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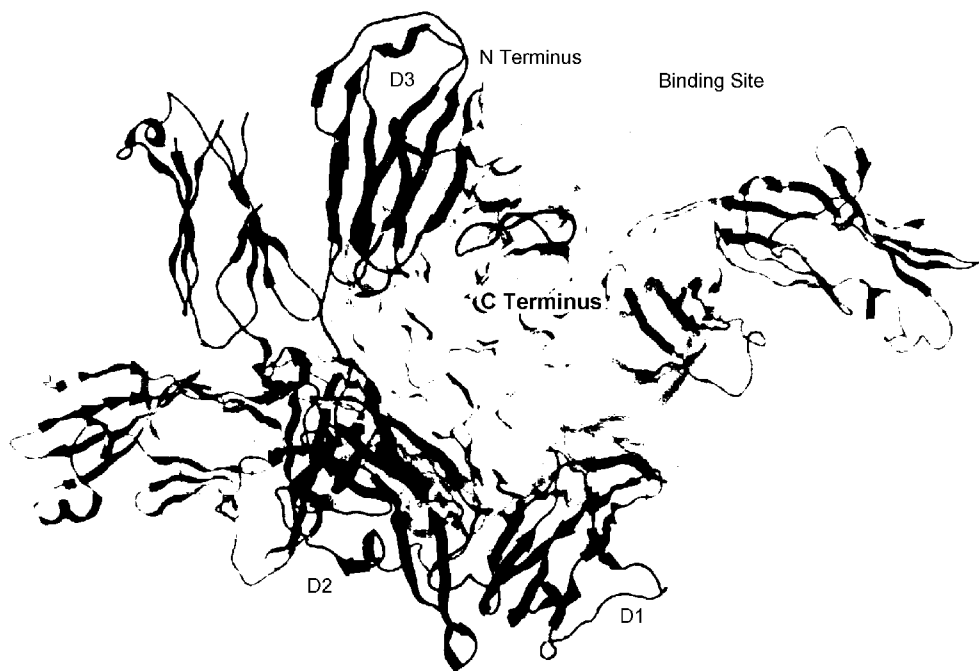


FIG. 1

(57) Abstract: Provided are methods of using a compound that binds to interleukin- 1 beta (IL- 1β) at a binding pocket of IL- 1β identified herein, which traps the IL- 1β and inhibits its interaction with interleukin- 1 receptor type I (IL-1R1).



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METHODS OF USING CYCLIC PEPTIDES FOR TRAPPING INTERLEUKIN-1 BETA**1. CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of U.S. Provisional Patent Application Nos. 63/507,984, filed June 13, 2023, and 63/612,878, filed December 20, 2023, the disclosure of each of which is incorporated by reference herein in its entirety.

2. SEQUENCE LISTING

[0002] This application contains a computer readable Sequence Listing which has been submitted in XML file format with this application, the entire content of which is incorporated by reference herein in its entirety. The Sequence Listing XML file submitted with this application is entitled “14463-089-228_SEQ_LISTING.xml”, was created on June 10, 2024, and is 46,471 bytes in size.

3. FIELD

[0003] The present disclosure relates to methods of using a compound, such as a cyclic peptide or compound of Formula (I), (II), (IIA), (III), (IIIA), or (IV), which binds to interleukin-1 beta (IL-1 β) to trap the IL-1 β from interacting with interleukin-1 receptor type I (IL-1R1).

4. BACKGROUND

[0004] Interleukin-1 beta (IL-1 β) signals by binding to its cell-surface receptor interleukin-1 receptor type I (IL-1R1) through interactions between IL-1 β and three binding domains (D1, D2, D3) of IL-1R1. The binding interaction of IL-1 β and IL-1R1 may be disrupted or inhibited by allosterically modifying the conformation of IL-1 β or by orthosterically binding to IL-1 β to competitively disrupt the binding interaction between IL-1 β and the D3 domain of IL-1R1. There is an ongoing need for continued development of compounds that are allosteric and/or orthosteric inhibitors of IL-1 β -induced IL-1R1 signaling.

5. SUMMARY

[0005] In one aspect, provided herein is a method of inhibiting binding of human interleukin-1 beta (IL-1 β) to a human interleukin-1 receptor type I (IL-1R1), comprising contacting the IL-1 β with a compound or pharmaceutically acceptable salt thereof that binds to a lipophilic binding pocket of the IL-1 β (SEQ ID NO:1).

[0006] In another aspect, provided herein is a method of inhibiting binding of human interleukin-1 beta (IL-1 β) to a human interleukin-1 receptor type I (IL-1R1), comprising contacting the IL-1 β with a compound or pharmaceutically acceptable salt thereof that binds to the IL-1 β at a binding pocket defined by amino acid residues Gly177-Leu178-Lys179-Glu180-Lys181-Asn182-Leu183-Tyr184 (SEQ ID NO:16) and Val201-Asp202-Pro203-Lys204-Asn205-Tyr206-Pro207 (SEQ ID NO:17) of the IL-1 β (SEQ ID NO:1).

[0007] In some embodiments, the compound allosterically or orthosterically inhibits the binding of the IL-1 β to the IL-1R1. In some embodiments, the compound inhibits the binding of the IL-1 β to a D3 domain of IL-1R1 (SEQ ID NO:7).

[0008] In some embodiments, the compound binds to one or both of residues Lys179 or Pro207 of the IL-1 β . In some embodiments, the compound comprises at least one moiety selected from: a) a pi-effect interaction moiety capable of accepting a cation-pi interaction from the sidechain of residue Lys179 of the IL-1 β ; or b) a pi-effect interaction moiety capable of accepting a polar-pi interaction from the backbone of residue Pro207 of the IL-1 β .

[0009] In some embodiments, the binding pocket further comprises Val119, Arg120, and/or Ser121 of the IL-1 β . In some embodiments, the compound binds to one or more of Val119, Arg120, Ser121, Pro203, or Lys204 of the IL-1 β .

[0010] In some embodiments, the compound comprises at least one or more moieties selected from: a) a H-bond interaction moiety capable of donating a H-bond to the backbone carbonyl of residue Val119 of the IL-1 β ; b) a pi-effect interaction moiety capable of accepting a cation-pi interaction from the sidechain of residue Arg120 of the IL-1 β ; c) a H-bond interaction moiety capable of donating a H-bond to the backbone carbonyl of residue Ser121 of the IL-1 β ; d) a H-bond interaction moiety capable of donating a H-bond to the backbone carbonyl of residue Pro203 of the IL-1 β ; or e) a H-bond interaction moiety capable of donating a H-bond to the backbone carbonyl of residue Lys204 of the IL-1 β .

[0011] In some embodiments, the compound comprises at least one or more moieties selected from: a) a H-bond interaction moiety capable of donating a H-bond to the backbone carbonyl of residue Val119 of the IL-1 β ; b) a pi-effect interaction moiety capable of accepting a cation-pi interaction from the sidechain of residue Arg120 of the IL-1 β ; c) a H-bond interaction moiety capable of donating a H-bond to the backbone carbonyl of residue Ser269 of the IL-1 β ; d) a H-bond interaction moiety capable of accepting a H-bond to the backbone carbonyl of residue Ser269 of the IL-1 β ; or e) a basic moiety capable of an electrostatic interaction with the c-terminal carboxylic acid of the IL-1 β .

[0012] In some embodiments, the compound comprises at least one moiety selected from: a) a H-bond interaction moiety capable of accepting a H-bond from the backbone NH of residue Arg120 of the IL-1 β ; b) a H-bond interaction moiety capable of accepting a H-bond from the sidechain of residue Arg120 of the IL-1 β ; c) a H-bond interaction moiety capable of accepting a H-bond from the backbone NH of residue Ser121 of the IL-1 β ; or d) a H-bond interaction moiety capable of accepting a H-bond from the sidechain of residue Lys204 of the IL-1 β .

[0013] In some embodiments, the compound binds to Tyr206 of the IL-1 β . In some embodiments, the compound comprises a H-bond interaction moiety capable of donating a H-bond to the backbone carbonyl of residue Tyr206 of the IL-1 β .

[0014] In some embodiments, the binding pocket further comprises Phe162 and/or Ser269 of the IL-1 β . The method of claim 20, wherein the compound binds to one or both of residues Phe162 or Ser269 of the IL-1 β .

[0015] In some embodiments, the compound comprises one or more moieties selected from: a) a pi-effect interaction moiety capable of donating a polar-pi interaction to residue Phe162 of the IL-1 β ; b) a H-bond interaction moiety capable of accepting a H-bond from the sidechain of residue Ser269 of the IL-1 β ; or c) a pi-effect interaction moiety capable of accepting a polar-pi interaction from residue Ser269 of the IL-1 β .

[0016] In some embodiments, the compound is a peptide. In some embodiments, the peptide is a cyclic peptide. In some embodiments, the peptide or cyclic peptide has a length of from 12 to 16 amino acid residues.

[0017] In some embodiments, the compound has a molecular weight of from about 1200 Da to about 3000 Da, from about 1500 Da to 2500 Da, or from about 1750 to about 2250 Da.

[0018] In another aspect, provided herein is a method of inhibiting binding of human IL-1 β to human IL-1R1, comprising contacting the IL-1 β with a compound that competes for binding to the IL-1R1, wherein the compound has a structure of Formula (I), (II), (IIA), (III), (IIIA), (IV), or a pharmaceutically acceptable salt thereof, wherein X¹, X², X³, A¹, A², R¹-R⁷, R^{8a}, R^{8b}, R^{9a}, R^{9b}, R¹⁰, R¹¹, R¹², R^{13a}, R^{13b}, and R¹⁴ are as herein described.

[0019] In another aspect, provided herein is a method of inhibiting binding of human IL-1 β to human IL-1R1, comprising contacting the IL-1 β with a compound that competes for binding to the IL-1R1, wherein the compound is a peptide having a sequence selected from: SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, or SEQ ID NO:15, or a pharmaceutically acceptable salt thereof.

[0020] In another aspect, provided herein is a method of inhibiting binding of human IL-1 β to human IL-1R1, comprising contacting the IL-1 β with a compound that competes for binding to the IL-1R1, wherein the compound is a peptide having a sequence selected from: Compound A, Compound B, Compound C, Compound D, Compound E, Compound F, Compound G, Compound H, or a pharmaceutically acceptable salt thereof.

6. BRIEF DESCRIPTION OF THE DRAWINGS

[0021] The foregoing summary, as well as the following detailed description of specific embodiments of the present application, will be better understood when read in conjunction with the appended drawings. It should be understood, however, that the application is not limited to the precise embodiments shown in the drawings.

[0022] **FIG. 1** depicts a binding site that has been identified on IL-1 β at which a compound as described herein can bind at in order to inhibit or disrupt the binding of IL-1 β to IL-1R1. The binding site shown is a lipophilic binding pocket located between the N-terminal and C-terminal domains of the tertiary structure of IL-1 β and is adjacent to the 3rd binding domain of IL-1R1.

[0023] **FIGs. 2A-2D** depict the numbering scheme for the amino acid residues of certain macrocyclic peptides of Formula (I), (II), (III), and (IV), respectively, as described herein.

[0024] **FIG. 3** depicts a three-dimensional cartoon plot of Compound A (SEQ ID NO:8) of the disclosure when bound at the lipophilic binding pocket of IL-1 β , as determined by X-ray crystallography. The side chains of amino acid positions 1, 2, 6, 7, and 10 of the macrocyclic

peptide are shown using stick representations and labeled. Amino acid residues Arg120, Ser121, Lys179, and Lys204 of the IL-1 β are labeled.

[0025] FIGS. 4A-4B depict two-dimensional diagrams of the binding interactions of Compound A (SEQ ID NO:8) to residues of the lipophilic binding pocket of IL-1 β , as determined by X-ray crystallography. FIG. 4A shows the binding interactions for the bottom portion (amino acids 1-7) of Compound A (SEQ ID NO:8) to residues of the binding pocket. FIG. 4B shows the binding interactions for the top portion (amino acids 8-14) of Compound A (SEQ ID NO:8) to residues of the binding pocket. Hydrogen bond interactions between the compound and an IL-1 β residue (acceptors/donors) are represented using dashed arrows, in which the arrowhead indicates the H-bond acceptor. Pi-effect interactions (*e.g.*, arene-H) are represented with dashed arrows having an H:benzene symbol.

[0026] FIG. 5 depicts a three-dimensional cartoon plot of Compound B (SEQ ID NO:9) of the disclosure when bound at the lipophilic binding pocket of IL-1 β , as determined by X-ray crystallography. The side chains of amino acid positions 1, 2, 6, 7, and 10 of the macrocyclic peptide are shown using stick representations and labeled. Amino acid residues Arg120, Ser121, Lys179, and Lys204 of the IL-1 β are labeled.

[0027] FIGS. 6A-6B depict two-dimensional diagrams of the binding interactions of Compound B (SEQ ID NO:9) to residues of the lipophilic binding pocket of IL-1 β , as determined by X-ray crystallography. FIG. 6A shows the binding interactions for the bottom portion (amino acids 1-7) of Compound B (SEQ ID NO:9) to residues of the binding pocket. FIG. 6B shows the binding interactions for the top portion (amino acids 8-14) of Compound B (SEQ ID NO:9) to residues of the binding pocket. Hydrogen bond interactions between the compound and an IL-1 β residue (acceptors/donors) are represented using dashed arrows, in which the arrowhead indicates the H-bond acceptor. Pi-effect interactions (*e.g.*, arene-H) are represented with dashed arrows having an H:benzene symbol.

[0028] FIG. 7 depicts a three-dimensional cartoon plot of Compound C (SEQ ID NO:10) of the disclosure when bound at the lipophilic binding pocket of IL-1 β , as determined by X-ray crystallography. The side chains of amino acid positions 1, 2, 6, 7, and 10 of the macrocyclic peptide are shown using stick representations and labeled. Amino acid residues Arg120, Ser121, Lys179, and Lys204 of the IL-1 β are labeled.

[0029] **FIGS. 8A-8B** depict two-dimensional diagrams of the binding interactions of Compound C (SEQ ID NO:10) to residues of the lipophilic binding pocket of IL-1 β , as determined by X-ray crystallography. FIG. 8A shows the binding interactions for the bottom portion (amino acids 1-7) of Compound C (SEQ ID NO:10) to residues of the binding pocket. FIG. 8B shows the binding interactions for the top portion (amino acids 8-14) of Compound C (SEQ ID NO:10) to residues of the binding pocket. Hydrogen bond interactions between the compound and an IL-1 β residue (acceptors/donors) are represented using dashed arrows, in which the arrowhead indicates the H-bond acceptor. Pi-effect interactions (*e.g.*, arene-H) are represented with dashed arrows having an H:benzene symbol.

[0030] **FIG. 9** depicts a three-dimensional cartoon plot of Compound D (SEQ ID NO:11) of the disclosure when bound at the lipophilic binding pocket of IL-1 β , as determined by X-ray crystallography. The side chains of amino acid positions 1, 2, 6, 7, and 10 of the macrocyclic peptide are shown using stick representations and labeled. Amino acid residues Arg120, Ser121, Lys179, and Lys204 of the IL-1 β are labeled.

[0031] **FIGS. 10A-10B** depict two-dimensional diagrams of the binding interactions of Compound D (SEQ ID NO:11) to residues of the lipophilic binding pocket of IL-1 β , as determined by X-ray crystallography. FIG. 10A shows the binding interactions for the bottom portion (amino acids 1-7) of Compound D (SEQ ID NO:11) to residues of the binding pocket. FIG. 10B shows the binding interactions for the top portion (amino acids 8-14) of Compound D (SEQ ID NO:11) to residues of the binding pocket. Hydrogen bond interactions between the compound and an IL-1 β residue (acceptors/donors) are represented using dashed arrows, in which the arrowhead indicates the H-bond acceptor. Pi-effect interactions (*e.g.*, arene-H) are represented with dashed arrows having an H:benzene symbol.

[0032] **FIG. 11** depicts a three-dimensional cartoon plot of Compound E (SEQ ID NO:12) of the disclosure when bound at the lipophilic binding pocket of IL-1 β , as determined by X-ray crystallography. The side chains of amino acid positions 1, 2, 6, 7, and 10 of the macrocyclic peptide are shown using stick representations and labeled. Amino acid residues Arg120, Ser121, Lys179, and Lys204 of the IL-1 β are labeled.

[0033] **FIGS. 12A-12B** depict two-dimensional diagrams of the binding interactions of Compound E (SEQ ID NO:12) to residues of the lipophilic binding pocket of IL-1 β , as determined by X-ray crystallography. FIG. 12A shows the binding interactions for the bottom

portion (amino acids 1-7) of Compound E (SEQ ID NO:12) to residues of the binding pocket. FIG. 12B shows the binding interactions for the top portion (amino acids 8-14) of Compound E (SEQ ID NO:12) to residues of the binding pocket. Hydrogen bond interactions between the compound and an IL-1 β residue (acceptors/donors) are represented using dashed arrows, in which the arrowhead indicates the H-bond acceptor. Pi-effect interactions (*e.g.*, arene-H) are represented with dashed arrows having an H:benzene symbol.

[0034] FIG. 13 depicts a three-dimensional cartoon plot of the lipophilic binding pocket of IL-1 β when bound to Compound A (SEQ ID NO:8), Compound B (SEQ ID NO:9), Compound C (SEQ ID NO:10), Compound D (SEQ ID NO:11), and Compound E (SEQ ID NO:12) of the disclosure, as determined by X-ray crystallography and presented as an overlay. The side chains of amino acid positions 1, 2, 6, 7, and 10 of the macrocyclic peptides are shown using stick representations and labeled. Amino acid residues Arg120, Ser121, Lys179, and Lys204 of the IL-1 β binding pocket are labeled.

[0035] FIG. 14 depicts a three-dimensional cartoon plot of Compound F (SEQ ID NO:13) of the disclosure when bound at the lipophilic binding pocket of IL-1 β , as determined by X-ray crystallography. The side chains of amino acid positions 1, 3, 6, 9, 10, and 15 of the macrocyclic peptide are shown using stick representations and labeled. Amino acid residues Arg120, Ser121, Lys179, and Lys204 of the IL-1 β binding pocket are labeled.

[0036] FIGS. 15A-15B depict two-dimensional diagrams of the binding interactions of Compound F (SEQ ID NO:13) to residues of the lipophilic binding pocket of IL-1 β , as determined by X-ray crystallography. FIG. 15A shows the binding interactions for the bottom portion (amino acids 1-8) of Compound F (SEQ ID NO:13) to residues of the binding pocket. FIG. 15B shows the binding interactions for the top portion (amino acids 9-15) of Compound F (SEQ ID NO:13) to residues of the binding pocket. Hydrogen bond interactions between the compound and an IL-1 β residue (acceptors/donors) are represented using dashed arrows, in which the arrowhead indicates the H-bond acceptor. Pi-effect interactions (*e.g.*, arene-H) are represented with dashed arrows having an H:benzene symbol.

[0037] FIG. 16 depicts a three-dimensional cartoon plot of Compound G (SEQ ID NO:14) of the disclosure when bound at the lipophilic binding pocket of IL-1 β , as determined by X-ray crystallography. The side chains of amino acid positions 1, 2, 6, 7, and 10 of the macrocyclic

peptide are shown using stick representations and labeled. Amino acid residues Arg120, Ser121, Lys179, and Lys204 of the IL-1 β binding pocket are labeled.

[0038] FIGS. 17A-17B depict two-dimensional diagrams of the binding interactions of Compound G (SEQ ID NO:14) to residues of the lipophilic binding pocket of IL-1 β , as determined by X-ray crystallography. FIG. 17A shows the binding interactions for the bottom portion (amino acids 1-7) of Compound G (SEQ ID NO:14) to residues of the binding pocket. FIG. 17B shows the binding interactions for the top portion (amino acids 8-14) of Compound G (SEQ ID NO:14) to residues of the binding pocket. Hydrogen bond interactions between the compound and an IL-1 β residue (acceptors/donors) are represented using dashed arrows, in which the arrowhead indicates the H-bond acceptor. Pi-effect interactions (*e.g.*, arene-H) are represented with dashed arrows having an H:benzene symbol.

[0039] FIG. 18 depicts a three-dimensional cartoon plot of Compound H (SEQ ID NO:15) of the disclosure when bound at the lipophilic binding pocket of IL-1 β , as determined by X-ray crystallography. The side chains of amino acid positions 1, 2, 6, 7, and 10 of the macrocyclic peptide are shown using stick representations and labeled. Amino acid residues Arg120, Ser121, Lys179, and Lys204 of the IL-1 β binding pocket are labeled.

[0040] FIGS. 19A-19B depict two-dimensional diagrams of the binding interactions of Compound H (SEQ ID NO:15) to residues of the lipophilic binding pocket of IL-1 β , as determined by X-ray crystallography. FIG. 19A shows the binding interactions for the bottom portion (amino acids 1-7) of Compound H (SEQ ID NO:15) to residues of the binding pocket. FIG. 19B shows the binding interactions for the top portion (amino acids 8-13) of Compound H (SEQ ID NO:15) to residues of the binding pocket. Hydrogen bond interactions between the compound and an IL-1 β residue (acceptors/donors) are represented using dashed arrows, in which the arrowhead indicates the H-bond acceptor. Pi-effect interactions (*e.g.*, arene-H) are represented with dashed arrows having an H:benzene symbol.

7. DETAILED DESCRIPTION

7.1 DEFINITIONS

[0041] Various publications, articles and patents are cited or described in the background and throughout the specification; each of these references is herein incorporated by reference in its entirety. Discussion of documents, acts, materials, devices, articles or the like which has been

included in the present specification is for the purpose of providing context for the invention. Such discussion is not an admission that any or all of these matters form part of the prior art with respect to any inventions disclosed or claimed.

[0042] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention pertains. Otherwise, certain terms used herein have the meanings as set forth in the specification.

[0043] It must be noted that as used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural reference unless the context clearly dictates otherwise.

[0044] Unless otherwise stated, any numerical values, such as a concentration or a concentration range described herein, are to be understood as being modified in all instances by the term “about.” Thus, a numerical value typically includes $\pm 10\%$ of the recited value. For example, a concentration of 1 mg/mL includes 0.9 mg/mL to 1.1 mg/mL. Likewise, a concentration range of 1% to 10% (w/v) includes 0.9% (w/v) to 11% (w/v). As used herein, the use of a numerical range expressly includes all possible subranges, all individual numerical values within that range, including integers within such ranges and fractions of the values unless the context clearly indicates otherwise.

[0045] Unless otherwise indicated, the term “at least” preceding a series of elements is to be understood to refer to every element in the series. Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the methods provided herein. Such equivalents are intended to be encompassed by the invention.

[0046] As used herein, the terms “comprises,” “comprising,” “includes,” “including,” “has,” “having,” “contains” or “containing,” or any other variation thereof, will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers and are intended to be non-exclusive or open-ended. For example, a composition, a mixture, a process, a method, an article, or an apparatus that comprises a list of elements is not necessarily limited to only those elements but can include other elements not expressly listed or inherent to such composition, mixture, process, method, article, or apparatus. Further, unless expressly stated to the contrary, “or” refers to an inclusive or and not to an exclusive or. For example, a condition A or B is satisfied by any one of the following: A is true

(or present) and B is false (or not present), A is false (or not present) and B is true (or present), and both A and B are true (or present).

[0047] As used herein, the conjunctive term “and/or” between multiple recited elements is understood as encompassing both individual and combined options. For instance, where two elements are conjoined by “and/or,” a first option refers to the applicability of the first element without the second. A second option refers to the applicability of the second element without the first. A third option refers to the applicability of the first and second elements together. Any one of these options is understood to fall within the meaning, and therefore satisfy the requirement of the term “and/or” as used herein. Concurrent applicability of more than one of the options is also understood to fall within the meaning, and therefore satisfy the requirement of the term “and/or.”

[0048] As used herein, the term “consists of,” or variations such as “consist of” or “consisting of,” as used throughout the specification and claims, indicate the inclusion of any recited integer or group of integers, but that no additional integer or group of integers can be added to the specified method, structure, or composition.

[0049] As used herein, the term “consists essentially of,” or variations such as “consist essentially of” or “consisting essentially of,” as used throughout the specification and claims, indicate the inclusion of any recited integer or group of integers, and the optional inclusion of any recited integer or group of integers that do not materially change the basic or novel properties of the specified method, structure, or composition. See M.P.E.P. § 2111.03.

[0050] As used herein, “subject” means any animal, preferably a mammal, most preferably a human. The term “mammal” as used herein, encompasses any mammal. Examples of mammals include, but are not limited to, cows, horses, sheep, pigs, cats, dogs, mice, rats, rabbits, guinea pigs, monkeys, humans, *etc.*, more preferably a human.

[0051] It should also be understood that the terms “about,” “approximately,” “generally,” “substantially,” and like terms, used herein when referring to a dimension or characteristic of a component of the methods provided herein, indicate that the described dimension/characteristic is not a strict boundary or parameter and does not exclude minor variations therefrom that are functionally the same or similar, as would be understood by one having ordinary skill in the art. At a minimum, such references that include a numerical parameter would include variations that, using mathematical and industrial principles accepted in the art (*e.g.*, rounding, measurement or other systematic errors, manufacturing tolerances, *etc.*), would not vary the least significant digit.

[0052] The terms “decrease,” “lower” or “reduce,” refer generally to the ability of a test molecule to mediate a reduced response (*i.e.*, downstream effect) when compared to the response mediated by a control or a vehicle. Decrease may be a statistically significant difference in the measured response between the test molecule and the control (or the vehicle), or a decrease in the measured response, such as a decrease of about 1.1, 1.2, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20 or 30 fold or more, such as 500, 600, 700, 800, 900 or 1000 fold or more.

[0053] The terms “enhance,” “promote” or “increase,” refer generally to the ability of the test molecule to mediate a greater response (*i.e.*, downstream effect) when compared to the response mediated by a control or a vehicle. Enhance may be a statistically significant difference in the measured response between the test molecule and control (or vehicle), or an increase in the measured response, such as an increase of about 1.1, 1.2, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20 or 30-fold or more, such as 500, 600, 700, 800, 900 or 1000-fold or more.

[0054] The term “recombinant” refers to polynucleotides, polypeptides, vectors, viruses, and other macromolecules that are prepared, expressed, created, or isolated by recombinant means.

[0055] The terms “specifically binds,” “specific binding,” “specifically binding” or “binds” refer to a compound as described herein binding to interleukin-1 receptor type I (IL-1R1), for example, at a binding pocket of IL-1R1 or to a specific residue of IL-1R1.

[0056] The term “subject” includes any human or nonhuman animal. “Nonhuman animal” includes all vertebrates, *e.g.*, mammals and non-mammals, such as nonhuman primates, sheep, dogs, cats, horses, cows, chickens, amphibians, reptiles, *etc.* The terms “subject” and “patient” can be used interchangeably herein.

[0057] As used throughout this disclosure, “a compound of the disclosure”, “a compound of the present disclosure” and “a compound disclosed herein” are used interchangeably are to be understood to include the disclosed cyclic peptides and compounds of Formulas (I), (II), (IIA), (III), (IIIA), and (IV). Reference to the compounds of Formula (I) includes the compounds of other generic formulas that fall within the scope of Formula (I) including, but not limited, to the compounds of Formula (IA). Reference to the compounds of Formula (II) includes the compounds of other generic formulas that fall within the scope of Formula (II) including, but not limited to, the compounds of Formula (IIA). Reference to the compounds of Formula (III) includes the compounds of other generic formulas that fall within the scope of Formula (III) including, but not limited to, the compounds of Formula (IIIA). Reference to the compounds of

Formula (IV) includes the compounds of other generic formulas that fall within the scope of Formula (IV). The compounds of Formulas (I), (II), (IIA), (III), (IIIA), and (IV) can form salts which are also within the scope of the present disclosure. Reference to a compound of the disclosure (or a compound of Formula (I), (II), (IIA), (III), (IIIA), or (IV)) herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula (I), (II), (IIA), (III), (IIIA), or (IV) contains both a basic moiety, such as, but not limited to an amino group, pyrrolidine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. In one embodiment, the salt is a pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salt. In another embodiment, the salt is other than a pharmaceutically acceptable salt. Salts of the compounds of Formula (I) may be formed, for example, by reacting a compound of Formula (I), (II), (IIA), (III), (IIIA), or (IV) with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

[0058] "Acyl" means an alkyl-C(O)- group, wherein alkyl is as defined below. The bond to the parent group is through the carbon atom of the carbonyl group.

[0059] "Alkyl", as well as other groups having the prefix "alk", such as alkoxy, and the like, means carbon chains which may be linear or branched, or combinations thereof, containing the indicated number of carbon atoms. For instance, a C₁-C₆ alkyl means an alkyl group having one (*i.e.*, methyl) up to 6 carbon atoms (*i.e.*, hexyl). In particular embodiments, linear alkyl groups have 1-6 carbon atoms and branched alkyl groups have 3-7 carbon atoms. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*- and *tert*-butyl, pentyl, hexyl, heptyl, octyl, nonyl and the like.

[0060] "Alkoxy" and "alkyl-O-" are used interchangeably and refer to an alkyl group linked to oxygen.

[0061] "Amino" means a H₂N- group. The bond to the parent group is through the nitrogen atom.

[0062] "Amino acid" refers to naturally occurring α -amino acids and their stereoisomers, as well as unnatural amino acids (such as β -amino acids and substituted amino acids) and their

stereoisomers. In the sequences given for the peptides (compounds) according to the present disclosure, the amino acid residues have their conventional meaning. Thus, "G" is glycine, "W" is tryptophan, "A" is alanine, "S" is serine, and so on. It is to be understood that "D" isomers are designated by a "d" before the one letter code or amino acid name, such that for example dA is the D isomer of L-alanine. Amino acid residues not encompassed by the foregoing have the definitions provided in the Table in the Examples section below.

[0063] "Arene," as used herein, refers to an aryl or heteroaryl.

[0064] "Aryl", as used herein, represents a monocyclic 6-membered or bicyclic 10-membered ring system, wherein at least one ring is aromatic, and all the ring atoms are carbon.

[0065] "Bicyclic ring system" refers to two joined rings. The rings may be fused, *i.e.*, share two adjacent atoms, or "spirocyclic", *i.e.*, share only a single atom.

[0066] "Carboxy" means a HO₂C- group. The bond to the parent group is through the carbon atom of the carbonyl component.

[0067] "Cycloalkyl" means a saturated cyclic hydrocarbon radical. In particular embodiments, the cycloalkyl group has 3-12 carbon atoms, forming 1-3 carbocyclic rings that are fused. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, and the like.

[0068] "Fluoroalkyl" includes mono-substituted as well as multiple fluoro-substituted alkyl groups, up to perfluoro substituted alkyl. For example, fluoromethyl, 1,1-difluoroethyl, trifluoromethyl or 1,1,1,2,2-pentafluorobutyl are included.

[0069] "Halogen" or "halo", unless otherwise indicated, includes fluorine (fluoro), chlorine (chloro), bromine (bromo) and iodine (iodo). In one embodiment, halo is fluoro (-F) or chloro (-Cl).

[0070] "Heterocycloalkyl" means a non-aromatic monocyclic, bicyclic, or tricyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. In some embodiments, heterocycloalkyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. In some embodiments, the nitrogen or sulfur atom of the heterocycloalkyl can be optionally oxidized to

the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiophenyl, and the like.

[0071] “Heteroaryl” refers to aromatic monocyclic, bicyclic, and tricyclic ring structures in which one or more atoms in the ring, the heteroatom(s), is an element other than carbon. Heteroatoms are typically O, S, or N atoms. Examples of heteroaromatic groups include pyridinyl, pyrimidinyl, pyrrolyl, pyridazinyl, isoxazolyl, thiazolyl, oxazolyl, indolyl, benzoxazolyl, benzothiazolyl, and imidazolyl.

[0072] When any variable (*e.g.*, RC¹) occurs more than one time in any constituent or in Formula (I), (II), (IIA), (III), (IIIA), or (IV) or other generic formulas herein, its definition on each occurrence is independent of its definition at every other occurrence. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. In choosing compounds of the present disclosure, one of ordinary skill in the art will recognize that the various substituents, *e.g.*, RC⁹, are to be chosen in conformity with well-known principles of chemical structure connectivity and stability. Unless expressly stated to the contrary, substitution by a named substituent is permitted on any atom in a ring (*e.g.*, aryl, a heteroaryl ring, or a saturated heteroaryl ring) provided such ring substitution is chemically allowed and results in a stable compound. A “stable” compound is a compound which can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (*e.g.*, therapeutic or prophylactic administration to a subject).

[0073] The term “substituted” shall be deemed to include multiple degrees of substitution by a named substituent. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally. By independently substituted, it is meant that the (two or more) substituents can be the same or different.

[0074] Unless expressly depicted or described otherwise, variables depicted in a structural formula with a “floating” bond, are permitted on any available carbon atom in the ring to which the variable is attached. When a moiety is noted as being “optionally substituted” in Formula (I), (II), (IIA), (III), (IIIA), or (IV) or any embodiment thereof, it means that Formula (I), (II), (IIA),

(III), (IIIA), or (IV) or the embodiment thereof encompasses compounds that contain the noted substituent (or substituents) on the moiety and also compounds that do not contain the noted substituent (or substituents) on the moiety.

[0075] The wavy line , as used herein, indicates a point of attachment to the rest of the compound.

[0076] Some of the compounds described herein may exist as tautomers which have different points of attachment of hydrogen accompanied by one or more double bond shifts. For example, a ketone and its enol form are keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of the present disclosure.

[0077] In the compounds of the disclosure, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present disclosure as described and claimed herein is meant to include all suitable isotopic variations of the compounds of the disclosure and embodiments thereof. For example, different isotopic forms of hydrogen (H) include protium (^1H) and deuterium (^2H , also denoted herein as D). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds of the disclosure can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

[0078] The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present disclosure is acidic (or has a functional group which may be anionic), its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Li^+ , Na^+ , and K^+ , alkaline earth metal cations such as Ca^{2+} , and Mg^{2+} , and other cations such as Al^{3+} and Zn^{2+} . Examples of suitable organic cations include, but are not limited to, ammonium ion (*i.e.*, NH_4^+) and substituted ammonium ions. Examples of

suitable substituted ammonium ions are those derived from methylamine, ethylamine, diethylamine, triethylamine and ethylenediamine. When a compound of the present disclosure is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic acids and organic acids. Example of such acid addition salts include salts formed from hydrohalic acids (*e.g.*, hydrochloric, hydrobromic, hydroiodic), formic acid, acetic acid, capric acid, and citric acids. Salts containing acetate, formate, caprate, chloride, or sodium salts are typical for use with the compounds of the present disclosure. In some embodiments, salts of compounds of the present disclosure can be formed by exchange well-known to those of ordinary skill in the art, such as by anion exchange, *e.g.*, replacement of trifluoroacetate ions with chloride ions.

[0079] Furthermore, compounds of the present disclosure may exist in amorphous form and/or one or more crystalline forms, and as such all amorphous and crystalline forms and mixtures thereof of the compounds of Formula (I), (II), (IIA), (III), (IIIA), or (IV), including the Examples, are intended to be included within the scope of the present disclosure. In addition, some of the compounds of the instant disclosure may form solvates with water (*i.e.*, a hydrate) or common organic solvents such as, but not limited to, acetic acid or acetonitrile. Such solvates and hydrates, particularly the pharmaceutically acceptable solvates and hydrates, of the instant compounds are likewise encompassed within the scope of this disclosure, along with un-solvated and anhydrous forms.

[0080] Any pharmaceutically acceptable pro-drug modification of a compound of this disclosure which results in conversion *in vivo* to a compound within the scope of this disclosure is also within the scope of this disclosure.

[0081] The present disclosure also relates to processes for the preparation of the compounds of Formula (I), (II), (IIA), (III), (IIIA), or (IV), which are described in the following Examples and by which the compounds of the disclosure are obtainable.

7.2 **METHODS**

[0082] In one aspect, provided herein is a method of inhibiting the binding of interleukin-1 beta (IL-1 β) to interleukin-1 receptor type I (IL-1R1), comprising contacting the IL-1 β with a compound as described herein or a pharmaceutically acceptable salt thereof.

[0083] In another aspect, provided herein is a method of inhibiting binding of IL-1 β to IL-1R, comprising contacting the IL-1 β with a compound as described herein or pharmaceutically acceptable salt thereof that competes for binding to the IL-1R1 (*e.g.*, the compound competes with IL-1 β for binding to IL-1R1).

[0084] In some embodiments of a method as described herein, a compound as described herein binds to IL-1 β at a binding pocket of IL-1 β , which inhibits the binding of IL-1 β to IL-1R1. In some embodiments, the binding pocket of IL-1 β is a lipophilic binding pocket and/or hydrophobic binding pocket of the IL-1 β .

[0085] In some embodiments of a method as described herein, a compound as described herein inhibits binding of IL-1 β to the A-site of IL-1R1 (*e.g.*, the A-site of IL-1R1 as described in Section 5.4). In some embodiments, inhibiting binding of IL-1 β to the A-site of IL-1R1 inhibits one or more biological functions of IL-1R1 (*e.g.*, inhibits propagation of inflammation, for example the propagation of inflammation in a subject). In some embodiments, a compound as described herein inhibits or reduces binding of IL-1 β to the D1 and/or D2 domain of IL-1R1. In some embodiments, inhibiting binding of IL-1 β to the D1 and/or D2 domain of IL-1R1 inhibits one or more biological functions of IL-1R1 (*e.g.*, inhibits propagation of inflammation, for example the propagation of inflammation in a subject).

[0086] In some embodiments of a method as described herein, a compound as described herein inhibits binding of IL-1 β to the B-site of IL-1R1 (*e.g.*, the B-site of IL-1R1 as described in Section 5.4). In some embodiments, inhibiting binding of IL-1 β to the B-site of IL-1R1 inhibits one or more biological functions of IL-1R1 (*e.g.*, inhibits propagation of inflammation, for example the propagation of inflammation in a subject). In some embodiments, a compound as described herein inhibits binding of IL-1 β to the D3 domain of IL-1R1. In some embodiments, inhibiting binding of IL-1 β to D3 domain of IL-1R1 inhibits one or more biological functions of IL-1R1 (*e.g.*, inhibits propagation of inflammation, for example the propagation of inflammation in a subject).

[0087] In some embodiments of a method as described herein, a compound as described herein inhibits binding of IL-1 β to both the A-site and B-site bindings sites of IL-1R1. In some embodiments, inhibiting binding of IL-1 β to both the A-site and B-site bindings sites of IL-1R1 inhibits one or more biological functions of IL-1R1 (*e.g.*, inhibits propagation of inflammation, for example the propagation of inflammation in a subject). In some embodiments, a compound

as described herein inhibits binding of IL-1 β to the D1, D2, and D3 domains of IL-1R1. In some embodiments, inhibiting binding of IL-1 β to the D1, D2, and D3 domains of IL-1R1 inhibits one or more biological functions of IL-1R1 (*e.g.*, inhibits propagation of inflammation, for example the propagation of inflammation in a subject).

[0088] In some embodiments, a compound as described herein orthosterically inhibits the binding of IL-1 β to IL-1R1. In some embodiments, orthosteric inhibition of IL-1R1 comprises binding of a compound as described herein to an orthosteric site (*e.g.*, primary binding site) of IL-1R1. In some embodiments, an orthosteric site (*e.g.*, primary binding site) is the active site of IL-1R1. In some embodiments, an orthosteric site (*e.g.*, primary binding site) of IL-1R1 is a binding site of IL-1R1 (*e.g.*, a binding site for a compound as described herein), which is the binding site of IL-1R1 that is specific for IL-1 β .

[0089] In some embodiments, a compound as described herein allosterically inhibits the binding of IL-1 β to IL-1R1. In some embodiments, allosteric inhibition of IL-1R1 comprises binding of a compound as described herein to an allosteric site (*e.g.*, secondary binding site) of IL-1R1. In some embodiments, an allosteric site (*e.g.*, secondary binding site) is not the active site of IL-1R1. In some embodiments, an allosteric site (*e.g.*, secondary binding site) of IL-1R1 is a binding site of IL-1R1 (*e.g.*, a binding site for a compound as described herein), which is not the binding site of IL-1R1 that is specific for IL-1 β .

[0090] In some embodiments of the methods described herein, the compound is a compound as described herein (*e.g.*, or the Examples). In some embodiments, the compound is a compound of structural Formula (I), (II), (IIA), (III), (IIIA), (IV), or their pharmaceutically acceptable salts, wherein X¹, X², X³, A¹, A², R¹-R⁷, R^{8a}, R^{8b}, R^{9a}, R^{9b}, R¹⁰, R¹¹, R¹², R^{13a}, R^{13b}, and R¹⁴ are as herein described.

7.3 INTERLEUKIN-1 BETA (IL-1B)

[0091] Interleukin-1 beta (IL-1 β) is a cytokine protein involved in inflammation. In some embodiments, IL-1 β is also known as: leukocytic pyrogen, leukocytic endogenous mediator, mononuclear cell factor, lymphocyte activating factor, IL1B, IL-1, IL1-BETA, IL1F2, or IL1beta. In some embodiments, the IL-1 β is encoded by the IL1B gene (*e.g.*, human IL1B gene). The precursor form of IL-1 β is cleaved by cytosolic caspase 1 (*e.g.*, interleukin 1 beta convertase) to produce a mature form of IL-1 β and a cleaved propeptide.

[0092] In some embodiments, the IL-1 β is a precursor form of IL-1 β . In some embodiments, the IL-1 β is a mature form of IL-1 β . In some embodiments, the mature form of IL-1 β does not comprise one or more or all of the amino acids of the propeptide of IL-1 β . In some embodiments, the IL-1 β (*e.g.*, precursor IL-1 β , propeptide of IL-1 β , or mature IL-1 β) is a human IL-1 β . In some embodiments, a precursor form of human IL-1 β comprises or consists of the amino acid sequence of the precursor form of human IL-1 β (*e.g.*, amino acids 1-269) as set forth at UniProt Accession No. P01584. In some embodiments, a precursor form of human IL-1 β comprises or consists of the amino acid sequence of SEQ ID NO:1. In some embodiments, a propeptide of human IL-1 β comprises or consists of the amino acid sequence of the propeptide of human IL-1 β (*e.g.*, amino acids 117-269) as set forth at UniProt Accession No. P01584. In some embodiments, a propeptide of human IL-1 β comprises or consists of the amino acid sequence of SEQ ID NO:2. In some embodiments, a mature form of human IL-1 β comprises or consists of the amino acid sequence of the mature form of human IL-1 β (*e.g.*, amino acids 117-269) as set forth at UniProt Accession No. P01584. In some embodiments, a mature form of human IL-1 β comprises or consists of the amino acid sequence of SEQ ID NO:3. Exemplary amino acid sequences of the forms of human IL-1 β are shown below in TABLE 1.

[0093] TABLE 1: Amino acid sequences for human IL-1 β

Name	Amino Acid Sequence
Human IL-1 β (precursor)	MAEVPELASEMMAYYSNEDDLFFEADGPKQMKCSFQDL DLCPLDGGI QLRISDHHYISKGFRQAASVVVAMDKLRKMLVPCPQTFQENDLSTFFPFIF EEPIFFDTWDNEAYVHDAPVRS LNCTLRDSQQKSLVMSGPYELKALHL QGQDMEQQVVFSMSFVQGEESNDKIPVALGLKEKNLYLSCVLKDDKPTL QLESVDPKNYPKKKMEKRFVFNKIEINN KLEFESAQFPNWIYSTSQAENM PVFLGGTKGGQDITDFTMQFVSS (SEQ ID NO:1)
Human IL-1 β (propeptide)	MAEVPELASEMMAYYSNEDDLFFEADGPKQMKCSFQDL DLCPLDGGI QLRISDHHYISKGFRQAASVVVAMDKLRKMLVPCPQTFQENDLSTFFPFIF EEPIFFDTWDNEAYVHD (SEQ ID NO:2)
Human IL-1 β (mature)	APVRS LNCTLRDSQQKSLVMSGPYELKALHLQGQDMEQQVVFSMSFVQ GEESNDKIPVALGLKEKNLYLSCVLKDDKPTLQLESVDPKNYPKKKMEK RFVFNKIEINN KLEFESAQFPNWIYSTSQAENMPVFLGGTKGGQDITDFT MQFVSS (SEQ ID NO:3)

[0094] It is contemplated that reference herein (*e.g.*, in a method described herein) to a specific amino acid residue number of the precursor form of IL-1 β may also refer to the corresponding residue of mature form of IL-1 β (*e.g.*, residue Val119 of the precursor form of IL-1 β refers to residue Val3 of the mature form of IL-1 β). The corresponding residue number of the

mature form of IL-1 β may be determined by subtracting the number of amino acids of the cleaved propeptide of IL-1 β (*e.g.*, 116 residues) from the specified residue number of the precursor form of IL-1 β .

7.3.1 IL-1 β Binding Pocket and Interaction Residues

[0095] A compound of the methods as described herein is capable of binding to IL-1 β at one or more binding pockets of the IL-1 β . In some embodiments, the binding pocket of IL-1 β is a lipophilic binding pocket of IL-1 β . In some embodiments, the binding pocket of IL-1 β is a hydrophobic binding pocket of IL-1 β . In some embodiments, the lipophilic or hydrophobic binding pocket of IL-1 β is recognizable from the primary sequence, secondary structure, or tertiary structure of the amino acid sequence of the IL-1 β . In some embodiments, the binding pocket of IL-1 β is the binding pocket of IL-1 β as shown in FIG. 1. In some embodiments, the binding pocket of IL-1 β is a binding pocket for a compound according to Formula (I), (II), (IIA), (III), (IIIA), (IV) as described herein, or their pharmaceutically acceptable salts, wherein X1, X2, X3, A1, A2, R1-R7, R8a, R8b, R9a, R9b, R10, R11, R12, R13a, R13b, and R14 are as herein described,

[0096] In some embodiments, the binding pocket of IL-1 β is defined by the residues of IL-1 β described herein as a binding pocket of IL-1 β (*e.g.*, a binding pocket of IL-1 β located between the N-terminal and C-terminal domains of the tertiary structure of IL-1 β , *e.g.*, as shown in FIG. 1). In some embodiments, the binding pocket of IL-1 β is at or adjacent to a D3 domain of IL-1R1 in an IL-1 β /IL-1R1 complex. In some embodiments, an IL-1 β /IL-1R1 complex is a macromolecular complex of IL-1 β bound to IL-1R1 formed in the absence a compound that inhibits IL-1 β /IL-1R1 complex formation (*e.g.*, a compound as described herein).

[0097] In some embodiments, the binding pocket of IL-1 β comprises or consists of the amino acid residues of Gly177-Leu178-Lys179-Glu180-Lys181-Asn182-Leu183-Tyr184 (SEQ ID NO:16) and/or Val201-Asp202-Pro203-Lys204-Asn205-Tyr206-Pro207 (SEQ ID NO:17) of IL-1 β . In some embodiments, the binding pocket of IL-1 β comprises or consists of the amino acid residues 177-184 and 201-207 of the IL-1 β (SEQ ID NO:1). In some embodiments, when a compound as described herein binds at a binding pocket of IL-1 β , all of the residues recited for the binding pocket of IL-1 β are bound by the compound. In some embodiments, when a compound as described herein binds at a binding pocket of IL-1 β , one or more but not all of the

residues recited for the binding pocket of IL-1 β are bound by the compound. In some embodiments, the binding pocket of IL-1 β further comprises additional IL-1 β residues, such as those additional residues of the binding pocket of IL-1 β as described herein.

[0098] In some embodiments, the binding between a residue of the binding pocket of IL-1 β and a compound as described herein is via a non-covalent interaction. In some embodiments, a non-covalent interaction as described herein may be donated by a residue of the binding pocket of the IL-1 β and accepted by the compound. In some embodiments, a non-covalent interaction as described herein may be donated by the compound and accepted by a residue of the binding pocket of the IL-1 β . For example, a pi-effect interaction may involve a cation from the binding pocket (*e.g.*, a hydrogen from the backbone of a residue of the binding pocket) being donated to and accepted by a pi orbital of the compound, to form a cation-pi interaction. Cation-pi interactions can occur between cationic sidechains of either a lysine or arginine and an aromatic. In some embodiments, a residue of the binding pocket of IL-1 β binds to a compound as described herein via a lipophilic interaction and/or hydrophobic interaction (*e.g.*, minimization of non-polar surface area exposure to polar molecules). In some embodiments, a residue of the binding pocket of IL-1 β binds to a compound as described herein via an electrostatic interaction (*e.g.*, Coulombic attraction interaction). In some embodiments, a residue of the binding pocket of IL-1 β binds to a compound as described herein via an ionic interaction (*e.g.*, electrovalent interaction). In some embodiments, a residue of the binding pocket of IL-1 β binds to a compound as described herein via a hydrogen bond (H-bond) interaction (*e.g.*, backbone or sidechain H-bond interaction). In some embodiments, a residue of the binding pocket of IL-1 β binds to a compound as described herein via a halogen bond interaction (*e.g.*, sidechain halogen bond interaction). In some embodiments, a residue of the binding pocket of IL-1 β binds to a compound as described herein via a Van der Waals interaction (*e.g.*, a dipole-dipole interaction; dipole-induced dipole interaction; or London dispersion forces). In some embodiments, a residue of the binding pocket of IL-1 β binds to a compound as described herein via a pi-effect interaction (*e.g.*, a pi-pi interaction; CH-pi interaction; cation-pi interaction; anion-pi interaction; or polar-pi interaction) to a residue of the IL-1 β . In some embodiments, a pi-effect interaction is a stacking interaction (*e.g.*, a pi-pi interaction). In some embodiments, the pi-effect interaction is a non-polar pi-effect interaction. In some embodiments, a polar-pi interaction is a polar hydrogen-pi interaction. In some embodiments, a polar-pi interaction is a polar nitrogen-pi

interaction. In some embodiments, a non-covalent interaction may be characterized as more than one type of non-covalent interaction as described herein.

[0099] In some embodiments, a residue of a binding pocket of IL-1 β as described herein binds to a compound at a functional group of a compound. In some embodiments, the functional group of the compound is a functional group on the sidechain or backbone moiety. In some embodiments, a functional group of the compound is an amino group (*e.g.*, NH group, NH₂ group, or NH₃⁺ group), carbonyl group, carboxylate group, or a cyclic pi-system of the compound (*e.g.*, an arene, aryl, or biaryl). In some embodiments, a residue of a binding pocket of IL-1 β as described herein binds to a compound at a site of the compound that is not a functional group of the compound.

[00100] In some embodiments, a binding pocket of IL-1 β comprises one or more of the amino acids corresponding to residues 177-184 and 201-207 of the IL-1 β (SEQ ID NO:1) and optionally one or more additional residue of the IL-1 β . In some embodiments, the binding pocket of IL-1 β is defined by one or more of amino acid residues Gly177-Leu178-Lys179-Glu180-Lys181-Asn182-Leu183-Tyr184 (SEQ ID NO:16) and Val201-Asp202-Pro203-Lys204-Asn205-Tyr206-Pro207 (SEQ ID NO:17) (*e.g.*, Gly177 through Tyr184 and Val201 through Pro207) of the IL-1 β (SEQ ID NO:1) and optionally one or more additional residue of the IL-1 β . In some embodiments, the one or more additional residue is selected from the group consisting of Val119, Arg120, Ser121, Phe162, and Ser269 of SEQ ID NO:1. In some embodiments, the one or more additional residue is selected from the group consisting of Val119, Arg120, Ser121, Phe162, Ser269, Ala117, Pro118, Leu122, Asn123, Ser159, and Phe266 of SEQ ID NO:1.

[00101] In some embodiments, the binding pocket of the IL-1 β further comprises the amino acid corresponding to residue 119 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of IL-1 β is further defined by amino acid residue Val119 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of the IL-1 β further comprises the amino acid corresponding to residue 120 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of IL-1 β is further defined by amino acid residue Arg120 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of the IL-1 β further comprises the amino acid corresponding to residue 121 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of IL-1 β is further defined by amino acid residue Ser121 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of the IL-1 β further comprises the

amino acid corresponding to residue 162 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of IL-1 β is further defined by amino acid residue Phe162 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of the IL-1 β further comprises the amino acid corresponding to residue 269 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of IL-1 β is further defined by amino acid residue Ser269 of the IL-1 β (SEQ ID NO:1).

[00102] In some embodiments, the binding pocket of the IL-1 β further comprises the amino acid corresponding to residue 117 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of IL-1 β is further defined by amino acid residue Ala117 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of the IL-1 β further comprises the amino acid corresponding to residue 118 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of IL-1 β is further defined by amino acid residue Pro118 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of the IL-1 β further comprises the amino acid corresponding to residue 122 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of IL-1 β is further defined by amino acid residue Leu122 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of the IL-1 β further comprises the amino acid corresponding to residue 123 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of IL-1 β is further defined by amino acid residue Asn123 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of the IL-1 β further comprises the amino acid corresponding to residue 159 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of IL-1 β is further defined by amino acid residue Ser159 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of the IL-1 β further comprises the amino acid corresponding to residue 266 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of IL-1 β is further defined by amino acid residue Phe266 of the IL-1 β (SEQ ID NO:1).

[00103] In some embodiments, the binding pocket of IL-1 β for a compound as described herein comprises or consists of one or more amino acids corresponding to residues selected from 119, 120, 121, 162, 179, 203, 204, 206, 207, or 269 of the IL-1 β (SEQ ID NO:1). In some embodiments, the binding pocket of IL-1 β for a compound as described herein comprises or consists of one or more amino acid residues selected from residues Val119, Arg120, Ser121, Phe162, Lys179, Pro203, Lys204, Tyr206, Pro207, or Ser269 of the IL-1 β (SEQ ID NO:1).

[00104] In certain embodiments, the binding pocket of IL-1 β for a compound as described herein comprises or consists of the amino acids corresponding to residues 119, 120, 121, 203, and 204 of the IL-1 β (SEQ ID NO:1). In certain embodiments, the binding pocket of IL-1 β for a compound as described herein comprises or consists of residues Val119, Arg120, Ser121, Pro203, and Lys204 of the IL-1 β (SEQ ID NO:1). In certain embodiments, the IL-1 β (SEQ ID NO:1) has no further interactions with the compound. In certain embodiments, the binding pocket of IL-1 β for a compound as described herein comprises or consists of one, two, three, four, or five amino acids corresponding to residues selected from 162, 179, 206, 207 or 269 of the IL-1 β (SEQ ID NO:1). In certain embodiments, the binding pocket of IL-1 β for a compound as described herein comprises or consists of one, two, three, four, or five residues selected from Phe162, Lys179, Tyr206, Pro207, or Ser269 of the IL-1 β (SEQ ID NO:1). In certain embodiments, the binding pocket of IL-1 β for a compound as described herein comprises or consists of at least the amino acid corresponding to residue 179 and/or residue 207 of the IL-1 β (SEQ ID NO:1). In certain embodiments, the binding pocket of IL-1 β comprises at least the amino acid corresponding to residue Lys179 and/or Pro207 of the IL-1 β (SEQ ID NO:1).

