

**RADIOPHARMACEUTICAL COMPOSITIONS TARGETING CARBONIC ANHYDRASE IX
AND USES THEREOF**

CROSS-REFERENCE

[0001] This application claims the benefit of U. S. Provisional Application Serial No. 63/499,666 filed May 2, 2023 which is hereby incorporated by reference in its entirety.

BACKGROUND

[0002] The expression of distinct proteins on the surface of tumor cells offers the opportunity to diagnose and characterize disease by probing the phenotypic identity and biochemical composition and activity of the tumor. Radioactive molecules that selectively bind to specific tumor cell surface proteins allow the use of noninvasive imaging techniques, such as molecular imaging or nuclear medicine, for detecting the presence and quantity of tumor associated proteins, thereby providing vital information related to the diagnosis and extent of disease, prognosis, and therapeutic management options. In addition, as radiopharmaceuticals can be prepared that are not only capable of imaging disease but also delivering a therapeutic radionuclide to the diseased tissue, therapy, in particular cancer therapy, can be realized. The selective expression of CA-IX on tumors in response to hypoxia makes it an attractive target to exploit for noninvasive imaging as well as targeted radiotherapy.

[0003] In order to grow beyond more than a few millimeters in diameter, tumor micrometastasis need to obtain a supply of oxygen to sustain the high metabolic rate characteristic of rapid growth, and do so by inducing the formation of new blood vessels. The distance that tumor cells reside from blood vessels is inversely proportional to the oxygen pressure of the tumor. Even when angiogenesis occurs and a blood supply is established, the less vascular interior region of the growing tumor mass remains hypoxic and eventually undergoes necrosis.

[0004] Hypoxia is associated with a poor response to radiation therapy, and leads to tumor resistance. Since oxygen is necessary for the cytotoxic actions of free radicals generated by radiation, higher, often incompatible, levels of radiation are required to promote damage to the tumor. Therefore, there is a need for non-invasive techniques to stratify patients based on cancer hypoxia who are not expected to respond to radiation therapy because of low oxygen, and who may be candidates for alternative hypoxia-activated chemotherapies that are becoming available. As hypoxia constitutes a major difference between the tumor and normal tissues, it can be exploited for the development of tumor specific probes.

[0005] Hypoxia is a potent stimulus for the expression of specific genes, several which function to trigger vasculogenesis and therefore supply oxygen to the tumor, increase metabolism to increase the oxygen extraction factor, and promote a favorable environment for tumor growth. The activation of hypoxia inducible genes is in part mediated by a transcription factor, HIF-1 α . Under normoxic conditions, HIF-1 α is hydroxylated on proline residues that reside in the oxygen induced degradation domain of the protein by proline hydroxylase. Hydroxyproline facilitates binding of Von-Hippel-Lindau Factor (VHL), a tumor suppressor that, when bound, promotes the ubiquitination and degradation of HIF-

1 α . During hypoxia, proline hydroxylase is inhibited, and VHL no longer binds HIF-1 α ; the now stabilized HIF-1 α translocates to the nucleus and associates with HIF-1 α . This heterodimeric transcription factor then binds to HIF-1 responsive DNA sequences in the promoter region of target genes including the carbonic anhydrase isoform CA-IX, as well as VEGF, erythropoietin, and glucose transporters.

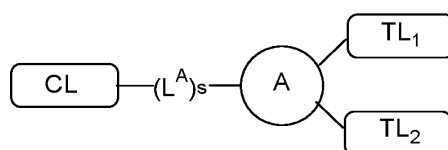
[0006] Carbonic anhydrases are a family of enzymes comprised of 16 isozymes that catalyze the reaction: $\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{HCO}_3^- + \text{H}^+$, and therefore play an important role in pH regulation. Specific isozymes are found either in the cytosol, anchored to the membrane, within the mitochondria, or secreted from the cell. The well-studied constitutively expressed isozyme, carbonic anhydrase II, is found in the cytosol of most cell types, and is the primary isoform responsible for the regulation of intracellular pH.

[0007] CA-IX is a membrane-anchored isoform of the enzyme with its catalytic domain in the extracellular space. It has a limited tissue distribution and is found at low levels primarily in the gastrointestinal tract. The expression of CA-IX is under the control of HIF-1 α , and this isozyme is highly expressed in tumors cells exposed to hypoxia both in vitro and in vivo. Increased CA-IX expression has been detected in carcinomas of the cervix, ovary, kidney, esophagus, lung, breast, and brain. CA-IX has been reported to promote extracellular acidification. The low extracellular pH as a result of the activity of CA-IX leads to tumorigenic transformation, chromosomal rearrangements, extracellular matrix breakdown, migration and invasion, induction of growth factors, protease activation, and chemoresistance.

[0008] Currently, many small molecule inhibitors for CA-IX show undesired side effects due to inhibition of other CA isozymes present in the target organ. There is a need for a CA-IX selective inhibitor to potentially reduce undesired side effects that may arise from inhibition of other, including non-membrane-associated, CA isozymes.

SUMMARY

[0009] Disclosed herein is a conjugate of Formula (A), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (A);

wherein:

TL₁ represents a 1st targeting moiety that binds to carbonic anhydrase IX;

TL₂ represents a 2nd targeting moiety that binds to carbonic anhydrase IX;

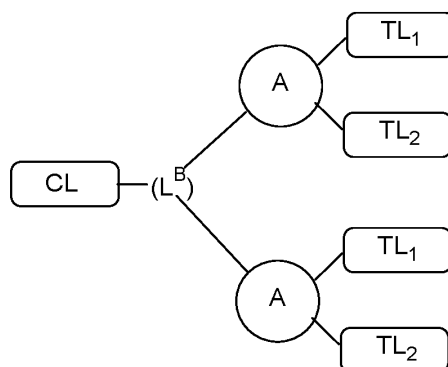
L^A represents a linker;

s is 0 or 1;

Ring A is an optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; and

CL represents a metal chelator.

[0010] Also disclosed herein is a conjugate of Formula (A'), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (A');

wherein:

each TL_1 independently represents a 1st targeting moiety that binds to carbonic anhydrase IX;

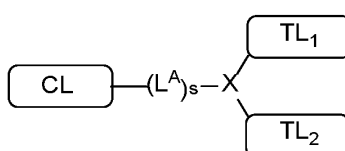
each TL_2 independently represents a 2nd targeting moiety that binds to carbonic anhydrase IX;

L^B represents a linker; and

each Ring A is independently an optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; and

CL represents a metal chelator.

[0011] Also disclosed herein is a conjugate of Formula (B), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (B);

wherein:

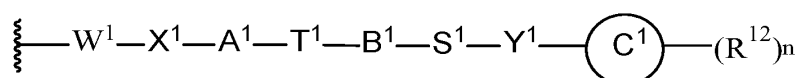
L^A represents a linker;

s is 0 or 1;

CL represents a metal chelator;

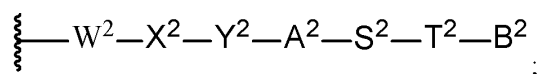
X is N, optionally substituted CH, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

TL_1 is of Formula (IB):



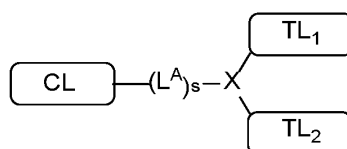
Formula (IB); and

TL₂ is of Formula (IIB):



Formula (IIB).

[0012] Also provided herein is a conjugate of Formula (C), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (C);

wherein:

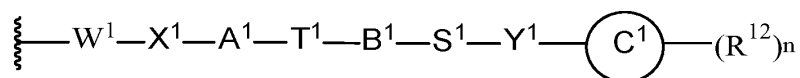
L^A represents a linker;

s is 0 or 1;

CL represents a metal chelator;

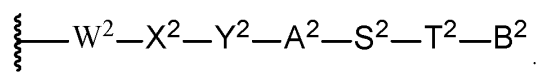
X is N, optionally substituted CH, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

TL₁ is of Formula (IC):



Formula (IC); and

TL₂ is of Formula (IIC):



Formula (IIC).

[0013] Also disclosed herein is a pharmaceutical composition comprising a radiopharmaceutical conjugate disclosed herein, and a pharmaceutically acceptable excipient or carrier.

[0014] In some embodiments, the pharmaceutical composition is formulated for intravenous administration to a subject.

[0015] Also disclosed herein is a method of diagnosing or imaging a disease or disorder in a subject in need thereof, the method comprising administering to the subject a radiopharmaceutical conjugate disclosed herein, or a pharmaceutical composition disclosed herein.

[0016] Also disclosed herein is a method of treating a disease or disorder in a subject in need thereof, the method comprising administering to the subject a radiopharmaceutical conjugate disclosed herein, or a pharmaceutical composition disclosed herein.

[0017] In some embodiments, the disease or disorder is a cancer.

[0018] In some embodiments, the cancer is a solid tumor cancer.

[0019] In some embodiments, the cancer is hypoxic.

[0020] In some embodiments, the cancer is clear cell renal cell carcinoma (ccRCC), endometrial cancer, basal cell carcinoma, liver cancer, colon cancer, gastric cancer, cervical squamous carcinoma, oral squamous cell carcinoma, pancreatic cancer, breast cancer, ovarian cancer, glioblastoma, head and neck cancer, or lung cancer.

[0021] In some embodiments, the cancer is cell renal cell carcinoma (ccRCC).

INCORPORATION BY REFERENCE

[0022] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] The novel features of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawing (also “figure” and “FIG.” herein), of which:

[0024] **FIG. 1** to **FIG. 19** illustrate the structures of representative metal chelators.

DETAILED DESCRIPTION

Definitions

[0025] In the following description, certain specific details are set forth to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the invention may be practiced without these details. In other instances, well-known structures have not been shown or described in detail to avoid unnecessarily obscuring descriptions of the embodiments. Unless the context requires otherwise, throughout the specification and claims which follow, the word “comprise” and variations thereof, such as, “comprises” and “comprising” are to be construed in an open, inclusive sense, that is, as “including, but not limited to.” Further, headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed invention.

[0026] Reference throughout this specification to “some embodiments” or “an embodiment” means that a particular feature, structure, or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearances of the phrases “in one embodiment” or “in an embodiment” in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments. Also, as used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the content clearly dictates

otherwise. It should also be noted that the term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise.

[0027] The terms below, as used herein, have the following meanings, unless indicated otherwise:

[0028] “oxo” refers to =O.

[0029] “Carboxyl” refers to -COOH.

[0030] “Cyano” refers to -CN.

[0031] “Alkyl” refers to a straight-chain, or branched-chain saturated hydrocarbon monoradical having from one to about ten carbon atoms, more preferably one to six carbon atoms. Examples include, but are not limited to methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl and hexyl, and longer alkyl groups, such as heptyl, octyl and the like. Whenever it appears herein, a numerical range such as “C₁-C₆ alkyl” or “C₁₋₆alkyl”, means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated. In some embodiments, the alkyl is a C₁₋₁₀alkyl. In some embodiments, the alkyl is a C₁₋₆alkyl. In some embodiments, the alkyl is a C₁₋₅alkyl. In some embodiments, the alkyl is a C₁₋₄alkyl. In some embodiments, the alkyl is a C₁₋₃alkyl. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkyl is optionally substituted with oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkyl is optionally substituted with halogen.

[0032] “Alkenyl” refers to a straight-chain, or branched-chain hydrocarbon monoradical having one or more carbon-carbon double-bonds and having from two to about ten carbon atoms, more preferably two to about six carbon atoms. The group may be in either the *cis* or *trans* conformation about the double bond(s), and should be understood to include both isomers. Examples include, but are not limited to ethenyl (-CH=CH₂), 1-propenyl (-CH₂CH=CH₂), isopropenyl [-C(CH₃)=CH₂], butenyl, 1,3-butadienyl and the like. Whenever it appears herein, a numerical range such as “C₂-C₆ alkenyl” or “C₂₋₆alkenyl”, means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkenyl” where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkenyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkenyl is optionally substituted with oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkenyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkenyl is optionally substituted with halogen.

[0033] “Alkynyl” refers to a straight-chain or branched-chain hydrocarbon monoradical having one or more carbon-carbon triple-bonds and having from two to about ten carbon atoms, more preferably from two to about six carbon atoms. Examples include, but are not limited to ethynyl, 2-propynyl, 2-butynyl, 1,3-butadiynyl and the like. Whenever it appears herein, a numerical range such as “C₂-C₆ alkynyl” or “C₂-₆alkynyl”, means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkynyl” where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkynyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkynyl is optionally substituted with oxo, halogen, -CN, -COOH, COOMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkynyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkynyl is optionally substituted with halogen.

[0034] “Alkylene” refers to a straight or branched divalent hydrocarbon chain. Unless stated otherwise specifically in the specification, an alkylene group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkylene is optionally substituted with oxo, halogen, -CN, -COOH, COOMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkylene is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkylene is optionally substituted with halogen.

[0035] “Alkoxy” refers to a radical of the formula -Oalkyl where alkyl is as defined above. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkoxy is optionally substituted with halogen, -CN, -COOH, COOMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkoxy is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkoxy is optionally substituted with halogen.

[0036] “Aryl” refers to a radical derived from a hydrocarbon ring system comprising 6 to 30 carbon atoms and at least one aromatic ring. The aryl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the aryl is bonded through an aromatic ring atom) or bridged ring systems. In some embodiments, the aryl is a 6- to 10-membered aryl. In some embodiments, the aryl is a 6-membered aryl (phenyl). Aryl radicals include, but are not limited to, aryl radicals derived from the hydrocarbon ring systems of anthrylene, naphthylene, phenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, as-indacene, s-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, an aryl may be optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some

embodiments, the aryl is optionally substituted with halogen, methyl, ethyl, -CN, -COOH, COOMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the aryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the aryl is optionally substituted with halogen.

[0037] “Cycloalkyl” refers to a partially or fully saturated, monocyclic, or polycyclic carbocyclic ring, which may include fused (when fused with an aryl or a heteroaryl ring, the cycloalkyl is bonded through a non-aromatic ring atom), spiro, or bridged ring systems. In some embodiments, the cycloalkyl is fully saturated. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to fifteen carbon atoms (e.g., C₃-C₁₅ fully saturated cycloalkyl or C₃-C₁₅ cycloalkenyl), from three to ten carbon atoms (e.g., C₃-C₁₀ fully saturated cycloalkyl or C₃-C₁₀ cycloalkenyl), from three to eight carbon atoms (e.g., C₃-C₈ fully saturated cycloalkyl or C₃-C₈ cycloalkenyl), from three to six carbon atoms (e.g., C₃-C₆ fully saturated cycloalkyl or C₃-C₆ cycloalkenyl), from three to five carbon atoms (e.g., C₃-C₅ fully saturated cycloalkyl or C₃-C₅ cycloalkenyl), or three to four carbon atoms (e.g., C₃-C₄ fully saturated cycloalkyl or C₃-C₄ cycloalkenyl). In some embodiments, the cycloalkyl is a 3- to 10-membered fully saturated cycloalkyl or a 3- to 10-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 3- to 6-membered fully saturated cycloalkyl or a 3- to 6-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 5- to 6-membered fully saturated cycloalkyl or a 5- to 6-membered cycloalkenyl. Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls include, for example, adamantyl, norbornyl, decalinyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin, trans-decalin, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, and 7,7-dimethyl-bicyclo[2.2.1]heptanyl. Partially saturated cycloalkyls include, for example cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Unless stated otherwise specifically in the specification, a cycloalkyl is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -COOH, COOMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the cycloalkyl is optionally substituted with halogen.

[0038] “Halo” or “halogen” refers to bromo, chloro, fluoro or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

[0039] “Haloalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, e.g., trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like.

[0040] “Hydroxyalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more hydroxyls. In some embodiments, the alkyl is substituted with one hydroxyl. In some embodiments, the alkyl is substituted with one, two, or three hydroxyls. Hydroxyalkyl include, for example,

hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, or hydroxypentyl. In some embodiments, the hydroxyalkyl is hydroxymethyl.

[0041] “Aminoalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more amines. In some embodiments, the alkyl is substituted with one amine. In some embodiments, the alkyl is substituted with one, two, or three amines. Aminoalkyl include, for example, aminomethyl, aminoethyl, aminopropyl, aminobutyl, or aminopentyl. In some embodiments, the aminoalkyl is aminomethyl.

[0042] “Heteroalkyl” refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, e.g., oxygen, nitrogen (e.g., -NH-, -N(alkyl)-), sulfur, phosphorus, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C₁-C₆ heteroalkyl wherein the heteroalkyl is comprised of 1 to 6 carbon atoms and one or more atoms other than carbon, e.g., oxygen, nitrogen (e.g., -NH-, -N(alkyl)-), sulfur, phosphorus, or combinations thereof wherein the heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. Examples of such heteroalkyl are, for example, -CH₂OCH₃, -CH₂CH₂OCH₃, -CH₂CH₂OCH₂CH₂OCH₃, -CH(CH₃)OCH₃, -CH₂NHCH₃, -CH₂N(CH₃)₂, -CH₂CH₂NHCH₃, or -CH₂CH₂N(CH₃)₂. Unless stated otherwise specifically in the specification, a heteroalkyl is optionally substituted for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heteroalkyl is optionally substituted with halogen.

[0043] “Heterocycloalkyl” refers to a 3- to 24-membered partially or fully saturated ring radical comprising 2 to 23 carbon atoms and from one to 8 heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, silicon, and sulfur. In some embodiments, the heterocycloalkyl is fully saturated. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heterocycloalkyl comprises one to three nitrogens. In some embodiments, the heterocycloalkyl comprises one or two nitrogens. In some embodiments, the heterocycloalkyl comprises one nitrogen. In some embodiments, the heterocycloalkyl comprises one nitrogen and one oxygen. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with an aryl or a heteroaryl ring, the heterocycloalkyl is bonded through a non-aromatic ring atom), spiro, or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heterocycloalkyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Representative heterocycloalkyls include, but are not limited to, heterocycloalkyls having from two to fifteen carbon atoms (e.g., C₂-C₁₅ fully saturated heterocycloalkyl or C₂-C₁₅ heterocycloalkenyl), from two to ten carbon atoms (e.g., C₂-C₁₀ fully saturated heterocycloalkyl or C₂-C₁₀ heterocycloalkenyl), from two to eight carbon atoms (e.g., C₂-

C₈ fully saturated heterocycloalkyl or C₂-C₈ heterocycloalkenyl), from two to seven carbon atoms (e.g., C₂-C₇ fully saturated heterocycloalkyl or C₂-C₇ heterocycloalkenyl), from two to six carbon atoms (e.g., C₂-C₆ fully saturated heterocycloalkyl or C₂-C₆ heterocycloalkenyl), from two to five carbon atoms (e.g., C₂-C₅ fully saturated heterocycloalkyl or C₂-C₅ heterocycloalkenyl), or two to four carbon atoms (e.g., C₂-C₄ fully saturated heterocycloalkyl or C₂-C₄ heterocycloalkenyl). Examples of such heterocycloalkyl radicals include, but are not limited to, aziridinyl, azetidiny, oxetanyl, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazoliny, imidazolidiny, isothiazolidiny, isoxazolidiny, morpholiny, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidiny, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidiny, quinuclidiny, thiazolidiny, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholiny, thiamorpholiny, 1-oxo-thiomorpholiny, 1,1-dioxo-thiomorpholiny, 1,3-dihydroisobenzofuran-1-yl, 3-oxo-1,3-dihydroisobenzofuran-1-yl, methyl-2-oxo-1,3-dioxol-4-yl, and 2-oxo-1,3-dioxol-4-yl. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides, and the oligosaccharides. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring). In some embodiments, the heterocycloalkyl is a 3- to 8-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 7-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 4- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 8-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 3- to 7-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 4- to 6-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered heterocycloalkenyl. Unless stated otherwise specifically in the specification, a heterocycloalkyl may be optionally substituted as described below, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the heterocycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -COOH, COOMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the heterocycloalkyl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heterocycloalkyl is optionally substituted with halogen.

[0044] “Heteroaryl” refers to a 5- to 14-membered ring system radical comprising one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, and sulfur, and at least one aromatic ring. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of

nitrogen and oxygen. In some embodiments, the heteroaryl comprises one to three nitrogens. In some embodiments, the heteroaryl comprises one or two nitrogens. In some embodiments, the heteroaryl comprises one nitrogen. The heteroaryl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the heteroaryl is bonded through an aromatic ring atom) or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. In some embodiments, the heteroaryl is a 5- to 10-membered heteroaryl. In some embodiments, the heteroaryl is a 5- to 6-membered heteroaryl. In some embodiments, the heteroaryl is a 6-membered heteroaryl. In some embodiments, the heteroaryl is a 5-membered heteroaryl. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothieryl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, isoindolyl, indolyl, isoindolyl, isoquinolyl, indolizyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolyl, quinuclidinyl, isoquinolyl, tetrahydroquinolyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e., thienyl). Unless stated otherwise specifically in the specification, a heteroaryl may be optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, -COOH, COOMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heteroaryl is optionally substituted with halogen.

[0045] The term “optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, “optionally substituted alkyl” means either “alkyl” or “substituted alkyl” as defined above. Further, an optionally substituted group may be un-substituted (e.g., -CH₂CH₃), fully substituted (e.g., -CF₂CF₃), mono-substituted (e.g., -CH₂CH₂F) or substituted at a level anywhere in-between fully substituted and mono-substituted (e.g., -CH₂CHF₂, -CH₂CF₃, -CF₂CH₃, -CFHCHF₂, etc.). It will be understood by those skilled in the art with respect to any group containing one or more substituents that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical and/or synthetically non-feasible. Thus, any substituents described should generally be understood as having a maximum molecular weight of about 1,000 daltons, and more typically, up to about 500 daltons.

[0046] The term “one or more” when referring to an optional substituent means that the subject group is optionally substituted with one, two, three, four, or more substituents. In some embodiments, the subject group is optionally substituted with one, two, three or four substituents. In some embodiments, the subject group is optionally substituted with one, two, or three substituents. In some embodiments, the subject group is optionally substituted with one or two substituents. In some embodiments, the subject group is optionally substituted with one substituent. In some embodiments, the subject group is optionally substituted with two substituents.

[0047] An “effective amount” or “therapeutically effective amount” refers to an amount of a compound administered to a mammalian subject, either as a single dose or as part of a series of doses, which is effective to produce a desired therapeutic effect.

[0048] “Treatment” of an individual (e.g. a mammal, such as a human) or a cell is any type of intervention used in an attempt to alter the natural course of the individual or cell. In some embodiments, treatment includes administration of a pharmaceutical composition, subsequent to the initiation of a pathologic event or contact with an etiologic agent and includes stabilization of the condition (e.g., condition does not worsen) or alleviation of the condition.

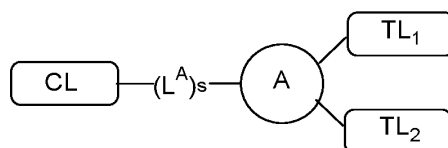
Compounds

[0049] Disclosed herein are conjugates targeting the CA-IX receptor and pharmaceutical compositions thereof. In some embodiments, the conjugate disclosed herein is selective for CA-IX over CA-XII.

[0050] The conjugates and compositions can be useful for treating cancer. The conjugates and compositions can also be useful in imaging and disease diagnosis.

[0051] In one aspect, described herein are conjugates that comprise a targeting ligand that binds to a CA-IX protein. In some embodiments, the conjugates described herein comprise a targeting ligand that binds to a CA-IX protein and a metal chelator that is configured to bind with a radionuclide. In some embodiments, the conjugates described herein comprises a radionuclide.

[0052] Disclosed herein is a conjugate of Formula (A), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (A);

wherein:

TL₁ represents a 1st targeting moiety that binds to carbonic anhydrase IX;

TL₂ represents a 2nd targeting moiety that binds to carbonic anhydrase IX;

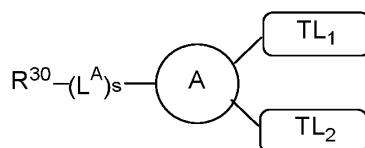
L^A represents a linker;

s is 0 or 1;

Ring A is an optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; and

CL represents a metal chelator.

[0053] Disclosed herein is a conjugate of Formula (AC), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (AC);

wherein:

TL₁ represents a 1st targeting moiety that binds to carbonic anhydrase IX;

TL₂ represents a 2nd targeting moiety that binds to carbonic anhydrase IX;

L^A represents a linker;

s is 0 or 1;

Ring A is an optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; and

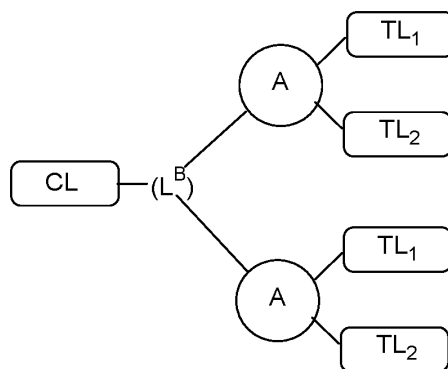
R³⁰ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted (e.g., with one or more R); or

R³⁰ is an albumin binding moiety or a payload moiety ;

wherein R^a, R^b, R^c, R^d, and R have their meanings as defined in Formula (IA).

[0054] In some embodiments, the conjugate compound of Formula (AC) comprises a covalently bound radioisotope.

[0055] Disclosed herein is a conjugate of Formula (A'), or a pharmaceutically acceptable salt or stereoisomer thereof:

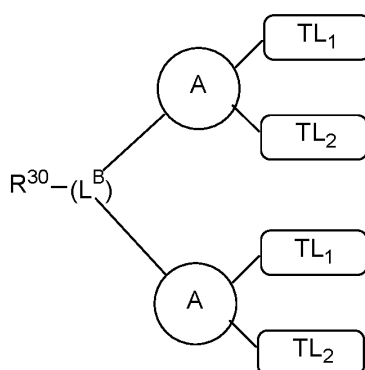


Formula (A');

wherein:

each TL_1 independently represents a 1st targeting moiety that binds to carbonic anhydrase IX;
 each TL_2 independently represents a 2nd targeting moiety that binds to carbonic anhydrase IX;
 L^B represents a linker; and
 each Ring A is independently an optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; and
 CL represents a metal chelator.

[0056] Disclosed herein is a conjugate of Formula (AC'), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (AC');

wherein:

each TL_1 independently represents a 1st targeting moiety that binds to carbonic anhydrase IX;
 each TL_2 independently represents a 2nd targeting moiety that binds to carbonic anhydrase IX;
 L^B represents a linker;
 each Ring A is independently an optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; and
 R^{30} is hydrogen, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-SF_5$, $-SH$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NR^bS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1 -

C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted (e.g., with one or more R); or

R³⁰ is an albumin binding moiety or a payload moiety ;

wherein R^a, R^b, R^c, R^d, and R have their meanings as defined in Formula (IA).

[0057] In some embodiments, the conjugate compound of Formula (AC') comprises a covalently bound radioisotope.

[0058] In some embodiments of a compound of Formula (A') or (AC'), each TL₁ is the same. In some embodiments of a compound of Formula (A') or (AC'), each TL₁ is different. In some embodiments of a compound of Formula (A') or (AC'), each TL₂ is the same. In some embodiments of a compound of Formula (A') or (AC'), each TL₂ is different. In some embodiments of a compound of Formula (A') or (AC'), each Ring A is the same. In some embodiments of a compound of Formula (A') or (AC'), each Ring A is different. In some embodiments of a compound of Formula (A') or (AC'), each TL₁ is independently a targeting moiety of Formula (IA). In some embodiments of a compound of Formula (A') or (AC'), each TL₂ is independently a targeting moiety of Formula (IIA).

[0059] In some embodiments of a compound of Formula (A), (AC), (A') or (AC'), Ring A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R; and each R is independently halogen, -CN, -OH, -SF₅, -SH, -S(=O)C₁-C₃alkyl, -S(=O)₂C₁-C₃alkyl, -S(=O)₂NH₂, -S(=O)₂NHC₁-C₃alkyl, -S(=O)₂N(C₁-C₃alkyl)₂, -NH₂, -NHC₁-C₃alkyl, -N(C₁-C₃alkyl)₂, -C(=O)C₁-C₃alkyl, -C(=O)OH, -C(=O)OC₁-C₃alkyl, -C(=O)NH₂, -C(=O)NHC₁-C₃alkyl, -C(=O)N(C₁-C₃alkyl)₂, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃haloalkyl, C₁-C₃haloalkoxy, C₁-C₃hydroxyalkyl, C₁-C₃aminoalkyl, C₁-C₃heteroalkyl, C₃-C₆cycloalkyl, or 3- to 6-membered heterocycloalkyl;

or two R on the same atom form an oxo.

[0060] In some embodiments of a compound of Formula (A), (AC), (A') or (AC'), Ring A is heterocycloalkyl optionally substituted with one or more R.

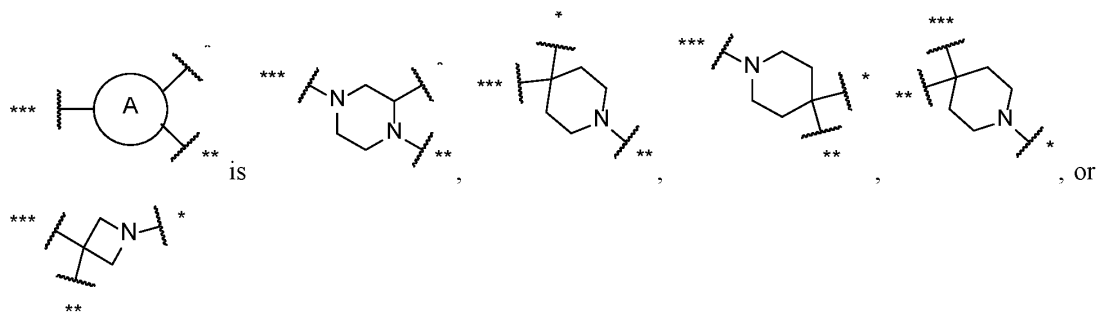
[0061] In some embodiments of a compound of Formula (A), (AC), (A') or (AC'), Ring A is monocyclic heterocycloalkyl optionally substituted with one or more R.

[0062] In some embodiments of a compound of Formula (A), (AC), (A') or (AC'), Ring A is bicyclic heterocycloalkyl optionally substituted with one or more R. In some embodiments of a compound of Formula (A), (AC), (A') or (AC'), Ring A is spirobicyclic heterocycloalkyl optionally substituted with one or more R.

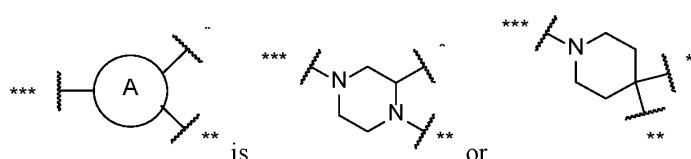
[0063] In some embodiments of a compound of Formula (A), (AC), (A') or (AC'), Ring A is 4- to 6-membered heterocycloalkyl optionally substituted with one or more R. In some embodiments of a compound of Formula (A), (AC), (A') or (AC'), Ring A is azetidiny, pyrrolidiny, piperidiny, or piperaziny, each optionally substituted with one or more R. In some embodiments of a compound of Formula (A), (AC), (A') or (AC'), Ring A is piperidiny or piperaziny, each optionally substituted with

one or more R. In some embodiments of a compound of Formula (A), (AC), (A') or (AC'), Ring A is piperidinyl optionally substituted with one or more R. In some embodiments of a compound of Formula (A), (AC), (A') or (AC'), Ring A is piperazinyl optionally substituted with one or more R.

[0064] In some embodiments of a compound of Formula (A), (AC), (A') or (AC'),

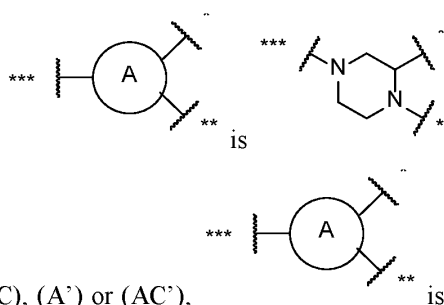


. In some embodiments of a compound of Formula (A), (AC), (A') or (AC'),

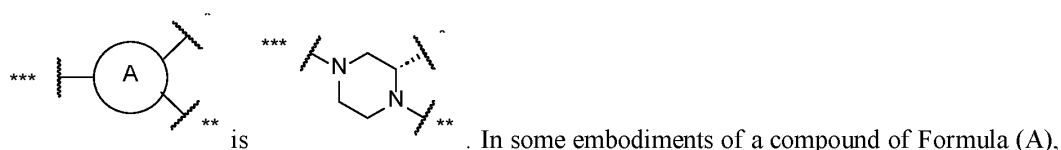
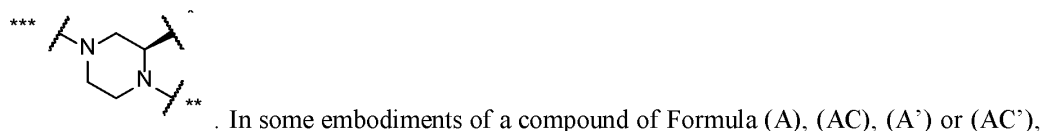


. In some embodiments of a

compound of Formula (A), (AC), (A') or (AC'),



embodiments of a compound of Formula (A), (AC), (A') or (AC'),

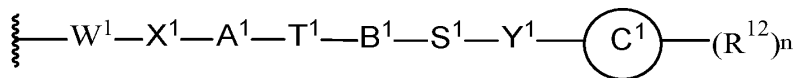


(AC), (A') or (AC'),

or Formula (AC), *** represents the attachment point of ring A to linker L^A. In some embodiments of Formula (A), when s is 0, *** represents the attachment point of ring A to metal chelator (CL). In some embodiments of Formula (AC), when s is 0, *** represents the attachment point of ring A to R³⁰. In some embodiments of Formula (A) or Formula (AC), ** represents the attachment point of ring A to TL₁, and * represents the attachment point of ring A to TL₂. In some embodiments of Formula (A) or Formula

(AC), * represents the attachment point of ring A to TL₁, and ** represents the attachment point of ring A to TL₂. In some embodiments of Formula (A') or Formula (AC'), *** represents the attachment point of ring A to linker L^B. In some embodiments of Formula (A') or Formula (AC'), ** represents the attachment point of ring A to a TL₁, and * represents the attachment point of ring A to a TL₂. In some embodiments of Formula (A') or Formula (AC'), * represents the attachment point of ring A to a TL₁, and ** represents the attachment point of ring A to a TL₂.

[0065] In some embodiments of a compound of Formula (A), (AC), (A') or (AC'), TL₁ is of Formula (IA):



Formula (IA);

wherein:

W¹ is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR¹¹-, -C(=O)-, -C(=O)NR¹¹-, -NR¹¹C(=O)-, -S(=O)₂NR¹¹-, or -NR¹¹S(=O)₂;

X¹ is C₁-C₁₀alkylene optionally substituted with one or more R and wherein one, two, three, or four carbon atoms of the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR¹¹-;

A¹ is absent, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R;

T¹ is absent or C₁-C₃alkylene optionally substituted with one or more R and wherein one carbon atom of the C₁-C₃alkylene is optionally replaced with -C(=O)-, -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR¹¹-;

B¹ is absent, C₁-C₁₀alkylene, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms in the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, -NR¹¹-;

S¹ is absent or C₁-C₃alkylene optionally substituted with one or more R and wherein one or two carbon atoms of the C₁-C₃alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR¹¹-;

Y¹ is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR¹¹-, -C(=O)-, -C(=O)NR¹¹-, -NR¹¹C(=O)-, -S(=O)₂NR¹¹-, or -NR¹¹S(=O)₂;

R¹¹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

Ring C¹ is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R¹² is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

n is 0, 1, 2, 3, 4, 5, or 6;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R;

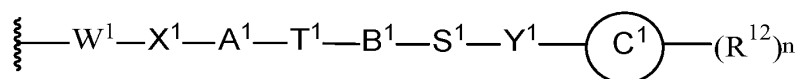
L is absent or C₁-C₃alkylene optionally substituted with one or more R; and

each R is independently halogen, -CN, -OH, -SF₅, -SH, -S(=O)C₁-C₃alkyl, -S(=O)₂C₁-C₃alkyl, -S(=O)₂NH₂, -S(=O)₂NHC₁-C₃alkyl, -S(=O)₂N(C₁-C₃alkyl)₂, -NH₂, -NHC₁-C₃alkyl, -N(C₁-C₃alkyl)₂, -C(=O)C₁-C₃alkyl, -C(=O)OH, -C(=O)OC₁-C₃alkyl, -C(=O)NH₂, -C(=O)NHC₁-C₃alkyl, -C(=O)N(C₁-C₃alkyl)₂, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃haloalkyl, C₁-C₃haloalkoxy, C₁-C₃hydroxyalkyl, C₁-C₃aminoalkyl, C₁-C₃heteroalkyl, C₃-C₆cycloalkyl, or 3- to 6-membered heterocycloalkyl;

or two R on the same atom form an oxo;

or two R on the same or different atoms are taken together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

[0066] In some embodiments of a compound of Formula (A), (AC), (A') or (AC'), TL₁ is of Formula (IA):



Formula (IA);

wherein:

W¹ is absent, -C(=O)-, or -C(=O)NR¹¹-;

X¹ is C₁-C₁₀alkylene;

A¹ is absent or heteroaryl optionally substituted with one or more R;

T¹ is absent;

B¹ is C₁-C₁₀alkylene or cycloalkyl;

S¹ is absent;

Y¹ is absent, -O-, -S-, -S(=O)₂-, -C(=O)NR¹¹-, or -NR¹¹C(=O)-;

R¹¹ is hydrogen;

Ring C¹ is heteroaryl;

each R¹² is independently halogen, -S(=O)₂NR^eR^d, or -NR^eR^d;

n is 0, 1, 2, or 3;

R^e and R^d are each independently hydrogen, C₁-C₆alkyl, -L-cycloalkyl, or -L-aryl, wherein each alkyl, cycloalkyl, and aryl is independently optionally substituted with one or more R;

L is absent or C₁-C₃alkylene; and

each R is independently C₁-C₃alkyl or C₁-C₃alkoxy.

[0067] In some embodiments of a compound of Formula (IA), W¹ is absent, -O-, -S-, -NR¹¹-, -C(=O)-, -C(=O)NR¹¹-, or -NR¹¹C(=O)-.

[0068] In some embodiments of a compound of Formula (IA), W¹ is absent, -C(=O)-, or -C(=O)NR¹¹-.

[0069] In some embodiments of a compound of Formula (IA), W¹ is absent.

[0070] In some embodiments of a compound of Formula (IA), W¹ is -C(=O)-.

[0071] In some embodiments of a compound of Formula (IA), W¹ is -C(=O)NR¹¹-.

[0072] In some embodiments of a compound of Formula (IA), X¹ is C₁-C₆alkylene optionally substituted with one or more R and wherein one or two carbon atoms of the C₁-C₆alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR¹¹-.

[0073] In some embodiments of a compound of Formula (IA), X¹ is C₁-C₆alkylene.

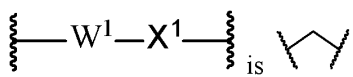
[0074] In some embodiments of a compound of Formula (IA), X¹ is C₁-C₄alkylene.

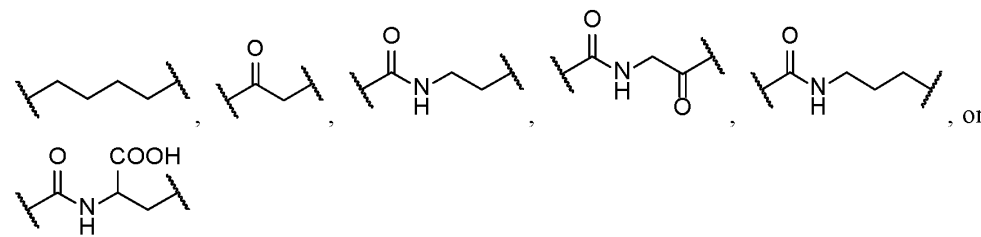
[0075] In some embodiments of a compound of Formula (IA), X¹ is -CH₂-.

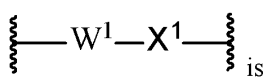
[0076] In some embodiments of a compound of Formula (IA), X¹ is -CH₂CH₂-.

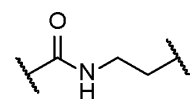
[0077] In some embodiments of a compound of Formula (IA), X¹ is -CH₂CH₂CH₂-.

[0078] In some embodiments of a compound of Formula (IA), X¹ is -CH₂CH₂CH₂CH₂-.

[0079] In some embodiments of a compound of Formula (IA),  is .



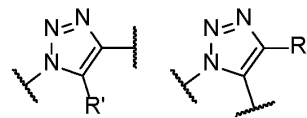
[0080] In some embodiments of a compound of Formula (IA),  is .



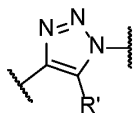
[0081] In some embodiments of a compound of Formula (IA), A¹ is absent.

[0082] In some embodiments of a compound of Formula (IA), A¹ is heteroaryl optionally substituted with one or more R.

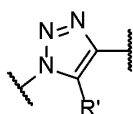
[0083] In some embodiments of a compound of Formula (IA), A¹ is triazolyl optionally substituted with one or more R. In some embodiments of a compound of Formula (IA), A¹ is unsubstituted triazolyl.



[0084] In some embodiments of a compound of Formula (IA), A¹ is



wherein R' is hydrogen or R. In some embodiments of a compound of Formula (IA), A¹ is

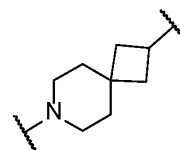


wherein R' is hydrogen or R. In some embodiments, R' is hydrogen.

[0085] In some embodiments of a compound of Formula (IA), A¹ is heterocycloalkyl optionally substituted with one or more R.

[0086] In some embodiments of a compound of Formula (IA), A¹ is monocyclic heterocycloalkyl optionally substituted with one or more R.

[0087] In some embodiments of a compound of Formula (IA), A¹ is bicyclic heterocycloalkyl optionally substituted with one or more R.



[0088] In some embodiments of a compound of Formula (IA), A¹ is

[0089] In some embodiments of a compound of Formula (IA), T¹ is absent or C₁-C₃alkylene.

[0090] In some embodiments of a compound of Formula (IA), T¹ is absent.

[0091] In some embodiments of a compound of Formula (IA), B¹ is C₁-C₁₀alkylene or cycloalkyl, wherein the alkylene and cycloalkyl is optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms in the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR¹¹-.

[0092] In some embodiments of a compound of Formula (IA), B¹ is C₁-C₁₀alkylene optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms in the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR¹¹-.

[0093] In some embodiments of a compound of Formula (IA), B¹ is C₁-C₁₀alkylene optionally substituted with one or more R.

[0094] In some embodiments of a compound of Formula (IA), B¹ is C₁-C₆alkylene.

[0095] In some embodiments of a compound of Formula (IA), B¹ is -CH₂CH₂CH₂-.

[0096] In some embodiments of a compound of Formula (IA), B¹ is -CH₂CH₂CH₂CH₂-.

[0097] In some embodiments of a compound of Formula (IA), B¹ is cycloalkyl optionally substituted with one or more R.

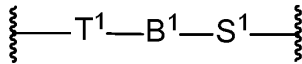
[0098] In some embodiments of a compound of Formula (IA), B¹ is a monocyclic cycloalkyl optionally substituted with one or more R.

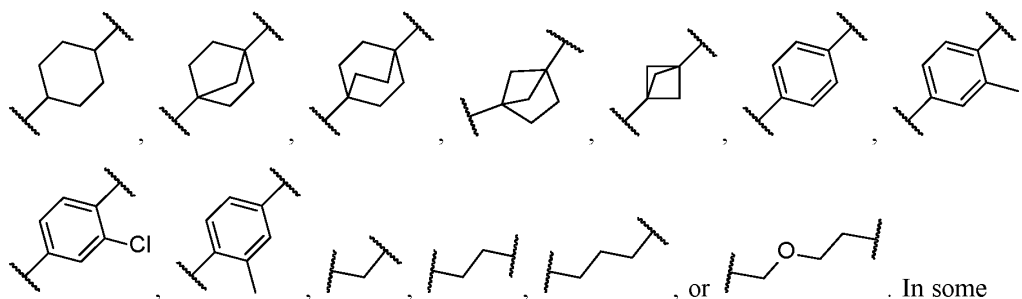
[0099] In some embodiments of a compound of Formula (IA), B¹ is a bicyclic cycloalkyl optionally substituted with one or more R.

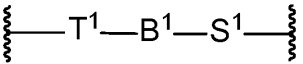
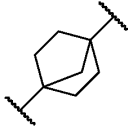
[00100] In some embodiments of a compound of Formula (IA), B¹ is bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, or bicyclo[2.1.1]hexanyl.

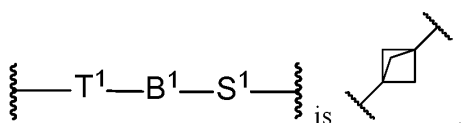
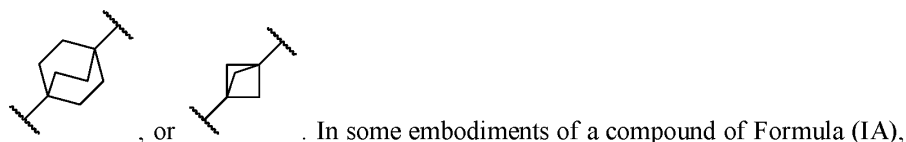
[00101] In some embodiments of a compound of Formula (IA), B¹ is bicyclo[1.1.1]pentanyl.

[00102] In some embodiments of a compound of Formula (IA), S¹ is absent.

[00103] In some embodiments of a compound of Formula (IA),  is



embodiments of a compound of Formula (IA),  is .

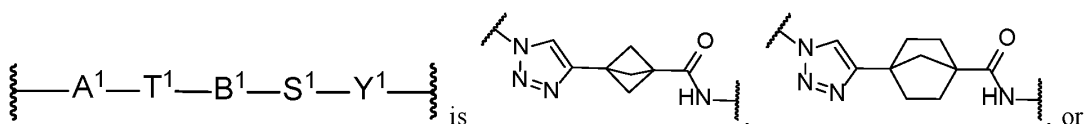


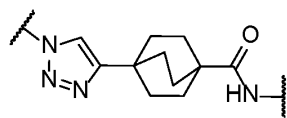
[00104] In some embodiments of a compound of Formula (IA), Y¹ is absent, -O-, -S-, -S(=O)₂-, -C(=O)NR¹¹-, or -NR¹¹C(=O)-.

[00105] In some embodiments of a compound of Formula (IA), Y¹ is -S(=O)₂-.

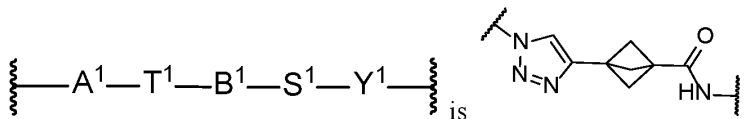
[00106] In some embodiments of a compound of Formula (IA), Y¹ is -C(=O)NR¹¹-.

[00107] In some embodiments of a compound of Formula (IA),





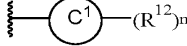
In some embodiments of a compound of Formula (IA),

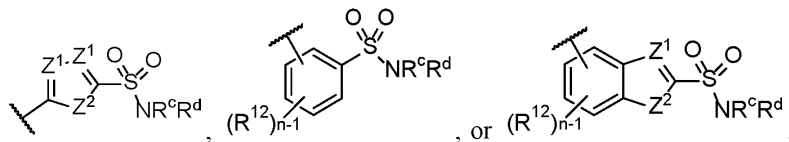


[00108] In some embodiments of a compound of Formula (IA), Ring C¹ is aryl or heteroaryl. In some embodiments of a compound of Formula (IA), Ring C¹ is phenyl or heteroaryl. In some embodiments of a compound of Formula (IA), Ring C¹ is heteroaryl. In some embodiments of a compound of Formula (IA), Ring C¹ is 5- to 12-membered heteroaryl. In some embodiments of a compound of Formula (IA), Ring C¹ is 5- to 10-membered heteroaryl. In some embodiments of a compound of Formula (IA), Ring C¹ is 5- to 6-membered heteroaryl. In some embodiments of a compound of Formula (IA), Ring C¹ is 7- to 10-membered heteroaryl. In some embodiments of a compound of Formula (IA), Ring C¹ is monocyclic heteroaryl. In some embodiments of a compound of Formula (IA), Ring C¹ thiadiazolyl or phenyl. In some embodiments of a compound of Formula (IA), Ring C¹ thiadiazolyl. In some embodiments of a compound of Formula (IA), Ring C¹ phenyl.

[00109] In some embodiments of a compound of Formula (IA), Ring C¹ is bicyclic heteroaryl.

[00110] In some embodiments of a compound of Formula (IA), Ring C¹ is benzothiazolyl or imidazothiadiazolyl.

[00111] In some embodiments of a compound of Formula (IA),  is



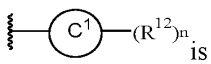
wherein each Z¹ is independently -N- or -CR^{12'}-;

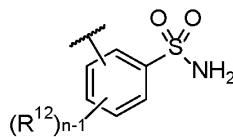
Z² is -O-, -S-, or -NR^{12''}-;

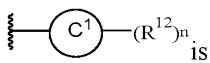
each R^{12'} is independently hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, cycloalkyl, or heterocycloalkyl; and

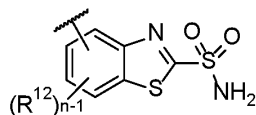
R^{12''} is hydrogen, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, cycloalkyl, or heterocycloalkyl.

[00112] In some embodiments, Z² is -O- or -S-. In some embodiments, Z² is -S-. In some embodiments, each Z¹ is -N-.

[00113] In some embodiments of a compound of Formula (IA),  is



. In some embodiments of a compound of Formula (IA),  is



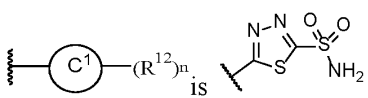
[00114] In some embodiments of a compound of Formula (IA), each R^{12} is independently halogen, -CN, -OH, -OR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, or C₁-C₆haloalkyl. In some embodiments of a compound of Formula (IA), one of R^{12} is -S(=O)₂NR^cR^d.

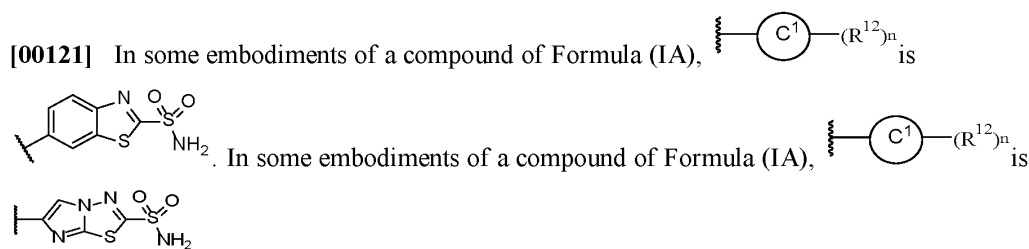
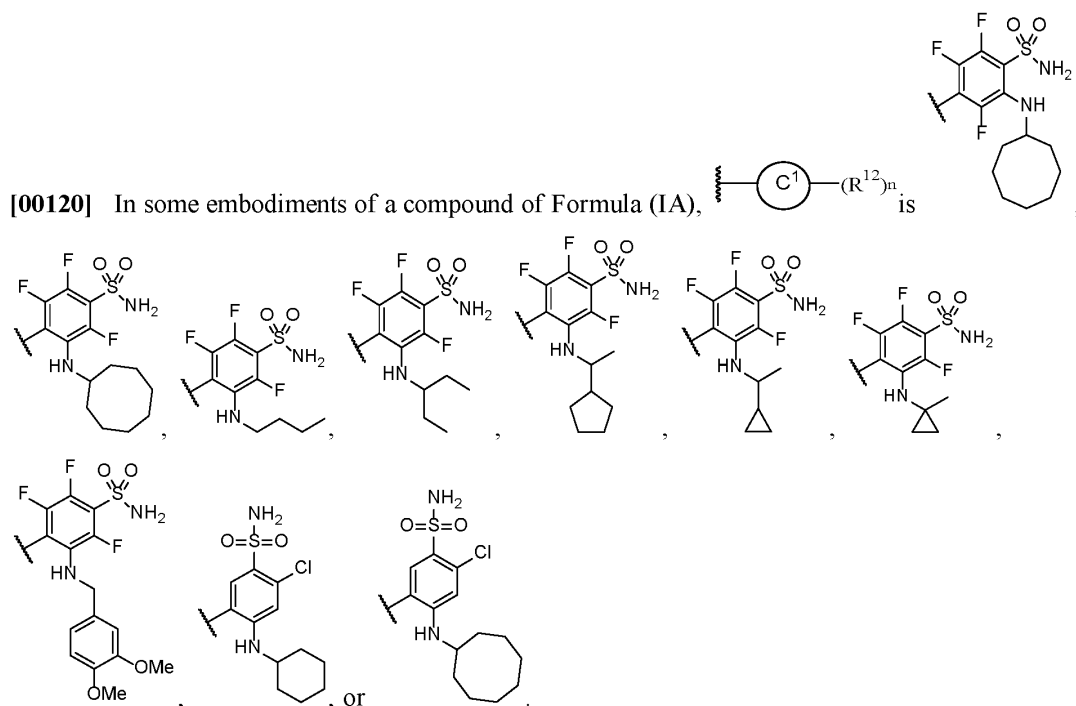
[00115] In some embodiments of a compound of Formula (IA), each R^{12} is independently halogen, -CN, -OH, -OR^a, -S(=O)R^a, -S(=O)₂R^a, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, or C₁-C₆haloalkyl.

[00116] In some embodiments of a compound of Formula (IA), each R^{12} is independently halogen, -S(=O)₂NR^cR^d, or -NR^cR^d.

[00117] In some embodiments of a compound of Formula (IA), each R^{12} is independently halogen or -NR^cR^d.

[00118] In some embodiments of a compound of Formula (IA), n is 0, 1, 2, 3, 4, or 5. In some embodiments of a compound of Formula (IA), n is 0, 1, 2, 3, or 4. In some embodiments of a compound of Formula (IA), n is 0, 1, 2, or 3. In some embodiments of a compound of Formula (IA), n is 0, 1, or 2. In some embodiments of a compound of Formula (IA), n is 0 or 1.

[00119] In some embodiments of a compound of Formula (IA),  is



[00122] In some embodiments of a compound of Formula (IA), R^{11} is hydrogen or C_1 - C_6 alkyl. In some embodiments of a compound of Formula (IIA), R^{11} is hydrogen.

[00123] In some embodiments of a compound of Formula (IA), each R^a is independently C_1 - C_6 alkyl;

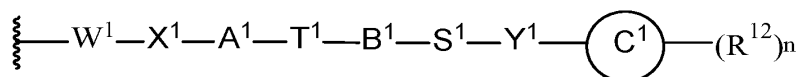
[00124] In some embodiments of a compound of Formula (IA), each R^b is independently hydrogen or C_1 - C_6 alkyl;

[00125] In some embodiments of a compound of Formula (IA), R^c and R^d are each independently hydrogen, C_1 - C_6 alkyl, -L-cycloalkyl, or -L-aryl, wherein each alkyl, cycloalkyl, and aryl is independently optionally substituted with one or more R.

[00126] In some embodiments of a compound of Formula (IA), L is absent or C_1 - C_3 alkylene. In some embodiments of a compound of Formula (IA), L is absent. In some embodiments of a compound of Formula (IA), L is C_1 - C_3 alkylene.

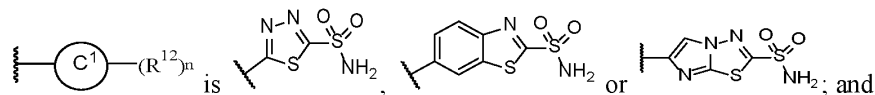
[00127] In some embodiments of a compound of Formula (IA), each R is independently C_1 - C_3 alkyl or C_1 - C_3 alkoxy.

[00128] In some embodiments of a compound of Formula (A), (AC), (A') or (AC'), TL_1 is of Formula (IA):



Formula (IA);

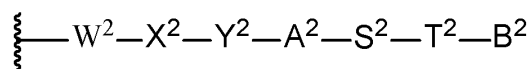
wherein



$\text{---}W^1-X^1-A^1-T^1-B^1-S^1-Y^1\text{---}$ are taken together to form a linking group that comprises 3 to 30 atoms (optionally, 5-25 atoms, 8-20 atoms, 8-15 atoms, or 10-14 atoms, or 8, 9, 10, 11, 12, 13, 14, or 15 atoms) in the linear chain.

[00129] In some embodiments, $\text{---}W^1-X^1-A^1-T^1-B^1-S^1-Y^1\text{---}$ are taken together to form a linking group that comprises 3 to 30 atoms in the linear chain, which are selected from C, N, and O. In some embodiments, the linking group comprises 3 to 30 atoms in the linear chain, including carbon, 1-5 N and 0-1 O. In some embodiments, the linking group comprises 3 to 30 atoms in the linear chain selected from N and C, including 2, 3, or 4 N. In some embodiments, the linking group comprises one or more cyclic groups, and the atoms in the linear chain comprises a part of the cyclic groups. In some embodiments, both A^1 and B^1 are cyclic groups. In some embodiments, the linking group comprises one or more groups selected from -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂-, optionally substituted C₁-C₁₀alkylene, optionally substituted C₁-C₁₀heteroalkylene, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl, or a combination thereof.

[00130] In some embodiments of a compound of Formula (A), (AC), (A') or (AC'), TL₂ is of Formula (IIA):



Formula (IIA);

wherein:

W^2 is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂;

X^2 is absent or C₁-C₁₀alkylene optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms of the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR²¹;

Y^2 is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂;

A² is absent, C₁-C₁₀alkylene, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²²; each R²² is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R; S² is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂;

T² is absent or C₁-C₁₀alkylene optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms of the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR²¹-;

R²¹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

(i) B² is absent;

or

(ii) B² is -N(R²³)₂;

each R²³ is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

or

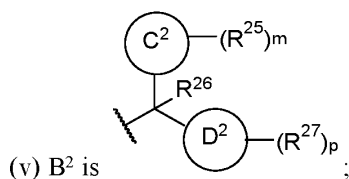
(iii) B² is -CF₃;

or

(iv) B² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²⁴;

each R²⁴ is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

or



Ring C² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R²⁵ is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R; m is 0, 1, 2, 3, or 4;

R²⁶ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl; Ring D² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R²⁷ is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R; p is 0, 1, 2, 3, or 4;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R;

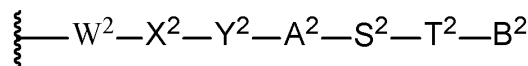
L is absent or C₁-C₃alkylene optionally substituted with one or more R; and

each R is independently halogen, -CN, -OH, -SF₅, -SH, -S(=O)C₁-C₃alkyl, -S(=O)₂C₁-C₃alkyl, -S(=O)₂NH₂, -S(=O)₂NHC₁-C₃alkyl, -S(=O)₂N(C₁-C₃alkyl)₂, -NH₂, -NHC₁-C₃alkyl, -N(C₁-C₃alkyl)₂, -C(=O)C₁-C₃alkyl, -C(=O)OH, -C(=O)OC₁-C₃alkyl, -C(=O)NH₂, -C(=O)NHC₁-C₃alkyl, -C(=O)N(C₁-C₃alkyl)₂, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃haloalkyl, C₁-C₃haloalkoxy, C₁-C₃hydroxyalkyl, C₁-C₃aminoalkyl, C₁-C₃heteroalkyl, C₃-C₆cycloalkyl, or 3- to 6-membered heterocycloalkyl;

or two R on the same atom form an oxo;

or two R on the same or different atoms are taken together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

[00131] In some embodiments of a compound of Formula (A), (AC), (A') or (AC'), TL₂ is of Formula (IIA):



Formula (IIA);

wherein:

W² is absent, -C(=O)-, or -NR²¹C(=O)-;

X² is C₁-C₁₀alkylene optionally substituted with one or more R;

Y² is absent, -NR²¹-, or -NR²¹C(=O)-;

A² is C₁-C₁₀alkylene, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²²;

each R²² is independently halogen, -CN, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆aminoalkyl;

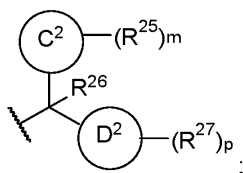
S² is absent, -NR²¹-, -C(=O)-, or -NR²¹C(=O)-;

T² is absent or C₁-C₁₀alkylene;

R²¹ is hydrogen;

B² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²⁴;

each R²⁴ is independently halogen, -OH, -SF₅, C₁-C₆alkyl, C₁-C₆haloalkyl, cycloalkyl, or heterocycloalkyl;



or B² is

Ring C² is aryl;

each R²⁵ is independently halogen, -OH, or C₁-C₆alkyl;

m is 0, 1, or 2;

R²⁶ is hydrogen or C₁-C₆alkyl;

Ring D² is aryl;

each R²⁷ is independently halogen, -OH, or C₁-C₆alkyl;

p is 0, 1, or 2;

each R^b is independently hydrogen or C₁-C₆alkyl;

R^c and R^d are each independently hydrogen or C₁-C₆alkyl; and

each R is independently -C(=O)OH or -C(=O)NH₂.

[00132] In some embodiments of a compound of Formula (IIA), W² is absent, -C(=O)-, or -NR²¹C(=O)-.

[00133] In some embodiments of a compound of Formula (IIA), W^2 is $-C(=O)-$. In some embodiments of a compound of Formula (IIA), W^2 is absent. In some embodiments of a compound of Formula (IIA), W^2 is $-C(=O)-$. In some embodiments of a compound of Formula (IIA), W^2 is $-NR^{21}C(=O)-$.

[00134] In some embodiments of a compound of Formula (IIA), X^2 is C_1-C_6 alkylene optionally substituted with one or more R.

[00135] In some embodiments of a compound of Formula (IIA), X^2 is C_1-C_4 alkylene optionally substituted with one or more R.

[00136] In some embodiments of a compound of Formula (IIA), X^2 is $-CH_2-$.

[00137] In some embodiments of a compound of Formula (IIA), X^2 is $-CH_2CH[C(=O)OH]-$ or $-CH_2CH[C(=O)NH_2]-$.

[00138] In some embodiments of a compound of Formula (IIA), X^2 is $-CH_2CH_2CH[C(=O)OH]-$ or $-CH_2CH_2CH[C(=O)NH_2]-$.

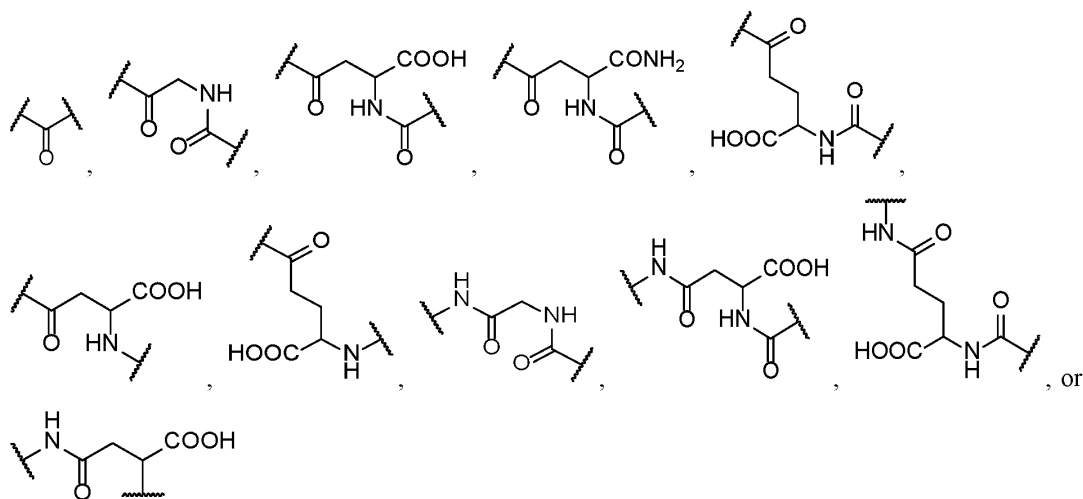
[00139] In some embodiments of a compound of Formula (IIA), X^2 is optionally substituted with one or more R, and wherein one or two carbon atoms of the C_1-C_{10} alkylene are replaced with $-S-$, $-S(=O)-$, $-S(=O)_2-$, $-O-$, or $-NR^{21}-$.

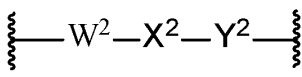
[00140] In some embodiments of a compound of Formula (IIA), Y^2 is absent, $-O-$, $-S-$, $-NR^{21}-$, $-C(=O)-$, $-C(=O)NR^{21}-$, or $-NR^{21}C(=O)-$.

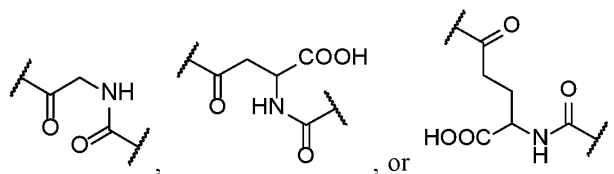
[00141] In some embodiments of a compound of Formula (IIA), Y^2 is absent, $-NR^{21}-$, or $-NR^{21}C(=O)-$.

[00142] In some embodiments of a compound of Formula (IIA), Y^2 is $-NR^{21}C(=O)-$.

[00143] In some embodiments of a compound of Formula (IIA), $\text{---}W^2-X^2-Y^2\text{---}$ is



[00144] In some embodiments of a compound of Formula (IIA),  is,



[00145] In some embodiments of a compound of Formula (IIA), A² is C₁-C₁₀alkylene, heterocycloalkyl, aryl, or heteroaryl, wherein the alkylene, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²².

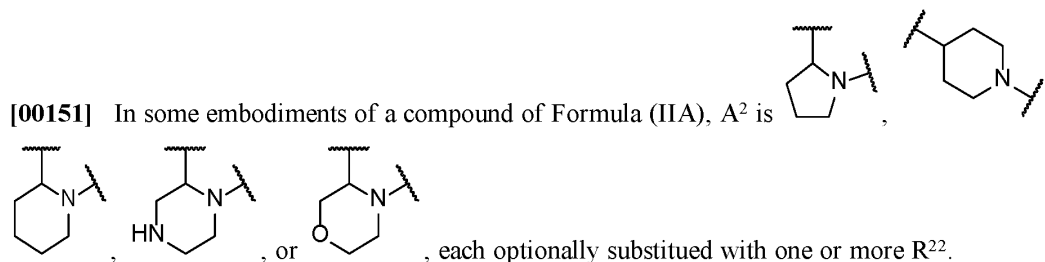
[00146] In some embodiments of a compound of Formula (IIA), A² is C₁-C₆alkylene optionally substituted with one or more R²².

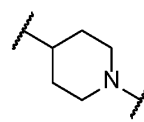
[00147] In some embodiments of a compound of Formula (IIA), A² is -CH₂CH[C(=O)OH]-.

[00148] In some embodiments of a compound of Formula (IIA), A² is heterocycloalkyl optionally substituted with one or more R²².

[00149] In some embodiments of a compound of Formula (IIA), A² is pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl, each optionally substituted with one or more R²².

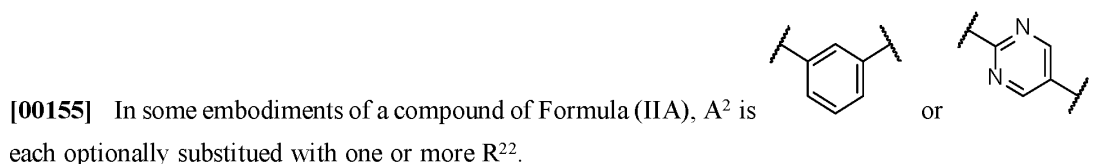
[00150] In some embodiments of a compound of Formula (IIA), A² is piperidinyl optionally substituted with one or more R²².

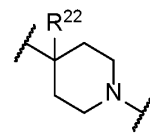


[00152] In some embodiments of a compound of Formula (IIA), A² is  optionally substituted with one or more R²².

[00153] In some embodiments of a compound of Formula (IIA), A² is aryl or heteroaryl, wherein the aryl and heteroaryl is optionally substituted with one or more R²².

[00154] In some embodiments of a compound of Formula (IIA), A² is phenyl, pyridinyl, pyrimidinyl, or pyrazinyl, each optionally substituted with one or more R²².





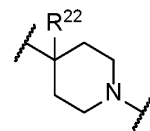
[00156] In some embodiments of a compound of Formula (IIA), A² is

[00157] In some embodiments of a compound of Formula (IIA), each R²² is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl.

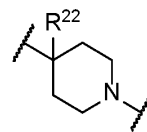
[00158] In some embodiments of a compound of Formula (IIA), each R²² is independently -CN, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, or C₁-C₆aminoalkyl.

[00159] In some embodiments of a compound of Formula (IIA), each R²² is independently -C(=O)OR^b or -C(=O)NR^cR^d.

[00160] In some embodiments of a compound of Formula (IIA), each R²² is independently -C(=O)NR^cR^d.

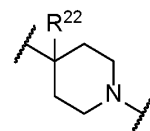


[00161] In some embodiments of a compound of Formula (IIA), A² is and R²² is halogen, -CN, -OH, -OR^a, -NR^cR^d, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl.

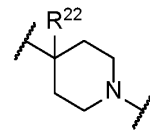


[00162] In some embodiments of a compound of Formula (IIA), A² is and R²² is -CN, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, or C₁-C₆aminoalkyl.

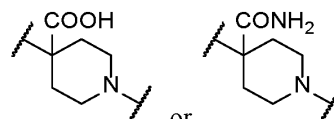
[00163]



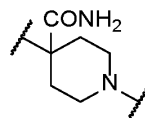
[00164] In some embodiments of a compound of Formula (IIA), A² is and R²² is -C(=O)OR^b or -C(=O)NR^cR^d.



[00165] In some embodiments of a compound of Formula (IIA), A² is and R²² is -C(=O)NR^cR^d.



[00166] In some embodiments of a compound of Formula (IIA), A² is



. In some embodiments of a compound of Formula (IIA), A² is

[00167] In some embodiments of a compound of Formula (IIA), S² is absent, -O-, -S-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, or -NR²¹C(=O)-.

[00168] In some embodiments of a compound of Formula (IIA), S² is absent, -NR²¹-, -C(=O)-, or -NR²¹C(=O)-.

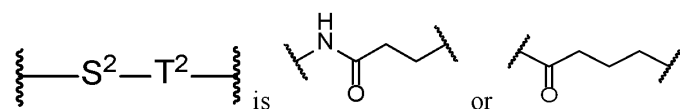
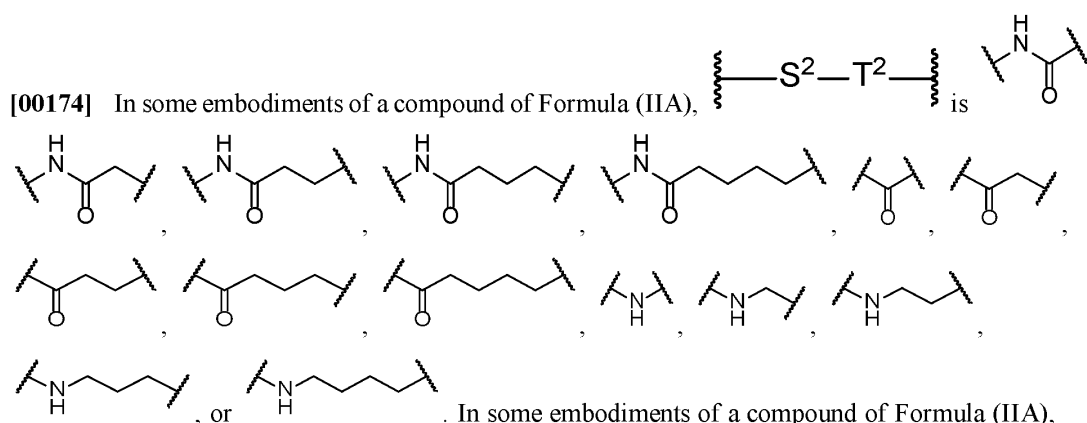
[00169] In some embodiments of a compound of Formula (IIA), S² is -C(=O)- or -NR²¹C(=O)-.

[00170] In some embodiments of a compound of Formula (IIA), T² is absent or C₁-C₆alkylene optionally substituted with one or more R.

[00171] In some embodiments of a compound of Formula (IIA), T² is C₁-C₆alkylene optionally substituted with one or more R.

[00172] In some embodiments of a compound of Formula (IIA), T² is -CH₂CH₂-.

[00173] In some embodiments of a compound of Formula (IIA), T² is -CH₂CH₂CH₂-.



[00175] In some embodiments of a compound of Formula (IIA), B² is absent.

[00176] In some embodiments of a compound of Formula (IIA), B² is -N(R²³)₂.

[00177] In some embodiments of a compound of Formula (IIA), B² is -CF₃.

[00178] In some embodiments of a compound of Formula (IIA), B² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²⁴.

[00179] In some embodiments of a compound of Formula (IIA), B² is cycloalkyl optionally substituted with one or more R²⁴.

[00180] In some embodiments of a compound of Formula (IIA), B² is monocyclic cycloalkyl optionally substituted with one or more R²⁴.

[00181] In some embodiments of a compound of Formula (IIA), B² is bicyclic cycloalkyl optionally substituted with one or more R²⁴.

[00182] In some embodiments of a compound of Formula (IIA), B² is phenyl optionally substituted with one or more R²⁴.

[00183] In some embodiments of a compound of Formula (IIA), B² is heteroaryl optionally substituted with one or more R²⁴.

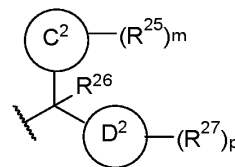
[00184] In some embodiments of a compound of Formula (IIA), B² is 5- to 10-membered heteroaryl (e.g., monocyclic or bicyclic heteroaryl) optionally substituted with one or more R²⁴.

[00185] In some embodiments of a compound of Formula (IIA), B² is 5- to 6-membered heteroaryl optionally substituted with one or more R²⁴.

[00186] In some embodiments of a compound of Formula (IIA), B² is indazolyl, phenyl, pyridyl, pyridinyl, pyrazinyl, pyridazinyl, cyclopropyl, cyclohexyl, cyclobutyl, cycloheptyl, pyrazolyl, oxazolyl, triazolyl, spiroheptanyl, or bicycloheptanyl.

[00187] In some embodiments of a compound of Formula (IIA), each R²⁴ is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, -SF₅, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R.

[00188] In some embodiments of a compound of Formula (IIA), each R²⁴ is independently halogen, -OH, C₁-C₆alkyl, or C₁-C₆haloalkyl.



[00189] In some embodiments of a compound of Formula (IIA), B² is wherein:

Ring C² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R²⁵ is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl,

heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R; m is 0, 1, 2, 3, or 4;

R²⁶ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl; Ring D² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R²⁷ is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -

$\text{NR}^b\text{C}(=\text{O})\text{OR}^b$, $-\text{NR}^b\text{S}(=\text{O})_2\text{R}^a$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^b$, $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_1\text{-C}_6\text{haloalkyl}$, $\text{C}_1\text{-C}_6\text{hydroxyalkyl}$, $\text{C}_1\text{-C}_6\text{aminoalkyl}$, $\text{C}_1\text{-C}_6\text{heteroalkyl}$, $\text{C}_2\text{-C}_6\text{alkenyl}$, $\text{C}_2\text{-C}_6\text{alkynyl}$, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl,

heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

p is 0, 1, 2, 3, or 4.

[00190] In some embodiments of a compound of Formula (IIA), Ring C^2 is phenyl.

[00191] In some embodiments of a compound of Formula (IIA), each R^{25} is independently halogen, -CN, -OH, $-\text{OR}^a$, $-\text{SF}_5$, -SH, $-\text{SR}^a$, $-\text{NR}^c\text{R}^d$, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_1\text{-C}_6\text{haloalkyl}$, or $\text{C}_1\text{-C}_6\text{hydroxyalkyl}$. In some embodiments of a compound of Formula (IIA), each R^{25} is independently halogen, -CN, -OH, $-\text{OR}^a$, $-\text{NR}^c\text{R}^d$, or $\text{C}_1\text{-C}_6\text{alkyl}$. In some embodiments of a compound of Formula (IIA), each R^{25} is independently -OH.

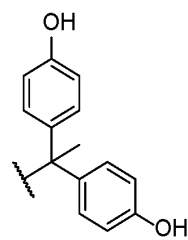
[00192] In some embodiments of a compound of Formula (IIA), m is 0 or 1. In some embodiments of a compound of Formula (IIA), m is 0, 1, or 2. In some embodiments of a compound of Formula (IIA), m is 0. In some embodiments of a compound of Formula (IIA), m is 1. In some embodiments of a compound of Formula (IIA), m is 2. In some embodiments of a compound of Formula (IIA), m is 3.

[00193] In some embodiments of a compound of Formula (IIA), Ring D^2 is phenyl.

[00194] In some embodiments of a compound of Formula (IIA), each R^{27} is independently halogen, -CN, -OH, $-\text{OR}^a$, $-\text{SF}_5$, -SH, $-\text{SR}^a$, $-\text{NR}^c\text{R}^d$, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_1\text{-C}_6\text{haloalkyl}$, or $\text{C}_1\text{-C}_6\text{hydroxyalkyl}$. In some embodiments of a compound of Formula (IIA), each R^{27} is independently halogen, -CN, -OH, $-\text{OR}^a$, $-\text{NR}^c\text{R}^d$, or $\text{C}_1\text{-C}_6\text{alkyl}$. In some embodiments of a compound of Formula (IIA), each R^{27} is independently -OH.

[00195] In some embodiments of a compound of Formula (IIA), p is 0 or 1. In some embodiments of a compound of Formula (IIA), p is 0, 1, or 2. In some embodiments of a compound of Formula (IIA), p is 0. In some embodiments of a compound of Formula (IIA), p is 1. In some embodiments of a compound of Formula (IIA), p is 2. In some embodiments of a compound of Formula (IIA), p is 3.

[00196] In some embodiments of a compound of Formula (IIA), R^{26} is hydrogen or $\text{C}_1\text{-C}_6\text{alkyl}$. In some embodiments of a compound of Formula (IIA), R^{26} is $\text{C}_1\text{-C}_6\text{alkyl}$.



[00197] In some embodiments of a compound of Formula (IIA), B^2 is

[00198] In some embodiments of a compound of Formula (IIA), R^{21} is hydrogen or $\text{C}_1\text{-C}_6\text{alkyl}$. In some embodiments of a compound of Formula (IIA), R^{21} is hydrogen.

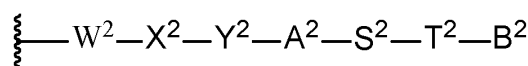
[00199] In some embodiments of a compound of Formula (IIA), each R^a is independently $\text{C}_1\text{-C}_6\text{alkyl}$;

[00200] In some embodiments of a compound of Formula (IIA), each R^b is independently hydrogen or $\text{C}_1\text{-C}_6\text{alkyl}$.

[00201] In some embodiments of a compound of Formula (IIA), R^c and R^d are each independently hydrogen or C₁-C₆alkyl.

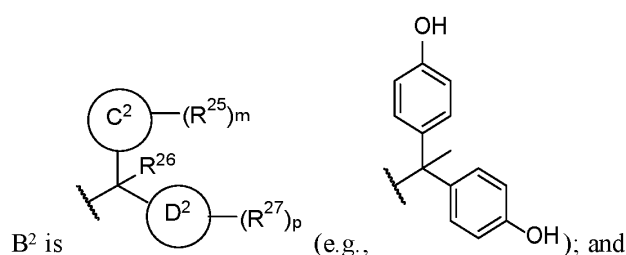
[00202] In some embodiments of a compound of Formula (IIA), each R is independently -C(=O)OH or -C(=O)NH₂.

[00203] In some embodiments of a compound of Formula (A), (AC), (A') or (AC'), TL₂ is of Formula (IIA):



Formula (IIA);

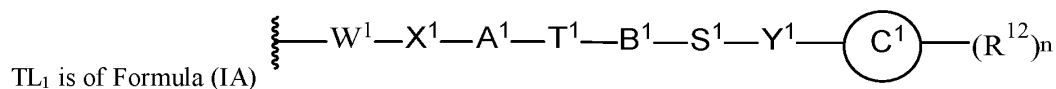
wherein



$\text{---} \text{W}^2 \text{---} \text{X}^2 \text{---} \text{Y}^2 \text{---} \text{A}^2 \text{---} \text{S}^2 \text{---} \text{T}^2 \text{---}$ are taken together to form a linking group that comprises 3 to 30 atoms (optionally, 5-25 atoms, 8-20 atoms, 8-15 atoms, or 10-14 atoms, or 8, 9, 10, 11, 12, 13, 14, or 15 atoms) in the linear chain.

[00204] In some embodiments, $\text{---} \text{W}^2 \text{---} \text{X}^2 \text{---} \text{Y}^2 \text{---} \text{A}^2 \text{---} \text{S}^2 \text{---} \text{T}^2 \text{---}$ together form a linking group that comprises 3 to 30 atoms in the linear chain, which are selected from C, N, and O. In some embodiments, the linking group comprises 3 to 30 atoms in the linear chain, including carbon, 1-5 N and 0-1 O. In some embodiments, the linking group comprises 3 to 30 atoms in the linear chain selected from N and C, including 2, 3, or 4 N. In some embodiments, the linking group comprises one or more cyclic groups, and the atoms in the linear chain comprises a part of the cyclic groups. In some embodiments, A² is a cyclic group. In some embodiments, the linking group comprises one or more groups selected from -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂-, optionally substituted C₁-C₁₀alkylene, optionally substituted C₁-C₁₀heteroalkylene, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl, or a combination thereof.

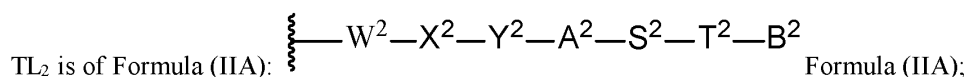
[00205] In some embodiments, disclosed herein is radiopharmaceutical conjugate comprising: (i) a radionuclide selected from Table 3 (e.g., ²²⁵Ac, ¹⁷⁷Lu, ⁶⁴Cu, and ⁶⁸Ga) and (ii) a compound of formula (A), or a salt thereof, wherein the CL is selected from a chelator of FIGs 1-19 (e.g., DOTA, DOTA-GA); s is 0; ring A is piperidinyl or piperazinyl, each is optionally substituted;



Formula (IA);

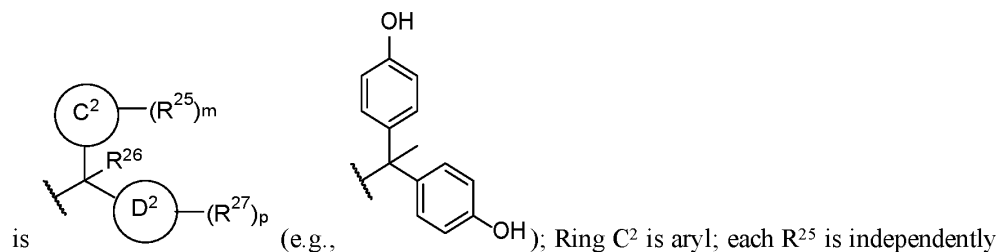
wherein:

W¹ is absent, -C(=O)-, or -C(=O)NR¹¹-; X¹ is C₁-C₁₀alkylene; A¹ is absent or heteroaryl (e.g., triazolyl) optionally substituted with one or more R; T¹ is absent; B¹ is C₁-C₁₀alkylene or cycloalkyl (e.g., bicyclo[1.1.1]pentanyl); S¹ is absent; Y¹ is absent, -O-, -S-, -S(=O)₂-, -C(=O)NR¹¹-, or -NR¹¹C(=O)-; R¹¹ is hydrogen; Ring C¹ is heteroaryl; each R¹² is independently halogen, -S(=O)₂NR^cR^d, or -NR^cR^d; and n is 0, 1, 2, or 3; and



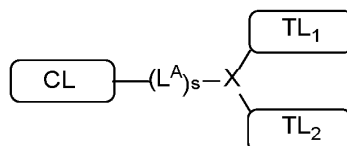
wherein:

W² is absent, -C(=O)-, or -NR²¹C(=O)-; X² is C₁-C₁₀alkylene optionally substituted with one or more R; Y² is absent, -NR²¹-, or -NR²¹C(=O)-; A² is C₁-C₁₀alkylene, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²²; each R²² is independently halogen, -CN, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, or C₁-C₆haloalkyl; S² is absent, -NR²¹-, -C(=O)-, or -NR²¹C(=O)-; T² is absent or C₁-C₁₀alkylene optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms of the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR²¹-; R²¹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl; B²



Ring C² is aryl; each R²⁵ is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, or C₁-C₆haloalkyl; m is 0, 1, or 2; R²⁶ is hydrogen, C₁-C₆alkyl, or C₁-C₆haloalkyl; Ring D² is aryl; each R²⁷ is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, or C₁-C₆haloalkyl; p is 0, 1, or 2.

[00206] Also disclosed herein is a conjugate of Formula (B), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (B);

wherein:

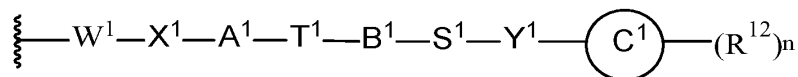
L^A represents a linker;

s is 0 or 1;

CL represents a metal chelator;

X is N, optionally substituted CH, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

TL₁ is of Formula (IB):



Formula (IB);

wherein:

W¹ is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR¹¹-, -C(=O)-, -C(=O)NR¹¹-, -NR¹¹C(=O)-, -S(=O)₂NR¹¹-, or -NR¹¹S(=O)₂;

X¹ is C₁-C₁₀alkylene optionally substituted with one or more R and wherein one, two, three, or four carbon atoms of the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR¹¹-;

A¹ is absent, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R;

T¹ is absent or C₁-C₃alkylene optionally substituted with one or more R and wherein one carbon atom of the C₁-C₃alkylene is optionally replaced with -C(=O)-, -S-, -S(=O)-, -S(=O)₂-, -O-, -NR¹¹-;

B¹ is cycloalkyl, heterocycloalkyl, or aryl, wherein the cycloalkyl, heterocycloalkyl, and aryl is optionally substituted with one or more R; or

B¹ is heteroaryl substituted with one or more R;

S¹ is absent or C₁-C₃alkylene optionally substituted with one or more R and wherein one or two carbon atoms of the C₁-C₃alkylene are optionally replaced with -C(=O)-, -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR¹¹-;

Y¹ is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR¹¹-, -C(=O)-, -C(=O)NR¹¹-, -NR¹¹C(=O)-, -S(=O)₂NR¹¹-, or -NR¹¹S(=O)₂;

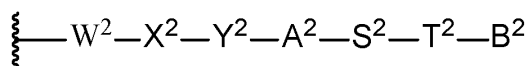
R¹¹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

Ring C¹ is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R¹² is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

n is 0, 1, 2, 3, 4, 5, or 6;

TL₂ is of Formula (IIB):



Formula (IIB);

wherein:

W² is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂;

X² is absent or C₁-C₁₀alkylene optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms of the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR²¹-;

Y² is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂;

A² is absent, C₁-C₁₀alkylene, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²²;

each R²² is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

S² is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂;

T² is absent or C₁-C₁₀alkylene optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms of the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR²¹-;

R²¹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

(i) B² is absent;

or

(ii) B² is -N(R²³)₂;

each R²³ is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

or

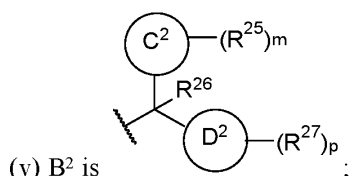
(iii) B² is -CF₃;

or

(iv) B² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²⁴;

each R^{24} is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

or



Ring C² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{25} is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

m is 0, 1, 2, 3, or 4;

R^{26} is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

Ring D² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{27} is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

p is 0, 1, 2, 3, or 4;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-

aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^e and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R;

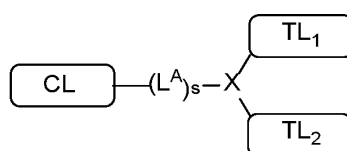
L is absent or C₁-C₃alkylene optionally substituted with one or more R; and

each R is independently halogen, -CN, -OH, -SF₅, -SH, -S(=O)C₁-C₃alkyl, -S(=O)₂C₁-C₃alkyl, -S(=O)₂NH₂, -S(=O)₂NHC₁-C₃alkyl, -S(=O)₂N(C₁-C₃alkyl)₂, -NH₂, -NHC₁-C₃alkyl, -N(C₁-C₃alkyl)₂, -C(=O)C₁-C₃alkyl, -C(=O)OH, -C(=O)OC₁-C₃alkyl, -C(=O)NH₂, -C(=O)NHC₁-C₃alkyl, -C(=O)N(C₁-C₃alkyl)₂, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃haloalkyl, C₁-C₃haloalkoxy, C₁-C₃hydroxyalkyl, C₁-C₃aminoalkyl, C₁-C₃heteroalkyl, C₃-C₆cycloalkyl, or 3- to 6-membered heterocycloalkyl;

or two R on the same atom form an oxo;

or two R on the same or different atoms are taken together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

[00207] Also disclosed herein is a conjugate of Formula (B), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (B);

wherein:

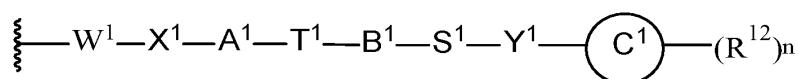
L^A represents a linker;

s is 0 or 1;

CL represents a metal chelator;

X is N, optionally substituted CH, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

TL₁ is of Formula (IB):



Formula (IB);

wherein:

W¹ is absent, -C(=O)-, or -C(=O)NR¹¹-;

X¹ is C₁-C₁₀alkylene;

A¹ is absent or heteroaryl optionally substituted with one or more R;

T¹ is absent;

B¹ is cycloalkyl;

S¹ is absent;

Y¹ is absent, -O-, -S-, -S(=O)₂-, -C(=O)NR¹¹-, or -NR¹¹C(=O)-;

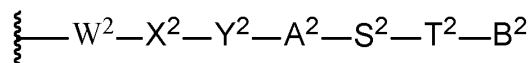
R¹¹ is hydrogen;

Ring C¹ is heteroaryl;

each R¹² is independently halogen, -S(=O)₂NR^cR^d, or -NR^cR^d; and

n is 0, 1, 2, or 3;

TL₂ is of Formula (IIB):



Formula (IIB);

wherein:

W² is absent, -C(=O)-, or -NR²¹C(=O)-;

X² is C₁-C₁₀alkylene optionally substituted with one or more R;

Y² is absent, -NR²¹-, or -NR²¹C(=O)-;

A² is C₁-C₁₀alkylene, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²²;

each R²² is independently halogen, -CN, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆aminoalkyl;

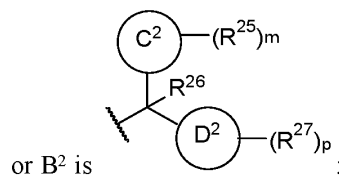
S² is absent, -NR²¹-, -C(=O)-, or -NR²¹C(=O)-;

T² is absent or C₁-C₁₀alkylene;

R²¹ is hydrogen;

B² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²⁴;

each R²⁴ is independently halogen, -OH, -SF₅, C₁-C₆alkyl, C₁-C₆haloalkyl, cycloalkyl, or heterocycloalkyl;



Ring C² is aryl;

each R²⁵ is independently halogen, -OH, or C₁-C₆alkyl;

m is 0, 1, or 2;

R²⁶ is hydrogen or C₁-C₆alkyl;

Ring D² is aryl;

each R²⁷ is independently halogen, -OH, or C₁-C₆alkyl;

p is 0, 1, or 2;

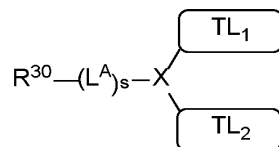
each R^b is independently hydrogen or C₁-C₆alkyl;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, -L-cycloalkyl, or -L-aryl, wherein each alkyl, cycloalkyl, and aryl is independently optionally substituted with one or more R;

L is absent or C₁-C₃alkylene; and

each R is independently C₁-C₃alkyl, C₁-C₃alkoxy, -C(=O)OH, or -C(=O)NH₂.

[00208] Disclosed herein is a conjugate of Formula (BC), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (BC)

wherein:

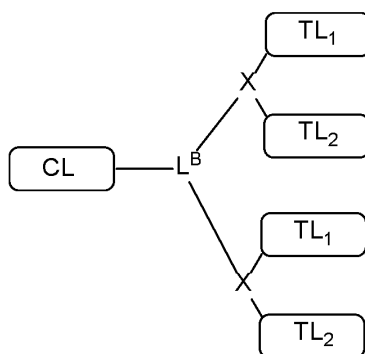
R³⁰ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted (e.g., with one or more R); or

R³⁰ is an albumin binding moiety or a payload moiety;

wherein the remaining groups have their meanings as defined in Formula (B).

[00209] In some embodiments, the conjugate compound of Formula (BC) comprises a covalently bound radioisotope.

[00210] Also disclosed herein is a conjugate of Formula (B'), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (B');

wherein:

L^B represents a linker;

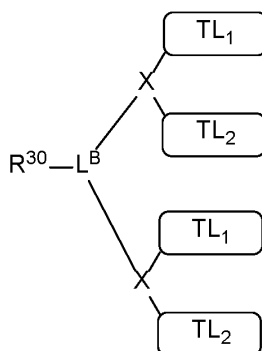
CL represents a metal chelator;

each X is independently N, optionally substituted CH, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each TL₁ represents a 1st targeting moiety that binds to carbonic anhydrase IX; and

each TL₂ represents a 2nd targeting moiety that binds to carbonic anhydrase IX.

[00211] Also disclosed herein is a conjugate of Formula (BC'), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (BC');

wherein:

L^B represents a linker;

each X is independently N, optionally substituted CH, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each TL₁ represents a 1st targeting moiety that binds to carbonic anhydrase IX;

each TL₂ represents a 2nd targeting moiety that binds to carbonic anhydrase IX;

R^{30} is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted (e.g., with one or more R); or

R^{30} is an albumin binding moiety or a payload moiety ;

wherein the remaining groups have their meanings as defined in Formula (B).

[00212] In some embodiments, the conjugate compound of Formula (BC') comprises a covalently bound radioisotope.

[00213] In some embodiments of a compound of Formula (B') or (BC'), each TL₁ is the same. In some embodiments of a compound of Formula (B') or (BC'), each TL₁ is different. In some embodiments of a compound of Formula (B') or (BC'), each TL₂ is the same. In some embodiments of a compound of Formula (B') or (BC'), each TL₂ is different. In some embodiments of a compound of Formula (B') or (BC'), each X is the same. In some embodiments of a compound of Formula (B') or (BC'), each X is different. In some embodiments of a compound of Formula (B') or (BC'), each TL₁ is independently a

targeting moiety of Formula (IB). In some embodiments of a compound of Formula (B') or (BC'), each TL₂ is independently a targeting moiety of Formula (IIB).

[00214] In some embodiments of a compound of Formula (B') or (BC'), each TL₁ is defined in Formula (B). In some embodiments of a compound of Formula (B') or (BC'), each TL₂ is defined in Formula (B).

[00215] In some embodiments of a compound of Formula (B), (BC), (B'), (BC') or (IB), T¹ is absent or C₁-C₃alkylene.

[00216] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IB), T¹ is absent.

[00217] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IB), B¹ is cycloalkyl optionally substituted with one or more R.

[00218] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IB), B¹ is a monocyclic cycloalkyl optionally substituted with one or more R.

[00219] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IB), B¹ is a bicyclic cycloalkyl optionally substituted with one or more R.

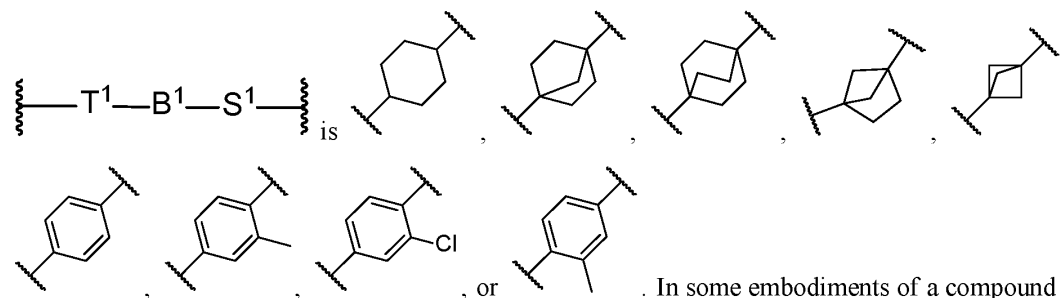
[00220] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IB), B¹ is bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, or bicyclo[2.1.1]hexanyl.

[00221] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IB), B¹ is bicyclo[1.1.1]pentanyl.

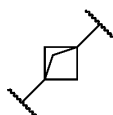
[00222] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IB), B¹ is heterocycloalkyl, which is optionally substituted with one or more R. In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IB), B¹ is aryl optionally substituted with one or more R. In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IB), B¹ is heteroaryl substituted with one or more R.

[00223] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IB), S¹ is absent.

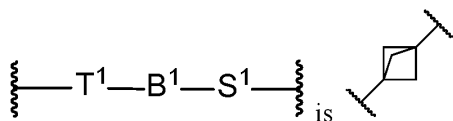
[00224] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IB),



Formula (B), (B'), (BC), (BC'), or (IB), is , or , or



. In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IB),



[00225] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), A² is C₁-C₁₀alkylene, heterocycloalkyl, aryl, or heteroaryl, wherein the alkylene, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²².

[00226] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), A² is C₆alkylene optionally substituted with one or more R²².

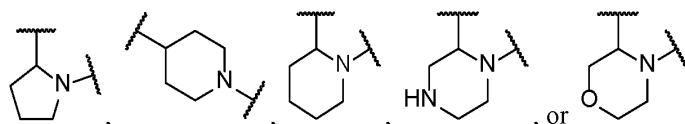
[00227] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), A² is -CH₂CH[C(=O)OH]-.

[00228] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), A² is heterocycloalkyl optionally substituted with one or more R²².

[00229] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), A² is pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl, each optionally substituted with one or more R²².

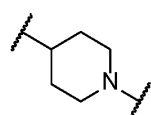
[00230] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), A² is piperidinyl optionally substituted with one or more R²².

[00231] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), A² is



, each optionally substituted with one or more R²².

[00232] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), A² is

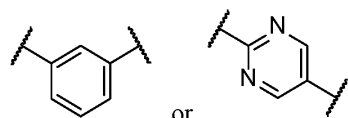


optionally substituted with one or more R²².

[00233] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), A² is aryl or heteroaryl, wherein the aryl and heteroaryl is optionally substituted with one or more R²².

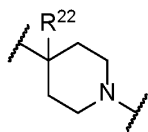
[00234] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), A² is phenyl, pyridinyl, pyrimidinyl, or pyrazinyl, each optionally substituted with one or more R²².

[00235] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), A² is



or , each optionally substituted with one or more R²².

[00236] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), A² is



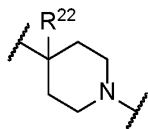
[00237] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), each R²² is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl.

[00238] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), each R²² is independently -CN, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, or C₁-C₆aminoalkyl.

[00239] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), each R²² is independently -C(=O)OR^b or -C(=O)NR^cR^d.

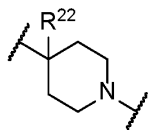
[00240] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), each R²² is independently -C(=O)NR^cR^d.

[00241] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), A² is



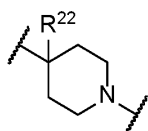
and R²² is halogen, -CN, -OH, -OR^a, -NR^cR^d, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl.

[00242] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), A² is



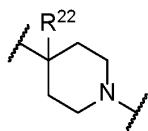
and R²² is -CN, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, or C₁-C₆aminoalkyl.

[00243] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), A² is



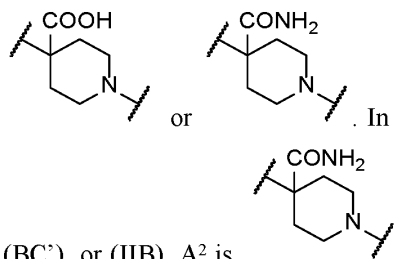
and R²² is -C(=O)OR^b or -C(=O)NR^cR^d.

[00244] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), A² is



and R²² is -C(=O)NR^cR^d.

[00245] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), A² is



(BC'), or (IIB), A² is

[00246] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), each R^a is independently C₁-C₆alkyl.

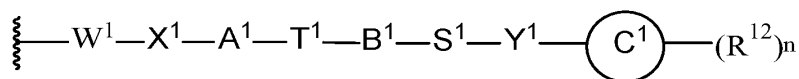
[00247] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), each R^b is independently hydrogen or C₁-C₆alkyl.

[00248] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), R^c and R^d are each independently hydrogen, C₁-C₆alkyl, -L-cycloalkyl, or -L-aryl, wherein each alkyl, cycloalkyl, and aryl is independently optionally substituted with one or more R.

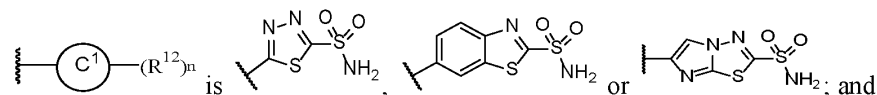
[00249] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), L is absent or C₁-C₃alkylene.

[00250] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), or (IIB), each R is independently C₁-C₃alkyl, C₁-C₃alkoxy, -C(=O)OH, or -C(=O)NH₂.

[00251] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), (IIB), (C), (C'), (CC), (CC'), or (IC), TL₁ has a structure of



wherein

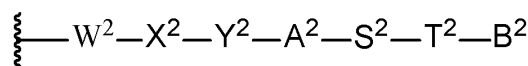


$\text{---W}^1\text{---X}^1\text{---A}^1\text{---T}^1\text{---B}^1\text{---S}^1\text{---Y}^1\text{---}$ are taken together to form a linking group that comprises 3 to 30 atoms (optionally, 5-25 atoms, 8-20 atoms, 8-15 atoms, or 10-14 atoms, or 8, 9, 10, 11, 12, 13, 14, or 15 atoms) in the linear chain. In some embodiments,

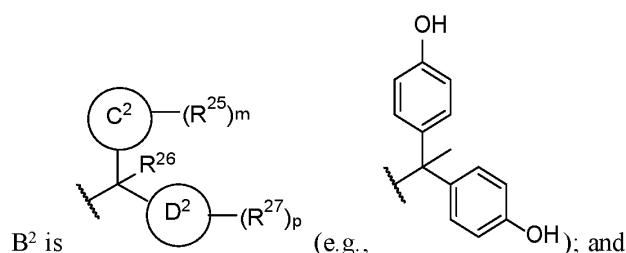
$\text{---W}^1\text{---X}^1\text{---A}^1\text{---T}^1\text{---B}^1\text{---S}^1\text{---Y}^1\text{---}$ are taken together to form a linking group that comprises 3 to 30 atoms in the linear chain, which are selected from C, N, and O. In some embodiments, the linking group comprises 3 to 30 atoms in the linear chain, including carbon, 1-5 N and 0-1 O. In some embodiments, the linking group comprises 3 to 30 atoms in the linear chain selected from N and C, including 2, 3, or 4 N. In some embodiments, the linking group comprises one or more cyclic groups, and the atoms in the linear chain comprises a part of the cyclic groups. In some embodiments, both A¹ and B¹

are cyclic groups. In some embodiments, the linking group comprises one or more groups selected from -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂-, optionally substituted C₁-C₁₀alkylene, optionally substituted C₁-C₁₀heteroalkylene, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl, or a combination thereof.

[00252] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), (IIB), (C), (C'), (CC), (CC'), or (IC), TL₂ is of the structure of



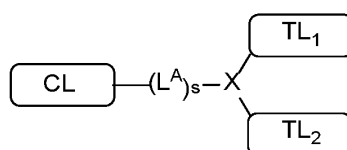
wherein



$\text{---}W^2-X^2-Y^2-A^2-S^2-T^2\text{---}$ are taken together to form a linking group that comprises 3 to 30 atoms (optionally, 5-25 atoms, 8-20 atoms, 8-15 atoms, or 10-14 atoms, or 8, 9, 10, 11, 12, 13, 14, or 15 atoms) in the linear chain. In some embodiments,

$\text{---}W^2-X^2-Y^2-A^2-S^2-T^2\text{---}$ together form a linking group that comprises 3 to 30 atoms in the linear chain, which are selected from C, N, and O. In some embodiments, the linking group comprises 3 to 30 atoms in the linear chain, including carbon, 1-5 N and 0-1 O. In some embodiments, the linking group comprises 3 to 30 atoms in the linear chain selected from N and C, including 2, 3, or 4 N. In some embodiments, the linking group comprises one or more cyclic groups, and the atoms in the linear chain comprises a part of the cyclic groups. In some embodiments, A² is a cyclic group. In some embodiments, the linking group comprises one or more groups selected from -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂-, optionally substituted C₁-C₁₀alkylene, optionally substituted C₁-C₁₀heteroalkylene, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl, or a combination thereof.

[00253] Also disclosed herein is a conjugate of Formula (C), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (C);

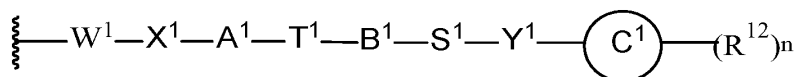
wherein:

 L^A represents a linker;

s is 0 or 1;

CL represents a metal chelator;

X is N, optionally substituted CH, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

 TL_1 is of Formula (IC):

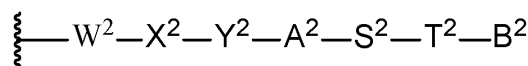
Formula (IC);

wherein:

 W^1 is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR¹¹-, -C(=O)-, -C(=O)NR¹¹-, -NR¹¹C(=O)-, -S(=O)₂NR¹¹-, or -NR¹¹S(=O)₂; X^1 is C₁-C₁₀alkylene optionally substituted with one or more R and wherein one, two, three, or four carbon atoms of the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR¹¹-; A^1 is absent, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R; T^1 is absent or C₁-C₃alkylene optionally substituted with one or more R and wherein one carbon atom of the C₁-C₃alkylene is optionally replaced with -C(=O)-, -S-, -S(=O)-, -S(=O)₂-, -O-, -NR¹¹-; B^1 is absent, C₁-C₁₀alkylene, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms in the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, -NR¹¹-; S^1 is absent or C₁-C₃alkylene optionally substituted with one or more R and wherein one or two carbon atoms of the C₁-C₃alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR¹¹-; Y^1 is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR¹¹-, -C(=O)-, -C(=O)NR¹¹-, -NR¹¹C(=O)-, -S(=O)₂NR¹¹-, or -NR¹¹S(=O)₂; R^{11} is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;Ring C^1 is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;each R^{12} is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

n is 0, 1, 2, 3, 4, 5, or 6;

TL₂ is of Formula (IIC):



Formula (IIC);

wherein:

W² is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂;

X² is absent or C₁-C₁₀alkylene optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms of the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR²¹-;

Y² is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂;

A² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²²;

each R²² is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

S² is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂;

T² is absent or C₁-C₁₀alkylene optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms of the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR²¹-;

R²¹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

(i) B² is absent;

or

(ii) B² is -N(R²³)₂;

each R²³ is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

or

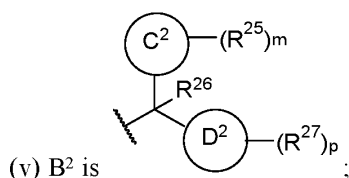
(iii) B² is -CF₃;

or

(iv) B² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²⁴;

each R^{24} is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

or



Ring C² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{25} is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

m is 0, 1, 2, 3, or 4;

R^{26} is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

Ring D² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{27} is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

p is 0, 1, 2, 3, or 4;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-

aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^e and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R;

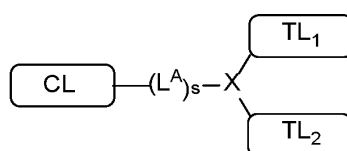
L is absent or C₁-C₃alkylene optionally substituted with one or more R; and

each R is independently halogen, -CN, -OH, -SF₅, -SH, -S(=O)C₁-C₃alkyl, -S(=O)₂C₁-C₃alkyl, -S(=O)₂NH₂, -S(=O)₂NHC₁-C₃alkyl, -S(=O)₂N(C₁-C₃alkyl)₂, -NH₂, -NHC₁-C₃alkyl, -N(C₁-C₃alkyl)₂, -C(=O)C₁-C₃alkyl, -C(=O)OH, -C(=O)OC₁-C₃alkyl, -C(=O)NH₂, -C(=O)NHC₁-C₃alkyl, -C(=O)N(C₁-C₃alkyl)₂, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃haloalkyl, C₁-C₃haloalkoxy, C₁-C₃hydroxyalkyl, C₁-C₃aminoalkyl, C₁-C₃heteroalkyl, C₃-C₆cycloalkyl, or 3- to 6-membered heterocycloalkyl;

or two R on the same atom form an oxo;

or two R on the same or different atoms are taken together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

[00254] Also disclosed herein is a conjugate of Formula (C), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (C);

wherein:

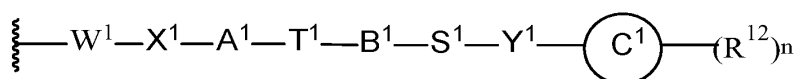
L^A represents a linker;

s is 0 or 1;

CL represents a metal chelator;

X is N, optionally substituted CH, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

TL₁ is of Formula (IC):



Formula (IC);

wherein:

W¹ is absent, -C(=O)-, or -C(=O)NR¹¹-;

X¹ is C₁-C₁₀alkylene;

A¹ is absent or heteroaryl optionally substituted with one or more R;

T¹ is absent;

B¹ is C₁-C₁₀alkylene or cycloalkyl;

S¹ is absent;

Y¹ is absent, -O-, -S-, -S(=O)₂-, -C(=O)NR¹¹-, or -NR¹¹C(=O)-;

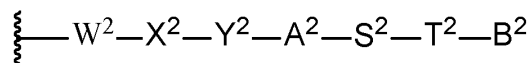
R¹¹ is hydrogen;

Ring C¹ is heteroaryl;

each R¹² is independently halogen, -S(=O)₂NR^cR^d, or -NR^cR^d; and

n is 0, 1, 2, or 3;

TL₂ is of Formula (IIC):



Formula (IIC);

wherein:

W² is absent, -C(=O)-, or -NR²¹C(=O)-;

X² is C₁-C₁₀alkylene optionally substituted with one or more R;

Y² is absent, -NR²¹-, or -NR²¹C(=O)-;

A² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²²;

each R²² is independently halogen, -CN, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆aminoalkyl;

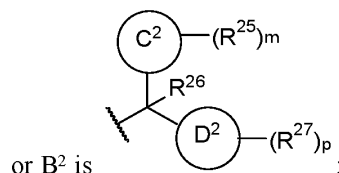
S² is absent, -NR²¹-, -C(=O)-, or -NR²¹C(=O)-;

T² is absent or C₁-C₁₀alkylene;

R²¹ is hydrogen;

B² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²⁴;

each R²⁴ is independently halogen, -OH, -SF₅, C₁-C₆alkyl, C₁-C₆haloalkyl, cycloalkyl, or heterocycloalkyl;



Ring C² is aryl;

each R²⁵ is independently halogen, -OH, or C₁-C₆alkyl;

m is 0, 1, or 2;

R²⁶ is hydrogen or C₁-C₆alkyl;

Ring D² is aryl;

each R²⁷ is independently halogen, -OH, or C₁-C₆alkyl;

p is 0, 1, or 2;

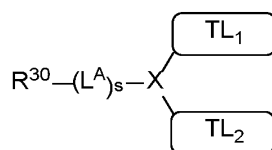
each R^b is independently hydrogen or C₁-C₆alkyl;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, -L-cycloalkyl, or -L-aryl, wherein each alkyl, cycloalkyl, and aryl is independently optionally substituted with one or more R;

L is absent or C₁-C₃alkylene; and

each R is independently C₁-C₃alkyl, C₁-C₃alkoxy, -C(=O)OH, or -C(=O)NH₂.

[00255] Disclosed herein is a conjugate of Formula (CC), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (CC)

wherein:

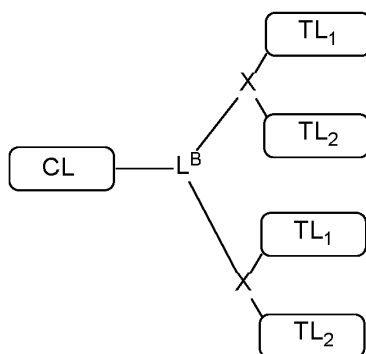
R³⁰ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted (e.g., with one or more R); or

R³⁰ is an albumin binding moiety or a payload moiety;

wherein the remaining groups have their meanings as defined in Formula (C).

[00256] In some embodiments, the conjugate compound of Formula (CC) comprises a covalently bound radioisotope.

[00257] Also disclosed herein is a conjugate of Formula (C'), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (C');

wherein:

L^B represents a linker;

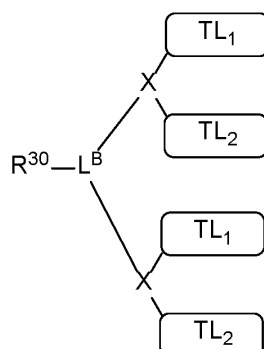
CL represents a metal chelator;

each X is independently N, optionally substituted CH, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each TL₁ represents a 1st targeting moiety that binds to carbonic anhydrase IX; and

each TL₂ represents a 2nd targeting moiety that binds to carbonic anhydrase IX.

[00258] Also disclosed herein is a conjugate of Formula (CC'), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (CC');

wherein:

L^B represents a linker;

each X is independently N, optionally substituted CH, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each TL₁ represents a 1st targeting moiety that binds to carbonic anhydrase IX;

each TL₂ represents a 2nd targeting moiety that binds to carbonic anhydrase IX; and

R³⁰ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted (e.g., with one or more R); or

R³⁰ is an albumin binding moiety or a payload moiety.

[00259] In some embodiments, the conjugate compound of Formula (CC') comprises a covalently bound radioisotope.

[00260] In some embodiments of a compound of Formula (C') or (CC'), each TL₁ is the same. In some embodiments of a compound of Formula (C') or (CC'), each TL₁ is different. In some embodiments of a compound of Formula (C') or (CC'), each TL₂ is the same. In some embodiments of a compound of Formula (C') or (CC'), each TL₂ is different. In some embodiments of a compound of Formula (C') or (CC'), each X is the same. In some embodiments of a compound of Formula (C') or (CC'), each X is different. In some embodiments of a compound of Formula (C') or (CC'), each TL₁ is independently a targeting moiety of Formula (IC). In some embodiments of a compound of Formula (C') or (CC'), each TL₂ is independently a targeting moiety of Formula (IIC).

[00261] In some embodiments of a compound of Formula (C') or (CC'), each TL₁ is defined in Formula (C). In some embodiments of a compound of Formula (C') or (CC'), each TL₂ is defined in Formula (C).

[00262] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IC), T¹ is absent or C₁-C₃alkylene.

[00263] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IC), T¹ is absent.

[00264] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IC), B¹ is C₁-C₁₀alkylene or cycloalkyl, wherein the alkylene and cycloalkyl is optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms in the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR¹¹-.

[00265] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IC), B¹ is C₁-C₁₀alkylene optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms in the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR¹¹-.

[00266] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IC), B¹ is C₁-C₁₀alkylene optionally substituted with one or more R.

[00267] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IC), B¹ is C₁-C₆alkylene.

[00268] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IC), B¹ is -CH₂CH₂CH₂-.

[00269] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IC), B¹ is -CH₂CH₂CH₂CH₂-.

[00270] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IC), B¹ is cycloalkyl optionally substituted with one or more R.

[00271] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IC), B¹ is a monocyclic cycloalkyl optionally substituted with one or more R.

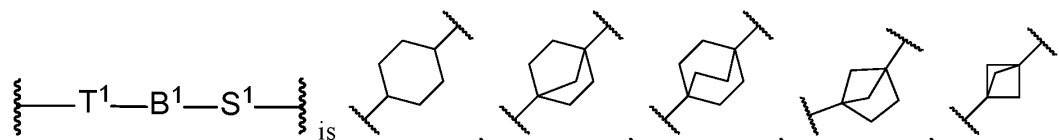
[00272] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IC), B¹ is a bicyclic cycloalkyl optionally substituted with one or more R.

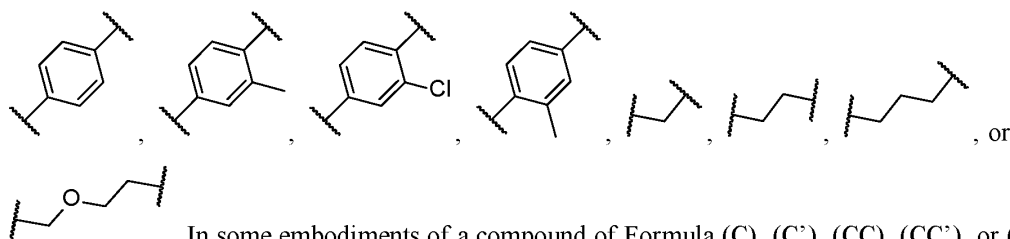
[00273] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IC), B¹ is bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, or bicyclo[2.1.1]hexanyl.

[00274] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IC), B¹ is bicyclo[1.1.1]pentanyl.

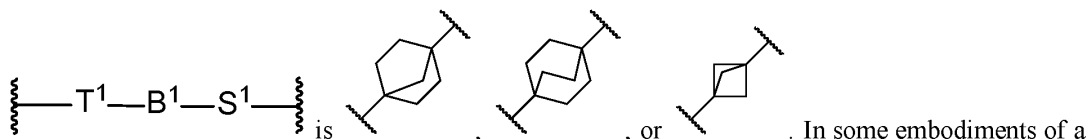
[00275] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IC), S¹ is absent.

[00276] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IC),





. In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IC),



compound of Formula (C), (C'), (CC), (CC'), or (IC), is .

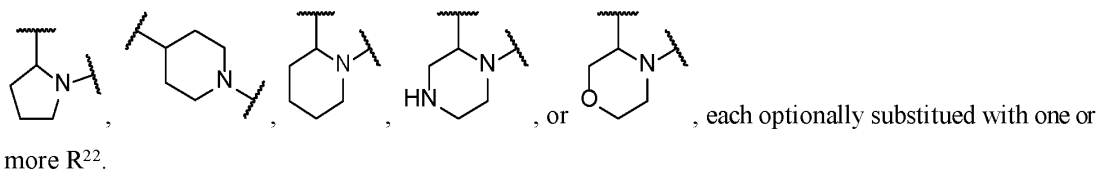
[00277] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), A² is heterocycloalkyl, aryl, or heteroaryl, wherein the heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²².

[00278] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), A² is heterocycloalkyl optionally substituted with one or more R²².

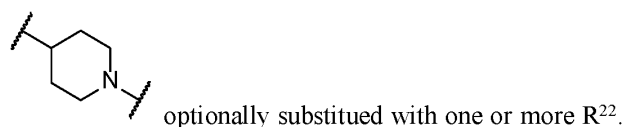
[00279] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), A² is pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl, each optionally substituted with one or more R²².

[00280] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), A² is piperidinyl optionally substituted with one or more R²².

[00281] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), A² is



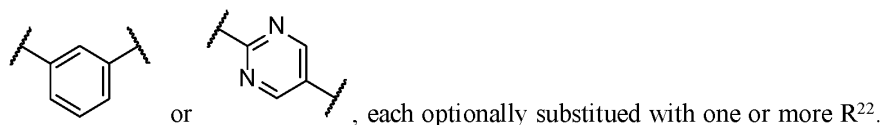
[00282] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), A² is



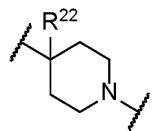
[00283] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), A² is aryl or heteroaryl, wherein the aryl and heteroaryl is optionally substituted with one or more R²².

[00284] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), A² is phenyl, pyridinyl, pyrimidinyl, or pyrazinyl, each optionally substituted with one or more R²².

[00285] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), A² is



[00286] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), A² is



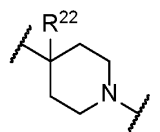
[00287] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), each R²² is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl.

[00288] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), each R²² is independently -CN, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, or C₁-C₆aminoalkyl.

[00289] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), each R²² is independently -C(=O)OR^b or -C(=O)NR^cR^d.

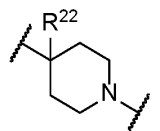
[00290] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), each R²² is independently -C(=O)NR^cR^d.

[00291] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), A² is



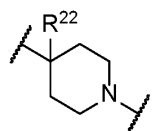
and R²² is halogen, -CN, -OH, -OR^a, -NR^cR^d, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl.

[00292] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), A² is



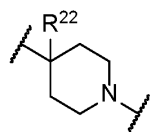
and R²² is -CN, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, or C₁-C₆aminoalkyl.

[00293] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), A² is



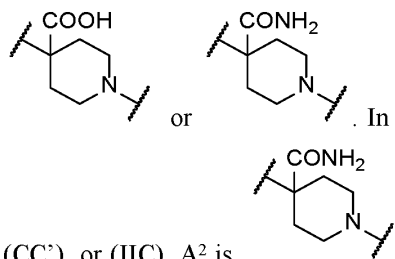
and R²² is -C(=O)OR^b or -C(=O)NR^cR^d.

[00294] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), A² is



and R²² is -C(=O)NR^cR^d.

[00295] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), A² is



In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), A² is

[00296] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), each R^a is independently or C₁-C₆alkyl.

[00297] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), each R^b is independently hydrogen or C₁-C₆alkyl.

[00298] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), R^c and R^d are each independently hydrogen, C₁-C₆alkyl, -L-cycloalkyl, or -L-aryl, wherein each alkyl, cycloalkyl, and aryl is independently optionally substituted with one or more R.

[00299] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), L is absent or C₁-C₃alkylene.

[00300] In some embodiments of a compound of Formula (C), (C'), (CC), (CC'), or (IIC), each R is independently C₁-C₃alkyl, C₁-C₃alkoxy, -C(=O)OH, or -C(=O)NH₂.

[00301] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), (C), (C'), (CC), or (CC'), X is CH. In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), (C), (C'), (CC), or (CC'), X is CH optionally substituted with halogen or C₁-C₆alkyl. In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), (C), (C'), (CC), or (CC'), X is N.

[00302] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), (C), (C'), (CC), or (CC'), X is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R; and each R is independently halogen, -CN, -OH, -SF₅, -SH, -S(=O)C₁-C₃alkyl, -S(=O)₂C₁-C₃alkyl, -

S(=O)₂NH₂, -S(=O)₂NHC₁-C₃alkyl, -S(=O)₂N(C₁-C₃alkyl)₂, -NH₂, -NHC₁-C₃alkyl, -N(C₁-C₃alkyl)₂, -C(=O)C₁-C₃alkyl, -C(=O)OH, -C(=O)OC₁-C₃alkyl, -C(=O)NH₂, -C(=O)NHC₁-C₃alkyl, -C(=O)N(C₁-C₃alkyl)₂, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃haloalkyl, C₁-C₃haloalkoxy, C₁-C₃hydroxyalkyl, C₁-C₃aminoalkyl, C₁-C₃heteroalkyl, C₃-C₆cycloalkyl, or 3- to 6-membered heterocycloalkyl;

or two R on the same atom form an oxo.

[00303] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), (C), (C'), (CC), or (CC'), X is optionally substituted heterocycloalkyl.

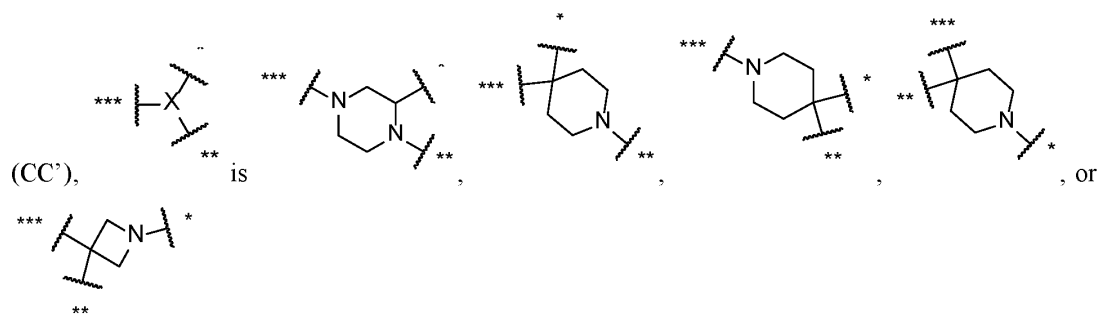
[00304] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), (C), (C'), (CC), or (CC'), X is heterocycloalkyl optionally substituted with one or more R.

[00305] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), (C), (C'), (CC), or (CC'), X is monocyclic heterocycloalkyl optionally substituted with one or more R.

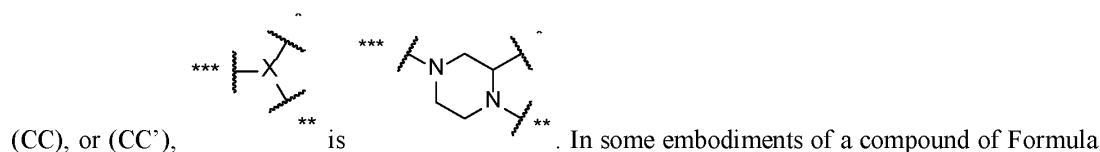
[00306] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), (C), (C'), (CC), or (CC'), X is bicyclic heterocycloalkyl optionally substituted with one or more R. In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), (C), (C'), (CC), or (CC'), X is spirobicyclic heterocycloalkyl optionally substituted with one or more

[00307] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), (C), (C'), (CC), or (CC'), X is 4- to 6-membered heterocycloalkyl optionally substituted with one or more R. In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), (C), (C'), (CC), or (CC'), X is azetidiny, pyrrolidinyl, piperidinyl, or piperazinyl, each optionally substituted with one or more R. In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), (C), (C'), (CC), or (CC'), X is piperidinyl or piperazinyl, each optionally substituted with one or more R. In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), (C), (C'), (CC), or (CC'), X is piperidinyl optionally substituted with one or more R. In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), (C), (C'), (CC), or (CC'), X is piperazinyl optionally substituted with one or more R.

[00308] In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), (C), (C'), (CC), or

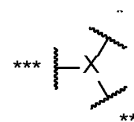


. In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), (C), (C'),

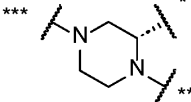


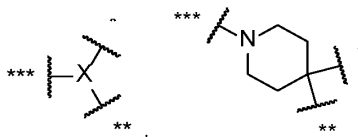



is In some



embodiments of a compound of Formula (B), (B'), (BC), (BC'), (C), (C'), (CC), or (CC'),

is . In some embodiments of a compound of Formula (B), (B'), (BC), (BC'), (C),

(C'), (CC), or (CC'),  is

[00309] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), W¹ is absent, -O-, -S-, -NR¹¹-, -C(=O)-, -C(=O)NR¹¹-, or -NR¹¹C(=O)-.

[00310] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), W¹ is absent, -C(=O)-, or -C(=O)NR¹¹-.

[00311] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), W¹ is absent.

[00312] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), W¹ is -C(=O)-.

[00313] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), W¹ is -C(=O)NR¹¹-.

[00314] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), X¹ is C₁-C₆alkylene optionally substituted with one or more R and wherein one or two carbon atoms of the C₁-C₆alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR¹¹-.

[00315] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), X¹ is C₁-C₆alkylene.

[00316] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), X¹ is C₁-C₄alkylene.

