INTEGRIN-TARGETING RADIOPHARMACEUTICALS AND USES THEREOF

1. BACKGROUND

[0001] In recent years, there has been a quickening in the pace of development of radiopharmaceuticals that target diagnostic biomarkers for use in targeted radionuclide imaging (TRI) and targeted radionuclide therapy (TRT). One of the most appealing benefits of TRI and TRT is the possibility for personalized medical care, optimized for patient and disease characteristics. Unlike conventional systemic chemotherapy, TRT allows radiation to be delivered directly to the targeted site of disease with potentially less toxicity from exposure of normal tissues.

[0002] Further improvements to disease treatment can be achieved by integrating imaging and therapy using diagnostic and therapeutic radiopharmaceuticals that access the same cellular structure and biologic process—that is, that share the same target—often referred to as theranostic pairs. The nuclear theranostic approach has sparked increasing interest and gained importance in parallel to the growth in molecular imaging and personalized medicine, helping to provide customized management for various diseases while improving patient selection, prediction of response and toxicity, and determination of prognosis but avoiding futile and costly diagnostic examinations.

[0003] Moreover, the availability of active and highly pure radiopharmaceuticals is essential for the development of nuclear medicine, including TRI and TRT. A variety of copper radionuclides have been used in the field of nuclear medicine, and they offer versatile choices for applications in radionuclide imaging (e.g., in radiotracers) and therapy.

[0004] Radionuclides can be used in personalized medicine, but their supply in quantity and quality for clinical applications represents a significant challenge. The use of specialty target "coins" (the often disk-like objects bearing a target metal that is bombarded with subatomic particles in order to produce radionuclides) that can produce radionuclide compositions having activity, at end of bombardment (EoB), end of production (EoP), end of synthesis (EoS – typically EoB + 2 hours), or at calibration, with high radionuclide purity is crucial for maximizing the potential of radiopharmaceuticals. Suitable target coin preparation and the

resulting quality of the produced radionuclide is one of the most important aspects in supply of medical grade radionuclides.

[0005] Development of the available diagnostic biomarkers for use in TRI and TRT is also an essential area of development. An important disease biomarker are integrins, a family of cell-adhesion molecules composed of two non-covalently linked heterodimeric α and β subunits. They mediate cell-to-cell and cell-to-extracellular matrix (ECM) interactions, providing adhesion and traction during cell movement. Integrins promote various signaling pathways that regulate diverse processes such as proliferation, migration, cell survival and differentiation. For this reason, their aberrant expression in cancer cells often favors the development of aggressive forms of malignancy.

[0006] Many studies have demonstrated that the αvβ6 integrin is absent or poorly expressed in healthy adult epithelia, but it is upregulated during embryogenesis, tissue repair, and carcinogenesis. It is involved in tumorigenesis and tumor progression (e.g. tumor invasion and metastasis). See. e.g., Transl Oncol. 2020 Jun; 13(6): 100773. In particular, αvβ6 has a role in mediating the epithelial-mesenchymal transition (EMT) of cancer. EMT is a highly conserved and fundamental process in which epithelial cells undergo morphogenetic transformation to escape from the rigid structural constraints provided by the tissue architecture and to adopt a phenotype more amenable to cell migration. EMT is characterized by the loss of cell adherence. αvβ6 promotes the invasiveness and aggressiveness of primary lesions, which subsequently lead to tumor metastasis and could be recognized as a biological hallmark of malignancy. It has been demonstrated that αvβ6 facilitates invasiveness and metastasis, also modulating cell surface proteolytic activity of metalloproteins (MMPs). (10.3390/cancers9090116; 10.1038/nrd.2015.10; 10.3390/cancers13071711; 10.1111/j.1365-2559.2004.01919.x; 10.1242/jcs.108.6.2241; 10.1158/2159-8290.CD-21-1059.

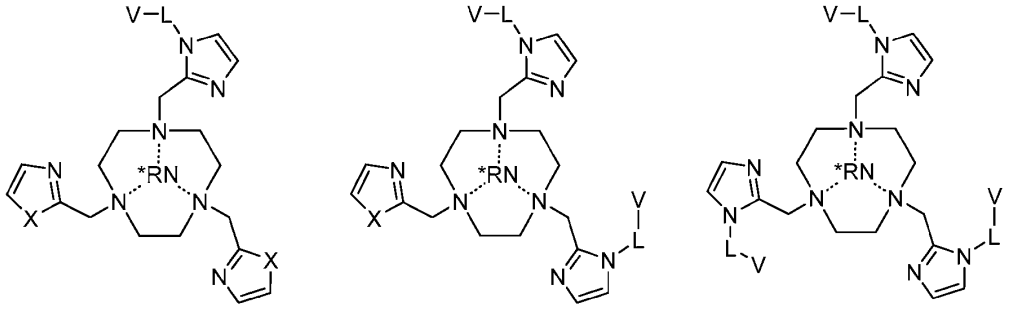
[0007] Integrin αvβ6 is an ideal target for treating aggressive types of cancer, such as pancreatic adenocarcinoma, lung adenocarcinoma, neck and head cancer, and squamous cell carcinoma (Fan D. et al. Front. Oncol., 2023 Volume 13). Inhibition of integrin αvβ6 also showed promising results in the treatment of idiopathic pulmonary fibroma (IPF) (Am J Respir Crit Care Med. 2022 Nov 1; 206(9): 1062–1063).

[0008] An object of the present disclosure is to provide compositions and methods that fully or in part overcome one or more of the issues recognized in the prior art encompassing radiopharmaceuticals, such as radiotracers and radio therapeutics, and their preparation and use in treating integrin associated cancers.

2. SUMMARY

[0009] The present disclosure relates to radioactive integrin-binding agents and their use in diagnosis and treatment of various diseases characterized by overexpression of integrin and subtypes of integrin.

[0010] In a first aspect of the present disclosure, a compound is provided, wherein the compound is of Formula I, II, or III:



(I) (II) (III)

or is a pharmaceutically acceptable salt thereof;

wherein:

*RN is an optionally present radionuclide;

each X is independently -S- or -NR^{a1}-; and

each R^{a1} is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group;

each V is a targeting moiety that binds to an integrin, such as $\alpha_v\beta_6$ integrin;

each L is independently a bond or a linking moiety;

[0011] In some embodiments, each X is -NR^{a1}-. In some embodiments, R^{a1} is hydrogen. In some embodiments, R^{a1} is an optionally substituted C_{1-6} aliphatic group.

[0012] In some embodiments, the radionuclide is selected from ^{61}Cu, ^{62}Cu, ^{64}Cu, and ^{67}Cu.

[0013] In a second aspect of the disclosure, a pharmaceutical composition is provided comprising a compound according to any one of the preceding embodiments and one or more pharmaceutically acceptable excipients.

[0014] In some embodiments, the compound is according to a compound set forth in Section 4.2.4 herein, wherein the compound comprises ^{61}Cu.

[0015] In some embodiments, the composition is characterized by one or more of:

an apparent molar activity of the compound of $\geq$ 3 MBq/nmol;

a radiochemical purity of $\geq$ 90%;

an activity concentration of $\geq$ 8 MBq/mL;

a radionuclidic purity at end of synthesis of $\geq$ 95%;

a radiocobalt radionuclidic purity at the end of synthesis of $\leq$ 0.05%; and

a ^{110m}Ag specific activity $\leq$ 0.1 Bq/g, a ^{108m}Ag specific activity $\leq$ 0.1 Bq/g, or a ^{109}Cd specific activity $\leq$ 0.1 Bq/g.

[0016] In some embodiments, the composition is characterized by an apparent molar activity of the compound of 35 MBq/nmol -2 GBq/nmol.

[0017] In some embodiments, the composition has a radiocobalt activity content at end of synthesis characterized by having a sum of radiocobalt of $\leq$ 0.05%.

[0018] In a third aspect, a method is provided for generating one or more images of a subject, the method comprising: administering to the subject an effective amount of a pharmaceutical composition according to a compound as provided herein the compound comprising a radionuclide suitable for generating an image; and generating one or more images of at least a part of the subject's body.

[0019] In a fourth aspect, a method is provided of detecting a disease in a subject, comprising:

(a) administering to a subject an effective amount of the pharmaceutical composition according to any of the provided embodiments;

(b) detecting the localization of the radionuclide; and

(c)determining the presence or absence of the disease based on the presence or absence of localization.

[0020] In a fifth aspect, a method is provided of determining the effect of cancer treatment on a subject afflicted with cancer comprising:

(a) administering to the subject an effective amount of a compound comprising a radionuclide according to a compound as provided herein, or a pharmaceutical composition comprising an effective amount of a compound comprising a radionuclide according to a compound as provided herein at an earlier time point and at a later time point;

(b) detecting the localization of the radionuclide at both the earlier time point and at a later time point; and

(c) determining the effect of the cancer treatment by comparing the amount of localization at the later time point to the amount of localization at the earlier time point.

[0021] In a sixth aspect, a method is provided of treating a disease in a patient in need thereof, comprising administering to the patient an effective amount of a compound as provided herein, or a pharmaceutical composition comprising a compound as provided herein.

[0022] In a seventh aspect, a theranostic method is provided comprising:

(a) administering to a subject an effective amount of a first compound comprising a ^{61}Cu radionuclide or a pharmaceutical composition comprising an effective amount of a first compound comprising a ^{61}Cu radionuclide;

(b) generating one or more images of the subject (e.g., of a certain region or part of the subject's body); and

(c) administering to the subject an effective amount of a second compound comprising a ^{67}Cu radionuclide or a pharmaceutical composition comprising an effective amount of a second compound comprising a ^{67}Cu radionuclide.

[0023] In some embodiments of the provided methods, the image is generated using positron emission tomography (PET), PET- computer tomography (PET-CT), or single-photon emission computerized tomography (SPECT).

[0024] In some embodiments of the provided methods, the disease is selected from cancers, inflammatory diseases, infectious diseases, and immune diseases. In some embodiments, the disease is cancer, and the cancer is selected from breast cancer (e.g., triple-negative breast cancer), pancreatic cancer, pancreatic adenocarcinoma, pancreatic ductal cancer (PDA), small intestine cancer, colon cancer, gastric cancer, rectal cancer, lung adenocarcinoma, lung cancer (e.g., non-small cell lung cancer), head and neck cancer, head and neck squamous cell carcinomas (HNSCCs), idiopathic pulmonary fibroma, ovarian cancer, hepatocellular carcinoma, epithelial cancer, esophageal cancer, hypopharynx cancer, nasopharynx cancer, larynx cancer, myeloma cells, bladder cancer, cholangiocellular carcinoma, clear cell renal carcinoma, neuroendocrine tumor, oncogenic osteomalacia, sarcoma, CUP (carcinoma of unknown primary), thymus carcinoma, desmoid tumors, glioma, astrocytoma, cervix carcinoma, and prostate cancer.

3. BRIEF DESCRIPTION OF THE DRAWINGS

[0025] These and other features, aspects, and advantages of the present disclosure will become better understood with regard to the following description, and accompanying drawings, where:

[0026] FIG. 1 illustrates with increasing magnification homogenous nickel coating having durable adhesion to a niobium coin upon completion of electroplating, as evaluated using a DINOLite digital microscope. Panel A, 20x magnification; panel B, 50x magnification; panel C, 250x magnification.

[0027] FIG. 2 shows samples of the coin provided according to the present disclosure with nickel deposited in the center of a niobium backing.

[0028] FIG. 3 displays the analysis of ^{61}Cu purity of [^{61}Cu]$CuCl_2$ solution obtained by irradiation of ^{nat}Ni on Nb backing with deuteron beam at 8.4 MeV for 3 h at 50 μA. The curved line corresponds to reduction in % purity of ^{61}Cu over time and the bars correspond to radiocobalt activity over time.

[0029] FIG. 4 displays an analysis of ^{61}Cu purity of [^{61}Cu]$CuCl_2$ solution obtained by irradiation of ^{60}Ni on Nb backing with a deuteron beam at 8.4 MeV for 3 h at 50 μA. The curved line corresponds to the reduction in % purity of ^{61}Cu over time, and the bars correspond to radiocobalt activity over time.

[0030] FIG. 5 presents the activity concentration of detected impurities in [^{61}Cu]$CuCl_2$ solutions produced according to various methods. The ext. coin (Ag, natNi) data was generated by irradiation of a commercially available ^{nat}Ni target on Ag backing. The (Nb, natNi) and (Nb, Ni-61) data were generated based on irradiation of Ni targets (natural and isotopically enriched in ^{61}Ni, respectively) electroplated according to the present disclosure on high-purity Nb backing. The activity concentration was assessed by gamma spectrometry and reported in Bq/g. The data shows that silver and cobalt isotopes are significantly reduced in the [^{61}Cu]$CuCl_2$ solution produced by irradiation of Ni targets electroplated according to the present disclosure on high-purity Nb backing.

[0031] FIG. 6 shows the significant reduction in the sum of radionuclidic impurities present in a [^{61}Cu]$CuCl_2$ solutions produced according to various methods. The ext. coin (Ag, natNi) data was generated based on irradiation of a commercially available ^{nat}Ni target on Ag backing. The (Nb, natNi) and (Nb, Ni-61) data were generated based on irradiation of Ni targets (natural and isotopically enriched in ^{61}Ni, respectively), electroplated according to the present disclosure on high-purity Nb backing. The radionuclidic impurities were determined by gamma spectrometry and reported in Bq/g (summed radionuclidic impurities). The presented data highlight in particular the reduction of overall impurities in the [^{61}Cu]$CuCl_2$ solution when produced in accordance with the present disclosure.

[0032] FIG. 7 illustrates the sustained high radionuclidic purity of a [^{61}Cu]$CuCl_2$ solution produced according to the present disclosure compared to a commercially available ^{nat}Ni target on a Ag backing (ext. coin (Ag, natNi)). The (Nb, natNi) and (Nb, Ni-61) coins were prepared by electrodeposition according to the present disclosure on high-purity Nb backing. The data was generated using gamma spectrometry and reported in Bq/g providing the summed radionuclidic purities at t = 0 h and at t = 12 h. The presented data highlight the superior quality of the [^{61}Cu]$CuCl_2$ solution when produced by irradiation of Ni targets electroplated according to the present disclosure on high purity Nb backing, where the purity after 12 hours is still well above the purity limits set by pharmacopeia for similar radionuclides for medical use.

[0033] FIG. 8 displays chemical impurities, as measured by ICP-MS, of the [^{61}Cu]$CuCl_2$ solution when produced by bombardment of ^{nat}Ni vs. ^{61}Ni when produced by irradiation of Ni targets electroplated according to the present disclosure on high-purity Nb backing.

4. DETAILED DESCRIPTION

4.1. Definitions

[0034] When describing the embodiments of the present disclosure, which may include compounds and pharmaceutically acceptable salts thereof, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated

[0035] It will be understood by those within the art that, in general, terms used herein, and especially in the appended claims (e.g., bodies of the appended claims) are generally intended as "open" terms (e.g., the term "including" should be interpreted as "including but not limited to," the term "having" should be interpreted as "having at least," the term "includes" should be interpreted as "includes but is not limited to," etc.). It will be further understood by those within the art that if a specific number of an introduced claim recitation is intended, such an intent will be explicitly recited in the claim, and in the absence of such recitation no such intent is present. For example, as an aid to understanding, the following appended claims may contain usage of the introductory phrases "at least one" and "one or more" to introduce claim recitations. However, the use of such phrases should not be construed to imply that the introduction of a claim recitation by the indefinite articles "a" or "an" limits any particular claim containing such introduced claim recitation to embodiments containing only one such recitation, even when the same claim includes the introductory phrases "one or more" or "at least one" and indefinite articles such as "a" or "an" (e.g., "a" and/or "an" should be interpreted to mean "at least one" or "one or more"); the same holds true for the use of definite articles used to introduce claim recitations. In addition, even if a specific number of an introduced claim recitation is explicitly recited, those skilled in the art will recognize that such recitation should be interpreted to mean at least the recited number (e.g., the bare recitation of "two recitations," without other modifiers, means at least two recitations, or two or more recitations). Furthermore, in those instances where a convention analogous to "at least one of A, B, and C, etc." is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (e.g., "a system having at least one of A, B, and C" would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). In those instances where a convention analogous to "at least one of A, B, or C, etc." is used, in general such a construction is intended in the sense one having

skill in the art would understand the convention (e.g., "a system having at least one of A, B, or C" would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). It will be further understood by those within the art that virtually any disjunctive word and/or phrase presenting two or more alternative terms, whether in the description, claims, or drawings, should be understood to contemplate the possibilities of including one of the terms, either of the terms, or both terms. For example, the phrase "A or B" will be understood to include the possibilities of "A" or "B" or "A and B."

[0036] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[0037] As will be understood by one skilled in the art, for any and all purposes, such as in terms of providing a written description, all ranges disclosed herein also encompass any and all possible sub-ranges and combinations of sub-ranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, etc. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, etc. As will also be understood by one skilled in the art all language such as "up to," "at least," "greater than," "less than," and the like include the number recited and refer to ranges which can be subsequently broken down into sub-ranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member. Thus, for example, a group having 1-3 articles refers to groups having 1, 2, or 3 articles. Similarly, a group having 1-5 articles refers to groups having 1, 2, 3, 4, or 5 articles, and so forth.

[0038] Compounds of this disclosure include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and

March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0039] The abbreviations used herein have their conventional meaning without the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

[0040] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocyclyl", "cycloaliphatic", or "cycloalkyl"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocyclyl" or "cycloalkyl") refers to a monocyclic C3-C7 hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0041] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substituted nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR+ (as in N-substituted pyrrolidinyl)).

[0042] The term "alkylene" refers to a divalent alkyl group. An "alkylene chain" is a polymethylene group, i.e., -(CH_2)n-, wherein n is a positive integer, for example, from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0043] A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -CN is attached through the carbon atom.

[0044] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, "C_1-C_6 alkyl" is intended to encompass C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl.

[0045] The term "acyl" as used herein refers to R-C(O)- groups such as, but not limited to, (alkyl)-C(O)-, (alkenyl)-C(O)-, (alkynyl)-C(O)-, (aryl)-C(O)-, (cycloalkyl)-C(O)-, (heteroaryl)-C(O)-, and (heterocyclyl)-C(O)-, wherein the group is attached to the parent molecular structure through the carbonyl functionality. In some embodiments, it is a C_1-C_{10} acyl radical which refers to the total number of chain or ring atoms of the, for example, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, or heteroaryl, portion plus the carbonyl carbon of acyl. For example, a C_4-acyl has three other ring or chain atoms plus carbonyl.

[0046] The term "alkenyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond, such as a straight or branched group of 2 8 carbon atoms, referred to herein as (C_2-C_8)alkenyl. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2 propyl 2-butenyl, and 4-(2-methyl-3-butene)-pentenyl.

[0047] The term "alkyl" as used herein refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1 to 8 carbon atoms, referred to herein as C_{1-8} alkyl. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, 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, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, and octyl. In some embodiments, "alkyl" is a straight-chain hydrocarbon. In some embodiments, "alkyl" is a branched hydrocarbon.

[0048] The term "alkoxy" means a straight or branched chain saturated hydrocarbon containing 1-12 carbon atoms containing a terminal "O" in the chain, e.g., -O(alkyl). Examples of alkoxy groups include, without limitation, methoxy, ethoxy, propoxy, butoxy, t-butoxy, or pentoxy groups.

[0049] The term "alkylene" as used herein refers to a divalent alkyl radical. Representative examples of C_{1-10} alkylene include, but are not limited to, methylene, ethylene, n-propylene, iso-propylene, n-butylene, sec-butylene, iso-butylene, tert-butylene, n-pentylene, isopentylene, neopentylene, n-hexylene, 3-methylhexylene, 2,2-dimethylpentylene, 2,3-dimethylpentylene, n-heptylene, n-octylene, n-nonylene and n-decylene.

[0050] The term "alkynyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond, such as a straight or branched group of 2-8 carbon atoms, referred to herein as (C_2-C_8)alkynyl. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, 4-methyl-1-butynyl, 4-propyl-2-pentynyl, and 4 butyl 2 hexynyl.

[0051] The term "aryl" herein refers to an all carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system. An aryl group may be selected from: monocyclic carbocyclic aromatic rings, for example, phenyl; bicyclic ring systems such as 7-12 membered, e.g., 9-10 membered, bicyclic ring systems wherein at least one ring is carbocyclic and aromatic, selected, for example, from naphthalene, indane, and 1,2,3,4-tetrahydroquinoline; and tricyclic ring systems such as 10-15 membered tricyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, fluorene. For example, the aryl group may be a 6-membered carbocyclic aromatic ring fused to a 5- to 7-membered cycloalkyl or heterocyclic ring optionally comprising at least one heteroatom selected from N, O, and S, provided that the point of attachment is at the carbocyclic aromatic ring when the carbocyclic aromatic ring is fused with a heterocyclic ring, and the point of attachment can be at the carbocyclic aromatic ring or at the cycloalkyl group when the carbocyclic aromatic ring is fused with a cycloalkyl group. Divalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. Divalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in "-yl" by removal of one hydrogen atom from the carbon atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, e.g., a naphthyl group with two points of attachment is termed naphthylidene.

[0052] The term "divalent" refers to a chemical moiety with two points of attachment. For example, a "divalent C_1-C_8 (or C_1-C_6) saturated or unsaturated, straight or branched hydrocarbon

chain" refers to divalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

[0053] As used herein, "determine" and grammatical derivatives thereof, refers to many methodologies, some of which are described herein which include a step of "determining". Those of ordinary skill in the art, reading the present specification, will appreciate that such "determining" can utilize or be accomplished through use of any of a variety of techniques available to those skilled in the art, including for example, specific techniques explicitly referred to herein. In some embodiments, determining involves manipulation of a physical sample. In some embodiments, determining involves consideration and/or manipulation of data or information, for example, utilizing a computer or other processing unit adapted to perform relevant analys(i/e)s. In some embodiments, determining involves receiving relevant information and/or materials from a source. In some embodiments, determining involves comparing one or more features of a sample or entity to a comparable reference.

[0054] The term "heteroaryl" refers to a group having 5 to 10 ring atoms, 5, 6, or 9 ring atoms; having 6, 10, or 14π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. The term "heteroaryl", as used herein, also includes groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring (or in the case of a divalent fused heteroarylene ring system, at least one radical or point of attachment is on a heteroaromatic ring). Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4H-quinolizinyl, carbozolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydrquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3-b]-1,4-oxazin-3(4H)-one. A heteroaryl group may be mono- or bicyclic. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring", "heteroaryl group", or "heteroaromatic", any of which terms include rings that are optionally substituted.

[0055] The term "cyano" as used herein refers to CN.