[00105] In certain embodiments, the binding pocket of IL-1 β for a compound as described herein comprises or consists of the amino acids corresponding to residues 119, 120, 121, 179, 203, 204, 206, 207, and 269 of the IL-1 β (SEQ ID NO:1). In certain embodiments, the binding pocket of IL-1 β for a compound as described herein comprises or consists of Val119, Arg120, Ser121, Lys179, Pro203, Lys204, Tyr206, Pro207, and Ser269 of the IL-1 β (SEQ ID NO:1).

[00106] In certain embodiments, the binding pocket of IL-1 β for a compound as described herein comprises or consists of the amino acids corresponding to residues 119, 120, 121, 179, 203, 204, and 206 of the IL-1 β (SEQ ID NO:1). In certain embodiments, the binding pocket of IL-1 β for a compound as described herein comprises or consists of IL-1 β to Val119, Arg120, Ser121, Lys179, Pro203, and Lys204 of the IL-1 β (SEQ ID NO:1).

[00107] In certain embodiments, the binding pocket of IL-1 β for a compound as described herein comprises or consists of the amino acids corresponding to residues 119, 120, 121, 162, 179, 203, 204, 206, 207, and 269 of the IL-1 β (SEQ ID NO:1). In certain embodiments, the binding pocket of IL-1 β for a compound as described herein comprises or consists of IL-1 β to Val119, Arg120, Ser121, Phe162, Lys179, Pro203, Lys204, Tyr206, Pro207, and Ser269 of the IL-1 β (SEQ ID NO:1).

[00108] In certain embodiments, the binding pocket of IL-1 β for a compound as described herein comprises or consists of the amino acids corresponding to residues 119, 120, 121, 179, 203, 204, 206, and 207 of the IL-1 β (SEQ ID NO:1). In certain embodiments, the binding pocket of IL-1 β for a compound as described herein comprises or consists of IL-1 β to Val119, Arg120, Ser121, Lys179, Pro203, Lys204, Tyr206, and Pro207 of the IL-1 β (SEQ ID NO:1).

[00109] In some embodiments, the binding of the compound at the binding pocket of IL-1 β to a specified residue is mediated by the backbone or sidechain of the specified residue (*e.g.*, a backbone NH, backbone carbonyl, or sidechain functional group of the specified IL-1 β residue interacts with the compound). In some embodiments, one or more residues of the binding pocket of IL-1 β mediates a non-covalent interaction with a compound as described herein. In some embodiments, the one or more residues of IL-1 β mediating the interaction between the binding pocket and a compound as described herein is selected from Val119, Arg120, Ser121, Phe162, Lys179, Pro203, Lys204, Tyr206, Pro207, or Ser269.

[00110] In some embodiments, a residue of the binding pocket of IL-1 β (*e.g.*, Val119, Arg120, Ser121, Phe162, Lys179, Pro203, Lys204, Tyr206, Pro207, or Ser269) mediates a non-covalent interaction with a compound as described herein. In some embodiments, a residue of the binding pocket of IL-1 β (*e.g.*, Val119, Arg120, Ser121, Phe162, Lys179, Pro203, Lys204, Tyr206, Pro207, or Ser269) mediates a lipophilic interaction and/or hydrophobic interaction with a compound as described herein. In some embodiments, a residue of the binding pocket of IL-1 β (*e.g.*, Val119, Arg120, Ser121, Phe162, Lys179, Pro203, Lys204, Tyr206, Pro207, or Ser269) mediates an electrostatic interaction with a compound as described herein. In some embodiments, a residue of the binding pocket of IL-1 β (*e.g.*, Val119, Arg120, Ser121, Phe162, Lys179, Pro203, Lys204, Tyr206, Pro207, or Ser269) mediates an ionic interaction with a compound as described herein. In some embodiments, a residue of the binding pocket of IL-1 β (*e.g.*, Val119, Arg120, Ser121, Phe162, Lys179, Pro203, Lys204, Tyr206, Pro207, or Ser269) mediates a hydrogen bond (H-bond) interaction with a compound as described herein. In some embodiments, a residue of the binding pocket of IL-1 β (*e.g.*, Val119, Arg120, Ser121, Phe162, Lys179, Pro203, Lys204, Tyr206, Pro207, or Ser269) mediates a halogen bond interaction with a compound as described herein. In some embodiments, a residue of the binding pocket of IL-1 β (*e.g.*, Val119, Arg120, Ser121, Phe162, Lys179, Pro203, Lys204, Tyr206, Pro207, or Ser269) mediates a Van der Waals interaction with a compound as described herein. In some

embodiments, a residue of the binding pocket of IL-1 β (*e.g.*, Val119, Arg120, Ser121, Phe162, Lys179, Pro203, Lys204, Tyr206, Pro207, or Ser269) mediates a Van der Waals interaction (*e.g.*, a dipole-dipole interaction; dipole-induced dipole interaction; or London dispersion force) with a compound as described herein. In some embodiments, a residue of the binding pocket of IL-1 β (*e.g.*, Val119, Arg120, Ser121, Phe162, Lys179, Pro203, Lys204, Tyr206, Pro207, or Ser269) mediates a pi-effect interaction (*e.g.*, a pi-pi interaction; CH-pi interaction; cation-pi interaction; anion-pi interaction; or polar-pi interaction) with a compound as described herein. In some embodiments, a residue of the binding pocket of IL-1 β (*e.g.*, Val119, Arg120, Ser121, Phe162, Lys179, Pro203, Lys204, Tyr206, Pro207, or Ser269) mediates more than one non-covalent interaction as described herein, which may be of different types.

[00111] In certain embodiments, residue Val119 of the IL-1 β mediates a hydrogen bond (H-bond) interaction with a compound as described herein. In certain embodiments, residue Arg120 of the IL-1 β mediates a hydrogen bond (H-bond) interaction with a compound as described herein. In certain embodiments, residue Ser121 of the IL-1 β mediates a hydrogen bond (H-bond) interaction with a compound as described herein. In certain embodiments, residue Pro203 of the IL-1 β mediates a hydrogen bond (H-bond) interaction with a compound as described herein. In certain embodiments, residue Lys204 of the IL-1 β mediates a hydrogen bond (H-bond) interaction with a compound as described herein. In certain embodiments, residue Tyr206 of the IL-1 β mediates a hydrogen bond (H-bond) interaction with a compound as described herein. In certain embodiments, residue Pro207 of the IL-1 β mediates a hydrogen bond (H-bond) interaction with a compound as described herein. In certain embodiments, residue Ser269 of the IL-1 β mediates a hydrogen bond (H-bond) interaction with a compound as described herein. Such hydrogen bond (H-bond) interactions may be mediated by the backbone (*e.g.*, NH group or carbonyl group) or side chain (*e.g.*, a functional group on the side chain, for example a carboxylate or OH group) of the IL-1 β residue.

[00112] In certain embodiments, residue Arg120 of the IL-1 β mediates a pi-effect (*e.g.*, CH-pi, cation-pi, or polar-pi) interaction with a compound as described herein. In certain embodiments, residue Phe162 of the IL-1 β mediates a pi-effect (*e.g.*, CH-pi, cation-pi, or polar-pi) interaction with a compound as described herein. In certain embodiments, residue Lys179 of the IL-1 β mediates a pi-effect (*e.g.*, CH-pi, cation-pi, or polar-pi) interaction with a compound as described herein. In certain embodiments, residue Pro207 of the IL-1 β mediates a pi-effect (*e.g.*,

CH- π , cation- π , or polar- π) interaction with a compound as described herein. In certain embodiments, residue Ser269 of the IL-1 β mediates a π -effect (*e.g.*, CH- π , cation- π , or polar- π) interaction with a compound as described herein. Such π -effect (*e.g.*, CH- π , cation- π , or polar- π) interactions may be mediated by the backbone (*e.g.*, NH group or carbonyl group) or side chain (*e.g.*, a functional group on the side chain, for example a hydrogen, OH, or amine) of the IL-1 β residue.

[00113] In certain embodiments, residue Lys204 of the IL-1 β mediates an ionic interaction with a compound as described herein. In certain embodiments, residue Ala117 of the IL-1 β mediates an ionic interaction with a compound as described herein. In certain embodiments, residue Arg120 of the IL-1 β mediates an ionic interaction with a compound as described herein. Such ionic interactions may be mediated by the backbone (*e.g.*, NH group or carbonyl group) or side chain (*e.g.*, a functional group on the side chain) of the IL-1 β residue.

[00114] In some embodiments, the binding pocket of IL-1 β comprises the residues of IL-1 β having a backbone or sidechain within five angstroms of the Van der Waals surface of Compound A when Compound A is bound to IL-1 β as determined by X-ray crystallography. In some embodiments, the binding pocket of IL-1 β comprises the residues of IL-1 β having a backbone or sidechain within five angstroms of the Van der Waals surface of Compound B when Compound B is bound to IL-1 β as determined by X-ray crystallography. In some embodiments, the binding pocket of IL-1 β comprises the residues of IL-1 β having a backbone or sidechain within five angstroms of the Van der Waals surface of Compound C when Compound C is bound to IL-1 β as determined by X-ray crystallography. In some embodiments, the binding pocket of IL-1 β comprises the residues of IL-1 β having a backbone or sidechain within five angstroms of the Van der Waals surface of Compound D when Compound D is bound to IL-1 β as determined by X-ray crystallography. In some embodiments, the binding pocket of IL-1 β comprises the residues of IL-1 β having a backbone or sidechain within five angstroms of the Van der Waals surface of Compound E when Compound E is bound to IL-1 β as determined by X-ray crystallography.

[00115] In certain embodiments, the binding interactions between the IL-1 β and compound as described herein are as depicted in any one of figures disclosed herein.

7.4 INTERLEUKIN-1 RECEPTOR TYPE I (IL-1R1)

[00116] Interleukin-1 receptor type I (IL-1R1) is a cytokine receptor for at least interleukin 1 alpha (IL-1 α), interleukin 1 beta (IL-1 β), and interleukin 1 receptor antagonist (IL-1RA). In some embodiments, IL-1R1 is also known as CD121A, D2S1473, IL-1R-alpha, IL1R1, P80, or interleukin 1 receptor type 1. IL-1R1 is one of two forms of the interleukin-1 receptor (*e.g.*, Type I and Type II). IL-1R1 functions, *inter alia*, to propagate the inflammatory effects of interleukin-1 (IL-1). In some embodiments, the IL-1R1 is encoded by the IL1R1 gene (*e.g.*, human IL1R1 gene).

[00117] In some embodiments, the IL-1R1 is a human IL-1R1. In some embodiments, IL-1R1 comprises or consists of the amino acid sequence of the full-length human IL-1R1 (*e.g.*, amino acids 1-569) as set forth at I Accession No. P14778. In some embodiments, human IL-1R1 comprises or consists of the amino acid sequence of SEQ ID NO:4. Human IL-1R1 comprises an ectodomain comprising three Ig-like domains: domain 1 (D1), domain 2 (D2), and domain 3 (D3). As shown in FIG. 1, IL-1R1 forms a tertiary structure that resembles a grasping hand in how it binds a cytokine (*e.g.*, IL-1 α , IL-1 β , or IL-1RA). The D1, D2, and D3 domains of IL-1R1 may form two distinct binding sites, the A-site of IL-1R1 and B-site of IL-1R1, which drive the interaction of IL-1R1 with IL-1 cytokines (*e.g.*, IL-1 β). The two domains D1 and D2 of IL-1R1 may together form the A-site binding site of IL-1R1. The D3 domain of IL-1R1 may form the B-site binding site of IL-1R1.

[00118] In some embodiments, the D1 domain of IL-1R1 comprises or consists of the amino acid sequence of the Ig-like C2-type 1 domain of human IL-1R1 (*e.g.*, amino acids 23-110) as set forth in UniProt Accession No. P14778. In some embodiments, the D1 domain of IL-1R1 comprises or consists of the amino acids 23-110 of SEQ ID NO:4. In some embodiments, the D1 domain of IL-1R1 comprises or consists of the amino acids sequence of SEQ ID NO:5. In some embodiments, the D2 domain of IL-1R1 comprises or consists of the amino acid sequence of the Ig-like C2-type 2 domain of human IL-1R1 (*e.g.*, amino acids 118-210) as set forth in UniProt Accession No. P14778. In some embodiments, the D2 domain of IL-1R1 comprises or consists of amino acids 118-210 of SEQ ID NO:4. In some embodiments, the D2 domain of IL-1R1 comprises or consists of the amino acid sequence of SEQ ID NO:6. In some embodiments, the D3 domain of IL-1R1 comprises or consists of the amino acid sequence of the Ig-like C2-type 3 domain of human IL-1R1 (*e.g.*, amino acids 226-I set forth at UniProt Accession No.

P14778. In some embodiments, the D3 domain of IL-1R1 comprises or consists of amino acids 226-328 of SEQ ID NO:4. In some embodiments, the D3 domain of IL-1R1 comprises or consists of the amino acid sequence of SEQ ID NO:6. Exemplary amino acid sequences of the full length human IL-1R1 and its D1, D2, and D3 domains are shown below in TABLE 2.

[00119] TABLE 2: Amino acid sequences for human IL-1R1

Name	Amino Acid Sequence
Human IL-1R type I	MKVLLRLICFIALLISSLEADKCKEREEKIILVSSANEIDVRPCPLNPNEHKGTITWYKDDSKTPVSTEQASRIHQHKEKLWFVPAKVEDSGHYVCVVRNS SYCLRIKISAKFVENEPNLCYNAQAIFKQKLPVAGDGGLVCPYMEFFKNE NNELPKLQWYKDCKPLLLDNIHFSGVKDRLIVMNVAEKHRGNYTCHAS YTYLGKQYPITRVIEFITLEENKPTRPVIVSPANETMEVDLGSQIQLICNVT GQLSDIAYWKWNGSVIDEDDPVLGEDYYSVENPANKRRSTLITVLNISEI ESRFYKHPFTCFAKNTHGIDAAYIQLIYPVTNFQKHMIGICVTLTVIIVCSV FIYKIFKIDIVLWYRDSCYDFLPIKASDGKTYDAYILYPKTVGEGSTSDCDI FVFKVLPEVLEKQCGYKLFIYGRDDYVGEDIVEVINENVKKSRRLLIILVR ETSGFSWLGGSSSEQIAMYNALVQDGIKVVLELEKIQDYEKMPESIKFIK QKHGAIRWSGDFTQGPQSAKTRFWKNVRYHMPVQRRSPSSKHQLLSPA TKEKLQREAHVPLG (SEQ ID NO:4)
D1 Domain of IL-1R1	CKEREEKIILVSSANEIDVRPCPLNPNEHKGTITWYKDDSKTPVSTEQASRIHQHKEKLWFVPAKVEDSGHYVCVVRNSSYCLRIKIS (SEQ ID NO:5)
D2 Domain of IL-1R1	PNLCYNAQAIFKQKLPVAGDGGLVCPYMEFFKNENNELPKLQWYKDCKPLLLDNIHFSGVKDRLIVMNVAEKHRGNYTCHASYTYLGKQYPIT (SEQ ID NO:6)
D3 Domain of IL-1R1	PVIVSPANETMEVDLGSQIQLICNVTGQLSDIAYWKWNGSVIDEDDPVLGEDYYSVENPANKRRSTLITVLNISEIESRFYKHPFTCFAKNTHGIDAAYIQLI (SEQ ID NO:7)

7.5 COMPOUNDS

[00120] Provided herein are compounds for inhibiting the binding of interleukin-1 beta (IL-1 β) to interleukin-1 receptor type I (IL-1R1). In some embodiments, a compound of the disclosure contacts IL-1 β to inhibit binding of the IL-1 β to IL-1R1. In some embodiments, a compound of the disclosure competes with the binding of IL-1 β to IL-1R1.

[00121] In some embodiments, a compound as described herein inhibits binding of IL-1 β to the A-site of IL-1R1, which inhibits one or more biological functions of IL-1R1. In some embodiments, a compound as described herein inhibits binding of IL-1 β to the D1 and/or D2 domain of IL-1R1, which inhibits one or more biological functions of IL-1R1. In some embodiments, a compound as described herein inhibits binding of IL-1 β to the B-site of IL-1R1, which inhibits one or more biological functions of IL-1R1. In some embodiments, a compound

as described herein inhibits binding of IL-1 β to the D3 domain of IL-1R1, which inhibits one or more biological functions of IL-1R1. In some embodiments, compound as described herein inhibits binding of IL-1 β to both the A-site and B-site of IL-1R1, which inhibits one or more biological functions of IL-1R1. In some embodiments, a compound as described herein inhibits binding of IL-1 β to the D1, D2, and D3 domains of IL-1R1, which inhibits one or more biological functions of IL-1R1. In some embodiments, the biological function of IL-1R1 is inflammation (*e.g.*, in a subject). In some embodiments, the biological function of IL-1R1 is expression of IL-6. In some embodiments, the biological function of IL-1R1 is expression of c-reactive protein (CRP).

[00122] In some embodiments, a compound as described herein is an orthosteric inhibitor of the binding of IL-1 β to IL-1R1. In some embodiments, the compound binds to an orthosteric site (*e.g.*, primary binding site) of IL-1 β for IL-1R. In some embodiments, the compound binds to the active site of IL-1 β for IL-1R.

[00123] In some embodiments, a compound as described herein is an allosteric inhibitor of the binding of IL-1 β to IL-1R1. In some embodiments, the compound binds to an allosteric site (*e.g.*, secondary binding site) of IL-1 β for IL-1R. In some embodiments, the compound does not bind to the active site of IL-1 β for IL-1R.

[00124] In some embodiments, a compound as described herein is a peptide. In some embodiments, the peptide comprises or consists of an amino acid sequence having a length of from 9 to 28 amino acids (*e.g.*, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28 amino acids). In some embodiments, the peptide comprises or consists of an amino acid sequence having a length of from 10 to 24 amino acid residues. In some embodiments, the peptide comprises or consists of an amino acid sequence having a length of from 11 to 20 amino acid residues. In some embodiments, the peptide comprises or consists of an amino acid sequence having a length of from 12 to 16 amino acid residues. In some embodiments, the peptide comprises or consists of an amino acid sequence having a length of from 13 to 15 amino acid residues. In some embodiments, the peptide comprises or consists of an amino acid sequence having a length of 14 amino acid residues.

[00125] In some embodiments, the peptide is a cyclic peptide. In some embodiments, the cyclic peptide comprises or consists of an amino acid sequence having a length of from 9 to 28 amino acid residues (*e.g.*, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27,

or 28 amino acids). In some embodiments, the cyclic peptide comprises or consists of an amino acid sequence having a length of from 10 to 24 amino acid residues. In some embodiments, the cyclic peptide comprises or consists of an amino acid sequence having a length of from 11 to 20 amino acid residues. In some embodiments, the cyclic peptide comprises or consists of an amino acid sequence having a length of from 12 to 16 amino acid residues. In some embodiments, the cyclic peptide comprises or consists of an amino acid sequence having a length of from 13 to 15 amino acid residues. In some embodiments, the cyclic peptide comprises or consists of an amino acid sequence having a length of 14 amino acid residues.

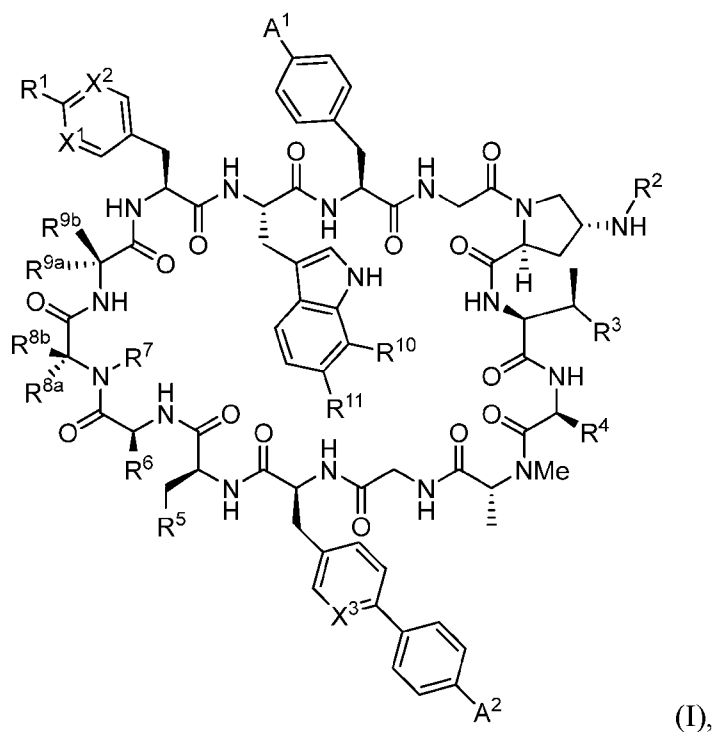
[00126] In some embodiments, the peptide is a macrocyclic peptide. In some embodiments, the cyclic peptide comprises or consists of an amino acid sequence having a length of from 9 to 28 amino acid residues (*e.g.*, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28 amino acids). In some embodiments, the macrocyclic peptide comprises or consists of an amino acid sequence having a length of from 10 to 24 amino acid residues. In some embodiments, the macrocyclic peptide comprises or consists of an amino acid sequence having a length of from 11 to 20 amino acid residues. In some embodiments, the macrocyclic peptide comprises or consists of an amino acid sequence having a length of from 12 to 16 amino acid residues. In some embodiments, the macrocyclic peptide comprises or consists of an amino acid sequence having a length of from 13 to 15 amino acid residues. In some embodiments, the macrocyclic peptide comprises or consists of an amino acid sequence having a length of 14 amino acid residues.

[00127] In some embodiments, a compound as described herein (*e.g.*, a peptide, cyclic peptide, or macrocyclic peptide) has a molecular weight of from about 1000 Da to about 3200 Da. In some embodiments, a compound as described herein (*e.g.*, a peptide, cyclic peptide, or macrocyclic peptide) has a molecular weight of from about 1200 Da to about 3000 Da. In some embodiments, a compound as described herein (*e.g.*, a peptide, cyclic peptide, or macrocyclic peptide) has a molecular weight of from about 1500 Da to about 2500 Da. In some embodiments, a compound as described herein (*e.g.*, a peptide, cyclic peptide, or macrocyclic peptide) has a molecular weight of from about 1750 Da to about 3000 Da. In some embodiments, a compound as described herein (*e.g.*, a peptide, cyclic peptide, or macrocyclic peptide) has a molecular weight of about the molecular weight of Compound A, Compound B, Compound C, Compound D, or Compound E.

[00128] In some embodiments, the compound is a compound as described herein (*e.g.*, or the Examples). In some embodiments, a compound as described herein that binds to IL-1 β at a binding pocket as described herein is a lipophilic compound comprising one or more lipophilic moieties. In some embodiments, a compound as described herein that binds to IL-1 β at a binding pocket as described herein is hydrophobic compound comprising one or more hydrophobic moieties.

[00129] In some embodiments of a method as described herein, the compound has a structure of Formula (I), or a pharmaceutically acceptable salt thereof, wherein X¹, X², X³, A¹, A², R¹-R⁷, R^{8a}, R^{8b}, R^{9a}, R^{9b}, R¹⁰, R¹¹, R¹², R^{13a}, R^{13b}, and R¹⁴ are as herein described.

[00130] In some embodiments of a method as described herein, the compound has a structure of Formula (I):



or a pharmaceutically acceptable salt thereof,
wherein:

R¹ is CH₃C(O)NH-CH₂CH₂-O- or C¹;

C¹ is:

- (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or

(ii) a 5- to 6-membered mono- or bicyclic, saturated cycloalkyl or heterocycloalkyl containing 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or

(iii) a 5- to 6-membered mono- or bicyclic cycloalkyl;

wherein C¹ is unsubstituted or substituted by 1 to 3 R^{C1} substituents independently selected from the group consisting of halo, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, carboxy, C₁-C₃ alkoxy, and C₂-C₃ acyl;

R² is H, C₁-C₃ alkyl, benzyl, or phenyl-CH₂CH₂-;

R³ is a 9- to 10-membered bicyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;

wherein R³ is unsubstituted or substituted by 1 to 3 R^{3a} substituents independently selected from the group consisting of halo, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, hydroxy and C₁-C₃ alkoxy;

R⁴ is C₁-C₃ alkyl, HO₂C-(CH₂)_m-, H₂NC(O)-(CH₂)_m-, (CH₃)₂NC(O)-(CH₂)_m-, or tetrazolyl-(CH₂)_m-;

R⁵ is amino, H₂N(CH₂)_n-, H₂NC(O)-(CH₂)_n-, CH₃C(O)NH-, CH₃C(O)NH(CH₂)_n-, C⁵, or C⁵-CH₂-;

C⁵ is:

(i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;

(ii) a 9- to 10-membered bicyclic aryl or heteroaryl, wherein said bicyclic heteroaryl contains 1 to 3 heteroatoms selected from the group consisting of N, O, and S;

(iii) a 5- to 6-membered monocyclic or 9- to 10-membered heterocycloalkyl, wherein said heterocycloalkyl is saturated or partially unsaturated, and contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;

(iv) a 5- to 6-membered monocyclic cycloalkyl; or

(v) 2,3-dihydroindolyl;

wherein C⁵ is unsubstituted or substituted by 1 to 3 R^{C5} substituents independently selected from the group consisting of halo, amino, hydroxy, C₁-C₃ alkyl, C₁-C₃

fluoroalkyl, C₁-C₃ alkoxy, H₂N-(CH₂)_k-, H₂NC(O)-(CH₂)_k-, H₂C=CH-CH₂O-, and phenyl;

R⁶ is H, C₁-C₅ alkyl, H₂N(CH₂)_p-, HOCH₂-, (CH₃)₂NCH₂-, H₃CO-(CH₂)_q-, or C⁶-CH₂-;

C⁶ is 5- or 6-membered monocyclic, saturated heterocycloalkyl containing 1 to 2 heteroatoms selected from the group consisting of N, O, and S; and wherein C⁶ is unsubstituted or substituted by 1 to 3 R^{C6} substituents independently selected from the group consisting of halo, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, hydroxy and C₁-C₃ alkoxy;

R⁷ is H or C₁-C₃ alkyl;

R^{8a} is H, C₁-C₅ alkyl, HOCH₂-, H₂N(CH₂)_r-, (CH₃)₃N⁺(CH₂)_r-, or CH₃C(O)NH(CH₂)_r-;

R^{8b} is H or C₁-C₃ alkyl;

R^{9a} is H or C₁-C₃ alkyl;

R^{9b} is H, C₁-C₅ alkyl, C⁹-CH₂-, or C⁹-CH₂CH₂-;

C⁹ is:

- (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or
- (ii) a 5- to 6-membered monocyclic, saturated cycloalkyl or heterocycloalkyl, wherein the heterocycloalkyl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;

wherein C⁹ is unsubstituted or substituted by 1 to 3 R^{C9} substituents independently selected from the group consisting of halo, amino, hydroxy, cyano, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, C₁-C₃ alkoxy, H₂N-(CH₂)_k-, H₂NC(O)-(CH₂)_k-, H₂NCH₂CH₂O-, CH₃C(O)NH-CH₂CH₂O-, and morpholinyl-CH₂CH₂O-;

R¹⁰ is H, halo, or C₁-C₃ alkyl;

R¹¹ is H, halo, or C₁-C₃ alkyl;

each occurrence of subscript k is independently 1 or 2;

subscript m is 1 or 2;

subscript n is 1, 2, 3, or 4;

subscript p is 1, 2, 3, or 4;

subscript q is 1 or 2;

subscript r is 1, 2, 3, or 4;

X¹, X², and X³ are independently C(H) or N; and

A¹ and A² are independently selected from the group consisting of HO₂C-, H₂NC(O)-, CH₃C(O)N(H)-, H₂NS(O)₂-, CH₃S(O)₂N(H)-, tetrazolyl, and 5-oxo oxadiazolyl.

[00131] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein:

R⁵ is amino, H₂N(CH₂)_n-, H₂NC(O)-(CH₂)_n-, C⁵, or C⁵-CH₂-,

C⁵ is:

- (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;
- (ii) a 9- to 10-membered bicyclic aryl or heteroaryl, wherein said bicyclic heteroaryl contains 1 to 3 heteroatoms selected from the group consisting of N, O, and S;
- (iii) a 5- to 6-membered monocyclic or 9- to 10-membered heterocycloalkyl, wherein said heterocycloalkyl is saturated or partially unsaturated, and contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or
- (iv) 2,3-dihydroindolyl;

wherein C⁵ is unsubstituted or substituted by 1 to 3 R^{C5} substituents independently selected from the group consisting of halo, amino, hydroxy, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, C₁-C₃ alkoxy, H₂N-(CH₂)_k-, H₂NC(O)-(CH₂)_k-, H₂C=CH-CH₂O-, and phenyl;

R⁶ is H, C₂-C₅ alkyl, H₂N(CH₂)_p-, HOCH₂-, (CH₃)₂NCH₂-, H₃CO-(CH₂)_q-, or C⁶-CH₂-;

R^{8a} is H, C₁-C₃ alkyl, HOCH₂-, or H₂N(CH₂)_r-;

R^{9a} is H;

R^{9b} is H, C₁-C₃ alkyl, C⁹-CH₂-, or C⁹-CH₂CH₂-;

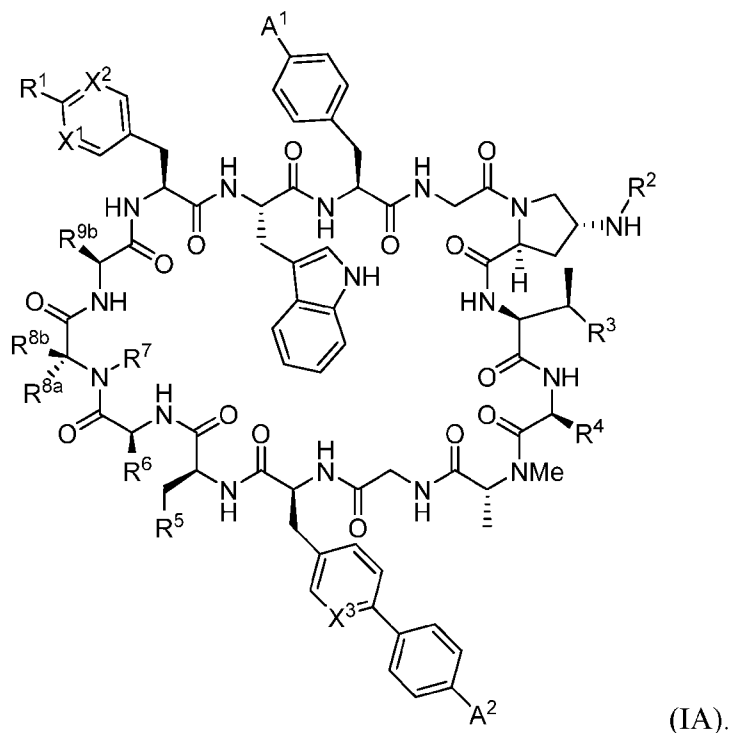
R¹⁰ is H;

R¹¹ is H;

subscript p is 1, 2, or 3; and

subscript r is 2, 3, or 4.

[00132] In some embodiments of a method as described herein, the compound of Formula (I) has the structural Formula (IA):



(IA).

[00133] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein:

C¹ is phenyl, pyrimidyl, or piperazinyl, wherein C¹ is unsubstituted or substituted by 1 to 2 R^{C1} substituents;

R³ is naphthyl or indolyl, wherein R³ is unsubstituted or substituted by 1 to 2 R^{3a} substituents;

C⁵ is phenyl, pyridyl, pyrimidyl, naphthyl, indolyl, 7-azaindolyl, indazolyl, 2,3-dihydroindolyl, piperidinyl, tetrahydropyranyl, or cyclohexyl, wherein C⁵ is unsubstituted or substituted by 1 to 2 R^{C5} substituents;

C⁶ is tetrahydropyranyl or morpholinyl; wherein C⁶ is unsubstituted or substituted by 1 to 2 R^{C6} substituents; and

C^{9a} is H or methyl;

C^{9b} is phenyl, pyridyl, cyclohexyl, morpholinyl, or piperidinyl, wherein C⁹ is unsubstituted or substituted by 1 to 2 R^{C9} substituents.

[00134] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein:

R¹ is C¹ wherein C¹ is phenyl, pyrimidyl, or piperazinyl, wherein C¹ is unsubstituted or substituted by 1 to 2 R^{C1} substituents;

R³ is naphthyl or indolyl, wherein R³ is unsubstituted or substituted by 1 to 2 R^{3a} substituents;

C⁵ is phenyl, pyridyl, pyrimidyl, naphthyl, indolyl, 7-azaindolyl, indazolyl, 2,3-dihydroindolyl, piperidinyl, tetrahydropyranyl, or cyclohexyl, wherein C⁵ is unsubstituted or substituted by 1 to 2 R^{C5} substituents;

C⁶ is tetrahydropyranyl or morpholinyl; wherein C⁶ is unsubstituted or substituted by 1 to 2 R^{C6} substituents; and

C^{9a} is H or methyl;

C^{9b} is phenyl, pyridyl, cyclohexyl, morpholinyl, or piperidinyl, wherein C⁹ is unsubstituted or substituted by 1 to 2 R^{C9} substituents.

[00135] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein:

X¹ and X² are C(H); and

R¹ is phenyl substituted by carboxy.

[00136] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein:

X¹ and X² are C(H); and

R¹ is CH₃C(O)NH-CH₂CH₂-O-.

[00137] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein R² is H.

[00138] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein R³ is indolyl substituted by one halo.

[00139] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein R³ is naphthyl.

[00140] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein R⁴ is HO₂C-(CH₂)_m-.

[00141] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein X^3 is C(H).

[00142] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein R^5 is $H_2N(CH_2)_n$ -, indole, 7-azaindole, naphthyl or pyridyl.

[00143] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein R^5 is $H_2N(CH_2)_n$ -, indole, naphthyl or pyridyl.

[00144] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein R^6 is H, $HOCH_2$ -, C_2 - C_5 alkyl or $H_2N(CH_2)_p$ -.

[00145] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein R^6 is C_2 - C_5 alkyl or $H_2N(CH_2)_p$ -.

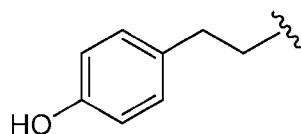
[00146] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein R^7 is H.

[00147] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein:

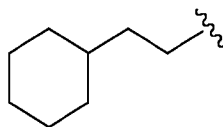
R^{8a} is methyl or $H_2NCH_2CH_2$ -, and

R^{8b} is H.

[00148] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein R^{9b} is

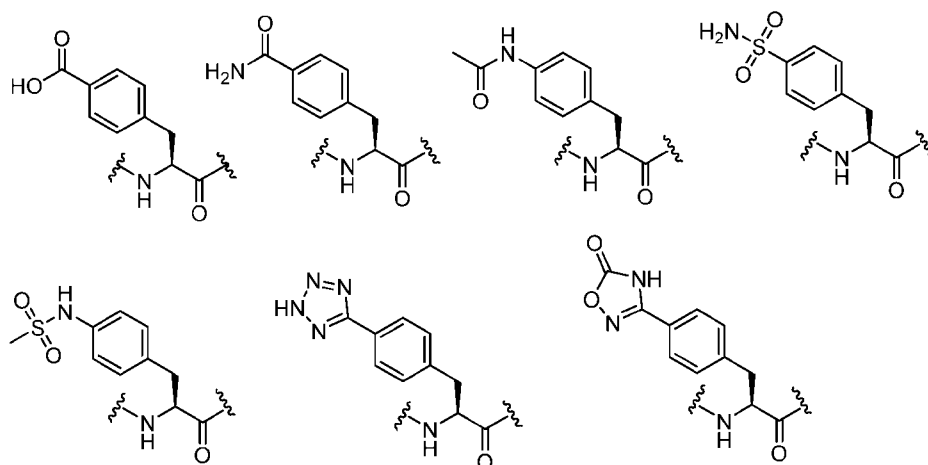


[00149] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein R^{9b} is

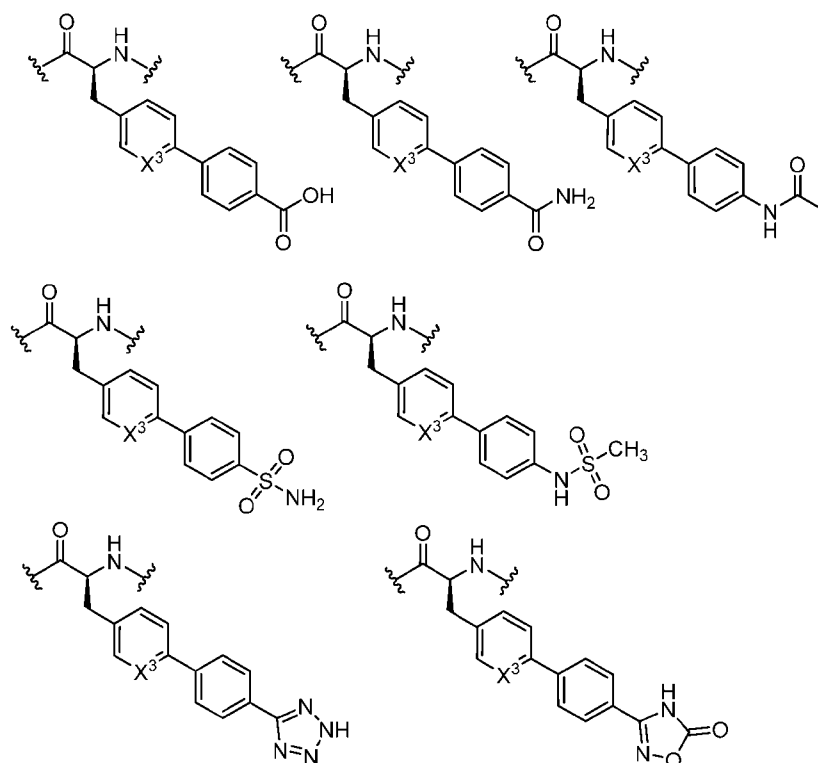


[00150] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein A^1 is selected from the group consisting of HO_2C -, $H_2NC(O)$ -, $CH_3C(O)N(H)$ -, $H_2NS(O)_2$ -, $CH_3S(O)_2N(H)$ -, tetrazolyl, and 5-oxo oxadiazolyl. Persons

skilled in chemistry will recognize that such moieties in the amino acid residue can be shown by the following substructures:



[00151] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein A² is selected from the group consisting of HO₂C-, H₂NC(O)-, CH₃C(O)N(H)-, H₂NS(O)₂-, CH₃S(O)₂N(H)-, tetrazolyl, and 5-oxo oxadiazolyl. Persons skilled in chemistry will recognize that such moieties in the amino acid residue can be shown by the following substructures:



[00152] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein:

R^{10} is H; and

R^{11} is H, F or Cl.

[00153] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein A^1 and A^2 are both HO_2C- (*i.e.*, carboxy).

[00154] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein:

R^1 is 4- $CH_3C(O)$ -piperazin-1-yl, $CH_3C(O)NH-CH_2CH_2-O-$, 5- CO_2H -pyrimidin-2-yl, or 4- CO_2H -phenyl;

R^2 is H, ethyl, benzyl, or phenyl- CH_2CH_2- ;

R^3 is naphth-1-yl, 4-fluoroindol-3-yl, or 4-chloroindol-3-yl;

R^4 is methyl, $HO_2C-(CH_2)_m-$, or $H_2NC(O)-(CH_2)_m-$;

R^5 is amino, $H_2N(CH_2)_n-$, naphth-1-yl, indol-3-yl, 7-aza-indol-3-yl, indazol-1-yl, 2,3-dihydroindol-1-yl, pyrid-3-yl, pyrid-4-yl, piperidin-4-yl, 3-aminomethylphenyl, 4-aminomethylphenyl, 3-aminophenyl, 4-aminophenyl, phenyl, pyrid-4-yl- CH_2- , pyrimidin-5-yl, tetrahydropyran-4-yl-, $H_2NC(O)-(CH_2)_2-$, 3-biphenyl, 3- $CH_2=CH-CH_2O$ -phenyl, $CH_3C(O)NH-$, $CH_3C(O)NH(CH_2)_3-$, or cyclohexyl;

R^6 is H, $(CH_3)_2CHCH_2-$, $(CH_3)_3CCH_2-$, $H_2N(CH_2)_p-$, $HOCH_2-$, $H_3CCH_2CH_2-$, morpholin-4-yl- CH_2- , tetrahydropyran-4-yl- CH_2- , $(CH_3)_2NCH_2-$, or $H_3CO-(CH_2)_q-$;

R^7 is H or methyl;

R^{8a} is H, methyl, $HOCH_2-$, $H_2N(CH_2)_r-$, $(CH_3)_3NCH_2CH_2-$, or $CH_3C(O)NH(CH_2)_4-$;

R^{8b} is H or methyl;

R^{9a} is H or methyl;

R^{9b} is H, methyl, $H_3CCH_2CH_2CH_2-$, 4-HO-phenyl- CH_2CH_2- , phenyl- CH_2CH_2- , cyclohexyl- CH_2CH_2- , 5-NC-pyrid-3-yl- CH_2CH_2- , 4-F₃C-phenyl- CH_2- , 3-F₃C-phenyl- CH_2- , 2-F₃C-phenyl- CH_2- , morpholin-4-yl- CH_2CH_2O -phenyl- CH_2- , 4-aminophenyl- CH_2- , 4,4-difluorocyclohexyl- CH_2- , 4- $H_2NCH_2CH_2O$ -phenyl- CH_2- ,

4-H₂NCH₂CH₂O-pyrid-3-yl-CH₂-, piperidin-4-yl-CH₂-, or
4-CH₃C(O)NH-CH₂CH₂O-phenyl-CH₂-;

R¹⁰ is H, fluoro, or methyl;

R¹¹ is H, fluoro, or chloro;

A¹ and A² are both HO₂C-; and

X¹, X², and X³ are C(H).

[00155] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein:

R¹ is 4-CH₃C(O)-piperazin-1-yl, CH₃C(O)NH-CH₂CH₂-O-, 5-CO₂H-pyrimidin-2-yl, or 4-CO₂H-phenyl;

R² is H, ethyl, benzyl, or phenyl-CH₂CH₂-;

R³ is naphth-1-yl, 4-fluoroindol-3-yl, or 4-chloroindol-3-yl;

R⁴ is methyl, HO₂C-(CH₂)_m-, or H₂N(O)C-(CH₂)_m-;

R⁵ is amino, H₂N(CH₂)_n-, naphth-1-yl, indol-3-yl, 7-aza-indol-3-yl, indazol-1-yl, 2,3-dihydroindol-1-yl, pyrid-3-yl, pyrid-4-yl, piperidin-4-yl, 3-aminomethylphenyl, 4-aminomethylphenyl, 3-aminophenyl, 4-aminophenyl, phenyl, pyrid-4-yl-CH₂-, pyrimidin-5-yl, tetrahydropyran-4-yl-, H₂N(O)C-(CH₂)₂-, 3-biphenyl, or 3-CH₂=CH-CH₂O-phenyl,

R⁶ is H, (CH₃)₂CHCH₂-, H₂N(CH₂)_p-, HOCH₂-, H₃CCH₂CH₂-, morpholin-4-yl-CH₂-, tetrahydropyran-4-yl-CH₂-, (CH₃)₂NCH₂-, or H₃CO-(CH₂)_q-;

R⁷ is H or methyl;

R^{8a} is H, methyl, HOCH₂-, or H₂N(CH₂)_r-;

R^{8b} is H or methyl;

R^{9a} is H;

R^{9b} is H, methyl, 4-HO-phenyl-CH₂CH₂-, phenyl-CH₂CH₂-, 5-NC-pyrid-3-yl-CH₂CH₂-, 4-F₃C-phenyl-CH₂-, 3-F₃C-phenyl-CH₂-, 2-F₃C-phenyl-CH₂-, morpholin-4-yl-CH₂CH₂O-phenyl-CH₂-, 4-aminophenyl-CH₂-, 4,4-difluorocyclohexyl-CH₂-, 4-H₂NCH₂CH₂O-phenyl-CH₂-,

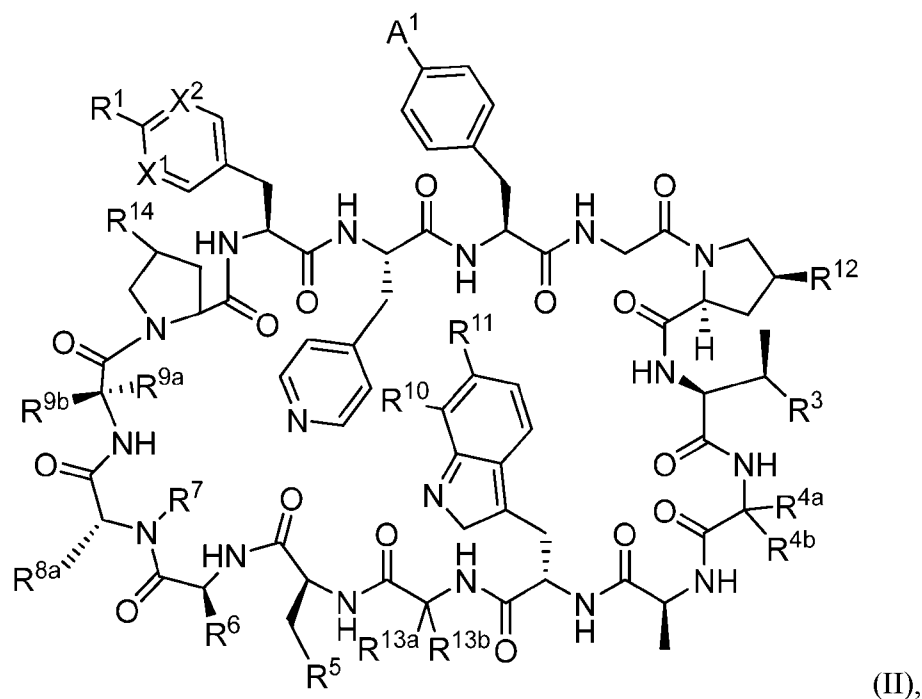
4-H₂NCH₂CH₂O-pyrid-3-yl-CH₂-, piperidin-4-yl-CH₂-, or

4-CH₃C(O)NH-CH₂CH₂O-phenyl-CH₂-;

R¹⁰ and R¹¹ are both H; and

A¹ and A² are both HO₂C-.

[00156] In some embodiments of a method as described herein, the compound has a structure of Formula (II):



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is CH₃C(O)NH-CH₂CH₂O- or C¹;

C¹ is:

- (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or
- (ii) a 5- to 6-membered mono- or bicyclic, saturated cycloalkyl or heterocycloalkyl containing 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or
- (iii) a 5- to 6-membered mono- or bicyclic cycloalkyl;

wherein C¹ is unsubstituted or substituted by 1 to 3 R^{C1} substituents independently selected from the group consisting of halo, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, HO₂C-, C₁-C₃ alkoxy, and C₂-C₃ acyl;

R³ is a 9- to 10-membered bicyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;

wherein R³ is unsubstituted or substituted by 1 to 3 R^{3a} substituents independently selected from the group consisting of halo, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, hydroxy and C₁-C₃ alkoxy;

R^{4a} and R^{4b} are independently C₁-C₃ alkyl, HO₂C-(CH₂)_m-, H₂NC(O)-(CH₂)_m-, (CH₃)₂NC(O)-(CH₂)_m-, or tetrazolyl-(CH₂)_m-;

R⁵ is hydroxyl, amino, H₂N(CH₂)_n-, H₂NC(O)-(CH₂)_n-, CH₃C(O)NH-, CH₃C(O)NH(CH₂)_n-, C⁵, or C⁵-CH₂-;

C⁵ is:

- (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;
- (ii) a 9- to 10-membered bicyclic aryl or heteroaryl, wherein said bicyclic heteroaryl contains 1 to 3 heteroatoms selected from the group consisting of N, O, and S;
- (iii) a 5- to 6-membered monocyclic or 9- to 10-membered heterocycloalkyl, wherein said heterocycloalkyl is saturated or partially unsaturated, and contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;
- (iv) a 5- to 6-membered monocyclic cycloalkyl; or
- (v) 2,3-dihydroindolyl;

wherein C⁵ is unsubstituted or substituted by 1 to 3 R^{C5} substituents independently selected from the group consisting of halo, amino, hydroxy, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, C₁-C₃ alkoxy, H₂N-(CH₂)_k-, H₂NC(O)-(CH₂)_k-, H₂C=CH-CH₂O-, and phenyl;

R⁶ is H, C₁-C₅ alkyl, H₂N(CH₂)_p-, H₂NC(O)(CH₂)_p-, HOCH₂-, (CH₃)₂NCH₂-, H₃CO-(CH₂)_q-, or C⁶-CH₂-;

C⁶ is 5- or 6-membered monocyclic, saturated heterocycloalkyl containing 1 to 2 heteroatoms selected from the group consisting of N, O, and S; and wherein C⁶ is unsubstituted or substituted by 1 to 3 R^{C6} substituents independently selected from

the group consisting of halo, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, hydroxy and C₁-C₃ alkoxy;

R⁷ is H or C₁-C₃ alkyl;

R^{8a} is H, C₁-C₅ alkyl, HOCH₂-, H₂N(CH₂)_r-, (CH₃)₃N⁺(CH₂)_r-, or CH₃C(O)NH(CH₂)_r-;

R^{9a} is H or C₁-C₃ alkyl;

R^{9b} is H, C₁-C₅ alkyl, C⁹-CH₂-, or C⁹-CH₂CH₂-;

C⁹ is:

- (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or
- (ii) a 5- to 6-membered monocyclic, saturated cycloalkyl or heterocycloalkyl, wherein the heterocycloalkyl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;

wherein C⁹ is unsubstituted or substituted by 1 to 3 R^{C9} substituents independently selected from the group consisting of halo, amino, hydroxy, cyano, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, C₁-C₃ alkoxy, H₂N-(CH₂)_k-, H₂NC(O)-(CH₂)_k-, H₂NCH₂CH₂O-, CH₃C(O)NH-CH₂CH₂O-, and morpholinyl-CH₂CH₂O-;

R¹⁰ is H, halo, or C₁-C₃ alkyl;

R¹¹ is H, halo, or C₁-C₃ alkyl;

R¹² is halo;

R^{13a} and R^{13b} are independently H or C₁-C₃ alkyl;

R¹⁴ is C₁-C₅ alkyl-;

C¹⁴ is:

- (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or
- (ii) a 5- to 6-membered monocyclic, saturated cycloalkyl or heterocycloalkyl, wherein the heterocycloalkyl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;

wherein C¹⁴ is unsubstituted or substituted by 1 to 3 R^{C14} substituents independently selected from the group consisting of halo, amino, hydroxy, cyano,

C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, C₁-C₃ alkoxy, H₂N-(CH₂)_k-, H₂NC(O)-(CH₂)_k-, H₂NCH₂CH₂O-, CH₃C(O)NH-CH₂CH₂O-, and morpholinyl-CH₂CH₂O-;

each occurrence of subscript k is independently 1 or 2;

subscript m is 1 or 2;

subscript n is 1, 2, 3, or 4;

subscript p is 1, 2, 3, or 4;

subscript q is 1 or 2;

subscript r is 1, 2, 3, or 4;

X¹ and X² are independently C(H) or N; and

A¹ is selected from the group consisting of HO₂C-, H₂NC(O)-, CH₃C(O)N(H)-, H₂NS(O)₂-, CH₃S(O)₂N(H)-, tetrazolyl, and 5-oxo oxadiazolyl.

[00157] In some embodiments of a method as described herein, the compound is a compound of Formula (II), wherein:

R¹ is C¹ wherein C¹ is:

- (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or
- (ii) a 5- to 6-membered mono- or bicyclic, saturated cycloalkyl or heterocycloalkyl containing 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or
- (iii) a 5- to 6-membered mono- or bicyclic cycloalkyl;

wherein C¹ is unsubstituted or substituted by 1 to 3 R^{C1} substituents independently selected from the group consisting of halo, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, HO₂C-, C₁-C₃ alkoxy, and C₂-C₃ acyl;

R³ is a 9- to 10-membered bicyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; wherein R³ is unsubstituted or substituted by 1 to 3 R^{3a} substituents independently selected from the group consisting of halo, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, hydroxy and C₁-C₃ alkoxy;

R^{4a} and R^{4b} are independently C₁-C₃ alkyl, HO₂C-(CH₂)_m-, H₂NC(O)-(CH₂)_m-, (CH₃)₂NC(O)-(CH₂)_m-, or tetrazolyl-(CH₂)_m-;

R⁵ is hydroxyl, amino, H₂N(CH₂)_n-, H₂NC(O)-(CH₂)_n-, CH₃C(O)NH-, or CH₃C(O)NH(CH₂)_n-;

R⁶ is H, C₁-C₅ alkyl, H₂N(CH₂)_p-, H₂NC(O)(CH₂)_p-, HOCH₂-, (CH₃)₂NCH₂-, or H₃CO-(CH₂)_q-;

R⁷ is H or C₁-C₃ alkyl;

R^{8a} is H or C₁-C₅ alkyl;

R^{9a} is H or C₁-C₃ alkyl;

R^{9b} is H or C₁-C₅ alkyl;

R¹⁰ is H, halo, or C₁-C₃ alkyl;

R¹¹ is H, halo, or C₁-C₃ alkyl;

R¹² is halo;

R^{13a} and R^{13b} are independently H or C₁-C₃ alkyl;

R¹⁴ is C₁-C₅ alkyl-C¹⁴; wherein C¹⁴ is:

- (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or
- (ii) a 5- to 6-membered monocyclic, saturated cycloalkyl or heterocycloalkyl, wherein the heterocycloalkyl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;

wherein C¹⁴ is unsubstituted or substituted by 1 to 3 R^{C14} substituents independently selected from the group consisting of halo, amino, hydroxy, cyano, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, C₁-C₃ alkoxy, H₂N-(CH₂)_k-, H₂NC(O)-(CH₂)_k-, H₂NCH₂CH₂O-, CH₃C(O)NH-CH₂CH₂O-, and morpholinyl-CH₂CH₂O-;

each occurrence of subscript k is independently 1 or 2;

subscript m is 1 or 2;

subscript n is 1, 2, 3, or 4;

subscript p is 1, 2, 3, or 4;

subscript q is 1 or 2;

subscript r is 1, 2, 3, or 4;

X¹ and X² are independently C(H) or N; and

A¹ is selected from the group consisting of HO₂C-, H₂NC(O)-, CH₃C(O)N(H)-, H₂NS(O)₂-, CH₃S(O)₂N(H)-, tetrazolyl, and 5-oxo oxadiazolyl.