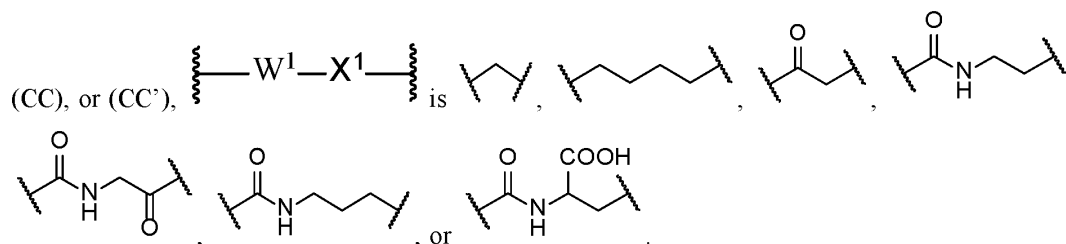
[00317] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), X¹ is -CH₂-.

[00318] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), X¹ is -CH₂CH₂-.

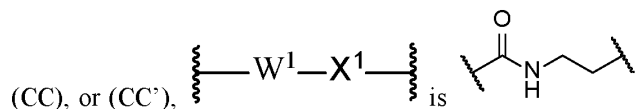
[00319] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), X¹ is -CH₂CH₂CH₂-.

[00320] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), X¹ is -CH₂CH₂CH₂CH₂-.

[00321] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'),



[00322] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'),

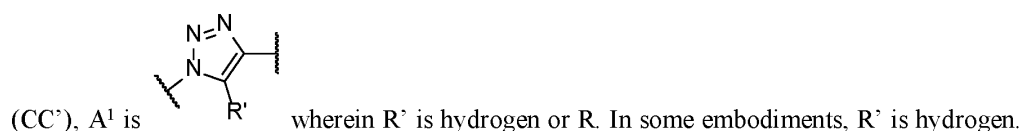
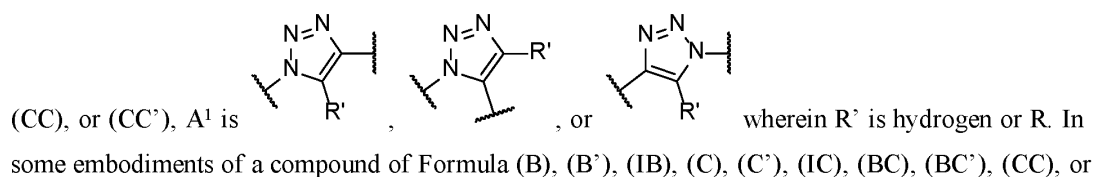


[00323] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), A¹ is absent.

[00324] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), A¹ is heteroaryl optionally substituted with one or more R.

[00325] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), A¹ is triazolyl optionally substituted with one or more R.

[00326] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'),

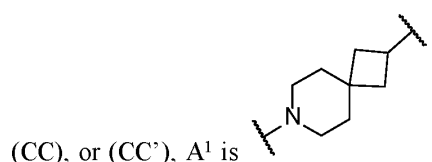


[00327] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), A¹ is heterocycloalkyl optionally substituted with one or more R.

[00328] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), A¹ is monocyclic heterocycloalkyl optionally substituted with one or more R.

[00329] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), A¹ is bicyclic heterocycloalkyl optionally substituted with one or more R.

[00330] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'),



[00331] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), T¹ is absent or C₁-C₃alkylene.

[00332] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), T¹ is absent.

[00333] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), B¹ is cycloalkyl optionally substituted with one or more R.

[00334] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), B¹ is a monocyclic cycloalkyl optionally substituted with one or more R.

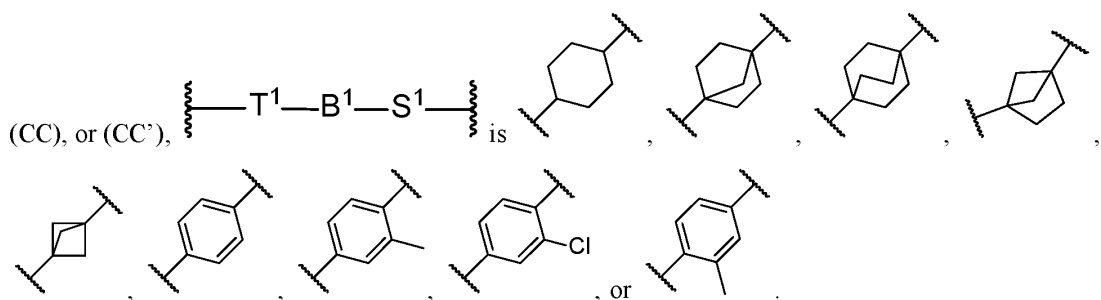
[00335] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), B¹ is a bicyclic cycloalkyl optionally substituted with one or more R.

[00336] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), B¹ is bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, or bicyclo[2.1.1]hexanyl.

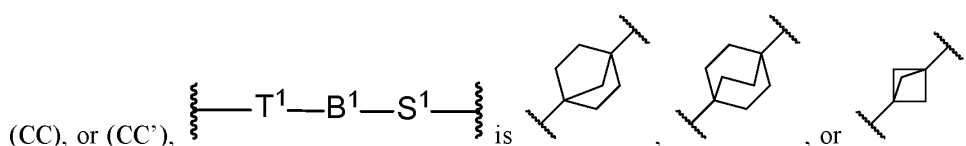
[00337] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), B¹ is bicyclo[1.1.1]pentanyl.

[00338] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), S¹ is absent.

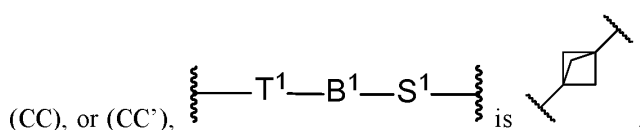
[00339] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'),



[00340] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'),



[00341] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'),

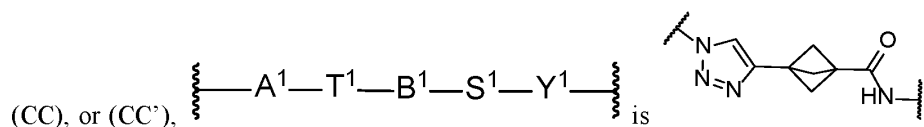


[00342] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), Y¹ is absent, -O-, -S-, -S(=O)₂-, -C(=O)NR¹¹-, or -NR¹¹C(=O)-.

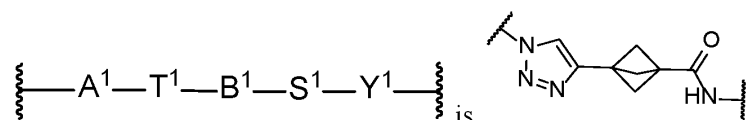
[00343] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), Y¹ is -S(=O)₂-.

[00344] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), Y¹ is -C(=O)NR¹¹-.

[00345] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'),



or In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'),

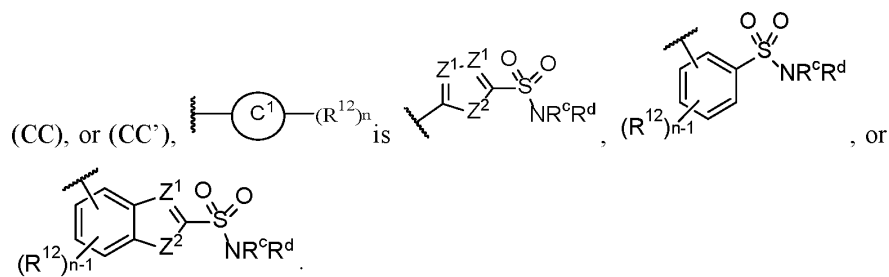


[00346] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), Ring C¹ is aryl or heteroaryl. In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), Ring C¹ is phenyl or heteroaryl. In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), Ring C¹ is heteroaryl. In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), Ring C¹ is 5- to 12-membered heteroaryl. In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), Ring C¹ is 5- to 10-membered heteroaryl. In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), Ring C¹ is 5- to 6-membered heteroaryl. In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), Ring C¹ is 7- to 10-membered heteroaryl. In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), Ring C¹ is monocyclic heteroaryl. In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), Ring C¹ thiadiazolyl or phenyl. In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), Ring C¹ thiadiazolyl. In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), Ring C¹ phenyl.

[00347] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), Ring C¹ is bicyclic heteroaryl.

[00348] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), Ring C¹ is benzothiazolyl or imidazothiadiazolyl.

[00349] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'),



wherein each Z^1 is independently -N- or $-\text{CR}^{12'}$ -;

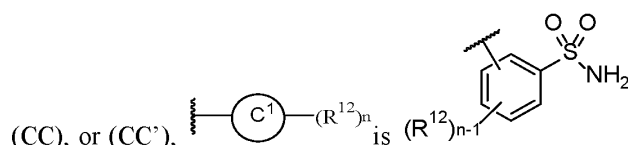
Z^2 is -O-, -S-, or $-\text{NR}^{12''}$ -;

each $\text{R}^{12'}$ is independently hydrogen, halogen, -CN, -OH, $-\text{OR}^{\text{a}}$, $-\text{NR}^{\text{c}} \text{R}^{\text{d}}$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, cycloalkyl, or heterocycloalkyl; and

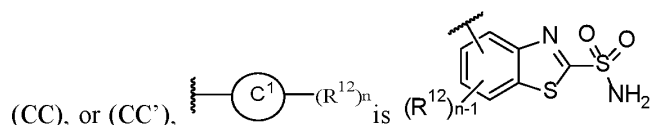
$\text{R}^{12''}$ is hydrogen, $-\text{S}(\text{O})\text{R}^{\text{a}}$, $-\text{S}(\text{O})_2\text{R}^{\text{a}}$, $-\text{S}(\text{O})_2\text{NR}^{\text{c}} \text{R}^{\text{d}}$, $-\text{C}(\text{O})\text{R}^{\text{a}}$, $-\text{C}(\text{O})\text{OR}^{\text{b}}$, $-\text{C}(\text{O})\text{NR}^{\text{c}} \text{R}^{\text{d}}$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, cycloalkyl, or heterocycloalkyl.

[00350] In some embodiments, Z^2 is -O- or -S-. In some embodiments, Z^2 is -S-. In some embodiments, each Z^1 is -N-.

[00351] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'),



[00352] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'),



[00353] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), each R^{12} is independently halogen, -CN, -OH, $-\text{OR}^{\text{a}}$, $-\text{S}(\text{O})\text{R}^{\text{a}}$, $-\text{S}(\text{O})_2\text{R}^{\text{a}}$, $-\text{S}(\text{O})_2\text{NR}^{\text{c}} \text{R}^{\text{d}}$, $-\text{NR}^{\text{c}} \text{R}^{\text{d}}$, $-\text{C}(\text{O})\text{R}^{\text{a}}$, $-\text{C}(\text{O})\text{OR}^{\text{b}}$, $-\text{C}(\text{O})\text{NR}^{\text{c}} \text{R}^{\text{d}}$, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl.

[00354] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), each R^{12} is independently halogen, -CN, -OH, $-\text{OR}^{\text{a}}$, $-\text{S}(\text{O})\text{R}^{\text{a}}$, $-\text{S}(\text{O})_2\text{R}^{\text{a}}$, $-\text{NR}^{\text{c}} \text{R}^{\text{d}}$, $-\text{C}(\text{O})\text{R}^{\text{a}}$, $-\text{C}(\text{O})\text{OR}^{\text{b}}$, $-\text{C}(\text{O})\text{NR}^{\text{c}} \text{R}^{\text{d}}$, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl.

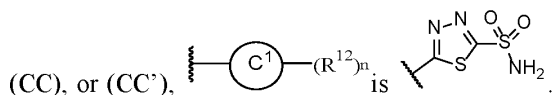
[00355] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), each R^{12} is independently halogen, $-\text{S}(\text{O})_2\text{NR}^{\text{c}} \text{R}^{\text{d}}$, or $-\text{NR}^{\text{c}} \text{R}^{\text{d}}$.

[00356] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), each R^{12} is independently halogen or $-\text{NR}^{\text{c}} \text{R}^{\text{d}}$. In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), one of R^{12} is $-\text{S}(\text{O})_2\text{NR}^{\text{c}} \text{R}^{\text{d}}$.

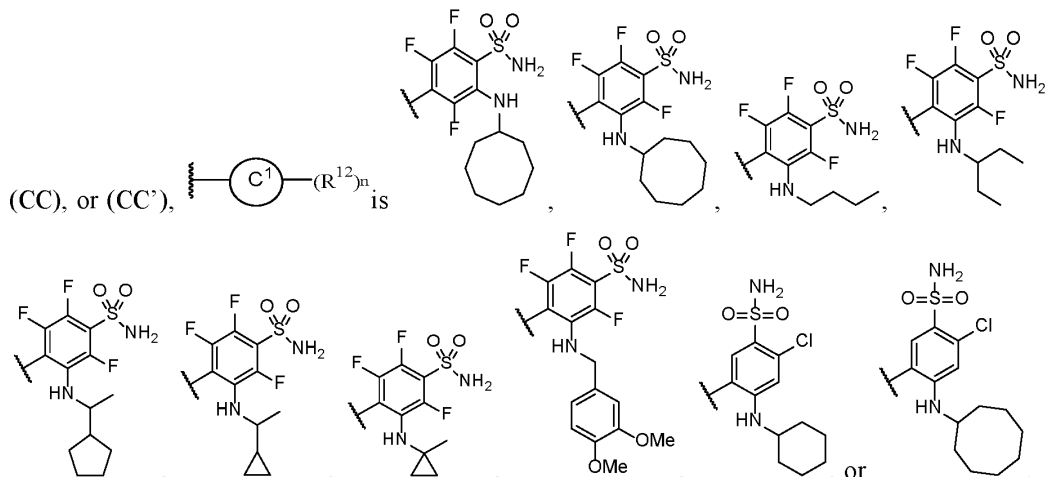
[00357] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), n is 0, 1, 2, 3, 4, or 5. In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), n is 0, 1, 2, 3, or 4. In some embodiments of a compound of

Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), n is 0, 1, 2, or 3. In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), n is 0, 1, or 2. In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'), (CC), or (CC'), n is 0 or 1.

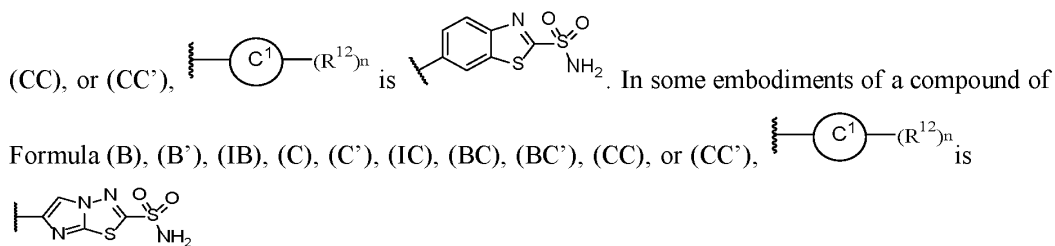
[00358] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'),



[00359] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'),



[00360] In some embodiments of a compound of Formula (B), (B'), (IB), (C), (C'), (IC), (BC), (BC'),



[00361] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), W² is absent, -C(=O)-, or -NR²¹C(=O)-.

[00362] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), W² is -C(=O)-.

[00363] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), W² is absent. In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), W² is -C(=O)-.

[00364] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), X² is C₁-C₆alkylene optionally substituted with one or more R.

[00365] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), X² is C₁-C₄alkylene optionally substituted with one or more R.

[00366] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), X² is -CH₂-.

[00367] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), X² is -CH₂CH[C(=O)OH]- or -CH₂CH[C(=O)NH₂]-.

[00368] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), X² is -CH₂CH₂CH[(C=O)OH]- or -CH₂CH₂CH[C(=O)NH₂]-.

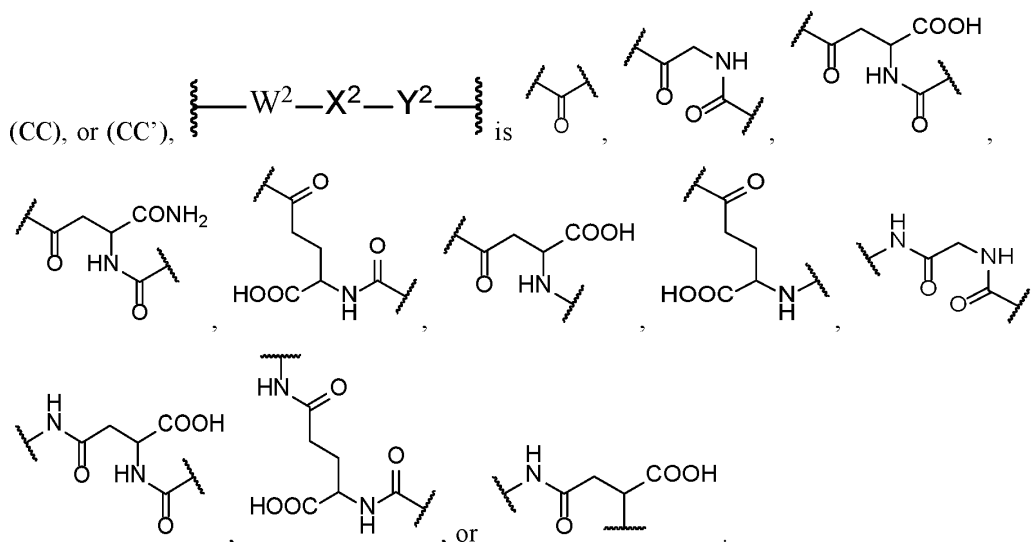
[00369] In embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), X² is optionally substituted with one or more R, and wherein one or two carbon atoms of the C₁-C₁₀alkylene are replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR²¹-.

[00370] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), Y² is absent, -O-, -S-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, or -NR²¹C(=O)-.

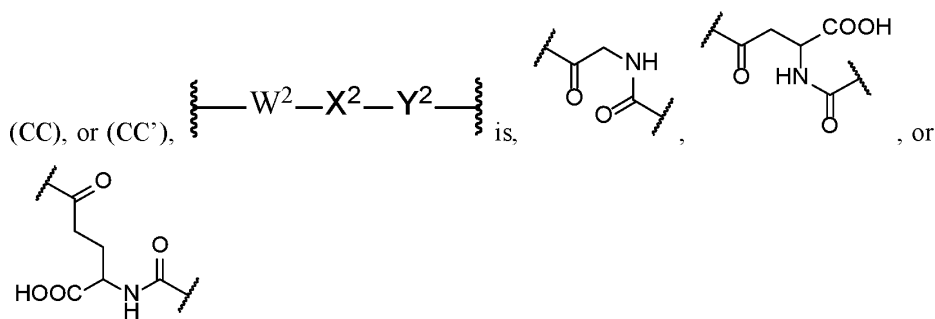
[00371] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), Y² is absent, -NR²¹-, or -NR²¹C(=O)-.

[00372] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), Y² is -NR²¹C(=O)-.

[00373] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'),



[00374] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'),



[00375] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), S² is absent, -O-, -S-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, or -NR²¹C(=O)-.

[00376] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), S² is absent, -NR²¹-, -C(=O)-, or -NR²¹C(=O)-.

[00377] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), S² is -C(=O)- or -NR²¹C(=O)-.

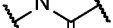
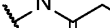
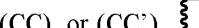
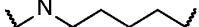
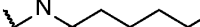
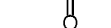
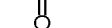
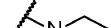
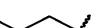
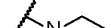
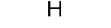
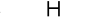
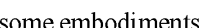
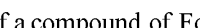
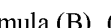
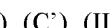
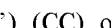
[00378] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), T² is absent or C₁-C₆alkylene optionally substituted with one or more R.

[00379] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), T² is C₁-C₆alkylene optionally substituted with one or more R.

[00380] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), T² is -CH₂CH₂-.

[00381] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), T² is -CH₂CH₂CH₂-.

[00382] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'),

(CC), or (CC'),  is , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , ,

$(CC')_n$ is or

[00383] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), B² is absent.

[00384] In embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), B² is -N(R²³)₂. In embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), B² is -CF₃.

[00385] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), B² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²⁴.

[00386] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), B² is cycloalkyl optionally substituted with one or more R²⁴.

[00387] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), B² is monocyclic cycloalkyl optionally substituted with one or more R²⁴.

[00388] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), B² is bicyclic cycloalkyl optionally substituted with one or more R²⁴.

[00389] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), B² is phenyl optionally substituted with one or more R²⁴.

[00390] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), B² is heteroaryl optionally substituted with one or more R²⁴.

[00391] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), B² is 5- to 10-membered heteroaryl (e.g., monocyclic or bicyclic heteroaryl) optionally substituted with one or more R²⁴.

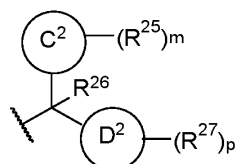
[00392] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), B² is 5- to 6-membered heteroaryl optionally substituted with one or more R²⁴.

[00393] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), B² is indazolyl, phenyl, pyridyl, pyridinyl, pyrazinyl, pyridazinyl, cyclopropyl, cyclohexyl, cyclobutyl, cycloheptyl, pyrazolyl, oxazolyl, triazolyl, spiroheptanyl, or bicycloheptanyl.

[00394] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), each R²⁴ is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, -SF₅, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R.

[00395] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), each R²⁴ is independently halogen, -OH, C₁-C₆alkyl, or C₁-C₆haloalkyl.

[00396] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'),



(CC), or (CC'), B² is

wherein:

Ring C² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R²⁵ is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl,

heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

m is 0, 1, 2, 3, or 4;

R²⁶ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

Ring D² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R²⁷ is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R; p is 0, 1, 2, 3, or 4.

[00397] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), Ring C² is phenyl.

[00398] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), each R²⁵ is independently halogen, -CN, -OH, -OR^a, -SF₅, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆hydroxyalkyl. In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), each R²⁵ is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, or C₁-C₆alkyl. In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), each R²⁵ is independently -OH.

[00399] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), m is 0 or 1. In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), m is 0, 1, or 2. In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), m is 0. In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), m is 1. In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), m is 2. In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), m is 3.

[00400] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), Ring D² is phenyl.

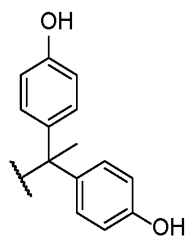
[00401] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), each R²⁷ is independently halogen, -CN, -OH, -OR^a, -SF₅, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆hydroxyalkyl. In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), each R²⁷ is independently halogen, -CN, -OH, -OR^a, -NR^cR^d, or C₁-C₆alkyl. In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), each R²⁷ is independently -OH.

[00402] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), p is 0 or 1. In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), p is 0, 1, or 2. In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), p is 0. In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), p is 1. In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), p is 2. In some

embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), p is 3.

[00403] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), R²⁶ is hydrogen or C₁-C₆alkyl. In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), R²⁶ is C₁-C₆alkyl.

[00404] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'),



(CC), or (CC'), B² is

[00405] In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), R¹¹ is hydrogen or C₁-C₆alkyl. In some embodiments of a compound of Formula (B), (B'), (IIB), (C), (C'), (IIC), (BC), (BC'), (CC), or (CC'), R¹¹ is hydrogen.

[00406] In some embodiments of a compound of Formula (A'), (A), (B), (B'), (C), (C'), (AC), (AC'), (BC), (BC'), (CC), or (CC'), TL₁ and TL₂ bind to different sites of the same carbonic anhydrase IX protein. In some embodiments of a compound of Formula (A'), (A), (B), (B'), (C), (C'), (AC), (AC'), (BC), (BC'), (CC), or (CC'), TL₁ is a targeting moiety that binds to a carbonic anhydrase IX protein at a first binding site. In some embodiments of a compound of Formula (A'), (A), (B), (B'), (C), (C'), (AC), (AC'), (BC), (BC'), (CC), or (CC'), TL₁ is a targeting moiety that binds to a carbonic anhydrase IX protein at a site that is different from the binding site of TL₂. In some embodiments of a compound of Formula (A'), (A), (B), (B'), (C), (C'), (AC), (AC'), (BC), (BC'), (CC), or (CC'), TL₂ is a targeting moiety that binds to carbonic anhydrase IX protein at a second binding site. In some embodiments of a compound of Formula (A'), (A), (B), (B'), (C), (C'), (AC), (AC'), (BC), (BC'), (CC), or (CC'), TL₂ is a targeting moiety that binds to a carbonic anhydrase IX protein at a site that is different from the binding site of TL₁.

[00407] In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), s is 0.

[00408] In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), s is 1.

[00409] In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), the linker comprises 1 to 30 intervening atoms selected from C, N, O, S, and Si between the metal chelator (CL) and the targeting ligand (TL).

[00410] In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), the linker comprises 1 to 20 intervening atoms selected from C, N, O, S, and Si between the metal chelator (CL) and the targeting ligand (TL).

[00411] In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), the linker comprises 1 to 10 intervening atoms selected from C, N, O, S, and Si between the metal chelator (CL) and the targeting ligand (TL).

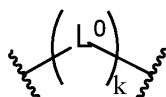
[00412] In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), the intervening atoms comprise C, N, or O. In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), the intervening atoms comprise at least one N atom.

[00413] In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), the intervening atoms comprise at least one O atom.

[00414] In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), the linker comprises one or more amino acid residues.

[00415] In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), the linker comprises one or more PEG moieties. In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), the linker comprises between 2 and 8 PEG moieties. In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), the linker comprises 2 PEG moieties. In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), the linker comprises 8 PEG moieties

[00416] In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), the linker L^A has a structure of Formula (L-1)



Formula (L-1),

wherein:

each L^0 is independently -O-, -NR^L-, -N(R^L)₂⁺-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, -S(=O)₂-, =CH-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -NR^LC(=S)NR^L-, -CR^L=N-, -N=CR^L-, -NR^LS(=O)₂-, -S(=O)₂NR^L-, -C(=O)NR^LS(=O)₂-, -S(=O)₂NR^LC(=O)-, cycloalkylene, heterocycloalkylene, arylene, heteroarylene, C₁-C₃₀alkylene, C₂-C₃₀alkenylene, C₂-C₃₀alkynylene, C₁-C₃₀heteroalkylene, -(C₁-C₃₀alkylene)-O-, -O-(C₁-C₃₀alkylene)-, -(C₁-C₃₀alkylene)-NR^L-, -NR^L-(C₁-C₃₀alkylene)-, -(C₁-C₃₀alkylene)-N(R^L)₂⁺-, or -N(R^L)₂⁺-(C₁-C₃₀alkylene)-; wherein each cycloalkylene, heterocycloalkylene, arylene, heteroarylene, alkylene, alkenylene, alkynylene, and heteroalkylene is optionally independently substituted with one or more R;

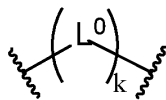
each R^L is independently hydrogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

k is 1-20;

each R is independently halogen, -CN, -OH, -SF₅, -SH, -S(=O)C₁-C₃alkyl, -S(=O)₂C₁-C₃alkyl, -S(=O)₂NH₂, -S(=O)₂NHC₁-C₃alkyl, -S(=O)₂N(C₁-C₃alkyl)₂, -NH₂, -NHC₁-C₃alkyl, -N(C₁-C₃alkyl)₂, -C(=O)C₁-C₃alkyl, -C(=O)OH, -C(=O)OC₁-C₃alkyl, -C(=O)NH₂, -C(=O)NHC₁-C₃alkyl, -C(=O)N(C₁-C₃alkyl)₂, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃haloalkyl, C₁-C₃haloalkoxy, C₁-C₃hydroxyalkyl, C₁-C₃aminoalkyl, C₁-C₃heteroalkyl, C₃-C₆cycloalkyl, or 3- to 6-membered heterocycloalkyl;

or two R on the same atom form an oxo.

[00417] In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), the linker L^A has a structure of Formula (L-1)



Formula (L-1),

wherein:

each L^0 is independently -O-, -NR^L-, -C(=O)-, -OC(=O)-, -C(=O)NR^L-, -NR^LC(=O)-, cycloalkylene, heterocycloalkylene, C₁-C₃₀alkylene, -(C₁-C₃₀alkylene)-O-, or -O-(C₁-C₃₀alkylene)-; wherein each cycloalkylene, heterocycloalkylene, and alkylene is optionally independently substituted with one or more R;

each R^L is independently hydrogen or C₁-C₄alkyl;

k is 1-20; and

R is independently -C(=O)OH.

[00418] In some embodiments of a compound of Formula (L-1), each L^0 is independently -O-, -NR^L-, -C(=O)-, -C(=O)O-, -OC(=O)-, -C(=O)NR^L-, -NR^LC(=O)-, cycloalkylene, heterocycloalkylene, C₁-C₃₀alkylene, C₁-C₃₀heteroalkylene, -(C₁-C₃₀alkylene)-O-, -O-(C₁-C₃₀alkylene)-, -(C₁-C₃₀alkylene)-NR^L-, or -NR^L-(C₁-C₃₀alkylene)-; wherein each cycloalkylene, heterocycloalkylene, alkylene, and heteroalkylene is optionally independently substituted with one or more R.

[00419] In some embodiments of a compound of Formula (L-1), each L^0 is independently -O-, -NR^L-, -C(=O)-, -C(=O)O-, -OC(=O)-, -C(=O)NR^L-, -NR^LC(=O)-, heterocycloalkylene, C₁-C₃₀alkylene, C₁-C₃₀heteroalkylene, -(C₁-C₃₀alkylene)-O-, or -O-(C₁-C₃₀alkylene)-; wherein each heterocycloalkylene, alkylene, and heteroalkylene is optionally independently substituted with one or more R.

[00420] In some embodiments of a compound of Formula (L-1), each L^0 is independently -O-, -NR^L-, -C(=O)-, -OC(=O)-, -NR^LC(=O)-, heterocycloalkylene, C₁-C₃₀alkylene, C₁-C₃₀heteroalkylene, or -O-(C₁-C₃₀alkylene)-; wherein each heterocycloalkylene, alkylene, and heteroalkylene is optionally independently substituted with one or more R.

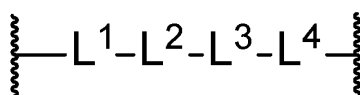
[00421] In some embodiments of a compound of Formula (L-1), each L^0 is independently -O-, -NR^L-, -C(=O)-, -OC(=O)-, -NR^LC(=O)-, heterocycloalkylene, C₁-C₆alkylene, C₁-C₆heteroalkylene, or -O-(C₁-C₆alkylene)-; wherein each heterocycloalkylene, alkylene, and heteroalkylene is optionally independently substituted with one or more R.

[00422] In some embodiments of a compound of Formula (L-1), each L^0 is independently -O-, -NR^L-, -C(=O)-, -OC(=O)-, -NR^LC(=O)-, heterocycloalkylene, C₁-C₄alkylene, C₁-C₄heteroalkylene, or -O-(C₁-C₄alkylene)-; wherein each heterocycloalkylene, alkylene, and heteroalkylene is optionally independently substituted with one or more R.

[00423] In some embodiments of a compound of Formula (L-1), each R^L is independently hydrogen or C₁-C₄alkyl. In some embodiments of a compound of Formula (L-1), each R^L is hydrogen.

[00424] In some embodiments of a compound of Formula (L-1), k is 1-15. In some embodiments of a compound of Formula (L-1), k is 1-14. In some embodiments of a compound of Formula (L-1), k is 1-13. In some embodiments of a compound of Formula (L-1), k is 1-12. In some embodiments of a compound of Formula (L-1), k is 1-11. In some embodiments of a compound of Formula (L-1), k is 1-10. In some embodiments of a compound of Formula (L-1), k is 1-9. In some embodiments of a compound of Formula (L-1), k is 1-8. In some embodiments of a compound of Formula (L-1), k is 1-7. In some embodiments of a compound of Formula (L-1), k is 1-6. In some embodiments of a compound of Formula (L-1), k is 1-5. In some embodiments of a compound of Formula (L-1), k is 1-4. In some embodiments of a compound of Formula (L-1), k is 1-3. In some embodiments of a compound of Formula (L-1), k is 1 or 2.

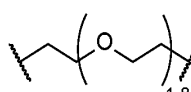
[00425] In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), the linker L^A has a structure of Formula (L-1a),



Formula (L-1a);

wherein:

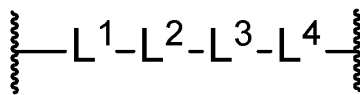
L^1 is absent, $-O-$, $-NR^L-$, $-N(R^L)_2^+$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, $-C(=O)-$, $-C(=O)O-$, $-OC(=O)-$, $-OC(=O)O-$, $-C(=O)NR^L-$, $-NR^LC(=O)-$, $-OC(=O)NR^L-$, $-NR^LC(=O)O-$, $-NR^LC(=O)NR^L-$, $-NR^LS(=O)_2-$, $-S(=O)_2NR^L-$, $-C(=O)NR^LS(=O)_2-$, or $-S(=O)_2NR^LC(=O)-$;

L^2 is , C_1-C_{10} alkylene, or heterocycloalkylene optionally substituted with one or more R;

L^3 is absent or C_1-C_{10} alkylene; and

L^4 is absent, $-O-$, $-NR^L-$, $-N(R^L)_2^+$, $-S-$, $-S(=O)-$, $-S(=O)_2-$, $-C(=O)-$, $-C(=O)O-$, $-OC(=O)-$, $-OC(=O)O-$, $-C(=O)NR^L-$, $-NR^LC(=O)-$, $-OC(=O)NR^L-$, $-NR^LC(=O)O-$, $-NR^LC(=O)NR^L-$, $-NR^LS(=O)_2-$, $-S(=O)_2NR^L-$, $-C(=O)NR^LS(=O)_2-$, or $-S(=O)_2NR^LC(=O)-$.

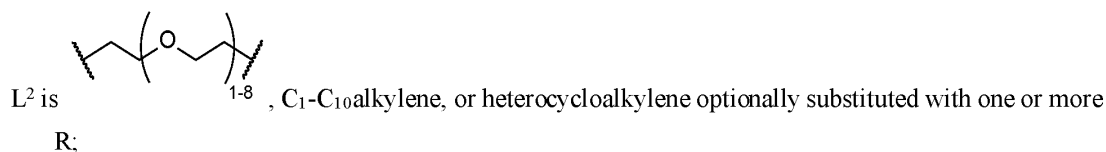
[00426] In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), the linker L^A has a structure of Formula (L-1a),



Formula (L-1a);

wherein:

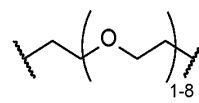
L^1 is absent, $-O-$, or $-NR^L-$;



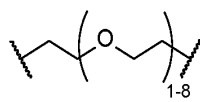
L³ is absent or C₁-C₁₀alkylene; and

L⁴ is absent, -O-, -NR^L-, -C(=O)-, -C(=O)O-, -OC(=O)-, -C(=O)NR^L-, or -NR^LC(=O)-.

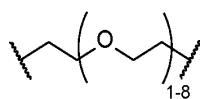
[00427] In some embodiments of a compound of Formula (L-1a), L¹ is absent, -O-, -NR^L-, -C(=O)-, -C(=O)O-, -OC(=O)-, -C(=O)NR^L-, or -NR^LC(=O)-. In some embodiments of a compound of Formula (L-1a), L¹ is absent, -O-, or -NR^L-. In some embodiments of a compound of Formula (L-1a), L¹ is absent or -NR^L-. In some embodiments of a compound of Formula (L-1a), L¹ is absent or -NH-.



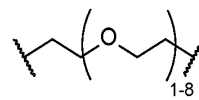
[00428] In some embodiments of a compound of Formula (L-1a), L² is ¹⁻⁸, C₁-C₆alkylene, or heterocycloalkylene optionally substituted with one or more R. In some embodiments of a



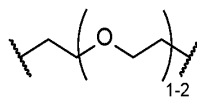
compound of Formula (L-1a), L² is ¹⁻⁸, C₁-C₄alkylene, or heterocycloalkylene optionally substituted with one or more R. In some embodiments of a compound of Formula (L-1a), L² is



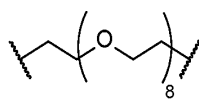
or heterocycloalkylene optionally substituted with one or more R.



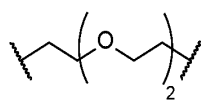
[00429] In some embodiments of a compound of Formula (L-1a), L² is . In some



embodiments of a compound of Formula (L-1a), L² is C_6H_4 or C_6H_2 . In some embodiments of a



compound of Formula (L-1a), L² is . In some embodiments of a compound of



Formula (L-1a), L^2 is

[00430] In some embodiments of a compound of Formula (L-1a), L² is C₁-C₁₀alkylene. In some embodiments of a compound of Formula (L-1a), L² is C₁-C₆alkylene. In some embodiments of a compound of Formula (L-1a), L² is C₁-C₄alkylene.

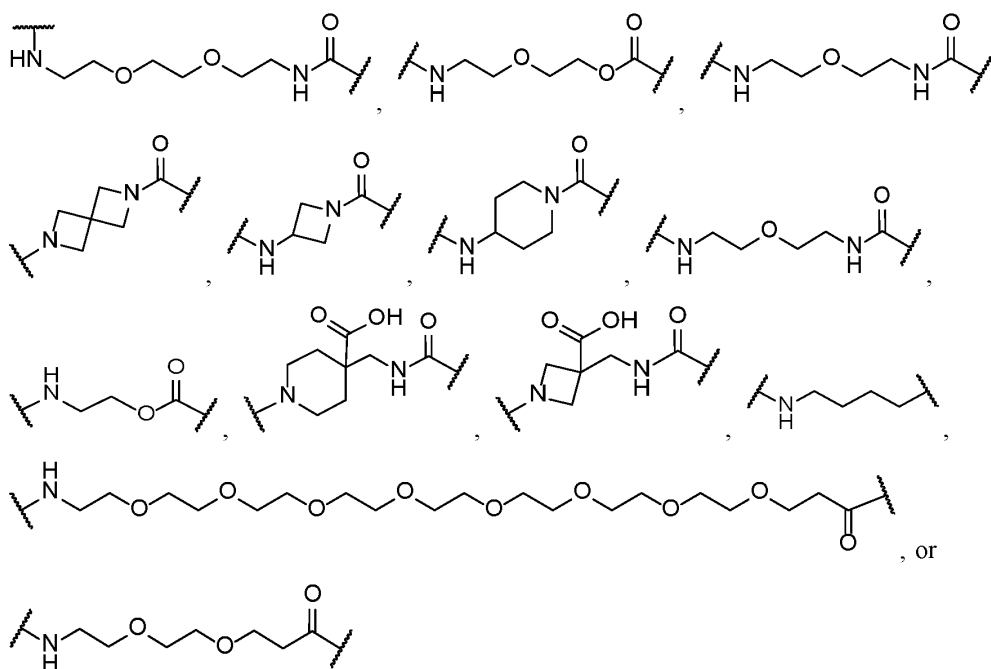
[00431] In some embodiments of a compound of Formula (L-1a), L² is heterocycloalkylene optionally substituted with one or more R. In some embodiments of a compound of Formula (L-1a), L² is monocyclic heterocycloalkylene optionally substituted with one or more R. In some embodiments of a compound of Formula (L-1a), L² is bicyclic heterocycloalkylene optionally substituted with one or more

R. In some embodiments of a compound of Formula (L-1a), L² is piperidinylene, azetidinylen, or diazaspироheptanylene; each optionally substituted with one or more R.

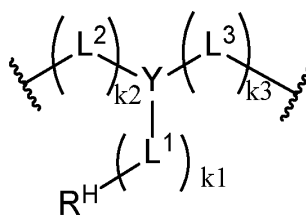
[00432] In some embodiments of a compound of Formula (L-1a), L³ is absent. In some embodiments of a compound of Formula (L-1a), L³ is -CH₂-.

[004333] In some embodiments of a compound of Formula (L-1a), L⁴ is absent, -O-, -NR^L-, -C(=O)-, -C(=O)O-, -OC(=O)-, -C(=O)NR^L-, or -NR^LC(=O)-. In some embodiments of a compound of Formula (L-1a), L⁴ is absent, -C(=O)-, -OC(=O)-, or -NR^LC(=O)-. In some embodiments of a compound of Formula (L-1a), L⁴ is absent, -C(=O)-, -OC(=O)-, or -NHC(=O)-.

[00434] In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), the linker L^A is



[00435] In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), the linker L^A has



the structure of Formula (L-2):

Formula (L-2);

wherein:

each L¹, L², and L³ is independently -O-, -NR^L-, -N(R^L)₂⁺-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, -S(=O)₂-, =CH-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -NR^LC(=S)NR^L-, -CR^L=N-, -N=CR^L-, -NR^LS(=O)₂-, -S(=O)₂NR^L-, -C(=O)NR^LS(=O)₂-, -S(=O)₂NR^LC(=O)-, C₃-C₁₅ cycloalkylene, C₁-C₁₂ heterocycloalkylene, arylene,

heteroarylene, C₁-C₃₀alkylene, C₂-C₃₀alkenylene, C₂-C₃₀alkynylene, C₁-C₃₀heteroalkylene, -(C₁-C₃₀alkylene)-O-, -O-(C₁-C₃₀alkylene)-, -(C₁-C₃₀alkylene)-NR^L-, -NR^L-(C₁-C₃₀alkylene)-, -(C₁-C₃₀alkylene)-N(R^L)₂⁺-, or -N(R^L)₂⁺-(C₁-C₃₀alkylene)-; wherein each cycloalkylene, heterocycloalkylene, arylene, heteroarylene, alkylene, alkenylene, alkynylene, and heteroalkylene is optionally independently substituted with one or more R;

R^H is a hydrophobic moiety;

Y is N or CR^L;

each R^L is independently hydrogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

k₁ is 0-20;

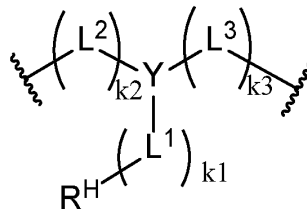
k₂ is 0-15;

k₃ is 0-15; and

each R is independently halogen, -CN, -OH, -SF₅, -SH, -S(=O)C₁-C₃alkyl, -S(=O)₂C₁-C₃alkyl, -S(=O)₂NH₂, -S(=O)₂NHC₁-C₃alkyl, -S(=O)₂N(C₁-C₃alkyl)₂, -NH₂, -NHC₁-C₃alkyl, -N(C₁-C₃alkyl)₂, -C(=O)C₁-C₃alkyl, -C(=O)OH, -C(=O)OC₁-C₃alkyl, -C(=O)NH₂, -C(=O)NHC₁-C₃alkyl, -C(=O)N(C₁-C₃alkyl)₂, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃haloalkyl, C₁-C₃haloalkoxy, C₁-C₃hydroxyalkyl, C₁-C₃aminoalkyl, C₁-C₃heteroalkyl, C₃-C₆cycloalkyl, or 3- to 6-membered heterocycloalkyl;

or two R on the same atom form an oxo.

[00436] In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), the linker L^A has the structure of Formula (L-2):



Formula (L-2);

wherein:

each L¹, L², and L³ is independently -O-, -NR^L-, or -C(=O)-;

R^H is a hydrophobic moiety;

Y is N or CR^L;

each R^L is independently hydrogen or C₁-C₄alkyl;

k₁ is 0-20;

k₂ is 0-15; and

k₃ is 0-15.

[00437] In some embodiments of a compound of Formula (L-2),

each L² and L³ is independently -O-, -NR^L-, -N(R^L)₂⁺-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-O-(CH₂CH₂)-O-(CH₂CH₂), or C₁-C₆alkylene optionally independently substituted with one or more R;

R^L is hydrogen or C₁-C₄ alkyl;

k₂ is 1-5; and

k₃ is 1-5.

[00438] In some embodiments of a compound of Formula (L-2),

each L¹ is independently -O-, -NR^L-, -N(R^L)₂+, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-,
-NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -O-(CH₂CH₂), or C₁-C₆alkylene
optionally independently substituted with one or more R;

R^L is hydrogen or C₁-C₄ alkyl;

k₁ is 1-15; and

k₂ is 1-15.

[00439] In some embodiments of a compound of Formula (L-2), each L² and L³ is independently -O-, -NR^L-, -N(R^L)₂+, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-,
-NR^LC(=O)O-, -NR^LC(=O)NR^L-, -O-(CH₂CH₂), or C₁-C₆alkylene optionally independently substituted with one or more R.

[00440] In some embodiments of a compound of Formula (L-2), each L² and L³ is independently -O-, -NR^L-, -C(=O)-, -C(=O)O-, -OC(=O)-, -C(=O)NR^L-, -NR^LC(=O)-, -O-(CH₂CH₂), or C₁-C₆alkylene
optionally independently substituted with one or more R.

[00441] In some embodiments of a compound of Formula (L-2), each L² and L³ is independently -O-, -NR^L-, -C(=O)-, -O-(CH₂CH₂), or C₁-C₆alkylene optionally independently substituted with one or more R.

[00442] In some embodiments of a compound of Formula (L-2), each L² and L³ is independently -O-, -NR^L-, or -C(=O)-.

[00443] In some embodiments of a compound of Formula (L-2), each L² and L³ is independently -NH- or -C(=O)-.

[00444] In some embodiments of a compound of Formula (L-2), each L¹ is independently -O-, -NR^L-, -N(R^L)₂+, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-,
-NR^LC(=O)O-, -NR^LC(=O)NR^L-, -O-(CH₂CH₂), or C₁-C₆alkylene optionally independently substituted with one or more R.

[00445] In some embodiments of a compound of Formula (L-2), each L¹ is independently -O-, -NR^L-, -C(=O)-, -C(=O)O-, -OC(=O)-, -C(=O)NR^L-, -NR^LC(=O)-, -O-(CH₂CH₂), or C₁-C₆alkylene optionally
independently substituted with one or more R;

[00446] In some embodiments of a compound of Formula (L-2), each L¹ is independently -C(=O)NR^L-, -NR^LC(=O)-, -O-(CH₂CH₂), or C₁-C₆alkylene optionally independently substituted with one or more R;

[00447] In some embodiments of a compound of Formula (L-2), each L¹ is independently -C(=O)NH-, -NHC(=O)-, -O-(CH₂CH₂), or C₁-C₆alkylene optionally independently substituted with one or more R.

[00448] In some embodiments of a compound of Formula (L-2), R^L is hydrogen or C₁-C₄ alkyl. In some embodiments of a compound of Formula (L-2), R^L is hydrogen.

[00449] In some embodiments of a compound of Formula (L-2), k₁ is 1-19. In some embodiments of a compound of Formula (L-2), k₁ is 1-18. In some embodiments of a compound of Formula (L-2), k₁ is 1-

17. In some embodiments of a compound of Formula (L-2), k1 is 1-16. In some embodiments of a compound of Formula (L-2), k1 is 1-15. In some embodiments of a compound of Formula (L-2), k1 is 1-14. In some embodiments of a compound of Formula (L-2), k1 is 1-13. In some embodiments of a compound of Formula (L-2), k1 is 1-12. In some embodiments of a compound of Formula (L-2), k1 is 1-11. In some embodiments of a compound of Formula (L-2), k1 is 1-10. In some embodiments of a compound of Formula (L-2), k1 is 1-9. In some embodiments of a compound of Formula (L-2), k1 is 1-8. In some embodiments of a compound of Formula (L-2), k1 is 1-7. In some embodiments of a compound of Formula (L-2), k1 is 1-6. In some embodiments of a compound of Formula (L-2), k1 is 1-5. In some embodiments of a compound of Formula (L-2), k1 is 1-4. In some embodiments of a compound of Formula (L-2), k1 is 1-3. In some embodiments of a compound of Formula (L-2), k1 is 1 or 2.

[00450] In some embodiments of a compound of Formula (L-2), k2 is 1-14. In some embodiments of a compound of Formula (L-2), k2 is 1-13. In some embodiments of a compound of Formula (L-2), k2 is 1-12. In some embodiments of a compound of Formula (L-2), k2 is 1-11. In some embodiments of a compound of Formula (L-2), k2 is 1-10. In some embodiments of a compound of Formula (L-2), k2 is 1-9. In some embodiments of a compound of Formula (L-2), k2 is 1-8. In some embodiments of a compound of Formula (L-2), k2 is 1-7. In some embodiments of a compound of Formula (L-2), k2 is 1-6. In some embodiments of a compound of Formula (L-2), k2 is 1-5. In some embodiments of a compound of Formula (L-2), k2 is 1-4. In some embodiments of a compound of Formula (L-2), k2 is 1-3. In some embodiments of a compound of Formula (L-2), k2 is 1 or 2.

[00451] In some embodiments of a compound of Formula (L-2), k3 is 1-14. In some embodiments of a compound of Formula (L-2), k3 is 1-13. In some embodiments of a compound of Formula (L-2), k3 is 1-12. In some embodiments of a compound of Formula (L-2), k3 is 1-11. In some embodiments of a compound of Formula (L-2), k3 is 1-10. In some embodiments of a compound of Formula (L-2), k3 is 1-9. In some embodiments of a compound of Formula (L-2), k3 is 1-8. In some embodiments of a compound of Formula (L-2), k3 is 1-7. In some embodiments of a compound of Formula (L-2), k3 is 1-6. In some embodiments of a compound of Formula (L-2), k3 is 1-5. In some embodiments of a compound of Formula (L-2), k3 is 1-4. In some embodiments of a compound of Formula (L-2), k3 is 1-3. In some embodiments of a compound of Formula (L-2), k3 is 1 or 2.

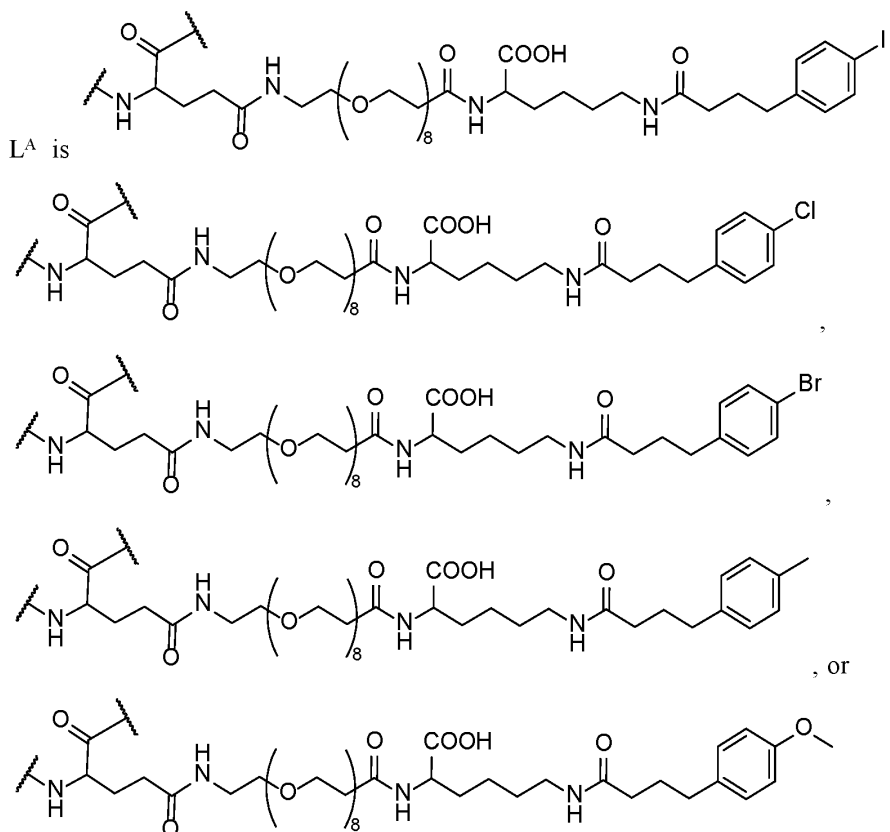
[00452] In some embodiments of a compound of Formula (L-2),

R^H is a fatty acid chain, a C₆-C₁₀ alkyl chain, a sterol, an aryl, or a heteroaryl; wherein the aryl and heteroaryl is optionally substituted with one or more R; and

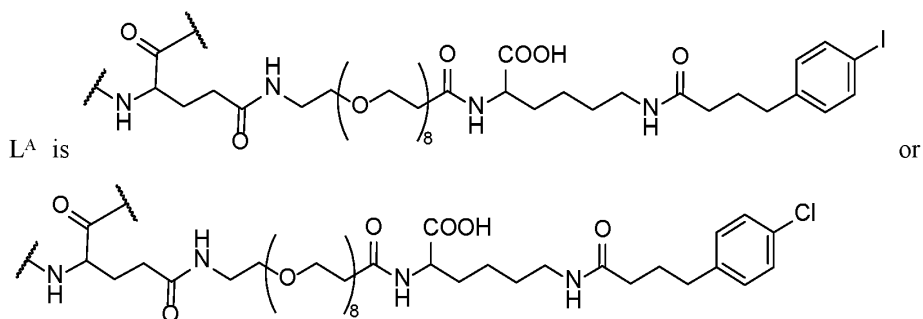
each R is independently halogen, -CN, -OH, -SF₅, -SH, -S(=O)C₁-C₃alkyl, -S(=O)₂C₁-C₃alkyl, -S(=O)₂NH₂, -S(=O)₂NHC₁-C₃alkyl, -S(=O)₂N(C₁-C₃alkyl)₂, -NH₂, -NHC₁-C₃alkyl, -N(C₁-C₃alkyl)₂, -C(=O)C₁-C₃alkyl, -C(=O)OH, -C(=O)OC₁-C₃alkyl, -C(=O)NH₂, -C(=O)NHC₁-C₃alkyl, -C(=O)N(C₁-C₃alkyl)₂, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃haloalkyl, C₁-C₃haloalkoxy, C₁-C₃hydroxyalkyl, C₁-C₃aminoalkyl, C₁-C₃heteroalkyl, C₃-C₆cycloalkyl, or 3- to 6-membered heterocycloalkyl.

[00453] In some embodiments of a compound of Formula (L-2), R^H is phenyl substituted with a halogen or a C₁-C₃ alkyl.

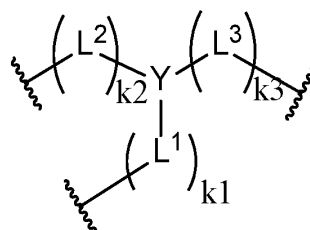
[00454] In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), the linker



[00455] In some embodiments of a compound of Formula (A), (B), (C), (AC), (BC), or (CC), the linker



[00456] In some embodiments of a compound of Formula (A'), (B'), (C'), (AC'), (BC'), or (CC'), the linker L^B has the structure of Formula (L-3):



Formula (L-3);

wherein:

each L^1 , L^2 , and L^3 is independently -O-, -NR^L-, -N(R^L)₂⁺-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, -S(=O)₂-, =CH-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -NR^LC(=S)NR^L-, -CR^L=N-, -N=CR^L-, -NR^LS(=O)₂-, -S(=O)₂NR^L-, -C(=O)NR^LS(=O)₂-, -S(=O)₂NR^LC(=O)-, C₃-C₁₅ cycloalkylene, C₁-C₁₂ heterocycloalkylene, arylene, heteroarylene, C₁-C₃₀alkylene, C₂-C₃₀alkenylene, C₂-C₃₀alkynylene, C₁-C₃₀heteroalkylene, -(C₁-C₃₀alkylene)-O-, -O-(C₁-C₃₀alkylene)-, -(C₁-C₃₀alkylene)-NR^L-, -NR^L-(C₁-C₃₀alkylene)-, -(C₁-C₃₀alkylene)-N(R^L)₂⁺-, or -N(R^L)₂⁺-(C₁-C₃₀alkylene)-; wherein each cycloalkylene, heterocycloalkylene, arylene, heteroarylene, alkylene, alkenylene, alkynylene, and heteroalkylene is optionally independently substituted with one or more R;

Y is N or CR^L;

each R^L is independently hydrogen, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

k₁ is 0-15;

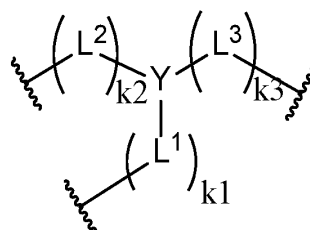
k₂ is 0-15;

k₃ is 0-15; and

each R is independently halogen, -CN, -OH, -SF₅, -SH, -S(=O)C₁-C₃alkyl, -S(=O)₂C₁-C₃alkyl, -S(=O)₂NH₂, -S(=O)₂NHC₁-C₃alkyl, -S(=O)₂N(C₁-C₃alkyl)₂, -NH₂, -NHC₁-C₃alkyl, -N(C₁-C₃alkyl)₂, -C(=O)C₁-C₃alkyl, -C(=O)OH, -C(=O)OC₁-C₃alkyl, -C(=O)NH₂, -C(=O)NHC₁-C₃alkyl, -C(=O)N(C₁-C₃alkyl)₂, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃haloalkyl, C₁-C₃haloalkoxy, C₁-C₃hydroxyalkyl, C₁-C₃aminoalkyl, C₁-C₃heteroalkyl, C₃-C₆cycloalkyl, or 3- to 6-membered heterocycloalkyl;

or two R on the same atom form an oxo.

[00457] In some embodiments of a compound of Formula (A'), (B'), (C'), (AC'), (BC'), or (CC'), the linker L^B has the structure of Formula (L-3):



Formula (L-3);

wherein:

each L^1 , L^2 , and L^3 is independently -O-, -NR^L-, -C(=O)-, C₁-C₃₀alkylene, -(C₁-C₃₀alkylene)-O-, or -O-(C₁-C₃₀alkylene)-;

Y is N or CR^L;

each R^L is independently hydrogen or C₁-C₄alkyl;

k₁ is 0-15;

k₂ is 0-15; and

k₃ is 0-15.

[00458] In some embodiments of a compound of Formula (L-3), each L^2 and L^3 is independently -O-, -NR^L-, -N(R^L)₂+, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -O-(CH₂CH₂), or C₁-C₆alkylene optionally independently substituted with one or more R.

[00459] In some embodiments of a compound of Formula (L-3), each L^2 and L^3 is independently -O-, -NR^L-, -C(=O)-, -C(=O)O-, -OC(=O)-, -C(=O)NR^L-, -NR^LC(=O)-, -O-(CH₂CH₂), or C₁-C₆alkylene optionally independently substituted with one or more R.

[00460] In some embodiments of a compound of Formula (L-3), each L^2 and L^3 is independently -O-, -NR^L-, -C(=O)-, -O-(CH₂CH₂), or C₁-C₆alkylene optionally independently substituted with one or more R.

[00461] In some embodiments of a compound of Formula (L-3), each L^2 and L^3 is independently -C(=O)-, -O-(CH₂CH₂), or C₁-C₆alkylene optionally independently substituted with one or more R.

[00462] In some embodiments of a compound of Formula (L-3), each L^2 and L^3 is independently -C(=O)-, -O-(CH₂CH₂), or C₁-C₆alkylene.

[00463] In some embodiments of a compound of Formula (L-3), each L^2 and L^3 is independently -C(=O)- or C₁-C₆alkylene.

[00464] In some embodiments of a compound of Formula (L-3), each L^1 is independently -O-, -NR^L-, -N(R^L)₂+, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -O-(CH₂CH₂), or C₁-C₆alkylene optionally independently substituted with one or more R.

[00465] In some embodiments of a compound of Formula (L-3), each L^1 is independently -O-, -NR^L-, -C(=O)-, -C(=O)O-, -OC(=O)-, -C(=O)NR^L-, -O-(CH₂CH₂), or C₁-C₆alkylene optionally independently substituted with one or more R.

[00466] In some embodiments of a compound of Formula (L-3), each L^1 is independently -O-, -NR^L-, -C(=O)-, -O-(CH₂CH₂), or C₁-C₆alkylene optionally independently substituted with one or more R.

[00467] In some embodiments of a compound of Formula (L-3), each L^1 is independently -NR^L-, -C(=O)-, or C₁-C₆alkylene optionally independently substituted with one or more R.

[00468] In some embodiments of a compound of Formula (L-3), each L^1 is independently -NR^L-.

[00469] In some embodiments of a compound of Formula (L-3), Y is N or CR^L. In some embodiments of a compound of Formula (L-3), Y is N. In some embodiments of a compound of Formula (L-3), Y is CR^L. In some embodiments of a compound of Formula (L-3), Y is CH.

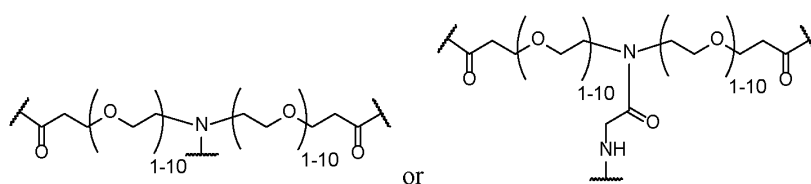
[00470] In some embodiments of a compound of Formula (L-3), k₁ is 1-15. In some embodiments of a compound of Formula (L-3), k₁ is 1-14. In some embodiments of a compound of Formula (L-3), k₁ is 1-13. In some embodiments of a compound of Formula (L-3), k₁ is 1-12. In some embodiments of a compound of Formula (L-3), k₁ is 1-11. In some embodiments of a compound of Formula (L-3), k₁ is 1-10. In some embodiments of a compound of Formula (L-3), k₁ is 1-9. In some embodiments of a compound of Formula (L-3), k₁ is 1-8. In some embodiments of a compound of Formula (L-3), k₁ is 1-7. In some embodiments of a compound of Formula (L-3), k₁ is 1-6. In some embodiments of a compound of Formula (L-3), k₁ is 1-5. In some embodiments of a compound of Formula (L-3), k₁ is 1-4. In some

embodiments of a compound of Formula (L-3), k_1 is 1-3. In some embodiments of a compound of Formula (L-3), k_1 is 1 or 2. In some embodiments of a compound of Formula (L-3), k_1 is 0-2. In some embodiments of a compound of Formula (L-3), k_1 is 0 or 1. In some embodiments of a compound of Formula (L-3), k_1 is 0. In some embodiments of a compound of Formula (L-3), k_1 is 1. In some embodiments of a compound of Formula (L-3), k_1 is 2. In some embodiments of a compound of Formula (L-3), k_1 is 3. In some embodiments of a compound of Formula (L-3), k_1 is 4.

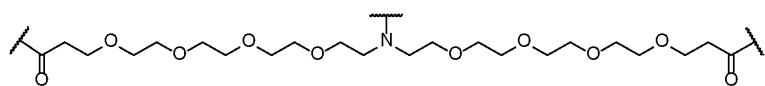
[00471] In some embodiments of a compound of Formula (L-3), k_2 is 1-14. In some embodiments of a compound of Formula (L-3), k_2 is 1-13. In some embodiments of a compound of Formula (L-3), k_2 is 1-12. In some embodiments of a compound of Formula (L-3), k_2 is 1-11. In some embodiments of a compound of Formula (L-3), k_2 is 1-10. In some embodiments of a compound of Formula (L-3), k_2 is 1-9. In some embodiments of a compound of Formula (L-3), k_2 is 1-8. In some embodiments of a compound of Formula (L-3), k_2 is 1-7. In some embodiments of a compound of Formula (L-3), k_2 is 1-6. In some embodiments of a compound of Formula (L-3), k_2 is 1-5. In some embodiments of a compound of Formula (L-3), k_2 is 1-4. In some embodiments of a compound of Formula (L-3), k_2 is 1-3. In some embodiments of a compound of Formula (L-3), k_2 is 1 or 2.

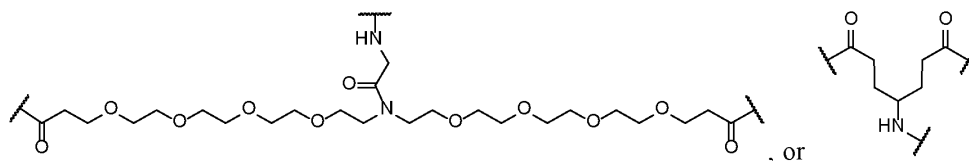
[00472] In some embodiments of a compound of Formula (L-3), k_3 is 1-14. In some embodiments of a compound of Formula (L-3), k_3 is 1-13. In some embodiments of a compound of Formula (L-3), k_3 is 1-12. In some embodiments of a compound of Formula (L-3), k_3 is 1-11. In some embodiments of a compound of Formula (L-3), k_3 is 1-10. In some embodiments of a compound of Formula (L-3), k_3 is 1-9. In some embodiments of a compound of Formula (L-3), k_3 is 1-8. In some embodiments of a compound of Formula (L-3), k_3 is 1-7. In some embodiments of a compound of Formula (L-3), k_3 is 1-6. In some embodiments of a compound of Formula (L-3), k_3 is 1-5. In some embodiments of a compound of Formula (L-3), k_3 is 1-4. In some embodiments of a compound of Formula (L-3), k_3 is 1-3. In some embodiments of a compound of Formula (L-3), k_3 is 1 or 2.

[00473] In some embodiments of a compound of Formula (A'), (B'), (C'), (AC'), (BC'), or (CC'), the linker L^B is



[00474] In some embodiments of a compound of Formula (A'), (B'), (C'), (AC'), (BC'), or (CC'), the linker L^B is





[00476] In some embodiments of a compound disclosed herein, each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, -L-cycloalkyl, or -L-heterocycloalkyl, wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, -L-cycloalkyl, or -L-heterocycloalkyl, wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl, wherein each alkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each R^b is independently hydrogen, C₁-C₆alkyl or C₁-C₆haloalkyl, wherein each alkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, each R^b is independently hydrogen, C₁-C₆alkyl, or C₁-C₆haloalkyl. In some embodiments of a compound disclosed herein, each R^b is independently hydrogen or C₁-C₆alkyl. In some embodiments of a compound disclosed herein, each R^b is independently hydrogen or C₁-C₆haloalkyl. In some embodiments of a compound disclosed herein, each R^b is hydrogen. In some embodiments of a compound disclosed herein, each R^b is independently C₁-C₆alkyl. In some embodiments of a compound disclosed herein, each R^b is independently C₁-C₆haloalkyl.

[00477] In some embodiments of a compound disclosed herein, each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, -L-cycloalkyl, or -L-heterocycloalkyl, wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally

substituted with one or more R. In some embodiments of a compound disclosed herein, R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, -L-cycloalkyl, or -L-heterocycloalkyl, wherein each alkyl, cycloalkyl, and heterocycloalkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl, wherein each alkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, R^c and R^d are each independently hydrogen, C₁-C₆alkyl or C₁-C₆haloalkyl, wherein each alkyl is independently optionally substituted with one or more R. In some embodiments of a compound disclosed herein, R^c and R^d are each independently hydrogen, C₁-C₆alkyl, or C₁-C₆haloalkyl. In some embodiments of a compound disclosed herein, R^c and R^d are each independently hydrogen or C₁-C₆alkyl. In some embodiments of a compound disclosed herein, R^c and R^d are each independently hydrogen or C₁-C₆haloalkyl. In some embodiments of a compound disclosed herein, R^c and R^d are each hydrogen. In some embodiments of a compound disclosed herein, R^c and R^d are each independently C₁-C₆alkyl. In some embodiments of a compound disclosed herein, R^c and R^d are each independently C₁-C₆haloalkyl.

[00478] In some embodiments of a compound disclosed herein, R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R.

[00479] In some embodiments of a compound disclosed herein, L is absent or C₁-C₃alkylene. In some embodiments of a compound disclosed herein, L is absent. In some embodiments of a compound disclosed herein, L is C₁-C₃alkylene. In some embodiments of a compound disclosed herein, L is -CH₂-. In some embodiments of a compound disclosed herein, L is -CH₂CH₂-. In some embodiments of a compound disclosed herein, L is -CH₂CH₂CH₂-.

[00480] In some embodiments of a compound disclosed herein, each R is independently halogen, -CN, -OH, -SF₅, -NH₂, -NHC₁-C₃alkyl, -N(C₁-C₃alkyl)₂, -C(=O)C₁-C₃alkyl, -C(=O)OH, -C(=O)OC₁-C₃alkyl, -C(=O)NH₂, -C(=O)NHC₁-C₃alkyl, -C(=O)N(C₁-C₃alkyl)₂, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃haloalkyl, C₁-C₃haloalkoxy, C₁-C₃hydroxyalkyl, C₁-C₃aminoalkyl, C₁-C₃heteroalkyl, C₃-C₆cycloalkyl, or 3- to 6-membered heterocycloalkyl. In some embodiments of a compound disclosed herein, each R is independently halogen, -CN, -OH, -SF₅, -NH₂, -NHC₁-C₃alkyl, -N(C₁-C₃alkyl)₂, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃haloalkyl, C₁-C₃haloalkoxy, C₁-C₃hydroxyalkyl, C₁-C₃aminoalkyl, C₁-C₃heteroalkyl, C₃-C₆cycloalkyl, or 3- to 6-membered heterocycloalkyl. In some embodiments of a compound disclosed herein, each R is independently halogen, -CN, -OH, -SF₅, -NH₂, -C(=O)C₁-C₃alkyl, -C(=O)OH, -C(=O)OC₁-C₃alkyl, -C(=O)NH₂, -C(=O)NHC₁-C₃alkyl, -C(=O)N(C₁-C₃alkyl)₂, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃haloalkyl, C₁-C₃haloalkoxy, C₁-C₃hydroxyalkyl, C₁-C₃aminoalkyl, C₁-C₃heteroalkyl, C₃-C₆cycloalkyl, or 3- to 6-membered heterocycloalkyl. In some embodiments of a compound disclosed herein, each R is independently halogen, -CN, -OH, -NH₂, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃haloalkyl, C₁-C₃haloalkoxy, C₁-C₃hydroxyalkyl, C₁-C₃aminoalkyl, C₁-C₃heteroalkyl, C₃-C₆cycloalkyl, or 3- to 6-membered heterocycloalkyl. In some embodiments of a compound disclosed herein, each R is independently halogen, -CN, -OH, -NH₂, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃haloalkyl, or C₁-C₃haloalkoxy. In some embodiments of a compound disclosed herein, each R is independently halogen, -CN, -OH, -

NH₂, C₁-C₃alkyl, or C₁-C₃haloalkyl. In some embodiments of a compound disclosed herein, each R is independently halogen, -CN, -OH, -C(=O)C₁-C₃alkyl, -C(=O)OH, -C(=O)OC₁-C₃alkyl, -C(=O)NH₂, -C(=O)NHC₁-C₃alkyl, -C(=O)N(C₁-C₃alkyl)₂, C₁-C₃alkyl, or C₁-C₃haloalkyl. In some embodiments of a compound disclosed herein, each R is independently halogen, -CN, -OH, -C(=O)OH, -C(=O)OC₁-C₃alkyl, C₁-C₃alkyl, or C₁-C₃haloalkyl. In some embodiments of a compound disclosed herein, each R is independently halogen, -CN, -OH, -C(=O)OH, -C(=O)OC₁-C₃alkyl, or C₁-C₃alkyl.

[00481] In some embodiments, disclosed herein is a radiopharmaceutical conjugate comprising a covalently bound radioisotope. In some embodiments of Formula (AC), (AC'), (BC), (BC'), (CC), or (CC'), R³⁰ comprises the covalently bound radioisotope. In some embodiments of Formula (AC), (BC), or (CC), TL₁ comprises the covalently bound radioisotope. In some embodiments of Formula (AC), (BC), or (CC), TL₂ comprises the covalently bound radioisotope. In some embodiments of Formula (AC), (BC), or (CC), L^A comprises the covalently bound radioisotope. In some embodiments of Formula (AC'), (BC'), or (CC'), one or both of the TL₁ groups comprise the covalently bound radioisotope. In some embodiments of Formula (AC'), (BC'), or (CC'), one or both of the TL₂ groups comprise the covalently bound radioisotope. In some embodiments of Formula (AC'), (BC'), or (CC'), L^B comprises the covalently bound radioisotope. In some embodiments of Formula (BC), (BC'), (CC), or (CC'), X comprises the covalently bound radioisotope.

[00482] In some embodiments of Formula (AC), (AC'), (BC), (BC'), (CC), or (CC'), R³⁰ is an albumin binding moiety.

[00483] In some embodiments of Formula (AC), (AC'), (BC), (BC'), (CC), or (CC'), R³⁰ is a payload moiety. In some embodiments, the payload moiety comprises a payload and a linker connecting the payload to group L^A or L^B. In some embodiments, the payload moiety is a payload having cytotoxic, therapeutic, or diagnostic properties. In some embodiments, the payload moiety comprises a radioisotope. In some embodiments, the payload moiety comprises a covalently bound radioisotope. In some embodiments, the payload moiety comprises a chelator. In some embodiments, the payload moiety comprises a chelator and a radioisotope bound to the chelator. In some embodiments, payload is a toxin. In some embodiments, payload is a therapeutic agent. In some embodiments, the payload moiety comprises a cleavable linker and a toxin (e.g., an auristatin, such as auristatin E or a derivative thereof). Exemplary cleavable linkers can be found in, e.g., U.S. Pat. No. 9962454B2.

[00484] In some embodiments, the toxin is a taxane, a topoisomerase inhibitor, a vinca alkaloid, or the like.

[00485] In some embodiments, the toxin can be selected from, for example, DNA minor groove binders (e.g., enediynes and lexitropsins, a CBI compound; see also U.S. Pat. No. 6,130,237), duocarmycins, taxanes (e.g., paclitaxel and docetaxel), puromycins, and vinca alkaloids. Other cytotoxic agents include, for example, CC-1065, SN-38, topotecan, morpholino-doxorubicin, rhizoxin, cyanomorpholino-doxorubicin, echinomycin, combretastatin, netropsin, epothilone A and B, estramustine, cryptophytins, cemadotin, maytansinoids, discodermolide, eleutherobin, and mitoxantrone.

[00486] In some embodiments, the toxin is an anti-tubulin agent. Examples of anti-tubulin agents include, auristatins, taxanes (e.g., Taxol® (paclitaxel), Taxotere® (docetaxel)), T67 (Tularik) and vinca alkyls (e.g., vincristine, vinblastine, vindesine, and vinorelbine). Examples of anti-tubulin agents further include, for example, baccatin derivatives, taxane analogs (e.g., epothilone A and B), nocodazole, colchicine and colcimid, estramustine, cryptophycins, cemadotin, maytansinoids, combretastatins, discodermolide, and eleutherobin.

[00487] In some embodiments, the toxin is a maytansinoid, another group of anti-tubulin agents. For example, in some embodiments, the maytansinoid is maytansine or DM-1.

[00488] In some embodiments, the toxin is a dolastatin. In some embodiments, the toxin is of the auristatin class. In some embodiments, the toxin is MMAE. In some embodiments, the toxin is AFP.

[00489] In some embodiments of Formula (AC), (AC'), (BC), (BC'), (CC), or (CC'), R³⁰ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted (e.g., with one or more R). In some embodiments of Formula (AC), (AC'), (BC), (BC'), (CC), or (CC'), R³⁰ is hydrogen.

[00490] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

Metal Chelator

[00491] In one aspect, described herein are conjugates that comprise a metal chelator, e.g., as represented by CL in the formulas described herein.

[00492] In some embodiments, the metal chelator binds with a radionuclide. In some embodiments, the conjugate described herein comprises two or more independent metal chelators, e.g., 2, 3, 4, 5, or more metal chelators. In some embodiments, the conjugate described herein comprises two metal chelators, which can be the same or different. In some embodiments, the conjugate described herein comprises two or more metal chelators. In some embodiments, the conjugate comprises two radionuclides bound to the metal chelators.

[00493] In some embodiments, the metal chelator is capable of binding a radioactive atom. The binding can be direct, e.g., the metal chelator can make hydrogen bonds or electrostatic interactions with the radioactive atom. The binding can also be indirect, e.g., the metal chelator binds to a molecule that comprises a radioactive atom. In some embodiments, the metal chelator comprises, or is, a macrocycle. In some embodiments, the metal chelator comprises, or is, 2,2',2'',2'''-(1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetic acid (DOTA) or 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA). In some

embodiments, the metal chelator comprises a macrocycle, e.g., a macrocycle comprising an oxygen atom and/or a nitrogen atom, DOTA, NOTA, one or more amines, one or more ethers, one or more carboxylic acids, EDTA, DTPA, TETA, DO3A, PCTA, or desferrioxamine.

[00494] In some embodiments, the metal chelator comprises a plurality of amines. In some embodiments, the metal chelator includes 4 or more nitrogen atoms, 4 or more carboxylic acid groups, or a combination thereof. In some embodiments, the metal chelator does not comprise S. In some embodiments, the metal chelator comprises a ring. In some embodiments, the ring comprises an oxygen atom and/or a nitrogen atom. In some embodiments, the metal chelator is a ring that includes 3 or more nitrogen atom, 3 or more carboxylic acid groups, or a combination thereof. In some embodiments, the metal chelator is polydentate.

[00495] In some embodiments, the metal chelator (or CL) described herein is DOTA, DOTA-GA, pBn-DOTA, pBn-SCN-DOTA, NH₂-DOTA, NH₂-DOTA-GA, p-NCS-Bn-DOTA-GA, p-NH₂-Bn-oxo-DO3A, p-SCN-Bn-oxo-DO3A, NOTA, NODA-GA, NH₂-NODA-GA, p-NCS-Bn-NODA-GA, p-NH₂-Bn-NOTA, p-SCN-Bn-NOTA, NCS-MP-NODA, NH₂-MPAA-NODA, PCTA, p-NH₂-Bn-PCTA, p-SCN-Bn-PCTA, p-SCN-Bn-HEHA, H₂-MACROPA-NCS, H₁-MACROPA, H₂-MACROPA-NH₂, H₄-OCTAPA, tetra-(S, S, S, S)-Me-DOTA, tetra-(S, S, S, S)-Et-DOTA, tetra-(S, S, S, S)-iBu-DOTA, or maleimide-nBu-DOTA.

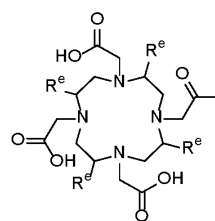
[00496] In some embodiments, the metal chelator (or CL) described herein comprises a cyclic chelating agent. Exemplary cyclic chelating agents include, but are not limited to, AAZTA, BAT, BAT-TM, Crown, Cyclen, DO2A, CB-DO2A, DO3A, H3HP-DO3A, Oxo-DO3A, p-NH₂-Bn-Oxo-DO3A, DOTA, DOTA-3py, DOTA-PA, DOTA-GA, DOTA-4AMP, DOTA-2py, DOTA-1py, p-SCN-Bn-DOTA, CHX-A"-EDTA, MeO-DOTA-NCS EDTA, DOTAMAP, DOTAGA, DOTAGA-anhydride, DOTMA, DOTASA, DOTAM, DOTP, CB-Cyclam, TE2A, CB-TE2A, CB-TE2P, DM-TE2A, MM-TE2A, NOTA, NOTP, HEHA, HEHA-NCS, p-SCN-Bn-HEHA, DTPA, CHX-A"-DTPA, p-NH₂-Bn-CHX-A"-DTPA, p-SCN-DTPA, p-SCN-Bz-Mx-DTPA, 1B4M-DTPA, p-SCN-Bn1B-DTPA, p-SCN-Bn-1B4M-DTPA, p-SCN-Bn-CHX-A"-DTPA, PEPA, p-SCN-Bn-PEPA, TETPA, DOTPA, DOTMP, DOTPM, t-Bu-calix[4]arene-tetracarboxylic acid, macropa, macropa-NCS, macropid, H₃L¹, H₃L⁴, H₂azapa, H₅decapa, bispa², H₄pypa, H₄octapa, H₄CHXoctapa, p-SCN-Bn-H₄octapa, p-SCN-Bn-H₄octapa, TTHA, p-NO₂-Bn-neunpa, H₄octox, H₂macropa, H₂bispa², H₄phospa, H₆phospa, p-SCN-Bn-H₆phospa, TETA, p-NO₂-Bn-TETA, TRAP, TPA, HBED, SHBED, HBED-CC, (HBED-CC)TFP, DMSA, DMPS, DHLA, lipoic acid, TGA, BAL, Bis-thioseminarabazones, p-SCN-NOTA, nNOTA, NODAGA, CB-TE1A1P, 3P-C-NETA-NCS, 3p-C-DEPA, 3P-C-DEPA-NCS, TCMC, PCTA, NODIA-Me, TACN, pycup1A1B, pycup2A, THP, DEDPA, H₂DEDPA, p-SCN-Bn-H₂DEDPA, p-SCN-Bn-TCMC, motexafin, NTA, NOC, 3p-C-NETA, p-NH₂-Bn-TE3A, SarAr, DiAmSar, SarAr-NCS, AmBaSar, BaBaSar, TACN-TM, CP256, C-NE3TA, C-NE3TA-NCS, NODASA, NETA-monoamide, C-NETA, NOPO, BPCA, p-SCN-Bn-DFO, DFO-ChX-Mal, DFO, DFO-IAC, DFO-BAC, DiP-LICAM, EC, SBAD, BAPEN, TACHPYR, NEC-SP, L^{py}, L¹, L², L³, and EuK-106. In some embodiments, the metal chelator is DOTA, TRITA, TETA, DOTA-MA, DO3A-HP, DOTMA, DOTA-pNB, DOTP, DOTMP, DOTE, DOTMPE, F-DOTMPE, DOTPP,

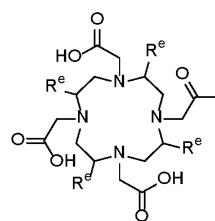
DOTBzP, DOTA-monoamide, p-NCS-DOTA, p-NCS-PADOTA, BAT, DO3TMP-Monoamide, p-NCS-TRITA, NOTA, or CHX-A"-DTPA. In some embodiments, the metal chelator described herein comprises an acyclic chelating agent. Exemplary acyclic chelating agents include, but are not limited to, DTA, CyEDTA, EDTMP, DTPMP, DTPA, CyDTPA, Cy2DTPA, DTPA-MA, DTPA-BA, and BOPA. In some embodiments, the metal chelator described herein comprises DOTA, DOTP, DOTMA, DOTAM, DTPA, NTA, EDTA, DO3A, DO2A, NOC, NOTA, TETA, TACN, DiAmSar, CB-Cyclam, CB-TE2A, DOTA-4AMP, or NOTP. In some embodiments, the metal chelator described herein comprises H₄pypa, H₄octox, H₄octapa, p-NO₂-Bn-neunpa, p-SCN-Bn-H₄neunpa, TTHA, 'Bu₄pypa-C7-NHS, H₄neunpa, H₂macropa, HP-DO3A, BT-DO3A, DO3A-Nprop, DO3AP, DO2A2P, DOA3P, DOTP, DOTPMB, DOTAMAE, DOTAMAP, DO3AM^{Bu}, DOTMA, TCE-DOTA, DEPA, PCTA, p-NO₂-Bn-PCTA, p-NO₂-Bn-DOTA, symPC2APA, symPCA2PA, asymPC2APA, asymPCA2PA, TRAP, AAZTA, DATA^m, THP, HEHA, or HBED.

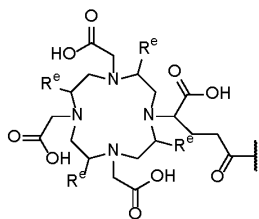
[00497] In some embodiments, the metal chelator (or CL) is DO3A. In some embodiments, the metal chelator is PEPA. In some embodiments, the metal chelator is EDTA. In some embodiments, the metal chelator is CHX-A"-DTPA. In some embodiments, the metal chelator is HEHA. In some embodiments, the metal chelator is DOTMP. In some embodiments, the metal chelator is t-Bu-calix[4]arene-tetracarboxylic acid. In some embodiments, the metal chelator is macropa. In some embodiments, the metal chelator is macropa-NCS. In some embodiments, the metal chelator is H₄pypa. In some embodiments, the metal chelator is H₄octapa. In some embodiments, the metal chelator is H₄CHXoctapa. In some embodiments, the metal chelator is DOTP. In some embodiments, the metal chelator is crown.

[00498] Exemplary metal chelators are further described in WO2012/174136; US20130183235A1; US20120219495A1; Ramogidaand et al., EJNMMI radiopharm. chem. 4, 21 (2019); Thiele et al., Cancer Biotherapy and Radiopharmaceuticals 2018; Li et al., Bioconjugate Chem. 2019, 30, 5, 1539-1553; and Baranyai et al., Eur. J. Inorg. Chem. 36-56 (2020), Dai et al., Nature Communications (2018) 9:857, each of which is incorporated by reference in its entirety.

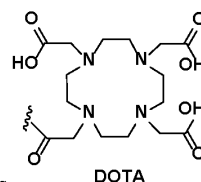
[00499] In some embodiments, the metal chelator (or CL) is DOTA. In some embodiments, the metal chelator is a chiral derivative of DOTA. In some embodiments, the metal chelator is 2,2',2'',2'''-((2S,5S,8S,11S)-2,5,8,11-tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetic acid.



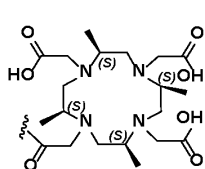
[00500] In some embodiments, the metal chelator (or CL) is , wherein each R^e is independently selected from hydrogen, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocycloalkyl, alkylaryl, alkylheteroaryl, or an amino acid side chain. In some embodiments, the metal chelator is



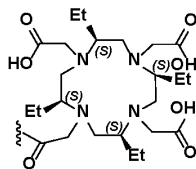
wherein each R^e is independently selected from hydrogen, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocycloalkyl, alkylaryl, alkylheteroaryl, or an amino acid side chain.



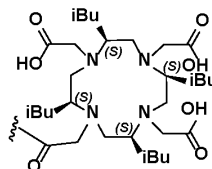
[00501] In some embodiments, the metal chelator (or CL) is



tetra-(S,S,S,S)-Me-DOTA,

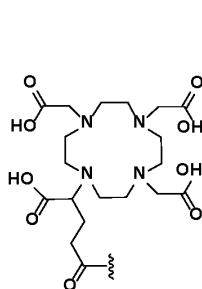


tetra-(S,S,S,S)-Et-DOTA, or

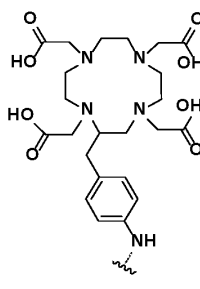


tetra-(S,S,S,S)-iBu-DOTA.

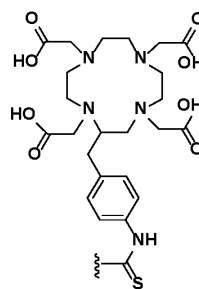
In some embodiments,



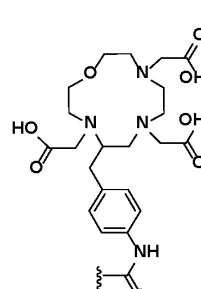
DOTA-GA,



pBn-DOTA,

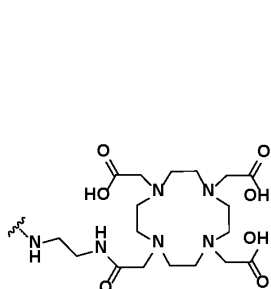


pBn-SCN-DOTA,

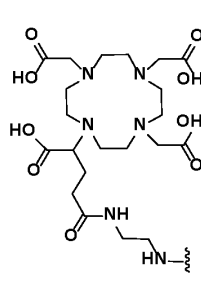


p-SCN-Bn-oxo-DO3A,

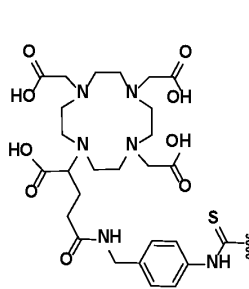
the metal chelator is



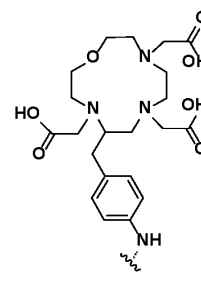
NH2-DOTA,



NH2-DOTA-GA,

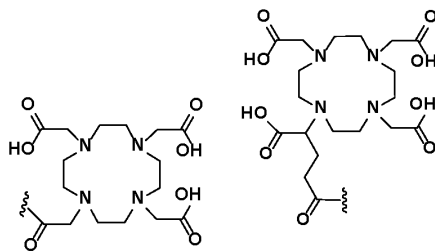


p-NCS-Bn-DOTA-GA,

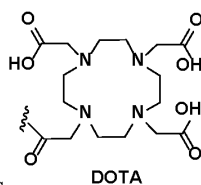


p-NH2-Bn-oxo-DO3A.

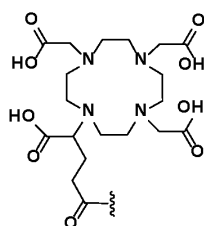
In



some embodiments, the metal chelator is DOTA or DOTA-GA. In some

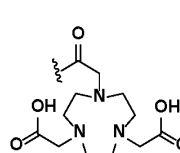


embodiments, the metal chelator is DOTA. In some embodiments, the metal chelator is

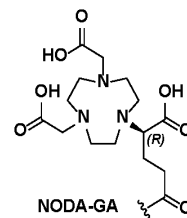


DOTA-GA

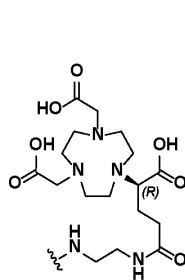
. In some embodiments, the metal chelator is



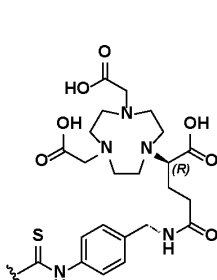
NOTA



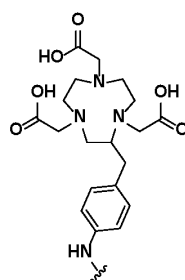
NODA-GA



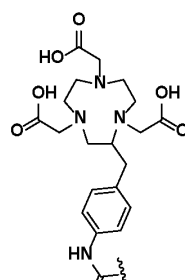
NH2-NODA-GA



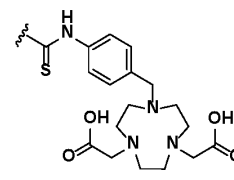
p-NCS-Bn-NODA-GA



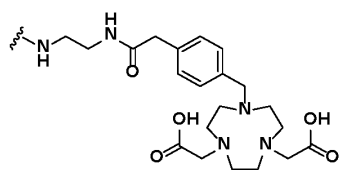
p-NH2-Bn-NOTA



p-SCN-Bn-NOTA



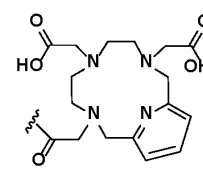
NCS-MP-NODA



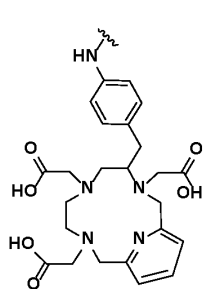
NH2-MPAA-NODA

or

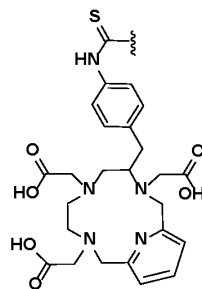
. In some embodiments, the metal chelator is



PCTA



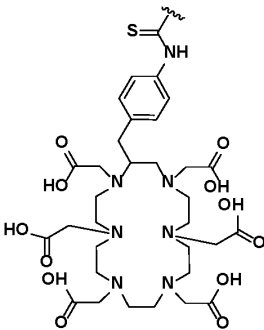
p-NH2-Bn-PCTA



p-SCN-Bn-PCTA

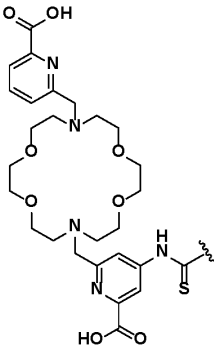
, or

. In some embodiments, the metal chelator (or CL) is

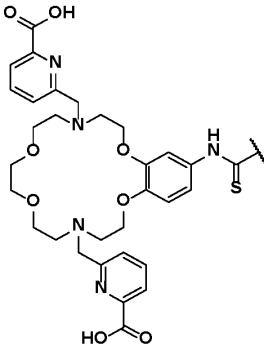


p-SCN-Bn-HEHA

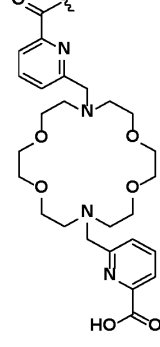
. In some embodiments, the metal chelator is



H2-MACROPA-NCS

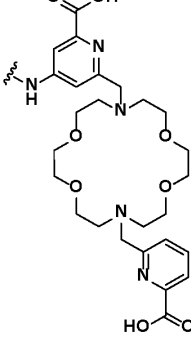


H2BZ MACROPA-NCS



H1-MACROPA

, or



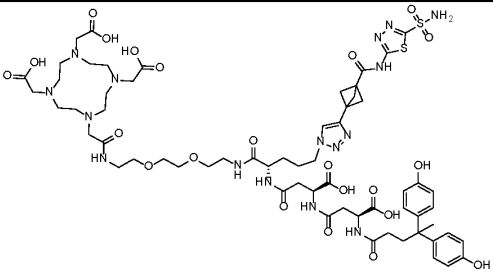
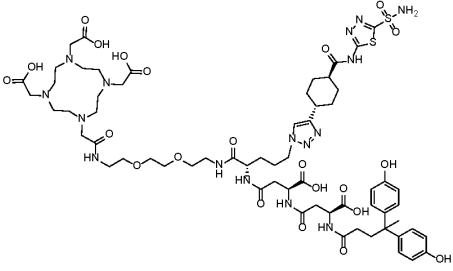
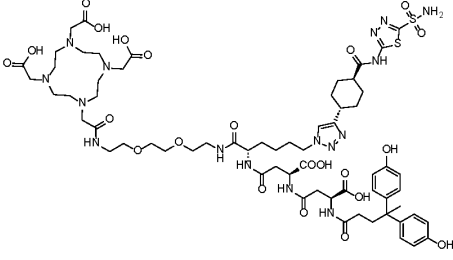
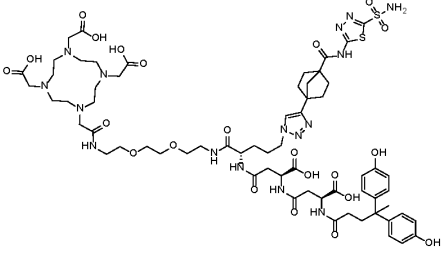
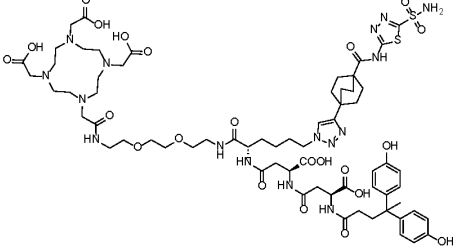
H2-MACROPA-NH2

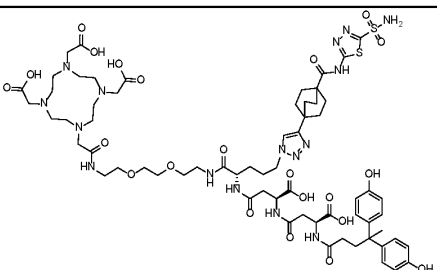
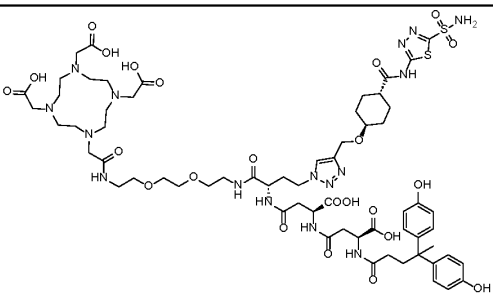
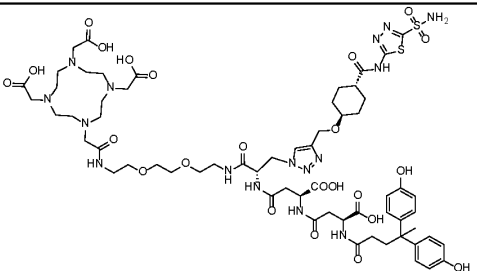
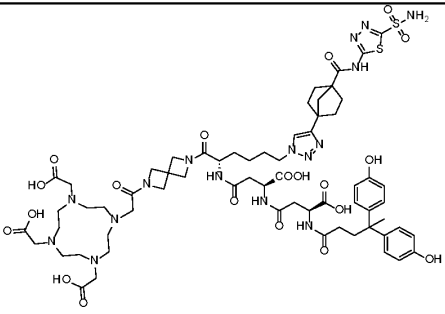
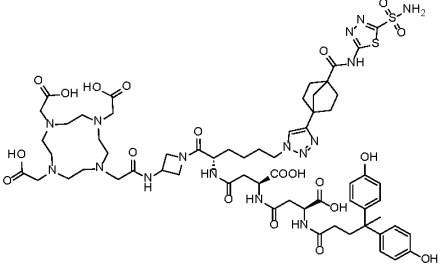
[00502] Exemplary metal chelators are also illustrated in FIG. 1 to FIG. 19.

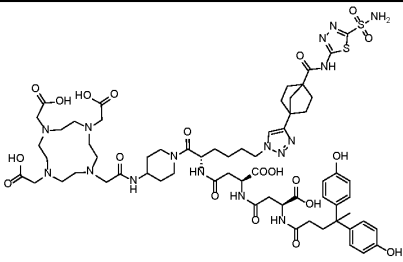
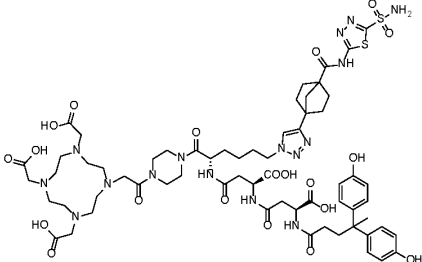
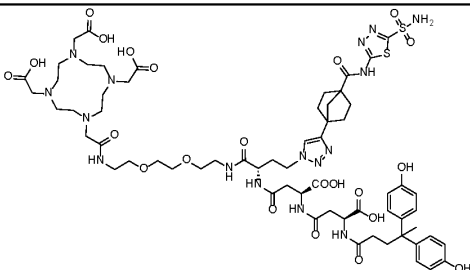
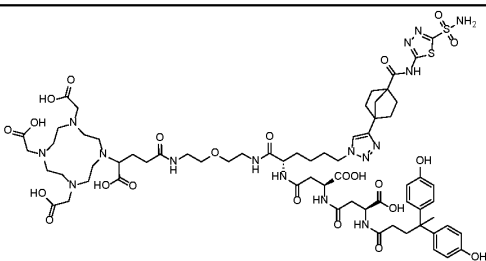
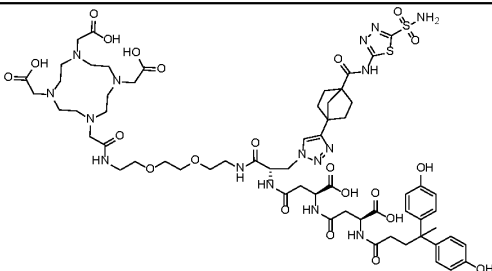
[00503] In some embodiments the conjugate disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, is one of the compounds in Table 1.

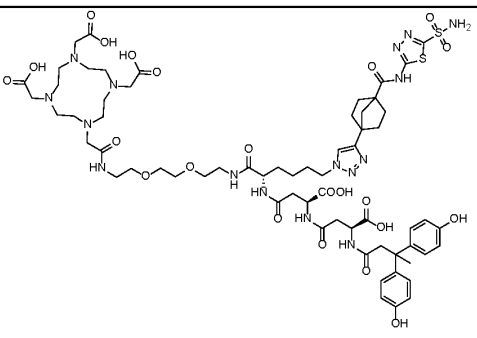
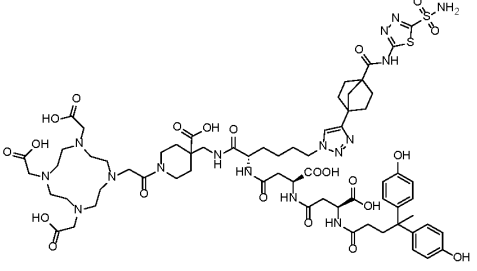
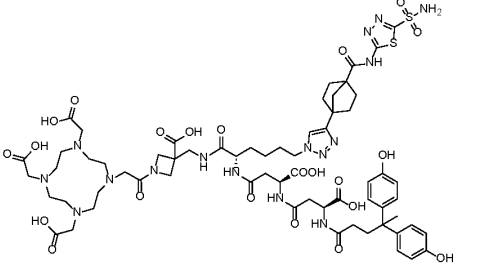
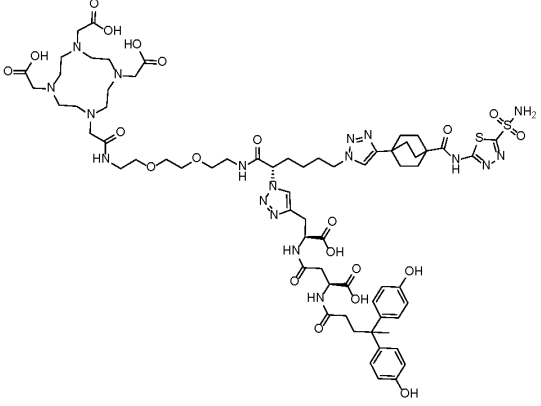
TABLE 1

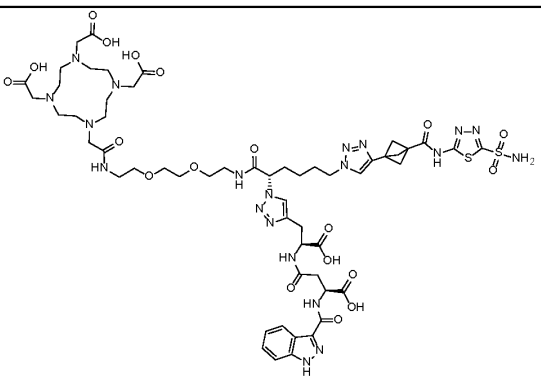
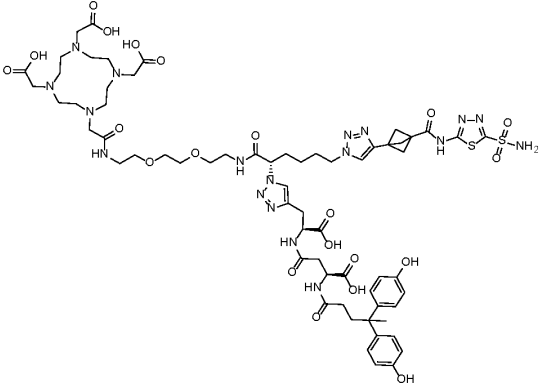
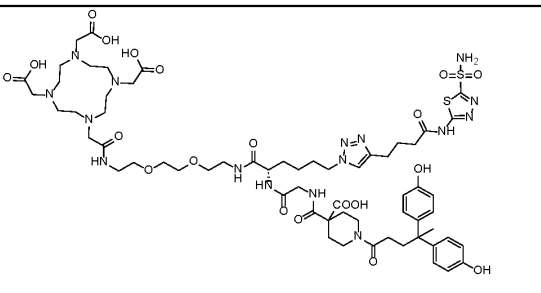
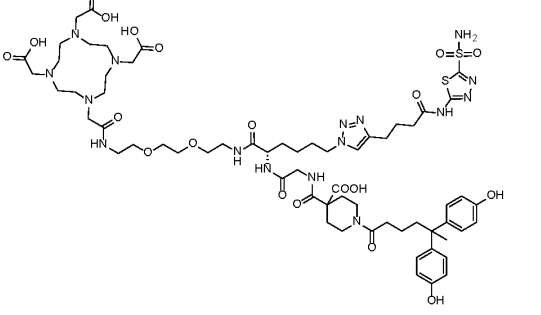
Compound	Structure
100	Chemical structure of compound 100, a conjugate of a macrocyclic chelator and a peptide sequence.
100.1	Chemical structure of compound 100.1, a conjugate of a macrocyclic chelator and a peptide sequence.

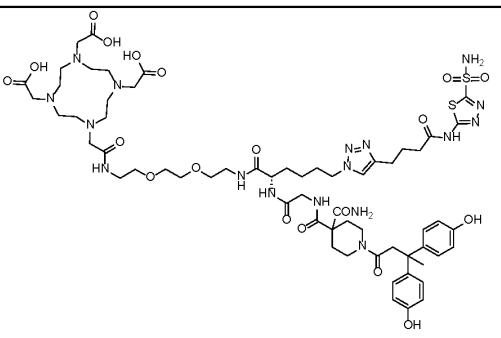
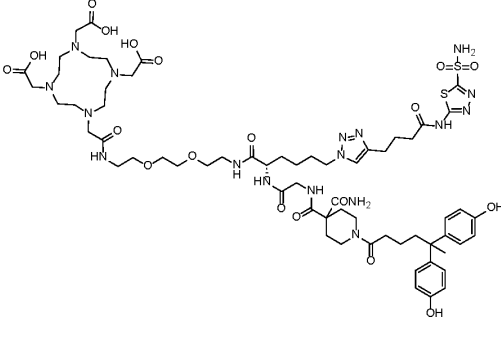
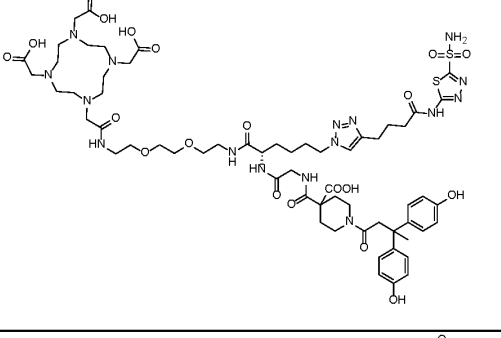
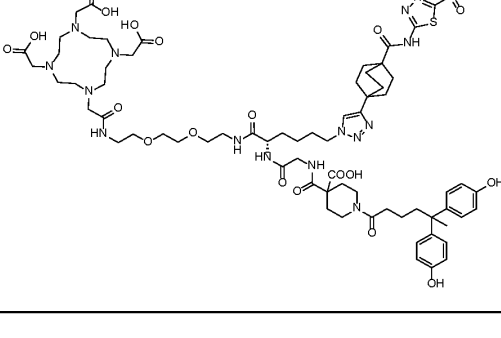
Compound	Structure
100.2	 Chemical structure of compound 100.2. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane core with two carboxylic acid groups. This core is linked via a long chain containing an amide, an ether, and another amide to a 1,2,4-triazole ring. The triazole is further connected to a cyclopropyl ring, which is substituted with a sulfonamide group (SO₂NH₂). The triazole also has a substituent that is a 1,3-bis(4-hydroxyphenyl)propan-1-one derivative.
100.3	 Chemical structure of compound 100.3. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane core with two carboxylic acid groups. This core is linked via a long chain containing an amide, an ether, and another amide to a 1,2,4-triazole ring. The triazole is further connected to a cyclohexyl ring, which is substituted with a sulfonamide group (SO₂NH₂). The triazole also has a substituent that is a 1,3-bis(4-hydroxyphenyl)propan-1-one derivative.
100.4	 Chemical structure of compound 100.4. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane core with two carboxylic acid groups. This core is linked via a long chain containing an amide, an ether, and another amide to a 1,2,4-triazole ring. The triazole is further connected to a cyclohexyl ring, which is substituted with a sulfonamide group (SO₂NH₂). The triazole also has a substituent that is a 1,3-bis(4-hydroxyphenyl)propan-1-one derivative.
100.5	 Chemical structure of compound 100.5. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane core with two carboxylic acid groups. This core is linked via a long chain containing an amide, an ether, and another amide to a 1,2,4-triazole ring. The triazole is further connected to a cyclopropyl ring, which is substituted with a sulfonamide group (SO₂NH₂). The triazole also has a substituent that is a 1,3-bis(4-hydroxyphenyl)propan-1-one derivative.
100.6	 Chemical structure of compound 100.6. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane core with two carboxylic acid groups. This core is linked via a long chain containing an amide, an ether, and another amide to a 1,2,4-triazole ring. The triazole is further connected to a cyclohexyl ring, which is substituted with a sulfonamide group (SO₂NH₂). The triazole also has a substituent that is a 1,3-bis(4-hydroxyphenyl)propan-1-one derivative.

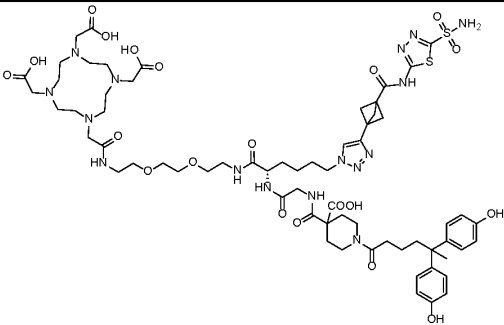
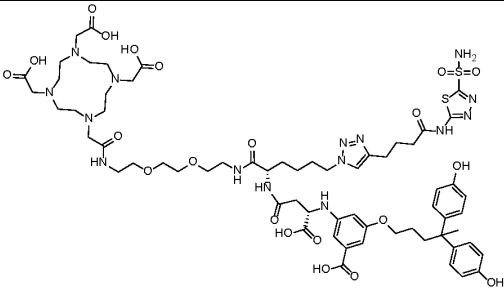
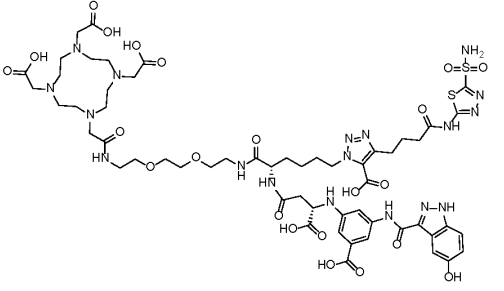
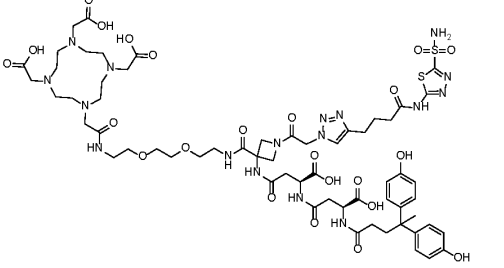
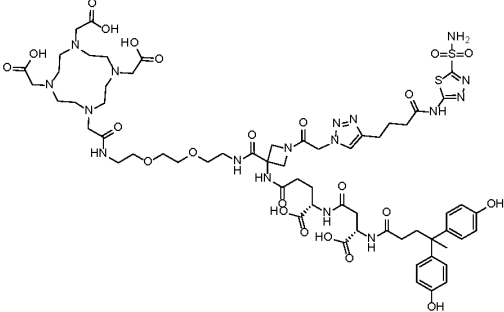
Compound	Structure
100.7	 Chemical structure of compound 100.7. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane-2,4,6,8-tetracarboxylic acid core. This core is linked via a long chain containing a 1,2,3-triazole ring to a 1,4-bis(4-hydroxyphenyl)-1,4-dimethyl-2,2-diphenylbutane moiety. The triazole ring is also connected to a 1,2,3-triazole-4-carboxamide-5-sulfonamide group.
100.8	 Chemical structure of compound 100.8. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane-2,4,6,8-tetracarboxylic acid core. This core is linked via a long chain containing a 1,2,3-triazole ring to a 1,4-bis(4-hydroxyphenyl)-1,4-dimethyl-2,2-diphenylbutane moiety. The triazole ring is also connected to a 1,2,3-triazole-4-carboxamide-5-sulfonamide group.
100.9	 Chemical structure of compound 100.9. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane-2,4,6,8-tetracarboxylic acid core. This core is linked via a long chain containing a 1,2,3-triazole ring to a 1,4-bis(4-hydroxyphenyl)-1,4-dimethyl-2,2-diphenylbutane moiety. The triazole ring is also connected to a 1,2,3-triazole-4-carboxamide-5-sulfonamide group.
100.10	 Chemical structure of compound 100.10. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane-2,4,6,8-tetracarboxylic acid core. This core is linked via a long chain containing a 1,2,3-triazole ring to a 1,4-bis(4-hydroxyphenyl)-1,4-dimethyl-2,2-diphenylbutane moiety. The triazole ring is also connected to a 1,2,3-triazole-4-carboxamide-5-sulfonamide group.
100.11	 Chemical structure of compound 100.11. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane-2,4,6,8-tetracarboxylic acid core. This core is linked via a long chain containing a 1,2,3-triazole ring to a 1,4-bis(4-hydroxyphenyl)-1,4-dimethyl-2,2-diphenylbutane moiety. The triazole ring is also connected to a 1,2,3-triazole-4-carboxamide-5-sulfonamide group.

Compound	Structure
100.12	 Chemical structure of compound 100.12. It features a central 1,3,5-triazine ring substituted with a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The triazine ring is also substituted with a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The structure includes a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The structure is a complex molecule with multiple functional groups, including a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group.
100.13	 Chemical structure of compound 100.13. It features a central 1,3,5-triazine ring substituted with a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The triazine ring is also substituted with a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The structure includes a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The structure is a complex molecule with multiple functional groups, including a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group.
100.14	 Chemical structure of compound 100.14. It features a central 1,3,5-triazine ring substituted with a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The triazine ring is also substituted with a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The structure includes a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The structure is a complex molecule with multiple functional groups, including a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group.
100.15	 Chemical structure of compound 100.15. It features a central 1,3,5-triazine ring substituted with a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The triazine ring is also substituted with a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The structure includes a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The structure is a complex molecule with multiple functional groups, including a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group.
100.16	 Chemical structure of compound 100.16. It features a central 1,3,5-triazine ring substituted with a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The triazine ring is also substituted with a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The structure includes a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The structure is a complex molecule with multiple functional groups, including a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group.

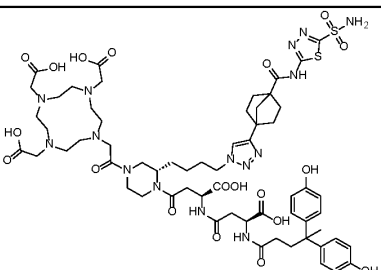
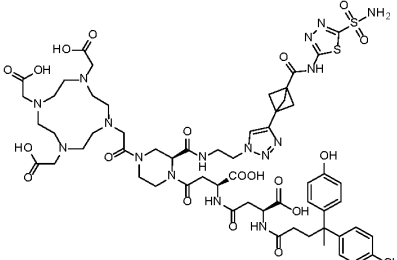
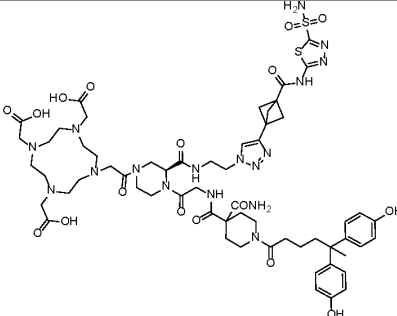
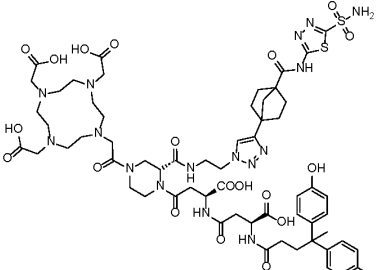
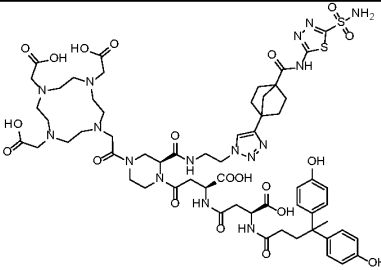
Compound	Structure
100.17	 Chemical structure of compound 100.17. It features a 12-membered macrocyclic ring with three amide bonds and two hydroxyl groups. This macrocycle is linked via an amide bond to a long chain containing a 1,2,4-triazole ring, a cyclohexane ring, and a sulfonamide group. The chain also includes a carboxylic acid group and a biphenyl moiety with two hydroxyl groups.
100.18	 Chemical structure of compound 100.18. It features a 12-membered macrocyclic ring with three amide bonds and two hydroxyl groups. This macrocycle is linked via an amide bond to a long chain containing a 1,2,4-triazole ring, a cyclohexane ring, and a sulfonamide group. The chain also includes a carboxylic acid group and a biphenyl moiety with two hydroxyl groups.
100.19	 Chemical structure of compound 100.19. It features a 12-membered macrocyclic ring with three amide bonds and two hydroxyl groups. This macrocycle is linked via an amide bond to a long chain containing a 1,2,4-triazole ring, a cyclohexane ring, and a sulfonamide group. The chain also includes a carboxylic acid group and a biphenyl moiety with two hydroxyl groups.
101	 Chemical structure of compound 101. It features a 12-membered macrocyclic ring with three amide bonds and two hydroxyl groups. This macrocycle is linked via an amide bond to a long chain containing a 1,2,4-triazole ring, a cyclohexane ring, and a sulfonamide group. The chain also includes a carboxylic acid group and a biphenyl moiety with two hydroxyl groups.

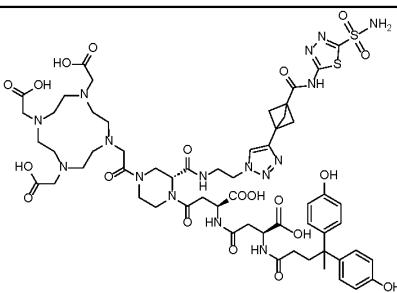
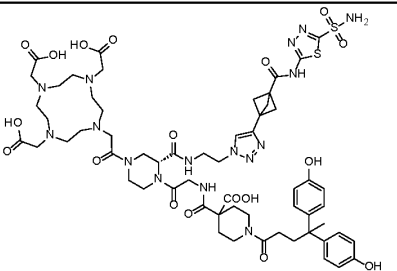
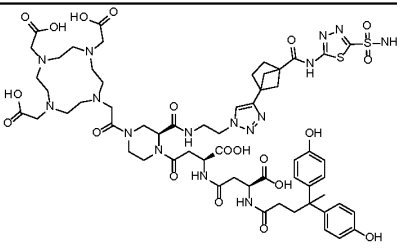
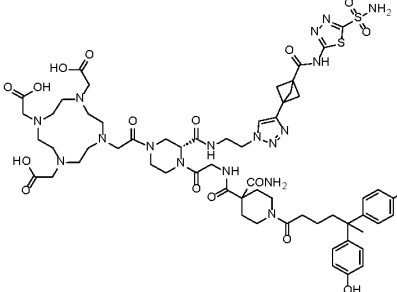
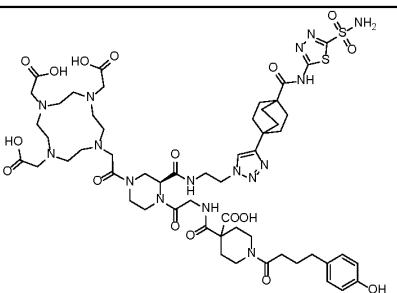
Compound	Structure
101.1	 Chemical structure of compound 101.1. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane-2,4,6,8-tetracarboxylic acid moiety linked via an amide bond to a long chain containing a 1,2,3-triazole ring, a cyclopropyl group, and a sulfonamide group (NH₂SO₂).
101.2	 Chemical structure of compound 101.2. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane-2,4,6,8-tetracarboxylic acid moiety linked via an amide bond to a long chain containing a 1,2,3-triazole ring, a cyclopropyl group, and a sulfonamide group (NH₂SO₂).
102	 Chemical structure of compound 102. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane-2,4,6,8-tetracarboxylic acid moiety linked via an amide bond to a long chain containing a 1,2,3-triazole ring, a cyclopropyl group, and a sulfonamide group (NH₂SO₂).
102.1	 Chemical structure of compound 102.1. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane-2,4,6,8-tetracarboxylic acid moiety linked via an amide bond to a long chain containing a 1,2,3-triazole ring, a cyclopropyl group, and a sulfonamide group (NH₂SO₂).

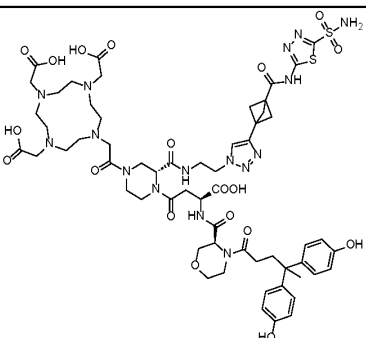
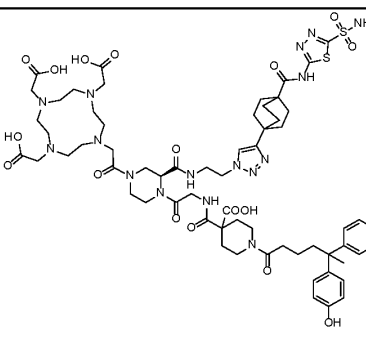
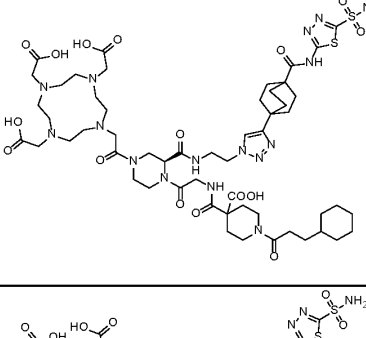
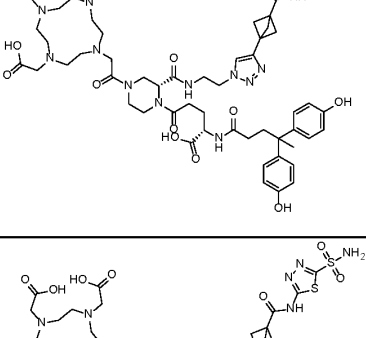
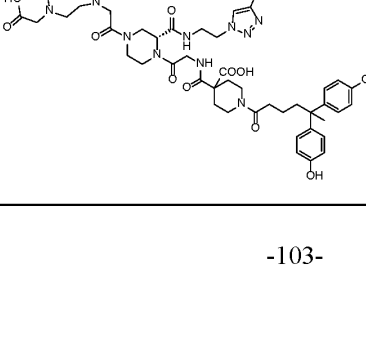
Compound	Structure
102.2	 Chemical structure of compound 102.2. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane core with two carboxylic acid groups. This core is linked via a long chain containing a tetrahydrofuran ring, an amide, and a diazole ring, to a side chain that includes a piperidine ring, a carboxamide group, and a 3,5-dihydroxybenzyl group. The side chain also terminates in a diazotetrazole moiety.
102.3	 Chemical structure of compound 102.3. It is similar to 102.2 but the side chain is modified, featuring a different arrangement of the piperidine ring and the terminal diazotetrazole group.
102.4	 Chemical structure of compound 102.4. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane core with two carboxylic acid groups. The side chain includes a piperidine ring, a carboxylic acid group, and a 3,5-dihydroxybenzyl group, terminating in a diazotetrazole moiety.
102.5	 Chemical structure of compound 102.5. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane core with two carboxylic acid groups. The side chain includes a piperidine ring, a carboxylic acid group, and a 3,5-dihydroxybenzyl group, terminating in a diazotetrazole moiety.

Compound	Structure
102.6	 Chemical structure of compound 102.6. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane core with two carboxylic acid groups. This core is linked via a long chain containing a 1,2,4-triazole ring, a 1,2,4,5-tetrazole ring, and a 1,2,4-triazole ring, to a 4-hydroxyphenyl group.
102.7	 Chemical structure of compound 102.7. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane core with two carboxylic acid groups. This core is linked via a long chain containing a 1,2,4-triazole ring, a 1,2,4,5-tetrazole ring, and a 1,2,4-triazole ring, to a 4-hydroxyphenyl group.
102.8	 Chemical structure of compound 102.8. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane core with two carboxylic acid groups. This core is linked via a long chain containing a 1,2,4-triazole ring, a 1,2,4,5-tetrazole ring, and a 1,2,4-triazole ring, to a 4-hydroxyphenyl group.
103	 Chemical structure of compound 103. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane core with two carboxylic acid groups. This core is linked via a long chain containing a 1,2,4-triazole ring, a 1,2,4,5-tetrazole ring, and a 1,2,4-triazole ring, to a 4-hydroxyphenyl group.
103.1	 Chemical structure of compound 103.1. It features a 1,3,5,7-tetraazabicyclo[3.3.1]nonane core with two carboxylic acid groups. This core is linked via a long chain containing a 1,2,4-triazole ring, a 1,2,4,5-tetrazole ring, and a 1,2,4-triazole ring, to a 4-hydroxyphenyl group.

Compound	Structure
103.2	
103.3	
103.4	
104	
104.1	

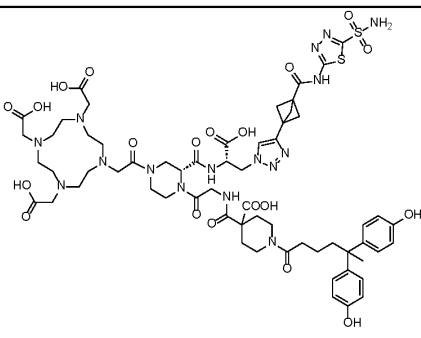
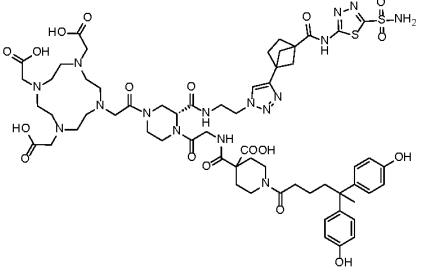
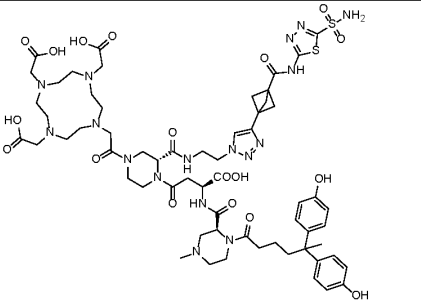
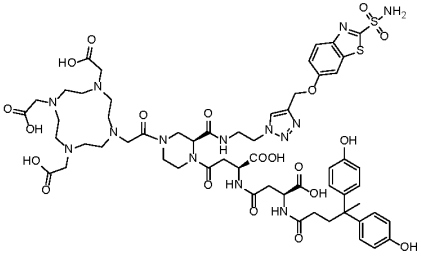
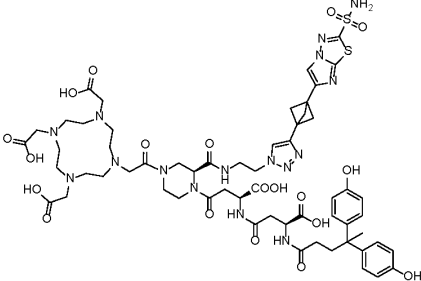
Compound	Structure
104.2	 Chemical structure of compound 104.2, featuring a complex molecule with multiple amide, ester, and sulfonamide groups, and a central bicyclic core.
106	 Chemical structure of compound 106, featuring a complex molecule with multiple amide, ester, and sulfonamide groups, and a central bicyclic core.
107	 Chemical structure of compound 107, featuring a complex molecule with multiple amide, ester, and sulfonamide groups, and a central bicyclic core.
107.1	 Chemical structure of compound 107.1, featuring a complex molecule with multiple amide, ester, and sulfonamide groups, and a central bicyclic core.
107.2	 Chemical structure of compound 107.2, featuring a complex molecule with multiple amide, ester, and sulfonamide groups, and a central bicyclic core.