[0056] The term "cycloalkyl" as used herein refers to a saturated or unsaturated cyclic, bicyclic, or bridged bicyclic hydrocarbon group of 3-16 carbons, or 3-8 carbons, referred to herein as "(C_3-C_8)cycloalkyl," derived from a cycloalkane. Exemplary cycloalkyl groups include, but are not limited to, cyclohexanes, cyclohexenes, cyclopentanes, and cyclopentenes. Cycloalkyl groups may be substituted with alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. Cycloalkyl groups can be fused to other cycloalkyl (saturated or partially unsaturated), aryl, or heterocyclyl groups, to form a bicycle, tetracycle, etc. The term "cycloalkyl" also includes bridged and spiro-fused cyclic structures which may or may not contain heteroatoms.

[0057] The terms "halo" or "halogen" as used herein refer to -F, -Cl, -Br, and/or -I.

[0058] "Haloalkyl" means an alkyl group substituted with one or more halogens. Examples of haloalkyl groups include, but are not limited to, trifluoromethyl, difluoromethyl, pentafluoroethyl, trichloromethyl, etc.

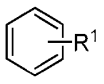
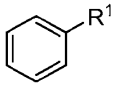
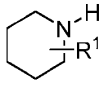
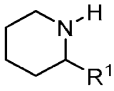
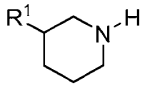
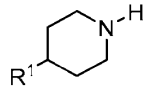
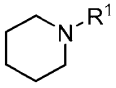
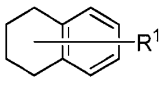
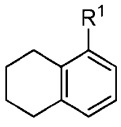
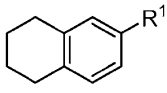
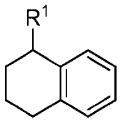
[0059] A "heterocyclyl" or "heterocyclic" group is a ring structure having from 3 to 12 atoms, for example 4 to 8 atoms, wherein one or more atoms are selected from the group consisting of N, O, and S wherein the ring N atom may be oxidized to N-O, and the ring S atom may be oxidized to SO or SO_2, the remainder of the ring atoms being carbon. The heterocyclyl may be a monocyclic, a bicyclic, a spirocyclic, or a bridged ring system. The heterocyclic group is independently optionally substituted on a ring nitrogen atom with alkyl, aralkyl, alkylcarbonyl, or on sulfur with lower alkyl. Examples of heterocyclic groups include, without limitation, epoxy, azetidinyl, aziridinyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, pyrrolidinonyl, piperidinyl, piperazinyl, imidazolidinyl, imidazopyridinyl, thiazolidinyl, dithianyl, trithianyl, dioxolanyl, oxazolidinyl, oxazolidinonyl, decahydroquinolinyl, piperidonyl, 4-piperidinonyl, quinuclidinyl, thiomorpholinyl, morpholinyl, azepanyl, oxazepanyl, azabicyclohexanyls, azabicycloheptanyl, azabicyclooctanyls, azabicyclononanyls (e.g., octahydroindolizinyl), azaspiroheptanyls, dihydro-1H,3H,5H-oxazolo[3,4-c]oxazolyl, tetrahydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizine], hexahydro-1H-pyrrolizinyl, hexahydro-1H-pyrrolo[2,1-c][1,4]oxazinyl, octahydroindolizinyl, oxaazaspirononanyls, oxaazaspirooctanyls,

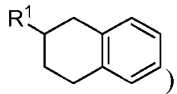
diazaspirononanyls, oxaazabiocycloheptanyls, hexahydropyrrolizinyl 4(1H)-oxide, tetrahydro-2H-thiopyranyl 1-oxide and tetrahydro-2H-thiopyranyl 1,1-dioxide. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms.

[0060] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation.

[0061] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0062] As used herein and unless otherwise specified, the suffix "-ene" is used to describe a divalent group. Thus, any of the terms above can be modified with the suffix "-ene" to describe a divalent version of that moiety. For example, a divalent carbocycle is "carbocyclylene", a divalent aryl ring is "arylene", a divalent benzene ring is "phenylene", a divalent heterocycle is "heterocyclylene", a divalent heteroaryl ring is "heteroarylene", a divalent alkyl chain is "alkylene", a divalent alkenyl chain is "alkylene", a divalent alkynyl chain is "alkynylene", and so forth.

[0063] As described herein, compounds of the disclosure may, when specified, contain "optionally substituted" moieties. In general, the term "substituted", whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. "Substituted" applies to one or more hydrogens that are either explicit or implicit from the structure (e.g.,  refers to at least ; and  refers to at least , , , or ). In addition, in a polycyclic ring system, substituents may, unless otherwise indicated, replace a hydrogen on any individual ring (e.g.,  refers to at least , , ,

or ). Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this disclosure are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their purification, detection, and, in some embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0064] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$; $-O(CH_2)_{0-4}C(O)OR^\circ$; $-O(CH_2)_{0-4}OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$, which may be substituted with R°, -CH=CHPh, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $-NO_2$; -CN; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)N(R^\circ)_2$; $-N(R^\circ)C(S)N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(S)N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)N(R^\circ)_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSi(R^\circ)_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)N(R^\circ)_2$; $-C(S)N(R^\circ)_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}OC(O)N(R^\circ)_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2N(R^\circ)_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)N(R^\circ)_2$; $-P(OR^\circ)_2$; $-P(O)(R^\circ)_2$; $-OP(O)(R^\circ)_2$; $-OP(O)(OR^\circ)_2$; $-SiR^\circ_3$; $-(C_{1-4}$ straight or branched alkylene)$O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene)$C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$-(5- to 6-membered heteroaryl ring), or a 5- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atoms(s), form a 3- to 12-membered

saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, which may be substituted as defined below.

[0065] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen; $-(CH_2)_{0-2}R^\bullet$; -(haloR$^\bullet$), $-(CH_2)_{0-2}OH$; $-(CH_2)_{0-2}OR^\bullet$; $-(CH_2)_{0-2}CH(OR^\bullet)_2$; -O(haloR$^\bullet$); -CN; $-N_3$; $-(CH_2)_{0-2}C(O)R^\bullet$; $-(CH_2)_{0-2}C(O)OH$; $-(CH_2)_{0-2}C(O)OR^\bullet$; $-(CH_2)_{0-2}SR^\bullet$; $-(CH_2)_{0-2}SH$; $-(CH_2)_{0-2}NH_2$; $-(CH_2)_{0-2}NHR^\bullet$; $-(CH_2)_{0-2}NR^\bullet_2$; $-NO_2$, $-SiR^\bullet_3$; $-OSiR^\bullet_3$; $-C(O)SR^\bullet$; -(C_{1-4} straight or branched alkylene)C(O)OR$^\bullet$, or -SSR$^\bullet$ wherein each R$^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5- to 6-memebered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[0066] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O; =S; $=NNR^\#_2$; $=NNHC(O)R^\#_2$; $=NNHC(O)OR^\#_2$; $=NNHS(O)_2R^\#_2$; $=NR^\#$; $=NOR^\#$; $-O(C(R^\#_2))_{2-3}O-$; or $-S(C(R^\#_2))_{2-3}S-$; wherein each independent occurrence of R$^\#$ is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(CR^\#_2)_{2-3}O-$, wherein each independent occurrence of R$^\#$ is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0067] Suitable substituents on the aliphatic group of R$^\#$ include halogen, -R$^\bullet$, -(haloR$^\bullet$), -OH, -OR$^\bullet$, -O(haloR$^\bullet$), -CN, -C(O)OH, -C(O)OR$^\bullet$, $-NH_2$, -NHR$^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each R$^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0068] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $-R^{\dagger}$, $-NR^{\dagger}_2$, $-C(O)R^{\dagger}$, $-C(O)OR^{\dagger}$, $-C(O)C(O)R^{\dagger}$, $-C(O)CH_2C(O)R^{\dagger}$, $-S(O)_2R^{\dagger}$, $-S(O)_2NR^{\dagger}_2$, $-C(S)NR^{\dagger}_2$, $-C(NH)NR^{\dagger}_2$, or $-N(R^{\dagger})S(O)_2R^{\dagger}_2$; wherein each $R^{\dagger}$ is independently hydrogen, C1-6 aliphatic which may be substituted as defined below, unsubstituted -OPh, or an unsubstituted 5- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or, notwithstanding the definition above, two independent occurrences or $R^{\dagger}$, taken together with their intervening atom(s) form an unsubstituted 3- to 12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0069] Suitable substituents on the aliphatic group of $R^{\dagger}$ are independently halogen, $-R^{\bullet}$, -(halo$R^{\bullet}$), -OH, $-OR^{\bullet}$, -O(halo$R^{\bullet}$), -CN, -C(O)OH, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or $-NO_2$, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5- to 6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0070] When the term "substituted" appears prior or after a list of possible substituted groups, it is intended that the term apply to every member of that group. For example, the phrase "substituted alkyl and aryl" is to be interpreted as "substituted alkyl and substituted aryl."

[0071] In addition to the disclosure herein, the term "substituted," when used to modify a specified group or radical, can also mean that one or more hydrogen atoms of the specified group or radical are each, independently of one another, replaced with the same or different substituent groups as defined herein.

[0072] In addition to the disclosure herein, in a certain embodiment, a group that is substituted has 1, 2, 3, or 4 substituents, 1, 2, or 3 substituents, 1 or 2 substituents, or 1 substituent.

[0073] Unless indicated otherwise, the nomenclature of substituents that are not explicitly defined herein are arrived at by naming the terminal portion of the functionality followed by the adjacent functionality toward the point of attachment. For example, the substituent "hydroxyalkyl" refers to the group HO-(alkyl)-.

[0074] As to any of the groups disclosed herein which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible. In addition, the subject compounds include all stereochemical isomers arising from the substitution of these compounds.

[0075] The term "oxo", as used herein, means an oxygen that is double bonded to a carbon atom thereby forming a carbonyl.

[0076] The terms "hydroxy" and "hydroxyl" as used herein refer to -OH.

[0077] Some of the compounds may exist with different points of attachment of hydrogen, referred to as "tautomers." For example, compounds including carbonyl $-CH_2C(O)-$ groups (keto forms) may undergo tautomerism to form hydroxyl -CH=C(OH)- groups (enol forms). Both keto and enol forms, individually as well as mixtures thereof, are also intended to be included where applicable.

[0078] The compounds, tautomers, solvates, or pharmaceutically acceptable salts of the disclosure may contain an asymmetric center and may thus exist as enantiomers. For example, where the compounds possess two or more asymmetric centers, they may additionally exist as diastereoisomers. Enantiomers and diastereoisomers fall within the broader class of stereoisomers. All such possible stereoisomers as substantially pure resolved enantiomers, racemic mixtures thereof, as well as mixtures of diastereoisomers are intended to be included in this disclosure. All stereoisomers of the compounds, tautomers, solvates, and pharmaceutically acceptable salts thereof are intended to be included. Unless specifically mentioned otherwise, reference to one isomer applies to any of the possible isomers. Whenever the isomeric composition is unspecified, all possible isomers are included.

[0079] Diastereomeric mixtures can be separated into their individual diastereoisomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereoisomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Enantiomers can also be separated by use of a chiral HPLC column.

[0080] "Stereoisomer" or "optical isomer" means a stable isomer that has at least one chiral atom or restricted rotation giving rise to perpendicular dissymmetric planes (e.g., certain biphenyls, allenes, and spiro compounds) and can rotate plane-polarized light. Because asymmetric centers and other chemical structure exist in the compounds of the disclosure which may give rise to stereoisomerism, the disclosure contemplates stereoisomers and mixtures thereof. The compounds of the disclosure and their salts include asymmetric carbon atoms and may therefore exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. Typically, such compounds will be prepared as a racemic mixture. If desired, however, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. As discussed in more detail below, individual stereoisomers of compounds are prepared by synthesis from optically active starting materials containing the desired chiral centers or by preparation of mixtures of enantiomeric products followed by separation or resolution, such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, use of chiral resolving agents, or direct separation of the enantiomers on chiral chromatographic columns. Starting compounds of particular stereochemistry are either commercially available or are made by the methods described below and resolved by techniques well-known in the art.

[0081] It is well-known in the art that the biological and pharmacological activity of a compound is sensitive to the stereochemistry of the compound. Thus, for example, enantiomers often exhibit strikingly different biological activity including differences in pharmacokinetic properties, including metabolism, protein binding, and the like, and pharmacological properties, including the type of activity displayed, the degree of activity, toxicity, and the like. Thus, one skilled in the art will appreciate that one enantiomer may be more active or may exhibit beneficial effects when enriched relative to the other enantiomer or when separated from the other enantiomer. Additionally, one skilled in the art would know how to separate, enrich, or selectively prepare the enantiomers of the compounds of this disclosure and the knowledge of the prior art.

[0082] Thus, although the racemic form of drug may be used, it is often less effective than administering an equal amount of enantiomerically pure drug; indeed, in some cases, one enantiomer may be pharmacologically inactive and would merely serve as a simple diluent. For example, although ibuprofen had been previously administered as a racemate, it has been shown

that only the S-isomer of ibuprofen is effective as an anti-inflammatory agent (in the case of ibuprofen, however, although the R-isomer is inactive, it is converted in vivo to the S-isomer, thus, the rapidity of action of the racemic form of the drug is less than that of the pure S-isomer). Furthermore, the pharmacological activities of enantiomers may have distinct biological activity. For example, S-penicillamine is a therapeutic agent for chronic arthritis, while R-penicillamine is toxic. Indeed, some purified enantiomers have advantages over the racemates, as it has been reported that purified individual isomers have faster transdermal penetration rates compared to the racemic mixture. See U.S. Pat. Nos. 5,114,946 and 4,818,541.

[0083] In some embodiments, the compound is a racemic mixture of (S)- and (R)-isomers. In other embodiments, provided herein is a mixture of compounds wherein individual compounds of the mixture exist predominately in an (S)- or (R)-isomeric configuration. For example, the compound mixture has an (S)-enantiomeric excess of greater than 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, or more. In other embodiments, the compound mixture has an (S)-enantiomeric excess of greater than 55% to 99.5%, greater than 60% to 99.5%, greater than 65% to 99.5%, greater than 70% to 99.5%, greater than 75% to 99.5%, greater than 80% to 99.5%, greater than 85% to 99.5%, greater than 90% to 99.5%, greater than 95% to 99.5%, greater than 96% to 99.5%, greater than 97% to 99.5%, greater than 98% to greater than 99.5%, greater than 99% to 99.5%, or more. In other embodiments, the compound mixture has an (R)-enantiomeric purity of greater than 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5% or more. In some other embodiments, the compound mixture has an (R)-enantiomeric excess of greater than 55% to 99.5%, greater than 60% to 99.5%, greater than 65% to 99.5%, greater than 70% to 99.5%, greater than 75% to 99.5%, greater than 80% to 99.5%, greater than 85% to 99.5%, greater than 90% to 99.5%, greater than 95% to 99.5%, greater than 96% to 99.5%, greater than 97% to 99.5%, greater than 98% to greater than 99.5%, greater than 99% to 99.5% or more.

[0084] Individual stereoisomers of compounds of the present disclosure can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic/chiral centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by: (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically

pure product from the auxiliary; (2) salt formation employing an optically active resolving agent; or (3) direct separation of the mixture of optical enantiomers on chiral chromatographic columns. Stereoisomeric mixtures can also be resolved into their component stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Stereoisomers can also be obtained from stereomerically-pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

[0085] Thus, if one enantiomer is pharmacologically more active, less toxic, or has a preferred disposition in the body than the other enantiomer, it would be therapeutically more beneficial to administer that enantiomer preferentially.

[0086] The term "pharmaceutically acceptable carrier" as used herein refers to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.

[0087] Additionally, as used herein refers to pharmaceutical excipients, for example, pharmaceutically, physiologically, acceptable organic or inorganic carrier substances suitable for enteral or parenteral application that do not deleteriously react with the active agent. Suitable pharmaceutically acceptable carriers include water, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, and carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethylcellulose, and polyvinylpyrrolidone. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the disclosure.

[0088] The term "pharmaceutically acceptable composition" as used herein refers to a composition comprising at least one compound as disclosed herein formulated together with one or more pharmaceutically acceptable carriers.

[0089] As used herein, the term "pharmaceutically acceptable salt(s)" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and

are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. Pharmaceutically acceptable salts of the compounds of this disclosure include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like. Pharmaceutically acceptable salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium, and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[0090] As used herein, "peptide receptor radionuclide therapy" (PRRT) refers to the use of one or more radiotherapeutic agents for the delivery of targeting radiation, usually by a chelated radionuclide, to a specific tissue or receptor associated with cancer. The targeting and selection of certain tissues over another is accomplished by specific peptide hormone receptors expressed or overexpressed on the surface of cancerous biomass.

[0091] As used herein, "activity" or "radioactivity" refers to a physical quantity defined as the number of radioactive transformations per second that occur in a particular compound or composition that contains one or more radioactive substances. The unit of activity used herein is the becquerel (Bq), which is defined equivalent to reciprocal seconds (1/seconds or s^{-1}).

[0092] As used herein, "activity concentration" refers to the total amount of radioactivity per unit volume. In some embodiments, activity concentration is expressed in Bq/L or magnitudes thereof (e.g., MBq/mL).

[0093] As used herein, "specific activity" refers to the activity of a radionuclide per unit mass or per unit volume. In certain embodiments, specific activity refers to the activity of a radionuclide per unit mass of the radiotracer. In certain embodiments, specific activity refers to the activity of a radionuclide per unit mass of the $[^{61}Cu]CuCl_2$ solution used to radiolabel a compound of the present disclosure. In certain embodiments, specific activity refers to the activity of a radionuclide per unit volume of the $[^{61}Cu]CuCl_2$ solution used to radiolabel a compound of the present disclosure. In certain embodiments, specific activity is measured at EoS.

[0094] As used herein, "effective amount," or "pharmaceutically effective amount," mean a sufficient amount of the pharmaceutical composition to provide the desired utility when administered to a subject. In some embodiments, an effective amount includes an amount of pharmaceutical composition sufficient to generate an image of subject. In some embodiments, an effective amount includes an amount of pharmaceutical composition sufficient to diagnose a disease in a subject. It is understood that for any given case, an appropriate "effective amount" can be determined by one of ordinary skill in the art using routine experimentation. For example, when administered in clinic, such pharmaceutical compositions will contain an amount of active ingredient effective to achieve the desired result (e.g., imaging cancerous tissue).

[0095] As used herein, the term "therapeutically effective amount" refers to an amount of a therapeutic agent that confers a therapeutic effect on the treated subject, at a reasonable benefit/risk ratio applicable to any medical treatment. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect). In particular, the "therapeutically effective amount" refers to an amount of a therapeutic agent effective to treat, ameliorate, or prevent a desired disease or condition, or to exhibit a detectable therapeutic or preventive effect, such as by ameliorating symptoms associated with the disease, preventing or delaying the onset of the disease or condition, and/or also lessening the severity or frequency of symptoms of the disease or condition. A therapeutically effective amount is commonly administered in a dosing regimen that may comprise multiple doses. For any particular therapeutic agent, a therapeutically effective amount

(and/or an appropriate unit dose within an effective dosing regimen) may vary, for example, depending on route of administration, on combination with other pharmaceutical agents. Also, the specific therapeutically effective amount (and/or unit dose) for any particular subject may depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific therapeutic agent employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and/or rate of excretion or metabolism of the specific therapeutic agent employed; the duration of the treatment; and like factors as is well known in the medical arts.

[0096] As used herein, "effective dose" refers to the internationally accepted central radiological risk metric quantity. The calculation of effective dose can be seen as a three-step process. First, the mean absorbed doses to organs and tissues are determined in gray (Gy; J kg^{-1}). Second, the absorbed doses are converted to equivalent doses in sievert (Sv) using tissue/organ radiation weighting factors (wR). The weighting factors were computed from radiation epidemiological data, and take into consideration that some organs (e.g., breasts, stomach, and, lungs) are more radiosensitive than others (e.g., brain and skin). The summing of organ/tissue equivalent doses, each weighted by the appropriate tissue weighting factor (wT), gives the effective dose, in Sv. The effective dose is therefore a risk metric, and not a dosimetric quantity *per se*.

[0097] As used herein, "molar activity" refers to the amount of radioactivity (e.g., number of nuclear disintegrations per second) per unit mole of the radiolabeled compound. In certain embodiments, molar activity is expressed in Bq/mol, e.g., MBq/nmol and is used where the molecular weight of the labelled material is known. The "apparent molar activity" (apparent Am) takes into account the amounts of the radiolabelled (compound A*) and non-radiolabelled radiotracer (compound A), radiolabelled impurities (compound B*) and non-radiolabelled impurities (compound B) and remaining precursor (compound C) present expressed in mol (or μmol). See, e.g., Luurtsema, G., *et al.* "EANM guideline for harmonisation on molar activity or specific activity of radiopharmaceuticals: impact on safety and imaging quality." *EJNMMI Radiopharm. Chem.* **6**, 34 (2021).

[0098] As used herein, "radiochemical purity" refers to the ratio, given as a percent, of radioactivity from the radionuclide in the pharmaceutical composition (e.g., the desired

radionuclide that is chelated in a radiotracer as described herein) to the total radioactivity of the composition that comprises the radiotracer. The majority of the radioactive isotope is attached to the tracer construct and is not free or attached to another chemical entity as these forms may have a different biodistribution. Radiochemical purity (RCP) measurements establish the content of impurities labelled with the same radionuclide used to prepare a radiopharmaceutical, but with a different chemical form.

[0099] Radiochemical purity is determined according to methods well known to those of skill in the art, e.g., radio-HPLC, iTLC. As is understood in the art, determination of radiochemical purity is not strictly quantitative, and it is calculated as the ratio between the peak area of the desired radiotracer and the overall area of all the detected peaks in the radiochromatogram (corrected for decay). The instrument used to determine radiochemical purity with HPLC (radio-HPLC) is a radiometric detector (radiodetector), which has an in-line detector connected in series with a UV or other physicochemical detector. The radiometric detector can be a Geiger-Müller probe, a scintillation detector, or a PIN diode. As compared with radio-HPLC it has the big advantage that all applied radioactivity is detected and there are no concerns with recovery.

[0100] As used herein, "radionuclidic purity" refers to the ratio, expressed as a percentage, of the radioactivity of a particular radionuclide to the total radioactivity of the sample, e.g., the starting material used to prepare a radiotracer. In certain embodiments, radionuclidic purity can be determined by high resolution gamma spectroscopy (e.g., high-purity germanium (HPGe) detector) on a sample after expiration, e.g. >8 hours or >3 weeks) and is then extrapolated (e.g., using the TENDLE-2019 database according to procedures well known in the art), and reported herein as the value at the end of synthesis (EoB+2hours) of the radionuclide.