[00158] In some embodiments of a method as described herein, the compound is a compound of Formula (II), wherein:

X¹ and X² are C(H); and

R¹ is phenyl substituted by carboxy.

[00159] In some embodiments of a method as described herein, the compound is a compound of Formula (II), wherein R³ is indolyl substituted by one halo.

[00160] In some embodiments of a method as described herein, the compound is a compound of Formula (II), wherein R⁶ is H, HOCH₂-, C₂-C₅ alkyl or H₂N(CH₂)_p-.

[00161] In some embodiments of a method as described herein, the compound is a compound of Formula (II), wherein R⁶ is C₂-C₅ alkyl or H₂N(CH₂)_p-.

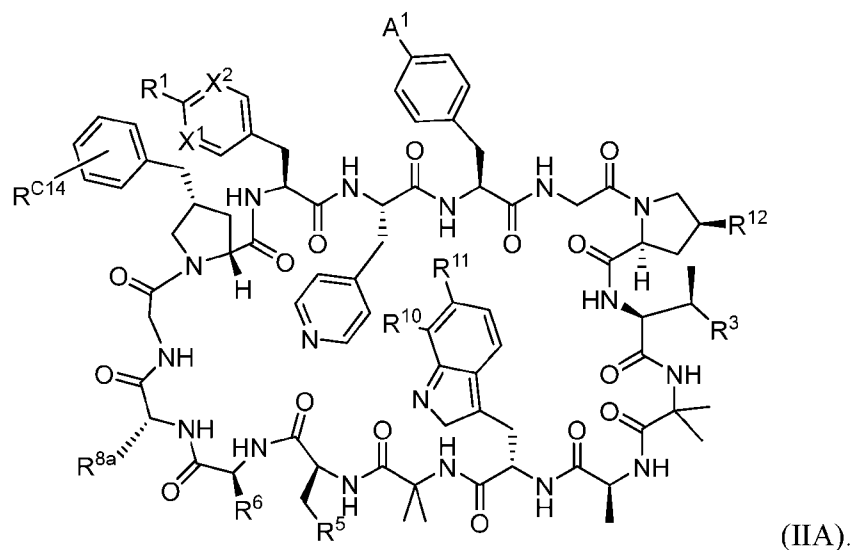
[00162] In some embodiments of a method as described herein, the compound is a compound of Formula (II), wherein:

R^{8a} is methyl or H₂NCH₂CH₂-; and

R^{8b} is H.

[00163] In some embodiments of a method as described herein, the compound is a compound of Formula (II), wherein R^{C14} is halo.

[00164] In some embodiments of a method as described herein, the compound has a structure of Formula (IIA):



[00165] In some embodiments of a method as described herein, the compound is a compound of Formula (II), wherein:

R¹ is C¹ wherein C¹ is phenyl unsubstituted or substituted by 1 to 2 R^{C1} substituents;

R³ is naphthyl or indolyl, wherein R³ is unsubstituted or substituted by 1 to 2 R^{3a} substituents;

R^{4a} and R^{4b} are independently C₁-C₃ alkyl;

R⁵ is hydroxyl, amino, H₂N(CH₂)_n-, H₂NC(O)-(CH₂)_n-, CH₃C(O)NH-, or CH₃C(O)NH(CH₂)_n-;

R⁶ is H, C₁-C₅ alkyl, H₂N(CH₂)_p-, H₂NC(O)(CH₂)_p-, HOCH₂-, (CH₃)₂NCH₂-, or H₃CO-(CH₂)_q-;

R⁷ is H;

R^{8a} is H;

R^{9a} is H;

R^{9b} is H;

R¹⁰ is H;

R¹¹ is H;

R¹² is halo;

R^{13a} and R^{13b} are independently H or C₁-C₃ alkyl;

R¹⁴ is C₁-C₅ alkyl-phenyl unsubstituted or substituted by 1 to 2 R^{C14} substituents;

wherein C^1 is unsubstituted or substituted by 1 to 3 R^{C1} substituents independently selected from the group consisting of halo, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, HO_2C -, C_1 - C_3 alkoxy, and C_2 - C_3 acyl;

R^2 is H, C_1 - C_3 alkyl, benzyl, or phenyl- CH_2CH_2 -;

R^3 is a 9- to 10-membered bicyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;

wherein R^3 is unsubstituted or substituted by 1 to 3 R^{3a} substituents independently selected from the group consisting of halo, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, hydroxy and C_1 - C_3 alkoxy;

R^4 is C_1 - C_3 alkyl, HO_2C -(CH_2) m -, $H_2NC(O)$ -(CH_2) m -, $(CH_3)_2NC(O)$ -(CH_2) m -, or tetrazolyl-(CH_2) m -;

R^5 is amino, $H_2N(CH_2)_n$ -, $H_2NC(O)$ -(CH_2) n -, $CH_3C(O)NH$ -, $CH_3C(O)NH(CH_2)_n$ -, C^5 , or C^5 - CH_2 -;

C^5 is:

- (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;
- (ii) a 9- to 10-membered bicyclic aryl or heteroaryl, wherein said bicyclic heteroaryl contains 1 to 3 heteroatoms selected from the group consisting of N, O, and S;
- (iii) a 5- to 6-membered monocyclic or 9- to 10-membered heterocycloalkyl, wherein said heterocycloalkyl is saturated or partially unsaturated, and contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;
- (iv) a 5- to 6-membered monocyclic cycloalkyl; or
- (v) 2,3-dihydroindolyl;

wherein C^5 is unsubstituted or substituted by 1 to 3 R^{C5} substituents independently selected from the group consisting of halo, amino, hydroxy, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, C_1 - C_3 alkoxy, H_2N -(CH_2) k -, $H_2NC(O)$ -(CH_2) k -, $H_2C=CH-CH_2O$ -, and phenyl;

R^6 is H, C_1 - C_5 alkyl, $H_2N(CH_2)_p$ -, $HOCH_2$ -, $(CH_3)_2NCH_2$ -, H_3CO -(CH_2) q -, or C^6 - CH_2 -;

C⁶ is 5- or 6-membered monocyclic, saturated heterocycloalkyl containing 1 to 2 heteroatoms selected from the group consisting of N, O, and S; and wherein C⁶ is unsubstituted or substituted by 1 to 3 R^{C6} substituents independently selected from the group consisting of halo, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, hydroxy and C₁-C₃ alkoxy;

R⁷ is H or C₁-C₃ alkyl;

R^{8a} is H, C₁-C₅ alkyl, HOCH₂-, H₂N(CH₂)_r-, (CH₃)₃N⁺(CH₂)_r-, or CH₃C(O)NH(CH₂)_r-;

R^{8b} is H or C₁-C₃ alkyl;

or R^{8b} is absent and R^{8a} and R⁷ are attached to form a 5- to 6-membered monocyclic, saturated cycloalkyl or heterocycloalkyl, wherein the heterocycloalkyl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S, wherein the 5- to 6-membered monocyclic, saturated cycloalkyl or heterocycloalkyl is unsubstituted or substituted by 1 to 3 R^{C8a} substituents independently selected from the group consisting of halo, amino, hydroxy, cyano, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, C₁-C₃ alkoxy, H₂N-(CH₂)_k-, H₂NC(O)-(CH₂)_k-, H₂NCH₂CH₂O-, CH₃C(O)NH-CH₂CH₂O-, and morpholinyl-CH₂CH₂O-;

R^{9a} is H or C₁-C₃ alkyl;

R^{9b} is H, C₁-C₅ alkyl, C⁹-CH₂-, or C⁹-CH₂CH₂-;

C⁹ is:

- (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or
- (ii) a 5- to 6-membered monocyclic, saturated cycloalkyl or heterocycloalkyl, wherein the heterocycloalkyl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;

wherein C⁹ is unsubstituted or substituted by 1 to 3 R^{C9} substituents independently selected from the group consisting of halo, amino, hydroxy, cyano, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, C₁-C₃ alkoxy, H₂N-(CH₂)_k-, H₂NC(O)-(CH₂)_k-, H₂NCH₂CH₂O-, CH₃C(O)NH-CH₂CH₂O-, and morpholinyl-CH₂CH₂O-;

or R^{9a} and R^{9b} are attached to form a 5- to 6-membered monocyclic, saturated cycloalkyl or heterocycloalkyl, wherein the heterocycloalkyl contains 1 to 2 heteroatoms selected from the

group consisting of N, O, and S, wherein the 5- to 6-membered monocyclic, saturated cycloalkyl or heterocycloalkyl is unsubstituted or substituted by 1 to 3 RC^{9ab} substituents independently selected from the group consisting of halo, amino, hydroxy, cyano, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, C_1 - C_3 -1,1'-biphenyl, C_1 - C_3 alkoxy, $H_2N-(CH_2)_k-$, $H_2NC(O)-(CH_2)_k-$, $H_2NCH_2CH_2O-$, $CH_3C(O)NH-CH_2CH_2O-$, and morpholinyl- CH_2CH_2O- ;

R^{10} is H, halo, or C_1 - C_3 alkyl;

R^{11} is H, halo, or C_1 - C_3 alkyl;

each occurrence of subscript k is independently 1 or 2;

subscript m is 1 or 2;

subscript n is 1, 2, 3, or 4;

subscript p is 1, 2, 3, or 4;

subscript q is 1 or 2;

subscript r is 1, 2, 3, or 4;

X^1 , X^2 , and X^3 are independently C(H) or N; and

A^1 and A^2 are independently selected from the group consisting of HO_2C- , $H_2NC(O)-$, $CH_3C(O)N(H)-$, $H_2NS(O)_2-$, $CH_3S(O)_2N(H)-$, tetrazolyl, and 5-oxo oxadiazolyl.

[00167] In some embodiments of a method as described herein, the compound is a compound of Formula (III), wherein:

R^1 is C^1 wherein C^1 is:

- (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or
- (ii) a 5- to 6-membered mono- or bicyclic, saturated cycloalkyl or heterocycloalkyl containing 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or
- (iii) a 5- to 6-membered mono- or bicyclic cycloalkyl;

wherein C^1 is unsubstituted or substituted by 1 to 3 RC^1 substituents independently selected from the group consisting of halo, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, HO_2C- , C_1 - C_3 alkoxy, and C_2 - C_3 acyl;

R^2 is H or C_1 - C_3 alkyl;

R³ is a 9- to 10-membered bicyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;

wherein R³ is unsubstituted or substituted by 1 to 3 R^{3a} substituents independently selected from the group consisting of halo, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, hydroxy and C₁-C₃ alkoxy;

R⁴ is C₁-C₃ alkyl, HO₂C-(CH₂)_m-, H₂NC(O)-(CH₂)_m-, (CH₃)₂NC(O)-(CH₂)_m-, or tetrazolyl-(CH₂)_m-;

R⁵ is C⁵ or C⁵-CH₂-, wherein C⁵ is:

- (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;
- (ii) a 9- to 10-membered bicyclic aryl or heteroaryl, wherein said bicyclic heteroaryl contains 1 to 3 heteroatoms selected from the group consisting of N, O, and S;
- (iii) a 5- to 6-membered monocyclic or 9- to 10-membered heterocycloalkyl, wherein said heterocycloalkyl is saturated or partially unsaturated, and contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;
- (iv) a 5- to 6-membered monocyclic cycloalkyl;
- (v) 2,3-dihydroindolyl;

wherein C⁵ is unsubstituted or substituted by 1 to 3 R^{C5} substituents independently selected from the group consisting of halo, amino, hydroxy, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, C₁-C₃ alkoxy, H₂N-(CH₂)_k-, H₂NC(O)-(CH₂)_k-, H₂C=CH-CH₂O-, and phenyl;

R⁶ is H, C₁-C₅ alkyl, H₂N(CH₂)_p-, HOCH₂-, (CH₃)₂NCH₂-, or H₃CO-(CH₂)_q-;

R⁷ is H or C₁-C₃ alkyl;

R^{8a} is H or C₁-C₅ alkyl;

R^{8b} is H or C₁-C₃ alkyl;

or R^{8b} is absent and R^{8a} and R⁷ are attached to form a 5- to 6-membered monocyclic, saturated cycloalkyl or heterocycloalkyl, wherein the heterocycloalkyl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S, wherein the 5- to 6-membered monocyclic, saturated cycloalkyl or heterocycloalkyl is unsubstituted or substituted by 1 to 3 R^{C8a} substituents

independently selected from the group consisting of halo, amino, hydroxy, cyano, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, C₁-C₃ alkoxy, H₂N-(CH₂)_k-, H₂NC(O)-(CH₂)_k-, H₂NCH₂CH₂O-, CH₃C(O)NH-CH₂CH₂O-, and morpholinyl-CH₂CH₂O-;

R^{9a} is H or C₁-C₃ alkyl;

R^{9b} is H or C₁-C₅ alkyl;

or R^{9a} and R^{9b} are attached to form a 5- to 6-membered monocyclic, saturated cycloalkyl or heterocycloalkyl, wherein the heterocycloalkyl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S, wherein the 5- to 6-membered monocyclic, saturated cycloalkyl or heterocycloalkyl is unsubstituted or substituted by 1 to 3 R^{C9ab} substituents independently selected from the group consisting of halo, amino, hydroxy, cyano, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, C₁-C₃-1,1'-biphenyl, C₁-C₃ alkoxy, H₂N-(CH₂)_k-, H₂NC(O)-(CH₂)_k-, H₂NCH₂CH₂O-, CH₃C(O)NH-CH₂CH₂O-, and morpholinyl-CH₂CH₂O-;

R¹⁰ is H, halo, or C₁-C₃ alkyl;

R¹¹ is H, halo, or C₁-C₃ alkyl;

each occurrence of subscript k is independently 1 or 2;

subscript m is 1 or 2;

subscript n is 1, 2, 3, or 4;

subscript p is 1, 2, 3, or 4;

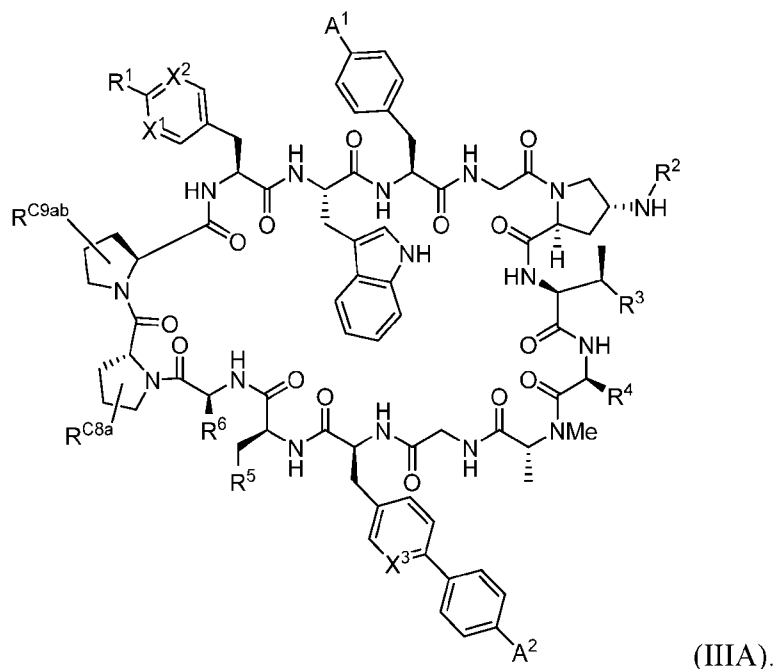
subscript q is 1 or 2;

subscript r is 1, 2, 3, or 4;

X¹, X², and X³ are independently C(H) or N; and

A¹ and A² are independently selected from the group consisting of HO₂C-, H₂NC(O)-, CH₃C(O)N(H)-, H₂NS(O)₂-, CH₃S(O)₂N(H)-, tetrazolyl, and 5-oxo oxadiazolyl.

[00168] In some embodiments of a method as described herein, the compound has a structure of Formula (IIIA):



[00169] In some embodiments of a method as described herein, the compound is a compound of Formula (III), wherein:

R¹ is C¹ wherein C¹ is phenyl unsubstituted or substituted by 1 to 2 R^{C1} substituents;

R² is H or C₁-C₃ alkyl;

R³ is naphthyl or indolyl, wherein R³ is unsubstituted or substituted by 1 to 2 R^{3a} substituents;

R⁴ is C₁-C₃ alkyl, HO₂C-(CH₂)_m-, H₂NC(O)-(CH₂)_m-, (CH₃)₂NC(O)-(CH₂)_m-, or tetrazolyl-(CH₂)_m-;

R⁵ is C⁵ or C⁵-CH₂-, wherein C⁵ is naphthyl or indolyl unsubstituted or substituted by 1 to 2 R^{C5} substituents;

R⁶ is H, C₁-C₅ alkyl, H₂N(CH₂)_p-, HOCH₂-, (CH₃)₂NCH₂-, or H₃CO-(CH₂)_q-;

R^{8b} is absent and R^{8a} and R⁷ are attached to form a pyrrolidinyl unsubstituted or substituted by 1 to 2 R^{C8a} substituents;

R^{9a} and R^{9b} are attached to form a pyrrolidinyl unsubstituted or substituted by 1 to 2 R^{C9ab} substituents;

R¹⁰ is H or C₁-C₃ alkyl;

R¹¹ is H or C₁-C₃ alkyl;

subscript m is 1 or 2;

X¹, X², and X³ are independently C(H) or N; and

A¹ and A² are independently selected from the group consisting of HO₂C-, H₂NC(O)-, or CH₃C(O)N(H)-.

[00170] In some embodiments of a method as described herein, the compound is a compound of Formula (III), wherein:

X¹ and X² are C(H); and

R¹ is phenyl substituted by carboxy.

[00171] In some embodiments of a method as described herein, the compound is a compound of Formula (III), wherein R² is H.

[00172] In some embodiments of a method as described herein, the compound is a compound of Formula (III), wherein R³ is indolyl substituted by one halo.

[00173] In some embodiments of a method as described herein, the compound is a compound of Formula (III), wherein R⁴ is HO₂C-(CH₂)_m-.

[00174] In some embodiments of a method as described herein, the compound is a compound of Formula (III), wherein X³ is C(H).

[00175] In some embodiments of a method as described herein, the compound is a compound of Formula (III), wherein R⁵ is H₂N(CH₂)_n-, indole, 7-azaindole, naphthyl or pyridyl.

[00176] In some embodiments of a method as described herein, the compound is a compound of Formula (III), wherein R⁵ is H₂N(CH₂)_n-, indole, naphthyl or pyridyl.

[00177] In some embodiments of a method as described herein, the compound is a compound of Formula (III), wherein R⁶ is H.

[00178] In some embodiments of a method as described herein, the compound is a compound of Formula (III), wherein R^{8b} is absent and R^{8a} and R⁷ are attached to form a pyrrolidinyl substituted by 1 to 2 R^{C8a} substituents.

[00179] In some embodiments of a method as described herein, the compound is a compound of Formula (III), wherein R^{9a} and R^{9b} are attached to form a pyrrolidinyl substituted by 1 to 2 R^{C9ab} substituents.

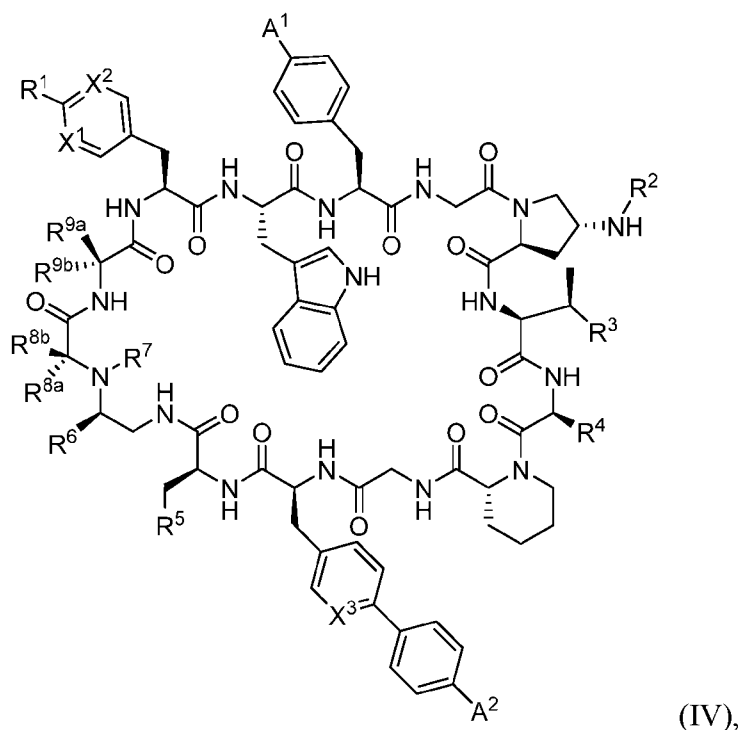
[00180] In some embodiments of a method as described herein, the compound is a compound of Formula (III), wherein R^{C9a} is hydroxyl.

[00181] In some embodiments of a method as described herein, the compound is a compound of Formula (III), wherein RC^{9ab} is C₁-C₃-1,1'-biphenyl.

[00182] In some embodiments of a method as described herein, the compound is a compound of Formula (III), wherein A^1 is $-CO_2H$.

[00183] In some embodiments of a method as described herein, the compound is a compound of Formula (III), wherein A^2 is $-CO_2H$.

[00184] In some embodiments of a method as described herein, the compound has a structure of Formula (IV):



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $CH_3C(O)NH-CH_2CH_2-O-$ or C^1 ;

C^1 is:

- (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or
- (ii) a 5- to 6-membered mono- or bicyclic, saturated cycloalkyl or heterocycloalkyl containing 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or
- (iii) a 5- to 6-membered mono- or bicyclic cycloalkyl;

wherein C^1 is unsubstituted or substituted by 1 to 3 RC^1 substituents independently selected from the group consisting of halo, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, HO_2C -, C_1 - C_3 alkoxy, and C_2 - C_3 acyl;

R^2 is H, C_1 - C_3 alkyl, benzyl, heteroaryl- $(CH_2)_m$ -C(O)-, or phenyl- CH_2CH_2 -, wherein said heteroaryl is a 5- to 6-membered monocyclic heteroaryl containing 1 to 2 heteroatoms selected from the group consisting of N, O, and S, wherein R^2 is unsubstituted or substituted by 1 to 3 RC^2 substituents independently selected from the group consisting of halo, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, HO_2C -, C_1 - C_3 alkoxy, and C_2 - C_3 acyl;

R^3 is a 9- to 10-membered bicyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;

wherein R^3 is unsubstituted or substituted by 1 to 3 R^{3a} substituents independently selected from the group consisting of halo, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, hydroxy and C_1 - C_3 alkoxy;

R^4 is C_1 - C_3 alkyl, HO_2C -(CH_2) $_m$ -, $H_2NC(O)$ -(CH_2) $_m$ -, $(CH_3)_2NC(O)$ -(CH_2) $_m$ -, or tetrazolyl-(CH_2) $_m$ -;

R^5 is amino, $H_2N(CH_2)_n$ -, $H_2NC(O)$ -(CH_2) $_n$ -, $CH_3C(O)NH$ -, $CH_3C(O)NH(CH_2)_n$ -, C^5 , or C^5 - CH_2 -,

C^5 is:

- (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;
- (ii) a 9- to 10-membered bicyclic aryl or heteroaryl, wherein said bicyclic heteroaryl contains 1 to 3 heteroatoms selected from the group consisting of N, O, and S;
- (iii) a 5- to 6-membered monocyclic or 9- to 10-membered heterocycloalkyl, wherein said heterocycloalkyl is saturated or partially unsaturated, and contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;
- (iv) a 5- to 6-membered monocyclic cycloalkyl;
- (v) 2,3-dihydroindolyl;

wherein C^5 is unsubstituted or substituted by 1 to 3 RC^5 substituents independently selected from the group consisting of halo, amino, hydroxy, C_1 - C_3 alkyl, C_1 - C_3

fluoroalkyl, C₁-C₃ alkoxy, H₂N-(CH₂)_k-, H₂NC(O)-(CH₂)_k-, H₂C=CH-CH₂O-, and phenyl;

R⁶ is H, C₁-C₅ alkyl, H₂N(CH₂)_p-, HOCH₂-, (CH₃)₂NCH₂-, H₃CO-(CH₂)_q-, or C⁶-CH₂-;

C⁶ is 5- or 6-membered monocyclic, saturated heterocycloalkyl containing 1 to 2 heteroatoms selected from the group consisting of N, O, and S; and wherein C⁶ is unsubstituted or substituted by 1 to 3 R^{C6} substituents independently selected from the group consisting of halo, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, hydroxy and C₁-C₃ alkoxy;

R⁷ is H or C₁-C₃ alkyl;

R^{8a} is H, C₁-C₅ alkyl, HOCH₂-, H₂N(CH₂)_r-, (CH₃)₃N⁺(CH₂)_r-, or CH₃C(O)NH(CH₂)_r-;

R^{8b} is H or C₁-C₃ alkyl;

R^{9a} is H or C₁-C₃ alkyl;

R^{9b} is H, C₁-C₅ alkyl, C⁹-CH₂-, or C⁹-CH₂CH₂-;

C⁹ is:

- (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or
- (ii) a 5- to 6-membered monocyclic, saturated cycloalkyl or heterocycloalkyl, wherein the heterocycloalkyl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;

wherein C⁹ is unsubstituted or substituted by 1 to 3 R^{C9} substituents independently selected from the group consisting of halo, amino, hydroxy, cyano, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, C₁-C₃ alkoxy, H₂N-(CH₂)_k-, H₂NC(O)-(CH₂)_k-, H₂NCH₂CH₂O-, CH₃C(O)NH-CH₂CH₂O-, and morpholinyl-CH₂CH₂O-;

R¹⁰ is H, halo, or C₁-C₃ alkyl;

R¹¹ is H, halo, or C₁-C₃ alkyl;

each occurrence of subscript k is independently 1 or 2;

subscript m is 1 or 2;

subscript n is 1, 2, 3, or 4;

subscript p is 1, 2, 3, or 4;

subscript q is 1 or 2;

subscript r is 1, 2, 3, or 4;

X¹, X², and X³ are independently C(H) or N; and

A¹ and A² are independently selected from the group consisting of HO₂C-, H₂NC(O)-, CH₃C(O)N(H)-, H₂NS(O)₂-, CH₃S(O)₂N(H)-, tetrazolyl, and 5-oxo oxadiazolyl.

[00185] In some embodiments of a method as described herein, the compound is a compound of Formula (IV), wherein:

R¹ is CH₃C(O)NH-CH₂CH₂-O-;

R² is heteroaryl-(CH₂)_m-C(O)-, wherein said heteroaryl is a 5- to 6-membered monocyclic heteroaryl containing 1 to 2 heteroatoms selected from the group consisting of N, O, and S, wherein R² is unsubstituted or substituted by 1 to 2 R^{C2} substituents;

R³ is a 9- to 10-membered bicyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; wherein R³ is unsubstituted or substituted by 1 to 3 R^{3a} substituents independently selected from the group consisting of halo, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, hydroxy and C₁-C₃ alkoxy;

R⁴ is C₁-C₃ alkyl, HO₂C-(CH₂)_m-, H₂NC(O)-(CH₂)_m-, (CH₃)₂NC(O)-(CH₂)_m-, or tetrazolyl-(CH₂)_m-;

R⁵ is C⁵ or C⁵-CH₂-, wherein C⁵ is:

- (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;
- (ii) a 9- to 10-membered bicyclic aryl or heteroaryl, wherein said bicyclic heteroaryl contains 1 to 3 heteroatoms selected from the group consisting of N, O, and S;
- (iii) a 5- to 6-membered monocyclic or 9- to 10-membered heterocycloalkyl, wherein said heterocycloalkyl is saturated or partially unsaturated, and contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;
- (iv) a 5- to 6-membered monocyclic cycloalkyl;
- (v) 2,3-dihydroindolyl;

wherein C^5 is unsubstituted or substituted by 1 to 3 RC^5 substituents independently selected from the group consisting of halo, amino, hydroxy, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, C_1 - C_3 alkoxy, $H_2N-(CH_2)_k$, $H_2NC(O)-(CH_2)_k$, $H_2C=CH-CH_2O$ -, and phenyl;

R^6 is H or C_1 - C_5 alkyl;

R^7 is H or C_1 - C_3 alkyl;

R^{8a} is H or C_1 - C_5 alkyl;

R^{8b} is H or C_1 - C_3 alkyl;

R^{9a} is H or C_1 - C_3 alkyl;

R^{9b} is H or C_1 - C_5 alkyl;

R^{10} is H, halo, or C_1 - C_3 alkyl;

R^{11} is H, halo, or C_1 - C_3 alkyl;

each occurrence of subscript k is independently 1 or 2;

subscript m is 1 or 2;

X^1 , X^2 , and X^3 are independently C(H) or N; and

A^1 and A^2 are independently selected from the group consisting of HO_2C -, $H_2NC(O)$ -, $CH_3C(O)N(H)$ -, $H_2NS(O)_2$ -, $CH_3S(O)_2N(H)$ -, tetrazolyl, and 5-oxo oxadiazolyl.

[00186] In some embodiments of a method as described herein, the compound is a compound of Formula (IV), wherein:

R^1 is $CH_3C(O)NH-CH_2CH_2-O$;

R^2 is benzyl, pyridinyl- $(CH_2)_m-C(O)$ -, or phenyl- CH_2CH_2 -, wherein said heteroaryl is a 5- to 6-membered monocyclic heteroaryl containing 1 to 2 heteroatoms selected from the group consisting of N, O, and S, wherein R^2 is unsubstituted or substituted by 1 to 3 RC^2 substituents independently selected from the group consisting of halo, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, HO_2C -, C_1 - C_3 alkoxy, and C_2 - C_3 acyl;

R^3 is naphthyl or indolyl, wherein R^3 is unsubstituted or substituted by 1 to 2 R^{3a} substituents;

R^4 is C_1 - C_3 alkyl, $HO_2C-(CH_2)_m$ -, $H_2NC(O)-(CH_2)_m$ -, $(CH_3)_2NC(O)-(CH_2)_m$ -, or tetrazolyl- $(CH_2)_m$;

R⁵ is C⁵ or C⁵-CH₂-, wherein C⁵ is naphthyl or indolyl unsubstituted or substituted by 1 to 2

RC⁵ substituents;

R⁶ is H or C₁-C₅ alkyl;

R⁷ is H or C₁-C₃ alkyl;

R^{8a} is H or C₁-C₅ alkyl;

R^{8b} is H or C₁-C₃ alkyl;

R^{9a} is H or C₁-C₃ alkyl;

R^{9b} is H or C₁-C₅ alkyl;

R¹⁰ is H or C₁-C₃ alkyl;

R¹¹ is H or C₁-C₃ alkyl;

subscript m is 1 or 2;

X¹, X², and X³ are independently C(H) or N; and

A¹ and A² are independently selected from the group consisting of HO₂C-, H₂NC(O)-,

CH₃C(O)N(H)-, H₂NS(O)₂-, CH₃S(O)₂N(H)-, tetrazolyl, and 5-oxo oxadiazolyl.

[00187] In some embodiments of a method as described herein, the compound is a compound of Formula (IV), wherein:

X¹ and X² are C(H); and

R¹ is CH₃C(O)NH-CH₂CH₂-O-.

[00188] In some embodiments of a method as described herein, the compound is a compound of Formula (IV), wherein R² is, pyridinyl-(CH₂)₂-C(O)-.

[00189] In some embodiments of a method as described herein, the compound is a compound of Formula (IV), wherein R³ is naphthyl.

[00190] In some embodiments of a method as described herein, the compound is a compound of Formula (IV), wherein R⁴ is HO₂C-(CH₂)_m-.

[00191] In some embodiments of a method as described herein, the compound is a compound of Formula (IV), wherein X³ is C(H).

[00192] In some embodiments of a method as described herein, the compound is a compound of Formula (IV), wherein R⁵ is H₂N(CH₂)_n-, indole, 7-azaindole, naphthyl or pyridyl.

[00193] In some embodiments of a method as described herein, the compound is a compound of Formula (IV), wherein R^5 is $H_2N(CH_2)_n$ -, indole, naphthyl or pyridyl.

[00194] In some embodiments of a method as described herein, the compound is a compound of Formula (IV), wherein R^6 is H.

[00195] In some embodiments of a method as described herein, the compound is a compound of Formula (IV), wherein R^7 is H.

[00196] In some embodiments of a method as described herein, the compound is a compound of Formula (IV), wherein R^{9a} is methyl.

[00197] In some embodiments of a method as described herein, the compound is a compound of Formula (IV), wherein R^{9b} is butyl.

[00198] In some embodiments of a method as described herein, the compound is a compound of Formula (IV), wherein A^1 is $-CO_2H$.

[00199] In some embodiments of a method as described herein, the compound is a compound of Formula (IV), wherein A^2 is $-CO_2H$.

[00200] In some embodiments of a method as described herein, the compound is a compound of Formula (I), wherein the compound is selected from the group consisting of SEQ ID NOS:8, 9, 10, 11, 12, 13, 14, 15.

[00201] In some embodiments, the compound is a peptide (*e.g.*, macrocyclic peptide) comprising the amino acid sequence of SEQ ID NO:8. In some embodiments, the compound is Compound A. In some embodiments, the compound is a peptide (*e.g.*, macrocyclic peptide) comprising the amino acid sequence of SEQ ID NO:9. In some embodiments, the compound is Compound B. In some embodiments, the compound is a peptide (*e.g.*, macrocyclic peptide) comprising the amino acid sequence of SEQ ID NO:10. In some embodiments, the compound is Compound C. In some embodiments, the compound is a peptide (*e.g.*, macrocyclic peptide) comprising the amino acid sequence of SEQ ID NO:11. In some embodiments, the compound is Compound D. In some embodiments, the compound is a peptide (*e.g.*, macrocyclic peptide) comprising the amino acid sequence of SEQ ID NO:12. In some embodiments, the compound is Compound E. In some embodiments, the compound is a peptide (*e.g.*, macrocyclic peptide) comprising the amino acid sequence of SEQ ID NO:13. In some embodiments, the compound is Compound F. In some embodiments, the compound is a peptide (*e.g.*, macrocyclic peptide)

comprising the amino acid sequence of SEQ ID NO:14. In some embodiments, the compound is Compound G. In some embodiments, the compound is a peptide (*e.g.*, macrocyclic peptide) comprising the amino acid sequence of SEQ ID NO:15. In some embodiments, the compound is Compound H.

[00202] While not being bound by any specific theory, the Applicant believes that the compounds of the disclosure trap interleukin-1 β , prevent signaling through the IL-1 receptor and hence reduce the downstream markers IL-6 and CRP.

7.5.1 Compound Interactions with IL-1 β

[00203] In some embodiments, a compound as described herein binds to IL-1 β at one or more binding pockets of IL-1 β . In some embodiments, a compound as described herein binds at a lipophilic binding pocket and/or hydrophobic binding pocket of the IL-1 β .

[00204] In some embodiments, a compound as described herein binds to IL-1 β at the residues of IL-1 β described herein as a binding pocket of IL-1 β (*e.g.*, a binding pocket of IL-1 β located between the N-terminal and C-terminal domains of IL-1 β). In some embodiments, a compound as described herein binds to a binding pocket of IL-1 β that is at or adjacent to the D3 domain of IL-1R1 when IL-1 β is complexed with IL-1R1. In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket comprising or consisting of the amino acid residues of Gly177-Leu178-Lys179-Glu180-Lys181-Asn182-Leu183-Tyr184 (SEQ ID NO:16) and/or Val201-Asp202-Pro203-Lys204-Asn205-Tyr206-Pro207 (SEQ ID NO:17) of IL-1 β . In some embodiments, a compound as described herein binds at a binding pocket of IL-1 β to all of the residues recited for the binding pocket of IL-1 β . In some embodiments, a compound as described herein binds at a binding pocket of IL-1 β to one or more but not all of the residues recited for the binding pocket of IL-1 β . In some embodiments, a compound as described herein binds at a binding pocket of IL-1 β comprising additional IL-1 β residues (*e.g.*, additional residues of the binding pocket described herein).

[00205] In some embodiments, a compound as described herein binds at the binding pocket of IL-1 β via a non-covalent interaction between a moiety of the compound and a residue of the binding pocket. In some embodiments, a moiety of the compound is capable of donating or accepting a non-covalent interaction as described herein. In some embodiments, a non-covalent interaction as described herein may be donated by a residue of the binding pocket of the IL-1 β

(*e.g.*, the backbone or sidechain of the residue) and accepted by the compound (*e.g.*, a moiety of the compound). In some embodiments, a non-covalent interaction as described herein may be donated by the compound (*e.g.*, a moiety of the compound) and accepted by a residue of the binding pocket of the IL-1 β (*e.g.*, the backbone or sidechain of the residue). For example, a hydrogen bond (H-bond) interaction may involve a hydrogen being donated by the compound (*e.g.*, a moiety of the compound) to and accepted by a residue of the binding pocket, to form a H-bond interaction. In some embodiments, a moiety of the compound is a functional group of the compound (*e.g.*, as described herein). In some embodiments, a moiety of the compound comprises multiple functional groups of the compound (*e.g.*, as described herein).

[00206] In some embodiments, a compound as described herein binds at the binding pocket of IL-1 β via a lipophilic interaction and/or hydrophobic interaction (*e.g.*, minimization of non-polar surface area exposure to polar molecules) to a residue of the IL-1 β . In some embodiments, a compound as described herein comprises a lipophilic interaction moiety and/or hydrophobic interaction moiety capable of accepting a lipophilic and/or hydrophobic interaction from a residue (*e.g.*, a backbone or sidechain of a residue) of a binding site of IL-1 β as described herein. In some embodiments, a compound as described herein comprises a lipophilic interaction moiety and/or hydrophobic interaction moiety capable of donating a lipophilic and/or hydrophobic interaction to a residue (*e.g.*, a backbone or sidechain of a residue) of a binding site of IL-1 β as described herein. In some embodiments, a compound as described herein binds at the binding pocket of IL-1 β through an electrostatic interaction (*e.g.*, Coulombic attraction interaction) to a residue of the IL-1 β . In some embodiments, a compound as described herein comprises an electrostatic interaction moiety capable of accepting an electrostatic interaction from a residue (*e.g.*, a backbone or sidechain of a residue) of a binding site of IL-1 β as described herein. In some embodiments, a compound as described herein comprises an electrostatic interaction moiety capable of donating an electrostatic interaction to a residue (*e.g.*, a backbone or sidechain of a residue) of a binding site of IL-1 β as described herein. In some embodiments, a compound as described herein binds at the binding pocket of IL-1 β through an ionic interaction (*e.g.*, electrovalent interaction) to a residue of the IL-1 β . In some embodiments, a compound as described herein comprises an ionic interaction moiety capable of accepting an ionic interaction from a residue (*e.g.*, a backbone or sidechain of a residue) of a binding site of IL-1 β as described herein. In some embodiments, a compound as described herein comprises an ionic interaction

moiety capable of donating an ionic interaction to a residue (*e.g.*, a backbone or sidechain of a residue) of a binding site of IL-1 β as described herein. In some embodiments, a compound as described herein binds at the binding pocket of IL-1 β through a hydrogen bond (H-bond) interaction (*e.g.*, backbone or sidechain H-bond interaction) to a residue of the IL-1 β . In some embodiments, a compound as described herein comprises a H-bond interaction moiety capable of accepting a H-bond interaction from a residue (*e.g.*, a backbone or sidechain of a residue) of a binding site of IL-1 β as described herein. In some embodiments, a compound as described herein comprises a H-bond interaction moiety capable of donating a H-bond interaction to a residue (*e.g.*, a backbone or sidechain of a residue) of a binding site of IL-1 β as described herein. In some embodiments, a compound as described herein binds at the binding pocket of IL-1 β through a halogen bond interaction (*e.g.*, sidechain halogen bond interaction) to a residue of the IL-1 β . In some embodiments, a compound as described herein comprises a halogen bond interaction moiety capable of accepting a halogen bond interaction from a residue (*e.g.*, a backbone or sidechain of a residue) of a binding site of IL-1 β as described herein. In some embodiments, a compound as described herein comprises a halogen bond interaction moiety capable of donating a halogen bond interaction to a residue (*e.g.*, a backbone or sidechain of a residue) of a binding site of IL-1 β as described herein. In some embodiments, a compound as described herein binds at the binding pocket of IL-1 β through a Van der Waals interaction (*e.g.*, a dipole-dipole interaction; dipole-induced dipole interaction; or London dispersion forces) to a residue of the IL-1 β . In some embodiments, a compound as described herein comprises a Van der Waals interaction moiety capable of accepting a Van der Waals interaction from a residue (*e.g.*, a backbone or sidechain of a residue) of a binding site of IL-1 β as described herein. In some embodiments, a compound as described herein comprises a Van der Waals interaction moiety capable of donating a Van der Waals interaction to a residue (*e.g.*, a backbone or sidechain of a residue) of a binding site of IL-1 β as described herein. In some embodiments, a compound as described herein binds at the binding pocket of IL-1 β through a pi-effect interaction (*e.g.*, a pi-pi interaction; CH-pi interaction; cation-pi interaction; anion-pi interaction; or polar-pi interaction) to a residue of the IL-1 β . In some embodiments, a compound as described herein comprises a pi-effect interaction moiety capable of accepting a pi-effect interaction from a residue (*e.g.*, a backbone or sidechain of a residue) of a binding site of IL-1 β as described herein. In some embodiments, a compound as described herein comprises a pi-

effect interaction moiety capable of donating a pi-effect interaction to a residue (*e.g.*, a backbone or sidechain of a residue) of a binding site of IL-1 β as described herein. In some embodiments, the pi-effect interaction is a stacking interaction (*e.g.*, a pi-pi interaction). In some embodiments, the pi-effect interaction is a non-polar pi-effect interaction. In some embodiments, the pi-effect interaction is a CH-pi interaction. In some embodiments, the pi-effect interaction is a polar-pi interaction. In some embodiments, the polar-pi interaction is a polar hydrogen-pi interaction. In some embodiments, a polar-pi interaction is a polar nitrogen-pi interaction. In some embodiments, the pi-effect interaction may be characterized as more than one type of pi-effect interaction as described herein. In some embodiments, the non-covalent interaction may be characterized as more than one type of non-covalent interaction as described herein.

[00207] In some embodiments, the non-covalent interaction moiety (*e.g.*, lipophilic interaction moiety, hydrophobic interaction moiety, electrostatic interaction moiety, ionic interaction moiety, H-bond interaction moiety, halogen bond interaction moiety, Van der Waals interaction moiety, or pi-effect interaction moiety) of the compound comprises a functional group of the compound, or a moiety, group, or substituent of the compound as described herein. In some embodiments, the non-covalent interaction moiety is an NH group, NH₂ group, NH₃ group, lone pair of electrons, OH group, carbonyl, carboxylate, arene (*e.g.*, aryl or biaryl), an atom such as H, N, O, F, Cl, or another group or atom defined herein or elsewhere as interacting non-covalently. For example, common donor and acceptor atoms for a H-bond non-covalent interaction include the period 2 elements, such as nitrogen (N), oxygen (O), and fluorine (F).

[00208] In some embodiments, a compound as described herein binds at a binding pocket of IL-1 β comprising one or more of the amino acids corresponding to residues 177-184 and 201-207 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds at a binding pocket of IL-1 β defined by amino acid residues Gly177-Leu178-Lys179-Glu180-Lys181-Asn182-Leu183-Tyr184 (SEQ ID NO:16) and Val201-Asp202-Pro203-Lys204-Asn205-Tyr206-Pro207 (SEQ ID NO:17) (*e.g.*, Gly177 through Tyr184 and Val201 through Pro207) of the IL-1 β (SEQ ID NO:1).

[00209] In some embodiments, a compound as described herein binds to one or both of the amino acids corresponding to residues selected from 179 or 207 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to one or both of the amino acid residues Lys179 or Pro207 of the IL-1 β (SEQ ID NO:1). In some embodiments, the compound

binds to one or both of the Lys179 or Pro207 via a moiety capable of interacting via a pi-effect interaction (*e.g.*, accepting a pi-effect interaction) with residue Lys179 and/or residue Pro207. In some embodiments, the moiety capable of interacting via a pi-effect interaction from residue Pro207 comprises an arene moiety. In some embodiments, the moiety capable of interacting via a pi-effect interaction from residue Pro207 comprises a biaryl moiety. In some embodiments, the biaryl moiety is a 9- to 10-membered bicyclic aryl or heteroaryl. In some embodiments, the heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S. In some embodiments, the 9- to 10-membered bicyclic aryl or heteroaryl is unsubstituted or substituted by 1 to 3 substituents independently selected from the group consisting of halo, C1-C3 alkyl, C1-C3 fluoroalkyl, hydroxy, and C1-C3 alkoxy. In some embodiments, the biaryl moiety is a substituted or unsubstituted indole or naphthyl.

[00210] In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket of IL-1 β that further comprises the amino acid corresponding to residue 119 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket of IL-1 β that is further defined by amino acid residue Val119 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket of IL-1 β that further comprises the amino acid corresponding to residue 120 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket of IL-1 β that is further defined by amino acid residue Arg120 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket of IL-1 β that further comprises the amino acid corresponding to residue 121 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket of IL-1 β that is further defined by amino acid residue Ser121 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket of IL-1 β that further comprises the amino acid corresponding to residue 203 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket of IL-1 β that is further defined by amino acid residue Pro203 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket of IL-1 β that further comprises the amino acid corresponding to residue 204 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-

1 β at a binding pocket of IL-1 β that is further defined by amino acid residue Lys204 of the IL-1 β (SEQ ID NO:1).

[00211] In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket that further comprises the amino acid corresponding to residue 162 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket that is further defined by amino acid residue Phe162 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket that further comprises the amino acid corresponding to residue 206 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket that is further defined by amino acid residue Tyr206 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket that further comprises the amino acid corresponding to residue 269 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket that is further defined by amino acid residue Ser269 of the IL-1 β (SEQ ID NO:1).

[00212] In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket that further comprises the amino acid corresponding to residue 117 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket that is further defined by amino acid residue Ala117 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket that further comprises the amino acid corresponding to residue 118 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket that is further defined by amino acid residue Pro118 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket that further comprises the amino acid corresponding to residue 122 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket that is further defined by amino acid residue Leu122 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket that further comprises the amino acid corresponding to residue 123 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket that is further defined by amino acid residue Asn123 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket that further comprises the

amino acid corresponding to residue 159 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket that is further defined by amino acid residue Ser159 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket that further comprises the amino acid corresponding to residue 266 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds to IL-1 β at a binding pocket that is further defined by amino acid residue Phe266 of the IL-1 β (SEQ ID NO:1).

[00213] In some embodiments, a compound as described herein binds at the binding pocket of IL-1 β to one or more amino acids corresponding to residues selected from 119, 120, 121, 162, 179, 203, 204, 206, 207, or 269 of the IL-1 β (SEQ ID NO:1). In some embodiments, a compound as described herein binds at the binding pocket of IL-1 β to one or more amino acid residues selected from residues Val119, Arg120, Ser121, Phe162, Lys179, Pro203, Lys204, Tyr206, Pro207, or Ser269 of the IL-1 β (SEQ ID NO:1).

[00214] In certain embodiments, a compound as described herein binds at the binding pocket of IL-1 β to the amino acids corresponding to residues 119, 120, 121, 203, and 204 of the IL-1 β (SEQ ID NO:1). In certain embodiments, a compound as described herein binds at the binding pocket of IL-1 β to residues Val119, Arg120, Ser121, Pro203, and Lys204 of the IL-1 β (SEQ ID NO:1). In certain embodiments, the compound has no further binding interactions with the IL-1 β (SEQ ID NO:1). In certain embodiments, the compound further binds at the binding pocket of IL-1 β to one, two, three, four, or five amino acids corresponding to residues selected from 162, 179, 206, 207 or 269 of the IL-1 β (SEQ ID NO:1). In certain embodiments, the compound further binds at the binding pocket of IL-1 β to one, two, three, four, or five residues selected from Phe162, Lys179, Tyr206, Pro207, or Ser269 of the IL-1 β (SEQ ID NO:1). In certain embodiments, a compound as described herein binds to IL-1 β at a binding pocket to at least the amino acid corresponding to residue 179 and/or residue 207 of the IL-1 β (SEQ ID NO:1). In certain embodiments, a compound as described herein binds to IL-1 β at a binding pocket that to at least the amino acid corresponding to residue Lys179 and/or Pro207 of the IL-1 β (SEQ ID NO:1).

[00215] In certain embodiments, a compound as described herein binds at the binding pocket of IL-1 β to the amino acids corresponding to residues 119, 120, 121, 179, 203, 204, 206, 207, and 269 of the IL-1 β (SEQ ID NO:1). In certain embodiments, a compound as described herein

binds at the binding pocket of IL-1 β to residues Val119, Arg120, Ser121, Lys179, Pro203, Lys204, Tyr206, Pro207, and Ser269 of the IL-1 β (SEQ ID NO:1).

[00216] In certain embodiments, a compound as described herein binds at the binding pocket of IL-1 β to the amino acids corresponding to residues 119, 120, 121, 179, 203, 204, and 206 of the IL-1 β (SEQ ID NO:1). In certain embodiments, a compound as described herein binds at the binding pocket of IL-1 β to residues Val119, Arg120, Ser121, Lys179, Pro203, and Lys204 of the IL-1 β (SEQ ID NO:1).

[00217] In certain embodiments, a compound as described herein binds at the binding pocket of IL-1 β to the amino acids corresponding to residues 119, 120, 121, 162, 179, 203, 204, 206, 207, and 269 of the IL-1 β (SEQ ID NO:1). In certain embodiments, a compound as described herein binds at the binding pocket of IL-1 β to residues Val119, Arg120, Ser121, Phe162, Lys179, Pro203, Lys204, Tyr206, Pro207, and Ser269 of the IL-1 β (SEQ ID NO:1).

[00218] In certain embodiments, a compound as described herein binds at the binding pocket of IL-1 β to the amino acids corresponding to residues 119, 120, 121, 179, 203, 204, 206, and 207 of the IL-1 β (SEQ ID NO:1). In certain embodiments, a compound as described herein binds at the binding pocket of IL-1 β to residues Val119, Arg120, Ser121, Lys179, Pro203, Lys204, Tyr206, and Pro207 of the IL-1 β (SEQ ID NO:1).

[00219] In some embodiments, the binding of the compound at the binding pocket of IL-1 β to a specified residue is mediated by the interaction of a moiety or functional group of a compound with the backbone or sidechain of the specified residue of IL-1 β . In some embodiments, a compound as described herein binds to one or more residues of the binding pocket of IL-1 β via a non-covalent interaction. In some embodiments, a compound as described herein binds to one or more residues of IL-1 β selected from Val119, Arg120, Ser121, Phe162, Lys179, Pro203, Lys204, Tyr206, Pro207, or Ser269.

[00220] In some embodiments, a compound as described herein binds at the binding pocket of IL-1 β to a residue of IL-1 β via a lipophilic interaction and/or hydrophobic interaction mediated by a lipophilic interaction moiety and/or hydrophobic interaction moiety of the compound. In some embodiments, a compound as described herein binds at the binding pocket of IL-1 β to a residue of IL-1 β via an electrostatic interaction mediated by an electrostatic interaction moiety of the compound. In some embodiments, a compound as described herein binds at the binding pocket of IL-1 β to a residue of IL-1 β via an ionic interaction mediated by an ionic interaction

moiety of the compound. In some embodiments, a compound as described herein binds at the binding pocket of IL-1 β to a residue of IL-1 β via a hydrogen bond (H-bond) interaction mediated by a H-bond interaction moiety of the compound. In some embodiments, a compound as described herein binds at the binding pocket of IL-1 β to a residue of IL-1 β via a halogen bond interaction mediated by a halogen bond interaction moiety of the compound. In some embodiments, a compound as described herein binds at the binding pocket of IL-1 β to a residue of IL-1 β via a Van der Waals interaction (*e.g.*, a dipole-dipole interaction; dipole-induced dipole interaction; or London dispersion force) mediated by a Van der Waals interaction moiety of the compound. In some embodiments, a compound as described herein binds at the binding pocket of IL-1 β to a residue of IL-1 β via a pi-effect interaction (*e.g.*, a pi-pi interaction; CH-pi interaction; cation-pi interaction; anion-pi interaction; or polar-pi interaction) mediated by a pi-effect interaction moiety of the compound. In some embodiments, the moiety of the compound comprises one or more functional groups of the compound (*e.g.*, as described herein). In some embodiments, a compound as described herein binds at the binding pocket of IL-1 β to a residue of IL-1 β via more than one non-covalent interaction as described herein, which may be of different types. In some embodiments, a moiety of the compound binds to a residue of IL-1 β via more than one non-covalent interaction as described herein, which may be of different types.

[00221] In some embodiments, a compound as described herein binds at the binding pocket of IL-1 β defined the amino acid residues Gly177-Leu178-Lys179-Glu180-Lys181-Asn182-Leu183-Tyr184 (SEQ ID NO:16) and Val201-Asp202-Pro203-Lys204-Asn205-Tyr206-Pro207 (SEQ ID NO:17) (*e.g.*, Gly177 through Tyr184 and Val201 through Pro207) of the IL-1 β (SEQ ID NO:1). In some embodiments, the compound binds to at least one additional residue of an IL-1 β binding pocket as described herein. In some embodiments, a compound as described herein binds at the binding pocket of IL-1 β as described herein to one or more residues selected from Val119, Arg120, Ser121, Phe162, Lys179, Pro203, Lys204, Tyr206, Pro207, or Ser269.