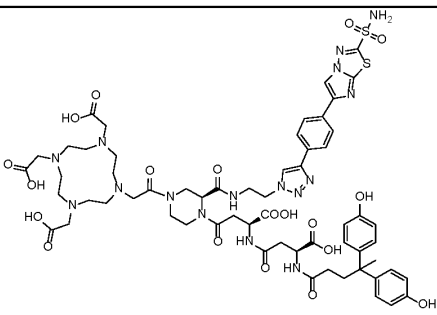
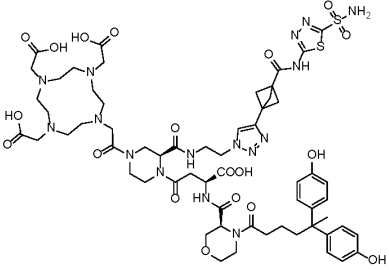
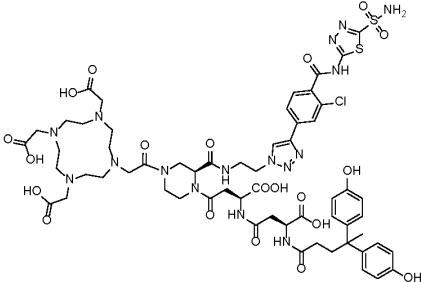
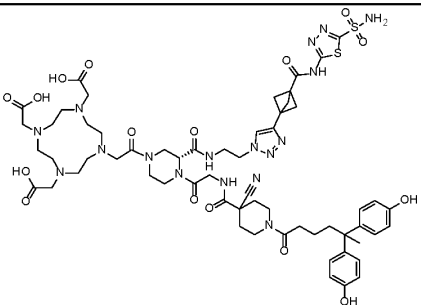
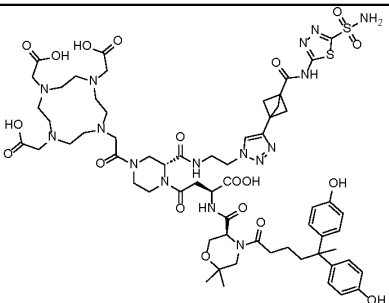
Compound	Structure
107.3	 Chemical structure of compound 107.3. It features a complex molecule with a central pyrazole ring system. The structure includes a 1,3,5-triazole ring substituted with a sulfonamide group (-SO₂NH₂) and a carboxylic acid group (-COOH). This is linked via a carbonyl group to a cyclohexane ring, which is further substituted with a carboxylic acid group (-COOH) and a side chain containing a 4-hydroxyphenyl group. The molecule also contains a 1,3,5-triazole ring and a 1,3,4-oxadiazole ring.
107.4	 Chemical structure of compound 107.4. It features a complex molecule with a central pyrazole ring system. The structure includes a 1,3,5-triazole ring substituted with a sulfonamide group (-SO₂NH₂) and a carboxylic acid group (-COOH). This is linked via a carbonyl group to a cyclohexane ring, which is further substituted with a carboxylic acid group (-COOH) and a side chain containing a 4-hydroxyphenyl group. The molecule also contains a 1,3,5-triazole ring and a 1,3,4-oxadiazole ring.
107.5	 Chemical structure of compound 107.5. It features a complex molecule with a central pyrazole ring system. The structure includes a 1,3,5-triazole ring substituted with a sulfonamide group (-SO₂NH₂) and a carboxylic acid group (-COOH). This is linked via a carbonyl group to a cyclohexane ring, which is further substituted with a carboxylic acid group (-COOH) and a side chain containing a 4-hydroxyphenyl group. The molecule also contains a 1,3,5-triazole ring and a 1,3,4-oxadiazole ring.
107.6	 Chemical structure of compound 107.6. It features a complex molecule with a central pyrazole ring system. The structure includes a 1,3,5-triazole ring substituted with a sulfonamide group (-SO₂NH₂) and a carboxylic acid group (-COOH). This is linked via a carbonyl group to a cyclohexane ring, which is further substituted with a carboxylic acid group (-COOH) and a side chain containing a 4-hydroxyphenyl group. The molecule also contains a 1,3,5-triazole ring and a 1,3,4-oxadiazole ring.
107.7	 Chemical structure of compound 107.7. It features a complex molecule with a central pyrazole ring system. The structure includes a 1,3,5-triazole ring substituted with a sulfonamide group (-SO₂NH₂) and a carboxylic acid group (-COOH). This is linked via a carbonyl group to a cyclohexane ring, which is further substituted with a carboxylic acid group (-COOH) and a side chain containing a 4-hydroxyphenyl group. The molecule also contains a 1,3,5-triazole ring and a 1,3,4-oxadiazole ring.

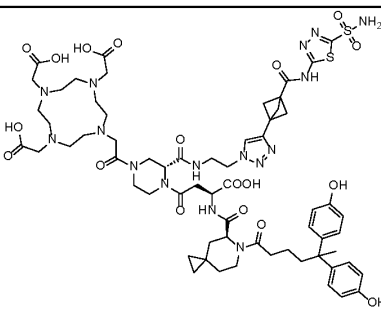
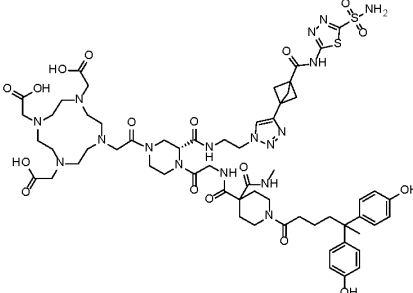
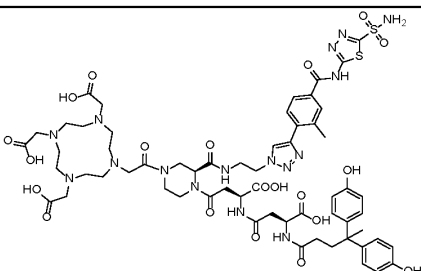
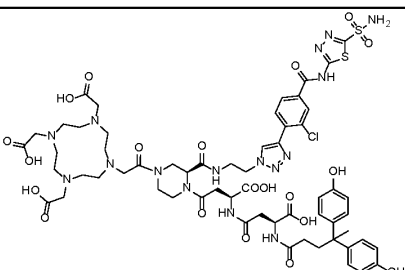
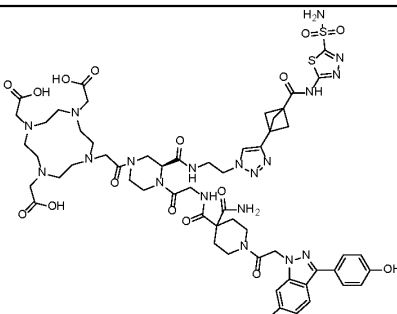
Compound	Structure
107.8	 Chemical structure of compound 107.8. It features a complex molecule with a central pyridine ring substituted with a carboxylic acid group and a side chain containing a 1,2,4-triazole ring. The triazole is linked to a cyclobutane ring, which is further connected to a sulfonamide group. Another side chain from the pyridine ring includes a carboxylic acid group and a side chain with a 1,2,4-triazole ring, which is linked to a cyclobutane ring, which is further connected to a sulfonamide group. The molecule also contains a 1,2,4-triazole ring and a sulfonamide group.
107.9	 Chemical structure of compound 107.9. It features a complex molecule with a central pyridine ring substituted with a carboxylic acid group and a side chain containing a 1,2,4-triazole ring. The triazole is linked to a cyclobutane ring, which is further connected to a sulfonamide group. Another side chain from the pyridine ring includes a carboxylic acid group and a side chain with a 1,2,4-triazole ring, which is linked to a cyclobutane ring, which is further connected to a sulfonamide group. The molecule also contains a 1,2,4-triazole ring and a sulfonamide group.
107.10	 Chemical structure of compound 107.10. It features a complex molecule with a central pyridine ring substituted with a carboxylic acid group and a side chain containing a 1,2,4-triazole ring. The triazole is linked to a cyclobutane ring, which is further connected to a sulfonamide group. Another side chain from the pyridine ring includes a carboxylic acid group and a side chain with a 1,2,4-triazole ring, which is linked to a cyclobutane ring, which is further connected to a sulfonamide group. The molecule also contains a 1,2,4-triazole ring and a sulfonamide group.
107.11	 Chemical structure of compound 107.11. It features a complex molecule with a central pyridine ring substituted with a carboxylic acid group and a side chain containing a 1,2,4-triazole ring. The triazole is linked to a cyclobutane ring, which is further connected to a sulfonamide group. Another side chain from the pyridine ring includes a carboxylic acid group and a side chain with a 1,2,4-triazole ring, which is linked to a cyclobutane ring, which is further connected to a sulfonamide group. The molecule also contains a 1,2,4-triazole ring and a sulfonamide group.
107.12	 Chemical structure of compound 107.12. It features a complex molecule with a central pyridine ring substituted with a carboxylic acid group and a side chain containing a 1,2,4-triazole ring. The triazole is linked to a cyclobutane ring, which is further connected to a sulfonamide group. Another side chain from the pyridine ring includes a carboxylic acid group and a side chain with a 1,2,4-triazole ring, which is linked to a cyclobutane ring, which is further connected to a sulfonamide group. The molecule also contains a 1,2,4-triazole ring and a sulfonamide group.

Compound	Structure
107.13	
107.14	
107.15	
107.16	
107.17	

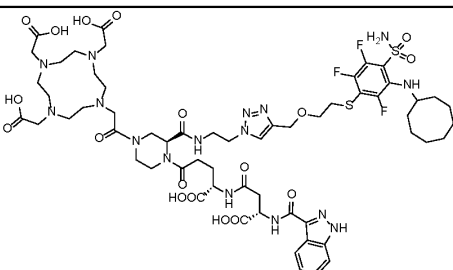
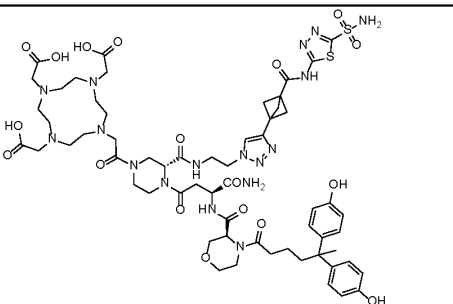
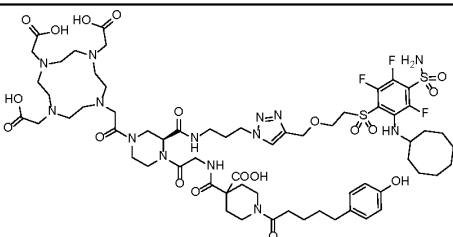
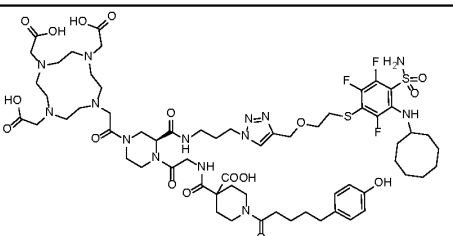
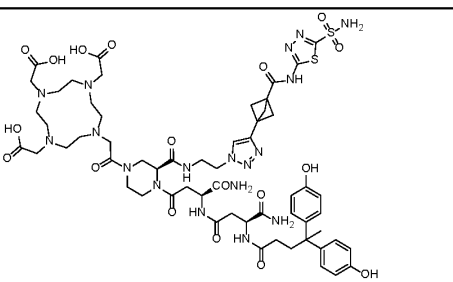
Compound	Structure
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107.19	
107.20	
107.21	
107.22	

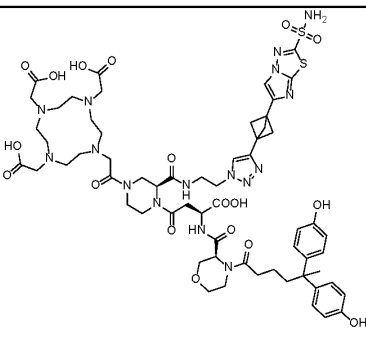
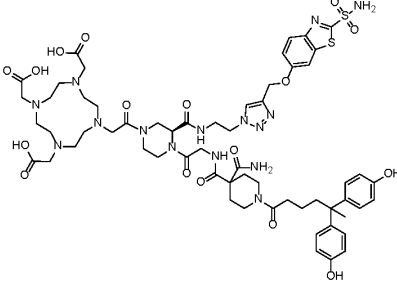
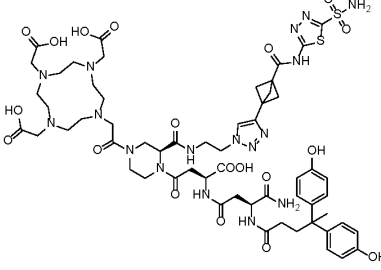
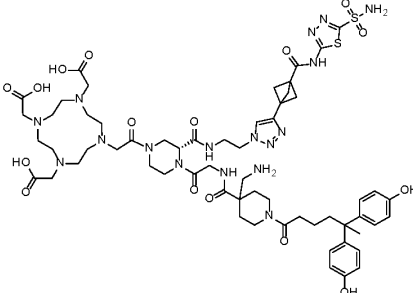
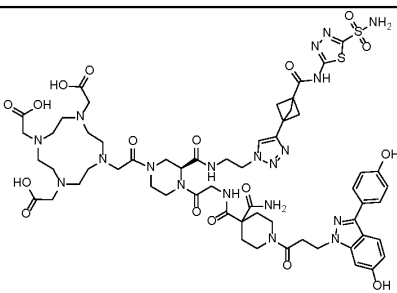
Compound	Structure
107.23	 Chemical structure of compound 107.23. It features a central pyrazole ring substituted with a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, and a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group. The structure also includes a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, and a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group.
107.24	 Chemical structure of compound 107.24. It features a central pyrazole ring substituted with a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, and a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group. The structure also includes a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, and a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group.
107.25	 Chemical structure of compound 107.25. It features a central pyrazole ring substituted with a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, and a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group. The structure also includes a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, and a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group.
107.26	 Chemical structure of compound 107.26. It features a central pyrazole ring substituted with a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, and a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group. The structure also includes a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, and a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group.
107.27	 Chemical structure of compound 107.27. It features a central pyrazole ring substituted with a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, and a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group. The structure also includes a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group, and a 1,3,4,5-tetrahydro-2H-pyrimidin-2-ylidene group.

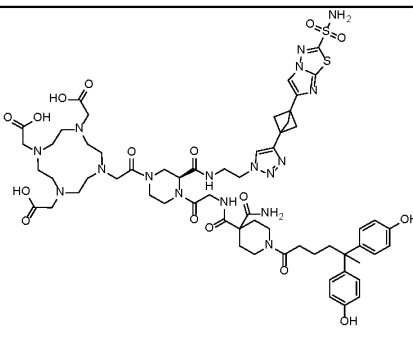
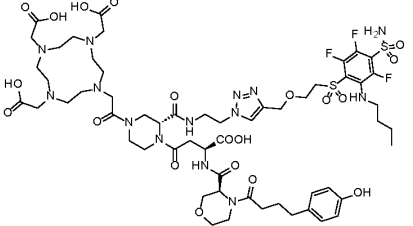
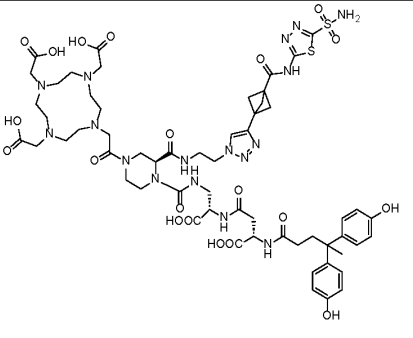
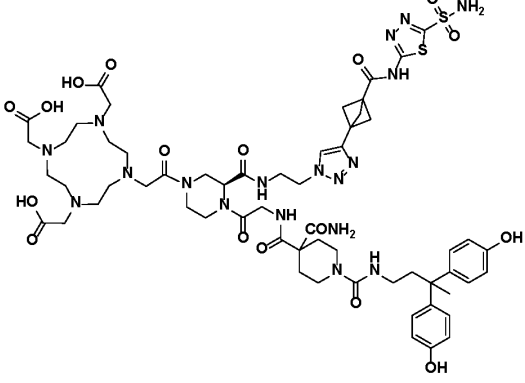
Compound	Structure
107.28	 Chemical structure of compound 107.28. It features a complex molecule with a central core containing a 1,3,5-triazine ring system. This core is substituted with a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The molecule also includes a sulfonamide group (SO₂NH₂) and a carboxylic acid group (COOH).
107.29	 Chemical structure of compound 107.29. It features a complex molecule with a central core containing a 1,3,5-triazine ring system. This core is substituted with a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The molecule also includes a sulfonamide group (SO₂NH₂) and a carboxylic acid group (COOH).
107.30	 Chemical structure of compound 107.30. It features a complex molecule with a central core containing a 1,3,5-triazine ring system. This core is substituted with a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The molecule also includes a sulfonamide group (SO₂NH₂) and a carboxylic acid group (COOH).
107.31	 Chemical structure of compound 107.31. It features a complex molecule with a central core containing a 1,3,5-triazine ring system. This core is substituted with a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The molecule also includes a sulfonamide group (SO₂NH₂) and a carboxylic acid group (COOH).
107.32	 Chemical structure of compound 107.32. It features a complex molecule with a central core containing a 1,3,5-triazine ring system. This core is substituted with a 4-hydroxyphenyl group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The molecule also includes a sulfonamide group (SO₂NH₂) and a carboxylic acid group (COOH).

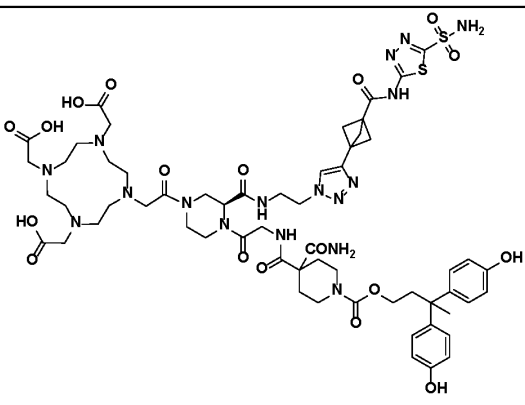
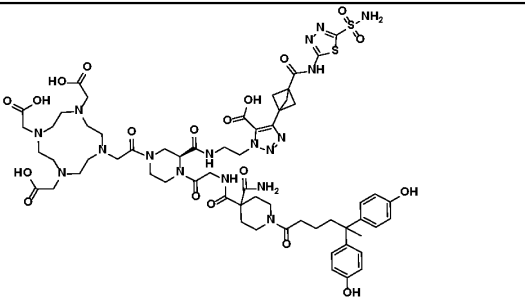
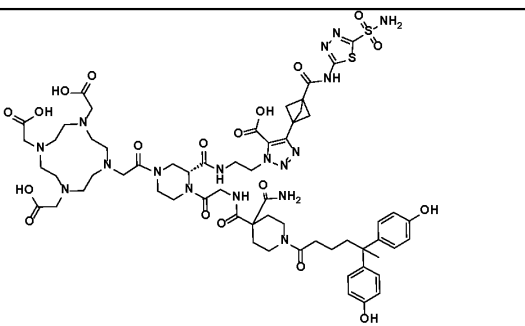
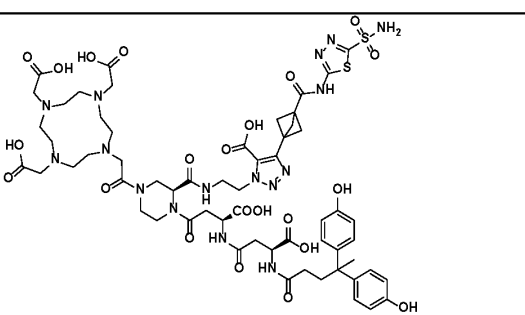
Compound	Structure
107.33	 Chemical structure of compound 107.33. It features a central pyrazole ring substituted with a 1,3,5-triazole-4-carboxamide group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The structure also includes a 1,3,5-triazole-4-carboxamide group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group.
107.34	 Chemical structure of compound 107.34. It features a central pyrazole ring substituted with a 1,3,5-triazole-4-carboxamide group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The structure also includes a 1,3,5-triazole-4-carboxamide group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group.
107.35	 Chemical structure of compound 107.35. It features a central pyrazole ring substituted with a 1,3,5-triazole-4-carboxamide group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The structure also includes a 1,3,5-triazole-4-carboxamide group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group.
107.36	 Chemical structure of compound 107.36. It features a central pyrazole ring substituted with a 1,3,5-triazole-4-carboxamide group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The structure also includes a 1,3,5-triazole-4-carboxamide group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group.
107.37	 Chemical structure of compound 107.37. It features a central pyrazole ring substituted with a 1,3,5-triazole-4-carboxamide group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group. The structure also includes a 1,3,5-triazole-4-carboxamide group, a 4-hydroxyphenyl group, and a 4-hydroxyphenyl group.

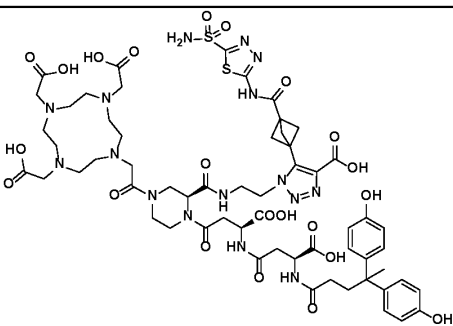
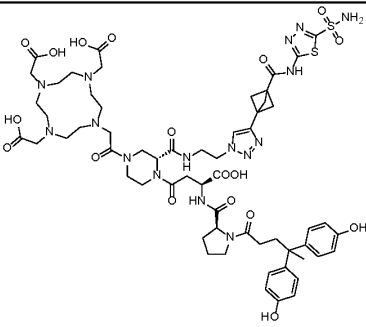
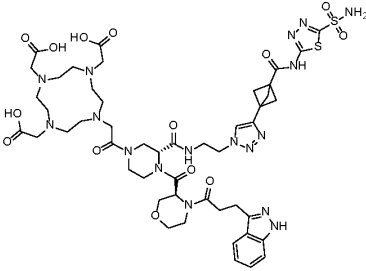
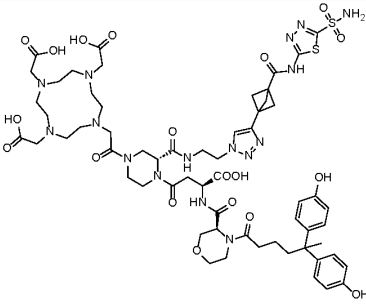
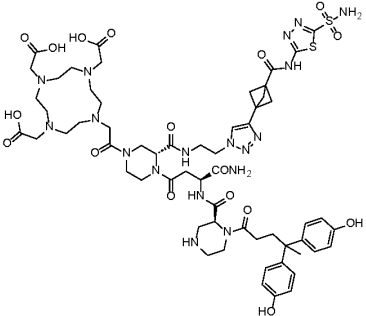
Compound	Structure
107.38	
107.39	
107.40	
107.41	
107.42	

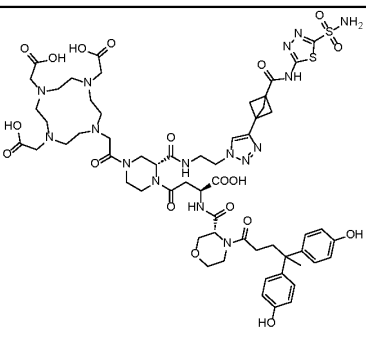
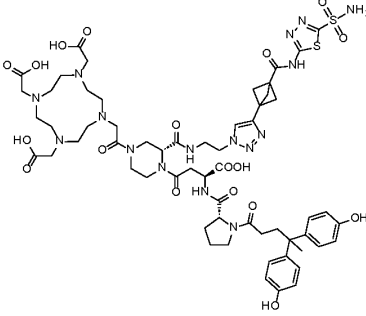
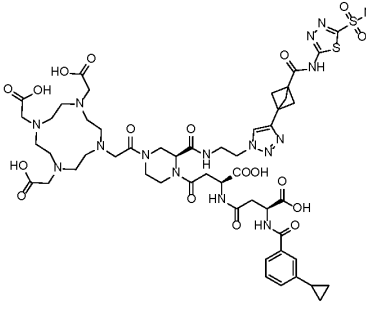
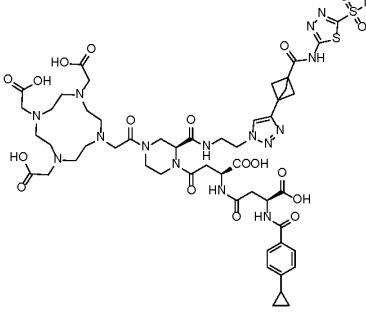
Compound	Structure
107.43	
107.44	
107.45	
107.46	
107.47	

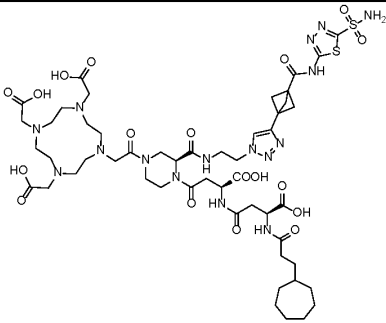
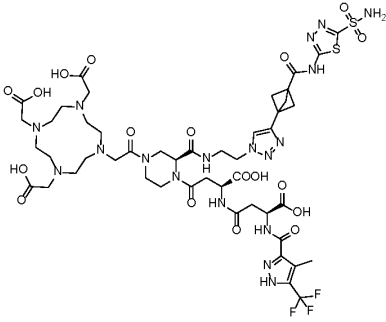
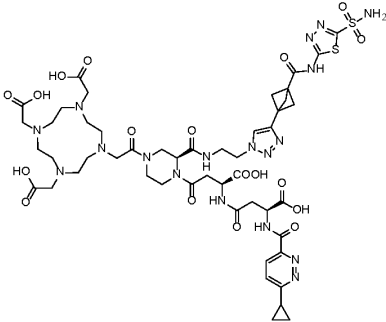
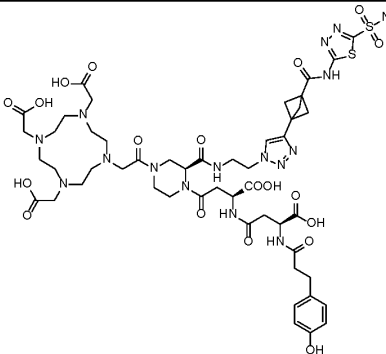
Compound	Structure
107.48	 Chemical structure of compound 107.48. It features a central macrocyclic core with multiple amide and ester linkages. The structure includes a 1,2,4-triazole ring, a 1,3,4-oxadiazole ring, and a 1,3,4-oxadiazole ring. It also contains a 1,3,4-oxadiazole ring, a 1,3,4-oxadiazole ring, and a 1,3,4-oxadiazole ring. The molecule is substituted with a 4-hydroxyphenyl group, a 3,4-dihydroxyphenyl group, and a 1,3,4-oxadiazole ring.
107.49	 Chemical structure of compound 107.49. It features a central macrocyclic core with multiple amide and ester linkages. The structure includes a 1,2,4-triazole ring, a 1,3,4-oxadiazole ring, and a 1,3,4-oxadiazole ring. It also contains a 1,3,4-oxadiazole ring, a 1,3,4-oxadiazole ring, and a 1,3,4-oxadiazole ring. The molecule is substituted with a 4-hydroxyphenyl group, a 3,4-dihydroxyphenyl group, and a 1,3,4-oxadiazole ring.
107.50	 Chemical structure of compound 107.50. It features a central macrocyclic core with multiple amide and ester linkages. The structure includes a 1,2,4-triazole ring, a 1,3,4-oxadiazole ring, and a 1,3,4-oxadiazole ring. It also contains a 1,3,4-oxadiazole ring, a 1,3,4-oxadiazole ring, and a 1,3,4-oxadiazole ring. The molecule is substituted with a 4-hydroxyphenyl group, a 3,4-dihydroxyphenyl group, and a 1,3,4-oxadiazole ring.
107.51	 Chemical structure of compound 107.51. It features a central macrocyclic core with multiple amide and ester linkages. The structure includes a 1,2,4-triazole ring, a 1,3,4-oxadiazole ring, and a 1,3,4-oxadiazole ring. It also contains a 1,3,4-oxadiazole ring, a 1,3,4-oxadiazole ring, and a 1,3,4-oxadiazole ring. The molecule is substituted with a 4-hydroxyphenyl group, a 3,4-dihydroxyphenyl group, and a 1,3,4-oxadiazole ring.
107.52	 Chemical structure of compound 107.52. It features a central macrocyclic core with multiple amide and ester linkages. The structure includes a 1,2,4-triazole ring, a 1,3,4-oxadiazole ring, and a 1,3,4-oxadiazole ring. It also contains a 1,3,4-oxadiazole ring, a 1,3,4-oxadiazole ring, and a 1,3,4-oxadiazole ring. The molecule is substituted with a 4-hydroxyphenyl group, a 3,4-dihydroxyphenyl group, and a 1,3,4-oxadiazole ring.

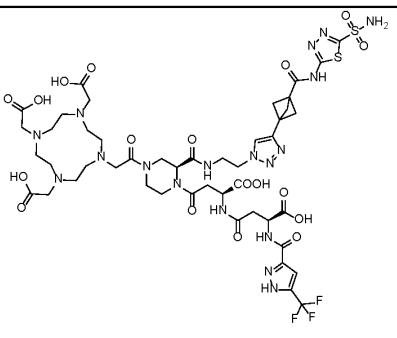
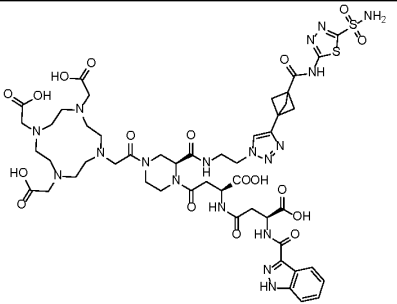
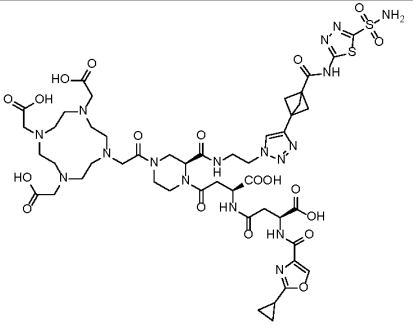
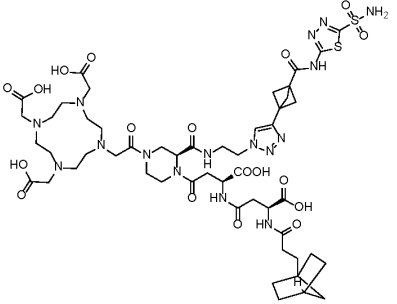
Compound	Structure
107.53	 Chemical structure of compound 107.53. It features a complex molecule with a central core containing multiple amide and ester linkages. The structure includes a 1,2,4-triazole ring system, a cyclopropyl group, and a 4-hydroxyphenyl group. A sulfonamide group (SO₂NH₂) is attached to the triazole ring. The molecule also contains several carboxylic acid and amide functional groups.
107.54	 Chemical structure of compound 107.54. It features a complex molecule with a central core containing multiple amide and ester linkages. The structure includes a 1,2,4-triazole ring system, a cyclopropyl group, and a 4-hydroxyphenyl group. A sulfonamide group (SO₂NH₂) is attached to the triazole ring. The molecule also contains several carboxylic acid and amide functional groups.
107.55	 Chemical structure of compound 107.55. It features a complex molecule with a central core containing multiple amide and ester linkages. The structure includes a 1,2,4-triazole ring system, a cyclopropyl group, and a 4-hydroxyphenyl group. A sulfonamide group (SO₂NH₂) is attached to the triazole ring. The molecule also contains several carboxylic acid and amide functional groups.
107.56	 Chemical structure of compound 107.56. It features a complex molecule with a central core containing multiple amide and ester linkages. The structure includes a 1,2,4-triazole ring system, a cyclopropyl group, and a 4-hydroxyphenyl group. A sulfonamide group (SO₂NH₂) is attached to the triazole ring. The molecule also contains several carboxylic acid and amide functional groups.

Compound	Structure
107.57	 Chemical structure of compound 107.57. It features a complex molecule with a central amide linkage. On the left, there is a bicyclic amine system with two carboxylic acid groups. This is connected via an amide bond to a central amide chain. The right side of the molecule includes a triazole ring, a cyclopropyl group, and a sulfonamide group. A side chain with two hydroxyl groups and a sulfonamide group is also present.
107.58	 Chemical structure of compound 107.58. It is similar to 107.57 but with a different side chain configuration. The central amide chain is connected to a triazole ring, which is further linked to a cyclopropyl group and a sulfonamide group. The side chain features two hydroxyl groups and a sulfonamide group.
107.59	 Chemical structure of compound 107.59. It is similar to 107.58 but with a different side chain configuration. The central amide chain is connected to a triazole ring, which is further linked to a cyclopropyl group and a sulfonamide group. The side chain features two hydroxyl groups and a sulfonamide group.
107.60	 Chemical structure of compound 107.60. It is similar to 107.59 but with a different side chain configuration. The central amide chain is connected to a triazole ring, which is further linked to a cyclopropyl group and a sulfonamide group. The side chain features two hydroxyl groups and a sulfonamide group.

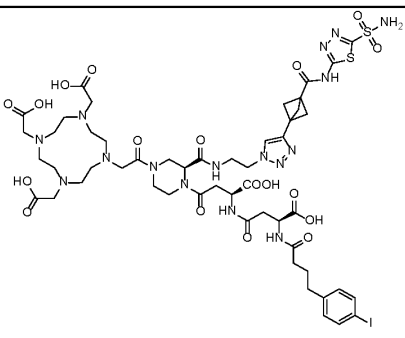
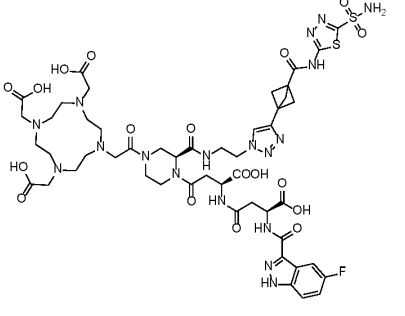
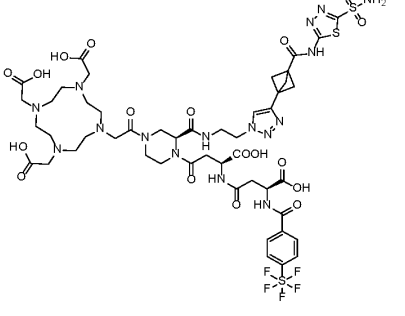
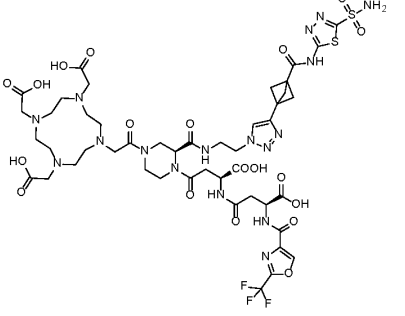
Compound	Structure
107.61	
108	
108.1	
108.2	
108.3	

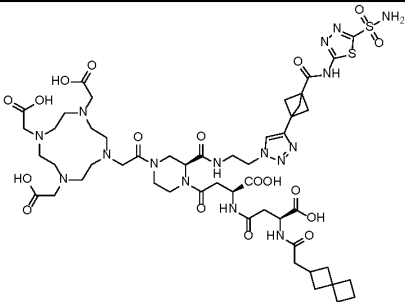
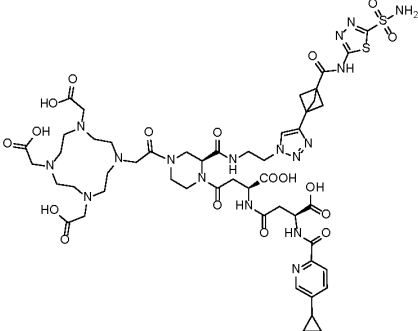
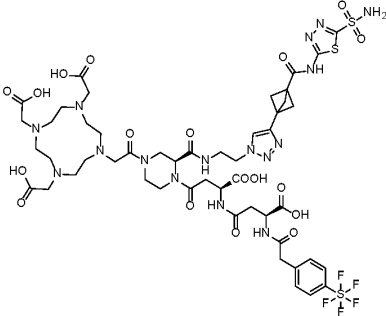
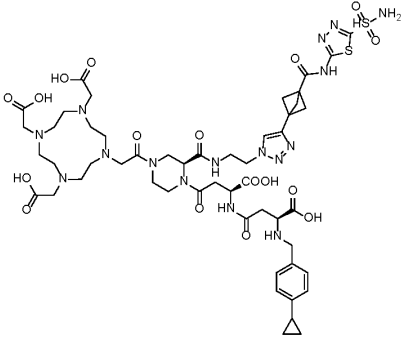
Compound	Structure
108.4	 Chemical structure of compound 108.4, featuring a complex molecule with multiple amide bonds, a carboxylic acid group, a sulfonamide group, and a biphenyl moiety.
108.5	 Chemical structure of compound 108.5, featuring a complex molecule with multiple amide bonds, a carboxylic acid group, a sulfonamide group, and a biphenyl moiety.
109	 Chemical structure of compound 109, featuring a complex molecule with multiple amide bonds, a carboxylic acid group, a sulfonamide group, and a biphenyl moiety.
109.1	 Chemical structure of compound 109.1, featuring a complex molecule with multiple amide bonds, a carboxylic acid group, a sulfonamide group, and a biphenyl moiety.

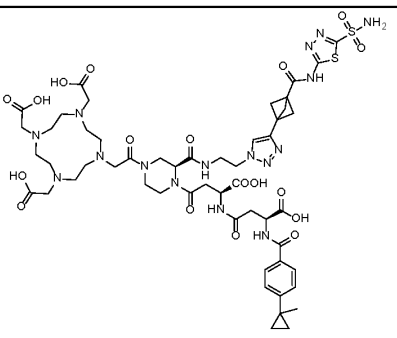
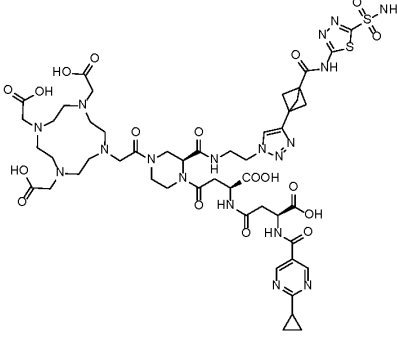
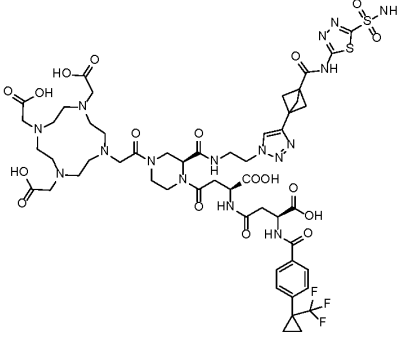
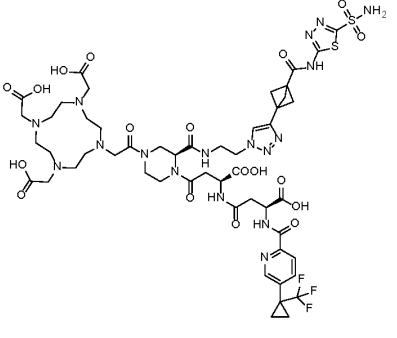
Compound	Structure
109.2	 Chemical structure of compound 109.2, featuring a complex polycyclic core with multiple amide and carboxylic acid groups. The structure includes a central bicyclic system with a carboxylic acid group, a sulfonamide group, and a cyclohexylmethyl group.
109.3	 Chemical structure of compound 109.3, featuring a complex polycyclic core with multiple amide and carboxylic acid groups. The structure includes a central bicyclic system with a carboxylic acid group, a sulfonamide group, and a 2,2,2-trifluoroethyl group.
109.4	 Chemical structure of compound 109.4, featuring a complex polycyclic core with multiple amide and carboxylic acid groups. The structure includes a central bicyclic system with a carboxylic acid group, a sulfonamide group, and a 2,2,2-trifluoroethyl group.
109.5	 Chemical structure of compound 109.5, featuring a complex polycyclic core with multiple amide and carboxylic acid groups. The structure includes a central bicyclic system with a carboxylic acid group, a sulfonamide group, and a 2,2,2-trifluoroethyl group.

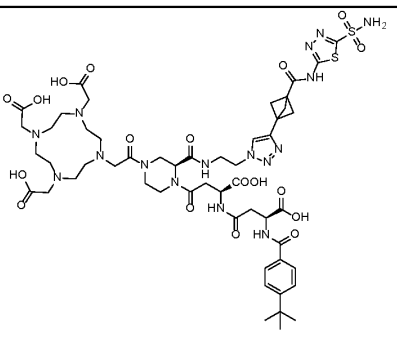
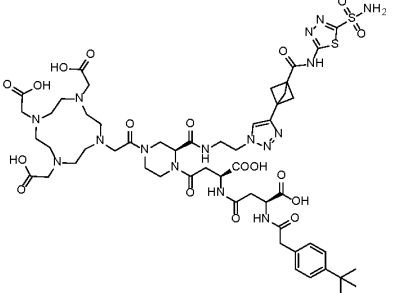
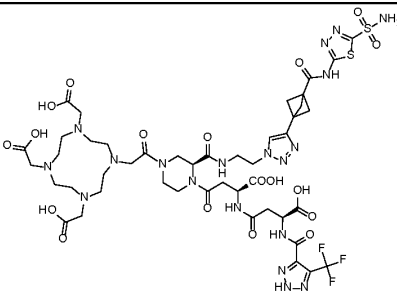
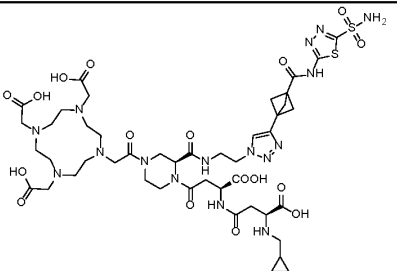
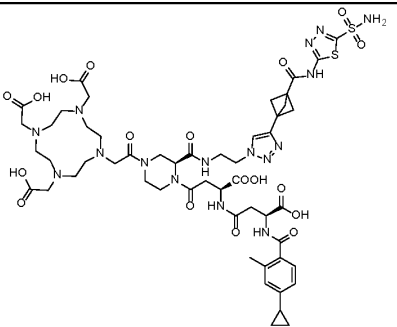
Compound	Structure
109.6	 Chemical structure of compound 109.6. It features a central macrocyclic core with multiple amide and ester linkages. The structure includes a 1,2,4-triazole ring, a cyclopropyl group, and a sulfonamide group (SO₂NH₂). A fluorinated phenyl ring is also present.
109.7	 Chemical structure of compound 109.7. It features a central macrocyclic core with multiple amide and ester linkages. The structure includes a 1,2,4-triazole ring, a cyclopropyl group, and a sulfonamide group (SO₂NH₂). A phenyl ring is also present.
109.8	 Chemical structure of compound 109.8. It features a central macrocyclic core with multiple amide and ester linkages. The structure includes a 1,2,4-triazole ring, a cyclopropyl group, and a sulfonamide group (SO₂NH₂). A furan ring is also present.
109.9	 Chemical structure of compound 109.9. It features a central macrocyclic core with multiple amide and ester linkages. The structure includes a 1,2,4-triazole ring, a cyclopropyl group, and a sulfonamide group (SO₂NH₂). A bicyclic system is also present.

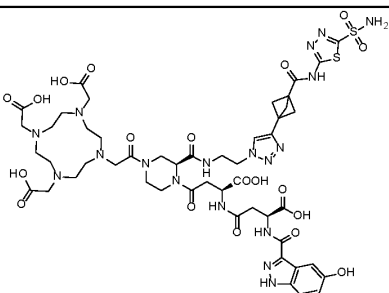
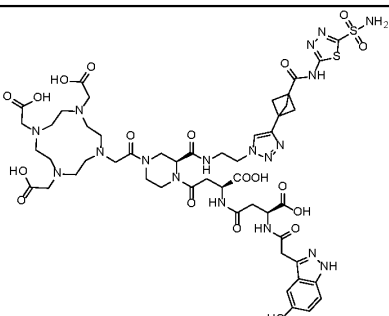
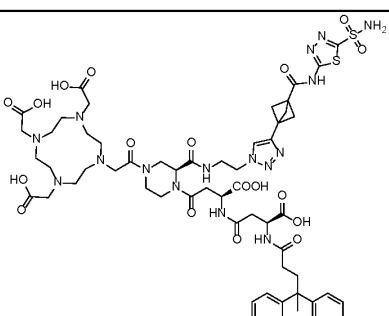
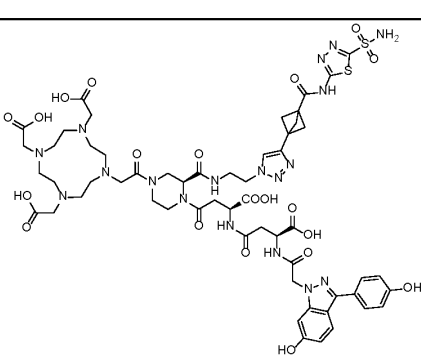
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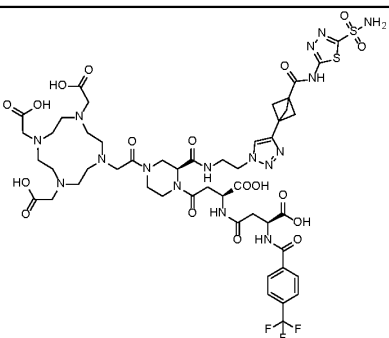
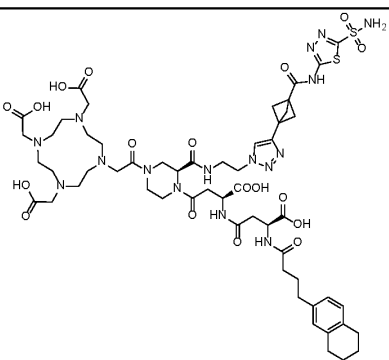
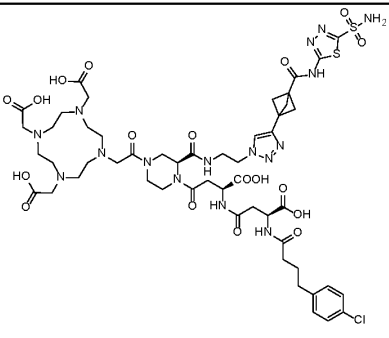
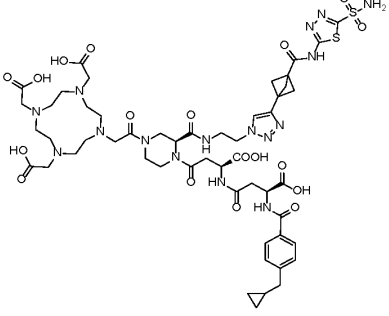
Compound	Structure
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109.15	
109.16	
109.17	

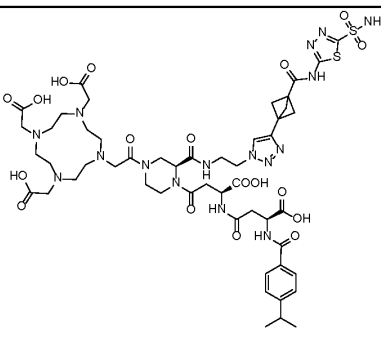
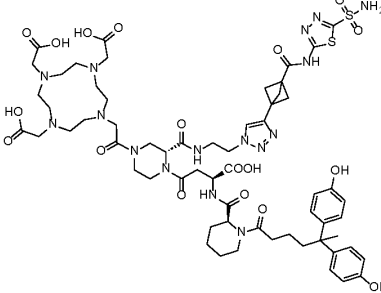
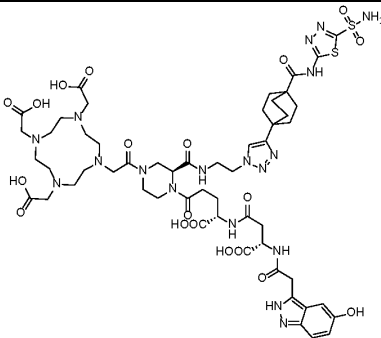
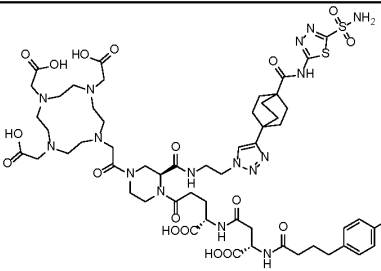
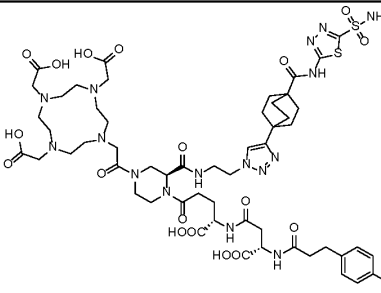
Compound	Structure
109.18	 Chemical structure of compound 109.18, featuring a complex polycyclic amide core with multiple carboxylic acid groups and a terminal sulfonamide group.
109.19	 Chemical structure of compound 109.19, featuring a complex polycyclic amide core with multiple carboxylic acid groups and a terminal sulfonamide group, with a pyridine ring substituent.
109.20	 Chemical structure of compound 109.20, featuring a complex polycyclic amide core with multiple carboxylic acid groups and a terminal sulfonamide group, with a trifluoromethyl group substituent.
109.21	 Chemical structure of compound 109.21, featuring a complex polycyclic amide core with multiple carboxylic acid groups and a terminal sulfonamide group, with a phenyl ring substituent.

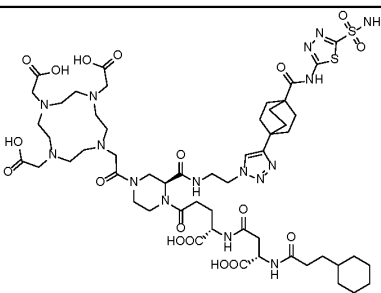
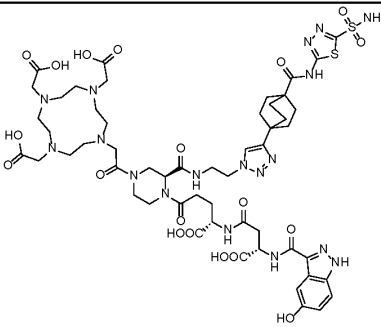
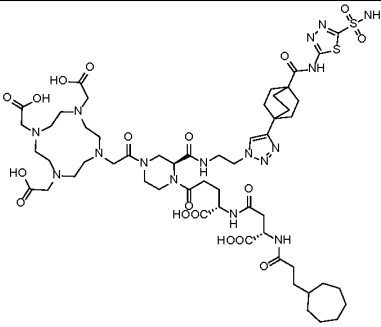
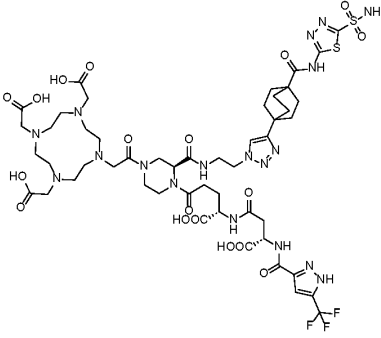
Compound	Structure
109.22	 Chemical structure of compound 109.22. It features a complex polycyclic core with multiple amide and carboxylic acid groups. A cyclopropyl ring is attached to the core, which is further substituted with a sulfonamide group (SO₂NH₂) and a phenyl ring. The structure is highly symmetrical and contains several nitrogen and oxygen atoms.
109.23	 Chemical structure of compound 109.23. It is similar to 109.22 but features a different substituent on the phenyl ring, specifically a pyridine ring.
109.24	 Chemical structure of compound 109.24. It is similar to 109.22 but features a different substituent on the phenyl ring, specifically a trifluoromethyl group (CF₃).
109.25	 Chemical structure of compound 109.25. It is similar to 109.22 but features a different substituent on the phenyl ring, specifically a trifluoromethyl group (CF₃) and a pyridine ring.

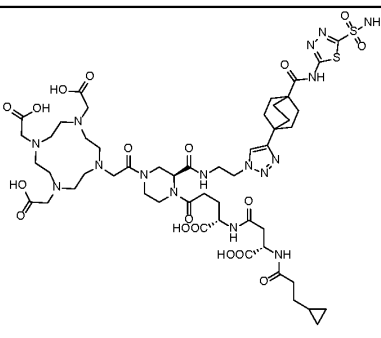
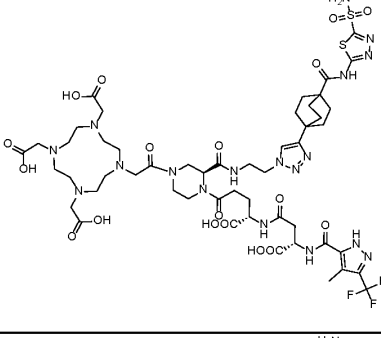
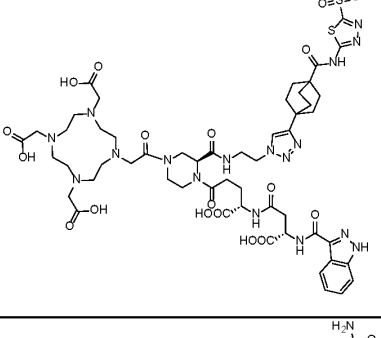
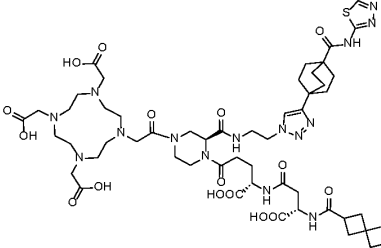
Compound	Structure
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109.27	
109.28	
109.29	
109.30	

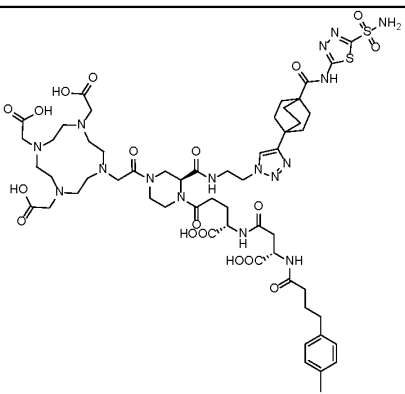
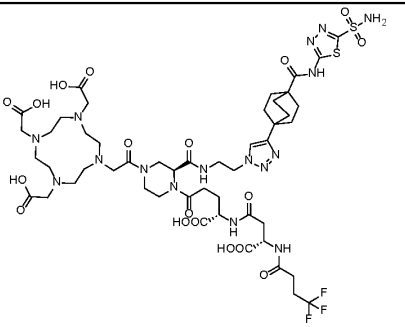
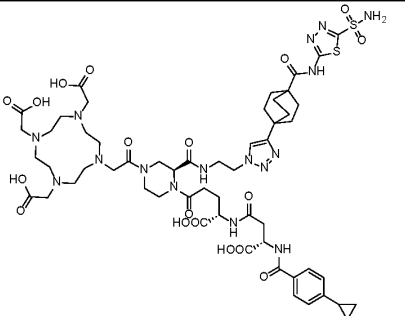
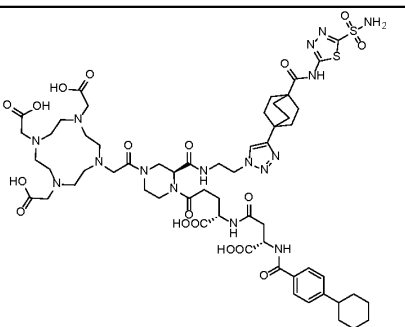
Compound	Structure
109.31	 Chemical structure of compound 109.31. It features a complex polycyclic core with multiple amide and carboxylic acid groups. A sulfonamide group is attached to the right side, and a hydroxyphenyl group is attached to the bottom right.
109.32	 Chemical structure of compound 109.32. It features a complex polycyclic core with multiple amide and carboxylic acid groups. A sulfonamide group is attached to the right side, and a hydroxyphenyl group is attached to the bottom right.
109.33	 Chemical structure of compound 109.33. It features a complex polycyclic core with multiple amide and carboxylic acid groups. A sulfonamide group is attached to the right side, and a hydroxyphenyl group is attached to the bottom right.
109.34	 Chemical structure of compound 109.34. It features a complex polycyclic core with multiple amide and carboxylic acid groups. A sulfonamide group is attached to the right side, and a hydroxyphenyl group is attached to the bottom right.

Compound	Structure
109.35	 Chemical structure of compound 109.35. It features a complex polycyclic core with multiple amide and carboxylic acid groups. A side chain includes a 1,2,4-triazole ring, a cyclobutane ring, and a sulfonamide group (SO₂NH₂). Another side chain contains a 4-(trifluoromethyl)phenyl group.
109.36	 Chemical structure of compound 109.36. It features a complex polycyclic core with multiple amide and carboxylic acid groups. A side chain includes a 1,2,4-triazole ring, a cyclobutane ring, and a sulfonamide group (SO₂NH₂). Another side chain contains a 4-(2-phenylethyl)phenyl group.
109.37	 Chemical structure of compound 109.37. It features a complex polycyclic core with multiple amide and carboxylic acid groups. A side chain includes a 1,2,4-triazole ring, a cyclobutane ring, and a sulfonamide group (SO₂NH₂). Another side chain contains a 4-(4-chlorophenylethyl)phenyl group.
109.38	 Chemical structure of compound 109.38. It features a complex polycyclic core with multiple amide and carboxylic acid groups. A side chain includes a 1,2,4-triazole ring, a cyclobutane ring, and a sulfonamide group (SO₂NH₂). Another side chain contains a 4-(cyclopropylethyl)phenyl group.

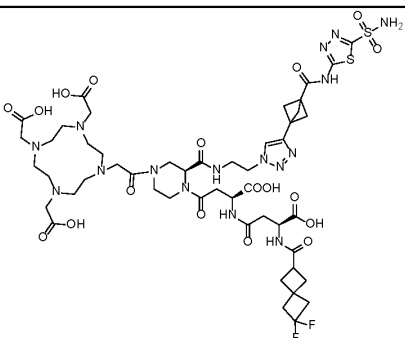
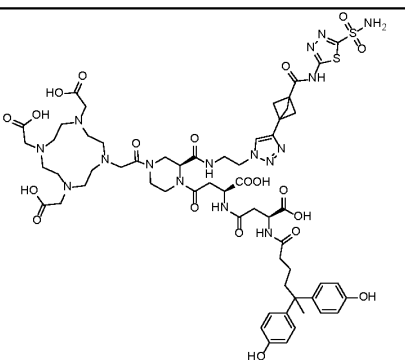
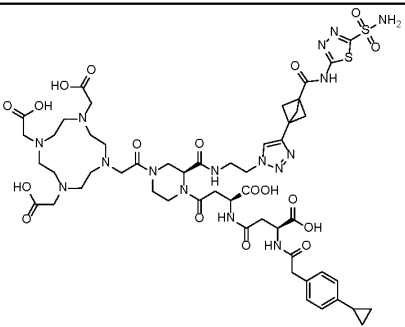
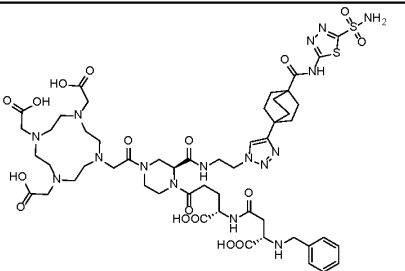
Compound	Structure
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109.40	
109.41	
109.42	
109.43	

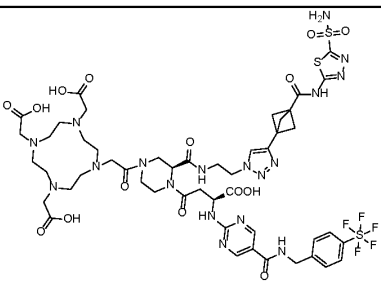
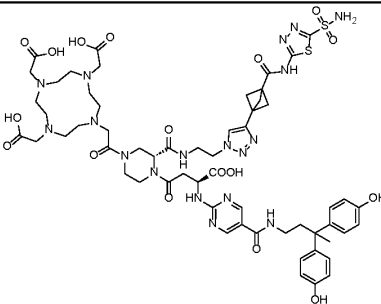
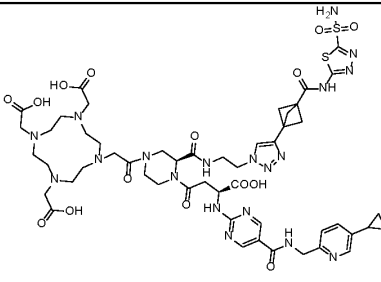
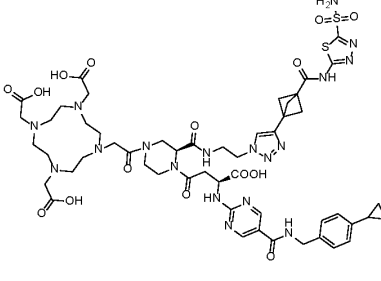
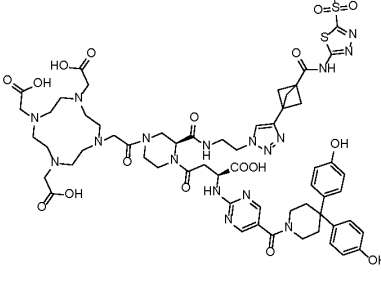
Compound	Structure
109.44	 Chemical structure of compound 109.44. It features a central bicyclic core with a carboxylic acid group, a sulfonamide group, and a cyclohexylmethyl group.
109.45	 Chemical structure of compound 109.45. It features a central bicyclic core with a carboxylic acid group, a sulfonamide group, and a 4-hydroxyphenyl group.
109.46	 Chemical structure of compound 109.46. It features a central bicyclic core with a carboxylic acid group, a sulfonamide group, and a cyclohexylmethyl group.
109.47	 Chemical structure of compound 109.47. It features a central bicyclic core with a carboxylic acid group, a sulfonamide group, and a 4-(trifluoromethyl)phenyl group.

Compound	Structure
109.48	
109.49	
109.50	
109.51	

Compound	Structure
109.52	
109.53	
109.54	
109.55	

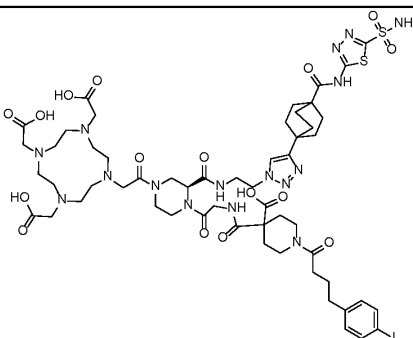
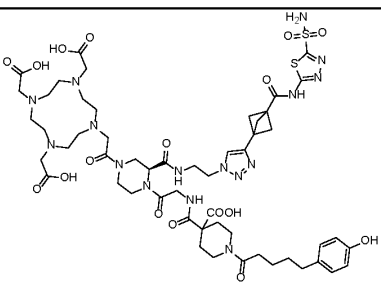
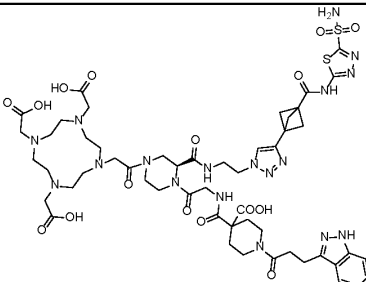
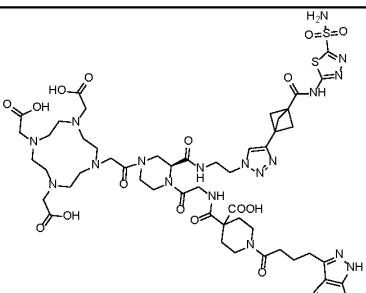
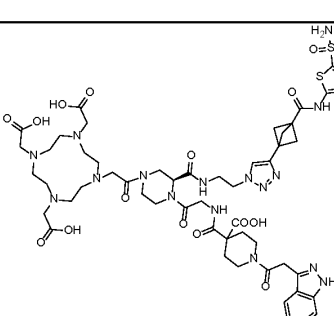
Compound	Structure
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109.57	
109.58	
109.59	
109.60	

Compound	Structure
109.61	
109.62	
109.63	
110	

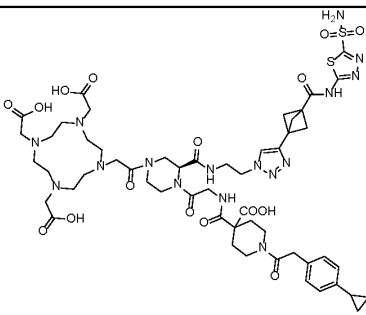
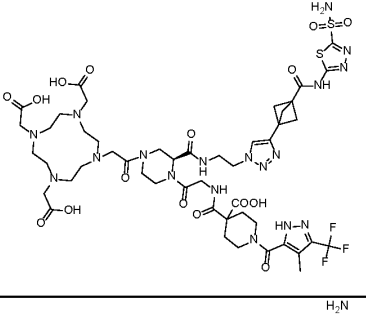
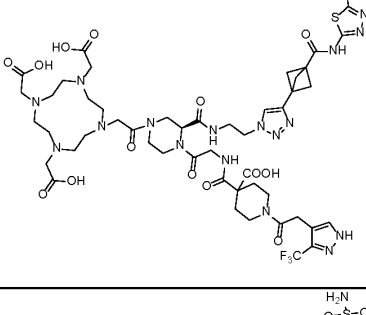
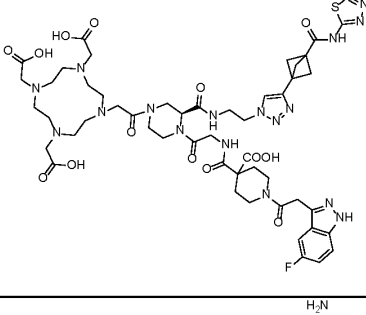
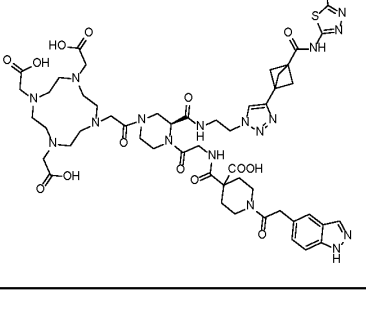
Compound	Structure
111	
111.1	
111.2	
111.3	
111.4	

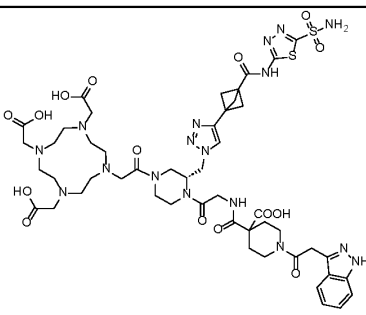
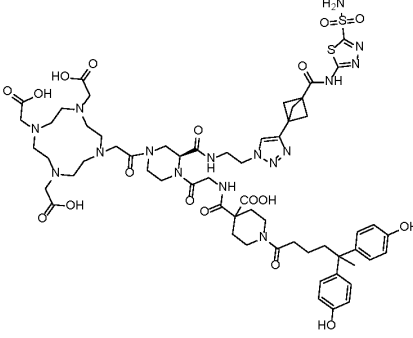
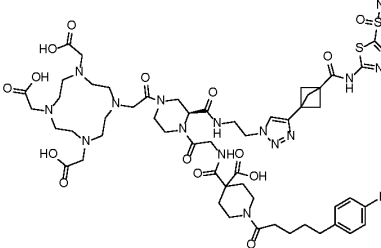
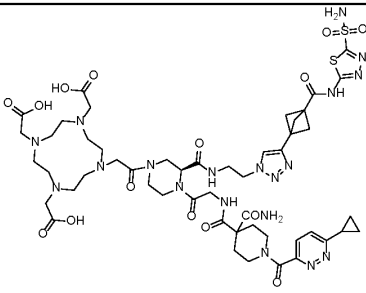
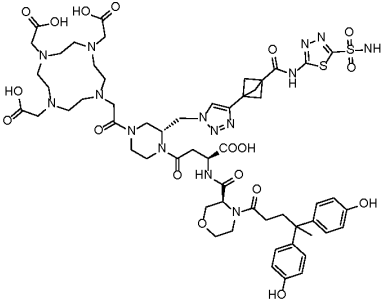
Compound	Structure
111.5	
111.6	
111.7	
111.8	
111.9	

Compound	Structure
111.10	
111.11	
111.12	
112	
112.1	

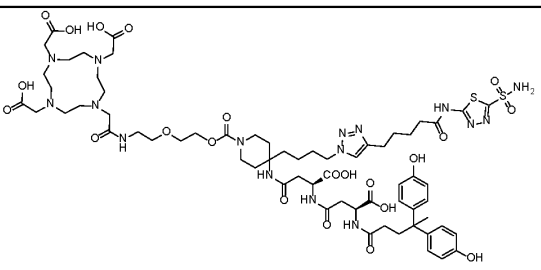
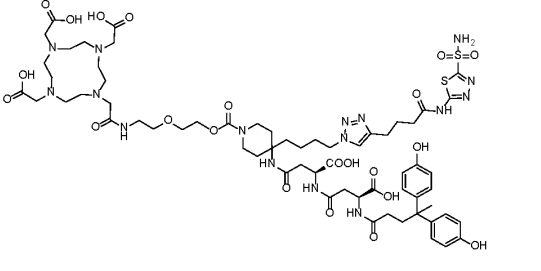
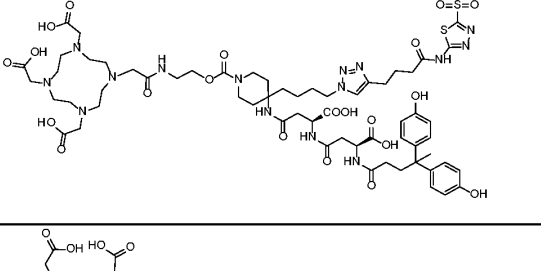
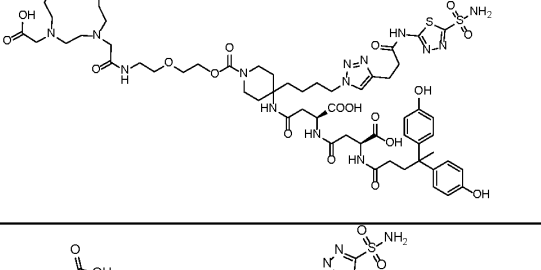
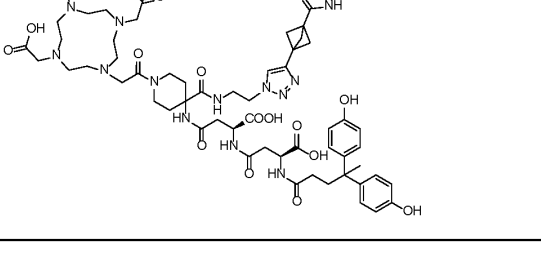
Compound	Structure
112.2	 Chemical structure of compound 112.2, featuring a complex polycyclic core with multiple amide and carboxylic acid groups. The structure includes a central bicyclic system with a carboxylic acid group, a sulfonamide group, and a phenyl ring substituted with a carboxylic acid group.
112.3	 Chemical structure of compound 112.3, featuring a complex polycyclic core with multiple amide and carboxylic acid groups. The structure includes a central bicyclic system with a carboxylic acid group, a sulfonamide group, and a phenyl ring substituted with a carboxylic acid group.
112.4	 Chemical structure of compound 112.4, featuring a complex polycyclic core with multiple amide and carboxylic acid groups. The structure includes a central bicyclic system with a carboxylic acid group, a sulfonamide group, and a phenyl ring substituted with a carboxylic acid group.
112.5	 Chemical structure of compound 112.5, featuring a complex polycyclic core with multiple amide and carboxylic acid groups. The structure includes a central bicyclic system with a carboxylic acid group, a sulfonamide group, and a phenyl ring substituted with a carboxylic acid group.
112.6	 Chemical structure of compound 112.6, featuring a complex polycyclic core with multiple amide and carboxylic acid groups. The structure includes a central bicyclic system with a carboxylic acid group, a sulfonamide group, and a phenyl ring substituted with a carboxylic acid group.

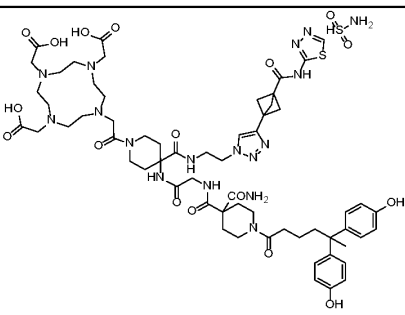
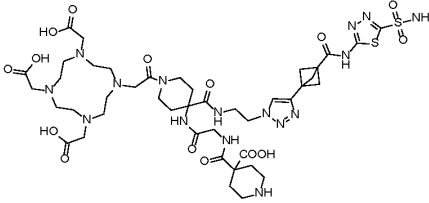
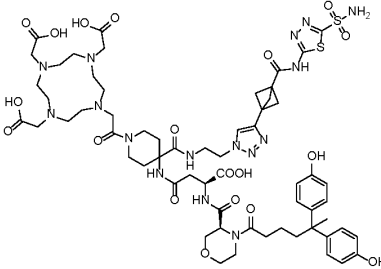
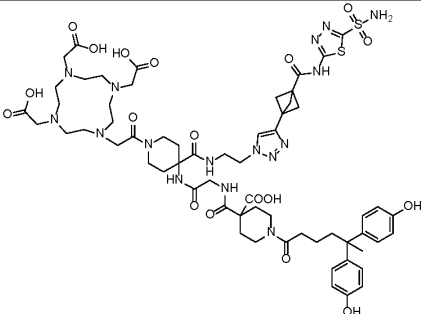
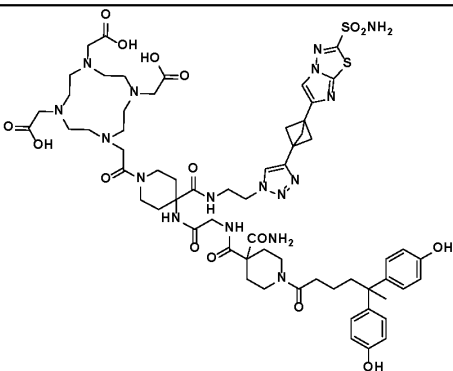
Compound	Structure
112.7	
112.8	
112.9	
112.10	
112.11	

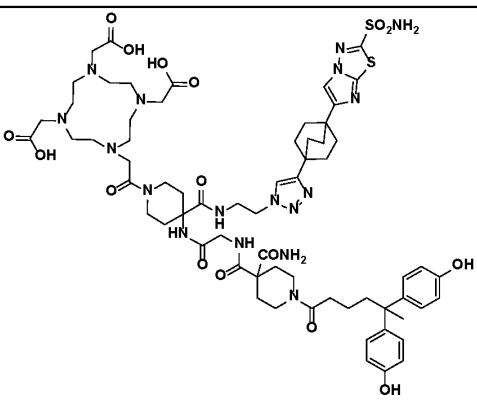
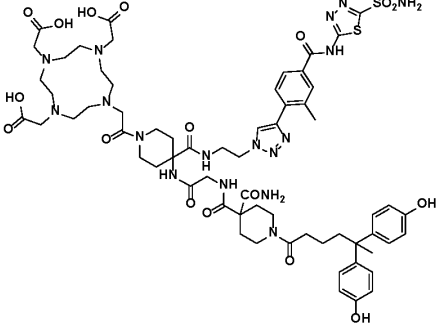
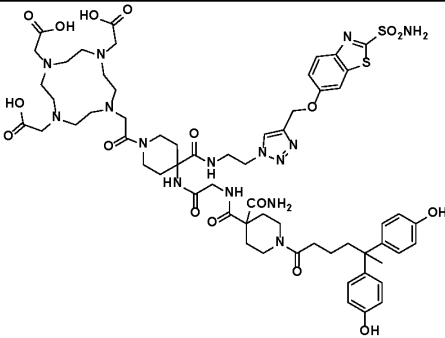
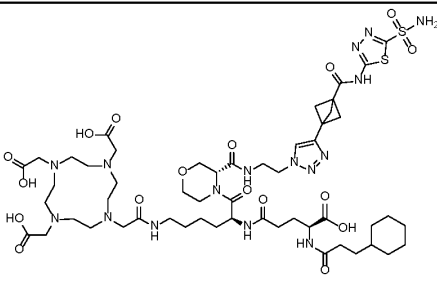
Compound	Structure
112.12	
112.13	
112.14	
112.15	
112.16	

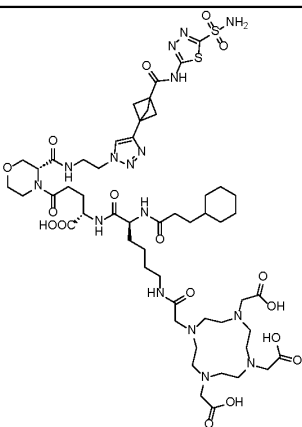
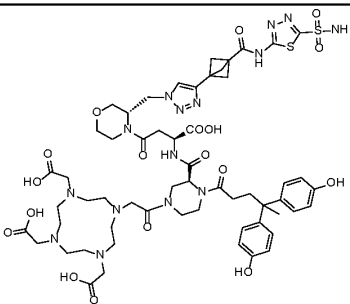
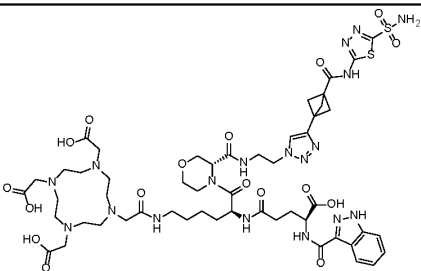
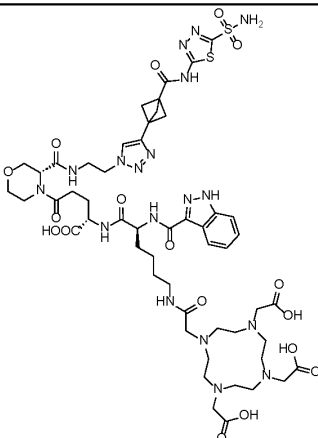
Compound	Structure
112.17	 Chemical structure of compound 112.17, featuring a complex molecule with multiple amide bonds, a cyclopropyl group, a sulfonamide group, and a pyrazole ring.
112.18	 Chemical structure of compound 112.18, featuring a complex molecule with multiple amide bonds, a cyclopropyl group, a sulfonamide group, and a pyrazole ring.
112.19	 Chemical structure of compound 112.19, featuring a complex molecule with multiple amide bonds, a cyclopropyl group, a sulfonamide group, and a pyrazole ring.
113	 Chemical structure of compound 113, featuring a complex molecule with multiple amide bonds, a cyclopropyl group, a sulfonamide group, and a pyrazole ring.
114	 Chemical structure of compound 114, featuring a complex molecule with multiple amide bonds, a cyclopropyl group, a sulfonamide group, and a pyrazole ring.

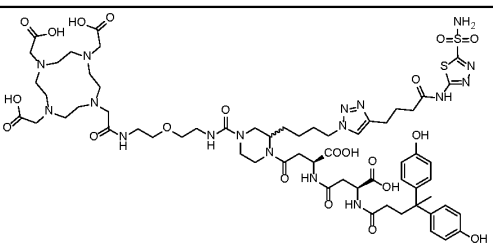
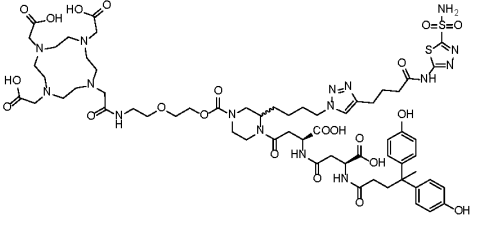
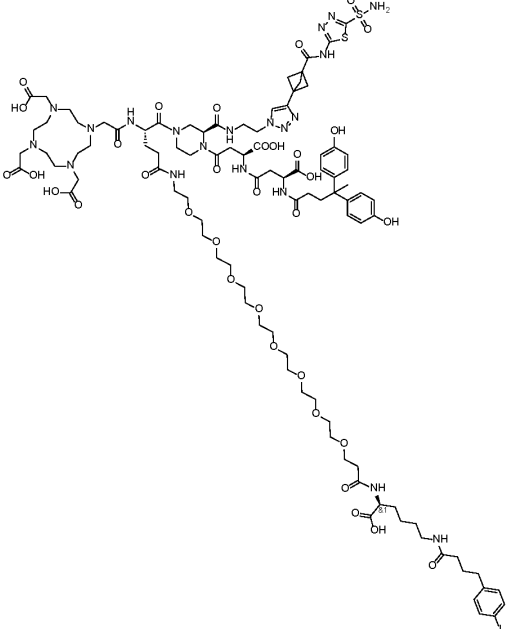
Compound	Structure
114.1	
114.2	
114.3	
115	
116	

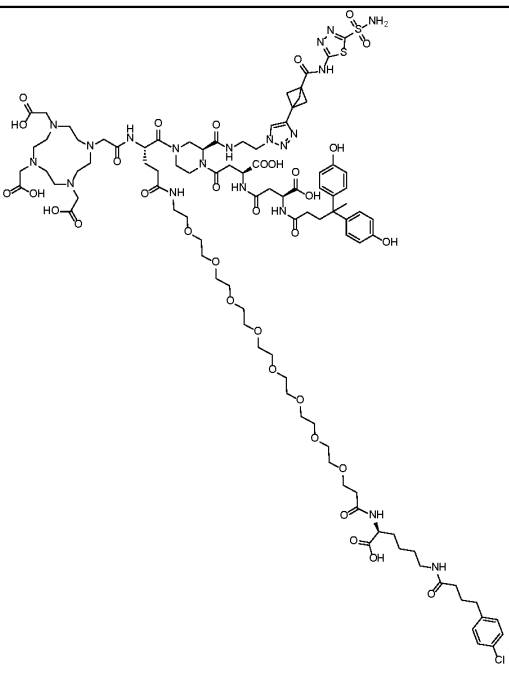
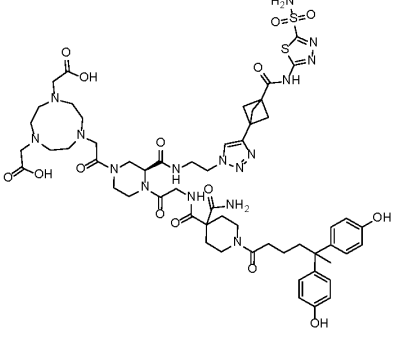
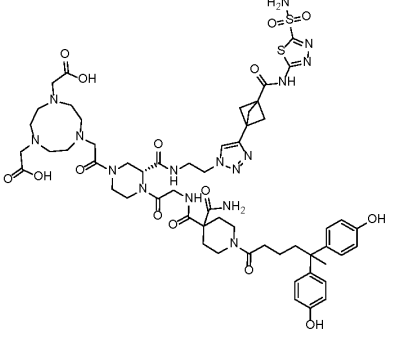
Compound	Structure
116.1	 Chemical structure of compound 116.1, featuring a complex molecule with multiple functional groups, including carboxylic acids, amides, and a sulfonamide group.
116.2	 Chemical structure of compound 116.2, featuring a complex molecule with multiple functional groups, including carboxylic acids, amides, and a sulfonamide group.
116.3	 Chemical structure of compound 116.3, featuring a complex molecule with multiple functional groups, including carboxylic acids, amides, and a sulfonamide group.
116.4	 Chemical structure of compound 116.4, featuring a complex molecule with multiple functional groups, including carboxylic acids, amides, and a sulfonamide group.
117	 Chemical structure of compound 117, featuring a complex molecule with multiple functional groups, including carboxylic acids, amides, and a sulfonamide group.

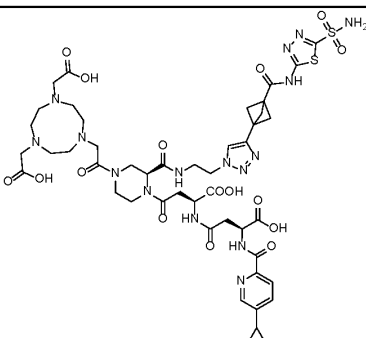
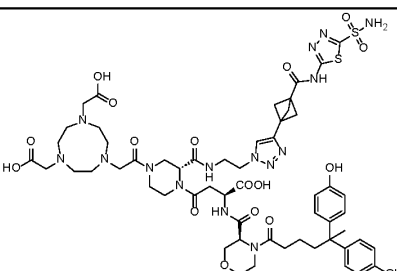
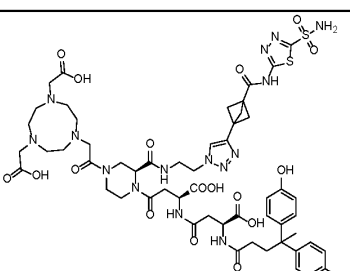
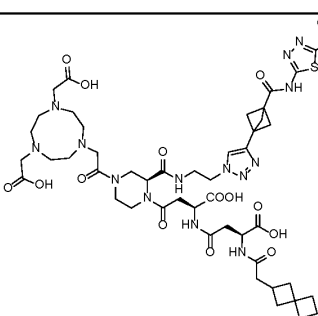
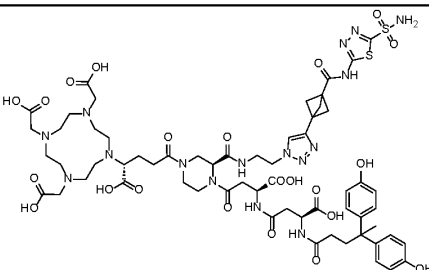
Compound	Structure
117.1	 Chemical structure of compound 117.1. It features a central bicyclic core with a carboxylic acid group, a sulfonamide group, and a phenyl ring with two hydroxyl groups.
117.2	 Chemical structure of compound 117.2. It features a central bicyclic core with a carboxylic acid group, a sulfonamide group, and a phenyl ring with two hydroxyl groups.
117.3	 Chemical structure of compound 117.3. It features a central bicyclic core with a carboxylic acid group, a sulfonamide group, and a phenyl ring with two hydroxyl groups.
117.4	 Chemical structure of compound 117.4. It features a central bicyclic core with a carboxylic acid group, a sulfonamide group, and a phenyl ring with two hydroxyl groups.
117.5	 Chemical structure of compound 117.5. It features a central bicyclic core with a carboxylic acid group, a sulfonamide group, and a phenyl ring with two hydroxyl groups.

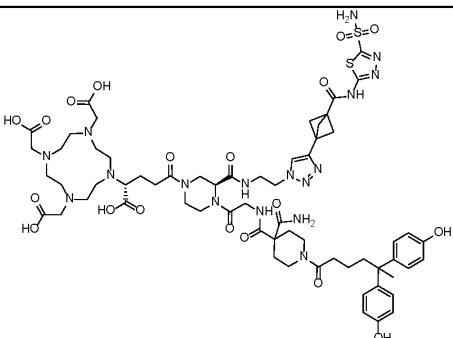
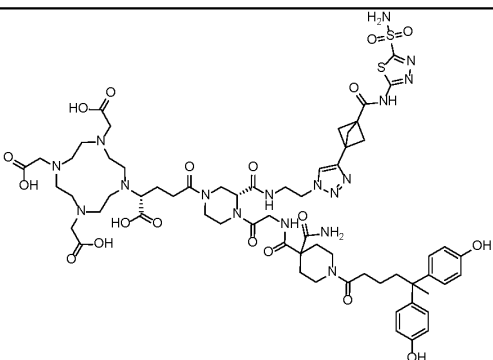
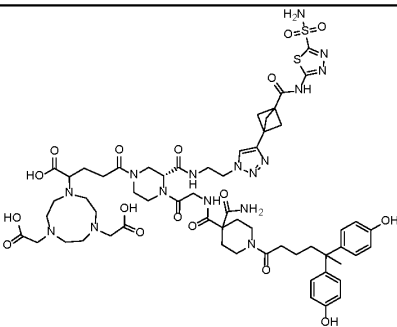
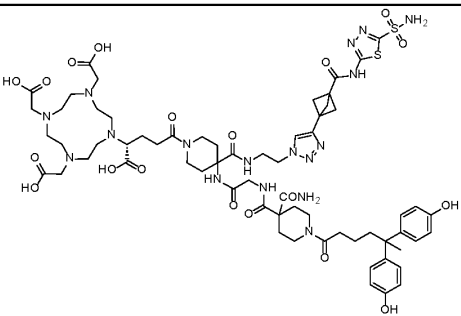
Compound	Structure
117.6	 Chemical structure of compound 117.6. It features a complex molecule with a central piperidine ring. Attached to this ring are various functional groups, including a carboxamide group (CONH₂), a carboxylic acid group (COOH), and a sulfonamide group (SO₂NH₂). The molecule also contains a biphenyl system with two hydroxyl groups (OH) and a thiazole ring.
117.7	 Chemical structure of compound 117.7. It features a complex molecule with a central piperidine ring. Attached to this ring are various functional groups, including a carboxamide group (CONH₂), a carboxylic acid group (COOH), and a sulfonamide group (SO₂NH₂). The molecule also contains a biphenyl system with two hydroxyl groups (OH) and a thiazole ring.
117.8	 Chemical structure of compound 117.8. It features a complex molecule with a central piperidine ring. Attached to this ring are various functional groups, including a carboxamide group (CONH₂), a carboxylic acid group (COOH), and a sulfonamide group (SO₂NH₂). The molecule also contains a biphenyl system with two hydroxyl groups (OH) and a thiazole ring.
118	 Chemical structure of compound 118. It features a complex molecule with a central piperidine ring. Attached to this ring are various functional groups, including a carboxamide group (CONH₂), a carboxylic acid group (COOH), and a sulfonamide group (SO₂NH₂). The molecule also contains a biphenyl system with two hydroxyl groups (OH) and a thiazole ring.

Compound	Structure
118.1	 Chemical structure of compound 118.1. It features a central 1,4-bis(methylene)pyrrolidine ring substituted with two carboxylic acid groups. This central ring is linked via amide bonds to two side chains. One side chain contains a 1,2,4-triazole ring, a cyclobutyl group, and a sulfonamide group. The other side chain contains a 1,2,4-triazole ring, a cyclobutyl group, and a carboxylic acid group.
118.2	 Chemical structure of compound 118.2. It features a central 1,4-bis(methylene)pyrrolidine ring substituted with two carboxylic acid groups. This central ring is linked via amide bonds to two side chains. One side chain contains a 1,2,4-triazole ring, a cyclobutyl group, and a sulfonamide group. The other side chain contains a 1,2,4-triazole ring, a cyclobutyl group, and a carboxylic acid group.
118.3	 Chemical structure of compound 118.3. It features a central 1,4-bis(methylene)pyrrolidine ring substituted with two carboxylic acid groups. This central ring is linked via amide bonds to two side chains. One side chain contains a 1,2,4-triazole ring, a cyclobutyl group, and a sulfonamide group. The other side chain contains a 1,2,4-triazole ring, a cyclobutyl group, and a carboxylic acid group.
118.4	 Chemical structure of compound 118.4. It features a central 1,4-bis(methylene)pyrrolidine ring substituted with two carboxylic acid groups. This central ring is linked via amide bonds to two side chains. One side chain contains a 1,2,4-triazole ring, a cyclobutyl group, and a sulfonamide group. The other side chain contains a 1,2,4-triazole ring, a cyclobutyl group, and a carboxylic acid group.

Compound	Structure
123	 Chemical structure of Compound 123, a complex molecule featuring a central core with multiple functional groups, including carboxylic acids, amides, and a sulfonamide group.
124	 Chemical structure of Compound 124, a complex molecule featuring a central core with multiple functional groups, including carboxylic acids, amides, and a sulfonamide group.
125	 Chemical structure of Compound 125, a complex molecule featuring a central core with multiple functional groups, including carboxylic acids, amides, and a sulfonamide group.

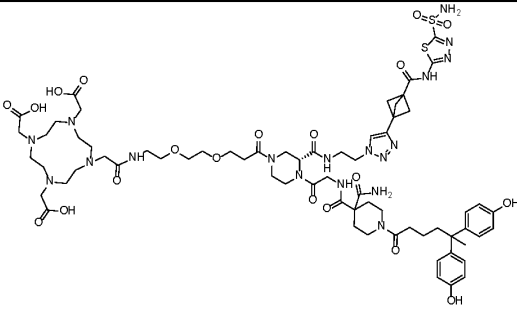
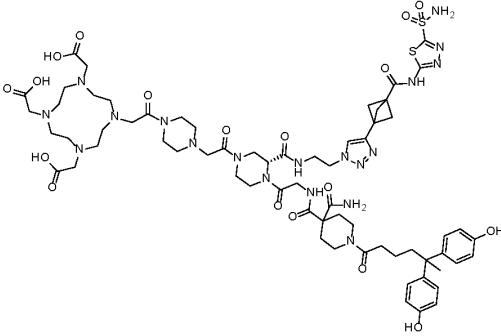
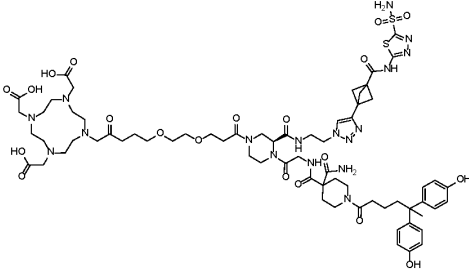
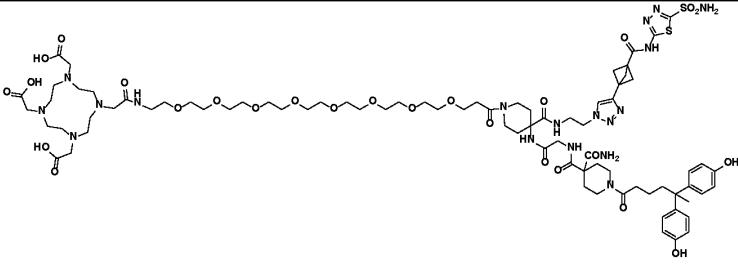
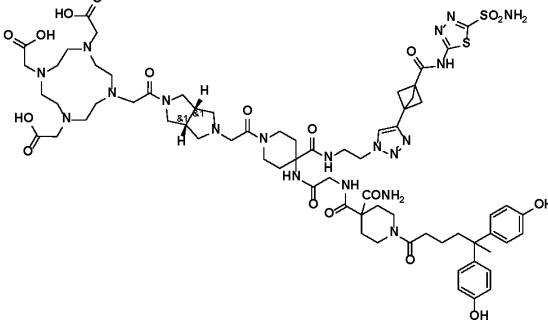
Compound	Structure
125.1	 Chemical structure of compound 125.1, a complex molecule featuring a long, flexible polyether chain. The chain is substituted with various functional groups, including a carboxylic acid, a hydroxyl group, a sulfonamide group, and a chlorophenyl group. The structure is highly branched and contains multiple amide and ester linkages.
126	 Chemical structure of compound 126, a complex molecule featuring a central core with multiple amide and ester linkages. The structure includes a carboxylic acid group, a hydroxyl group, and a sulfonamide group. The molecule is highly branched and contains multiple amide and ester linkages.
126.1	 Chemical structure of compound 126.1, a complex molecule featuring a central core with multiple amide and ester linkages. The structure includes a carboxylic acid group, a hydroxyl group, and a sulfonamide group. The molecule is highly branched and contains multiple amide and ester linkages.

Compound	Structure
126.2	 Chemical structure of compound 126.2, featuring a complex molecule with a central amide linkage, a carboxylic acid group, a sulfonamide group, and a pyridine ring.
126.3	 Chemical structure of compound 126.3, featuring a complex molecule with a central amide linkage, a carboxylic acid group, a sulfonamide group, and a pyridine ring.
126.4	 Chemical structure of compound 126.4, featuring a complex molecule with a central amide linkage, a carboxylic acid group, a sulfonamide group, and a pyridine ring.
126.5	 Chemical structure of compound 126.5, featuring a complex molecule with a central amide linkage, a carboxylic acid group, a sulfonamide group, and a pyridine ring.
127	 Chemical structure of compound 127, featuring a complex molecule with a central amide linkage, a carboxylic acid group, a sulfonamide group, and a pyridine ring.

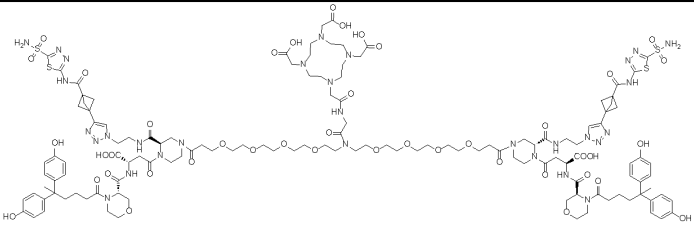
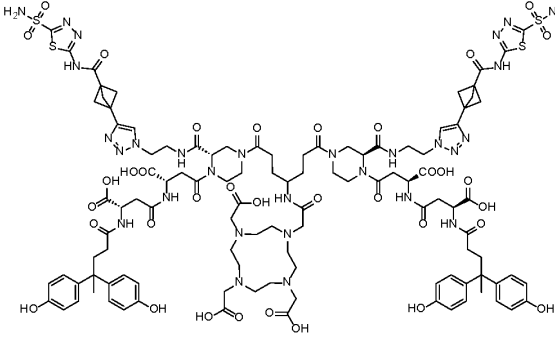
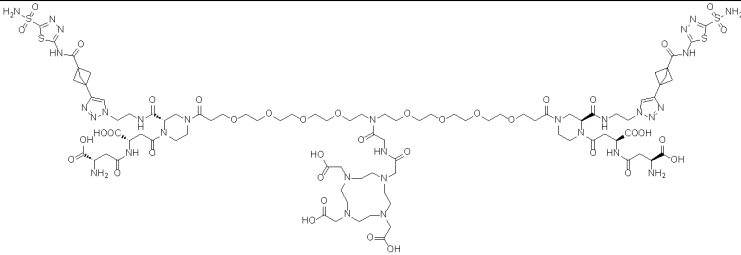
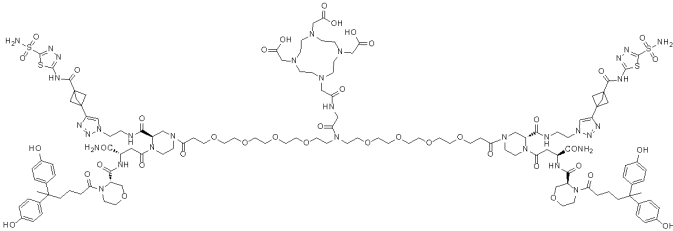
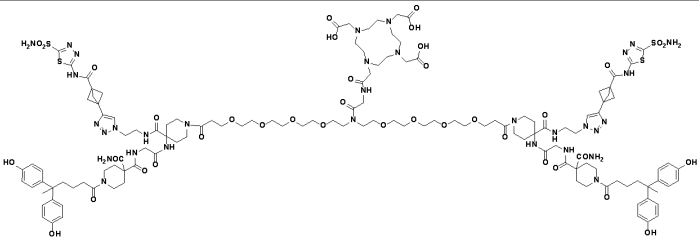
Compound	Structure
127.1	 Chemical structure of compound 127.1, featuring a complex molecule with multiple rings, including a cyclohexane ring, a piperidine ring, and a triazole ring. It also contains a sulfonamide group and a hydroxyl group.
127.2	 Chemical structure of compound 127.2, featuring a complex molecule with multiple rings, including a cyclohexane ring, a piperidine ring, and a triazole ring. It also contains a sulfonamide group and a hydroxyl group.
127.3	 Chemical structure of compound 127.3, featuring a complex molecule with multiple rings, including a cyclohexane ring, a piperidine ring, and a triazole ring. It also contains a sulfonamide group and a hydroxyl group.
127.4	 Chemical structure of compound 127.4, featuring a complex molecule with multiple rings, including a cyclohexane ring, a piperidine ring, and a triazole ring. It also contains a sulfonamide group and a hydroxyl group.

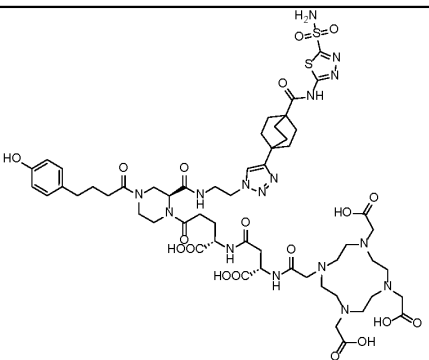
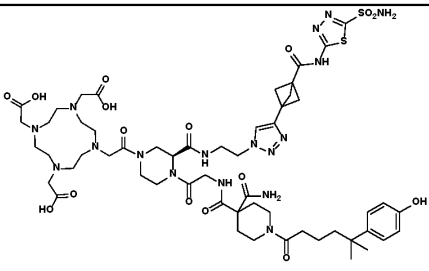
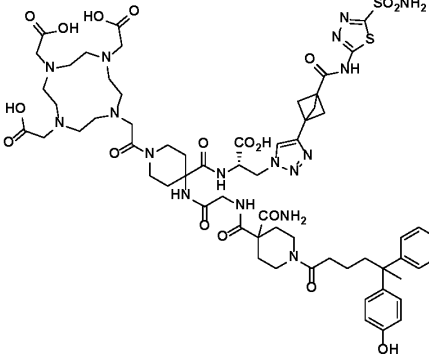
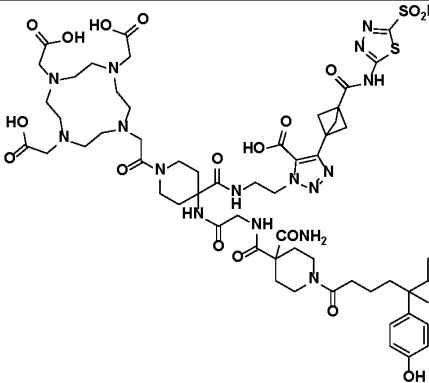
Compound	Structure
127.5	
127.6	
127.7	
127.8	

Compound	Structure
127.9	
128	
128.1	
129	
129.1	

Compound	Structure
129.2	
129.3	
129.4	
129.5	
129.6	

Compound	Structure
129.7	
130	
131	
131.1	
131.2	

Compound	Structure
131.3	 Chemical structure of compound 131.3, a long-chain molecule featuring multiple amide, ester, and sulfonamide groups, with terminal hydroxyl and sulfonamide groups.
131.4	 Chemical structure of compound 131.4, a complex molecule with multiple amide, ester, and sulfonamide groups, and terminal hydroxyl and sulfonamide groups.
131.5	 Chemical structure of compound 131.5, a long-chain molecule featuring multiple amide, ester, and sulfonamide groups, with terminal hydroxyl and sulfonamide groups.
131.6	 Chemical structure of compound 131.6, a long-chain molecule featuring multiple amide, ester, and sulfonamide groups, with terminal hydroxyl and sulfonamide groups.
131.7	 Chemical structure of compound 131.7, a long-chain molecule featuring multiple amide, ester, and sulfonamide groups, with terminal hydroxyl and sulfonamide groups.

Compound	Structure
132	
133	
134	
135	

Compound	Structure
136	

[00504] In some embodiments the conjugate disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, is one of the compounds in Table 2.

TABLE 2

Structures

Further Forms of Compounds Disclosed Herein

Isomers/Stereoisomers

[00505] In some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the corresponding mixtures thereof. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the R configuration, or S configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some embodiments, the compounds

described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred. In some embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization.

Isotopically enriched compounds

[00506] Unless otherwise stated, compounds described herein may exhibit their natural isotopic abundance, 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. All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are encompassed within the scope of the present disclosure. For example, hydrogen has three naturally occurring isotopes, denoted ^1H (protium), ^2H (deuterium), and ^3H (tritium). Protium is the most abundant isotope of hydrogen in nature. Enriching for deuterium may afford some therapeutic advantages, such as increased *in vivo* half-life and/or exposure, or may provide a compound useful for investigating *in vivo* routes of drug elimination and metabolism.

[00507] For example, the compounds described herein may be artificially enriched in one or more particular isotopes. In some embodiments, the compounds described herein may be artificially enriched in one or more isotopes that are not predominantly found in nature. In some embodiments, the compounds described herein may be artificially enriched in one or more isotopes selected from deuterium (^2H), tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). In some embodiments, the compounds described herein are artificially enriched in one or more isotopes selected from ^2H , ^{11}C , ^{13}C , ^{14}C , ^{15}C , ^{12}N , ^{13}N , ^{15}N , ^{16}N , ^{16}O , ^{17}O , ^{14}F , ^{15}F , ^{16}F , ^{17}F , ^{18}F , ^{33}S , ^{34}S , ^{35}S , ^{36}S , ^{35}Cl , ^{37}Cl , ^{79}Br , ^{81}Br , ^{131}I , and ^{125}I . In some embodiments, the abundance of the enriched isotopes is independently at least 1%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% by molar.

[00508] In some embodiments, the compound is deuterated in at least one position. In some embodiments, the compounds disclosed herein have some or all of the ^1H atoms replaced with ^2H atoms.

[00509] The methods of synthesis for deuterium-containing compounds are known in the art and include, by way of non-limiting example only, the procedure described in U.S. Patent Nos. 5,846,514 and 6,334,997, and the following synthetic methods. For example, deuterium substituted compounds may be synthesized using various methods such as described in: Dean, Dennis C.; Editor. Recent Advances in the Synthesis and Applications of Radiolabeled Compounds for Drug Discovery and Development. [In: Curr., Pharm. Des., 2000; 6(10)] 2000, 110 pp; George W.; Varma, Rajender S. The Synthesis of

Radiolabeled Compounds via Organometallic Intermediates, Tetrahedron, 1989, 45(21), 6601-21; and Evans, E. Anthony. Synthesis of radiolabeled compounds, J. Radioanal. Chem., 1981, 64(1-2), 9-32.

[00510] Deuterated starting materials are readily available and are subjected to the synthetic methods described herein to provide for the synthesis of deuterium-containing compounds. Large numbers of deuterium-containing reagents and building blocks are available commercially from chemical vendors, such as Aldrich Chemical Co.

Pharmaceutically acceptable salts

[00511] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[00512] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds disclosed herein or stereoisomer thereof, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[00513] Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral, organic acid or inorganic base, such salts including, acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, γ -hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-naphthalenesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylate, undecanoate, and xylenesulfonate.

[00514] Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluenesulfonic acid, tartaric

acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid and muconic acid. In some embodiments, other acids, such as oxalic, while not in themselves pharmaceutically acceptable, are employed in the preparation of salts useful as intermediates in obtaining the compounds disclosed herein or stereoisomer thereof and their pharmaceutically acceptable acid addition salts.

[00515] In some embodiments, those compounds described herein which comprise a free acid group react with a suitable base, such as the hydroxide, carbonate, bicarbonate, sulfate, of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, tertiary, or quaternary amine. Representative salts include the alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, and magnesium, and aluminum salts and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4} \text{ alkyl})_4$, and the like.

[00516] Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they contain. In some embodiments, water or oil-soluble or dispersible products are obtained by such quaternization.

Tautomers

[00517] In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. Tautomers are compounds that are interconvertible by migration of a hydrogen atom, accompanied by a switch of a single bond and adjacent double bond. In bonding arrangements where tautomerization is possible, a chemical equilibrium of the tautomers will exist. All tautomeric forms of the compounds disclosed herein are contemplated. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH.

Radiopharmaceutical Conjugates

[00518] Disclosed herein are radiopharmaceutical conjugate comprising a conjugate disclosed herein bound to a radionuclide. Generally, the type of radionuclide used in a therapeutic radiopharmaceutical can be tailored to the specific type of cancer, the type of targeting moiety (e.g., binding peptide), etc. Radionuclides that undergo α -decay produce particles composed of two neutrons and two protons, and radionuclides that undergo β -decay emit energetic electrons from their nuclei. Some radionuclides can also undergo electron capture and emit Auger electrons. In some embodiments, the conjugate comprises an alpha particle-emitting radionuclide. Alpha radiation can cause direct, irreparable double-strand DNA breaks compared with gamma and beta radiation, which can cause single-stranded breaks via indirect

DNA damage. The range of these particles in tissue and the half-life of the radionuclide can also be considered in designing the radiopharmaceutical conjugate. Tables 3 below illustrates some properties of exemplary radionuclides.

Table 3. Exemplary radionuclides

Radionuclide	Emission/Decay	Exemplary application-- Therapeutics (Tx) or Diagnostics (Dx)	Exemplary methods of binding the radionuclide to a radiopharmaceutical conjugate (e.g., through a Chelator or bound to the conjugate through a Covalent bond)
Ac-225	Alpha	Tx	Chelator
As-70	Positron	Dx	Covalent
As-71	Positron	Dx	Covalent
As-72	Positron	Dx	Covalent
As-73	Electron Capture	Dx	Covalent
As-74	Positron	Dx	Covalent
As-76	Beta	Tx	Covalent
As-77	Beta	Tx	Covalent
At-211	Alpha	Tx	Covalent
Bi-209	Alpha	Tx	Chelator
Bi-212	Alpha	Tx	Chelator
Bi-213	Alpha	Tx	Chelator
Br-76	Positron	Dx	Covalent
Ce-134	Electron Capture	Dx	Chelator
Cu-61	Positron	Dx	Chelator
Cu-62	Positron	Dx	Chelator
Cu-64	Positron	Dx	Chelator
Cu-67	Beta	Tx	Chelator
Fr-223	Alpha	Tx	Chelator
Ga-68	Positron	Dx	Chelator
Gd-148	Alpha	Tx	Chelator
Ho-166	Beta/gamma	Tx/Dx	Chelator
I-123	Electron Capture	Dx	Covalent
I-124	Positron	Dx	Covalent
I-125	Electron Capture	Dx	Covalent
I-131	Beta	Tx	Covalent
In-111	Beta/Electron Capture	Tx/Dx	Chelator
Lu-177	Beta	Tx	Chelator
Pb-212	Alpha	Tx	Chelator
Pm-153	Beta	Tx	Chelator
Po-213	Alpha	Tx	Chelator
Ra-223	Alpha	Tx	Chelator
Ra-224	Alpha	Tx	Chelator
Rh-105	Beta	Tx	Chelator
Sm-153	Beta	Tx	Chelator
Tb-149	Alpha	Tx	Chelator
Tb-152	Positron	Dx	Chelator
Tb-161	Beta	Tx/Dx	Chelator
Tc-99m	Gamma/Isomeric Transition	Dx	Chelator
Th-227	Alpha	Tx	Chelator
Th-229	Alpha	Tx	Chelator

Radionuclide	Emission/Decay	Exemplary application-- Therapeutics (Tx) or Diagnostics (Dx)	Exemplary methods of binding the radionuclide to a radiopharmaceutical conjugate (e.g., through a Chelator or bound to the conjugate through a Covalent bond)
Tm-167	Beta/Electron Capture	Tx	Chelator
Y-90	Beta	Tx	Chelator
Yb-175	Beta	Tx	Chelator
Zr-89	Positron	Dx	Chelator

[00519] In some embodiments, the radiopharmaceutical conjugate described herein comprises a radionuclide selected from Table 3. In some embodiments, disclosed herein are conjugates comprising a compound of Table 1, or a salt or stereoisomer thereof, complexed with a radionuclide selected from Table 3. In some embodiments, disclosed herein are compositions comprising a compound of Table 1, or a salt or stereoisomer thereof, complexed with a radionuclide selected from Table 3. In some embodiments, disclosed herein are conjugates comprising a compound of Table 2, or a salt or stereoisomer thereof, complexed with a radionuclide selected from Table 3. In some embodiments, disclosed herein are compositions comprising a compound of Table 2, or a salt or stereoisomer thereof, complexed with a radionuclide selected from Table 3.

[00520] In some embodiments, the radiopharmaceutical conjugate described herein comprises one or more independent radionuclides. In some embodiments, the radiopharmaceutical conjugate comprises two radionuclides. In some embodiments, each of the one or more radionuclides is bound to the metal chelator of the radiopharmaceutical conjugate. In some embodiments, two radionuclides of the radiopharmaceutical conjugate are bound to the same metal chelator. In some embodiments, two radionuclides of the radiopharmaceutical conjugate are bound to two independent metal chelators. In some embodiments, each of the one or more radionuclides is an alpha particle-emitting radionuclide.

[00521] In some embodiments, the radiopharmaceutical conjugate described herein comprises an alpha particle-emitting radionuclide. In some embodiments, the radiopharmaceutical conjugate comprises an alpha-particle emitting radionuclide bound to the metal chelator. In some embodiments, the alpha particle-emitting radionuclide is actinium-225 (^{225}Ac), radium-223 (^{223}Ra), radium-224 (^{224}Ra), bismuth-209 (^{209}Bi), bismuth-213 (^{213}Bi), gadolinium-148 (^{148}Gd), terbium-149 (^{149}Tb), polonium-213 (^{213}Po), francium-223 (^{223}Fr), thorium-227 (^{227}Th), thorium-229 (^{229}Th), or lead-212 (^{212}Pb). In some embodiments, the alpha particle-emitting radionuclide is selected from ^{225}Ac , ^{223}Ra , ^{209}Bi , ^{213}Bi , ^{148}Gd , ^{149}Tb , ^{213}Po , ^{223}Fr , ^{227}Th , ^{229}Th , and ^{212}Pb . In some embodiments, the alpha particle-emitting radionuclide is ^{225}Ac . In some embodiments, the alpha particle-emitting radionuclide is ^{213}Bi . In some embodiments, the alpha particle-emitting radionuclide is ^{212}Bi . In some embodiments, the alpha particle-emitting radionuclide is ^{212}Pb . In some embodiments, the alpha particle-emitting radionuclide is ^{224}Ra . In some embodiments, the alpha particle-emitting radionuclide is ^{223}Ra . In some embodiments, the alpha particle-emitting radionuclide is ^{227}Th . In some embodiments, the alpha particle-emitting radionuclide is ^{149}Tb .

[00522] In some embodiments, the radiopharmaceutical conjugate described herein comprises a radionuclide selected from ^{62}Cu , ^{64}Cu , ^{67}Cu , ^{90}Y , ^{109}Pd , ^{111}Ag , ^{134}Ce , ^{149}Pm , ^{153}Sm , ^{166}Ho , $^{99\text{m}}\text{Tc}$, ^{67}Ga , ^{68}Ga , ^{111}In , ^{90}Y , ^{177}Lu , ^{186}Re , ^{188}Re , ^{197}Au , ^{198}Au , ^{199}Au , ^{105}Rh , ^{165}Ho , ^{161}Tb , ^{149}Pm , ^{153}Pm , ^{44}Sc , ^{47}Sc , ^{213}Po , ^{212}Pb , ^{209}Bi , ^{212}Bi , ^{213}Bi , ^{225}Ac , $^{117\text{m}}\text{Sn}$, ^{67}Ga , ^{149}Tb , ^{152}Tb , ^{167}Tm , ^{175}Yb , ^{223}Ra , ^{223}Fr , ^{227}Th , ^{229}Th , ^{201}Tl , ^{148}Gd , ^{160}Gd , ^{148}Nd , ^{89}Sr , and ^{89}Zr . In some embodiments, the radionuclide is selected from ^{62}Cu , ^{64}Cu , ^{67}Cu , ^{68}Ga , ^{89}Zr , ^{90}Y , $^{99\text{m}}\text{Tc}$, ^{105}Rh , ^{111}In , ^{134}Ce , ^{148}Gd , ^{149}Tb , ^{152}Tb , ^{153}Pm , ^{167}Tm , ^{175}Yb , ^{177}Lu , ^{209}Bi , ^{212}Pb , ^{213}Po , ^{213}Bi , ^{223}Ra , ^{223}Fr , ^{227}Th , ^{225}Ac , and ^{229}Th . In some embodiments, the radionuclide is ^{225}Ac . In some embodiments, the radionuclide is a decay daughter of ^{225}Ac such as ^{221}Fr , ^{217}At , ^{213}Bi , ^{213}Po , ^{209}Tl , ^{209}Pb , or ^{209}Bi . In some embodiments, the radiopharmaceutical conjugate comprises two ^{225}Ac radionuclides. In some embodiments, the radionuclide is ^{177}Lu . In some embodiments, the radiopharmaceutical conjugate comprises two ^{177}Lu radionuclides. In some embodiments, the radionuclide is no-carrier added (i.e., non-carrier-added or n.c.a.) ^{177}Lu . In some embodiments, the radionuclide is no-carrier added (i.e., non-carrier-added or n.c.a.) ^{225}Ac . In some embodiments, the radionuclide is ^{177}Lu free of long-lived radioactive contaminants and byproducts. In some embodiments, the radionuclide is a non-carrier-added radionuclide. In some embodiments, the radionuclide is a pseudo-radiometal. In some embodiments, the pseudo-radiometal is aluminum - ^{18}F fluoride (^{18}F AlF) complex.

[00523] In some embodiments, the radiopharmaceutical conjugate described herein comprises a beta particle-emitting radionuclide. In some embodiments, the radiopharmaceutical conjugate comprises a beta particle-emitting radionuclide bound to the metal chelator. In some embodiments, the beta particle-emitting radionuclide is copper-67, rhodium-105, ytterbium-175, thulium-167, promethium-153, yttrium-90, samarium-153, or lutetium-177. In some embodiments, the beta particle emitting radionuclide is copper-67, yttrium-90, samarium-153, or lutetium-177. In some embodiments, the beta particle emitting radionuclide is lutetium-177.

[00524] In some embodiments, the radiopharmaceutical conjugate described herein comprises a gamma particle-emitting radionuclide. In some embodiments, the radiopharmaceutical conjugate comprises a gamma particle-emitting radionuclide bound to the metal chelator. In some embodiments, the gamma particle-emitting radionuclide is indium-111 or tin-117m.

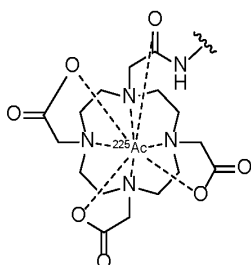
[00525] In some embodiments, the radiopharmaceutical conjugate described herein comprises a positron particle-emitting radionuclide. In some embodiments, the radiopharmaceutical conjugate comprises a positron particle-emitting radionuclide bound to the metal chelator. In some embodiments, the positron-emitting radionuclide is gallium-68, copper-61, copper-62, copper-64, zirconium-89, or terbium-152. In some embodiments, the radionuclide is zirconium-89. In some embodiments, the radionuclide is gallium-68.

[00526] In some embodiments, a conjugate described herein comprises a radionuclide suitable for imaging or diagnostic purposes. In some embodiments, the radionuclide suitable for imaging is selected from ^{62}Cu , ^{64}Cu , ^{89}Zr , ^{134}Ce , ^{152}Tb , ^{68}Ga , ^{111}In , and $^{99\text{m}}\text{Tc}$. In some embodiments, the radionuclide is suitable PET imaging. In some embodiments, the radionuclide suitable for PET imaging is selected from ^{62}Cu , ^{64}Cu , ^{89}Zr , ^{134}Ce , ^{152}Tb , and ^{68}Ga . In some embodiments, the radionuclide is suitable for SPECT

imaging. In some embodiments, the radionuclide suitable for SPECT imaging is selected from ^{111}In and $^{99\text{m}}\text{Tc}$.

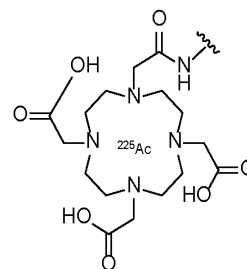
[00527] In some embodiments, radiopharmaceutical conjugates described herein do not contain any hot radionuclide, i.e., a cold conjugate. For example, in some cases, a radionuclide can be replaced with a surrogate (e.g., ^{225}Ac replaced with lanthanum) for testing and experimental purposes. In some embodiments, hot lutetium (Lu-177) is replaced with a cold Lutetium (Lu-175).

[00528] A metal chelator such as DOTA can interact with a radionuclide (e.g., ^{177}Lu or ^{225}Ac) via one or more functional groups and/or atoms. For example, the metal chelator can interact with a radionuclide via a nitrogen and/or an oxygen atom. As another example, the metal chelator can interact with a radionuclide via carbonyl, carboxylic acid, amino, and/or amide groups of the metal chelator. In some embodiments, the interaction of the metal chelator and a radionuclide of the conjugates disclosed herein



can be illustrated as

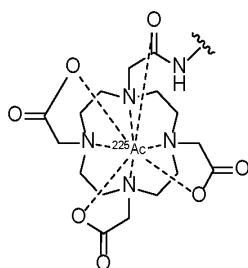
. In some embodiments, the interaction of the metal chelator



and a radionuclide of the conjugates disclosed herein can be illustrated as

. In

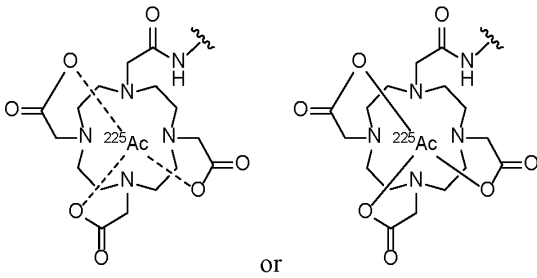
some embodiments, the interaction of the metal chelator and a radionuclide of the conjugates disclosed



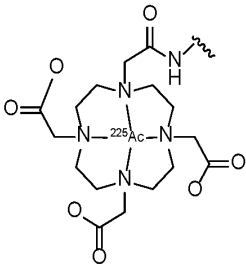
herein can be illustrated as

. In some embodiments, the interaction of the metal

chelator and a radionuclide of the conjugates disclosed herein can be illustrated as

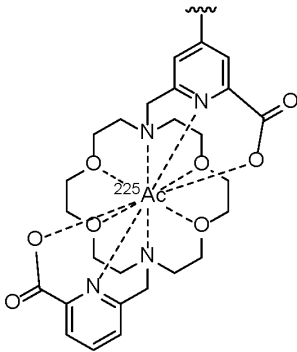


. In some embodiments, the interaction of the metal



chelator and a radionuclide of the conjugates disclosed herein are illustrated as

In some embodiments, the interaction of the metal chelator and a radionuclide of the conjugates disclosed



herein are illustrated as

. In some embodiments, the radionuclide exists in a

positive oxidation state e.g., $^{225}\text{Ac}^{3+}$, $^{177}\text{Lu}^{3+}$. In some embodiments, for example in certain aqueous conditions, the radionuclide exists in a salt form, e.g., as $^{225}\text{Ac}^{3+}$, $^{177}\text{Lu}^{3+}$. In some embodiments, for example in certain acidic aqueous conditions, the radionuclide exists in a salt form, e.g., as $^{225}\text{Ac}^{3+}$, $^{177}\text{Lu}^{3+}$. In some embodiments, the conjugate is in a salt form. In some embodiments, one or more of the carboxylic acid groups of the conjugate may exist as carboxylate anions. In some embodiments, one or more of the carboxylate anions of the conjugate may coordinate to the radionuclide. A person of ordinary skill would appreciate that the dissociation of an acid depends on the pH value of the environment and its pK value. Accordingly, in some embodiments, the conjugate described herein can exist in a completely ionized, partially ionized, or non-ionized form.

[00529] In some embodiments, the radiopharmaceutical conjugate is selected from a conjugate found in table 4a or 4b.