[0101] As used herein, "chemical purity," refers to the molar percent of the identified or desired entity to all entities in the sample. The radionuclide compositions prepared by the disclosed methods herein exhibit high chemical purity, which facilitates the production of radiopharmaceuticals with high radiochemical purity. Radiochemical purity, as understood herein, is the ratio or percent of reactivity from the desired radionuclide in the radiopharmaceutical to the total radioactivity of the sample that includes the radiopharmaceutical. Non-radioactive isotopes of metals ("cold" metals) will not contribute to the total radioactivity of a sample, but they can compete with the desired radionuclide for

inclusion in the radiopharmaceutical, e.g., competing for chelation sites in the radiopharmaceutical.

[0102] Chemical names were generated using PerkinElmer ChemDraw® Professional, version 17.

[0103] The compounds of the disclosure may contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as geometric isomers, enantiomers or diastereomers. The term "stereoisomers" when used herein consist of all geometric isomers, enantiomers or diastereomers. These compounds may be designated by the symbols "R" or "S," depending on the configuration of substituents around the stereogenic carbon atom. The present disclosure encompasses various stereoisomers of these compounds and mixtures thereof. Stereoisomers include enantiomers and diastereomers. Mixtures of enantiomers or diastereomers may be designated "(±)" in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly. In some embodiments, an enantiomer or stereoisomer may be provided substantially free of the corresponding enantiomer.

[0104] As used herein, "cancer" refers to diseases, disorders, and conditions that involve abnormal cell growth with the potential to invade or spread to other parts of the body. Exemplary cancers include, but are not limited to, breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer, and esophageal cancer.

[0105] The terms "cancer", "malignancy", "neoplasm", tumor", and "carcinoma", are used herein to refer to cells that exhibit relatively abnormal, uncontrolled, and/or autonomous growth, so that they exhibit an aberrant growth phenotype characterized by a significant loss of control of cell proliferation. In some embodiments, a tumor may be or comprise cells that are pre-cancerous (e.g., benign), malignant, pre-metastatic, metastatic, and/or non-metastatic. The present disclosure specifically identifies certain cancers to which its teachings may be particularly relevant. In some embodiments, a relevant cancer may be characterized by a solid tumor. In some embodiments, a relevant cancer may be characterized by a hematologic tumor. In general, examples of different types of cancers known in the art include, for example, hematopoietic cancers including leukemias, lymphomas (Hodgkin's and non-Hodgkin's), myelomas and myeloproliferative disorders; sarcomas, melanomas, adenomas, carcinomas of solid tissue, squamous cell carcinomas of the mouth, throat, larynx, and lung, liver cancer, genitourinary

cancers such as prostate, cervical, bladder, uterine, and endometrial cancer and renal cell carcinomas, bone cancer, pancreatic cancer, skin cancer, cutaneous or intraocular melanoma, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, head and neck cancers, breast cancer, gastro-intestinal cancers and nervous system cancers, benign lesions such as papillomas, and the like.

[0106] As used herein, the term "subject" refers to an organism, typically an animal (e.g., a mammal). A subject also refers to for example, primates (e.g., humans, male or female), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds, and the like. In some embodiments, the subject is a primate. In some embodiments, the subject is a human. In some embodiments, a subject is susceptible to a disease, disorder, or condition. In some embodiments, a subject may display one or more symptoms or characteristics of a disease, disorder, or condition. In some embodiments, a subject does not display any symptom or characteristic of a disease, disorder, condition. In some embodiments, a subject is someone with one or more features characteristic of susceptibility to or risk of a disease, disorder, or condition. In some embodiments, a subject is a patient. In some embodiments, a subject is an individual to whom diagnosis and/or therapy is and/or has been administered.

[0107] As used herein, the term "susceptible" refers to a subject who is vulnerable to a disease, disorder, or condition or is at risk for developing a disease, disorder, or condition. In some embodiments, a subject who is susceptible to a disease, disorder, or condition does not display any symptoms of the disease, disorder, or condition. In some embodiments, a subject who is susceptible to a disease, disorder, or condition has not been diagnosed with the disease, disorder, or condition. In some embodiments, a subject who is susceptible to a disease, disorder, or condition. In some embodiments, a risk of developing a disease, disorder, and/or condition is a population-based risk (e.g., family members of the subject suffering from the disease, disorder, or condition).

[0108] A "dosing regimen" (or "therapeutic regimen"), as that term is used herein, is a set of unit doses (typically more than one) that are administered individually to a subject, typically separated by periods of time. In some embodiments, a given therapeutic agent has a recommended dosing regimen, which may involve one or more doses. In some embodiments, a dosing regimen comprises a plurality of doses each of which are separated from one another by a

time period of the same length; in some embodiments, a dosing regimen comprises a plurality of doses and at least two different time periods separating individual doses.

[0109] As will be understood from context, a "reference" compound is one that is sufficiently similar to a particular compound of interest to permit a relevant comparison. In some embodiments, information about a reference compound is obtained simultaneously with information about a particular compound. In some embodiments, comparison of a particular compound of interest with a reference compound establishes identity with, similarity to, or difference of the particular compound of interest relative to the compound.

[0110] As used herein, the phrase "therapeutic agent" refers to any agent that has a therapeutic effect and/or elicits a desired biological and/or pharmacological effect, when administered to a subject.

[0111] As used herein, the term "treat," "treating," or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treat," "treating," or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, "treat," "treating," or "treatment" refers to modulating the disease or disorder, either physically (e.g., through stabilization of a discernible symptom), physiologically, (e.g., through stabilization of a physical parameter), or both. In yet another embodiment, "treat," "treating," or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder.

[0112] As used herein, a subject is "in need of" a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.

[0113] The term "radioactivity" (also referred to as activity, or total activity) as used herein refers to a physical quantity defined as the number of radioactive transformations per second that occur in a particular radionuclide. The unit of radioactivity used herein is the becquerel (symbol Bq), which is defined equivalent to reciprocal seconds (1/seconds or s^{-1}).

[0114] As used herein, "operably linked" refers to a juxtaposition wherein the components described are in a relationship permitting them to function in their intended manner. A control

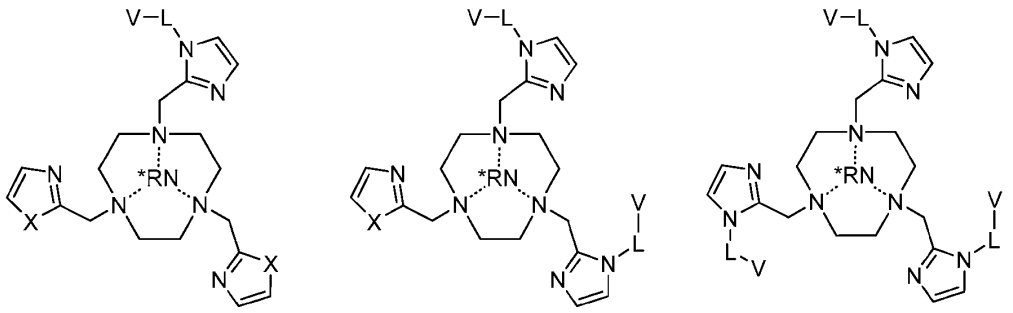
element "*operably linked*" to a functional element is associated in such a way that expression and/or activity of the functional element is achieved under conditions compatible with the control element. In some embodiments, "*operably linked*" control elements are contiguous (e.g., covalently linked) with the according elements of interest; in some embodiments, control elements act in *trans* to or otherwise at or from the functional element of interest.

[0115] As used herein, "therapeutic agent" refers to an agent that when administered to a subject, has a therapeutic effect and/or elicits a desired biological and/or pharmacological effect. In some embodiments, a therapeutic agent is any substance that can be used to alleviate, ameliorate, relieve, inhibit, prevent, delay onset of, reduce severity of, and/or reduce incidence of oner or more symptoms or features of a disease, disorder, and/or condition.

4.2. Integrin Targeted Compounds

[0116] An aspect of the present disclosure is the provision of integrin targeted radiopharmaceutical compounds and precursors thereof. These compounds comprise a targeting moiety that binds to an integrin as described herein. In some embodiments, the compound comprises a radionuclide, such as ^{61}Cu.

[0117] In some embodiments, the present disclosure provides a compound, wherein the compound is of Formula I, II, or III:



(I) (II) (III)

or is a pharmaceutically acceptable salt thereof;

wherein:

*RN is an optionally present radionuclide as described in Section 4.2.3 Radionuclide;

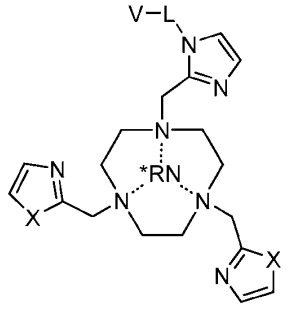
each X is independently -S- or -NR^{a1}-; and

each R^{a1} is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group;

each V is a targeting moiety that binds to an integrin, such as $\alpha_v\beta_6$ integrin, as described in Section 4.2.1 Targeting Moiety;

each L is independently a bond or a linking moiety as described in Section 4.2.2 Linking Moiety;

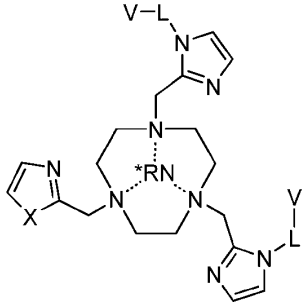
[0118] In some embodiments, the compound is of Formula I:



(I)

or is a pharmaceutically acceptable salt thereof.

[0119] In some embodiments, the compound is of Formula II:



(II)

or is a pharmaceutically acceptable salt thereof.

[0120] In some embodiments of Formula I or II, each X is $-NR^{a1}-$.

[0121] In some embodiments of Formula I or II, R^{a1} is hydrogen.

[0122] In some embodiments of Formula I or II, R^{a1} is an optionally substituted C_{1-6} aliphatic group.

[0123] In some embodiments of Formula I or II, R^{a1} is an optionally substituted C_{1-4} aliphatic group.

[0124] In some embodiments of Formula I or II, R^{a1} is an optionally substituted C_{1-3} aliphatic group.

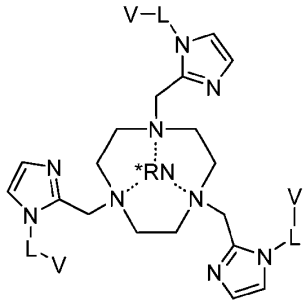
[0125] In some embodiments of Formula I or II, R^{a1} is an optionally substituted C_{1-6} alkyl group.

[0126] In some embodiments of Formula I or II, R^{a1} is an optionally substituted C_{1-4} alkyl group.

[0127] In some embodiments of Formula I or II, R^{a1} is an optionally substituted C_{1-3} alkyl group.

[0128] In some embodiments of Formula I or II, R^{a1} is an optionally substituted C_{1-6} cycloalkyl group.

[0129] In some embodiments, the compound is of Formula III:



(III)

or is a pharmaceutically acceptable salt thereof.

4.2.1. Targeting Moiety

[0130] Integrins, consisting of two noncovalently bound transmembrane α and β subunits, are an important molecular family involved in tumor angiogenesis. Integrin αvβ3 is highly expressed on activated endothelial cells, new-born vessels as well as some tumor cells, but is not present in resting endothelial cells and most normal organ systems, making it a suitable target for anti-angiogenic therapy.

[0131] In embodiments of a compound of Formulae I, II, or III, the targeting moiety comprises one or more functionalities that bind to integrin. In some embodiments, the targeting moiety comprises one or more functionalities that bind to one or more integrin subtypes (e.g., αvβ3, αvβ5, or αvβ6).

[0132] In some embodiments of a compound of Formulae I, II, or III, the targeting moiety comprises a peptide that binds to a αvβ3 integrin. In some embodiments, the targeting moiety is selected from an RGD-peptide, SC-68448, SCH221153, and S-247 (as depicted below). In some embodiments, the targeting moiety comprises a dimeric RGD-peptide E-[c(RGDfK)]$_2$, formed by two cyclic pentapeptides c(RGDfK) linked via a glutamic acid residue. In some embodiments, the targeting moiety comprises c(RGDfV). In these embodiments, f stands for D-phenylalanine. In some embodiments, the targeting moiety comprises cilengitide, a cyclized RGD-containing pentapeptide, c(RGDf[NMe]V) (as depicted below). In some embodiments, the targeting moiety comprises a disintegrin, a family of low molecular weight (47–84 amino acids) RGD containing cysteine-rich peptides derived from viper venoms.

[0133] In some embodiments, each targeting moiety is independently selected from an antibody, an RGD-peptide, a cysteine knot peptide, an integrin αvβ6 agonist, and an integrin αvβ6 antagonist.

[0134] In some embodiments, at least one targeting moiety comprises cilengitide, tirofiban, JSM-6427, risuteganib, GSK3008348, SDM17, GLPG0187, CWHM-12, nesvategrast, bexotegrast, EMD527040, MK-0429, Tyr$_2$, A20FMDV2, SFITGv6, SFLAP3, R$_0$1-MG-F2, echistatin, MK-0429, TDI-3761, TDI-4161, 29P, iRGD, c8, c[FRGDLAFp(NMe)K(Ac)], or Tyr$_{12}$.

[0135] In some embodiments, at least one targeting moiety comprises an RGD-peptide. In some embodiments, at least one targeting moiety is an RGD-peptide comprising $\overline{\text{Arg-Gly-Asp-(Xaa)}_n\text{-Xaa}}$, wherein n is an integer from 1 to 6, and wherein Xaa is an optionally substituted amino acid selected from aspartic acid, glutamic acid, α-glutamic acid, γ-glutamic acid, tyrosine, alanine, valine, leucine, isoleucine, phenylalanine, cyclohexylglycine, cyclopentylglycine, cyclobutylglycine, cyclopropylglycine, cyclohexylalanine, cyclopentylalanine, cyclobutylalanine, and cyclopropylalanine. In some embodiments, n is an integer from 1 to 5. In some embodiments, n is an integer from 1 to 4. In some embodiments, n is an integer from 1 to 3. In some embodiments, n is an integer from 1 to 2. In some embodiments, n is 1, 2, 3, 4, or 5.

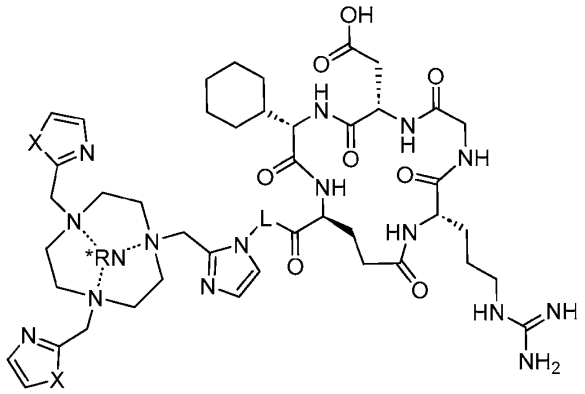
[0136] In some embodiments, at least one targeting moiety is an RGD-peptide comprising [Arg-Gly-Asp-Xaa-Xaa] or [Arg-Gly-Asp-Glu-Xaa].

[0137] In some embodiments, at least one targeting moiety is an RGD-peptide comprising [Arg-Gly-Asp-γ-Glu-Xaa], [Arg-Gly-Asp-γ-Glu-Chg], [Arg-Gly-Asp-γ-Glu-Val], [Arg-Gly-Asp-γ-Glu-Leu], or [Arg-Gly-Asp-γ-Glu-Ile]. In some embodiments, at least one targeting moiety comprising an RGD-peptide sequence covalently attached through any appropriately functionalized amino acid residue.

[0138] In some embodiments, the RGD-peptide is selected from: cilengitide, SDM17, Tyr_2, A20FMDV2, SFITGv6, SFLAP3, R_01-MG-F2, echistatin, iRGD, c8, c[FRGDLAFp(NMe)K(Ac)], and Tyr_{12}.

[0139] In some embodiments, the RGD-peptide is SDM17.

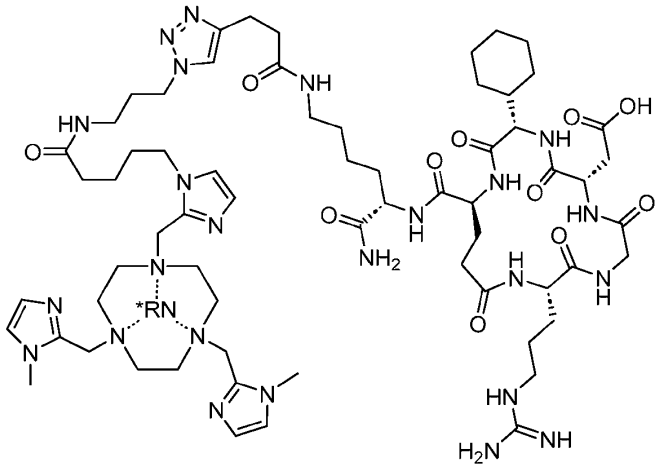
[0140] In some embodiments, the compound is of Formula IB:



(IB)

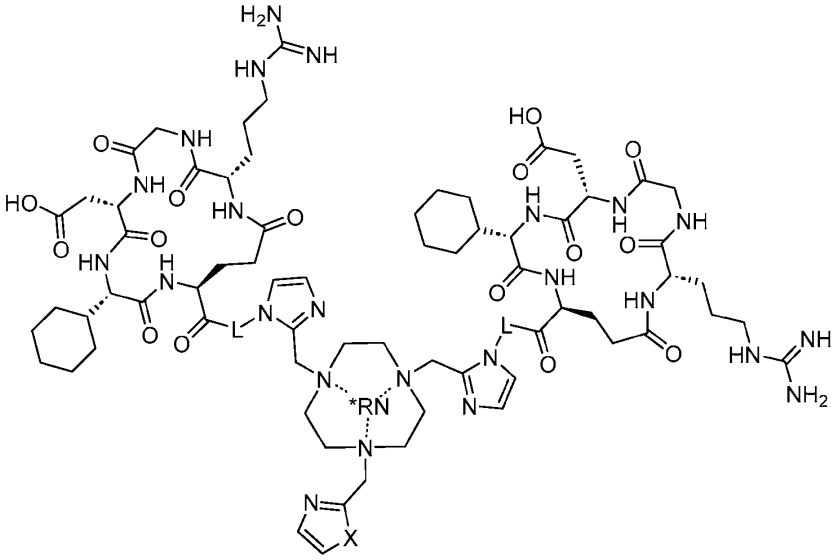
or is a pharmaceutically acceptable salt thereof.

[0141] In some embodiments, the compound is of the structure:



or is a pharmaceutically acceptable salt thereof.

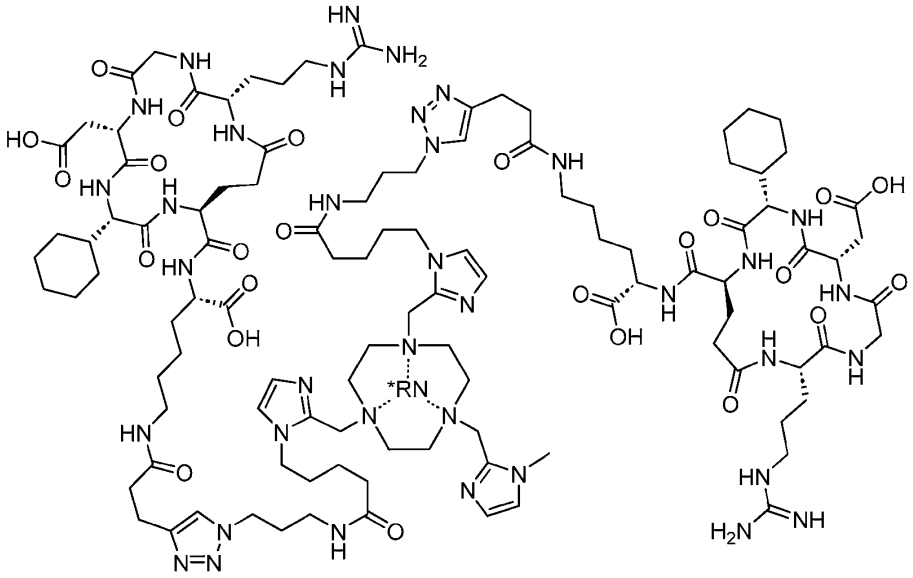
[0142] In some embodiments, the compound is of Formula IIB:



(IIB)

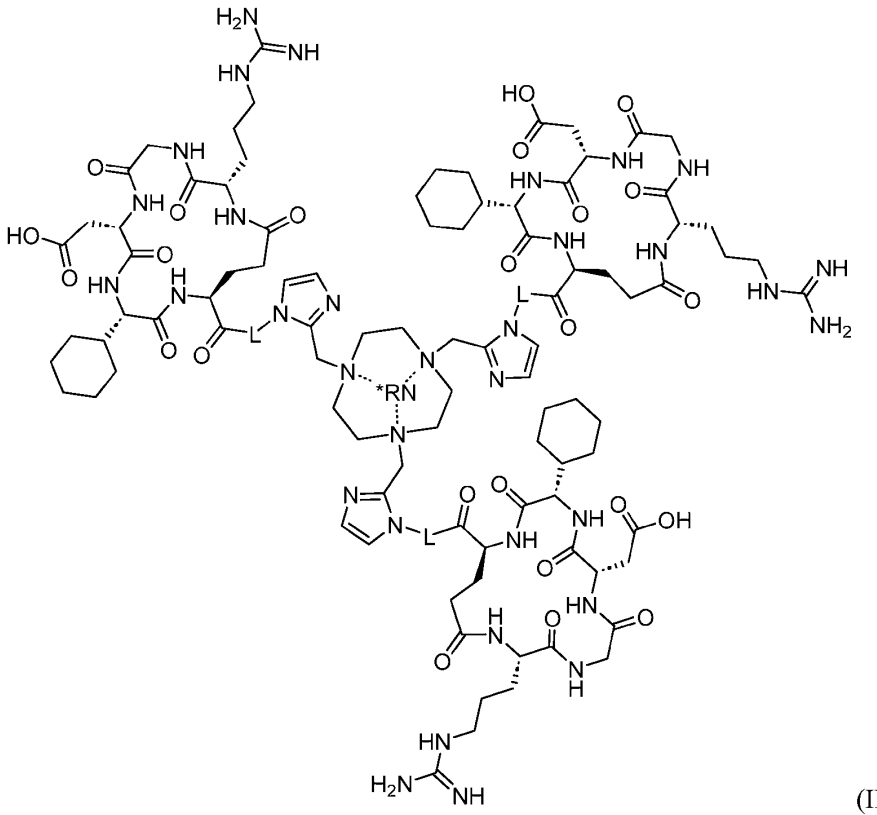
or is a pharmaceutically acceptable salt thereof.

[0143] In some embodiments, the compound is of the structure:



or is a pharmaceutically acceptable salt thereof.