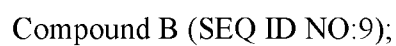
[00222] In certain embodiments, a compound as described herein binds to residue Val119 of the IL-1 β via a hydrogen bond (H-bond) interaction. In certain embodiments, a compound as described herein binds to residue Arg120 of the IL-1 β via a hydrogen bond (H-bond) interaction. In certain embodiments, a compound as described herein binds to residue Ser121 of the IL-1 β via a hydrogen bond (H-bond) interaction. In certain embodiments, a compound as described herein binds to residue Pro203 of the IL-1 β via a hydrogen bond (H-bond) interaction. In certain

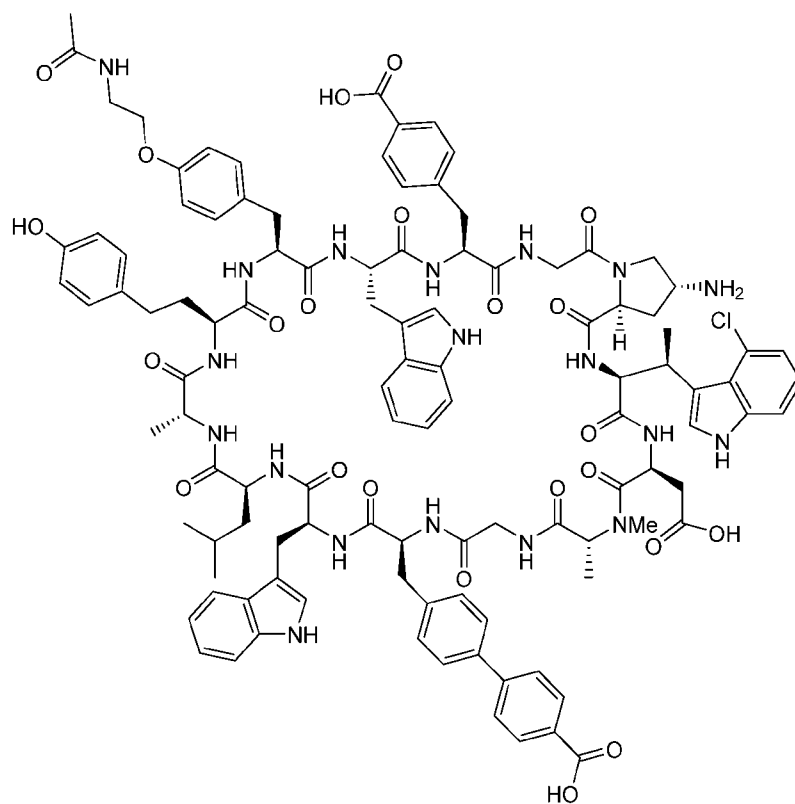
embodiments, a compound as described herein binds to residue Lys204 of the IL-1 β via a hydrogen bond (H-bond) interaction. In certain embodiments, a compound as described herein binds to residue Tyr206 of the IL-1 β via a hydrogen bond (H-bond) interaction. In certain embodiments, a compound as described herein binds to residue Pro207 of the IL-1 β via a hydrogen bond (H-bond) interaction. In certain embodiments, a compound as described herein binds to residue Ser269 of the IL-1 β via a hydrogen bond (H-bond) interaction. In embodiments, the hydrogen bond (H-bond) interaction is mediated by a NH group, carbonyl group, carboxylate group, oxygen, or other functional group of the compound (*e.g.*, as described herein).

[00223] In certain embodiments, a compound as described herein binds to residue Arg120 of the IL-1 β via a pi-effect (*e.g.*, CH-pi, cation-pi, or polar-pi) interaction. In certain embodiments, a compound as described herein binds to residue Phe162 of the IL-1 β via a pi-effect (*e.g.*, CH-pi, cation-pi, or polar-pi) interaction. In certain embodiments, a compound as described herein binds to residue Arg179 of the IL-1 β via a pi-effect (*e.g.*, CH-pi, cation-pi, or polar-pi) interaction. In certain embodiments, a compound as described herein binds to residue Pro207 of the IL-1 β via a pi-effect (*e.g.*, CH-pi, cation-pi, or polar-pi) interaction. In certain embodiments, a compound as described herein binds to residue Ser269 of the IL-1 β via a pi-effect (*e.g.*, CH-pi, cation-pi, or polar-pi) interaction. In some embodiments, the pi-effect (*e.g.*, CH-pi, cation-pi, or polar-pi) interaction is mediated a functional group of the compound (*e.g.*, a functional group as described herein).

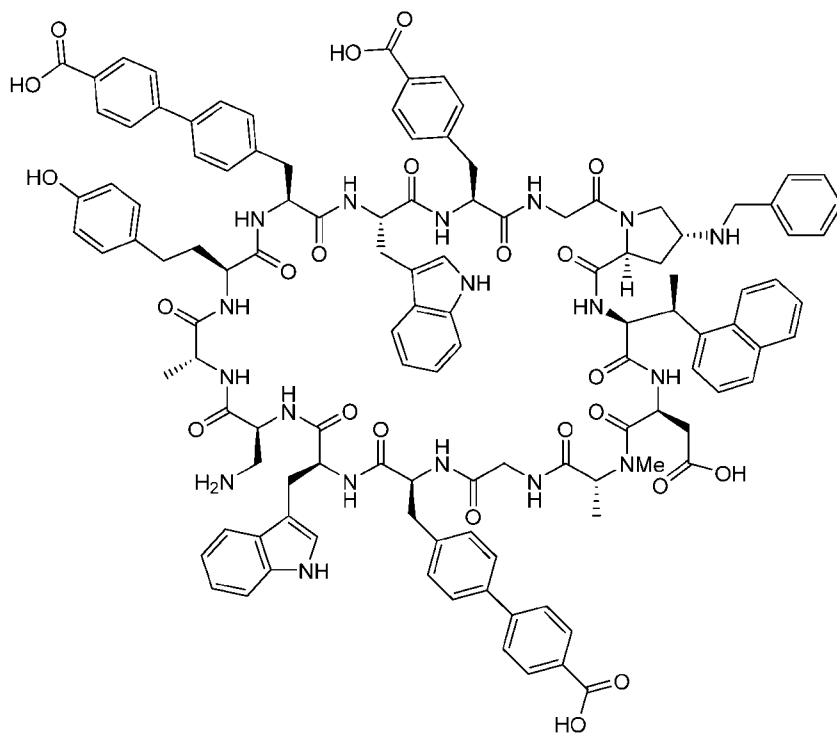
[00224] In certain embodiments, a compound as described herein binds to residue Lys204 of the IL-1 β via an ionic interaction. In certain embodiments, a compound as described herein binds to residue Ala117 of the IL-1 β via an ionic interaction. In certain embodiments, a compound as described herein binds to residue Arg120 of the IL-1 β via an ionic interaction. Such ionic interactions may be mediated a functional group of the compound (*e.g.*, as described herein).

[00225] In certain embodiments, the binding interactions between the compound and IL-1 β are as depicted in any one of figures disclosed herein.

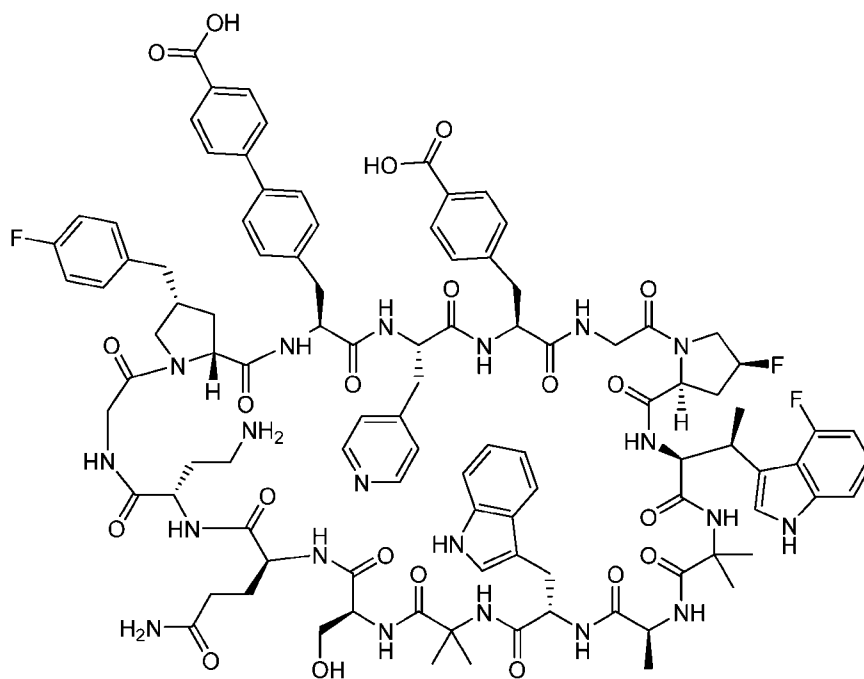




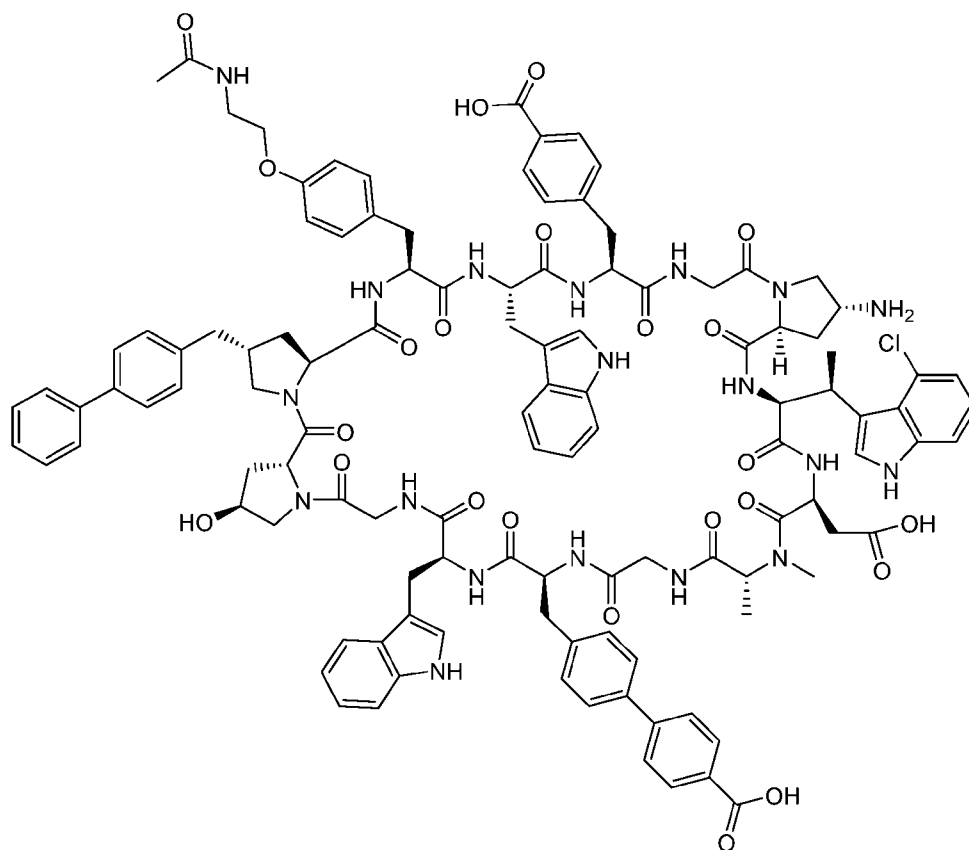
Compound D (SEQ ID NO:11).



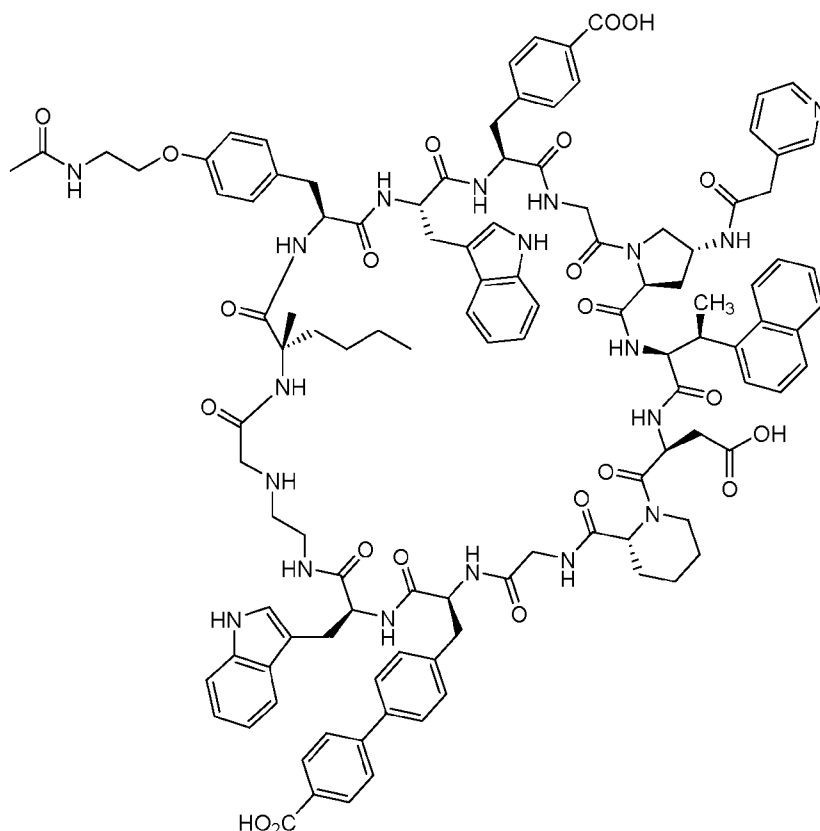
Compound E (SEQ ID NO:12).



Compound F (SEQ ID NO:13).



Compound G (SEQ ID NO:14).



Compound H (SEQ ID NO:15).

8.2 EXAMPLE 2: EXEMPLARY SYNTHESIS OF CERTAIN COMPOUNDS THAT BIND TO IL1B

[00227] The compounds described herein can be prepared according to the procedures of the following schemes and examples, using appropriate materials and are further exemplified by the following specific examples. The examples also include methods for testing such compounds in cellular assays. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the disclosure.

[00228] The examples further illustrate details for the preparation of the compounds of the present disclosure. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. For instance, in some cases, the order of carrying out the steps of reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. Starting materials and intermediates for the final compounds are purchased, made from known

procedures, or as otherwise illustrated. The examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosure.

[00229] NMR data were obtained on a 300 MHz or 400 MHz instrument in CDCl₃, DMSO-*d*₆, or Methanol-*d*₄ with the chemical shifts reported relative to tetramethylsilane standard.

Resonance signals are reported by the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet or overlap of non-equivalent resonances. Coupling constants (*J*) are reported in Hertz (Hz).

[00230] Throughout the synthetic schemes and examples, abbreviations and acronyms may be used with the following meanings in TABLE 3 unless otherwise indicated:

[00231] TABLE 3: Abbreviations

Abbreviation	Definition
1Nal	3-(1-Naphthyl)-l-alanine
3Pal4Ph4CO2H	(S)-4-(5-(2-amino-2-carboxyethyl)pyridin-2-yl)benzoic acid
4Pal	(2S)-2-amino-3-(4-pyridyl)propanoic acid
A	L-Alanine
AA	Amino acid
AcOH	Acetic acid
Aib	2-amino-2-methyl-propanoic acid
Ac ₂ O	Acetic anhydride
AlaTHP4	(S)-2-amino-3-(tetrahydro-2H-pyran-4-yl)propanoic acid
Alloc-OSu	N-(Allyloxycarbonyloxy)succinimide
aMeNle	(S)-2-amino-2-methylhexanoic acid
Bip4CO2H	L-Biphenylalanine-4-carboxylic acid or (S)-4'-(2-amino-2-carboxyethyl)-[1,1'-biphenyl]-4-carboxylic acid
BnBr	Benzyl bromide
Boc	<i>tert</i> -Butoxy-carbonyl
Boc ₂ O	Di- <i>tert</i> -butyl dicarbonate
Bu ₃ SNH	Tributyltin hydride
CBz	Benzyl chloroformate
CDCl ₃	Deuterated chloroform
CRP	C-reactive protein
D	L-Aspartic acid
dA	D-Alanine
Dab	(2S)-2,4-diaminobutanoic acid

Abbreviation	Definition
Dap	L-2,3-diaminopropionic acid
DCE	Dichloroethane
DCM	Dichloromethane
deNC2NH2Gly	(2-aminoethyl)glycine
DIAD	Diisopropyl azodicarboxylate
DIC	<i>N,N'</i> -Diisopropylcarbodiimide
DIPEA	<i>N,N</i> -Diisopropylethylamine or Hunig's base
DMA	<i>N,N</i> -Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
dNMeA	D- <i>N</i> -methyl-Alanine
dPip	(R)-piperidine-2-carboxylic acid
dProc4Bn4F	(2R,4R)-4-[(4-fluorophenyl)methyl]pyrrolidine-2-carboxylic acid
dProt4OH	(2R,4S)-4-hydroxypyrrolidine-2-carboxylic acid
E	L-Glutamic acid
Eq.	Equivalents
ES	Electrospray
ESI	Electrospray ionization
EtOAc	Ethyl acetate
F	L-Phenylalanine
Fmoc	9H-fluoren-9-ylmethoxycarbonyl
G	Glycine
h	hour(s)
h3Pal5CN	(S)-2-amino-4-(5-cyanopyridin-3-yl)butanoic acid
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate or N-[(Dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide
HFIP	Hexafluoroisopropanol
HPLC	High-performance liquid chromatography
hY	L-homoTyrosine
Im	1H-imidazole
K	L-Lysine
L	L-Leucine
MeCN	Acetonitrile

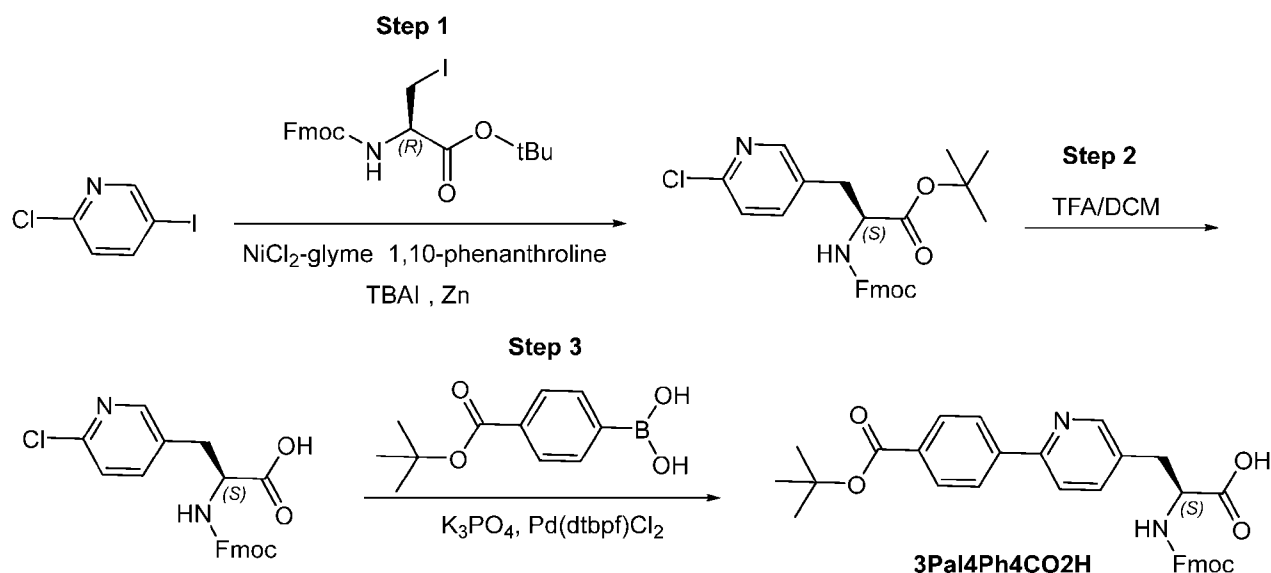
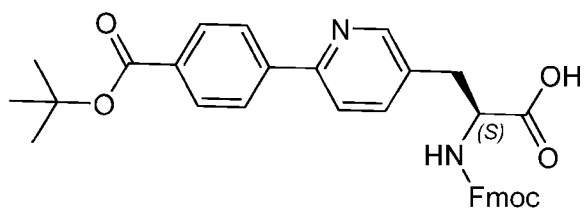
Abbreviation	Definition
MeOH	Methanol
min	Minute
MS	Mass spectrometry
N	L-Asparagine
NiCl ₂ -glyme	Nickel(II) chloride ethylene glycol dimethyl ether complex
NIS	N-iodosuccinimide
NMP	<i>N</i> -Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
NsCl	4-Nitrobenzenesulfonyl chloride
o.n.	Over night
OMpe	β-methylpentyl ester
Orn	L-Ornithine
OSu	O-succinimide
Oxyma	Ethyl cyano(hydroxyimino)acetate
Pd(dtbpf)Cl ₂	[1,1'-Bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II)
PE	Petroleum ether
PfTrpB-0B2	Engineered tryptophan synthase from <i>Pyrococcus furiosus</i>
PfTrpB-4D11	Engineered tryptophan synthase from <i>Pyrococcus furiosus</i>
PfTrpB-7E6	Engineered tryptophan synthase from <i>Pyrococcus furiosus</i>
Phe4COOH	L-phenylalanine-4-carboxylic acid or (S)-4-(2-amino-2-carboxyethyl)benzoic acid
PLP	3-hydroxy-2-methyl-5-([phosphonoxy]methyl)-4-pyridinecarboxaldehyde or pyridoxal 5-phosphate
pOMePhSH	4-methoxybenzenethiol
PPh ₃	Triphenylphosphine
Proc4F	(2S,4S)-4-fluoropyrrolidine-2-carboxylic acid
Prot4CH2Bip	(2S,4R)-4-([1,1'-biphenyl]-4-ylmethyl)pyrrolidine-2-carboxylic acid
Prot4NH ₂	(2S,4R)-4-aminopyrrolidine-2-carboxylic acid
Prot4NHBn	(2S,4R)-4-(benzylamino)pyrrolidine-2-carboxylic acid
Prot4NHCO ₃ Py	(2S,4R)-4-(2-(pyridin-3-yl)acetamido)pyrrolidine-2-carboxylic acid
psi	Pound-force per square inch
PyAOP	(7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
Q	L-Glutamine
RMS	Root mean square
RP	Reverse phase

Abbreviation	Definition
rpm	Revolutions per minute
rt	Room temperature
S	L-Serine
sbMe1NaI	(2S,3S)-2-amino-3-(naphthalen-1-yl)butanoic acid
sbMeW4Cl	(2S,3S)-2-amino-3-(4-chloro-1H-indol-3-yl)butanoic acid
sbMeW4F	(2S,3S)-2-amino-3-(4-fluoro-1H-indol-3-yl)butanoic acid
SFC	Supercritical fluid chromatography
SPPS	Solid-Phase Peptide Synthesis
<i>t</i> Bu	<i>tert</i> -Butyl
<i>t</i> -BuOH	<i>tert</i> -Butanol
Tba	(S)-2-amino-4,4-dimethylpentanoic acid
TBAB	Tetrabutylammonium bromide
TBAI	Tetrabutylammonium iodide
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIS	Triisopropylsilane
TyrEtNAc	L-Tyrosine <i>O</i> -ethyl acetamide or (S)-3-(4-(2-acetamidoethoxy)phenyl)-2-aminopropanoic acid
UPLC	Ultra Performance Liquid Chromatography or Ultrahigh Pressure Liquid Chromatography
W	L-Tryptophan

8.2.1 Intermediate Syntheses:

[00232] The amino acids used to synthesize the Final Compounds as described in Section 8.2.2 may be prepared by the following methods and are also commercially available.

8.2.1.1 Synthetic Scheme 1

**3Pal4Ph4CO2H**

(S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino-3-(6-(4-(tert-butoxycarbonyl)phenyl)pyridin-3-yl)propanoic acid

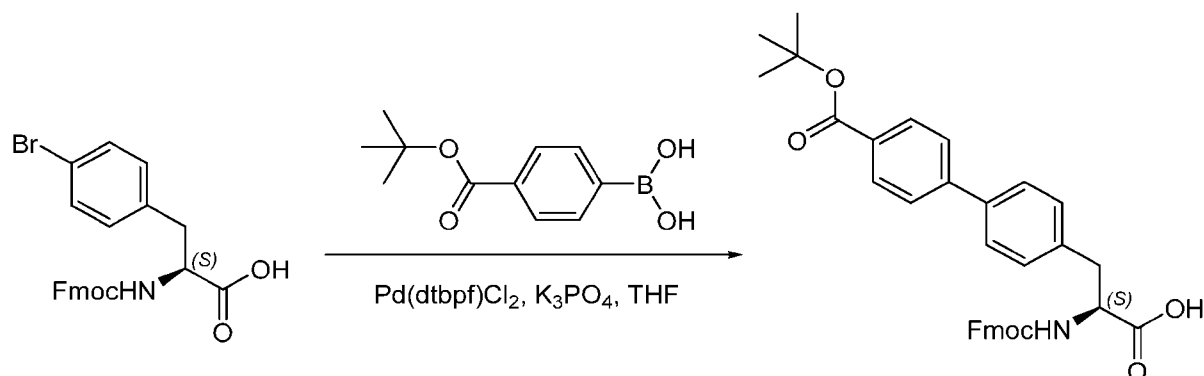
[00233] Step 1: To a stirred solution of NiCl₂-glyme (0.918 g, 4.18 mmol) in DMA (100 mL) was added 1,10-phenanthroline (0.905 g, 4.18 mmol) at rt under nitrogen atmosphere. The resulted solution was stirred at 50 °C for 1 h. 2-Chloro-5-iodopyridine (5 g, 20.88 mmol), *tert*-butyl (*R*)-2-(((9*H*-fluoren-9-yl)methoxy)carbonyl)amino-3-iodopropanoate (12.36 g, 25.06 mmol), TBAI (8.01 g, 20.88 mmol) and Zn (2.73 g, 41.8 mmol) were added to the mixture above at rt and the resulted mixture was stirred at 25 °C for 2 h. The reaction was quenched with H₂O (200 mL), extracted with EtOAc (2 x 500 mL). The combined organic layer was washed with brine (3 x 200 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluted with 0 - 30% EtOAc in PE to give *tert*-butyl (*S*)-2-(((9*H*-fluoren-9-

yl)methoxy)carbonyl)amino)-3-(6-chloropyridin-3-yl)propanoate. MS ESI calculated for $C_{27}H_{28}ClN_2O_4$ $[M + H]^+$ 479.17, found 479.20.

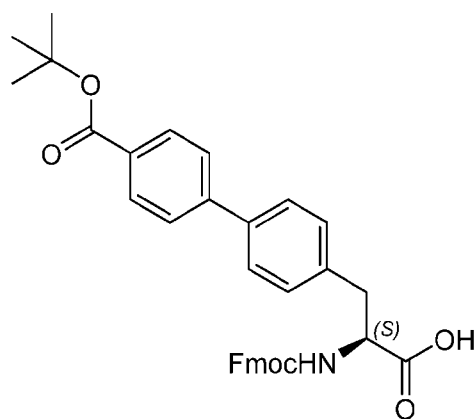
[00234] Step 2: To a stirred solution of *tert*-butyl (*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(6-chloropyridin-3-yl)propanoate (5 g, 10.48 mmol) in DCM (5 mL) was added TFA (10 mL) at rt. The solution was stirred at 25 °C for 1 h. The solvent was concentrated under reduced pressure and the residue was purified by RP-flash with the following conditions: Column: Flash C18 (330 g); Mobile Phase A: water (0.1% TFA), Mobile Phase B: MeCN; (Gradient: 5% B hold 5 min, up to 30% B within 15 min, 30% B hold 5 min; up to 95% B within 20 min, 95% B hold 10 min); Flow rate: 90 mL/min; Detector: UV 210 nm; RT = 40 min. The product-containing fractions were collected and evaporated in vacuo to give (*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(6-chloropyridin-3-yl)propanoic acid. MS ESI calculated for $C_{23}H_{20}ClN_2O_4$ $[M + H]^+$ 423.10, found 423.10.

[00235] Step 3: To a stirred solution of (*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(6-chloropyridin-3-yl)propanoic acid (3 g, 7.09 mmol) in THF (25 mL) and water (5 mL) were added (4-(*tert*-butoxycarbonyl)phenyl)boronic acid (1.890 g, 8.51 mmol) and K_3PO_4 (7.53 g, 35.5 mmol) at 25 °C under nitrogen. The resultant solution was stirred at 25 °C for 10 min. $Pd(dtbpf)Cl_2$ (0.694 g, 1.064 mmol) was added to the solution and the mixture was then stirred at 60 °C for 16 h. The reaction was cooled to rt and quenched with H_2O (200 mL) and extracted with EtOAc (2 x 500 mL). The combined organic layer was washed with brine (3 x 200 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by RP-flash with the following conditions: Column: Flash C18 (330 g); Mobile Phase A: water (0.1% TFA), Mobile Phase B: MeCN; (Gradient: 5% B hold 5 min, up to 60% B within 15 min, 60% B hold 15 min; up to 95% B within 10 min, 95% B hold 10 min); Flow rate: 90 mL/min; Detector: UV 210 nm; RT = 55 min. The product-containing fractions were collected and evaporated in vacuo to give (*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(6-(4-(*tert*-butoxycarbonyl)phenyl)pyridin-3-yl)propanoic acid. MS ESI calculated for $C_{34}H_{33}N_2O_6$ $[M + H]^+$ 565.23, found 565.15; ^1H NMR (400 MHz, Methanol-*d*₄) δ 8.66 (d, J = 1.9 Hz, 1H), 8.12 - 8.07 (m, 3H), 7.99 - 7.92 (m, 3H), 7.77 (d, J = 7.5 Hz, 2H), 7.59 - 7.56 (m, 2H), 7.37 - 7.33 (m, 2H), 7.30 - 7.22 (m, 2H), 4.60 - 4.56 (m, 1H), 4.29 - 4.27 (m, 2H), 4.14 - 4.10 (m, 1H), 3.45 - 3.41 (m, 1H), 3.14 - 3.10 (m, 1H), 1.62 (s, 9H).

8.2.1.2 Synthetic Scheme 2



Bip4CO2H

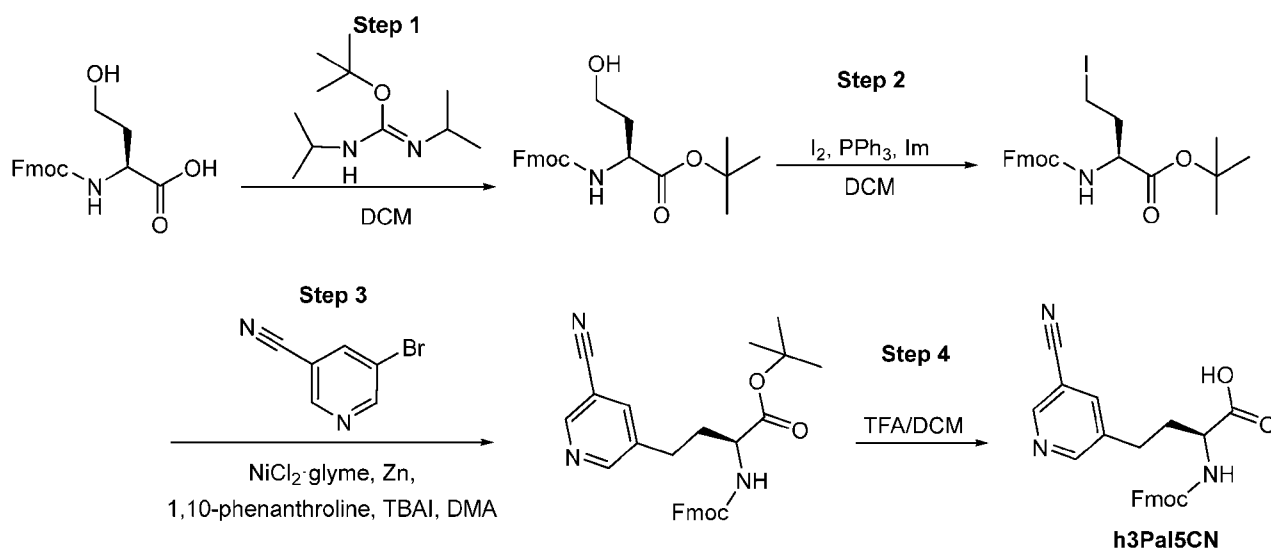


(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4'-(tert-butoxycarbonyl)-[1,1'-biphenyl]-4-yl)propanoic acid

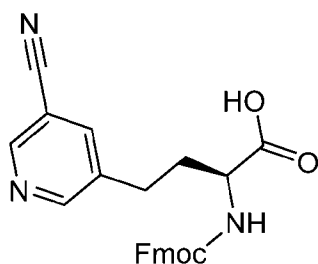
[00236] Argon gas was bubbled through a mixture of (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-bromophenyl)propanoic acid (6 g, 12.87 mmol), (4-(tert-butoxycarbonyl)phenyl)boronic acid (4.29 g, 19.30 mmol) and K₃PO₄ (8.19 g, 38.6 mmol) in THF (40 mL) for 10 min, then [1,1'-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium (II) (0.839 g, 1.287 mmol) was added. After the resulting mixture was stirred at 50 °C for 16 h, it was diluted with EtOAc (300 mL) and washed with aqueous saturated NaHCO₃ (3 x 80 mL), brine (2 x 40 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with gradient 0% - 50% EtOAc in PE. The product-containing fractions were collected and *roto*-evaporated *in vacuo*. The residue was re-purified by combi-Flash with the following conditions: Column: C18 gel column (330 g), 20-35 μm; Mobile Phase A: 0.5% aq. TFA; Mobile Phase B:

MeCN; (Gradient: 0% B hold 10 min, up to 62.3% B within 25 min, 62.3% B hold 6.2 min; up to 95% B within 2 min, 95% B hold 10 min); Flow rate: 90 mL/min; Detector: UV 254 & 210 nm; RT: 32.32 min. The product-containing fractions were collected and concentrated under reduced pressure to afford (*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4'-(*tert*-butoxycarbonyl)-[1,1'-biphenyl]-4-yl)propanoic acid. MS ESI calculated for C₃₅H₃₄NO₆ [M + 1]⁺ 564.23, found 564.15. ¹H NMR (300 MHz, Methanol-*d*₄) δ 7.97 - 7.95 (m, 2H), 7.78 - 7.76 (m, 2H), 7.61 - 7.53 (m, 6H), 7.38 - 7.21 (m, 2H), 4.51 - 4.11 (m, 4H), 3.32 - 3.25 (m, 1H), 3.03 - 2.95 (m, 1H), 1.61 (s, 9H).

8.2.1.3 Synthetic Scheme 3



h3Pal5CN



(*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-(5-cyanopyridin-3-yl)butanoic acid

[00237] Step 1: To a stirred solution of (((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-homoserine (15 g, 43.9 mmol) in DCM (200 mL) at rt was added *tert*-butyl (*Z*)-*N,N'*-diisopropylcarbamimidate (35.2 g, 176 mmol). The solution was stirred at 30 °C for 4 h. The

solid was filtered out and the filtrate was concentrated under reduced pressure. The residue was purified by a silica gel column chromatography, eluted with 0 - 32% EtOAc in PE to afford *tert*-butyl (((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-homoserinate. MS ESI calculated for C₂₃H₂₈NO₅ [M + H]⁺ 398.19, found 398.15. ¹H NMR (300 MHz, CDCl₃) δ 7.81 - 7.74 (m, 2H), 7.64 - 7.56 (m, 2H), 7.45 - 7.37 (m, 2H), 7.37 - 7.28 (m, 2H), 5.61 (d, *J* = 7.7 Hz, 1H), 4.54 - 4.32 (m, 3H), 4.22 (t, *J* = 6.9 Hz, 1H), 3.76 - 3.52 (m, 2H), 2.25 - 2.07 (m, 1H), 1.71 - 1.55 (m, 1H), 1.48 (s, 9H).

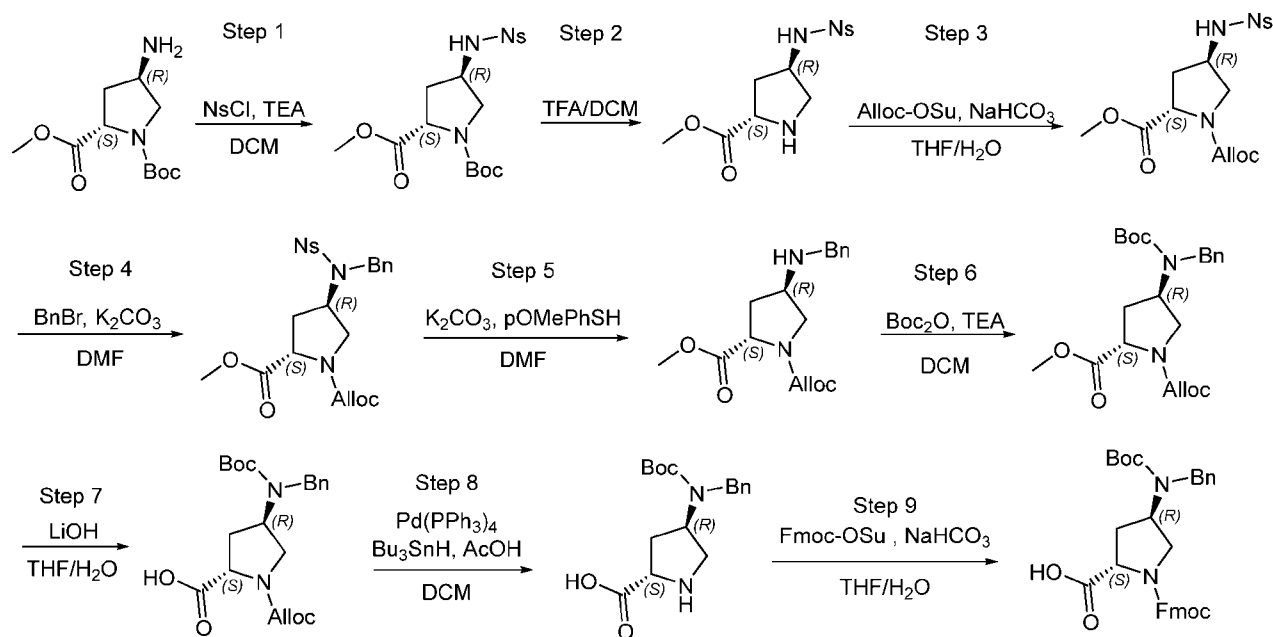
[00238] Step 2: To a stirred solution of PPh₃ (12.67 g, 48.3 mmol) and 1*H*-imidazole (4.38 g, 64.4 mmol) in DCM (200 mL) was added I₂ (12.26 g, 48.3 mmol) at rt under nitrogen atmosphere. The mixture was stirred at rt for 10 min. *Tert*-butyl (((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-homoserinate (12.8 g, 32.2 mmol) was added to the mixture and stirred at 25 °C for 2 h. The solvent was concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluted with 0 - 18% EtOAc in PE to afford *tert*-butyl (*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-iodobutanoate. MS ESI calculated for C₂₃H₂₆INO₄Na [M + Na]⁺ 530.09 found 530.20. ¹H NMR (300 MHz, CDCl₃) δ 7.83 - 7.71 (m, 2H), 7.65 - 7.56 (m, 2H), 7.47 - 7.36 (m, 2H), 7.36 - 7.28 (m, 2H), 5.35 (d, *J* = 8.3 Hz, 1H), 4.52 - 4.35 (m, 2H), 4.34 - 4.16 (m, 2H), 3.21 - 3.04 (m, 2H), 2.52 - 2.32 (m, 1H), 2.28 - 2.07 (m, 1H), 1.48 (s, 9H).

[00239] Step 3: To a stirred solution of 1,10-phenanthroline (1.083 g, 6.01 mmol) in DMA (300 mL) was added NiCl₂-glyme (1.321 g, 6.01 mmol) at rt under argon atmosphere. The mixture was stirred at 50 °C for 1 h then cooled to rt. Then *tert*-butyl (*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-iodobutanoate (15.25 g, 30.1 mmol), 5-bromonicotinonitrile (5.5 g, 30.1 mmol), TBAI (15.25 g, 30.1 mmol) and zinc (3.93 g, 60.1 mmol) were added to the mixture at rt and stirred at 35 °C for 2.5 h. The mixture was cooled to rt and diluted with water (500 mL) and EtOAc (800 mL). The solid was filtered out and the organic layer was separated. The organic layer was washed with brine (3 x 150 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by a silica gel column chromatography, eluted with 0 - 40% EtOAc in PE to afford *tert*-butyl (*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-(5-cyanopyridin-3-yl)butanoate. MS ESI calculated for C₂₉H₃₀N₃O₄ [M + H]⁺ 484.22, found 484.20. ¹H NMR (300 MHz, CDCl₃) δ

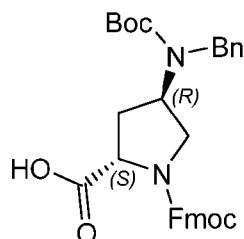
8.75 (s, 1H), 8.66 (s, 1H), 7.87 - 7.71 (m, 3H), 7.61 (d, $J = 7.4$ Hz, 2H), 7.47 - 7.28 (m, 4H), 5.40 (d, $J = 7.8$ Hz, 1H), 4.55 - 4.37 (m, 2H), 4.36 - 4.18 (m, 2H), 2.85 - 2.59 (m, 2H), 2.26 - 2.08 (m, 1H), 2.02 - 1.82 (m, 1H), 1.49 (s, 9H).

[00240] Step 4: To a stirred solution of *tert*-butyl (*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-(5-cyanopyridin-3-yl)butanoate (7.5 g, 15.51 mmol) in DCM (50 mL) was added TFA (100 mL) at rt. The solution was stirred at 25 °C for 3 h then concentrated under reduced pressure. The residue was purified by RP-flash with the following conditions: C18 column, 330 g, 5% -5% in 10 min, 5% - 55% in 40 min, 55% -55% in 10 min, MeCN in water (0.05% TFA) to give (*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-(5-cyanopyridin-3-yl)butanoic acid. MS ESI calculated for $C_{25}H_{22}N_3O_4$ $[M + H]^+$ 428.15, found 428.05. ^1H NMR (400 MHz, DMSO- d_6) δ 12.78 (br, 1H), 8.87 (s, 1H), 8.75 (s, 1H), 8.18 (s, 1H), 7.92 - 7.90 (m, 2H), 7.76 - 7.73 (m, 3H), 7.44 - 7.33 (m, 4H), 4.39 - 4.20 (m, 3H), 3.94 - 3.89 (m, 1H), 2.79 - 2.67 (m, 2H), 2.09 - 1.89 (m, 2H).

8.2.1.4 Synthetic Scheme 4



Prot4NHBn



(2S,4R)-1-(((9H-fluoren-9-yl)methoxy)carbonyl)-4-(benzylamino)pyrrolidine-2-carboxylic acid

[00241] Step 1: To a mixture of 1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-aminopyrrolidine-1,2-dicarboxylate (10 g, 40.9 mmol) in DCM (100 mL) were added TEA (14.26 mL, 102 mmol) and NsCl (10.89 g, 49.1 mmol) at rt. The reaction was stirred at rt for 4 h. The resulting solution was quenched with water (150 mL) and extracted with EtOAc (3 x 300 mL). The organic layers were combined, washed with brine (2 x 150 mL), dried over anhydrous Na₂SO₄, and filtered.

The filtrate was concentrated in vacuum. The residue was purified by silica gel chromatography, eluting with a gradient of EtOAc in PE from 0% to 45% afford 1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-((4-nitrophenyl)sulfonamido)pyrrolidine-1,2-dicarboxylate. MS ESI calculated for

C₁₇H₂₄N₃O₈S [M + H - Boc]⁺ 330.12, found 330.10. ¹H NMR (400 MHz, CDCl₃) δ 8.18 - 8.16 (m, 1H), 7.91 - 7.87 (m, 1H), 7.79 - 7.75 (m, 2H), 4.40 - 4.29 (m, 1H), 4.18 - 4.15 (m, 1H), 3.72 (s, 3H), 3.66 - 3.62 (m, 1H), 3.26 - 3.19 (m, 1H), 2.29 - 2.15 (m, 2H), 1.38 (s, 9H).

[00242] Step 2: To a mixture of 1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-((4-nitrophenyl)sulfonamido)pyrrolidine-1,2-dicarboxylate (17 g, 39.6 mmol) in DCM (60 mL) was added TFA (30 mL, 389 mmol) at ambient temperature. The reaction was stirred at ambient temperature for 2 h then concentrated under vacuum to afford methyl (2*S*,4*R*)-4-((4-nitrophenyl)sulfonamido)pyrrolidine-2-carboxylate. MS ESI calculated for C₁₂H₁₆N₃O₆S [M + H]⁺ 330.07, found 330.10.

[00243] Step 3: To a solution of methyl (2*S*,4*R*)-4-((4-nitrophenyl)sulfonamido)pyrrolidine-2-carboxylate (18.5 g, 39.3 mmol) in THF (150 mL) and water (150 mL) were added NaHCO₃ (16.52 g, 197 mmol) and Alloc-OSu (5.46 mL, 35.4 mmol) at ambient temperature. The reaction was stirred at ambient temperature for 4 h then diluted with water (100 mL) and extracted with EtOAc (3 x 250 mL). The organic layers were combined, washed with brine (2 x 150 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated in vacuum. The residue was purified by silica gel chromatography, eluting with a gradient of EtOAc in PE from 0% to

55% to afford 1-allyl 2-methyl (2*S*,4*R*)-4-((4-nitrophenyl)sulfonamido)pyrrolidine-1,2-dicarboxylate. MS ESI calculated for $C_{16}H_{20}N_3O_8S$ $[M + H]^+$ 414.09, found 413.95. ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 - 8.15 (m, 1H), 7.91 - 7.88 (m, 1H), 7.82 - 7.77 (m, 2H), 5.84 - 5.70 (m, 1H), 5.30 - 5.16 (m, 2H), 4.58 - 4.52 (m, 2H), 4.50 - 4.48 (m, 1H), 4.47 - 4.15 (m, 1H), 3.78 - 3.73 (m, 4H), 3.32 - 3.28 (m, 1H), 2.30 - 2.19 (m, 2H).

[00244] Step 4: To a solution of 1-allyl 2-methyl (2*S*,4*R*)-4-((4-nitrophenyl)sulfonamido)pyrrolidine-1,2-dicarboxylate (8.1 g, 19.59 mmol) in DMF (100 mL) were added (bromomethyl)benzene (4.02 g, 23.51 mmol) and K_2CO_3 (8.12 g, 58.8 mmol) at ambient temperature. The reaction was stirred at ambient temperature for 4 h, then quenched with water (100 mL) and extracted with EtOAc (3 x 250 mL). The organic layers were combined, washed with brine (4 x 200 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography, eluting with a gradient of EtOAc in PE from 0% to 55% to afford 1-allyl 2-methyl (2*S*,4*R*)-4-((*N*-benzyl-4-nitrophenyl)sulfonamido)pyrrolidine-1,2-dicarboxylate. MS ESI calculated for $C_{23}H_{26}N_3O_8S$ $[M + H]^+$ 504.14, found 504.20. ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 - 7.84 (m, 1H), 7.68 - 7.67 (m, 2H), 7.66 - 7.55 (m, 1H), 7.29 - 7.23 (m, 5H), 5.85 - 5.75 (m, 1H), 5.25 - 5.18 (m, 2H), 4.19 - 4.15 (m, 6H), 3.73 - 3.25 (m, 5H), 2.23 - 2.15 (m, 2H).

[00245] Step 5: To a solution of 1-allyl 2-methyl (2*S*,4*R*)-4-((*N*-benzyl-4-nitrophenyl)sulfonamido)pyrrolidine-1,2-dicarboxylate (9.3 g, 18.47 mmol) in DMF (40 mL) were added 4-methoxybenzenethiol (3.11 g, 22.16 mmol) and K_2CO_3 (7.66 g, 55.4 mmol) at ambient temperature. The reaction was stirred at ambient temperature for 1 h, then diluted with water (100 mL) and extracted with EtOAc (3 x 150 mL). The organic layers were combined, washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4 , and filtered. The residue was purified by RP-flash with the following conditions: Column: Flash C18 (330 g); Mobile Phase A: water (0.05% TFA), Mobile Phase B: MeCN; (Gradient: 5% B hold 5 min, up to 32% B within 15 min, 32% B hold 6 min; up to 95% B within 5 min, 95% B hold 5 min); Flow rate: 90 mL/min; Detector: UV 210 nm; RT = 36 min. The product-containing fractions were collected and concentrated in vacuum to give 1-allyl 2-methyl (2*S*,4*R*)-4-(benzylamino)pyrrolidine-1,2-dicarboxylate. MS ESI calculated for $C_{17}H_{23}N_2O_4$ $[M + H]^+$

319.16, found 319.10. ^1H NMR (300 MHz, CDCl_3) δ 7.39 - 7.34 (m, 5H), 5.90 - 5.85 (m, 1H), 5.32 - 5.17 (m, 2H), 4.60 - 4.36 (m, 3H), 3.96 - 3.57 (m, 8H), 2.07 - 1.99 (m, 2H).

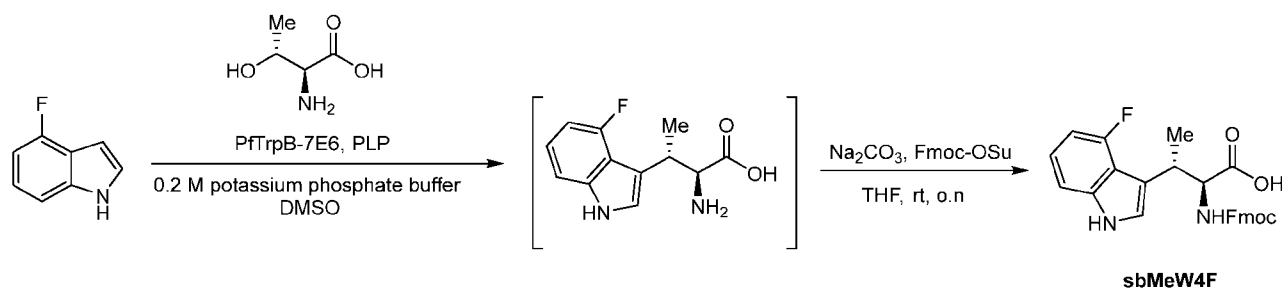
[00246] Step 6: To a solution of 1-allyl 2-methyl (2*S*,4*R*)-4-(benzylamino)pyrrolidine-1,2-dicarboxylate (4.5 g, 12.72 mmol) in DCM (40 mL) were added Boc_2O (4.16 g, 19.08 mmol) and TEA (5.32 mL, 38.2 mmol) at ambient temperature. The reaction was stirred at ambient temperature for 4 h then quenched with water (30 mL) and extracted with EtOAc (3 x 200 mL). The organic layers were combined, washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography, eluting with a gradient of EtOAc in PE from 0% to 40% to afford 1-allyl 2-methyl (2*S*,4*R*)-4-(benzyl(*tert*-butoxycarbonyl)amino)pyrrolidine-1,2-dicarboxylate. MS ESI calculated for $\text{C}_{22}\text{H}_{31}\text{N}_2\text{O}_6$ $[\text{M} + \text{H}]^+$ 419.21, found 419.15. ^1H NMR (300 MHz, CDCl_3) δ 7.34 - 7.15 (m, 5H), 5.90 - 5.85 (m, 1H), 5.25 - 5.18 (m, 2H), 4.58 - 4.32 (m, 6H), 3.74 - 3.44 (m, 5H), 2.49 - 2.38 (m, 1H), 2.12 - 1.99 (m, 1H), 1.42 (s, 9H).

[00247] Step 7: To a mixture of 1-allyl 2-methyl (2*S*,4*R*)-4-(benzyl(*tert*-butoxycarbonyl)amino)pyrrolidine-1,2-dicarboxylate (3 g, 5.73 mmol) in THF (15 mL) was added LiOH (11.47 mL, 11.47 mmol, 1 M in water) at 0 °C. The reaction was stirred at ambient temperature for 2 h, then acidified with aqueous HCl to pH 3~4 and extracted with EtOAc (3 x 150 mL). The organic layers were combined, washed with brine (2 x 80 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under vacuum to afford (2*S*,4*R*)-1-((allyloxy)carbonyl)-4-(benzyl(*tert*-butoxycarbonyl)amino)pyrrolidine-2-carboxylic acid. MS ESI calculated for $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_6$ $[\text{M} + \text{H}]^+$ 405.19, found 405.30. ^1H NMR (300 MHz, CDCl_3) δ 7.35 - 7.14 (m, 5H), 5.89 - 5.75 (m, 1H), 5.14 - 5.19 (m, 2H), 4.61 - 4.30 (m, 6H), 3.82 - 3.32 (m, 2H), 2.47 - 2.18 (m, 2H), 1.42 (s, 9H).

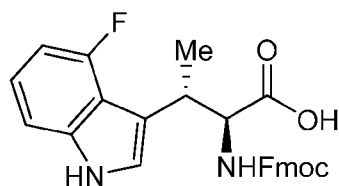
[00248] Step 8: To a mixture of (2*S*,4*R*)-1-((allyloxy)carbonyl)-4-(benzyl(*tert*-butoxycarbonyl)amino)pyrrolidine-2-carboxylic acid (2.6 g, 5.46 mmol) in DCM (150 mL) were added AcOH (0.751 mL, 13.11 mmol) and $\text{Pd}(\text{Ph}_3\text{P})_4$ (0.126 g, 0.109 mmol) at ambient temperature. And then to the reaction was added Bu_3SnH (1.749 g, 6.01 mmol). After the reaction was stirred at ambient temperature for 4 h, it was concentrated under reduced pressure to afford (2*S*,4*R*)-4-(benzyl(*tert*-butoxycarbonyl)amino)pyrrolidine-2-carboxylic acid. MS ESI calculated for $\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_4$ $[\text{M} + \text{H}]^+$ 321.17, found 321.15.

[00249] Step 9: To a mixture of (2*S*,4*R*)-4-(benzyl(*tert*-butoxycarbonyl)amino)pyrrolidine-2-carboxylic acid (3.2 g, 4.99 mmol) in THF (50 mL) and water (50 mL) was added NaHCO₃ (2.098 g, 24.97 mmol) to a pH of 8~9. And then Fmoc-OSu (1.516 g, 4.49 mmol) was added to the reaction. The resulting mixture was stirred at ambient temperature for 4 h then acidified with aqueous HCl to pH 3~4 and extracted with EtOAc (3 x 200 mL). The organic layers were combined, washed with brine (2 x 100 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under vacuum to afford crude product. The residue was purified by RP-flash with the following conditions: Column: Flash C18 (330 g); Mobile Phase A: water (0.05% TFA), Mobile Phase B: MeCN; (Gradient: 5% B hold 5 min, up to 70% B within 25 min, 70% B hold 8 min; up to 95% B within 2 min, 95% B hold 5 min); Flow rate: 90 mL/min; Detector: UV 210 nm; RT = 45 min. The product-containing fractions were collected and concentrated in vacuum to give (2*S*,4*R*)-1-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-4-(benzyl(*tert*-butoxycarbonyl)amino)pyrrolidine-2-carboxylic acid. MS ESI calculated for C₃₂H₃₅N₂O₆ [M + H]⁺ 543.24, found 543.20. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.93 (s, 2H), 7.88 (d, *J* = 7.6 Hz, 2H), 7.61 - 7.57 (m, 2H), 7.43 - 7.18 (m, 9H), 4.43 - 4.15 (m, 8H), 3.53 - 3.25 (m, 2H), 2.51 - 2.50 (m, 1H), 2.03 - 1.92 (m, 1H), 1.37 (s, 2H).