TABLE 4a	
Radiopharmaceutical conjugate	
Compound	Radionuclide
100	Ac-225
100.1	Ac-225

TABLE 4b	
Radiopharmaceutical conjugate	
Compound	Radionuclide
100	Lu-177
100.1	Lu-177

TABLE 4a	
Radiopharmaceutical conjugate	
Compound	Radionuclide
100.2	Ac-225
100.3	Ac-225
100.4	Ac-225
100.5	Ac-225
100.6	Ac-225
100.7	Ac-225
100.8	Ac-225
100.9	Ac-225
100.10	Ac-225
100.11	Ac-225
100.12	Ac-225
100.13	Ac-225
100.14	Ac-225
100.15	Ac-225
100.16	Ac-225
100.17	Ac-225
100.18	Ac-225
100.19	Ac-225
101	Ac-225
101.1	Ac-225
101.2	Ac-225
102	Ac-225
102.1	Ac-225
102.2	Ac-225
102.3	Ac-225
102.4	Ac-225
102.5	Ac-225
102.6	Ac-225
102.7	Ac-225
102.8	Ac-225
103	Ac-225
103.1	Ac-225
103.2	Ac-225
103.3	Ac-225
103.4	Ac-225
104	Ac-225
104.1	Ac-225
104.2	Ac-225
106	Ac-225
107	Ac-225
107.1	Ac-225
107.2	Ac-225
107.3	Ac-225
107.4	Ac-225
107.5	Ac-225
107.6	Ac-225
107.7	Ac-225
107.8	Ac-225
107.9	Ac-225
107.10	Ac-225
107.11	Ac-225

TABLE 4b	
Radiopharmaceutical conjugate	
Compound	Radionuclide
100.2	Lu-177
100.3	Lu-177
100.4	Lu-177
100.5	Lu-177
100.6	Lu-177
100.7	Lu-177
100.8	Lu-177
100.9	Lu-177
100.10	Lu-177
100.11	Lu-177
100.12	Lu-177
100.13	Lu-177
100.14	Lu-177
100.15	Lu-177
100.16	Lu-177
100.17	Lu-177
100.18	Lu-177
100.19	Lu-177
101	Lu-177
101.1	Lu-177
101.2	Lu-177
102	Lu-177
102.1	Lu-177
102.2	Lu-177
102.3	Lu-177
102.4	Lu-177
102.5	Lu-177
102.6	Lu-177
102.7	Lu-177
102.8	Lu-177
103	Lu-177
103.1	Lu-177
103.2	Lu-177
103.3	Lu-177
103.4	Lu-177
104	Lu-177
104.1	Lu-177
104.2	Lu-177
106	Lu-177
107	Lu-177
107.1	Lu-177
107.2	Lu-177
107.3	Lu-177
107.4	Lu-177
107.5	Lu-177
107.6	Lu-177
107.7	Lu-177
107.8	Lu-177
107.9	Lu-177
107.10	Lu-177
107.11	Lu-177

TABLE 4a	
Radiopharmaceutical conjugate	
Compound	Radionuclide
107.12	Ac-225
107.13	Ac-225
107.14	Ac-225
107.15	Ac-225
107.16	Ac-225
107.17	Ac-225
107.18	Ac-225
107.19	Ac-225
107.20	Ac-225
107.21	Ac-225
107.22	Ac-225
107.23	Ac-225
107.24	Ac-225
107.25	Ac-225
107.26	Ac-225
107.27	Ac-225
107.28	Ac-225
107.29	Ac-225
107.30	Ac-225
107.31	Ac-225
107.32	Ac-225
107.33	Ac-225
107.34	Ac-225
107.35	Ac-225
107.36	Ac-225
107.37	Ac-225
107.38	Ac-225
107.39	Ac-225
107.40	Ac-225
107.41	Ac-225
107.42	Ac-225
107.43	Ac-225
107.44	Ac-225
107.45	Ac-225
107.46	Ac-225
107.47	Ac-225
107.48	Ac-225
107.49	Ac-225
107.50	Ac-225
107.51	Ac-225
107.52	Ac-225
107.53	Ac-225
107.54	Ac-225
107.55	Ac-225
107.56	Ac-225
107.57	Ac-225
107.58	Ac-225
107.59	Ac-225
107.60	Ac-225
107.61	Ac-225
108	Ac-225

TABLE 4b	
Radiopharmaceutical conjugate	
Compound	Radionuclide
107.12	Lu-177
107.13	Lu-177
107.14	Lu-177
107.15	Lu-177
107.16	Lu-177
107.17	Lu-177
107.18	Lu-177
107.19	Lu-177
107.20	Lu-177
107.21	Lu-177
107.22	Lu-177
107.23	Lu-177
107.24	Lu-177
107.25	Lu-177
107.26	Lu-177
107.27	Lu-177
107.28	Lu-177
107.29	Lu-177
107.30	Lu-177
107.31	Lu-177
107.32	Lu-177
107.33	Lu-177
107.34	Lu-177
107.35	Lu-177
107.36	Lu-177
107.37	Lu-177
107.38	Lu-177
107.39	Lu-177
107.40	Lu-177
107.41	Lu-177
107.42	Lu-177
107.43	Lu-177
107.44	Lu-177
107.45	Lu-177
107.46	Lu-177
107.47	Lu-177
107.48	Lu-177
107.49	Lu-177
107.50	Lu-177
107.51	Lu-177
107.52	Lu-177
107.53	Lu-177
107.54	Lu-177
107.55	Lu-177
107.56	Lu-177
107.57	Lu-177
107.58	Lu-177
107.59	Lu-177
107.60	Lu-177
107.61	Lu-177
108	Lu-177

TABLE 4a	
Radiopharmaceutical conjugate	
Compound	Radionuclide
108.1	Ac-225
108.2	Ac-225
108.3	Ac-225
108.4	Ac-225
108.5	Ac-225
109	Ac-225
109.1	Ac-225
109.2	Ac-225
109.3	Ac-225
109.4	Ac-225
109.5	Ac-225
109.6	Ac-225
109.7	Ac-225
109.8	Ac-225
109.9	Ac-225
109.10	Ac-225
109.11	Ac-225
109.12	Ac-225
109.13	Ac-225
109.14	Ac-225
109.15	Ac-225
109.16	Ac-225
109.17	Ac-225
109.18	Ac-225
109.19	Ac-225
109.20	Ac-225
109.21	Ac-225
109.22	Ac-225
109.23	Ac-225
109.24	Ac-225
109.25	Ac-225
109.26	Ac-225
109.27	Ac-225
109.28	Ac-225
109.29	Ac-225
109.30	Ac-225
109.31	Ac-225
109.32	Ac-225
109.33	Ac-225
109.34	Ac-225
109.35	Ac-225
109.36	Ac-225
109.37	Ac-225
109.38	Ac-225
109.39	Ac-225
109.40	Ac-225
109.41	Ac-225
109.42	Ac-225
109.43	Ac-225
109.44	Ac-225
109.45	Ac-225

TABLE 4b	
Radiopharmaceutical conjugate	
Compound	Radionuclide
108.1	Lu-177
108.2	Lu-177
108.3	Lu-177
108.4	Lu-177
108.5	Lu-177
109	Lu-177
109.1	Lu-177
109.2	Lu-177
109.3	Lu-177
109.4	Lu-177
109.5	Lu-177
109.6	Lu-177
109.7	Lu-177
109.8	Lu-177
109.9	Lu-177
109.10	Lu-177
109.11	Lu-177
109.12	Lu-177
109.13	Lu-177
109.14	Lu-177
109.15	Lu-177
109.16	Lu-177
109.17	Lu-177
109.18	Lu-177
109.19	Lu-177
109.20	Lu-177
109.21	Lu-177
109.22	Lu-177
109.23	Lu-177
109.24	Lu-177
109.25	Lu-177
109.26	Lu-177
109.27	Lu-177
109.28	Lu-177
109.29	Lu-177
109.30	Lu-177
109.31	Lu-177
109.32	Lu-177
109.33	Lu-177
109.34	Lu-177
109.35	Lu-177
109.36	Lu-177
109.37	Lu-177
109.38	Lu-177
109.39	Lu-177
109.40	Lu-177
109.41	Lu-177
109.42	Lu-177
109.43	Lu-177
109.44	Lu-177
109.45	Lu-177

TABLE 4a	
Radiopharmaceutical conjugate	
Compound	Radionuclide
109.46	Ac-225
109.47	Ac-225
109.48	Ac-225
109.49	Ac-225
109.50	Ac-225
109.51	Ac-225
109.52	Ac-225
109.53	Ac-225
109.54	Ac-225
109.55	Ac-225
109.56	Ac-225
109.57	Ac-225
109.58	Ac-225
109.59	Ac-225
109.60	Ac-225
109.61	Ac-225
109.62	Ac-225
109.63	Ac-225
110	Ac-225
111	Ac-225
111.1	Ac-225
111.2	Ac-225
111.3	Ac-225
111.4	Ac-225
111.5	Ac-225
111.6	Ac-225
111.7	Ac-225
111.8	Ac-225
111.9	Ac-225
111.10	Ac-225
111.11	Ac-225
111.12	Ac-225
112	Ac-225
112.1	Ac-225
112.2	Ac-225
112.3	Ac-225
112.4	Ac-225
112.5	Ac-225
112.6	Ac-225
112.7	Ac-225
112.8	Ac-225
112.9	Ac-225
112.10	Ac-225
112.11	Ac-225
112.12	Ac-225
112.13	Ac-225
112.14	Ac-225
112.15	Ac-225
112.16	Ac-225
112.17	Ac-225
112.18	Ac-225

TABLE 4b	
Radiopharmaceutical conjugate	
Compound	Radionuclide
109.46	Lu-177
109.47	Lu-177
109.48	Lu-177
109.49	Lu-177
109.50	Lu-177
109.51	Lu-177
109.52	Lu-177
109.53	Lu-177
109.54	Lu-177
109.55	Lu-177
109.56	Lu-177
109.57	Lu-177
109.58	Lu-177
109.59	Lu-177
109.60	Lu-177
109.61	Lu-177
109.62	Lu-177
109.63	Lu-177
110	Lu-177
111	Lu-177
111.1	Lu-177
111.2	Lu-177
111.3	Lu-177
111.4	Lu-177
111.5	Lu-177
111.6	Lu-177
111.7	Lu-177
111.8	Lu-177
111.9	Lu-177
111.10	Lu-177
111.11	Lu-177
111.12	Lu-177
112	Lu-177
112.1	Lu-177
112.2	Lu-177
112.3	Lu-177
112.4	Lu-177
112.5	Lu-177
112.6	Lu-177
112.7	Lu-177
112.8	Lu-177
112.9	Lu-177
112.10	Lu-177
112.11	Lu-177
112.12	Lu-177
112.13	Lu-177
112.14	Lu-177
112.15	Lu-177
112.16	Lu-177
112.17	Lu-177
112.18	Lu-177

TABLE 4a	
Radiopharmaceutical conjugate	
Compound	Radionuclide
112.19	Ac-225
113	Ac-225
114	Ac-225
114.1	Ac-225
114.2	Ac-225
114.3	Ac-225
115	Ac-225
116	Ac-225
116.1	Ac-225
116.2	Ac-225
116.3	Ac-225
116.4	Ac-225
117	Ac-225
117.1	Ac-225
117.2	Ac-225
117.3	Ac-225
117.4	Ac-225
117.5	Ac-225
117.6	Ac-225
117.7	Ac-225
117.8	Ac-225
118	Ac-225
118.1	Ac-225
118.2	Ac-225
118.3	Ac-225
118.4	Ac-225
119	Ac-225
120	Ac-225
121	Ac-225
121.1	Ac-225
122	Ac-225
123	Ac-225
124	Ac-225
125	Ac-225
125.1	Ac-225
126	Ac-225
126.1	Ac-225
126.2	Ac-225
126.3	Ac-225
126.4	Ac-225
126.5	Ac-225
127	Ac-225
127.1	Ac-225
127.2	Ac-225
127.3	Ac-225
127.4	Ac-225
127.5	Ac-225
127.6	Ac-225
127.7	Ac-225
127.8	Ac-225
127.9	Ac-225

TABLE 4b	
Radiopharmaceutical conjugate	
Compound	Radionuclide
112.19	Lu-177
113	Lu-177
114	Lu-177
114.1	Lu-177
114.2	Lu-177
114.3	Lu-177
115	Lu-177
116	Lu-177
116.1	Lu-177
116.2	Lu-177
116.3	Lu-177
116.4	Lu-177
117	Lu-177
117.1	Lu-177
117.2	Lu-177
117.3	Lu-177
117.4	Lu-177
117.5	Lu-177
117.6	Lu-177
117.7	Lu-177
117.8	Lu-177
118	Lu-177
118.1	Lu-177
118.2	Lu-177
118.3	Lu-177
118.4	Lu-177
119	Lu-177
120	Lu-177
121	Lu-177
121.1	Lu-177
122	Lu-177
123	Lu-177
124	Lu-177
125	Lu-177
125.1	Lu-177
126	Lu-177
126.1	Lu-177
126.2	Lu-177
126.3	Lu-177
126.4	Lu-177
126.5	Lu-177
127	Lu-177
127.1	Lu-177
127.2	Lu-177
127.3	Lu-177
127.4	Lu-177
127.5	Lu-177
127.6	Lu-177
127.7	Lu-177
127.8	Lu-177
127.9	Lu-177

TABLE 4a Radiopharmaceutical conjugate	
Compound	Radionuclide
128	Ac-225
128.1	Ac-225
129	Ac-225
129.1	Ac-225
129.2	Ac-225
129.3	Ac-225
129.4	Ac-225
129.5	Ac-225
129.6	Ac-225
129.7	Ac-225
130	Ac-225
131	Ac-225
131.1	Ac-225
131.2	Ac-225
131.3	Ac-225
131.4	Ac-225
131.5	Ac-225
131.6	Ac-225
131.7	Ac-225
132	Ac-225
133	Ac-225
134	Ac-225
135	Ac-225
136	Ac-225

TABLE 4b Radiopharmaceutical conjugate	
Compound	Radionuclide
128	Lu-177
128.1	Lu-177
129	Lu-177
129.1	Lu-177
129.2	Lu-177
129.3	Lu-177
129.4	Lu-177
129.5	Lu-177
129.6	Lu-177
129.7	Lu-177
130	Lu-177
131	Lu-177
131.1	Lu-177
131.2	Lu-177
131.3	Lu-177
131.4	Lu-177
131.5	Lu-177
131.6	Lu-177
131.7	Lu-177
132	Lu-177
133	Lu-177
134	Lu-177
135	Lu-177
136	Lu-177

* The radionuclide of Table 4a and Table 4b is bound to the chelator of the corresponding compound.

[00530] In some embodiments, the radiopharmaceutical conjugate is selected from a conjugate found in table 5a or 5b.

TABLE 5a Radiopharmaceutical conjugate	
Compound	Radionuclide
100	Cu-64
100.1	Cu-64
100.2	Cu-64
100.3	Cu-64
100.4	Cu-64
100.5	Cu-64
100.6	Cu-64
100.7	Cu-64
100.8	Cu-64
100.9	Cu-64
100.10	Cu-64
100.11	Cu-64
100.12	Cu-64
100.13	Cu-64
100.14	Cu-64
100.15	Cu-64
100.16	Cu-64
100.17	Cu-64
100.18	Cu-64

TABLE 5b Radiopharmaceutical conjugate	
Compound	Radionuclide
100	Ga-68
100.1	Ga-68
100.2	Ga-68
100.3	Ga-68
100.4	Ga-68
100.5	Ga-68
100.6	Ga-68
100.7	Ga-68
100.8	Ga-68
100.9	Ga-68
100.10	Ga-68
100.11	Ga-68
100.12	Ga-68
100.13	Ga-68
100.14	Ga-68
100.15	Ga-68
100.16	Ga-68
100.17	Ga-68
100.18	Ga-68

TABLE 5a		TABLE 5b	
Radiopharmaceutical conjugate		Radiopharmaceutical conjugate	
Compound	Radionuclide	Compound	Radionuclide
100.19	Cu-64	100.19	Ga-68
101	Cu-64	101	Ga-68
101.1	Cu-64	101.1	Ga-68
101.2	Cu-64	101.2	Ga-68
102	Cu-64	102	Ga-68
102.1	Cu-64	102.1	Ga-68
102.2	Cu-64	102.2	Ga-68
102.3	Cu-64	102.3	Ga-68
102.4	Cu-64	102.4	Ga-68
102.5	Cu-64	102.5	Ga-68
102.6	Cu-64	102.6	Ga-68
102.7	Cu-64	102.7	Ga-68
102.8	Cu-64	102.8	Ga-68
103	Cu-64	103	Ga-68
103.1	Cu-64	103.1	Ga-68
103.2	Cu-64	103.2	Ga-68
103.3	Cu-64	103.3	Ga-68
103.4	Cu-64	103.4	Ga-68
104	Cu-64	104	Ga-68
104.1	Cu-64	104.1	Ga-68
104.2	Cu-64	104.2	Ga-68
106	Cu-64	106	Ga-68
107	Cu-64	107	Ga-68
107.1	Cu-64	107.1	Ga-68
107.2	Cu-64	107.2	Ga-68
107.3	Cu-64	107.3	Ga-68
107.4	Cu-64	107.4	Ga-68
107.5	Cu-64	107.5	Ga-68
107.6	Cu-64	107.6	Ga-68
107.7	Cu-64	107.7	Ga-68
107.8	Cu-64	107.8	Ga-68
107.9	Cu-64	107.9	Ga-68
107.10	Cu-64	107.10	Ga-68
107.11	Cu-64	107.11	Ga-68
107.12	Cu-64	107.12	Ga-68
107.13	Cu-64	107.13	Ga-68
107.14	Cu-64	107.14	Ga-68
107.15	Cu-64	107.15	Ga-68
107.16	Cu-64	107.16	Ga-68
107.17	Cu-64	107.17	Ga-68
107.18	Cu-64	107.18	Ga-68
107.19	Cu-64	107.19	Ga-68
107.20	Cu-64	107.20	Ga-68
107.21	Cu-64	107.21	Ga-68
107.22	Cu-64	107.22	Ga-68
107.23	Cu-64	107.23	Ga-68
107.24	Cu-64	107.24	Ga-68
107.25	Cu-64	107.25	Ga-68
107.26	Cu-64	107.26	Ga-68
107.27	Cu-64	107.27	Ga-68
107.28	Cu-64	107.28	Ga-68

TABLE 5a		TABLE 5b	
Radiopharmaceutical conjugate		Radiopharmaceutical conjugate	
Compound	Radionuclide	Compound	Radionuclide
107.29	Cu-64	107.29	Ga-68
107.30	Cu-64	107.30	Ga-68
107.31	Cu-64	107.31	Ga-68
107.32	Cu-64	107.32	Ga-68
107.33	Cu-64	107.33	Ga-68
107.34	Cu-64	107.34	Ga-68
107.35	Cu-64	107.35	Ga-68
107.36	Cu-64	107.36	Ga-68
107.37	Cu-64	107.37	Ga-68
107.38	Cu-64	107.38	Ga-68
107.39	Cu-64	107.39	Ga-68
107.40	Cu-64	107.40	Ga-68
107.41	Cu-64	107.41	Ga-68
107.42	Cu-64	107.42	Ga-68
107.43	Cu-64	107.43	Ga-68
107.44	Cu-64	107.44	Ga-68
107.45	Cu-64	107.45	Ga-68
107.46	Cu-64	107.46	Ga-68
107.47	Cu-64	107.47	Ga-68
107.48	Cu-64	107.48	Ga-68
107.49	Cu-64	107.49	Ga-68
107.50	Cu-64	107.50	Ga-68
107.51	Cu-64	107.51	Ga-68
107.52	Cu-64	107.52	Ga-68
107.53	Cu-64	107.53	Ga-68
107.54	Cu-64	107.54	Ga-68
107.55	Cu-64	107.55	Ga-68
107.56	Cu-64	107.56	Ga-68
107.57	Cu-64	107.57	Ga-68
107.58	Cu-64	107.58	Ga-68
107.59	Cu-64	107.59	Ga-68
107.60	Cu-64	107.60	Ga-68
107.61	Cu-64	107.61	Ga-68
108	Cu-64	108	Ga-68
108.1	Cu-64	108.1	Ga-68
108.2	Cu-64	108.2	Ga-68
108.3	Cu-64	108.3	Ga-68
108.4	Cu-64	108.4	Ga-68
108.5	Cu-64	108.5	Ga-68
109	Cu-64	109	Ga-68
109.1	Cu-64	109.1	Ga-68
109.2	Cu-64	109.2	Ga-68
109.3	Cu-64	109.3	Ga-68
109.4	Cu-64	109.4	Ga-68
109.5	Cu-64	109.5	Ga-68
109.6	Cu-64	109.6	Ga-68
109.7	Cu-64	109.7	Ga-68
109.8	Cu-64	109.8	Ga-68
109.9	Cu-64	109.9	Ga-68
109.10	Cu-64	109.10	Ga-68
109.11	Cu-64	109.11	Ga-68

TABLE 5a		TABLE 5b	
Radiopharmaceutical conjugate		Radiopharmaceutical conjugate	
Compound	Radionuclide	Compound	Radionuclide
109.12	Cu-64	109.12	Ga-68
109.13	Cu-64	109.13	Ga-68
109.14	Cu-64	109.14	Ga-68
109.15	Cu-64	109.15	Ga-68
109.16	Cu-64	109.16	Ga-68
109.17	Cu-64	109.17	Ga-68
109.18	Cu-64	109.18	Ga-68
109.19	Cu-64	109.19	Ga-68
109.20	Cu-64	109.20	Ga-68
109.21	Cu-64	109.21	Ga-68
109.22	Cu-64	109.22	Ga-68
109.23	Cu-64	109.23	Ga-68
109.24	Cu-64	109.24	Ga-68
109.25	Cu-64	109.25	Ga-68
109.26	Cu-64	109.26	Ga-68
109.27	Cu-64	109.27	Ga-68
109.28	Cu-64	109.28	Ga-68
109.29	Cu-64	109.29	Ga-68
109.30	Cu-64	109.30	Ga-68
109.31	Cu-64	109.31	Ga-68
109.32	Cu-64	109.32	Ga-68
109.33	Cu-64	109.33	Ga-68
109.34	Cu-64	109.34	Ga-68
109.35	Cu-64	109.35	Ga-68
109.36	Cu-64	109.36	Ga-68
109.37	Cu-64	109.37	Ga-68
109.38	Cu-64	109.38	Ga-68
109.39	Cu-64	109.39	Ga-68
109.40	Cu-64	109.40	Ga-68
109.41	Cu-64	109.41	Ga-68
109.42	Cu-64	109.42	Ga-68
109.43	Cu-64	109.43	Ga-68
109.44	Cu-64	109.44	Ga-68
109.45	Cu-64	109.45	Ga-68
109.46	Cu-64	109.46	Ga-68
109.47	Cu-64	109.47	Ga-68
109.48	Cu-64	109.48	Ga-68
109.49	Cu-64	109.49	Ga-68
109.50	Cu-64	109.50	Ga-68
109.51	Cu-64	109.51	Ga-68
109.52	Cu-64	109.52	Ga-68
109.53	Cu-64	109.53	Ga-68
109.54	Cu-64	109.54	Ga-68
109.55	Cu-64	109.55	Ga-68
109.56	Cu-64	109.56	Ga-68
109.57	Cu-64	109.57	Ga-68
109.58	Cu-64	109.58	Ga-68
109.59	Cu-64	109.59	Ga-68
109.60	Cu-64	109.60	Ga-68
109.61	Cu-64	109.61	Ga-68
109.62	Cu-64	109.62	Ga-68

TABLE 5a		TABLE 5b	
Radiopharmaceutical conjugate		Radiopharmaceutical conjugate	
Compound	Radionuclide	Compound	Radionuclide
109.63	Cu-64	109.63	Ga-68
110	Cu-64	110	Ga-68
111	Cu-64	111	Ga-68
111.1	Cu-64	111.1	Ga-68
111.2	Cu-64	111.2	Ga-68
111.3	Cu-64	111.3	Ga-68
111.4	Cu-64	111.4	Ga-68
111.5	Cu-64	111.5	Ga-68
111.6	Cu-64	111.6	Ga-68
111.7	Cu-64	111.7	Ga-68
111.8	Cu-64	111.8	Ga-68
111.9	Cu-64	111.9	Ga-68
111.10	Cu-64	111.10	Ga-68
111.11	Cu-64	111.11	Ga-68
111.12	Cu-64	111.12	Ga-68
112	Cu-64	112	Ga-68
112.1	Cu-64	112.1	Ga-68
112.2	Cu-64	112.2	Ga-68
112.3	Cu-64	112.3	Ga-68
112.4	Cu-64	112.4	Ga-68
112.5	Cu-64	112.5	Ga-68
112.6	Cu-64	112.6	Ga-68
112.7	Cu-64	112.7	Ga-68
112.8	Cu-64	112.8	Ga-68
112.9	Cu-64	112.9	Ga-68
112.10	Cu-64	112.10	Ga-68
112.11	Cu-64	112.11	Ga-68
112.12	Cu-64	112.12	Ga-68
112.13	Cu-64	112.13	Ga-68
112.14	Cu-64	112.14	Ga-68
112.15	Cu-64	112.15	Ga-68
112.16	Cu-64	112.16	Ga-68
112.17	Cu-64	112.17	Ga-68
112.18	Cu-64	112.18	Ga-68
112.19	Cu-64	112.19	Ga-68
113	Cu-64	113	Ga-68
114	Cu-64	114	Ga-68
114.1	Cu-64	114.1	Ga-68
114.2	Cu-64	114.2	Ga-68
114.3	Cu-64	114.3	Ga-68
115	Cu-64	115	Ga-68
116	Cu-64	116	Ga-68
116.1	Cu-64	116.1	Ga-68
116.2	Cu-64	116.2	Ga-68
116.3	Cu-64	116.3	Ga-68
116.4	Cu-64	116.4	Ga-68
117	Cu-64	117	Ga-68
117.1	Cu-64	117.1	Ga-68
117.2	Cu-64	117.2	Ga-68
117.3	Cu-64	117.3	Ga-68
117.4	Cu-64	117.4	Ga-68

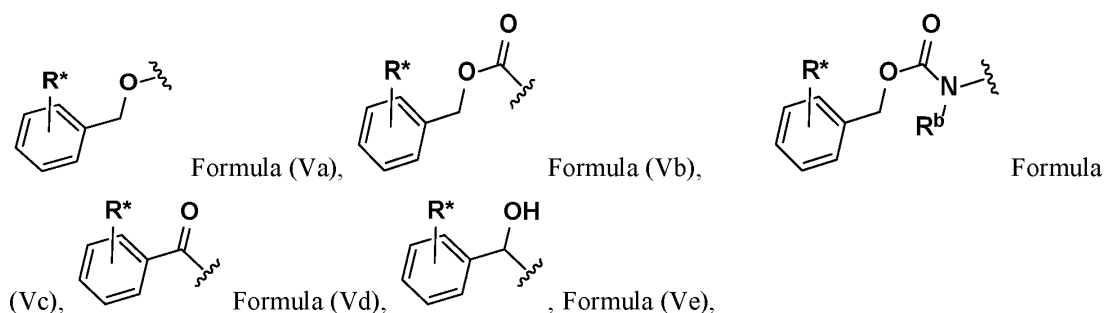
TABLE 5a		TABLE 5b	
Radiopharmaceutical conjugate		Radiopharmaceutical conjugate	
Compound	Radionuclide	Compound	Radionuclide
117.5	Cu-64	117.5	Ga-68
117.6	Cu-64	117.6	Ga-68
117.7	Cu-64	117.7	Ga-68
117.8	Cu-64	117.8	Ga-68
118	Cu-64	118	Ga-68
118.1	Cu-64	118.1	Ga-68
118.2	Cu-64	118.2	Ga-68
118.3	Cu-64	118.3	Ga-68
118.4	Cu-64	118.4	Ga-68
119	Cu-64	119	Ga-68
120	Cu-64	120	Ga-68
121	Cu-64	121	Ga-68
121.1	Cu-64	121.1	Ga-68
122	Cu-64	122	Ga-68
123	Cu-64	123	Ga-68
124	Cu-64	124	Ga-68
125	Cu-64	125	Ga-68
125.1	Cu-64	125.1	Ga-68
126	Cu-64	126	Ga-68
126.1	Cu-64	126.1	Ga-68
126.2	Cu-64	126.2	Ga-68
126.3	Cu-64	126.3	Ga-68
126.4	Cu-64	126.4	Ga-68
126.5	Cu-64	126.5	Ga-68
127	Cu-64	127	Ga-68
127.1	Cu-64	127.1	Ga-68
127.2	Cu-64	127.2	Ga-68
127.3	Cu-64	127.3	Ga-68
127.4	Cu-64	127.4	Ga-68
127.5	Cu-64	127.5	Ga-68
127.6	Cu-64	127.6	Ga-68
127.7	Cu-64	127.7	Ga-68
127.8	Cu-64	127.8	Ga-68
127.9	Cu-64	127.9	Ga-68
128	Cu-64	128	Ga-68
128.1	Cu-64	128.1	Ga-68
129	Cu-64	129	Ga-68
129.1	Cu-64	129.1	Ga-68
129.2	Cu-64	129.2	Ga-68
129.3	Cu-64	129.3	Ga-68
129.4	Cu-64	129.4	Ga-68
129.5	Cu-64	129.5	Ga-68
129.6	Cu-64	129.6	Ga-68
129.7	Cu-64	129.7	Ga-68
130	Cu-64	130	Ga-68
131	Cu-64	131	Ga-68
131.1	Cu-64	131.1	Ga-68
131.2	Cu-64	131.2	Ga-68
131.3	Cu-64	131.3	Ga-68
131.4	Cu-64	131.4	Ga-68
131.5	Cu-64	131.5	Ga-68

TABLE 5a		TABLE 5b	
Radiopharmaceutical conjugate		Radiopharmaceutical conjugate	
Compound	Radionuclide	Compound	Radionuclide
131.6	Cu-64	131.6	Ga-68
131.7	Cu-64	131.7	Ga-68
132	Cu-64	132	Ga-68
133	Cu-64	133	Ga-68
134	Cu-64	134	Ga-68
135	Cu-64	135	Ga-68
136	Cu-64	136	Ga-68

* The radionuclide of Table 5a and Table 5b is bound to the chelator of the corresponding compound.

[00531] In some embodiments, disclosed herein is a radiopharmaceutical conjugate comprising a covalently bound radioisotope. In some embodiments of Formula (AC), (AC'), (BC), (BC'), (CC), or (CC'), R³⁰ comprises the covalently bound radioisotope. In some embodiments of Formula (AC), (BC), or (CC), TL₁ comprises the covalently bound radioisotope. In some embodiments of Formula (AC), (BC), or (CC), TL₂ comprises the covalently bound radioisotope. In some embodiments of Formula (AC), (BC), or (CC), L^A comprises the covalently bound radioisotope. In some embodiments of Formula (AC'), (BC'), or (CC'), one or both of the TL₁ groups comprise the covalently bound radioisotope. In some embodiments of Formula (AC'), (BC'), or (CC'), one or both of the TL₂ groups comprise the covalently bound radioisotope. In some embodiments of Formula (AC'), (BC'), or (CC'), L^B comprises the covalently bound radioisotope. In some embodiments of Formula (BC), (BC'), (CC), or (CC'), X comprises the covalently bound radioisotope. In some embodiments, the covalently bound radioisotope is selected from ¹¹C, ¹³N, ¹⁵O, ¹⁸F, ⁷⁰As, ⁷¹As, ⁷²As, ⁷³As, ⁷⁴As, ⁷⁶As, ⁷⁷As, ⁷⁶Br, ¹²³I, ¹²⁴I, ¹²⁵I, ¹³¹I, and ²¹¹At. In some embodiments, the covalently bound radioisotope is ¹³¹I. In some embodiments, the covalently bound radioisotope is ²¹¹At. In some embodiments, the covalently bound radioisotope is ¹⁸F.

[00532] In some embodiments, a compound of Formula (AC), (AC'), (BC), (BC'), (CC), or (CC'), or a pharmaceutically acceptable salt or a stereoisomer thereof comprises a covalently bound radioisotope (designated as R*), and wherein the compound comprises a structure represented in Formula (Va), Formula (Vb), Formula (Vc), Formula (Vd), or Formula (Ve):



wherein,

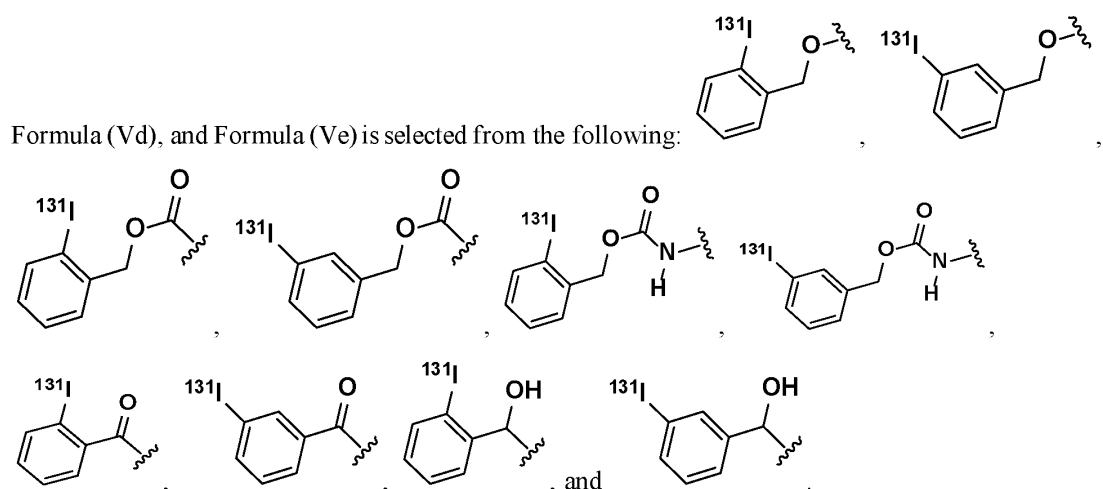
R* is a covalently bound radioisotope (e.g., such as fluorine-18 (¹⁸F), iodine-131 (¹³¹I), iodine-123 (¹²³I), iodine-124 (¹²⁴I), iodine-125 (¹²⁵I), or astatine-211 (²¹¹At)); and

R^b is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, C₂-C₉heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl is optionally substituted (e.g., optionally substituted with one or more R as described herein).

[00533] In some embodiments of Formula (AC), (AC'), (BC), (BC'), (CC), or (CC'), R³⁰ comprises a structure represented in Formula (Va), Formula (Vb), Formula (Vc), Formula (Vd), or Formula (Ve).

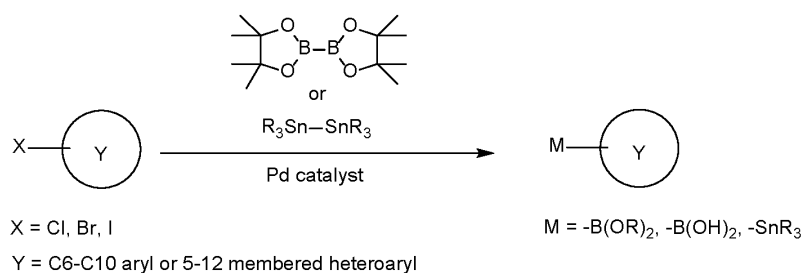
[00534] In some embodiments of Formula (Va), Formula (Vb), Formula (Vc), Formula (Vd), or Formula (Ve), the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl are independently optionally substituted by one or more halogen, amino, -OH, -NO₂, oxo, -CN, C₁₋₃ alkoxy, C₁₋₃ alkyl and C₁₋₃ haloalkyl. In some embodiments, R^b is hydrogen. In some embodiments, R^b is C₁-C₄alkyl. In some embodiments, R^b is C₁-C₄cycloalkyl. In some embodiments, R* is ¹³¹I.

[00535] In some embodiments, a structure represented in Formula (Va), Formula (Vb), Formula (Vc),



[00536] In some embodiments, radiopharmaceutical conjugates comprising covalently bound radionuclides described herein can be synthesized from a boronic acid, boronate, or stannane precursor. Boronic acid, boronate, and stannane precursors can be formed according to the following general reaction:

[00537] Reaction 1:

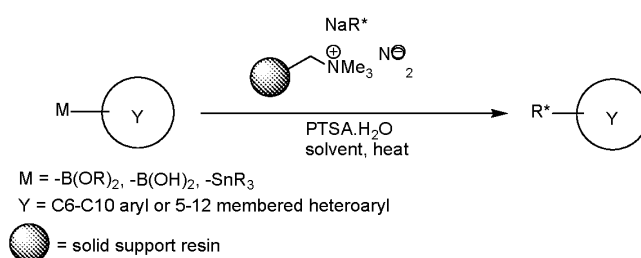


where R is a variable chemical moiety, for example alkyl or hydrogen. A halogen on ring Y, for example chloro, bromo, or iodo, can undergo a palladium mediated coupling reaction with a boronic acid,

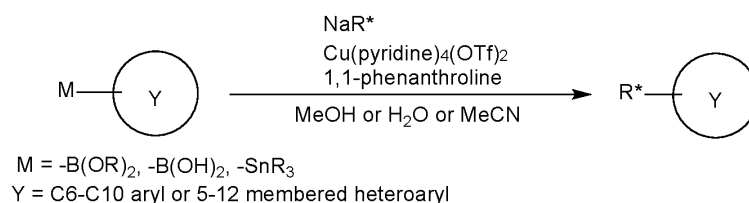
boronate, or stannane compound to form an intermediate compound wherein group M has replaced halogen X.

[00538] A radioisotope, for example R*, such as fluorine-18 (^{18}F), iodine-131 (^{131}I), iodine-123 (^{123}I), iodine-124 (^{124}I), iodine-125 (^{125}I), or astatine-211 (^{211}At), or any other radioisotope of Table 5A and Table 5B can be formed, for example, from the intermediate compound according to the following general reactions:

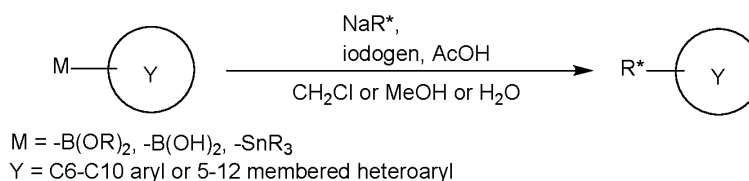
[00539] Reaction 2:



[00540] Reaction 3:

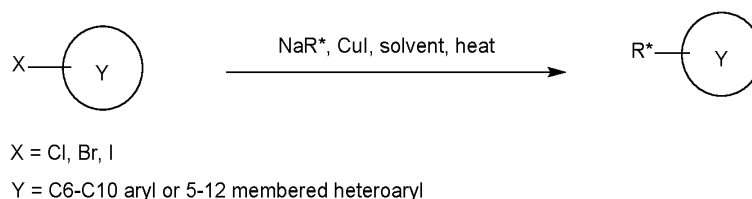


[00541] Reaction 4:



where R is a variable chemical moiety, for example alkyl or hydrogen.

[00542] In some embodiments, radiolabeled conjugates described herein can be synthesized from a chloro, bromo, or iodo precursor according to the following general reaction:



where R* is a radioisotope, for example, fluorine-18 (^{18}F), iodine-131 (^{131}I), iodine-123 (^{123}I), iodine-124 (^{124}I), iodine-125 (^{125}I), astatine-211 (^{211}At), or a radioisotope of Table 5A and Table 5B.

[00543] The radiolabeling reactions depicted above are used as example procedures in the synthesis of radiolabeled conjugates described herein. Additional reactions, including nucleophilic substitution, electrophilic substitution, isotopic exchanges, bromine-radioiodine exchange, radioiododestannylation, radioiododeboronation, and transition metal mediated halogen exchange are contemplated and

procedures can be found in Berdal et al., "Investigation on the reactivity of nucleophilic radiohalogens with arylboronic acids in water: access to an efficient single-step method for the radioiodination and astatination of antibodies" *Chemical Science* 2021, 12, 1458, and Dubost et al., "Recent Advances in Synthetic Methods for Radioiodination" *J. Org. Chem.*, 2020, 85, 13, 8300-8310, both of which are incorporated by reference herein in their entirety.

Method of Treatment

[00544] Disclosed herein are methods of treating a CA-IX-mediated disease or disorder in a subject in need thereof, the method comprising administering to the subject a radiopharmaceutical conjugate disclosed herein. In some embodiments, the CA-IX-mediated disease or disorder is cancer.

[00545] Disclosed herein are methods of treating cancer in a subject in need thereof, the method comprising administering to the subject a radiopharmaceutical conjugate disclosed herein.

[00546] In some embodiments, the cancer is a solid tumor. In some embodiments, the cancer is a relapsed or refractory cancer. In some embodiments, the cancer is a metastatic cancer. In some embodiments, the cancer is hypoxic.

[00547] In some embodiments, the cancer includes any of various malignant neoplasms characterized by the proliferation of anaplastic cells that tend to invade surrounding tissue and metastasize to new body sites. Non-limiting examples of cancers suitable for treatment using the radiopharmaceutical conjugate disclosed herein include anal cancer, appendix cancer, bile duct cancer, bladder cancer, bone cancer, breast cancer, cancer of the central nervous system, cervical cancer, choriocarcinomas, colon cancer, colorectal cancer, esophageal cancer, fibrosarcoma, gall bladder cancer, gastrointestinal carcinoid tumors, glioma, head and neck cancers, leukemia (e.g., acute lymphocytic leukemia, chronic lymphocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, or hairy cell leukemia), liver cancer, lung cancer, lymphoma (e.g., non-Hodgkin's lymphoma, Hodgkin's lymphoma, B-cell lymphoma, or Burkitt's lymphoma), multiple myeloma, neuroblastoma, oral squamous cell carcinoma, osteogenic sarcomas, ovarian cancer, pancreatic cancer, pleural cancer, prostate cancer, rectal cancer, renal cancer (e.g., renal cell carcinoma), skin cancer (e.g., melanoma) small intestine cancer, stomach (gastric) cancer, testicular cancer, and thyroid cancer.

[00548] In some embodiments, the cancer is clear cell renal cell carcinoma (ccRCC), endometrial cancer, basal cell carcinoma, liver cancer, colon cancer, gastric cancer, cervical squamous carcinoma, oral squamous cell carcinoma, pancreatic cancer, breast cancer, ovarian cancer, glioblastoma, head and neck cancer, or lung cancer. In some embodiments, the cancer is clear cell renal cell carcinoma (ccRCC). In some embodiments, the lung cancer is squamous cell lung cancer or non-cell small lung cancer. In some embodiments, the pancreatic cancer is ductal carcinoma. In some embodiments, the lung cancer is squamous cell lung cancer.

[00549] In some embodiments, provided herein are methods for killing a cell comprising contacting the cell with a radiopharmaceutical conjugate or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments, the cell expresses a CA-IX receptor. In some embodiments, the

radiopharmaceutical conjugate or a pharmaceutically acceptable salt or stereoisomer thereof releases a number of alpha particles by natural radioactive decay. In some embodiments, the radiopharmaceutical conjugate or a pharmaceutically acceptable salt or stereoisomer thereof releases a number of beta particles, gamma rays, and/or Auger electrons by natural radioactive decay. The radiopharmaceutical conjugate described herein can kill a cell by radiation. In some embodiments, the radiopharmaceutical conjugate kills the cell directly by radiation. In some embodiments, the radiopharmaceutical conjugate kills the cell by inducing double-stranded DNA breaks. In some embodiments, the cell is a cancer cell. In some embodiments, the method comprises killing a cell with an alpha-particle emitting radionuclide. After contacting a cell, the radiopharmaceutical conjugate described herein can be internalized by the cell. The internalization can be mediated by cell receptors, cell membrane endocytosis, etc. In some embodiments, the radiopharmaceutical conjugate or a pharmaceutically acceptable salt or stereoisomer thereof is configured to treat cancer by ablating tumor cells.

[00550] In addition to the methods of treatment described above, the radiopharmaceutical conjugates and compositions described herein can be used to image, and/or as part of a treatment for diseases. Conjugates for imaging applications, e.g., single-photon emission computed tomography (SPECT) and positron emission tomography (PET), can comprise a radionuclide suitable for use as imaging isotopes (e.g., Dx in Table 3) such as the isotopes in Table 3. Accordingly, the radiopharmaceutical conjugate can be administered as a companion diagnostic.

[00551] In one aspect, described herein is a method of treatments that comprises administering a first radiopharmaceutical conjugate and a second radiopharmaceutical conjugate. The first radiopharmaceutical conjugate can be used as companion diagnostics and the second radiopharmaceutical conjugate can be used for therapeutics. In some embodiments, the first radiopharmaceutical conjugate and the second radiopharmaceutical conjugate have the same structure except for the radionuclide. In some embodiments, the first radiopharmaceutical conjugate comprises a gamma particle emitting radionuclide. In some embodiments, the first radiopharmaceutical conjugate comprises a radionuclide marked Dx of Table 3. In some embodiments, the first radiopharmaceutical conjugate comprises a radionuclide selected from Lu-177, In-111, Ga-68, Cu-64, and Zr-89. In some embodiments, the second radiopharmaceutical conjugate comprises an alpha or beta-particle emitting radionuclide. In some embodiments, the second radiopharmaceutical conjugate comprises a radionuclide marked Tx of Table 3. In some embodiments, the second radiopharmaceutical conjugate comprises Ac-225. In some embodiments, the method comprises administering (i) a first radiopharmaceutical conjugate comprising a radionuclide configured for companion diagnostic (such as PET imaging) and (ii) a second radiopharmaceutical conjugate comprising a radionuclide selected from an alpha or beta-particle emitter, wherein the first and the second radiopharmaceutical conjugate have the same structure except for the radionuclide.

[00552] In one aspect, described herein is a method of diagnosing or imaging a cancer in a subject in need thereof, comprising administering to the subject a radiopharmaceutical conjugate or a pharmaceutical composition described herein.

[00553] In some embodiments, the subject is 1 to 100 years old. In some embodiments, the subject is 5 to 10, 5 to 15, 5 to 18, 5 to 25, 5 to 35, 5 to 45, 5 to 55, 5 to 65, 5 to 75, 10 to 15, 10 to 18, 10 to 25, 10 to 35, 10 to 45, 10 to 55, 10 to 65, 10 to 75, 15 to 18, 15 to 25, 15 to 35, 15 to 45, 15 to 55, 15 to 65, 15 to 75, 18 to 25, 18 to 35, 18 to 45, 18 to 55, 18 to 65, 18 to 75, 25 to 35, 25 to 45, 25 to 55, 25 to 65, 25 to 75, 35 to 45, 35 to 55, 35 to 65, 35 to 75, 45 to 55, 45 to 65, 45 to 75, 55 to 65, 55 to 75, or 65 to 75 years old. In some embodiments, the subject is at least 5, 10, 15, 18, 25, 35, 45, 55, or 65 years old. In some embodiments, the subject is at most 10, 15, 18, 25, 35, 45, 55, 65, or 75 years old.

Dosing

[00554] In certain embodiments, the compositions containing the radiopharmaceutical conjugates described herein are administered for therapeutic treatments. In certain therapeutic applications, the radiopharmaceutical conjugates described herein are administered to a patient already suffering from a disease or disorder, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or disorder. Amounts effective for this use depend on the severity and course of the disease or disorder, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. The amount of radiopharmaceutical conjugates described herein or a pharmaceutically acceptable salt or stereoisomer thereof and/or pharmaceutical compositions administered can be sufficient to deliver a therapeutically effective dose of the particular subject. In some embodiments, radiopharmaceutical conjugate dosages can be between about 0.1 pg and about 50 mg per kilogram of body weight. In some embodiments, the dose of the radiopharmaceutical conjugate or a pharmaceutically acceptable salt or stereoisomer thereof described herein for the described methods is about 0.001 mg to about 1000 mg per dose for the subject being treated.

[00555] In some cases, the elimination profile of the conjugate can be adjusted by a reversible binding between the conjugate and a plasma protein such as albumin. A suitable affinity between the conjugate and the plasma protein can utilize the plasma protein as a reservoir for the conjugates, attaching and preserving the conjugates at high concentration and releasing the conjugates at a lower concentration, thereby improving elimination profile. In some embodiments, a dissociation constant (K_d) between the conjugate and human serum albumin is at most 500 μM , as determined at room temperature in human serum condition. In some embodiments, the K_d is from about 0.1 nM to about 1000 μM . In some embodiments, the K_d is at most 100 μM . In some embodiments, the K_d is at most 15 μM . In some embodiments, the K_d is from about 1 nM to about 10 μM . In some embodiments, the K_d is from about 10 nM to about 10 μM . In some embodiments, the K_d is from about 50 nM to about 1 μM . In some embodiments, the K_d is from about 100 nM to about 10 μM .

Routes of Administration

[00556] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical

administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

Pharmaceutical Compositions/Formulations

[00557] The compounds described herein are administered to a subject in need thereof, either alone or in combination with pharmaceutically acceptable carriers, excipients, or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. In some embodiments, the compounds described herein are administered to animals.

[00558] In another aspect, provided herein are pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt or stereoisomer thereof, and at least one pharmaceutically acceptable excipient. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable excipients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Dekker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999), herein incorporated by reference for such disclosure.

EXAMPLES

A: Synthesis of the Compounds

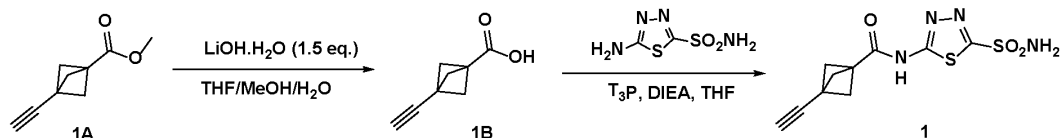
General Information

[00559] ¹H NMR spectra were recorded on either a Bruker Avance III 400 (400 MHz), or Bruker Avance 300 (400 MHz) spectrometer. Chemical shifts are reported in ppm with solvent resonance as the internal standard (CDCl₃: 7.27 ppm, DMSO-*d*₆: 2.50 ppm, CD₃OD: 3.31 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), and coupling constants (Hz).

[00560] Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO₂, 1000 mesh) or by column chromatography (silica gel, 1000 mesh). Thin layer chromatography (TLC) was performed on 20-25 μm silica gel glass backed plates. Preparative TLC was performed on a 40-45 μm silica gel glass backed plates. Visualization was performed using ultraviolet light (254 nm), iodide, or KMnO₄ in water.

A1. Synthesis of Intermediate 1

Scheme A1.



1.1 Preparation of compound 1B

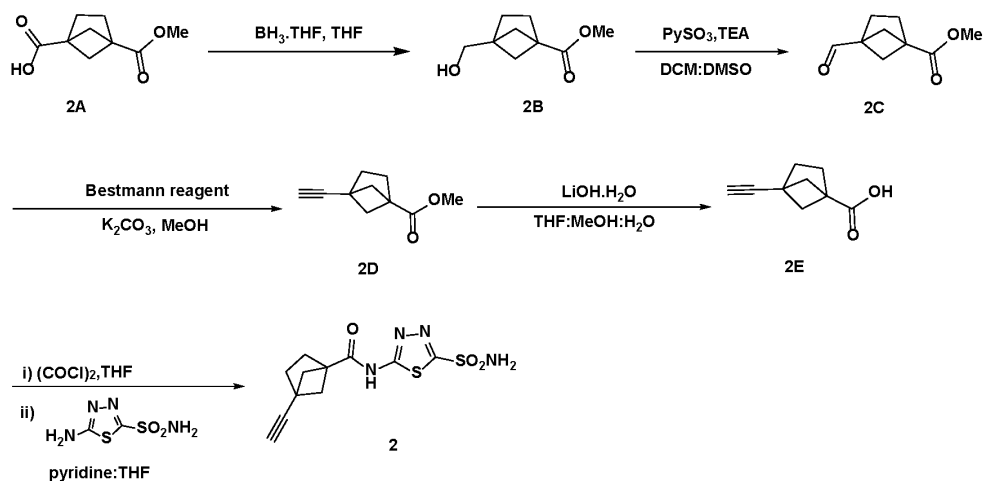
[00561] A solution of methyl 3-ethynylbicyclo[1.1.1]pentane-1-carboxylate (6.5 g, 43.3 mmol, 1 *eq*) and LiOH.H₂O (2.72 g, 64.9 mmol, 1.5 *eq*) in THF (20 mL), MeOH (20 mL) and H₂O (20 mL) was stirred at 20°C for 1h. The reaction mixture was concentrated under reduced pressure to remove organics and the aqueous phase adjusted to pH = 5 by the addition of 1 M HCl. White solid precipitated and was filtered. The filter cake collected and dried under reduced pressure to give **compound 1B** (5.4 g, 92% yield) as a white solid; LCMS [M+H]: 137.1; ¹H NMR (400 MHz, DMSO-d₆) δ 12.51 (s, 1 H), 3.12 (s, 1 H), 2.21 (s, 6 H).

1.2 Preparation of Intermediate 1

[00562] To a solution of **compound 1B** (7.0 g, 51.4 mmol, 1 *eq*) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (9.27 g, 51.4 mmol, 1 *eq*) in THF (40 mL) and DIEA (44.8 mL, 257 mmol, 5 *eq*) was added dropwise a solution of T₃P (36.7 mL, 61.7 mmol, 50% w/w solution in EtOAc, 1.2 *eq*) in THF (4 mL) at 20°C. The mixture was stirred at 20°C for 2h. The mixture was diluted with H₂O (40 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was triturated with H₂O (20 mL), filtered, and concentrated under reduced pressure to give **Intermediate 1** (6.0 g, 39% yield) as a white solid; LCMS [M+H]: 299.0; ¹H NMR (400 MHz, DMSO-d₆) δ 13.17 (br s, 1H), 8.32 (s, 2H), 3.19 (s, 1H), 2.40 (s, 6H).

A2. Synthesis of Intermediate 2

Scheme A2.



1.3. Preparation of compound 2B

[00563] To a solution of **compound 2A** (3.5 g, 19.0 mmol, 1 *eq*) in THF (50 mL) was added 1M BH₃.THF (17.1 mL, 0.9 *eq*) at -20°C. The mixture was stirred at 0 °C for 0.5 h, quenched by addition of

MeOH (20 mL) at 0 °C and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 2B** (2.0 g, 62% yield) as a white oil; ¹H NMR (400 MHz, CDCl₃) δ 3.71 (s, 2H), 3.68 (s, 3H), 1.99 - 1.94 (m, 2H), 1.80 (br d, *J* = 1.4 Hz, 2H), 1.68 - 1.63 (m, 2H), 1.41 (dd, *J* = 1.9, 4.1 Hz, 2H).

1.4. Preparation of compound 2C

[00564] To a solution of **compound 2B** (3.1 g, 18.2 mmol, 1 *eq*) in DCM (30 mL) was added TEA (25.4 mL, 182 mmol, 10 *eq*) and a solution of PySO₃ (8.70 g, 54.6 mmol, 3 *eq*) in DMSO (10 mL). The mixture was stirred at 25 °C for 16h. The residue was diluted with H₂O (50 mL) and extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure to give crude **compound 2C** (3.0 g, 98% yield) as a yellow oil which was used directly in the next reaction.

1.5. Preparation of compound 2D

[00565] To a solution of compound **2C** (3.0 g, 17.8 mmol, 1 *eq*) and Bestmann reagent (4.11 g, 21.4 mmol, 1.2 *eq*) in MeOH (30 mL) was added K₂CO₃ (4.93 g, 35.7 mmol, 2 *eq*) at 0°C. The mixture was stirred at 25 °C for 2h. The reaction mixture was partitioned between MTBE (150 mL) and H₂O (300 mL). The organic phase was separated, washed with brine (3 × 50 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 2D** (1.7 g, 58% yield) as a white oil; ¹H NMR (400 MHz, CDCl₃) δ 3.62 (s, 3H), 2.19 (s, 1H), 2.01 - 1.97 (m, 2H), 1.87 (s, 4H), 1.62 (dd, *J* = 2.0, 4.2 Hz, 2H).

1.6. Preparation of compound 2E

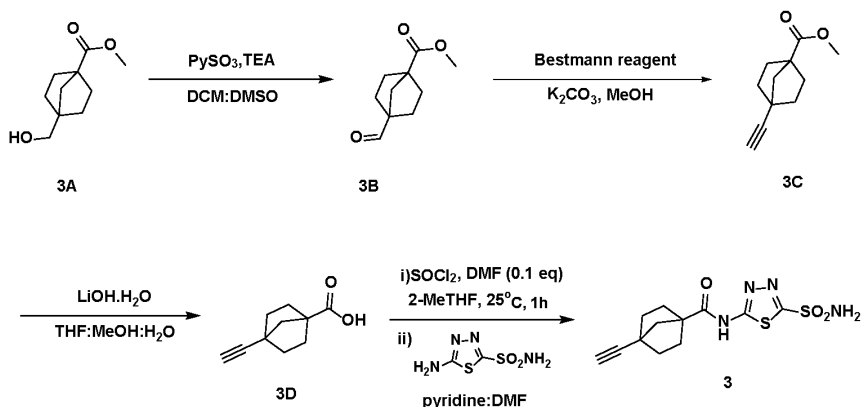
[00566] To a solution of **compound 2D** (1.6 g, 9.74 mmol, 1 *eq*) in 2:2:1 THF:MeOH:H₂O (10 mL) was added LiOH·H₂O (818 mg, 19.5 mmol, 2 *eq*). The mixture was stirred at 25 °C for 4h. The reaction mixture was concentrated under reduced pressure, the residue diluted with H₂O (8 mL) and acidified with 1M HCl (150 mL). White solids precipitated, the suspension filtered and the filtrate concentrated under reduced pressure to give **compound 2E** (1.6 g, 98% yield, 90% purity) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 2.24 (s, 1H), 2.02 (br s, 2H), 1.91 (s, 4H), 1.66 (dd, *J* = 1.9, 4.1 Hz, 2H).

1.7. Preparation of Intermediate 2

[00567] To a solution of **compound 2E** (1.0 g, 6.7 mmol, 1 *eq*) in DCM (5 mL) was added oxalyl dichloride (991 μL, 11.3 mmol, 1.7 *eq*) at 0°C. The mixture was stirred at 25 °C for 1h. The mixture was quenched with the addition of MeOH and concentrated under reduced pressure. The yellow oil was taken up in THF (10 mL) and added to a solution of 5-amino-1,3,4-thiadiazole-2-sulfonamide (1.23 g, 6.85 mmol) and pyridine (2.63 mL, 32.6 mmol) in THF (10 mL) at 0°C. The solution was stirred at 15°C for 1h and concentrated under reduced pressure. The residue was triturated with H₂O (120 mL) at 15°C for 20 min to give **Intermediate 2** (2.0 g, 98% yield) as a white solid; LCMS [*M*+*H*]: 313.0; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.97 (s, 1H), 8.33 (s, 2H), 3.21 (s, 1H), 2.11 (br d, *J* = 1.3 Hz, 2H), 2.02 - 1.98 (m, 2H), 1.92 - 1.87 (m, 2H), 1.79 (dd, *J* = 1.9, 4.0 Hz, 2H).

A3. Synthesis of Intermediate 3

Scheme A3.



1.8 Preparation of compound **3B**

[00568] To a solution of **compound 3A** (9.0 g, 24.4 mmol, 1 *eq*) and TEA (68 mL, 244 mmol, 10 *eq*) in DCM (100 mL) was added a solution of PySO_3 (23.3 g, 73.3 mmol, 3 *eq*) in DMSO (40 mL) at 0°C. The mixture was stirred at 15°C for 15 min then 30°C for 16 h. The mixture was diluted with DCM (100 mL) and extracted with H₂O (10 × 50 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give crude **compound 3B** (3.8 g) as colorless oil.

1.9 Preparation of compound **3C**

[00569] To a solution of **compound 3B** (8.5 g, 23.3 mmol, 1 *eq*) and Bestmann reagent (10.8 g, 28.0 mmol, 1.2 *eq*) in MeOH (90 mL) was added K_2CO_3 (12.9 g, 46.7 mmol, 2 *eq*) at 0°C. The mixture was stirred at 25°C for 2h. The mixture was diluted with MTBE (80 mL) and extracted with H₂O (3 × 50 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , petroleum ether:EtOAc) to give **compound 3C** (7.3 g, 88% yield) as a white solid.

1.10 Preparation of compound **3D**

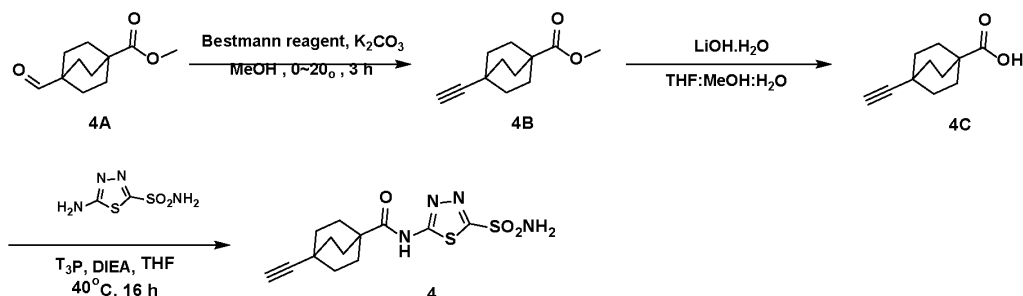
[00570] To a solution of **compound 3C** (7.3 g, 20.5 mmol, 1 *eq*) in 2:2:1 THF:MeOH:H₂O (25 mL) was added $\text{LiOH} \cdot \text{H}_2\text{O}$ (2.58 g, 30.7 mmol, 1.5 *eq*). The mixture was stirred at 30°C for 4h and concentrated under reduced pressure. The residue was diluted with H₂O (8 mL) and acidified with 1M HCl (150 mL). White solids precipitated, the suspension filtered, and the filtrate concentrated under reduced pressure to give **compound 3D** (6.1 g, 91% yield) as a white solid.

1.11 Preparation of Intermediate **3**

[00571] To a solution of **compound 3D** (6.10 g, 18.6 mmol, 1 *eq*) in 2-MeTHF (30 mL) was added DMF (286 μL , 1.86 mmol, 0.1 *eq*) and SOCl_2 (5.38 mL, 37.2 mmol, 2 *eq*) at 0°C. The mixture was stirred at 25°C for 1h and concentrated under reduced pressure. The residue in DMF (20 mL) was added dropwise to a solution of 5-amino-1,3,4-thiadiazole-2-sulfonamide (8.04 g, 44.6 mmol, 1.2 *eq*) and pyridine (9.0 mL, 112 mmol, 3 *eq*) in DMF (20 mL) at 0°C. The solution was stirred at 15°C for 1h and the reaction mixture concentrated under reduced pressure. The residue was triturated with H₂O (120 mL) at 15°C for 20 min to give **Intermediate 3** (10.3 g, 85% yield) as a white solid; LCMS [$\text{M}+\text{H}$]: 327.0; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.83 (s, 1H), 8.32 (s, 2H), 3.08 (d, $J = 1.1$ Hz, 1H), 2.03 - 1.94 (m, 4H), 1.88 - 1.66 (m, 6H).

A4. Synthesis of Intermediate 4

Scheme A4.



1.12 Preparation of compound 4B

[00572] To a mixture of **compound 4A** (2.0 g, 10.2 mmol, 1 *eq*) and Bestmann reagent (2.35 g, 12.2 mmol, 1.2 *eq*) in MeOH (50 mL) and K₂CO₃ (2.82 g, 20.4 mmol, 2 *eq*) was added at 0°C. The mixture was stirred at 0°C for 2 h, and then stirred at 20°C for 1 h. The reaction mixture diluted with water (50 mL) and extracted with MTBE (3 × 50 mL). The combined organic layer was washed with brine (25 mL), dried (Na₂SO₄), filtered and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 4B** (1.82 g, 93% yield) as a white solid; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 3.64 (s, 3H), 2.09 (s, 1H), 1.80 (s, 12H).

1.13 Preparation of compound 4C

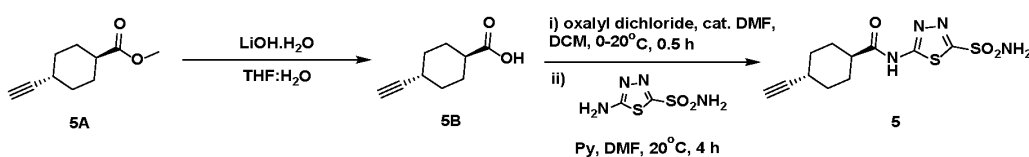
[00573] To a solution of **compound 4B** (1.82 g, 9.47 mmol, 1 *eq*) in 1:1:1 THF:MeOH:H₂O (60 mL) was added LiOH.H₂O (1.39 g, 33.1 mmol, 3.5 *eq*). The mixture was stirred at 15°C for 3 h. The reaction mixture was washed with 1M HCl (43 mL), filtered and concentrated under reduced pressure to give **compound 4C** (1.58 g, 94% yield) as a white solid; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 7.27 (s, 1H), 2.10 (s, 1H), 1.85 - 1.80 (m, 12H).

1.14 Preparation of Intermediate 4

[00574] T₃P (2.50 mL, 4.21 mmol, 50% purity, 1.5 *eq*) was added dropwise at 0°C to a mixture of **compound 4C** (500 mg, 2.81 mmol, 1 *eq*), 5-amino-1,3,4-thiadiazole-2-sulfonamide (607 mg, 3.37 mmol, 1.2 *eq*) and DIEA (1.47 mL, 8.42 mmol, 3 *eq*) in THF (10 mL). The mixture was stirred at 40°C for 16 h, diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The crude product was triturated with EtOAc at 15°C for 5 min to give **Intermediate 4** (131 mg, 14% yield) as a white solid; LCMS [M+H]: 341.1.

A5. Synthesis of Intermediate 5

Scheme A5.

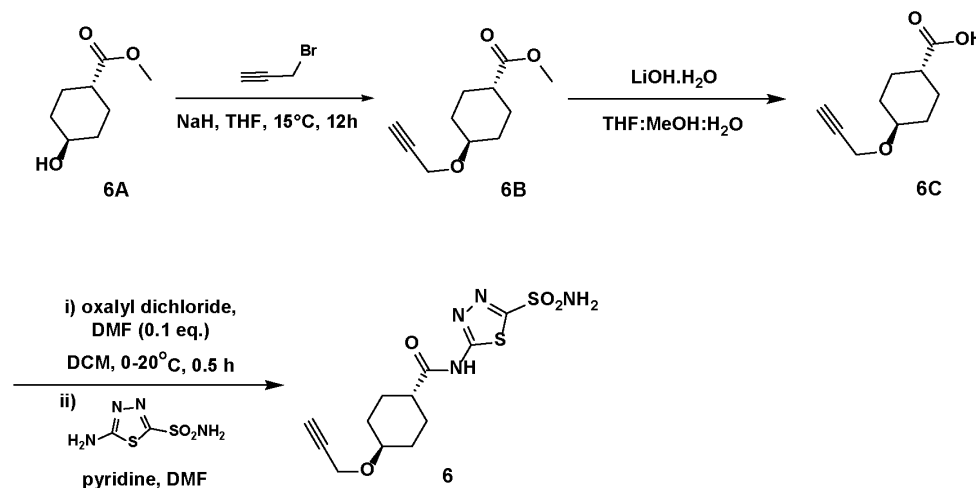


1.15 Preparation of compound 5B

[00575] To a solution of **compound 5A** (2.0 g, 12.0 mmol, 1 *eq*) in THF (10 mL) and H₂O (10 mL) was added LiOH·H₂O (656 mg, 15.6 mmol, 1.3 *eq*). The mixture was stirred at 20°C for 2h and concentrated under reduced pressure. The residue was diluted with H₂O (8 mL) and *acidified* with 1 M HCl (30 mL). The white precipitate was filtered, and the filtrate concentrated under reduced pressure. The residue was recrystallization from H₂O to give **compound 5B** (1.72 g, 94% yield) as a white solid; LCMS [M+H]: 153.1; ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 2.31 (d, *J* = 2.32 Hz, 1 H) 2.26 (br d, *J* = 3.42 Hz, 2 H), 1.98 (br d, *J* = 9.78 Hz, 4 H), 1.32 - 1.50 (m, 5 H).

1.16 Preparation of Intermediate 5

[00576] To a solution of **compound 5B** (1.52 g, 9.99 mmol, 1 *eq*) in DCM (5 mL) was added DMF (77 μL, 999 μmol, 0.1 *eq*) and oxalyl chloride (870 μL, 9.99 mmol, 1 *eq*) at 0°C. The reaction mixture was stirred at 20°C for 30 min and concentrated under reduced pressure. The oil was taken up in DMF (5 mL) and added to a solution of 5-amino-1,3,4-thiadiazole-2-sulfonamide (1.80 g, 9.96 mmol, 1 *eq*) and pyridine (804 μL, 9.96 mmol, 1 *eq*) in DMF (3 mL) at 0°C. The solution was stirred at 20°C for 4 h, diluted with EtOAc (100 mL) and extracted with H₂O (3 × 50 mL). The combined organic layers were washed with brine (2 × 30 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was further purified by recrystallization from H₂O (10 mL) to give **Intermediate 5** (3.03 g, 97% yield) as a white solid; LCMS [M+H]: 315.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.98 (s, 1 H), 8.31 (s, 2 H), 2.73 (s, 1 H), 2.31 (br dd, *J*=12.9, 2.0 Hz, 2 H), 1.84 - 2.02 (m, 4 H), 1.23 - 1.52 (m, 4 H).

A6. Synthesis of Intermediate 6**Scheme A6.****1.17 Preparation of compound 6B**

[00577] To a solution of **compound 6A** (12.5 g, 79.0 mmol, 1 *eq*) in THF (250 mL) was added NaH (3.79 g, 94.8 mmol, 60% purity, 1.2 *eq*) at 0°C under a nitrogen atmosphere. 3-Bromoprop-1-yne (17 mL, 158 mmol, 80% purity, 2 *eq*) was added dropwise and the reaction stirred at 15°C for 12h. The

mixture was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 6B** (2.5 g, 8.1% yield) as a yellow oil.

1.18 Preparation of compound 6C

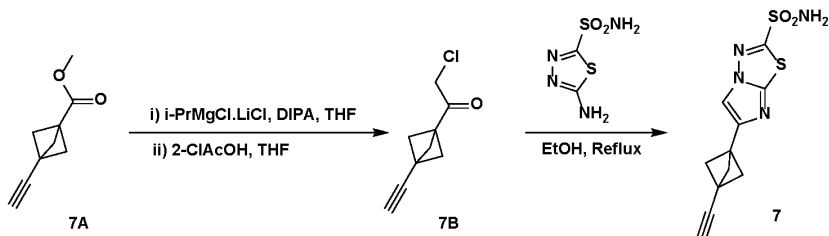
[00578] To a solution of **compound 6B** (2.5 g, 12.7 mmol, 1.0 *eq*) in 1:1:1 THF:MeOH:H₂O (15 mL) was added LiOH.H₂O (535 mg, 12.74 mmol, 1 *eq*) at 15°C under a nitrogen atmosphere. The mixture was stirred at 15°C for 12h. The reaction was concentrated under reduced pressure. The residue was adjusted pH to 5-6 with 1M HCl (15 mL) and filtered. The filter cake was dried under vacuum to give **compound 6C** (1.4 g, 30% yield) as yellow solid; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 4.20 (d, 2H), 3.56 - 3.43 (m, 1H), 2.42 (t, *J* = 2.3 Hz, 1H), 2.37 - 2.28 (m, 1H), 2.16 - 2.02 (m, 4H), 1.57 - 1.48 (m, 2H), 1.37 - 1.32 (m, 2H).

1.19 Preparation of Intermediate 6

[00579] Oxalyl chloride (576 μL, 6.59 mmol, 1 *eq*) was added dropwise to a solution of **compound 6C** (1.2 g, 6.59 mmol, 1 *eq*) and DMF (51 μL, 659 μmol, 0.1 *eq*) in DCM (12 mL) at 0°C. The mixture was stirred at 20°C for 0.5h and concentrated under reduced pressure. The yellow oil was taken up in DCM (8 mL) and added to a solution of 5-amino-1,3,4-thiadiazole-2-sulfonamide (1.17 g, 6.48 mmol, 1 *eq*) and pyridine (523 μL, 6.48 mmol, 1 *eq*) in DMF (8 mL) at 0°C. The mixture was stirred at 20°C for 1h, poured into H₂O (50 mL), stirred at 20°C for 10 min, filtered and the filter cake dried under reduced pressure. The crude product was triturated with 1:1 petroleum ether:MTBE (20 mL) at 20°C for 20 min to give **Intermediate 6** (1.3 g, 51% yield, 88% purity) as a yellow solid; ¹H NMR (400 MHz, METHANOL-*d*₄) δ 4.21 (d, *J* = 2.5 Hz, 2 H) 3.54 (tt, *J* = 10.7, 4.2 Hz, 1 H) 2.82 (t, *J* = 2.4 Hz, 1 H) 2.5 (tt, *J* = 11.8, 3.6 Hz, 1 H) 2.12 - 2.23 (m, 2 H) 1.96 - 2.07 (m, 2 H) 1.54 - 1.69 (m, 2 H) 1.25 - 1.38 (m, 2 H).

A7. Synthesis of Intermediate 7

Scheme A7.



1.20 Preparation of compound 7B

[00580] 1.3 M *i*-PrMgCl.LiCl (18.4 mL, 9 *eq*) was added dropwise to DIPA (3.76 mL, 26.6 mmol, 10 *eq*) and the mixture stirred at 10°C for 3h. A solution of **compound 7A** (400 mg, 2.66 mmol, 1 *eq*) and 2-chloroacetic acid (899 μL, 7.99 mmol, 3 *eq*) in THF (9 mL) was added to the reaction mixture at 0°C. The reaction stirred at 0°C for 0.5h and then warmed to 10°C for 1 h. The reaction mixture was quenched by addition of 1M HCl (30 mL) at 0°C and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **compound 7B**

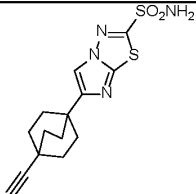
(372 mg, 83% yield) as a white solid; ^1H NMR (400 MHz, METHANOL- d_4) δ 4.44 - 4.35 (m, 2H), 2.51 (s, 1H), 2.34 (s, 6H).

1.21 Preparation of Intermediate 7

[00581] A mixture of **compound 7B** (280 mg, 1.66 mmol, 1 *eq*) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (299 mg, 1.66 mmol, 1 *eq*) was heated in EtOH (4 mL) at 80°C for 24h under a nitrogen atmosphere. The reaction mixture was filtered and concentrated under reduced pressure. The residue was triturated with EtOAc at 10°C for 10 min to give a white solid. The solid was dissolved in MeOH (3 mL) and 1 M NaHCO_3 (995 μL) was added. The mixture was stirred at 65 °C for 0.5h under a nitrogen atmosphere, the reaction mixture cooled to room temperature, filtered and the filtrate concentrated under reduced pressure. The residue was triturated with H_2O at 15°C for 10 min to give **Intermediate 7** (183 mg, 62% yield) as a white solid; ^1H NMR (400 MHz, METHANOL- d_4) δ 7.88 (s, 1H), 2.48 (s, 1H), 2.35 (s, 6H).

[00582] Intermediates in **table 7.1** were prepared by procedures depicted in **scheme A7**.

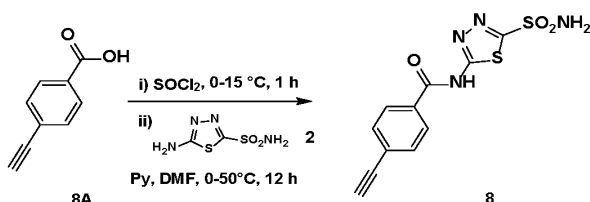
Table 7.1.

Intermediate	Structure	m/z
7.1		[M+H] ⁺ : 337.1

[00583]

A8. Synthesis of Intermediate 8

Scheme A8.



1.22 Preparation of Intermediate 8

[00584] **Compound 8A** (2.0 g, 13.7 mmol, 1 *eq*) was added to SOCl_2 (20 mL) at 0°C under a nitrogen atmosphere and the mixture stirred at 15 °C for 1 h. The reaction mixture was concentrated under reduced pressure and taken up in DMF (20 mL):pyridine (2.21 mL, 27.3 mmol, 2 *eq*). 5-Amino-1,3,4-thiadiazole-2-sulfonamide (2.25 g, 13.7 mmol, 1 *eq*) was added at 0°C and the mixture stirred at 50°C for 12 h. The crude product was triturated with H_2O at 15°C for 10 min and triturated with EtOAc at 15°C for 10 min to give crude **Intermediate 8** (4.2 g) as a yellow solid; LCMS [M+H]⁺: 309.0; ^1H NMR (400 MHz, DMSO- d_6) δ 13.85 - 13.34 (m, 1H), 8.38 (s, 2H), 8.14 (br d, J = 8.3 Hz, 2H), 7.68 (br d, J = 8.1 Hz, 2H), 4.59 - 4.42 (m, 1H).

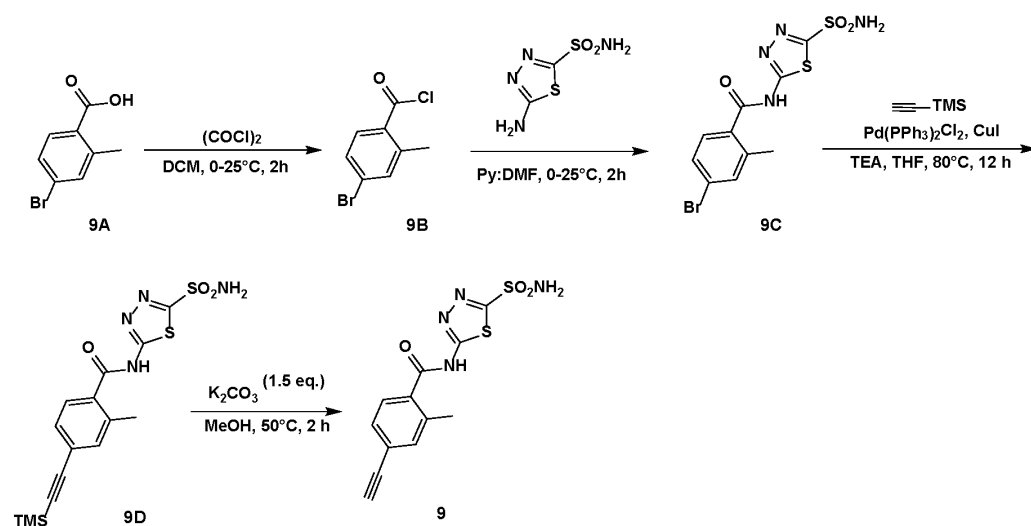
[00585] Intermediates in **table 6.1** were prepared by procedures depicted in **scheme A8**.

Table 6.1.

Intermediate	Structure	m/z
8.1		[M+H]: 323.2
8.2		[M+H]: 342.9/344.9

A9. Synthesis of Intermediate 9

Scheme A9.



1.23 Preparation of compound 9B

[00586] To a solution of **compound 9A** (2.50 g, 11.6 mmol, 1 *eq*) in DCM (50 mL) was added (COCl)₂ (5.09 mL, 58.1 mmol, 5 *eq*) and DMF (1.5 mL) at 0°C and the mixture was stirred at 25°C for 2 h. The reaction was repeated. The two reactions were combined and concentrated under reduced pressure to give crude **compound 9B** (5.4 g) as a yellow oil that was used directly in the next reaction.

1.24 Preparation of compound 9C

[00587] To a solution of 5-amino-1,3,4-thiadiazole-2-sulfonamide (2.97 g, 16.5 mmol, 1 *eq*) in DMF (54 mL) was added pyridine (1.33 mL, 16.5 mmol, 1 *eq*). A solution of **compound 9B** (2.69 g, 11.5 mmol, 0.7 *eq*) in DMF (10 mL) was added at 0°C and the mixture stirred at 25°C for 2 h. The reaction was repeated and combined. The reaction mixture was poured into H₂O (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried (Na₂SO₄),

filtered and concentrated under reduced pressure. The residue was purified by *prep*-HPLC (column: Phenomenex luna C18 (250*70mm, 15 μ m); mobile phase: [H₂O (0.1%TFA)-ACN];gradient:24%-54% B over 28.0 min) to give **compound 9C** (3.0 g, 24% yield) as white solid; LCMS [M+2H]: 379.0.

1.25 Preparation of compound 9D

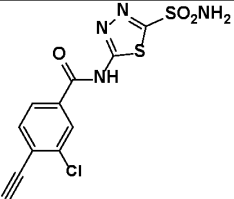
[00588] To a solution of **compound 9C** (1.2 g, 3.18 mmol, 1 *eq*) in THF (24 mL) was added Pd(PPh₃)₂Cl₂ (223 mg, 318 μ mol, 0.1 *eq*), CuI (121 mg, 636 μ mol, 0.2 *eq*), TEA (2.53 mL, 18.2 mmol) and ethyl(trimethyl)silane (1.32 mL, 9.54 mmol). The mixture stirred at 80°C for 12h. The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **compound 9D** (2.4 g, 83% yield, 87% purity) as yellow solid; LCMS [M+H]: 395.2.

1.26 Preparation of Intermediate 9

[00589] To a solution of **compound 9D** (2.0 g, 5.07 mmol, 1 *eq*) in MeOH (40 mL) was added K₂CO₃ (1.05 g, 7.60 mmol, 1.5 *eq*) at 50°C, and the mixture was stirred at 50°C for 2 h. The mixture was adjusted to pH=3 with 1M HCl, the solid filtered and the filter cake concentrated to give **intermediate 9** (1.4 g, 86% yield) as a yellow solid that was used directly in the next reaction; LCMS [M+H]: 323.1; ¹H NMR (400 MHz, DMSO-d₆) δ 13.52 (br s, 1H), 8.38 (s, 2H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.52 - 7.40 (m, 2H), 4.40 (s, 1H), 2.40 (s, 3H).

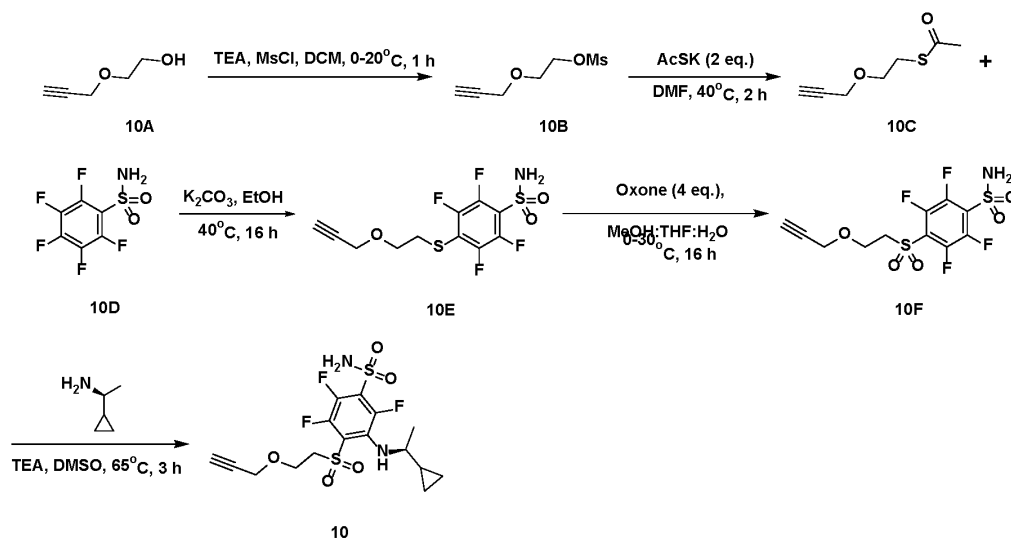
[00590] Intermediates in **table 6.2** were prepared by procedures depicted in **scheme A9**.

Table 6.2.

Intermediate	Structure	m/z
9.1		[M+H]: 343.2/345.1

A10. Synthesis of Intermediate 10

Scheme A10.



1. 27 Preparation of compound 10B

[00591] To a solution of **compound 10A** (10 g, 99.9 mmol, 1 *eq*) in DCM (100 mL) were added TEA (27.8 mL, 200 mmol, 2 *eq*) and MsCl (11.6 mL, 150 mmol, 1.5 *eq*) at 0°C under a nitrogen atmosphere. The mixture was stirred at 20°C for 1 h. The reaction mixture was washed with NaHCO₃ (50 mL), NH₄Cl (50 mL), H₂O (20 mL) and brine (20 mL). The organic layer was dried (Na₂SO₄), filtered, and concentrated under reduced pressure to give **compound 10B** (17.8 g, 100% yield) as a yellow oil; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 4.44 - 4.36 (m, 2H), 4.25 - 4.17 (m, 2H), 3.85 - 3.73 (m, 2H), 3.10 - 3.03 (m, 3H), 2.52 - 2.42 (m, 1H).

1. 28 Preparation of compound 10C

[00592] To a solution of **compound 10B** (17.8 g, 99.9 mmol, 1 *eq*) in DMF (200 mL) was added potassium ethanethioate (22.8 g, 200 mmol, 2 *eq*) at 20°C under a nitrogen atmosphere. The mixture was stirred at 40°C for 2 h. The residue was dissolved in EtOAc (500 mL), washed with H₂O (2 × 100 mL) and brine (2 × 100 mL). The organic phase was dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 10C** (9.2 g, 58% yield) as a light yellow liquid; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 4.16 (d, *J* = 2.4 Hz, 2H), 3.66 (t, *J* = 6.4 Hz, 2H), 3.11 (t, *J* = 6.4 Hz, 2H), 2.44 (t, *J* = 2.4 Hz, 1H), 2.34 (s, 3H).

1. 29 Preparation of compound 10E

[00593] To a solution of **compound 10C** (7.11 g, 44.9 mmol, 1 *eq*) and **compound 10D** (11.1 g, 44.9 mmol, 1 *eq*) in EtOH (100 mL) was added K₂CO₃ (31.1 g, 225 mmol, 5 *eq*) at 20°C. The mixture was stirred at 40°C for 16 h. The reaction mixture was diluted with H₂O (160 mL) and extracted with EtOAc (3 × 400 mL). The combined organic layer was dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **compound 10E** (6.4 g, 41% yield) as a white solid; LCMS [M+H]⁺: 344.0. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.39 (s, 2H), 4.10 (d, *J* = 2.4 Hz, 2H), 3.64 (t, *J* = 5.8 Hz, 2H), 3.38 (t, *J* = 2.4 Hz, 1H), 3.24 (t, *J* = 5.8 Hz, 2H).

1.30 Preparation of compound 10F

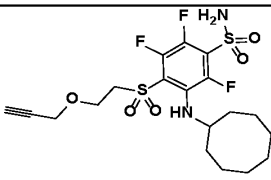
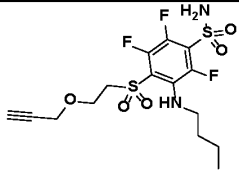
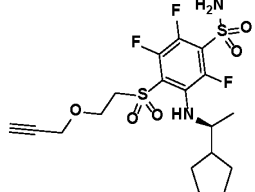
[00594] To a solution of **compound 10E** (2.0 g, 5.83 mmol, 1 *eq*) in MeOH (24 mL) and THF (8 mL) was added Oxone (14.3 g, 23.3 mmol, 4 *eq*) in H₂O (16 mL) at 0°C. The mixture was stirred at 30°C for 16 h. The reaction mixture was diluted with H₂O (30 mL) and extracted with DCM (2 × 50 mL). The combined organic layer was dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **compound 10F** (1.4 g, 64% yield) as a white solid; LCMS [M-H]⁺: 373.9; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.61 (s, 2H), 4.02 (d, *J* = 2.4 Hz, 2H), 3.96 - 3.90 (m, 2H), 3.89 - 3.84 (m, 2H), 3.36 (t, *J* = 2.4 Hz, 1H).

1.31 Preparation of Intermediate 10

[00595] To a solution of **compound 10F** (1.2 g, 3.20 mmol, 1 *eq*) in DMSO (12 mL) was added TEA (890 μL, 6.39 mmol, 2 *eq*) and (*S*)-1-cyclopropylethan-1-amine (408 mg, 4.80 mmol, 1.5 *eq*) under a nitrogen atmosphere. The mixture was stirred at 65°C for 3 h. The residue was diluted with H₂O (30 mL) and extracted with DCM (3 × 30 mL). The combined organic layer was washed with brine (2 × 10 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **Intermediate 10** (840 mg, 60% yield) as a yellow oil; LCMS [M-H]⁺: 439.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.32 (s, 2H), 6.51 (br d, *J* = 8.6 Hz, 1H), 4.05 (d, *J* = 2.4 Hz, 2H), 3.86 (d, *J* = 1.8 Hz, 4H), 3.39 (t, *J* = 2.4 Hz, 1H), 3.14 (td, *J* = 6.4, 8.4 Hz, 1H), 1.29 - 1.08 (m, 5H), 0.97 - 0.78 (m, 1H), 0.51 - 0.35 (m, 2H), 0.28 - 0.14 (m, 2H).

Intermediates in **table 6.3** were prepared by procedures depicted in **Scheme A10**.

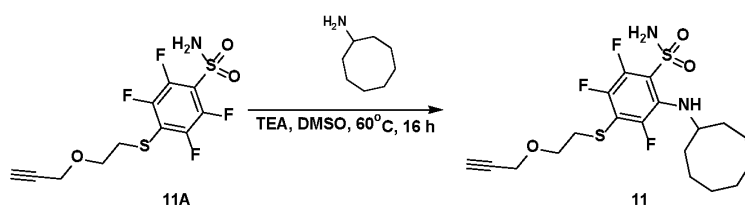
Table 6.3.

Intermediate	Structure	m/z	¹ H NMR
10.1		[M-H] ⁺ : 481.4	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.31 (s, 2H), 6.60 (br d, <i>J</i> = 8.6 Hz, 1H), 4.05 (d, <i>J</i> = 2.4 Hz, 2H), 3.84 (s, 4H), 3.78 (br dd, <i>J</i> = 3.8, 7.8 Hz, 1H), 3.38 (t, <i>J</i> = 2.4 Hz, 1H), 1.92 - 1.79 (m, 2H), 1.74 - 1.43 (m, 12H)
10.2		[M-H] ⁺ : 427.0	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.26 (br s, 2H), 6.56 (br t, <i>J</i> = 4.4 Hz, 1H), 4.08 - 4.01 (m, 2H), 3.90 - 3.79 (m, 3H), 3.38 (t, <i>J</i> = 2.4 Hz, 1H), 3.37 - 3.26 (m, 2H), 1.63 - 1.48 (m, 2H), 1.43 - 1.26 (m, 2H), 1.01 - 0.84 (m, 3H)
10.3		[M-H] ⁺ : 467.4	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.31 (s, 2H), 6.53 (br d, <i>J</i> = 9.0 Hz, 1H), 4.07 - 4.03 (m, 2H), 3.84 (s, 4H), 3.65 - 3.54 (m, 1H), 3.38 (s, 1H), 1.95 - 1.45 (m, 7H), 1.35 - 1.21 (m, 2H), 1.14 - 1.07 (m, 3H).

Intermediate	Structure	m/z	¹ H NMR
10.4		[M-H] ⁺ : 441.3	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.31 (br s, 2H), 6.49 (br d, <i>J</i> = 9.0 Hz, 1H), 4.05 (d, <i>J</i> = 2.4 Hz, 2H), 3.85 (s, 4H), 3.61 - 3.48 (m, 1H), 3.38 (t, <i>J</i> = 2.4 Hz, 1H), 1.63 - 1.38 (m, 4H), 0.97 - 0.82 (m, 6H).

A11. Synthesis of Intermediate 11

Scheme A11.

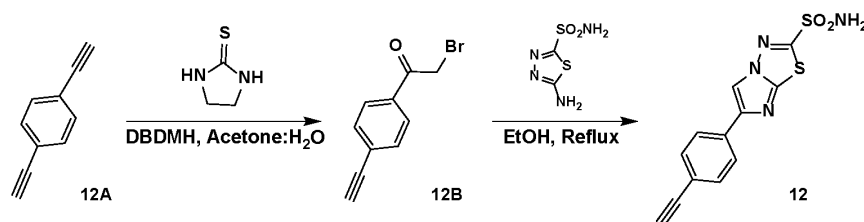


1.32 Preparation of intermediate 11

[00596] To a solution of **compound 11A** (1.7 g, 4.95 mmol, 1 *eq*) in DMSO (17 mL) was added TEA (1.38 mL, 9.90 mmol, 2 *eq*) and cyclooctanamine (1.26 g, 9.90 mmol, 2 *eq*). The mixture was stirred at 60°C for 16h, diluted with H₂O (40 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layer was dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **intermediate 11** (1.4 g, 63% yield) as a yellow oil; LCMS [M-H]⁺: 449.4; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.10 (s, 2H), 6.38 - 6.25 (m, 1H), 4.11 (d, *J* = 2.4 Hz, 2H), 3.71 (br dd, *J* = 3.8, 7.8 Hz, 1H), 3.61 (t, *J* = 6.2 Hz, 2H), 3.38 (t, *J* = 2.4 Hz, 1H), 3.17 (t, *J* = 6.2 Hz, 2H), 1.87 - 1.74 (m, 2H), 1.70 - 1.59 (m, 2H), 1.57 - 1.37 (m, 10H).

A12. Synthesis of Intermediate 12

Scheme A12.



1.33 Preparation of compound 12B

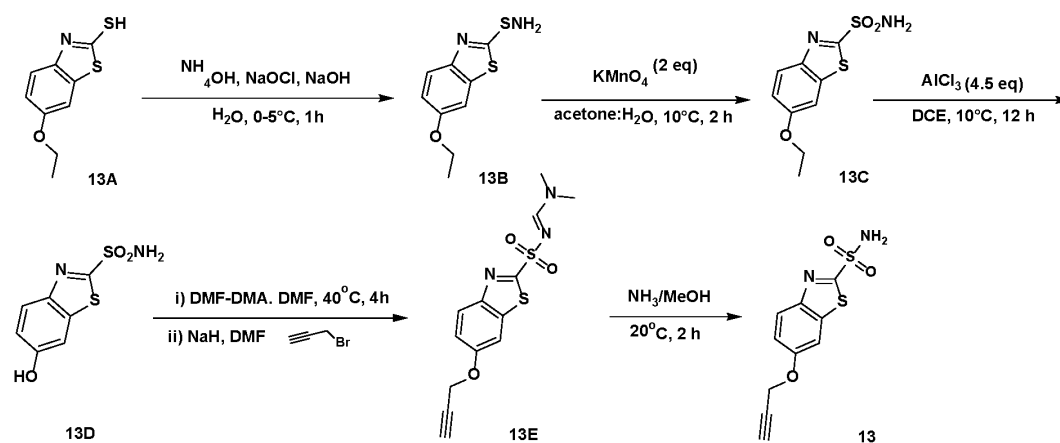
[00597] To a solution of **compound 12A** (4.0 g, 31.7 mmol, 1 *eq*) in acetone (160 mL) and H₂O (2.8 mL) was added DBDMH (9.07 g, 31.7 mmol, 1 *eq*) and imidazolidine-2-thione (486 mg, 4.76 mmol, 0.15 *eq*) at 25 °C. The reaction was stirred at 45 °C for 12 h, filtered and the filtrate concentrated under reduced pressure. The residue was purified by silica gel chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 12B** (3.8 g, 54% yield) as yellow solid; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.96 (2 H, d, *J* = 8.44 Hz) 7.61 (2 H, d, *J* = 8.44 Hz) 4.44 (2 H, s) 3.30 (1 H, s).

1.34 Preparation of Intermediate 12

[00598] To a solution of **compound 12B** (1.9 g, 8.52 mmol, 1 *eq*) in EtOH (19 mL) was added 5-amino-1,3,4-thiadiazole-2-sulfonamide (1.53 g, 8.52 mmol, 1 *eq*) and the mixture stirred at 80 °C for 12 h. The procedure was repeated. The two batches were combined and filtered. The filter cake was collected and purified by *prep*-HPLC (column: Phenomenex Titank C18 Bulk 250*70mm 10u; mobile phase: [H₂O(0.1%TFA)-ACN]; gradient:25%-65% B over 20.0 min) to give **Intermediate 12** (2.0 g, 39% yield) as yellow solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.96 (s, 1H), 8.75 (s, 2H), 7.97 – 7.88 (m, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 4.25 (s, 1H).

A13. Synthesis of Intermediate 13

Scheme A13.



1.35 Preparation of compound 13B

[00599] To a solution of **compound 13A** (2.0 g, 9.47 mmol, 1 *eq*) and NaOH (398 mg, 9.94 mmol, 1.05 *eq*) in H₂O (24 mL) was added NH₃·H₂O (7.24 mL, 52.6 mmol, 28% purity, 5.6 *eq*) dropwise. NaClO (3.44 mL, 2.93 mmol, 5.3% purity) was added dropwise at 0°C and the resulting mixture stirred at 0-5 °C for 1 h. The mixture was filtered and the filter cake washed with H₂O (3 mL) to give crude **compound 13B** (2.78 g) as a white solid; LCMS [M+H]⁺: 227.0; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.64 - 7.54 (m, 2H), 7.03 - 6.95 (m, 1H), 4.88 (s, 2H), 4.13 - 4.02 (m, 2H), 1.34 (t, *J* = 7.0 Hz, 3H).

1.36 Preparation of compound 13C

[00600] To a solution of **compound 13B** (2.78 g, 12.3 mmol, 1 *eq*) in acetone (60 mL) and H₂O (60 mL) was added a solution of KMnO₄ (3.88 g, 24.6 mmol, 2 *eq*) in H₂O (90 mL) dropwise at 0°C. The reaction mixture was stirred at 10 °C for 2h. The mixture was treated with activated carbon and 10 N NaOH (4 mL), stirred for 30 min, filtered, and washed with EtOAc (50 mL). To the filtrate was added H₂O (50 mL), the mixture extracted with EtOAc (3 × 50 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 13C** (2.1 g, 66% yield) as a white solid; LCMS [M+H]⁺: 259.0; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.24 (s, 2H), 8.03 (d, *J* = 9.1 Hz, 1H), 7.79 (d, *J* = 2.5 Hz, 1H), 7.29 - 7.19 (m, 1H), 4.20 - 4.06 (m, 2H), 1.38 (t, *J* = 7.0 Hz, 3H).

1.37 Preparation of compound 13D

[00601] To a mixture of **compound 13C** (2.5 g, 9.68 mmol, 1 *eq*) in DCE (39 mL) was added AlCl_3 (2.38 mL, 43.6 mmol, 4.5 *eq*) and the mixture stirred at 25°C for 12h under a nitrogen atmosphere. The reaction was quenched with H_2O (6 mL) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , petroleum ether:EtOAc) to give **compound 13D** (2.13 g, 96% yield) as a white solid; LCMS $[\text{M}+\text{H}]^+$: 230.9; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.22 (s, 1H), 8.18 (s, 2H), 7.95 (d, $J = 8.9$ Hz, 1H), 7.50 (d, $J = 2.4$ Hz, 1H), 7.14 - 7.07 (m, 1H).

1.38 Preparation of compound 13E

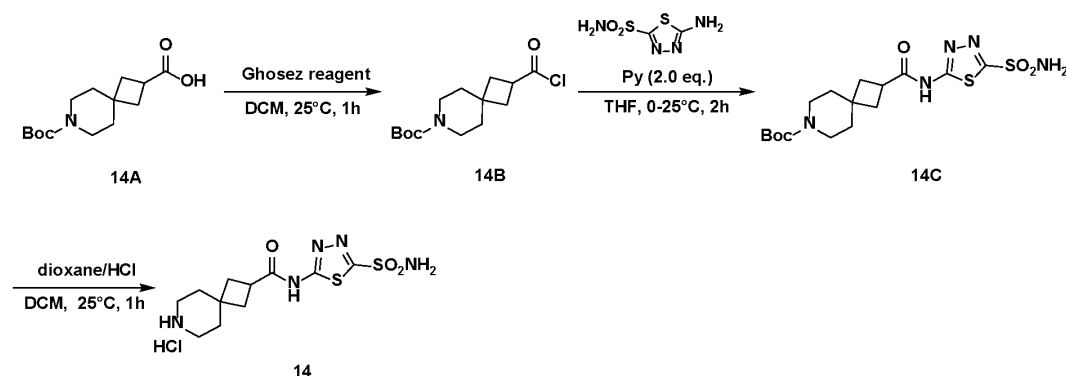
[00602] To a solution of **compound 13D** (0.5 g, 2.17 mmol, 1 *eq*) in DMF (5 mL) was added **DMF-DMA** (1.91 mL, 14.4 mmol) at 20°C. The mixture was stirred at 40°C for 4 h. The mixture was concentrated, the residue dissolved in DMF (5 mL), NaH (130 mg, 3.26 mmol, 60% purity, 1.50 *eq*) added at 0°C and the mixture stirred at 0°C for 0.5 h. 3-Bromoprop-1-yne (373 μL , 3.46 mmol, 1.59 *eq*) in DMF (0.5 mL) was added at 0°C, the mixture stirred at 20°C for 2h and the residue poured into a mixture of water (5 mL) and EtOAc (5 mL). The mixture was filtered, the filter cake collected, dissolved in DCM (10 mL), and washed with saturated aqueous NaHCO_3 (3×8 mL). The residue was purified by column chromatography (SiO_2 , DCM/MeOH) to give **compound 13E** (240 mg, 34% yield) as a brown solid; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.37 (s, 1 H), 8.06 (br d, $J=9.0$ Hz, 1 H), 7.74 - 7.88 (m, 1 H), 7.28 (br dd, $J=9.01, 2.00$ Hz, 1 H), 4.92 (br d, $J=1.75$ Hz, 2 H), 3.63 (s, 1 H), 3.24 (s, 3 H), 2.99 (s, 3 H).

1.39 Preparation of Intermediate 13

[00603] To a solution of **compound 13E** (0.24 g, 742 μmol , 1 *eq*) in NH_3/MeOH (10 mL) was stirred at 20°C for 2 h. The mixture was adjusted to pH = 2 with conc. HCl and concentrated under reduced pressure. The solid was triturated with ice-water (5 mL), filtered and the filter cake was concentrated to give **Intermediate 13** (0.16 g, 80% yield) as a yellow solid; LCMS $[\text{M}+\text{H}]^+$: 269.0.

A14. Synthesis of Intermediate 14

Scheme A14.



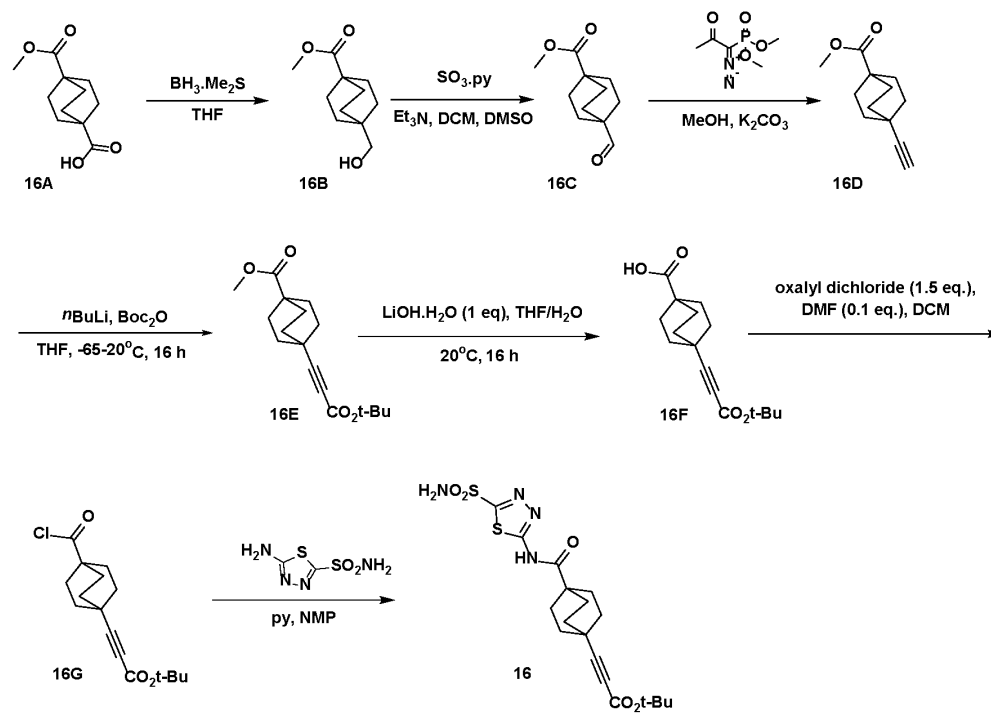
1.40 Preparation of compound 14B

[00604] To a solution of **compound 14A** (20 g, 74.3 mmol, 1 *eq*) in DCM (300 mL) was added Ghosez reagent (11.8 mL, 89.1 mmol, 1.2 *eq*), and the mixture stirred at 25 °C for 1h. The reaction mixture was concentrated under reduced pressure to give **compound 14B** (21 g, 98% yield) as a yellow oil that was used directly in the next reaction.

(m, 1H), 9.49 (br s, 2H), 8.34 (s, 2H), 8.10 (br d, $J = 8.8$ Hz, 2H), 7.11 (br d, $J = 9.0$ Hz, 2H), 3.70 - 3.59 (m, 4H), 3.19 (br s, 4H).

A16. Synthesis of Intermediate 16

Scheme A16.



1.45 Preparation of compound 16B

[00609] Compound **16A** (20 g, 94.2 mmol, 1 eq) was taken up in THF (200 mL). The mixture degassed and purged with nitrogen 3 times, cooled to 0°C , 10 M borane methylsulfanylmethane (23.6 mL, 2.5 eq) added dropwise for 15 minutes. The reaction was stirred at 20°C for 2 h. The reaction mixture was quenched by addition of MeOH (200 mL) at 20°C and concentrated under reduced pressure to give crude **Compound 16B** (18.7 g) as a colorless oil; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 4.35 (t, $J = 5.6$ Hz, 1H), 3.55 (s, 3H), 3.02 (d, $J = 5.4$ Hz, 2H), 1.75 - 1.57 (m, 6H), 1.42 - 1.27 (m, 6H).

1.46 Preparation of compound 16C

[00610] To a solution of **compound 16B** (18.7 g, 94.2 mmol, 1 eq) in DCM (160 mL) was added TEA (131 mL, 942 mmol, 10 eq) at 20°C . Pyridine;sulfur trioxide (45 g, 283 mmol, 3 eq) was dissolved in DMSO (100 mL), stirred for 15 minutes at 20°C then added to the reaction mixture at 0°C . The mixture was stirred at 30°C for 16 h, diluted with DCM (200 mL). The combined organic layers were washed with H_2O (3×200 mL) and brine (2×200 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give crude **compound 16C** (18.5 g) as a yellow oil; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.41 (s, 1H), 3.58 (s, 3H), 1.80 - 1.68 (m, 6H), 1.64 - 1.54 (m, 6H).

1.47 Preparation of compound 16D

[00611] To a solution of **compound 16C** (18.5 g, 94.2 mmol, 1 eq) in MeOH (185 mL) was added K_2CO_3 (26.0 g, 188 mmol, 2 eq) and 1-diazo-1-dimethoxyphosphoryl-propan-2-one (21.7 g, 113 mmol,

1.2 eq) at 0°C then the mixture stirred at 0°C for 2 h. The reaction mixture was poured into H₂O (150 mL) and extracted with MTBE (3 × 150 mL). The combined organic layers were washed with brine (150 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **compound 16D** (14 g, 77% yield) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.56 (s, 3H), 2.89 (s, 1H), 1.70 (s, 12H).

1.48 Preparation of compound 16E

[00612] **Compound 16D** (5.0 g, 26.0 mmol, 1 eq) was taken up in THF (500 mL). The suspension was degassed under reduced pressure and purged with nitrogen several times. The solution was cooled to below -65°C and 2.5 M n-BuLi (12.5 mL) was added dropwise over 30 min under a nitrogen atmosphere. The mixture was stirred at -65°C for 30 min then Boc₂O (6.27 mL, 27.3 mmol) was added at -65°C. The mixture was warmed to 20°C and stirred for 16 h. The mixture was cooled to 0°C then NH₄Cl (50 mL) was added and stirred at 0°C for 10 min. The mixture was stirred at 20°C for 30 min. The aqueous phase extracted with EtOAc (3 × 200 mL) and the combined organic phase was washed with brine (2 × 100 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **compound 16E** (2.4 g, 32% yield) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.57 (s, 3H), 1.80 - 1.66 (m, 12H), 1.41 (s, 9H).

1.49 Preparation of compound 16F

[00613] To a mixture of **compound 16E** (2.20 g, 7.52 mmol, 1 eq) in THF (20 mL) and H₂O (5 mL) was added LiOH.H₂O (316 mg, 7.52 mmol, 1 eq) at 20°C under a nitrogen atmosphere. The mixture was stirred at 20°C for 16 h. The reaction mixture was poured into water (50 mL) and the aqueous phase was extracted with EtOAc (150 mL). The aqueous phase adjusted with 1M HCl to pH = 4-5 and extracted with EtOAc (2 × 150 mL). The combined organic phase was washed with brine (2 × 100 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure to give **compound 16F** (1.5 g, 72% yield) as a white solid; LCMS [M-H]: 277.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.14 (br s, 1H), 1.72 (q, *J* = 9.6 Hz, 12H), 1.42 (s, 9H).

1.50 Preparation of compound 16G

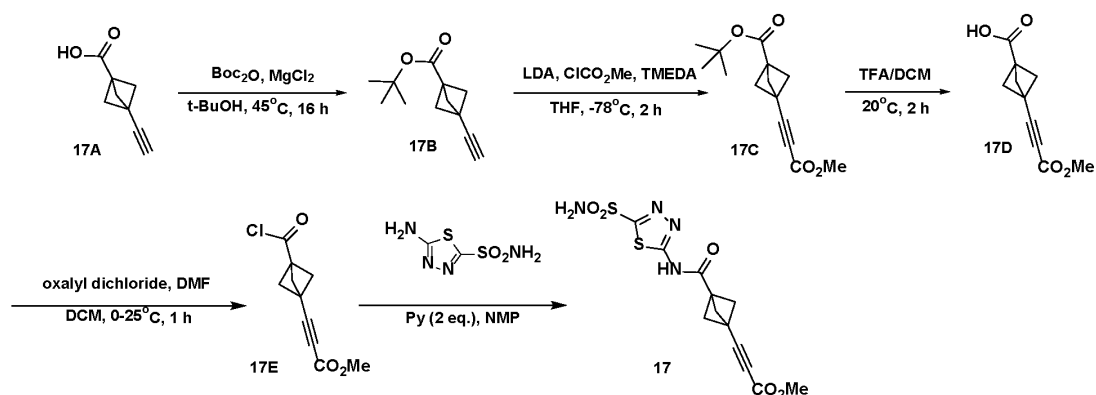
[00614] To a mixture of **compound 16F** (650 mg, 2.34 mmol, 1 eq) in DCM (8 mL) was added oxalyl chloride (307 μL, 3.50 mmol, 1.5 eq) and DMF (18 μL, 234 μmol) at 20°C under a nitrogen atmosphere. The mixture was stirred at 20°C for 1 h and concentrated under reduced pressure to give crude **compound 16G** (1.39 g) as a white solid.

1.51 Preparation of Intermediate 16

[00615] To a mixture of 5-amino-1,3,4-thiadiazole-2-sulfonamide (838 mg, 2.32 mmol, 1 eq) in NMP (8 mL) was added pyridine (375 μL, 4.65 mmol) and **compound 16G** (690 mg, 2.32 mmol, 1 eq) dropwise over 30 min at 0°C under a nitrogen atmosphere. The mixture was stirred at 20°C for 16 h, H₂O (40 mL) added at 20°C, the mixture filtered and the filter cake dried under reduced pressure. The crude product was washed with MTBE (2 × 10 mL) to give crude **Intermediate 16** (2.3 g) as a light brown solid; LCMS [M+H]: 441.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.69 (br s, 1H), 8.30 (s, 2H), 1.91 - 1.74 (m, 12H), 1.49 - 1.33 (m, 9H).

A17. Synthesis of Intermediate 17

Scheme A17.



1.52 Preparation of compound 17B

[00616] To a solution of compound 17A (2.95 g, 21.7 mmol) in $t\text{-BuOH}$ (50 mL) was added MgCl_2 (89 μL , 2.17 mmol) and Boc_2O (5.97 mL, 26 mmol). The mixture was stirred at 45°C for 16 h, quenched by addition of NaHCO_3 (20 mL) at 25°C , the combined organic layers washed with DCM (60 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2 , Petroleum ether: EtOAc) to give compound 17B (5.0 g, 60% yield) as a white solid; ^1H NMR (400 MHz, CDCl_3) δ = 2.28 (s, 6H), 2.11 (s, 1H), 1.44 (s, 9H).

1.53 Preparation of compound 17C

[00617] 2M LDA (4.94 mL) was added slowly to a solution of compound 17B (1.0 g, 4.94 mmol) in THF (100 mL) and TMEDA (75 μL , 494 μmol) at -78°C and stirred at -78°C for 1 h. Methyl carbonochloridate (382 μL , 4.94 mmol) was added at -78°C and the mixture stirred at -78°C for 1 h. The reaction mixture was quenched by addition of NH_4Cl (100 mL) at 20°C for 30 min, and extracted with EtOAc (2×200 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2 , EtOAc :Petroleum ether) to give compound 17C (5.3 g, 86% yield) as a white solid; ^1H NMR (400 MHz, CDCl_3) δ 3.77 (s, 3 H) 2.34 (s, 6 H) 1.43 (s, 9 H).

1.54 Preparation of compound 17D

[00618] A solution of compound 17C (3.0 g, 12 mmol) in DCM (15 mL) and TFA (15 mL) was stirred at 20°C for 2 h. The reaction mixture was concentrated under reduced pressure to give crude compound 17D (4.4 g, TFA) as a white solid that was used without further purification; ^1H NMR (400 MHz, CDCl_3) δ 3.78 (s, 3 H) 2.44 (s, 6 H).

1.55 Preparation of compound 17E

[00619] To a solution of compound 17D (3.3 g, 17.0 mmol) in DCM (33 mL) was added DMF (131 μL , 1.70 mmol). Oxalyl dichloride (1.79 mL, 20.4 mmol) was added at 0°C , the mixture stirred at 25°C for 1 h and concentrated under reduced pressure to give compound 17E (3.6 g, 99% yield) as a white solid.

1.56 Preparation of intermediate 5

[00620] To a solution of **intermediate 17E** (3.1 g, 16.9 mmol) in NMP (60 mL) was added Py (2.73 mL, 34 mmol). 5-Amino-1,3,4-thiadiazole-2-sulfonamide (3.6 g, 16.9 mmol) in NMP (60 mL) was added to the mixture under N₂ at 0°C. The mixture was stirred at 25°C for 1h, the crude product triturated with H₂O at 25°C for 15 min and filtered. The filter cake was concentrated under reduced pressure to give **intermediate 17** (4.0 g, 66% yield) as a white solid; LCMS [M+H]⁺ = 357.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.24 (br s, 1H), 8.34 (s, 2H), 3.71 (s, 3H), 2.52 (s, 6H).

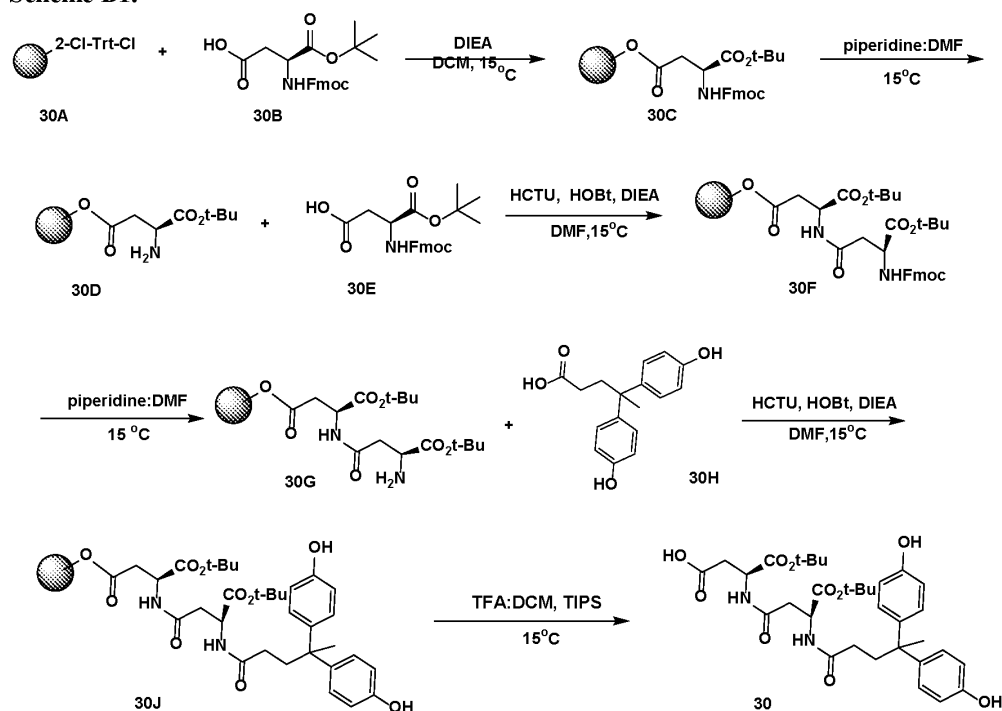
Intermediates in **table 6.4** were prepared according to literature procedures.

Table 6.4.

Compound	Structure
17.1	
17.2	
17.3	

B1. Synthesis of Intermediate 30

Scheme B1.



2.1 Synthesis of compound 30C

[00621] To a mixture of **2-Cl-Trt-Cl resin** (110 g, 110 mmol/g) in DCM (1000 mL) was added a solution of **compound 30B** (45.3 g, 110 mmol, 1 *eq*), DIEA (38.3 mL, 220 mmol, 2 *eq*) in DCM (500

mL) at 15°C. The mixture was shaken at 15°C for 16h under a nitrogen atmosphere. The reaction mixture was filtered, the filter cake washed with DCM (3 × 1000 mL), DMF (2 × 1000 mL), MeOH (3 × 1000 mL) and DMF (2 × 1000 mL), the resin dried with nitrogen to give **compound 30C** that was used directly in the next reaction.

2.2 Synthesis of compound 30D

[00622] A mixture of **compound 30C** in piperidine (200 mL) and DMF (800 mL) was shaken at 15°C for 10 min under a nitrogen atmosphere and the mixture filtered. The procedure was repeated four times, the cake washed with DCM (2 × 1000 mL) and DMF (2 × 1000 mL), the resin dried with nitrogen to give **compound 30D** that was used directly in the next reaction.

2.3 Synthesis of compound 30F

[00623] A mixture of **compound 30E** (61.7 g, 150 mmol, 1.5 eq), HCTU (62.1 g, 150 mmol, 1.5 eq), HOBT (20.3 g, 150 mmol, 1.5 eq) and DIEA (29.6 mL, 170 mmol, 1.7 eq) in DMF (1000 mL) was stirred at 15°C for 30 min. The above mixture was added to a solution of **Compound 30D** in DMF (1000 mL) and the mixture shaken at 15°C for 2 h. The mixture was filtered, the cake washed with DMF (1000 mL), DCM (3 × 1000 mL) and DMF (2 × 1000 mL), the resin dried with nitrogen to give **compound 30F** that was used directly in the next reaction.

2.4 Synthesis of compound 30G

[00624] A mixture of **compound 30F** in piperidine (200 mL) and DMF (800 mL) was shaken at 15°C for 10 min under a nitrogen atmosphere and the mixture filtered. This procedure was repeated four times, the cake washed with DCM (2 × 1000 mL) and DMF (2 × 1000 mL), the resin dried with nitrogen to give **compound 30G** that was used directly in the next reaction.

2.5 Synthesis of compound 30J

A mixture of **compound 30H** (43.0 g, 150 mmol, 1.5 eq), HCTU (62.1 g, 150 mmol, 1.5 eq), HOBT (20.3 g, 150 mmol, 1.5 eq), DIEA (29.6 mL, 1.7 eq) in DMF (1000 mL) was stirred at 15°C for 30 min. The mixture was added to a solution of **compound 30G** in DMF (1000 mL) and the mixture shaken at 15 °C for 2 h. The mixture was filtered, the cake washed with DMF (1000 mL), DCM (3 × 1000 mL) and DMF (2 × 1000 mL). The resin was dried with nitrogen to give **compound 30J** that was used directly in the next reaction.

2.6 Synthesis of compound 30

[00625] A solution of **compound 30J** in DCM (1000 mL), TFA (10 mL) and TIPS (10 mL) was shaken at 15°C for 10 min. This procedure was repeated three times to ensure completion of the cleavage. The resin was washed with THF (1000 mL), the mixture filtered, the combined organic layer washed with NaHCO₃ (34 g in 500 mL H₂O), the organic layer dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 30** (50 g) as a yellow solid; LCMS [M+H]⁺: 629.5.

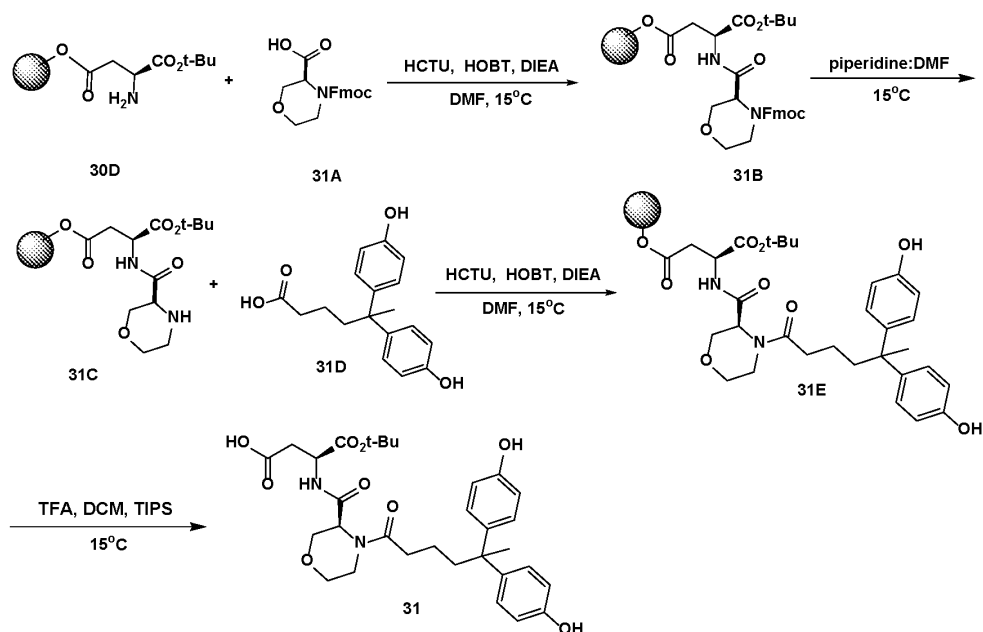
[00626] Compounds in **table 7.1** were prepared by procedures depicted in **Scheme B1**.

Table 7.1.

Intermediate	Structure	m/z
30.1		[M+H]: 472.4
30.2		[M+H]: 348.1
30.3		[M+H]: 362.2
30.4		[M+H]: 513.5
30.5		[M+H]: 761.4

B2. Synthesis of Intermediate 31

Scheme B2.



2.9 Synthesis of compound 31B

[00627] A mixture of **compound 31A** (8.59 g, 24.3 mmol, 1.5 *eq*), HOBT (3.28 g, 24.3 mmol, 1.5 *eq*), HCTU (10.1 g, 24.3 mmol, 1.5 *eq*) and DIEA (4.80 mL, 27.5 mmol, 1.7 *eq*) in DMF (50 mL) was stirred

at 15°C for 30 min. The mixture was added to a solution of **compound 30D** in DMF (50 mL), and the mixture shaken at 15°C for 2 h. The mixture was filtered and the cake washed with DMF (100 mL), DCM (3 × 100 mL) and DMF (2 × 100 mL). The resin was dried with nitrogen to give **compound 31B** which was used directly in the next reaction.

2.10 Synthesis of compound 31C

[00628] A mixture of **compound 31B** in piperidine (20 mL) and DMF (80 mL) was shaken at 15°C for 10 min under a nitrogen atmosphere and the mixture filtered. The procedure was repeated four times. The cake was washed with DCM (2 × 100 mL) and DMF (2 × 100 mL), the resin dried with nitrogen to give **compound 31C** which was used directly in the next reaction.

2.11 Synthesis of compound 31E

[00629] To a mixture of **compound 31C** (3.1 g, 5.35 mmol, 1 eq) and **compound 31D** (2.41 g, 8.03 mmol, 1.5 eq) in DMF (50 mL) was added DIEA (1.59 mL, 9.10 mmol, 1.7 eq), HOBt (1.09 g, 8.03 mmol, 1.5 eq) and HCTU (3.32 g, 8.03 mmol, 1.5 eq). The mixture was shaken at 25°C for 1 h. The mixture was filtered. The cake was washed with DMF (100 mL), DCM (3 × 100 mL) and DMF (2 × 100 mL). The resin dried with nitrogen to give **compound 31B** which was used directly in the next reaction.

2.12 Synthesis of compound 31

[00630] To a solution of **compound 31E** (4.6 g, 5.34 mmol, 1 eq) in DCM (100 mL) was added TFA (1 mL) and TIPS (1 mL). The reaction was shaken for 10 min at 15°C and the mixture filtered. The procedure was repeated three times. THF (100 mL) was added and shaken for 10 min at 15°C. The mixture was filtered, washed with NaHCO₃ (3.4 g in 50 mL H₂O), the organic layer dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 31** (1.4 g, 45% yield) as a yellow solid; LCMS [M+H]⁺: 585.3.

[00631] Compounds in **table 7.2** were prepared by procedures depicted in **scheme B2**.

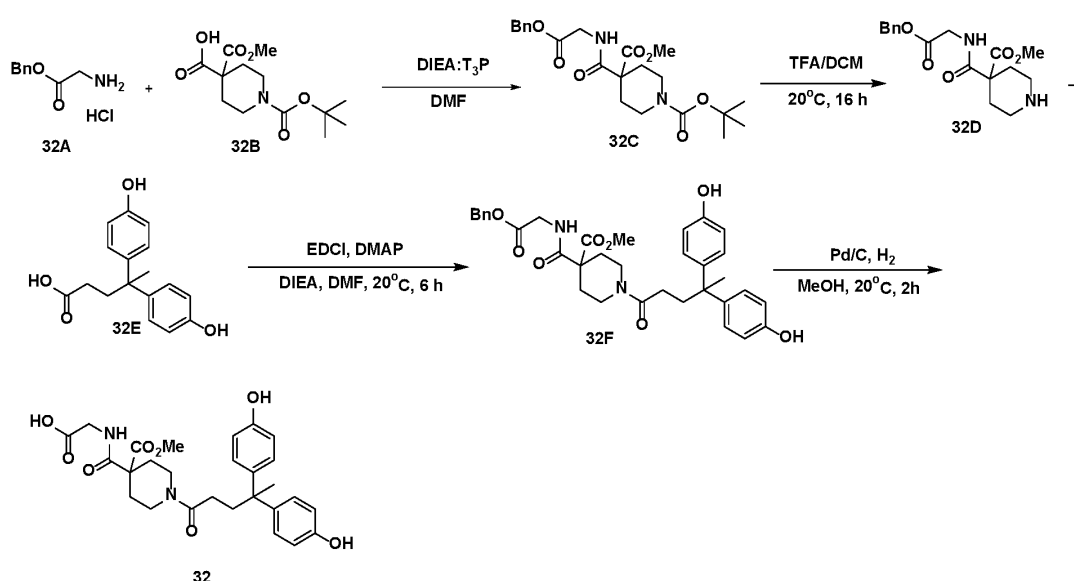
Table 7.2.

Compound	Structure	m/z
31.1		[M+H] ⁺ : 583.4
31.2		[M+H] ⁺ : 598.5
31.3		[M+H] ⁺ : 613.4

Compound	Structure	m/z
31.4		[M+Na] ⁺ : 631.4
31.5		[M+H] ⁺ : 670.4

B3. Synthesis of Intermediate 32

Scheme B3.



2.13 Synthesis of compound 32C

[00632] To a mixture of **compound 32B** (2.59 g, 9.02 mmol, 1.0 *eq*) and **compound 32A** (2.0 g, 9.92 mmol, 1.1 *eq*) in DMF (30 mL) was added DIPEA (7.85 mL, 45.1 mmol, 5 *eq*) and T₃P (10.7 mL, 18.0 mmol, 50% purity, 2 *eq*) at 20°C under a nitrogen atmosphere. The mixture was stirred at 20°C for 2 h. The reaction mixture was poured into water (60 mL). The aqueous phase was extracted with EtOAc (3 × 80 mL). The combined organic phase was washed with brine (2 × 80 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (petroleum ether:EtOAc) to give **compound 32C** (4.0 g, 57% yield, 56% purity) as a colorless oil.

2.14 Synthesis of compound 32D

[00633] To a mixture of **compound 32C** (3.30 g, 7.60 mmol, 1 *eq*) in DCM (30 mL) was added TFA (10 mL) in one portion at 20°C under a nitrogen atmosphere. The mixture was stirred at 20°C for 16 h and concentrated under reduced pressure to give crude **compound 32D** (2.5 g) as colorless oil; ¹H NMR

(400 MHz, METHANOL- d_4) δ 7.47 - 7.27 (m, 5H), 5.17 (s, 2H), 3.99 (s, 2H), 3.74 (s, 3H), 3.28 - 3.14 (m, 4H), 2.46 - 2.24 (m, 4H).

2.15 Synthesis of compound 32F

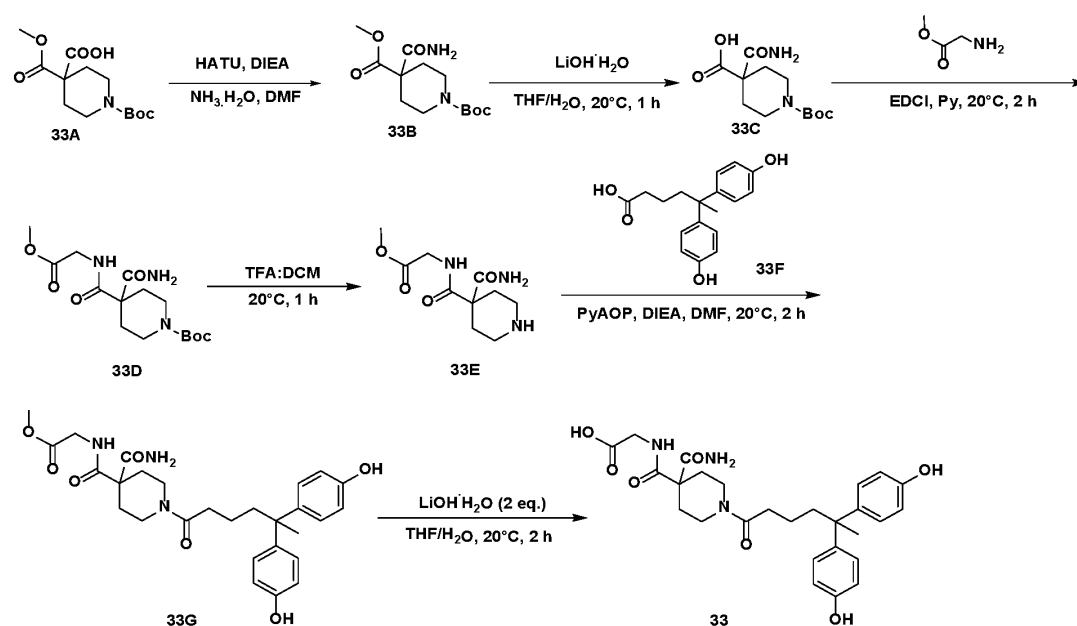
[00634] To a mixture of **compound 32D** (2.4 g, 7.18 mmol, 1 *eq*) and **compound 32E** (2.06 g, 7.18 mmol, 1 *eq*) in DCM (5 mL) was added DMAP (175 mg, 1.44 mmol, 0.2 *eq*), DIEA (5.00 mL, 28.7 mmol, 4 *eq*) and EDCI (2.06 g, 10.8 mmol, 1.5 *eq*) in one portion at 20°C under a nitrogen atmosphere. The mixture was stirred at 20°C for 6 h. The reaction mixture was poured into water (80 mL), the aqueous phase extracted with DCM (3 $\times$ 120 mL), the combined organic phase washed with brine (2 $\times$ 80 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2 , Petroleum ether:EtOAc) to give **compound 32F** (3.6 g, 69% yield, 83% purity) as a white solid; ^1H NMR (400 MHz, METHANOL- d_4) δ 7.40 - 7.19 (m, 5H), 7.08 - 6.97 (m, J = 8.6 Hz, 4H), 6.70 (d, J = 8.8 Hz, 4H), 5.13 (s, 2H), 4.58 (s, 2H), 3.95 (s, 2H), 3.68 (s, 3H), 3.55 - 3.40 (m, 2H), 3.11 (q, J = 4.8 Hz, 2H), 2.33 - 2.24 (m, 2H), 2.14 - 2.04 (m, 2H), 1.96 (br d, J = 4.4 Hz, 2H), 1.55 (s, 3H).

2.16 Synthesis of compound 32

[00635] To a solution of **compound 32F** (3.2 g, 5.31 mmol, 1 *eq*) in MeOH (35 mL) was added Pd/C (600 mg, 5.31 mmol, 10% purity, 1 *eq*) under a nitrogen atmosphere. The suspension was degassed under vacuum and purged with hydrogen 3 times. The mixture was stirred under a hydrogen atmosphere (15 psi) at 20°C for 2h. The reaction mixture was filtered and the filtrate concentrated under reduced pressure to give **intermediate 32** (2.6 g, 96% yield) as a white solid; ^1H NMR (400 MHz, METHANOL- d_4) δ 7.02 (d, J = 8.6 Hz, 4H), 6.69 (d, J = 8.4 Hz, 4H), 3.92 - 3.83 (m, 2H), 3.80 - 3.67 (m, 4H), 3.40 - 3.34 (m, 3H), 3.24 - 3.10 (m, 1H), 2.39 - 2.18 (m, 2H), 2.18 - 1.97 (m, 6H).

B4. Synthesis of Intermediate 33

Scheme B4.