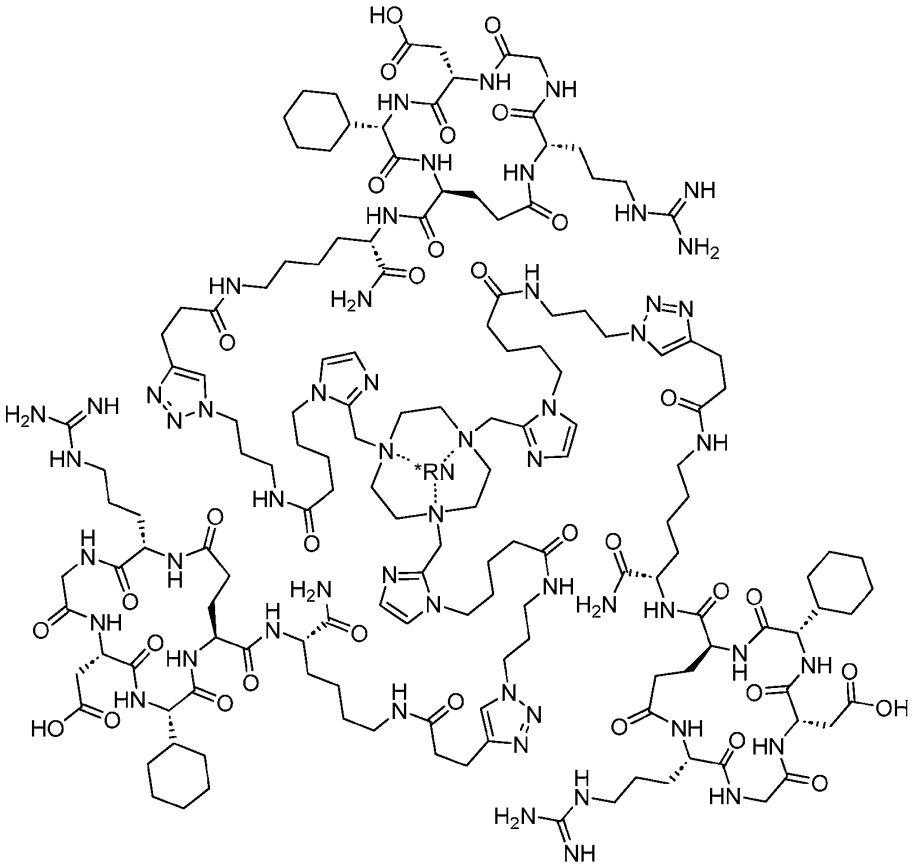
[0144] In some embodiments, the compound is of Formula IIIB:



(IIIB)

or is a pharmaceutically acceptable salt thereof.

[0145] In some embodiments, the compound has the structure:



or is a pharmaceutically acceptable salt thereof.

4.2.2. Linking Moiety

[0146] In some embodiments, the present disclosure provides a compound of Formula I, IB, II, IIB, III or IIIB wherein:

each L is independently a bond or a linking moiety;

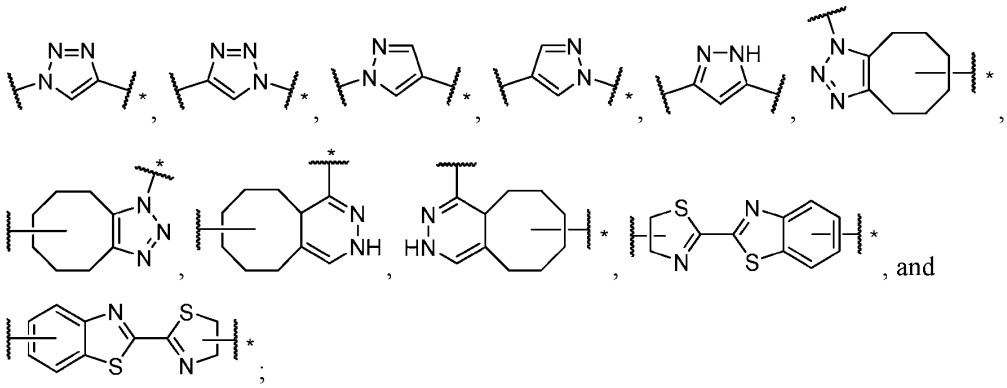
each linking moiety independently comprises a divalent PEG-containing moiety or an optionally substituted, saturated or partially unsaturated, straight or branched divalent aliphatic C_{1-50} hydrocarbon chain, wherein one or more carbon atoms in the chain are optionally replaced by a divalent group independently selected from -O-, $-NR^{a2}-$, $-N^{+}(R^{a2})_2-$, -S-, -S(O)-, $-S(NR^{a2})-$, $-S(O)_2-$, $S(O)(NR^{a2})-$, $-S(NR^{a})_2-$, -C(O)-, -C(S)-, and $-Cy^{A}-$;

each Cy^A independently comprises an optionally substituted ring system selected from a 3- to 12-membered saturated or partially unsaturated carbocyclene; a phenylene; a 3- to 12-membered saturated or partially unsaturated heterocyclene having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5- to 6-membered heteroarylene having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a combination of any of these ring systems including fused variants thereof; and

each R^{a2} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group.

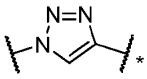
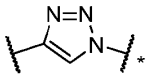
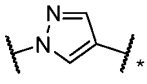
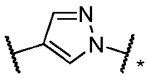
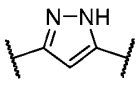
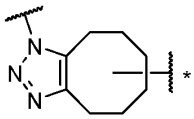
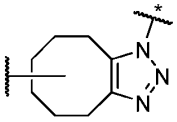
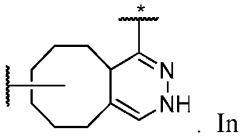
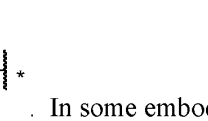
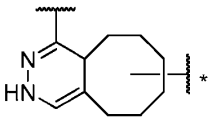
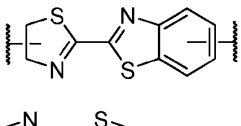
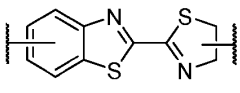
[0147] In some embodiments, R^{a2} is an optionally substituted C_{1-4} aliphatic group. In some embodiments, R^{a2} is an optionally substituted C_{1-3} aliphatic group. In some embodiments, R^{a2} is an optionally substituted C_{1-6} alkyl group. In some embodiments, R^{a2} is an optionally substituted C_{1-4} alkyl group. In some embodiments, R^{a2} is an optionally substituted C_{1-3} alkyl group. In some embodiments, R^{a2} is an optionally substituted C_{1-6} cycloalkyl group. In some embodiments, each L is a linking moiety, optionally comprising a divalent PEG moiety.

[0148] In some embodiments, at least one linking moiety comprises a Cy^A group selected from



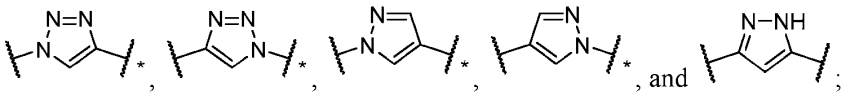
, and ;

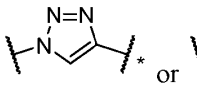
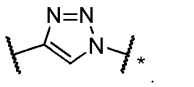
wherein * represents the direction of connection toward V.

[0149] In some embodiments, at least one linking moiety comprises . In some embodiments, at least one linking moiety comprises . In some embodiments, at least one linking moiety comprises . In some embodiments, at least one linking moiety comprises . In some embodiments, at least one linking moiety comprises . In some embodiments, at least one linking moiety comprises . In some embodiments, at least one linking moiety comprises . In some embodiments, at least one linking moiety comprises . In some embodiments, at least one linking moiety comprises . In some embodiments, at least one linking moiety comprises . In some embodiments, at least one linking moiety comprises . In some embodiments, at least one linking moiety comprises .

[0150] In some embodiments, at least one linking moiety comprises a Cy^A group that is a 5- or 6-membered heteroarylene having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0151] In some embodiments, the 5- or 6-membered heteroarylene is selected from:

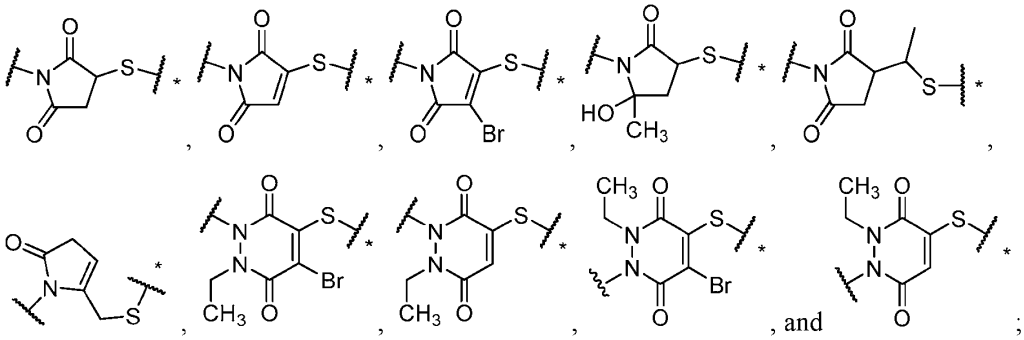


wherein * represents the direction of connection toward V. In some embodiments, the 5- or 6-membered heteroarylene is:  or .

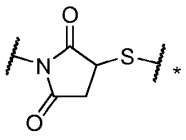
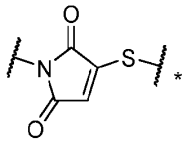
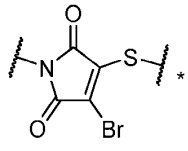
[0152] In some embodiments, the 5- to 6-membered heteroarylene comprises a divalent form of 1,2,3-triazole.

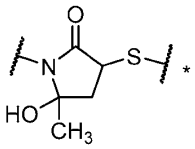
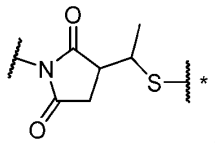
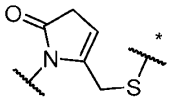
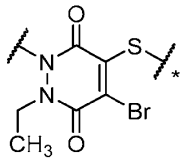
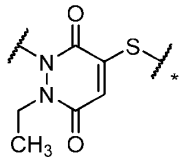
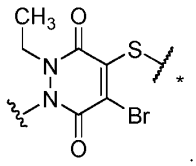
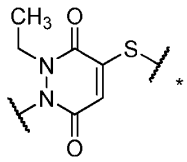
[0153] In some embodiments, at least one linking moiety comprises a Cy^A group that is a 3- to 7-membered saturated or partially unsaturated heterocyclene having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0154] In some embodiments, the 3- to 7-membered heterocyclene is selected from:



wherein * represents the direction of connection toward V.

[0155] In some embodiments, at least one, at least two, or all three linking moiety comprises . In some embodiments, at least one linking moiety comprises . In some embodiments, at least one linking moiety comprises . In some

embodiments, at least one linking moiety comprises . In some embodiments, at least one linking moiety comprises . In some embodiments, at least one linking moiety comprises . In some embodiments, at least one linking moiety comprises . In some embodiments, at least one linking moiety comprises . In some embodiments, at least one linking moiety comprises . In some embodiments, at least one linking moiety comprises .

[0156] In some embodiments, the 3- to 7-membered heterocyclene is a divalent form of succinimide, maleimide, or pyridazinedione.

[0157] In some embodiments, at least one linking moiety comprises at least one occurrence of -C(O)NR^{a2}-*, such as -C(O)NH-*, wherein * represents the direction of connection toward V.

[0158] In some embodiments, at least one linking moiety comprises two occurrences of -C(O)NR^{a2}-*, such as -C(O)NH-*.

[0159] In some embodiments, at least one linking moiety comprises an optionally substituted -C$_{1\text{-}6}$alkyl-C(O)NR^{a2}-*, such as -C$_{1\text{-}6}$alkyl-C(O)NH-*.

[0160] In some embodiments, at least one linking moiety comprises an optionally substituted -C_{1-6}alkyl-C(O)NR^{a2}-C_{1-6}alkyl-*, such as -C_{1-6}alkyl-C(O)NH-C_{1-6}alkyl-*.

[0161] In some embodiments, at least one linking moiety comprises an optionally substituted -C_{1-6}alkyl-HetAr-C_{1-6}alkyl-*, wherein HetAr is a divalent form of 1,2,3-triazole.

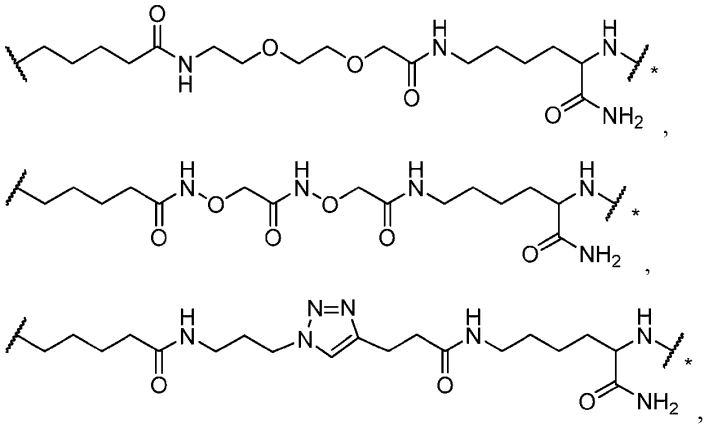
[0162] In some embodiments, at least one linking moiety comprises an optionally substituted -C(O)NR^{a2}-C_{1-6}alkyl-HetAr-C_{1-6}alkyl-C(O)NR^{a2}-*, such as -C(O)NH-C_{1-6}alkyl-HetAr-C_{1-6}alkyl-C(O)NH-*.

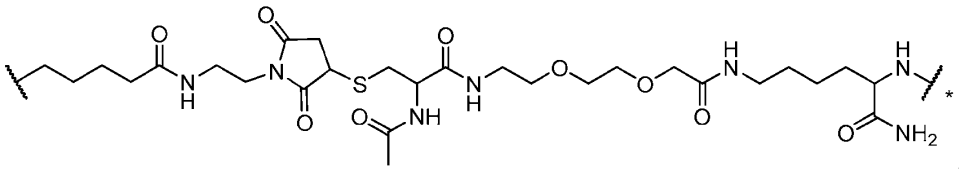
[0163] In some embodiments, at least one linking moiety comprises an optionally substituted -C_{1-6}alkyl-C(O)NR^{a2}-C_{1-6}alkyl-HetAr-C_{1-6}alkyl-C(O)NR^{a2}-C_{1-6}alkyl-*, such as -C_{1-6}alkyl-C(O)NH-C_{1-6}alkyl-HetAr-C_{1-6}alkyl-C(O)NH-C_{1-6}alkyl-*.

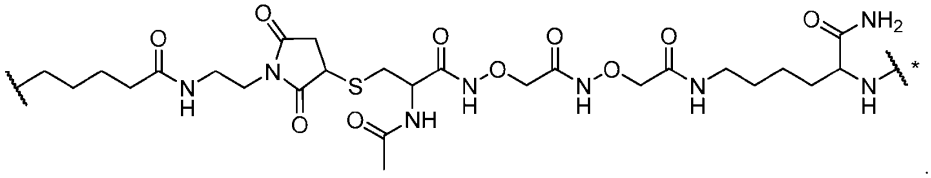
[0164] In some embodiments, at least one linking moiety comprises an optionally substituted -NH-$PEG_{(1-3)}$-C(O)-$AA_{(1-3)}$-, -NH-$AA_{(1-3)}$-C(O)-$AA_{(1-3)}$-, -NH-$AA_{(1-3)}$-$PEG_{(1-3)}$-C(O)-$AA_{(1-3)}$-, or -NH-$AA_{(1-3)}$-C(O)-$AA_{(1-3)}$- (written from the N-to-C direction);

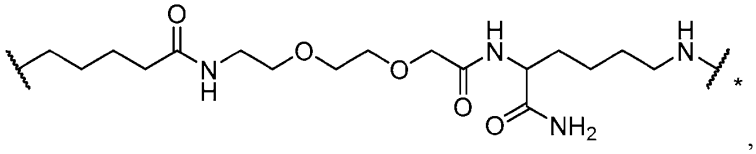
wherein each AA is independently selected from an optionally substituted -NH-PEG_2-C(O)-ε-Lys-NH-, -NH-Aoa-Aoa-C(O)-ε-Lys-NH-, -NH-Cys-PEG_2-(CH_2)C(O)-ε-Lys-NH-, and -NH-Cys-Aoa-Aoa-C(O)-ε-Lys-NH- (written from the N-to-C direction).

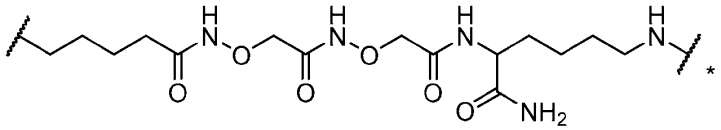
[0165] In some embodiments, at least one linking moiety is selected from the following, wherein * represents the direction of connection toward V:

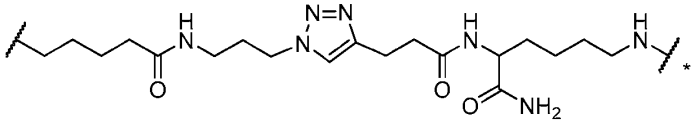


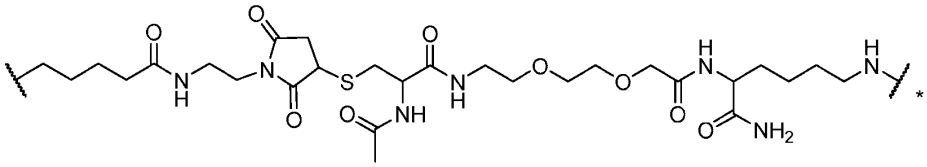

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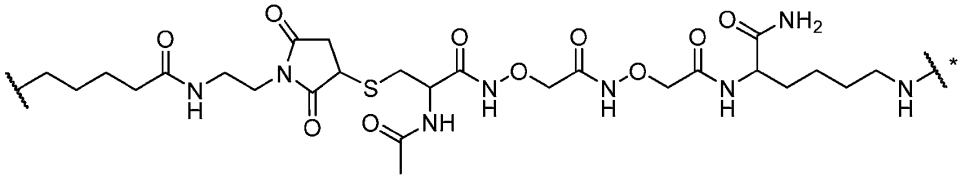

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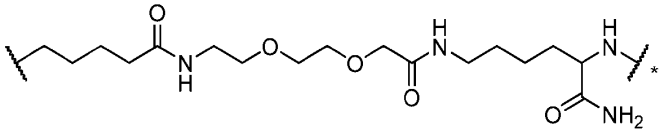

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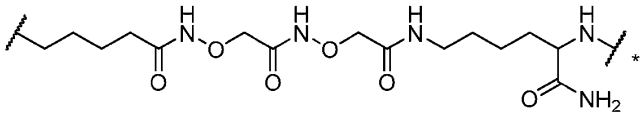

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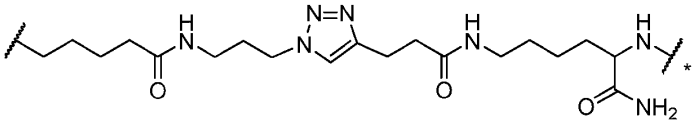

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[0166] In some embodiments, at least one linking moiety is

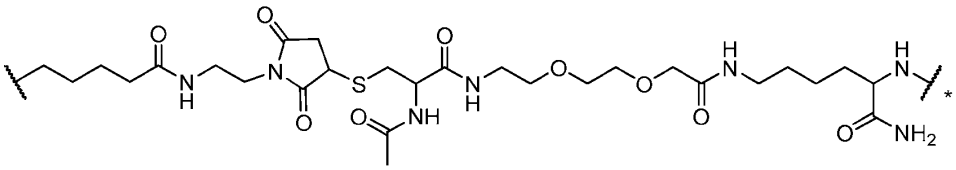

. In some embodiments, at least one



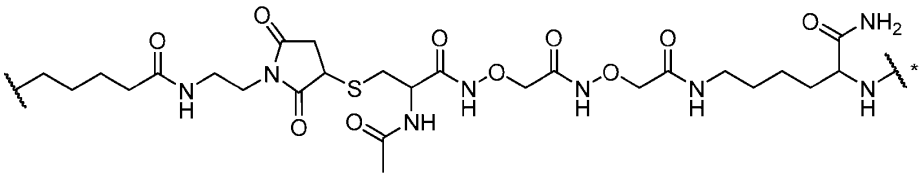
linking moiety is . In some embodiments, at least one linking moiety is



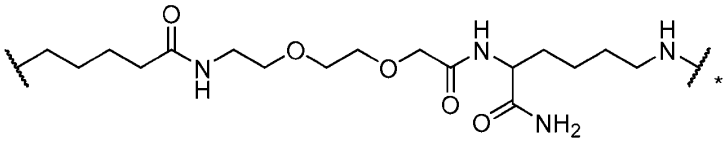
. In some embodiments, at least one linking moiety is



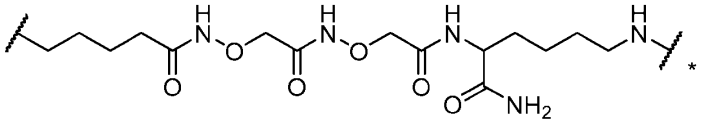
. In some embodiments, at least one linking moiety is



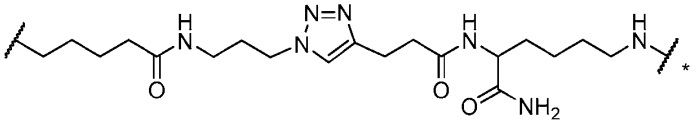
. In some embodiments, at least one linking moiety is



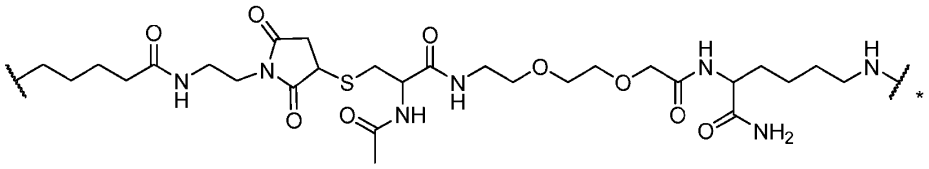
. In some embodiments, at least one linking moiety is



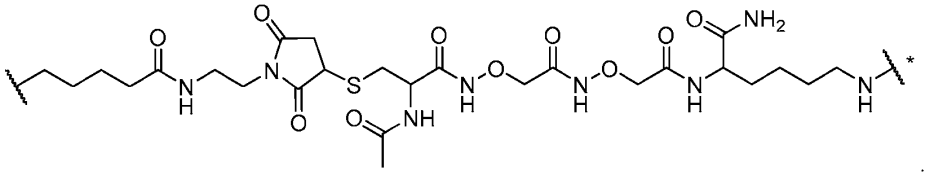
. In some embodiments, at least one linking moiety is



. In some embodiments, at least one linking moiety is

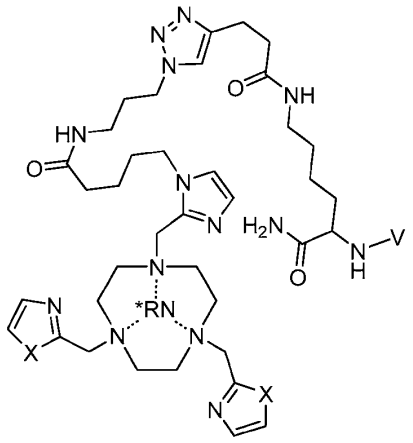


. In some embodiments, at least one linking moiety is



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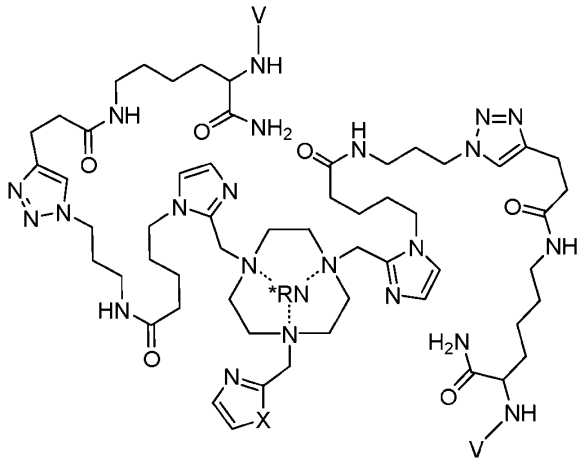
[0167] In some embodiments, the compound is of Formula IA:



(IA)

or is a pharmaceutically acceptable salt thereof.