8.2.1.5 Synthetic Scheme 5



sbMeW4F

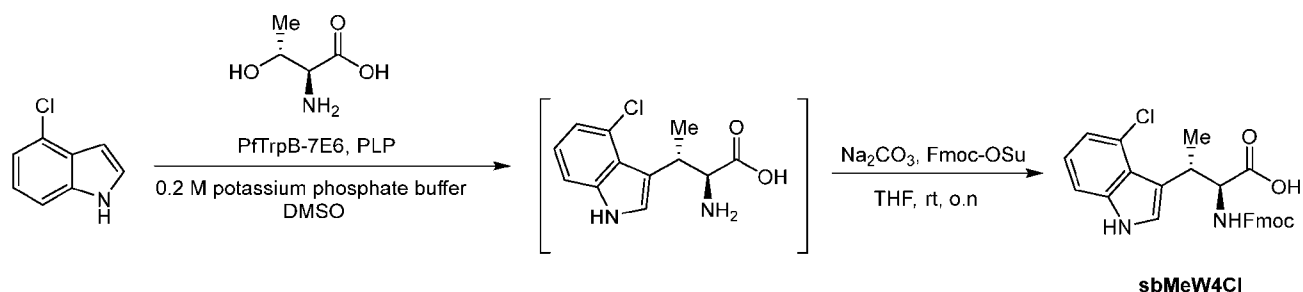


(2*S*,3*S*)-2-amino-3-(4-fluoro-1*H*-indol-3-yl)butanoic acid

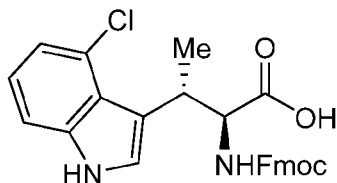
[00250] Into a 1-L 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 4-fluoro-1H-indole (10 g, 1.00 eq.), L-threonine (10.6 g, 1.20 eq.), DMSO (100 mL), potassium phosphate buffer (0.2 M, 300 mL, pH = 7.4). The reaction mixture was heated to 65 °C, then PfTrpB-7E6 (2.5 g, 25 wt.%) and 3-hydroxy-2-methyl-5-([phosphonooxy]methyl)-4-pyridinecarboxaldehyde (0.078 g, 0.004 eq.) were added. The resulting solution was stirred overnight at 65 °C. The mixture was then cooled to rt and used directly in the next step.

[00251] Into the above reaction mixture, THF (100 mL), sodium carbonate (23.56 g, 3.0 eq.) and 2,5-dioxopyrrolidin-1-yl 9H-fluoren-9-ylmethyl carbonate (29.96 g, 1.20 eq.) were added at 0 °C. The resulting solution was stirred overnight at rt. The pH was adjusted to 4 by 3 M HCl and the solid precipitate was filtered away. The resulting solution was extracted with EtOAc (3 x 500 mL). The organic fractions were combined, and washed with brine (1 L), dried over anhydrous sodium sulfate, and concentrated under vacuum. The mixture was applied onto a silica gel column with MeOH:DCM = 1:5. HPLC-MS: (ES, m/z): [M+1]: 459. ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.60 (s, 1H), 11.15 (s, 1H), 7.87 (d, J = 7.6 Hz, 2H), 7.76 – 7.49 (m, 3H), 7.47 – 7.34 (m, 2H), 7.34 – 7.16 (m, 4H), 7.03 (td, J = 7.9, 5.0 Hz, 1H), 6.73 (dd, J = 11.8, 7.7 Hz, 1H), 4.36 (t, J = 8.5 Hz, 1H), 4.31 – 4.02 (m, 3H), 3.51 (q, J = 7.4 Hz, 1H), 1.31 (d, J = 7.0 Hz, 4H), 0.78 (s, 1H).

8.2.1.6 Synthetic Scheme 6



sbMeW4Cl

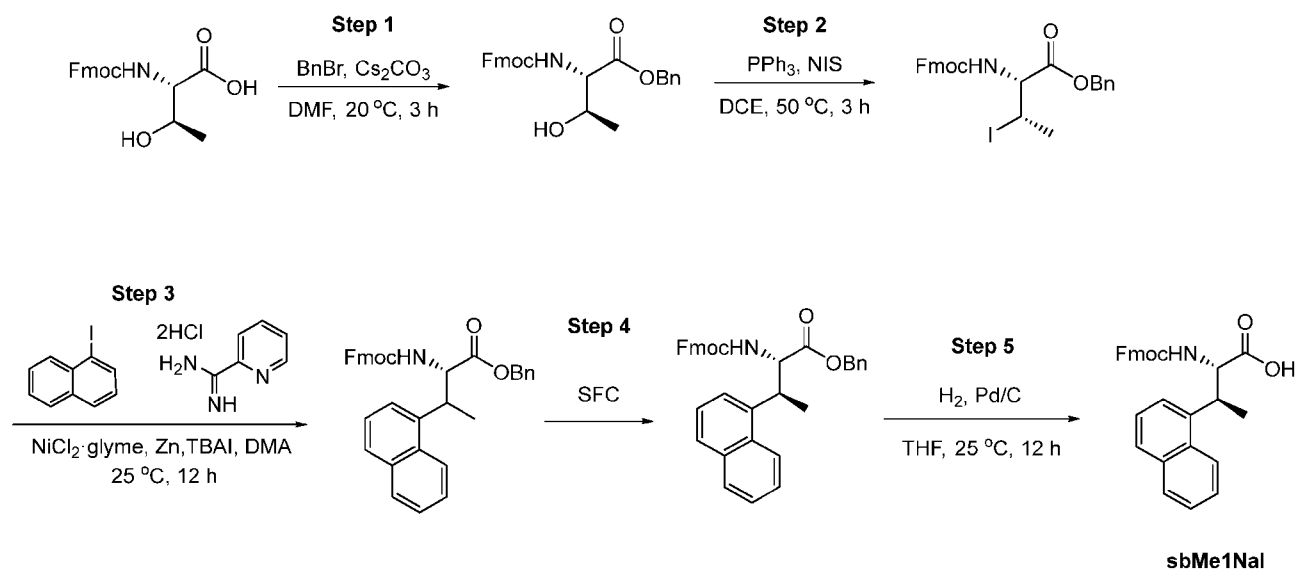


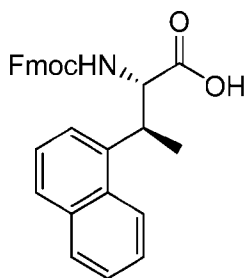
(2S,3S)-2-amino-3-(4-chloro-1H-indol-3-yl)butanoic acid

[00252] Into a 1-L 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 4-chloro-1H-indole (10g, 1.00 eq.), L-threonine (14.09 g, 1.8 eq.), DMSO (100 mL), potassium phosphate buffer (0.2 M, 300 mL, PH = 7.4), the reaction mixture was heated to 65 °C, then PfTrpB-7E6 (7.5g, 25 wt.%) and 3-hydroxy-2-methyl-5-([phosphonooxy]methyl)-4-pyridinecarboxaldehyde (174 mg, 0.01 eq.) were added. The resulting solution was stirred for 36 h at 65 °C. The mixture was then cooled to rt and used directly in the next step.

[00253] Into the above reaction mixture, THF (100 mL), sodium carbonate (20.9 g, 3.0 eq.) and 2,5-dioxopyrrolidin-1-yl 9H-fluoren-9-ylmethyl carbonate (31.0 g, 1.40 eq.) were added at 0 °C. The resulting solution was stirred overnight at rt. The pH was adjusted to 4 by 3 M HCl, and the solid precipitate was filtered away. The resulting solution was extracted with EtOAc (3 x 500 mL). The organic fractions were combined, and washed with brine (1 L), dried over anhydrous sodium sulfate, and concentrated under vacuum. HPLC-MS: (ES, m/z): [M+1]: 475

8.2.1.7 Synthetic Scheme 7

**sbMe1Nal**



(2S,3S)-2-amino-3-(naphthalen-1-yl)butanoic acid

[00254] Step 1: To a solution of (2S,3R)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-hydroxybutanoic acid (250 g, 1.00 eq.) in DMF (1.5 L) was added benzyl bromide (250 g, 2.00 eq.) dropwise at 20 °C. Then, cesium carbonate (477 g, 2.00 eq.) was added, and the solution was stirred at 20°C for 3 h. The reaction was poured into ice H₂O (3 L) and extracted with EtOAc (500 mL x 3). The organic phase was washed with 3% LiCl solution (500 mL x 2) and brine (500 mL), dried over sodium sulfate and concentrated under vacuum at 40 °C. The crude product was triturated with methyl tert-butyl ether:PE = 6:1. ¹H NMR (400 MHz, CDCl₃): δ 7.77 (d, J = 7.6 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.31-7.36 (m, 10H), 5.65-5.71 m, 1H), 5.13-5.31 (m, 3H), 4.39-4.43 (m, 3H), 4.22-4.25 (m, 1H), 1.25 (d, J = 6.4 Hz, 3H)

[00255] Step 2: To a 3-neck round-bottom flask was added (2S,3R)-benzyl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-hydroxybutanoate (125 g, 1.00 eq.) and DCE (750 mL) with an inert atmosphere of nitrogen. The reaction was cooled to 0 °C followed by the addition of NIS (195 g, 3.00 eq.) and PPh₃ (228 g, 3.00 eq.). The temperature was raised to 50 °C and the reaction mixture was stirred for 3 h. The reaction was poured into ice H₂O (500 mL) and extracted with DCM (500 mL x 2). The organic phase was dried over sodium sulfate and concentrated under vacuum at 40°C. The residue was purified by silica gel column chromatography (PE/EtOAc = 1/0 to 0/1). ¹H NMR (400 MHz, CDCl₃): δ 7.78 (d, J = 7.6 Hz, 2H), 7.68 (d, J = 7.2 Hz, 2H), 7.33-7.43 (m, 9H), 5.27-5.68 (m, 1H), 5.21-5.23 (m, 2H), 4.39-4.52 (m, 3H), 4.25-4.38 (m, 1H), 1.91-1.95 (m, 3H).

[00256] Step 3: To a 3-neck round-bottom flask was placed 2-((((9H-fluoren-9-yl) methoxy) carbonyl)amino)-3-iodobutanoate, 1-iodonaphthalene (42.2 g, 1.20 eq.), TBAI (76.7 g, 1.50 eq.), Zn (19.0 g, 2.10 eq.) and DMA (750 mL). To a second 3-neck round-bottom flask was placed picolinimidamide.2HCl (42.2 g, 1.20 eq.), NiCl₂.glyme (7.61 g, 0.25 eq.) and DMA (750 mL) at

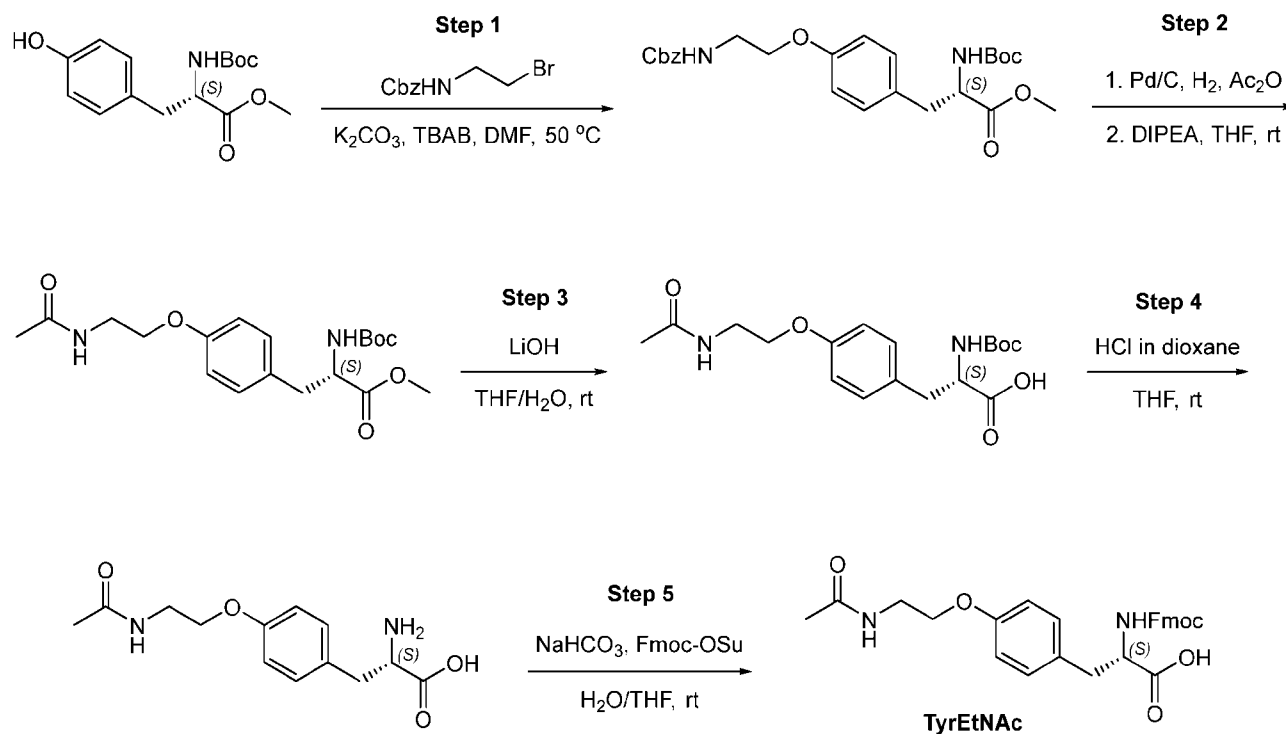
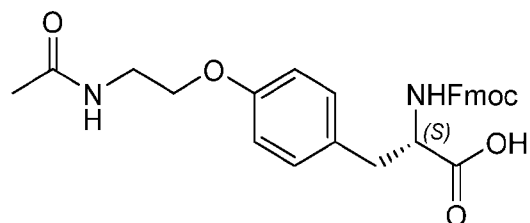
25 °C. Under argon, the contents of the second flask were added to the first flask. The resulting mixture was then stirred for 12 h at 25 °C. The reaction was poured into ice H₂O (3 L) and extracted with EtOAc (1 L x 2). The organic phase was dried over sodium sulfate and concentrated under vacuum at 40 °C. The crude product was purified by reversed-phase HPLC (MeCN:H₂O). HPLC-MS: [M+23]: 564. ¹H NMR (400 MHz, CDCl₃) δ: 8.17-8.24 (m, 1H), 8.15-8.17 (m, 1H), 7.77-7.87 (m, 2H), 7.76-7.77 (m, 4H), 7.30-7.41 (m, 10H), 5.30-5.38 (m, 1H), 4.96-5.04 (m, 3H), 4.85-4.87 (m, 1H), 4.30-4.34 (m, 1H), 4.18-4.26 (m, 4H), 1.43-1.45 (m, 3H).

[00257] Step 4: 143 g of (2S)-benzyl 2-((((9H-fluoren-9-yl) methoxy) carbonyl) amino)-3-(naphthalen-1-yl)butanoate was separated by SFC. The organic phase was concentrated under vacuum at 35 °C.

[00258] Peak 1: (2S,3R)-benzyl 2-((((9H-fluoren-9-yl)methoxy)carbonyl) amino)-3-(naphthalene-1-yl)butanoate. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.11-8.12 (m, 2H), 8.10-8.11 (m, 1H), 7.88-7.90 (m, 2H), 7.54-7.88 (m, 1H), 7.44-7.53 (m, 2H), 7.42-7.44 (m, 4H), 7.33-7.42 (m, 3H), 7.27-7.33 (m, 6H), 7.08-7.09 (m, 2H), 4.91-4.94 (m, 1H), 4.79- 4.82 (m, 1H), 4.58 (t, *J* = 8.0 Hz), 4.17-4.25 (m, 4H), 1.39 (d, *J* = 6.8 Hz, 3H). Peak 2: (2S,3S)-benzyl 2-((((9H-fluoren-9-yl)methoxy) carbonyl) amino)-3-(naphthalen-1-yl)butanoate. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.92-8.15 (m, 1H), 7.86-7.92 (m, 1H), 7.84-7.86 (m, 1H), 7.57-7.84 (m, 2H), 7.56-7.57 (m, 1H), 7.41-7.54 (m, 4H), 7.30-7.38 (m, 4H), 7.27-7.30 (m, 7H), 5.08-5.14 (m, 2H), 4.65 (t, *J* = 8.0 Hz), 4.23-4.26 (m, 1H), 4.05-4.18 (m, 3H), 1.30 (d, *J* = 6.8 Hz, 3H).

[00259] Step 5: To a 3-neck round-bottom flask was added (2S,3S)-benzyl 2-((((9H-fluoren-9-yl) methoxy) carbonyl)amino)-3-(naphthalen-1-yl)butanoate (40.0 g, 1.00 eq.) and THF (200 mL). 10% wet Pd/C (7.00 g) was added, and the reaction was purged 3 times with H₂ and stirred at 25 °C for 12 h under H₂ (15 psi). The reaction was filtered through a celite pad and concentrated under vacuum at 35 °C. The crude product was triturated with PE at 25 °C for 1 h. After filtration, the filter cake was dissolved in MeCN (100 mL) and concentrated under vacuum at 35 °C to remove residual solvent. HPLC-MS: [M+23]: 474. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.78 (s, 1H), 8.23 (d, *J* = 7.6 Hz, 1H), 7.86-7.88 (m, 1H), 7.80-7.86 (m, 2H), 7.61-7.80 (m, 2H), 7.55-7.59 (m, 4H), 7.481-7.55 (m, 1H), 7.40-7.48 (m, 3H), 7.27-7.29 (m, 2H), 4.28-4.60 (m, 1H), 4.24-4.28 (m, 1H), 4.17-4.24 (m, 2H), 4.04-4.15 (m, 1H), 1.36 (d, *J* = 6.8 Hz, 3H).

8.2.1.8 Synthetic Scheme 8

**TyrEtNAc**

L-Tyrosine *O*-ethyl acetamide or (S)-3-(4-(2-acetamidoethoxy)phenyl)-2-aminopropanoic acid

[00260] Step 1: To a stirred solution of methyl (*tert*-butoxycarbonyl)-L-tyrosinate (10.0 g, 33.9 mmol), benzyl (2-bromoethyl)carbamate (26.2 g, 102 mmol) and TBAB (5.46 g, 16.93 mmol) in DMF (150 mL) was added potassium carbonate (14.04 g, 102 mmol) at rt. The mixture was then stirred at 50 °C for 24 h. The mixture was cooled to rt, quenched with water (250 mL), and extracted with EtOAc (2 x 500 mL). The combined organic layers were washed with brine (3 x 150 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography, eluted with 0 - 30% EtOAc in PE. MS ESI calculated for C₂₅H₃₂N₂O₇ [M + Na]⁺ 495.22, found 495.10; ¹H NMR (300 MHz, CDCl₃) δ 7.38 - 7.32 (m, 5H), 7.04 (d, *J* = 8.4

Hz, 2H), 6.81 (d, $J = 8.4$ Hz, 2H), 5.31 (br, 1H), 5.21 (s, 2H), 4.97 (br, 1H), 4.56 - 4.53 (m, 1H), 4.03 (t, $J = 5.0$ Hz, 2H), 3.72 (s, 3H), 3.64 - 3.58 (m, 2H), 3.06 - 3.01 (m, 2H), 1.43 (s, 9H).

[00261] Step 2: To a stirred solution of methyl (*S*)-3-(4-(2-(((benzyloxy)carbonyl)amino)ethoxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (16.0 g, 33.9 mmol) and acetic anhydride (6.39 mL, 67.7 mmol) in THF (200 mL) was added Pd/C (3.60 g, 33.9 mmol, dry, 10%wt) at rt under nitrogen atmosphere. The mixture was degassed with hydrogen 3 times and stirred at 20 °C for 4 h. DIPEA (17.74 mL, 102 mmol) was added to the mixture and stirred at 20 °C for 1 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 0 - 3% MeOH in DCM. MS ESI calculated for $C_{19}H_{28}N_2O_6$ $[M + Na]^+$ 403.19, found 403.10; ^1H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, $J = 8.4$ Hz, 2H), 6.85 - 6.80 (m, 2H), 5.99 (br, 1H), 5.32 (br, 1H), 4.99 - 4.97 (m, 1H), 4.02 (t, $J = 5.0$ Hz, 2H), 3.72 (s, 3H), 3.69 - 3.63 (m, 2H), 3.10 - 2.89 (m, 2H), 2.02 (s, 3H), 1.42 (s, 9H).

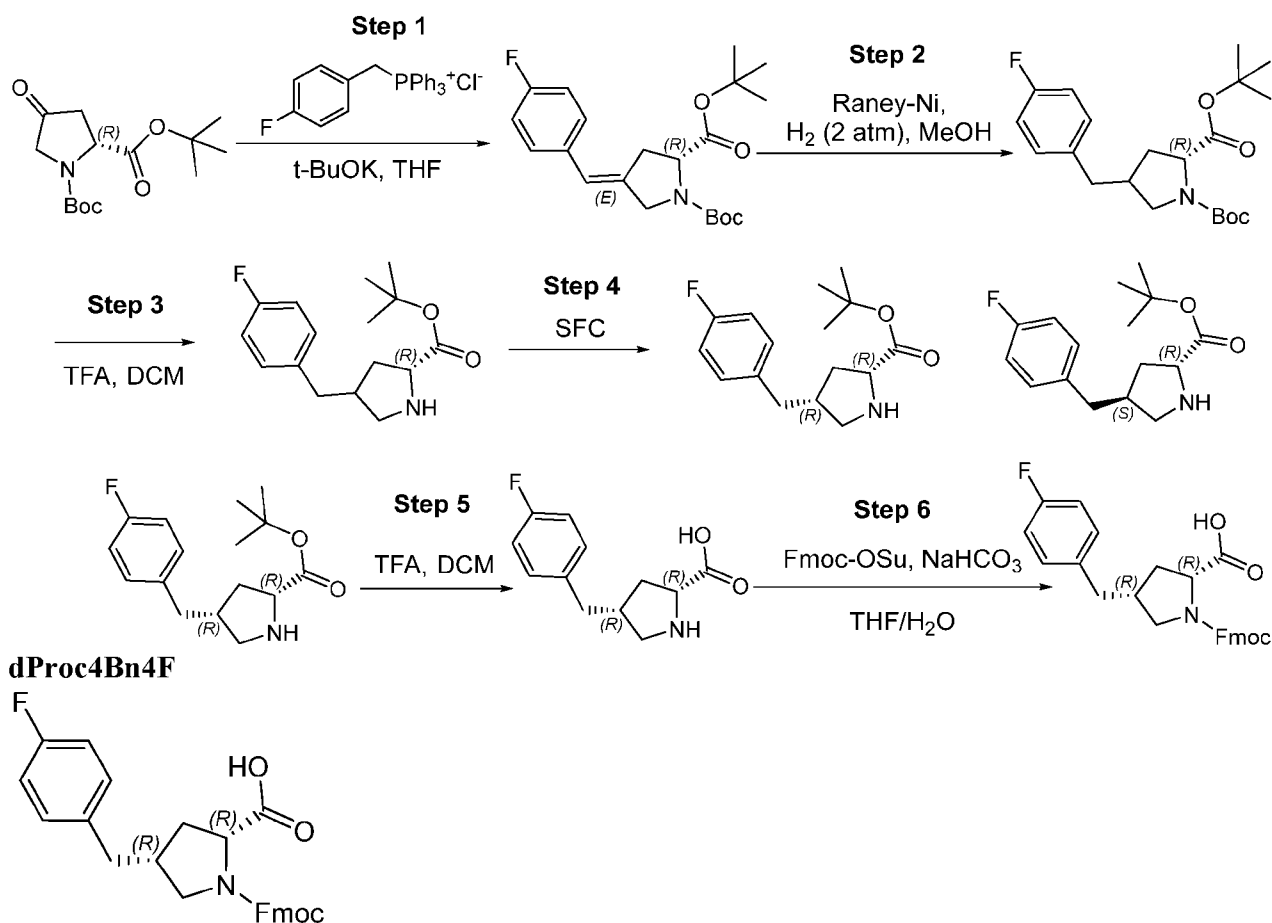
[00262] Step 3: To a stirred solution of methyl (*S*)-3-(4-(2-acetamidoethoxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (12.5 g, 32.9 mmol) THF (100 mL) was added lithium hydroxide (65.7 mL, 65.7 mmol, 1 N in water) at rt. The solution was stirred at 20 °C for 2 h. The pH of the solution was adjusted to 3 with 1 N HCl. The aqueous layer was extracted with EtOAc (2 x 250 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. MS ESI $[M + H]^+$: 367.10.

[00263] Step 4: To a stirred solution of (*S*)-3-(4-(2-acetamidoethoxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoic acid (12.5 g, 30.7 mmol) in THF (20 mL) was added 4 N HCl in dioxane (200 mL) at rt. The solution was stirred at 20 °C for 1 h. The solvent was concentrated under reduced pressure. MS ESI $[M + H]^+$: 267.05.

[00264] Step 5: To a stirred mixture of (*S*)-3-(4-(2-acetamidoethoxy)phenyl)-2-aminopropanoic acid hydrochloride (9.50 g, 25.1 mmol) and $NaHCO_3$ (10.54 g, 126 mmol) in THF (100 mL) and water (100 mL) was added Fmoc-OSu (7.62 g, 22.59 mmol) at rt. The mixture was stirred at 20 °C for 1 h. The pH value of the solution was adjusted to 3 with 1 N HCl. The aqueous phase was extracted with EtOAc (2 x 500 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous sodium bicarbonate, and filtered. The filtrate was concentrated under reduced pressure, and the residue was recrystallized from EtOAc

(200 mL). The solid was collected by filtration and dried under vacuum. MS ESI $[M + H]^+$: 489.05; ^1H NMR (300 MHz, Methanol- d_4) δ 7.79 (d, $J = 7.6$ Hz, 2H), 7.62-7.57 (m, 2H), 7.42-7.26 (m, 4H), 7.17-7.14 (m, 2H), 6.83 (d, $J = 8.4$ Hz, 2H), 4.41-4.31 (m, 2H), 4.29-4.10 (m, 2H), 3.96 (t, $J = 4.8$ Hz, 2H), 3.51 (t, $J = 5.4$ Hz, 2H), 3.19-3.13 (m, 1H), 2.92-2.84 (m, 1H), 1.94 (s, 3H).

8.2.1.9 Synthetic Scheme 9



(2R,4R)-1-(((9H-Fluoren-9-yl)methoxy)carbonyl)-4-(4-fluorobenzyl)pyrrolidine-2-carboxylic acid

[00265] Step 1: To a mixture of (4-fluorobenzyl)triphenylphosphonium chloride (17.82 g, 43.8 mmol) in THF (30 mL) was added potassium 2-methylpropan-2-olate (4.92 g, 43.8 mmol) under argon. The reaction was stirred at room temperature for 1 h. To the mixture was added a solution of di-*tert*-butyl (*R*)-4-oxopyrrolidine-1,2-dicarboxylate (5 g, 17.52 mmol) in THF (20 mL). The reaction was stirred at room temperature for 2 h. The resulting solution was quenched with water (50 mL) and extracted with ethyl acetate (3 x 300 mL). The organic layers

were combined, washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate and filtrated. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel chromatography, eluted with a gradient of ethyl acetate: petroleum ether – 0:1 to 1:5 to afford di-*tert*-butyl (*R, E*)-4-(4-fluorobenzylidene)pyrrolidine-1,2-dicarboxylate (4.8 g, 12.72 mmol, 73% yield) as a colorless oil. MS ESI calculated for $C_{21}H_{29}FNO_4$ $[M + H]^+$ 378.21, found 378.20.

[00266] Step 2: To a mixture of di-*tert*-butyl (*R, E*)-4-(4-fluorobenzylidene)pyrrolidine-1,2-dicarboxylate (5 g, 13.25 mmol) in MeOH (50 mL) was added Raney Ni (1.2 g, 20.45 mmol) at room temperature under argon. The suspension was degassed under vacuum and purged with H_2 several times; the reaction solution was stirred for 6 h at room temperature under 2 atm H_2 .

LCMS showed major was product. The resulting solution was filtrated. The filtrate was concentrated *in vacuo* to afford di-*tert*-butyl (2*R*)-4-(4-fluorobenzyl)pyrrolidine-1,2-dicarboxylate (4.5 g, 11.86 mmol, 90% yield) as a colorless oil. MS ESI calculated for $C_{21}H_{31}FNO_4$ $[M + H]^+$ 380.22, found 380.20.

[00267] Step 3: To a stirred solution of di-*tert*-butyl (2*R*)-4-(4-fluorobenzyl)pyrrolidine-1,2-dicarboxylate (4.5 g, 11.86 mmol) in TFA (10 mL) and DCM (25 mL) at room temperature. The solution was stirred at room temperature for 1 h. The solvent was concentrated under reduced pressure and the residue was purified by RP flash with the following conditions: Column: Flash C 18 (330 g); Mobile Phase A: water (0.1% TFA), Mobile Phase B: ACN; (Gradient: 5% B hold 5 min, up to 42% B within 15 min, 42% B hold 5 min; up to 95% B within 5 min, 95% B hold 5 min); Flow rate: 90 mL/min; Detector: UV 210 nm; RT = 26 min. The product-containing fractions were collected and *roto*-evaporated *in vacuo* to give *tert*-butyl (2*R*)-4-(4-fluorobenzyl)pyrrolidine-2-carboxylate (2.8 g, 10.02 mmol, 85% yield) as a light yellow oil. MS ESI calculated for $C_{16}H_{23}FNO_2$ $[M + H]^+$ 280.17, found 280.25.

[00268] Step 4: *tert*-butyl (2*R*)-4-(4-fluorobenzyl)pyrrolidine-2-carboxylate (2.8 g, 10.02 mmol) was separated by *Prep*-SFC with the following conditions: Column: Lux Cellulose-4, 4.6*50 mm, 3 μ m; Mobile Phase A: Hex(0.1% $NH_3 \cdot H_2O$), Mobile Phase B: MeOH Preparative; Flow rate: 1.0 mL/min; Gradient: 30% B; Column Temperature: 25 °C; Back Pressure: 100 bar; 190 nm; RT1: 3.42 min; RT2: 4.16 min. The fractions of first peak (RT1: 3.42 min) were collected and *roto*-evaporated *in vacuo* to give *tert*-butyl (2*R, 4S*)-4-(4-fluorobenzyl)pyrrolidine-2-carboxylate (300 mg, 1.074 mmol, 11% yield) as a yellow oil. MS ESI calculated for

$C_{16}H_{23}FNO_2$ $[M + H]^+$ 280.17, found 280.25. The fractions of second peak (RT2: 4.16min) were collected and *roto*-evaporated *in vacuo* to give *tert*-butyl (2*R*,4*R*)-4-(4-fluorobenzyl)pyrrolidine-2-carboxylate (2.1 g, 7.52 mmol, 75% yield) as a yellow oil. MS ESI calculated for $C_{16}H_{23}FNO_2$ $[M + H]^+$ 280.17, found 280.25. ^1H NMR (400 MHz, Methanol- d_4) δ 7.25 - 7.21 (m, 2H), 7.05 - 7.01 (m, 2H), 4.35 - 4.31 (m, 1H), 3.43 - 3.39 (m, 1H), 3.08 - 3.03 (m, 1H), 2.78 - 2.77 (m, 2H), 2.76 - 2.72 (m, 1H), 2.48 - 2.47 (m, 1H), 1.77 - 1.74 (m, 1H), 1.52 (s, 9H).

[00269] Step 5: The solution of *tert*-butyl (2*R*,4*R*)-4-(4-fluorobenzyl)pyrrolidine-2-carboxylate (2.1 g, 7.52 mmol) in CH_2Cl_2 (10 mL) and TFA (10.00 mL) was stirred at 25 °C for 3 hours. The reaction progress was monitored by LCMS. The reaction mixture was concentrated *in vacuo* to give crude (2*R*,4*R*)-4-(4-fluorobenzyl)pyrrolidine-2-carboxylic acid (1.678 g, ~ 7.52 mmol, 100 % yield) as a yellow solid. MS ESI calculated for $C_{12}H_{15}FNO_2$ $[M + H]^+$ 224.11, found 224.15.

[00270] Step 6: To a solution of (2*R*,4*R*)-4-(4-fluorobenzyl)pyrrolidine-2-carboxylic acid (1.678 g, 7.52 mmol) in THF (10 mL) and Water (10.00 mL) were added Sodium bicarbonate (3.95 g, 47.0 mmol) and *N*-(9-fluorenylmethoxycarbonyloxy)succinimide (2.86 g, 8.47 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 h then extracted with Ethyl acetate (3 x 200 mL). The combined organic layer was washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4 and filtrated. The filtrate was concentrated and was purified by Column: Flash C 18 (120 g); Mobile Phase A: water (0.1% TFA), Mobile Phase B: ACN; (Gradient: 5% B hold 5 min, up to 65% B within 25 min, 65% B hold 2.6 min; up to 95% B within 2 min, 95% B hold 5 min); Flow rate: 70 mL/min; Detector: UV 210 nm; RT = 26 min. The product-containing fractions were collected and *roto*-evaporated *in vacuo* to give (2*R*,4*R*)-1-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-4-(4-fluorobenzyl)pyrrolidine-2-carboxylic acid (2.6866 g, 6.03 mmol, 80% yield) as a white solid. MS ESI calculated for $C_{27}H_{25}FNO_4$ $[M + H]^+$ 446.18, found 446.25. ^1H NMR (300 MHz, Methanol- d_4) δ 7.78 - 7.71 (m, 2H), 7.63 - 7.53 (m, 2H), 7.39 - 7.26 (m, 4H), 7.21 - 7.14 (m, 2H), 7.07 - 6.97 (m, 2H), 4.39 - 4.37 (m, 1H), 4.32 - 4.14 (m, 3H), 3.68 - 3.32 (m, 1H), 3.22 - 2.96 (m, 1H), 2.71 - 2.37 (m, 2H), 2.43 - 2.36 (m, 2H), 1.81 - 1.62 (m, 1H).

8.2.2 Preparation of Final Compounds:

A. Generalized Procedure for Synthesizing Linear Peptide Precursors

[00271] Peptides in TABLE 4 were synthesized using standard solid-phase synthesis using Fmoc/*t*Bu chemistry as exemplified in Chan, W.C.; White, P.D. “Fmoc Solid-Phase Synthesis: a Practical Approach”, Oxford University Press, Oxford, 2000; Steward, J.; Young, J. “Solid Phase Peptide Synthesis”, Pierce Chemical Company, Rockford, 1984.; Benoiton, N.L. “Chemistry of Peptide Synthesis”, CRC Press, New York, 2006; and Lloyd-Williams, P.; Albericio, F.; Giralt, E. “Chemical Approaches to the Synthesis of Peptides and Proteins”, CRC Press, New York, 1997.

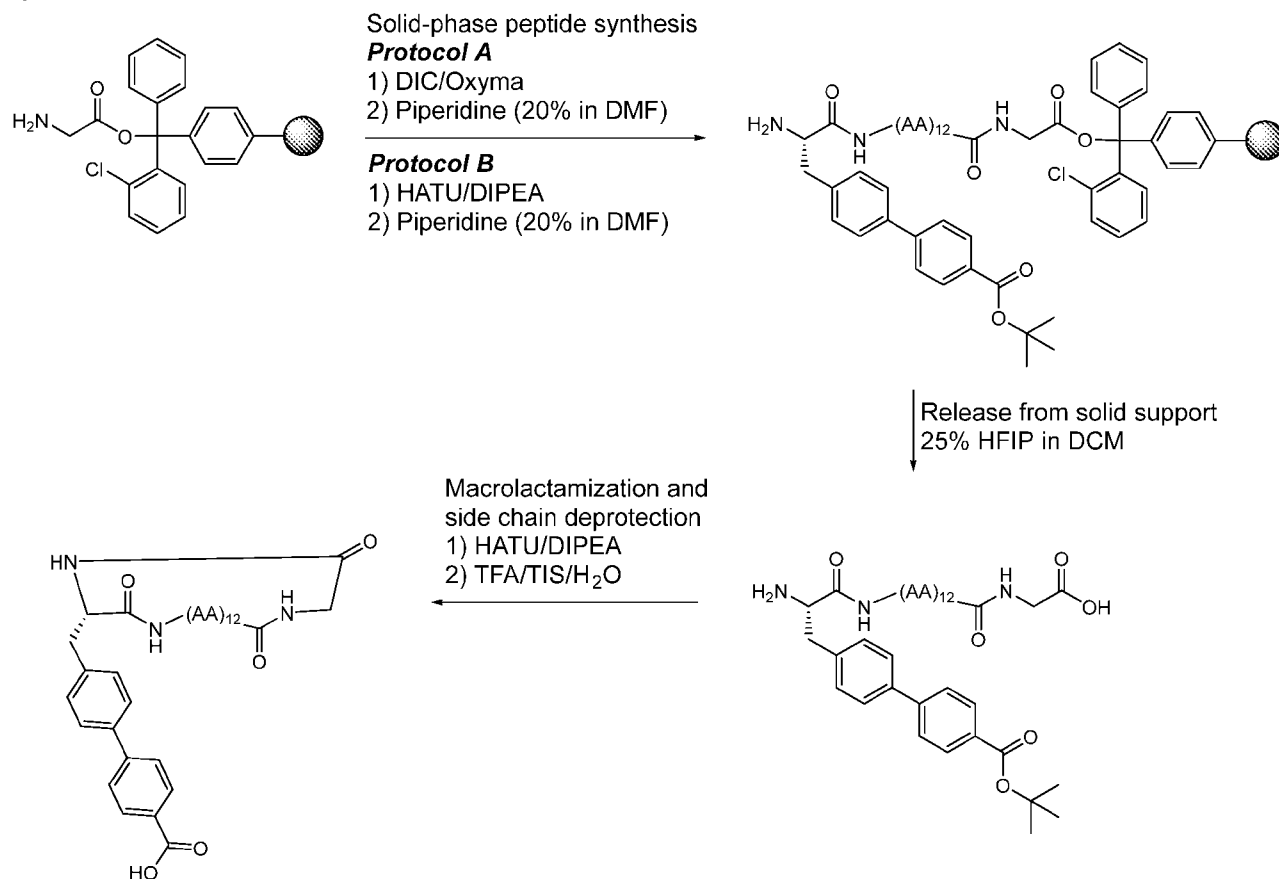
[00272] During peptide chain elongation, the α -amino group of each amino acid was protected with a 9*H*-fluoren-9-ylmethoxycarbonyl group (Fmoc). To avoid any side reactions during the chain elongation steps, any reactive amino acid side chains also carry acid-labile protecting groups, effectively masking the reactive groups until removal upon treatment with strong acid. After completion of each coupling step, the Fmoc group of the *N*-terminal amino acid was removed with piperidine or 4-methylpiperidine and the resin was thoroughly washed to prepare for the coupling of the subsequent Fmoc-protected amino acid derivative.

[00273] The side chain protecting groups used were: *tert*-butyl (*t*Bu) for S, hY, Bip4CO₂H, Phe4COOH, F4pcCCA, F4ptCCA, F4bcpA; *tert*-butoxy-carbonyl (Boc) for Dap, dDab, dK, dOrn, K, Prot4NH₂, dDap, daMeDab; and, β -methylpentyl ester (OMpe) for D.

[00274] Fmoc-protected amino acids were typically obtained from vendors such as Sigma-Aldrich, Novabiochem, Chem-Impex, and Combi-Block.

B. Synthetic Procedures used to Prepare Cyclic Peptides

Synthetic Scheme



Solid-Phase Synthesis of Peptides Protocol A

[00275] Peptides were synthesized on a Liberty Blue™ synthesizer from CEM Corporation, using standard solid-phase synthesis using Fmoc/tBu chemistry as summarized above in Scheme 25. *N,N'*-Diisopropylcarbodiimide (DIC) with ethyl cyano(hydroxyimino)acetate (Oxyma) were used as coupling agents to form the amide bond between the free amino terminus of the resin-bound protected peptide and the carboxylic acid of the Fmoc-protected amino acid.

[00276] H-Gly-loaded 2-chlorotrityl resin (200-400 mesh, 0.79 mmol/g loading, 1% cross-linked polystyrene, Novabiochem) was used for synthesis. All the amino acids were dissolved at a 0.2 M concentration in DMF (*N,N*-dimethylformamide). The amino acids were activated with equimolar amounts of Oxyma solution (0.5 M in DMF), and a 2-fold molar excess of DIC solution (1.0 M in DMF). Alternatively, amino acids were dissolved at a 0.125 M concentration in DMF (*N,N*-dimethylformamide). The amino acids were activated with equimolar amounts of

Oxyma Pure solution (0.125 M in DMF; with 0.05 M DIEA), and a 2-fold molar excess of DIC solution (0.25 M in DMF). Reactions were typically performed at the 25 μ mol scale.

[00277] Every synthesis cycle included: Fmoc-amino acid deprotection by 20% piperidine in DMF (90 °C microwave assisted heating, 2 min) and coupling (potentially repeated twice for difficult couplings) with Fmoc-protected amino acid/DIC/Oxyma (5, 5, and 10 eq respectively; 90 °C microwave assisted heating, 2 min or 4 min). Cycles of Fmoc deprotection and Fmoc-protected amino acid coupling were repeated with the desired monomers until the full linear peptide was formed.

Solid-Phase Synthesis of Peptides Protocol B

[00278] Alternatively, peptides were synthesized on a Biotage® Syro II peptide synthesizer using standard solid-phase synthesis using Fmoc/*t*Bu chemistry as summarized above in Scheme 25. HATU with DIPEA were used as coupling agents to create the amide bond between the free amino terminus of the resin-bound protected peptide and the carboxylic acid of the Fmoc-protected amino acid. H-Gly-loaded 2-chlorotrityl resin (200-400 mesh, 0.79 mmol/g loading, 1% cross-linked polystyrene, Novabiochem) was used for synthesis. All the amino acids were dissolved at a 0.2 M concentration in 1:1 DMF:NMP. Reactions were typically performed at the 12 μ mol scale.

[00279] Every synthesis cycle included: (1) Coupling (repeated twice) with Fmoc-protected amino acid/HATU/DIPEA (4, 4 and 8 eq, respectively; rt; 15 min). The mixture was filtered, and the peptidyl resin was washed with DMF (2 x 1 mL); (2) Fmoc deprotection (repeated three times): 20% 4-methyl piperidine in DMF (1 mL; rt; 3 min). The mixture was filtered, and the peptidyl resin was washed with DMF (4 x 1 mL). Cycles of Fmoc deprotection and Fmoc-protected amino acid coupling were repeated with the desired monomers until the full linear peptide was formed.

Selective Cleavage of Protected Peptide and Macrolactamization

[00280] For the cleavage of the protected linear peptide from the solid support, the peptidyl resin (~16 mg) was treated with 25% hexafluoroisopropanol (HFIP) in DCM for 20 min at rt, filtered, and the solvent was removed under reduced pressure. The resulting residue was dissolved in DMF (5 mL). HATU (0.44 eq) and DIPEA (2.5 eq) were added. The mixture was stirred for 5 min at rt. Then an additional 0.66 eq of HATU was added. Upon completion of the macrolactamization, monitored by UPLC-MS, the solvent was removed under reduced pressure.

Final side chain deprotection

[00281] A solution of TFA/H₂O/TIS (90/8/2, v/v/v, 1 mL) was added to the crude protected cyclic peptide. The mixture was stirred for 10 min at rt. Cold diethyl ether (15 mL) was added to the solution. The peptide was precipitated by centrifugation (3200 rpm, -10 °C). The precipitate was washed with diethyl ether (2 x 10 mL) and dried under vacuum overnight to give the crude deprotected cyclic peptide as a solid.

HPLC Purification

[00282] Purification was performed by preparative reversed-phase high performance liquid chromatography (RP-HPLC) on Waters X-Bridge Prep C18 OBD Prep column (130 Å, 5 µm, column size 19 * 100 mm) using a Waters MS-Directed AutoPurification HPLC/MS system. Mobile phase: (A) 0.16% TFA in HPLC water and (B) 0.16% TFA in HPLC acetonitrile; flow rate: 25 mL/min; UV wavelength λ = 215 nm; gradient: 25-50% B over 5 min. Alternatively purification was performed on Waters CSH-C18 Column (19 x 250mm, 5 µm) using an Agilent, with 1290 infinity II preparative LC system and LC-MSD XT mass spectrometer. Mobile phase: (A) 0.1% formic acid in HPLC water and (B) 0.1% formic acid in HPLC acetonitrile; flow rate: 25 mL/min; UV wavelength λ = 215 nm; gradient: 20% B over 2.5 min, 55% B over 2.5-20 min. UV absorbing fractions containing the target m/z ions were collected and the fractions containing product were confirmed by LC/MS.

[00283] Confirmation of identity and purity assessment of final compounds were performed by UPLC-MS, which was measured by a reverse phase Waters Acquity UPLC-MS system. Column: Waters XSelect CSH C18 Column (130 Å, 2.5 µm, column size 2.1 * 50 mm). Mobile phase: (A) 0.05% TFA in HPLC water and (B) 0.05% TFA in HPLC acetonitrile; injection volume: 1 µL; flow rate: 1 mL/min; UV wavelength λ = 215 nm; gradient: 5-100% B in 5 min. Lyophilization of combined fractions containing pure peptide resulted in the final cyclized product as a powder.

8.2.3 Biological Assays:**Procedure for IL-6 Assay in MRC5 cells**

[00284] The inhibition of IL-1 β induced IL-6 secretion was evaluated in MRC5 cells. Recombinant human IL-1 β (BioLegend 579404) at 2X EC₈₀ concentration was prepared in seeding medium, EMEM (ATCC 30-2003) with 0.025% BSA (Sigma A9576), 1X

penicillin/streptomycin (Gibco 15070-063), 1X NEAA (Gibco 11140-050), 1X GlutaMax (Gibco 35050-061), and 1X sodium pyruvate (Gibco 11360-070). 20 μ L of IL-1 β was added to a 384-well collagen-coated plate (Corning 354664) and pre-incubated at ambient temperature for 1 h with 200 nL of compound dispensed using an ECHO 555 liquid handler. Human lung fibroblast MRC5 cells (ATCC CCL-171) were added at a density of 3000 cells / 20 μ L per well. The cells were prepared by passaging three times in growth medium, EMEM (ATCC 30-2003) with 10% fetal bovine serum (Gibco 16140-071), 1X penicillin/streptomycin (Gibco 15070-063), 1X NEAA (Gibco 11140-050), 1X GlutaMax (Gibco 35050-061), and 1X sodium pyruvate (Gibco 11360-070) in collagen-coated T175 flasks (Greiner 661950) and harvested in seeding medium after 5 minutes of 0.25% trypsin-EDTA (Gibco 25200-056) digestion. The 384-well collagen-coated plate, containing a final volume of 40 μ L, was incubated at 37 °C, 5% CO₂ overnight. 5 μ L of the conditioned medium was transferred to a 384-well AlphaLISA plate (PerkinElmer 6005350) for detection of IL-6 using the human AlphaLISA IL-6 kit (PerkinElmer AL223F) as per the manufacturer's protocol. 20 μ L of the acceptor bead/biotinylated antibody mix was added to the 384-well AlphaLISA plate and incubated for 1 h at ambient temperature. The donor bead mix was protected from light and 25 μ L was added to the plate and incubated for 30 minutes at ambient temperature. The AlphaLISA plate was read on an EnVision multimode plate reader (Perkin Elmer model 2104) using the AlphaScreen setting (laser excitation at 680 nm and emission at 570 nm). Dose response curves and IC₅₀ values were analyzed using a 4-parameter logistic equation in Spotfire software (Tibco, Palo Alto, CA).

[00285] The amino acid sequences, biological activities (MRC IC₅₀s), calculated monoisotopic masses, molecular formulas, calculated molecular weights and mass spectral data ([M+H]⁺ or [M+2H]²⁺) of compound A-H (SEQ ID NOS:8, 9, 10, 11, 12, 13, 14, and 15) are provided below in TABLE 4.

[00286] TABLE 4: Properties of Selected Compounds of the Disclosure

SEQ ID NO.	Sequence	MRC5 IC50 (nM)	Exact Mass (Da)	Molecular Formula	Molecular Weight (g/mol)	Measured Mass (Da)	Observed ion
8	Bip4CO2H-W-Phe4COOH-G-Prot4NH2-SbMe1Nal-D-dNMeA-G-Bip4CO2H-AlaTHP4-Dap-dA-h3Pal5CN	0.0112	2047.85697	C108H117N19O23	2049.2	1025.5	[M+2H]/2+
9	Bip4CO2H-W-Phe4COOH-G-Prot4NH2-SbMeW4F-D-dNMeA-G-Bip4CO2H-K-L-dA-hY	0.046	2044.8836	C107H121FN18O23	2046.21	1024.7	[M+2H]/2+
10	TyrEtNAc-W-Phe4COOH-G-Prot4NH2-SbMeW4Cl-D-dNMeA-G-Bip4CO2H-1Nal-L-dA-hY	0.04984	2110.8697	C111H123CN18O23	2112.72	1056.5	[M+2H]/2+
11	TyrEtNAc-W-Phe4COOH-G-Prot4NH2-SbMeW4Cl-D-dNMeA-G-Bip4CO2H-W-L-dA-hY	0.04831	2099.86495	C109H122CN19O23	2101.7	1051.3	[M+2H]/2+
12	Bip4CO2H-W-Phe4COOH-G-Prot4NH2-SbMe1Nal-D-dNMeA-G-Bip4CO2H-W-Dap-dA-hY	0.0157	2158.89302	C118H122N18O23	2160.34	1081.0	[M+2H]/2+
13	Bip4CO2H-4Pal-Phe4COOH-G-Proc4F-SbMeW4F-A1b-A-W-Aib-S-Q-Dab-G-dProc4Bn4F	0.736	2000.84978	C101H115F3N20O21	2002.11	1001.43	[M+2H]/2+
14	TyrEtNAc-W-Phe4COOH-G-Prot4NH2-SbMeW4Cl-D-dNMeA-G-Bip4CO2H-W-G-dProt4OH-Prot4CH2Bip	0.01639	2171.86495	C115H122CN19O23	2173.77	1087.11	[M+2H]/2+
15	TyrEtNAc-W-Phe4COOH-G-Prot4NHCO3Py-SbMe1Nal-D-dPip-G-Bip4CO2H-W-deNC2NH2Gly-aMeNle	0.01	2087.9247	C112H125N19O22	2089.31	1045.9	[M+2H]/2+

8.3 EXAMPLE 3: CRYSTALLOGRAPHIC CHARACTERIZATION OF A COMPOUND A/IL-1 β COMPLEX

Crystallography Protocol

[00287] IL-1 β was recombinantly expressed and purified by chromatography. For co-crystallization, the ligand (*e.g.*, Compound A) was dissolved in 100% deuterated DMSO at a concentration of 100 mM and diluted 50-fold with the IL-1 β protein sample at 20 mg/ml to achieve approximately a 2-to-1 ligand to protein molar ratio. After 1 h incubation, the sample was divided into 2 aliquots, and a solution of 125 mM zinc chloride solution was added to one of the aliquots to a final concentration of 1 mM. Broad screening of crystallization conditions was performed using commercially available screens at 18 °C. Screening set-up was performed using a Mosquito (TTP Labtech) dispensing 200 nL of sample solution with or without exogenous zinc in two separate sub-wells, to which 100-200 nL of precipitant solution was added. The mixture was incubated at 18 °C in a RockImager (Formulatrix). Crystals appeared between a time period of 2 to 45 days. For flash-freezing and data collection, a cryoprotectant solution at a pH and a precipitant concentration matching the crystallization conditions and augmented with 20% v/v glycerol was added to the crystallization drop. The crystals were then harvested with a LithoLoop (Molecular Dimensions) and flash-frozen in liquid nitrogen.

[00288] Data collection was performed either at the Industrial Macromolecular Consortium Association (IMCA) beamline at the Advanced Photon Source (APS), or at the macromolecular crystallography beam line at the Canadian Light Source (CLS). Data were processed using the autoPROC (Global Phasing) software with calls to XDS, POINTLESS (CCP4) and STARANISO (Global Phasing) for integration, space group determination and scaling, respectively. The structure was solved by molecular replacement using the MOLREP program (CCP4). Structures were refined using COOT (CCP4) and autoBUSTER (Global Phasing). The crystallographic parameters for the Compound A/IL-1 β complex are shown below in TABLE 5.

[00289] TABLE 5: Crystallographic parameters for Compound A/IL-1 β complex

Parameter	Compound A
R-work	26.9
R-free	24.6
# of non-H atoms	5732
# protein non-H atoms	4872

Parameter	Compound A
# ligands atom	600
# waters	254
# protein residues	586
RMS bonds (Å)	0.008
RMS angles (Å)	1.16
% Ramachandran favored	97.7%
% Ramachandran outliers	0.0%
Macromolecule(s) average B	41.1
Solvent average B	35.7
Ligand average B	31.8

[00290] A three-dimensional cartoon representation of Compound A bound at the lipophilic binding pocket of IL-1 β is shown in FIG. 3, which depicts the side chains of amino acid positions 1, 2, 6, 7, and 10 of the macrocyclic peptide using stick representations. Amino acid residues Arg120, Ser121, Lys179, and Lys204 of the IL-1 β are labeled. An overlay of the Compound A/IL-1 β complex with other compounds complexed with IL-1 β is shown in FIG. 13.

[00291] A two-dimensional representation of the contact map of Compound A and IL-1 β residue interactions is shown in FIGS. 4A-4B. FIG. 4A shows the binding interactions for the bottom portion (amino acids 1-7) of Compound A to residues of the binding pocket. FIG. 4B shows the binding interactions for the top portion (amino acids 8-14) of Compound A to residues of the binding pocket.

8.4 EXAMPLE 4: CRYSTALLOGRAPHIC CHARACTERIZATION OF A COMPOUND B/IL-1B COMPLEX

[00292] Co-crystals of IL-1 β and Compound B were prepared and analyzed in accordance with the protocol of Example 3 (*e.g.*, the crystallography methods of Section 8.3). The crystallographic parameters for the Compound B/IL-1 β complex are shown below in TABLE 6.