2.17 Synthesis of compound 33B

[00636] To a solution of **compound 33A** (60 g, 209 mmol, 1 *eq*) in DMF (500 mL) was added HATU (83 g, 219 mmol, 1.1 *eq*) and DIEA (109 mL, 627 mmol, 3 *eq*). The mixture was stirred at 20°C for 0.5 h, NH₃·H₂O (34.5 mL, 251 mmol, 1.2 *eq*) added at 20°C and stirred at 20°C for 1 h. The reaction mixture was extracted with EtOAc (4 × 500 mL). The combined organic layers were washed with (3 × 200 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM:MeOH) to give **compound 33B** (60 g, 92% yield) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.45 - 7.14 (m, 2H), 3.65 (s, 3H), 3.52 - 3.39 (m, 2H), 3.10 (br s, 2H), 1.98 - 1.80 (m, 4H), 1.48 - 1.29 (m, 9H).

2.18 Synthesis of compound 33C

[00637] To a solution of **compound 33B** (50 g, 175 mmol, 1 *eq*) in THF (300 mL) and H₂O (100 mL) was added LiOH·H₂O (14.7 g, 349 mmol, 2 *eq*) at 20°C. The mixture was stirred at 20°C for 1h and concentrated under reduced pressure to remove organics. 1N HCl was added to adjust reaction mixture to pH=2-3, filtered and concentrated under reduced pressure to give crude **compound 33C** (57 g) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.91 - 12.68 (m, 1H), 7.19 (s, 2H), 3.40 (ddd, *J* = 4.0, 6.2, 13.4 Hz, 2H), 3.15 (br d, *J* = 8.8 Hz, 2H), 1.96 - 1.78 (m, 4H), 1.38 (s, 9H).

2.19 Synthesis of compound 33D

[00638] To a solution of **compound 33C** (55 g, 101 mmol, 1 *eq*) and methyl glycinate (27.9 g, 111 mmol, 1.1 *eq*) in pyridine (400 mL) was added EDCI (46.5 g, 121 mmol, 1.2 *eq*) at 20°C. The mixture was stirred at 20°C for 2h and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM:MeOH) to give crude **compound 33D** (66.5 g) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.13 (br t, *J* = 5.6 Hz, 1H), 7.30 - 6.99 (m, 2H), 3.82 (br d, *J* = 5.5 Hz, 2H), 3.62 (s, 3H), 3.50 - 3.37 (m, 2H), 3.16 (br s, 2H), 2.08 - 1.91 (m, 2H), 1.88 - 1.73 (m, 2H), 1.39 (s, 9H).

2.20 Synthesis of compound 33E

[00639] To a solution of **compound 33D** (60 g, 175 mmol, 1 *eq*) in DCM (300 mL) was added TFA (100 mL) at 20°C. The mixture was stirred at 20°C for 1h and concentrated under reduced pressure. The crude product was triturated with THF at 20°C for 10 min to give **compound 33E** (53 g, 82% yield, TFA) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.51 - 8.37 (m, 2H), 7.52 - 7.11 (m, 2H), 3.85 (br d, *J* = 5.8 Hz, 2H), 3.64 (s, 3H), 3.11 (br s, 2H), 3.00 (br s, 2H), 2.24 (br d, *J* = 13.6 Hz, 2H), 2.11 - 1.99 (m, 2H).

2.21 Synthesis of compound 33F

[00640] To a solution of 5-oxohexanoic acid (92 mL, 768 mmol, 1 *eq*) in H₂O (24.9 mL, 1.38 mol, 1.8 *eq*) was added phenol (135 mL, 1.54 mol, 2 *eq*), the mixture cooled to 0°C, H₂SO₄ (73.7 mL, 1.38 mol, 1.8 *eq*) was added dropwise for 15 min at 0°C, the reaction stirred at 50°C for 96 h, poured into water (2000 mL) and stirred for 10 minutes. The aqueous phase was extracted with EtOAc (3 × 2000 mL). The combined organic phase was washed with water (6 × 1000 mL), combined aqueous phase extracted with ethyl acetate (6 × 1000 mL), organics dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/EtOAc) and further purified

by *prep*-HPLC (column: Phenomenex Titank C18 Bulk 250*150mm 10u; mobile phase: [H₂O (10mM NH₄HCO₃)-ACN]; gradient: 1%-25% B over 20.0 min) to give **compound 33F** (128 g, 18% yield) as a white solid; LCMS [M-H]: 299.0; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.95 (br s, 1H), 9.13 (br s, 2H), 6.94 (d, *J* = 8.6 Hz, 4H), 6.64 (d, *J* = 8.6 Hz, 4H), 2.16 (br t, *J* = 7.4 Hz, 2H), 2.03 - 1.85 (m, 2H), 1.48 (s, 3H), 1.35 - 1.16 (m, 2H).

2.22 Synthesis of compound 33G

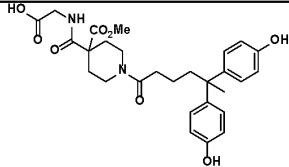
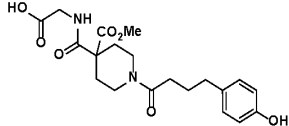
[00641] To a solution of **compound 33E** (40 g, 112 mmol, 1 *eq*, TFA) and **compound 33F** (33.6 g, 112 mmol, 1 *eq*) in DMF (300 mL) was added DIEA (58.5 mL, 336 mmol, 3 *eq*) and PYAOP (61.3 g, 118 mmol, 1.1 *eq*) at 20°C. The mixture was stirred at 20°C for 2h, H₂O (600 mL) added and then the mixture extracted with EtOAc (3 × 300 mL). The combined organic layers were washed with brine (3 × 150 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM:MeOH) to give **compound 33G** (60 g, 89% yield, 87% purity) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.15 - 9.07 (m, 2H), 8.15 (t, *J* = 5.8 Hz, 1H), 7.26 - 7.04 (m, 2H), 6.97 - 6.89 (m, 4H), 6.63 (d, *J* = 8.6 Hz, 4H), 3.83 (d, *J* = 5.8 Hz, 2H), 3.62 (s, 3H), 3.47 - 3.39 (m, 1H), 3.29 - 3.22 (m, 1H), 3.17 (d, *J* = 5.3 Hz, 2H), 2.29 - 2.21 (m, 2H), 2.07 - 1.90 (m, 4H), 1.88 - 1.72 (m, 2H), 1.48 (s, 3H), 1.26 (d, *J* = 1.1 Hz, 2H).

2.23 Synthesis of intermediate 33

[00642] To a solution of **compound 33G** (40 g, 76.1 mmol, 1 *eq*) in THF (120 mL) and H₂O (40 mL) was added LiOH.H₂O (6.39 g, 152 mmol, 2 *eq*) at 20°C. The mixture was stirred at 20 °C for 2 h. LCMS showed **Compound 33G** was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove THF. The pH was adjusted to 2-3 with 1N HCl and concentrated under reduced pressure to give **intermediate 33** (36 g, 92% yield) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.07 - 13.19 (m, 1 H) 9.00 - 9.36 (m, 2 H) 8.09 (br t, *J* = 5.6 Hz, 1 H) 7.12 - 7.25 (m, 2 H) 6.93 (d, *J* = 8.6 Hz, 4 H) 6.63 (d, *J* = 8.6 Hz, 4 H) 3.74 (br d, *J* = 5.75 Hz, 2 H) 3.57 - 3.66 (m, 1 H) 3.45 (br s, 1 H) 3.19 - 3.29 (m, 2 H) 2.24 (br t, *J* = 7.2 Hz, 2 H) 1.89 - 2.06 (m, 4 H) 1.74 - 1.87 (m, 2 H) 1.47 (s, 3 H) 1.17 - 1.30 (m, 2 H).

[00643] Compounds in **table 7.3** were prepared by procedures depicted in **scheme B4**.

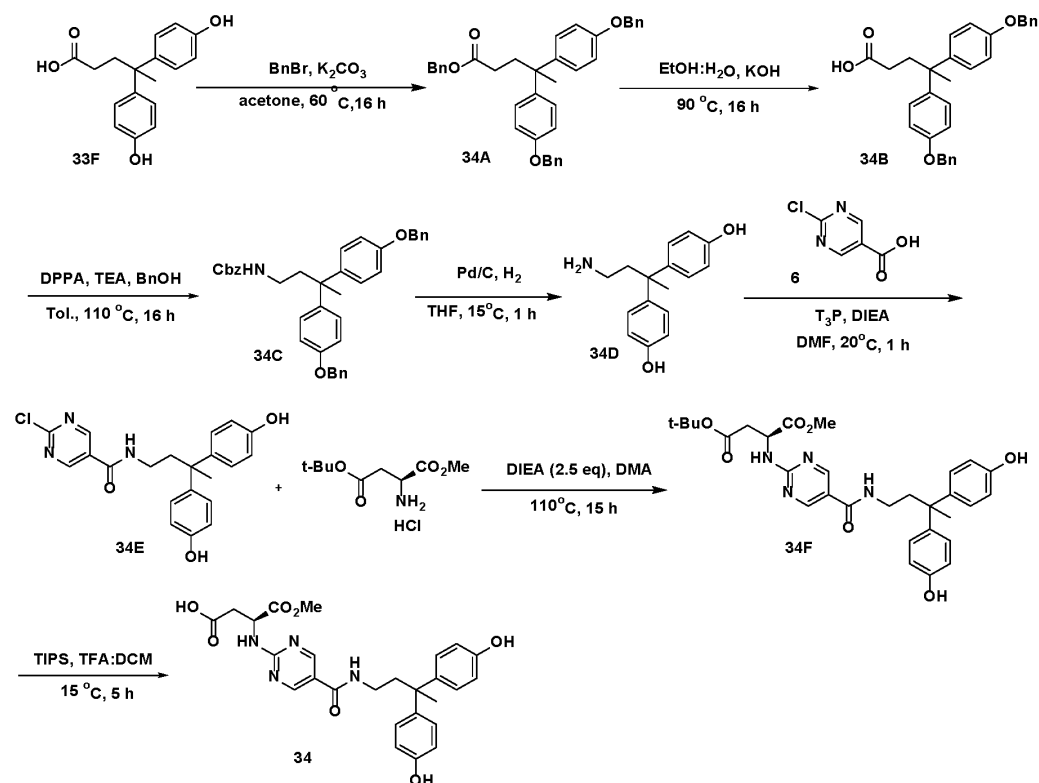
Table 7.3.

Compound	Structure	m/z
33.1		[M+H]: 527.2
33.2		[M+H]: 407.3

Compound	Structure	m/z
33.3		[M+H] ⁺ : 383.2
33.4		[M+H] ⁺ : 494.2
33.5		[M+H] ⁺ : 526.3
33.6		[M+H] ⁺ : 421.3

B5. Synthesis of Intermediate 34

Scheme B5.



2.24 Synthesis of compound 34A

[00644] To a solution of **compound 33F** (15.0 g, 52.4 mmol, 1 *eq*) in acetone (150 mL) was added K₂CO₃ (43.4 g, 314 mmol, 6 *eq*) and bromomethylbenzene (37.3 mL, 314 mmol, 6 *eq*). The

mixture was stirred at 60 °C for 16h. Additional bromomethylbenzene (37.3 mL, 314 mmol, 6 *eq*) was added and the mixture stirred at 60 °C for 14 h. The reaction mixture was quenched by addition of H₂O (40 mL) at 15°C, diluted with H₂O (50 mL) and extracted with EtOAc (2 × 120 mL). The combined organic layers were washed with brine (100 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 34A** (18.1 g, 62%) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.48 - 7.27 (m, 15H), 7.07 (d, *J* = 8.9 Hz, 4H), 6.92 (d, *J* = 8.8 Hz, 4H), 5.08 - 5.00 (m, 6H), 2.37 - 2.29 (m, 2H), 2.15 - 2.05 (m, 2H), 1.51 (s, 3H).

2.25 Synthesis of compound 34B

[00645] To a solution of **compound 34A** (17 g, 31 mmol, 1 *eq*) in H₂O (40 mL) was added KOH (9.42 g, 168 mmol, 5.5 *eq*) and EtOH (120 mL). The mixture was stirred at 90 °C for 16 h. The reaction mixture was diluted with MTBE (150 mL) and extracted with MTBE (2 × 40 mL). To the mixture was added aqueous citric acid solution until the reaction mixture pH = 4. The combined organic layers were washed with brine (150 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure to give **compound 34B** (14.3 g, 100% yield) as a colorless oil; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.49 - 7.30 (m, 9H), 7.14 - 7.04 (m, 4H), 6.91 (d, *J* = 8.8 Hz, 4H), 5.09 - 5.02 (m, 4H), 3.10 - 3.05 (m, 1H), 2.29 - 2.21 (m, 2H), 2.02 (br s, 3H), 1.56 - 1.44 (m, 3H).

2.26 Synthesis of compound 34C

[00646] To a solution of **compound 34B** (13.3 g, 28.5 mmol, 1 *eq*) in toluene (10 mL) was added TEA (11.9 mL, 85.4 mmol, 3 *eq*), BnOH (8.9 mL, 85.4 mmol, 3 *eq*) and DPPA (6.17 mL, 28.5 mmol, 1 *eq*). The mixture was stirred at 110 °C for 15 h. The reaction mixture was extracted with MTBE (2 × 100 mL), washed with 1M NaOH (2 × 150 mL), 0.5 M HCl (200 mL), brine (150 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 34C** (10.5 g, 65%) as a colorless oil.

2.27 Synthesis of compound 34D

[00647] A suspension of **compound 34C** (4.7 g, 8.22 mmol, 1 *eq*) in THF (100 mL) was degassed under vacuum and purged with nitrogen three times. Then Pd/C (2.5 g, 8.22 mmol, 10% purity, 1 *eq*) was added slowly. The suspension was degassed and purged with hydrogen 3 times and the mixture was stirred at 15 °C for 4 h. The reaction mixture was filtered and the filtrate concentrated under reduced pressure to give crude **compound 34D** (4.8 g) as a pink solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.95 - 6.80 (m, 4H), 6.63 (br d, *J* = 8.5 Hz, 4H), 3.63 - 3.56 (m, 1H), 2.34 - 2.26 (m, 2H), 2.08 - 2.00 (m, 2H), 1.80 - 1.71 (m, 1H), 1.47 (s, 3H).

2.28 Synthesis of compound 34E

[00648] A suspension of **compound 34D** (4.3 g, 16.7 mmol, 1 *eq*), 2-chloropyrimidine-5-carboxylic acid (2.65 g, 16.7 mmol, 1 *eq*), DIEA (14.6 mL, 83.6 mmol, 5 *eq*) and DMF (40 mL) was degassed under reduced pressure and purged with nitrogen three times. Then T₃P (14.9 mL, 25.1 mmol, 50% purity, 1.5 *eq*) was added slowly and the mixture stirred at 15°C for 2 h. The reaction mixture was quenched by addition of H₂O (15 mL) at 20°C, diluted with H₂O (30 mL) and extracted with EtOAc (100 mL). The

combined organic layers were washed with brine (50 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **compound 34E** (3.33 g, 50% yield) as a colorless oil; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.20 - 9.15 (m, 2H), 9.05 (s, 2H), 8.75 (t, *J* = 5.3 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 4H), 6.66 (d, *J* = 8.7 Hz, 4H), 3.12 - 2.98 (m, 2H), 2.30 - 2.18 (m, 2H), 1.56 (s, 3H).

2.29 Synthesis of compound 34F

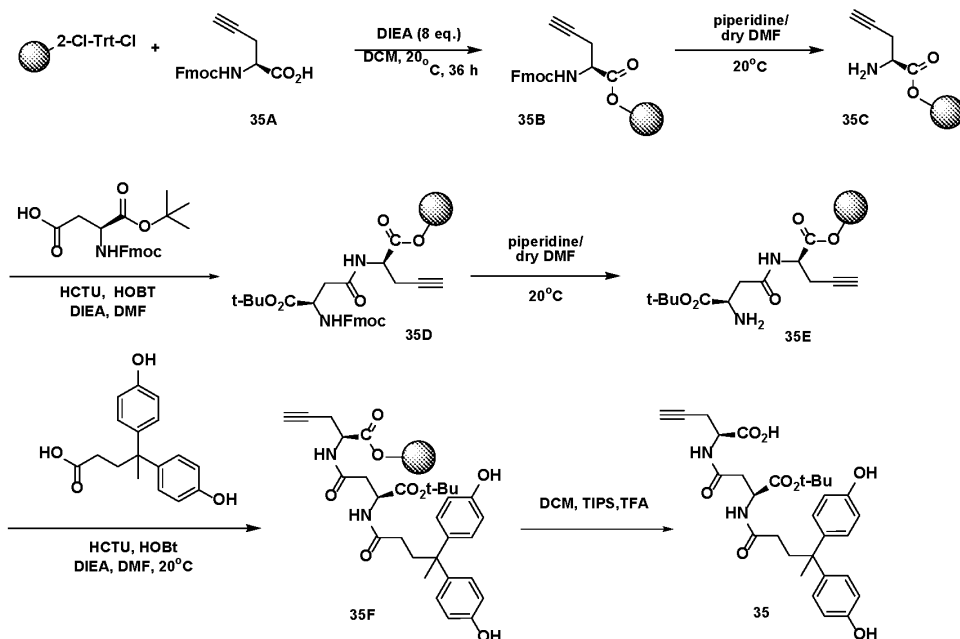
[00649] To a solution of **compound 34E** (2.93 g, 7.36 mmol, 1 *eq*) in DMA (30 mL) was added DIEA (3.21 mL, 18.4 mmol, 2.5 *eq*) and 4-(*tert*-butyl) 1-methyl L-aspartate HCl (1.94 g, 8.10 mmol, 1.1 *eq*). The mixture was stirred at 110°C for 16 h. The reaction mixture was quenched by addition of H₂O (5 mL) at 15°C. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **compound 34F** (2.88 g, 69%) as a yellow oil; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.15 (s, 2H), 8.68 (s, 2H), 8.25 (t, *J* = 5.3 Hz, 1H), 8.04 - 7.99 (m, 1H), 6.99 (d, *J* = 8.6 Hz, 4H), 6.66 (d, *J* = 8.6 Hz, 4H), 4.91 (dt, *J* = 6.1, 8.0 Hz, 1H), 3.61 (s, 3H), 3.01 (td, *J* = 5.4, 10.4 Hz, 2H), 2.85 - 2.77 (m, 1H), 2.75 - 2.68 (m, 1H), 2.24 - 2.15 (m, 2H), 1.55 (s, 3H), 1.36 (s, 9H).

2.30 Synthesis of compound 34

[00650] To a solution of **compound 34F** (2.5 g, 4.43 mmol, 1 *eq*) in DCM (18 mL) was added TIPS (18.2 mL, 88.6 mmol, 20 *eq*) and TFA (6.0 mL, 81.0 mmol). The mixture was stirred at 15°C for 5 h. The reaction mixture was concentrated under reduced pressure, washed with H₂O (2 × 25 mL), extracted with EtOAc (2 × 75 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure to give **compound 34** (2.4 g, crude) as a yellow solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.54 - 12.34 (m, 1H), 9.21 - 9.11 (m, 2H), 8.68 (br s, 2H), 8.25 (br s, 1H), 8.03 (br d, *J* = 8.0 Hz, 1H), 6.99 (br d, *J* = 8.4 Hz, 4H), 6.66 (br d, *J* = 8.3 Hz, 4H), 4.93 - 4.82 (m, 1H), 3.61 (s, 3H), 3.00 (br s, 2H), 2.89 - 2.69 (m, 2H), 2.25 - 2.15 (m, 2H), 1.55 (br s, 3H), 1.06 - 0.93 (m, 1H).

B6. Synthesis of Intermediate 35

Scheme B6



2.31 Synthesis of compound 35B

[00651] To a solution of **compound 35A** (10 g, 29.8 mmol, 1.0 *eq*) in DCM (100 mL) was added 2-Cl-Trt-Cl resin (9.34 g, 29.8 mmol, 1.0 *eq*), and DIEA (41.6 mL, 239 mmol, 8 *eq*). The mixture was stirred at 20°C for 36 hours under a nitrogen atmosphere. The reaction mixture was filtered, the cake washed with DCM (3 × 200 mL), DMF (2 × 200 mL), MeOH (3 × 200 mL) and DMF (200 mL), the resin dried with nitrogen to give **compound 35B** which was used directly in the next reaction.

2.32 Synthesis of compound 35C

[00652] A mixture of **compound 35B** (5.0 g, 14.9 mmol, 1.0 *eq*) in piperidine (20 mL) and DMF (100 mL) was shaken at 20°C for 10 minutes under a nitrogen atmosphere, and the mixture filtered. The procedure was repeated four times. The cake was washed with DCM (2 × 100 mL), DMF (2 × 100 mL), the resin dried with nitrogen to give **compound 35C** which was used directly in the next reaction.

2.33 Synthesis of compound 35D

[00653] To a solution of (*S*)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-(tert-butoxy)-4-oxobutanoic acid (9.22 g, 22.4 mmol, 1.5 *eq*) in DMF (50 mL) was added HCTU (9.27 g, 22.4 mmol, 1.5 *eq*), HOBT (3.03 g, 22.4 mmol, 1.5 *eq*) and DIEA (7.81 mL, 44.8 mmol, 3 *eq*). The mixture stirred at 20°C for 0.5 h. **Compound 35C** (1.69 g, 14.9 mmol, 1 *eq*) was added and the mixture stirred at 20°C for 1h under a nitrogen atmosphere. The mixture was filtered, the cake washed with DMF (3 × 100 mL), DCM (5 × 100 mL), and DMF (100 mL). The resin was dried with nitrogen to give **compound 35D** which was used directly in the next reaction.

2.34 Synthesis of compound 35E

[00654] A mixture of **compound 35D** (7.57 g, 14.9 mmol, 1.0 *eq*) in piperidine (20 mL) and DMF (100 mL) was shaken at 20°C for 10 minutes under a nitrogen atmosphere, and the mixture filtered. The procedure was repeated four times. The cake was washed with DCM (2 × 100 mL) and DMF (2 × 100

mL), the resin was dried with nitrogen to give **compound 35E** which was used directly in the next reaction.

2.35 Synthesis of compound 35F

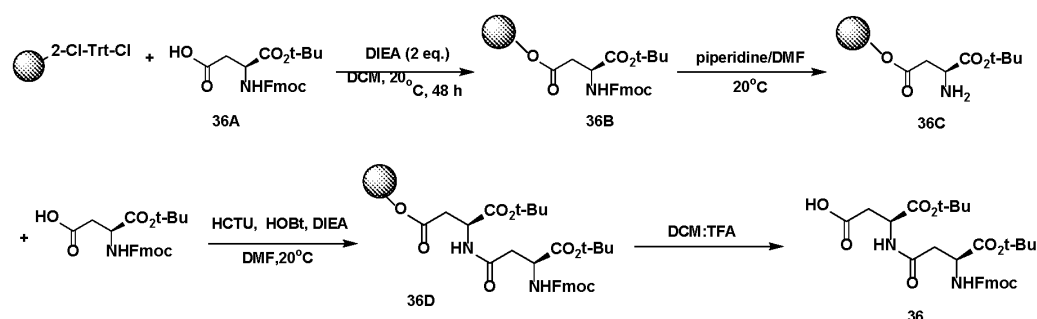
[00655] To a solution of 4,4-bis(4-hydroxyphenyl)pentanoic acid (4.08 g, 15.0 mmol, 1 *eq*) in DMF (50 mL) was added HCTU (5.89 g, 15 mmol, 1 *eq*), HOBT (1.92 mg, 15 mmol, 1 *eq*) and DIEA (2.98 mL, 17.09 mmol, 1.2 *eq*). To the mixture was added **compound 35F** (4.25 g, 14.95 mmol, 1 *eq*) and the mixture stirred at 20°C for 1h under a nitrogen atmosphere. The mixture was filtered, the cake washed with DMF (3 × 100 mL) and DCM (5 × 100 mL), the resin dried with nitrogen to give **compound 35F** which was used directly in the next reaction.

2.36 Synthesis of Intermediate 35

[00656] A solution of **compound 35F** (13.2 g, 23.8 mmol, 1 *eq*) in DCM (100 mL), TFA (1 mL) and TIPS (2.5 mL) was stirred at 20°C for 10 minutes. The procedure was repeated three times. THF (100 mL) was added and stirred at 20°C for 10 min. The mixture was filtered, washed with NaHCO₃ until the reaction mixture pH=7, the organic layer dried (Na₂SO₄), filtered and concentrated under reduced pressure to give crude **Intermediate 35** (3.24 g); LCMS [M+H]: 553.4; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.89 (br s, 1H), 9.15 (s, 2H), 8.28 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 4H), 6.64 (d, *J* = 8.6 Hz, 4H), 4.44 - 4.30 (m, 2H), 2.80 (t, *J* = 2.4 Hz, 1H), 2.54 (br t, *J* = 4.8 Hz, 4H), 2.21 - 2.12 (m, 2H), 1.91 - 1.80 (m, 2H), 1.46 (s, 3H), 1.36 (s, 9H).

B7. Synthesis of Intermediate 36

Scheme B7.



2.37 Preparation of compound 36B

[00657] To a solution of **compound 36A** (30 g, 72.9 mmol, 1.0 *eq*) in DCM (300 mL) was added 2-Cl-Trt-Cl resin (22.8 g, 72.9 mmol, 1 *eq*), and DIEA (25.4 mL, 146 mmol, 2 *eq*). The mixture was stirred at 20 °C for 48h under a nitrogen atmosphere. The reaction mixture was filtered and the cake washed with DCM (3 × 300 mL), DMF (2 × 300 mL), MeOH (3 × 300 mL) and DMF (300 mL). The resin was dried with nitrogen to give **compound 36B** which was used directly in the next reaction.

2.38 Preparation of compound 36C

[00658] A mixture of **compound 36B** (30 g, 72.9 mmol, 1.0 *eq*) in piperidine (20 mL) and DMF (100 mL) was shaken at 20°C for 10 min under a nitrogen atmosphere and the mixture filtered. A sample of

the filtrate (0.1 mL) was added to water (0.5 mL) and the mixture turned to a white suspension. This procedure was repeated four times until the mixture of the filtrate and water was a transparent liquid. The cake was then washed with DCM (2 × 300 mL), DMF (2 × 300 mL), the resin dried with nitrogen to give **compound 36C** which was used directly in the next reaction.

2.39 Preparation of compound 36D

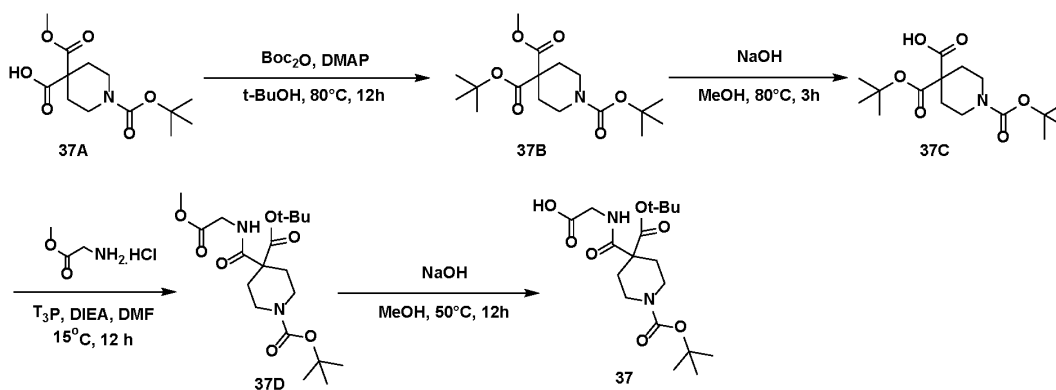
[00659] To a solution of (*S*)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-(tert-butoxy)-4-oxobutanoic acid (45.0 g, 109 mmol, 1.5 *eq*) in DMF (240 mL) was added HCTU (45 g, 109 mmol, 1.5 *eq*), HOBt (14.8 g, 109 mmol, 1.5 *eq*) and DIEA (25.4 mL, 146 mmol, 2 *eq*). The mixture was stirred at 20°C for 0.5 h, **compound 36C** (13.8 g, 72.9 mmol, 1 *eq*) added and the mixture stirred at 20°C for 1h under a nitrogen atmosphere. The mixture was filtered, the cake washed with DMF (3 × 300 mL), DCM (5 × 300 mL), and DMF (300 mL), the resin dried with nitrogen to give **compound 36D** which was used directly in the next reaction.

2.40 Preparation of Intermediate 36

[00660] To a solution of **compound 36D** (42.5 g, 72.9 mmol, 1.0 *eq*) in DCM (100 mL) and TFA (1 mL) was stirred at 20°C for 10 min. This procedure was repeated three times to ensure completion of the cleavage. DCM (300 mL) was added to the reaction mixture and the reaction stirred at 20°C for 10 min. The mixture was filtered, the filtrate diluted with MeOH and washed with saturated NaHCO₃ solution (pH = 7), the organic layer dried (Na₂SO₄), filtered and concentrated to give **Intermediate 36** (40 g) as a white solid; LCMS [M+H]⁺: 583.4; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.06 (br d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.47 (br d, *J* = 7.2 Hz, 2H), 7.27 (br d, *J* = 8.4 Hz, 1H), 7.22 - 7.15 (m, 2H), 7.13 - 7.06 (m, 2H), 4.29 - 4.20 (m, 1H), 4.12 - 3.93 (m, 4H), 2.40 - 2.30 (m, 4H), 1.14 (br d, *J* = 2.8 Hz, 18H).

B8. Synthesis of Compound 37

Scheme B8.



2.41 Synthesis of compound 37B

[00661] To a solution of **compound 37A** (10.0 g, 34.8 mmol, 1 *eq*) and Boc₂O (20 mL, 87.1 mmol, 2.50 *eq*) in *t*-BuOH (20 mL) was added DMAP (1.28 g, 10.4 mmol, 0.3 *eq*) at 15°C under a nitrogen atmosphere. The mixture was stirred at 80°C for 12 h then concentrated under reduced pressure and

purified by chromatography column (SiO₂, petroleum ether:EtOAc) to give **compound 37B** (11 g, 92% yield) as a white solid.

2.42 Synthesis of compound 37C

[00662] To a solution of **compound 37B** (11 g, 32.0 mmol, 1 *eq*) in MeOH (12 mL) was added 3M NaOH (10.7 mL, 1 *eq*) at 15°C under a nitrogen atmosphere. The mixture was stirred at 80°C for 3h and concentrated under reduced pressure. The aqueous solution was adjusted to pH=2 with 1M HCl (30 mL), filtered and the filter cake concentrated under reduced pressure to give **compound 37C** (10 g, 95% yield) as a white solid that was used directly in the next reaction; ¹H NMR (400 MHz, CHLOROFORM-d) δ 3.56 - 3.36 (m, 4H), 2.13 - 1.97 (m, 4H), 1.47 (d, *J* = 3.9 Hz, 18H).

2.43 Synthesis of compound 37D

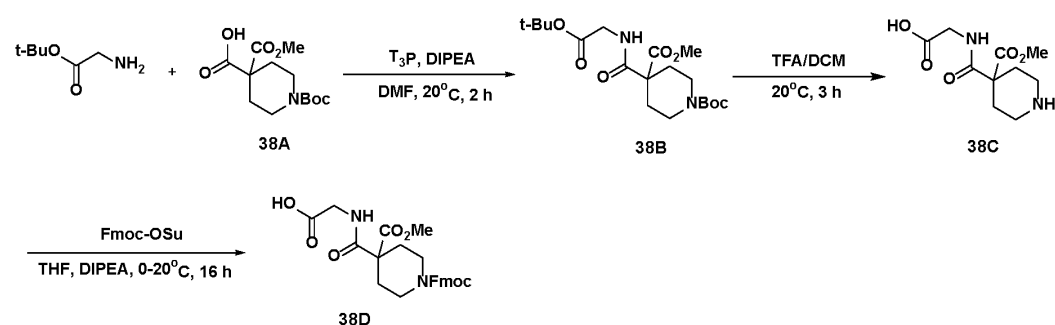
[00663] To a solution of **compound 37C** (8.8 g, 26.7 mmol, 1 *eq*) and methyl glycinate hydrochloride (8.39 g, 67 mmol, 2.5 *eq*, HCl) in DMF (9 mL) were added T₃P (31.8 mL, 53.4 mmol, 50% purity, 2 *eq*) and DIEA (27.9 mL, 160 mmol, 6 *eq*) at 15°C under a nitrogen atmosphere. The mixture was stirred at 15°C for 12h and concentrated under reduced pressure. Brine (60 mL) was added. The reaction was extracted with DCM (3 × 60 mL), the organics dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by chromatography column (SiO₂, petroleum ether:EtOAc) to give **compound 37D** (10 g, 93% yield) as a yellow oil.

2.44 Synthesis of compound 37

[00664] To a solution of **compound 37D** (9.0 g, 22.5 mmol, 1 *eq*) in MeOH (10 mL) was added 2M NaOH (16.9 mL, 1.5 *eq*) at 15°C under a nitrogen atmosphere. The mixture was stirred at 50°C for 12h and concentrated under reduced pressure to remove organics. The remaining aqueous solution was adjusted to pH=2 with 1M HCl (15 mL) and extracted with DCM (3 × 30 mL). The organic phase was dried (Na₂SO₄) and concentrated under reduced pressure to give **Intermediate 37** (8.5 g, 98% yield) as a white solid that was used directly in the next reaction.

B9. Synthesis of Intermediate 38

Scheme B9.



2.45 Preparation of compound 38B

[00665] To a solution of *tert*-butyl glycinate (2.74 g, 21 mmol, 1 *eq*) in DMF (60 mL) was added **compound 38A** (6.0 g, 21 mmol, 1 *eq*) and DIEA (18 mL, 104 mmol, 5 *eq*). T₃P (18.6 mL, 31.3 mmol, 50% purity, 1.5 *eq*) was added to the reaction mixture slowly and the reaction mixture stirred at 20°C for

2h. The reaction mixture was quenched by the addition of H₂O (20 mL) at 25°C, concentrated under reduced pressure, the residue diluted with H₂O (150 mL) and extracted with EtOAc (300 mL). The combined organic layers were washed with H₂O (100mL), brine (100 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 38B** (14 g, 84% yield) as an off-white solid; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 6.48 (br s, 1H), 3.91 (d, *J* = 4.8 Hz, 2H), 3.84 - 3.68 (m, 5H), 3.11 (br s, 2H), 2.25 - 2.10 (m, 2H), 2.10 - 1.94 (m, 2H), 1.49 - 1.42 (m, 18H).

2.46 Preparation of compound 38C

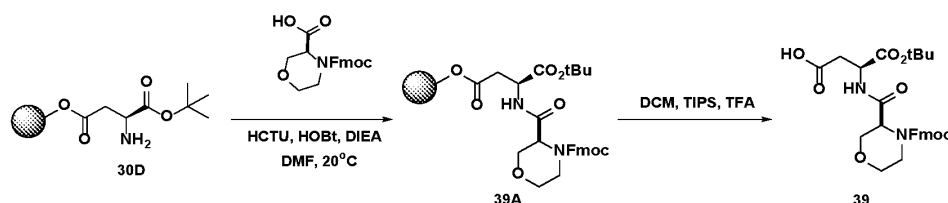
[00666] To a mixture of **compound 38B** (12 g, 30 mmol, 1 *eq*) in DCM (90 mL) was added TFA (30 mL) at 20°C under a nitrogen atmosphere. The mixture was stirred at 20°C for 3h and concentrated under reduced pressure to give **compound 38C** (8.5 g, crude) as a colorless oil; LCMS [*M*+*H*]: 245.0; ¹H NMR (400 MHz, METHANOL-*d*₄) δ 3.91 (s, 3H), 3.30 - 3.16 (m, 5H), 2.42 - 2.19 (m, 6H).

2.47 Preparation of intermediate 38D

[00667] To a mixture of **compound 38C** (8.5 g, 34.8 mmol, 1 *eq*) in THF (80 mL) was added DIEA (30 mL, 174 mmol, 5 *eq*) at 0°C under a nitrogen atmosphere. The mixture was stirred at 0°C for 15 min, then Fmoc-OSu (36.4 g, 108 mmol, 3.1 *eq*) added at 0°C. The mixture was stirred at 20°C for 16 h, poured into NaHCO₃ (20 mL) and the aqueous phase extracted with EtOAc (3 × 100 mL). The aqueous phase was adjust to pH=3-4 with 1M HCl, the mixture extracted with EtOAc (3 × 200 mL), the combined organic phase washed with brine (2 × 100 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure to give **intermediate 38** (12 g, 74% yield) as a white solid; LCMS [*M*+*H*]: 467.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.15 (t, *J* = 5.8 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.45 - 7.31 (m, 4H), 4.40 (br d, *J* = 6.0 Hz, 2H), 4.34 - 4.20 (m, 1H), 3.72 (d, *J* = 5.8 Hz, 2H), 3.66 (s, 3H), 3.35 (m, 2H), 3.23 (m, 2H), 1.95 - 1.72 (m, 4H).

B10. Synthesis of Intermediate 39

Scheme B10.



2.50 Preparation of compound 39A

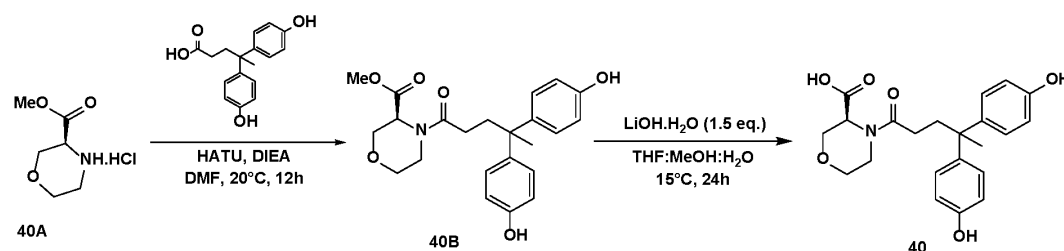
[00668] To a solution of (*S*)-4-(((9H-fluoren-9-yl)methoxy)carbonyl)morpholine-3-carboxylic acid (11.2 g, 31.6 mmol, 1.3 *eq*) in DMF (100 mL) was added HCTU (10.1 g, 24.3 mmol, 1 *eq*), HOBT (3.29 g, 24.3 mmol, 1 *eq*) and DIEA (6.35 mL, 36.5 mmol, 1.5 *eq*), and the mixture stirred at 20°C for 0.5 h. **Compound 30D** (4.6 g, 24.3 mmol, 1 *eq*) was added and the mixture stirred at 20°C for 1h under a nitrogen atmosphere. The mixture was filtered, and the cake washed with DMF (3 × 100 mL), DCM (5 × 100 mL) and DMF (100 mL), the resin dried with nitrogen to give **compound 39A** which was used directly in the next reaction.

2.51 Preparation of Intermediate 39

[00669] A solution of **compound 39A** in DCM (100 mL), TFA (1 mL) and TIPS (2.5 mL) was stirred at 15°C for 10 minutes. This procedure was repeated three times, THF (100 mL) added and stirred at 15°C for 10 min. The mixture was filtered, the filtrate diluted in MeOH, washed with NaHCO₃ (pH = 7), the organic layer dried (Na₂SO₄), filtered and concentrated to give crude **Intermediate 39** (8.7 g); LCMS [M+H]: 525.3.

B11. Synthesis of Intermediate 40

Scheme B11.



2.54 Synthesis of compound 40B

[00670] To a solution of **compound 40A** (2.0 g, 11.0 mmol, 1 *eq*) and 4,4-bis(4-hydroxyphenyl)pentanoic acid (3.2 g, 11.0 mmol, 1 *eq*) in DMF (30 mL) was added HATU (4.19 g, 11.0 mmol, 1 *eq*) and DIEA (9.59 mL, 55.1 mmol, 5 *eq*). The mixture was stirred at 20 °C for 12 h. The reaction mixture was diluted with EtOAc (45 mL), extracted with a saturated NH₄Cl solution (12 mL) and a saturated Na₂CO₃ solution (12 mL). The combined organic layers were washed with brine (9 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 40B** (4.5 g, 99% yield) as a white solid; LCMS [M+H]: 414.4.

2.55 Synthesis of Intermediate 40

[00671] A solution of **compound 40B** (4.5 g, 10.9 mmol, 1 *eq*) and LiOH.H₂O (457 mg, 10.9 mmol, 1 *eq*) in THF (15 mL), MeOH (15 mL) and H₂O (15 mL) was stirred at 15°C for 24 h. The reaction mixture was concentrated under reduced pressure to remove organics. The aqueous phase was adjusted to pH = 5 with 1 M HCl. Precipitated white solids were filtered and the cake dried under reduced pressure to give **Intermediate 40** (3.0 g, 69% yield) as a white solid; LCMS [M+H]: 400.4.

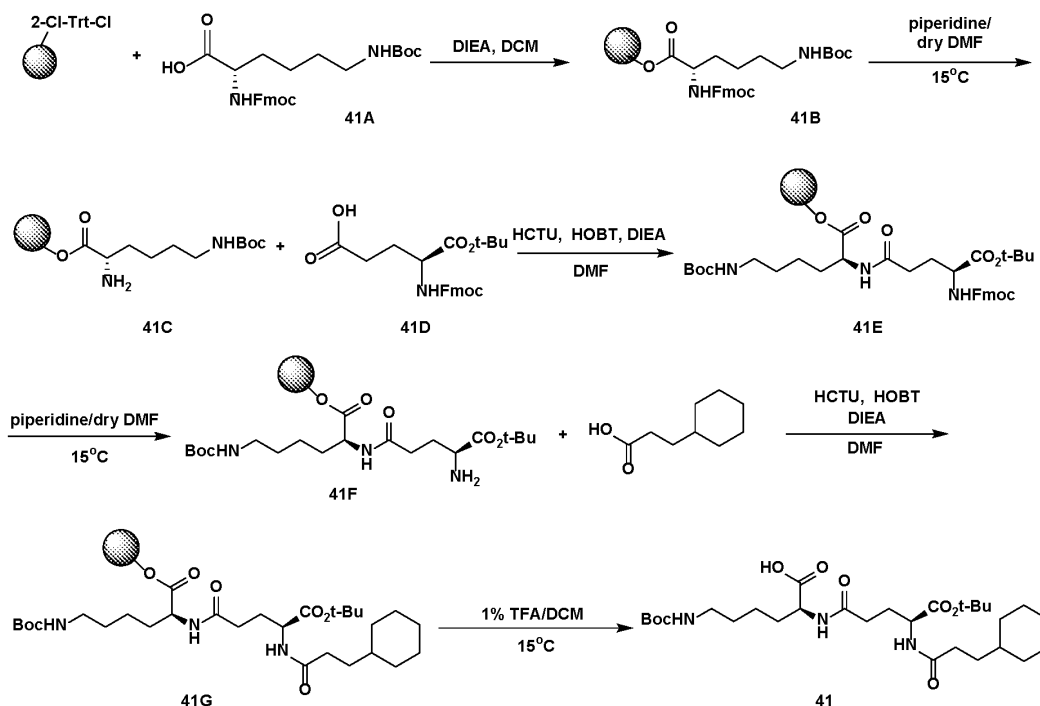
[00672] Compounds in **table 7.4** were prepared by procedures depicted in **scheme B11**.

Table 7.4.

Intermediate	Structure	m/z
40.1		[M+H]: 384.2

Intermediate	Structure	m/z
40.2		[M+H] ⁺ : 384.2
40.3		[M+H] ⁺ : 400.2
40.4		[M+H] ⁺ : 374.2
40.5		[M+H] ⁺ : 388.3
40.6		[M+H] ⁺ : 499.3
40.7		[M+H] ⁺ : 670.4

B12. Synthesis of Intermediate 41**Scheme B12.**



2.56 Synthesis of compound 41B

[00673] To a mixture of 2-Cl-Trt-Cl resin (4.46 g, 14.2 mmol, 1 *eq*) in DCM (70 mL) was added a solution of **compound 41A** (10 g, 21.3 mmol, 1.5 *eq*) and DIEA (4.96 mL, 28.5 mmol, 2 *eq*) in DCM (70 mL) at 25°C and the mixture shaken for 36h under a nitrogen atmosphere. The reaction mixture was filtered, the filter cake washed with DCM (3 × 100 mL), DMF (2 × 100 mL), MeOH (3 × 100 mL) and DMF (2 × 100 mL), the resin dried with nitrogen and used directly in the next reaction.

2.57 Synthesis of compound 41C

[00674] A mixture of **compound 41B** (20 g, 26.8 mmol, 1 *eq*) in piperidine (20 mL) and DMF (80 mL) was shaken at 25°C for 10 min under a nitrogen atmosphere, the mixture filtered and the procedure repeated four times. The cake was washed with DCM (2 × 100 mL) and DMF (2 × 100 mL), the resin dried with nitrogen and used directly in the next reaction.

2.58 Synthesis of compound 41E

[00675] To a mixture of **compound 41D** (8.54 g, 20.1 mmol, 1.5 *eq*) in DMF (100 mL) was added DIEA (3.96 mL, 22.8 mmol, 1.7 *eq*), HOBT (2.71 g, 20.1 mmol, 1.5 *eq*) and HCTU (8.30 g, 20.1 mmol, 1.5 *eq*) at 25°C. The mixture was stirred at 25°C for 30 min, added to a solution of **compound 41C** (7.0 g, 13.4 mmol, 1 *eq*) in DMF (100 mL), and the mixture shaken at 25°C for 1h. The mixture was filtered, the cake washed with DMF (100 mL), DCM (3 × 100 mL) and DMF (2 × 100 mL), the resin dried with nitrogen and used directly in the next reaction.

2.59 Synthesis of compound 41F

[00676] A mixture of **compound 41E** (14.1 g, 15.2 mmol, 1.0 *eq*) in piperidine (20 mL) and DMF (80 mL) was shaken at 15°C for 10 min under a nitrogen atmosphere, and the mixture filtered. The

procedure was repeated four times, the cake washed with DCM (2×100 mL) and DMF (2×100 mL), the resin dried with nitrogen and used directly in the next reaction.

2.60 Synthesis of compound 41G

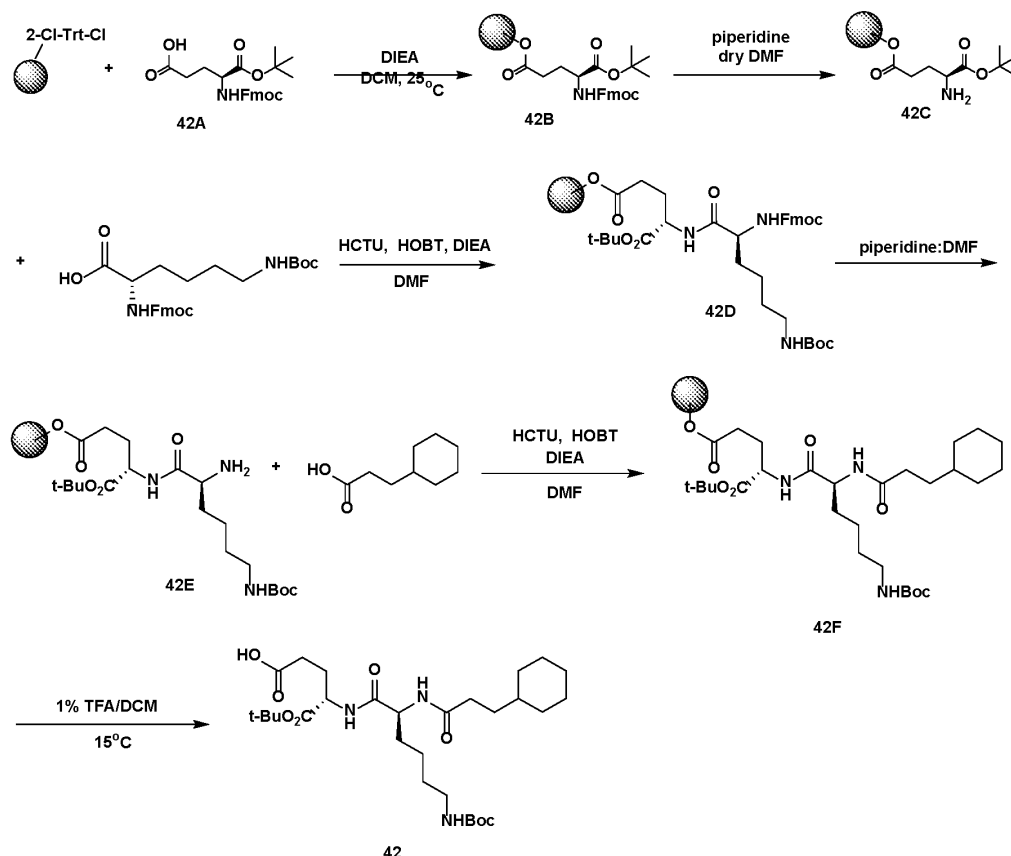
[00677] To a mixture of 3-cyclohexylpropanoic acid (3.81 mL, 22.2 mmol, 1.5 *eq*) in DMF (50 mL) was added DIEA (4.39 mL, 25.2 mmol, 1.7 *eq*), HOBt (3.00 g, 22.2 mmol, 1.5 *eq*) and HCTU (9.20 g, 22.2 mmol, 1.5 *eq*) at 25°C. The mixture was stirred at 25°C for 30 min, the mixture added to a solution of **compound 41F** (10.5 g, 14.8 mmol, 1 *eq*) in DMF (50 mL), and the reaction shaken at 25°C for 1h. The mixture was filtered, the cake washed with DMF (100 mL), DCM (3×100 mL) and DMF (2×100 mL), the resin dried with nitrogen and used directly in the next reaction.

2.61 Synthesis of Intermediate 41

[00678] To a solution of **compound 41G** (12 g, 14.18 mmol, 1 *eq*) in DCM (100 mL) was added TFA (1 mL) at 15°C for 10 min, and the mixture filtered. This procedure was repeated three times, THF (100 mL) was added, and the reaction shaken for 10 min at 15°C. The mixture was filtered, washed with aq. NaHCO_3 (5.6 g in 50 mL H_2O), the organic layer dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , petroleum ether:EtOAc) to give **Intermediate 41** (6.2 g, 77% yield) as a yellow solid; LCMS $[\text{M}+\text{H}]^+$: 570.5; ^1H NMR (400 MHz, CD_3OD) δ 4.39 - 4.32 (m, 1H), 4.25 (dd, $J = 4.9, 9.4$ Hz, 1H), 3.04 (t, $J = 6.7$ Hz, 2H), 2.37 - 2.31 (m, 2H), 2.30 - 2.21 (m, 2H), 2.20 - 2.05 (m, 1H), 1.95 - 1.81 (m, 2H), 1.80 - 1.62 (m, 6H), 1.61 - 1.49 (m, 3H), 1.47 (s, 9H), 1.43 (s, 9H), 1.40 - 1.35 (m, 1H), 1.34 - 1.23 (m, 4H), 1.23 - 1.13 (m, 2H), 0.98 - 0.86 (m, 2H).

B13. Synthesis of Intermediate 42

Scheme B13.



2.62 Synthesis of compound 42B

[00679] To a mixture of 2-Cl-Trt-Cl resin (9.82 g, 31.3 mmol, 1.0 *eq*) in DCM (70 mL) was added a solution of **compound 42A** (20.0 g, 47.0 mmol, 1.5 *eq*), DIEA (10.9 mL, 62.7 mmol, 2 *eq*) in DCM (70 mL) at 25°C, and the mixture shaken at 25°C for 36h under a nitrogen atmosphere. The reaction mixture was filtered, the filter cake washed with DCM (3 × 100 mL), DMF (2 × 100 mL), MeOH (3 × 100 mL) and DMF (2 × 100 mL), the resin dried with nitrogen and used directly in the next reaction.

2.63 Synthesis of compound 42C

[00680] A mixture of **compound 42B** (22 g, 31.3 mmol, 1.0 *eq*) in piperidine (20 mL) and DMF (80 mL) was shaken at 25°C for 10 min under a nitrogen atmosphere, and the mixture filtered. The procedure was repeated four times, the cake washed with DCM (2 × 100 mL) and DMF (2 × 100 mL), the resin dried with nitrogen and used directly in the next reaction.

2.64 Synthesis of compound 42D

[00681] To a mixture of N2-((9H-fluoren-9-yl)methoxy)carbonyl)-N6-(tert-butoxycarbonyl)-L-lysine (22.0 g, 46.9 mmol, 1.5 *eq*) in DMF (100 mL) was added DIEA (9.3 mL, 53.1 mmol, 1.7 *eq*), HOBT (6.33 g, 46.9 mmol, 1.5 *eq*) and HCTU (19.4 g, 46.9 mmol, 1.5 *eq*) at 25°C. The mixture was stirred at 25°C for 30 min. The mixture was added to a solution of **compound 42C** (15.0 g, 31.3 mmol, 1 *eq*) in DMF (100 mL), and the mixture was shaken at 25°C for 1 h. The mixture was filtered, the cake washed with

DMF (100 mL), DCM (3×100 mL) and DMF (2×100 mL), the resin dried with nitrogen and used directly in the next reaction.

2.65 Synthesis of compound 42E

[00682] A mixture of **compound 42D** (10.0 g, 10.8 mmol, 1.0 *eq*) in piperidine (20 mL) and DMF (80 mL) was shaken at 15°C for 10 min under a nitrogen atmosphere, and the mixture filtered. The procedure was repeated four times, the cake was washed with DCM (2×100 mL) and DMF (2×100 mL), the resin dried with nitrogen and used directly in the next reaction.

2.66 Synthesis of compound 42F

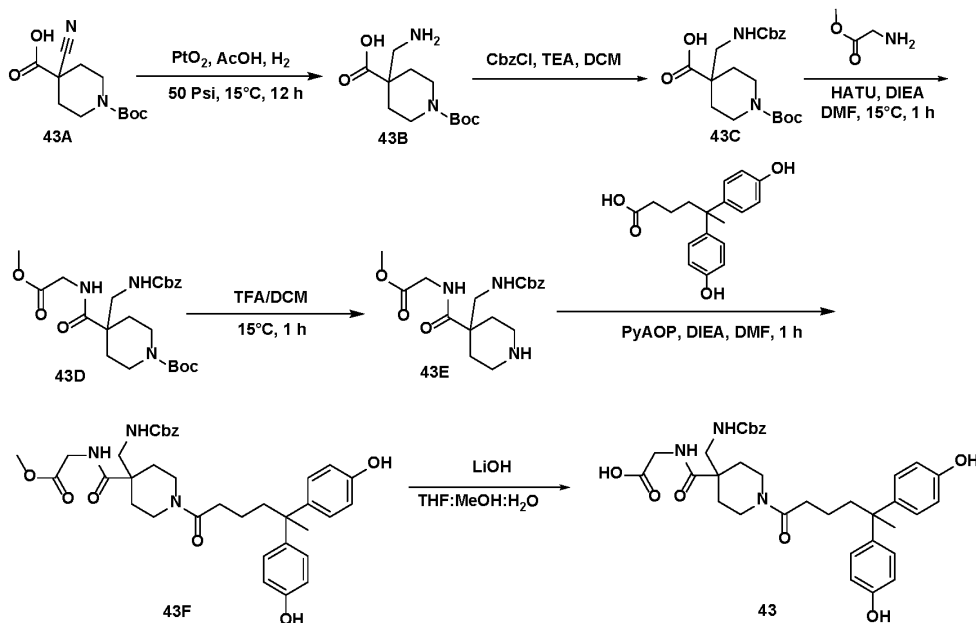
[00683] To a mixture of 3-cyclohexylpropanoic acid (2.76 mL, 16.1 mmol, 1.5 *eq*) in DMF (50 mL) was added DIEA (3.18 mL, 18.2 mmol, 1.7 *eq*), HOBt (2.17 g, 16.1 mmol, 1.5 *eq*) and HCTU (6.66 g, 16.1 mmol, 1.5 *eq*) at 25°C. The mixture was stirred at 25°C for 30 min, added to a solution of **compound 42E** (7.6 g, 10.7 mmol, 1 *eq*) in DMF (50 mL), and the mixture shaken at 25°C for 1 h. The mixture was filtered, the cake washed with DMF (100 mL), DCM (3×100 mL) and DMF (2×100 mL), the resin dried with nitrogen and used directly in the next reaction.

2.67 Synthesis of Intermediate 42

[00684] To a solution of **compound 42F** (9.0 g, 10.6 mmol, 1 *eq*) in DCM (100 mL) was added TFA (1 mL) at 15°C for 10 min and the mixture filtered. The procedure was repeated three times, THF (100 mL) was added, the reaction shaken for 10 min at 15°C and the mixture filtered. The mixture was washed with aq. NaHCO₃ (3.4 g in 50 mL H₂O), the organic layer dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **Intermediate 42** (6.0 g, 99% yield) as a yellow oil; LCMS [M+H]: 570.5; ¹H NMR (400 MHz, CHLOROFORM-d) δ 7.45 - 7.31 (m, 1H), 6.45 (br d, *J* = 2.9 Hz, 1H), 4.83 - 4.68 (m, 1H), 4.57 - 4.37 (m, 2H), 3.20 - 3.07 (m, 2H), 2.52 - 2.36 (m, 2H), 2.29 - 2.17 (m, 3H), 2.12 - 1.97 (m, 1H), 1.89 - 1.76 (m, 2H), 1.74 - 1.59 (m, 6H), 1.55 - 1.49 (m, 3H), 1.48 - 1.42 (m, 18H), 1.30 (br d, *J* = 8.7 Hz, 5H), 0.97 - 0.80 (m, 2H).

B14. Synthesis of Intermediate 43

Scheme B14.



2.68 Synthesis of compound 43B

[00685] To a solution of **compound 43A** (2.8 g, 11.0 mmol, 1 *eq*) in AcOH (20 mL) was added PtO_2 (300 mg, 1.32 mmol, 0.12 *eq*). The mixture was stirred at 15°C for 12h under a hydrogen atmosphere (50 Psi). The reaction mixture was filtered and the filtrate concentrated under reduced pressure to give **compound 43B** (2.8 g, 98% yield) as a colorless oil; LCMS $[\text{M}+\text{Na}]$: 281.2.

2.69 Synthesis of compound 43C

[00686] To a solution of **compound 43B** (3.8 g, 14.7 mmol, 1 *eq*) in DCM (40 mL) was added DIEA (3.07 mL, 17.7 mmol, 1.2 *eq*) and CbzCl (2.21 mL, 15.5 mmol, 1.05 *eq*) at 0°C. The mixture was stirred at 15°C for 1h, concentrated under reduced pressure and the residue purified by column chromatography (SiO_2 , DCM/MeOH) to give **compound 43C** (3.5 g, 61% yield) as a colorless oil; LCMS $[\text{M}-100+1]$: 293.3; ^1H NMR (400 MHz, CHLOROFORM-d) δ 7.29 (s, 5H), 5.15 - 4.95 (m, 2H), 4.61 (s, 7H), 4.04 (q, $J = 7.1$ Hz, 2H), 3.74 - 3.58 (m, 1H), 3.06 - 2.91 (m, 2H), 2.57 (d, $J = 10.1$ Hz, 1H), 1.66 - 1.52 (m, 2H), 1.44 - 1.33 (m, 9H).

2.70 Synthesis of compound 43D

[00687] To a solution of **compound 43C** (3.0 g, 7.64 mmol, 1 *eq*) and methyl glycinate (960 mg, 7.64 mmol, 1 *eq*, HCl) in DMF (30 mL) was added DIEA (3.99 mL, 22.9 mmol, 3 *eq*) and HATU (2.91 g, 7.64 mmol, 1 *eq*) at 15°C. The reaction mixture was stirred at 15°C for 1h, H_2O (50 mL) added and extracted with EtOAc (2×50 mL). The combined organic phase was dried (Na_2SO_4), concentrated under reduced pressure and the residue purified by column chromatography (SiO_2 , petroleum ether:EtOAc) to give **compound 43D** (5.0 g) as a yellow solid; LCMS $[\text{M}-100+\text{H}]$: 364.2; ^1H NMR (400 MHz, CHLOROFORM-d) δ 7.43 - 7.31 (m, 5H), 6.15 (t, $J = 5.6$ Hz, 1H), 5.74 - 5.65 (m, 1H), 5.11 (s, 2H), 4.04 (d, $J = 5.1$ Hz, 2H), 3.82 - 3.74 (m, 5H), 3.67 (d, $J = 12.4$ Hz, 2H), 3.40 (br s, 2H), 3.25 (t, $J = 9.8$ Hz, 2H), 1.96 - 1.88 (m, 2H), 1.45 (s, 9H).

2.71 Synthesis of compound 43E

[00688] To a solution of **compound 43D** (2.2 g, 4.75 mmol, 1 *eq*) in DCM (6 mL) was added TFA (2 mL) stirred at 15°C. The mixture was stirred at 15°C for 1h, H₂O (20 mL) added and extracted with MTBE (3 × 10 mL). The water phase was adjusted to pH=11 with aq. K₂CO₃ and extracted with DCM (3 × 30 mL). The combined organic phase was dried (Na₂SO₄) and concentrated under reduced pressure to give **compound 43E** (1.2 g, 70% yield) as a white solid; LCMS [M+H]: 364.1.

2.72 Synthesis of compound 43F

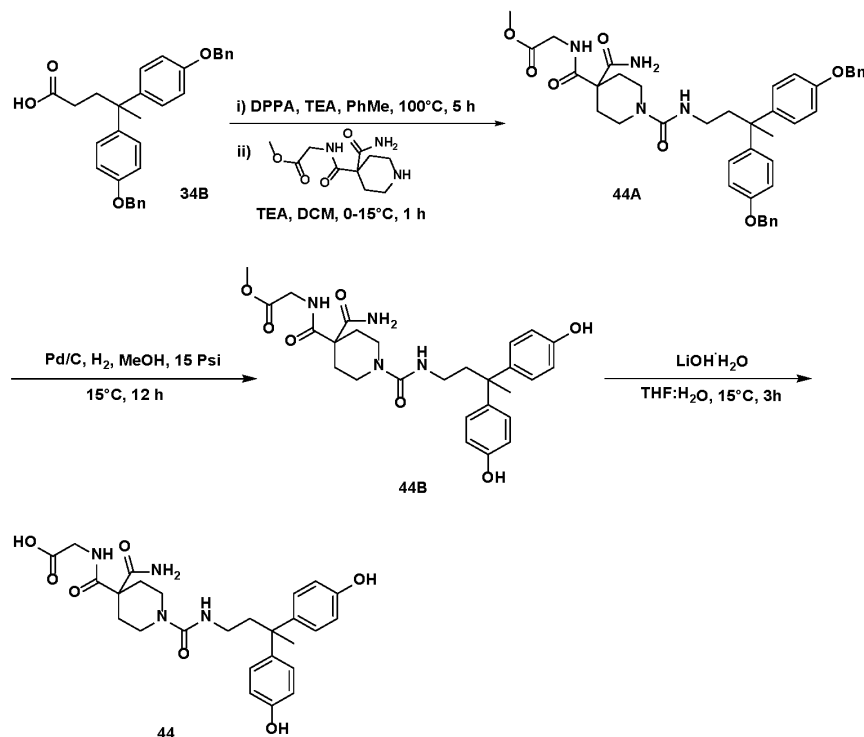
[00689] To a solution of **compound 43E** (3.0 g, 8.32 mmol, 1 *eq*) and 5,5-*bis*(4-hydroxyphenyl)hexanoic acid (2.5 g, 8.32 mmol, 1 *eq*) in DMF (10 mL) was added DIEA (3.23 g, 24.97 mmol, 4.35 mL, 3 *eq*) and PyAOP (4.55 g, 8.73 mmol, 1.05 *eq*) at 15°C. The mixture was stirred at 15°C for 1h, diluted with water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (30 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc and DCM:MeOH) to give **compound 43E** (6.0 g, 81% yield, 72% purity) as a yellow oil; LCMS [M+1]: 646.4.

2.73 Synthesis of Intermediate 43

[00690] To a solution of **compound 43E** (6.5 g, 10.07 mmol, 1 *eq*) in THF (5 mL), MeOH (5 mL) and H₂O (5 mL) was added LiOH (1.21 g, 50.3 mmol, 5 *eq*) at 15°C. The mixture was stirred at 15°C for 3h, H₂O (10 mL) added, and the mixture adjusted to pH=2 with 2N HCl (~15 mL). The suspension was filtered and the filter cake concentrated under reduced pressure to give **Intermediate 43** (5.0 g, 79% yield) as a white solid; LCMS [M+H]: 632.4.

B15. Synthesis of Intermediate 44

Scheme B15.



2. 76 Synthesis of compound 44A

[00691] To a solution of **compound 34B** (3.0 g, 6.42 mmol, 1 *eq*) in toluene (45 mL) was added TEA (3.58 mL, 25.7 mmol, 4 *eq*) and DPPA (1.52 mL, 7.08 mmol, 1.1 *eq*). The mixture was stirred at 100 °C for 5h, methyl (4-carbamoylpiperidine-4-carbonyl)glycinate (1.95 g, 5.46 mmol, 0.85 *eq*, TFA salt) and TEA (2.98 mL, 21.4 mmol) in DCM (20 mL) added at 0 °C, and the reaction stirred at 0 °C for 1h under a nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **compound 44A** (3.03 g, 67% yield) as a white solid; LCMS [M+H]: 707.5.

2. 77 Synthesis of compound 44B

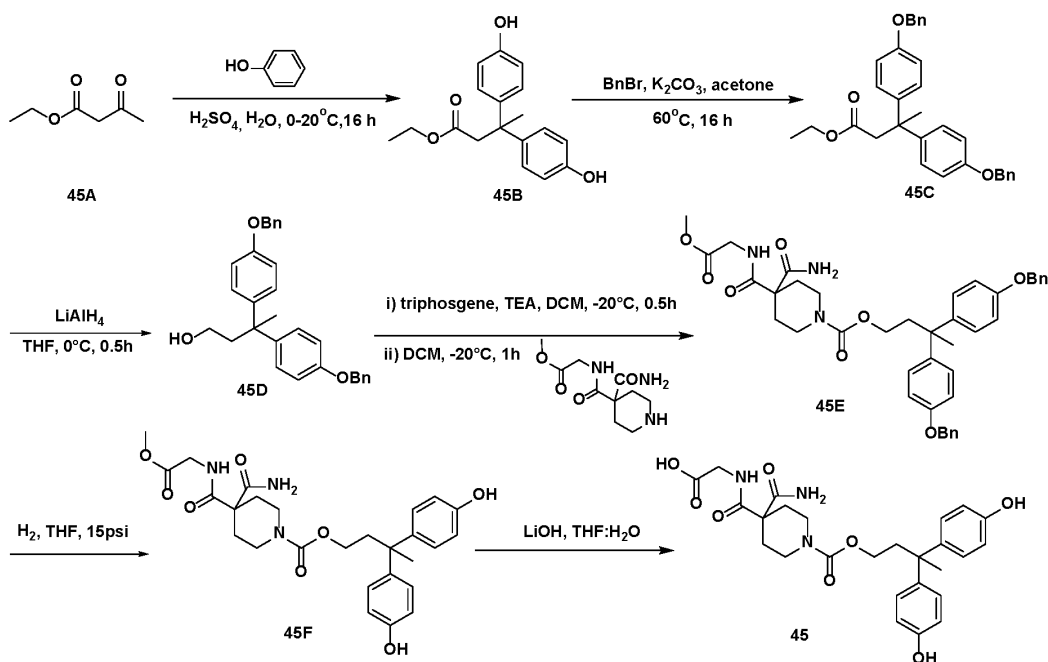
[00692] To a solution of **compound 44A** (4.5 g, 6.36 mmol, 1 *eq*) in MeOH (50 mL) was added Pd/C (4.0 g, 10% purity). The suspension was degassed and purged with hydrogen 3 times. The mixture was stirred under a hydrogen atmosphere (15 Psi) at 15 °C for 12h, filtered and the filtrate concentrated under reduced pressure to give crude **compound 44B** (3.35 g, crude) as a white solid; LCMS [M+H]: 527.4.

2. 78 Synthesis of Intermediate 44

[00693] To a solution of **compound 44B** (3.36 g, 3.19 mmol, 1 *eq*) in THF (15 mL) and H₂O (15 mL) was added LiOH·H₂O (803 mg, 19.1 mmol, 3 *eq*). The mixture was stirred at 15°C for 3h and concentrated under reduced pressure to remove the THF. The mixture was adjusted to pH=2 with 2M HCl. The mixture was concentrated under reduced pressure to give **intermediate 44** (3.27 g, crude) as a yellow solid; LCMS [M+H]: 513.3.

B16. Synthesis of Intermediate 45

Scheme B16.



2.79 Synthesis of compound 45B

[00694] To a solution of **compound 45A** (9.71 mL, 76.8 mmol, 1 *eq*), phenol (13.5 mL, 154 mmol, 2 *eq*) in H₂O (3.46 mL, 192 mmol, 2.5 *eq*) was added H₂SO₄ (7.54 mL, 141 mmol, 1.84 *eq*) dropwise at 0°C for 15 min. The mixture was stirred at 20°C for 16 h, diluted with H₂O (300 mL) and extracted with EtOAc (300 mL). The organic layer was washed with NaHCO₃ (2 × 200 mL) and H₂O (200 mL), the organic layer dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **compound 45B** (17.4 g, 38% yield) as a colorless oil; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 7.05 (d, *J* = 8.6 Hz, 4H), 6.71 (d, *J* = 8.6 Hz, 4H), 4.98 (s, 2H), 3.91 (q, *J* = 7.2 Hz, 2H), 3.07 (s, 2H), 1.81 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 3H).

2.80 Synthesis of compound 45C

[00695] To a solution of **compound 45B** (12 g, 40.0 mmol, 1 *eq*), BnBr (47.5 mL, 400 mmol, 10 *eq*) and K₂CO₃ (55 g, 400 mmol, 10 *eq*) in acetone (120 mL) was degassed and purged with nitrogen 3 times, and stirred at 60°C for 16 h under a nitrogen atmosphere. The reaction mixture was diluted with H₂O (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with NaHCO₃ (3 × 50 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **compound 45C** (9.0 g, 58% yield) as a colorless oil; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 7.41 - 7.27 (m, 8H), 7.27 - 7.16 (m, 2H), 7.08 - 7.01 (m, 4H), 6.87 - 6.78 (m, 4H), 4.97 (s, 4H), 3.82 (q, *J* = 7.2 Hz, 2H), 3.00 (s, 2H), 1.76 (s, 3H), 0.92 (t, *J* = 7.2 Hz, 3H).

2.81 Synthesis of compound 45D

[00696] To a solution of **compound 45C** (6.0 g, 15.4 mmol, 1 *eq*) in THF (60 mL) was added 2.5 M LiAlH₄ (12.3 mL, 2 *eq*) at 0°C under a nitrogen atmosphere. The mixture was stirred at 0°C for 0.5 h,

quenched with H₂O (30 mL) and stirred at 20°C for 30 min. The mixture was extracted with EtOAc (2 × 50 mL), the combined organic phase washed with brine (2 × 50 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **compound 45D** (5.0 g, 93% yield) as a white solid; ¹H NMR (400 MHz, CHLOROFORM-d) δ 7.43 - 7.15 (m, 10H), 7.05 (d, *J* = 8.8 Hz, 4H), 6.82 (d, *J* = 8.8 Hz, 4H), 4.96 (s, 4H), 3.46 (t, *J* = 7.4 Hz, 2H), 2.32 (t, *J* = 7.4 Hz, 2H), 1.55 (s, 3H).

2.82 Synthesis of compound 45E

[00697] To a solution of **compound 45D** (4.0 g, 11.5 mmol, 1 *eq*) in DCM (60 mL) was added TEA (6.39 mL, 45.9 mmol, 4 *eq*) and triphosgene (2.04 g, 6.89 mmol, 0.6 *eq*) at -20°C, and the mixture stirred for 0.5 h. Methyl (4-carbamoylpiperidine-4-carbonyl)glycinate (4.10 g, 11.48 mmol, 1 *eq*, TFA) was added at -20°C and the reaction stirred at -20°C for 1h. H₂O (50 mL) was added, and the reaction extracted with DCM (3 × 30 mL). The combined organic phase was dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column (SiO₂, EtOAc to DCM;MeOH) to give **compound 45E** (5.0 g, 83% yield) as a white solid; LCMS [*M*+1]: 708.5; ¹H NMR (400 MHz, CHLOROFORM-d) δ 7.42 - 7.21 (m, 10H), 7.08 - 7.01 (m, 4H), 6.84 - 6.77 (m, 4H), 4.99 - 4.92 (m, 4H), 3.94 - 3.84 (m, 4H), 3.70 - 3.66 (m, 3H), 3.53 (ddd, *J* = 3.8, 8.2, 17.5 Hz, 2H), 3.38 - 3.19 (m, 2H), 2.35 (t, *J* = 7.3 Hz, 2H), 1.97 (br s, 2H), 1.57 (s, 3H).

2.83 Synthesis of compound 45F

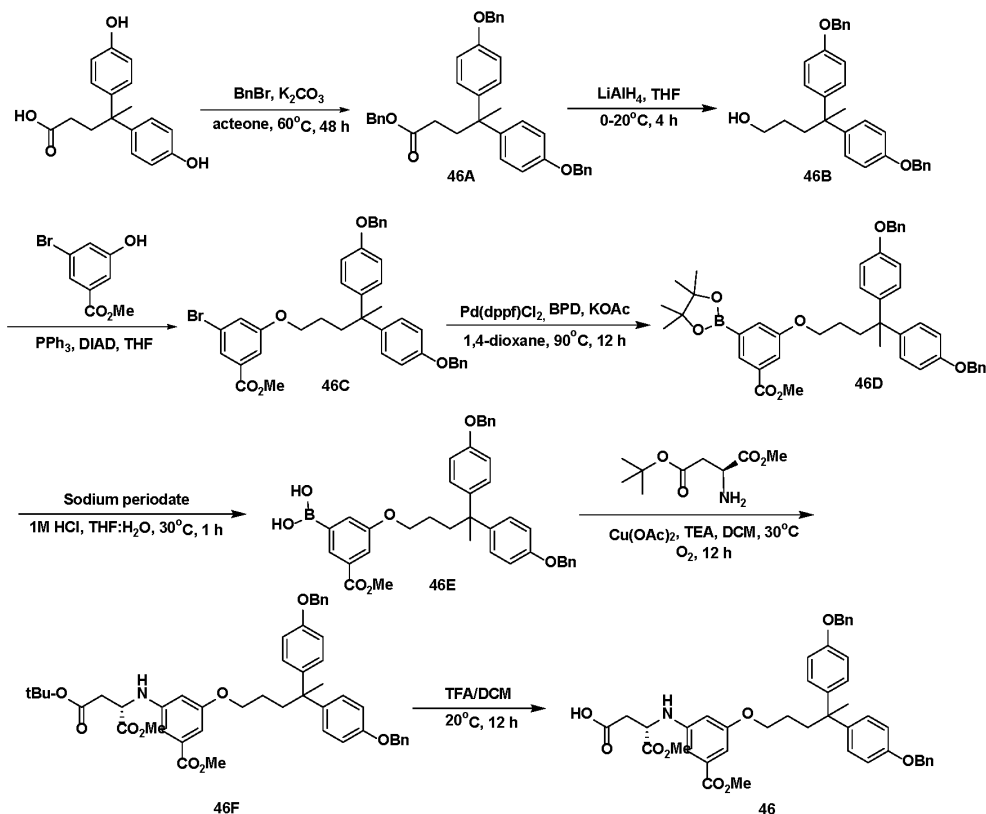
[00698] To a solution of **compound 45E** (4.5 g, 6.36 mmol, 1 *eq*) in THF (60 mL) was added Pd/C (0.7 g, 658 μmol, 10% purity). The mixture was stirred at 20°C for 5h under a hydrogen atmosphere (15 psi), filtered and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether::EtOAc to DCM/MeOH) to give **compound 45F** (3.3 g, 98% yield) as a white solid; LCMS [*M*+H]: 528.3; ¹H NMR (400 MHz, DMSO-d₆) δ 9.18 (s, 2H), 8.21 - 8.09 (m, 1H), 6.96 (d, *J* = 8.5 Hz, 4H), 6.65 (d, *J* = 8.5 Hz, 4H), 3.83 (d, *J* = 5.5 Hz, 2H), 3.67 - 3.60 (m, 5H), 3.43 (dd, *J* = 5.5, 9.0 Hz, 2H), 3.17 (t, *J* = 10.3 Hz, 2H), 2.31 (t, *J* = 7.3 Hz, 2H), 2.06 - 1.94 (m, 2H), 1.88 - 1.78 (m, 2H), 1.52 (s, 3H).

2.84 Synthesis of compound 45

[00699] To a solution of **compound 45F** (3.0 g, 5.69 mmol, 1 *eq*) in THF (5 mL) and H₂O (5 mL) was added LiOH (545 mg, 22.8 mmol, 4 *eq*) at 15°C. The mixture was stirred at 15°C for 3 h, concentrated under reduced pressure, H₂O (5 mL) added to the residue and 2N HCl (~5 mL) added to pH=2. The suspension was filtered and concentrated under reduced pressure to give **Intermediate 45** (2.9 g, 99% yield) as a white solid; LCMS [*M*+H]: 514.3.

B17. Synthesis of intermediate 46

Scheme B17.



2.85 Synthesis of compound 46A

[00700] To a mixture of 4,4-bis(4-hydroxyphenyl)pentanoic acid (10.0 g, 34.9 mmol, 1 *eq*) and K₂CO₃ (24.1 g, 174.6 mmol, 5.0 *eq*) in acetone (100 mL) was added BnBr (20.7 mL, 175 mmol, 5.0 *eq*) at 20°C. The mixture was stirred at 60°C for 48 h, filtered and concentrated under reduced pressure. The residue was diluted with EtOAc (100 mL), the organic layer washed with H₂O (30 mL) and brine (30 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, **Petroleum ether:EtOAc**) to give **compound 46A** (15.5 g, 80% yield) as a white solid; ¹H NMR (400 MHz, CDCl₃-d) δ 7.46 - 7.30 (m, 15H), 7.10 (s, 4H), 6.89 (d, *J* = 8.8 Hz, 4H), 5.07 (s, 2H), 5.03 (s, 4H), 2.48 - 2.41 (m, 2H), 2.21 - 2.14 (m, 2H), 1.58 (s, 3H).

2.86 Synthesis of compound 46B

[00701] A mixture of LiAlH₄ (2.8 g, 75.1 mmol, 4.0 *eq*) in THF (50 mL) was stirred at 0°C for 10 minutes under a nitrogen atmosphere. **Compound 46A** (10.4 g, 18.7 mmol, 1.0 *eq*) in THF (50 mL) was added dropwise, the temperature warmed to 20°C and stirred for 4 h. The reaction mixture was quenched by addition of H₂O (2.8 mL), 15% NaOH (2.8 mL) and H₂O (8.0 mL) at 0°C. The mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, **Petroleum ether:EtOAc**) to give **compound 46B** (8.2 g, 97% yield) as a white solid; ¹H NMR (400 MHz, CDCl₃-d) δ 7.51 - 7.32 (m, 10H), 7.14 (d, *J* = 8.8 Hz, 4H), 6.90 (d, *J* = 8.8 Hz, 4H), 5.05 (s, 4H), 3.61 (t, *J* = 6.6 Hz, 2H), 2.17 - 2.09 (m, 2H), 1.62 (s, 3H), 1.44 - 1.34 (m, 2H).

2.87 Synthesis of compound 46C

[00702] To a solution of **compound 46B** (6.0 g, 13.2 mmol, 1.0 *eq*) and methyl 3-bromo-5-hydroxybenzoate (3.1 g, 13.2 mmol, 1.0 *eq*) in THF (60 mL) was added PPh₃ (5.2 g, 19.9 mmol, 1.5 *eq*) at 15°C. The mixture was degassed and purged with nitrogen 3 times. DIAD (4.0 g, 19.8 mmol, 3.8 mL, 1.5 *eq*) was added dropwise at 0°C, the mixture stirred at 0°C for 1h under a nitrogen atmosphere and concentrated under reduced pressure. The residue was diluted with EtOAc (100 mL), the organic layer washed with NaHCO₃ (30 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **compound 46C** (7.1 g, 81% yield) as a yellow oil; ¹H NMR (400 MHz, CDCl₃-*d*) δ 7.75 (s, 1H), 7.49 - 7.31 (m, 11H), 7.22 - 7.19 (m, 1H), 7.14 (d, *J* = 8.8 Hz, 4H), 6.90 (d, *J* = 8.8 Hz, 4H), 5.05 (s, 4H), 3.96 - 3.89 (m, 5H), 2.26 - 2.18 (m, 2H), 1.64 (m, 5H).

2.88 Synthesis of compound 46D

[00703] To a solution of **compound 46C** (5.7 g, 8.5 mmol, 1.0 *eq*) in 1,4-dioxane (57 mL) was added BPD (5.4 g, 21.4 mmol, 2.5 *eq*), KOAc (2.9 g, 29.9 mmol, 3.5 *eq*) and Pd(dppf)Cl₂ (627 mg, 856 μmol, 0.1 *eq*). The mixture was degassed and purged with nitrogen 3 times, stirred at 90°C for 12h under a nitrogen atmosphere and concentrated under reduced pressure. The residue was diluted with EtOAc (60 mL), the organic layer washed with H₂O (20 mL), brine (20 mL), dried (Na₂SO₄), filtered, concentrated under reduced pressure and purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give crude **compound 46D** (7.6 g) as a colorless oil; ¹H NMR (400 MHz, CDCl₃-*d*) δ 8.05 (s, 1H), 7.62 (dd, *J* = 1.6, 2.4 Hz, 1H), 7.50 (d, *J* = 2.6 Hz, 1H), 7.47 - 7.31 (m, 10H), 7.14 (d, *J* = 8.8 Hz, 4H), 6.89 (d, *J* = 8.8 Hz, 4H), 5.04 (s, 4H), 4.00 - 3.95 (m, 2H), 3.91 (s, 3H), 2.26 - 2.20 (m, 2H), 1.66 - 1.57 (m, 5H), 1.36 (s, 12H).

2.89 Synthesis of compound 46E

[00704] To a solution of **compound 46D** (720 mg, 1.0 mmol, 1.0 *eq*) and sodium periodate (97.9 μL, 1.7 mmol, 1.7 *eq*) in THF (32 mL) and H₂O (8 mL) was added 1M HCl (5.7 mL, 5.7 *eq*). The mixture was stirred at 30°C for 1 h, diluted with brine (20 mL), and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with Na₂SO₃ (20 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure to give a crude **compound 46E** (669 mg) as a white solid; LCMS [M-H]:629.2; ¹H NMR (400 MHz, CDCl₃-*d*) δ 8.43 (s, 1H), 7.90 (d, *J* = 2.0 Hz, 1H), 7.75 (d, *J* = 1.0 Hz, 1H), 7.46 - 7.29 (m, 10H), 7.19 - 7.12 (m, 4H), 6.92 - 6.86 (m, 4H), 5.06 - 4.99 (m, 4H), 4.10 - 4.01 (m, 2H), 3.98 - 3.92 (m, 3H), 2.32 - 2.20 (m, 2H), 1.74 - 1.61 (m, 5H).

2.90 Synthesis of compound 46F

[00705] To a solution of **compound 46E** (2.1 g, 3.3 mmol, 1.0 *eq*) and 4-(*tert*-butyl) 1-methyl L-aspartate (1.3 g, 6.6 mmol, 2.0 *eq*) in DCM (21 mL) were added 4Å molecular sieves (2.1 g), TEA (464 μL, 3.3 mmol, 1.0 *eq*) and Cu(OAc)₂ (3.0 g, 16.6 mmol, 5.0 *eq*) at 30°C. The mixture was degassed and purged with oxygen 3 times and stirred at 30°C for 12h under an oxygen atmosphere. The reaction mixture was diluted with DCM (80 mL), filtered, the combined organic layers washed with NaHCO₃ (20 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give crude **compound 46F** (2.1 g) as a

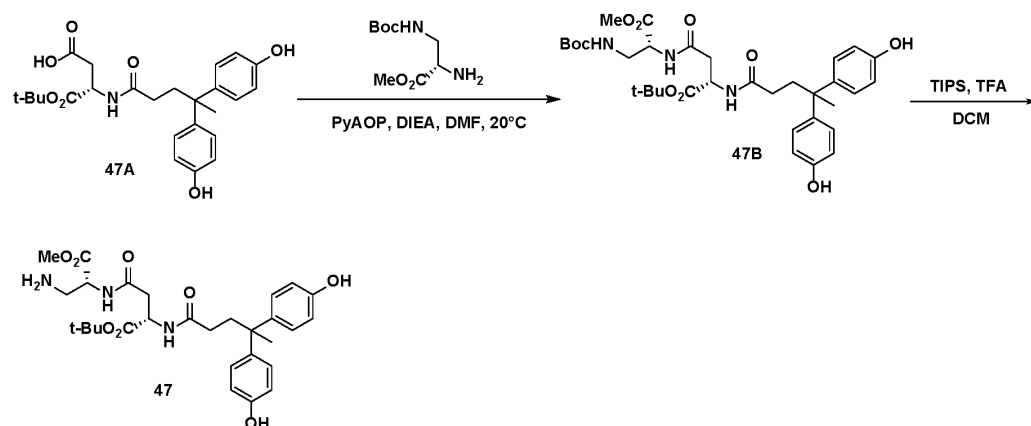
yellow solid; LCMS [M+H]:788.5; ^1H NMR (400 MHz, CDCl_3 -*d*) δ 7.45 - 7.33 (m, 10H), 7.14 (br d, J = 8.8 Hz, 4H), 6.94 (d, J = 2.0 Hz, 2H), 6.89 (br d, J = 8.8 Hz, 4H), 6.36 (s, 1H), 5.05 - 5.02 (m, 4H), 4.43 - 4.38 (m, 1H), 3.92 - 3.87 (m, 5H), 3.76 (s, 3H), 2.87 - 2.75 (m, 2H), 2.25 - 2.17 (m, 2H), 1.66 - 1.59 (m, 5H), 1.44 (s, 9H)

2.91 Synthesis of compound 46

[00706] A mixture of **compound 46F** (1.9 g, 2.4 mmol, 1.0 *eq*) in TFA (9 mL) and DCM (45 mL) was stirred at 20°C for 12h under a nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography (SiO_2 , Petroleum ether:EtOAc) to give crude **compound 46** (1.9 g) as a yellow oil; LCMS [M+H]:732.4; ^1H NMR (400 MHz, CDCl_3 -*d*) δ 7.46 - 7.31 (m, 10H), 7.13 (br d, J = 8.8 Hz, 4H), 6.96 (br s, 2H), 6.89 (br d, J = 8.8 Hz, 4H), 6.37 (br s, 1H), 5.03 (s, 4H), 4.46 (br t, J = 5.0 Hz, 1H), 3.93 - 3.86 (m, 5H), 3.77 (s, 3H), 2.99 - 2.93 (m, 2H), 2.23 - 2.17 (m, 2H), 1.65 - 1.56 (m, 5H).

B18. Synthesis of intermediate 47

Scheme B18.



2.92 Synthesis of compound 47B

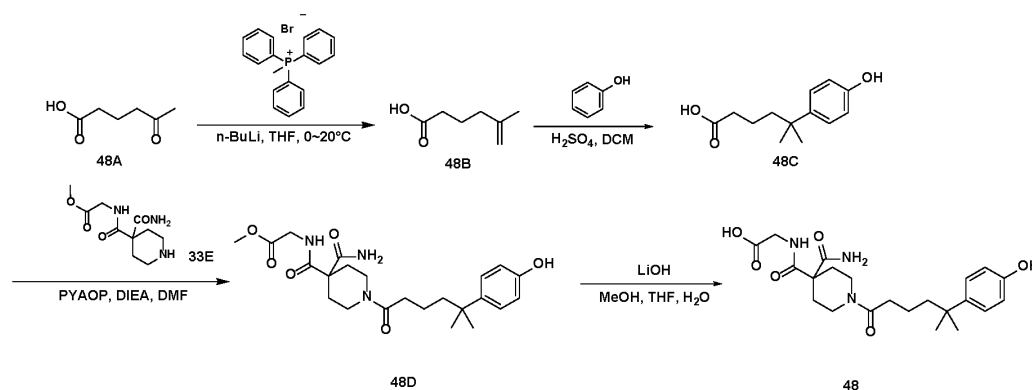
[00707] To a mixture of methyl (*S*)-2-amino-3-((tert-butoxycarbonyl)amino)propanoate (2.0 g, 9.16 mmol, 1 *eq*) and **compound 47A** (4.19 g, 9.16 mmol, 1 *eq*) in DMF (20 mL) was added DIEA (3.19 mL, 18.3 mmol, 2 *eq*) and PYAOP (5.26 g, 10.1 mmol, 1.1 *eq*) in one portion at 20°C under a nitrogen atmosphere. The mixture was stirred at 20°C for 1h, poured into water (50 mL) and extracted with EtOAc (3 × 100 mL). The combined organic phase was washed with brine (2 × 100 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2 , DCM:MeOH) to give **compound 47B** (3.4 g, 51% yield, 90% purity) as light yellow solid; LCMS [M+H]: 658.4; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.14 (s, 2H), 6.97 - 6.88 (m, J = 8.8 Hz, 4H), 6.64 (d, J = 8.6 Hz, 4H), 4.39 (br d, J = 6.4 Hz, 1H), 4.32 - 4.22 (m, 1H), 3.72 (s, 3H), 3.23 (br t, J = 6.0 Hz, 2H), 2.61 - 2.51 (m, 1H), 2.47 - 2.41 (m, 1H), 2.23 - 2.10 (m, 2H), 1.91 - 1.79 (m, 2H), 1.45 (s, 3H), 1.35 (s, 18H)

2.93 Synthesis of compound 47

[00708] To a mixture of **compound 47B** (2.4 g, 3.65 mmol, 1 *eq*) in DCM (60 mL) was added triisopropylsilane (15.0 mL, 73 mmol, 20 *eq*) and TFA (1.90 mL, 25.5 mmol, 7 *eq*) in one portion at 20°C under a nitrogen atmosphere. The mixture was stirred at 20°C for 16 h, poured into water (20 mL) and the aqueous phase extracted with ethyl acetate (3 × 50 mL). The combined organic phase was washed with NaHCO₃ (3 × 30 mL), brine (2 × 30 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **Intermediate 47** (800 mg, 39% yield) as a light yellow solid; LCMS [M+H]⁺: 558.4; ¹H NMR (400 MHz, METHANOL-*d*₄) δ 7.05 - 6.97 (m, 4H), 6.72 - 6.64 (m, 4H), 4.59 (dd, *J* = 5.6, 6.8 Hz, 1H), 4.45 (dd, *J* = 4.8, 7.2 Hz, 1H), 3.74 - 3.69 (m, 3H), 3.09 - 2.97 (m, 1H), 2.95 - 2.85 (m, 1H), 2.73 (dd, *J* = 6.2, 7.8 Hz, 2H), 2.40 - 2.32 (m, 2H), 2.06 - 2.02 (m, 2H), 1.55 (s, 3H), 1.45 (s, 9H).

B18. Synthesis of intermediate 48

Scheme B19.



2.94 Synthesis of compound 48B

[00709] To a solution of methyltriphenylphosphonium bromide (247 g, 692 mmol) in THF (600 mL) was added 2.5 M *n*-BuLi (277 mL, 693 mmol) at 0°C. The mixture was stirred at 0°C for 1 h, **compound 48A** (28 mL, 231 mmol) in THF (100 mL) was added dropwise and the reaction stirred at 20°C for 12h. The reaction mixture was quenched by addition of saturated NH₄Cl solution (200 mL) at 0°C, diluted with H₂O (500 mL) and extracted with EtOAc (3 x 500 mL). The combined organic layers were washed with brine (3 x 500 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **compound 48B** (25 g, 95%) as a white oil; ¹H NMR (400 MHz, CDCl₃) δ 11.72 (br s, 1H), 4.73 (br d, *J* = 19.9 Hz, 2H), 2.36 (t, *J* = 7.5 Hz, 2H), 2.11 - 2.04 (m, 2H), 1.79 (quin, *J* = 7.5 Hz, 2H), 1.73 (s, 3H).

2.95 Synthesis of compound 48C

[00710] To a solution of **compound 48B** (5.0 g, 39.0 mmol) and phenol (17.1 mL, 195 mmol) in DCM (150 mL) was added H₂SO₄ (10.4 mL, 195 mmol) at -20°C. The mixture was stirred at 0°C for 0.5h and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **compound 48C** (1.5 g, 17% yield) as a white solid; LCMS: [M-1]⁺ = 221.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.92 (br s, 1 H) 9.10 (s, 1 H) 7.10 (d, *J* = 8.8 Hz, 2 H) 6.67 (d, *J* = 8.6 Hz, 2 H) 2.08 (t, *J* = 7.4 Hz, 2 H) 1.46 - 1.57 (m, 2 H) 1.22 (br d, *J* = 3.8 Hz, 2 H) 1.19 (s, 6 H).

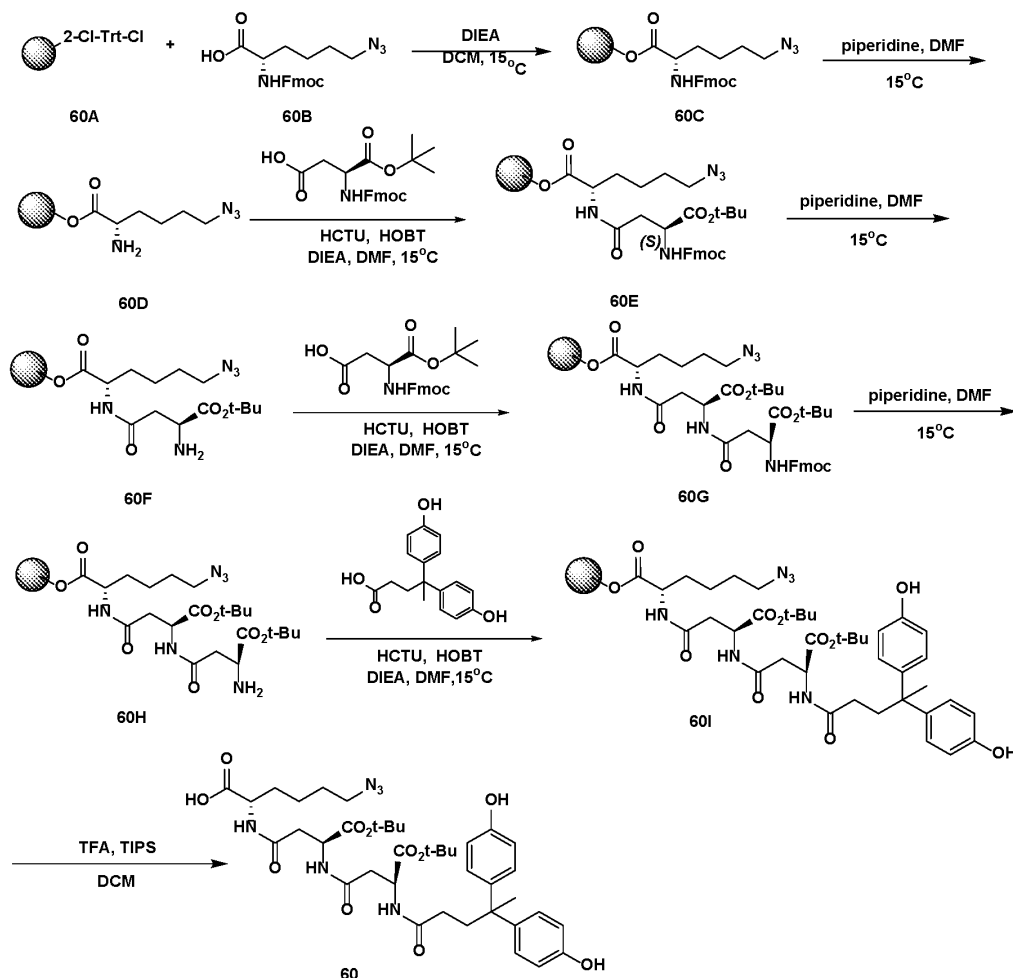
2.96 Synthesis of compound 48D

[00711] To a solution of **Compound 48C** (1.35 g, 6.07 mmol) and **Compound 33E** (1.70 g, 6.98 mmol, 1.15 *eq*) in DMF (20 mL) was added DIEA (3.17 mL, 18.2 mmol) and PyAOP (3.80 g, 7.29 mmol, 1.2 *eq*) at 20°C. The mixture was stirred at 20°C for 1 h. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM:MeOH) to give **Compound 48D** (1.5 g, 55% yield) as a white solid; LCMS [M+H]⁺ = 448.5; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.10 (s, 1 H) 8.15 (t, *J* = 5.8 Hz, 1 H) 7.23 (s, 1 H) 7.11 (d, *J* = 8.6 Hz, 2 H) 7.07 (s, 1 H) 6.67 (d, *J* = 8.6 Hz, 2 H) 3.83 (d, *J* = 5.8 Hz, 2 H) 3.62 (s, 4 H) 3.38 - 3.49 (m, 1 H) 3.21 - 3.31 (m, 1 H) 3.14 (br d, *J* = 3.6 Hz, 1 H) 2.18 (br t, *J* = 7.4 Hz, 2 H) 1.93 - 2.07 (m, 2 H) 1.72 - 1.90 (m, 2 H) 1.48 - 1.57 (m, 2 H) 1.22 - 1.29 (m, 2 H) 1.20 (s, 6 H).

2.97 Synthesis of compound 48

[00712] To a solution of **Compound 48D** (1.0 g, 2.23 mmol, 1 *eq*) in THF (3 mL), MeOH (3 mL) and H₂O (3 mL) was added LiOH·H₂O (141 mg, 3.35 mmol) at 20 °C. The mixture was stirred at 20°C for 1h. The reaction mixture was concentrated under reduced pressure to remove organics. The aqueous phase was adjusted to pH=5 with 1 M HCl, the resulting solid filtered and the filter cake dried under reduced pressure to give **compound 48** (850 mg, 88% yield) as a white solid; LCMS [M+H]⁺ = 434.5; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.08 (t, *J* = 5.8 Hz, 1H), 7.27 - 7.12 (m, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.67 (d, *J* = 8.6 Hz, 2H), 3.74 (d, *J* = 5.8 Hz, 2H), 3.70 - 3.56 (m, 2H), 3.54 - 3.29 (m, 2H), 3.23 (br t, *J* = 10.1 Hz, 1H), 3.13 (br t, *J* = 10.1 Hz, 1H), 2.17 (br t, *J* = 7.4 Hz, 2H), 2.08 - 1.92 (m, 2H), 1.90 - 1.71 (m, 2H), 1.56 - 1.46 (m, 2H), 1.18 (s, 6H).

C1. Synthesis of Intermediate 60**Scheme C1.**



3.1 Preparation of compound 60C

[00713] To a mixture of 2-Cl-Trt-Cl resin (15.5 g, 1.09 mmol/g) in DCM (100 mL) was added DIEA (17.5 g, 135 mmol, 8 *eq*) and **compound 60B** in DCM (100 mL) at 15°C, and the mixture was shaken at 15°C for 16h under a nitrogen atmosphere. The reaction mixture was filtered, and the filter cake washed with DCM (3 × 300 mL), DMF (2 × 300 mL), MeOH (3 × 300 mL) and DMF (2 × 300 mL), the resin dried with nitrogen and used directly in the next reaction.

3.2 Preparation of compound 60D

[00714] A mixture of **compound 60C** in piperidine (20 mL) and DMF (80 mL) was shaken at 15°C for 10 min under a nitrogen atmosphere. The procedure was repeated four times, the cake washed with DCM (2 × 300 mL) and DMF (2 × 300 mL), the resin dried with nitrogen and used directly in the next reaction.

3.3 Preparation of compound 60E

[00715] A mixture of **compound 60D** (10.3 g, 25.1 mmol, 1.5 *eq*), HCTU (10.4 g, 25.1 mmol, 1.5 *eq*), HOBT (3.39 g, 25.1 mmol, 1.5 *eq*) and DIEA (6.49 g, 50.2 mmol, 3 *eq*) in DMF (100 mL) was stirred at 15°C for 30 min. The solution was added to a solution of **compound 60E** in DMF (100 mL) at 15°C and the mixture shaken at 15°C for 2h. The mixture was filtered, the cake washed with DMF (200 mL), DCM (3 × 200 mL) and DMF (2 × 200 mL), the resin dried with nitrogen and used directly in the next reaction.

3.4 Preparation of compound 60F

[00716] A mixture of **compound 60E** in piperidine (20 mL) and DMF (80 mL) was shaken at 15°C for 10 min under a nitrogen atmosphere. The procedure was repeated four times, the cake washed with DCM (2 × 300 mL) and DMF (2 × 300 mL), the resin dried with nitrogen and used directly in the next reaction.

3.5 Preparation of compound 60G

[00717] A mixture of **compound 60F** (10.3 g, 24.9 mmol, 1.5 eq), HCTU (10.3 g, 24.9 mmol, 1.5 eq), HOBt (3.37 g, 24.9 mmol, 1.5 eq), DIEA (8.68 mL, 49.8 mmol, 3 eq) in DMF (100 mL) was stirred at 15°C for 30 min. The mixture was added to a solution of (*S*)-3-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-(tert-butoxy)-4-oxobutanoic acid in DMF (100 mL) and shaken at 15°C for 2 h. The mixture was filtered, the cake washed with DMF (100 mL), DCM (3 × 200 mL) and DMF (2 × 100 mL), the resin dried with nitrogen and used directly in the next reaction.

3.6 Preparation of compound 60H

[00718] A mixture of **compound 60G** in piperidine (20 mL) and DMF (80 mL) was shaken at 15°C for 2h under a nitrogen atmosphere. The procedure was repeated four times, the cake washed with DCM (2 × 30 mL) and DMF (2 × 30 mL), the resin dried with nitrogen and used directly in the next reaction.

3.7 Preparation of compound 60I

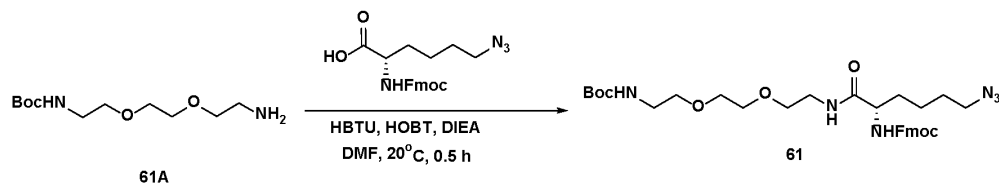
[00719] A mixture of 4,4-*bis*(4-hydroxyphenyl)pentanoic acid (4.74 g, 16.6 mmol, 1 eq), HCTU (6.85 g, 16.6 mmol, 1 eq), HOBt (2.24 g, 16.6 mmol, 1 eq) and DIEA (8.65 mL, 49.7 mmol, 3 eq) in DMF (60 mL) was stirred at 15°C for 1 min. The mixture was added to a solution of **compound 60H** in DMF (130 mL) and shaken at 15°C for 0.5 h. The mixture was filtered, the cake washed with DMF (300 mL), DCM (3 × 300 mL), DMF (2 × 300 mL) and DCM (2 × 300 mL), the resin dried with nitrogen and used directly in the next reaction.

3.8 Preparation of intermediate 60

[00720] To a solution of **compound 60I** in DCM (100 mL) was added TFA (1 mL) and TIPS (2.5 mL), and the reaction mixture stirred at 15°C for 10 min. The procedure was repeated three times, THF (100 mL) added and stirred at 15°C for 10 min. The mixture was filtered, the filtrate diluted in MeOH, washed with NaHCO₃ (3.4 g in 50 mL H₂O), the organic layer dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **intermediate 60** (14 g, purity 85%). A portion (7.0 g) of **intermediate 60** was further purified by *prep*-HPLC (column: Phenomenex luna C18 (250*70mm, 15 um); mobile phase: [water (FA)-ACN]; B%: 40%-70%, 20 min) to give **intermediate 60** (2.7 g) as a white solid; LCMS [M+H]⁺: 783.4; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.63 (br s, 1 H) 9.15 (s, 2 H) 8.08 - 8.22 (m, 2 H) 7.90 (br d, *J*=7.60 Hz, 1 H) 6.93 (br d, *J*=8.40 Hz, 4 H) 6.64 (br d, *J*=8.80 Hz, 4 H) 4.41 (quin, *J*=6.80 Hz, 2 H) 4.19 (td, *J*=8.00, 5.20 Hz, 1 H) 3.29 (t, *J*=6.40 Hz, 2 H) 2.52 - 2.60 (m, 3 H) 2.39 - 2.47 (m, 1 H) 2.12 - 2.23 (m, 2 H) 1.80 - 1.91 (m, 2 H) 1.63 - 1.76 (m, 1 H) 1.48 - 1.62 (m, 3 H) 1.46 (s, 3 H) 1.35 (s, 20 H).

C2. Synthesis of Intermediate 61

Scheme C2.



[00721]3.9 Preparation of Intermediate 61

[00722] To a solution of *N*2-(((9H-fluoren-9-yl)methoxy)carbonyl)-*N*6-diazo-L-lysine (1.0 g, 2.54 mmol, 1 *eq*) in DMF (10 mL) was added HBTU (962 mg, 2.54 mmol, 1 *eq*), HOBT (343 mg, 2.54 mmol, 1 *eq*) and DIEA (1.32 mL, 7.61 mmol, 3 *eq*). **Compound 61A** (755 mg, 3.04 mmol, 1.2 *eq*) was added to the mixture, the reaction stirred at 20°C for 0.5 h, diluted with H₂O (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (30 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **Intermediate 61** (1.55 g, 83% yield, 84.6% purity) as a light yellow oil; LCMS [M+H]⁺: 625.3; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.60 (br d, *J* = 7.4 Hz, 2H), 7.47 - 7.36 (m, 2H), 7.35 - 7.28 (m, 2H), 6.73 - 6.49 (m, 1H), 5.73 - 5.39 (m, 1H), 5.16 - 4.82 (m, 1H), 4.53 - 4.27 (m, 2H), 4.25 - 4.19 (m, 1H), 3.68 - 3.49 (m, 9H), 3.47 - 3.38 (m, 1H), 3.27 (br t, *J* = 6.6 Hz, 4H), 1.92 - 1.79 (m, 3H), 1.62 (dt, *J* = 6.6, 13.6 Hz, 2H), 1.43 (br s, 11H).

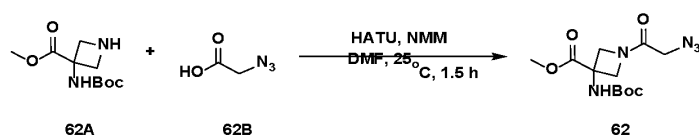
[00723] Compounds in **table 8.1** were prepared by procedures depicted in **scheme C2**.

Table 8.1.

Intermediate	Structure	m/z
61.1		[M+H] ⁺ : 583.4

C3. Synthesis of Intermediate 62

Scheme C3.

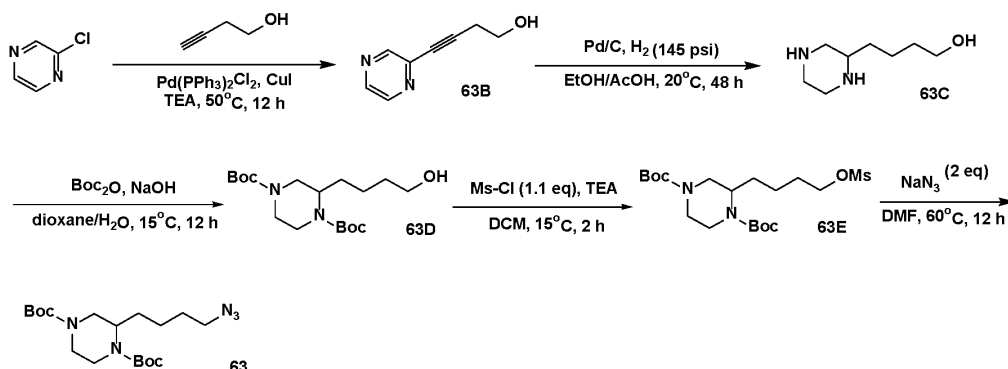


3.10 Synthesis of Intermediate 62

[00724] To a solution of **compound 62B** in DMF (60 mL) was added HATU (11.9 g, 31.3 mmol, 1.2 *eq*) at -30°C and the mixture was stirred at 25°C for 0.5 h. A solution of **compound 62A** (6.0 g, 26.1 mmol, 1 *eq*) in DMF (6 mL) and NMM (8.59 mL, 78.2 mmol, 3 *eq*) was added and the mixture stirred at 25°C for 1 h. The mixture was extracted with EtOAc (2 × 200 mL), the combined organic layer washed with brine (150 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **compound 62** (5.0 g, 61% yield) as a white solid.

C4. Synthesis of Intermediate 63

Scheme C4.



3.11 Synthesis of compound 63B

[00725] To a solution of 2-chloropyrazine (7.81 mL, 87.3 mmol, 1 *eq*) and but-3-yn-1-ol (8.59 mL, 114 mmol, 1.3 *eq*) in TEA (50 mL) was added CuI (299 mg, 1.57 mmol, 0.018 *eq*) and Pd(PPh₃)₂Cl₂ (1.10 g, 1.57 mmol, 0.018 *eq*) at 15°C, and the mixture stirred in a sealed tube at 50 °C for 12 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (SiO₂, **petroleum ether: EtOAc**) to give **compound 63B** (21.8 g, 84% yield) as a yellow solid; LCMS [M+H]: 149.2; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.64 (s, 1H), 8.53 - 8.49 (m, 1H), 8.46 (d, *J* = 2.4 Hz, 1H), 3.89 (t, *J* = 6.3 Hz, 2H), 2.77 (t, *J* = 6.3 Hz, 2H), 2.49 (br s, 1H).

3.12 Synthesis of compound 63C

[00726] To a solution of **compound 63B** (20 g, 135 mmol, 1 *eq*) in EtOH (250 mL) and AcOH (10 mL) was added Pd/C (10 g, 10% purity) under a nitrogen atmosphere. The mixture was stirred at 20°C under a hydrogen atmosphere (145 psi) for 48 h. The mixture was filtered and concentrated to give crude **compound 63C** (40 g) as a yellow solid; LCMS [M+H]: 159.5; ¹H NMR (400 MHz, DMSO-*d*₆) δ 3.37 (t, *J* = 6.3 Hz, 1H), 2.97 - 2.81 (m, 2H), 2.78 - 2.57 (m, 2H), 2.32 (t, *J* = 11.4 Hz, 1H), 1.84 (s, 7H), 1.44 - 1.21 (m, 4H).

3.13 Synthesis of compound 63D

[00727] To a solution of **compound 63C** (30 g, 190 mmol, 1 *eq*) in dioxane (240 mL) and H₂O (90 mL) was added NaOH (22.8 g, 569 mmol, 3 *eq*) and Boc₂O (109 mL, 474 mmol, 2.5 *eq*) at 15°C, and the mixture stirred at 15°C for 12 h. The reaction mixture was quenched by addition of a saturated NH₄Cl solution (100 mL) at 20°C and extracted with DCM (2 × 80 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, **petroleum ether:EtOAc**) to give **compound 63D** (30 g, 44% yield) as yellow oil; LCMS [M-155]: 203.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ 4.35 (t, *J* = 4.6 Hz, 1H), 4.03 - 3.84 (m, 2H), 3.81 (d, *J* = 13.4 Hz, 1H), 3.71 (d, *J* = 11.3 Hz, 1H), 3.37 (q, 2H), 3.31 (s, 1H), 2.99 - 2.63 (m, 3H), 1.39 (s, 18H), 1.38 - 1.32 (m, 2H), 1.32 - 1.17 (m, 2H).

3.14 Synthesis of compound 63E

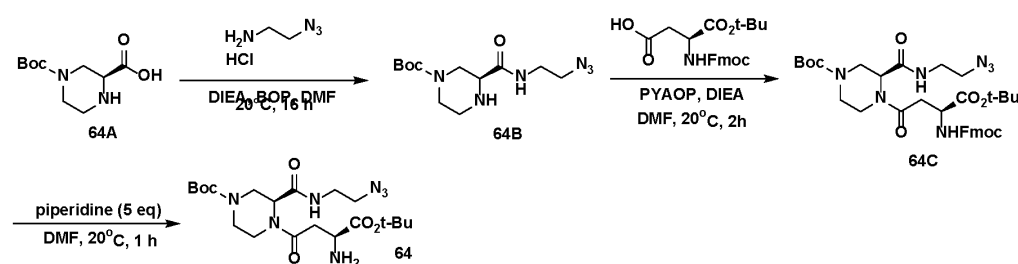
[00728] To a solution of **compound 63D** (5.0 g, 14.0 mmol, 1 *eq*) in DCM (50 mL) was added TEA (2.91 mL, 20.9 mmol, 1.5 *eq*) and MsCl (1.19 mL, 15.3 mmol, 1.1 *eq*) at 0°C, and the mixture stirred at 15°C for 2 h. The reaction mixture was quenched with aq. NH₄Cl (100 mL) and extracted with DCM (2 × 50 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated under reduced pressure to give crude **compound 63E** (6.0 g) as a yellow oil; ¹H NMR (400 MHz, DMSO-d₆) δ 4.18 (t, *J* = 6.3 Hz, 2H), 4.06 - 3.66 (m, 4H), 3.32 (s, 1H), 3.14 (s, 3H), 3.05 (q, 6H), 1.68 (q, 2H), 1.40 (s, 18H).

3.15 Synthesis of compound 63

[00729] To a solution of **compound 63E** (36 g, 82.5 mmol, 1 *eq*) in DMF (150 mL) was added NaN₃ (10.7 g, 165 mmol, 2 *eq*) at 15°C, and the mixture stirred at 60 °C for 12h. The mixture was diluted with water (300 mL) and extracted with EtOAc (300 mL). The organic layer was washed with water (2 × 100 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, **petroleum ether:EtOAc**) to give **compound 63** (22 g, 70% yield) as a colorless oil; ¹H NMR (400 MHz, DMSO-d₆) δ 4.04 - 3.84 (m, 2H), 3.80 (d, *J* = 13.4 Hz, 2H), 3.73 (d, *J* = 11.2 Hz, 1H), 3.03 - 2.60 (m, 4H), 1.55 (q, 3H), 1.48 - 1.45 (m, 1H), 1.40 (s, 18H), 1.34 - 1.27 (m, 1H), 1.27 - 1.19 (m, 1H).

C5. Synthesis of Intermediate 64

Scheme C5.



3.16 Preparation of compound 64B

[00730] To a solution of 2-azidoethan-1-amine hydrochloride (13.3 g, 109 mmol, 1.0 *eq*) in DMF (250 mL) was added DIEA (47.3 mL, 271 mmol, 2.5 *eq*), **compound 64A** (25 g, 109 mmol, 1 *eq*) and BOP (52.8 g, 119 mmol, 1.1 *eq*), and the mixture stirred at 20°C for 16 h. The reaction mixture was quenched by addition of H₂O (10 mL) at 20°C, diluted with H₂O (250 mL) and extracted with EtOAc (2 × 300 mL). The combined organic layers were washed with a saturated NH₄Cl solution (150 mL), NaHCO₃ solution (150 mL) and brine (250 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM:MeOH) to give **compound 64B** (27.4 g, 63% yield, 75% purity) as an orange oil; ¹H NMR (400 MHz, CHLOROFORM-d) δ 7.24 (br s, 1H), 4.11 - 3.99 (m, 1H), 3.51 - 3.39 (m, 5H), 3.21 - 3.12 (m, 3H), 3.04 (br d, *J* = 12.8 Hz, 2H), 2.92 - 2.80 (m, 1H), 1.46 (s, 9H).

3.17 Synthesis of intermediate 64C

[00731] To a solution of **compound 64B** (6.00 g, 12.1 mmol, 60% purity, 1 *eq*), (S)-3-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-(tert-butoxy)-4-oxobutanoic acid (4.96 g, 12.07 mmol, 1 *eq*) in DMF (60 mL) was added DIEA (4.20 mL, 24.1 mmol, 2 *eq*) and PyAOP (6.92 g, 13.3 mmol, 1.1 *eq*). The mixture

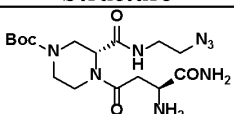
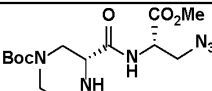
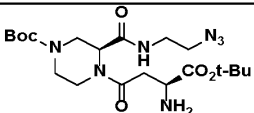
was stirred at 20°C for 2 h, quenched by the addition of H₂O (50 mL) at 20°C and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (20 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 64C** (8.0 g, 96% yield) as a white solid; LCMS [M+H]⁺: 692; ¹H NMR (400 MHz, DMSO-d₆) δ 8.33 (br s, 1H), 8.17 - 8.11 (m, 1H), 7.89 (br d, *J* = 7.4 Hz, 2H), 7.70 (br d, *J* = 7.4 Hz, 2H), 7.46 - 7.38 (m, 3H), 7.36 - 7.27 (m, 2H), 4.75 (br s, 1H), 4.41 - 4.14 (m, 5H), 3.73 (br d, *J* = 11.8 Hz, 2H), 3.40 - 3.30 (m, 4H), 3.27 - 3.13 (m, 2H), 1.45 - 1.30 (m, 18H).

3.18 Synthesis of intermediate 64

[00732] To a solution of **compound 64C** (5.0 g, 7.23 mmol, 1 *eq*) in DMF (60 mL) was added piperidine (3.57 mL, 36.1 mmol, 5 *eq*), the mixture stirred at 20°C for 1h and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM:MeOH) to give crude **Intermediate 64** (3.6 g) as a white solid; LCMS [M+H]⁺: 470.3; ¹H NMR (400 MHz, DMSO-d₆) δ 8.42 - 8.19 (m, 1H), 4.28 (br d, *J* = 13.8 Hz, 1H), 3.85 - 3.69 (m, 3H), 3.56 - 3.41 (m, 2H), 3.30 - 3.07 (m, 5H), 3.04 - 2.98 (m, 1H), 2.86 - 2.76 (m, 2H), 1.49 - 1.29 (m, 18H).

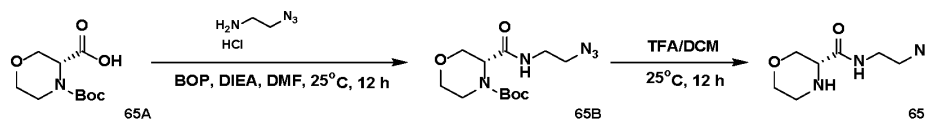
[00733] Compounds in **table 8.2** were prepared by procedures depicted in **scheme C5**.

Table 8.2.

Intermediate	Structure	m/z
64.1		[M+H] ⁺ : 413.3
64.2		[M+H] ⁺ : 357.3
64.3		[M+H] ⁺ : 470.3

C6. Synthesis of Intermediate 65

Scheme C6.



3.19 Preparation of compound 65B

[00734] To a solution of **compound 65A** (10 g, 43.2 mmol, 1 *eq*), 2-azidoethan-1-amine hydrochloride (5.30 g, 43.2 mmol, 1 *eq*) in DMF (50 mL) was added BOP (21.0 g, 47.6 mmol, 1.1 *eq*) and DIEA (30.1 mL, 173 mmol, 4 *eq*). The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 65B** (11.4 g, 88% yield) as a yellow oil; LCMS [M-100]⁺: 200; ¹H NMR

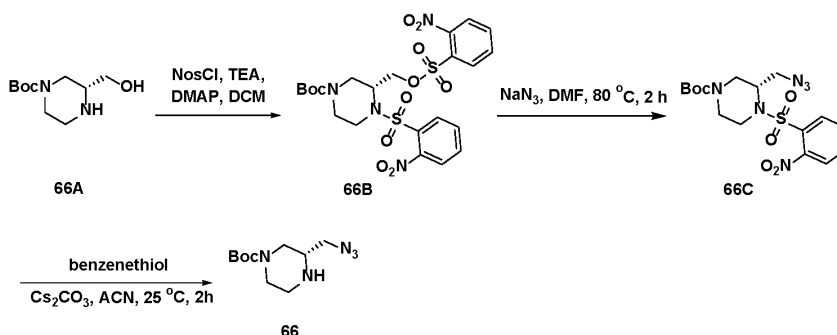
(400 MHz, DMSO- d_6) δ 8.15 (br s, 1H), 4.31 - 4.09 (m, 2H), 3.76 (br s, 1H), 3.61 - 3.50 (m, 2H), 3.36 (br s, 3H), 3.24 (br s, 2H), 1.36 (br s, 9H).

3.20 Preparation of Intermediate 65

[00735] To a solution of **compound 65B** (11.4 g, 38.2 mmol, 1 *eq*) in DCM (90 mL) was added TFA (30 mL) and the mixture stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give crude **Intermediate 65** (7.61 g) as an oil; LCMS [M+H]⁺: 200.2; ¹H NMR (400 MHz, CHLOROFORM- d) δ 8.51 (br d, J = 4.5 Hz, 1H), 4.52 (br dd, J = 3.7, 10.5 Hz, 1H), 4.24 - 4.17 (m, 1H), 4.02 (br d, J = 11.7 Hz, 1H), 3.87 (br t, J = 11.7 Hz, 1H), 3.75 (br t, J = 11.6 Hz, 1H), 3.70 - 3.60 (m, 1H), 3.48 (br dd, J = 4.2, 10.4 Hz, 3H), 3.40 - 3.33 (m, 3H).

C7. Synthesis of Intermediate 66

Scheme C7.



3.21 Preparation of compound 66B

[00736] To a solution of **compound 66A** (25 g, 116 mmol, 1 *eq*) in DCM (500 mL) was added NosCl (79.4 g, 358 mmol, 3.1 *eq*), DMAP (141 mg, 1.16 mmol, 0.01 *eq*) and TEA (64.4 mL, 462 mmol, 4 *eq*) at 25 °C. The mixture was stirred at 25 °C for 12 h, poured into water (500 mL) and the aqueous phase extracted with DCM (3 × 500 mL). The combined organic phase was washed with brine (2 × 500 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by *prep*-HPLC (column: Welch Xtimate C18 250*100mm#10um; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 45%-75%, 20 min) to give **compound 66B** (40 g, 59% yield) as a yellow solid.

3.22 Preparation of compound 66C

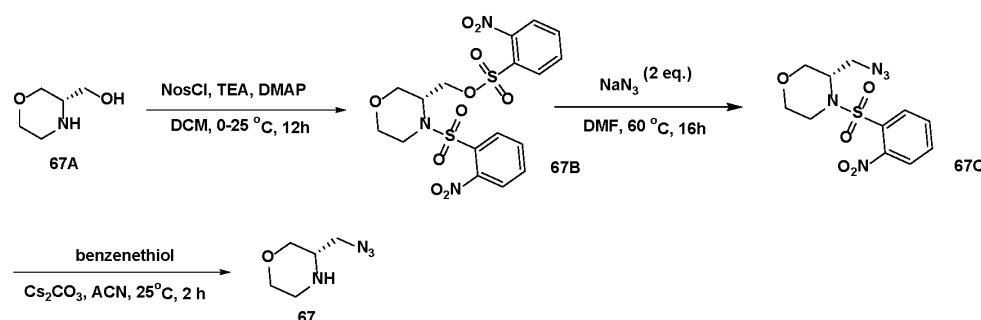
[00737] To a solution of **compound 66B** (10 g, 17.1 mmol, 1 *eq*) in DMF (100 mL) was added NaN₃ (2.22 g, 34.1 mmol, 2 *eq*) and the mixture stirred at 80 °C for 2 h. The mixture was diluted with water (500 mL) and extracted with EtOAc (300 mL). The organic layer was washed with brine (2 × 200 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 66C** (8.4 g, 58% yield) as a light yellow solid; ¹H NMR (400 MHz, CDCl₃) δ 8.19 - 8.04 (m, 1H), 7.87 - 7.64 (m, 3H), 4.22 - 4.11 (m, 1H), 3.99 (s, 1H), 3.79 - 3.58 (m, 1H), 3.54 - 3.37 (m, 2H), 3.27 - 3.15 (m, 1H), 3.03 (d, J = 11.8 Hz, 1H), 2.93 - 2.66 (m, 1H), 1.52 - 1.42 (m, 9H).

3.23 Preparation of Intermediate 66

[00738] To a mixture of **compound 66C** (8.0 g, 18.8 mmol, 1 *eq*) in ACN (80 mL) was added benzenethiol (3.83 mL, 37.5 mmol, 2 *eq*) and Cs₂CO₃ (12.2 g, 37.5 mmol, 2 *eq*) at 25 °C under a nitrogen atmosphere. The mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched by addition of a 2 M NaOH solution (200 mL) at 25°C and extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine (200 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 66** (8.2 g, 56% yield) as a light yellow solid; ¹H NMR (400 MHz, CDCl₃) δ 3.89 (d, *J* = 7.8 Hz, 2H), 3.42 (dd, *J* = 4.4, 12.2 Hz, 1H), 3.26 (dd, *J* = 7.7, 12.1 Hz, 1H), 2.98 (d, *J* = 11.5 Hz, 1H), 2.93 - 2.84 (m, 1H), 2.83 - 2.69 (m, 2H), 2.61 (s, 1H), 1.46 (s, 9H).

C8. Synthesis of Intermediate 9

Scheme C8.



3.24 Preparation of compound 67B

[00739] To a solution of **compound 67A** (6.0 g, 39.1 mmol, 1 *eq*) in DCM (60 mL) was added TEA (21.8 mL, 156 mmol, 4 *eq*) and DMAP (48 mg, 391 μmol, 0.01 *eq*). 2-Nitrobenzenesulfonyl chloride (26.8 g, 121 mmol) was added at 0 °C, the mixture stirred at 25°C for 12 h, extracted with DCM (2 × 10 mL), the combined organic phase washed with brine (10 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether:EtOAc) to give **compound 67B** (11 g, 56% yield) as a yellow oil; ¹H NMR (400 MHz, DMSO-d₆) δ 8.09 - 8.17 (m, 3H), 8.04 (td, *J*=7.75, 1.38 Hz, 1H), 7.92 - 7.99 (m, 2H), 7.79 - 7.92 (m, 2H), 4.99 (br s, 1H), 4.51 (dd, *J*=10.19, 7.07 Hz, 1H), 4.37 (dd, *J*=10.19, 7.69 Hz, 1H), 4.12 (td, *J*=7.19, 2.63 Hz, 1H), 3.85 (d, *J*=12.13 Hz, 1H), 3.77 (dd, *J*=11.51, 2.63 Hz, 1H), 3.50 - 3.56 (m, 1H), 3.38 - 3.47 (m, 1H), 3.16 - 3.25 (m, 1H).

3.25 Preparation of compound 67C

[00740] To a solution of **compound 67B** (4.0 g, 8.21 mmol, 1 *eq*) in DMF (40 mL) was added NaN₃ (1.07 g, 16.4 mmol, 2 *eq*) at 25°C. The mixture was stirred at 60°C for 16 h, quenched by addition of a saturated K₂CO₃ solution at 25°C until the reaction mixture pH =9, and extracted with EtOAc (2 × 20 mL). The combined organic phase was washed with brine (20 mL), dried (Na₂SO₄) and concentrated under reduced pressure. (The aqueous phase was quenched with sodium hypochlorite aqueous solution (160 ml)). The residue was purified by silica gel chromatography (petroleum ether:EtOAc) to give **compound 67C** (3.8 g, 69% yield) as a yellow oil; ¹H NMR (400 MHz, DMSO-d₆) δ 8.15 (dd, *J*=7.72,

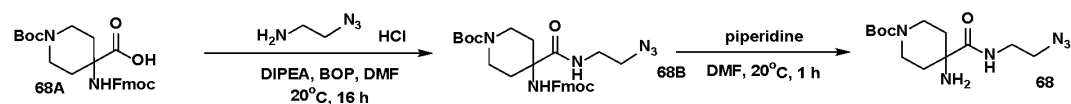
1.57 Hz, 1H), 7.98 - 8.03 (m, 1H), 7.83 - 7.95 (m, 2H), 3.91 - 3.98 (m, 1H), 3.67 - 3.82 (m, 3H), 3.52 - 3.64 (m, 2H), 3.37 - 3.48 (m, 2H), 3.19 (td, $J=11.86$, 3.14 Hz, 1H).