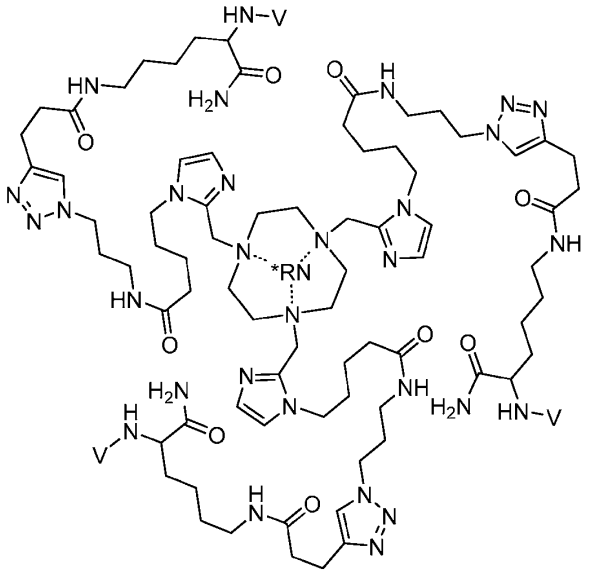
[0168] In some embodiments, the compound is of Formula IIA:



(IIA)

or is a pharmaceutically acceptable salt thereof.

[0169] In some embodiments, the compound is of Formula IIIA:



(IIIA)

or is a pharmaceutically acceptable salt thereof.

4.2.3. Radionuclide

[0170] In embodiments of the present disclosure, a compound of Formula I, IA, IB, II, IIA, IIB, III, IIIA, and IIIB, is provided, wherein the compound further comprises a radionuclide (*RN) that is chelated by the chelating moiety.

[0171] In some embodiments, *RN is selected from ^{225}Ac, ^{51}Cr, ^{66}Ga, ^{67}Ga, ^{68}Ga, [^{18}F]AlF, ^{111}In, ^{113m}In, ^{52m}Mn, ^{99m}Tc, ^{186}Re, ^{188}Re, ^{139}La, ^{140}La, ^{175}Yb, ^{179}Yb, ^{153}Sm, ^{177m}Sn, ^{166}Ho, ^{86}Y, ^{88}Y, ^{90}Y, ^{149}Pm, ^{165}Dy, ^{169}Er, ^{177}Lu, ^{52}Fe, ^{43}Sc, ^{44}Sc, ^{46}Sc, ^{47}Sc, ^{142}Pr, ^{157}Gd, ^{159}Gd, ^{212}Bi, ^{213}Bi, ^{72}As, ^{77}As, ^{97}Ru, ^{109}Pd, ^{105}Rh, ^{101m}Rh, ^{119}Sb, ^{197}Hg, ^{151}Eu, ^{153}Eu, ^{169}Eu, ^{201}Tl, ^{149}Tb, ^{152}Tb, ^{155}Tb, ^{161}Tb, ^{203}Pb, ^{212}Pb, ^{151}Pm, ^{153}Pm, ^{142}Pr, ^{143}Pr, ^{55}Co, ^{60}Cu, ^{61}Cu, ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{62}Zn, ^{188}Re, ^{198}Au, ^{199}Au, ^{227}Th, ^{111}Ag, ^{199}Ag, ^{211}At, ^{223}Ra, ^{88}Zr, and ^{89}Zr.

[0172] In some embodiments, *RN is selected from ^{225}Ac, ^{68}Ga, [^{18}F]AlF, ^{111}In, ^{99m}Tc, ^{177}Lu, ^{212}Pb, ^{61}Cu, ^{64}Cu, and ^{67}Cu.

[0173] In some embodiments, *RN is selected from ^{61}Cu, ^{64}Cu, and ^{67}Cu.

[0174] In some embodiments, *RN is ^{61}Cu.

4.2.4. Additional Embodiments

[0175] In some embodiments, the present disclosure provides for compounds having the structure:

NOTI-TVA-[NR-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_3$;

NOTI-Me-DVA-[NR-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_2$;

NOTI-Me_2-MVA-NR-$(PEG)_2$-CH_2-C(O)-Lys-SDM17;

NOTI-TVA-[NR-$(CH_2)_3$-triazolylene-$(CH_2)_2$-C(O)-Lys-SDM17]$_3$;

NOTI-Me-DVA-[NR-$(CH_2)_3$-triazolylene-$(CH_2)_2$-C(O)-Lys-SDM17]$_2$;

NOTI-Me_2-MVA-NR-$(CH_2)_3$-triazolylene-$(CH_2)_2$-C(O)-Lys-SDM17;

NOTI-TVA-[$(Aoa)_2$-Lys-SDM17]$_3$;

NOTI-Me-DVA-[$(Aoa)_2$-Lys-SDM17]$_2$;

NOTI-Me_2-MVA-$(Aoa)_2$-Lys-SDM17;

NOTI-TVA-[$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_3$;

NOTI-Me-DVA-[$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_2$;

NOTI-Me_2-MVA-$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(PEG)_2$-CH_2-C(O)-Lys-SDM17;

NOTI-TVA-[$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(Aoa)_2$-Lys-SDM17]$_3$;

NOTI-Me-DVA-[$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(Aoa)_2$-Lys-SDM17]$_2$; or

NOTI-Me_2-MVA-$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(Aoa)_2$-Lys-SDM17;

or a pharmaceutically acceptable salt thereof.

[0176] In some embodiments, the present disclosure provides compounds with a NOTI-derived chelating moiety that chelates a radionuclide (*RN), the compounds having the structure:

*RN-NOTI-TVA-[NR-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_3$;

*RN-NOTI-Me-DVA-[NR-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_2$;

*RN-NOTI-Me_2-MVA-NR-$(PEG)_2$-CH_2-C(O)-Lys-SDM17;

*RN-NOTI-TVA-[NR-$(CH_2)_3$-triazolylene-$(CH_2)_2$-C(O)-Lys-SDM17]$_3$;

*RN-NOTI-Me-DVA-[NR-$(CH_2)_3$-triazolylene-$(CH_2)_2$-C(O)-Lys-SDM17]$_2$;

*RN-NOTI-Me_2-MVA-NR-$(CH_2)_3$-triazolylene-$(CH_2)_2$-C(O)-Lys-SDM17;

*RN-NOTI-TVA-[$(Aoa)_2$-Lys-SDM17]$_3$;

*RN-NOTI-Me-DVA-[$(Aoa)_2$-Lys-SDM17]$_2$;

*RN-NOTI-Me_2-MVA-$(Aoa)_2$-Lys-SDM17;

*RN-NOTI-TVA-[$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_3$;

*RN-NOTI-Me-DVA-[$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_2$;

*RN-NOTI-Me_2-MVA-S(NAc)Cys-$(PEG)_2$-CH_2-C(O)-Lys-SDM17;

*RN-NOTI-TVA-[$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(Aoa)_2$-Lys-SDM17]$_3$;

*RN-NOTI-Me-DVA-[$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(Aoa)_2$-Lys-SDM17]$_2$; or

*RN-NOTI-Me_2-MVA-$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(Aoa)_2$-Lys-SDM17;

or a pharmaceutically acceptable salt thereof.

[0177] In some embodiments, the present disclosure provides compounds with a NOTI-derived chelating moiety that chelates ^{61}Cu, the compounds having the structure:

[^{61}Cu]Cu-NOTI-TVA-[NR-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_3$;

[^{61}Cu]Cu-NOTI-Me-DVA-[NR-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_2$;

[^{61}Cu]Cu-NOTI-Me$_2$-MVA-NR-(PEG)$_2$-CH$_2$-C(O)-Lys-SDM17;

[^{67}Cu]Cu-NOTI-TVA-[NR-(PEG)$_2$-CH$_2$-C(O)-Lys-SDM17]$_3$;

[^{67}Cu]Cu-NOTI-Me-DVA-[NR-(PEG)$_2$-CH$_2$-C(O)-Lys-SDM17]$_2$;

[^{67}Cu]Cu-NOTI-Me$_2$-MVA-NR-(PEG)$_2$-CH$_2$-C(O)-Lys-SDM17;

[^{61}Cu]Cu-NOTI-TVA-[NR-(CH$_2$)$_3$-triazolylene-(CH$_2$)$_2$-C(O)-Lys-SDM17]$_3$;

[^{61}Cu]Cu-NOTI-Me-DVA-[NR-(CH$_2$)$_3$-triazolylene-(CH$_2$)$_2$-C(O)-Lys-SDM17]$_2$;

[^{61}Cu]Cu-NOTI-Me$_2$-MVA-NR-(CH$_2$)$_3$-triazolylene-(CH$_2$)$_2$-C(O)-Lys-SDM17;

[^{67}Cu]Cu-NOTI-TVA-[NR-(CH$_2$)$_3$-triazolylene-(CH$_2$)$_2$-C(O)-Lys-SDM17]$_3$;

[^{67}Cu]Cu-NOTI-Me-DVA-[NR-(CH$_2$)$_3$-triazolylene-(CH$_2$)$_2$-C(O)-Lys-SDM17]$_2$;

[^{67}Cu]Cu-NOTI-Me$_2$-MVA-NR-(CH$_2$)$_3$-triazolylene-(CH$_2$)$_2$-C(O)-Lys-SDM17;

[^{61}Cu]Cu-NOTI-TVA-[(Aoa)$_2$-Lys-SDM17]$_3$;

[^{61}Cu]Cu-NOTI-Me-DVA-[(Aoa)$_2$-Lys-SDM17]$_2$;

[^{61}Cu]Cu-NOTI-Me$_2$-MVA-(Aoa)$_2$-Lys-SDM17;

[^{67}Cu]Cu-NOTI-TVA-[(Aoa)$_2$-Lys-SDM17]$_3$;

[^{67}Cu]Cu-NOTI-Me-DVA-[(Aoa)$_2$-Lys-SDM17]$_2$;

[^{67}Cu]Cu-NOTI-Me$_2$-MVA-(Aoa)$_2$-Lys-SDM17;

[^{61}Cu]Cu-NOTI-TVA-[(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(PEG)$_2$-CH$_2$-C(O)-Lys-SDM17]$_3$;

[^{61}Cu]Cu-NOTI-Me-DVA-[(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(PEG)$_2$-CH$_2$-C(O)-Lys-SDM17]$_2$;

[^{61}Cu]Cu-NOTI-Me$_2$-MVA-(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(PEG)$_2$-CH$_2$-C(O)-Lys-SDM17;

[^{67}Cu]Cu-NOTI-TVA-[(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(PEG)$_2$-CH$_2$-C(O)-Lys-SDM17]$_3$;

[^{67}Cu]Cu-NOTI-Me-DVA-[(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(PEG)$_2$-CH$_2$-C(O)-Lys-SDM17]$_2$;

[^{67}Cu]Cu-NOTI-Me$_2$-MVA-(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(PEG)$_2$-CH$_2$-C(O)-Lys-SDM17;

[^{61}Cu]Cu-NOTI-TVA-[(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(Aoa)$_2$-Lys-SDM17]$_3$;

[^{61}Cu]Cu-NOTI-Me-DVA-[(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(Aoa)$_2$-Lys-SDM17]$_2$;

[^{61}Cu]Cu-NOTI-Me$_2$-MVA-(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(Aoa)$_2$-Lys-SDM17;

[^{67}Cu]Cu-NOTI-TVA-[(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(Aoa)$_2$-Lys-SDM17]$_3$;

[^{67}Cu]Cu-NOTI-Me-DVA-[(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(Aoa)$_2$-Lys-SDM17]$_2$; or

[^{67}Cu]Cu-NOTI-Me$_2$-MVA-(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(Aoa)$_2$-Lys-SDM17;

or a pharmaceutically acceptable salt thereof.

4.3. Pharmaceutical Compositions

[0178] In another aspect, the present disclosure provides pharmaceutical compositions comprising a compound of the present disclosure, including a compound of any one of Formula I, IA, IB, II, IIA, IIB, III, IIIA, and IIIB, or a salt thereof, and any of the compound embodiments in Section 4.2.4, in combination with a pharmaceutically acceptable excipient (e.g., carrier). In some embodiments, the compound further comprises a radionuclide, *RN.

[0179] A "pharmaceutically acceptable carrier", as used herein refers to pharmaceutical excipients, for example, pharmaceutically, physiologically, acceptable organic or inorganic carrier substances suitable for enteral or parenteral application that do not deleteriously react with the active agent. Suitable pharmaceutically acceptable carriers include water, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, and carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethylcellulose, and polyvinylpyrrolidone. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the disclosure.

[0180] The compounds of the disclosure can be administered alone or can be coadministered to the subject. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). The preparations can

also be combined, when desired, with other active substances (e.g., to reduce metabolic degradation).

[0181] In some embodiments, a compound as described herein can be incorporated into a pharmaceutical composition for administration by methods known to those skilled in the art and described herein for provided compounds.

[0182] In some embodiments, the pharmaceutical composition comprising a compound according to of any one of Formula II (and all subgenera Formulae I, IIa, IIb, IIc, and III), further comprising ^{61}Cu, wherein the composition is characterized by one or more of:

an apparent molar activity of the compound of ≥ 35 MBq/nmol;

an activity concentration of ≥ 8 MBq/mL

a [^{61}Cu]Cu radionuclidic purity at end of synthesis of ≥ 95%,

a radiocobalt activity content at end of synthesis of ≤ 0.05%,

a ^{110m}Ag specific activity ≤ 0.1 Bq/g,

a ^{108m}Ag specific activity ≤ 0.1 Bq/g, or

a ^{109}Cd specific activity ≤ 0.1 Bq/g.

4.3.1. Properties

[0183] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure (e.g., Formula II, inclusive of Formulae I, IIa, IIb, IIc, and III), the compound further comprising ^{61}Cu, the composition has an apparent molar activity of the compound of 1 to 280 MBq/nmol, e.g., 5 to 265 MBq/nmol, 10 to 250 MBq/nmol, 15 to 235 MBq/nmol, 20 to 220 MBq/nmol, 25 to 205 MBq/nmol, 30 to 190 MBq/nmol, 35 to 175 MBq/nmol, 40 to 160 MBq/nmol, 45 to 150 MBq/nmol, 50 to 135 MBq/nmol, 55 to 120 MBq/nmol, 1 to 50 MBq/nmol, 2 to 48 MBq/nmol, 4 to 46 MBq/nmol, 6 to 44 MBq/nmol, 8 to 42 MBq/nmol, 10 to 40 MBq/nmol, 12 to 38 MBq/nmol, 14 to 36 MBq/nmol, 16 to 34 MBq/nmol, 18 to 32 MBq/nmol, 20 to 30 MBq/nmol, or 22 to 28 MBq/nmol. In some embodiments, the composition has an apparent molar activity of the compound of 24 MBq/nmol ± 3 MBq/nmol.

[0184] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the compound further comprising ^{61}Cu, the composition has an apparent molar activity of the compound of ≥ 35 MBq/nmol, ≥ 40 MBq/nmol, ≥ 45 MBq/nmol, ≥ 50 MBq/nmol, ≥ 55 MBq/nmol, ≥ 60 MBq/nmol, ≥ 65 MBq/nmol, ≥ 70 MBq/nmol, ≥ 75 MBq/nmol, ≥ 80 MBq/nmol, ≥ 85 MBq/nmol, ≥ 90 MBq/nmol, ≥ 95 MBq/nmol, ≥ 100 MBq/nmol, ≥ 105 MBq/nmol, ≥ 110 MBq/nmol, ≥ 115 MBq/nmol, ≥ 120 MBq/nmol, ≥ 125 MBq/nmol, ≥ 130 MBq/nmol, ≥ 135 MBq/nmol, ≥ 140 MBq/nmol, ≥ 145 MBq/nmol, ≥ 150 MBq/nmol, ≥ 155 MBq/nmol, ≥ 160 MBq/nmol, ≥ 165 MBq/nmol, ≥ 170 MBq/nmol, ≥ 175 MBq/nmol, ≥ 180 MBq/nmol, ≥ 185 MBq/nmol, ≥ 190 MBq/nmol, ≥ 195 MBq/nmol, or ≥ 200 MBq/nmol.

[0185] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the compound further comprising ^{61}Cu, the composition has an apparent molar activity of the compound of 1 to 250 MBq/nmol, for example, 1 to 200 MBq/nmol, 1 to 150 MBq/nmol, 1 to 100 MBq/nmol, 1 to 50 MBq/nmol, 50 to 250 MBq/nmol, 50 to 200 MBq/nmol, 50 to 150 MBq/nmol, 50 to 100 MBq/nmol, 100 to 250 MBq/nmol, 100 to 150 MBq/nmol, 150 to 250 MBq/nmol, 150 to 200 MBq/nmol, or 200 to 250 MBq/nmol. In some embodiments, the radiotracer composition is characterized by apparent molar activity of the compound of 1 to 150 MBq/nmol.

[0186] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the compound further comprising ^{61}Cu, the composition has an apparent molar activity of the compound of ≥ 90 MBq/nmol, ≥ 88 MBq/nmol, ≥ 86 MBq/nmol, ≥ 84 MBq/nmol, ≥ 82 MBq/nmol, ≥ 80 MBq/nmol, ≥ 78 MBq/nmol, ≥ 76 MBq/nmol, ≥ 74 MBq/nmol, ≥ 72 MBq/nmol, ≥ 70 MBq/nmol, ≥ 68 MBq/nmol, ≥ 66 MBq/nmol, ≥ 64 MBq/nmol, ≥ 62 MBq/nmol, ≥ 60 MBq/nmol, ≥ 58 MBq/nmol, ≥ 56 MBq/nmol, ≥ 54 MBq/nmol, ≥ 52 MBq/nmol, ≥ 50 MBq/nmol, ≥ 48 MBq/nmol, ≥ 46 MBq/nmol, ≥ 44 MBq/nmol, or ≥ 42 MBq/nmol.

[0187] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the compound further comprising ^{61}Cu, the composition has an apparent molar activity of the compound of ≥ 3 MBq/nmol, ≥ 4 MBq/nmol, ≥ 5 MBq/nmol, ≥ 6 MBq/nmol, ≥ 7 MBq/nmol, ≥ 8 MBq/nmol, ≥ 9 MBq/nmol, ≥ 10 MBq/nmol, ≥ 11 MBq/nmol,

≥ 12 MBq/nmol, ≥ 13 MBq/nmol, ≥ 14 MBq/nmol, ≥ 15 MBq/nmol, ≥ 16 MBq/nmol, ≥ 17 MBq/nmol, ≥ 18 MBq/nmol, or ≥ 19 MBq/nmol.

[0188] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the compound further comprising ^{61}Cu, the composition has an apparent molar activity of the compound of ≥ 3 MBq/nmol, ≥ 5 MBq/nmol, ≥ 10 MBq/nmol, ≥ 15 MBq/nmol, ≥ 20 MBq/nmol, ≥ 25 MBq/nmol, ≥ 30 MBq/nmol, ≥ 35 MBq/nmol, ≥ 40 MBq/nmol, ≥ 45 MBq/nmol, ≥ 50 MBq/nmol, ≥ 55 MBq/nmol, ≥ 60 MBq/nmol, ≥ 65 MBq/nmol, ≥ 70 MBq/nmol, ≥ 75 MBq/nmol, ≥ 80 MBq/nmol, ≥ 85 MBq/nmol, ≥ 90 MBq/nmol, ≥ 95 MBq/nmol, ≥ 100 MBq/nmol, ≥ 105 MBq/nmol, ≥ 110 MBq/nmol, ≥ 115 MBq/nmol, ≥ 120 MBq/nmol, ≥ 125 MBq/nmol, 130 MBq/nmol, 135 MBq/nmol, 140 MBq/nmol, 145 MBq/nmol, 150 MBq/nmol, 155 MBq/nmol, ≥ 160 MBq/nmol, ≥ 165 MBq/nmol, ≥ 170 MBq/nmol, ≥ 175 MBq/nmol, ≥ 180 MBq/nmol, ≥ 185 MBq/nmol, ≥ 190 MBq/nmol, ≥ 195 MBq/nmol, ≥ 200 MBq/nmol, ≥ 205 MBq/nmol, ≥ 210 MBq/nmol, ≥ 215 MBq/nmol, 220 ≥ MBq/nmol, ≥ 225 MBq/nmol, ≥ 230 MBq/nmol, ≥ 235 MBq/nmol, ≥ 240 MBq/nmol, ≥ 245 MBq/nmol, ≥ 250 MBq/nmol, ≥ 255 MBq/nmol, ≥ 260 MBq/nmol, ≥ 265 MBq/nmol, ≥ 270 MBq/nmol, ≥ 275 MBq/nmol, or ≥ 280 MBq/nmol. In some embodiments, the composition has an apparent molar activity of the compound of ≥ 24 MBq/nmol.