[00293] TABLE 6: Crystallographic parameters for Compound B/IL-1 β complex

Parameter	Compound B
R-work	31.0
R-free	35.7

Parameter	Compound B
# of non-H atoms	2761
# protein non-H atoms	2412
# ligands atom	298
# waters	51
# protein residues	302
RMS bonds (Å)	0.008
RMS angles (Å)	1.08
% Ramachandran favored	92.6%
% Ramachandran outliers	3.0%
Macromolecule(s) average B	37.6
Solvent average B	25.7
Ligand average B	32.9

[00294] A three-dimensional cartoon representation of Compound B bound at the lipophilic binding pocket of IL-1 β is shown in FIG. 5, which depicts the side chains of amino acid positions 1, 2, 6, 7, and 10 of the macrocyclic peptide using stick representations. Amino acid residues Arg120, Ser121, Lys179, and Lys204 of the IL-1 β are labeled. An overlay of the Compound B/IL-1 β complex with other compounds complexed with IL-1 β is shown in FIG. 13.

[00295] A two-dimensional representation of the contact map of Compound B and IL-1 β residue interactions is shown in FIGS. 6A-6B. FIG. 6A shows the binding interactions for the bottom portion (amino acids 1-7) of Compound B to residues of the binding pocket. FIG. 6B shows the binding interactions for the top portion (amino acids 8-14) of Compound B to residues of the binding pocket.

8.5 **EXAMPLE 5: CRYSTALLOGRAPHIC CHARACTERIZATION OF A COMPOUND C/IL-1 β COMPLEX**

[00296] Co-crystals of IL-1 β and Compound C were prepared and analyzed in accordance with the protocol of Example 3 (*e.g.*, the crystallography methods of Section 8.3). The crystallographic parameters for the Compound C/IL-1 β complex are shown below in TABLE 7.

[00297] TABLE 7: Crystallographic parameters for Compound C/IL-1 β complex

Parameter	Compound C
R-work	30.6
R-free	24.3
# of non-H atoms	4103
# protein non-H atoms	3642
# ligands atom	459
# waters	0
# protein residues	451
RMS bonds (Å)	0.009
RMS angles (Å)	1.18
% Ramachandran favored	91.1%
% Ramachandran outliers	0.7%
Macromolecule(s) average B	56.6
Solvent average B	-
Ligand average B	54.8

[00298] A three-dimensional cartoon representation of Compound C bound at the lipophilic binding pocket of IL-1 β is shown in FIG. 7, which depicts the side chains of amino acid positions 1, 2, 6, 7, and 10 of the macrocyclic peptide using stick representations. Amino acid residues Arg120, Ser121, Lys179, and Lys204 of the IL-1 β are labeled. An overlay of the Compound C/IL-1 β complex with other compounds complexed with IL-1 β is shown in FIG. 13.

[00299] A two-dimensional representation of the contact map of Compound C and IL-1 β residue interactions is shown in FIGS. 8A-8B. FIG. 8A shows the binding interactions for the bottom portion (amino acids 1-7) of Compound C to residues of the binding pocket. FIG. 8B shows the binding interactions for the top portion (amino acids 8-14) of Compound C to residues of the binding pocket.

8.6 EXAMPLE 6: CRYSTALLOGRAPHIC CHARACTERIZATION OF A COMPOUND D/IL-1 β COMPLEX

[00300] Co-crystals of IL-1 β and Compound D were prepared and analyzed in accordance with the protocol of Example 3 (*e.g.*, the crystallography methods of Section 8.3). The crystallographic parameters for the Compound D/IL-1 β complex are shown below in TABLE 8.

[00301] TABLE 8: Crystallographic parameters for Compound D/IL-1 β complex

Parameter	Compound D
R-work	29.9
R-free	26.0
# of non-H atoms	3819
# protein non-H atoms	3519
# ligands atom	256
# waters	39
# protein residues	443
RMS bonds (Å)	0.008
RMS angles (Å)	1.16
% Ramachandran favored	88.3%
% Ramachandran outliers	3.2%
Macromolecule(s) average B	38.1
Solvent average B	21.9
Ligand average B	37.0

[00302] A three-dimensional cartoon representation of Compound D bound at the lipophilic binding pocket of IL-1 β is shown in FIG. 9, which depicts the side chains of amino acid positions 1, 2, 6, 7, and 10 of the macrocyclic peptide using stick representations. Amino acid residues Arg120, Ser121, Lys179, and Lys204 of the IL-1 β are labeled. An overlay of the Compound D/IL-1 β complex with other compounds complexed with IL-1 β is shown in FIG. 13.

[00303] A two-dimensional representation of the contact map of Compound D and IL-1 β residue interactions is shown in FIGS. 10A-10B. FIG. 10A shows the binding interactions for the bottom portion (amino acids 1-7) of Compound D to residues of the binding pocket. FIG. 10B shows the binding interactions for the top portion (amino acids 8-14) of Compound D to residues of the binding pocket.

8.7 EXAMPLE 7: CRYSTALLOGRAPHIC CHARACTERIZATION OF A COMPOUND E/IL-1 β COMPLEX

[00304] Co-crystals of IL-1 β and Compound E prepared and analyzed in accordance with the protocol of Example 3 (e.g., the crystallography methods of Section 8.3). The crystallographic parameters for the Compound E/IL-1 β complex are shown below in TABLE 9.

[00305] TABLE 9: Crystallographic parameters for Compound E/IL-1 β complex

Parameter	Compound E
R-work	25.1
R-free	23.7
# of non-H atoms	1494
# protein non-H atoms	1218
# ligands atom	159
# waters	117
# protein residues	153
RMS bonds (Å)	0.010
RMS angles (Å)	1.23
% Ramachandran favored	95.4%
% Ramachandran outliers	0.7%
Macromolecule(s) average B	34.1
Solvent average B	40.2
Ligand average B	30.5

[00306] A three-dimensional cartoon representation of Compound E bound at the lipophilic binding pocket of IL-1 β is shown in FIG. 11, which depicts the side chains of amino acid positions 1, 2, 6, 7, and 10 of the macrocyclic peptide using stick representations. Amino acid residues Arg120, Ser121, Lys179, and Lys204 of the IL-1 β are labeled. An overlay of the Compound E/IL-1 β complex with other compounds complexed with IL-1 β is shown in FIG. 13. An overlay of the Compound E/IL-1 β complex with other compounds complexed with IL-1 β is shown in FIG. 13.

[00307] A two-dimensional representation of the contact map of Compound E and IL-1 β residue interactions is shown in FIGS. 12A-12B. FIG. 12A shows the binding interactions for the bottom portion (amino acids 1-7) of Compound E to residues of the binding pocket. FIG. 12B shows the binding interactions for the top portion (amino acids 8-14) of Compound E to residues of the binding pocket.

8.8 **EXAMPLE 8: CRYSTALLOGRAPHIC CHARACTERIZATION OF A COMPOUND F/IL-1 β COMPLEX**

[00308] Co-crystals of IL-1 β and Compound F prepared and analyzed in accordance with the protocol of Example 3 (e.g., the crystallography methods of Section 8.3). The crystallographic parameters for the Compound F/IL-1 β complex are shown below in TABLE 10.

[00309] TABLE 10: Crystallographic parameters for Compound F/IL-1 β complex

Parameter	Compound F
R-work	25.2
R-free	27.0
# of non-H atoms	8584
# protein non-H atoms	7134
# ligands atom	870
# waters	310
# protein residues	893
RMS bonds (Å)	0.008
RMS angles (Å)	1.13
% Ramachandran favored	98.7%
% Ramachandran outliers	0%
Macromolecule(s) average B	50.0
Solvent average B	46.7
Ligand average B	50.0

[00310] A three-dimensional cartoon representation of Compound F bound at the lipophilic binding pocket of IL-1 β is shown in FIG. 14, which depicts the side chains of amino acid positions 1, 3, 6, 7, 10, and 15 of the macrocyclic peptide using stick representations. Amino acid residues Arg120, Ser121, Lys179, and Lys204 of the IL-1 β are labeled.

[00311] A two-dimensional representation of the contact map of Compound F and IL-1 β residue interactions is shown in FIGS. 15A-15B. FIG. 15A shows the binding interactions for the bottom portion (amino acids 1-7) of Compound F to residues of the binding pocket. FIG. 15B shows the binding interactions for the top portion (amino acids 8-13) of Compound F to residues of the binding pocket.

8.9 **EXAMPLE 9: CRYSTALLOGRAPHIC CHARACTERIZATION OF A COMPOUND G/IL-1 β COMPLEX**

[00312] Co-crystals of IL-1 β and Compound G prepared and analyzed in accordance with the protocol of Example 3 (e.g., the crystallography methods of Section 8.3). The crystallographic parameters for the Compound G/IL-1 β complex are shown below in TABLE 11.

[00313] TABLE 11: Crystallographic parameters for Compound G/IL-1 β complex

Parameter	Compound G
R-work	21.8
R-free	24.5
# of non-H atoms	1477
# protein non-H atoms	1239
# ligands atom	158
# waters	77
# protein residues	157
RMS bonds (Å)	0.008
RMS angles (Å)	1.16
% Ramachandran favored	98.0%
% Ramachandran outliers	0%
Macromolecule(s) average B	49.4
Solvent average B	48.2
Ligand average B	54.8

[00314] A three-dimensional cartoon representation of Compound G bound at the lipophilic binding pocket of IL-1 β is shown in FIG. 16, which depicts the side chains of amino acid positions 1, 2, 6, 7, and 10 of the macrocyclic peptide using stick representations. Amino acid residues Arg120, Ser121, Lys179, and Lys204 of the IL-1 β are labeled.

[00315] A two-dimensional representation of the contact map of Compound G and IL-1 β residue interactions is shown in FIGS. 17A-17B. FIG. 17A shows the binding interactions for the bottom portion (amino acids 1-7) of Compound F to residues of the binding pocket. FIG. 17B shows the binding interactions for the top portion (amino acids 8-14) of Compound G to residues of the binding pocket.

8.10 **EXAMPLE 10: CRYSTALLOGRAPHIC CHARACTERIZATION OF A COMPOUND H/IL-1 β COMPLEX**

[00316] Co-crystals of IL-1 β and Compound H prepared and analyzed in accordance with the protocol of Example 3 (e.g., the crystallography methods of Section 8.3). The crystallographic parameters for the Compound H/IL-1 β complex are shown below in TABLE 12.

[00317] TABLE 12: Crystallographic parameters for Compound H/IL-1 β complex

Parameter	Compound H
R-work	20.1
R-free	22.3
# of non-H atoms	1515
# protein non-H atoms	1228
# ligands atom	153
# waters	132
# protein residues	155
RMS bonds (Å)	0.010
RMS angles (Å)	1.15
% Ramachandran favored	98.7%
% Ramachandran outliers	0%
Macromolecule(s) average B	50.3
Solvent average B	49.1
Ligand average B	52.0

[00318] A three-dimensional cartoon representation of Compound H bound at the lipophilic binding pocket of IL-1 β is shown in FIG. 18, which depicts the side chains of amino acid positions 1, 2, 6, 7, and 10 of the macrocyclic peptide using stick representations. Amino acid residues Arg120, Ser121, Lys179, and Lys204 of the IL-1 β are labeled.

[00319] A two-dimensional representation of the contact map of Compound H and IL-1 β residue interactions is shown in FIGS. 19A-19B. FIG. 19A shows the binding interactions for the bottom portion (amino acids 1-8) of Compound F to residues of the binding pocket. FIG. 19B shows the binding interactions for the top portion (amino acids 9-15) of Compound G to residues of the binding pocket.

CLAIMS

WHAT IS CLAIMED:

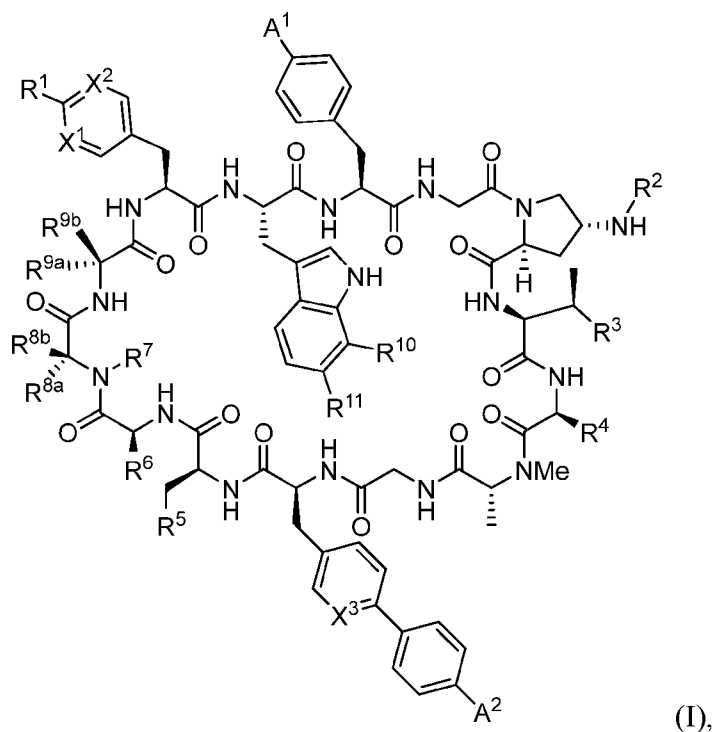
1. A method of inhibiting binding of human interleukin-1 beta (IL-1 β) to a human interleukin-1 receptor type I (IL-1R1), comprising contacting the IL-1 β with a compound or pharmaceutically acceptable salt thereof that binds to the IL-1 β at a binding pocket defined by amino acid residues Gly177-Leu178-Lys179-Glu180-Lys181-Asn182-Leu183-Tyr184 (SEQ ID NO:16) and Val201-Asp202-Pro203-Lys204-Asn205-Tyr206-Pro207 (SEQ ID NO:17) of the IL-1 β (SEQ ID NO:1).
2. The method of claim 1, wherein the compound allosterically inhibits the binding of the IL-1 β to the IL-1R1.
3. The method of claim 1 or 2, wherein the compound orthosterically inhibits the binding of the IL-1 β to the IL-1R1.
4. The method of any one of claims 1-3, wherein the compound inhibits the binding of the IL-1 β to a D3 domain of IL-1R1 (SEQ ID NO:7).
5. The method of any one of claims 1-4, wherein the compound binds to one or both of residues Lys179 or Pro207 of the IL-1 β .
6. The method of claim 5, wherein the compound comprises at least one moiety selected from:
 - a) a pi-effect interaction moiety capable of accepting a cation-pi interaction from the sidechain of residue Lys179 of the IL-1 β ;
 - b) a pi-effect interaction moiety capable of accepting a polar-pi interaction from the backbone of residue Pro207 of the IL-1 β .
7. The method of claim 6, wherein:
 - a) the pi-effect interaction moiety capable of accepting the cation-pi interaction from residue Lys179 is an arene;
 - b) the pi-effect interaction moiety capable of accepting the polar-pi interaction from residue Pro207 is an arene.

8. The method of claim 7, wherein the one or more arenes are biaryl moieties.
9. The method of claim 8, wherein the one or more biaryl moieties comprises a 9- to 10-membered bicyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; wherein the 9- to 10-membered bicyclic aryl or heteroaryl is unsubstituted or substituted by 1 to 3 substituents independently selected from the group consisting of halo, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, hydroxy, and C₁-C₃ alkoxy.
10. The method of claim 8 or 9, wherein the one or more biaryl moieties comprises a substituted or unsubstituted indole or naphthyl.
11. The method of any one of claims 1-10, wherein the binding pocket further comprises Val119, Arg120, Ser121, and/or Ser269 of the IL-1 β .
12. The method of any one of claims 1-10, wherein the binding pocket further comprises Val119, Arg120, and/or Ser121 of the IL-1 β .
13. The method of any one of claims 1-11, wherein the compound binds to one or more of Val119, Arg120, Ser121, Pro203, Lys204, and Ser269 of the IL-1 β .
14. The method of claim 13, wherein the compound comprises at least one or more moieties selected from:
 - a) a H-bond interaction moiety capable of donating a H-bond to the backbone carbonyl of residue Val119 of the IL-1 β ;
 - b) a pi-effect interaction moiety capable of accepting a cation-pi interaction from the sidechain of residue Arg120 of the IL-1 β ;
 - c) a H-bond interaction moiety capable of donating a H-bond to the backbone carbonyl of residue Ser121 of the IL-1 β ;
 - d) a H-bond interaction moiety capable of donating a H-bond to the backbone carbonyl of residue Pro203 of the IL-1 β ; or
 - e) a H-bond interaction moiety capable of donating a H-bond to the backbone carbonyl of residue Lys204 of the IL-1 β .

15. The method of claim 13, wherein the compound comprises at least one or more moieties selected from
- a) a H-bond interaction moiety capable of donating a H-bond to the backbone carbonyl of residue Val119 of the IL-1 β ;
 - b) a pi-effect interaction moiety capable of accepting a cation-pi interaction from the sidechain of residue Arg120 of the IL-1 β ;
 - c) c) a H-bond interaction moiety capable of donating a H-bond to the backbone carbonyl of residue Ser269 of the IL-1 β ;
 - d) d) a H-bond interaction moiety capable of accepting a H-bond to the backbone carbonyl of residue Ser269 of the IL-1 β ; or
 - e) e) a basic moiety capable of an electrostatic interaction with the c-terminal carboxylic acid of the IL-1 β .
16. The method of claim 14, wherein:
- a) the H-bond donor moiety capable of donating the H-bond to the backbone carbonyl of residue Val119 of the IL-1 β comprises a backbone NH group;
 - b) the pi-effect interaction moiety capable of accepting the cation-pi interaction from the sidechain of residue Arg120 of the IL-1 β comprises an arene;
 - c) the H-bond donor moiety capable of donating the H-bond to the backbone carbonyl of residue Ser121 of the IL-1 β comprises a backbone NH group;
 - d) the H-bond donor moiety capable of donating the H-bond to the backbone carbonyl of residue Pro203 of the IL-1 β comprises a backbone NH group;
 - e) the H-bond donor moiety capable of donating the H-bond to the backbone carbonyl of residue Lys204 of the IL-1 β comprises a sidechain NH₃⁺ or NH₂⁺ group.
17. The method of any one of claims 13-16, wherein the compound comprises at least one moiety selected from:
- a) a H-bond interaction moiety capable of accepting a H-bond from the backbone NH of residue Arg120 of the IL-1 β ;
 - b) a H-bond interaction moiety capable of accepting a H-bond from the sidechain of residue Arg120 of the IL-1 β ;

- c) a H-bond interaction moiety capable of accepting a H-bond from the backbone NH of residue Ser121 of the IL-1 β ; or
 - d) a H-bond interaction moiety capable of accepting a H-bond from the sidechain of residue Lys204 of the IL-1 β .
18. The method of claim 17, wherein:
- a) the H-bond interaction moiety capable of accepting the H-bond from the backbone NH of residue Arg120 of the IL-1 β comprises a carbonyl group;
 - b) the H-bond interaction moiety capable of accepting a H-bond from the sidechain of residue Arg120 of the IL-1 β comprises a carboxylate group;
 - c) the H-bond interaction moiety capable of accepting the H-bond from the backbone NH of residue Ser121 of the IL-1 β comprises a carbonyl group; or
 - d) the H-bond interaction moiety capable of accepting the H-bond from the sidechain of residue Lys204 of the IL-1 β comprises a carbonyl group or a carboxylate group.
19. The method of any one of claims 1-18, wherein the compound binds to Tyr206 of the IL-1 β .
20. The method of claim 19, wherein the compound comprises a H-bond interaction moiety capable of donating a H-bond to the backbone carbonyl of residue Tyr206 of the IL-1 β .
21. The method of claim 20, wherein the H-bond interaction moiety capable of donating the H-bond to the backbone carbonyl of residue Tyr206 of the IL-1 β comprises a backbone NH group.
22. The method of any one of claims 1-21, wherein the binding pocket further comprises Phe162 and/or Ser269 of the IL-1 β .
23. The method of claim 22, wherein the compound binds to one or both of residues Phe162 or Ser269 of the IL-1 β .
24. The method of claim 23, wherein the compound comprises one or more moieties selected from:

- a) a pi-effect interaction moiety capable of donating a polar-pi interaction to residue Phe162 of the IL-1 β ;
 - b) a H-bond interaction moiety capable of accepting a H-bond from the sidechain of residue Ser269 of the IL-1 β ; or
 - c) a pi-effect interaction moiety capable of accepting a polar-pi interaction from residue Ser269 of the IL-1 β .
25. The method of claim 24, wherein
- a) the pi-effect interaction moiety capable of donating a polar-pi interaction to residue Phe162 of the IL-1 β comprises a backbone NH moiety;
 - b) the H-bond interaction moiety capable of accepting the H-bond from the sidechain OH of residue Ser269 of the IL-1 β comprises an oxygen; or
 - c) the pi-effect interaction moiety capable of accepting the polar-pi interaction from residue Ser269 of the IL-1 β comprises an arene.
26. The method of any one of claims 1-25, wherein the compound is a peptide.
27. The method of claim 26, wherein the peptide is a cyclic peptide.
28. The method of claim 27, wherein the cyclic peptide has a length of from 12 to 16 amino acid residues.
29. The method of any one of claims 1-28, wherein the compound has a molecular weight of from about 1200 Da to about 3000 Da, from about 1500 Da to 2500 Da, or from about 1750 to about 2250 Da.
30. A method of inhibiting binding of human IL-1 β to human IL-1R1, comprising contacting the IL-1 β with a compound that competes for binding to the IL-1R1, wherein the compound has a structure of Formula (I):



wherein:

R¹ is CH₃C(O)NH-CH₂CH₂-O- or C¹;

C¹ is:

- (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or
- (ii) a 5- to 6-membered mono- or bicyclic, saturated cycloalkyl or heterocycloalkyl containing 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or
- (iii) a 5- to 6-membered mono- or bicyclic cycloalkyl;

wherein C¹ is unsubstituted or substituted by 1 to 3 R^{C1} substituents independently selected from the group consisting of halo, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, carboxy, C₁-C₃ alkoxy, and C₂-C₃ acyl;

R² is H, C₁-C₃ alkyl, benzyl, or phenyl-CH₂CH₂-;

R³ is a 9- to 10-membered bicyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;

wherein R^3 is unsubstituted or substituted by 1 to 3 R^{3a} substituents independently selected from the group consisting of halo, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, hydroxy and C_1 - C_3 alkoxy;

R^4 is C_1 - C_3 alkyl, $HO_2C-(CH_2)_m-$, $H_2NC(O)-(CH_2)_m-$, $(CH_3)_2NC(O)-(CH_2)_m-$, or tetrazolyl- $(CH_2)_m-$;

R^5 is amino, $H_2N(CH_2)_n-$, $H_2NC(O)-(CH_2)_n-$, $CH_3C(O)NH-$, $CH_3C(O)NH(CH_2)_n-$, C^5 , or C^5-CH_2- ,

C^5 is:

- (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;
- (ii) a 9- to 10-membered bicyclic aryl or heteroaryl, wherein said bicyclic heteroaryl contains 1 to 3 heteroatoms selected from the group consisting of N, O, and S;
- (iii) a 5- to 6-membered monocyclic or 9- to 10-membered heterocycloalkyl, wherein said heterocycloalkyl is saturated or partially unsaturated, and contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;
- (iv) a 5- to 6-membered monocyclic cycloalkyl; or
- (v) 2,3-dihydroindolyl;

wherein C^5 is unsubstituted or substituted by 1 to 3 RC^5 substituents independently selected from the group consisting of halo, amino, hydroxy, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, C_1 - C_3 alkoxy, $H_2N-(CH_2)_k-$, $H_2NC(O)-(CH_2)_k-$, $H_2C=CH-CH_2O-$, and phenyl;

R^6 is H, C_1 - C_5 alkyl, $H_2N(CH_2)_p-$, $HOCH_2-$, $(CH_3)_2NCH_2-$, $H_3CO-(CH_2)_q-$, or C^6-CH_2- ;

C^6 is 5- or 6-membered monocyclic, saturated heterocycloalkyl containing 1 to 2 heteroatoms selected from the group consisting of N, O, and S; and wherein C^6 is unsubstituted or substituted by 1 to 3 RC^6 substituents independently selected from the group consisting of halo, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, hydroxy and C_1 - C_3 alkoxy;

R^7 is H or C_1 - C_3 alkyl;

R^{8a} is H, C_1 - C_5 alkyl, $HOCH_2-$, $H_2N(CH_2)_r-$, $(CH_3)_3N^+(CH_2)_r-$, or $CH_3C(O)NH(CH_2)_r-$;

R^{8b} is H or C₁-C₃ alkyl;

R^{9a} is H or C₁-C₃ alkyl;

R^{9b} is H, C₁-C₅ alkyl, C⁹-CH₂-, or C⁹-CH₂CH₂-;

C⁹ is:

- (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or
- (ii) a 5- to 6-membered monocyclic, saturated cycloalkyl or heterocycloalkyl, wherein the heterocycloalkyl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S;

wherein C⁹ is unsubstituted or substituted by 1 to 3 R^{C9} substituents independently selected from the group consisting of halo, amino, hydroxy, cyano, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, C₁-C₃ alkoxy, H₂N-(CH₂)_k-, H₂NC(O)-(CH₂)_k-, H₂NCH₂CH₂O-, CH₃C(O)NH-CH₂CH₂O-, and morpholinyl-CH₂CH₂O-;

R¹⁰ is H, halo, or C₁-C₃ alkyl;

R¹¹ is H, halo, or C₁-C₃ alkyl;

each occurrence of subscript k is independently 1 or 2;

subscript m is 1 or 2;

subscript n is 1, 2, 3, or 4;

subscript p is 1, 2, 3, or 4;

subscript q is 1 or 2;

subscript r is 1, 2, 3, or 4;

X¹, X², and X³ are independently C(H) or N; and

A¹ and A² are independently selected from the group consisting of HO₂C-, H₂NC(O)-, CH₃C(O)N(H)-, H₂NS(O)₂-, CH₃S(O)₂N(H)-, tetrazolyl, and 5-oxo oxadiazolyl; or a pharmaceutically acceptable salt thereof.

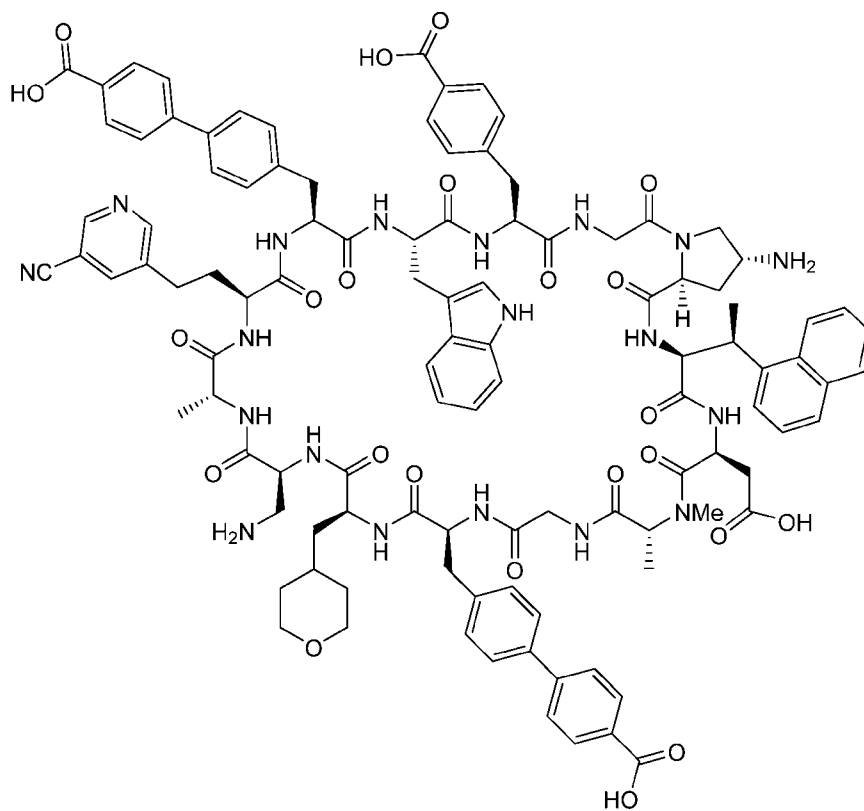
31. A method of inhibiting binding of human IL-1 β to human IL-1R1, comprising contacting the IL-1 β with a compound that competes for binding to the IL-1R1, wherein the compound is a peptide having a sequence selected from:

- a) Bip4CO₂H-W-Phe4COOH-G-Prot4NH₂-SbMe1Nal-D-dNMeA-G-Bip4CO₂H-AlaTHP4-Dap-dA-h3Pal5CN (SEQ ID NO:8);
- b) Bip4CO₂H-W-Phe4COOH-G-Prot4NH₂-SbMeW4F-D-dNMeA-G-Bip4CO₂H-K-L-dA-hY (SEQ ID NO:9);
- c) TyrEtNAc-W-Phe4COOH-G-Prot4NH₂-SbMeW4Cl-D-dNMeA-G-Bip4CO₂H-1Nal-L-dA-hY (SEQ ID NO:10);
- d) TyrEtNAc-W-Phe4COOH-G-Prot4NH₂-SbMeW4Cl-D-dNMeA-G-Bip4CO₂H-W-L-dA-hY (SEQ ID NO:11); or
- e) Bip4CO₂H-W-Phe4COOH-G-Prot4NHBn-SbMe1Nal-D-dNMeA-G-Bip4CO₂H-W-Dap-dA-hY (SEQ ID NO:12);
- f) Bip4CO₂H-4Pal-Phe4COOH-G-Proc4F-SbMeW4F-Aib-A-W-Aib-S-Q-Dab-G-dProc4Bn4F (SEQ ID NO:13);
- g) TyrEtNAc-W-Phe4COOH-G-Prot4NH₂-SbMeW4Cl-D-dNMeA-G-Bip4CO₂H-W-G-dProt4OH-Prot4CH₂Bip (SEQ ID NO:14);
- h) TyrEtNAc-W-Phe4COOH-G-Prot4NHCO₃Py-SbMe1Nal-D-dPip-G-Bip4CO₂H-W-deNC₂NH₂Gly-aMeNle (SEQ ID NO:15);

or a pharmaceutically acceptable salt thereof.

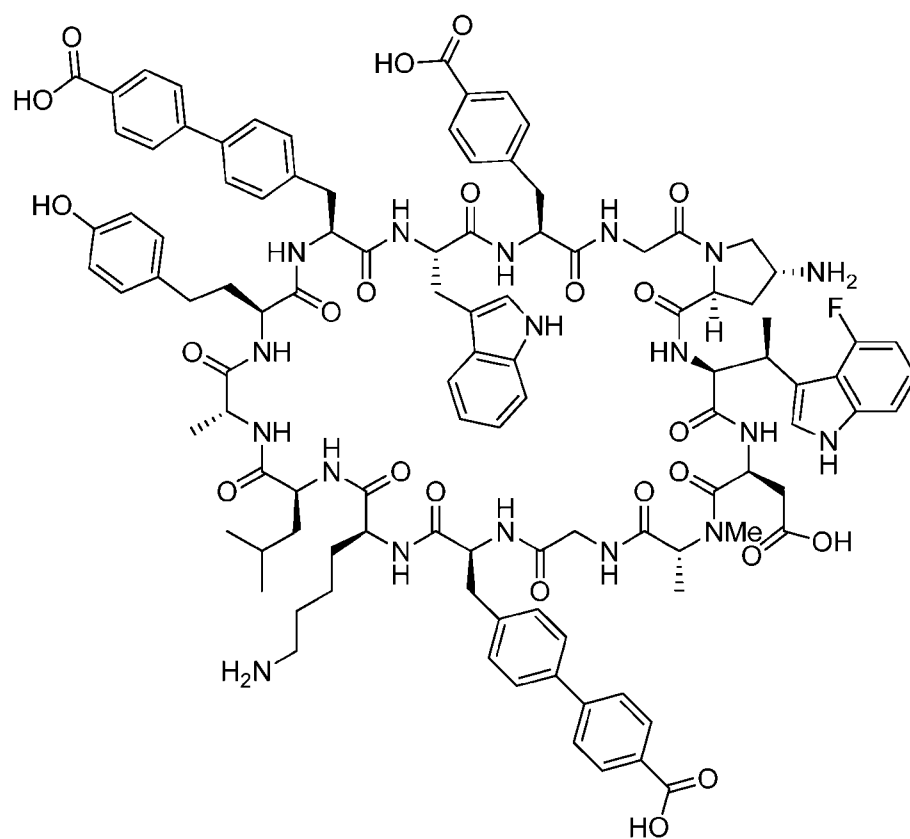
32. A method of inhibiting binding of human IL-1 β to human IL-1R1, comprising contacting the IL-1 β with a compound that competes for binding to the IL-1R1, wherein the compound has a structural formula of:

a)



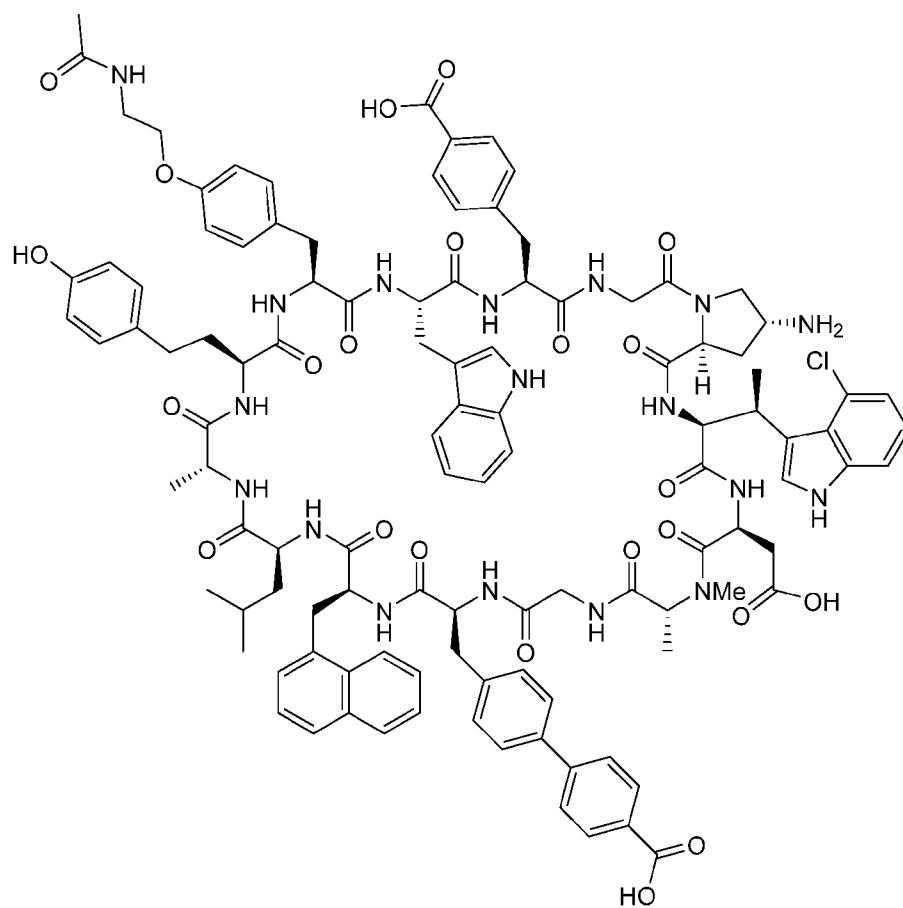
Compound A (SEQ ID NO:8);

b)



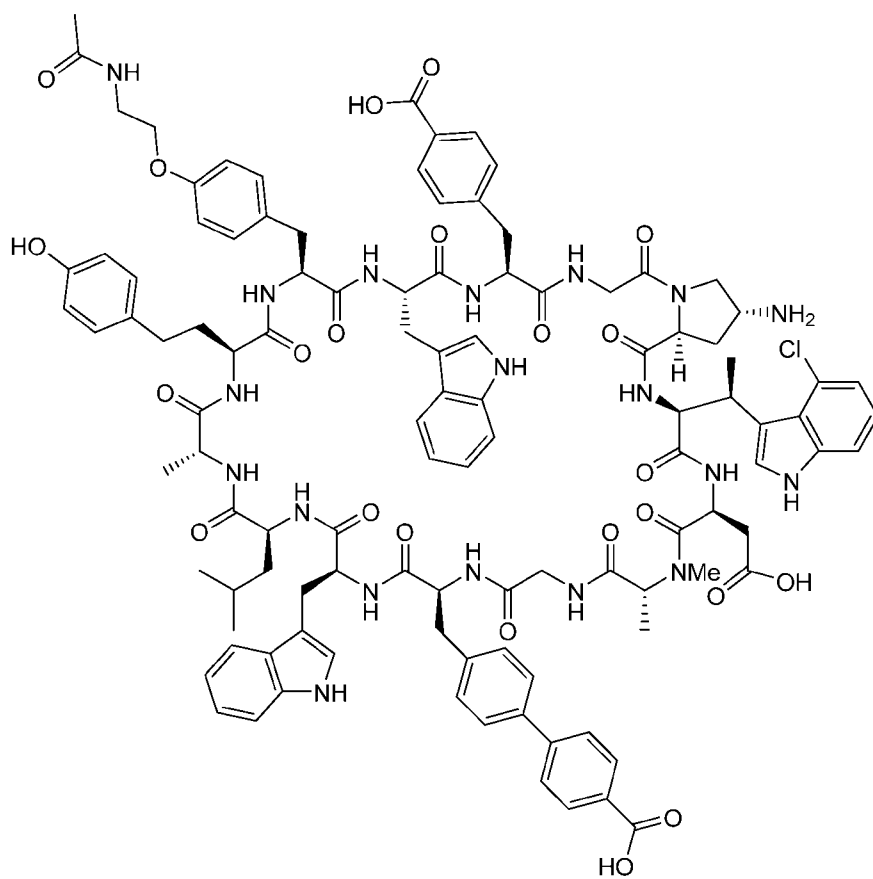
Compound B (SEQ ID NO:9);

c)



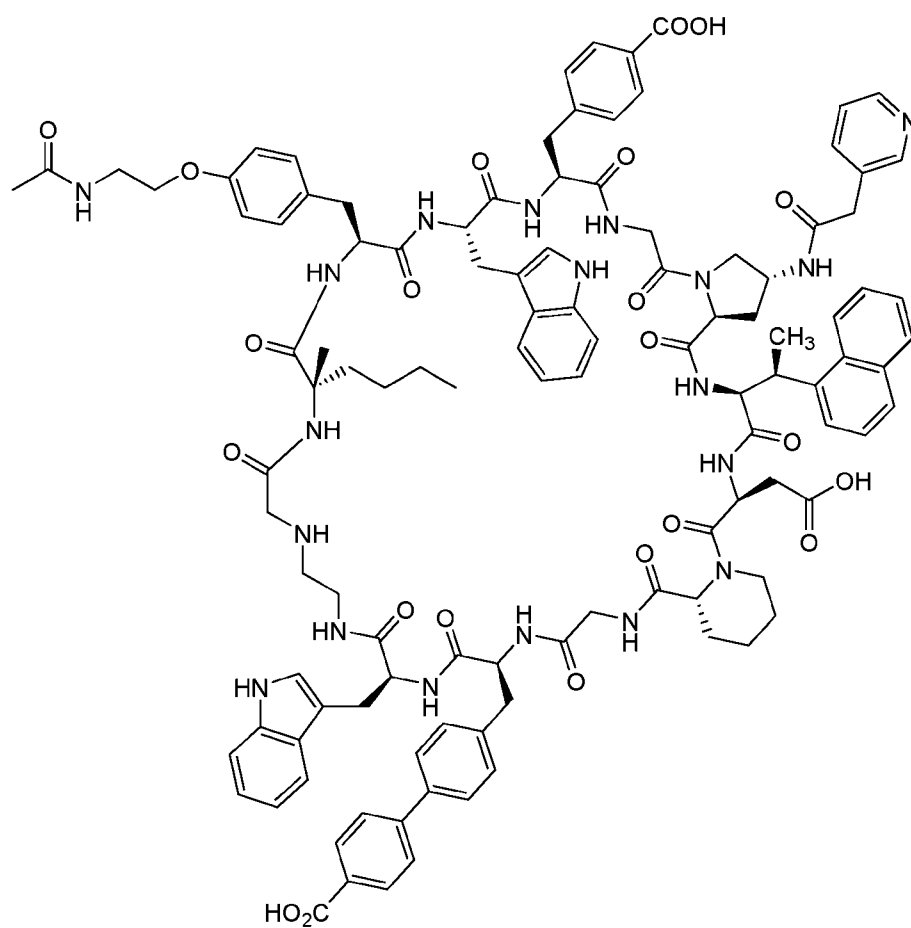
Compound C (SEQ ID NO:10);

d)



Compound D (SEQ ID NO:11);

h)



Compound H (SEQ ID NO:15);

or a pharmaceutically acceptable salt thereof.