3.26 Preparation of Intermediate 67

[00741] To a solution of **compound 67C** (1.0 g, 3.06 mmol, 1 *eq*) in ACN (14 mL) was added Cs_2CO_3 (1.99 g, 6.11 mmol, 2 *eq*) and benzenethiol (623 μL , 6.11 mmol, 2 *eq*). The mixture was stirred at 25 °C for 2 h, quenched by addition of a 2 M NaOH solution at 25 °C (15 mL), and extracted with EtOAc (2 $\times$ 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. (The aqueous phase was quenched with sodium hypochlorite aqueous solution). The residue was purified by column chromatography (SiO_2 , petroleum ether:EtOAc) to give **Intermediate 67** (500 mg, 69% yield, 60% purity) as a yellow oil; ^1H NMR (400 MHz, DMSO- d_6) δ 3.59 - 3.69 (m, 2H), 3.23 - 3.36 (m, 2H), 3.16 - 3.23 (m, 1H), 3.10 (dd, $J=10.8$, 9.3 Hz, 1H), 2.76 - 2.83 (m, 1H), 2.65 - 2.75 (m, 2H).

C9. Synthesis of Intermediate 68

Scheme C9.



3.27 Preparation of compound 68B

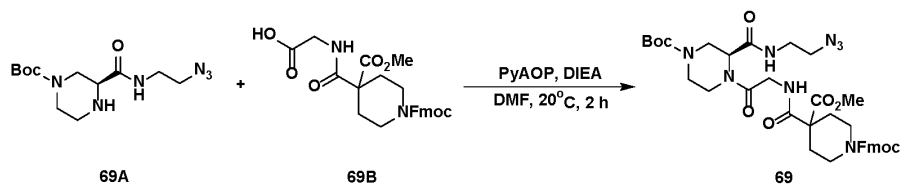
[00742] To a mixture of **2-azidoethan-1-amine HCl** (1.31 g, 10.7 mmol, 1 *eq*) in DMF (40 mL) was added DIEA (2.1 mL, 11.8 mmol, 1.1 *eq*) and the mixture stirred at 20 °C for 10 minutes. To the reaction mixture was added **compound 68A** (5.0 g, 10.72 mmol, 1 *eq*) and BOP (4.74 g, 10.72 mmol, 1 *eq*) at 20 °C. The mixture was stirred at 20 °C for 16 h, poured into water (50 mL), the aqueous phase extracted with EtOAc (3 $\times$ 200 mL), the combined organics washed with brine (2 $\times$ 100 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , petroleum ether:EtOAc) to give **compound 68B** (11.8 g, 69% yield) as a white solid; ^1H NMR (400 MHz, DMSO- d_6) δ 7.95 - 7.86 (m, 2H), 7.82 (br s, 1H), 7.74 (br d, $J=7.2$ Hz, 2H), 7.50 (br s, 1H), 7.47 - 7.28 (m, 4H), 4.34 - 4.14 (m, 3H), 3.64 (br d, $J=12.0$ Hz, 2H), 3.32 - 3.15 (m, 4H), 3.01 (br s, 2H), 1.89 (br s, 2H), 1.77 (br t, $J=10.2$ Hz, 2H), 1.40 (s, 9H).

3.28 Preparation of Intermediate 68

[00743] To a mixture of **compound 68B** (5.4 g, 10.1 mmol, 1 *eq*) in DMF (100 mL) was added piperidine (4.99 mL, 50.5 mmol, 5 *eq*) in one portion at 20 °C. The mixture was stirred at 20 °C for 1 h and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , petroleum ether:EtOAc) to give **Intermediate 68** (4.5 g, 71% yield) as a light-yellow solid; ^1H NMR (400 MHz, CHLOROFORM- d) δ 8.04 (br s, 1H), 4.08 - 3.90 (m, 2H), 3.49 - 3.40 (m, 4H), 3.06 (br t, $J=12.2$ Hz, 2H), 2.16 (ddd, $J=4.6$, 11.8, 13.8 Hz, 2H), 1.47 (s, 9H), 1.42 - 1.32 (m, 2H).

C10. Synthesis of Intermediate 69

Scheme C10.

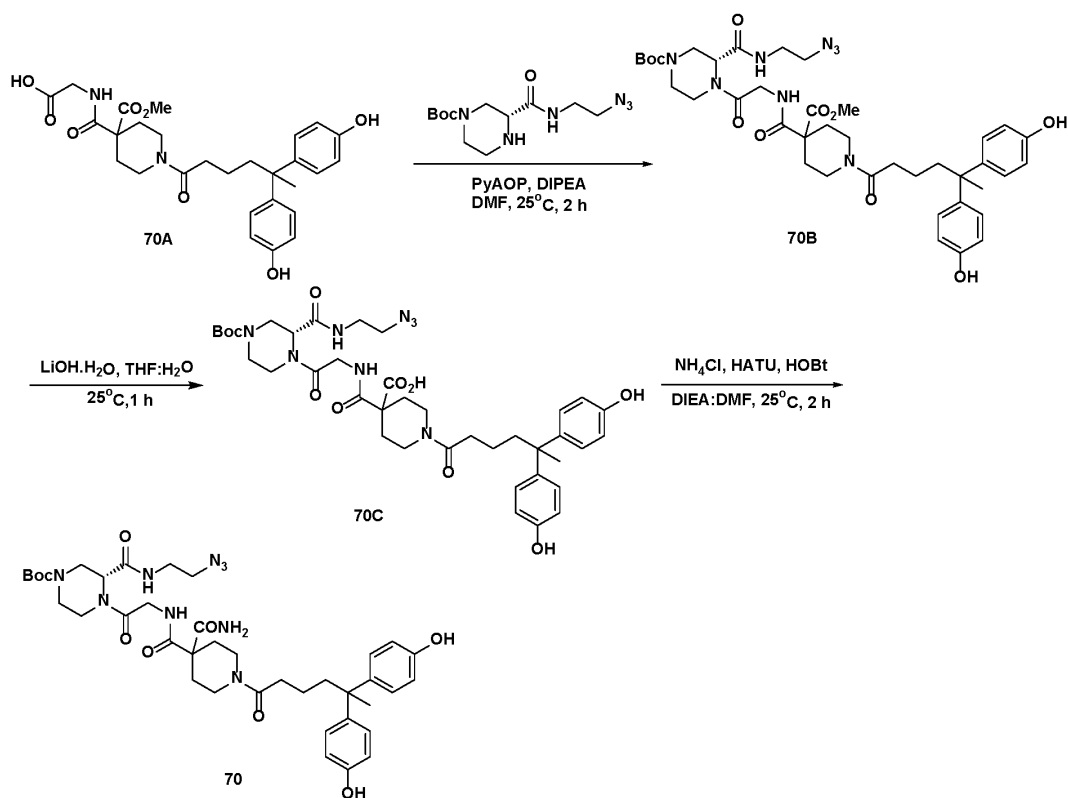


3.29 Synthesis of intermediate 69

[00744] To a mixture of **compound 69A** (2.13 g, 4.29 mmol, 1 *eq*) and **compound 69B** (2.0 g, 4.29 mmol, 1 *eq*) in DMF (15 mL) was added PyAOP (2.46 g, 4.72 mmol, 1.1 *eq*) and DIEA (1.49 mL, 8.57 mmol, 2 *eq*) at 20°C under a nitrogen atmosphere. The mixture was stirred at 20°C for 2h and the reaction mixture concentrated under reduced pressure. The crude product was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give crude **compound 69** (7.6 g) as a white solid; LCMS [M-100]: 647.4; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.24 - 8.11 (m, 1H), 7.98 - 7.78 (m, 2H), 7.68 - 7.55 (m, 1H), 7.48 - 7.26 (m, 2H), 4.71 (br d, *J* = 1.4 Hz, 1H), 4.46 - 4.20 (m, 2H), 4.18 - 4.07 (m, 1H), 3.93 - 3.81 (m, 1H), 3.69 - 3.58 (m, 3H), 3.22 (br s, 13H), 2.07 - 1.69 (m, 4H), 1.47 - 1.12 (m, 15H).

C11. Synthesis of Intermediate 70

Scheme C11.



3.30 Synthesis of compound 70B

[00745] To a solution of *tert*-butyl (R)-3-((2-azidoethyl)carbamoyl)piperazine-1-carboxylate (933 mg, 3.13 mmol, 1 *eq*) and **compound 70A** (1.65 g, 3.13 mmol, 1 *eq*) in DMF (18 mL) was added DIEA (1.36 mL, 7.82 mmol, 2.5 *eq*) and PyAOP (1.79 g, 3.44 mmol, 1.1 *eq*). The mixture was stirred at 25°C for 2

h, partitioned between EtOAc (50 mL) and H₂O (10 mL), the organic phase washed with brine (2 × 5 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM:MeOH) to give crude **compound 70B** (1.62 g) as a white solid; LCMS [M+H]⁺:807.4; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.12 (s, 2H), 8.19 (br t, *J*= 5.4 Hz, 1H), 7.93 - 7.86 (m, 1H), 6.93 (d, *J*= 8.6 Hz, 4H), 6.62 (d, *J*= 8.6 Hz, 4H), 4.71 (br s, 1H), 4.33 - 4.20 (m, 1H), 4.14 (br d, *J*= 5.0 Hz, 1H), 4.07 - 3.98 (m, 1H), 3.94 - 3.81 (m, 1H), 3.74 - 3.61 (m, 4H), 3.58 - 3.42 (m, 3H), 3.39 - 3.33 (m, 2H), 3.30 - 3.20 (m, 3H), 3.17 (d, *J*= 5.4 Hz, 2H), 3.14 (br s, 1H), 3.01 (br dd, *J*= 2.6, 6.6 Hz, 1H), 2.30 - 2.21 (m, 2H), 1.97 - 1.89 (m, 4H), 1.47 (s, 3H), 1.37 (s, 9H), 1.28 - 1.17 (m, 3H).

3.31 Synthesis of compound 70C

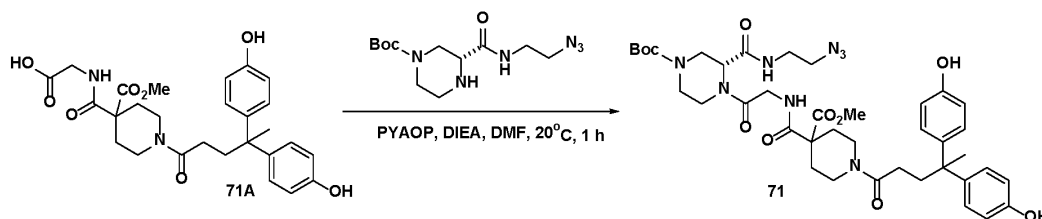
[00746] To a solution of **compound 70B** (1.4 g, 1.74 mmol, 1 *eq*) in THF (8 mL) and H₂O (8 mL) was added LiOH·H₂O (218 mg, 5.21 mmol, 3 *eq*). The mixture was stirred at 25°C for 1 h, the reaction mixture concentrated under reduced pressure and the aqueous phase adjusted to pH=5-6 with aq. HCl. The reaction mixture was concentrated under reduced pressure to give **compound 70C** (1.36 g, 99% yield) as a white solid; LCMS [M+H]⁺:793.4; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.37 - 8.91 (m, 1H), 8.18 (br t, *J*= 5.4 Hz, 1H), 7.91 (br s, 1H), 6.93 (d, *J*= 8.6 Hz, 4H), 6.63 (d, *J*= 8.6 Hz, 4H), 4.72 (br s, 1H), 4.31 (br d, *J*= 12.4 Hz, 1H), 4.16 - 3.86 (m, 3H), 3.80 - 3.53 (m, 5H), 3.51 - 3.43 (m, 2H), 3.30 - 3.07 (m, 7H), 2.24 (br t, *J*= 7.2 Hz, 2H), 2.05 - 1.74 (m, 7H), 1.47 (s, 4H), 1.37 (s, 9H), 1.24 (br d, *J*= 5.4 Hz, 2H).

3.32 Synthesis of intermediate 70

[00747] To a solution of **compound 70C** (1.36 g, 1.72 mmol, 1 *eq*) in DMF (14 mL) was added NH₄Cl (110 mg, 2.06 mmol, 1.2 *eq*), DIEA (598 μL, 3.43 mmol, 2 *eq*), HATU (652 mg, 1.72 mmol, 1 *eq*) and HOBt (278 mg, 2.06 mmol, 1.2 *eq*). The reaction mixture was stirred at 25°C for 2h and concentrated under reduced pressure. The residue was purified by reversed-phase HPLC to give **intermediate 70** (900 mg, 66% yield) as a white solid; LCMS [M+H]⁺:792.7; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.31 - 8.92 (m, 1H), 8.21 (br s, 1H), 7.95 (br s, 1H), 7.45 (br s, 1H), 7.24 (br s, 1H), 6.93 (d, *J*= 8.6 Hz, 4H), 6.63 (d, *J*= 8.6 Hz, 4H), 4.72 (br s, 1H), 4.39 - 4.09 (m, 2H), 3.91 (br dd, *J*= 5.0, 16.8 Hz, 1H), 3.80 - 3.61 (m, 4H), 3.35 (br d, *J*= 5.4 Hz, 3H), 3.29 - 3.07 (m, 6H), 2.24 (br s, 2H), 2.09 - 1.76 (m, 7H), 1.47 (s, 3H), 1.38 (s, 9H), 1.22 (br s, 2H).

C12. Synthesis of Intermediate 71

Scheme C12.



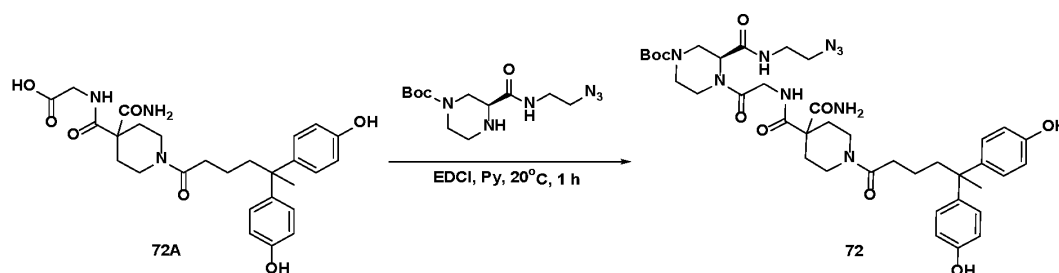
3.33 Synthesis of intermediate 71

[00748] To a mixture of *tert*-butyl (*R*)-3-((2-azidoethyl)carbamoyl)piperazine-1-carboxylate (450 mg, 1.51 mmol, 1 *eq*) and **compound 71A** (773 mg, 1.51 mmol, 1 *eq*) in DMF (5 mL) was added DIEA (657 μL, 3.77 mmol, 2.5 *eq*) and PyAOP (865 mg, 1.66 mmol, 1.1 *eq*) at 20°C under a nitrogen atmosphere.

The mixture was stirred at 20 °C for 1 h, poured into water (80 mL) and extracted with EtOAc (3 × 120 mL). The combined organic phase was washed with brine (2 × 20 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified by column chromatography (DCM:MeOH) to give **intermediate 71** (850 mg, 71% yield) as a white solid; ¹H NMR (400 MHz, METHANOL-*d*₄) δ 7.02 (br d, *J* = 8.4 Hz, 5H), 6.69 (br d, *J* = 7.6 Hz, 4H), 4.10 (q, *J* = 7.0 Hz, 4H), 3.94 - 3.84 (m, 1H), 3.83 - 3.67 (m, 5H), 3.65 - 3.53 (m, 1H), 3.44 - 3.36 (m, 4H), 3.33 - 3.30 (m, 8H), 3.28 - 3.10 (m, 3H), 2.37 - 2.24 (m, 2H), 2.15 - 2.05 (m, 4H), 1.46 (s, 9H).

C13. Synthesis of Intermediate 72

Scheme C13.

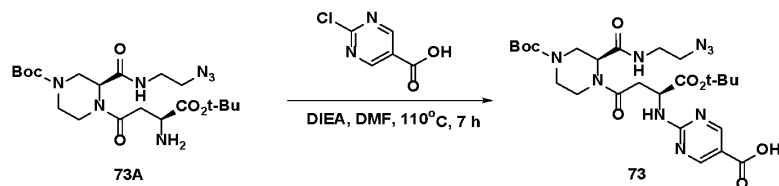


3.34 Synthesis of Intermediate 72

[00749] To a solution of *tert*-butyl (*S*)-3-((2-azidoethyl)carbamoyl)piperazine-1-carboxylate (10.1 g, 33.7 mmol, 1.5 *eq*) and **compound 72A** (11.5 g, 22.5 mmol, 1 *eq*) in pyridine (105 mL) was added EDCI (8.62 g, 45 mmol, 2 *eq*). The mixture was stirred at 20°C for 1h and concentrated under reduced pressure. The reaction was repeated and the combined residues were purified by column chromatography (SiO₂, EtOAc:MeOH) to give **Intermediate 72** (23 g, 64.6% yield) as a white solid; LCMS [*M*+*H*]: 792.5; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.13 (s, 2H), 8.23 (br t, *J* = 5.4 Hz, 1H), 7.97 (br s, 1H), 7.46 (br s, 1H), 7.24 (br s, 1H), 6.93 (d, *J* = 8.6 Hz, 4H), 6.63 (d, *J* = 8.6 Hz, 4H), 4.72 (br s, 1H), 4.35 - 4.13 (m, 2H), 3.92 (br dd, *J* = 4.8, 16.8 Hz, 1H), 3.83 - 3.62 (m, 3H), 3.52 - 3.41 (m, 2H), 3.35 (br s, 2H), 3.21 (br d, *J* = 11.8 Hz, 3H), 3.12 (br d, *J* = 4.8 Hz, 2H), 2.24 (br t, *J* = 7.2 Hz, 2H), 2.09 - 1.72 (m, 6H), 1.47 (s, 3H), 1.38 (s, 9H), 1.28 - 1.18 (m, 2H).

C14. Synthesis of Intermediate 73

Scheme C14.



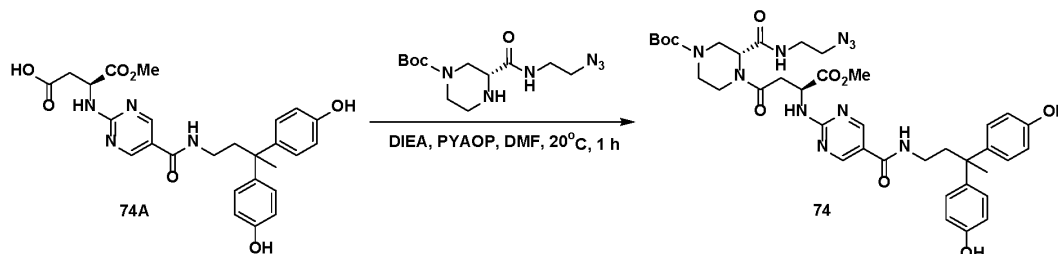
3.35 Synthesis of intermediate 73

[00750] To a solution of **compound 73A** (4.7 g, 10.0 mmol, 1 *eq*), 2-chloropyrimidine-5-carboxylic acid (1.59 g, 10.0 mmol, 1 *eq*) in DMF (50 mL) was added DIEA (5.23 mL, 30.0 mmol, 3 *eq*). The mixture was stirred at 110°C for 7h and the reaction mixture concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM:MeOH) to give **compound 8** (5.4 g, 46%

yield) as a white oil; LCMS [M+H]:592.2; ^1H NMR (400 MHz, DMSO- d_6) δ 12.82 (br s, 1H), 8.79 - 8.67 (m, 2H), 8.16 (br t, J = 5.4 Hz, 1H), 8.04 - 7.83 (m, 1H), 4.80 - 4.68 (m, 2H), 4.38 - 4.13 (m, 1H), 3.82 - 3.64 (m, 2H), 3.54 - 3.41 (m, 1H), 3.37 - 3.33 (m, 2H), 3.19 (s, 1H), 3.17 - 2.91 (m, 3H), 2.87 - 2.77 (m, 1H), 1.43 - 1.31 (m, 18H).

C15. Synthesis of Intermediate 74

Scheme C15.

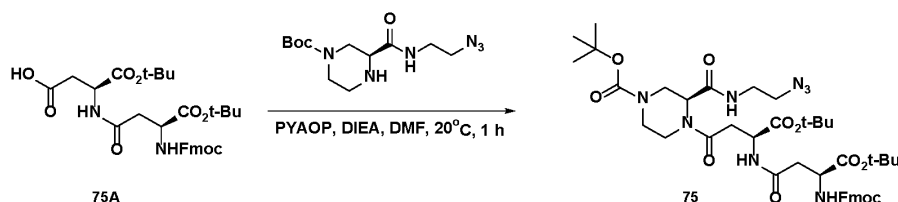


3.36 Synthesis of Intermediate 74

[00751] To a mixture of **compound 74A** (2.4 g, 4.72 mmol, 1 *eq*) and *tert*-butyl (*R*)-3-((2-azidoethyl)carbamoyl)piperazine-1-carboxylate (1.69 g, 5.66 mmol, 1.2 *eq*) in DMF (3 mL) was added DIEA (2.06 mL, 2.5 *eq*) and PyAOP (2.71 g, 5.19 mmol, 1.1 *eq*). The suspension was degassed under reduced pressure and purged with nitrogen 3 times. The mixture was stirred at 20 °C for 1 h, quenched by addition of H₂O (15 mL) at 20°C, diluted with H₂O (20 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine (20 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM:MeOH) to give **intermediate 74** (1.9 g, 51% yield) as a white solid.

C16. Synthesis of Intermediate 75

Scheme C16.



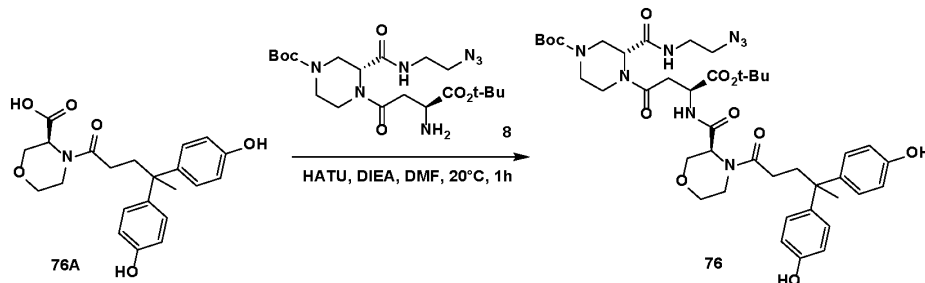
3.37 Synthesis of Intermediate 75

[00752] To a solution of *tert*-butyl (*S*)-3-((2-azidoethyl)carbamoyl)piperazine-1-carboxylate (20.0 g, 35.5 mmol, 1 *eq*) and **compound 75A** (21.5 g, 36.9 mmol, 1.0 *eq*) in DMF (200 mL) was added PyAOP (19.2 g, 36.9 mmol, 1.1 *eq*) and DIEA (11.7 mL, 67.0 mmol, 2 *eq*). The mixture was stirred at 20°C for 1h, the reaction mixture poured into water (300 mL) and extracted with EtOAc (3 × 100 mL). The combined organic phase was washed with a saturated NH₄Cl solution (100mL), a saturated NaHCO₃ solution (100 mL) and brine (100 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **Intermediate 75** (18 g, 62% yield) as a yellow oil; LCMS [M+H]: 863.6; ^1H NMR (400 MHz, METHANOL- d_4) δ 7.80 (br d, J = 7.4 Hz, 2H), 7.68 (br d, J = 7.4 Hz, 2H), 7.44 - 7.35 (m, 2H), 7.31 (s, 2H), 4.88 (br s, 2H), 4.74

- 4.61 (m, 1H), 4.54 - 4.17 (m, 5H), 3.93 - 3.73 (m, 2H), 3.61 - 3.48 (m, 1H), 3.38 (br d, $J = 5.2$ Hz, 3H), 3.29 - 2.65 (m, 7H), 1.52 - 1.37 (m, 27H).

C17. Synthesis of Intermediate 76

Scheme C17.

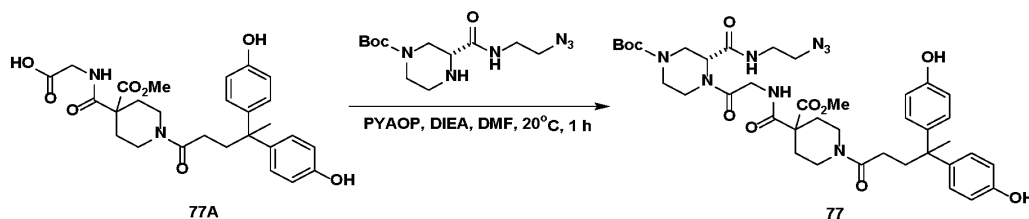


3.38 Synthesis of Intermediate 76

[00753] To a solution of **compound 76A** (0.50 g, 1.25 mmol, 1 *eq*) and *tert*-butyl (*R*)-4-((*S*)-3-amino-4-(*tert*-butoxy)-4-oxobutanoyl)-3-((2-azidoethyl)carbamoyl)piperazine-1-carboxylate (588 mg, 1.25 mmol, 1 *eq*) in DMF (3 mL) was added HATU (476 mg, 1.25 mmol, 1 *eq*) and DIEA (654 μ L, 3.76 mmol, 3 *eq*) at 20°C. The reaction mixture was stirred at 20°C for 1 h, diluted with EtOAc (4 mL), washed with aq. NH_4Cl (2 mL), aq. Na_2CO_3 (2 mL) and brine (3 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , petroleum ether:EtOAc) to give **Intermediate 76** (1.0 g, 94% yield) as a white solid; LCMS $[\text{M}+\text{H}]$: 851.4.

C18. Synthesis of Intermediate 77

Scheme C18



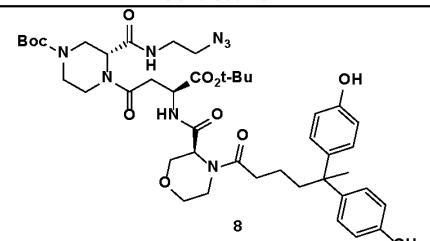
3.39 Synthesis of Intermediate 77

[00754] To a mixture of *tert*-butyl (*R*)-3-((2-azidoethyl)carbamoyl)piperazine-1-carboxylate (450 mg, 1.51 mmol, 1 *eq*) and **compound 77A** (773 mg, 1.51 mmol, 1 *eq*) in DMF (5 mL) was added DIEA (657 μ L, 3.77 mmol, 2.5 *eq*) and PyAOP (865 mg, 1.66 mmol, 1.1 *eq*) at 20°C under a nitrogen atmosphere. The mixture was stirred at 20 °C for 1 h, poured into water (80 mL) and the aqueous phase extracted with EtOAc (3 $\times$ 120 mL). The combined organic phase was washed with brine (2 $\times$ 20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (**DCM:MeOH**) to give **Intermediate 77** (850 mg, 71% yield) as white solid; ^1H NMR (400 MHz, $\text{METHANOL-}d_4$) δ 7.02 (br d, $J = 8.4$ Hz, 5H), 6.69 (br d, $J = 7.6$ Hz, 4H), 4.10 (q, $J = 7.0$

Hz, 4H), 3.94 - 3.84 (m, 1H), 3.83 - 3.67 (m, 5H), 3.65 - 3.53 (m, 1H), 3.44 - 3.36 (m, 4H), 3.33 - 3.30 (m, 8H), 3.28 - 3.10 (m, 3H), 2.37 - 2.24 (m, 2H), 2.15 - 2.05 (m, 4H), 1.46 (s, 9H).

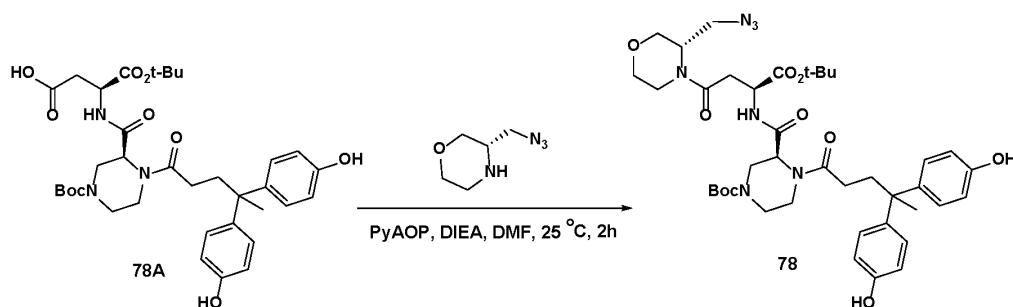
Compounds in **table 8.4** were prepared by procedures depicted in **scheme C18**.

Table 8.4.

Compound	Structure	m/z
77.1		[M+H] ⁺ : 865.3

C19. Synthesis of Intermediate 78

Scheme C19.

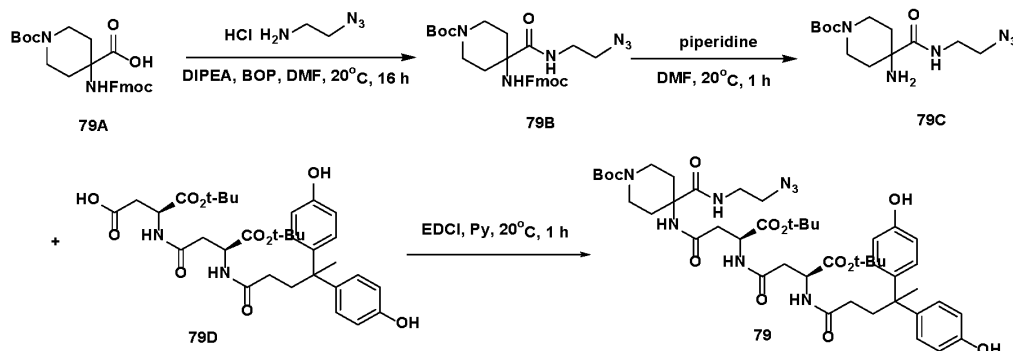


3.40 Synthesis of Intermediate 78

[00755] To a solution of (S)-3-(azidomethyl)morpholine (500 mg, 3.52 mmol, 1 *eq*) and **compound 78A** (1.88 g, 2.81 mmol, 0.8 *eq*) in DMF (5 mL) was added PyAOP (1.47 g, 2.81 mmol, 0.8 *eq*) and DIEA (1.84 mL, 10.6 mmol, 3 *eq*). The mixture was stirred at 25 °C for 2h and extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine (20 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO₂, petroleum ether:EtOAc) to give **Intermediate 78** (710 mg, 25% yield) as a yellow solid; ¹H NMR (400 MHz, DMSO-d₆) δ 9.16 (d, *J*=2.3 Hz, 1H), 8.03 - 8.29 (m, 1H), 7.95 (s, 1H), 6.95 (br d, *J*=8.4 Hz, 4H), 6.64 (br d, *J*=8.4 Hz, 4H), 4.83 (br s, 1H), 4.32 - 4.60 (m, 2H), 4.09 - 4.30 (m, 1H), 3.69 - 3.96 (m, 3H), 3.38 - 3.62 (m, 4H), 3.23 - 3.29 (m, 1H), 3.08 - 3.19 (m, 1H), 2.97 - 3.08 (m, 1H), 2.86 - 2.92 (m, 3H), 2.73 (s, 2H), 2.20 (br d, *J*=5.0 Hz, 2H), 2.02 - 2.15 (m, 2H), 1.44 - 1.54 (m, 3H), 1.36 (d, *J*=1.6 Hz, 18H).

C20. Synthesis of Intermediate 79

Scheme C20.



3.41 Synthesis of compound 79B

[00756] To a mixture of 2-azidoethan-1-amine (1.31 g, 10.7 mmol, 1 *eq*) in DMF (40 mL) was added DIEA (2.1 mL, 11.8 mmol, 1.1 *eq*), the mixture stirred at 20 °C for 10 minutes, **compound 79A** (5.0 g, 10.7 mmol, 1 *eq*) and BOP (4.74 g, 10.7 mmol, 1 *eq*) added at 20 °C and the reaction stirred at 20°C for 16 h. The reaction mixture was poured into water (50 mL), the aqueous phase extracted with EtOAc (3 × 200 mL), the combined organics washed with brine (2 × 100 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 79B** (11.8 g, 69% yield) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.95 - 7.86 (m, 2H), 7.82 (br s, 1H), 7.74 (br d, *J* = 7.2 Hz, 2H), 7.50 (br s, 1H), 7.47 - 7.28 (m, 4H), 4.34 - 4.14 (m, 3H), 3.64 (br d, *J* = 12.0 Hz, 2H), 3.32 - 3.15 (m, 4H), 3.01 (br s, 2H), 1.89 (br s, 2H), 1.77 (br t, *J* = 10.2 Hz, 2H), 1.40 (s, 9H).

3.42 Synthesis of compound 79C

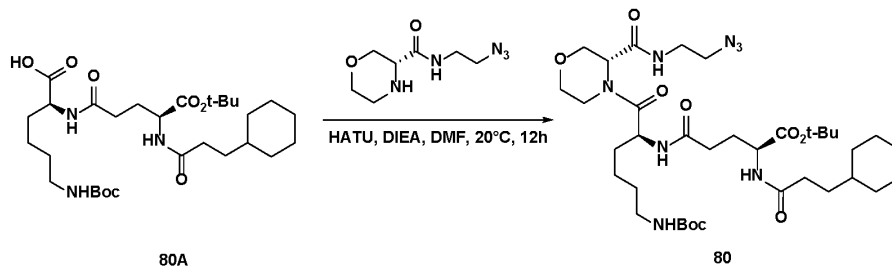
[00757] To a mixture of **compound 79B** (5.4 g, 10.1 mmol, 1 *eq*) in DMF (100 mL) was added piperidine (4.99 mL, 50.5 mmol, 5 *eq*) in one portion at 20°C. The mixture was stirred at 20°C for 1h and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 79C** (4.5 g, 71% yield) as a light yellow solid; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.04 (br s, 1H), 4.08 - 3.90 (m, 2H), 3.49 - 3.40 (m, 4H), 3.06 (br t, *J* = 12.2 Hz, 2H), 2.16 (ddd, *J* = 4.6, 11.8, 13.8 Hz, 2H), 1.47 (s, 9H), 1.42 - 1.32 (m, 2H).

3.43 Synthesis of Intermediate 79

[00758] To a solution of **compound 79C** (160 mg, 512 μmol, 1 *eq*) in pyridine (3.5 mL) was added **compound 79D** (354 mg, 563 μmol, 1.1 *eq*) and EDCI (196 mg, 1.02 mmol, 2 *eq*) at 20°C for 1 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **Intermediate 79** (360 mg, 76% yield) as a white solid; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 7.14 - 6.83 (m, 7H), 6.81 - 6.62 (m, 5H), 4.90 - 4.57 (m, 2H), 3.94 - 3.77 (m, 2H), 3.54 - 3.31 (m, 4H), 3.12 - 2.98 (m, 2H), 2.76 - 2.58 (m, 3H), 2.48 - 2.27 (m, 3H), 2.06 - 1.90 (m, 6H), 1.70 (br s, 4H), 1.50 - 1.38 (m, 27H).

C21. Synthesis of Intermediate 80

Scheme C21.



3.45 Synthesis of Intermediate 80

[00759] To a solution of (*R*)-*N*-(2-azidoethyl)morpholine-3-carboxamide (825 mg, 2.63 mmol, 1 *eq*, TFA) and **compound 80A** (1.5 g, 2.63 mmol, 1 *eq*) in DMF (15 mL) was added HATU (1.00 g, 2.63 mmol, 1 *eq*) and DIEA (1.38 mL, 7.90 mmol, 3 *eq*). The mixture was stirred at 20°C for 12 h, diluted with EtOAc (20 mL) and extracted with H₂O (10 mL). The combined organic layers were washed with brine (9 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM:MeOH) to give **Intermediate 80** (1.75 g, 89% yield) as a white solid; LCMS; [M+H]⁺: 751.5.

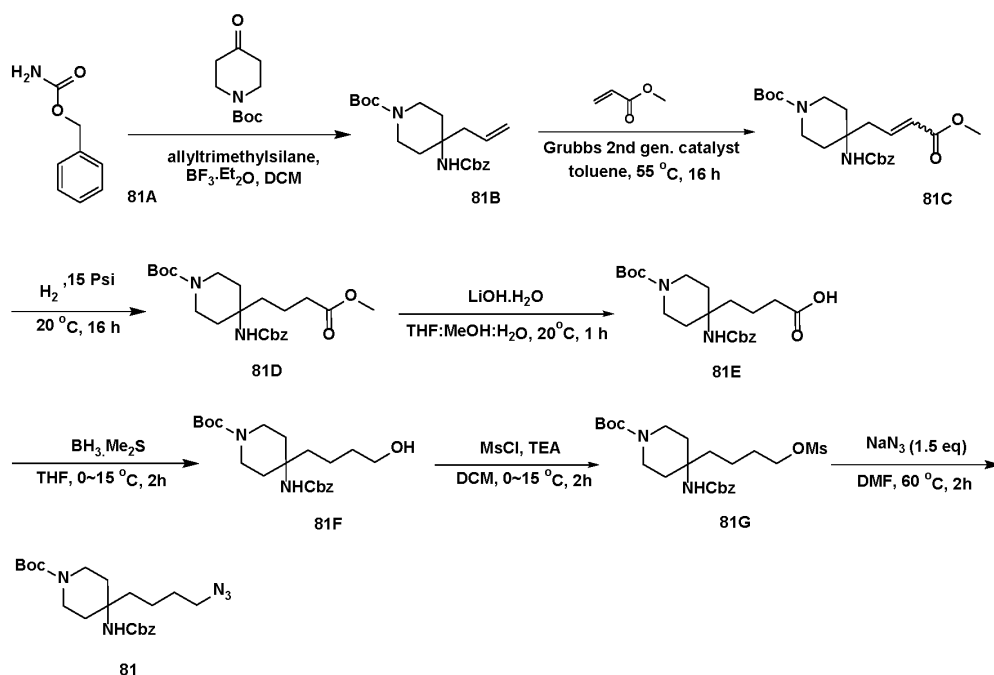
[00760] Compounds in **table 8.5** were prepared by procedures depicted in **scheme C21**.

Table 8.5.

Compound	Structure	m/z
80.1		[M+H] ⁺ : 751.4

C22. Synthesis of Intermediate 81

Scheme C22.



3.46 Synthesis of compound 81B

[00761] To a solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (100 g, 502 mmol, 1 *eq*), **compound 81A** (91.0 g, 602 mmol, 1.2 *eq*) and allyl(trimethyl)silane (96.1 mL, 602 mmol, 1.2 *eq*) in DCM (1000 mL) was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (74.3 mL, 602 mmol, 1.2 *eq*) dropwise at 0°C . The solution was stirred at 0°C for 40 min and 30°C for 16 h. The reaction was concentrated under reduced pressure, the residue diluted with EtOAc (1000 mL), washed with NaHCO_3 (300 mL) and brine (200 mL), the organics dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , Petroleum ether:EtOAc) to give **compound 81B** (89 g, 23% yield) as a light-yellow oil.

3.47 Synthesis of compound 81C

[00762] To a solution of **compound 81B** (63 g, 168 mmol, 1 *eq*) in toluene (630 mL) was added methyl acrylate (76 mL, 841 mmol, 5 *eq*) and Grubbs 2nd generation catalyst (14.3 g, 16.8 mmol, 0.1 *eq*). The mixture was stirred at 55°C for 16 h and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , petroleum ether:EtOAc) to give **compound 81C** (54 g, 71% yield) as a colorless oil.

3.48 Synthesis of compound 81D

[00763] To a solution of **compound 81C** (54 g, 125 mmol, 1 *eq*) in EtOAc (48 mL) was added PtO_2 (18.4 g, 81.2 mmol, 0.65 *eq*) at 20°C . The mixture was stirred at 20°C for 16 h under a hydrogen atmosphere (15 psi). The mixture was filtered, and the filtrate concentrated under reduced pressure to give **compound 81D** (54 g, 38% yield) as an oil.

3.49 Synthesis of compound 81E

[00764] To a solution of **compound 81D** (54 g, 124 mmol, 1 *eq*) in THF (225 mL), MeOH (225 mL) and H₂O (160 mL) was added LiOH.H₂O (20.9 g, 497 mmol, 4 *eq*). The mixture was stirred at 20°C for 2h, adjusted to pH=4 with a saturated citric acid solution, extracted with EtOAc (3 × 300 mL), the organic phase washed with brine (150 mL), dried (Na₂SO₄), filtered and concentrated to give **compound 81E** (54 g, 83% yield) as a white solid.

3.50 Synthesis of compound 81F

[00765] To a solution of **compound 81E** (34 g, 81 mmol, 1 *eq*) in THF (340 mL) was added BH₃-Me₂S (28.3 mL, 283 mmol, 3.5 *eq*) dropwise at 0°C. The mixture was stirred at 15°C for 2h, the reaction quenched with an aqueous ammonium chloride (30 mL) and extracted with EtOAc (3 × 300 mL). The organics were washed with brine (150 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM:MeOH) to give **compound 81F** (20 g, 55% yield) as a brown oil.

3.51 Synthesis of compound 81G

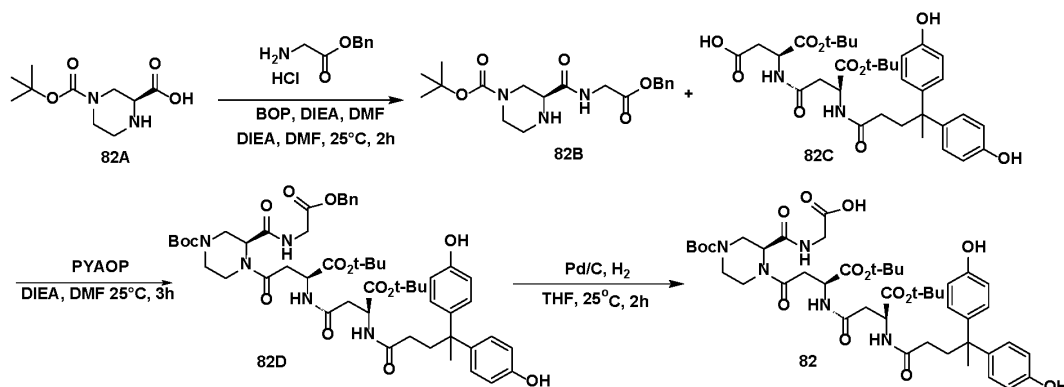
[00766] To a solution of **compound 81F** (21 g, 51.7 mmol, 1 *eq*) in DCM (210 mL) was added TEA (21.6 mL, 155 mmol, 3 *eq*) and MsCl (6.00 mL, 77 mmol, 1.5 *eq*) dropwise at 0°C. The mixture was stirred at 15°C for 2h. The mixture was quenched with aq. NH₄Cl (50 mL) and extracted with DCM (3 × 200 mL). The organic phase was washed with brine (100 mL), dried (Na₂SO₄), filtered and concentrated to give **compound 81G** (25 g, crude) as a brown oil.

3.52 Synthesis of Intermediate 81

[00767] To a solution of **compound 81G** (35.7 g, 73.7 mmol, 1 *eq*) in DMF (350 mL) was added NaN₃ (7.18 g, 111 mmol, 1.5 *eq*). The mixture was stirred at 60°C for 2h, diluted with H₂O (500 mL), extracted with EtOAc (3 × 200 mL), the organic layers washed with brine (3 × 100 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. (The aqueous phase was poured into H₂O (1000 mL) and NaClO (1000 mL) added slowly, the mixture was stirred at 20°C for 16h and discarded). The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **Intermediate 81** (21 g, 63% yield) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 7.33 - 7.22 (m, 5H), 5.05 - 4.93 (s, 2H), 4.51 - 4.39 (s, 1H), 3.80 - 3.62 (s, 2H), 3.23 - 3.13 (m, 2H), 3.03 - 2.87 (m, 2H), 1.97 - 1.85 (m, 2H), 1.73 - 1.61 (m, 2H), 1.54 - 1.47 (m, 2H), 1.47 - 1.40 (m, 2H), 1.38 (s, 9H), 1.31 - 1.19 (m, 2H).

C23. Synthesis of Intermediate 82

Scheme C23.



3.53 Synthesis of compound 82B

[00768] To a solution of benzyl glycinate (4.82 g, 23.9 mmol, 1.1 *eq*) in DMF (50 mL) was added DIEA (15.1 mL, 86.9 mmol, 4 *eq*), **compound 82A** (5.0 g, 21.7 mmol, 1 *eq*) and BOP (10.6 g, 23.9 mmol, 1.1 *eq*). The mixture was stirred at 25°C for 2 h, poured into water (50 mL) and the aqueous phase extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by *prep*-HPLC (column: Phenomenex luna C18 (250*70mm, 10 μ m); mobile phase: [water (TFA)-ACN]; gradient: 15%-50% B over 20 min) to give **compound 82B** (1.5 g, 14% yield, TFA) as a white solid.

3.54 Synthesis of compound 82D

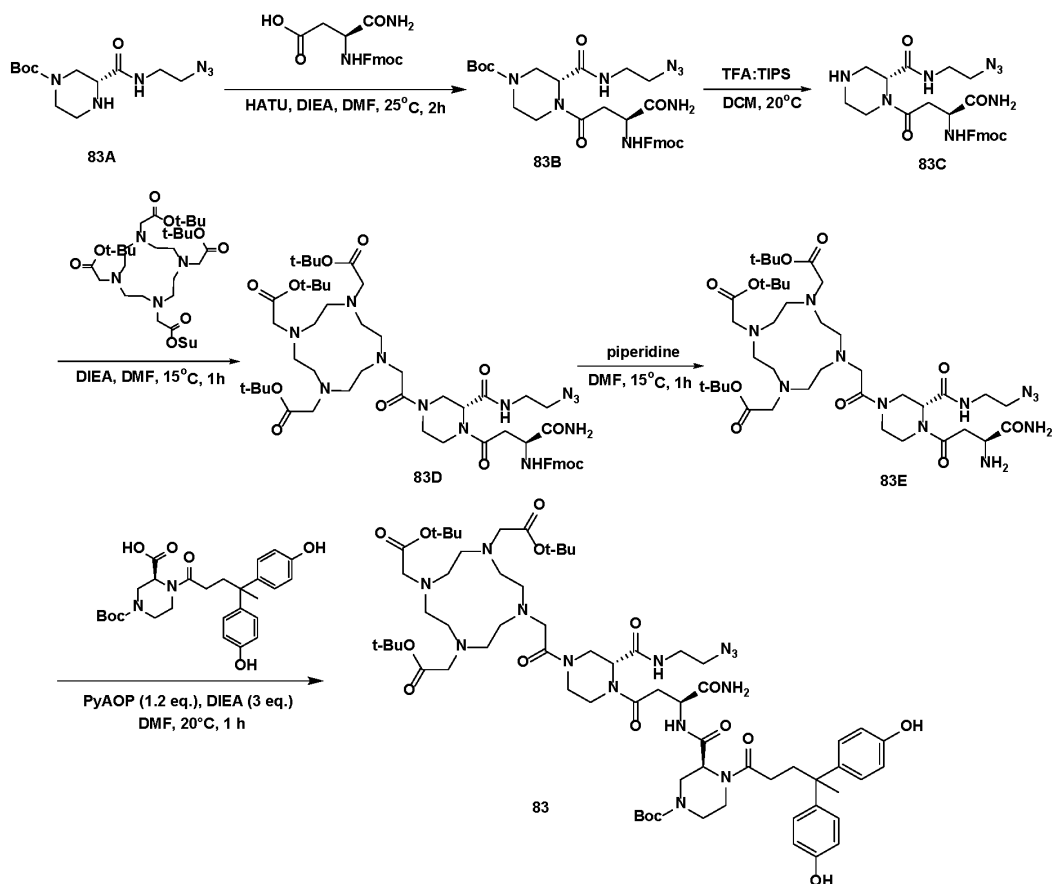
[00769] To a solution of **compound 82C** (1.50 g, 2.38 mmol, 1 *eq*) in DMF (18 mL) was added DIEA (1.25 mL, 7.15 mmol, 3 *eq*) and **compound 82B** (0.9 g, 2.38 mmol, 1 *eq*), followed by PyAOP (1.37 g, 2.62 mmol, 1.1 *eq*). The mixture was stirred at 25°C for 3 h in 2 batches. The reaction mixture was poured into H₂O (50 mL), extracted with EtOAc (3 × 50 mL), combined organics washed with brine (100 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 82D** (1.3 g, 28% yield, 75% purity) as a white solid; LCMS: [M+H]:988.7; ¹H NMR (400 MHz, CDCl₃) δ 8.03 (s, 2H), 7.33 (br d, *J* = 2.1 Hz, 3H), 6.95 (d, *J* = 7.4 Hz, 4H), 6.71 - 6.65 (m, 4H), 5.13 (br s, 2H), 4.94 - 4.65 (m, 3H), 4.56 - 4.31 (m, 1H), 4.26 - 4.12 (m, 1H), 3.99 - 3.77 (m, 2H), 3.65 - 3.51 (m, 1H), 3.45 - 3.27 (m, 1H), 3.21 - 3.02 (m, 2H), 2.97 (s, 6H), 2.89 (s, 7H), 2.76 - 2.61 (m, 2H), 2.48 - 2.29 (m, 2H), 2.05 - 1.91 (m, 2H), 1.87 - 1.61 (m, 2H), 1.52 - 1.43 (m, 17H).

3.55 Synthesis of Intermediate 82

[00770] To a solution of Pd/C (2.7 g, 10% purity) in THF (27 mL) was added **compound 82D** (1.3 g, 1.32 mmol, 1 *eq*), and the mixture stirred at 25°C for 2 h under a hydrogen atmosphere (15 psi). The mixture was filtered and concentrated under reduced pressure to give crude **Intermediate 82** as a white solid; LCMS [M+H]:898.6; ¹H NMR (400 MHz, CDCl₃) δ 8.03 (s, 2H), 6.69 (br s, 2H), 5.66 - 5.56 (m, 1H), 4.91 - 4.77 (m, 1H), 4.04 - 3.93 (m, 3H), 3.76 (t, *J* = 6.4 Hz, 2H), 2.97 (s, 6H), 2.89 (s, 6H), 2.80 - 2.65 (m, 2H), 2.31 - 2.24 (m, 2H), 2.00 - 1.84 (m, 7H), 1.53 - 1.43 (m, 23H).

C24. Synthesis of Intermediate 83

Scheme C24.



3.56 Synthesis of compound **83B**

[00771] To a solution of **compound 83A** (8.92 g, 29.9 mmol, 2 eq) and (*S*)-3-(((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-amino-4-oxobutanoic acid (5.3 g, 15.0 mmol, 1 eq) in DMF (25 mL) was added HATU (6.82 g, 18 mmol, 1.2 eq) and DIEA (7.82 mL 44.9 mmol, 3 eq) at 25°C . The mixture was stirred at 25°C for 2h, the reaction extracted with DCM (3 x 40 mL) and the combined organic layers washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by *prep*-HPLC (column: Welch Xtimate C18 180*70mm#10um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 30%-60%, 15min) to give **compound 83B** (3.8 g, 40% yield); LCMS $[\text{M}+\text{H}]$: 635.4; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.02 - 8.12 (m, 1H), 7.86 - 7.92 (m, 2H), 7.67 - 7.74 (m, 2H), 7.36 - 7.45 (m, 3H), 7.26 - 7.36 (m, 3H), 7.09 (br s, 1H), 4.71 - 4.88 (m, 1H), 4.16 - 4.43 (m, 5H), 3.64 - 3.84 (m, 2H), 3.35 - 3.53 (m, 2H), 3.02 - 3.22 (m, 2H), 2.65 - 2.85 (m, 2H), 1.31 - 1.45 (m, 9H).

3.57 Synthesis of compound **83C**

[00772] To a solution of **compound 83B** (1.95 g, 3.07 mmol, 1 eq) in DCM (16 mL) was added TFA (4 mL) and TIPS (6.31 mL, 30.7 mmol, 10 eq) at 20°C . The mixture was stirred at 20°C for 1h and concentrated under reduced pressure to give crude **compound 83C** (1.99 g) as a white solid; LCMS $[\text{M}+\text{H}]$: 535.3.

3.58 Synthesis of compound **83D**

[00773] To a solution of **compound 83C** (2.76 g, 4.26 mmol, 1 *eq*, TFA) in DMF (30 mL) was added tri-*tert*-butyl 2,2',2''-(10-(2-((2,5-dioxopyrrolidin-1-yl)oxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (7.13 g, 10.6 mmol, 2.5 *eq*) and DIEA (1.48 mL, 8.51 mmol, 2 *eq*) at 15°C. The mixture was stirred at 15°C for 1h, filtered, concentrated under reduced pressure and the residue purified by column chromatography (SiO₂, DCM:MeOH) to give **compound 83D** (4.2 g, 91% yield) as a white solid; LCMS [M+H]: 1089.6.

3.59 Synthesis of compound 83E

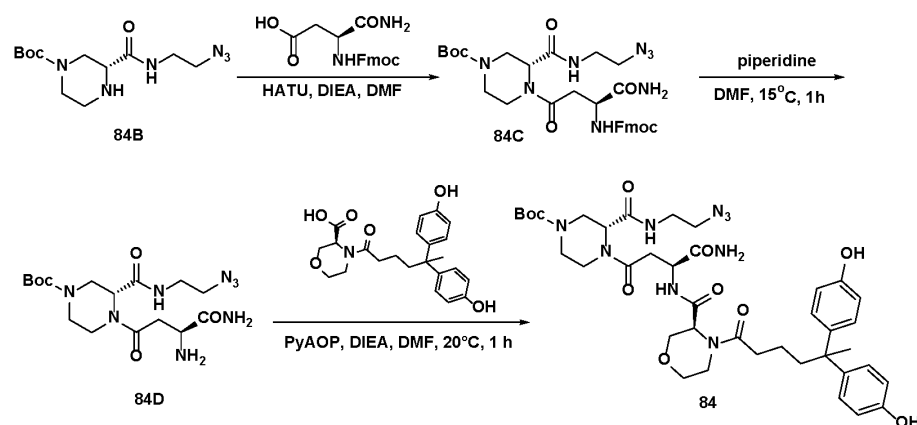
[00774] To a solution of **compound 83D** (4.2 g, 3.86 mmol, 1 *eq*) in DMF (20 mL) was added piperidine (400 μ L, 4.05 mmol, 1.05 *eq*). The mixture was stirred at 15°C for 1h, concentrated under reduced pressure and the residue purified by column chromatography (SiO₂, DCM:MeOH) to give **compound 83E** (2.0 g, 60% yield) as a white solid; LCMS [M+H]: 867.5.

3.61 Synthesis of Intermediate 83

[00775] To a solution of (*S*)-1-(4,4-bis(4-hydroxyphenyl)pentanoyl)-4-(*tert*-butoxycarbonyl)piperazine-2-carboxylic acid (831 mg, 1.67 mmol, 0.85 *eq*) and **compound 83E** (1.7 g, 1.96 mmol, 1 *eq*) in DMF (20 mL) was added PYAOP (1.23 g, 2.4 mmol, 1.2 *eq*) and DIEA (1.02 mL, 5.88 mmol, 3 *eq*) at 20°C. The mixture was stirred at 20°C for 1h, diluted with water (15 mL) and extracted with EtOAc (3 $\times$ 20 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **Intermediate 83** (2.1 g, 79% yield) as a white solid; LCMS [M+H]: 1347.9.

C25. Synthesis of Compound 84

Scheme C25.



3.62 Synthesis of compound 84C

[00776] To a solution of **compound 84B** (4.13 g, 13.8 mmol, 1 *eq*) and (*S*)-3-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-amino-4-oxobutanoic acid (4.9 g, 13.8 mmol, 1 *eq*) in DMF (100 mL) was added HATU (6.31 g, 16.6 mmol, 1.2 *eq*) and DIEA (7.23 mL, 41.5 mmol, 3 *eq*) at 20°C. The mixture was stirred at 20°C for 1h and directly by *prep*-HPLC (column: Welch Xtimate C18

250*100mm#10um;mobile phase: [water(NH₄HCO₃)-ACN];B%: 25%-55%,20min) directly to give **compound 84C** (2.5 g, 28% yield) as a white solid; LCMS [M+H]:635.4.

3.63 Synthesis of compound 84D

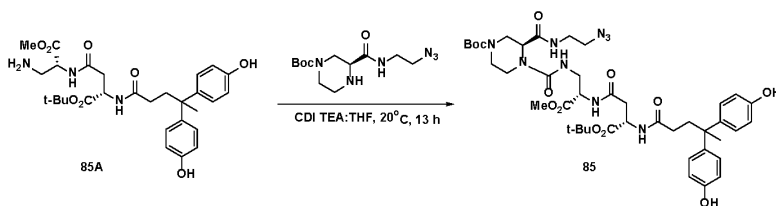
[00777] To a solution of **compound 84C** (2.0 g, 3.2 mmol, 1 *eq*) in DMF (20 mL) was added piperidine (327 μ L, 3.31 mmol, 1.05 *eq*) at 15°C. The mixture was stirred at 15°C for 1h, concentrated under reduced pressure and purified by column chromatography (SiO₂, DCM:MeOH) to give **compound 84D** (1.07 g, 82% yield) as a white solid; LCMS [M+H]:413.2.

3.64 Synthesis of Intermediate 84

[00778] To a solution of (*S*)-4-(5,5-bis(4-hydroxyphenyl)hexanoyl)morpholine-3-carboxylic acid (1.56 g, 3.78 mmol, 1.2 *eq*) and **compound 84D** (1.3 g, 3.15 mmol, 1 *eq*) in DMF (20 mL) was added DIEA (1.65 mL, 9.46 mmol, 3 *eq*) and PYAOP (1.97 g, 3.78 mmol, 1.2 *eq*) at 20°C. The mixture was stirred at 20°C for 1h, water (15 mL) added, extracted with EtOAc (3 $\times$ 20 mL), combined organics washed with brine (10 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give crude **Intermediate 84** (5.0 g) as a white solid that was used directly in the next reaction; LCMS [M+H]: 808.5.

C26. Synthesis of Intermediate 85

Scheme C26.

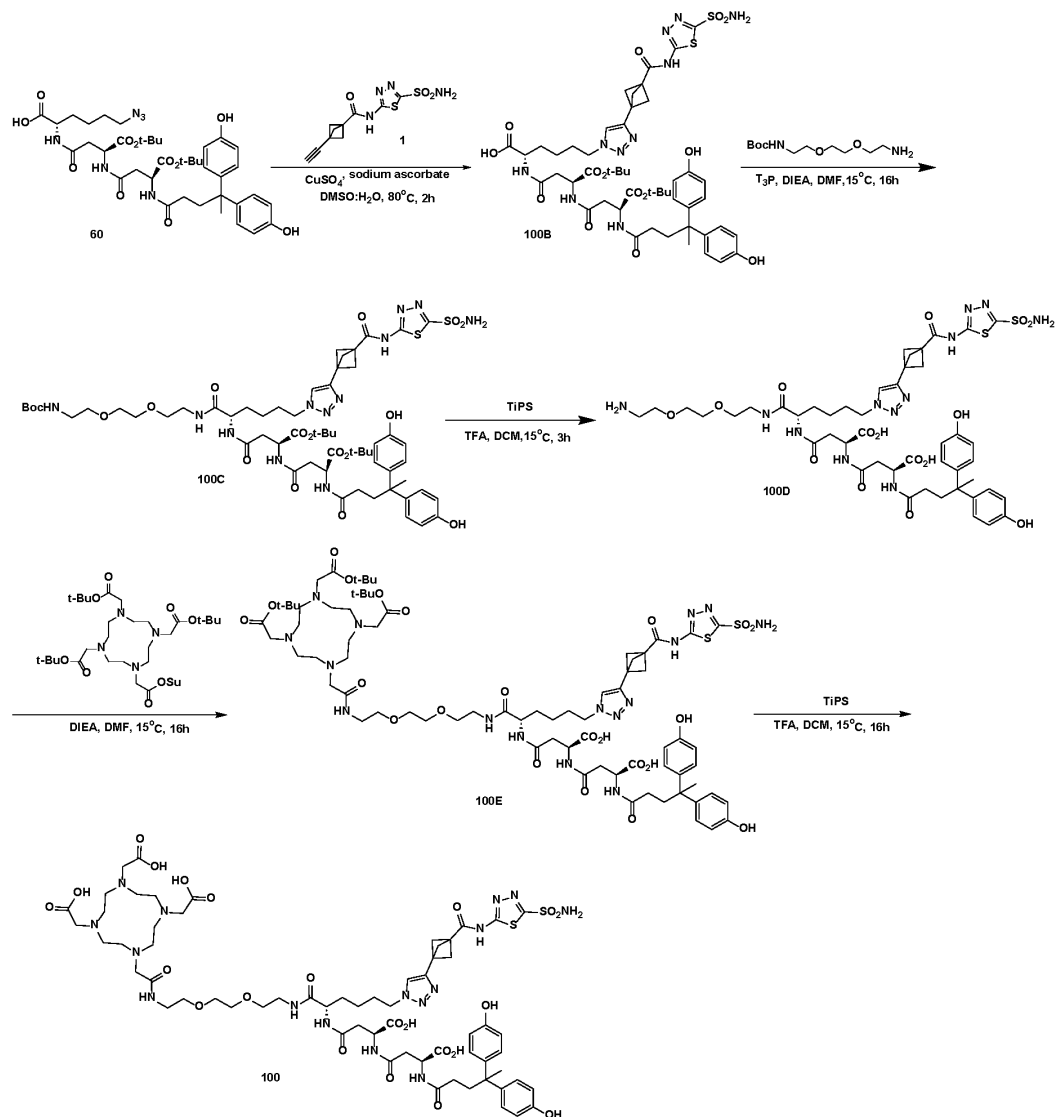


3.65 Synthesis of Intermediate 85

[00779] To a mixture of *tert*-butyl (*S*)-3-((2-azidoethyl)carbamoyl)piperazine-1-carboxylate (631 mg, 1.06 mmol, 1 *eq*) in DMF (2 mL) was added TEA (147 μ L, 1.06 mmol, 1 *eq*) and CDI (172 mg, 1.06 mmol, 1 *eq*) and the mixture stirred at 20°C for 1 h. **Compound 85A** (590 mg, 1.06 mmol, 1 *eq*) was added in one portion at 20°C under a nitrogen atmosphere and the mixture stirred at 20°C for 12 h. The reaction mixture was poured into water (50 mL), the aqueous phase extracted with EtOAc (5 $\times$ 100 mL), the combined organic phase washed with brine (2 $\times$ 50 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO₂, DCM:MeOH) to give **Intermediate 85** (1.2 g, 76% yield, 59% purity) as a light yellow solid; LCMS [M+H]:882.4; ¹H NMR (400 MHz, DMSO-d₆) δ 9.14 (br s, 2H), 8.18 (br d, *J* = 7.2 Hz, 1H), 8.09 (s, 1H), 8.03 - 7.86 (m, 2H), 7.17 (s, 2H), 6.93 (br d, *J* = 8.6 Hz, 4H), 6.64 (d, *J* = 8.6 Hz, 4H), 4.45 - 4.35 (m, 1H), 4.32 - 4.25 (m, 1H), 3.57 (s, 3H), 3.49 - 3.35 (m, 4H), 3.30 - 3.16 (m, 5H), 3.08 (br d, *J* = 9.4 Hz, 2H), 2.56 (br s, 1H), 2.47 - 2.39 (m, 1H), 2.22 - 2.11 (m, 2H), 1.91 - 1.79 (m, 2H), 1.45 (s, 3H), 1.42 - 1.31 (m, 18H).

D1. Synthesis of Compound 100

Scheme D1.



4.1. Synthesis of compound 100B

[00780] To a solution of **Intermediate 60** (551 mg, 493 μmol , 70% purity, 1.05 *eq*) in DMSO (5 mL) was added **Intermediate 1** (200 mg, 469 μmol , 1 *eq*), then sodium ascorbate (93 mg, 469 μmol , 1 *eq*) and CuSO_4 (3.60 μL , 23.5 μmol , 0.05 *eq*) in H_2O (2.5 mL). The reaction mixture was stirred at 80°C for 2h, diluted with EtOAc (50 mL), extracted with H_2O (4 x 30 mL), combined organic layers washed with NH_4Cl (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by *prep*-HPLC (FA condition, column: Phenomenex Luna C18 75*30mm*3 μm ; mobile phase: [water(FA)-ACN]; B%: 30%-60%, 8min) to give **compound 100B** (353 mg, 68% yield) as a white solid; LCMS $[\text{M}+\text{H}]$: 1081.2.

4.2. Synthesis of compound 100C

[00781] To a mixture of **compound 100B** (323 mg, 299 μmol , 1 *eq*), T_3P (355 μL , 597 μmol , 2 *eq*) and DIEA (312 μL , 1.79 mmol, 6 *eq*) in DMF (1 mL) was added *tert*-butyl N-[2-[2-(2-aminoethoxy)ethoxy]ethyl]carbamate (111 mg, 448 μmol , 1.5 *eq*) in one portion at 15°C under a nitrogen

atmosphere. The mixture was stirred at 15°C for 16 h, diluted with H₂O (50 mL), extracted with EtOAc (4 x 30 mL), the combined organic layers washed with brine (20 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure to give **compound 100C** (290 mg, 74% yield) as an oil; LCMS [M+H]: 1311.5.

4.3. Synthesis of compound 100D

[00782] A mixture of **compound 100C** (270 mg, 206 μmol, 1 *eq*), TIPS (423 μL, 2.06 mmol, 10 *eq*) in DCM (2 mL) and TFA (2 mL) was degassed and purged with nitrogen 3 times, and the mixture stirred at 15°C for 3h under a nitrogen atmosphere. The mixture was concentrated under reduced pressure, the residue triturated with MTBE (3 mL) at 15°C for 5 min and filtered to give crude **compound 100D** (242 mg, TFA salt) as a white solid; LCMS [M+H]: 1099.2.

4.4. Synthesis of compound 100E

[00783] To a solution of **compound 100D** (210 mg, 173 μmol, 1 *eq*, TFA), tri-*tert*-butyl 2,2',2''-(10-(2-((2,5-dioxopyrrolidin-1-yl)oxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (116 mg, 173 μmol, 1 *eq*) in DMF (2 mL) was added DIEA (301 μL, 1.73 mmol, 10 *eq*). The mixture was stirred at 15°C for 16h and the mixture concentrated under reduced pressure. The residue was triturated with MTBE (3 mL) and filtered to give crude **compound 100E** (289 mg) as a white solid; LCMS [M+H]: 1653.8.

4.5. Synthesis of Compound 100

[00784] A mixture of **compound 100E** (289 mg, 175 μmol, 1 *eq*), triisopropylsilane (359 μL, 1.75 mmol, 10 *eq*) in DCM (3 mL) and TFA (3 mL) was degassed and purged with nitrogen 3 times, and the mixture stirred at 15°C for 16h under a nitrogen atmosphere. The mixture was concentrated under reduced pressure and purified by *prep*-HPLC (FA condition; column: Phenomenex Luna C18 200*40mm*10um; mobile phase: [water (FA)-ACN]; B%: 5%-35%, 8min) to give **compound 100** (115 mg, 14% yield, FA salt); LCMS [M+H]: 1485.6; ¹H NMR (400 MHz, DMSO-d₆) δ 9.39 - 9.06 (m, 1H), 8.41 - 8.27 (m, 2H), 8.23 - 8.09 (m, 3H), 8.04 - 7.94 (m, 2H), 7.94 - 7.86 (m, 1H), 6.95 - 6.89 (m, 4H), 6.67 - 6.62 (m, 4H), 4.53 - 4.41 (m, 2H), 4.25 (br t, *J* = 6.8 Hz, 2H), 4.21 - 4.13 (m, 1H), 3.50 - 3.39 (m, 18H), 3.27 - 3.11 (m, 13H), 3.03 - 2.94 (m, 10H), 2.67 (br d, *J* = 1.6 Hz, 4H), 2.63 - 2.54 (m, 3H), 2.43 (s, 6H), 2.20 - 2.12 (m, 2H), 1.89 - 1.82 (m, 2H), 1.80 - 1.72 (m, 2H), 1.69 - 1.61 (m, 1H), 1.55 - 1.49 (m, 1H), 1.48 - 1.43 (m, 3H), 1.29 - 1.19 (m, 2H).

[00785] Compounds in **table 9.1** were prepared by procedures depicted in **Scheme D1**.

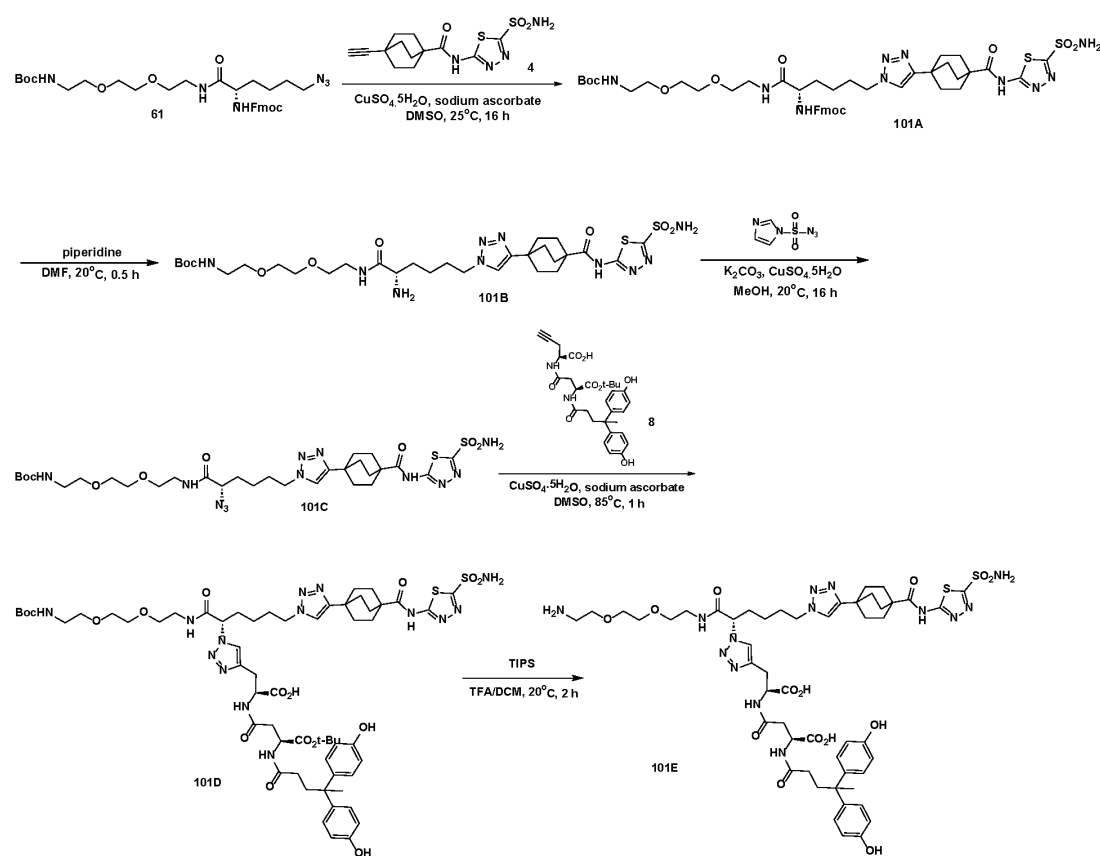
Table 9.1.

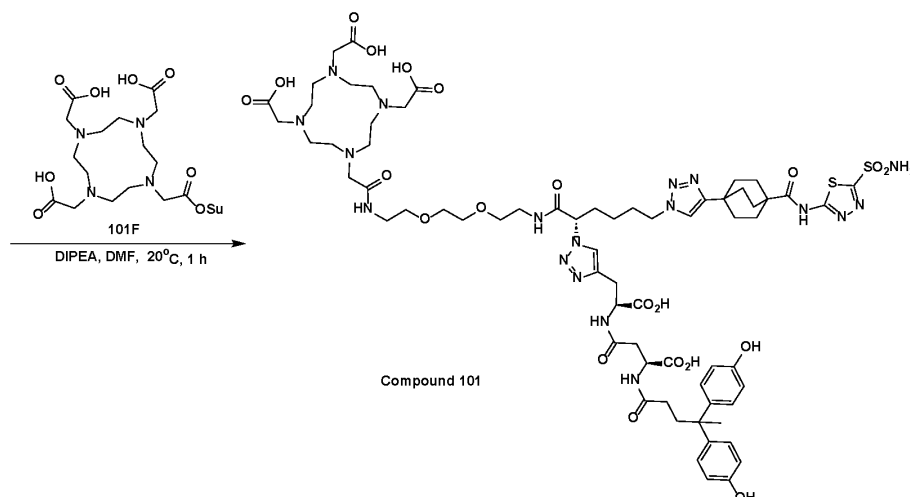
Compound	m/z
100.1	[M+H]:1513.3
100.2	[M+H]:1471.3
100.3	[M+H]:1487.4
100.4	[M+H]:1501.3
100.5	[M+H]:1499.3
100.6	[M+H]:1527.3
100.7	[M+H]:1513.4
100.8	[M+H]:1503.3
100.9	[M+H]:1489.3

Compound	m/z
100.10	[M+H]:1463.3
100.11	[M+H]:1437.3
100.12	[M+H]:1465.3
100.13	[M+H]:1451.3
100.14	[M+H]:1485.3
100.15	[M+H]:1541.4
100.16	[M+H]:1471.3
100.17	[M/2+H]: 750.3
100.18	[M+H]:1523.3
100.19	[M/2+H]:1495.4

D2. Synthesis of Compound 101

Scheme D2.





4.6 Preparation of compound 101A

[00786] To a solution of **Intermediate 61** (1.15 g, 1.84 mmol, 1 *eq*) and **Intermediate 4** (689 mg, 2.02 mmol, 1.1 *eq*) in DMSO (10 mL) was added sodium ascorbate (365 mg, 1.84 mmol, 1 *eq*) and CuSO₄·5H₂O (46 mg, 184 μmol, 0.1 *eq*). The mixture was stirred at 25°C for 16 h. The reaction mixture was added dropwise into H₂O (30 mL) and aq. NH₄Cl solution (10 mL), and the mixture stirred at 20°C for 1 h. The mixture was filtered, and the filter cake dried to give **compound 101A** (1.4 g, 68% yield) as a white solid; LCMS [M+H]: 965.3.

4.7 Preparation of compound 101B

[00787] To a solution of **compound 101A** (1.3 g, 1.35 mmol, 1 *eq*) in DMF (17 mL) was added piperidine (665 μL, 6.73 mmol, 5 *eq*). The mixture was stirred at 20°C for 0.5 h and concentrated under reduced pressure. The crude product was triturated with MTBE (20 mL) to give **compound 101B** (820 mg, 71% yield, 87% purity) as a light green solid; LCMS [M+H]: 743.3; ¹H NMR (400 MHz, DMSO-d₆) δ 7.79 (br s, 2H), 7.44 - 7.09 (m, 1H), 6.77 (br s, 3H), 4.26 (br d, *J* = 1.4 Hz, 2H), 3.50 (br s, 5H), 3.36 (br s, 6H), 3.07 (s, 4H), 1.80 (br s, 12H), 1.67 - 1.49 (m, 3H), 1.37 (s, 9H), 1.10 (s, 3H).

4.8 Preparation of compound 101C

[00788] To a solution of **compound 101B** (820 mg, 1.10 mmol, 1 *eq*) in MeOH (8 mL) was added K₂CO₃ (229 mg, 1.66 mmol, 1.5 *eq*), CuSO₄·5H₂O (14 mg, 55.2 μmol, 0.05 *eq*) and 1*H*-imidazole-1-sulfonyl azide (229 mg, 1.32 mmol, 1.2 *eq*). The mixture was stirred at 20°C for 16 h, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM:MeOH) and re-purified by prep-TLC (SiO₂, DCM:MeOH) to give **compound 101C** (250 mg, 29% yield) as a white solid; LCMS [M+H]: 769.3; ¹H NMR (400 MHz, DMSO-d₆) δ 13.08 - 12.39 (m, 1H), 8.30 (br s, 1H), 8.26 (br t, *J* = 5.6 Hz, 1H), 7.84 (s, 1H), 6.77 (br t, *J* = 5.6 Hz, 1H), 4.28 (t, *J* = 7.0 Hz, 2H), 3.71 (t, *J* = 7.0 Hz, 1H), 3.50 (s, 4H), 3.45 - 3.39 (m, 2H), 3.38 - 3.34 (m, 3H), 3.28 - 3.22 (m, 2H), 3.17 (d, *J* = 4.6 Hz, 1H), 3.05 (q, *J* = 6.0 Hz, 2H), 2.01 - 1.89 (m, 5H), 1.87 - 1.77 (m, 8H), 1.75 - 1.62 (m, 2H), 1.36 (s, 9H), 1.31 - 1.15 (m, 2H).

4.9 Preparation of compound 101D

[00789] To a solution of **compound 101C** (176 mg, 228 μ mol, 1 *eq*) and (*S*)-2-((*S*)-3-(4,4-*bis*(4-hydroxyphenyl)pentanamido)-4-(*tert*-butoxy)-4-oxobutanamido)pent-4-ynoic acid (277 mg, 502 μ mol, 2.2 *eq*) in DMSO (4 mL) was added CuSO₄·5H₂O (5.70 mg, 22.8 μ mol, 0.1 *eq*) and sodium ascorbate (45 mg, 228 μ mol, 1 *eq*). The mixture was stirred at 85°C for 1 h, the reaction mixture added dropwise into H₂O (15 mL) and aq. NH₄Cl solution (5 mL), and the mixture stirred at 20°C for 1 h. The mixture was filtered and the filter cake dried to give **compound 101D** (220 mg, 55% yield, 75% purity) as a light brown solid; LCMS [M+H]: 1321.5; ¹H NMR (400 MHz, DMSO-d₆) δ 9.16 (br s, 2H), 8.52 (br s, 1H), 8.30 - 8.03 (m, 2H), 8.00 - 7.91 (m, 1H), 7.89 - 7.80 (m, 1H), 7.77 - 7.58 (m, 1H), 6.92 (br d, *J* = 7.8 Hz, 4H), 6.75 (br s, 1H), 6.63 (br d, *J* = 8.0 Hz, 4H), 5.37 - 5.12 (m, 1H), 4.38 (br s, 2H), 4.23 (br d, *J* = 6.4 Hz, 2H), 3.48 (s, 5H), 3.44 - 3.32 (m, 1H), 3.23 (br s, 2H), 3.05 (br d, *J* = 5.6 Hz, 3H), 2.97 - 2.79 (m, 1H), 2.42 (br d, *J* = 4.4 Hz, 1H), 2.17 (br s, 2H), 1.94 (br s, 6H), 1.90 - 1.70 (m, 9H), 1.53 - 1.42 (m, 3H), 1.36 - 1.22 (m, 17H), 1.08 (br s, 2H).

4.10 Preparation of compound 101E

[00790] To a solution of **compound 101D** (170 mg, 129 μ mol, 1 *eq*) in DCM (1.5 mL) was added TIPS (528 μ L, 2.57 mmol, 20 *eq*) and TFA (1.5 mL). The mixture was stirred at 20°C for 2 h. The reaction mixture was concentrated under reduced pressure and the residue triturated with MTBE (15 mL) at 20°C for 30 min. The mixture was filtered, and the filter cake dried to give crude **compound 101E** (220 mg) as a green solid; LCMS [M+H]: 1165.4; ¹H NMR (400 MHz, DMSO-d₆) δ 12.68 (br s, 1H), 9.76 - 8.89 (m, 1H), 8.50 (br t, *J* = 5.2 Hz, 1H), 8.31 (s, 1H), 8.25 (br s, 1H), 8.02 - 7.86 (m, 2H), 7.83 - 7.69 (m, 3H), 6.91 (br d, *J* = 8.6 Hz, 4H), 6.63 (br d, *J* = 8.2 Hz, 4H), 5.23 (br t, *J* = 7.6 Hz, 1H), 4.60 - 4.35 (m, 2H), 4.22 (br t, *J* = 5.8 Hz, 2H), 3.62 - 3.49 (m, 5H), 3.46 - 3.36 (m, 2H), 3.23 (br d, *J* = 5.6 Hz, 2H), 3.07 (s, 2H), 3.01 - 2.93 (m, 2H), 2.68 - 2.54 (m, 1H), 2.46 - 2.35 (m, 1H), 2.22 - 2.12 (m, 2H), 2.01 - 1.91 (m, 6H), 1.90 - 1.68 (m, 9H), 1.44 (s, 3H), 1.10 (s, 5H), 1.05 - 1.01 (m, 3H), 1.00 - 0.82 (m, 2H).

4.11 Preparation of Compound 101

[00791] To a solution of **compound 101E** (100 mg, 85.8 μ mol, 1 *eq*) in DMF (2 mL) was added DIEA (75 μ L, 429 μ mol, 5 *eq*) and **compound 101F** (86 mg, 172 μ mol, 2 *eq*) at 20°C, and the mixture stirred at 20°C for 1h. The reaction mixture was quenched by the addition of H₂O (0.1 mL) and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*3 μ m; mobile phase: [water (TFA)-ACN]; B%: 1%-40%, 8min) and further purified by *prep*-HPLC (column: C18-1 150*30mm*5 μ m; mobile phase: [water (FA)-ACN]; B%: 5%-35%, 20min) to give **Compound 101** (5.2 mg, 3.9% yield); LCMS [M+H]: 1551.4; ¹H NMR (400 MHz, DMSO-d₆) δ 9.51 - 8.99 (m, 1H), 8.76 - 8.57 (m, 1H), 8.37 - 8.20 (m, 3H), 8.14 (br s, 1H), 7.98 - 7.85 (m, 2H), 7.78 (s, 1H), 6.90 (s, 4H), 6.63 (br d, *J* = 8.2 Hz, 4H), 5.26 (br t, *J* = 7.6 Hz, 1H), 4.47 - 4.38 (m, 2H), 4.21 (br d, *J* = 5.8 Hz, 3H), 3.02 (br s, 30H), 2.71 - 2.54 (m, 8H), 2.47 - 2.39 (m, 2H), 2.23 - 2.10 (m, 3H), 2.08 - 1.69 (m, 21H), 1.44 (s, 4H), 1.18 - 0.98 (m, 3H).

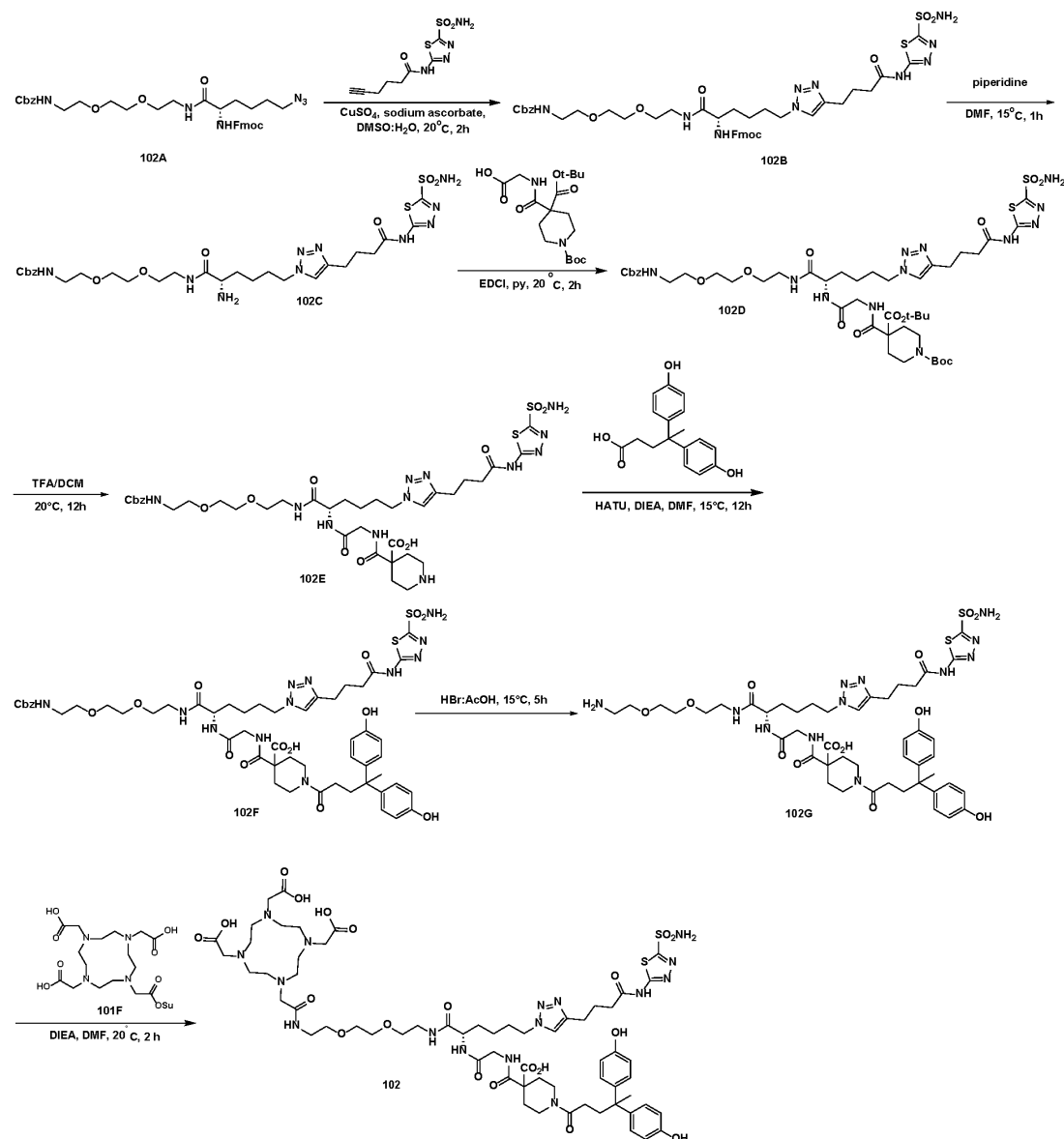
[00792] Compounds in **table 9.2** were prepared by procedures depicted in **scheme D2**.

Table 9.2.

Compound	m/z
101.1	[M+H] ⁺ : 1385.7
101.2	[M+H] ⁺ : 1509.8

D3. Synthesis of Compound 102

Scheme D3.



4.12 Preparation of compound 102B

[00793] To a solution of **compound 102A** (13 g, 19.7 mmol, 1 *eq*) and *N*-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)hex-5-ynamide (5.41 g, 19.7 mmol, 1 *eq*) in DMSO (30 mL) were added sodium ascorbate (3.91 g, 19.7 mmol, 1 *eq*) and CuSO₄ (303 μ L, 1.97 mmol, 0.1 *eq*) in H₂O (10 mL) at 20°C under a nitrogen atmosphere. The mixture was stirred at 20°C for 2h, poured into H₂O (80 mL), extracted with DCM (3 $\times$ 150 mL). The combined organic phase was dried (Na₂SO₄) and concentrated

under reduced pressure. The residue was purified by chromatography column (SiO₂, DCM:MeOH) to give **compound 102B** (18.1 g, 98% yield) as a yellow solid; LCMS [M+H]: 933.2; ¹H NMR (400 MHz, CHLOROFORM-d) δ 7.73 (d, J = 7.5 Hz, 2H), 7.55 (d, J = 3.8 Hz, 2H), 7.41 - 7.28 (m, 8H), 7.16 - 6.90 (m, 2H), 6.21 - 6.12 (m, 1H), 6.06 - 5.94 (m, 1H), 5.59 - 5.46 (m, 1H), 5.17 - 4.97 (m, 2H), 4.43 - 4.09 (m, 6H), 3.62 - 3.27 (m, 12H), 2.83 (dd, J = 4.1, 6.8 Hz, 1H), 2.20 - 2.07 (m, 2H), 1.88 - 1.70 (m, 5H), 1.59 (br s, 1H), 1.41 - 1.24 (m, 3H).

4.13 Preparation of compound 102C

[00794] To a solution of **compound 102B** (8.0 g, 8.57 mmol, 1 *eq*) in DMF (10 mL) was added piperidine (847 μ L, 8.57 mmol, 1 *eq*) at 20°C under a nitrogen atmosphere. The mixture was stirred at 20°C for 2h and purified directly by chromatography column (SiO₂, EtOAc:MeOH) to give **compound 102C** (4.5 g, 74% yield) as a green solid; LCMS [M+H]: 711.2; ¹H NMR (400 MHz, DMSO-d₆) δ 7.85 (br s, 1H), 7.39 - 7.23 (m, 6H), 5.00 (s, 2H), 4.27 (br s, 2H), 3.53 - 3.08 (m, 21H), 2.65 (d, J = 5.4 Hz, 2H), 2.01 - 1.67 (m, 6H), 1.12 (d, J = 6.0 Hz, 2H).

4.14 Preparation of compound 102D

[00795] To a solution of **compound 102C** (1.6 g, 4.14 mmol, 1 *eq*) and (1,4-bis(*tert*-butoxycarbonyl)piperidine-4-carbonyl)glycine (2.94 g, 4.14 mmol, 1 *eq*) in pyridine (10 mL) was added EDCI (1.59 g, 8.18 mmol, 2 *eq*) at 20°C under a nitrogen atmosphere. The mixture was stirred at 20°C for 2h and concentrated under reduced pressure. The residue was purified by chromatography column (SiO₂, DCM:MeOH) to give **compound 102D** (4.0 g) as a yellow solid; LCMS [M+H]: 1079.5.

4.15 Preparation of compound 102E

[00796] To a solution of **compound 102D** (3.7 g, 3.43 mmol, 1 *eq*) in DCM (5 mL) was added TFA (10 mL) and the reaction stirred at 20°C for 12h. The reaction mixture was concentrated under reduced pressure to give crude **compound 102E** (3.1 g, 98% yield) as a yellow oil that was used directly in the next reaction.

4.16 Preparation of compound 102F

[00797] To a solution of **compound 102E** (1.0 g, 1.08 mmol, 1 *eq*) and 4,4-bis(4-hydroxyphenyl)pentanoic acid (310 mg, 1.08 mmol, 1 *eq*) in DMF (5 mL) were added DIEA (566 μ L, 3.25 mmol, 3 *eq*) and HATU (412 mg, 1.08 mmol, 1 *eq*) at 20°C under a nitrogen atmosphere. The reaction mixture was stirred for 12h at 15 °C, concentrated under reduced pressure and the residue purified by chromatography column (SiO₂, DCM:MeOH) to give **compound 102F** (1.8 g, 98% yield) as a yellow solid; LCMS [M+H]: 1191.6.

4.17 Preparation of compound 102G

[00798] **Compound 102F** (1.4 g, 1.18 mmol, 1 *eq*) in HBr/AcOH (1.18 mmol, 10 mL, 20% purity, 1 *eq*) was stirred at 20°C for 2h. The reaction mixture was concentrated under reduced pressure and the residue triturated with MeCN (5 mL), filtered and the filter cake concentrated to give crude **compound 102G** (1.1 g, 71% yield) as a yellow solid that was used directly in the next reaction; LCMS [M+H]: 1057.3.

4.19 Preparation of Compound 102

[00799] To a solution of **compound 102G** (0.7 g, 483 μ mol, 73% purity, 1 *eq*) in DMF (5 mL) was added DIEA (253 μ L, 1.45 mmol, 3 *eq*) and 2,2',2''-(10-(2-((2,5-dioxopyrrolidin-1-yl)oxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (242 mg, 483 μ mol, 1 *eq*) at 20°C under a nitrogen atmosphere. The mixture was stirred at 20°C for 2h and the reaction mixture concentrated under reduced pressure. The residue was purified by *prep*-HPLC (column: Phenomenex luna C18 (250*70mm, 15 μ m); mobile phase: [water(TFA)-ACN]; B%: 10%-40%, 22min) to give **Compound 102** (0.15 g, 22% yield); LCMS [M+H]⁺: 1443.4; ¹H NMR (400 MHz, DMSO-d₆) δ 13.07 - 12.96 (m, 1H), 9.23 - 9.15 (m, 1H), 8.50 - 8.37 (m, 1H), 8.35 - 8.28 (m, 2H), 8.08 - 7.94 (m, 2H), 7.90 - 7.76 (m, 2H), 6.99 - 6.88 (m, 4H), 6.72 - 6.59 (m, 4H), 4.28 - 4.17 (m, 3H), 4.03 - 3.66 (m, 8H), 3.63 - 3.56 (m, 4H), 3.50 (s, 5H), 3.43 (t, *J* = 5.5 Hz, 4H), 3.37 (t, *J* = 6.0 Hz, 4H), 3.29 - 3.23 (m, 4H), 3.18 (d, *J* = 5.4 Hz, 9H), 3.09 - 3.04 (m, 3H), 2.70 - 2.55 (m, 5H), 2.20 - 2.13 (m, 2H), 2.04 - 1.91 (m, 6H), 1.89 - 1.73 (m, 4H), 1.52 (br s, 2H), 1.48 (s, 3H), 1.26 - 1.17 (m, 2H).

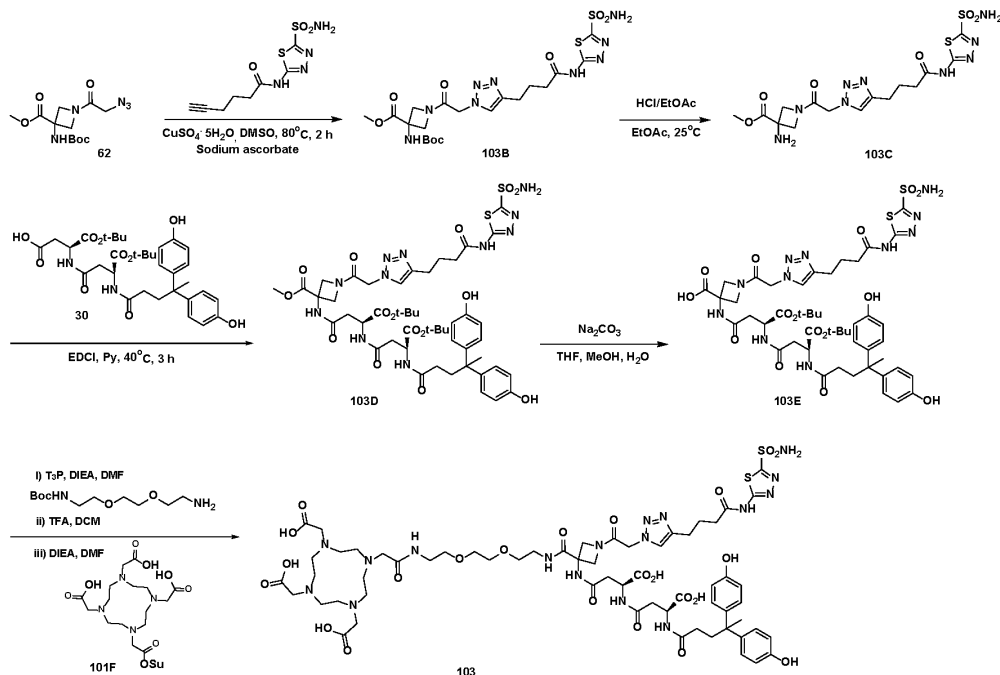
[00800] Compounds in **table 9.3** were prepared by procedures depicted in **scheme D3**.

Table 9.3.

Compound	m/z
102.1	[M+H] ⁺ : 1457.4
102.2	[M+H] ⁺ : 1428.5
102.3	[M+2H] ⁺ : 1456.3
102.4	[M+H] ⁺ : 1429.3
102.5	[M+H] ⁺ : 1523.4
102.6	[M+H] ⁺ : 1481.3
102.7	[M+H] ⁺ : 1468.3
102.8	[M+H] ⁺ : 1417.7

D4. Synthesis of Compound 103

Scheme D4.



4.20 Preparation of compound 103B

[00801] To a solution of **compound 62** (1.0 g, 3.19 mmol, 1 *eq*) in DMSO (2 mL) was added sodium ascorbate (696 mg, 3.51 mmol, 1.1 *eq*), *N*-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)hex-5-ynamide (1.01 g, 3.67 mmol, 1.15 *eq*) and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (48 mg, 192 μmol , 0.06 *eq*). The mixture was stirred at 80°C for 2h, extracted with EtOAc (2×200 mL), combined organics washed with brine (150 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give **compound 103B** (1.4 g, 75% yield) as a white solid; LCMS $[\text{M}+\text{H}]$: 588.1.

4.21 Preparation of compound 103C

[00802] To a solution of **Compound 103B** (1.3 g, 2.21 mmol, 1 *eq*) in EtOAc (10 mL) was added 4 M HCl in EtOAc (10 mL). The mixture was stirred at 25°C for 1h, the reaction mixture filtered and concentrated under reduced pressure to give **compound 103C** (1 g, 93% yield) as a white solid; LCMS $[\text{M}+\text{H}]$: 488.0.

4.22 Preparation of compound 103D

[00803] To a solution of **compound 103C** (1.0 g, 2.05 mmol, 1 *eq*) in pyridine (2 mL) was added EDCI (786 mg, 4.10 mmol, 2 *eq*) and **compound 30** (645 mg, 1.03 mmol, 0.5 *eq*). The mixture was stirred at 40°C for 3h, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , MeOH:DCM) to give **compound 103D** (800 mg, 18% yield) as a white solid; LCMS $[\text{M}+\text{H}]$: 1098.4.

4.23 Preparation of compound 103E

[00804] To a solution of **compound 103D** (700 mg, 637 μmol , 1 *eq*) in THF (9 mL), H_2O (1 mL) and MeOH (1 mL) was added Na_2CO_3 (270 mg, 2.55 mmol, 4 *eq*). The mixture was stirred at 25°C for 1h,

the reaction mixture adjusted to pH=7 with 1M HCl, filtered and concentrated under reduced pressure to give **compound 103E** (500 mg, 72% yield) as a white solid; LCMS [M+H]: 1084.5.

4.47 Preparation of Compound 103

[00805] **Compound 103** was prepared as per reactions previously depicted; LCMS [M+H]: 1488.3.

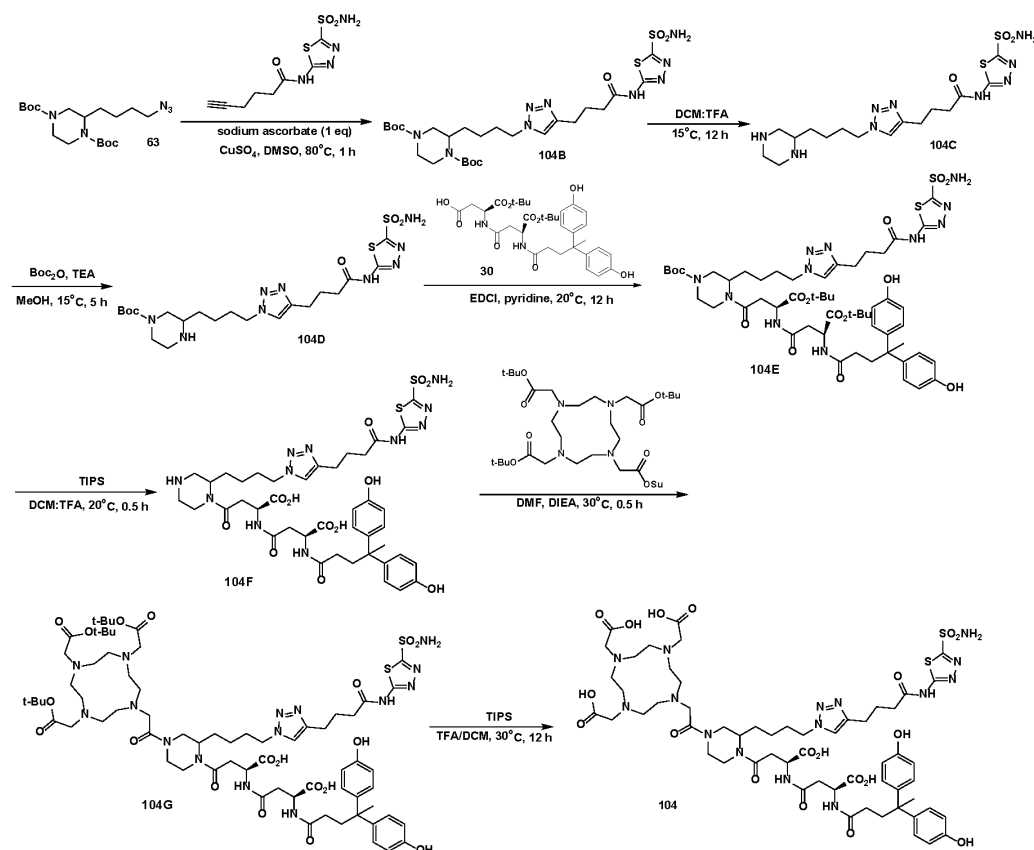
[00806] Compounds in **table 9.4** were prepared by procedures depicted in **scheme D4**.

Table 9.4.

Compound	m/z
103.1	[M+H]:1502.3
103.2	[M+H]:1530.2
103.3	[M+H]:1474.3
103.4	[M+H]:1502.3

D5. Synthesis of Compound 104

Scheme D5.



4.24 Synthesis of compound 9

[00807] To a solution of **compound 63** (10.0 g, 26.1 mmol, 1 *eq*) and *N*-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)hex-5-ynamide (5.72 g, 20.9 mmol, 0.8 *eq*) in DMSO (80 mL) was added sodium ascorbate (5.17 g, 26.1 mmol, 1 *eq*) and CuSO₄·5H₂O (325.55 mg, 1.30 mmol, 0.05 *eq*) at 15°C, and the mixture stirred at 80°C for 1h. The reaction mixture was poured into H₂O (160 mL) and aq. NH₄Cl solution (10 mL),

filtered and the filter cake concentrated under reduced pressure to give **compound 104B** (17.2 g, 99% yield) as a blue oil; LCMS [M+H]:658.2; ¹H NMR (400 MHz, DMSO-d₆) δ 8.25 (br s, 2H), 7.82 (s, 1H), 4.24 (t, *J* = 6.6 Hz, 2H), 4.01 - 3.60 (m, 4H), 2.93 - 2.71 (m, 2H), 2.68 - 2.53 (m, 4H), 1.90 (m, 2H), 1.84 - 1.67 (m, 2H), 1.56 - 1.39 (m, 2H), 1.37 - 1.29 (m, 18H), 1.22 - 1.00 (m, 2H).

4.25 Synthesis of compound 104C

[00808] A mixture of **compound 104B** (17.2 g, 26.1 mmol, 1 *eq*) in DCM (15 mL) and TFA (15 mL) was stirred at 15°C for 12 h. The reaction mixture was concentrated under reduced pressure to give **compound 104C** (19.5 g, 73% yield, TFA salt) as a yellow solid; LCMS [M+H]:458.1; ¹H NMR (400 MHz, DMSO-d₆) δ 7.88 (br s, 1H), 4.29 (t, *J* = 6.5 Hz, 2H), 3.33 (t, *J* = 6.7 Hz, 1H), 2.90 - 2.52 (m, 10H), 2.05 - 1.86 (m, 2H), 1.78 (br s, 2H), 1.38 (br s, 2H), 1.31 - 1.17 (m, 2H).

4.26 Synthesis of compound 104D

[00809] To a solution of **compound 104C** (13.0 g, 28.3 mmol, 1 *eq*) and TEA (19.7 mL, 142 mmol, 5 *eq*) in MeOH (100 mL) was added Boc₂O (6.5 mL, 28.3 mmol, 1 *eq*) in MeOH (50 mL) at 15°C, and the mixture stirred at 15°C for 5 h. The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography (SiO₂, EtOAc:MeOH) to give **compound 104D** (12.5 g, 79% yield) as a red oil; LCMS [M+H]:558.2; ¹H NMR (400 MHz, DMSO-d₆) δ 7.88 (s, 1H), 4.30 (t, *J* = 7.0 Hz, 2H), 3.83 (d, *J* = 13.2 Hz, 3H), 3.01 - 2.91 (m, 2H), 2.91 - 2.77 (m, 2H), 2.66 (t, *J* = 7.5 Hz, 2H), 2.59 (t, *J* = 7.3 Hz, 2H), 1.98 - 1.90 (m, 2H), 1.81 (q, 2H), 1.53 - 1.45 (m, 2H), 1.39 (s, 9H), 1.34 - 1.25 (m, 2H).

4.27 Synthesis of compound 104E

[00810] To a solution of **compound 104D** (5.4 g, 9.7 mmol, 1 *eq*) and **Intermediate 30** (6.09 g, 9.68 mmol, 1 *eq*) in pyridine (20 mL) was added EDCI (3.71 g, 19.4 mmol, 2 *eq*) at 15°C, and the mixture stirred at 20°C for 12h. The reaction mixture was concentrated under reduced pressure, the residue purified by column chromatography (SiO₂, EtOAc:MeOH) and *prep*-HPLC (column: Phenomenex luna C18 (250*70mm, 15 μm); mobile phase: [water (FA)-ACN]; B%: 40%-70%, 20 min) to give **compound 104E** (700 mg) as a white solid; LCMS [M+H]:1168.6; ¹H NMR (400 MHz, DMSO-d₆) δ 13.27 - 12.60 (m, 1H), 9.15 (s, 2H), 8.28 (br s, 2H), 8.13 (d, *J* = 6.8 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.96 - 7.88 (m, 1H), 7.85 (s, 1H), 6.92 (d, *J* = 8.3 Hz, 4H), 6.64 (d, *J* = 8.5 Hz, 4H), 4.50 (br d, *J* = 5.1 Hz, 1H), 4.44 - 4.32 (m, 2H), 4.32 - 4.18 (m, 2H), 3.94 - 3.72 (m, 2H), 3.58 (dd, *J* = 2.1, 11.1 Hz, 1H), 3.08 (t, *J* = 11.7 Hz, 1H), 2.74 - 2.53 (m, 8H), 2.21 - 2.11 (m, 2H), 1.99 - 1.88 (m, 2H), 1.88 - 1.71 (m, 4H), 1.54 - 1.41 (m, 5H), 1.41 - 1.29 (m, 28H), 1.26 - 1.08 (m, 2H).

4.28 Synthesis of compound 104F

[00811] To a solution of **compound 104E** (200 mg, 171 μmol, 1 *eq*) in DCM (1 mL) was added TIPS (352 μL, 1.71 mmol, 10 *eq*) and TFA (1 mL), and the mixture stirred at 15°C for 12h. The reaction mixture was concentrated under reduced pressure and the residue triturated with MTBE at 20°C for 0.5h to give crude **compound 104F** (200 mg, TFA) as yellow solid; LCMS [M+H]:956.2.

4.29 Synthesis of compound 104G

[00812] To a solution of **compound 104F** (210 mg, 220 μ mol, 1 *eq*) and DIEA (383 μ L, 2.20 mmol, 10 *eq*) in DMF (3 mL) was added tri-*tert*-butyl 2,2',2''-(10-(2-((2,5-dioxopyrrolidin-1-yl)oxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (221 mg, 329 μ mol, 1.5 *eq*), and the mixture stirred at 30°C for 0.5 h. The reaction mixture was concentrated under reduced pressure and the residue triturated with ACN at 20°C to give **compound 104G** (230 mg, 69% yield) as a yellow solid; LCMS [M+H]: 1511.2.

4.30 Synthesis of Compound 104

[00813] To a solution of **compound 104G** (230 mg, 152 μ mol, 1 *eq*) in DCM (1 mL) was added TIPS (313 μ L, 1.52 mmol, 10 *eq*) and TFA (2 mL), and the mixture stirred at 30°C for 12h. The reaction mixture was concentrated under reduced pressure and the residue purified by *prep*-HPLC (column: Phenomenex Luna C18 150*30mm*5 μ m; mobile phase: [water (TFA)-ACN]; B%: 5%-25%, 8 min) to give **Compound 104** (90 mg, 43% yield); LCMS [M+H]: 1342.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.00 (br s, 1H), 12.84 - 12.39 (m, 2H), 9.30 - 9.04 (m, 1H), 8.32 (s, 2H), 8.23 - 8.04 (m, 1H), 7.92 (t, *J* = 7.7 Hz, 1H), 7.81 (dd, *J* = 2.8, 7.3 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 4H), 6.64 (d, *J* = 8.6 Hz, 4H), 4.68 - 4.55 (m, 1H), 4.53 - 4.43 (m, 2H), 4.33 - 4.09 (m, 6H), 4.07 - 3.86 (m, 4H), 3.80 - 3.50 (m, 8H), 3.47 - 3.22 (m, 10H), 3.20 - 2.98 (m, 9H), 2.77 - 2.55 (m, 8H), 2.22 - 2.12 (m, 2H), 1.94 (q, 2H), 1.88 - 1.70 (m, 4H), 1.45 (s, 3H), 1.29 - 1.09 (m, 2H).

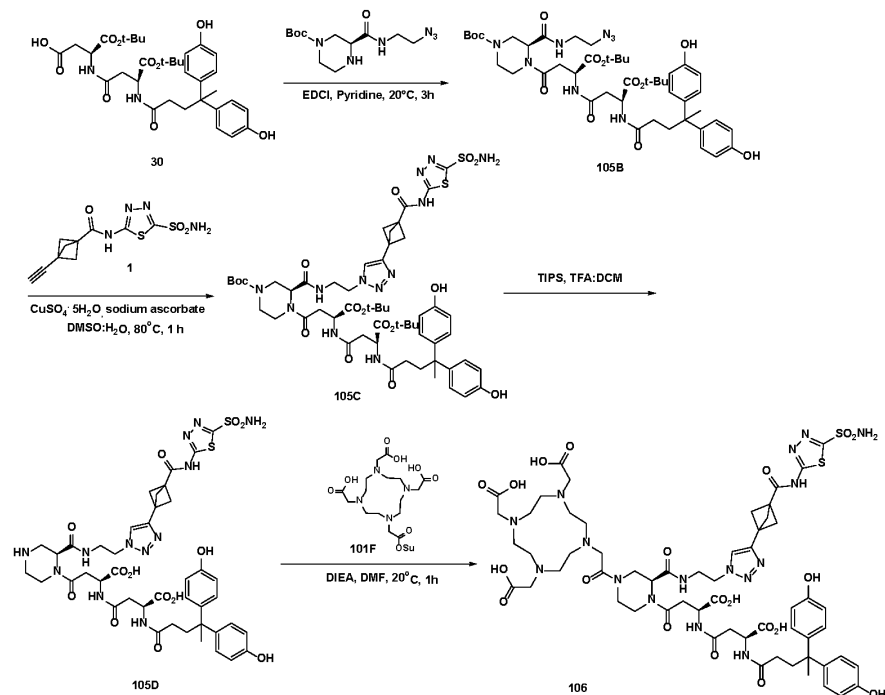
[00814] Compounds in **table 9.5** were prepared by procedures depicted in **scheme D5**.

Table 9.5.

Compound	m/z
104.1	[M+H]: 1394.6
104.2	[M+H]: 1394.3

D6. Synthesis of Compound 106

Scheme D6.



4.31 Synthesis of compound 106B

[00815] To a solution of *tert*-butyl (*S*)-3-((2-azidoethyl)carbamoyl)piperazine-1-carboxylate (300 mg, 1.01 mmol, 1 *eq*) and **compound 30** (316 mg, 503 μ mol, 0.5 *eq*) in pyridine (5 mL) was added EDCI (231 mg, 1.21 mmol, 1.2 *eq*) at 25°C. The mixture was stirred at 20 °C for 3h. The reaction was extracted with EtOAc (3 $\times$ 40 mL), the combined organic layers washed with brine (3 $\times$ 10 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether:EtOAc) to give **compound 106B** (0.59 g, 65% yield) as a white solid; LCMS [M+H]: 909.5.

4.32 Synthesis of compound 106C

[00816] To a solution of **compound 106B** (500 mg, 550 μ mol, 1 *eq*) and **compound 1** (164 mg, 550 μ mol, 1 *eq*) in DMSO (5 mL) and H₂O (1 mL) was added CuSO₄·5H₂O (6.87 mg, 27.5 μ mol, 0.05 *eq*) and sodium ascorbate (120 mg, 605 μ mol, 1.1 *eq*) at 20°C. The mixture was stirred at 80 °C for 1h. The reaction mixture was concentrated under reduced pressure and recrystallization from H₂O (15 mL) to give **compound 106C** (590 mg, 89% yield) as a green solid; LCMS [M+H]: 1207.5.

4.33 Synthesis of compound 106D

[00817] To a solution of **compound 106C** (0.5 g, 414 μ mol, 1 *eq*) in DCM (5 mL) and TFA (5 mL) was added TIPS (851 μ L, 4.14 mmol, 10 *eq*) at 20°C. The reaction mixture was stirred at 20 °C for 2h, concentrated under reduced pressure and the residue triturated with MTBE at 20°C for 10 min to give **compound 106D** (414 μ mol, 99% yield, TFA salt) as a green solid; LCMS [M+H]: 995.3.

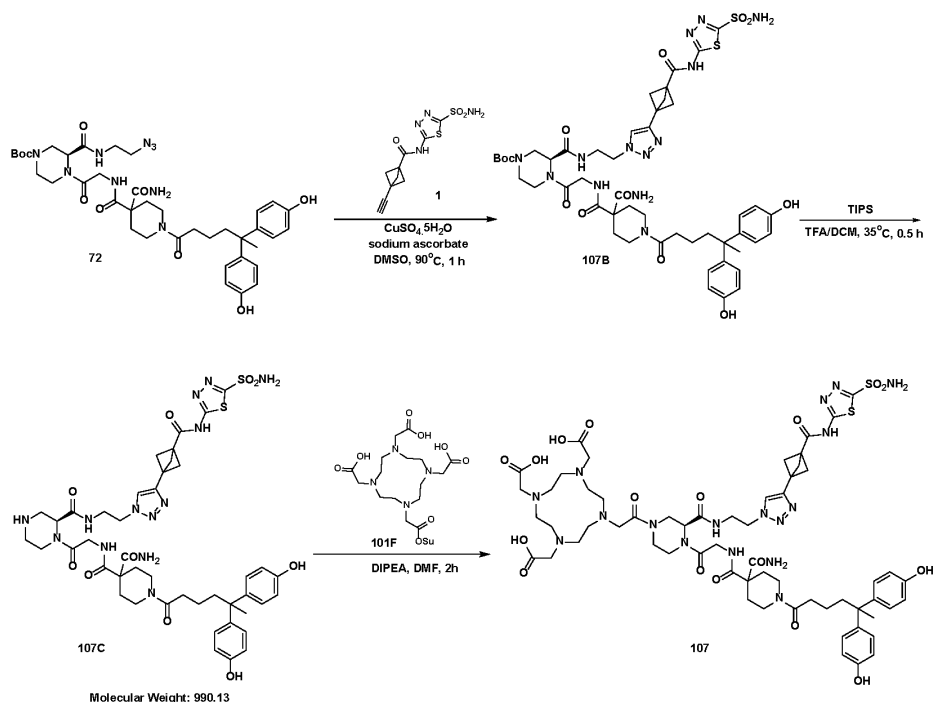
4.34 Synthesis of Compound 106

[00818] To a solution of **compound 106D** (0.45 g, 452 μ mol, 1 *eq*) in DMF (5 mL) was added DIEA (788 μ L, 4.52 mmol, 10 *eq*) and 2,2',2''-(10-(2-((2,5-dioxopyrrolidin-1-yl)oxy)-2-oxoethyl)-1,4,7,10-

tetraazacyclododecane-1,4,7-triyl)triacetic acid (272 mg, 543 μ mol, 1.2 *eq*) at 20°C. The mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated under reduced pressure and the residue purified by *prep*-HPLC (PhenomenexC18 80*30mm*3ummobile phase: [water (TFA)-ACN]; B%: 5%-35%, 8min.) to give **Compound 106** (130 mg, 21% yield); LCMS [M+H]: 1381.5; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.33 - 12.27 (m, 3H), 9.28 - 8.98 (m, 1H), 8.40 - 8.24 (m, 2H), 8.23 - 7.98 (m, 1H), 7.98 - 7.74 (m, 2H), 6.92 (br d, *J* = 8.3 Hz, 4H), 6.64 (d, *J* = 8.7 Hz, 4H), 5.00 - 4.72 (m, 1H), 4.68 - 3.95 (m, 11H), 3.85 - 3.50 (m, 9H), 3.20 - 2.78 (m, 15H), 2.71 - 2.55 (m, 5H), 2.44 (s, 7H), 2.19 - 2.03 (m, 1H), 2.19 - 1.82 (m, 2H), 1.45 (s, 3H).

D7. Synthesis of Compound 107

Scheme D7.



4.35 Synthesis of compound 107B

[00819] To a solution of **Intermediate 72** (11.5 g, 13.1 mmol, 1 *eq*) and **compound 1** (3.51 g, 11.8 mmol, 0.9 *eq*) in DMSO (57 mL) was added CuSO₄·5H₂O (653 mg, 2.61 mmol, 0.2 *eq*) and sodium ascorbate (5.18 g, 26.1 mmol, 2 *eq*). The mixture was stirred at 90°C for 1h. The reaction was repeated and combined. Silica gel (26 g) was added to the reaction mixture was stirred at 40°C for 0.5 h. The mixture was filtered and the filtrate was added dropwise to H₂O (230 mL) and NH₄Cl (60 mL) at 20°C over 10 min. The mixture was filtered, the filter cake washed with H₂O (300 mL) and the filter cake concentrated under reduced pressure. The residue was dissolved in DCM (130 mL) and MeOH (130 mL). Silica gel (26 g) was added into the mixture and stirred at 40°C for 0.5h. The mixture was filtered and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM:MeOH) to give **compound 107B** (23 g, 80% yield) as a white solid; LCMS [M+H]: 1090.6; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.19 (br s, 1H), 9.11 (s, 2H), 8.32 (br s, 3H), 7.93 (br s, 2H), 7.50 -

7.39 (m, 1H), 7.25 (brs, 1H), 6.93 (d, $J = 8.6$ Hz, 4H), 6.62 (d, $J = 8.8$ Hz, 4H), 4.70 (br s, 1H), 4.51 - 4.00 (m, 5H), 3.98 - 3.84 (m, 1H), 3.80 - 3.39 (m, 7H), 3.24 - 3.04 (m, 4H), 2.70 - 2.63 (m, 1H), 2.46 - 2.35 (m, 7H), 2.24 (br t, $J = 6.8$ Hz, 2H), 2.09 - 1.73 (m, 7H), 1.47 (s, 3H), 1.38 (s, 9H), 1.23 (br s, 3H).

4.36 Synthesis of Compound 107C

[00820] To a solution of **compound 107B** (11.5 g, 10.6 mmol, 1 eq) in DCM (60 mL) was added triisopropylsilane (43.3 mL, 211 mmol, 20 eq) and TFA (60 mL) and the reaction mixture stirred at 35°C for 0.5 h. The reaction was repeated and combined. The mixture was concentrated under reduced pressure, the residue triturated with MTBE (100 mL) at 20°C for 20 min twice, the mixture filtered and the filter cake concentrated under reduced pressure to give **compound 107C** (27 g, 93% yield, 3 TFA) as a white solid; LCMS [M+H]: 990.6; ^1H NMR (400 MHz, DMSO- d_6) δ 13.20 (s, 1H), 9.49 - 9.26 (m, 1H), 8.72 - 8.51 (m, 1H), 8.35 (s, 2H), 8.22 (br s, 1H), 8.02 (s, 1H), 7.95 - 7.83 (m, 1H), 7.38 (br s, 1H), 7.34 - 7.26 (m, 1H), 7.18 - 6.99 (m, 1H), 6.93 (d, $J = 8.6$ Hz, 4H), 6.62 (d, $J = 8.6$ Hz, 4H), 5.15 - 4.82 (m, 1H), 4.53 - 4.33 (m, 2H), 4.31 - 4.09 (m, 1H), 4.04 - 3.80 (m, 2H), 3.67 (br d, $J = 11.0$ Hz, 1H), 3.64 - 3.48 (m, 3H), 3.45 - 3.15 (m, 5H), 3.13 - 2.95 (m, 1H), 2.85 (br d, $J = 9.0$ Hz, 1H), 2.47 - 2.40 (m, 6H), 2.25 (br t, $J = 7.2$ Hz, 2H), 2.07 - 1.78 (m, 6H), 1.47 (s, 3H), 1.29 - 1.16 (m, 2H).

4.37 Synthesis of Compound 107

2,2',2''-(10-(2-((2,5-Dioxopyrrolidin-1-yl)oxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (897 mg, 1.18 mmol, 1.3 eq) was added to a solution of **compound 107C** (1.0 g, 0.91 mmol, 1eq), DIEA (790 μL , 4.54 mmol, 5eq), and DMF (10 mL) at 0 °C. The mixture stirred at 0 °C for 10 minutes and stirred at room temperature for 2 h. The reaction was purified directly by *prep*-HPLC (5-45% CH₃CN in water with 0.5% AcOH) to give **Compound 107** (642 mg, 51%); LCMS [M/2+H]: 688.9; ^1H NMR (400 MHz, DMSO) δ 9.22 (s, 2H), 8.48 (s, 1H), 8.27 (m, 2H), 8.06 (s, 1H), 7.90 (m, 1H), 7.47 (m, 1H), 7.33 - 7.23 (m, 1H), 6.92 (d, $J = 8.4$ Hz, 4H), 6.62 (d, $J = 8.3$ Hz, 4H), 4.72 (m, 1H), 4.42 (d, $J = 6.2$ Hz, 2H), 4.20 (m, 3H), 4.02 - 3.63 (m, 6H), 3.51 (m, 13H), 3.21 (m, 4H), 2.78 (m, 13H), 2.45 - 2.37 (m, 6H), 2.24 (m, 2H), 1.94 (s, 3H), 1.81 (m, 2H), 1.47 (s, 3H), 1.22 (t, $J = 8.2$ Hz, 2H).

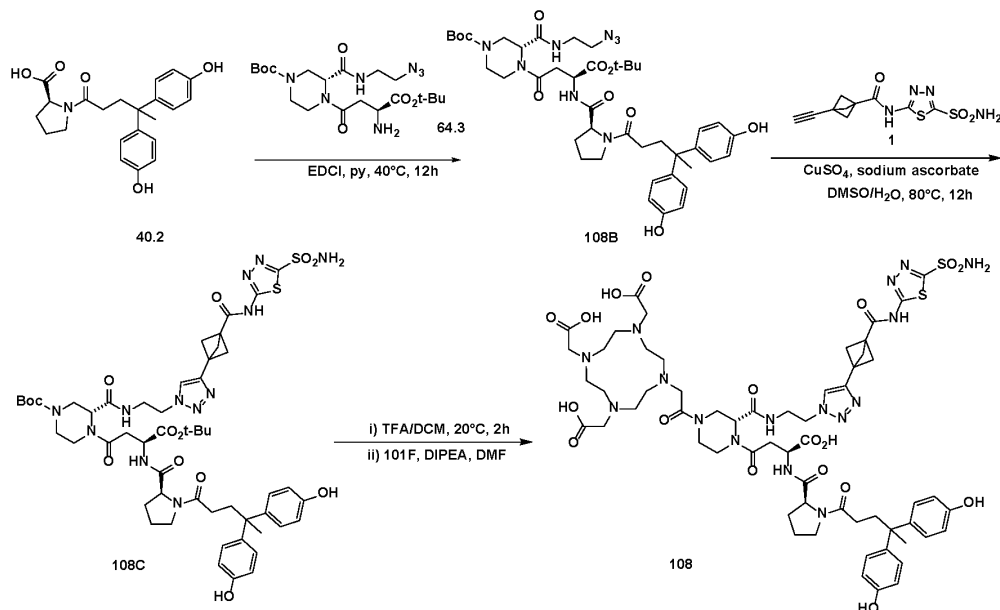
[00821] Compounds in **table 9.6** were prepared by procedures depicted in **scheme D7**.

Table 9.6.

Compound	m/z
107.1	[M+H]:1409.2
107.2	[M+H]:1410.3
107.3	[M+H]:1381.2
107.4	[M+H]:1363.3
107.5	[M+H]:1395.6
107.6	[M+H]:1376.5
107.7	[M+H]: 1299.3
107.8	[M+H]:1379.3
107.9	[M+H]:1419.3
107.10	[M+H]:1275.3
107.11	[M+H]:1280.2
107.12	[M+H]:1377.3
107.13	[M+H]:1395.4
107.14	[M+H]:1338.2
107.15	[M+H]:1509.8

Compound	m/z
107.16	[M+H]: 1170.5
107.17	[M+H]:1156.3
107.18	[M+H]:1154.3
107.19	[M+H]:1378.7
107.20	[M+H]: 1421.8
107.21	[M+H]:1381.3
107.22	[M+H]:1391.4
107.23	[M+H]:1421.5
107.24	[M+H]:1391.5
107.25	[M+H]:1406.6
107.26	[M+H]:1351.5
107.27	[M+H]: 1377.5
107.28	[M+H]:1387.4
107.29	[M+H]:1393.6
107.30	[M+H]:1425.4
107.31	[M+H]:1358.5
107.32	[M+H]:1421.6
107.33	[M+H]:1417.6
107.34	[M+H]:1390.5
107.35	[M+H]:1405.3
107.36	[M+H]:1425.3
107.37	[M/2+H]: 680.8
107.38	[M+H]:1380.6
107.39	[M+H]:1395.3
107.40	[M+H]:1405.4
107.41	[M+H]: 1417.7
107.42	[M+H]: 1443.8
107.43	[M+H]: 1423.7
107.44	[M+H]:1392.5
107.45	[M/2+H]:1469.7
107.46	[M+H]: 1437.8
107.47	[M+H]: 1379.6
107.48	[M+H]: 1389.7
107.49	[M+H]: 1346.6
107.50	[M+H]: 1380.6
107.51	[M+H]: 1362.7
107.52	[M+H]: 1374.7
107.53	[M+H]: 1372.8
107.54	[M+H]: 1403.3
107.55	[M+H]: 1396.4
107.56	[M+H]: 1377.3
107.57	[M+H]: 1378.9
107.58	[M/2+H]: 710.8
107.59	[M/2+H]: 711.2
107.60	[M/2+H]: 713.7
107.61	[M/2+H]: 713.7

D8. Synthesis of Compound 108**Scheme D8.**



4.38 Synthesis of compound 108B

[00822] To a solution of **compound 40.2** (470 mg, 1.23 mmol, 0.8 *eq*) and **compound 64.3** in pyridine (10 mL) was added EDCI (353 mg, 1.84 mmol, 1.2 *eq*) at 25°C. The mixture was stirred at 40°C for 12h and the reaction mixture concentrated under reduced pressure. Water (20 mL) was added, the mixture extracted with EtOAc (3 × 50 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether:EtOAc) to give **compound 108B** (730 mg, 57% yield) as a yellow oil; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.15 - 1.28 (m, 1 H) 1.33 - 1.41 (m, 22 H) 1.49 (br s, 2 H) 1.64 - 1.74 (m, 1 H) 1.80 (d, *J* = 2.93 Hz, 2 H) 1.98 - 2.01 (m, 1 H) 2.15 - 2.23 (m, 2 H) 2.67 - 2.74 (m, 1 H) 2.87 - 2.95 (m, 1 H) 3.13 (dd, *J* = 12.72, 3.67 Hz, 1 H) 3.17 (d, *J* = 5.14 Hz, 1 H) 3.23 - 3.30 (m, 2 H) 3.70 (d, *J* = 12.96 Hz, 1 H) 3.99 - 4.12 (m, 1 H) 4.19 - 4.33 (m, 2 H) 4.45 - 4.57 (m, 1 H) 4.70 - 4.79 (m, 1 H) 6.59 - 6.69 (m, 4 H) 6.89 - 6.98 (m, 4 H) 7.90 - 8.04 (m, 1 H) 8.12 - 8.23 (m, 1 H) 9.11 - 9.18 (m, 2 H).