[0189] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the compound further comprising ^{61}Cu, the composition has an apparent molar activity of the compound of 1 to 250 MBq/nmol, for example, 1 to 200 MBq/nmol, 1 to 150 MBq/nmol, 1 to 100 MBq/nmol, 1 to 50 MBq/nmol, 50 to 250 MBq/nmol, 50 to 200 MBq/nmol, 50 to 150 MBq/nmol, 50 to 100 MBq/nmol, 100 to 250 MBq/nmol, 100 to 150 MBq/nmol, 150 to 250 MBq/nmol, 150 to 200 MBq/nmol, or 200 to 250 MBq/nmol.

[0190] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the compound further comprising ^{61}Cu, the composition has an apparent molar activity of the compound of 35 to 250 MBq/nmol, for example, 35 to 200 MBq/nmol, 35 to 150 MBq/nmol, 35 to 100 MBq/nmol, 35 to 50 MBq/nmol, 37 to 250 MBq/nmol, 37 to 200 MBq/nmol, 37 to 150 MBq/nmol, 37 to 100 MBq/nmol, 37 to 50 MBq/nmol, 40 to 250 MBq/nmol, 40 to 200 MBq/nmol, 40 to 150 MBq/nmol, 40 to 100 MBq/nmol, or 40 to 50 MBq/nmol.

[0191] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the compound further comprising ^{61}Cu, the composition has an apparent molar activity of the compound of 35, 36, 37, 38, 39, 40, 41, 42, 43, 45, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 MBq/nmol or greater. For example, in some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the compound further comprising ^{61}Cu, the composition has an apparent molar activity of the compound of 37 or greater, 54 or greater, 67 or greater.

[0192] In some embodiments of the pharmaceutical composition is characterized by an activity concentration of $\geq$ 8 MBq/mL. In some embodiments, the composition is characterized by an activity concentration of 8 to 10 MBq/mL, 10 to 20 MBq/mL, 20 to 30 MBq/mL, 30 to 40 MBq/mL, 40 to 50 MBq/mL, 50 to 60 MBq/mL, 60 to 70 MBq/mL, 70 to 80 MBq/mL, 80 to 90 MBq/mL, 90 to 100 MBq/mL, 100 to 110 MBq/mL, 110 to 120 MBq/mL, 120 to 130 MBq/mL, 130 to 140 MBq/mL, 140 to 150 MBq/mL, 150 to 160 MBq/mL, 160 to 170 MBq/mL, 170 to 180 MBq/mL, 180 to 190 MBq/mL, 190 to 200 MBq/mL, 200 to 210 MBq/mL, 210 to 220 MBq/mL, 220 to 230 MBq/mL, 230 to 240 MBq/mL, 240 to 250 MBq/mL, 250 to 260 MBq/mL, 260 to 270 MBq/mL, 270 to 280 MBq/mL, 280 to 290 MBq/mL, 290 to 300 MBq/mL, 300 to 310 MBq/mL, 310 to 320 MBq/mL, 320 to 330 MBq/mL, 330 to 340 MBq/mL, 340 to 350 MBq/mL, 350 to 360 MBq/mL, 360 to 370 MBq/mL, 370 to 380 MBq/mL, 380 to 390 MBq/mL, 390 to 400 MBq/mL, 400 to 410 MBq/mL, 410 to 420 MBq/mL, 420 to 430 MBq/mL, 430 to 440 MBq/mL, 440 to 450 MBq/mL, 450 to 460 MBq/mL, 460 to 470 MBq/mL, 470 to 480 MBq/mL, 480 to 490 MBq/mL, 490 to 500 MBq/mL, 500 to 510 MBq/mL, 510 to 520 MBq/mL, 520 to 530 MBq/mL, 530 to 540 MBq/mL, 540 to 550 MBq/mL, 550 to 560 MBq/mL, 560 to 570 MBq/mL, 570 to 580 MBq/mL, 580 to 590 MBq/mL, 590 to 600 MBq/mL, 600 to 610 MBq/mL, 610 to 620 MBq/mL, 620 to 630 MBq/mL, 630 to 640 MBq/mL, 640 to 650 MBq/mL, 650 to 660 MBq/mL, 660 to 670 MBq/mL, 670 to 680 MBq/mL, 680 to 690 MBq/mL, 690 to 700 MBq/mL, 700 to 710 MBq/mL, 710 to 720 MBq/mL, 720 to 730 MBq/mL, 730 to 740 MBq/mL, 740 to 750 MBq/mL, 750 to 760 MBq/mL, 760 to 770 MBq/mL, 770 to 780 MBq/mL, 780 to 790 MBq/mL, 790 to 800 MBq/mL, 800 to 810 MBq/mL, 810 to 820 MBq/mL, 820 to 830 MBq/mL, 830 to 840 MBq/mL, 840 to 850 MBq/mL, 850 to 860 MBq/mL, 860 to 870

MBq/mL, 870 to 880 MBq/mL, 880 to 890 MBq/mL, 890 to 900 MBq/mL, 900 to 910 MBq/mL, 910 to 920 MBq/mL, 920 to 930 MBq/mL, 930 to 940 MBq/mL, 940 to 950 MBq/mL, 950 to 960 MBq/mL, 960 to 970 MBq/mL, 970 to 980 MBq/mL, 980 to 990 MBq/mL, or 990 to 1000 MBq/mL.

[0193] In some embodiments of the pharmaceutical composition is characterized by an activity concentration of ≥ 8 MBq/mL. In some embodiments, the composition is characterized by an activity concentration of 5 to 500 MBq/mL, 20 to 480 MBq/mL, 40 to 460 MBq/mL, 60 to 440 MBq/mL, 80 to 420 MBq/mL, 100 to 400 MBq/mL, 120 to 380 MBq/mL, 140 to 360 MBq/mL, 160 to 340 MBq/mL, 180 to 320 MBq/mL, or 200 to 300 MBq/mL.

[0194] In some embodiments of the pharmaceutical composition is characterized by an activity concentration of ≥ 3 MBq/mL, ≥ 4 MBq/mL, ≥ 5 MBq/mL, ≥ 6 MBq/mL, ≥ 7 MBq/mL, ≥ 8 MBq/mL, ≥ 9 MBq/mL, ≥ 10 MBq/mL, ≥ 12 MBq/mL, ≥ 15 MBq/mL, ≥ 20 MBq/mL, ≥ 25 MBq/mL, ≥ 30 MBq/mL, ≥ 35 MBq/mL, ≥ 40 MBq/mL, ≥ 45 MBq/mL, ≥ 50 MBq/mL, ≥ 55 MBq/mL, ≥ 60 MBq/mL, ≥ 65 MBq/mL, ≥ 70 MBq/mL, ≥ 75 MBq/mL, ≥ 80 MBq/mL, ≥ 85 MBq/mL, ≥ 90 MBq/mL, ≥ 95 MBq/mL, ≥ 100 MBq/mL, ≥ 105 MBq/mL, ≥ 110 MBq/mL, ≥ 115 MBq/mL, ≥ 120 MBq/mL, ≥ 125 MBq/mL, 130 MBq/mL, 135 MBq/mL, 140 MBq/mL, 145 MBq/mL, 150 MBq/mL, 155 MBq/mL, ≥ 160 MBq/mL, ≥ 165 MBq/mL, ≥ 170 MBq/mL, ≥ 175 MBq/mL, ≥ 180 MBq/mL, ≥ 185 MBq/mL, ≥ 190 MBq/mL, ≥ 195 MBq/mL, ≥ 200 MBq/mL, ≥ 205 MBq/mL, ≥ 210 MBq/mL, ≥ 215 MBq/mL, 220 ≥ MBq/mL, ≥ 225 MBq/mL, ≥ 230 MBq/mL, ≥ 235 MBq/mL, ≥ 240 MBq/mL, ≥ 245 MBq/mL, ≥ 250 MBq/mL, ≥ 255 MBq/mL, ≥ 260 MBq/mL, ≥ 265 MBq/mL, ≥ 270 MBq/mL, ≥ 275 MBq/mL, or ≥ 280 MBq/mL.

[0195] In some embodiments, the activity concentration of the resulting pharmaceutical composition may be diluted (e.g., by a factor of 3 to 10) as long as the activity concentration is ≥ 8 MBq/mL. In some embodiments, a composition has an activity concentration 8 to 20 MBq/mL, 9 to 19 MBq/mL, 10 to 18 MBq/mL, 11 to 19 MBq/mL, 12 to 18 MBq/mL, 13 to 15 MBq/mL, 14 to 15 MBq/mL, 8 to 14 MBq/mL, 8 to 13 MBq/mL, 8 to 12 MBq/mL, 8 to 11 MBq/mL, 8 to 10 MBq/mL, 8 to 9 MBq/mL, 9 to 14 MBq/mL, 10 to 13 MBq/mL, or 11 to 12 MBq/mL.

[0196] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by an activity concentration 35 to 75 MBq/mL.

[0197] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by a ^{61}[Cu]Cu radionuclidic purity at end of synthesis of ≥ 95%, e.g., ≥ 96%, ≥ 97%, ≥ 98%, or ≥ 99%. In some embodiments, the composition is characterized by a ^{61}[Cu]Cu radionuclidic purity at end of synthesis of ≥ 97%.

[0198] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized a ^{61}[Cu]Cu radionuclidic purity at end of synthesis of ≥ 98%, e.g., ≥ 99%, ≥ 99.5%, ≥ 99.6%, ≥ 99.7%, ≥ 99.8%, or ≥ 99.9%. In some embodiments, the composition is a characterized a ^{61}[Cu]Cu radionuclidic purity at end of synthesis of ≥ 99.99%.

[0199] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized a radiocobalt radionuclidic purity [sum of all isotopes present] at end of synthesis of ≤ 0.05%, ≤ 0.02%, or ≤ 0.01%, e.g., ≤ 0.005% or, ≤ 0.001%.

[0200] In some embodiments of the pharmaceutical composition is characterized by at least one of the ^{56}[Co]Co radiocobalt activity content or ^{58}[Co]Co radiocobalt activity content at end of synthesis of ≤ 1500 Bq/g, e.g., ≤ 1200 Bq/g, ≤ 1000 Bq/g, ≤ 800 Bq/g, ≤ 400 Bq/g, or ≤ 200 Bq/g.

[0201] In some embodiments of the pharmaceutical composition is characterized by at least one of the ^{56}[Co]Co radiocobalt activity content or ^{58}[Co]Co radiocobalt activity content at end of synthesis from 200 Bq/g to 1500 Bq/g, e.g., from 200 Bq/g to 1200 Bq/g, from 200 Bq/g to 1000 Bq/g, from 200 Bq/g to 800 Bq/g, from 200 to 600 Bq/g, or from 200 Bq/g to 400 Bq/g.

[0202] In some embodiments of the pharmaceutical composition comprising is characterized by a ^{58}[Co]Co radiocobalt activity content at end of synthesis of ≤ 100 Bq/g, e.g., ≤ 50 Bq/g, ≤ 25 Bq/g, ≤ 10 Bq/g, ≤ 8 Bq/g, ≤ 4 Bq/g, or ≤ 2 Bq/g.

[0203] In some embodiments of the pharmaceutical composition is characterized by a ^{56}[Co]Co radiocobalt activity content at end of synthesis of ≤ 100 Bq/g, e.g., ≤ 50 Bq/g, ≤ 25 Bq/g, ≤ 10 Bq/g, ≤ 8 Bq/g, ≤ 4 Bq/g, or ≤ 2 Bq/g.

[0204] In some embodiments of the pharmaceutical composition is characterized by a ^{56}[Co]Co radiocobalt activity content at end of synthesis of from 1 Bq/g to 100 Bq/g, e.g., from 1 Bq/g to 50 Bq/g, from 1 Bq/g to 25 Bq/g, from 1 Bq/g to 10 Bq/g, from 1 Bq/g to 8 Bq/g, or from 1 Bq/g to 4 Bq/g.

[0205] In some embodiments of the pharmaceutical composition is characterized by a ^{58}[Co]Co radiocobalt activity content at end of synthesis of $\leq$ 100 Bq/g, e.g., $\leq$ 50 Bq/g, $\leq$ 25 Bq/g, $\leq$ 10 Bq/g, $\leq$ 8 Bq/g, $\leq$ 4 Bq/g, or $\leq$ 2 Bq/g.

[0206] In some embodiments of the pharmaceutical composition is characterized by a ^{58}[Co]Co radiocobalt activity content at end of synthesis of from 1 Bq/g to 100 Bq/g, e.g., from 1 Bq/g to 50 Bq/g, from 1 Bq/g to 25 Bq/g, from 1 Bq/g to 10 Bq/g, from 1 Bq/g to 8 Bq/g, or from 1 Bq/g to 4 Bq/g.

[0207] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by ^{110m}Ag in an amount $\leq$ 0.1 Bq/g. In some embodiments, the pharmaceutical composition is characterized by ^{108m}Ag in an amount $\leq$ 0.1 Bq/g. In some embodiments, the pharmaceutical composition is characterized by ^{109}Cd in an amount $\leq$ 0.1 Bq/g.

[0208] In some embodiments, the pharmaceutical composition comprises at least two of: an amount of ^{110m}Ag $\leq$ 0.1 Bq/g, an amount of ^{108m}Ag $\leq$ 0.1 Bq/g, and an amount of ^{109}Cd $\leq$ 0.1 Bq/g. In some embodiments, the pharmaceutical composition comprises an amount of ^{110m}Ag $\leq$ 0.1 Bq/g, an amount of ^{108m}Ag $\leq$ 0.1 Bq/g, and an amount of ^{109}Cd $\leq$ 0.1 Bq/g.

[0209] In some embodiments, the pharmaceutical composition comprises radionuclidic impurities in a sum of $\leq$ 1200 Bq/g, e.g., $\leq$ 1000 Bq/g, $\leq$ 800 Bq/g, or $\leq$ 500 Bq/g.

[0210] In certain embodiments, the pharmaceutical composition has at least one of a ^{56}[Co]Co specific activity or ^{58}[Co]Co specific activity at end of synthesis of $\leq$ 1,500 Bq/g, e.g., $\leq$ 1,200 Bq/g, $\leq$ 1,000 Bq/g, $\leq$ 800 Bq/g, $\leq$ 400 Bq/g, or $\leq$ 200 Bq/g.

[0211] In certain embodiments, the pharmaceutical composition has at least one of a ^{56}[Co]Co specific activity or ^{58}[Co]Co specific activity at end of synthesis from 200 Bq/g to 1,500 Bq/g, e.g., from 200 Bq/g to 1,200 Bq/g, from 200 Bq/g to 1,000 Bq/g, from 200 Bq/g to 800 Bq/g, from 200 to 600 Bq/g, or from 200 Bq/g to 400 Bq/g.

[0212] In certain embodiments, the pharmaceutical composition has a ^{56}[Co]Co specific activity of ≤ 100 Bq/g, e.g., ≤ 50 Bq/g, ≤ 25 Bq/g, ≤ 10 Bq/g, ≤ 8 Bq/g, ≤ 4 Bq/g, or ≤ 2 Bq/g.

[0213] In certain embodiments, the pharmaceutical composition has a ^{56}[Co]Co specific activity of from 1 Bq/g to 100 Bq/g, e.g., from 1 Bq/g to 50 Bq/g, from 1 Bq/g to 25 Bq/g, from 1 Bq/g to 10 Bq/g, from 1 Bq/g to 8 Bq/g, or from 1 Bq/g to 4 Bq/g.

[0214] In certain embodiments, the pharmaceutical composition has a ^{58}[Co]Co specific activity of ≤ 100 Bq/g, e.g., ≤ 50 Bq/g, ≤ 25 Bq/g, ≤ 10 Bq/g, ≤ 8 Bq/g, ≤ 4 Bq/g, or ≤ 2 Bq/g.

[0215] In certain embodiments, the pharmaceutical composition has a ^{58}[Co]Co specific activity of from 1 Bq/g to 100 Bq/g, e.g., from 1 Bq/g to 50 Bq/g, from 1 Bq/g to 25 Bq/g, from 1 Bq/g to 10 Bq/g, from 1 Bq/g to 8 Bq/g, or from 1 Bq/g to 4 Bq/g.

[0216] In certain embodiments, the pharmaceutical composition is characterized by a ^{110m}Ag specific activity ≤ 0.1 Bq/g. In certain embodiments, the pharmaceutical composition is characterized by a ^{108m}Ag specific activity ≤ 0.1 Bq/g. In certain embodiments, the pharmaceutical composition is characterized by a ^{109}Cd specific activity ≤ 0.1 Bq/g.

[0217] In certain embodiments, the pharmaceutical composition is characterized by at least two of: a ^{110m}Ag specific activity ≤ 0.1 Bq/g, a ^{108m}Ag specific activity ≤ 0.1 Bq/g, and a ^{109}Cd specific activity ≤ 0.1 Bq/g. In certain embodiments, the pharmaceutical composition is characterized by a ^{110m}Ag specific activity of ≤ 0.1 Bq/g, a ^{108m}Ag specific activity ≤ 0.1 Bq/g, and a ^{109}Cd specific activity ≤ 0.1 Bq/g.

[0218] In certain embodiments, the sum of the specific activities of the radionuclidic impurities in the pharmaceutical composition is ≤ 8,000 Bq/g, e.g., ≤ 5,000 Bq/g, ≤ 3,000 Bq/g, ≤ 1200 Bq/g, ≤ 1,000 Bq/g, ≤ 800 Bq/g, or ≤ 500 Bq/g.

[0219] In certain embodiments, the pharmaceutical composition comprises Al in an amount ≤ 1.2 ng/MBq. In certain embodiments, the pharmaceutical composition comprises Co in an amount ≤ 0.2 ng/MBq. In certain embodiments, the pharmaceutical composition comprises Fe in an amount ≤ 1.7 ng/MBq. In certain embodiments, the pharmaceutical composition comprises Pb in an amount ≤ 0.8 ng/MBq. In certain embodiments, the pharmaceutical composition comprises Zn in an amount ≤ 0.8 ng/MBq. In certain embodiments, the pharmaceutical composition comprises one

or more of: an amount of Al ≤ 1.2 ng/MBq, an amount of Co ≤ 0.2 ng/MBq, an amount of Fe ≤ 1.7 ng/MBq, an amount of Pb ≤ 0.8 ng/MBq, or an amount of Zn ≤ 0.8 ng/MBq.

[0220] In certain embodiments, the pharmaceutical composition has an activity concentration ≥ 10 MBq/mL, e.g., ≥ 20 MBq/mL, ≥ 30 MBq/mL, ≥ 40 MBq/mL, ≥ 50 MBq/mL, ≥ 60 MBq/mL, ≥ 70 MBq/mL, ≥ 80 MBq/mL, or ≥ 90 MBq/mL.

[0221] In certain embodiments, the pharmaceutical composition has an activity concentration from 10 MBq/mL to 100 MBq/mL, e.g., from 10 MBq/mL to 50 MBq/mL, from 10 MBq/mL to 100 MBq/mL, or from 40 MBq/mL to 90 MBq/mL.

[0222] In certain embodiments, the pharmaceutical composition has an activity concentration ≥ 10 MBq/mL, e.g., ≥ 20 MBq/mL, ≥ 30 MBq/mL, ≥ 40 MBq/mL, ≥ 50 MBq/mL, or ≥ 60 MBq/mL.

[0223] In certain embodiments, the pharmaceutical composition has an activity concentration from 10 MBq/mL to 60 MBq/mL, e.g., from 10 MBq/mL to 50 MBq/mL, from 10 MBq/mL to 40 MBq/mL, from 10 MBq/mL to 30 MBq/mL, from 10 MBq/mL to 20 MBq/mL, from 20 MBq/mL to 60 MBq/mL, from 20 MBq/mL to 50 MBq/mL, from 20 MBq/mL to 40 MBq/mL, from 20 MBq/mL to 30 MBq/mL, from 30 MBq/mL to 60 MBq/mL, from 30 MBq/mL to 50 MBq/mL, from 30 MBq/mL to 40 MBq/mL, from 40 MBq/mL to 60 MBq/mL, from 40 MBq/mL to 50 MBq/mL, or from 50 MBq/mL to 60 MBq/mL.

[0224] In certain embodiments, the apparent molar activity of the compound is ≥ 1 MBq/nmol, e.g., ≥ 10 MBq/nmol, ≥ 20 MBq/nmol, ≥ 30 MBq/nmol, or ≥ 50 MBq/nmol. In certain embodiments, the apparent molar activity of the compound is from 1 MBq/nmol to 50 MBq/nmol, e.g., from 1 MBq/nmol to 30 MBq/nmol, from 1 MBq/nmol to 20 MBq/nmol, from 1 MBq/nmol to 10 MBq/nmol, from 10 MBq/nmol to 50 MBq/nmol, from 10 MBq/nmol, to 30 MBq/nmol, from 10 MBq/nmol to 20 MBq/nmol, from 20 MBq/nmol to 50 MBq/nmol, from 20 MBq/nmol to 40 MBq/nmol, or from 20 MBq/nmol to 30 MBq/nmol.

[0225] In certain embodiments, the molar activity of the compound is ≥ 1 MBq/nmol, e.g., ≥ 10 MBq/nmol, ≥ 20 MBq/nmol, ≥ 30 MBq/nmol, or ≥ 50 MBq/nmol. In certain embodiments, the molar activity of the compound is from 1 MBq/nmol to 50 MBq/nmol, e.g., from 1 MBq/nmol to 30 MBq/nmol, from 1 MBq/nmol to 20 MBq/nmol, from 1 MBq/nmol to 10 MBq/nmol, from 10 MBq/nmol to 50 MBq/nmol, from 10 MBq/nmol, to 30 MBq/nmol, from 10 MBq/nmol to 20

MBq/nmol, from 20 MBq/nmol to 50 MBq/nmol, from 20 MBq/nmol to 40 MBq/nmol, or from 20 MBq/nmol to 30 MBq/nmol.

[0226] In certain embodiments, the pH of the pharmaceutical composition is from 5 to 7, e.g., from 5 to 6, from 5.5 to 6.5, or from 6 to 7. In certain embodiments, the pH of the pharmaceutical composition is 5, 6, or 7 +/- 0.1.

[0227] In some embodiments, a composition provided is characterized by a specific activity of ≥ 0.5 GBq/mg, e.g., ≥ 1 GBq/mg, ≥ 1.5 GBq/mg, ≥ 2.0 GBq/mg, ≥ 3.0 GBq/mg, ≥ 4.0 GBq/mg, ≥ 5.0 GBq/mg, ≥ 6.0 GBq/mg, ≥ 7.0 GBq/mg, ≥ 8.0 GBq/mg, ≥ 9.0 GBq/mg, or ≥ 10.0 GBq/mg.