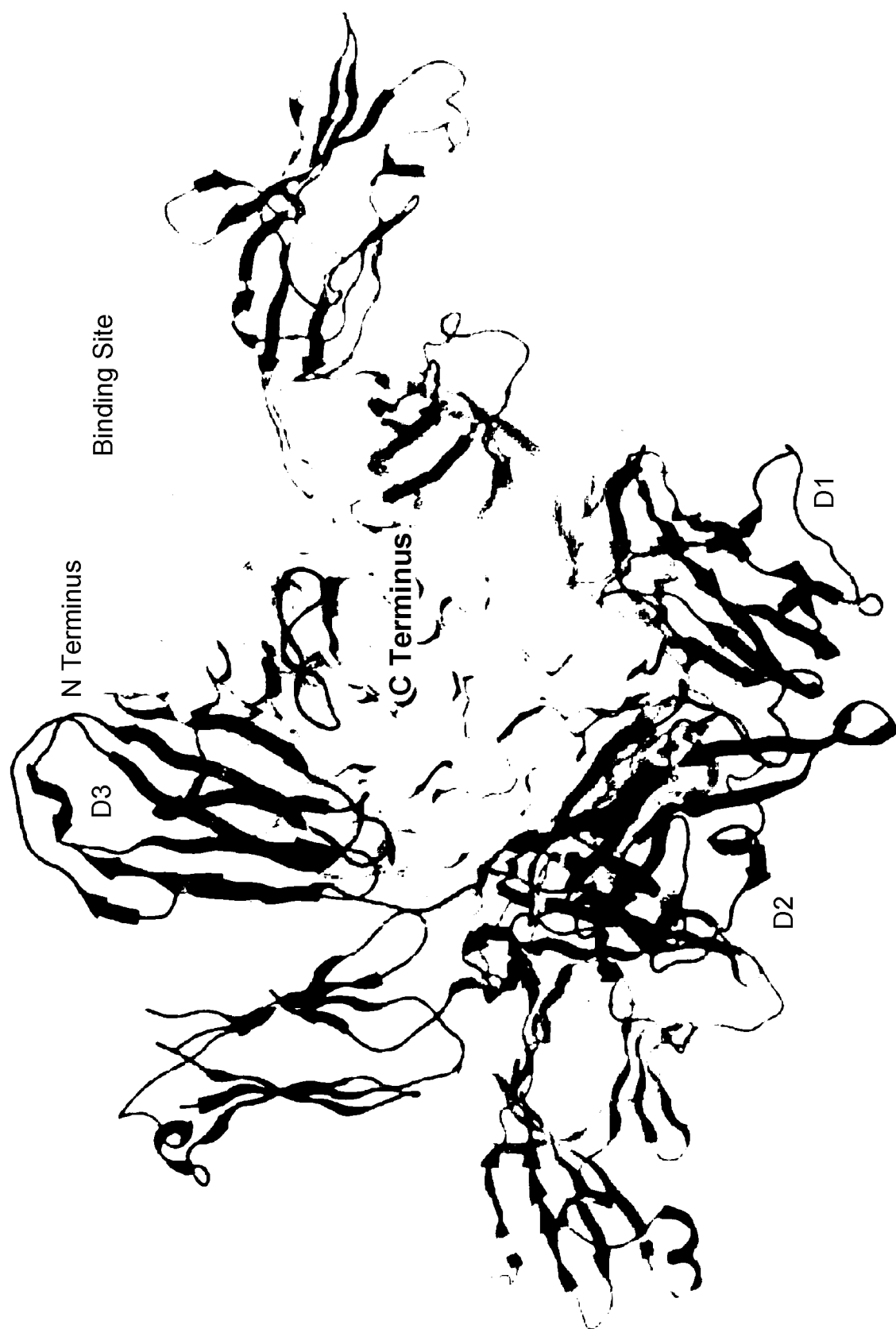


FIG. 1

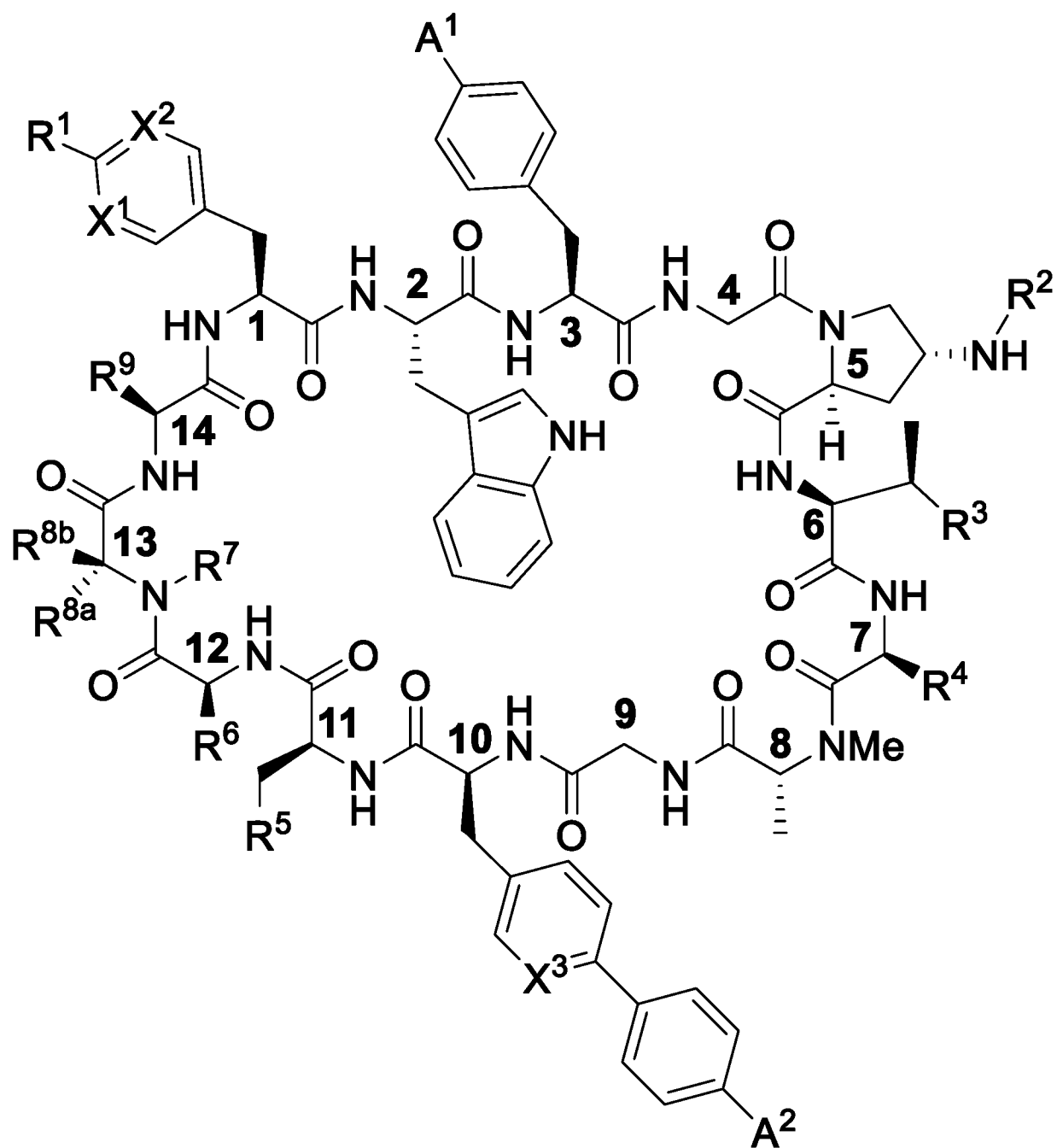


FIG. 2A

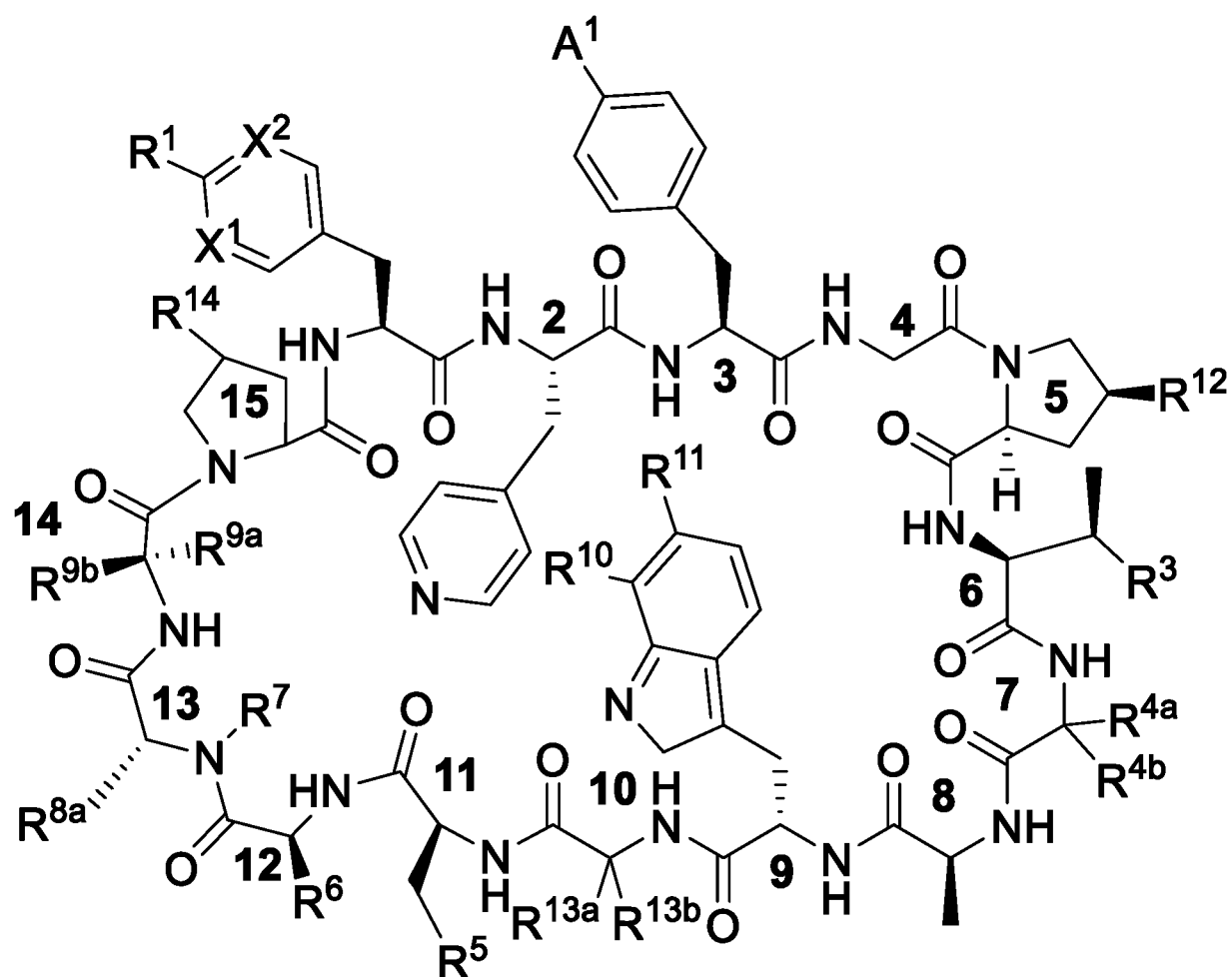


FIG. 2B

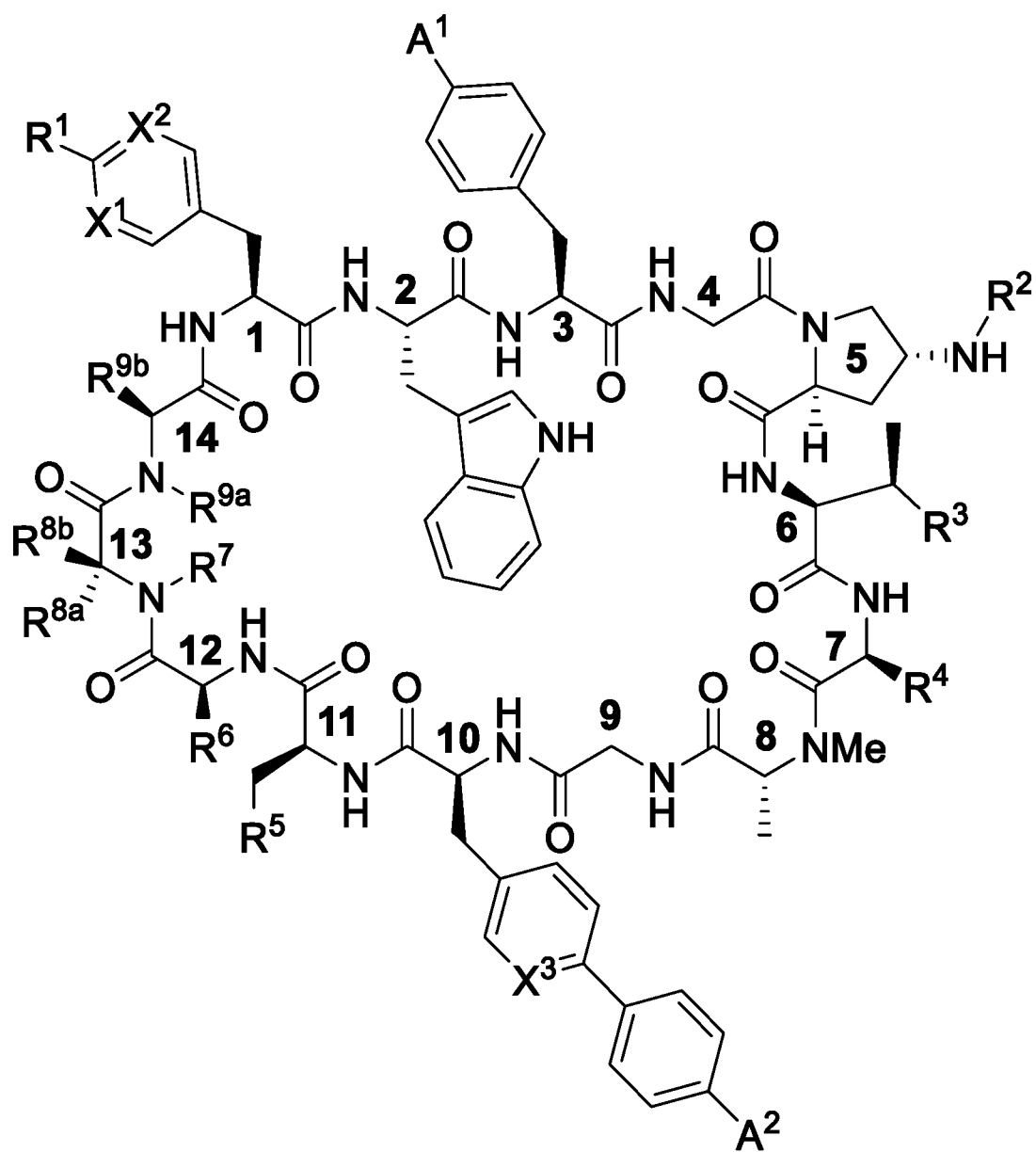


FIG. 2C

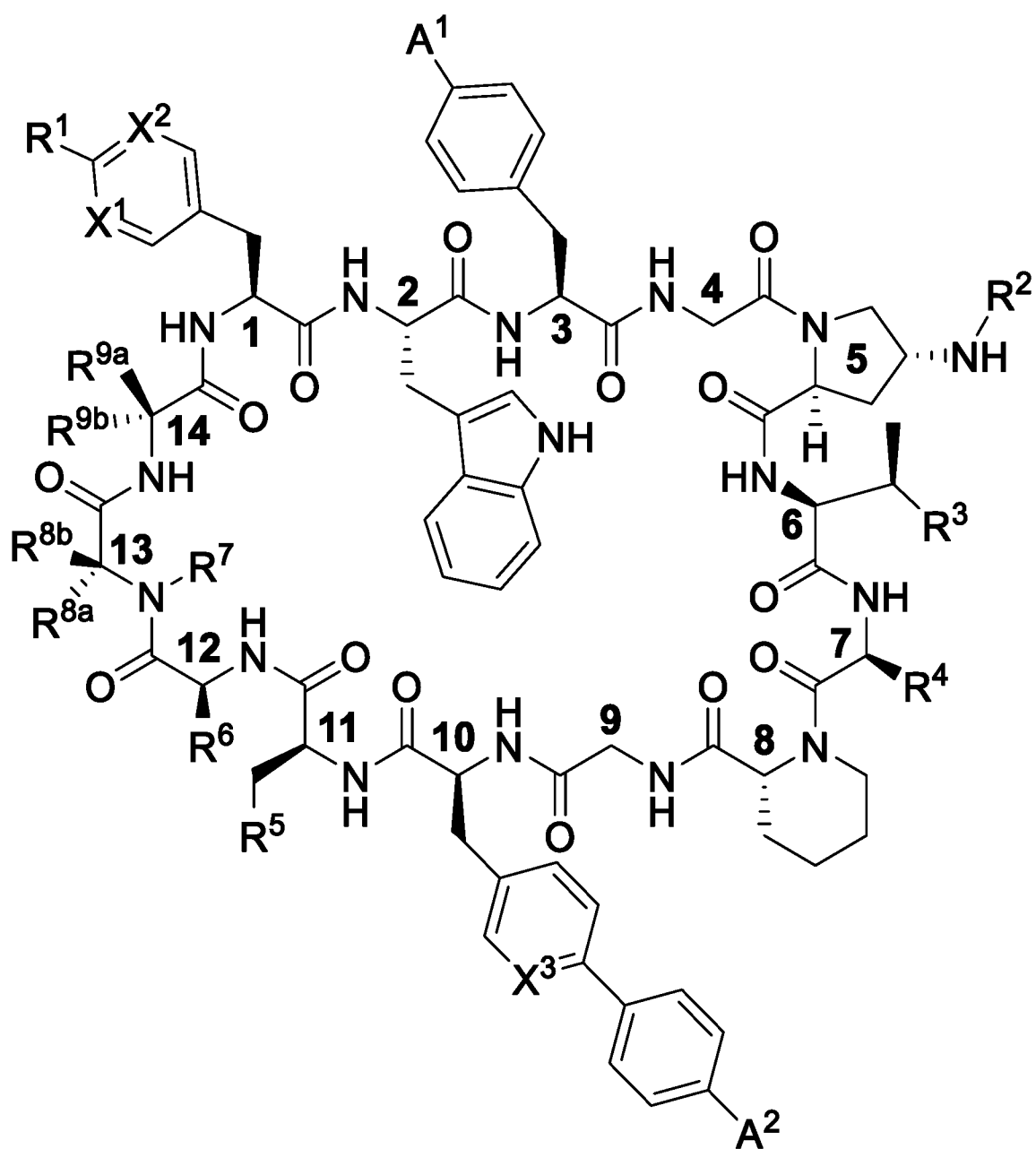


FIG. 2D

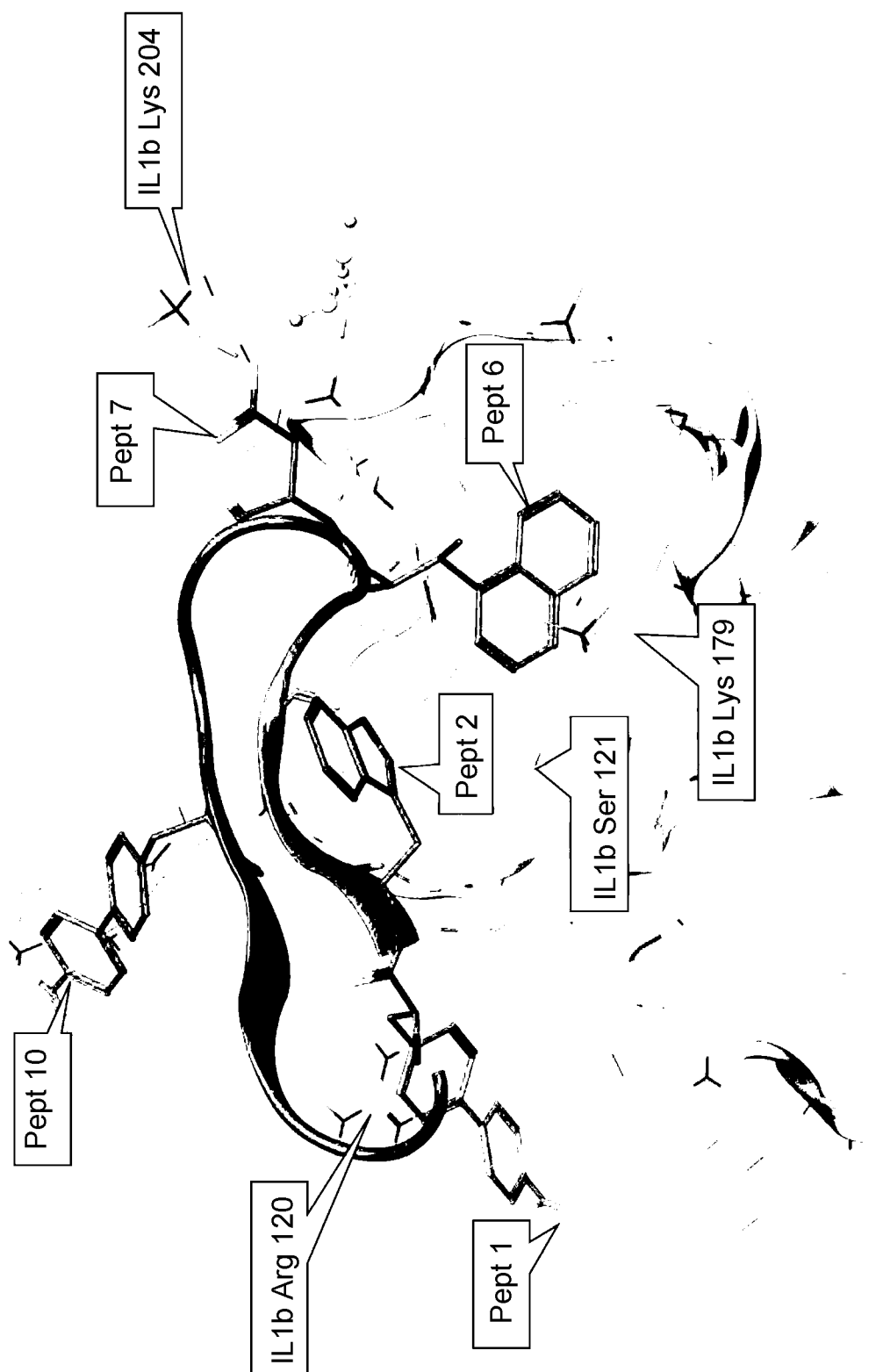
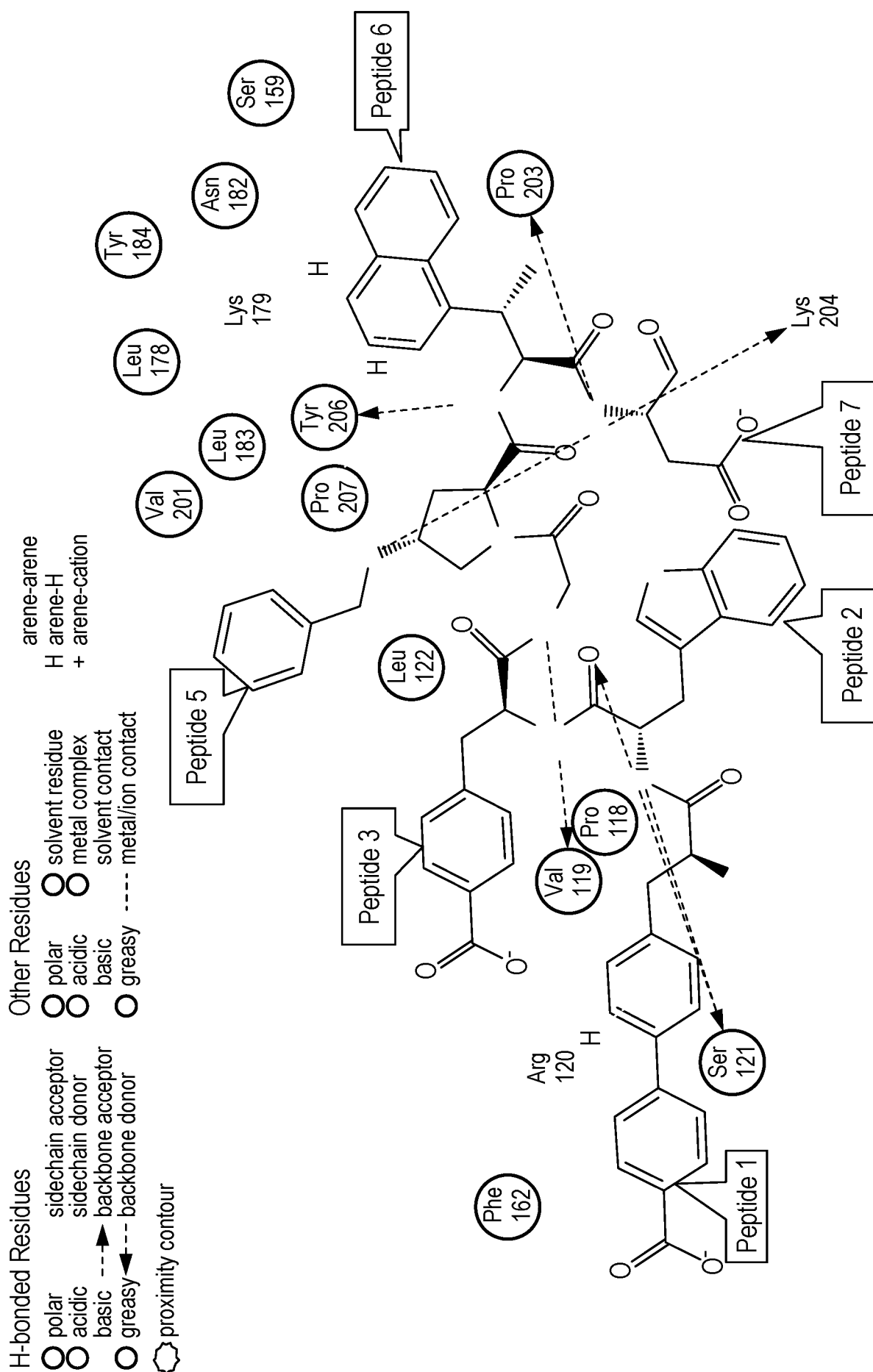


FIG. 3



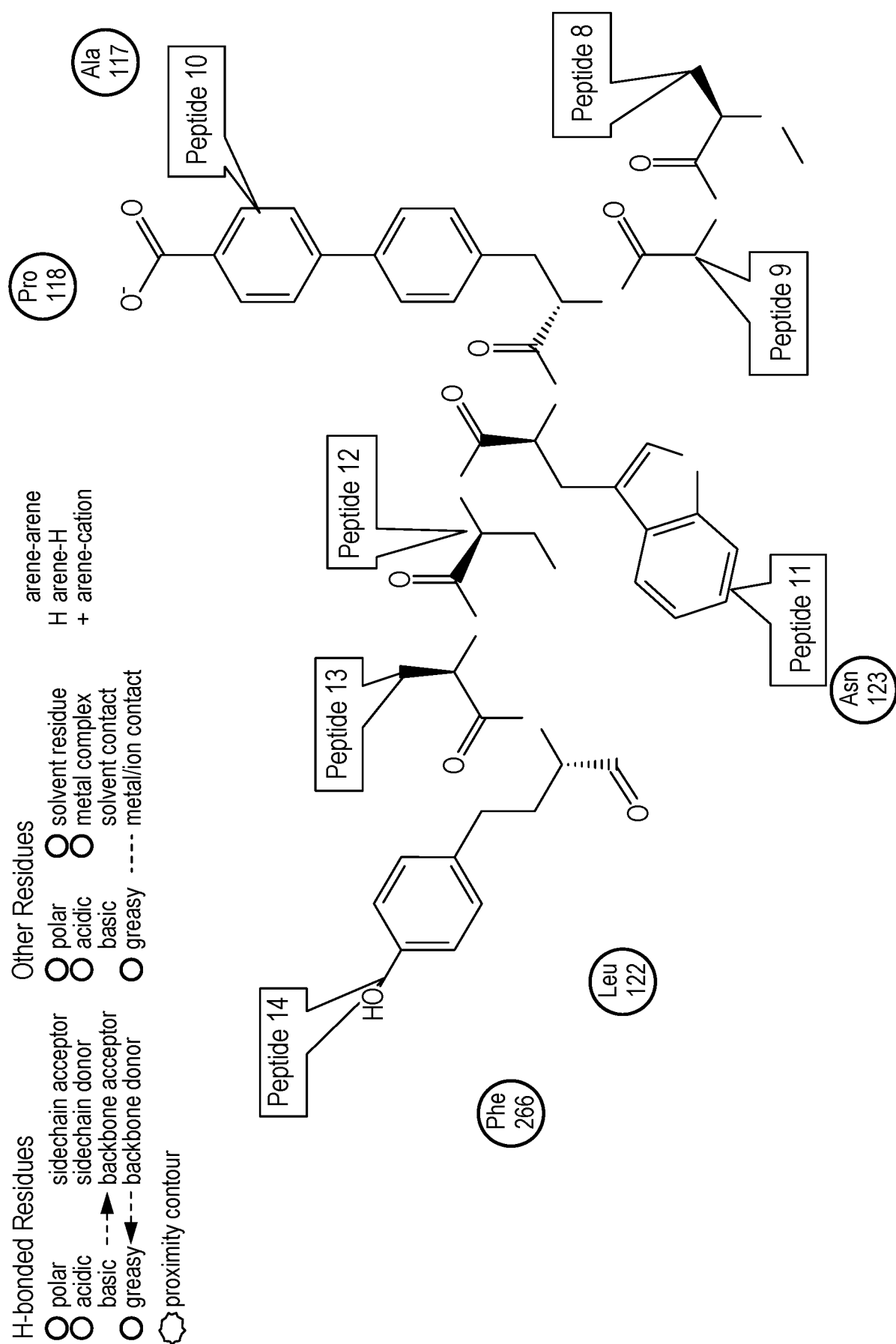


FIG. 4B

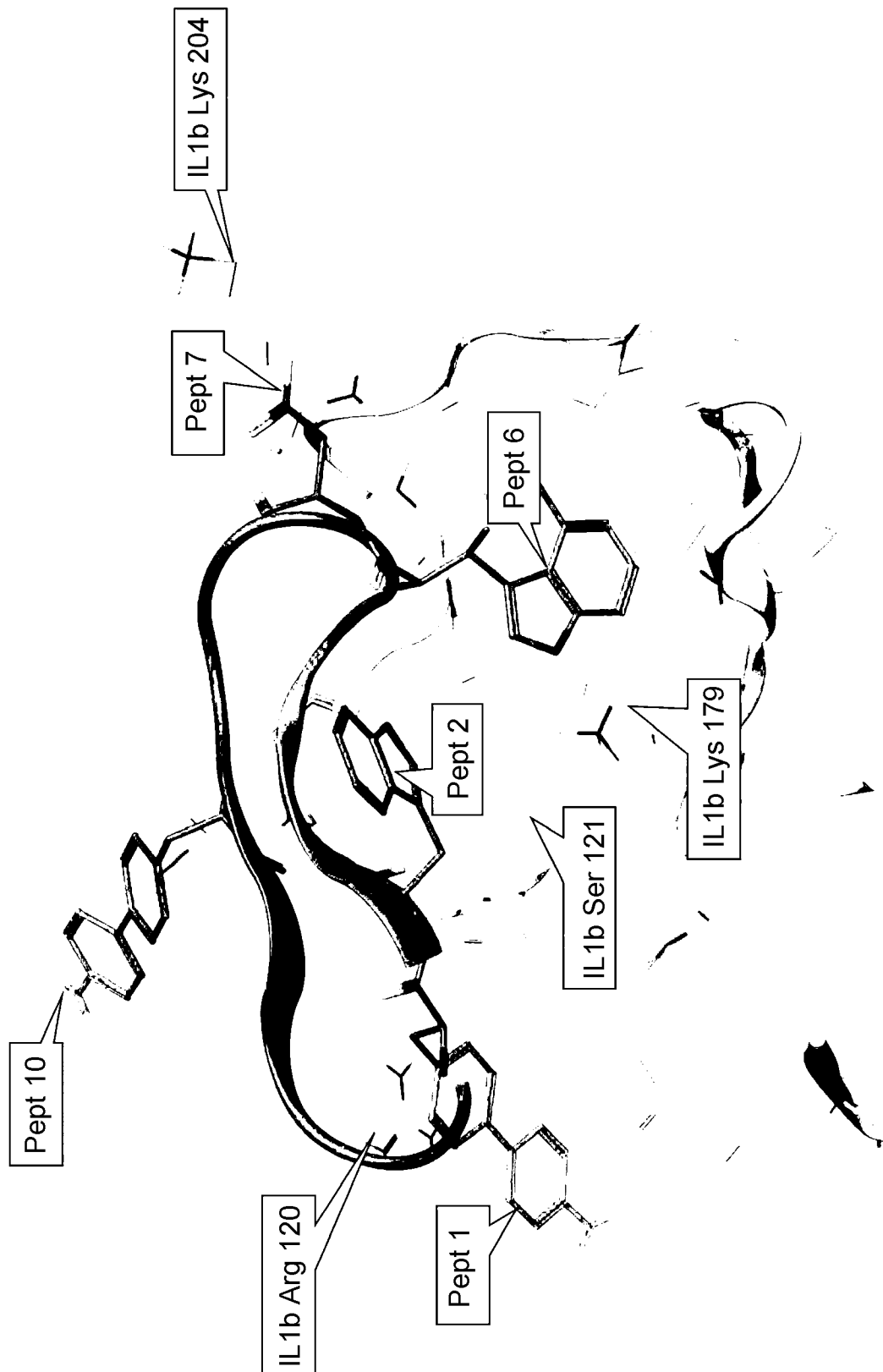
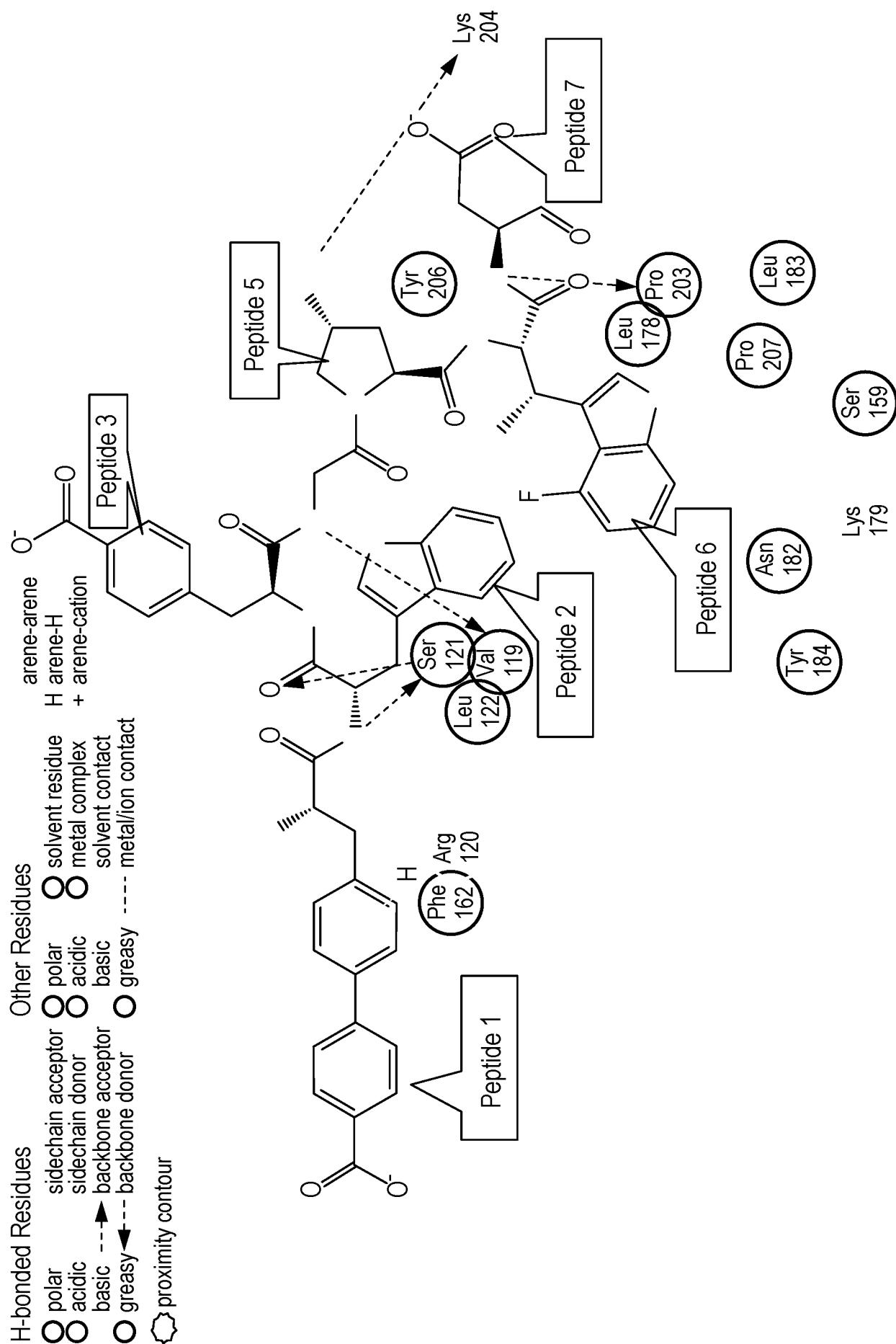


FIG. 5



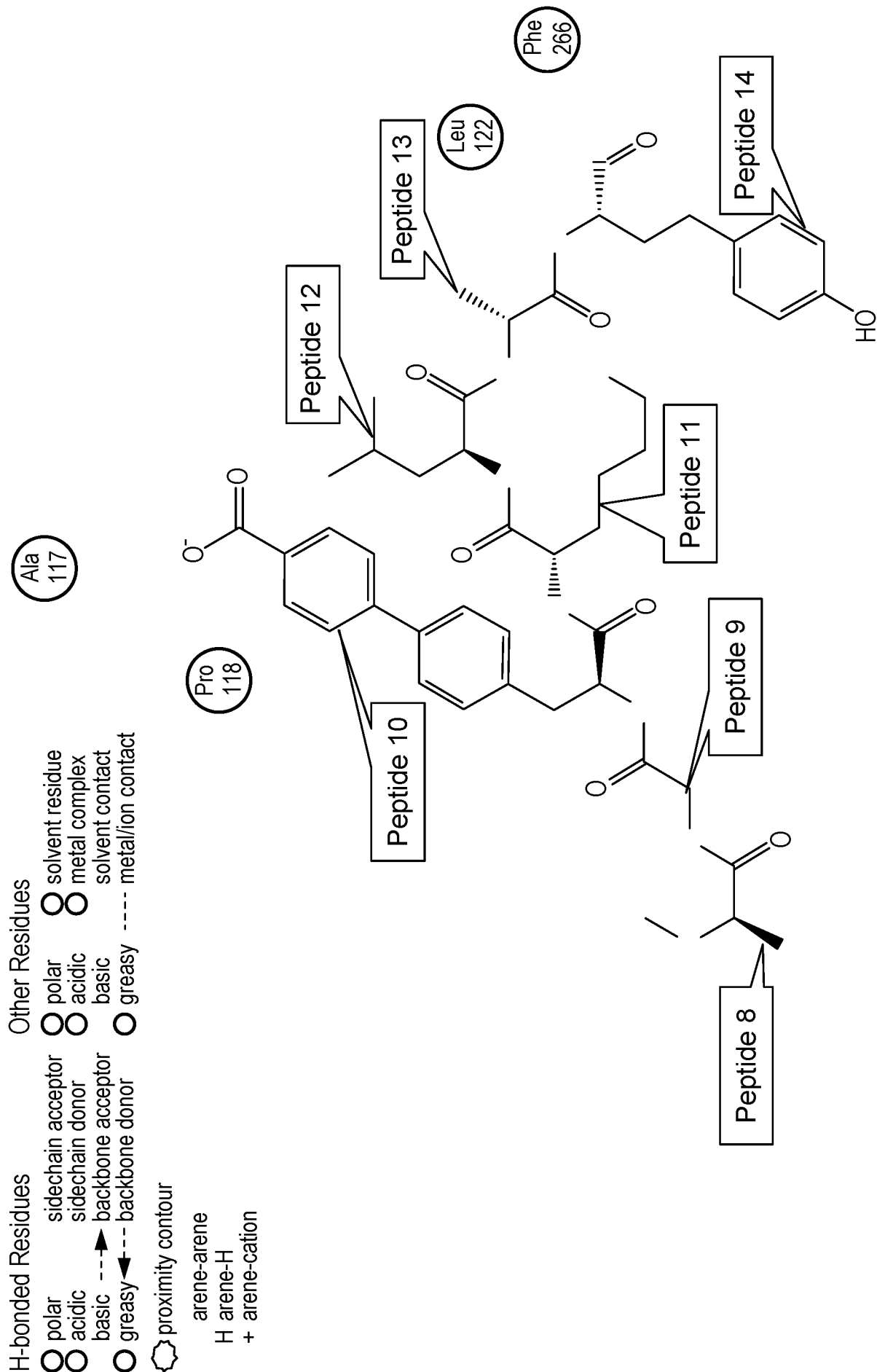


FIG. 6B

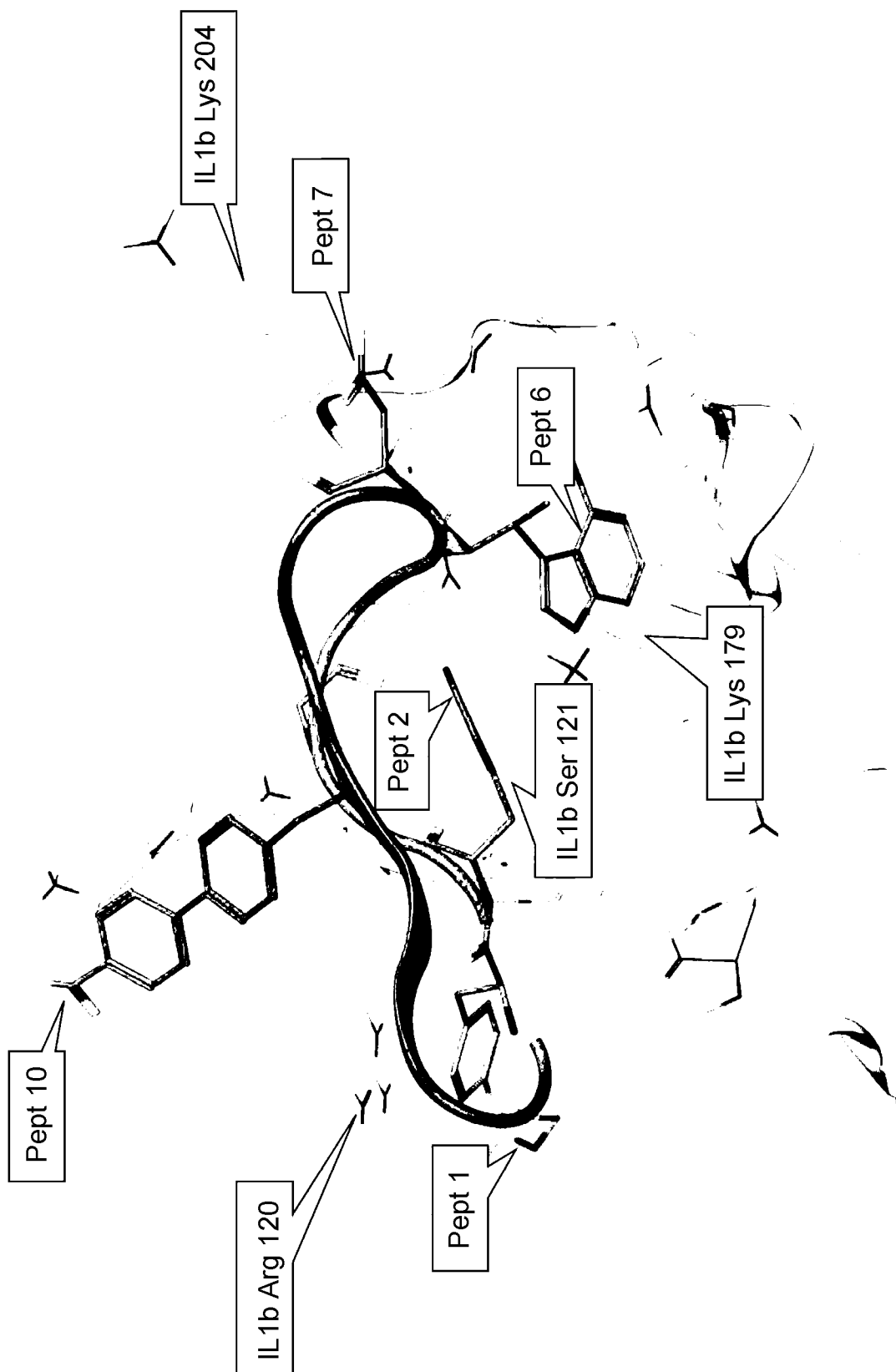
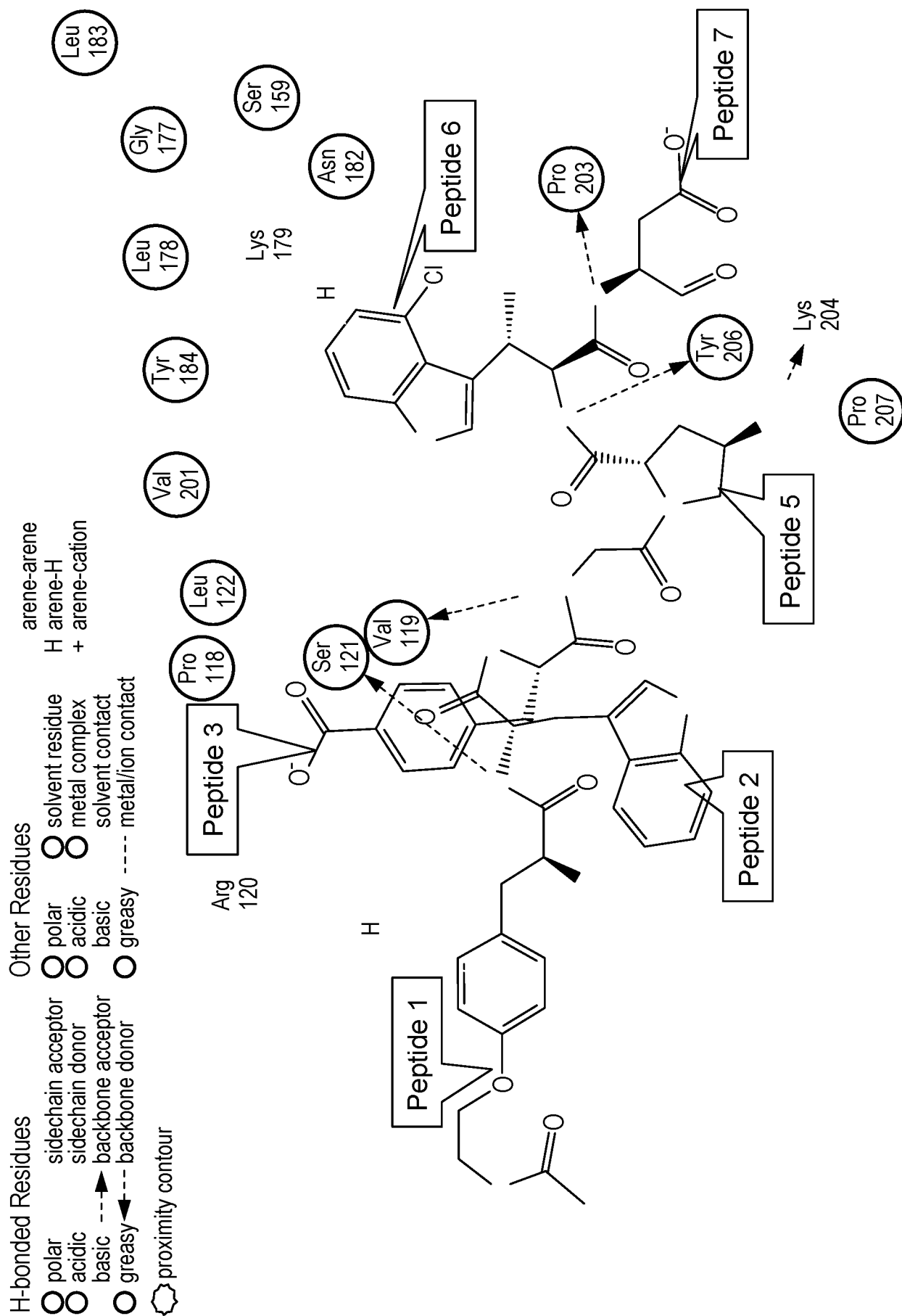


FIG. 7



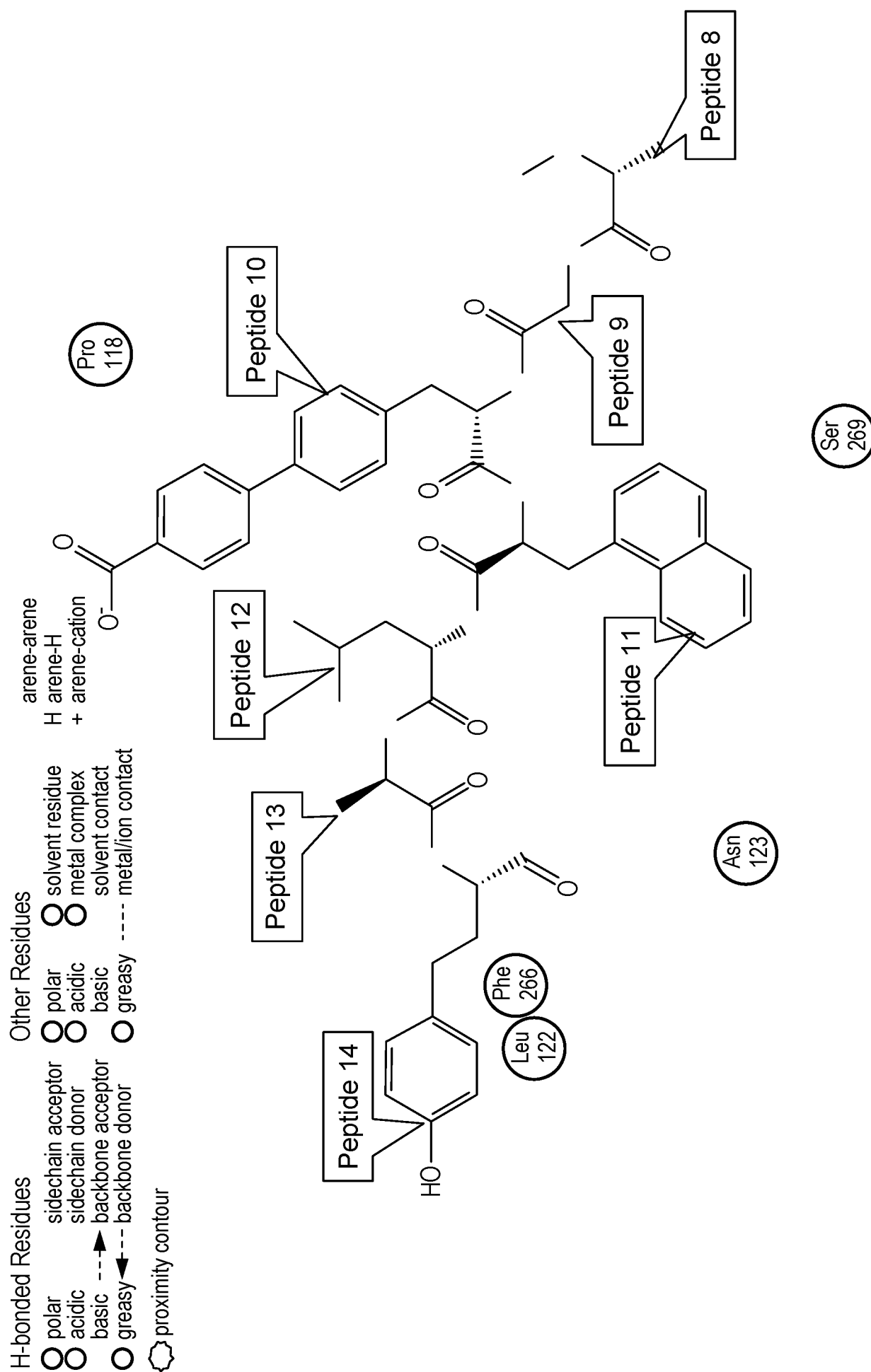


FIG. 8B

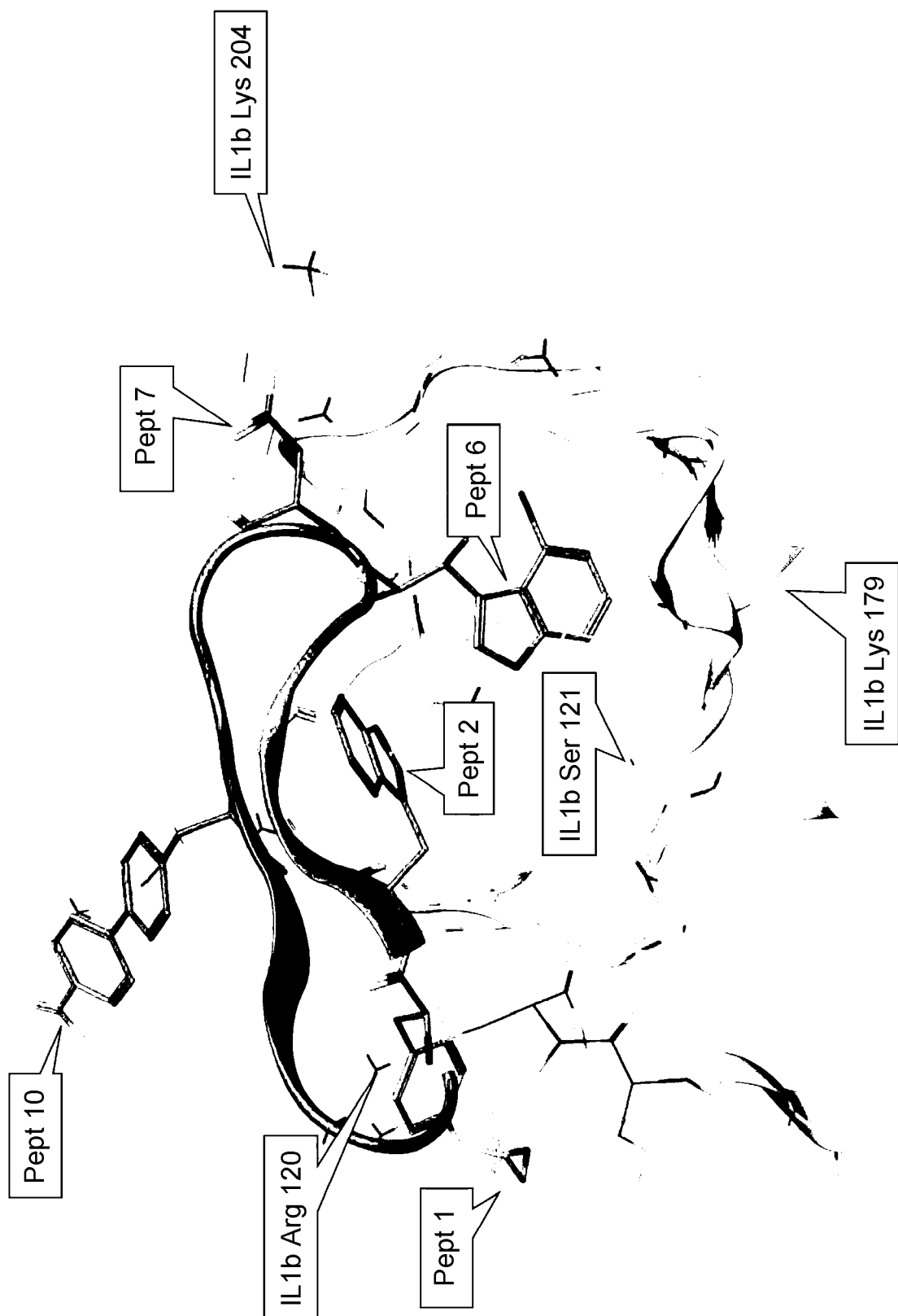


FIG. 9

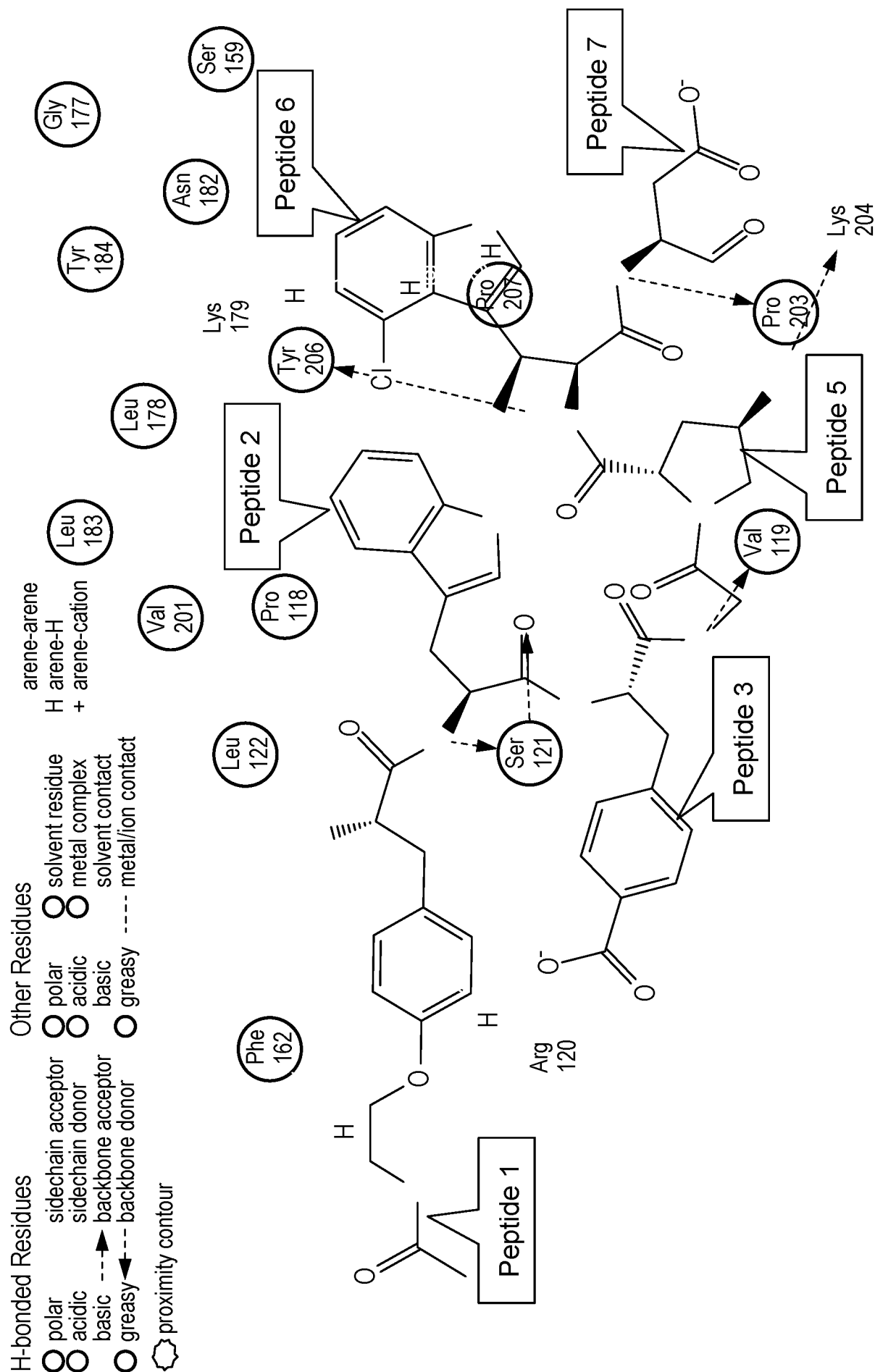
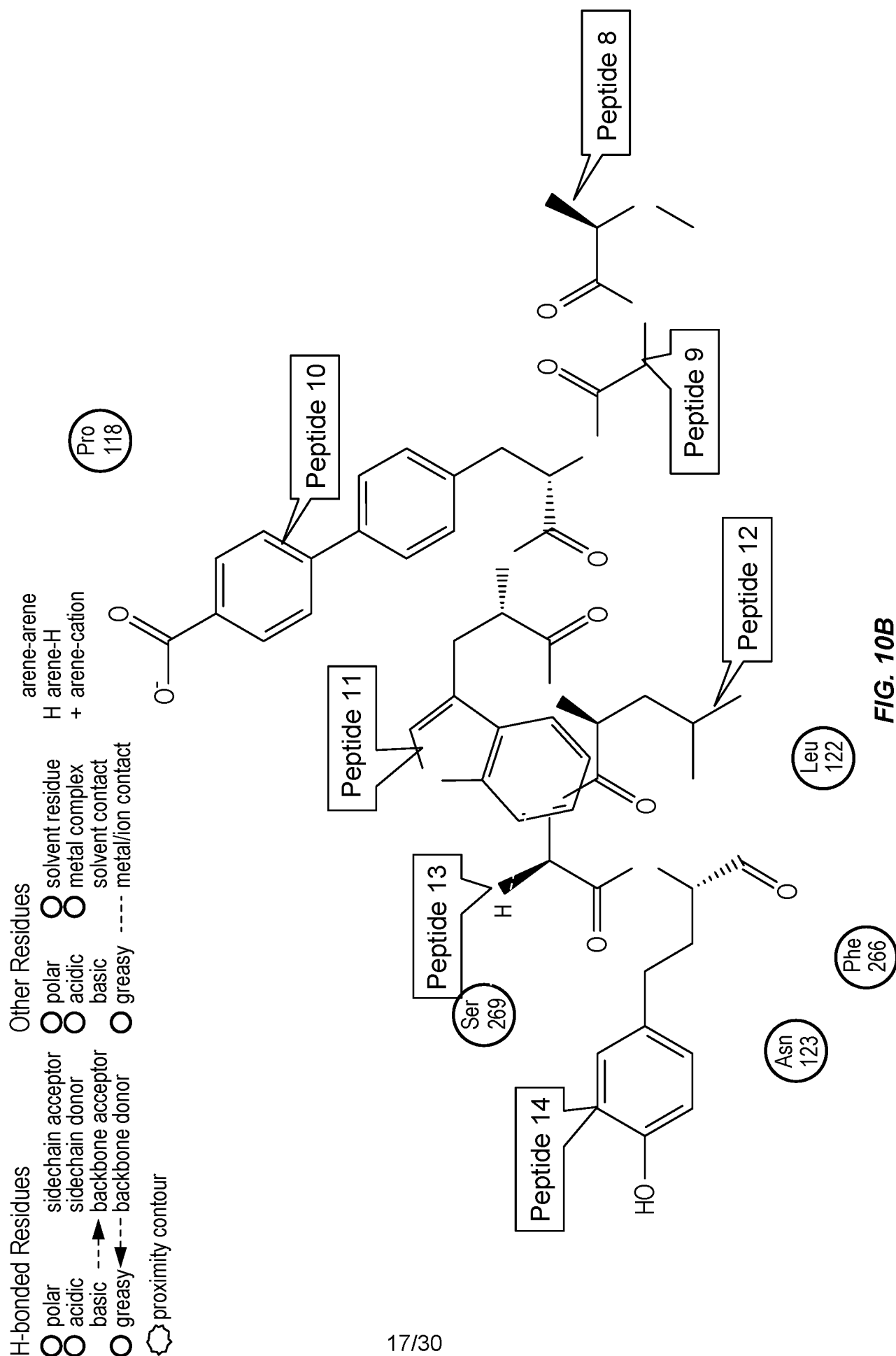


FIG. 10A



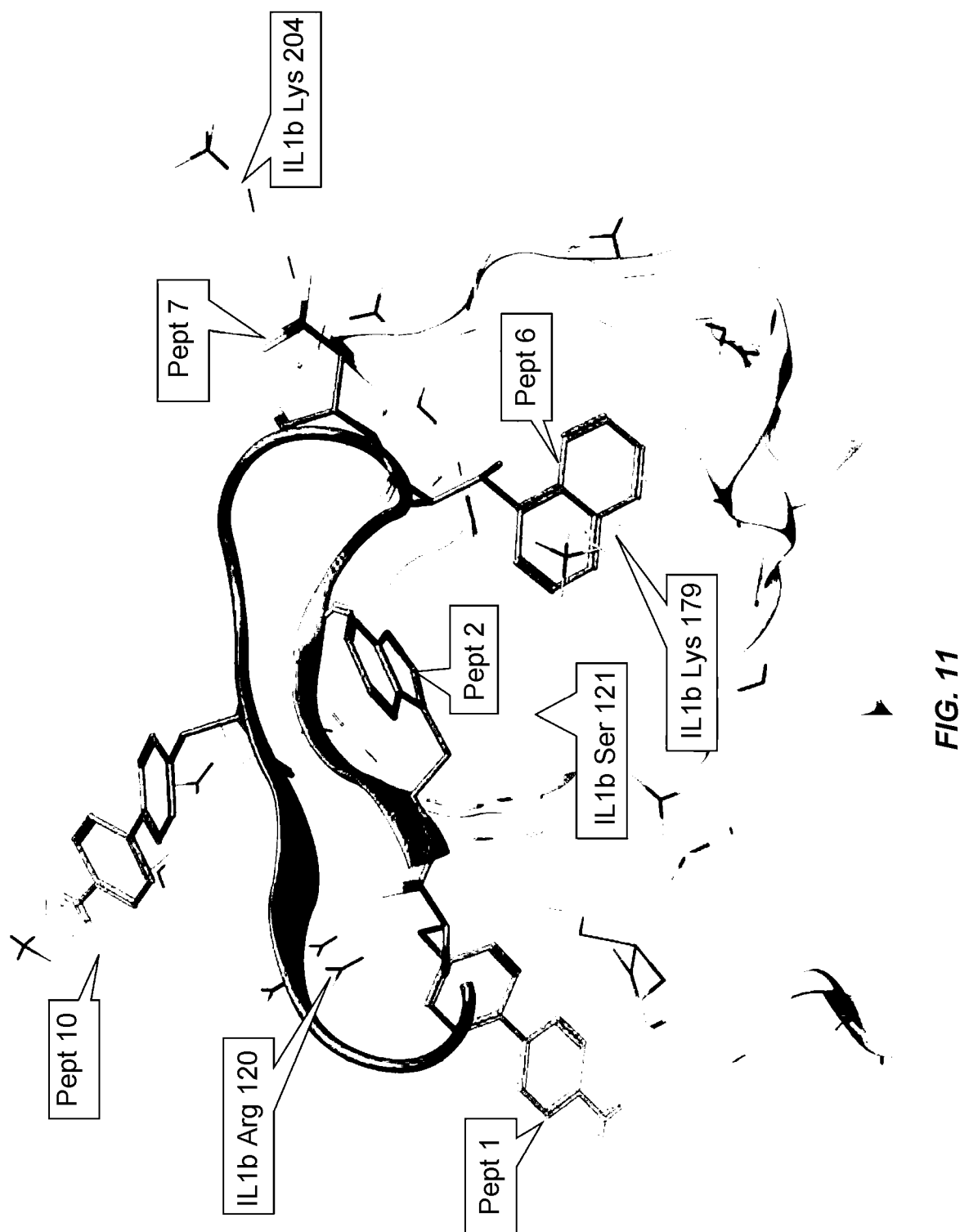


FIG. 11

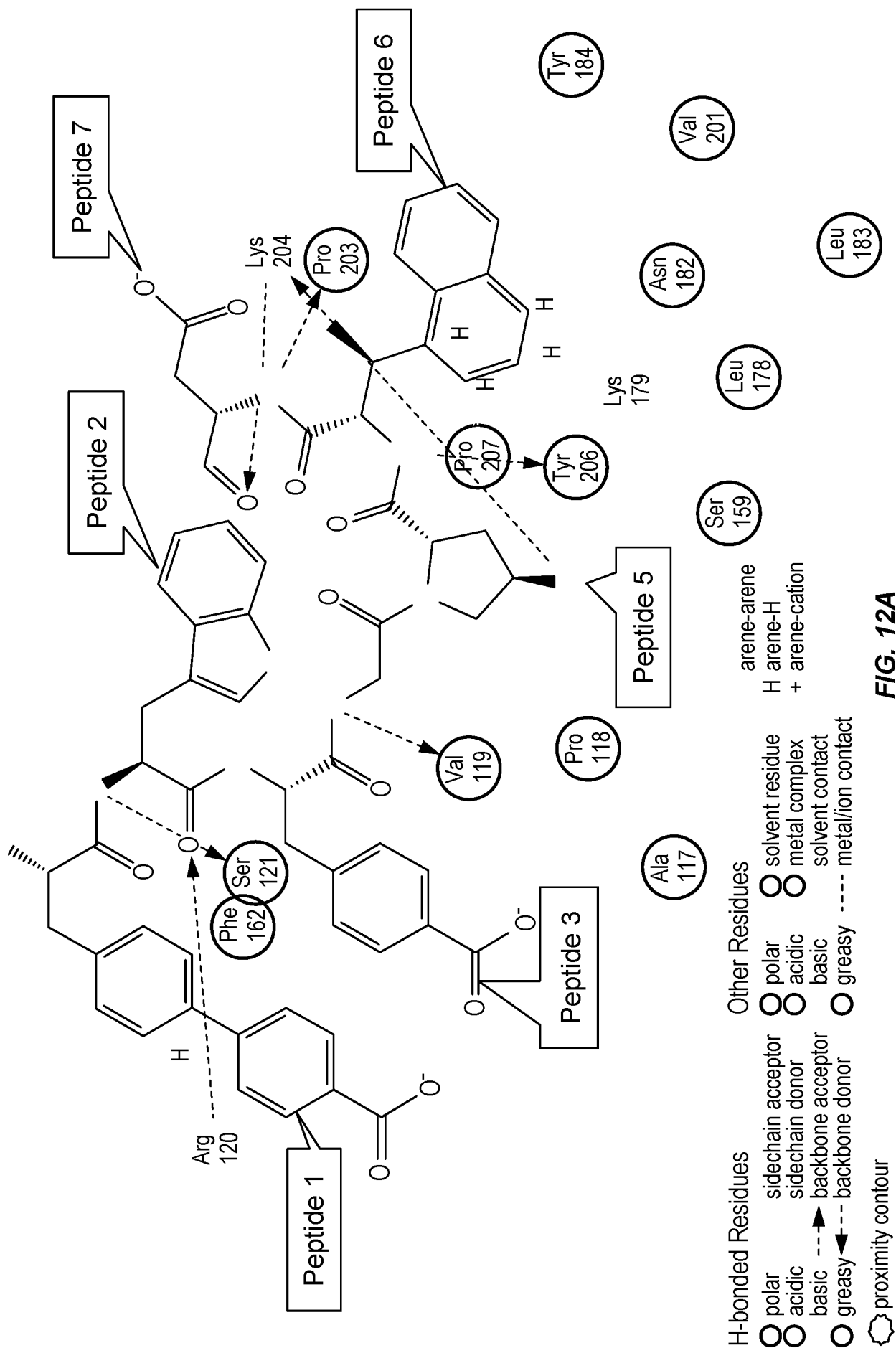


FIG. 12A

- H-bonded Residues**
- polar
 - acidic
 - basic
 - greasy
 - sidechain acceptor
 - sidechain donor
 - backbone acceptor
 - backbone donor
 - proximity contour
- Other Residues**
- polar
 - acidic
 - basic
 - greasy
 - solvent residue
 - metal complex
 - solvent contact
 - metal/ion contact
- arene-arene
H arene-H
+ arene-cation