4.39 Synthesis of compound 108C

[00823] To a solution of **compound 1** (214 mg, 719 μmol, 1 *eq*) and **compound 108B** (600 mg, 719 μmol, 1 *eq*) in DMSO (6 mL) was added a solution of CuSO₄ (5.5 μL, 36 μmol, 0.05 *eq*) and sodium ascorbate (142 mg, 719 μmol, 1 *eq*) in H₂O (1.2 mL) at 25°C. The mixture was stirred at 80°C for 12h. The mixture was poured into an NH₄Cl solution (20 mL) and stirred at 25°C for 15 min, filtered, filter cake dried and triturated with H₂O (10 mL) to give **compound 108C** (640 mg, 79% yield) as a yellow solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.18 - 1.28 (m, 1 H) 1.31 - 1.41 (m, 20 H) 1.47 (br s, 2 H) 1.62 - 1.74 (m, 1 H) 1.74 - 1.89 (m, 3 H) 1.90 - 2.03 (m, 2 H) 2.08 - 2.26 (m, 2 H) 2.44 (br s, 6 H) 2.54 (br s, 1 H) 2.63 - 2.77 (m, 1 H) 2.86 - 3.08 (m, 1 H) 3.10 - 3.22 (m, 2 H) 3.62 - 3.82 (m, 3 H) 4.01 - 4.15 (m, 1 H) 4.17 - 4.29 (m, 2 H) 4.29 - 4.41 (m, 2 H) 4.43 - 4.57 (m, 2 H) 4.62 - 4.73 (m, 1 H) 6.59 - 6.69 (m, 4 H) 6.93 (d, *J* = 7.70 Hz, 4 H) 7.90 - 8.00 (m, 1 H) 8.12 - 8.23 (m, 1 H) 8.26 - 8.36 (m, 2 H) 9.11 - 9.20 (m, 2 H) 12.95 - 13.46 (m, 1 H).

4.40 Synthesis of Compound 108

[00824] Compound 108 was prepared from compound 10 as previously depicted; LCMS [M+H]: 1363.4.

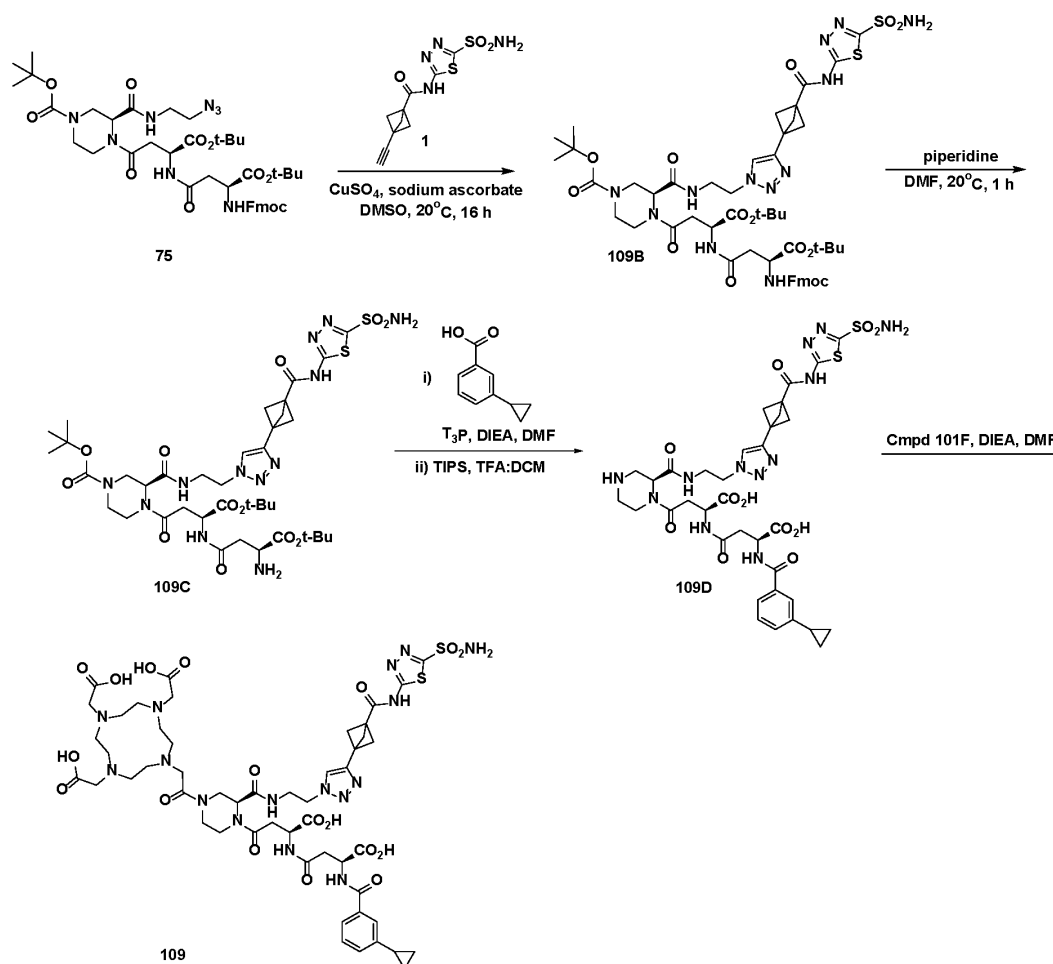
[00825] Compounds in table 9.7 were prepared by procedures depicted in scheme D8.

Table 9.7.

Compound	m/z
108.1	[M+H]:1168.3
108.2	[M+H]:1393.7
108.3	[M+H]:1377.7
108.4	[M+H]:1379.3
108.5	[M+H]:1363.2

D9. Synthesis of Compound 109

Scheme D9.



4.41 Synthesis of compound 109B

[00826] To a solution of compound 75 (18 g, 20.9 mmol, 1 eq) and Intermediate 1 (5.91 g, 19.8 mmol, 0.95 eq) in DMSO (90 mL) was added CuSO₄·5H₂O (521 mg, 2.09 mmol, 0.1 eq) and sodium

ascorbate (4.13 g, 20.9 mmol, 1.0 *eq*). The mixture was stirred at 20°C for 16 h, poured into an NH₄Cl solution (100 g in 400 mL water), stirred for 20 min at 20°C, filtered and the filter cake dried under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM:MeOH) to give **compound 109B** (18 g, 95% yield) as a white solid; LCMS [M+H]: 1161.4; ¹H NMR (400 MHz, METHANOL-*d*₄) δ 8.02 - 7.82 (m, 1H), 7.78 (br d, *J* = 7.6 Hz, 2H), 7.64 (brs, 2H), 7.37 (s, 2H), 7.29 (s, 2H), 4.82 - 4.62 (m, 2H), 4.61 - 4.43 (m, 3H), 4.41 - 4.14 (m, 4H), 3.86 - 3.48 (m, 4H), 3.35 (s, 6H), 3.28 - 3.06 (m, 2H), 3.04 - 2.70 (m, 4H), 2.58 - 2.40 (m, 7H), 1.55 - 1.33 (m, 27H).

4.42 Synthesis of compound 109C

[00827] To a solution of **compound 109B** (18 g, 19 mmol, 1 *eq*) in DMF (90 mL) was added piperidine (3.79 mL, 38.3 mmol, 2 *eq*). The mixture was stirred at 20°C for 1h, MTBE (90 mL) added and the residue purified by *prep*-TLC (SiO₂, DCM:MeOH) to give **compound 109C** (10.5 g, 96% yield) as a white solid; LCMS [M+H]: 939.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.73 - 7.55 (m, 3H), 7.51 - 6.02 (m, 1H), 4.83 - 3.95 (m, 5H), 3.91 - 3.25 (m, 5H), 3.25 - 3.09 (m, 5H), 3.03 - 2.59 (m, 2H), 2.37 (br s, 6H), 1.57 - 1.03 (m, 27H).

4.43 Synthesis of compound 109D

[00828] Propylphosphonic anhydride (38 μL, 50% in DMF, 128 μmol, 1.5 *eq*) was added to a solution of **compound 109C** (80 mg, 85.2 μmol, 1.0 *eq*), 3-cyclopropylbenzoic acid (18 mg, 111 μmol, 1.3 *eq*), DIEA (37 μL, 212 μmol, 2.5 *eq*), and DMF (1 mL). The mixture stirred for 2h, diluted with EtOAc, washed with water and brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was dissolved in a solution of trifluoroacetic acid (0.4 mL), tris(propan-2-yl)silane (0.4 mL) and DCM (1.2 mL) added and the reaction stirred at room temperature overnight. The mixture was concentrated under reduced pressure and the residue purified by *prep*-HPLC (15-35% CH₃CN in water with 0.1% TFA) to give **compound 109D** (40 mg, 48%) as a white powder; LCMS [M+H]: 871.3; ¹H NMR (400 MHz, DMSO) δ 13.22 (s, 1H), 12.76 (s, 2H), 8.62 - 8.25 (m, 5H), 8.12 - 7.94 (m, 2H), 7.64 - 7.46 (m, 2H), 7.39 - 7.17 (m, 2H), 5.10 (d, *J* = 4.6 Hz, 1H), 4.74 (q, *J* = 7.1 Hz, 1H), 4.67 - 4.58 (m, 1H), 4.50 - 4.29 (m, 3H), 3.90 (d, *J* = 14.3 Hz, 1H), 3.73 - 3.42 (m, 3H), 3.27 (t, *J* = 13.5 Hz, 2H), 3.03 - 2.71 (m, 4H), 2.66 (dd, *J* = 15.5, 7.1 Hz, 1H), 2.43 (s, 6H), 1.97 (tt, *J* = 9.1, 5.2 Hz, 1H), 1.03 - 0.90 (m, 2H), 0.72 (d, *J* = 5.2 Hz, 2H).

4.44 Synthesis of Compound 109

[00829] **Compound 109** is synthesized from **compound 109D** by procedures depicted in **scheme D9**; LCMS [M/2+H]: 629.4.

[00830] Compounds in **table 9.8** were prepared by procedures depicted in **Scheme D9**.

Table 9.8.

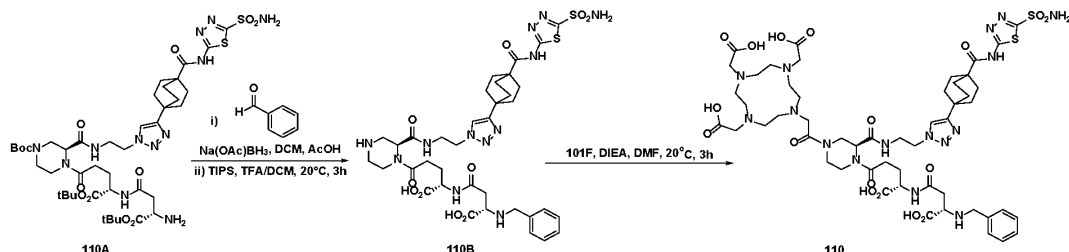
Compound	m/z
109.1	[M/2+H]: 629.3
109.2	[M/2+H]: 633.4
109.3	[M/2+H]: 645.3
109.4	[M/2+H]: 630.3
109.5	[M/2+H]: 631.2
109.6	[M/2+H]: 638.3

Compound	m/z
109.7	[M/2+H]: 629.3
109.8	[M/2+H]: 624.8
109.9	[M/2+H]: 632.4
109.10	[M/2+H]: 636.3
109.11	[M/2+H]: 645.3
109.12	[M/2+H]: 629.8
109.13	[M/2+H]: 557.3
109.14	[M/2+H]: 693.3
109.15	[M/2+H]: 638.3
109.16	[M/2+H]: 672.3
109.17	[M/2+H]: 638.7
109.18	[M/2+H]: 625.3
109.19	[M/2+H]: 629.8
109.20	[M/2+H]: 679.3
109.21	[M/2+H]: 622.2
109.22	[M/2+H]: 636.3
109.23	[M/2+H]: 630.3
109.24	[M/2+H]: 663.8
109.25	[M/2+H]: 663.8
109.26	[M/2+H]: 637.3
109.27	[M/2+H]: 644.3
109.28	[M/2+H]: 638.7
109.29	[M/2+H]: 584.3
109.30	[M/2+H]: 636.3
109.31	[M/2+H]: 637.3
109.32	[M/2+H]: 644.3
109.33	[M/2+H]: 683.4
109.34	[M/2+H]: 690.4
109.35	[M/2+H]: 643.3
109.36	[M/2+H]: 657.4
109.37	[M/2+H]: 647.3
109.38	[M/2+H]: 636.3
109.39	[M/2+H]: 630.3
109.40	[M+H]: 1392.4
109.41	[M/2+H]: 672.4
109.42	[M/2+H]: 666.3
109.43	[M+H]: 1317.3
109.44	[M+H]: 1307.3
109.45	[M/2+H]: 665.4
109.46	[M/2+H]: 661.4
109.47	[M/2+H]: 666.3
109.48	[M/2+H]: 633.4
109.49	[M/2+H]: 673.3
109.50	[M/2+H]: 657.3
109.51	[M/2+H]: 646.3
109.52	[M/2+H]: 721.3
109.53	[M/2+H]: 647.3
109.54	[M/2+H]: 657.4
109.55	[M/2+H]: 678.4
109.56	[M/2+H]: 657.9
109.57	[M/2+H]: 660.4
109.58	[M/2+H]: 700.3
109.59	[M/2+H]: 666.8
109.60	[M/2+H]: 585.3

Compound	m/z
109.61	[M/2+H]: 636.3
109.62	[M/2+H]: 698.3
109.63	[M/2+H]: 636.4

D10. Synthesis of Compound 110

Scheme D10.



4.45 Synthesis of compound 110B

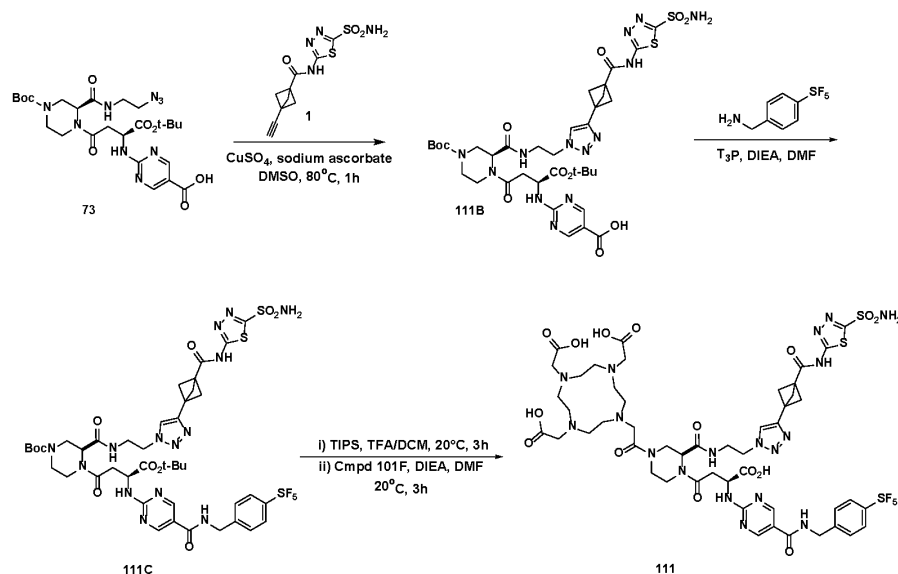
[00831] Benzaldehyde (20 μ L, 197 μ L, 2 eq) was added to a solution of **compound 110A** (100 mg, 100 μ mol, 1 eq), DCM (2 mL), and acetic acid (0.5 mL). The mixture stirred at room temperature for 1h, sodium triacetoxyborohydride (76 mg, 402 μ L, 4 eq) added at 0 °C and the reaction stirred at room temperature overnight. The mixture diluted with EtOAc, washed with water, and saturated NaHCO₃ solution. The organic layer was dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue was dissolved in a solution of trifluoroacetic acid (0.2 mL), tris(propan-2-yl)silane (0.2 mL), and DCM (1.2 mL) and stirred overnight. The reaction mixture was concentrated and the residue purified by *prep*-HPLC (10-30% CH₃CN in water with 0.1% TFA) to give **compound 110B** (63 mg, 72%) as a white powder; LCMS [M+H]: 873.4; ¹H NMR (400 MHz, DMSO) δ 12.71 (s, 1H), 9.30 (d, *J* = 28.8 Hz, 3H), 8.70 – 8.43 (m, 3H), 8.34 (s, 2H), 8.18 (t, *J* = 5.9 Hz, 1H), 7.84 (d, *J* = 24.4 Hz, 1H), 7.53 – 7.38 (m, 5H), 5.14 (s, 1H), 4.74 (s, 1H), 4.44 (dd, *J* = 13.7, 6.2 Hz, 2H), 4.32 (q, *J* = 7.9 Hz, 1H), 4.21 (d, *J* = 15.7 Hz, 3H), 3.87 (d, *J* = 14.2 Hz, 1H), 3.66 (d, *J* = 12.6 Hz, 1H), 3.52 (d, *J* = 6.3 Hz, 2H), 3.34 (t, *J* = 13.3 Hz, 1H), 3.21 – 2.96 (m, 3H), 2.85 (d, *J* = 40.9 Hz, 3H), 2.43 (d, *J* = 7.7 Hz, 1H), 2.28 (s, 1H), 2.09 – 1.92 (m, 6H), 1.84 (t, *J* = 7.7 Hz, 7H).

4.46 Synthesis of compound 110

[00832] **Compound 110** is synthesized from **compound 110B** by procedures depicted in **scheme D10**; LCMS [M/2+H]: 630.3.

D11. Synthesis of Compound 111

Scheme D11.



4.47 Synthesis of compound 111B

[00833] To a solution of **compound 73** (4.0 g, 6.76 mmol, 1 *eq*) and **compound 1** (1.80 g, 6.02 mmol, 0.89 *eq*) in DMSO (40 mL) was added sodium (2*R*)-2-[(2*R*)-3,4-dihydroxy-5-oxo-2H-furan-2-yl]-2-hydroxy-ethanolate (2.68 g, 13.5 mmol, 2 *eq*) and CuSO₄·5H₂O (169 mg, 676 μmol, 0.1 *eq*). The mixture was stirred at 80 °C for 1 h, the crude product triturated with an NH₄Cl solution (200 mL H₂O, 40 g NH₄Cl) at 20 °C for 10 min, the filter cake washed with H₂O (20 mL) and the filter cake concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM:MeOH) to give **compound 111B** (4.0 g, 66% yield) as a white solid; LCMS [M+H]: 890.3.

4.48 Synthesis of compound 111C

[00834] 1-[4-(Pentafluoro-λ⁶-sulfanyl)phenyl]methanamine (40 mg, 170 μmol, 1.1 *eq*) and DIEA (81 μl, 463 μmol, 3*eq*) were added to a solution of **compound 111B** (137 mg, 154 μmol, 1 *eq*) in DMF (4 mL). 1-Propanephosphonic anhydride solution (116 μl, 386 μmol, 2.5) was added dropwise, the solution stirred at room temperature for 30 min and the reaction mixture purified directly by *prep*-HPLC (C18, Luna 30x150mm, 0-40% CH₃CN/H₂O+ 0.1% Formic acid) to give **compound 111C** (80 mg, 47% yield) as a white solid; [M+H]: 1105.3.

4.49 Synthesis of compound 111

[00835] **Compound 111** was synthesized from **compound 111C** by procedures depicted in **scheme D11**; LCMS [M/2+H]: 630.2.

[00836] Compounds in **table 9.10** were prepared by procedures depicted in **scheme D11**.

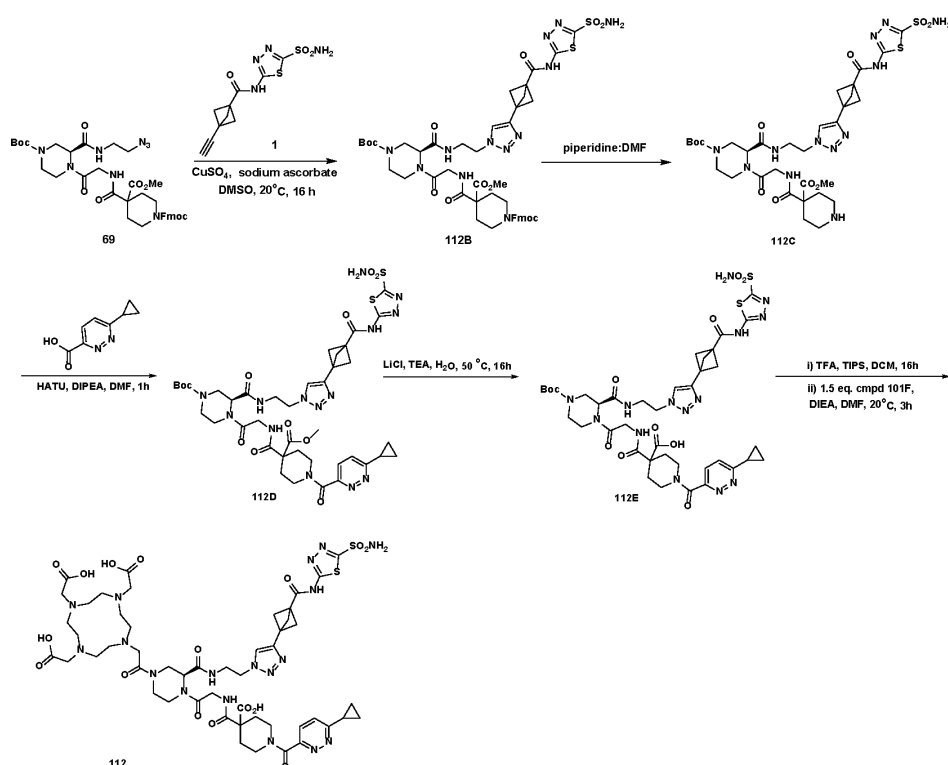
Table 9.10

Compound	m/z
111.1	[M+H]: 1359.3
111.2	[M/2+H]: 625.8
111.3	[M+H]: 1249.4
111.4	[M/2+H]: 686.4
111.5	[M/2+H]: 634.8

Compound	m/z
111.6	[M/2+H]: 630.3
111.7	[M/2+H]: 646.3
111.8	[M/2+H]: 630.3
111.9	[M+H]: 1227.3
111.10	[M+H]: 1249.3
111.11	[M/2+H]: 632.4
111.12	[M+H]: 1162.3

D12. Synthesis of Compound 112

Scheme D12.



4.50 Synthesis of intermediate 112B

[00837] To a mixture of **compound 69** (4.0 g, 5.36 mmol, 1 *eq*) and **compound 1** (1.36 g, 4.55 mmol, 0.85 *eq*) in DMSO (40 mL) was added CuSO₄·5H₂O (134 mg, 536 μmol, 0.1 *eq*) and sodium ascorbate (1.06 g, 5.36 mmol, 1 *eq*) in one portion at 20°C under a nitrogen atmosphere. The mixture was stirred at 20°C for 16 h, the reaction mixture poured into H₂O (320 mL) and aq. NH₄Cl (80 mL), and the mixture filtered. The filter cake was purified by column chromatography (SiO₂, DCM:MeOH) to give **compound 112B** (6.6 g, 58% yield) as a white solid; LCMS [M+H]: 1045.5.

4.51 Synthesis of compound 112C

[00838] To a solution of **compound 112B** (7.0 g, 6.7 mmol, 1 *eq*) in DMF (70 mL) was added piperidine (13.2 mL, 134 mmol) and the mixture stirred at 20°C for 1 h. MTBE (210 mL) was added, and the reaction stirred at 20°C for 10 min. The suspension was filtered, and the filter cake concentrated

under reduced pressure. The solid was purified by chromatography column (SiO₂, DCM:MeOH) to give a blue solid. The crude product was dissolved in DCM (50 mL) and MeOH (50 mL), silica gel (10 g) added and the reaction stirred at 40°C for 0.5h (residual copper removal), the mixture filtered and the process repeated three times. The filtrate was concentrated under reduced pressure to give **compound 112C** (10 g, 60% yield) as a white solid; LCMS [M+H]: 823.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.34 - 8.11 (m, 2H), 8.06 - 7.51 (m, 3H), 4.65 (br s, 1H), 4.39 (br s, 2H), 4.33 - 4.19 (m, 2H), 4.15 - 3.87 (m, 1H), 3.86 - 3.71 (m, 3H), 3.70 - 3.64 (m, 3H), 3.52 (br s, 1H), 3.24 - 3.08 (m, 4H), 3.04 - 2.91 (m, 3H), 2.40 - 2.26 (m, 2H), 2.25 - 2.15 (m, 6H), 2.13 - 1.95 (m, 2H), 1.71 - 1.48 (m, 1H), 1.37 (s, 9H).

4.52 Synthesis of compound 112D

[00839] 6-Cyclopropylpyridazine-3-carboxylic acid (31 mg, 190 μmol, 1.1 *eq*) was added to **compound 112C** (130 mg, 158 μmol, 1 *eq*) in DMF (4 mL). HATU (72 mg, 190 μmol, 1.2 *eq*) and DIEA (82 μl) were added dropwise, and the solution stirred at room temperature for 1 h. The reaction was purified directly by *prep*-HPLC (prep C18, Luna 30x150mm, 10-60% CH₃CN/H₂O+ 0.1% Formic acid) to give **compound 112D** (65 mg, 42% yield) as a white solid; [M+H]: 969.3.

4.53 Synthesis of compound 112E

[00840] Triethylamine (44 μl, 315 μmol, 3 *eq*) was added followed by lithium chloride (13 mg, 315 μmol, 3 *eq*) to a solution of **compound 112D** (65 mg, 63 μmol, 1 *eq*) in water (1mL). The reaction solution was stirred at 50°C for 16h and directly purified by *prep*-HPLC (C18, Luna 30x150mm, 30-50% CH₃CN:H₂O, 0.1% Formic acid) to give **compound 112E** (25 mg, 41%) as a white solid; [M+H]: 955.3.

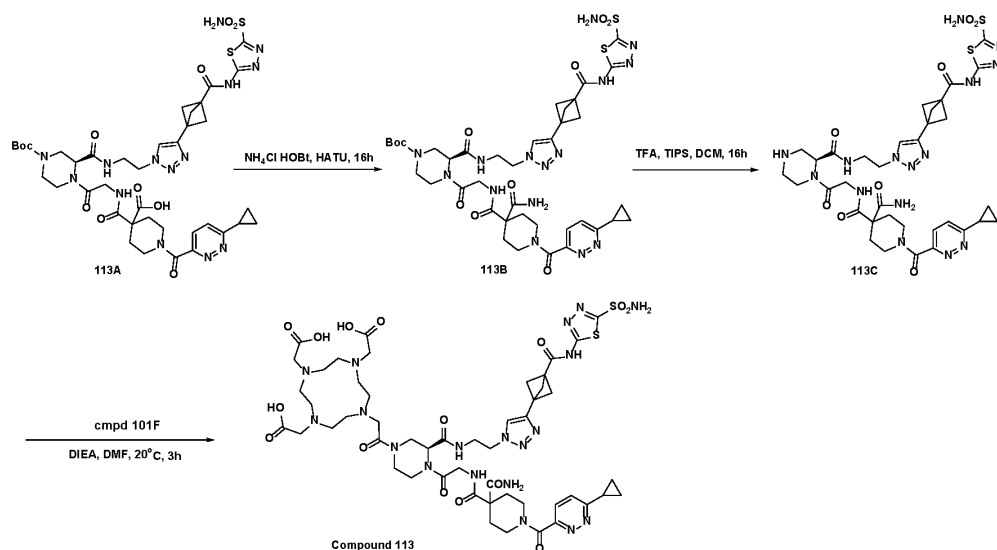
4.54 Synthesis of Compound 112

[00841] **Compound 112** was prepared from **compound 112E** by protocols previously depicted; LCMS [M+H]: 1241.3.

[00842] Compounds in **table 9.11** were prepared by procedures depicted in **scheme D12**.

Table 9.11

Compound	m/z
112.1	[M/2+H]: 627.3
112.2	[M/2+H]: 705.1
112.3	[M/2+H]: 636.3
112.4	[M/2+H]: 634.4
112.5	[M/2+H]: 641.3
112.6	[M/2+H]: 627.3
112.7	[M+H]: 1247.5
112.8	[M/2+H]: 616.3
112.9	[M/2+H]: 620.4
112.10	[M/2+H]: 620.3
112.11	[M/2+H]: 629.3
112.12	[M/2+H]: 627.4
112.13	[M/2+H]: 636.3
112.14	[M/2+H]: 636.3
112.15	[M/2+H]: 636.3
112.16	[M/2+H]: 627.3
112.17	[M+H]: 1196.6
112.18	[M/2+H]: 689.4
112.19	[M/2+H]: 691.3

D13. Synthesis of Compound 113**Scheme D13.****4.55 Synthesis of compound 113B**

[00843] Ammonium chloride (1.3 mg, 25.1 μmol , 1.2 *eq*), HOBt (2.0 mg, 15.1 μmol , 1.2 *eq*), HATU (4.7 mg, 12.6 μmol , 1 *eq*) and DIEA (5.5 μl , 31.4 μmol , 3 *eq*) were added to a solution of **compound 113A** (12 mg, 12.6 μmol , 1 *eq*) in DMF (1 mL). The solution was stirred at room temperature for 16h and directly purified by *prep*-HPLC (C18, Luna 30x150mm, 20-60% $\text{CH}_3\text{CN}:\text{H}_2\text{O} + 0.1\%$ Formic acid) to give **compound 113B** (7 mg, 58% yield) as a white solid; $[\text{M}+\text{H}]^+$: 954.4.

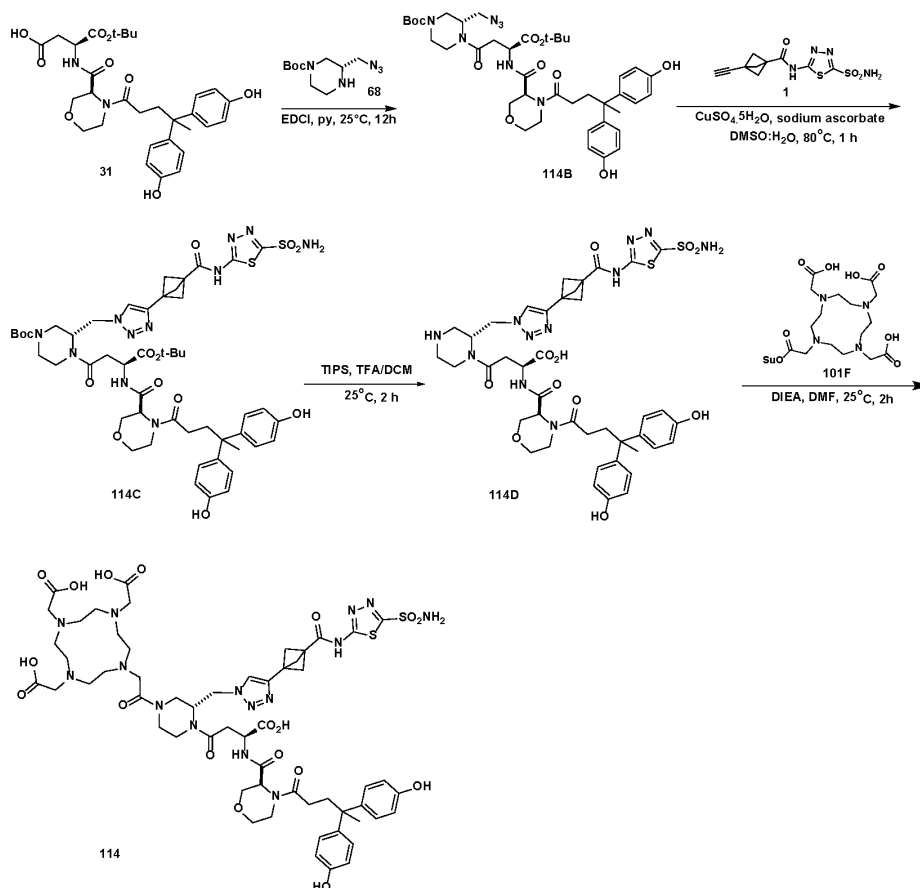
4.56 Synthesis of compound 113C

[00844] Tris(isopropyl)silane (4.5 μl , 22 μmol , 3 *eq*) and trifluoroacetic acid (1.7 μl , 22 μmol , 3 *eq*) were added to a solution of **compound 113B** (7.0 mg, 7.3 μmol , 1 *eq*) in DCM (1 mL). The reaction was stirred at room temperature for 16h and concentrated under reduced pressure with toluene 3 times to give **compound 113C** (6.0 mg, 95% yield) as a white powder; $[\text{M}+\text{H}]^+$: 854.5.

4.57 Synthesis of Compound 113

[00845] **Compound 113** was prepared from **compound 113C** by protocols previously depicted; LCMS $[\text{M}/2+\text{H}]^+$: 620.4.

D14. Synthesis of Compound 114**Scheme D14.**



4.58 Synthesis of Compound 114B

[00846] To a solution of **compound 68** (650 mg, 2.69 mmol, 1 *eq*) and **compound 31** (1.54 g, 2.69 mmol, 1 *eq*) in pyridine (10 mL) was added EDCI (620 mg, 3.23 mmol, 1.2 *eq*). The mixture was stirred at 25°C for 12h and concentrated under reduced pressure. The residue was purified by *prep*-HPLC (Phenomenex Luna 80*30mm*3um; mobile phase:[water(HCl)-ACN];B%: 40%-70%,8min) to give **compound 114B** (0.91 g, 43% yield) as a white solid; LCMS [M+H]: 794.4.

4.59 Synthesis of compound 114C

[00847] To a solution of **compound 114B** (0.86 g, 1.08mmol, 1 *eq*) and **compound 1** (323 mg, 1.08 mmol, 1 *eq*) in DMSO (10 mL) and H₂O (2 mL) was added CuSO₄·5H₂O (13.5 mg, 0.05 *eq*) and sodium ascorbate (230 mg, 1.1 *eq*). The mixture was stirred at 80°C for 1 h, concentrated under reduced pressure and the residue purified by re-crystallization at 0°C (H₂O) to give **compound 114C** (1.1 g, 93% yield) as a white solid; LCMS [M+H]: 1092.4.

4.60 Synthesis of compound 114D

[00848] To a solution of **compound 114C** (1.00 g, 916 μmol, 1 *eq*) in DCM (10 mL) was added TFA (2.0 mL, 27.0 mmol, 30 *eq*) and TIPS (1.88 mL, 9.16 mmol, 10 *eq*), and the mixture stirred at 25°C for 2h. The reaction mixture was concentrated under reduced pressure and the crude product triturated with MTBE at 20 °C for 10 min to give **compound 114D** (760 mg, 89% yield) as a green solid; LCMS [M+H]: 936.3.

4.61 Synthesis of Compound 114

[00849] To a solution of **compound 114D** (760 mg, 812 μ mol, 1 *eq*) in DMF (10 mL) was added DIEA (1.41 mL, 8.12 mmol, 10 *eq*) and **compound 101F** (937 mg, 1.87 mmol, 2.3 *eq*). The mixture was stirred at 25 °C for 2h and concentrated under reduced pressure. The residue was purified by *prep*-HPLC (Phenomenex luna C18 100*40mm*5 μ m; mobile phase: [water(TFA)-ACN]; B%: 1%-35%, 8min) to give **Compound 114** (100 mg, 9.3% yield); LCMS [M+H]: 1322.7.

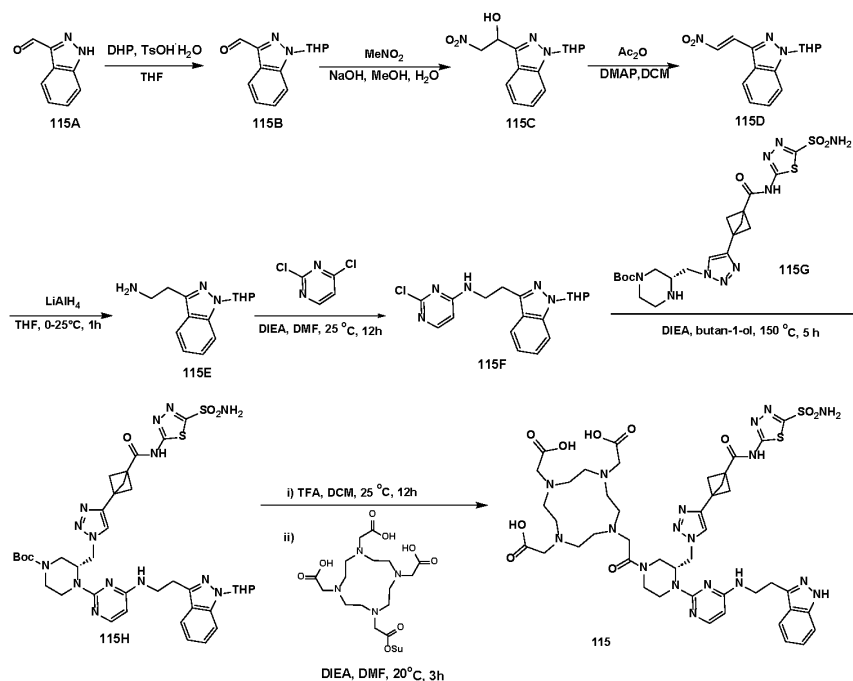
[00850] Compounds in **table 9.13** were prepared by procedures depicted in **scheme D14**.

Table 9.13.

Compound	m/z
114.1	[M+H]:1212.3
114.2	[M+H]:1097.3
114.3	[M+H]:1111.3

D15. Synthesis of Compound 115

Scheme D15.



4.62 Synthesis of compound 115B

[00851] To a solution of **compound 115A** (10 g, 68.4 mmol, 1 *eq*) in THF (140 mL) was added DHP (9.38 mL, 103 mmol, 1.5 *eq*) and TsOH.H₂O (1.30 g, 6.84 mmol, 0.1 *eq*), and the mixture stirred at 80°C for 2h. The reaction mixture was poured into ice-water (100 mL), the aqueous phase extracted with EtOAc (3 x 100 mL), the combined organic phase washed with brine (100 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (SiO₂, Petroleum ether:EtOAc) to give **compound 115B** (12 g, 75% yield) as white oil; LCMS [M+H]: 231.1;

¹H NMR (400 MHz, CDCl₃) δ ppm 10.27 (1 H, s) 8.31 (1 H, d, *J*=8.19 Hz) 7.68 (1 H, d, *J*=8.44 Hz) 7.48 (1 H, t, *J*=7.70 Hz) 7.37 (1 H, m) 5.85 (1 H, dd, *J*=8.93, 2.81 Hz) 4.03 (1 H, m) 3.79 (1 H, m) 2.59 (1 H, m) 2.16 (2 H, m) 1.77 (3 H, m).

[00852] 4.63 Synthesis of compound 115C

[00853] To a solution of **compound 115B** (9.0 g, 39.1 mmol, 1 *eq*) and MeNO₂ (2.74 mL, 50.8 mmol, 1.3 *eq*) in MeOH (90 mL) was added a solution of NaOH (3.44 g, 86 mmol, 2.2 *eq*) in H₂O (9 mL) dropwise at 0°C. The reaction mixture was stirred at 0°C for 0.5h, quenched with 1M HCl (60 mL), the aqueous phase was extracted with EtOAc (3 x 100 mL), the combined organic phase washed with brine (100 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (SiO₂, Petroleum ether/EtOAc) to give **compound 115C** (9.7 g, 74% yield, 87% purity) as a yellow oil; LCMS [M+H]⁺: 292.1; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.84 (1 H, ddd, *J*=8.17, 1.85, 0.95 Hz) 7.58 (1 H, dd, *J*=8.46, 3.81 Hz) 7.43 (1 H, ddd, *J*=8.31, 7.12, 0.89 Hz) 7.21 (1 H, m) 5.84 (1 H, ddd, *J*=8.76, 7.57, 3.46 Hz) 5.68 (1 H, dt, *J*=9.45, 2.85 Hz) 4.92 (2 H, m) 4.02 (1 H, m) 3.74 (1 H, td, *J*=10.88, 2.92 Hz) 3.16 (1 H, m) 2.50 (1 H, m) 2.14 (1 H, m) 2.01 (1 H, m) 1.72 (3 H, m).

4.64 Synthesis of compound 115D

[00854] To a solution of **compound 115C** (9.7 g, 33.3 mmol, 1 *eq*) in DCM (97 mL) was added Ac₂O (3.12 mL, 33.3 mmol, 1 *eq*) and DMAP (203 mg, 1.66 mmol, 0.05 *eq*), and the mixture stirred at 25°C for 2h. The mixture was poured into ice-water (100 mL), the aqueous phase extracted with DCM (3 x 100 mL), the combined organic phase washed with brine (100 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure to give crude **compound 115D** (10 g) as a yellow solid which was used directly in the next reaction.

4.65 Synthesis of compound 115E

[00855] A solution of **compound 115D** (4.0 g, 14.6 mmol, 1 *eq*) in THF (40 mL) was added to a stirred solution of 1M LiAlH₄ (58.6 mL, 4 *eq*) in THF (56 mL) dropwise at 0°C and the reaction mixture stirred at 25°C for 1h. The mixture was poured into ice-water (100 mL), the aqueous phase extracted with EtOAc (3 x 100 mL), the combined organic phase washed with NH₄Cl solution (100 mL) and brine (100 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure to give crude **compound 115E** (3.2 g) as a yellow oil that was used directly in the next reaction; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.68 (1 H, d, *J*=8.13 Hz) 7.55 (1 H, d, *J*=8.38 Hz) 7.39 (1 H, m) 7.16 (1 H, m) 5.67 (1 H, dd, *J*=9.88, 2.63 Hz) 4.07 (1 H, m) 3.75 (1 H, m) 3.14 (3 H, m) 2.58 (1 H, m) 2.10 (2 H, m) 1.72 (4 H, m).

4.66 Synthesis of compound 115F

[00856] To a stirred solution of 2,4-dichloropyrimidine (1.94 g, 13.0 mmol, 1 *eq*) in anhydrous DMSO (32 mL) at 25°C under a nitrogen atmosphere was added DIEA (4.54 mL, 26.1 mmol, 2 *eq*) and **compound 115E** (3.2 g, 13.0 mmol, 1 *eq*) slowly. The mixture was stirred at 25°C for 12h, poured into ice-water (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic phase was washed with brine (20 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by chromatography column (SiO₂, Petroleum ether:EtOAc) to give **compound 115F** (2.4 g, 43% yield, 83% purity) as a yellow solid; ¹H NMR (400 MHz, CDCl₃) δ 7.94 (1 H, m) 7.66 (1 H, d, *J*=7.5 Hz)

7.56 (1 H, d, $J=8.4$ Hz) 7.40 (1 H, m) 7.17 (1 H, t, $J=7.5$ Hz) 6.22 (1 H, m) 5.84 (1 H, br s) 5.67 (1 H, dd, $J=9.8, 2.51$ Hz) 4.08 (1 H, m) 3.78 (3 H, m) 3.25 (2 H, t, $J=6.5$ Hz) 2.55 (1 H, m) 2.16 (1 H, m) 2.05 (1 H, m) 1.74 (4 H, m).

4.67 Synthesis of compound 115H

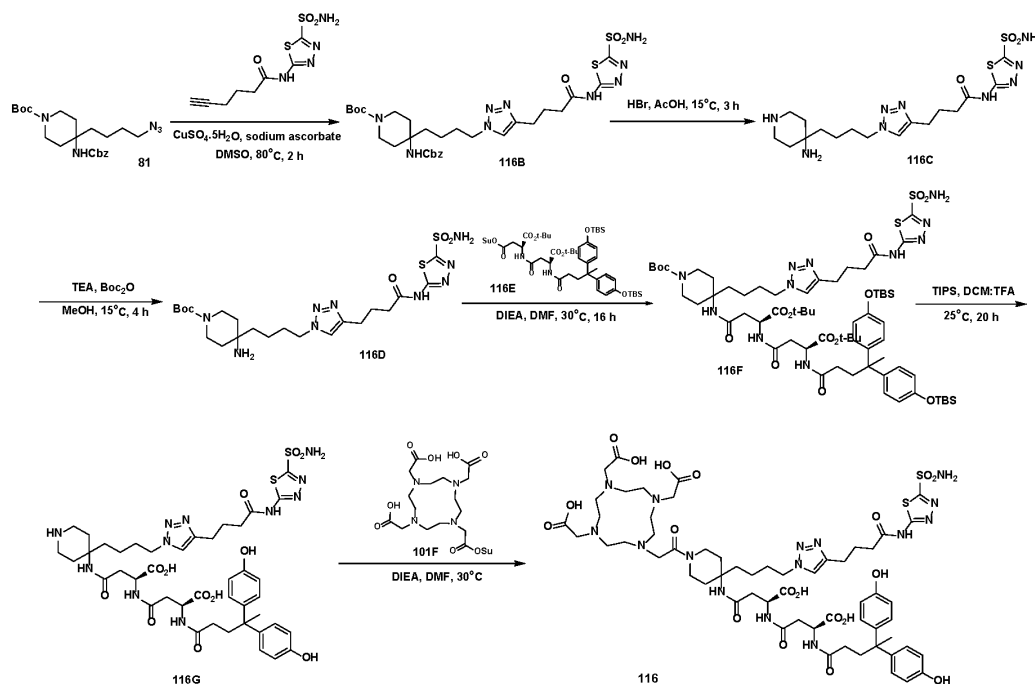
[00857] To a solution of **compound 115G** (650 mg, 1.20 mmol, 1 *eq*) in butan-1-ol (1.5 mL) were added DIEA (1.05 mL, 6.02 mmol, 5 *eq*) and **compound 115F** (539 mg, 1.20 mmol, 1 *eq*), and the mixture stirred at 150°C for 5h. The reaction mixture was concentrated under reduced pressure and the residue purified by *prep*-HPLC (column: Waters Xbridge BEH C18 250*50mm*10um; mobile phase: [water(NH₄HCO₃)-ACN]:B%: 30%- 60%, 10min) to give **compound 115H** (270 mg, 26% yield) as a yellow solid; LCMS [M+H]: 861.2; ¹H NMR (400 MHz, CDCl₃) δ ppm 7.64 (2 H, d, $J=7.75$ Hz) 7.52 (1 H, dd, $J=8.32, 4.44$ Hz) 7.38 (2 H, m) 7.13 (1 H, td, $J=7.38, 2.88$ Hz) 5.65 (2 H, d, $J=10.01$ Hz) 4.53 (3 H, m) 4.10 (3 H, m) 3.74 (3 H, m) 3.36 (1 H, t, $J=11.38$ Hz) 3.20 (2 H, m) 3.10 (1 H, m) 2.96 (1 H, m) 2.56 (7 H, m) 2.05 (3 H, m) 1.73 (4 H, m) 1.53 (9 H, s).

4.68 Preparation of Compound 115

[00858] **Compound 115** was prepared from **compound 115H** as previously depicted; LCMS [M+H]: 1063.3.

D16. Synthesis of Compound 116

Scheme D16.



4.69 Synthesis of compound 81

[00859] To a solution of **compound 81** (2.0 g, 4.63 mmol, 1 *eq*) in DMSO (30 mL) was added *N*-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)hex-5-ynamide (1.14 g, 4.17 mmol, 0.9 *eq*), sodium ascorbate (1.01 g, 5.10 mmol, 1.1 *eq*) and CuSO₄ (37 mg, 232 μ mol, 0.05 *eq*) in H₂O (15 mL) at 20°C, and the mixture

stirred at 80°C for 2h. The mixture was added to H₂O (100 mL), filtered, and the filter cake concentrated under reduced pressure to give **compound 116B** (2.3 g, 63% yield) as a brown solid; LCMS [M+H]: 706.2; ¹H NMR (400 MHz, METHANOL-*d*₄) δ 7.79 - 7.69 (m, 1H), 7.41 - 7.27 (m, 5H), 5.12 - 4.99 (m, 2H), 4.35 - 4.23 (m, 2H), 3.85 - 3.68 (m, 2H), 3.38 - 3.33 (m, 1H), 3.28 - 3.20 (m, 1H), 3.07 - 2.94 (m, 2H), 2.82 - 2.73 (m, 2H), 2.63 - 2.55 (m, 2H), 2.15 - 2.00 (m, 4H), 1.89 - 1.77 (m, 2H), 1.74 - 1.64 (m, 2H), 1.47 - 1.42 (m, 9H), 1.39 - 1.32 (m, 2H), 1.30 - 1.20 (m, 2H).

4.70 Synthesis of compound 116C

[00860] A mixture of **Compound 116B** (5.0 g, 7.08 mmol, 1 *eq*) and HBr (25 mL, 33% purity) in AcOH (15 mL) was degassed and purged with nitrogen 3 times, and the mixture stirred at 15°C for 3h under a nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure and the residue diluted with MeOH (15 mL). A basic resin was added to the mixture and stirred at 15°C for 0.5h. The mixture was filtered through a celite pad, the filter cake rinsed with MeOH and the filtrate concentrated under reduced pressure to give crude **compound 116C** (3.34 g) as a light blue solid; LCMS [M+H]: 472.2; ¹H NMR (400 MHz, METHANOL-*d*₄) δ 7.79 (s, 1H), 7.53 - 7.45 (m, 3H), 4.38 (t, *J* = 6.8 Hz, 2H), 3.12 - 2.99 (m, 2H), 2.94 (dd, *J* = 2.4, 13.0 Hz, 2H), 2.83 (s, 4H), 2.76 (t, *J* = 7.4 Hz, 2H), 2.47 (br s, 2H), 2.10 - 1.99 (m, 2H), 1.63 (br s, 2H), 1.57 - 1.43 (m, 4H), 1.40 - 1.24 (m, 2H).

4.71 Synthesis of intermediate 116D

[00861] To a solution of **compound 116C** (3.34 g, 7.08 mmol, 1 *eq*) in MeOH (30 mL) was added TEA (4.93 mL, 35.4 mmol, 5 *eq*) at 15°C. The mixture was stirred at 15°C for 10 min, Boc₂O (1.63 mL, 7.08 mmol, 1 *eq*) added dropwise at 0°C and the reaction stirred at 15°C for 4h. The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography (SiO₂, DCM:MeOH) to give **intermediate 116D** (3.2 g, 79% yield) as a light-yellow solid; LCMS [M+H]: 572.2; ¹H NMR (400 MHz, METHANOL-*d*₄) δ 7.78 (s, 1H), 4.37 (s, 2H), 3.63 - 3.44 (m, 2H), 3.39 - 3.35 (m, 1H), 3.34 (br s, 1H), 2.75 (t, *J* = 7.5 Hz, 2H), 2.47 (t, *J* = 7.4 Hz, 2H), 2.05 (t, *J* = 7.4 Hz, 2H), 1.91 (br s, 1H), 1.87 (br s, 1H), 1.52 - 1.45 (m, 3H), 1.44 (s, 9H), 1.29 (s, 5H).

4.72 Synthesis of intermediate 116F

[00862] To a solution of **compound 116D** (500 mg, 875 μmol, 1 *eq*) in DMF (1 mL) was added DIEA (609 μL, 3.50 mmol, 4 *eq*) and **compound 116E** (1.25 g, 1.31 mmol, 1.5 *eq*). The mixture was stirred at 30°C for 16h and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM:MeOH) to give **compound 116F** (155 mg, 13% yield); LCMS [M+H]: 1411.1; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.01 (s, 1H), 8.33 (s, 2H), 8.22 (d, *J* = 7.7 Hz, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.84 (s, 1H), 7.31 (s, 1H), 7.01 (d, *J* = 8.6 Hz, 4H), 6.73 (d, *J* = 8.6 Hz, 4H), 4.43 - 4.32 (m, 2H), 4.24 (t, *J* = 7.1 Hz, 2H), 3.64 - 3.54 (m, 2H), 2.98 - 2.90 (m, 1H), 2.88 (br s, 1H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.61 - 2.57 (m, 2H), 2.48 - 2.39 (m, 2H), 2.23 - 2.18 (m, 2H), 2.10 - 2.00 (m, 2H), 1.96 - 1.91 (m, 2H), 1.89 - 1.84 (m, 2H), 1.58 (d, *J* = 7.9 Hz, 6H), 1.50 (s, 3H), 1.36 - 1.34 (m, 27H), 1.22 (d, *J* = 6.1 Hz, 2H), 1.15 - 1.10 (m, 2H), 0.93 (s, 18H), 0.16 - 0.16 (m, 12H).

4.73 Synthesis of compound 116G

[00863] To a solution of **compound 116F** (150 mg, 106 μ mol, 1 *eq*) in DCM (1 mL) was added TIPS (131 μ L, 638 μ mol, 6 *eq*) and TFA (1 mL). The mixture was stirred at 15°C for 16h, TFA (1 mL) added at 15 °C, the mixture stirred at 25°C for 20h and concentrated under reduced pressure. The residue was triturated with MTBE at 15°C for 10 min to give crude **compound 116G** (130 mg) as a white solid; LCMS [M+H]: 970.5; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.02 (s, 1H), 8.44 - 8.37 (m, 1H), 8.34 (s, 2H), 8.28 (d, *J* = 7.7 Hz, 1H), 7.93 (d, *J* = 8.1 Hz, 1H), 7.85 (s, 1H), 7.52 (s, 1H), 6.92 (d, *J* = 8.3 Hz, 4H), 6.64 (d, *J* = 8.6 Hz, 4H), 4.53 - 4.42 (m, 2H), 4.30 - 4.20 (m, 2H), 3.13 - 3.08 (m, 2H), 2.99 (br d, *J* = 1.3 Hz, 2H), 2.69 - 2.56 (m, 8H), 2.48 - 2.37 (m, 2H), 2.27 - 2.11 (m, 4H), 1.97 - 1.91 (m, 2H), 1.89 - 1.81 (m, 2H), 1.77 - 1.58 (m, 4H), 1.45 (s, 3H), 1.26 - 1.12 (m, 2H), 1.05 - 1.03 (m, 2H), 0.96 - 0.86 (m, 2H).

4.74 Synthesis of Compound 116

[00864] To a solution of **compound 116G** (110 mg, 113 μ mol, 1 *eq*) in DMF (1 mL) were added DIEA (198 μ L, 1.13 mmol, 10 *eq*) and **compound 101F** (57 mg, 113 μ mol, 1 *eq*). The reaction mixture was stirred at 30°C for 6h and concentrated under reduced pressure. The residue was purified by *prep*-HPLC (TFA condition: column: Phenomenex Luna C18 150*30mm*5 μ m; mobile phase: [water (TFA)-ACN] B%: 15%-35% 8min) to give **compound 116** (45 mg, 29% yield); LCMS [M+H]: 1356.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.00 (br s, 1H), 12.91 - 12.28 (m, 3H), 9.29 - 9.05 (m, 1H), 8.32 (s, 2H), 8.23 (d, *J* = 7.7 Hz, 1H), 7.94 - 7.89 (m, 1H), 7.83 (s, 1H), 7.48 (br s, 1H), 6.92 (d, *J* = 8.2 Hz, 4H), 6.64 (d, *J* = 8.5 Hz, 4H), 4.53 - 4.44 (m, 2H), 4.28 - 4.17 (m, 4H), 4.11 (br s, 2H), 4.00 (d, *J* = 11.0 Hz, 1H), 3.61 (d, *J* = 3.3 Hz, 2H), 3.51 - 3.34 (m, 8H), 3.28 (d, *J* = 4.3 Hz, 2H), 3.17 - 2.93 (m, 10H), 2.88 - 2.79 (m, 1H), 2.69 - 2.54 (m, 8H), 2.41 - 2.36 (m, 2H), 2.35 - 2.30 (m, 1H), 2.21 - 2.08 (m, 4H), 1.99 - 1.91 (m, 2H), 1.89 - 1.81 (m, 2H), 1.77 - 1.68 (m, 2H), 1.65 (d, *J* = 6.9 Hz, 2H), 1.45 (s, 3H), 1.34 (t, *J* = 10.0 Hz, 1H), 1.27 - 1.10 (m, 3H).

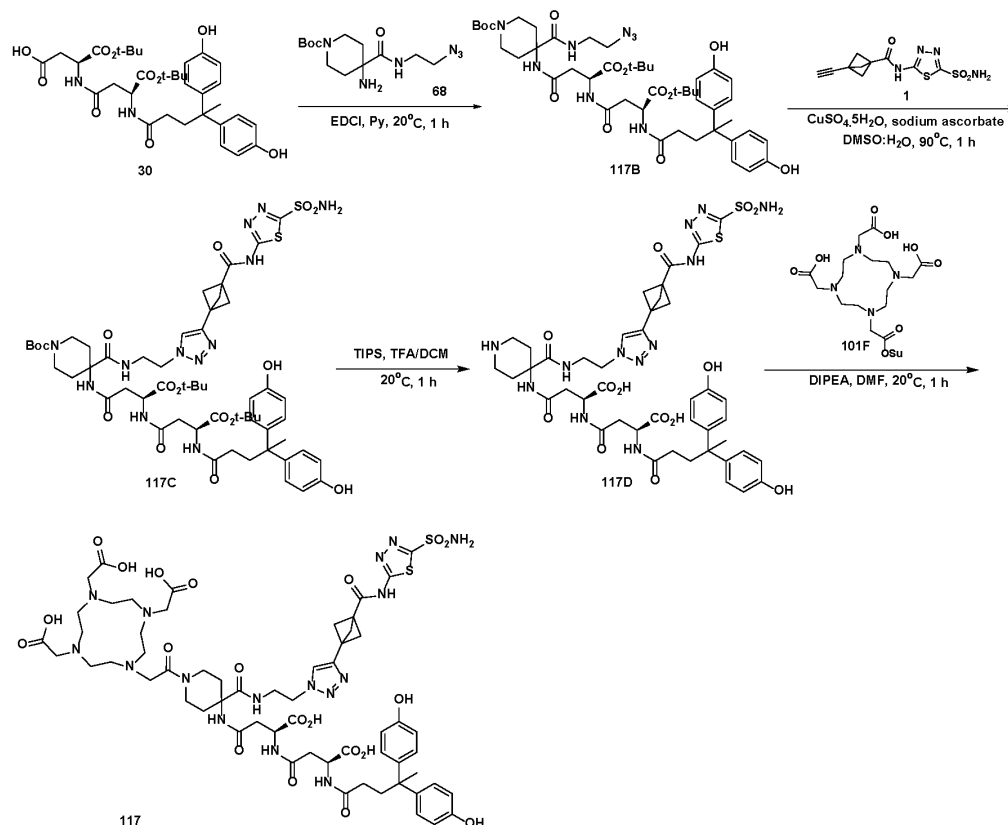
[00865] Compounds in **table 9.14** were prepared by procedures previously depicted.

Table 9.14.

Compound	m/z
116.1	[M+H]:1501.3
116.2	[M+H]:1487.3
116.3	[M+H]:1443.3
116.4	[M+H]:1473.3

D17. Synthesis of Compound 117

Scheme D17.



4.75 Synthesis of compound 117B

[00866] To a solution of **compound 68** (160 mg, 512 μ mol, 1 *eq*) in pyridine (3.5 mL) was added **compound 30** (354 mg, 563 μ mol, 1.1 *eq*) and EDCI (196 mg, 1.02 mmol, 2 *eq*) and the reaction stirred at 20°C for 1h. The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography (SiO₂, DCM:MeOH) to give **compound 117B** (360 mg, 76% yield) as a white solid; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 7.14 - 6.83 (m, 7H), 6.81 - 6.62 (m, 5H), 4.90 - 4.57 (m, 2H), 3.94 - 3.77 (m, 2H), 3.54 - 3.31 (m, 4H), 3.12 - 2.98 (m, 2H), 2.76 - 2.58 (m, 3H), 2.48 - 2.27 (m, 3H), 2.06 - 1.90 (m, 6H), 1.70 (br s, 4H), 1.50 - 1.38 (m, 27H).

4.76 Synthesis of compound 117C

[00867] To a solution of **compound 117B** (290 mg, 314 μ mol, 1 *eq*) and **compound 1** (94 mg, 314 μ mol, 1 *eq*) in DMSO (3 mL) was added CuSO₄·5H₂O (16 mg, 63 μ mol, 0.2 *eq*) and sodium ascorbate (124 mg, 628 μ mol, 2 *eq*). The reaction mixture was stirred at 90°C for 1h, poured into a H₂O (12 mL) and NH₄Cl solution (3 mL), and stirred for 20 min. The mixture was filtered and the solid concentrated under reduced pressure. The crude product was washed with MTBE (2 $\times$ 5 mL) to give crude **compound 117C** (160 mg) as a white solid; ¹H NMR (400 MHz, MeOH-*d*₄) δ 7.93 (br s, 1H), 7.09 - 6.93 (m, 4H), 6.74 - 6.59 (m, 4H), 4.70 - 4.44 (m, 5H), 3.88 - 3.74 (m, 3H), 3.69 - 3.47 (m, 3H), 3.16 - 2.98 (m, 2H), 2.87 - 2.44 (m, 10H), 2.39 - 2.28 (m, 2H), 2.15 - 1.94 (m, 3H), 1.93 - 1.79 (m, 3H), 1.61 - 1.50 (m, 4H), 1.47 - 1.36 (m, 27H).

4.77 Synthesis of compound 117D

[00868] To a solution of **compound 117C** (160 mg, 131 μmol , 1 *eq*) in DCM (2.5 mL) and TFA (1 mL) was added triisopropylsilane (538 μL , 2.62 mmol, 20 *eq*) at 20°C, and the mixture stirred at 20°C for 1 h. The reaction mixture was concentrated under reduced pressure, the residue triturated with MTBE (2 mL), the suspension filtered, and the filter cake washed with MTBE (2 $\times$ 1 mL). The filter cake was concentrated under reduced pressure to give **compound 117D** (130 mg, 98% yield) as a green solid; ^1H NMR (400 MHz, MeOH-d_4) δ 7.00 (br d, J = 8.6 Hz, 4H), 6.66 (br d, J = 8.6 Hz, 4H), 4.58 - 4.45 (m, 1H), 3.67 - 3.58 (m, 2H), 2.66 (s, 9H), 2.54 (br d, J = 8.6 Hz, 6H), 2.43 (s, 4H), 2.34 (br dd, J = 6.4, 9.3 Hz, 2H), 2.27 - 2.20 (m, 3H), 2.04 (br dd, J = 8.6, 11.8 Hz, 2H), 1.59 - 1.48 (m, 4H), 1.19 (s, 6H).

4.78 Synthesis of Compound 117

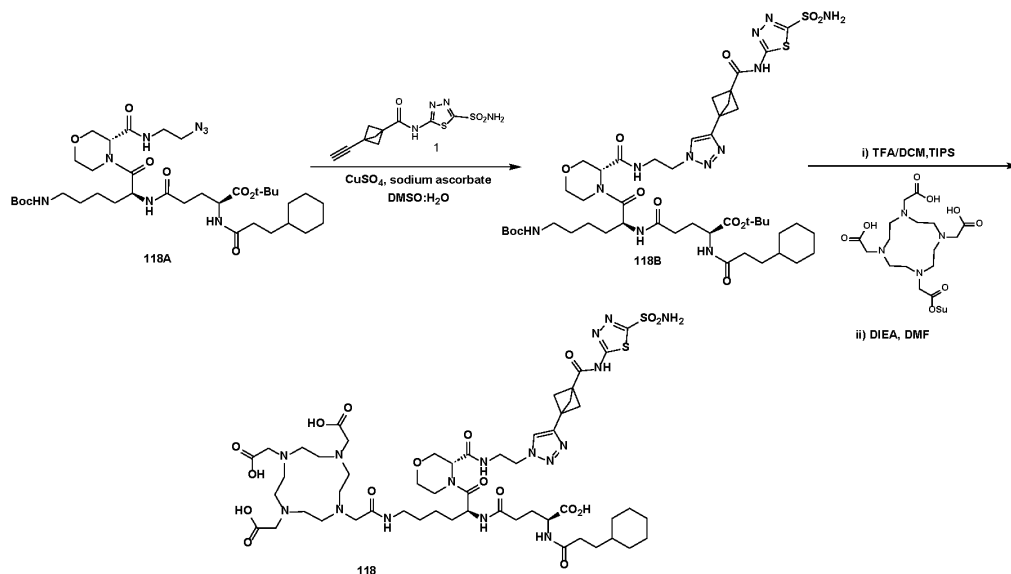
[00869] To a solution of **compound 117D** (130 mg, 129 μmol , 1 *eq*) in DMF (1 mL) was added DIEA (224 μL , 1.29 mmol, 10 *eq*) and **compound 101F** (226 mg, 451 μmol , 3.5 *eq*) under a nitrogen atmosphere. The mixture was stirred at 20°C for 1h, the reaction mixture quenched by the addition of H_2O (1 mL) and concentrated under reduced pressure. The crude product was purified by *prep*-HPLC (column: Phenomenex luna C18 100*40mm*5 μm ; mobile phase: [water(TFA)-ACN]:gradient:5%-35% B over 8 min) to give **Compound 117** (19 mg, 11% yield); LCMS $[\text{M}/2+\text{H}]$: 698.5; ^1H NMR (400 MHz, DMSO-d_6) δ 9.19 - 9.12 (m, 1H), 8.34 (s, 2H), 8.31 - 8.25 (m, 1H), 8.20 - 8.10 (m, 1H), 7.93 (s, 2H), 7.77 - 7.67 (m, 1H), 6.92 (d, J = 7.8 Hz, 4H), 6.64 (d, J = 8.6 Hz, 4H), 4.49 (br d, J = 6.4 Hz, 2H), 4.35 (br s, 2H), 4.21 - 3.92 (m, 4H), 3.71 - 3.49 (m, 8H), 3.16 (s, 12H), 3.12 - 2.95 (m, 10H), 2.66 (s, 4H), 2.42 (s, 7H), 2.36 - 2.35 (m, 1H), 2.32 (s, 1H), 2.17 (br dd, J = 6.8, 9.2 Hz, 2H), 2.02 - 1.91 (m, 2H), 1.90 - 1.78 (m, 3H), 1.77 - 1.65 (m, 1H), 1.45 (s, 3H).

[00870] Compounds in **table 9.15** were prepared by procedures depicted in **scheme D17**.

Table 9.15.

Compound	m/z
117.1	$[\text{M}+\text{H}]$: 1391.6
117.2	$[\text{M}/2+\text{H}]$: 555.3
117.3	$[\text{M}+\text{H}]$: 1407.7
117.4	$[\text{M}+\text{H}]$: 1391.5
117.5	$[\text{M}/2+\text{H}]$: 694.0
117.6	$[\text{M}/2+\text{H}]$: 715.1
117.7	$[\text{M}+\text{H}]$: 1415.0
117.8	$[\text{M}+\text{H}]$: 1360.9

D18. Synthesis of Compound 118**Scheme D18.**



4.79 Preparation of compound 118B

[00871] To a solution of **compound 118A** (1.1 g, 1.03 mmol, 70% purity, 1 *eq*) and **compound 1** (306 mg, 1.03 mmol, 1 *eq*) in DMSO (20 mL) was added a solution of sodium ascorbate (203 mg, 1.03 mmol, 1 *eq*) and CuSO₄·5H₂O (25.6 mg, 103 μmol, 0.1 *eq*) in H₂O (4 mL) in one portion at 20°C. The mixture was stirred at 80°C for 1h and triturated with water at 20°C for 5 min to give **compound 118B** (730 mg, 68% yield) as a green solid; LCMS [M+H]⁺: 1049.2.

4.80 Preparation of Compound 118

[00872] **Compound 118** was prepared from **compound 118B** as previously depicted; LCMS [M+H]⁺: 1279.5; ¹H NMR (400 MHz, DMSO-d₆) δ 0.78 - 0.88 (m, 2 H) 1.09 - 1.31 (m, 6 H) 1.34 - 1.50 (m, 5 H) 1.53 - 1.78 (m, 8 H) 1.87 - 1.98 (m, 1 H) 2.09 - 2.22 (m, 4 H) 2.40 - 2.45 (m, 6 H) 3.09 (b r s, 11 H) 3.27 - 3.41 (m, 12 H) 3.70 - 3.95 (m, 7 H) 4.02 - 4.33 (m, 5 H) 4.37 - 4.57 (m, 3 H) 4.64 - 4.72 (m, 1 H) 7.84 - 7.92 (m, 1 H) 8.03 - 8.09 (m, 1 H) 8.12 - 8.26 (m, 1 H) 8.30 - 8.37 (m, 3 H) 8.40 - 8.47 (m, 1 H) 13.15 - 13.28 (m, 1 H).

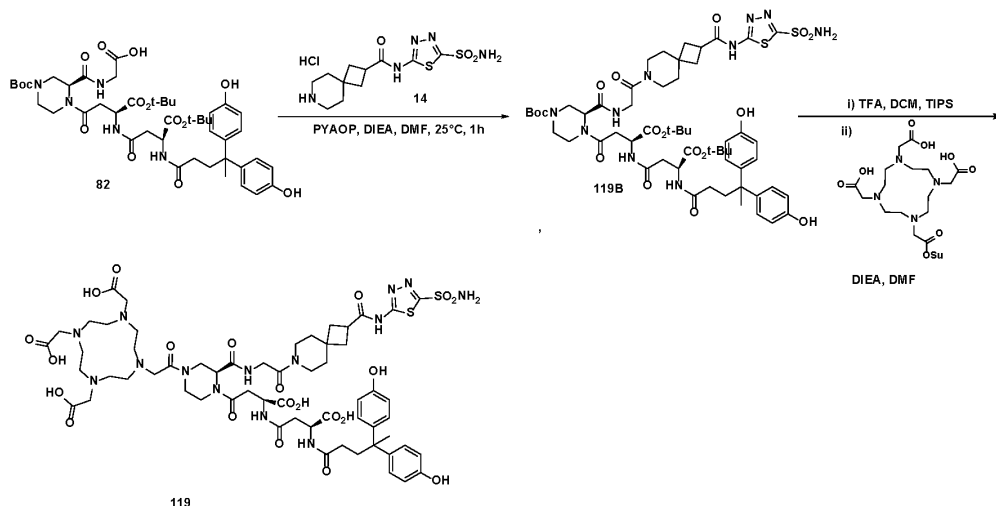
[00873] Compounds in **table 9.16** were prepared by procedures depicted in Scheme D18.

Table 9.16.

Compound	m/z
118.1	[M+H] ⁺ :1279.7
118.2	[M+H] ⁺ : 1322.7
118.3	[M+H] ⁺ :1285.7
118.4	[M+H] ⁺ :1285.7

D19. Synthesis of Compound 119

Scheme D19.



4.81 Preparation of compound 119B

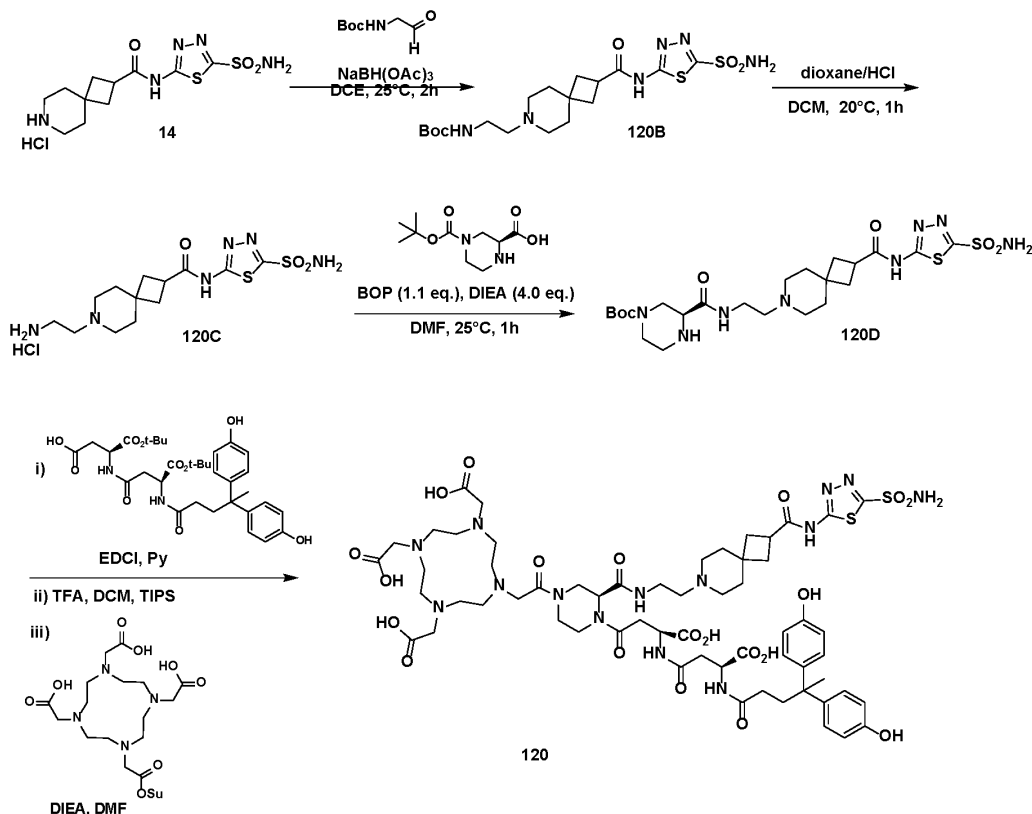
[00874] To a solution of **compound 14** (294 mg, 668 μ mol, 1 *eq*, HCl) in DMF (7 mL) was added DIEA (349 μ L, 2.00 mmol, 3 *eq*), **compound 82** (0.60 g, 668 μ mol, 1 *eq*), and PyAOP (383 mg, 735 μ mol, 1.1 *eq*). The mixture was stirred at 25°C for 1 h. The reaction was repeated and combined. The reaction mixture was poured into H₂O (100 mL), the aqueous layer extracted with EtOAc (3 $\times$ 30 mL), the combined organic layers were washed with brine (100 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by chromatography column (EtOAc:MeOH) to give **compound 118B** (1.0 g, 54% yield, 87% purity) as a white solid.

4.82 Preparation of Compound 119

[00875] **Compound 119** was prepared from **compound 119B** as previously depicted; LCMS [M+H]: 1385.5; ¹H NMR (400 MHz, DMSO-d₆) δ 13.11 - 12.29 (m, 3H), 9.30 - 9.09 (m, 1H), 8.39 - 8.01 (m, 3H), 8.00 - 7.80 (m, 2H), 6.93 (d, *J* = 8.3 Hz, 4H), 6.64 (d, *J* = 8.5 Hz, 4H), 5.11 - 4.83 (m, 1H), 4.73 - 4.38 (m, 3H), 4.29 - 3.53 (m, 16H), 3.19 - 2.80 (m, 19H), 2.69 - 2.60 (m, 3H), 2.37 - 2.28 (m, 1H), 2.21 - 1.96 (m, 7H), 1.90 - 1.81 (m, 2H), 1.62 - 1.37 (m, 7H).

D20. Synthesis of Compound 120

Scheme D20.



4.86 Preparation of compound 120B

[00876] To a solution of **compound 14** (25.7 g, 69.9 mmol, 1 *eq*, HCl salt) in DCE (257 mL) was added a solution of *tert*-butyl (2-oxoethyl)carbamate (13.3 g, 83.8 mmol, 1.2 *eq*) in DCE (64 mL) at 0°C . NaBH(OAc)_3 (22.2 g, 105 mmol, 1.5 *eq*) was added, the mixture stirred at 25°C for 2h and poured into saturated aqueous NaHCO_3 (100 mL). The organic layer was separated, the aqueous layer extracted with DCM (3×100 mL), the combined organic layers washed with brine (3×100 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography column (EtOAc:MeOH) to give **compound 120B** (12 g, 36% yield) as a light-yellow solid.

4.87 Preparation of compound 120C

[00877] To a solution of **compound 120B** (9.5 g, 20.0 mmol, 1 *eq*) in DCM (100 mL) was added 4M HCl in dioxane (95 mL), the mixture stirred at 20°C for 1h and concentrated under reduced pressure to give crude **compound 120C** (8.5 g, HCl salt) as a white solid. The product was used directly.

4.88 Preparation of compound 120D

[00878] To a solution of **compound 120C** (2.4 g, 5.84 mmol, 1 *eq*, HCl) in DMF (48 mL) was added DIEA (4.07 mL, 23.4 mmol, 4 *eq*), (*S*)-4-(*tert*-butoxycarbonyl)piperazine-2-carboxylic acid (1.34 g, 5.84 mmol, 1 *eq*) and BOP (2.84 g, 6.42 mmol, 1.1 *eq*). The mixture was stirred at 25°C for 1h. The reaction was repeated twice and the 3 reaction mixtures combined, filtered and the filtrate purified by *prep*-HPLC (column: Welch Xtimate C18 180*70mm#10um; mobile phase: $[\text{H}_2\text{O}(0.1\%\text{TFA})\text{-ACN}]$; gradient: 5%-

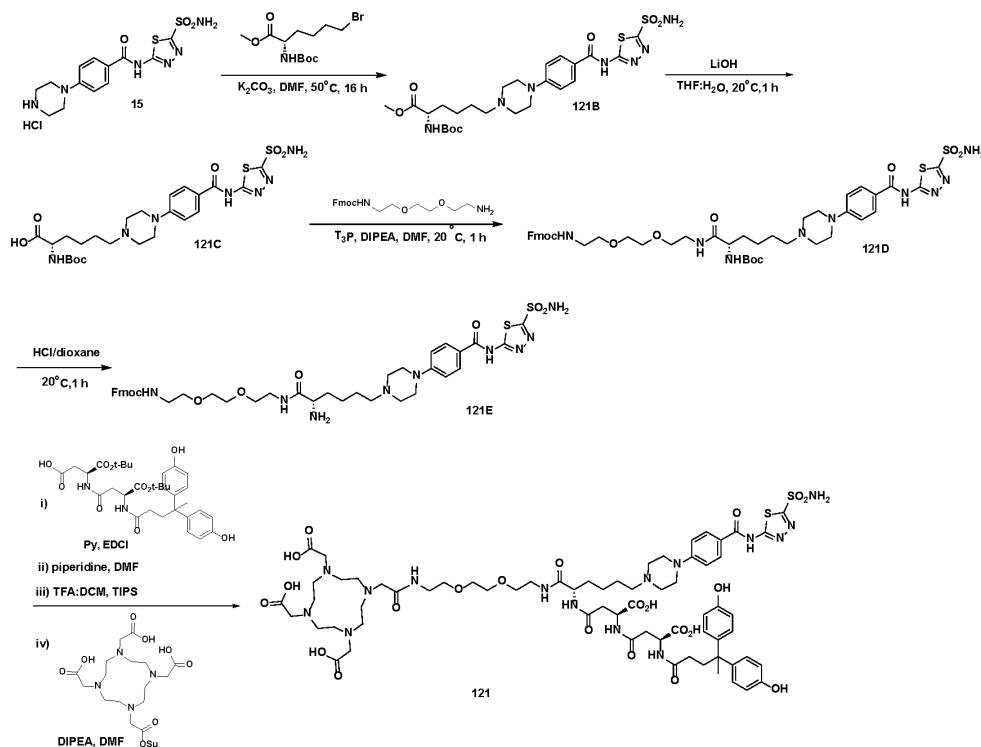
35% B over 20.0 min) to give **compound 120D** (3.0 g, 29% yield) as a white solid; LCMS [M+H]: 587.4.

4.89 Preparation of Compound 120

[00879] **Compound 120** was prepared from **Compound 120D** as previously depicted; LCMS [M+H]: 1371.4.

D21. Synthesis of Compound 121

Scheme D21.



4.90 Preparation of compound 121B

[00880] To a solution of **compound 15** (1.89 g, 5.13 mmol, 1 *eq*) in DMF (20 mL) was added K₂CO₃ (2.84 g, 20.5 mmol, 4 *eq*) and methyl (S)-6-bromo-2-((tert-butoxycarbonyl)amino)hexanoate (1.83 g, 5.64 mmol, 1.1 *eq*). The mixture was stirred at 50°C for 16 h, the aqueous phase acidified to pH=7 with aqueous HCl and the aqueous phase extracted with 5:1 DCM:IPA (2 × 30 mL). The combined organic phase was dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM:MeOH) to give **compound 121B** (813 mg, 23% yield, 90% purity) as a white solid; LCMS [M+H]: 612.3; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.09 - 12.59 (m, 1H), 8.26 (s, 2H), 8.05 (d, *J* = 9.0 Hz, 2H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 9.0 Hz, 2H), 3.99 - 3.90 (m, 1H), 3.62 (s, 3H), 3.37 (br s, 4H), 3.17 (d, *J* = 5.2 Hz, 5H), 2.41 - 2.28 (m, 2H), 1.73 - 1.54 (m, 2H), 1.41 - 1.26 (m, 12H).

4.91 Preparation of compound 121C

[00881] To a solution of **compound 121B** (710 mg, 1.16 mmol, 1 *eq*) in THF (2 mL) and H₂O (2 mL) was added LiOH (83 mg, 3.48 mmol, 3 *eq*). The mixture was stirred at 20°C for 1 h and concentrated

under reduced pressure. The aqueous layer was acidified to pH=5 with 1N HCl, filtered and the filter cake concentrated under reduced pressure to give crude **compound 121C** (852 mg) as a white solid; LCMS [M+H]: 598.3.

¹H NMR (400 MHz, DMSO-*d*₆) δ 13.14 - 12.03 (m, 1H), 8.28 (s, 2H), 8.11 - 8.01 (m, 2H), 7.06 (br d, *J* = 8.8 Hz, 2H), 3.86 (dt, *J* = 5.0, 8.4 Hz, 1H), 3.50 (br d, *J* = 1.4 Hz, 8H), 2.81 (br s, 3H), 2.69 - 2.54 (m, 2H), 1.75 - 1.48 (m, 3H), 1.43 - 1.30 (m, 9H).

4.92 Preparation of compound 121D

[00882] To a solution of **compound 121C** (791 mg, 1.32 mmol, 1 *eq*) in DMF (8 mL) was added (9H-fluoren-9-yl)methyl (2-(2-(2-aminoethoxy)ethoxy)ethyl)carbamate (538 mg, 1.32 mmol, 1 *eq*), DIPEA (576 μL, 3.31 mmol, 2.5 *eq*) and T₃P (4.73 mL, 7.94 mmol, 50% purity, 6 *eq*). The mixture was stirred at 20°C for 1 h, the reaction mixture quenched by addition of H₂O (10 mL) at 25°C and concentrated under reduced pressure. The residue was diluted with H₂O (10 mL) and extracted with EtOAc (20 mL), the combined organic layers washed with brine (10 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM:MeOH) to give **compound 121D** (300 mg, 23% yield, 95% purity) as a white solid; LCMS [M+H]: 950.4; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.15 - 12.69 (m, 1H), 8.26 (s, 2H), 8.04 (d, *J* = 9.0 Hz, 2H), 7.88 (d, *J* = 7.4 Hz, 2H), 7.81 (t, *J* = 5.6 Hz, 1H), 7.68 (d, *J* = 7.4 Hz, 2H), 7.44 - 7.38 (m, 2H), 7.36 - 7.28 (m, 3H), 7.01 (br d, *J* = 9.0 Hz, 2H), 6.77 (br d, *J* = 8.2 Hz, 1H), 4.29 (d, *J* = 6.8 Hz, 2H), 4.23 - 4.17 (m, 1H), 3.93 - 3.84 (m, 1H), 3.50 (s, 4H), 3.44 - 3.33 (m, 9H), 3.28 - 3.20 (m, 1H), 3.20 - 3.09 (m, 3H), 2.39 - 2.28 (m, 2H), 1.65 - 1.54 (m, 1H), 1.53 - 1.40 (m, 3H), 1.37 (s, 9H), 1.31 - 1.19 (m, 2H).

4.93 Preparation of compound 121E

[00883] 4M HCl/dioxane (4 mL) was added to a solution of **compound 121D** (187 mg, 197 μmol, 1 *eq*) in dioxane (4 mL) and the mixture stirred at 20°C for 1 h. The reaction mixture was concentrated under reduced pressure to give crude **compound 121E** (257 mg) as a white solid; LCMS [M+H]: 850.4; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.27 - 13.11 (m, 1H), 11.34 (br s, 1H), 8.68 (br t, *J* = 5.4 Hz, 1H), 8.37 - 8.26 (m, 5H), 8.10 (br d, *J* = 8.8 Hz, 2H), 7.89 (d, *J* = 7.4 Hz, 2H), 7.69 (d, *J* = 7.4 Hz, 2H), 7.45 - 7.38 (m, 2H), 7.38 - 7.29 (m, 3H), 7.16 - 7.09 (m, 2H), 4.29 (br d, *J* = 6.8 Hz, 2H), 4.23 - 4.18 (m, 1H), 4.10 (br d, *J* = 13.0 Hz, 2H), 3.83 - 3.72 (m, 1H), 3.52 (s, 5H), 3.49 - 3.36 (m, 6H), 3.20 - 3.01 (m, 6H), 1.86 - 1.68 (m, 4H), 1.41 - 1.28 (m, 2H).

4.94 Preparation of compound 121

[00884] **Compound 121** was prepared from **compound 121E** as previously depicted; LCMS [M+H]: 1512.6.

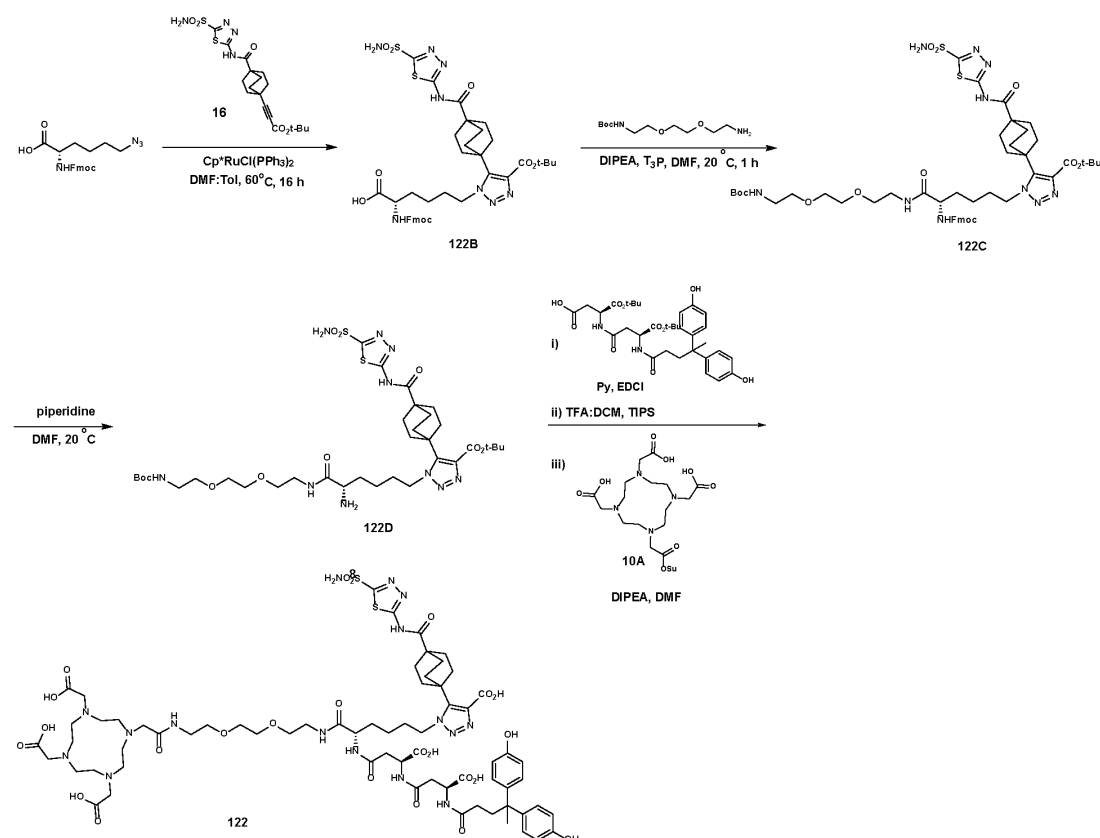
[00885] Compounds in **table 9.17** were prepared by procedures depicted in Scheme **D21**.

Table 9.17.

Compound	m/z
121.1	[M+H]:1511.7

D22. Synthesis of Compound 122

Scheme D22.



4.95 Preparation of compound 122B

[00886] To a mixture of **compound 16** (400 mg, 908 μmol , 1 *eq*) and $N^2-(((9H\text{-fluoren-9-yl})\text{methoxy})\text{carbonyl})\text{-}N^6\text{-diazo-L-lysine}$ (358 mg, 908 μmol , 1 *eq*) in DMF (12 mL) and toluene (3 mL) was added $\text{Cp}^*\text{RuCl}(\text{PPh}_3)_2$ (217 mg, 272 μmol , 0.3 *eq*) at 20°C under a nitrogen atmosphere. The mixture was stirred at 60°C for 16h and concentrated under reduced pressure. The residue was purified by *prep*-HPLC (column: Waters Xbridge BEH C18 100*30mm*10 μm ; mobile phase: $[\text{H}_2\text{O}(10\text{mM } \text{NH}_4\text{HCO}_3)\text{-ACN}]$; gradient: 25%-55% B over 8.0 min) to give **compound 122B** (360 mg, 24% yield) as a light yellow solid; LCMS $[\text{M}+\text{H}]$: 835.3; ^1H NMR (400 MHz, DMSO-d_6) δ 7.88 (br d, $J = 7.2$ Hz, 2H), 7.72 (br d, $J = 7.2$ Hz, 2H), 7.40 (br t, $J = 7.0$ Hz, 2H), 7.32 (br t, $J = 7.2$ Hz, 2H), 4.47 (br t, $J = 7.0$ Hz, 2H), 4.36 - 4.15 (m, 3H), 3.93 (br d, $J = 3.6$ Hz, 1H), 2.11 - 1.71 (m, 16H), 1.63 - 1.51 (m, 9H), 1.49 - 1.33 (m, 3H).

4.96 Preparation of compound 122C

[00887] T_3P (278 μL , 467 μmol , 50% purity, 1.5 *eq*) were added slowly to a solution of **compound 122B** (260 mg, 311 μmol , 1 *eq*), *tert*-butyl (2-(2-(2-aminoethoxy)ethoxy)ethyl)carbamate (77 mg, 311 μmol , 1 *eq*), DIEA (108 μL , 623 μmol , 2 *eq*) and DMF (6 mL). The reaction mixture was stirred at 20°C for 1 h, quenched by addition of H_2O (10 mL) at 25°C and the reaction mixture concentrated under reduced pressure. The residue was diluted with H_2O (20 mL) and extracted with EtOAc (80 mL). The combined organic layers were washed with H_2O (30 mL), brine (30 mL), dried (Na_2SO_4), filtered and

concentrated under reduced pressure. The crude product was purified by column chromatography (SiO₂, DCM:MeOH) to give crude **compound 122C** (400 mg) as a light yellow solid; LCMS [M+H]: 1065.6; ¹H NMR (400 MHz, METHANOL-d₄) δ 7.82 - 7.71 (m, 2H), 7.71 - 7.55 (m, 2H), 7.42 - 7.24 (m, 4H), 4.65 - 4.47 (m, 2H), 4.47 - 4.32 (m, 2H), 4.23 (br d, *J* = 6.8 Hz, 1H), 4.15 - 4.06 (m, 1H), 3.65 - 3.43 (m, 9H), 3.38 (br t, *J* = 5.2 Hz, 2H), 3.20 (br t, *J* = 5.6 Hz, 3H), 2.25 - 2.08 (m, 7H), 2.06 - 1.81 (m, 11H), 1.59 (s, 9H), 1.41 (s, 9H).

4.97 Preparation of compound 122D

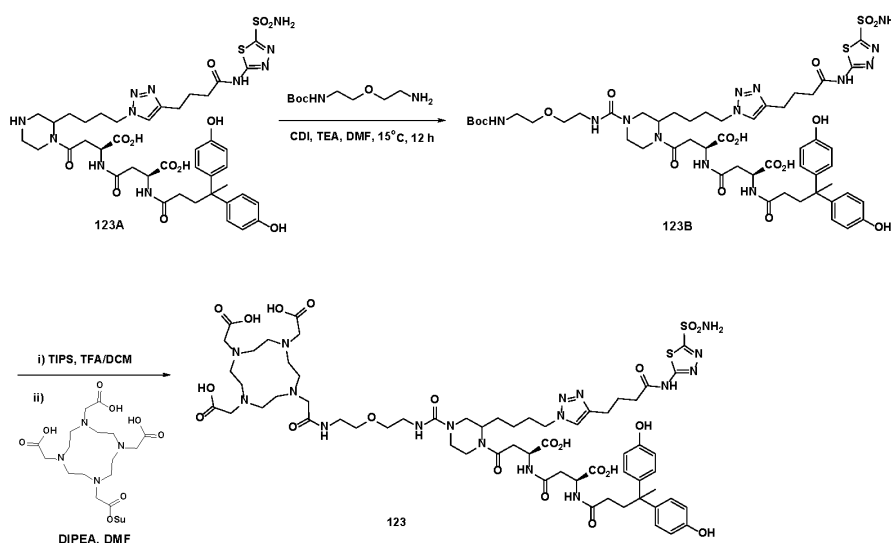
[00888] To a mixture of **compound 122C** (400 mg, 375 μmol, 1 *eq*) in DMF (5 mL) was added piperidine (185 μL, 1.88 mmol, 5 *eq*) in one portion at 20°C under a nitrogen atmosphere. The mixture was stirred at 20°C for 1h and concentrated under reduced pressure. The residue was washed with MTBE (3 × 10 mL) to give crude **compound 122D** (360 mg) as a light yellow solid; LCMS [M+H]: 843.4; ¹H NMR (400 MHz, METHANOL-d₄) δ 4.59 (br t, *J* = 7.4 Hz, 1H), 3.70 - 3.46 (m, 7H), 3.44 - 3.35 (m, 3H), 3.26 - 3.18 (m, 4H), 3.16 - 3.06 (m, 1H), 2.25 - 2.11 (m, 5H), 2.07 - 1.93 (m, 6H), 1.83 - 1.64 (m, 4H), 1.42 (s, 9H), 1.25 - 1.14 (m, 9H).

4.98 Preparation of Compound 122

[00889] **Compound 122** was prepared from **compound 122D** as previously depicted; LCMS [M+H]: 1571.7.

D23. Synthesis of Compound 123

Scheme D23.



4.99 Synthesis of compound 123B

[00890] To a solution of *tert*-butyl (2-(2-aminoethoxy)ethyl)carbamate (60 mg, 294 μmol, 1 *eq*) and TEA (41 μL, 294 μmol, 1 *eq*) in DMF (1 mL) was added CDI (48 mg, 294 μmol, 1 *eq*) at 15°C, and the mixture stirred at 15°C for 1 h. A solution of **compound 123A** (314 mg, 294 μmol, 1 *eq*, TFA) and TEA (41 μL, 294 μmol, 1 *eq*) in DMF (1 mL) was added and the mixture stirred at 15°C for 11 h. The reaction mixture was concentrated under reduced pressure and the residue purified by *prep*-TLC (SiO₂,

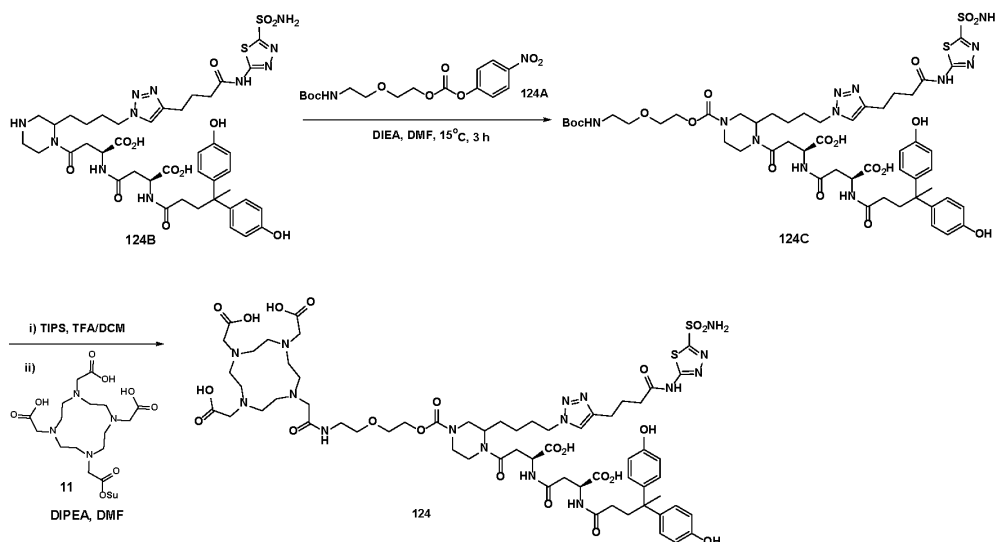
EtOAc:MeOH) to give **compound 123B** (260 mg, 75% yield) as white solid; LCMS [M+H]: 1186.8; ¹H NMR (400 MHz, DMSO-d₆) δ 8.28 - 8.11 (m, 1H), 7.93 - 7.85 (m, 1H), 7.63 (s, 2H), 7.01 (s, 3H), 6.92 (d, *J* = 8.5 Hz, 4H), 6.76 (t, *J* = 5.3 Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 4H), 6.55 (br s, 1H), 4.50 - 4.33 (m, 2H), 4.31 - 4.10 (m, 4H), 3.94 - 3.75 (m, 3H), 3.71 - 3.57 (m, 1H), 3.17 (s, 6H), 3.05 (q, *J* = 5.4 Hz, 3H), 2.89 (s, 1H), 2.73 (s, 2H), 2.70 - 2.59 (m, 4H), 2.40 (br s, 2H), 2.22 - 2.13 (m, 2H), 1.97 - 1.82 (m, 4H), 1.82 - 1.66 (m, 2H), 1.47 - 1.41 (m, 3H), 1.36 (s, 9H), 1.34 - 1.21 (m, 2H).

4.100 Synthesis of Compound 123

[00891] **Compound 123** was prepared from **compound 123B** as previously depicted; LCMS [M+H]: 1472.3; ¹H NMR (400 MHz, DMSO-d₆) δ 12.99 (br s, 2H), 9.16 (br s, 1H), 8.54 (br s, 1H), 8.32 (s, 2H), 8.16 - 8.01 (m, 1H), 7.96 - 7.87 (m, 1H), 7.87 - 7.81 (m, 1H), 6.92 (d, *J* = 8.5 Hz, 4H), 6.64 (d, *J* = 8.5 Hz, 4H), 4.57 (d, *J* = 5.0 Hz, 1H), 4.51 - 4.43 (m, 1H), 4.42 - 4.32 (m, 1H), 4.29 - 4.19 (m, 3H), 4.18 - 4.03 (m, 4H), 3.95 - 3.77 (m, 6H), 3.71 - 3.48 (m, 5H), 3.48 - 3.32 (m, 10H), 3.29 - 3.16 (m, 6H), 3.11 (br s, 6H), 2.86 - 2.53 (m, 10H), 2.21 - 2.12 (m, 2H), 2.00 - 1.88 (m, 2H), 1.88 - 1.81 (m, 2H), 1.81 - 1.70 (m, 2H), 1.56 - 1.34 (m, 5H), 1.29 - 1.06 (m, 2H).

D24. Synthesis of Compound 124

Scheme D24.



4.101 Synthesis of compound 124A

[00892] To a solution of *tert*-butyl (2-(2-hydroxyethoxy)ethyl)carbamate (200 mg, 974 μmol, 1 *eq*) and TEA (271 μL, 1.95 mmol, 2 *eq*) in THF (5 mL) was added 4-nitrophenyl carbonochloridate (216 mg, 1.07 mmol, 1.1 *eq*) at 15°C, and the mixture stirred at 15 °C for 12 h. The reaction mixture was concentrated under reduced pressure, the residue diluted with H₂O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by *prep*-TLC (SiO₂, EtOAc:petroleum ether) to give **compound 124A** (190 mg, 53% yield) as a colorless oil; ¹H NMR (400 MHz, CHLOROFORM-d) δ 8.32 - 8.27 (m,

2H), 7.44 - 7.37 (m, 2H), 4.93 (br s, 1H), 4.48 - 4.42 (m, 2H), 3.82 - 3.74 (m, 2H), 3.60 (t, $J = 5.1$ Hz, 2H), 3.36 (q, $J = 5.1$ Hz, 2H), 1.46 (s, 9H).

4.102 Synthesis of compound 124C

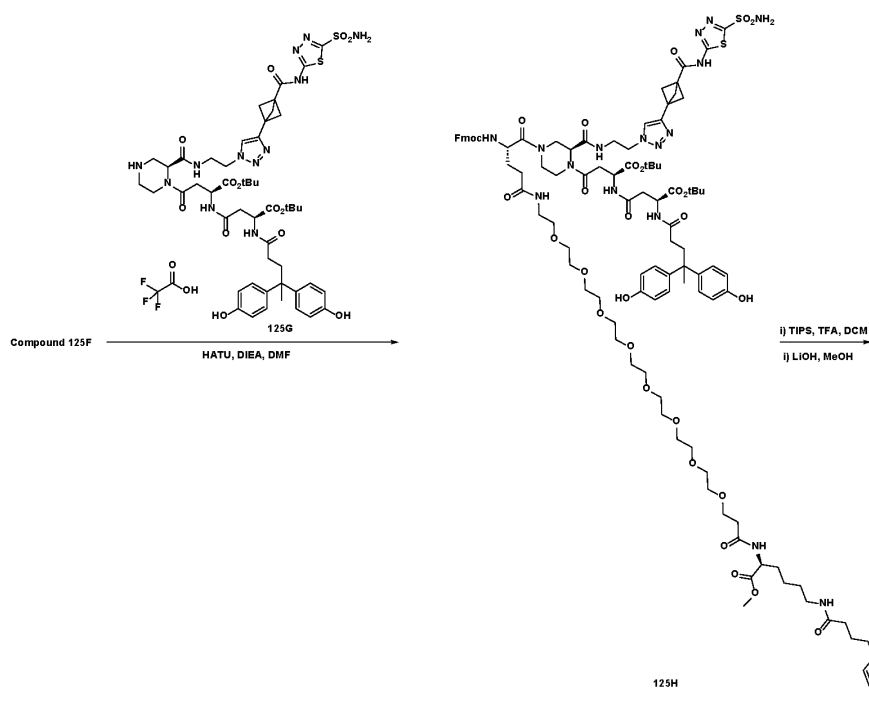
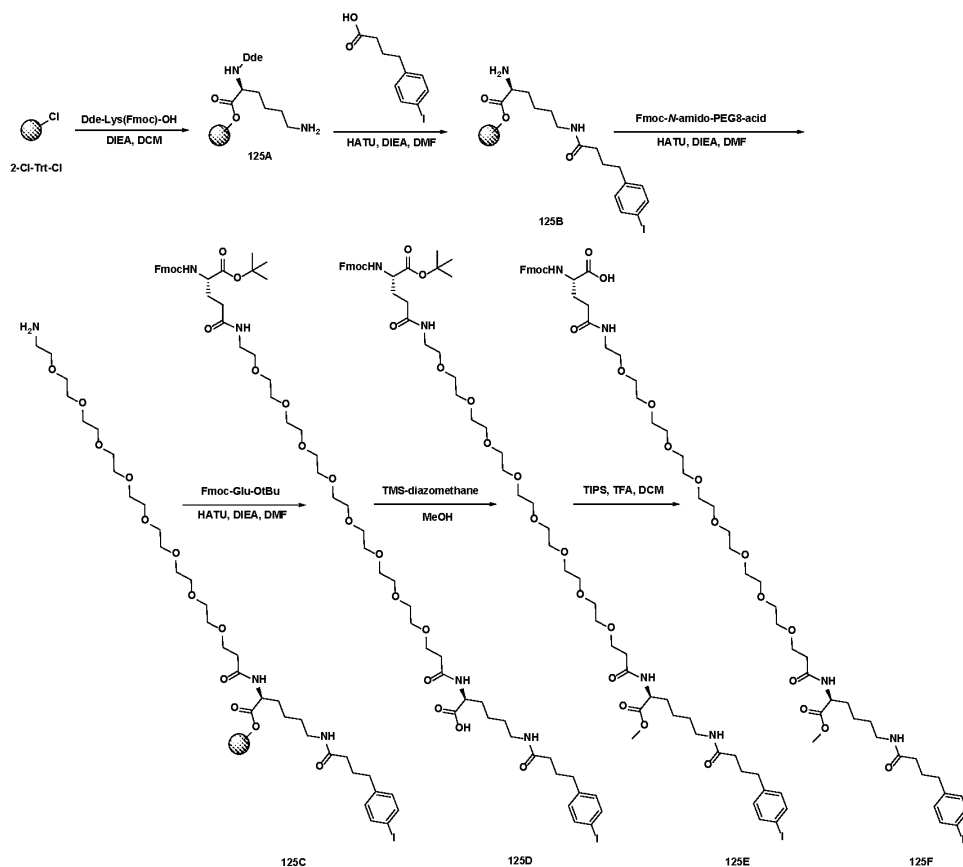
[00893] To a solution of **compound 124B** (350 mg, 327 μmol , TFA) and DIEA (132 μL , 756 μmol , 2 *eq*) in DMF (3 mL) was added **compound 124A** (140 mg, 378 μmol , 1 *eq*) at 15°C, and the mixture stirred at 15°C for 3h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by *prep*-TLC (SiO_2 , EtOAc:MeOH) to give **compound 124C** (330 mg, 74% yield) as a colorless solid; LCMS [$\text{M}+\text{H}$]: 1187.4; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.29 - 8.01 (m, 2H), 7.96 - 7.83 (m, 1H), 7.70 - 7.56 (m, 1H), 6.92 (br d, $J = 8.3$ Hz, 4H), 6.63 (br d, $J = 8.3$ Hz, 4H), 4.49 - 4.34 (m, 2H), 4.32 - 4.17 (m, 4H), 4.15 - 4.06 (m, 2H), 3.96 - 3.64 (m, 4H), 3.59 - 3.53 (m, 2H), 3.42 - 3.36 (m, 2H), 3.18 - 3.13 (m, 7H), 3.10 - 3.01 (m, 4H), 2.70 - 2.59 (m, 4H), 2.43 - 2.37 (m, 2H), 2.20 - 2.12 (m, 2H), 1.95 - 1.83 (m, 4H), 1.47 - 1.40 (m, 3H), 1.35 (s, 9H), 1.32 - 1.21 (m, 2H).

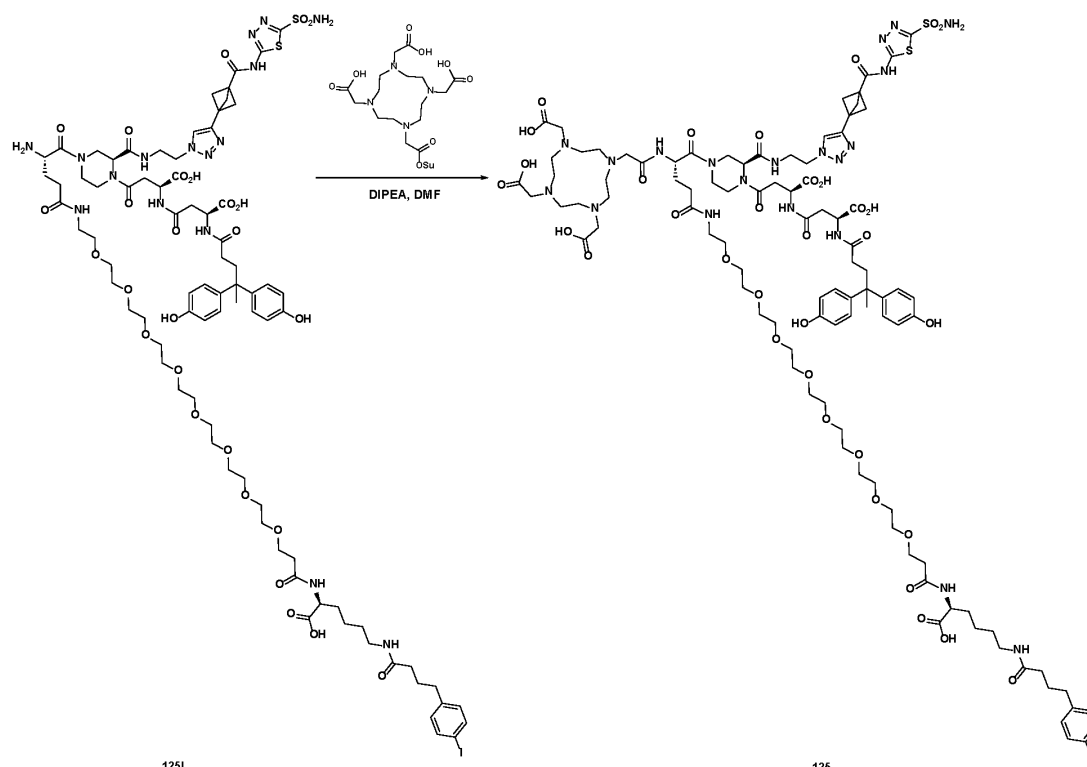
4.103 Synthesis of Compound 124

[00894] **Compound 124** was prepared from **compound 124C** from procedures previously depicted; LCMS [$\text{M}+\text{H}$]: 1473.4; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.13 - 12.91 (m, 1H), 9.15 (d, $J = 6.4$ Hz, 2H), 8.50 (d, $J = 1.9$ Hz, 1H), 8.32 (s, 2H), 8.19 - 8.02 (m, 1H), 7.92 (t, $J = 6.5$ Hz, 1H), 7.87 - 7.81 (m, 1H), 6.92 (d, $J = 8.3$ Hz, 4H), 6.64 (d, $J = 8.5$ Hz, 4H), 4.57 (dd, $J = 2.3, 3.4$ Hz, 1H), 4.51 - 4.39 (m, 2H), 4.30 - 4.21 (m, 2H), 4.16 - 4.09 (m, 2H), 3.59 (br s, 8H), 3.54 (d, $J = 6.4$ Hz, 2H), 3.50 - 3.43 (m, 4H), 3.27 (d, $J = 5.5$ Hz, 8H), 3.15 - 2.99 (m, 10H), 2.72 - 2.56 (m, 10H), 2.36 - 2.31 (m, 2H), 2.21 - 2.12 (m, 2H), 1.94 (quin, $J = 7.3$ Hz, 2H), 1.89 - 1.74 (m, 4H), 1.45 (s, 5H), 1.21 - 1.10 (m, 2H).

D25. Synthesis of Compound 125

Scheme D25.





4.104 Preparation of compound 125A

[00895] 2-Cl-Trt-Cl resin (6.8 g, 1.0 mmol/g, 6.8 mmol, 1.7 *eq*) was added to a mixture of Dde-Lys(Fmoc)-OH (2.1 g, 4 mmol, 1 *eq*), DIEA (2.8 mL, 16 mmol, 4 *eq*), and DCM (3 mL) and agitated for 2 h. MeOH (3 mL) was added, the reaction mixture agitated for 30 min, filtered and the filter cake washed with 17:2:1 DCM:MeOH:DIEA (3 x 50 mL), DCM (3 x 80 mL), and DMF (2 x 80 mL). The reaction mixture was agitated with 20% piperidine in DMF (70 mL). The mixture was filtered, and the process repeated 5 times. The filter cake was washed with DCM (3 x 70 mL) and DMF (2 x 70 mL) to give **compound 125A**.

4.105 Preparation of compound 125B

[00896] A solution of 4-(4-iodophenyl)butanoic acid (3.5 g, 12 mmol, 3 *eq*), HATU (3.0 g, 8 mmol, 2 *eq*), DIEA (6.3 mL, 36 mmol, 9 *eq*), and DMF (70 mL) was added to **compound 125A** (4 mmol). The mixture was agitated for 62h and the reaction solution removed via filtration. The filter cake was washed with DMF (70 mL), DCM (3 x 70 mL), and DMF (2 x 70 mL). The reaction mixture was agitated with 2% hydrazine in DMF (75 mL). The mixture was filtered, and the process repeated 3 times. The filter cake was washed with DMF (70 mL), DCM (2 x 70 mL) and DMF (2 x 70 mL) to give **compound 125B**.

4.106 Preparation of compound 125C

[00897] A solution of Fmoc-*N*-amido-PEG8-acid (5.0 g, 7.5 mmol, 1.9 *eq*), HATU (2.9 g, 7.6 mmol, 1.9 *eq*), DIEA (6.3 mL, 36 mmol, 9 *eq*) and DMF (70 mL) was added to **compound 125B** (4 mmol). The mixture was agitated for 2h and the reaction solution removed via filtration. The filter cake was washed with DMF (70 mL), DCM (3 x 70 mL), and DMF (2 x 70 mL). The reaction was agitated with

20% piperidine in DMF (70 mL). The mixture was filtered, and this process was repeated 5 times. The filter cake was washed with DCM (2 x 70 mL) and DMF (2 x 70 mL) to give **compound 125C**.

4.107 Preparation of compound 125D

[00898] A solution of Fmoc-Glu-OrBu (5.1 g, 12 mmol, 3 *eq*), HATU (3.0 g, 8 mmol, 2 *eq*), DIEA (6.3 mL, 36 mmol, 9 *eq*), and DMF (70 mL) was added to **compound 125C** (4 mmol). The mixture was agitated for 2h and the reaction solution removed via filtration. The filter cake was washed with DMF (70 mL) and DCM (3 x 70 mL). The resin was cleaved via 5 min agitation with 20% HFP in DCM (70 mL). The mixture was filtered and this process was repeated 4 times. The filter cake was washed with DCM (70 mL). The filtrate were combined, concentrated under reduced pressure and purified by flash chromatography (EtOAc:DCM then MeOH:DCM) to give **compound 125D** (2.6 g, 52%) as a yellow solid; LCMS [M+H]: 1249.4; ¹H NMR (400 MHz, DMSO) δ 12.54 (s, 1H), 8.09 (d, *J* = 7.7 Hz, 1H), 7.90 (d, *J* = 7.4 Hz, 3H), 7.73 (h, *J* = 6.7 Hz, 4H), 7.65 – 7.58 (m, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.01 (d, *J* = 7.8 Hz, 2H), 4.27 (dt, *J* = 21.6, 6.6 Hz, 3H), 4.19 – 4.09 (m, 2H), 3.89 (t, *J* = 7.3 Hz, 1H), 3.58 (t, *J* = 6.7 Hz, 2H), 3.47 (s, 26H), 3.40 (t, *J* = 6.2 Hz, 2H), 3.23 – 3.13 (m, 5H), 3.00 (q, *J* = 6.7 Hz, 2H), 2.48 (s, 1H), 2.36 (p, *J* = 7.6 Hz, 2H), 2.17 (t, *J* = 7.7 Hz, 2H), 2.04 (t, *J* = 7.4 Hz, 2H), 1.93 (d, *J* = 8.3 Hz, 1H), 1.76 (q, *J* = 7.6 Hz, 3H), 1.68 (d, *J* = 8.0 Hz, 1H), 1.60 – 1.49 (m, 1H), 1.39 (s, 10H), 1.28 (d, *J* = 7.8 Hz, 2H).

4.108 Preparation of compound 125E

[00899] TMS-diazomethane (10.5 mL, 10% in hexane) was added to a solution of **compound 125D** (2.6 g, 2.1 mmol, 1 *eq*) in MeOH (10 mL) and stirred at room temperature for 5 min. TMS-diazomethane (8.0 mL, 10% in Hexane) was then added, the mixture stirred at room temperature for 5 min and concentrated under reduced pressure. The residue was purified by silica gel chromatography (MeOH:DCM) to give **compound 125E** (2.2 g, 85%) as a yellow solid; LCMS [(M-*t*Bu)+H]: 1207.3; ¹H NMR (400 MHz, DMSO) δ 8.23 (d, *J* = 7.5 Hz, 1H), 7.90 (d, *J* = 7.4 Hz, 3H), 7.72 (dq, *J* = 13.9, 8.0 Hz, 4H), 7.65 – 7.60 (m, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.01 (d, *J* = 7.7 Hz, 2H), 4.35 – 4.09 (m, 5H), 3.88 (d, *J* = 6.5 Hz, 1H), 3.62 – 3.55 (m, 5H), 3.47 (s, 27H), 3.40 (t, *J* = 6.2 Hz, 2H), 3.23 – 3.16 (m, 3H), 3.00 (q, *J* = 6.5 Hz, 2H), 2.48 (s, 1H), 2.37 (q, *J* = 7.0 Hz, 2H), 2.17 (t, *J* = 7.7 Hz, 2H), 2.04 (t, *J* = 7.4 Hz, 2H), 1.93 (d, *J* = 8.1 Hz, 1H), 1.76 (q, *J* = 7.6 Hz, 3H), 1.65 (t, *J* = 7.1 Hz, 1H), 1.61 – 1.52 (m, 1H), 1.39 (d, *J* = 1.8 Hz, 11H), 1.27 (s, 2H).

4.109 Preparation of compound 125F

[00900] **Compound 125E** (2.2 g, 1.8 mmol, 1 *eq*) was dissolved in a solution of trifluoroacetic acid (2 mL), tris(propan-2-yl)silane (2 mL), and DCM (6 mL). The mixture was stirred at room temperature overnight, concentrated, and then purified by *prep*-HPLC (40-65% CH₃CN in water with 0.1% FA). The material was stirred with MP-Carbonate in THF and MeOH overnight. The mixture was filtered and the filtrate concentrate to give **Compound 125F** (1.2 g, 56%) as a white powder; LCMS [M+H]: 1207.4; ¹H NMR (400 MHz, DMSO) δ 12.64 (s, 1H), 8.23 (d, *J* = 7.3 Hz, 1H), 7.90 (d, *J* = 7.4 Hz, 3H), 7.79 – 7.70 (m, 3H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.63 (dd, *J* = 8.3, 2.3 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.05 – 6.96 (m, 2H), 4.30 – 4.17 (m, 4H), 3.99 – 3.88 (m, 1H), 3.64 – 3.54 (m, 5H), 3.54 – 3.43

(m, 27H), 3.41 – 3.37 (m, 3H), 3.19 (d, $J = 6.0$ Hz, 2H), 3.00 (d, $J = 6.6$ Hz, 2H), 2.48 (s, 2H), 2.36 (p, $J = 7.5$ Hz, 2H), 2.18 (t, $J = 7.7$ Hz, 2H), 2.03 (t, $J = 7.4$ Hz, 2H), 1.97 (s, 1H), 1.76 (q, $J = 7.3$ Hz, 3H), 1.69 – 1.51 (m, 2H), 1.35 (d, $J = 7.4$ Hz, 2H), 1.27 (s, 2H).

4.110 Preparation of compound 125H

[00901] **Compound 125G** (56 mg, 42.6 μ mol, 1 *eq*) was added to a solution of **Compound 125F** (59.6 μ L, 1.4 *eq*), HATU (21 mg, 55.4 μ mol, 1.3 *eq*), DIEA (23 μ L, 132 μ mol, 3.1 *eq*), and DMF (1 mL). The mixture was stirred at room temperature for 1h and purified by *prep*-HPLC (40-70% CH₃CN in water with 0.1% TFA) to give **compound 125H** (88 mg, 90%) as a white foam; LCMS [M/2+H]: 1148.8.

4.111 Preparation of compound 125I

[00902] **Compound 125H** (88 mg, 38.3 μ mol, 1 *eq*) was dissolved in a solution of trifluoroacetic acid (0.4 mL), tris(propan-2-yl)silane (0.4 mL), and DCM (1.2 mL). The mixture was stirred at room temperature overnight and concentrated under reduced pressure. The crude material was diluted with THF (1.5 mL), MeOH (0.75 mL), and a 2.0 M LiOH solution (0.2 mL), the mixture heated at 50 °C for 1 h, concentrated under reduced pressure, and purified by *prep*-HPLC (30-50% CH₃CN in water with 0.1% TFA) to give **compound 125I** (48 mg, 64%) as a white powder; LCMS [M/2+H]: 974.7.

4.112 Preparation of Compound 125

[00903] **Compound 125** was prepared from **compound 125** from procedures previously depicted; LCMS [M/2+H]: 1167.7.

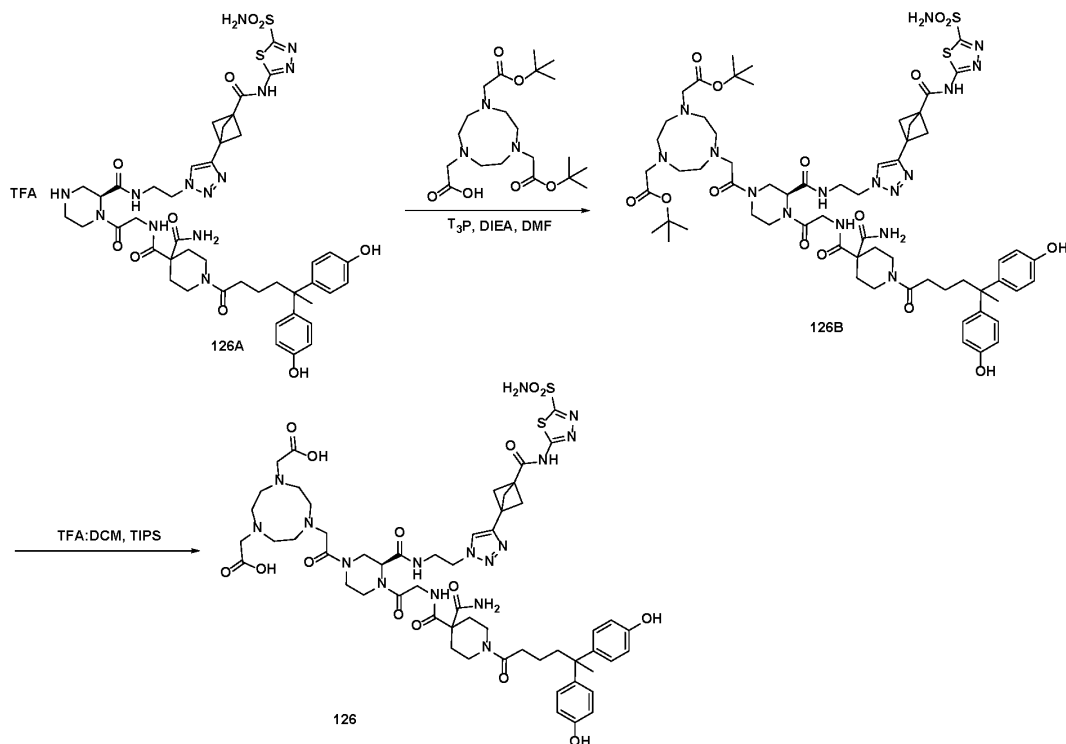
[00904] Compounds in **table 9.18** were prepared by procedures depicted in Scheme D24.

Table 9.18.

Compound	m/z
125.1	[M/2+H]: 1121.8

D26. Synthesis of Compound 126

Scheme D26.



4.113 Preparation of compound 126B

[00905] Propylphosphonic anhydride (50% in DMF, 270 μL , 906 μmol , 2 *eq*) was added to a solution of **compound 126A** (500 mg, 453 μmol , 1.0 *eq*), 2-(4,7-bis(2-(*tert*-butoxy)-2-oxoethyl)-1,4,7-triazonan-1-yl)acetic acid (245 mg, 589 μmol , 1.3 *eq*), DIEA (316 μL , 1.81 mmol, 4 *eq*), and DMF (2.5 mL) at 0 °C. The reaction was stirred at room temperature for 15 min and purified directly by *prep*-HPLC (30–50% CH_3CN in water with 0.1% TFA) to give **compound 126B** (472 mg, 75%) as a white foam; LCMS $[\text{M}/2+\text{H}]$: 694.5; ^1H NMR (400 MHz, DMSO) δ 13.23 (s, 1H), 9.91 (s, 1H), 8.37 (s, 3H), 8.06 (d, $J = 2.6$ Hz, 1H), 8.00 – 7.79 (m, 2H), 7.48 – 7.26 (m, 2H), 6.93 (d, $J = 8.6$ Hz, 4H), 6.63 (d, $J = 8.4$ Hz, 4H), 4.96–4.71 (m, 1H), 4.50 – 3.69 (m, 9H), 3.69 – 3.36 (m, 9H), 3.25 (d, $J = 12.2$ Hz, 10H), 2.97 – 2.64 (m, 7H), 2.44 (d, $J = 4.6$ Hz, 6H), 2.24 (d, $J = 7.5$ Hz, 2H), 2.05 – 1.76 (m, 6H), 1.54 – 1.30 (m, 20H), 1.27 – 1.18 (m, 2H).

4.114 Preparation of Compound 126

[00906] **Compound 126B** (468 mg) was dissolved in trifluoroacetic acid (0.9 mL), tris(propan-2-yl)silane (0.9 mL), and DCM (2.7 mL) was added and was stirred at 40 °C for 4 h. The mixture was concentrated, basified with an NH_4OH solution, and purified by *prep*-HPLC (10–45% CH_3CN in water with 0.5% AcOH) to give **Compound 126** (231 mg, 54%); LCMS $[\text{M}/2+\text{H}]$: 638.4; ^1H NMR (400 MHz, DMSO) δ 11.95 (s, 1H), 9.22 (s, 2H), 8.42 – 8.09 (m, 3H), 8.03 – 7.83 (m, 2H), 7.46 (s, 1H), 7.29 (m, 1H), 6.92 (d, $J = 8.6$ Hz, 4H), 6.63 (d, $J = 8.4$ Hz, 4H), 4.62 (m, 1H), 4.47 – 4.12 (m, 4H), 3.97 (m, 1H), 3.68 (m, 4H), 3.52 (s, 6H), 3.19 (s, 3H), 3.05 (s, 4H), 2.91 (m, 9H), 2.42 (m, 8H), 2.24 (s, 3H), 1.94 (s, 3H), 1.78 (m, 2H), 1.47 (s, 3H), 1.23 (m, 2H).

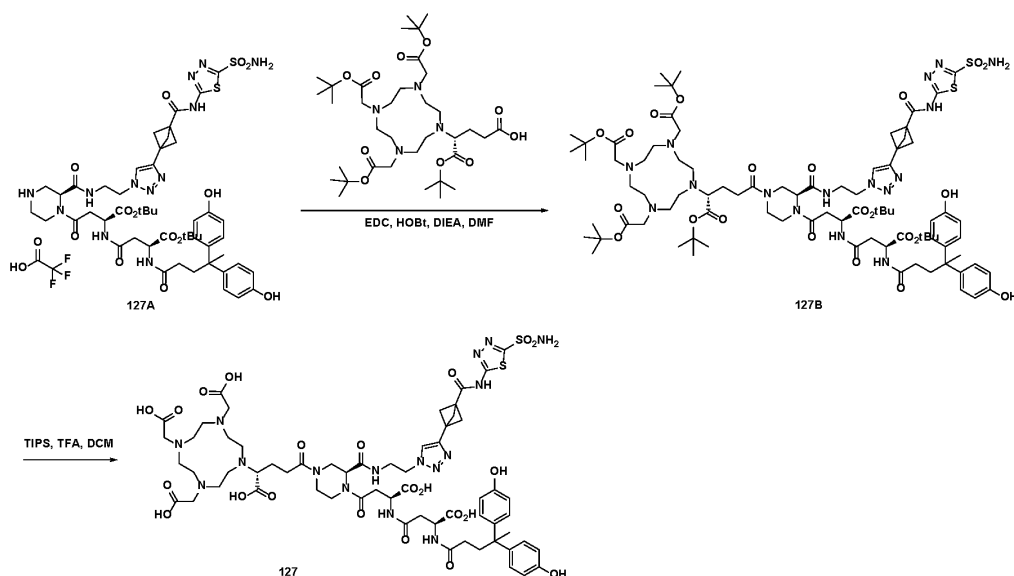
[00907] Compounds in **table 9.19** were prepared by procedures depicted in Scheme **D25**.

Table 9.19.

Compound	m/z
126.1	[M/2+H]: 638.3
126.2	[M/2+H]: 579.2
126.3	[M/2+H]: 646.8
126.4	[M/2+H]: 640.8
126.5	[M/2+H]: 574.8

D27. Synthesis of Compound 127

Scheme D27.

**4.115 Preparation of compound 127B**

[00908] **Compound 127A** (75 mg, 61.4 μmol , 1 *eq*) was added to a solution of (*R*)-5-(*tert*-butoxy)-5-oxo-4-(4,7,10-tris(2-(*tert*-butoxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)pentanoic acid (60 mg, 85.6 μmol , 1.4 *eq*), EDCI (30 mg, 156 μmol , 2.6 *eq*), HOBt (15 mg, 111 μmol , 1.8 *eq*), DIEA (70 μL , 402 μmol , 6.5 *eq*), and DMF (1.0 mL) at 0 °C. The mixture was warmed to room temperature over 2h and purified by *prep*-HPLC (20-75% CH_3CN in water with 0.1% TFA) to give **compound 127B** (58 mg, 53%) as a white foam; LCMS [M/2+H]: 895.9.