[0228] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by a specific activity of 0.5 to 10.0 GBq/mg, for example, 1.0 to 10.0 GBq/mg, 2.0 to 10.0 GBq/mg, 3.0 to 10.0 GBq/mg, 4.0 to 10.0 GBq/mg, 5.0 to 10.0 GBq/mg, 6.0 to 10.0 GBq/mg, 7.0 To 10.0 GBq/mg, 8.0 to 10.0 GBq/mg, 9.0 to 10.0 GBq/mg, 0.5 to 5.0 GBq/mg, 1.0 to 5.0 GBq/mg, 2.0 to 5.0 GBq/mg, 3.0 to 5.0 GBq/mg, or 4.0 to 5.0 GBq/mg.

[0229] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by a specific activity of 0.5 to 1.9 GBq/mg, 0.55 to 1.85 GBq/mg, 0.6 to 1.8 GBq/mg, 0.65 to 1.75 GBq/mg, 0.7 to 1.7 GBq/mg, 0.75 to 1.65 GBq/mg, 0.8 to 1.6 GBq/mg, 0.85 to 1.55 GBq/mg, 0.9 to 1.5 GBq/mg, 0.95 to 1.45 GBq/mg, 1 to 1.4 GBq/mg, 1.05 to 1.35 GBq/mg, 1.1 to 1.3 GBq/mg, 1.15 to 1.25 GBq/mg, 0.6 to 1.3 GBq/mg, 0.65 to 1.25 GBq/mg, 0.7 to 1.2 GBq/mg, 0.75 to 1.15 GBq/mg, 0.8 to 1.1 GBq/mg, or 0.85 to 1.05 GBq/mg.

[0230] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by a specific activity of at least 0.5 GBq/mg, e.g., at least 1 GBq/mg, at least 1.5 GBq/mg, at least 2.0 GBq/mg, at least 3.0 GBq/mg, at least 4.0 GBq/mg, at least 5.0 GBq/mg, at least 6.0 GBq/mg, at least 7.0 GBq/mg, at least 8.0 GBq/mg, at least 9.0 GBq/mg, or at least 10.0 GBq/mg.

[0231] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by a specific activity from 0.5 GBq/mg to 10.0 GBq/mg, such as, for example, from 1.0 GBq/mg to 10.0 GBq/mg, from 2.0

GBq/mg to 10.0 GBq/mg, from 3.0 GBq/mg to 10.0 GBq/mg, from 4.0 GBq/mg to 10.0 GBq/mg, from 5.0 GBq/mg to 10.0 GBq/mg, from 6.0 GBq/mg to 10.0 GBq/mg, from 7.0 GBq/mg to 10.0 GBq/mg, from 8.0 GBq/mg to 10.0 GBq/mg, from 9.0 GBq/mg to 10.0 GBq/mg, from 0.5 GBq/mg to 5.0 GBq/mg, from 1.0 GBq/mg to 5.0 GBq/mg, from 2.0 GBq/mg to 5.0 GBq/mg, from 3.0 GBq/mg to 5.0 GBq/mg, or from 4.0 GBq/mg to 5.0 GBq/mg.

[0232] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by a specific activity from 0.5 GBq/mg to 1.9 GBq/mg, from 0.55 GBq/mg to 1.85 GBq/mg, from 0.6 GBq/mg to 1.8 GBq/mg, from 0.65 GBq/mg to 1.75 GBq/mg, from 0.7 GBq/mg to 1.7 GBq/mg, from 0.75 GBq/mg to 1.65 GBq/mg, from 0.8 GBq/mg to 1.6 GBq/mg, from 0.85 GBq/mg to 1.55 GBq/mg, from 0.9 GBq/mg to 1.5 GBq/mg, from 0.95 GBq/mg to 1.45 GBq/mg, from 1 GBq/mg to 1.4 GBq/mg, from 1.05 GBq/mg to 1.35 GBq/mg, from 1.1 GBq/mg to 1.3 GBq/mg, from 1.15 GBq/mg to 1.25 GBq/mg, from 0.6 GBq/mg to 1.3 GBq/mg, from 0.65 GBq/mg to 1.25 GBq/mg, from 0.7 to 1.2 GBq/mg, 0.75 to 1.15 GBq/mg, 0.8 to 1.1 GBq/mg, or 0.85 GBq/mg to 1.05 GBq/mg.

[0233] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by a specific activity from 0.7 GBq/mg to 1.2 GBq/mg, from 0.75 GBq/mg to 1.15 GBq/mg, from 0.8 GBq/mg to 1.1 GBq/mg, or from 0.85 GBq/mg to 1.05 GBq/mg.

[0234] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by a specific activity of $\geq$ 0.5 GBq/mg, e.g., $\geq$ 1 GBq/mg, $\geq$ 1.5 GBq/mg, $\geq$ 2.0 GBq/mg, $\geq$ 3.0 GBq/mg, $\geq$ 4.0 GBq/mg, $\geq$ 5.0 GBq/mg, $\geq$ 6.0 GBq/mg, $\geq$ 7.0 GBq/mg, $\geq$ 8.0 GBq/mg, $\geq$ 9.0 GBq/mg, or $\geq$ 10.0 GBq/mg.

[0235] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by a specific activity of 0.5 to 10.0 GBq/mg, for example, 1.0 to 10.0 GBq/mg, 2.0 to 10.0 GBq/mg, 3.0 to 10.0 GBq/mg, 4.0 to 10.0 GBq/mg, 5.0 to 10.0 GBq/mg, 6.0 to 10.0 GBq/mg, 7.0 To 10.0 GBq/mg, 8.0 to 10.0 GBq/mg, 9.0 to 10.0 GBq/mg, 0.5 to 5.0 GBq/mg, 1.0 to 5.0 GBq/mg, 2.0 to 5.0 GBq/mg, 3.0 to 5.0 GBq/mg, or 4.0 to 5.0 GBq/mg.

[0236] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by a specific activity of 0.5 to 1.9 GBq/mg, 0.55 to 1.85 GBq/mg, 0.6 to 1.8 GBq/mg, 0.65 to 1.75 GBq/mg, 0.7 to 1.7 GBq/mg, 0.75 to 1.65 GBq/mg, 0.8 to 1.6 GBq/mg, 0.85 to 1.55 GBq/mg, 0.9 to 1.5 GBq/mg, 0.95 to 1.45 GBq/mg, 1 to 1.4 GBq/mg, 1.05 to 1.35 GBq/mg, 1.1 to 1.3 GBq/mg, 1.15 to 1.25 GBq/mg, 0.6 to 1.3 GBq/mg, 0.65 to 1.25 GBq/mg, 0.7 to 1.2 GBq/mg, 0.75 to 1.15 GBq/mg, 0.8 to 1.1 GBq/mg, or 0.85 to 1.05 GBq/mg.

[0237] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by a specific activity of at least 0.5 GBq/mg, e.g., at least 1 GBq/mg, at least 1.5 GBq/mg, at least 2.0 GBq/mg, at least 3.0 GBq/mg, at least 4.0 GBq/mg, at least 5.0 GBq/mg, at least 6.0 GBq/mg, at least 7.0 GBq/mg, at least 8.0 GBq/mg, at least 9.0 GBq/mg, or at least 10.0 GBq/mg.

[0238] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by a specific activity from 0.5 GBq/mg to 10.0 GBq/mg, such as, for example, from 1.0 GBq/mg to 10.0 GBq/mg, from 2.0 GBq/mg to 10.0 GBq/mg, from 3.0 GBq/mg to 10.0 GBq/mg, from 4.0 GBq/mg to 10.0 GBq/mg, from 5.0 GBq/mg to 10.0 GBq/mg, from 6.0 GBq/mg to 10.0 GBq/mg, from 7.0 GBq/mg to 10.0 GBq/mg, from 8.0 GBq/mg to 10.0 GBq/mg, from 9.0 GBq/mg to 10.0 GBq/mg, from 0.5 GBq/mg to 5.0 GBq/mg, from 1.0 GBq/mg to 5.0 GBq/mg, from 2.0 GBq/mg to 5.0 GBq/mg, from 3.0 GBq/mg to 5.0 GBq/mg, or from 4.0 GBq/mg to 5.0 GBq/mg.

[0239] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by a specific activity from 0.5 GBq/mg to 1.9 GBq/mg, from 0.55 GBq/mg to 1.85 GBq/mg, from 0.6 GBq/mg to 1.8 GBq/mg, from 0.65 GBq/mg to 1.75 GBq/mg, from 0.7 GBq/mg to 1.7 GBq/mg, from 0.75 GBq/mg to 1.65 GBq/mg, from 0.8 GBq/mg to 1.6 GBq/mg, from 0.85 GBq/mg to 1.55 GBq/mg, from 0.9 GBq/mg to 1.5 GBq/mg, from 0.95 GBq/mg to 1.45 GBq/mg, from 1 GBq/mg to 1.4 GBq/mg, from 1.05 GBq/mg to 1.35 GBq/mg, from 1.1 GBq/mg to 1.3 GBq/mg, from 1.15 GBq/mg to 1.25 GBq/mg, from 0.6 GBq/mg to 1.3 GBq/mg, from 0.65 GBq/mg to 1.25 GBq/mg.

[0240] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by a specific activity from of 0.7 to 1.2 GBq/mg, 0.75 to 1.15 GBq/mg, 0.8 to 1.1 GBq/mg, or 0.85 GBq/mg to 1.05 GBq/mg.

[0241] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by a specific activity from 0.7 GBq/mg to 1.2 GBq/mg, from 0.75 GBq/mg to 1.15 GBq/mg, from 0.8 GBq/mg to 1.1 GBq/mg, or from 0.85 GBq/mg to 1.05 GBq/mg.

[0242] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by a specific activity of ≥ 0.5 GBq/μg, e.g., ≥ 1 GBq/μg, ≥ 1.5 GBq/μg, ≥ 2.0 GBq/μg, ≥ 3.0 GBq/μg, ≥ 4.0 GBq/μg, ≥ 5.0 GBq/μg, ≥ 6.0 GBq/μg, ≥ 7.0 GBq/μg, ≥ 8.0 GBq/μg, ≥ 9.0 GBq/μg, or ≥ 10.0 GBq/μg.

[0243] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by a specific activity of 0.5 to 10.0 GBq/μg, for example, 1.0 to 10.0 GBq/μg, 2.0 to 10.0 GBq/μg, 3.0 to 10.0 GBq/μg, 4.0 to 10.0 GBq/μg, 5.0 to 10.0 GBq/μg, 6.0 to 10.0 GBq/μg, 7.0 To 10.0 GBq/μg, 8.0 to 10.0 GBq/μg, 9.0 to 10.0 GBq/μg, 0.5 to 5.0 GBq/μg, 1.0 to 5.0 GBq/μg, 2.0 to 5.0 GBq/μg, 3.0 to 5.0 GBq/μg, or 4.0 to 5.0 GBq/μg.

[0244] In some embodiments, t a composition provided herein as a specific activity of 0.5 to 1.9 GBq/μg, 0.55 to 1.85 GBq/μg, 0.6 to 1.8 GBq/μg, 0.65 to 1.75 GBq/μg, 0.7 to 1.7 GBq/μg, 0.75 to 1.65 GBq/μg, 0.8 to 1.6 GBq/μg, 0.85 to 1.55 GBq/μg, 0.9 to 1.5 GBq/μg, 0.95 to 1.45 GBq/μg, 1 to 1.4 GBq/μg, 1.05 to 1.35 GBq/μg, 1.1 to 1.3 GBq/μg, 1.15 to 1.25 GBq/μg, 0.6 to 1.3 GBq/μg, 0.65 to 1.25 GBq/μg, 0.7 to 1.2 GBq/μg, 0.75 to 1.15 GBq/μg, 0.8 to 1.1 GBq/μg, or 0.85 to 1.05 GBq/μg.

[0245] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by a specific activity of at least 0.5 GBq/μg, e.g., at least 1 GBq/μg, at least 1.5 GBq/μg, at least 2.0 GBq/μg, at least 3.0 GBq/μg, at least 4.0 GBq/μg, at least 5.0 GBq/μg, at least 6.0 GBq/μg, at least 7.0 GBq/μg, at least 8.0 GBq/μg, at least 9.0 GBq/μg, or at least 10.0 GBq/μg.

[0246] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by a specific activity from 0.5 GBq/μg to 10.0 GBq/μg, such as, for example, from 1.0 GBq/μg to 10.0 GBq/μg, from 2.0 GBq/μg to 10.0 GBq/μg, from 3.0 GBq/μg to 10.0 GBq/μg, from 4.0 GBq/μg to 10.0 GBq/μg, from 5.0 GBq/μg to 10.0 GBq/μg, from 6.0 GBq/μg to 10.0 GBq/μg, from 7.0 GBq/μg to 10.0 GBq/μg, from 8.0 GBq/μg to 10.0 GBq/μg, from 9.0 GBq/μg to 10.0 GBq/μg, from 0.5 GBq/μg to 5.0 GBq/μg, from 1.0 GBq/μg to 5.0 GBq/μg, from 2.0 GBq/μg to 5.0 GBq/μg, from 3.0 GBq/μg to 5.0 GBq/μg, or from 4.0 GBq/μg to 5.0 GBq/μg.

[0247] In some embodiments of the pharmaceutical composition comprising a compound according to the present disclosure, the composition is characterized by a specific activity from 0.5 GBq/μg to 1.9 GBq/μg, from 0.55 GBq/μg to 1.85 GBq/μg, from 0.6 GBq/μg to 1.8 GBq/μg, from 0.65 GBq/μg to 1.75 GBq/μg, from 0.7 GBq/μg to 1.7 GBq/μg, from 0.75 GBq/μg to 1.65 GBq/μg, from 0.8 GBq/μg to 1.6 GBq/μg, from 0.85 GBq/μg to 1.55 GBq/μg, from 0.9 GBq/μg to 1.5 GBq/μg, from 0.95 GBq/μg to 1.45 GBq/μg, from 1 GBq/μg to 1.4 GBq/μg, from 1.05 GBq/μg to 1.35 GBq/μg, from 1.1 GBq/μg to 1.3 GBq/μg, from 1.15 GBq/μg to 1.25 GBq/μg, from 0.6 GBq/μg to 1.3 GBq/μg, from 0.65 GBq/μg to 1.25 GBq/μg, is characterized by a specific activity of 0.7 to 1.2 GBq/μg, 0.75 to 1.15 GBq/μg, 0.8 to 1.1 GBq/μg, or 0.85 GBq/μg to 1.05 GBq/μg.

[0248] In some embodiments a composition provided herein as a specific activity from 0.7 GBq/μg to 1.2 GBq/μg, from 0.75 GBq/μg to 1.15 GBq/μg, from 0.8 GBq/μg to 1.1 GBq/μg, or from 0.85 GBq/μg to 1.05 GBq/μg.

[0249] In some embodiments, the composition is characterized by radiochemical purity of ≥ 90%. In some embodiments, the composition is characterized by radiochemical purity of ≥ 91%, ≥ 92%, ≥ 93%, ≥94%, 95%, ≥ 96%, ≥ 97%, ≥ 98%, or ≥ 99%. In some embodiments, the composition is characterized by radiochemical purity ≥ 90%. In some embodiments, the composition is characterized by radiochemical purity of ≥ 95%. In some embodiments, the composition is characterized by radiochemical purity of ≥ 96%. In some embodiments, the composition is characterized by radiochemical purity of ≥ 98%.

[0250] In some embodiments, the composition provided is characterized by a radiochemical purity of ≥ 94.0%, ≥ 94.5%, ≥ 95.0%, ≥ 95.5%, ≥ 96.0%, ≥ 96.5%, ≥ 97.0%, ≥ 97.5%, ≥ 98.0%, ≥ 98.5%, ≥ 99.0%, or ≥ 99.5%.

[0251] In some embodiments, the composition provided is characterized by a radiochemical purity of ≥ 95.2%, ≥ 95.4%, ≥ 95.6%, ≥ 95.8%, ≥ 96%, ≥ 96.2%, ≥ 96.4%, ≥ 96.6%, ≥ 96.8%, ≥ 97%, ≥ 97.2%, ≥ 97.4%, ≥ 97.6%, ≥ 97.8%, ≥ 98%, ≥ 98.2%, ≥ 98.4%, ≥ 98.6%, ≥ 98.8%, ≥ 99%, ≥ 99.2%, ≥ 99.4%, ≥ 99.6%, or ≥ 99.8%.

[0252] In some embodiments, the pharmaceutical composition according to the present disclosure has a chemical purity of ≥ 99.0% by mole. In some embodiments, the pharmaceutical composition is prepared according to the methods provided herein.

[0253] In some embodiments, the pharmaceutical composition is characterized by one or more of the following:

Fe ≤ 2 μg/L;

^{69}Cu and ^{65}Cu together are ≤ 1 μg/L;

Zn(II) ≤ 2 μg/L;

Sn(IV) ≤ 0.01 μg/L;

Ti(IV) ≤ 0.01 μg/L;

Al(III) ≤ 2 μg/L;

As ≤ 1 μg/L;

Ni ≤ 1 μg/L; and

wherein any one of Cr, Cd, Co, and Y is ≤ 0.1 μg/mL.

[0254] In some embodiments, the pharmaceutical composition is characterized by comprising Fe ≤ 2 μg/L. In some embodiments, iron is present in ≤ 3 μg/L, ≤ 2.9 μg/L, ≤ 2.8 μg/L, ≤ 2.7 μg/L, ≤ 2.6 μg/L, ≤ 2.5 μg/L, ≤ 2.4 μg/L, ≤ 2.3 μg/L, ≤ 2.2 μg/L, ≤ 2.1 μg/L, ≤ 2 μg/L, ≤ 1.9 μg/L, ≤ 1.8 μg/L, ≤ 1.7 μg/L, ≤ 1.6 μg/L, ≤ 1.5 μg/L, ≤ 1.4 μg/L, ≤ 1.3 μg/L, ≤ 1.2 μg/L, ≤ 1.1 μg/L, ≤ 1 μg/L, ≤ 0.9 μg/L, ≤ 0.8 μg/L, ≤ 0.7 μg/L, ≤ 0.6 μg/L, ≤ 0.5 μg/L, ≤ 0.4 μg/L, ≤ 0.3 μg/L, ≤ 0.2 μg/L, or ≤ 0.1 μg/L.

[0255] In some embodiments, the pharmaceutical composition is characterized by comprising Cu (non-radioactive) ≤ 1 μg/L. In some embodiments, Cu (non-radioactive) is present in ≤ 2 μg/L, ≤ 1.9 μg/L, ≤ 1.8 μg/L, ≤ 1.7 μg/L, ≤ 1.6 μg/L, ≤ 1.5 μg/L, ≤ 1.4 μg/L, ≤ 1.3 μg/L, ≤ 1.2 μg/L, ≤ 1.1 μg/L, ≤ 1 μg/L, ≤ 0.9 μg/L, ≤ 0.8 μg/L, ≤ 0.7 μg/L, ≤ 0.6 μg/L, ≤ 0.5 μg/L, ≤ 0.4 μg/L, ≤ 0.3 μg/L, ≤ 0.2 μg/L, or ≤ 0.1 μg/L.

[0256] In some embodiments, the pharmaceutical composition is characterized by comprising Ni ≤ 1 μg/L. In some embodiments, nickel is present in ≤ 4.5 μg/L, ≤ 4.4 μg/L, ≤ 4.3 μg/L, ≤ 4.2 μg/L, ≤ 4.1 μg/L, ≤ 4 μg/L, ≤ 3.9 μg/L, ≤ 3.8 μg/L, ≤ 3.7 μg/L, ≤ 3.6 μg/L, ≤ 3.5 μg/L, ≤ 3.4 μg/L, ≤ 3.3 μg/L, ≤ 3.2 μg/L, ≤ 3.1 μg/L, ≤ 3 μg/L, ≤ 2.9 μg/L, ≤ 2.8 μg/L, ≤ 2.7 μg/L, ≤ 2.6 μg/L, ≤ 2.5 μg/L, ≤ 2.4 μg/L, ≤ 2.3 μg/L, ≤ 2.2 μg/L, ≤ 2.1 μg/L, ≤ 2 μg/L, ≤ 1.9 μg/L, ≤ 1.8 μg/L, ≤ 1.7 μg/L, ≤ 1.6 μg/L, ≤ 1.5 μg/L, ≤ 1.4 μg/L, ≤ 1.3 μg/L, ≤ 1.2 μg/L, ≤ 1.1 μg/L, ≤ 1 μg/L, ≤ 0.9 μg/L, ≤ 0.8 μg/L, ≤ 0.7 μg/L, ≤ 0.6 μg/L, ≤ 0.5 μg/L, ≤ 0.4 μg/L, ≤ 0.3 μg/L, ≤ 0.2 μg/L, or ≤ 0.1 μg/L.

[0257] In certain embodiments, the pharmaceutical composition has an apparent molar activity ≥ 8 MBq/nmol, e.g., ≥ 20 MBq/nmol, ≥ 30 MBq/nmol, ≥ 40 MBq/nmol, ≥ 50 MBq/nmol, ≥ 75 MBq/nmol, ≥ 100 MBq/nmol, ≥ 200 MBq/nmol, ≥ 300 MBq/nmol, ≥ 400 MBq/nmol, or ≥ 500 MBq/nmol.

[0258] In certain embodiments, the pharmaceutical composition has an apparent molar activity from 8 MBq/nmol to 600 MBq/nmol, e.g., from 8 MBq/nmol to 600 MBq/nmol, from 8 MBq/nmol to 500 MBq/nmol, from 8 MBq/nmol to 400 MBq/nmol, from 8 MBq/nmol to 300 MBq/nmol, from 8 MBq/nmol to 200 MBq/nmol, from 8 MBq/nmol to 100 MBq/nmol, from 30 MBq/nmol to 600 MBq/nmol, from 30 MBq/nmol to 500 MBq/nmol, from 30 MBq/nmol to 400 MBq/nmol, from 30 MBq/nmol to 300 MBq/nmol, from 30 MBq/nmol to 200 MBq/nmol, from 30 MBq/nmol to 100 MBq/nmol, from 30 MBq/nmol, from 100 MBq/nmol to 600 MBq/nmol, from 100 MBq/nmol to 500 MBq/nmol, from 100 MBq/nmol to 400 MBq/nmol, from 100 MBq/nmol to 300 MBq/nmol, or from 100 MBq/nmol to 200 MBq/nmol.

[0259] In certain embodiments, the pharmaceutical composition has an apparent molar activity from 8 MBq/nmol to 40 MBq/nmol, e.g., from 8 MBq/nmol to 30 MBq/nmol, from 8 MBq/nmol to 20 MBq/nmol, from 20 MBq/nmol to 40 MBq/nmol, from 20 MBq/nmol to 30 MBq/nmol, or from 30 MBq/nmol to 40 MBq/nmol.