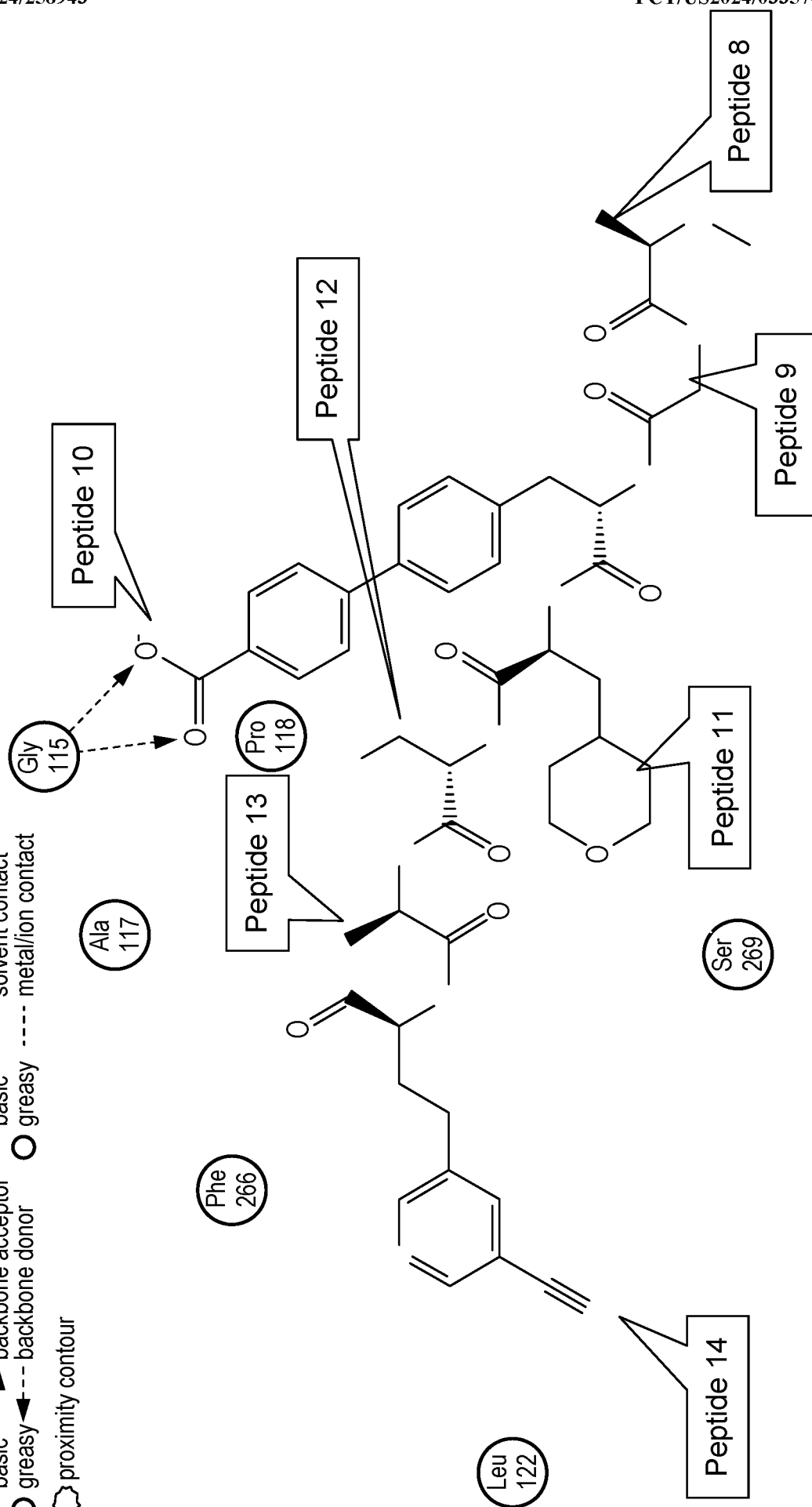


FIG. 12B

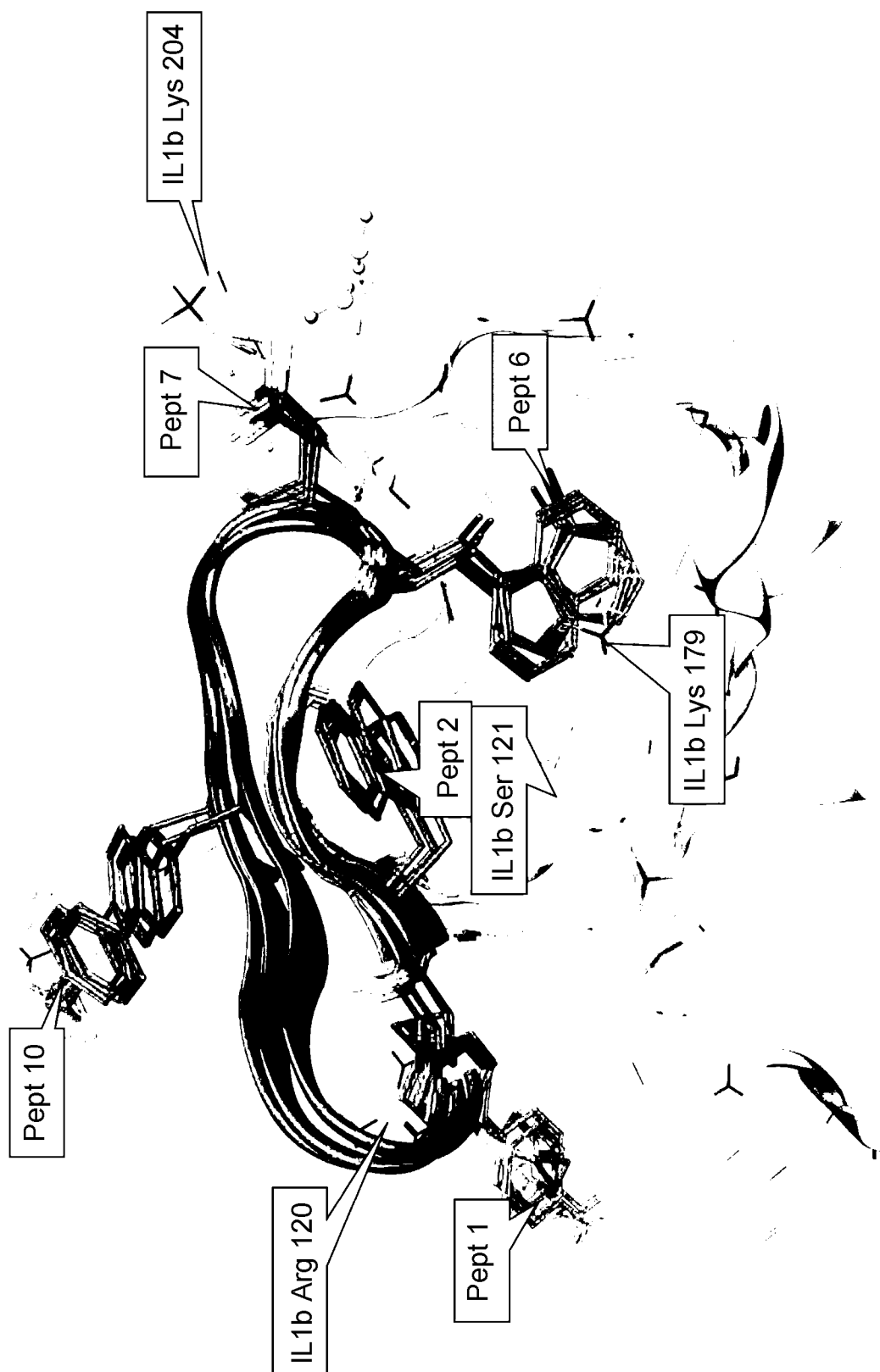


FIG. 13

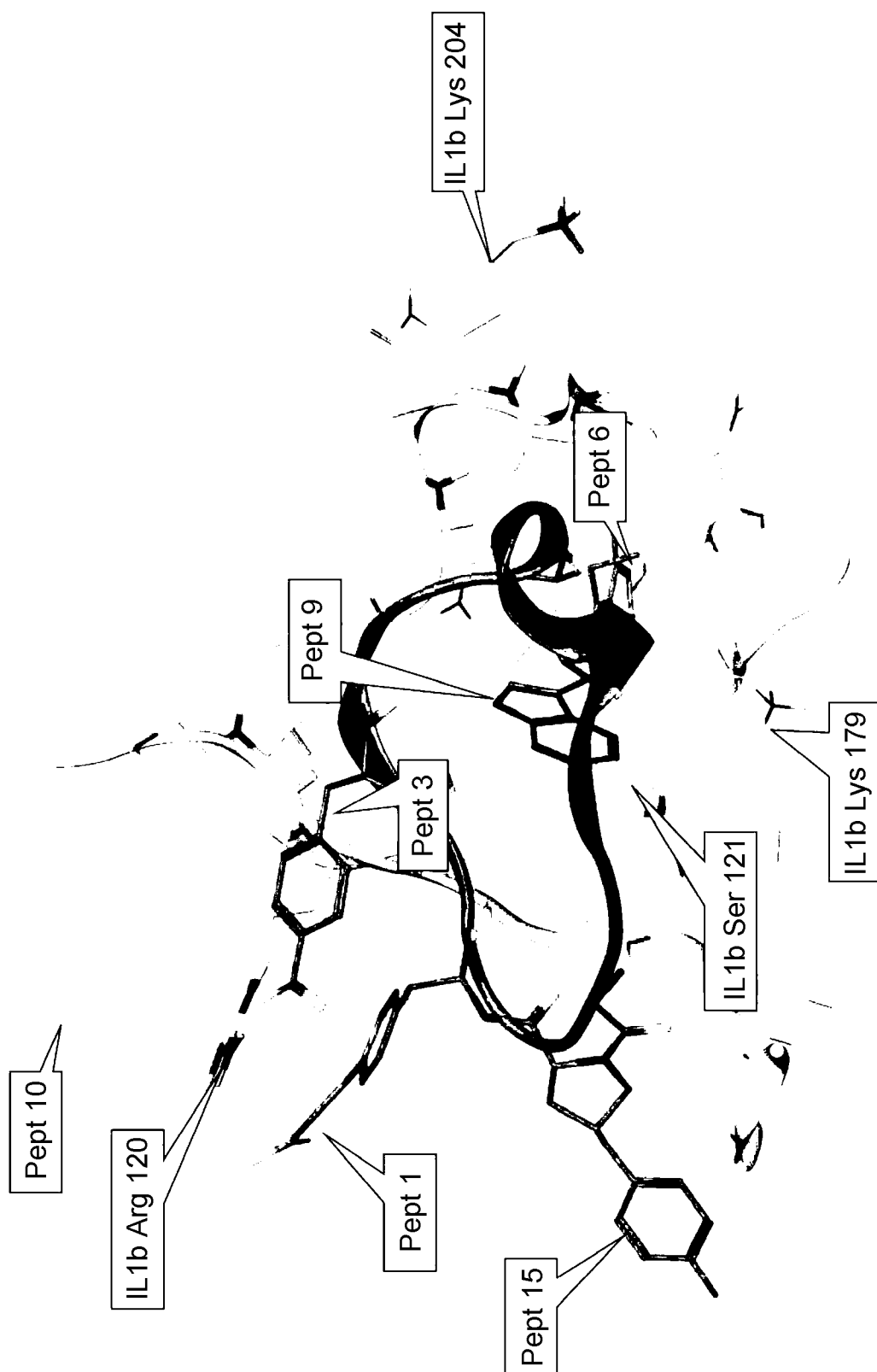
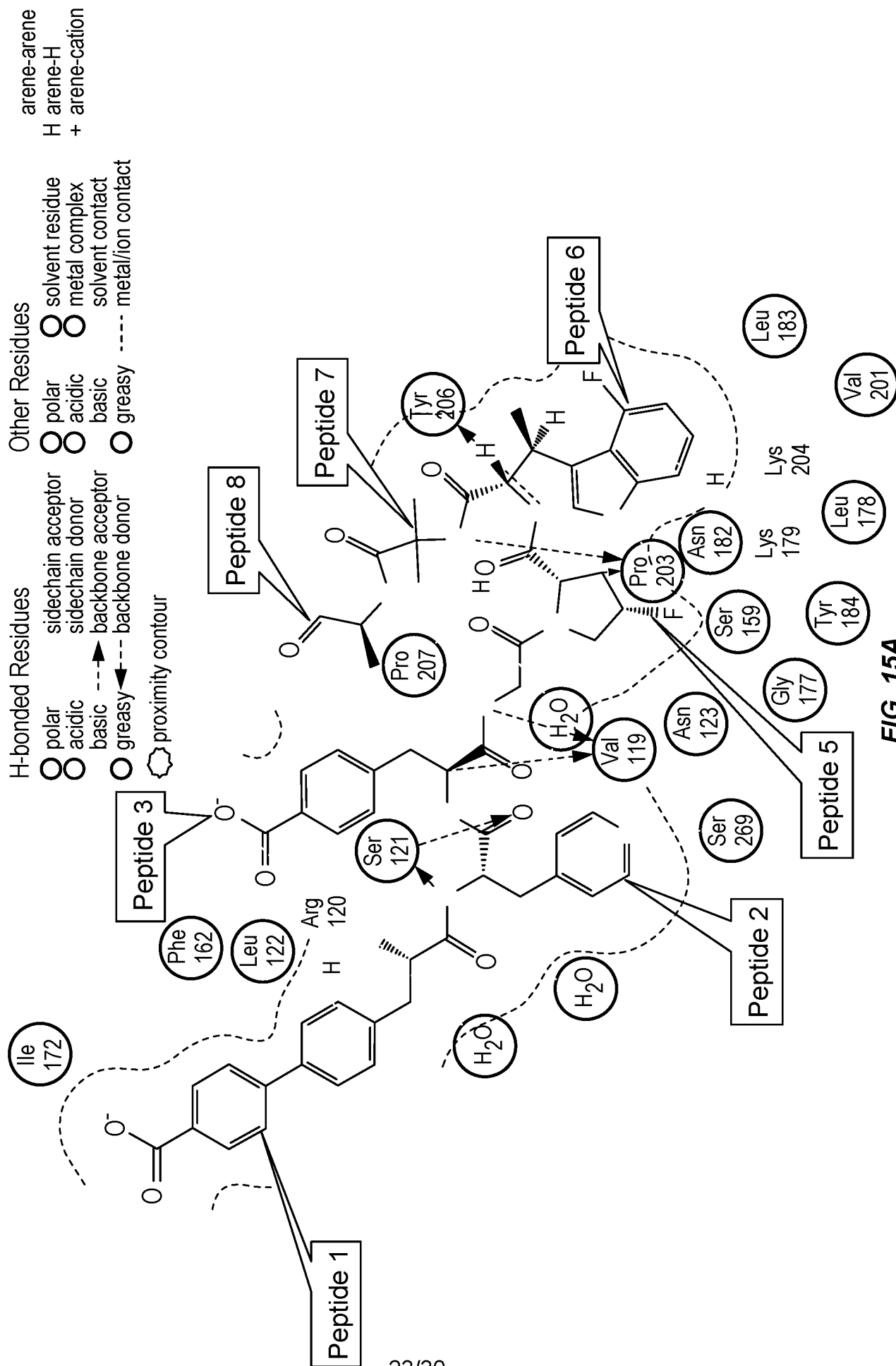


FIG. 14



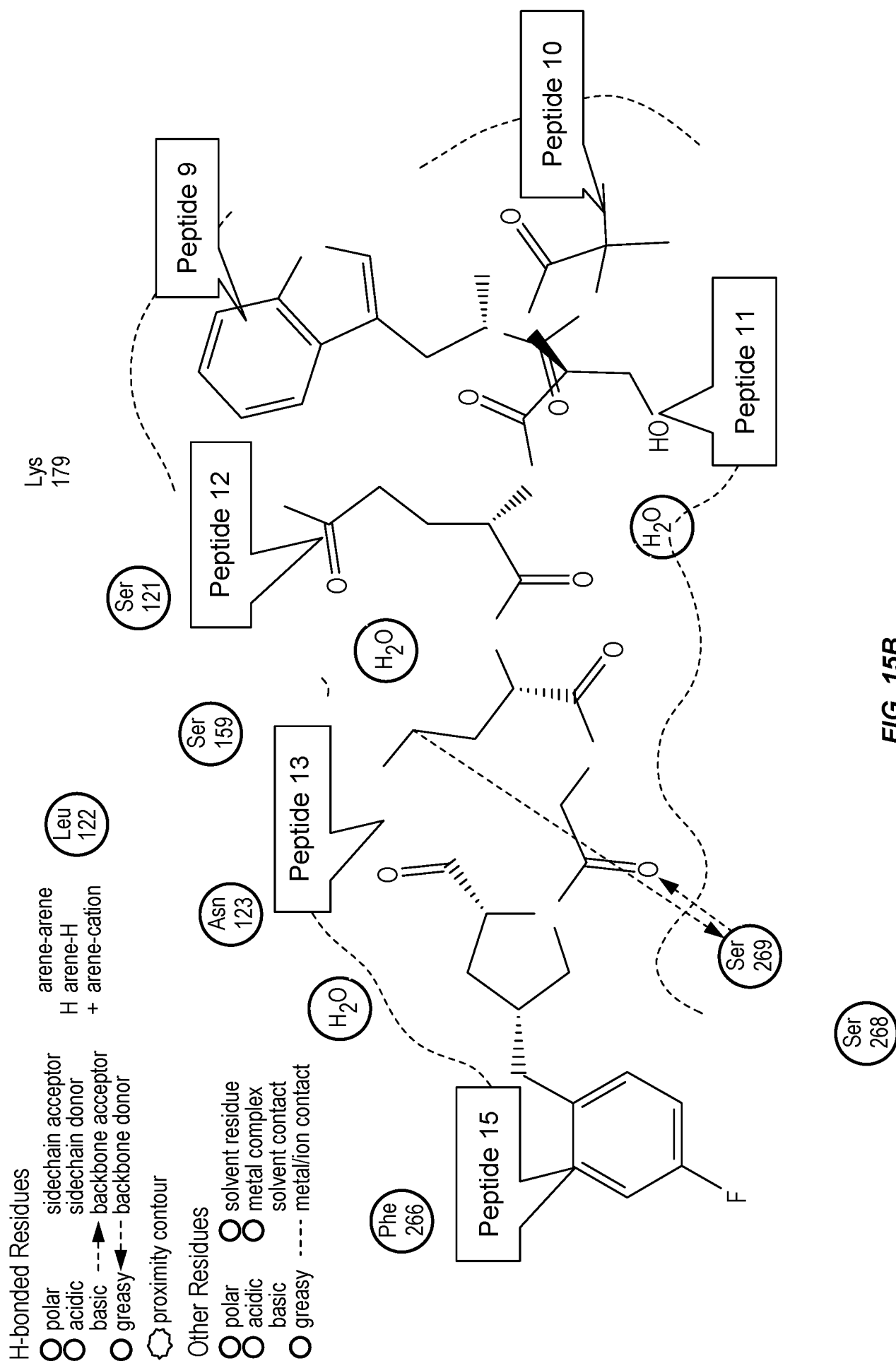


FIG. 15B

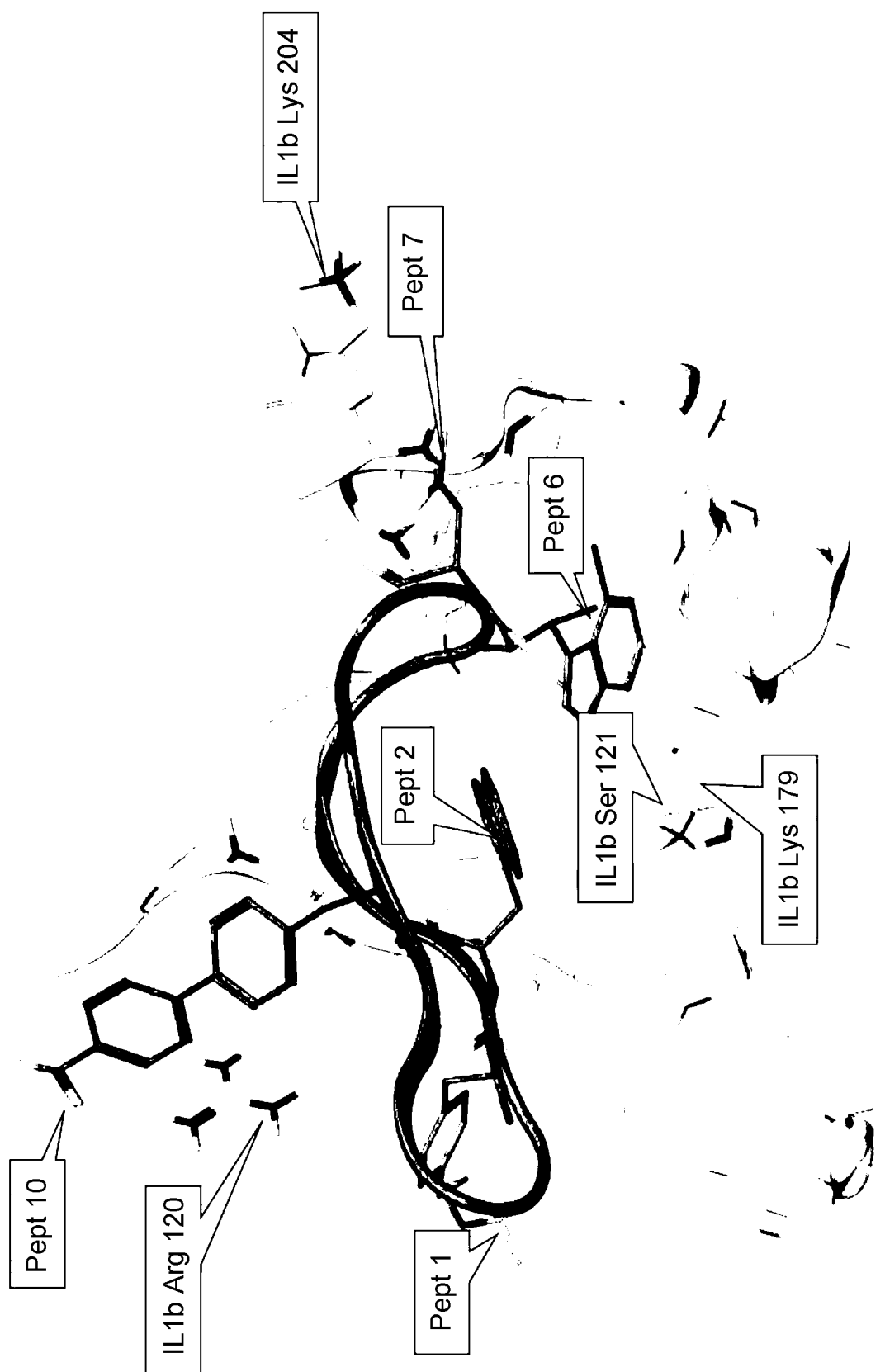


FIG. 16

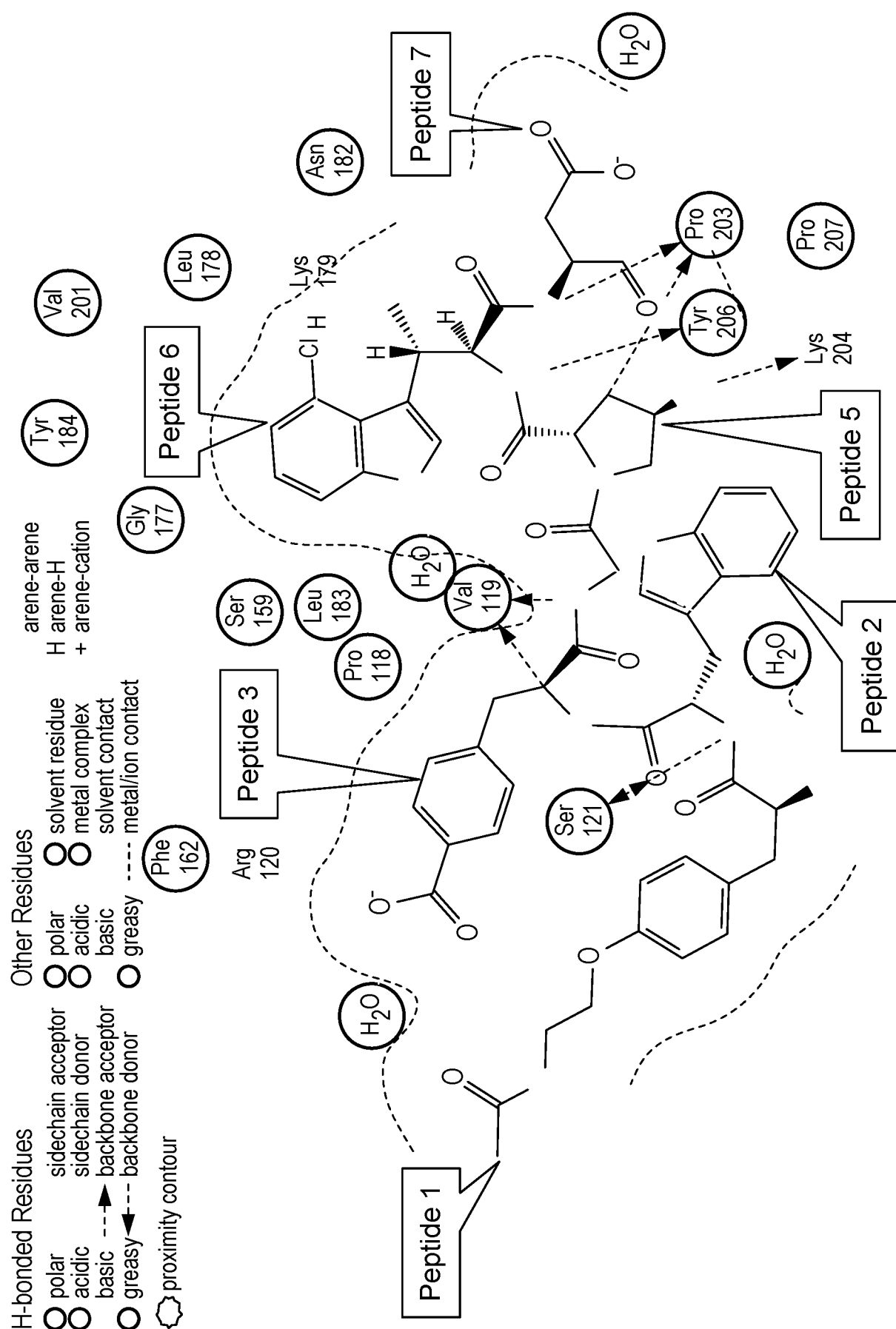


FIG. 17A

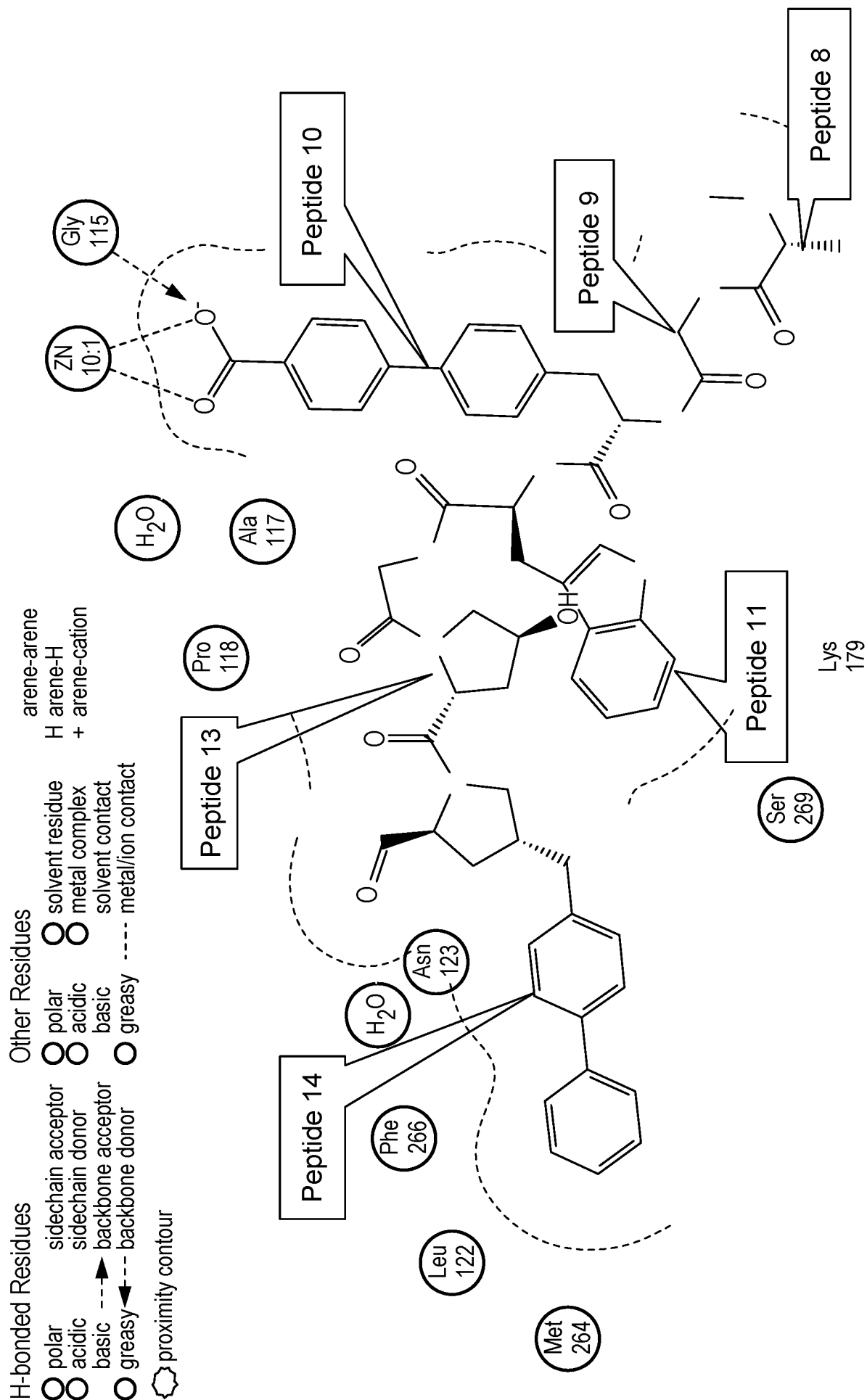


FIG. 17B

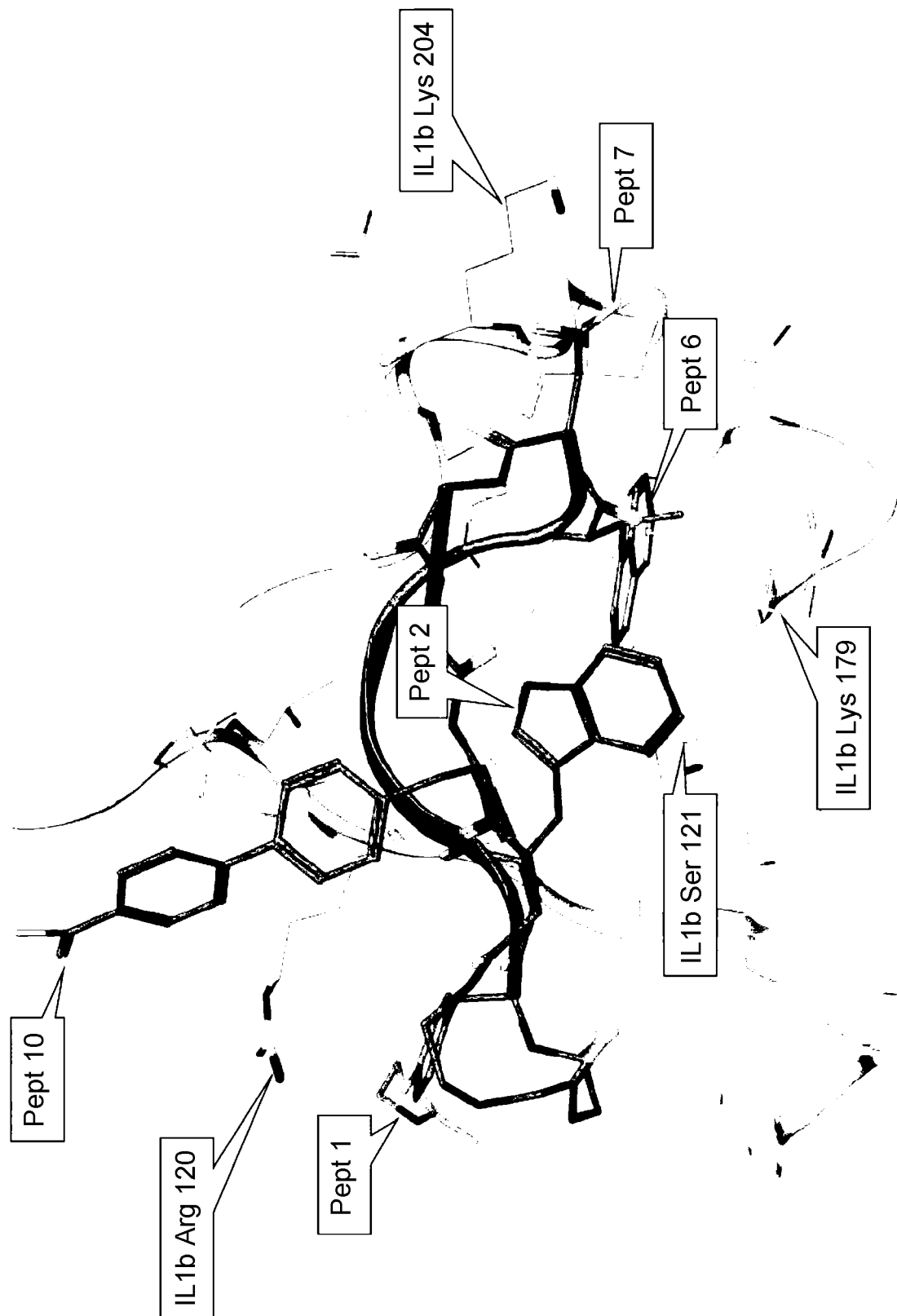


FIG. 18

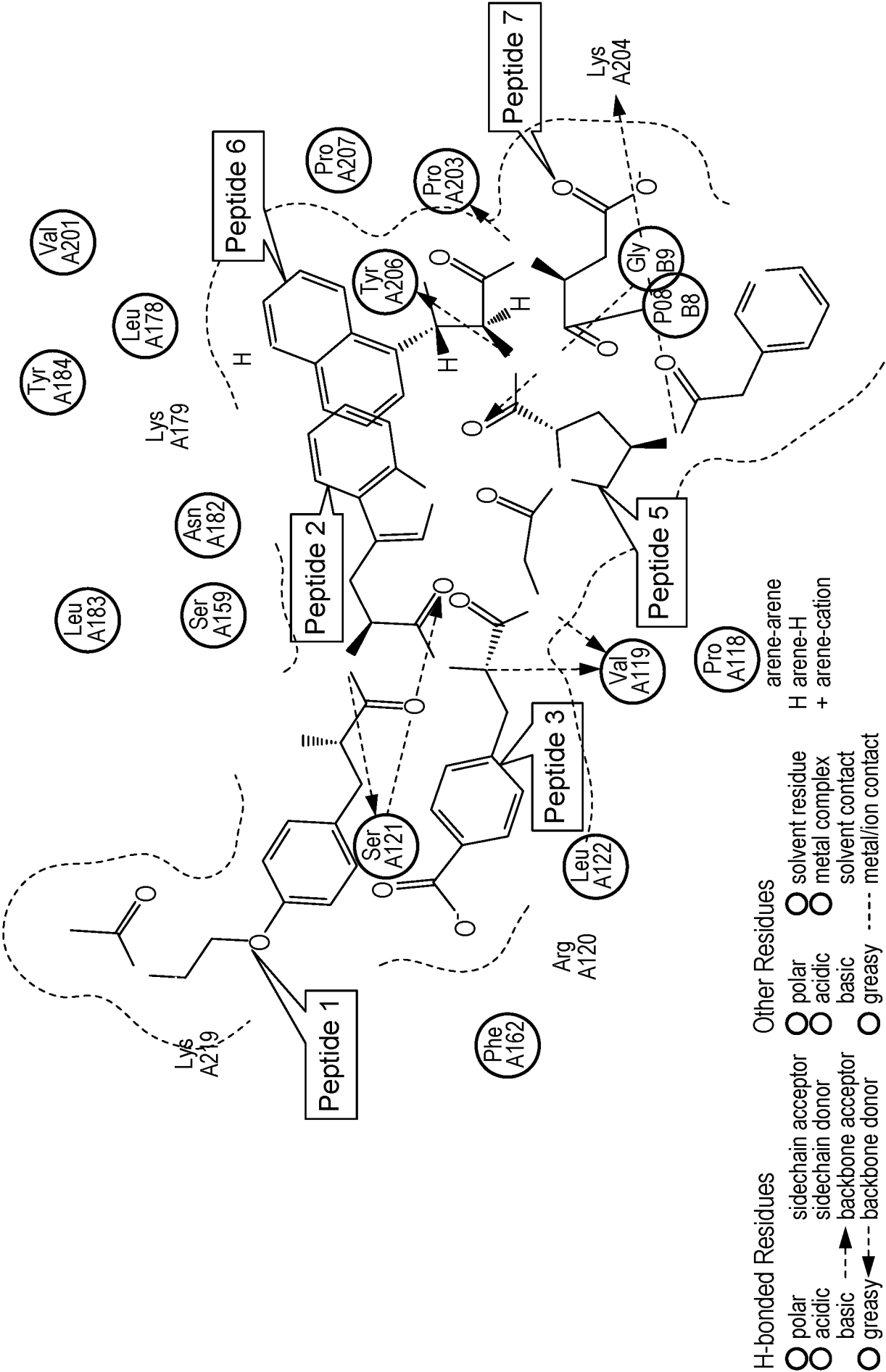
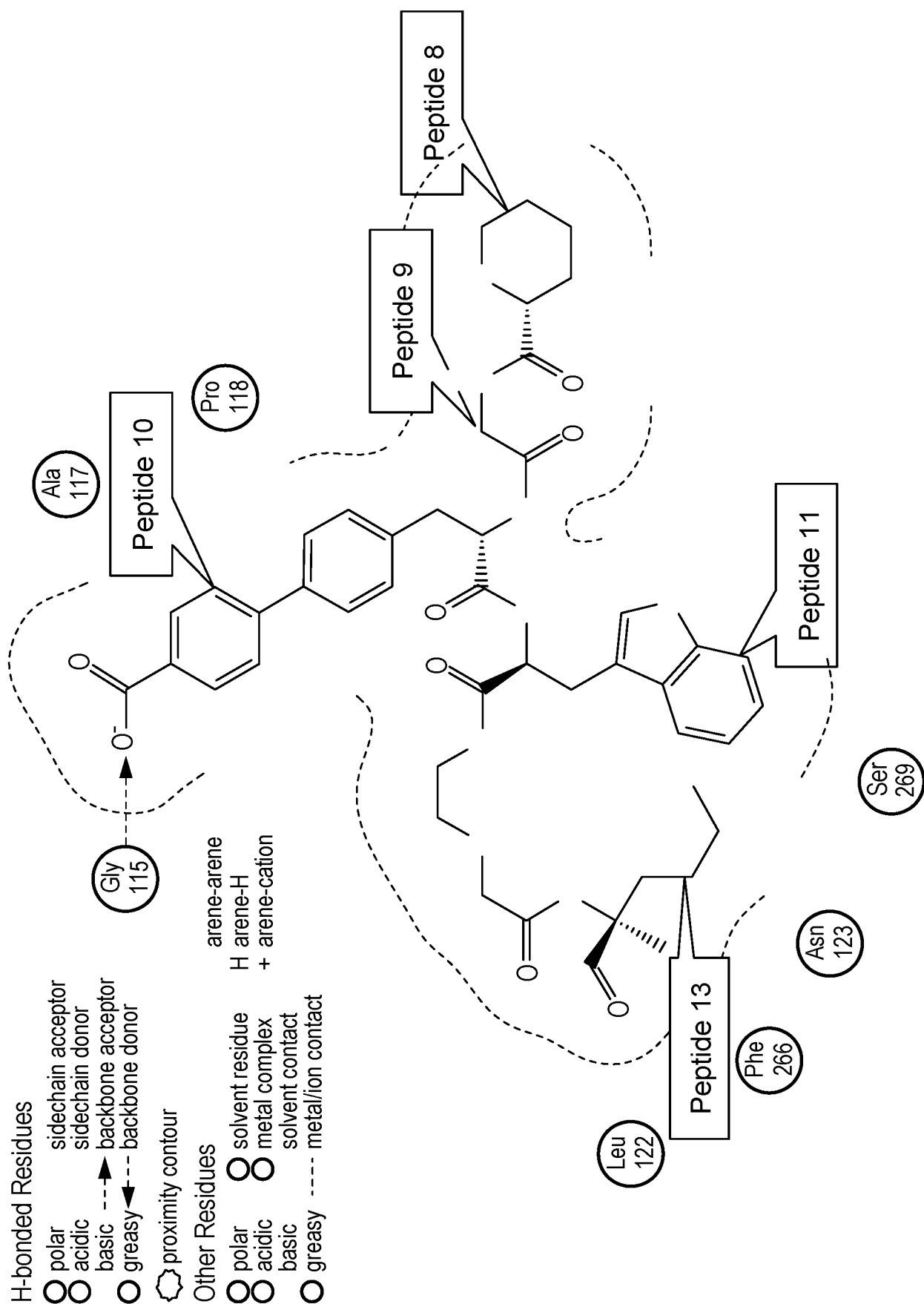


FIG. 19A



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/033570

A. CLASSIFICATION OF SUBJECT MATTERIPC: **A61K 38/12** (2024.01); **A61P 29/00** (2024.01); **A61K 38/10** (2024.01)CPC: **A61K 38/12**; **A61K 38/10**; **A61P 29/00**

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

See Search History Document

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	US 2022/0089724 A1 (AUTOLUS LIMITED) 24 March 2022 (24.03.2022) entire document	1-3, 30-32
A	US 2022/0144906 A1 (BIOASIS TECHNOLOGIES INC.) 12 May 2022 (12.05.2022) entire document	1-3, 30-32
A	US 2022/0220195 A1 (CELL MEDICA INC.) 14 July 2022 (14.07.2022) entire document	1-3, 30-32
A	US 2019/0048072 A1 (NOVARTIS AG) 14 February 2019 (14.02.2019) entire document	1-3, 30-32
A	US 2014/0004125 A1 (XOMA TECHNOLOGY LTD.) 02 January 2014 (02.01.2014) entire document	1-3, 30-32

☐ 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

"D" document cited by the applicant in the international application

"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

16 August 2024 (16.08.2024)

Date of mailing of the international search report

11 October 2024 (11.10.2024)

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

Authorized officer

MATOS
TAINA

Facsimile No. 571-273-8300

Telephone No. 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/033570

Box No. I **Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)**

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)),
☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/033570

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.: **4-29**
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:

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 1-3 and 30-32 are drawn to methods for inhibiting binding of human interleukin-1 beta (IL-1B) to a human interleukin-1 receptor type I (IL-1R1).

The first invention of Group I+ is restricted to a compound selected to be SEQ ID NO:8, and methods comprising the same. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the peptide sequences listed in instant claim 31. It is believed that claims 1-3, and 30-32 read on this first named invention and thus these claims will be searched without fee to the extent that they read on SEQ ID NO:8.

Applicant is invited to elect additional IL-1R1 binding peptides and their respective, corresponding, SEQ ID NOs to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be a compound selected to be SEQ ID NO:9, and methods comprising the same. Additional IL-1R1 binding peptides and their respective, corresponding, SEQ ID NOs 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+ formulas do not share a significant structural element responsible for inhibiting IL-1 beta binding IL-1R1, requiring the selection of alternative inhibitor compounds where "A method of inhibiting binding of human TL-10 to human IL-1R1, comprising contacting the IL-1 beta with a compound that competes for binding to the IL-1R1, wherein the compound has a structure of Formula (I): (see structure, instant claim 30) wherein: R1 is CH₃C(O)NH-CH₂CH₂-O- or C1; C1 is: (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or (ii) a 5- to 6-membered mono- or bicyclic, saturated cycloalkyl or heterocycloalkyl containing 1 to 2 heteroatoms

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

selected from the group consisting of N, O, and S; or (iii) a 5- to 6-membered mono- or bicyclic cycloalkyl; wherein C1 is unsubstituted or substituted by 1 to 3 RC1 substituents independently selected from the group consisting of halo, C1-C3 alkyl, C1-C3 fluoroalkyl, carboxy, C1-C3 alkoxy, and C2-C3 acyl; R2 is H, C1-C3 alkyl, benzyl, or phenyl-CH₂CH₂-; R3 is a 9- to 10-membered bicyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; wherein R3 is unsubstituted or substituted by 1 to 3 R3a substituents independently selected from the group consisting of halo, C1-C3 alkyl, C1-C3 fluoroalkyl, hydroxy and C1-C3 alkoxy; R4 is C1-C3 alkyl, HO₂C-(CH₂)_m-, H₂NC(O)-(CH₂)_m-, (CH₃)₂NC(O)-(CH₂)_m-, or tetrazolyl-(CH₂)_m-; R5 is amino, H₂N(CH₂)_n-, H₂NC(O)-(CH₂)_n-, CH₃C(O)NH-, CH₃C(O)NH(CH₂)_n-, C5, or C5-CH₂-, C5 is: (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; (ii) a 9- to 10-membered bicyclic aryl or heteroaryl, wherein said bicyclic heteroaryl contains 1 to 3 heteroatoms selected from the group consisting of N, O, and S; (iii) a 5- to 6-membered monocyclic or 9- to 10-membered heterocycloalkyl, wherein said heterocycloalkyl is saturated or partially unsaturated, and contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; (iv) a 5- to 6-membered monocyclic cycloalkyl; or (v) 2,3-dihydroindolyl; wherein C5 is unsubstituted or substituted by 1 to 3 RC5 substituents independently selected from the group consisting of halo, amino, hydroxy, C1-C3 alkyl, C1-C3 fluoroalkyl, C1-C3 alkoxy, H₂N-(CH₂)_k-, H₂NC(O)-(CH₂)_k-, H₂C=CH-CH₂O-, and phenyl; R6 is H, C1-C5 alkyl, H₂N(CH₂)_p-, HOCH₂-, (CH₃)₂NCH₂-, H₃CO-(CH₂)_q-, or C6-CH₂-; C6 is 5- or 6-membered monocyclic, saturated heterocycloalkyl containing 1 to 2 heteroatoms selected from the group consisting of N, O, and S; and wherein C6 is unsubstituted or substituted by 1 to 3 RC6 substituents independently selected from the group consisting of halo, C1-C3 alkyl, C1-C3 fluoroalkyl, hydroxy and C1-C3 alkoxy; R7 is H or C1-C3 alkyl; R8a is H, C1-C5 alkyl, HOCH₂-, H₂N(CH₂)_r-, (CH₃)₃N(CH₂)_r-, or CH₃C(O)NH(CH₂)_r-; R8b is H or C1-C3 alkyl; R9a is H or C1-C3 alkyl; R9b is H, C1-C5 alkyl, C9-CH₂-, or C9-CH₂CH₂-; C9 is: (i) a 5- to 6-membered monocyclic aryl or heteroaryl, wherein said heteroaryl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; or (ii) a 5- to 6-membered monocyclic, saturated cycloalkyl or heterocycloalkyl, wherein the heterocycloalkyl contains 1 to 2 heteroatoms selected from the group consisting of N, O, and S; wherein C9 is unsubstituted or substituted by 1 to 3 RC9 substituents independently selected from the group consisting of halo, amino, hydroxy, cyano, C1-C3 alkyl, C1-C3 fluoroalkyl, C1-C3 alkoxy, H₂N-(CH₂)_k-, H₂NC(O)-(CH₂)_k-, H₂NCH₂CH₂O-, CH₃C(O)NH-CH₂CH₂O-, and morpholinyl-CH₂CH₂O-; R10 is H, halo, or C1-C3 alkyl; R11 is H, halo, or C1-C3 alkyl; each occurrence of subscript k is independently 1 or 2; subscript m is 1 or 2; subscript n is 1, 2, 3, or 4; subscript p is 1, 2, 3, or 4; subscript q is 1 or 2; subscript r is 1, 2, 3, or 4; X1, X2, and X3 are independently C(H) or N; and A1 and A2 are independently selected from the group consisting of HO₂C-, H₂NC(O)-, CH₃C(O)N(H)-, H₂NS(O)₂-, CH₃S(O)₂N(H)-, tetrazolyl, and 5-oxo oxadiazolyl; or a pharmaceutically acceptable salt thereof.”

Additionally, even if Groups I+ were considered to share the technical features of discloses a method of inhibiting binding of human interleukin-1 beta (IL-1B) to a human interleukin-1 receptor type 1 (IL-1R1), comprising contacting the IL-1B with a compound or pharmaceutically acceptable salt thereof that binds to the IL-1B at a binding pocket. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2014/0004125 A1 to Xoma Technology Ltd. discloses a method of inhibiting binding of human interleukin-1 beta (IL-1B) to a human interleukin-1 receptor type 1 (IL-1R1) (the present invention neutralize the biological activity of IL-1 beta connected with the signaling function of IL-1 receptor type I (IL-1RI) bound by the IL-1 beta, Para. [0048]; IL-1 beta /IL-1RI binding assays, the permitting or blocking of IL-1 beta binding to IL-1 receptor type I may be determined by comparing the binding of IL-1 beta to IL-1RI in the presence or absence of IL-1 beta antibodies or IL-1 beta binding fragments thereof. Blocking is identified in the assay readout as a designated reduction of IL-1 beta binding to IL-1 receptor type I in the presence of anti-IL-1 beta antibodies, Para. [0097]), comprising contacting the IL-1B with a compound or pharmaceutically acceptable salt thereof that binds to the IL-1B at a binding pocket (the present invention neutralize the biological activity of IL-1 beta connected with the signaling function of IL-1 receptor type I (IL-1RI) bound by the IL-1 beta, Para. [0048]; IL-1 beta /IL-1RI binding assays, the permitting or blocking of IL-1 beta binding to IL-1 receptor type I may be determined by comparing the binding of IL-1 beta to IL-1RI in the presence or absence of IL-1 beta antibodies or IL-1 beta binding fragments thereof. Blocking is identified in the assay readout as a designated reduction of IL-1 beta binding to IL-1 receptor type I in the presence of anti-IL-1 beta antibodies, Para. [0097]).

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/033570

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.

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.: **1-3, 30-32**

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.