4.116 Preparation of Compound 127

[00909] **Compound 127B** (58 mg, 32 μmol , 1 *eq*) was dissolved in a solution of trifluoroacetic acid (0.4 mL), tris(propan-2-yl)silane (0.4 mL), and DCM (1.2 mL). The mixture was stirred at room temperature overnight, concentrated under reduced pressure and purified by *prep*-HPLC (10-30% CH_3CN in water with 0.1% TFA) to **Compound 127** (7.0 mg, 14%); LCMS [M/2+H]: 727.4.

[00910] Compounds in **table 9.20** were prepared by procedures depicted in Scheme D26.

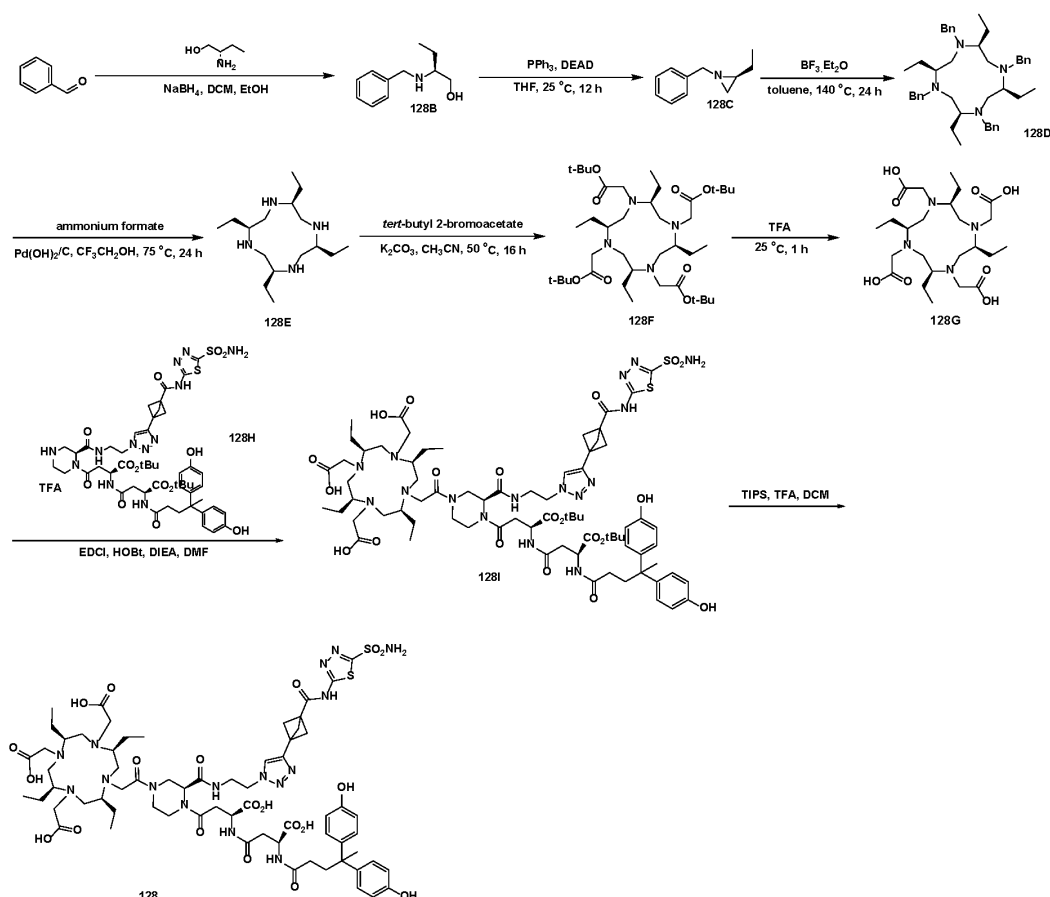
Table 9.20.

Compound	m/z
127.1	[M/2+H]: 724.8

Compound	m/z
127.2	[M/2+H]: 724.8
127.3	[M/2+H]: 674.3
127.4	[M/2+H]: 732.0
127.5	[M/2+H]: 730.1
127.6	[M/2+H]: 751.2
127.7	[M/2+H]: 744.1
127.8	[M/2+H]: 743.0
127.9	[M/2+H]: 717.0

D28. Synthesis of Compound 128

Scheme D28.



4.117 Preparation of compound 128B

[00911] To a solution of (2*S*)-2-aminobutan-1-ol (89.4 mL, 942 mmol, 1 *eq*) in DCM (1000 mL) was added benzaldehyde (95 mL, 942 mmol, 1 *eq*) at 0°C, and the mixture stirred at 25°C for 2 h. Na₂SO₄ was added to the mixture, the reaction filtered and the filtrate concentrated under reduced pressure. The residue was taken up in EtOH (1600 mL), NaBH₄ (40.8 g, 1.08 mol, 1.14 *eq*) added portion wise at 0°C and the mixture stirred at 25°C for 2 h. The reaction was added to a saturated aqueous solution of NH₄Cl (1000 mL) at 0°C, the residue stirred at 0°C for 1h and concentrated under reduced pressure. The mixture

was basified with 1N NaOH to pH = 9, the aqueous phase extracted with EtOAc (3 × 1000mL). The combined organic layers were washed with brine (2000 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The crude was suspended in EtOAc (500mL), stirred at 20 °C for 20 min, filtered, the cake washed with EtOAc (2 × 300 mL) and dried under reduced pressure to give **compound 128B** (125 g, 68% yield) as a white solid; ¹H NMR (400MHz, CDCl₃) δ 7.36 - 7.32 (m, 4H), 7.30 - 7.23 (m, 1H), 3.88 - 3.75 (m, 2H), 3.67 (dd, *J*=4.0, 10.6 Hz, 1H), 3.34 (dd, *J*=6.4, 10.8 Hz, 1H), 2.69 - 2.59 (m, 1H), 2.39 - 1.83 (m, 2H), 1.66 - 1.35 (m, 2H), 0.94 (t, *J*=7.6 Hz, 3H).

4.118 Preparation of compound 128C

[00912] To a solution of **compound 128B** (60 g, 335 mmol, 1 *eq*) in THF (600 mL) was added PPh₃ (123 g, 469 mmol, 1.4 *eq*) and DEAD (85.2 mL, 469 mmol, 1.4 *eq*) at 0°C, and the mixture stirred at 25°C for 12h under a nitrogen atmosphere. Water (1000 mL) was added, the residue adjusted to pH=3 with 1M HCl at 0°C, extracted with EtOAc (3 × 500 mL), the pH of the aqueous phase adjusted to pH=8 by adding ammonia water at 0°C, and extracted with DCM (3 × 500 mL). The combined organics were dried (Na₂SO₄), filtered and concentrated under reduced pressure to give **compound 128C** (53 g, 98% yield) as a white solid; ¹H NMR (400MHz, CDCl₃) δ 7.27 (s, 4H), 7.21 - 7.15 (m, 1H), 3.50 - 3.18 (m, 2H), 1.55 (d, *J* = 2.8 Hz, 1H), 1.40 - 1.28 (m, 4H), 0.81 (t, *J* = 7.4 Hz, 3H).

4.119 Preparation of compound 128D

[00913] To a solution of **compound 128C** (30 g, 186 mmol, 1 *eq*) in toluene (420 mL) was added BF₃·Et₂O (155 μL, 3.72 mmol, 0.02 *eq*), and the mixture stirred under reflux at 140 °C for 24 h. The reaction was cooled, saturated sodium bicarbonate (300mL) added, the reaction concentrated under reduced pressure and the residue purified by recrystallization in EtOAc (300 mL). The solid was washed with water (300 mL) to give crude **compound 128D** (8.1 g) as a colorless oil.

4.120 Preparation of compound 128E

[00914] To a solution of **compound 128D** (8.0 g, 12.4 mmol, 1 *eq*) in CF₃CH₂OH (240 mL) was added Pd(OH)₂/C (5.0 g, 20% purity) and ammonium formate (10.2 g, 161 mmol, 13 *eq*). The reaction was heated at 75°C for 24 h under a nitrogen atmosphere, filtered and the filtrate concentrated under reduced pressure to give crude **compound 128E** (4.3 g) as a colorless oil; ¹H NMR (400MHz, CDCl₃) δ 2.75 (dd, *J*=2.0, 13.0 Hz, 4H), 2.47 - 2.30 (m, 8H), 1.64 - 1.49 (m, 4H), 1.25 - 1.14 (m, 4H), 0.87 (t, *J*=7.6 Hz, 12H).

4.121 Preparation of compound 128F

To a solution of **compound 128E** (8.5 g, 29.9 mmol, 1 *eq*) in CH₃CN (85 mL) was added K₂CO₃ (28.9 g, 209 mmol, 7 *eq*) and *tert*-butyl 2-bromoacetate (26.5 mL, 179 mmol, 6 *eq*) at 0°C, and the mixture stirred at 50°C for 16 h under a nitrogen atmosphere. The mixture was cooled to room temperature and filtered, the filtrate concentrated, the residue dissolved in 2M HCl (600 mL) and extracted with EtOAc (300 mL). The pH of the aqueous phase was adjusted to pH=8 by adding ammonia water and the aqueous layer extracted with dichloromethane (2 × 300 mL) to give **compound 128F** (9.72 g, 44% yield) as a yellow solid; ¹H NMR (400MHz, CDCl₃) δ 3.28 - 3.17 (m, 4H), 3.04 - 2.74 (m, 10H), 2.71 - 2.55 (m, 3H), 2.18 - 2.07 (m, 5H), 1.43 - 1.39 (m, 36H), 1.35 - 1.25 (m, 3H), 0.96 - 0.84 (m, 16H).

4.122 Preparation of compound 128G

[00915] To a solution of **compound 128F** (14 g, 18.9 mmol) was added TFA (700 mL) at 25°C, the mixture stirred at 25°C for 1h under a nitrogen atmosphere and concentrated under reduced pressure. The residue was purified by *prep*-HPLC (column: Phenomenex C18 250*70mm 10u; mobile phase: [water(TFA)-ACN]; B%: 0%-30%, 20 min) to give **compound 128G TFA salt** (6.19 g, 34% yield, 4TFA); ¹H NMR (400MHz, D₂O) δ 4.11 (br d, *J* = 15.0 Hz, 3H), 3.84 (br d, *J* = 15.6 Hz, 4H), 3.70 - 3.31 (m, 5H), 3.18 (br d, *J* = 17.6 Hz, 5H), 2.91 (br d, *J* = 10.8 Hz, 2H), 2.86 - 2.72 (m, 1H), 1.95 (br dd, *J* = 7.4 Hz, 4H), 1.59 - 1.19 (m, 4H), 1.13 - 0.82 (m, 12H); and **compound 128G** (1.61g, 3.12 mmol, 17% yield) as a white solid; ¹H NMR (400MHz, D₂O) δ 4.04 (br s, 3H), 3.85 (br d, *J* = 18.2 Hz, 4H), 3.70 - 3.32 (m, 5H), 3.18 (br d, *J* = 17.6 Hz, 5H), 2.90 (br d, *J* = 10.0 Hz, 2H), 2.86 - 2.74 (m, 1H), 1.95 (br d, *J* = 5.6 Hz, 4H), 1.42 (br s, 4H), 1.11 - 0.85 (m, 12H).

4.123 Preparation of compound 128I

[00916] **Compound 128H** (75 mg, 61.4 μmol, 1 *eq*) was added to a solution of **compound 128G** (35 mg, 67.7 μmol, 1.1 *eq*), EDCI (30 mg, 156 μmol, 2.6 *eq*), HOBT (15 mg, 98 μmol, 1.6 *eq*), DIEA (70 μL, 402 μmol, 6.5 *eq*), and DMF (1 mL) at 0 °C. The mixture stirred at 0 °C to room temperature over 1h and then purified by *prep*-HPLC (30-50% CH₃CN in water with 0.1% TFA) to give **compound 128I** (13 mg, 13%) as a white solid; LCMS [M/2+H]⁺: 803.5.

4.124 Preparation of Compound 128

[00917] **Compound 128I** (13 mg, 8 μmol, 1 *eq*) was dissolved in a solution of trifluoroacetic acid (0.2 mL), tris(propan-2-yl)silane (0.2 mL) and DCM (0.6 mL). The mixture was stirred at room temperature overnight, concentrated under reduced pressure and purified by *prep*-HPLC (20-40% CH₃CN in water with 0.1% TFA) to give **Compound 128** (7 mg, 54%); LCMS [M/2+H]⁺: 747.4.

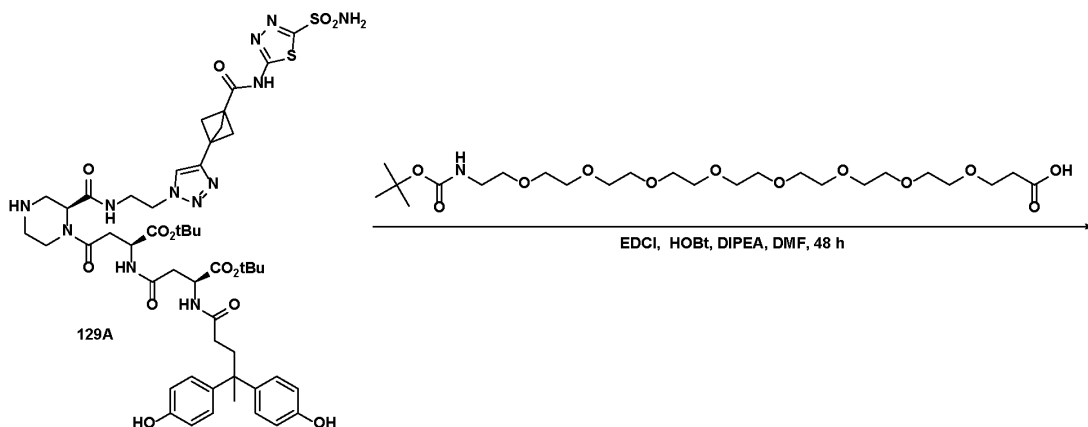
[00918] Compounds in **table 9.21** were prepared by procedures depicted in Scheme D27.

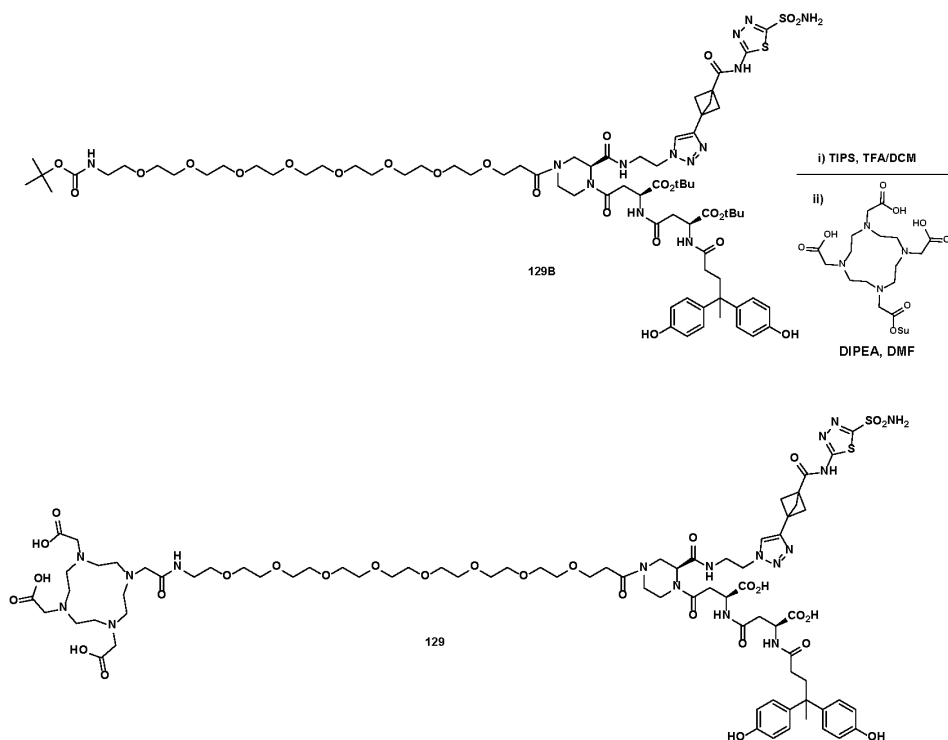
Table 9.21.

Compound	m/z
128.1	[M/2+H] ⁺ : 745.0

D29. Synthesis of Compound 129

Scheme D29.





4.125 Preparation of compound 129B

[00919] 3-([(Ethyylimino)methylidene]amino)-*N,N*-dimethylpropan-1-amine (32.6 mg, 170 μ mol, 2.3 *eq*) was added to 1-([(*tert*-butoxy)carbonyl]amino)-3,6,9,12,15,18,21,24-octaooxaheptacosan-27-oic acid (44 mg, 81.2 μ mol, 1.1 *eq*) in DMF (1.5mL, 19.4 mmol). 1H-1,2,3-Benzotriazol-1-ol (14 mg, 103 μ mol, 1.4 *eq*) and ethylbis(propan-2-yl)amine (0.39 mL, 222 μ mol, 3 *eq*) were added and the reaction stirred at room temperature for 15 min. Compound 129A (82 mg, 73.9 μ mol, 1 *eq*) was added, the reaction stirred at room temperature for 48h and directly purified by *prep*-HPLC (C18, Luna 30x150mm, 30-70% CH₃CN/H₂O+ 0.1% Formic acid) to give **compound 129B** as a white foam (26 mg, 22% yield); LCMS ([M-Boc]-[*t*Bu])/2+H): 738.0.

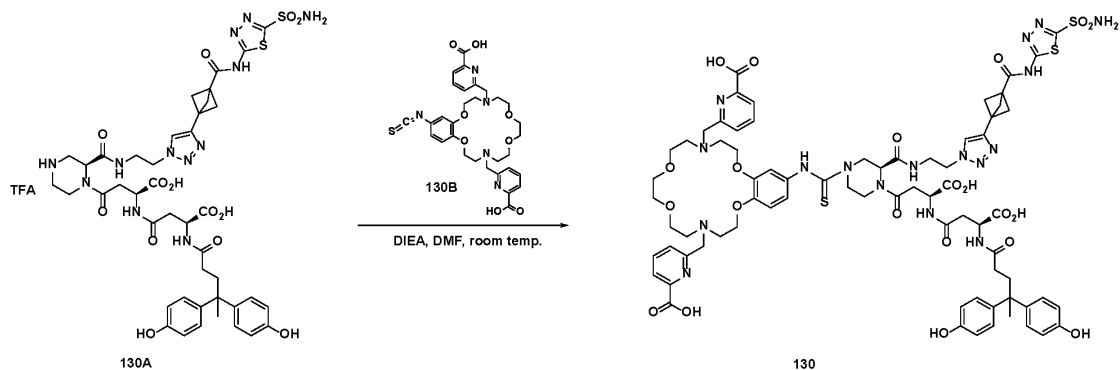
4.126 Preparation of compound 129

[00920] **Compound 129** was prepared from **compound 129B** as previously depicted; LCMS [M/2+H]: 902.8.

[00921] Compounds in **table 9.22** were prepared by procedures depicted in Scheme D28.

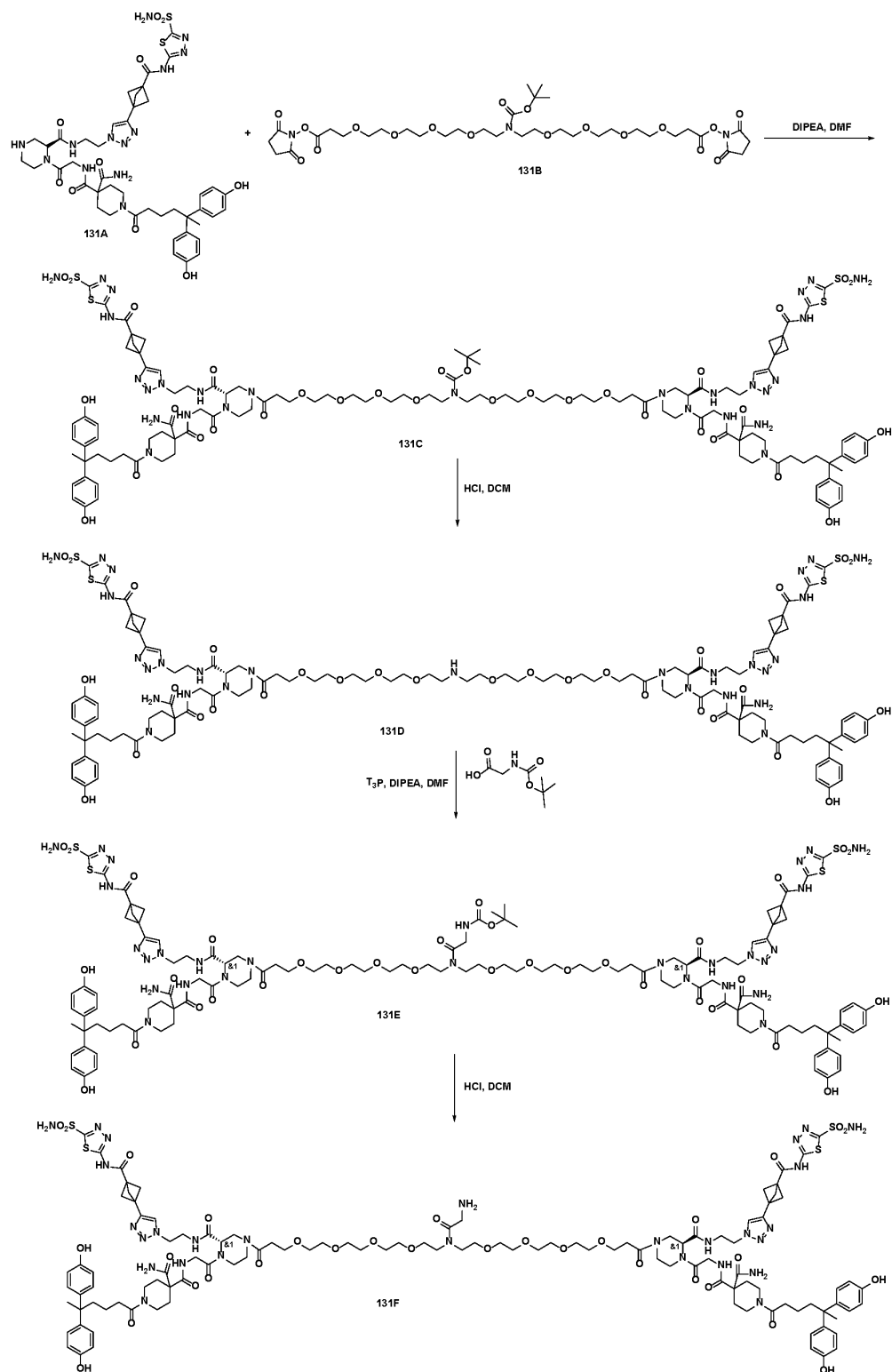
Table 9.22.

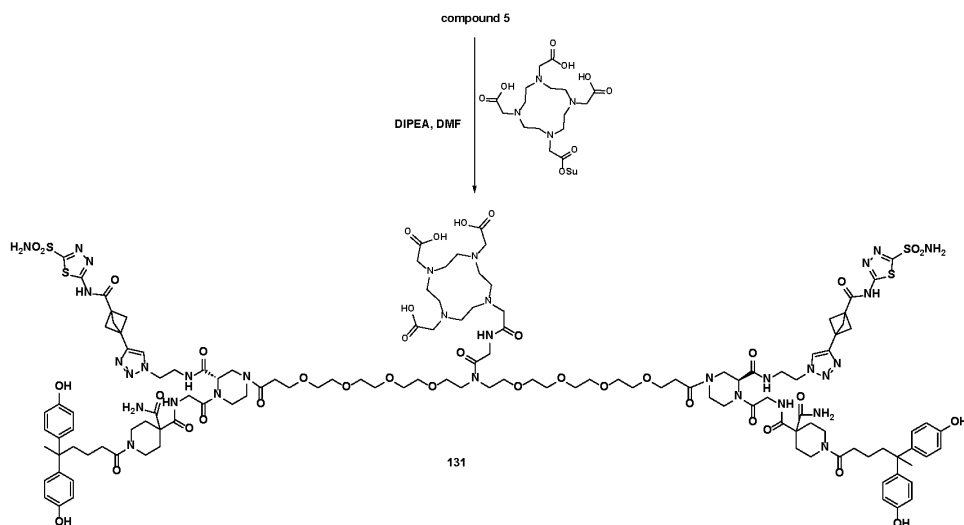
Compound	m/z
129.1	[M/2+H]: 900.5
129.2	[M/2+H]: 768.5
129.3	[M/2+H]: 751.5
129.4	[M/2+H]: 768.6
129.5	[M/2+H]: 907.7
129.6	[M/2+H]: 772.1
129.7	[M/2+H]: 765.1

D30. Synthesis of Compound 130**Scheme D30.**

[00922] **Compound 130A** (30 mg, 27 μmol) and **compound 130B** (35 mg, 54 μmol) were dissolved in DMF (450 μL) and DIEA (75 μL) and the reaction mixture stirred at room temperature overnight. The reaction was purified directly by *prep.* HPLC (10-40% ACN/ H_2O gradient, TFA modifier) to give **Compound 130** (17.5 mg, 40% yield); LCMS [$\text{M}/2+\text{H}$]: 816.2.

D31. Synthesis of Compound 131**Scheme D31.**





4.128 Preparation of compound 131C

[00923] To a solution of *bis*{2-[2-(2-{2-[3-(2,5-dioxo-1-pyrrolidinyloxy)-3-oxopropoxy]ethoxy}ethoxy)ethoxy]ethyl}amino-*tert*-butylformylate (38 mg, 47 μ mol, 1 *eq*) in DMF (1.5 mL) was added **compound 131A** (182 mg, 165 μ mol, 3.5 *eq*) followed by ethyl*bis*(propan-2-yl)amine (369 μ L, 2.1 mmol). The resulting solution stirred at room temperature for 16h and purified directly by *prep*-HPLC (C18, Luna 30x150mm, 30-70% CH₃CN/H₂O+ 0.1% Trifluoroacetic acid) to give **compound 131C** as a white solid (38 mg, 32% yield); LCMS [M-Boc/2+H]: 1229.2.

4.129 Preparation of compound 131D

[00924] 4N HCl in dioxane (20 μ L, 14.9 μ mol, 5 *eq*) was added to a solution of **compound 131C** (38 mg, 14.9 μ mol) in DCM (1mL) and stirred at room temperature for 6h. The reaction was concentrated under reduced pressure to give crude **compound 131D** (33 mg) as a white solid; LCMS [M/2+H]: 1229.2.

4.130 Preparation of compound 131E

[00925] **Compound 131D** (33 mg, 9.0 μ mol) was taken up in DMF (1.5 mL), (*tert*-butoxycarbonylamino)acetic acid (2.8 mg, 15.9 μ mol, 1.2 *eq*) followed by *N*-ethyl*bis*(isopropyl)amine (7.0 μ L, 40 μ mol, 3 *eq*) and 2,4,6-tripropyl-1,3,5,2 λ^5 ,4 λ^5 ,6 λ^5 -trioxatriphosphinane-2,4,6-trione (10 μ L, 33 μ mol, 2.5 *eq*) were added dropwise. The resulting solution was stirred at room temperature for 0.5h and purified directly by *prep*-HPLC (C18, Luna 30x150mm, 25-60% CH₃CN/H₂O+ 0.1% TFA) to give **compound 131E** as a white solid (25 mg, 72% yield); LCMS[M-Boc/3+H]: 838.9.

4.131 Preparation of compound 131F

[00926] 4N HCl in dioxane (12 μ L, 48 μ mol, 5*eq*) was added to a solution of **compound 131E** (25 mg, 10 μ mol) in DCM (1mL) and stirred at room temperature for 16h. The reaction was concentrated under reduced pressure to give crude **compound 131F** as white solid (10 mg); LCMS [M/2+H]: 838.7.

4.132 Preparation of Compound 131

[00927] **Compound 131** was prepared from **compound 131F** using procedures previously depicted. LCMS [M/3+H]: 967.8.

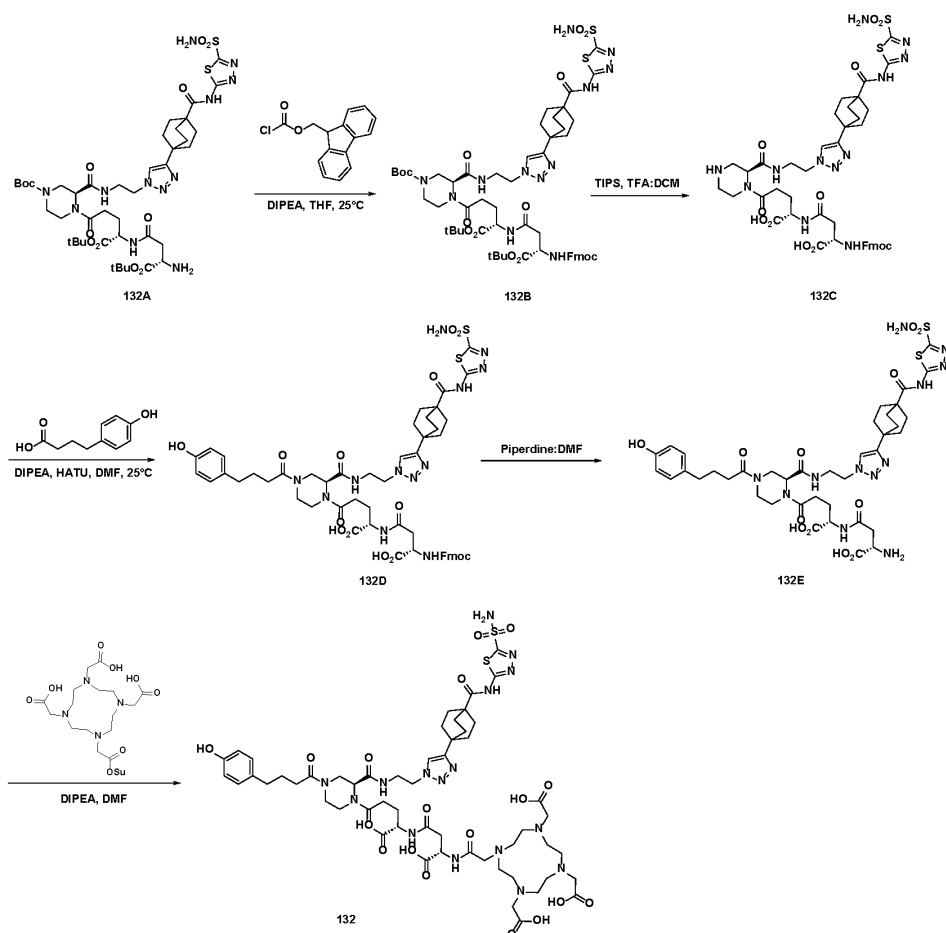
[00928] Compounds in **table 9.23** were prepared by procedures depicted in Scheme D29.

Table 9.23.

Compound	m/z
131.1	[M/3+H]: 952.2
131.2	[M/3+H]: 970.3
131.3	[M+H]/3: 978.3
131.4	[M/3+H]: 839.2
131.5	[M/3+H]: 792.1
131.6	[M/3+H]: 977.6
131.7	[M/3+H]: 977.2

D32. Synthesis of Compound 132

Scheme D32.



4.135 Preparation of compound 132B

[00929] (9H-fluoren-9-yl)methyl carbonochloridate (27 mg, 112 μ mol, 1.1 eq) and DIPEA (37 μ l, 212 μ mol, 2.1 eq) were added to a stirred solution of **compound 132A** (100 mg, 0.1 mmol, 1 eq) in THF (1 mL). The reaction was stirred at room temperature for 30 min, diluted with EtOAc, washed with water and brine, dried (Na_2SO_4), filtered and to give crude **compound 132B** (122 mg) that was used directly in the next reaction; [M+H]: 1217.4.

4.136 Preparation of compound 132C

[00930] Tris(isopropyl)silane (0.8 mL) and TFA (0.8 mL) were added to a stirred solution of **compound 132B** (122 mg, 0.1 mmol, 1 eq) in DCM (0.6 mL). The reaction was stirred at room temperature for 17h and concentrated under reduced pressure. The reaction was purified by *prep*-HPLC (Luna C18 30x150mm column, 25-50% ACN/H₂O +0.1%TFA) to give **compound 132C** (69 mg) as a white powder; [M+H]: 1005.4.

4.137 Preparation of compound 132D

[00931] HATU (20mg, 52.5 μ mol, 1.2 eq) and DIPEA (23 μ L, 131 μ mol, 3 eq) were added to a stirred solution of 4-(4-hydroxyphenyl)butanoic acid (8 mg, 44 μ mol, 1 eq) in DMF (1.2 mL). The reaction solution was stirred at room temperature for 20 min, **compound 132C** (44 mg, 43 μ mol, 1 eq) added and the crude reaction stirred at room temperature for 16 h. The reaction was quenched with 1N HCl (10 mL), the aqueous layer extracted with EtOAc (2 $\times$ 8 mL), the combined organics washed with brine (10 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure to give crude **compound 132D** (38 mg, 74% yield); [M+H]: 1168.3.

4.138 Preparation of compound 132E

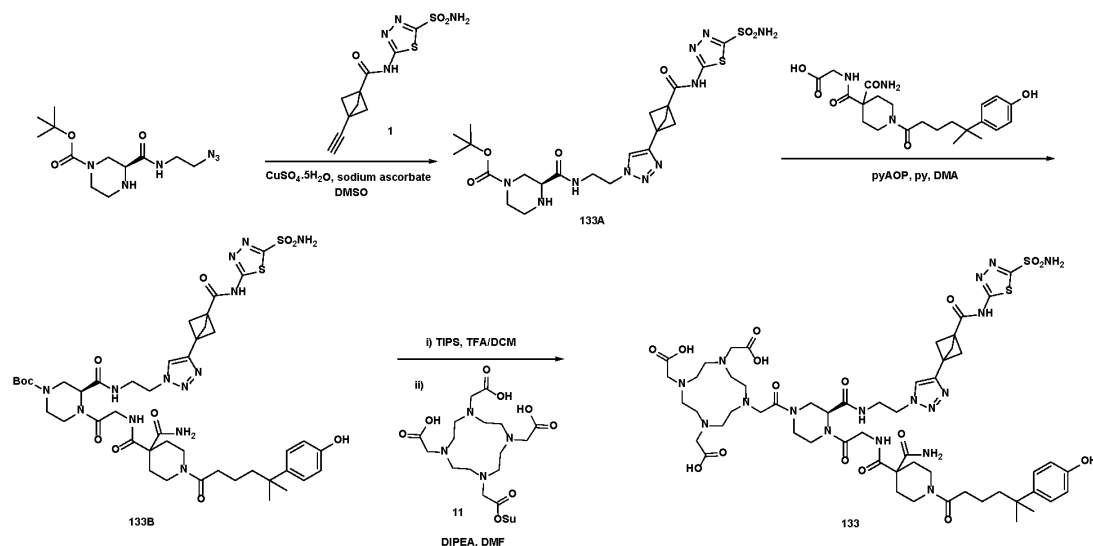
[00932] Piperidine (5.0 μ L, 48.8 μ mol, 1.5 eq) was added to a stirred solution of **compound 132D** (38 mg, 32.6 μ mol, 1 eq) in DMF (0.5 mL). The reaction was stirred at room temperature for 0.5h and purified directly by *prep*-HPLC (Luna C18 30x150mm column, 0-50% ACN/H₂O +0.1%TFA) to give **compound 132E** (20 mg, 65% yield); [M+H]: 946.3.

4.139 Preparation of Compound 132

[00933] **Compound 132** was prepared from **compound 132E** using procedures previously depicted; LCMS [M/2+H]: 666.2.

D33. Synthesis of Compound 133

Scheme D33.



4.140 Preparation of compound 133A

[00934] To a solution of *tert*-butyl (*S*)-3-((2-azidoethyl)carbamoyl)piperazine-1-carboxylate (85.0 g, 279 mmol) and **compound 1** (68.3 g, 228 mmol) in DMSO (845 mL) was added CuSO₄·5H₂O (3.49 g, 13.9 mmol) and sodium ascorbate (55.4 g, 279 mmol). The mixture was stirred at 25 °C for 8 h. The reaction mixture was quenched by addition of H₂O (700 mL) at 25 °C, and extracted with DCM (5 × 500 mL). The combined organic layers were filtered and concentrated under reduced pressure. The residue was added dropwise to H₂O (3000 mL) at 5 °C and the green solid was collected by filtration. The crude product was triturated with MeOH (750 mL) at 25 °C for 12 h to give **compound 133A** (132 g) as an off-white solid; LCMS [M+H]⁺ = 597.3; ¹H NMR (400MHz, CD₃OD) δ 7.91 (s, 1H), 4.56 (m, 2H), 3.77 - 3.75 (m, 1H), 3.70 - 3.67 (m, 1H), 2.96 - 2.93 (m, 3H), 2.67 - 2.65 (m, 1H), 2.52 (s, 6H), 1.46 (s, 9H).

4.141 Preparation of compound 133B

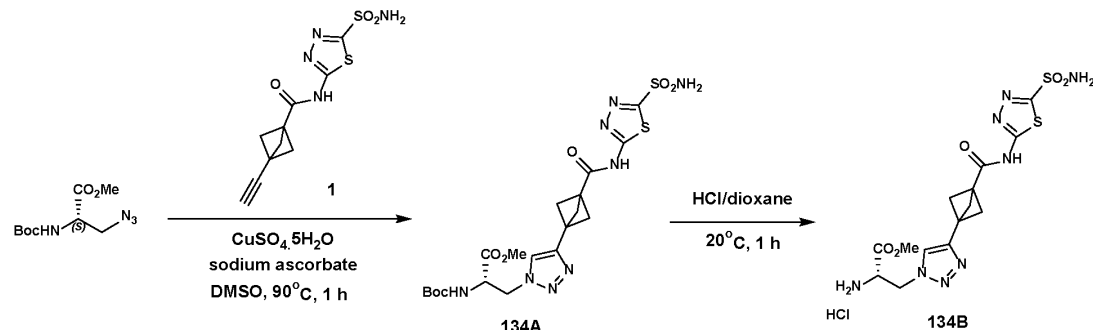
[00935] To a stirred solution of (4-carbamoyl-1-(5-(4-hydroxyphenyl)-5-methylhexanoyl)piperidine-4-carbonyl)glycine (141 mg, 0.33 mmol) in anhydrous DMA (1.5 mL), PyAOP (282 mg, 0.54 mmol) was added followed by pyridine (0.70 mL, 8.7 mmol) and the resulting heated to 40 °C, **Compound 133A** (130 mg, 0.22 mmol) was slowly added to the solution portion wise over 5 min. The resulting solution was stirred at room temperature for 1h and directly purified by *prep*-HPLC to afford **compound 133B** as a white solid (180 mg, 82% yield); [M+H]⁺ = 1012.5.

4.142 Preparation of Compound 133

[00936] Compound **133** was prepared from **Compound 133B** as previously depicted; LCMS [M/2+H]: 650.0.

D34. Synthesis of Compound 134

Scheme D34.

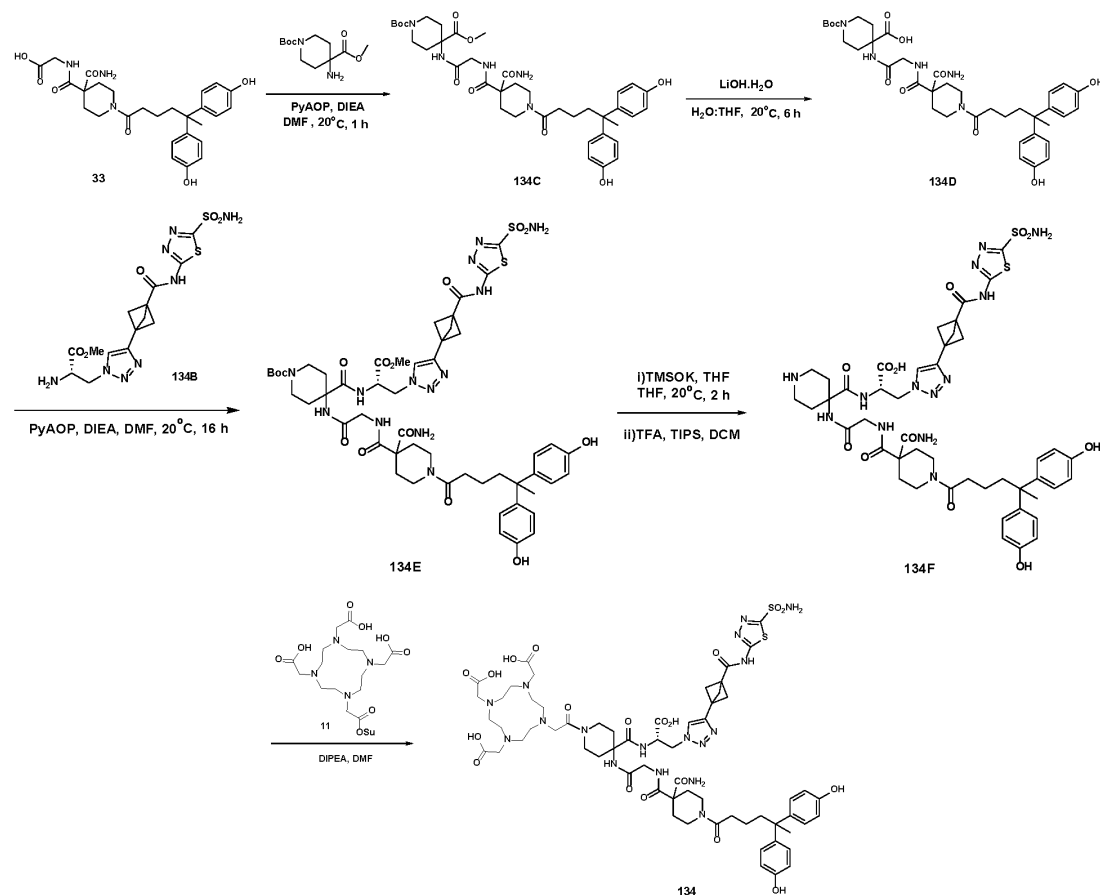


Preparation of compound 134A

[00937] To a solution of methyl (*S*)-3-azido-2-((tert-butoxycarbonyl)amino)propanoate (200 mg, 819 μmol) and **compound 1** (244 mg, 819 μmol) in DMSO (2 mL) was added CuSO₄·5H₂O (41 mg, 164 μmol) and sodium ascorbate (324 mg, 1.64 mmol). The mixture was stirred at 90°C for 1 h. The crude product was triturated with H₂O (8 mL) and NH₄Cl (2 mL) at 20°C for 10 min, the filter cake washed with H₂O (10 mL), and the filter cake concentrated under reduced pressure to give crude **compound 134A** (450 mg) as a white solid; LCMS [M+H]⁺ = 543.2; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.49 - 8.05 (m, 2H), 8.02 - 7.87 (m, 1H), 7.43 (br d, *J* = 8.0 Hz, 1H), 4.78 - 4.65 (m, 1H), 4.61 - 4.48 (m, 2H), 3.66 (s, 3H), 2.42 (br s, 6H), 1.33 (s, 9H).

Preparation of compound 134B

[00938] A solution of **compound 134A** (400 mg, 737 μmol) in 4M HCl in dioxane (4 mL) was stirred at 20°C for 1 h and concentrated under reduced pressure to give crude **compound 134B** (500 mg, 3HCl) as a white solid; LCMS: $[M-1]^- = 441.0$; ^1H NMR (400 MHz, DMSO- d_6) δ 13.22 (br s, 1H), 8.92 (br s, 2H), 8.36 (s, 2H), 8.07 (s, 1H), 4.95 - 4.82 (m, 2H), 4.69 (br s, 1H), 3.78 - 3.70 (m, 3H), 2.45 (s, 6H).

Scheme D35.**Preparation of compound 134C**

[00939] To a solution of 1-(*tert*-butyl) 4-methyl 4-aminopiperidine-1,4-dicarboxylate (353 mg, 1.37 mmol) and **compound 33** (700 mg, 1.37 mmol) in DMF (10 mL) was added **PyAOP** (785 mg, 1.51 mmol) and **DIEA** (715 μL , 4.11 mmol). The mixture was stirred at 20°C for 1 h, diluted with **H₂O** (50 mL) and extracted with **EtOAc** (3×30 mL). The combined organic layers were washed with brine (3×10 mL), dried (**Na₂SO₄**), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (**SiO₂**, **MeOH:DCM**) to give crude **compound 134C** (825 mg) as a white solid; LCMS $[M+H]^+ = 752.3$.

Preparation of compound 134D

[00940] To a solution of **compound 134C** (700 mg, 931 μmol) in **THF** (3.5 mL) and **H₂O** (3.5 mL) was added **LiOH.H₂O** (117 mg, 2.79 mmol). The mixture was stirred at 20°C for 6 h and organics removed

under reduced pressure. The reaction mixture was adjusted to pH=4, the solid separated and concentrated under reduced pressure to give **compound 134D** (680 mg, 99% yield) as a white solid: LCMS $[M+H]^+ = 738.6$.

Preparation of compound 134E

[00941] To a solution of **compound 134D** (484 mg, 655 μ mol) and **compound 134B** (580 mg, 1.31 mmol) in DMF (4.8 mL) was added PyAOP (376 mg, 721 μ mol) and DIEA (342 μ L, 1.97 mmol). The mixture was stirred at 20°C for 16 h. The reaction mixture was concentrated under reduced pressure to give crude **compound 134E** (761 mg) as a yellow oil: LCMS $[M+H]^+ = 1162.7$.

Preparation of compound 134F

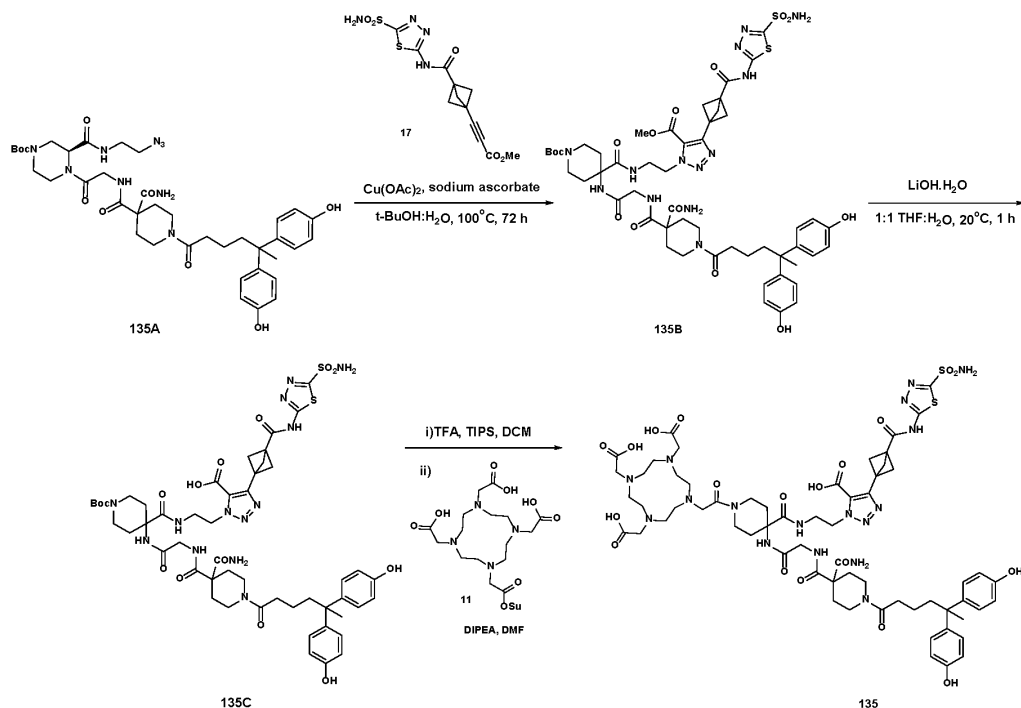
[00942] To a solution of **compound 134E** (740 mg, 637 μ mol) in THF (8 mL) was added TMSOK (408 mg, 3.18 mmol). The mixture was stirred at 20°C for 1 h, the reaction mixture adjusted to pH=6 and concentrated under reduced pressure. The residue was taken up in DCM (4 mL), triisopropylsilane (2.58 mL, 12.5 mmol) and TFA (4 mL) added and the reaction stirred at 20°C for 1 h. The reaction mixture was concentrated under reduced pressure and purified by *prep*- HPLC to give **compound 134F** (81 mg, 12% yield) as a white solid; LCMS $[M+H]^+ = 1048.6$; ^1H NMR (400 MHz, DMSO-*d*₆) δ 13.19 (s, 2H), 9.12 (s, 2H), 8.54 (br d, $J = 3.8$ Hz, 1H), 8.35 (s, 2H), 8.32 - 8.21 (m, 2H), 8.07 (br d, $J = 7.4$ Hz, 1H), 7.89 (d, $J = 2.6$ Hz, 1H), 7.37 (br d, $J = 12.0$ Hz, 2H), 6.93 (br d, $J = 8.6$ Hz, 4H), 6.62 (d, $J = 8.6$ Hz, 4H), 4.81 (br d, $J = 10.2$ Hz, 1H), 4.66 - 4.48 (m, 2H), 3.79 (br d, $J = 4.4$ Hz, 3H), 3.51 (br s, 1H), 3.18 (br s, 3H), 3.08 - 2.84 (m, 3H), 2.42 (s, 6H), 2.31 - 2.15 (m, 3H), 2.02 (br d, $J = 11.4$ Hz, 5H), 1.96 - 1.73 (m, 4H), 1.47 (s, 3H), 1.23 (br s, 2H).

Preparation of compound 134

[00943] **Compound 134** was prepared from **compound 134F** using procedures previously depicted; LCMS $[M+H]^+ = 1434.9$.

D35. Synthesis of Compound 135

Scheme D36.



Preparation of compound 135B

[00944] To a solution of **compound 17** (747 mg, 2.10 mmol) and **compound 135A** (1.3 g, 1.61 mmol) in $t\text{-BuOH}$ (7 mL) and H_2O (0.7 mL) was added $\text{Cu}(\text{OAc})_2$ (117 mg, 645 μmol) and sodium ascorbate (256 mg, 1.29 mmol) in $t\text{-BuOH}$ (7 mL) under a nitrogen atmosphere at 20°C . The mixture was stirred at 100°C for 72 h and concentrated under reduced pressure. The residue was purified by *prep*-HPLC followed by *prep*-SFC to separate the triazole regioisomers to give **compound 135B** (900 mg, 60%) as a white solid; LCMS $[\text{M}+\text{H}]^+ = 1162.4$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.93 - 13.46 (m, 1 H), 9.12 (s, 2 H), 8.13 - 8.36 (m, 3 H), 8.06 (s, 1 H), 7.64 (br t, $J=5.8$ Hz, 1 H), 7.22 - 7.43 (m, 2 H), 6.93 (d, $J=8.6$ Hz, 4 H), 6.63 (d, $J=8.6$ Hz, 4 H), 4.65 (br t, $J=5.8$ Hz, 2 H), 3.94 (s, 3 H), 3.70 - 3.85 (m, 5 H), 3.57 - 3.68 (m, 2 H), 3.42 - 3.56 (m, 3 H), 3.07 - 3.14 (m, 1 H), 2.82 - 3.03 (m, 3 H), 2.24 (br t, $J=7.2$ Hz, 2 H), 1.89 - 2.10 (m, 4 H), 1.70 - 1.88 (m, 4 H), 1.63 (br t, $J=10.6$ Hz, 2 H), 1.47 (s, 3 H), 1.39 (s, 9 H), 1.20 - 1.25 (m, 2 H).

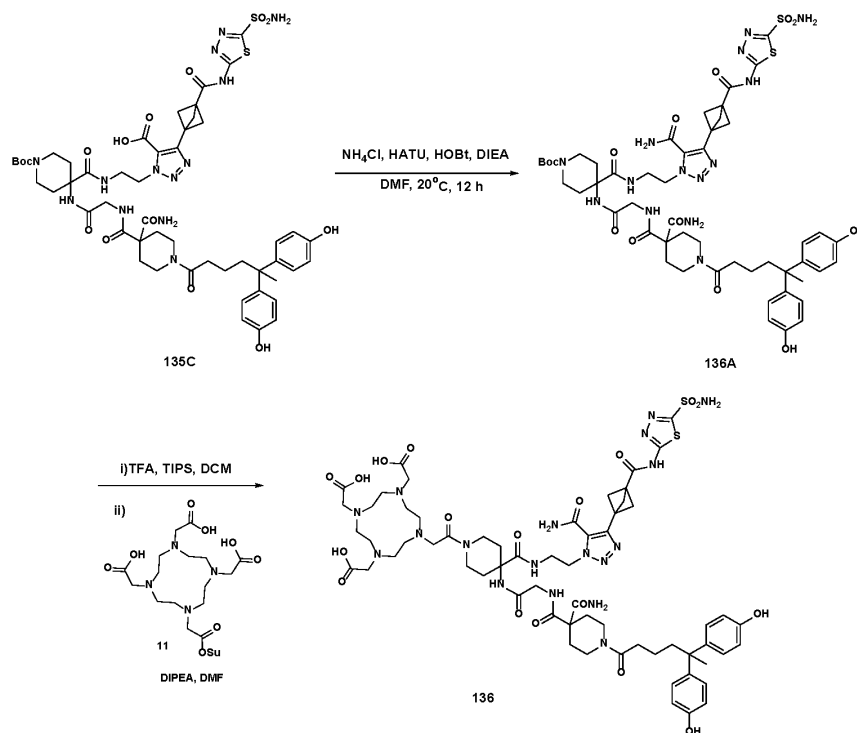
Preparation of compound 135C

[00945] To a solution of **compound 135B** (350 mg, 301 μmol) in THF (2 mL) and H_2O (2 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (51 mg, 1.20 mmol). The mixture was stirred at 20°C for 1 h and concentrated under reduced pressure to give crude **compound 135C** (350 mg) as a white solid; LCMS $[\text{M}+\text{H}]^+ = 1148.5$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.97 - 13.32 (m, 1 H), 9.02 - 9.28 (m, 2 H), 8.48 - 8.80 (m, 1 H), 8.34 (s, 2 H), 7.76 - 8.09 (m, 1 H), 7.53 (br s, 1 H), 7.30 (br s, 1 H), 6.93 (br d, $J=8.41$ Hz, 4 H), 6.62 (br d, $J=8.41$ Hz, 4 H), 4.46 - 4.96 (m, 1 H), 3.83 (br s, 3 H), 3.65 (br s, 2 H), 3.02 - 3.20 (m, 5 H), 2.89 (br d, $J=6.65$ Hz, 4 H), 2.42 (br d, $J=4.14$ Hz, 2 H), 2.24 (br s, 2 H), 2.15 (br s, 2 H), 1.74 - 2.01 (m, 7 H), 1.67 (br s, 2 H), 1.46 (br s, 3 H), 1.38 (s, 9 H), 1.23 (br s, 3 H).

[00946]

Preparation of compound 135

[00947] **Compound 135** was prepared from **compound 135C** using procedures previously depicted; LCMS $[M+H]^+ = 1435.0$.

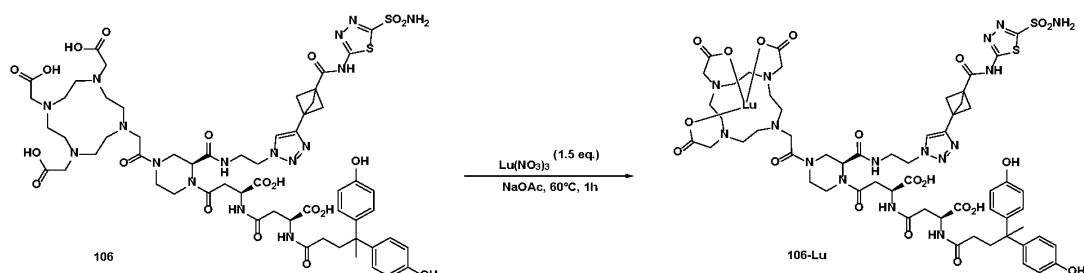
D36. Synthesis of Compound 136**Scheme D37.****Preparation of compound 136A**

[00948] To a solution of **compound 135C** (150 mg, 131 μmol) and NH_4Cl (21 mg, 392 μmol) in DMF (1.5 mL) was added DIEA (46 μL , 261 μmol), HOBT (35 mg, 261 μmol) and HATU (99 mg, 261 μmol). The mixture was stirred at 20°C for 12 h and concentrated under reduced pressure. The crude product was purified by *prep*-HPLC to give **compound 136A** (30 mg) as a white solid; LCMS: $[M+H]^+ = 1147.6$.

Preparation of compound 136

[00949] **Compound 136** was prepared from **compound 136A** using procedures previously depicted; LCMS $[M+H]^+ = 1434.1$.

E1. Synthesis of Compound 106-Lu**Scheme E1.**

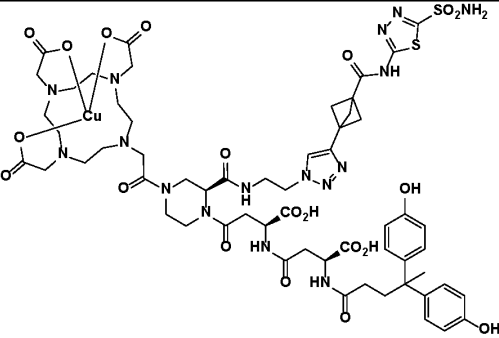
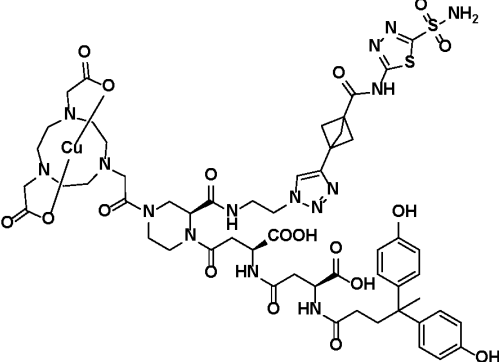


[00950] To a solution of **Compound 106** (80 mg, 57.9 μmol , 1 *eq*) in H_2O (1 mL) was added NaOAc (16 mg, 195 μmol , 3.4 *eq*) and $\text{Lu}(\text{NO}_3)_3$ (32.9 mg, 89 μmol , 1.5 *eq*), the mixture stirred at 60°C for 1h and concentrated under reduced pressure. The residue was purified by *prep*-HPLC (PhenomenexC18 150*30mm*5um; mobile phase: [water (TFA)-ACN]; B%: 10%-30%, 8min) to give **Compound 106-Lu** (30.3 mg, 34% yield) as a white solid; LCMS $[\text{M}+\text{H}]$: 1553.4; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.66 - 13.16 (m, 1H), 12.86 - 12.42 (m, 1H), 9.39 - 9.02 (m, 1H), 8.59 - 7.61 (m, 5H), 6.91 (b r d, $J = 8.3$ Hz, 4H), 6.64 (b r d, $J = 7.2$ Hz, 4H), 5.07 - 4.65 (m, 2H), 4.58 - 4.35 (m, 4H), 4.31 - 3.91 (m, 5H), 3.43 - 3.28 (m, 6H), 3.24 - 3.06 (m, 3H), 2.71 - 2.69 (m, 1H), 3.04 - 2.69 (m, 10H), 2.69 - 2.53 (m, 10H), 2.47 - 2.40 (m, 6H), 2.35 - 2.31 (m, 1H), 2.16 (b r t, $J = 7.1$ Hz, 2H), 1.84 (b r d, $J = 6.5$ Hz, 2H), 1.44 (br s, 3H).

[00951] Compounds in **table 10.1** were prepared by procedures depicted in **scheme E1** using the appropriate inorganic salt; Lanthanum trichloride, gallium tris(nitrate) monohydrate or copper dichloride.

Table 10.1.

Compound	Structure	m/z
106-La		$[\text{M}/2+\text{H}]$: 759.1
106-Ga		$[\text{M}/2+\text{H}]$: 724.3

Compound	Structure	m/z
106-Cu		[M/2+H] ⁺ : 721.8
126-Cu		[M/2+H] ⁺ : 671.3

F1. Radiolabeling Protocols

General protocol for ¹⁷⁷Lu Radiolabeling of empty-DOTA construct

[00952] A 35 mCi aliquot of ¹⁷⁷LuCl₃ was added to the reaction vessel followed by addition of 10% ethanol in 0.4M NaOAc buffer (1.0 mL; pH=5.0) and the empty-DOTA construct (1.0 µg/µL, 32 µL). The resulting mixture was heated and mixed with a thermal mixer at 70°C for 0.5h. After 0.5h, the reaction mixture was allowed to cool at room temperature for 3 min. Then the reaction mixture was diluted with 4.8 mL of a pre-mixed formulation buffer. To assess the radiochemical purity, 60 µCi of the ¹⁷⁷Lu labeled product was injected on a rad-HPLC. At the end of the synthesis (EOS), the radiochemical purity and specific activity was determined. HPLC column: Aeris 3.6 µm PEPTIDE XB-C18 100, LC Column, 150 x 4.6 mm (00F-4507-E0). Flow 1.0mL/min. HPLC column Aeris 3.6 µm PEPTIDE XB-C18 100, LC Column, 150 x 4.6 mm (00F-4507-E0). Solvent A was H₂O/0.05% TFA and solvent B was CH₃CN/0.05% TFA. Elution was conducted at flow rate of 1.0 mL/min with gradient from 5 to 95% B over 16 min.

General protocol for ²²⁵Ac Radiolabeling of empty-DOTA construct

[00953] A ²²⁵Ac(NO₃)₃ powder was diluted with 0.5M HCl to achieve a concentration of 10 µCi/µL. 100µCi aliquot of the 10 µCi/µL ²²⁵Ac-chloride solution was added to the reaction vessel followed by addition of 10% ethanol in 0.4M NaOAc buffer (200 µL, pH=6.2) and 27.5 µg of the empty-DOTA construct (1.0 µg/µL, 27.5 µL). The resulting mixture was heated and mixed with a thermal mixer at 90°C for 0.5 h. After 0.5h, the reaction mixture was allowed to cool at room temperature for 3 min. The reaction mixture was diluted with 1.0 mL of a pre-mixed formulation buffer. The radiochemical purity

was determined at 5 $\mu\text{Ci/nmol}$ by radio thin-layer chromatography (radio-TLC). TLC plate: Agilent Technologies Chromatography paper (Cat number A120B12); mobile phase: 50mM DTPA, pH=5.56.

General protocol for ^{64}Cu Radiolabeling of empty-NOTA construct

[00954] $^{64}\text{CuCl}_2$ in 0.1M HCl was reconstituted with 0.4M NaOAc pH=6.2 to achieve a concentration of 0.2 mCi/ μL . A 7.14 mCi aliquot of the $^{64}\text{CuCl}_2$ solution was added to the reaction vessel followed by addition of 10% ethanol in 0.4M NaOAc buffer (200 μL ; pH=6.2) and the empty-NOTA construct (1.0 $\mu\text{g}/\mu\text{L}$, 6.0 μL). The resulting mixture was heated and mixed with a thermal mixer at 50°C for 0.5h. After 0.5h, the reaction mixture was allowed to cool at room temperature for 3 min. Then the reaction was diluted with 4.8 mL of a pre-mixed formulation buffer. To assess the radiochemical purity, 10 μCi of the product was injected on a rad-HPLC. At the end of the synthesis (EOS), the radiochemical purity and specific activity was determined. HPLC column: Aeris 3.6 μm PEPTIDE XB-C18 100, LC Column, 150 x 4.6 mm (00F-4507-E0). Solvent A was $\text{H}_2\text{O}/0.05\%$ TFA and solvent B was $\text{CH}_3\text{CN}/0.05\%$ TFA. Elution was conducted at flow rate of 1.0 mL/min with gradient from 5 to 95% B over 16 min.

G1. Surface Plasmon Resonance Assay Conditions for hCA-IX and hCA-XII

[00955] Surface Plasmon Resonance (SPR) experiments were conducted on a Biacore 8K instrument (Cytiva, Marlborough, MA) to determine the binding kinetics of the compound to recombinant human CA-IX (Acro, CA9-H82E3) and CA-XII (Creative BioMart, CA12-261H) proteins. The ligands were diluted to 10 $\mu\text{g}/\text{mL}$ in PBS-P+ buffer (20 mM phosphate buffer, pH 7.4, with 2.7 mM KCl, 137 mM NaCl, and 0.05% Tween 20) and captured on Series S Streptavidin Sensor Chips (Cytiva, 29699621) to 1200-1800 response units (RU) using a flow rate of 5 $\mu\text{L}/\text{min}$ and injection times of 180 seconds for human CA-IX and 75 seconds for human CA-XII. Analyte binding was evaluated using a single-cycle kinetics method over 9 analyte concentrations (100-0.39 nM) in PBS-P+ buffer with 1% DMSO using a 50 $\mu\text{L}/\text{min}$. flow rate, 120 second association time, and 1200 second dissociation time. The flow cell temperature was set to 25 °C. Analyte binding curves were fit to a 1:1 binding kinetic model in Biacore Insight Evaluation software (version 4.0.8.20368) following reference flow cell subtraction and DMSO correction to derive the association and dissociation binding constants. The data is presented in table 11.

TABLE 11

Conjugates Tested Comprising a compound and, when indicated, a chelated metal		CAIX KD	CAXII KD	Ratio (CAXII/CAIX)
Compound	Chelated Metal			
100	Lu-175	B	D	***
100.1	Lu-175	A	B	*
100.2	Lu-175	B	D	***
100.3	Lu-175	A	C	**
100.4	Lu-175	A	C	*
100.5	Lu-175	A	A	*
100.6	Lu-175	A	B	**
100.7	Lu-175	A	B	*
100.8	Lu-175	A	C	*
100.9	Lu-175	A	B	*

Conjugates Tested Comprising a compound and, when indicated, a chelated metal		CAIX KD	CAXII KD	Ratio (CAXII/CAIX)
Compound	Chelated Metal			
100.10	Lu-175	A	A	*
100.11	Lu-175	A	A	*
100.12	Lu-175	A	A	*
100.13	Lu-175	A	A	*
100.14	Lu-175	A	A	*
100.15	Lu-175	A	A	*
100.16	Lu-175	A	A	*
100.17	Lu-175	A	A	*
100.18	Lu-175	A	A	*
100.19	Lu-175	A	A	*
101	Lu-175	A	A	*
101.1	Lu-175	A	C	**
101.2	Lu-175	A	C	***
102	Lu-175	B	D	**
102.1	Lu-175	A	D	***
102.2	Lu-175	C	D	*
102.3	None	A	D	***
102.4	Lu-175	A	C	**
102.5	Lu-175	A	C	***
102.6	Lu-175	A	D	***
102.7	Lu-175	A	C	***
102.8	Lu-175	A	B	*
103	Lu-175	B	C	*
103.1	Lu-175	B	C	*
103.2	Lu-175	B	C	*
103.3	Lu-175	C	D	*
103.4	Lu-175	C	C	*
104	Lu-175	B	C	*
104.1	None	A	A	*
104.2	None	A	A	*
106	Lu-175	A	C	***
107	Lu-175	A	D	****
107.1	Lu-175	A	A	*
107.2	Lu-175	A	A	*
107.3	Lu-175	B	D	***
107.4	Lu-175	B	D	***
107.5	Lu-175	A	A	*
107.6	Lu-175	A	D	****
107.7	Lu-175	A	B	*
107.8	Lu-175	B	D	***
107.9	Lu-175	A	B	*
107.10	Lu-175	A	A	*
107.11	Lu-175	A	D	***
107.12	Lu-175	B	D	****
107.13	Lu-175	B	D	***
107.14	Lu-175	A	A	*
107.15	Lu-175	B	D	***
107.16	Lu-175	B	C	**
107.17	Lu-175	A	B	*

Conjugates Tested Comprising a compound and, when indicated, a chelated metal		CAIX KD	CAXII KD	Ratio (CAXII/CAIX)
Compound	Chelated Metal			
107.18	Lu-175	C	D	***
107.19	Lu-175	B	D	****
107.20	Lu-175	ND	ND	
107.21	Lu-175	B	D	***
107.22	Lu-175	B	D	***
107.23	Lu-175	A	D	***
107.24	Lu-175	B	C	*
107.25	Lu-175	A	D	****
107.26	Lu-175	A	D	***
107.27	Lu-175	A	A	***
107.28	Lu-175	A	A	***
107.29	Lu-175	A	D	****
107.30	Lu-175	A	B	**
107.31	Lu-175	B	D	****
107.32	Lu-175	A	D	****
107.33	Lu-175	A	D	****
107.34	Lu-175	A	D	****
107.35	Lu-175	A	D	***
107.36	Lu-175	A	D	***
107.37	Lu-175	D	D	***
107.38	Lu-175	A	D	****
107.39	Lu-175	A	D	***
107.40	Lu-175	ND	A	
107.41	Lu-175	B	D	***
107.42	Lu-175	A	C	*
107.43	Lu-175	C	D	****
107.44	Lu-175	A	D	****
107.45	Lu-175	A	C	*
107.46	Lu-175	D	ND	
107.47	Lu-175	B	D	****
107.48	Lu-175	A	B	****
107.49	Lu-175	A	D	****
107.50	Lu-175	A	D	***
107.51	Lu-175	B	D	****
107.52	Lu-175	B	D	****
107.53	None	A	C	****
107.54	Lu-175	C	D	*
107.55	Lu-175	A	C	***
107.56	Lu-175	B	D	****
107.57	Lu-175	B	D	****
107.58	Lu-175	A	D	****
107.59	Lu-175	A	D	****
107.60	Lu-175	A	C	**
107.61	Lu-175	B	D	**
108	Lu-175	B	D	***
108.1	Lu-175	C	D	***
108.2	Lu-175	A	D	****
108.3	Lu-175	C	D	****
108.4	Lu-175	B	D	***

Conjugates Tested Comprising a compound and, when indicated, a chelated metal		CAIX KD	CAXII KD	Ratio (CAXII/CAIX)
Compound	Chelated Metal			
108.5	Lu-175	C	D	***
109	Lu-175	A	C	**
109.1	Lu-175	A	C	*
109.2	Lu-175	A	B	**
109.3	Lu-175	A	A	*
109.4	Lu-175	A	C	**
109.5	Lu-175	B	C	**
109.6	Lu-175	A	C	**
109.7	Lu-175	A	C	*
109.8	Lu-175	B	C	*
109.9	Lu-175	A	B	*
109.10	Lu-175	A	C	***
109.11	Lu-175	A	C	***
109.12	Lu-175	B	C	*
109.13	Lu-175	A	C	***
109.14	Lu-175	A	C	***
109.15	Lu-175	A	C	**
109.16	Lu-175	A	C	**
109.17	Lu-175	C	D	*
109.18	Lu-175	A	B	*
109.19	Lu-175	A	B	*
109.20	Lu-175	A	C	**
109.21	Lu-175	A	D	***
109.22	Lu-175	B	C	*
109.23	Lu-175	C	D	*
109.24	Lu-175	B	C	*
109.25	Lu-175	A	C	***
109.26	Lu-175	B	C	*
109.27	Lu-175	B	C	*
109.28	Lu-175	A	B	*
109.29	Lu-175	C	D	***
109.30	Lu-175	A	C	**
109.31	Lu-175	A	C	**
109.32	Lu-175	A	D	***
109.33	Lu-175	B	D	***
109.34	Lu-175	A	C	**
109.35	Lu-175	B	C	*
109.36	Lu-175	B	C	**
109.37	Lu-175	A	C	***
109.38	Lu-175	A	C	**
109.39	Lu-175	B	C	*
109.40	Lu-175	A	D	****
109.41	Lu-175	A	A	*
109.42	Lu-175	A	A	*
109.43	Lu-175	A	A	*
109.44	Lu-175	A	A	*
109.45	Lu-175	A	A	*
109.46	Lu-175	A	A	*
109.47	Lu-175	A	A	*

Conjugates Tested Comprising a compound and, when indicated, a chelated metal		CAIX KD	CAXII KD	Ratio (CAXII/CAIX)
Compound	Chelated Metal			
109.48	Lu-175	A	A	*
109.49	Lu-175	A	A	*
109.50	Lu-175	A	A	*
109.51	Lu-175	A	A	*
109.52	Lu-175	A	A	*
109.53	Lu-175	A	A	*
109.54	Lu-175	A	A	**
109.55	Lu-175	A	A	*
109.56	Lu-175	A	B	*
109.57	Lu-175	A	A	*
109.58	Lu-175	A	A	***
109.59	Lu-175	A	A	*
109.60	Lu-175	A	B	***
109.61	Lu-175	B	C	*
109.62	None	A	D	***
109.63	None	A	C	***
110	Lu-175	A	A	*
111	Lu-175	C	D	***
111.1	Lu-175	B	D	***
111.2	Lu-175	C	D	***
111.3	Lu-175	B	D	***
111.4	Lu-175	C	D	***
111.5	Lu-175	C	D	***
111.6	Lu-175	C	D	***
111.7	Lu-175	C	D	***
111.8	Lu-175	C	D	***
111.9	Lu-175	B	D	***
111.10	Lu-175	C	D	***
111.11	Lu-175	B	D	***
111.12	Lu-175	C	D	***
112	Lu-175	C	D	***
112.1	Lu-175	C	D	***
112.2	Lu-175	A	C	*
112.3	Lu-175	B	D	***
112.4	Lu-175	C	D	***
112.5	Lu-175	C	D	***
112.6	Lu-175	B	D	***
112.7	Lu-175	A	D	***
112.8	Lu-175	A	C	***
112.9	Lu-175	A	D	****
112.10	Lu-175	A	D	***
112.11	Lu-175	C	D	****
112.12	Lu-175	B	D	***
112.13	Lu-175	B	D	****
112.14	Lu-175	C	D	***
112.15	Lu-175	B	D	***
112.16	Lu-175	C	D	***
112.17	Lu-175	A	B	*
112.18	Lu-175	B	D	****

Conjugates Tested Comprising a compound and, when indicated, a chelated metal		CAIX KD	CAXII KD	Ratio (CAXII/CAIX)
Compound	Chelated Metal			
112.19	Lu-175	A	D	***
113	Lu-175	C	D	****
114	Lu-175	B	D	***
114.1	Lu-175	B	D	***
114.2	Lu-175	B	D	***
114.3	Lu-175	B	D	***
115	Lu-175	C	D	***
116	Lu-175	B	C	*
116.1	Lu-175	B	C	*
116.2	Lu-175	B	C	*
116.3	Lu-175	B	C	*
116.4	Lu-175	C	D	**
117	Lu-175	B	D	***
117.1	Lu-175	A	D	****
117.2	None	ND	ND	
117.3	Lu-175	A	D	****
117.4	Lu-175	B	D	****
117.5	Lu-175	A	C	****
117.6	Lu-175	A	B	****
117.7	Lu-175	A	D	****
117.8	Lu-175	A	D	****
118	Lu-175	B	C	**
118.1	Lu-175	B	D	***
118.2	Lu-175	B	D	***
118.3	Lu-175	C	C	*
118.4	Lu-175	B	D	***
119	Lu-175	C	D	**
120	None	ND	ND	
121	Lu-175	A	D	****
121.1	Lu-175	B	D	****
122	Lu-175	B	B	*
123	Lu-175	B	C	*
124	Lu-175	C	C	*
125	Lu-175	B	D	**
125.1	Lu-175	C	D	***
126	Cu (cold)	A	D	****
126.1	Cu (cold)	A	D	****
126.2	Cu (cold)	A	C	***
126.3	Cu (cold)	A	D	***
126.4	Cu (cold)	A	D	***
126.5	Cu (cold)	A	B	***
127	Lu-175	A	D	***
127.1	Lu-175	A	D	****
127.2	Lu-175	A	D	****
127.3	Cu (cold)	A	D	****
127.4	Lu-175	A	D	****
127.5	Lu-175	A	C	****
127.6	Lu-175	A	A	****
127.7	Lu-175	A	D	****

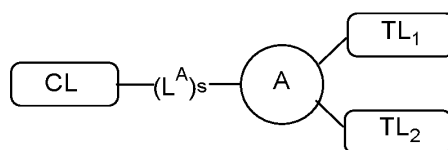
Conjugates Tested Comprising a compound and, when indicated, a chelated metal		CAIX KD	CAXII KD	Ratio (CAXII/CAIX)
Compound	Chelated Metal			
127.8	Lu-175	A	D	****
127.9	Lu-175	A	D	****
128	Lu-175	A	D	***
128.1	Lu-175	A	D	****
129	Lu-175	B	D	***
129.1	Lu-175	A	D	****
129.2	Lu-175	A	D	****
129.3	Lu-175	A	D	****
129.4	None	A	D	****
129.5	Lu-175	A	D	****
129.6	Lu-175	A	D	****
129.7	Lu-175	A	D	****
130	None	A	C	***
131	Lu-175	A	C	****
131.1	None	A	A	*
131.2	None	A	A	**
131.3	Lu-175	A	A	****
131.4	None	A	A	*
131.5	Lu-175	A	A	*
131.6	Lu-175	A	B	****
131.7	Lu-175	A	B	****
132	Lu-175	A	B	*
133	Lu-175	A	D	****
134	Lu-175	A	D	****
135	Lu-175	A	D	****
136	Lu-175	A	D	****

CAIX KD (nM)	CAXII KD (nM)	Ratio (CAXII/CAIX)
0 < A ≤ 1	0 < A ≤ 1	1 < * ≤ 5
1 < B ≤ 2.5	1 < B ≤ 2.5	5 < ** ≤ 10
2.5 < C ≤ 10	2.5 < C ≤ 10	10 < *** ≤ 50
10 < D	10 < D	50 < ****
ND: not determined	ND: not determined	

CLAIMS

WHAT IS CLAIMED:

1. A conjugate of Formula (A), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (A);

wherein:

TL₁ represents a 1st targeting moiety that binds to carbonic anhydrase IX;

TL₂ represents a 2nd targeting moiety that binds to carbonic anhydrase IX;

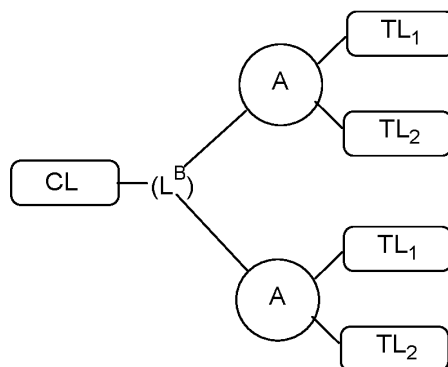
L^A represents a linker;

s is 0 or 1;

Ring A is an optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; and

CL represents a metal chelator.

2. A conjugate of Formula (A'), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (A');

wherein:

each TL₁ independently represents a 1st targeting moiety that binds to carbonic anhydrase IX;

each TL₂ independently represents a 2nd targeting moiety that binds to carbonic anhydrase IX;

L^B represents a linker; and

each Ring A is independently an optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; and

CL represents a metal chelator.

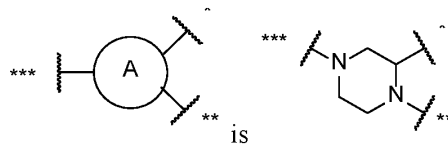
3. The conjugate of claim 1 or 2, wherein:

Ring A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R; and

each R is independently halogen, -CN, -OH, -SF₅, -SH, -S(=O)C₁-C₃alkyl, -S(=O)₂C₁-C₃alkyl, -

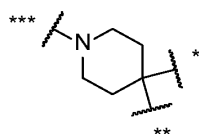
S(=O)₂NH₂, -S(=O)₂NHC₁-C₃alkyl, -S(=O)₂N(C₁-C₃alkyl)₂, -NH₂, -NHC₁-C₃alkyl, -N(C₁-C₃alkyl)₂, -

or two R on the same atom form an oxo.



-
- or

-
- The figure shows two chemical structures. On the left is the structure of poly(2-vinylpyridine), consisting of a central circle labeled 'A' with four bonds extending from it: one to the left labeled '***', one to the right labeled '**', and two to the top and bottom labeled 'n'. On the right is the structure of poly(2-vinylpyridine-co-vinylcarbazole), which is a bicyclic system with two nitrogen atoms, labeled with '***' and '**' at the top and bottom, and 'n' at the right side.



- $$\text{---W}^1\text{---X}^1\text{---A}^1\text{---T}^1\text{---B}^1\text{---S}^1\text{---Y}^1\text{---}\textcircled{\text{C}^1}\text{---}(\text{R}^{12})_n$$

wherein:

B¹ is absent, C₁-C₁₀alkylene, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms in the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, -NR¹¹-;

S¹ is absent or C₁-C₃alkylene optionally substituted with one or more R and wherein one or two carbon atoms of the C₁-C₃alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR¹¹-;

Y¹ is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR¹¹-, -C(=O)-, -C(=O)NR¹¹-, -NR¹¹C(=O)-, -S(=O)₂NR¹¹-, or -NR¹¹S(=O)₂;

R¹¹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

Ring C¹ is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R¹² is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl,

heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

n is 0, 1, 2, 3, 4, 5, or 6;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R;

L is absent or C₁-C₃alkylene optionally substituted with one or more R; and

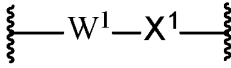
each R is independently halogen, -CN, -OH, -SF₅, -SH, -S(=O)C₁-C₃alkyl, -S(=O)₂C₁-C₃alkyl, -S(=O)₂NH₂, -S(=O)₂NHC₁-C₃alkyl, -S(=O)₂N(C₁-C₃alkyl)₂, -NH₂, -NHC₁-C₃alkyl, -N(C₁-C₃alkyl)₂, -C(=O)C₁-C₃alkyl, -C(=O)OH, -C(=O)OC₁-C₃alkyl, -C(=O)NH₂, -C(=O)NHC₁-C₃alkyl, -C(=O)N(C₁-C₃alkyl)₂, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃haloalkyl, C₁-C₃haloalkoxy, C₁-C₃hydroxyalkyl, C₁-C₃aminoalkyl, C₁-C₃heteroalkyl, C₃-C₆cycloalkyl, or 3- to 6-membered heterocycloalkyl;

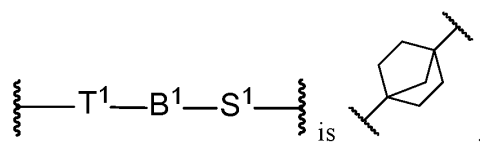
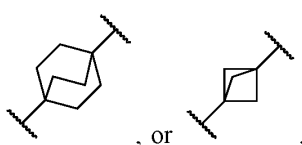
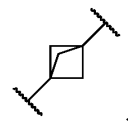
or two R on the same atom form an oxo;

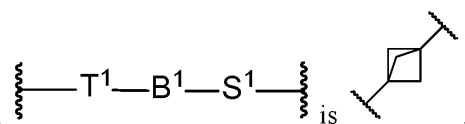
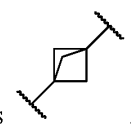
or two R on the same or different atoms are taken together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

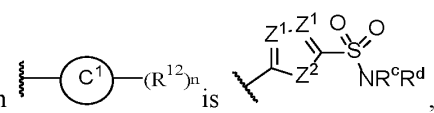
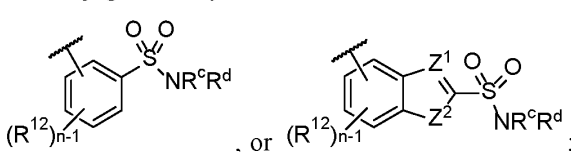
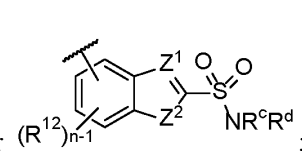
7. The conjugate of claim 6, wherein W¹ is absent, -C(=O)-, or -C(=O)NR¹¹-.

8. The conjugate of claim 6 or 7, wherein X¹ is C₁-C₄alkylene.

9. The conjugate of claim 6, wherein  is , , , , , , , ,

19. The conjugate of any one of claims 12-18 wherein  is  , or  .

20. The conjugate of any one of claims 12-19, wherein  is  .
21. The conjugate of any one of claims 6-20, wherein Y¹ is absent, -O-, -S-, -S(=O)₂-, -C(=O)NR¹¹-, or -NR¹¹C(=O)-.
22. The conjugate of any one of claims 6-21, wherein Ring C¹ is heteroaryl or phenyl.
23. The conjugate of any one of claims 6-21, wherein Ring C¹ is monocyclic heteroaryl.
24. The conjugate of any one of claims 6-21, wherein Ring C¹ is bicyclic heteroaryl.

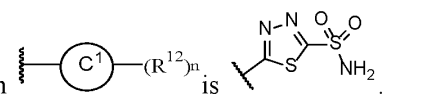
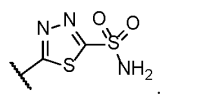
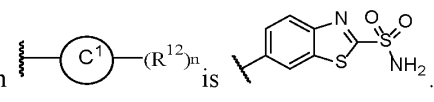
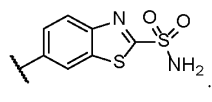
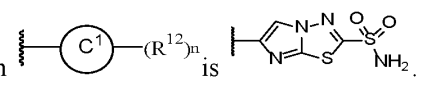
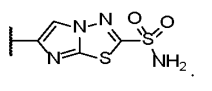
25. The conjugate of any one of claims 6-21, wherein  is  , or  ;

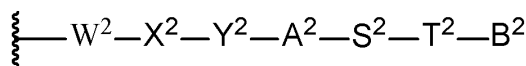
wherein each Z¹ is independently -N- or -CR^{12'}-;

Z² is -O-, -S-, or -NR^{12''}-;

each R^{12'} is independently hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, cycloalkyl, or heterocycloalkyl; and

R^{12''} is hydrogen, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, cycloalkyl, or heterocycloalkyl.

26. The conjugate of any one of claims 6-21, wherein  is  .
27. The conjugate of any one of claims 6-21, wherein  is  .
28. The conjugate of any one of claims 6-21, wherein  is  .
29. The conjugate of any one of claims 1-28, wherein TL₂ is of Formula (IIA):



Formula (IIA);

wherein:

W² is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂;

X² is absent or C₁-C₁₀alkylene optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms of the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR²¹-;

Y² is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂;

A² is absent, C₁-C₁₀alkylene, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²²;

each R²² is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl,

heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

S² is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂;

T² is absent or C₁-C₁₀alkylene optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms of the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR²¹-;

R²¹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

(i) B² is absent;

or

(ii) B² is -N(R²³)₂;

each R²³ is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

or

(iii) B² is -CF₃;

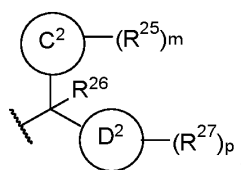
or

(iv) B² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²⁴;

each R²⁴ is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl,

heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

or



(v) B² is

Ring C² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R²⁵ is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

m is 0, 1, 2, 3, or 4;

R²⁶ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

Ring D² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R²⁷ is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

p is 0, 1, 2, 3, or 4;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R;

L is absent or C₁-C₃alkylene optionally substituted with one or more R; and

each R is independently halogen, -CN, -OH, -SF₅, -SH, -S(=O)C₁-C₃alkyl, -S(=O)₂C₁-C₃alkyl, -S(=O)₂NH₂, -S(=O)₂NHC₁-C₃alkyl, -S(=O)₂N(C₁-C₃alkyl)₂, -NH₂, -NHC₁-C₃alkyl, -N(C₁-C₃alkyl)₂, -C(=O)C₁-C₃alkyl, -C(=O)OH, -C(=O)OC₁-C₃alkyl, -C(=O)NH₂, -C(=O)NHC₁-C₃alkyl, -C(=O)N(C₁-C₃alkyl)₂, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃haloalkyl, C₁-C₃haloalkoxy, C₁-C₃hydroxyalkyl, C₁-C₃aminoalkyl, C₁-C₃heteroalkyl, C₃-C₆cycloalkyl, or 3- to 6-membered heterocycloalkyl;

or two R on the same atom form an oxo;

or two R on the same or different atoms are taken together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

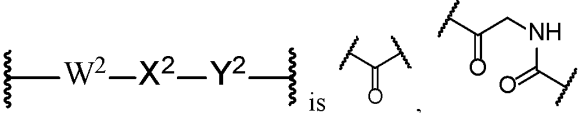
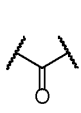
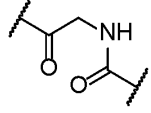
30. The conjugate of claim 29, wherein W² is absent, -C(=O)-, or -NR²¹C(=O)-.

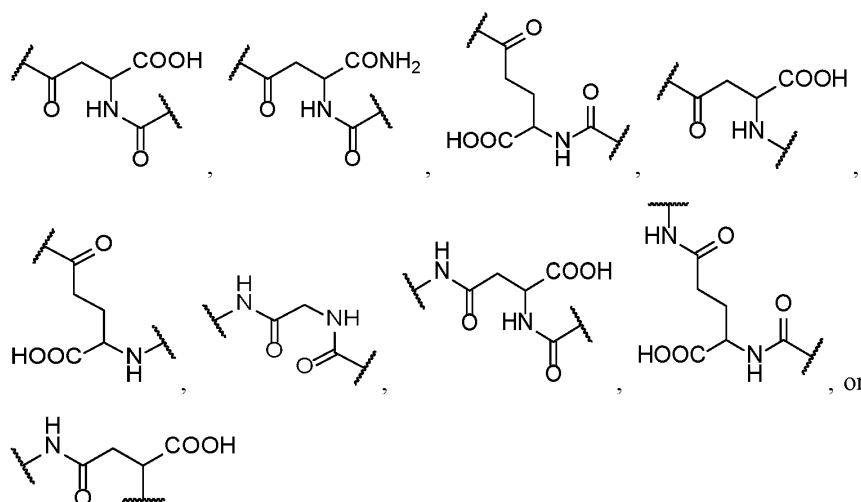
31. The conjugate of claim 29 or 30, wherein X² is C₁-C₄alkylene optionally substituted with one or more R.

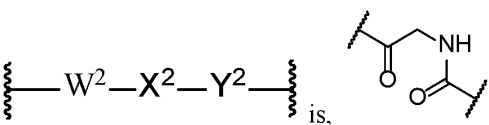
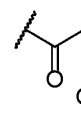
32. The conjugate of any one of claims 29-31, wherein X² is -CH₂-.

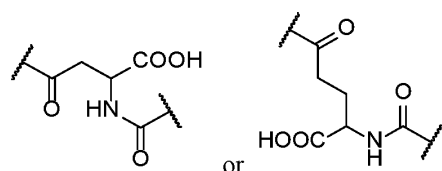
33. The conjugate of any one of claims 29-32, wherein Y² is absent, -NR²¹-, or -NR²¹C(=O)-.

34. The conjugate of any one of claims 29-33, wherein Y² is -NR²¹C(=O)-.

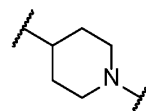
35. The conjugate of claim 29, wherein  is , .



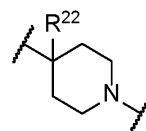
36. The conjugate of claim 29, wherein  is, ,



37. The conjugate of any one of claims 29-36, wherein A^2 is C_1 - C_6 alkylene optionally substituted with one or more R^{22} .
38. The conjugate of any one of claims 29-36, wherein A^2 is heterocycloalkyl optionally substituted with one or more R^{22} .
39. The conjugate of any one of claims 29-36, wherein A^2 is pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl, each optionally substituted with one or more R^{22} .
40. The conjugate of any one of claims 29-36, wherein A^2 is piperidinyl optionally substituted with one or more R^{22} .



41. The conjugate of any one of claims 29-36, wherein A^2 is optionally substituted with one or more R^{22} .

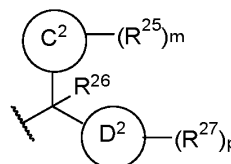


42. The conjugate of any one of claims 29-36, wherein A^2 is
43. The conjugate of any one of claims 29-42, wherein each R^{22} is independently $-C(=O)OR^b$ or $-C(=O)NR^cR^d$.
44. The conjugate of any one of claims 29-43, wherein each R^{22} is independently $-C(=O)NR^cR^d$.
45. The conjugate of any one of claims 29-44, wherein S^2 is absent, $-NR^{21}-$, $-C(=O)-$, or $-NR^{21}C(=O)-$.
46. The conjugate of any one of claims 29-45, wherein T^2 is absent or C_1 - C_6 alkylene optionally substituted with one or more R .

47. The conjugate of claim 45 or 46, wherein $\text{---}S^2\text{---}T^2\text{---}$ is
-

48. The conjugate of any one of claims 45-47, wherein $\text{---}S^2\text{---}T^2\text{---}$ is
-
- or
-

49. The conjugate of any one of claims 29-48, wherein B² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²⁴.
50. The conjugate of any one of claims 29-49, wherein each R²⁴ is independently halogen, -OH, C₁-C₆alkyl, or C₁-C₆haloalkyl.



51. The conjugate of any one of claims 29-48, wherein B² is wherein:

Ring C² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R²⁵ is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

m is 0, 1, 2, 3, or 4;

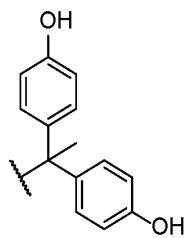
R²⁶ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

Ring D² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

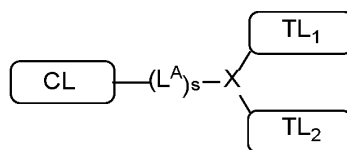
each R²⁷ is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

and

p is 0, 1, 2, 3, or 4.



52. The conjugate of any one of claims 29-48, wherein B² is
53. A conjugate of Formula (B), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (B);

wherein:

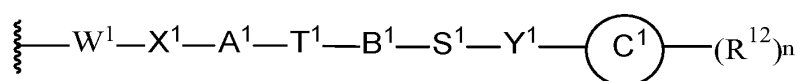
L^A represents a linker;

s is 0 or 1;

CL represents a metal chelator;

X is N, optionally substituted CH, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

TL_1 is of Formula (IB):



Formula (IB);

wherein:

W^1 is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR¹¹-, -C(=O)-, -C(=O)NR¹¹-, -NR¹¹C(=O)-, -S(=O)₂NR¹¹-, or -NR¹¹S(=O)₂;

X^1 is C₁-C₁₀alkylene optionally substituted with one or more R and wherein one, two, three, or four carbon atoms of the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR¹¹-;

A^1 is absent, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R;

T^1 is absent or C₁-C₃alkylene optionally substituted with one or more R and wherein one carbon atom of the C₁-C₃alkylene is optionally replaced with -C(=O)-, -S-, -S(=O)-, -S(=O)₂-, -O-, -NR¹¹-;

B^1 is cycloalkyl, heterocycloalkyl, or aryl, wherein the cycloalkyl, heterocycloalkyl, and aryl is optionally substituted with one or more R; or

B^1 is heteroaryl substituted with one or more R;

S^1 is absent or C₁-C₃alkylene optionally substituted with one or more R and wherein one or two carbon atoms of the C₁-C₃alkylene are optionally replaced with -C(=O)-, -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR¹¹-;

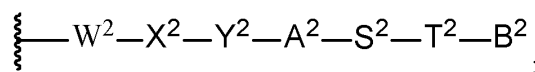
Y^1 is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR¹¹-, -C(=O)-, -C(=O)NR¹¹-, -NR¹¹C(=O)-, -S(=O)₂NR¹¹-, or -NR¹¹S(=O)₂;

R¹¹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

Ring C¹ is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R¹² is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl,

C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R; n is 0, 1, 2, 3, 4, 5, or 6; TL₂ is of Formula (IIB):



Formula (IIB);

wherein:

W² is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂;

X² is absent or C₁-C₁₀alkylene optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms of the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR²¹-;

Y² is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂;

A² is absent, C₁-C₁₀alkylene, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²²;

each R²² is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

S² is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂;

T² is absent or C₁-C₁₀alkylene optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms of the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR²¹-;

R²¹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

(i) B² is absent;

or

(ii) B² is -N(R²³)₂;

each R²³ is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

or

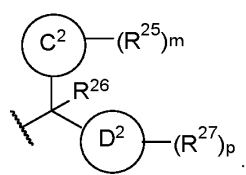
(iii) B² is -CF₃;

or

(iv) B² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²⁴;

each R²⁴ is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

or



(v) B² is

Ring C² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R²⁵ is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

m is 0, 1, 2, 3, or 4;

R²⁶ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

Ring D² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R²⁷ is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

p is 0, 1, 2, 3, or 4;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-

heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R;

L is absent or C₁-C₃alkylene optionally substituted with one or more R; and

each R is independently halogen, -CN, -OH, -SF₅, -SH, -S(=O)C₁-C₃alkyl, -S(=O)₂C₁-C₃alkyl, -S(=O)₂NH₂, -S(=O)₂NHC₁-C₃alkyl, -S(=O)₂N(C₁-C₃alkyl)₂, -NH₂, -NHC₁-C₃alkyl, -N(C₁-C₃alkyl)₂, -C(=O)C₁-C₃alkyl, -C(=O)OH, -C(=O)OC₁-C₃alkyl, -C(=O)NH₂, -C(=O)NHC₁-C₃alkyl, -C(=O)N(C₁-C₃alkyl)₂, C₁-C₃alkyl, C₁-C₃alkoxy, C₁-C₃haloalkyl, C₁-C₃haloalkoxy, C₁-C₃hydroxyalkyl, C₁-C₃aminoalkyl, C₁-C₃heteroalkyl, C₃-C₆cycloalkyl, or 3- to 6-membered heterocycloalkyl;

or two R on the same atom form an oxo;

or two R on the same or different atoms are taken together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

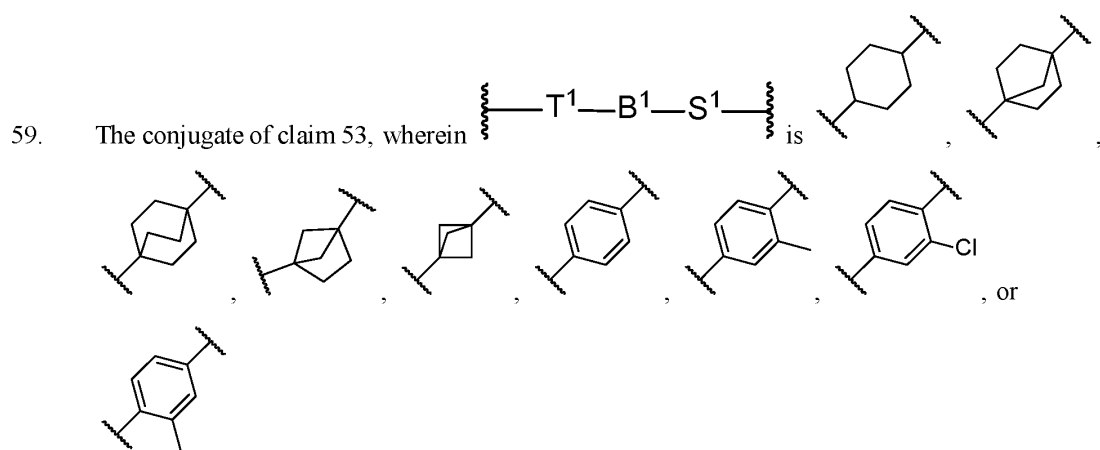
54. The conjugate of claim 53, wherein T¹ is absent or C₁-C₃alkylene.

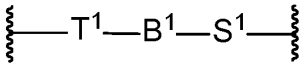
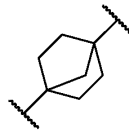
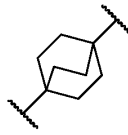
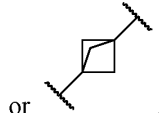
55. The conjugate of claim 53 or 54, wherein B¹ is cycloalkyl optionally substituted with one or more R.

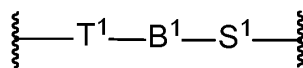
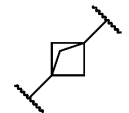
56. The conjugate of any one of claims 53-55, wherein B¹ is bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, or bicyclo[2.1.1]hexanyl.

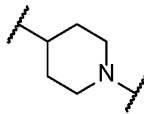
57. The conjugate of any one of claims 53-55, wherein B¹ is bicyclo[1.1.1]pentanyl.

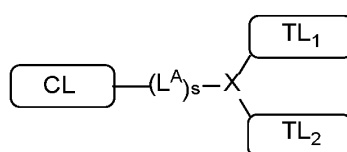
58. The conjugate of any one of claims 53-57, wherein S¹ is absent.



60. The conjugate of claim 53, wherein  is , ,
or .

61. The conjugate of claim 53, wherein  is .
62. The conjugate of any one of claims 53-61, wherein A² is C₁-C₆alkylene optionally substituted with one or more R²².
63. The conjugate of any one of claims 53-61, wherein A² is heterocycloalkyl optionally substituted with one or more R²².
64. The conjugate of any one of claims 53-61, wherein A² is pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl, each optionally substituted with one or more R²².
65. The conjugate of any one of claims 53-61, wherein A² is piperidinyl optionally substituted with one or more R²².

66. The conjugate of any one of claims 53-61, wherein A² is  optionally substituted with one or more R²².
67. The conjugate of any one of claims 53-66, wherein each R²² is independently -C(=O)OR^b or -C(=O)NR^cR^d.
68. The conjugate of any one of claims 53-67, wherein each R²² is independently -C(=O)NR^cR^d.
69. A conjugate of Formula (C), or a pharmaceutically acceptable salt or stereoisomer thereof:



Formula (C);

wherein:

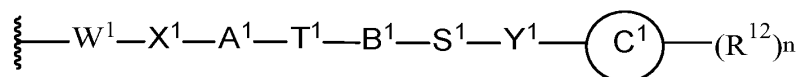
L^A represents a linker;

s is 0 or 1;

CL represents a metal chelator;

X is N, optionally substituted CH, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

TL₁ is of Formula (IC):



Formula (IC);

wherein:

W¹ is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR¹¹-, -C(=O)-, -C(=O)NR¹¹-, -NR¹¹C(=O)-, -S(=O)₂NR¹¹-, or -NR¹¹S(=O)₂;

X¹ is C₁-C₁₀alkylene optionally substituted with one or more R and wherein one, two, three, or four carbon atoms of the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR¹¹-;

A¹ is absent, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R;

T¹ is absent or C₁-C₃alkylene optionally substituted with one or more R and wherein one carbon atom of the C₁-C₃alkylene is optionally replaced with -C(=O)-, -S-, -S(=O)-, -S(=O)₂-, -O-, -NR¹¹-;

B¹ is absent, C₁-C₁₀alkylene, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the alkylene, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms in the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, -NR¹¹-;

S¹ is absent or C₁-C₃alkylene optionally substituted with one or more R and wherein one or two carbon atoms of the C₁-C₃alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR¹¹-;

Y¹ is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR¹¹-, -C(=O)-, -C(=O)NR¹¹-, -NR¹¹C(=O)-, -S(=O)₂NR¹¹-, or -NR¹¹S(=O)₂;

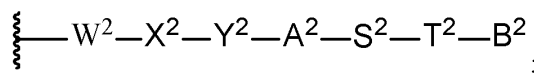
R¹¹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

Ring C¹ is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R¹² is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

n is 0, 1, 2, 3, 4, 5, or 6;

TL₂ is of Formula (IIC):



Formula (IIC);

wherein:

W² is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂;

X² is absent or C₁-C₁₀alkylene optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms of the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR²¹-;

Y² is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂-;

A² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²²;

each R²² is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

S² is absent, -O-, -S-, -S(=O)-, -S(=O)₂-, -NR²¹-, -C(=O)-, -C(=O)NR²¹-, -NR²¹C(=O)-, -S(=O)₂NR²¹-, or -NR²¹S(=O)₂-;

T² is absent or C₁-C₁₀alkylene optionally substituted with one or more R, and wherein one, two, three, or four carbon atoms of the C₁-C₁₀alkylene are optionally replaced with -S-, -S(=O)-, -S(=O)₂-, -O-, or -NR²¹-;

R²¹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

(i) B² is absent;

or

(ii) B² is -N(R²³)₂;

each R²³ is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

or

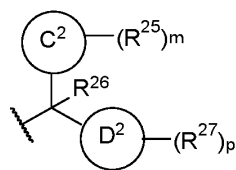
(iii) B² is -CF₃;

or

(iv) B² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R²⁴;

each R²⁴ is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

or



(v) B² is ;

Ring C² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R²⁵ is independently halogen, -CN, -NO₂, -OH, -ORᵃ, -OC(=O)Rᵃ, -OC(=O)ORᵇ, -OC(=O)NRᶜRᵈ, -SF₅, -SH, -SRᵃ, -S(=O)Rᵃ, -S(=O)₂Rᵃ, -S(=O)₂NRᶜRᵈ, -NRᶜRᵈ, -NRᵇC(=O)NRᶜRᵈ, -NRᵇC(=O)Rᵃ, -NRᵇC(=O)ORᵇ, -NRᵇS(=O)₂Rᵃ, -C(=O)Rᵃ, -C(=O)ORᵇ, -C(=O)NRᶜRᵈ, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

m is 0, 1, 2, 3, or 4;

R²⁶ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

Ring D² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R²⁷ is independently halogen, -CN, -NO₂, -OH, -ORᵃ, -OC(=O)Rᵃ, -OC(=O)ORᵇ, -OC(=O)NRᶜRᵈ, -SF₅, -SH, -SRᵃ, -S(=O)Rᵃ, -S(=O)₂Rᵃ, -S(=O)₂NRᶜRᵈ, -NRᶜRᵈ, -NRᵇC(=O)NRᶜRᵈ, -NRᵇC(=O)Rᵃ, -NRᵇC(=O)ORᵇ, -NRᵇS(=O)₂Rᵃ, -C(=O)Rᵃ, -C(=O)ORᵇ, -C(=O)NRᶜRᵈ, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

p is 0, 1, 2, 3, or 4;

each Rᵃ is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

each Rᵇ is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

Rᶜ and Rᵈ are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, -L-cycloalkyl, -L-heterocycloalkyl, -L-aryl, or -L-heteroaryl, wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more R;

or Rᶜ and Rᵈ are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more R;

L is absent or C₁-C₃alkylene optionally substituted with one or more R; and

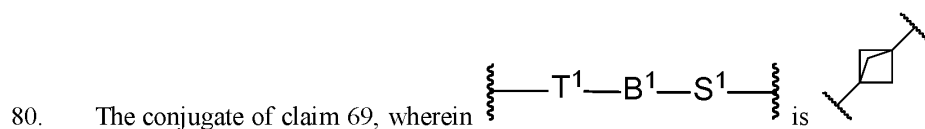
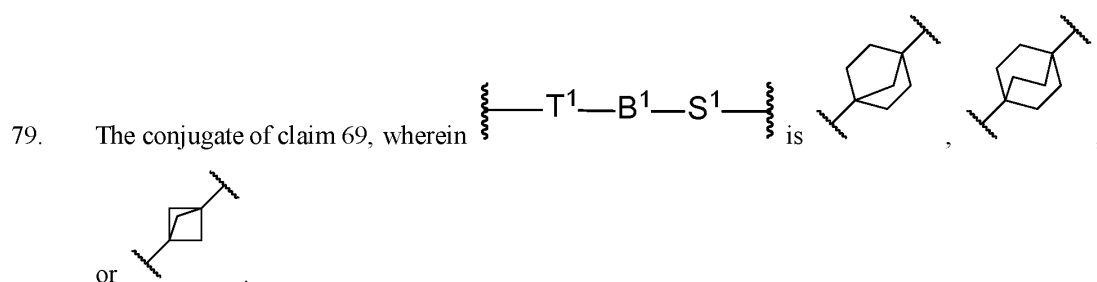
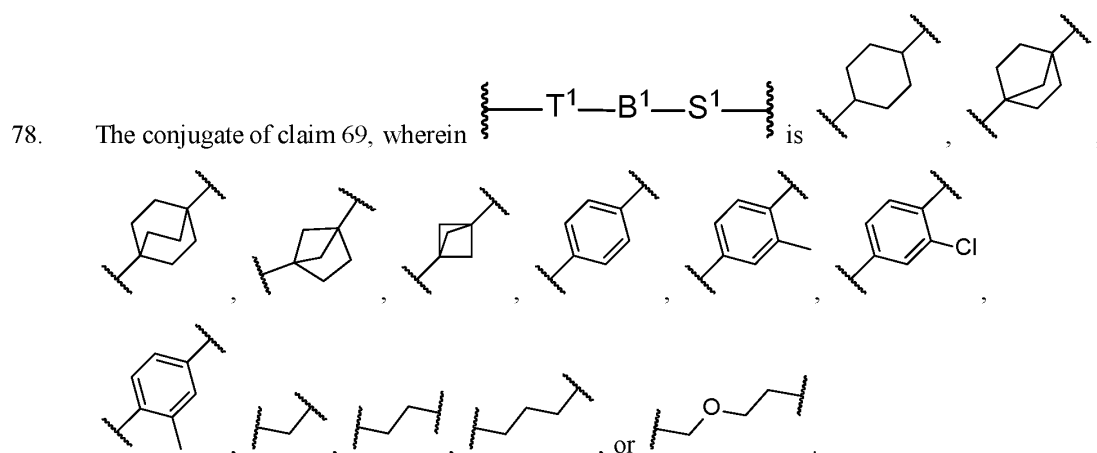
each R is independently halogen, -CN, -OH, -SF₅, -SH, -S(=O)C₁-C₃alkyl, -S(=O)₂C₁-C₃alkyl, -S(=O)₂NH₂, -S(=O)₂NHC₁-C₃alkyl, -S(=O)₂N(C₁-C₃alkyl)₂, -NH₂, -NHC₁-C₃alkyl, -N(C₁-C₃alkyl)₂, -

$C(=O)C_1-C_3alkyl$, $-C(=O)OH$, $-C(=O)OC_1-C_3alkyl$, $-C(=O)NH_2$, $-C(=O)NHC_1-C_3alkyl$, $-C(=O)N(C_1-C_3alkyl)_2$, C_1-C_3alkyl , $C_1-C_3alkoxy$, $C_1-C_3haloalkyl$, $C_1-C_3haloalkoxy$, $C_1-C_3hydroxyalkyl$, $C_1-C_3aminoalkyl$, $C_1-C_3heteroalkyl$, $C_3-C_6cycloalkyl$, or 3- to 6-membered heterocycloalkyl;

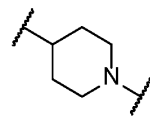
or two R on the same atom form an oxo;

or two R on the same or different atoms are taken together to form a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

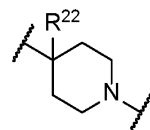
70. The conjugate of claim 69, wherein T^1 is absent.
71. The conjugate of claim 69 or 70, wherein B^1 is $C_1-C_6alkylene$.
72. The conjugate of any one of claims 69-71, wherein B^1 is cycloalkyl optionally substituted with one or more R.
73. The conjugate of any one of claims 69-71, wherein B^1 is a monocyclic cycloalkyl optionally substituted with one or more R.
74. The conjugate of any one of claims 69-71, wherein B^1 is a bicyclic cycloalkyl optionally substituted with one or more R.
75. The conjugate of any one of claims 69-71, wherein B^1 is bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, or bicyclo[2.1.1]hexanyl.
76. The conjugate of any one of claims 69-71, wherein B^1 is bicyclo[1.1.1]pentanyl.
77. The conjugate of any one of claims 69-76, wherein S^1 is absent.



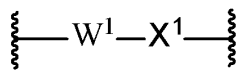
81. The conjugate of any one of claims 69-80, wherein A² is heterocycloalkyl optionally substituted with one or more R²².
82. The conjugate of any one of claims 69-80, wherein A² is pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl, each optionally substituted with one or more R²².
83. The conjugate of any one of claims 69-80, wherein A² is piperidinyl optionally substituted with one or more R²².

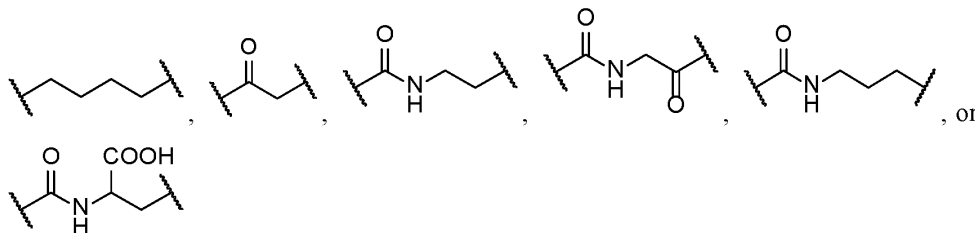


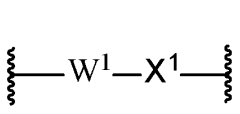
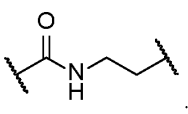
84. The conjugate of any one of claims 69-80, wherein A² is optionally substituted with one or more R²².

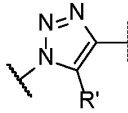
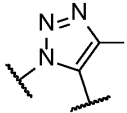


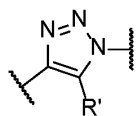
85. The conjugate of any one of claims 69-80, wherein A² is
86. The conjugate of any one of claims 69-85, wherein each R²² is independently -C(=O)OR^b or -C(=O)NR^cR^d.
87. The conjugate of any one of claims 69-86, wherein each R²² is independently -C(=O)NR^cR^d.
88. The conjugate of any one of claims 53-87, wherein X is CH.
89. The conjugate of any one of claims 53-87, wherein X is optionally substituted heterocycloalkyl.
90. The conjugate of any one of claims 53-89, wherein W¹ is absent, -C(=O)-, or -C(=O)NR¹¹-.
91. The conjugate of any one of claims 53-90, wherein X¹ is C₁-C₄alkylene.

92. The conjugate of any one of claims 53-91, wherein  is .



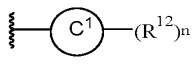
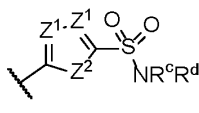
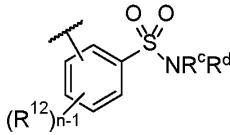
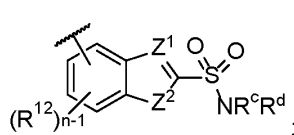
93. The conjugate of any one of claims 53-92, wherein  is .
94. The conjugate of any one of claims 53-93, wherein A¹ is heteroaryl optionally substituted with one or more R.
95. The conjugate of any one of claims 53-93, wherein A¹ is triazolyl optionally substituted with one or more R.

96. The conjugate of any one of claims 53-92, wherein A¹ is , , or



wherein R' is hydrogen or R.

97. The conjugate of any one of claims 53-96, wherein T¹ is absent or C₁-C₃alkylene.
 98. The conjugate of any one of claims 53-97, wherein Y¹ is absent, -O-, -S-, -S(=O)₂-, -C(=O)NR¹¹-, or -NR¹¹C(=O)-.
 99. The conjugate of any one of claims 53-98, wherein Ring C¹ is heteroaryl or phenyl.
 100. The conjugate of any one of claims 53-98, wherein Ring C¹ is monocyclic heteroaryl.
 101. The conjugate of any one of claims 53-98, wherein Ring C¹ is bicyclic heteroaryl.

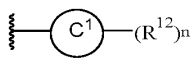
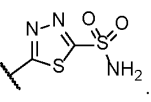
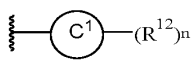
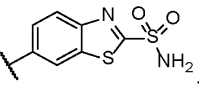
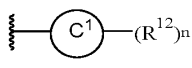
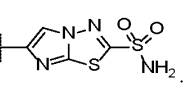
102. The conjugate of any one of claims 53-98, wherein  is , , or ;

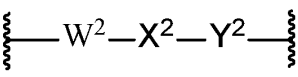
wherein each Z¹ is independently -N- or -CR^{12'}-;

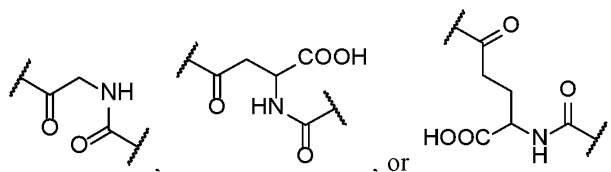
Z² is -O-, -S-, or -NR^{12''}-;

each R^{12'} is independently hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, cycloalkyl, or heterocycloalkyl; and

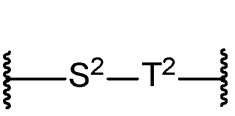
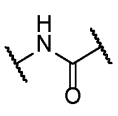
R^{12''} is hydrogen, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, cycloalkyl, or heterocycloalkyl.

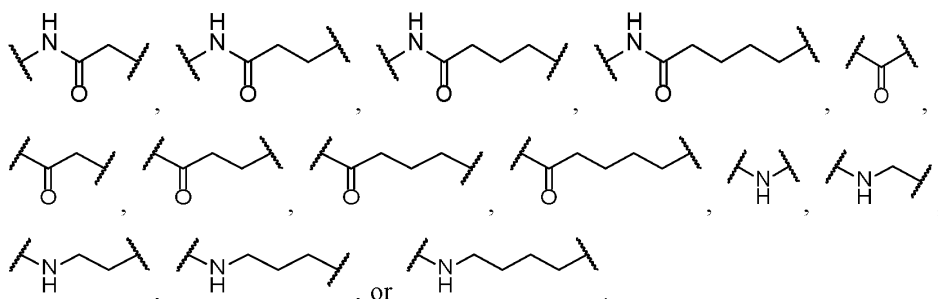
103. The conjugate of any one of claims 53-98, wherein  is .
104. The conjugate of any one of claims 53-98, wherein  is .
105. The conjugate of any one of claims 53-98, wherein  is .
106. The conjugate of any one of claims 53-105, wherein W² is absent, -C(=O)-, or -NR²¹C(=O)-.
 107. The conjugate of any one of claims 53-106, wherein X² is C₁-C₄alkylene optionally substituted with one or more R.
 108. The conjugate of any one of claims 53-107, wherein X² is -CH₂-.
 109. The conjugate of any one of claims 53-108, wherein Y² is absent, -NR²¹-, or -NR²¹C(=O)-.
 110. The conjugate of any one of claims 53-109, wherein Y² is -NR²¹C(=O)-.

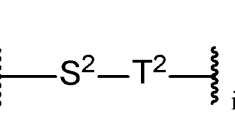
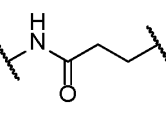
111. The conjugate of any one of claims 53-110, wherein  is,

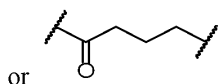


112. The conjugate of any one of claims 53-111, wherein S^2 is absent, $-NR^{21}-$, $-C(=O)-$, or $-NR^{21}C(=O)-$.
113. The conjugate of any one of claims 53-112, wherein T^2 is absent or C_1 - C_6 alkylene optionally substituted with one or more R.

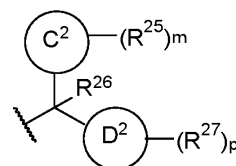
114. The conjugate of any one of claims 53-113, wherein  is .



115. The conjugate of any one of claims 53-114, wherein  is .



116. The conjugate of any one of claims 53-115, wherein B^2 is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally substituted with one or more R^{24} .
117. The conjugate of any one of claims 53-116, wherein each R^{24} is independently halogen, $-OH$, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl.



118. The conjugate of any one of claims 53-115, wherein B^2 is wherein:

Ring C^2 is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{25} is independently halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-SF_5$, $-SH$, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-$

NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

m is 0, 1, 2, 3, or 4;

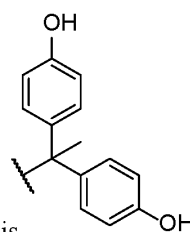
R²⁶ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₁-C₆heteroalkyl;

Ring D² is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

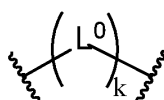
each R²⁷ is independently halogen, -CN, -NO₂, -OH, -OR^a, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -SF₅, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -NR^bS(=O)₂R^a, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R;

and

p is 0, 1, 2, 3, or 4.



119. The conjugate of any one of claims 53-115, wherein B² is
120. The conjugate of any one of claims 1-119, wherein s is 0.
121. The conjugate of any one of claims 1-119, wherein s is 1.
122. The conjugate of any one of claims 1-119 or 121, wherein the linker L^A has a structure of Formula (L-1)



Formula (L-1),

wherein:

each L⁰ is independently -O-, -NR^L-, -N(R^L)₂⁺-, -OP(=O)(OR^L)O-, -S-, -S(=O)-, -S(=O)₂-, =CH-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -NR^LC(=S)NR^L-, -CR^L=N-, -N=CR^L-, -NR^LS(=O)₂-, -S(=O)₂NR^L-, -C(=O)NR^LS(=O)₂-, -S(=O)₂NR^LC(=O)-, cycloalkylene, heterocycloalkylene, arylene, heteroarylene, C₁-C₃₀alkylene, C₂-C₃₀alkenylene, C₂-C₃₀alkynylene, C₁-C₃₀heteroalkylene, -(C₁-C₃₀alkylene)-O-, -O-(C₁-C₃₀alkylene)-, -(C₁-C₃₀alkylene)-NR^L-, -NR^L-(C₁-C₃₀alkylene)-, -(C₁-C₃₀alkylene)-N(R^L)₂⁺-, or -N(R^L)₂⁺-(C₁-C₃₀alkylene)-; wherein each cycloalkylene, heterocycloalkylene, arylene, heteroarylene, alkylene, alkenylene, alkynylene, and heteroalkylene is optionally independently substituted with one or more R;

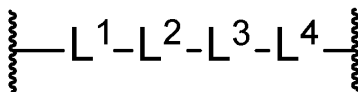
each R^L is independently hydrogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

k is 1-20; and

each R is independently halogen, -CN, -OH, -SF₅, -SH, -S(=O) C_1 - C_3 alkyl, -S(=O)₂ C_1 - C_3 alkyl, -S(=O)₂NH₂, -S(=O)₂NHC C_1 - C_3 alkyl, -S(=O)₂N(C_1 - C_3 alkyl)₂, -NH₂, -NHC C_1 - C_3 alkyl, -N(C_1 - C_3 alkyl)₂, -C(=O) C_1 - C_3 alkyl, -C(=O)OH, -C(=O)OC C_1 - C_3 alkyl, -C(=O)NH₂, -C(=O)NHC C_1 - C_3 alkyl, -C(=O)N(C_1 - C_3 alkyl)₂, C_1 - C_3 alkyl, C_1 - C_3 alkoxy, C_1 - C_3 haloalkyl, C_1 - C_3 haloalkoxy, C_1 - C_3 hydroxyalkyl, C_1 - C_3 aminoalkyl, C_1 - C_3 heteroalkyl, C_3 - C_6 cycloalkyl, or 3- to 6-membered heterocycloalkyl;

or two R on the same atom form an oxo.

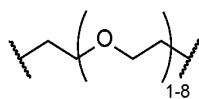
123. The conjugate of claim 122, wherein the linker L^A has a structure of Formula (L-1a),



Formula (L-1a);

wherein:

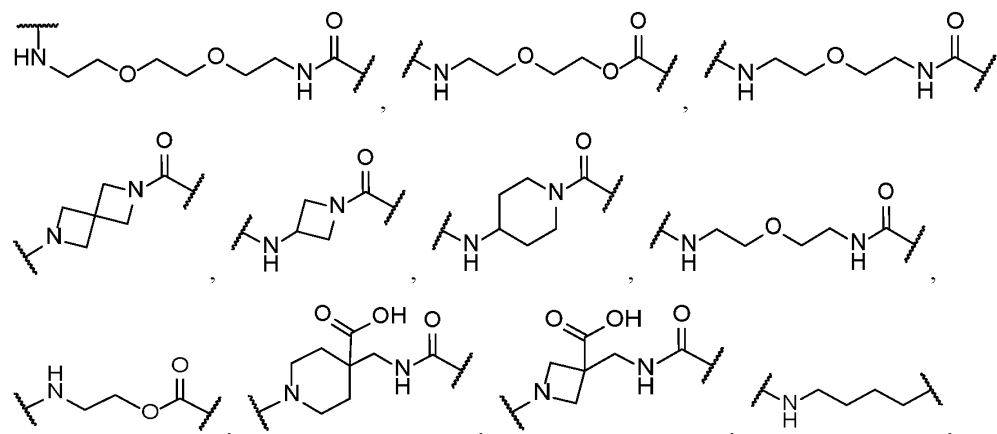
L^1 is absent, -O-, -NR^L-, -N(R^L)₂⁺-, -S-, -S(=O)-, -S(=O)₂-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -NR^LS(=O)₂-, -S(=O)₂NR^L-, -C(=O)NR^LS(=O)₂-, or -S(=O)₂NR^LC(=O)-;

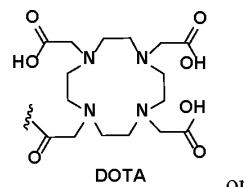
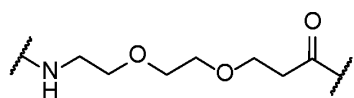
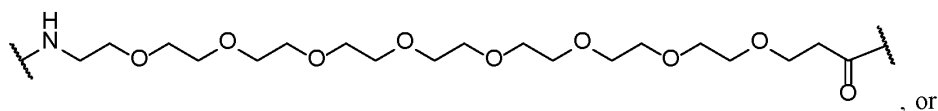
L^2 is ₁₋₈, C_1 - C_{10} alkylene, or heterocycloalkylene optionally substituted with one or more R;

L^3 is absent or C_1 - C_{10} alkylene; and

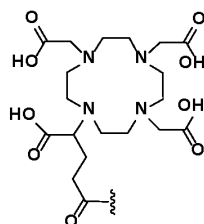
L^4 is absent, -O-, -NR^L-, -N(R^L)₂⁺-, -S-, -S(=O)-, -S(=O)₂-, -C(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)O-, -C(=O)NR^L-, -NR^LC(=O)-, -OC(=O)NR^L-, -NR^LC(=O)O-, -NR^LC(=O)NR^L-, -NR^LS(=O)₂-, -S(=O)₂NR^L-, -C(=O)NR^LS(=O)₂-, or -S(=O)₂NR^LC(=O)-.

124. The conjugate of any one of claims 1-119 or 121-123, wherein the linker L^A is





125. The conjugate of claim 124, wherein the metal chelator is



DOTA-GA

126. The conjugate of any one of claims 1-125, wherein the conjugate is found in table 1.
127. The conjugate of any one of claims 1-126, further comprising a radionuclide bound to the metal chelator to form a radiopharmaceutical conjugate.
128. The radiopharmaceutical conjugate of claim 127, wherein the radionuclide is an alpha particle-emitting radionuclide.
129. The radiopharmaceutical conjugate of claim 128, wherein the alpha particle-emitting radionuclide is Ac-225.
130. The radiopharmaceutical conjugate of claim 127, wherein the radionuclide is a beta particle-emitting radionuclide.
131. The radiopharmaceutical conjugate of claim 130, wherein the beta particle-emitting radionuclide is lutetium-177.
132. The radiopharmaceutical conjugate of claim 127, wherein the radionuclide is a positron-emitting radionuclide.
133. A conjugate having a structure of Formula (AC), (AC'), (BC), (BC'), (CC), or (CC'), wherein each of the formula is described herein.
134. A pharmaceutical composition comprising a radiopharmaceutical conjugate of any one of claims 128-133, and a pharmaceutically acceptable excipient or carrier.
135. A method of diagnosing or imaging a disease or disorder in a subject in need thereof, the method comprising administering to the subject the radiopharmaceutical conjugate of any one of claims 128-133, or the pharmaceutical composition of claim 134.

136. A method of treating a disease or disorder in a subject in need thereof, the method comprising administering to the subject the radiopharmaceutical conjugate of any one of claims 128-133, or the pharmaceutical composition of claim 134.
137. The method of claim 135 or 136, wherein the disease or disorder is a cancer.
138. The method of claim 137, wherein the cancer is hypoxic.
139. The method of any one of claim 137 or 138, wherein the cancer is cell renal cell carcinoma (ccRCC).