[0260] In certain embodiments, the pH of the pharmaceutical composition is from 5 to 7, e.g., from 5 to 6, 5.5 to 6.5, or from 6 to 7. In certain embodiments, the pH of the pharmaceutical composition is 5, 6, or 7 +/- 0.1.

[0261] In some embodiments, the pharmaceutical composition is an embodiment as described above, further characterized by one or more of: an activity concentration of 0.60-0.66 GBq/mL at EoB + 2 hours; an apparent molar activity of the compound of 10 - 100 MBq/nmol at EoB + 2 hours; and an activity of > 500 MBq at EoB + 2hrs. An embodiment, as described above, further characterized by one or more of: an activity concentration of > 25 MBq/mL at EoB + 2 hours, an apparent molar activity of the compound of 10 - 150 MBq/nmol at EoB + 2 hours, and an activity of > 150 MBq at the EoB + 2hrs.

[0262] An embodiment as described above, further characterized by one or more of: an activity concentration of 0.60-0.66 GBq/mL at EoB + 2 hours; an apparent molar activity of the compound of 10 - 100 MBq/nmol at EoB + 2 hours; and an activity at end of synthesis of > 500 MBq.

4.3.2. Excipients

[0263] In certain embodiments, the pharmaceutical composition comprises one or more excipients.

[0264] In certain embodiments, the pharmaceutical composition comprises sodium chloride. In certain embodiments, sodium chloride is present in a concentration from 0.5 mg/mL to 50 mg/mL, e.g., from 5 mg/mL to 10 mg/mL, from 10 mg/mL to 30 mg/mL, or from 20 mg/mL to 50 mg/mL.

[0265] In certain embodiments, the pharmaceutical composition comprises ethanol. In certain embodiments, ethanol is present in an amount ≤ 10% v/v, e.g., ≤ 8% v/v, ≤ 5% v/v, or ≤ 3% v/v.

[0266] In certain embodiments, the pharmaceutical composition comprises ascorbic acid or a salt thereof, ethanol, and sodium chloride.

[0267] In certain embodiments, the pharmaceutical composition comprises 20-100 μg radiopharmaceutical, 5-20 mg ascorbic acid, 0.1-1 mL ethanol, and 1-10 mL isotonic saline solution.

[0268] In certain embodiments, the pharmaceutical composition comprises 20-30 μg radiopharmaceutical, 5-10 mg ascorbic acid, 0.1-0.5 mL ethanol, and 1-5 mL isotonic saline solution.

[0269] In certain embodiments, the pharmaceutical composition comprises 50-75 μg radiopharmaceutical, 15-20 mg ascorbic acid, 0.5-1 mL ethanol, and 5-10 mL isotonic saline solution.

[0270] In certain embodiments, the pharmaceutical composition comprises sodium bicarbonate. In certain embodiments, the pharmaceutical composition comprises sodium acetate. In certain embodiments, the pharmaceutical composition comprises a metal scavenger, e.g., EDTA .

4.3.3. Formulations

[0271] Compounds of the present disclosure can be prepared and administered in a wide variety of oral, parenteral, and topical dosage forms. Thus, the compounds of the present disclosure can be administered by injection (e.g., intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally). In some embodiments, compounds of the present disclosure are administered orally. Also, the compounds described herein can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present disclosure can be administered transdermally. It is also envisioned that multiple routes of administration (e.g., intramuscular, oral, transdermal) can be used to administer compounds of the disclosure. Accordingly, the present disclosure also provides pharmaceutical compositions comprising pharmaceutically acceptable carrier or excipient and one or more compounds of the disclosure.

[0272] For preparing pharmaceutical compositions from the compounds of the present disclosure, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances that may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

[0273] In powders, the carrier is finely divided solid in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

4.4. Imaging, Diagnosis and Treatment

[0274] The present disclosure provides methods for imaging subjects suspected of having or diagnosed with a disease associated with increased expression of αvβ6-integrin, the method comprising administering an effective amount of a pharmaceutical composition of the present disclosure and generating one or more radiographic images of the subject.

[0275] In another aspect, the present disclosure provides methods for determining a subject's response to a treatment over time, e.g., a subject previously diagnosed with a disease associated with increased expression of αvβ6-integrin.

[0276] In certain embodiments, the method comprises:

(a) administering an effective amount of a pharmaceutical composition of the present disclosure to a subject diagnosed with an integrin-expressing disease or disorder at an earlier time point and at a later time point;

(b) generating one or more radiographic images of the subject at the earlier time point and at the later time point;

(c) determining the amount of localization of the radionuclide in the one or more radiographic images of the subject at the earlier time point and at the later time point; and

(d) determining the subject's response to the cancer treatment by comparing the amount of localization of the radionuclide in the one or more radiographic images of the subject at the earlier time point and at the later time point.

[0277] In some embodiments, the method of generating one or more images of a subject, the method comprising administering to the subject an effective amount of a pharmaceutical composition as provided herein and generating one or more images of at least a part of the subject's body.

[0278] In some embodiments, the image is generated using positron emission tomography (PET), PET- computer tomography (PET-CT), or single-photon emission computerized tomography (SPECT).

[0279] In some embodiments, the method is further comprising determining the presence or absence of a disease in the subject based on the presence or absence of localization of the radionuclide in the one or more images of the subject's body.

[0280] In some embodiments, when the subject is determined to have a disease, the method further comprises administering to the subject a therapeutically effective amount of a pharmaceutical composition as provided herein.

[0281] In some embodiments, the disease is selected from cancers, inflammatory diseases, infectious diseases, and immune diseases.

[0282] In some embodiments, the disease is cancer, and the cancer is selected from breast cancer (e.g., triple-negative breast cancer), pancreatic cancer, pancreatic adenocarcinoma, pancreatic ductal cancer (PDA), small intestine cancer, colon cancer, gastric cancer, rectal cancer, lung adenocarcinoma, lung cancer (e.g., non-small cell lung cancer), head and neck cancer, head and neck squamous cell carcinomas (HNSCCs), idiopathic pulmonary fibroma, ovarian cancer, hepatocellular carcinoma, epithelial cancer, esophageal cancer, hypopharynx cancer, nasopharynx cancer, larynx cancer, myeloma cells, bladder cancer, cholangiocellular carcinoma, clear cell renal carcinoma, neuroendocrine tumor, oncogenic osteomalacia, sarcoma, CUP (carcinoma of unknown primary), thymus carcinoma, desmoid tumors, glioma, astrocytoma, cervix carcinoma, and prostate cancer.

[0283] In some embodiments, the cancer is selected from pancreatic adenocarcinoma, pancreatic ductal cancer (PDA), lung adenocarcinoma, head and neck squamous cell carcinomas (HNSCCs), and idiopathic pulmonary fibroma.

[0284] In some embodiments, a method of detecting a disease in a subject is provided, the method comprising:

(a) administering to a subject an effective amount of the pharmaceutical composition as provided herein;

(b) detecting the localization of the radionuclide; and

(c) determining the presence or absence of the disease based on the presence or absence of localization.

[0285] In some embodiments, the detecting is by positron emission tomography (PET), PET-computer tomography (PET-CT), or single-photon emission computerized tomography (SPECT).

[0286] In some embodiments, the disease is associated with increased expression of αvβ6-integrin. In some embodiments, the disease is preferably fibrosis or cancer. In some embodiments, the disease is selected from cancers, inflammatory diseases, infectious diseases, and immune diseases.

[0287] In some embodiments, the disease is cancer. In some embodiments, the cancer is selected from breast cancer (e.g., triple-negative breast cancer), pancreatic cancer, small intestine cancer, colon cancer, gastric cancer, rectal cancer, lung cancer (e.g., non-small cell lung cancer), head and neck cancer, ovarian cancer, hepatocellular carcinoma, epithelial cancer, esophageal cancer, hypopharynx cancer, nasopharynx cancer, larynx cancer, myeloma cells, bladder cancer, cholangiocellular carcinoma, clear cell renal carcinoma, neuroendocrine tumor, oncogenic osteomalacia, sarcoma, CUP (carcinoma of unknown primary), thymus carcinoma, desmoid tumors, glioma, astrocytoma, cervix carcinoma, and prostate cancer.

[0288] Also provided is a method of determining the effect of cancer treatment on a subject afflicted with cancer comprising:

(a) administering to the subject an effective amount of a compound comprising a radionuclide as provided herein, or a pharmaceutical composition comprising an effective amount of a compound comprising a radionuclide as provided herein at an earlier time point and at a later time point;

(b) detecting the localization of the radionuclide at both the earlier time point and at a later time point; and

(c) determining the effect of the cancer treatment by comparing the amount of localization at the later time point to the amount of localization at the earlier time point.

[0289] In some embodiments, the localization of the compound is detected using positron emission tomography (PET), PET- computer tomography (PET-CT), or single-photon emission computerized tomography (SPECT).

[0290] In some embodiments, the earlier time point is before commencing the cancer treatment and the later time point is at least two weeks after commencing the cancer treatment.

[0291] In some embodiments, the cancer is selected from breast cancer (e.g., triple-negative breast cancer), pancreatic cancer, small intestine cancer, colon cancer, gastric cancer, rectal cancer, lung cancer (e.g., non-small cell lung cancer), head and neck cancer, ovarian cancer, hepatocellular carcinoma, epithelial cancer, esophageal cancer, hypopharynx cancer, nasopharynx cancer, larynx cancer, myeloma cells, bladder cancer, cholangiocellular carcinoma, clear cell renal carcinoma, neuroendocrine tumor, oncogenic osteomalacia, sarcoma, CUP (carcinoma of unknown primary), thymus carcinoma, desmoid tumors, glioma, astrocytoma, cervix carcinoma, and prostate cancer.

[0292] Provided is a method of treating a disease in a subject in need thereof, comprising administering to the subject an effective amount of a compound according to the present disclosure, or a pharmaceutical composition comprising a compound according to the present disclosure.

[0293] In some embodiments, the disease is selected from cardiovascular diseases, liver fibrosis and cirrhosis, arthritic disorders (e.g., rheumatoid arthritis), IgG4-related disease, pulmonary fibrosis and interstitial lung disease, Crohn's disease, tuberculosis, sarcoidosis, and periprosthetic joint infections.

[0294] Also provided is a theranostic method comprising:

(a) administering to a subject an effective amount of a first compound comprising: a ^{61}Cu radionuclide or a pharmaceutical composition comprising an effective amount of a first compound comprising a ^{61}Cu radionuclide,

(b) generating one or more images of the subject (e.g., of a certain region or part of the subject's body); and

(c) administering to the subject an effective amount of a second compound comprising a ^{67}Cu radionuclide or a pharmaceutical composition comprising an effective amount of a second compound comprising a ^{67}Cu radionuclide.

[0295] The present disclosure provides compounds (Section 4.2) and pharmaceutical compositions (Section 4.3) comprising the same for use in medicine, i.e., for use in treatment. The present disclosure further provides the use of any compounds (e.g., including a compound of any one of Formula I, IA, IB, II, IIA, IIB, III, IIIA, and IIIB, or a salt thereof, and any of the

compound embodiments in Section 4.2.4,) described herein for diagnostic and therapeutic methods, which would be beneficial to treatment of the disease, if associated with increased expression of αvβ6-integrin, preferably fibrosis or cancer is selected from cancers, inflammatory diseases, infectious diseases, and immune diseases.

[0296] In some embodiments, the disease is cancer, and the cancer is selected from breast cancer (e.g., triple-negative breast cancer), pancreatic cancer, small intestine cancer, colon cancer, gastric cancer, rectal cancer, lung cancer (e.g., non-small cell lung cancer), head and neck cancer, ovarian cancer, hepatocellular carcinoma, epithelial cancer, esophageal cancer, hypopharynx cancer, nasopharynx cancer, larynx cancer, myeloma cells, bladder cancer, cholangiocellular carcinoma, clear cell renal carcinoma, neuroendocrine tumor, oncogenic osteomalacia, sarcoma, CUP (carcinoma of unknown primary), thymus carcinoma, desmoid tumors, glioma, astrocytoma, cervix carcinoma, and prostate cancer.

[0297] In some embodiments, the methods comprise administering to a subject in need thereof (e.g., a subject such as a human patient, for example with edema) any of the compounds described herein or a pharmaceutically acceptable salt thereof. In some embodiments, the methods comprise administering a compound of including a compound of any one of Formula I, IA, IB, II, IIA, IIB, III, IIIA, and IIIB, or a salt thereof, and any of the compound embodiments in Section 4.2.4, or a pharmaceutically acceptable salt or composition thereof, to a subject in need thereof. In some embodiments, the method comprises administering a pharmaceutical composition comprising a compound of including a compound of any one of Formula I, IA, IB, II, IIA, IIB, III, IIIA, and IIIB, or a salt thereof, and any of the compound embodiments in Section 4.2.4, or a pharmaceutically acceptable salt to a subject in need thereof.

[0298] For any provided compound or pharmaceutical composition, the effective amount (e.g., the diagnostically effective or therapeutically effective amount) can be initially determined from cell culture assays and/or animal testing. Target concentrations will be those concentrations of active compound(s) that are capable of diagnosing, monitoring, and/or treating cancer in a patient or subject.

[0299] Therapeutic efficacy of the compound may be determined from animal models. The dosage in humans can be adjusted during the clinical trials via dose escalation studies by monitoring safety and efficacy.

[0300] Dosages may be varied depending upon the requirements of the patient and the compound or pharmaceutical composition being employed. The dose administered to a patient, in the context of the present disclosure, should be sufficient to affect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side effects.

[0301] In one aspect, compounds provided herein display one or more improved pharmacokinetic (PK) properties (e.g., Cmax, tmax, Cmin, t1/2, AUC, CL, bioavailability, etc.) when compared to a reference compound.

[0302] In some embodiments, a compound of the disclosure or a pharmaceutical composition comprising the same is provided as a unit dose.

[0303] In a further aspect, the present disclosure provides a novel radiopharmaceutical and/or a novel radiopharmaceutical composition as provided herein above for use in a method of imaging, diagnosing and/or staging cancer.

[0304] In some embodiments, the cancer is selected from breast cancer (e.g., triple-negative breast cancer), pancreatic cancer, small intestine cancer, colon cancer, gastric cancer, rectal cancer, lung cancer (e.g., non-small cell lung cancer), head and neck cancer, ovarian cancer, hepatocellular carcinoma, epithelial cancer, esophageal cancer, hypopharynx cancer, nasopharynx cancer, larynx cancer, myeloma cells, bladder cancer, cholangiocellular carcinoma, clear cell renal carcinoma, neuroendocrine tumor, oncogenic osteomalacia, sarcoma, CUP (carcinoma of unknown primary), thymus carcinoma, desmoid tumors, glioma, astrocytoma, cervix carcinoma, and prostate cancer.

[0305] In some embodiments, the methods comprise administering to a subject in need thereof (e.g., a subject such as a human patient) any of the compounds described herein or a pharmaceutically acceptable salt thereof. In some embodiments, the methods comprise administering a compound of Formula I, IA, IB, II, IIA, IIB, III, IIIA, and IIIB, or a salt thereof, and any of the compound embodiments in Section 4.2.4, as provided herein or a pharmaceutically acceptable salt or composition of any of these, to a subject in need thereof. In some embodiments, the method comprises administering a pharmaceutical composition comprising a compound of Formula I, IA, IB, II, IIA, IIB, III, IIIA, and IIIB, or a salt thereof,

and any of the compound embodiments in Section 4.2.4, as provided herein or a pharmaceutically acceptable salt to a subject in need thereof.

4.5. Theranostics

[0306] In an aspect of the present disclosure, a theranostic method comprises the use of a pair of *Cu radiopharmaceuticals ("theranostic pair"), as provided herein, for both imaging/diagnosis of a disease and for treating the disease in the same patient, wherein the theranostic pair of radiopharmaceuticals differ only in the radionuclide, i.e., they are different radioisotopes. In some embodiments, the theranostic pair comprises a γ or positron emitting radionuclide in the radiopharmaceutical for imaging/diagnosis (e.g., with PET, PET-CT, or SPECT) and a β emitting radionuclide in the radiopharmaceutical for therapy.

[0307] In some embodiments, the theranostic pair comprises ^{61}Cu (for imaging/diagnosis) and ^{67}Cu (for therapy). In some embodiments, this is referred to as a ^{61}/^{67}Cu theranostic pair.

[0308] Some embodiments of the theranostic method comprise the administration of a diagnostic form of the radiopharmaceutical (e.g., wherein *Cu is ^{61}Cu for PET or wherein *Cu is ^{67}Cu for SPECT), enabling expression of the therapeutic target to be visualized in vivo with a companion imaging method before switching to the radiolabeled therapeutic counterpart, e.g., wherein *Cu is ^{64}Cu or ^{67}Cu.

[0309] In some embodiments, a theranostic method comprises the steps of:

(a) administering to a subject an effective amount of a first pharmaceutical composition according to Section 4.3 herein;

(b) generating one or more images of the subject (e.g., of a certain region or part of the subject); and

(c) administering to the subject an effective amount of a second pharmaceutical composition.

[0310] In some embodiments, the first composition comprises a radionuclide known to be useful for imaging. In some embodiments, *RN is ^{61}Cu.

[0311] In some embodiments, the second pharmaceutical composition comprises the compound of Formula II, wherein *RN is ^{67}Cu. In some embodiments, wherein the second pharmaceutical

composition comprises a compound selected from Table B, Table F or Table I or is a pharmaceutically acceptable salt thereof.

[0312] In some embodiments, a theranostic method comprises the steps of:

(a) administering to a subject an effective amount of a compound comprising a ^{61}Cu radionuclide described herein or a pharmaceutical composition comprising the same;

(b) generating one or more images of the subject (e.g., of a certain region or part of the subject's body); and

(c) administering to the subject an effective amount of a compound comprising a radionuclide described herein or a pharmaceutical composition comprising the same, wherein the compounds of step (a) and (c) differ only in radioisotopic identity.

[0313] In some embodiments, the amount of compound comprising a ^{61}Cu radionuclide described herein or pharmaceutical composition comprising the same administered in step (a) is effective to generate one or more images of subject (i.e., a "detectably effective amount"). In some embodiments, the amount of compound comprising a ^{61}Cu radionuclide described herein or pharmaceutical composition comprising the same administered in step (a) is effective to diagnose the presence or absence of a disease (i.e., a "diagnostically effective amount").

[0314] In some embodiments, the method further comprises determining, via the one or more images of the subject, the presence or absence of a disease in the subject based on the presence or absence of localization of the ^{61}Cu radionuclide in the subject's body. In instances where the subject is not determined to have a disease, step (c) in the method is not performed.

[0315] In some embodiments, the method further comprises calculating an effective therapeutic amount of the compound comprising a ^{67}Cu radionuclide described herein to administer to the subject in step (c). In some embodiments, the method further comprises calculating an effective therapeutic dose of the compound comprising a ^{67}Cu radionuclide described herein to administer to the subject in step (c).

[0316] In some embodiments, the amount of compound comprising a ^{67}Cu radionuclide described herein or a pharmaceutical composition comprising the same administered in step (c)

is effective therapeutically to treat the disease in the subject (i.e., a "therapeutically effective amount").

[0317] In some embodiments, a theranostic method comprises:

(a) generating one or more images of a subject (e.g., of a certain region or part of the subject's body), comprising administering to the subject an effective amount of a compound comprising a ^{61}Cu radionuclide described herein or a pharmaceutical composition comprising the same;

(b) determining, via the one or more images of the subject, the presence or absence of a disease in the subject based on the presence or absence of localization of the ^{61}Cu radionuclide in the subject's body; and

(c) administering to the subject, when the presence of a disease in the subject is determined, an effective amount of a compound comprising a ^{67}Cu radionuclide described herein, or a pharmaceutical composition comprising the same, wherein the compounds in step (a) and (c) differ only in the radionuclide identity.

[0318] In some embodiments, a theranostic method comprises the steps of:

(a) administering to a subject an effective amount of a compound comprising a ^{61}Cu radionuclide described herein or a pharmaceutical composition comprising the same;

(b) generating one or more images of the subject (e.g., of a certain region or part of the subject's body); and

(c) administering to the subject an effective amount of a compound comprising a radionuclide known in the art to be effective for treating a disease.

4.6. Methods of Making Compositions

[0319] In some embodiments, the method of making the compounds and compositions according to Formula II (and all subgenera Formulae I, IIa, IIb, IIc, and III), the compound further comprising ^{61}Cu, as provided herein comprises the step of

(a) combining a high purity ^{61}Cu[Cu] solution with:

(b) a compound as provided herein, e.g., according to Formula II (and all subgenera

Formulae I, IIa, IIb, IIc, and III), wherein the compound does not comprise *RN.

[0320] In some embodiments, the combining occurs in a reaction time of 15 min at elevated temperature (80-95°C). In some embodiments, the combining occurs in a reaction time of 15 min at room temperature. In some embodiments, the combining occurs in a reaction time 2-5 min at room temperature. In certain of these embodiments, the combining occurs in a suitable buffer solution (e.g., ammonium acetate buffer, 0.5M, pH=8).

[0321] In some embodiments, no further purification step is necessary to remove uncomplexed ^{61}Cu[Cu] the reaction mixture, allowing direct use of the formed compound.

[0322] Radiochemical yield is the amount of activity in the product expressed as the percentage (%) of starting activity used in the considered process (e.g., synthesis, separation, etc.). The quantity of both must relate to the same radionuclide and be decay corrected to the same point in time before the calculation is made (see also Appendix A). It should be understood, that under this definition, the radiochemical yield is only related to the considered radionuclide, and it does not include compounds labelled with all radionuclides that may undergo the same reaction as the radionuclide of interest (e.g., ^{68}Ge in ^{68}Ga preparations). 'Radiochemical yield', calculated using decay-corrected radioactivity values for products and starting compounds, is identical to the concept of 'chemical yield'. Logically, the reference time for correction of decay must be identical to describe a particular reaction, irrespective of whether it is chosen to be the end of the radionuclide production, the end of bombardment, the start of synthesis, the end of synthesis, or any other convenient reference time point.

[0323] In some embodiments, a composition produced by the provided method of making a compound is characterized by radiolabeling yield at the end of labeling of ≥ 80%. In further embodiments, the composition is characterized by radiolabeling yield of ≥ 95% or greater. In further embodiments, the composition is characterized by radiolabeling yield of ≥ 95% at room temperature.

[0324] In some embodiments, the composition provided is characterized by a radiolabeling yield of greater than 85%, e.g., greater than 85.5%, 86.0%, 86.5%, 87.0%, 87.5%, 88.0%, 88.5%, 89.0%, 89.5%, 90.0%, 90.5%, 91.0%, 91.5%, 92.0%, 92.5%, 93.0%, 93.5%, 94.0%, 94.5%, 95.0%, 95.5%, 96.0%, 96.5%, 97.0%, 97.5%, 98.0%, 98.5%, 99.0%, or 99.5%. In some embodiments, the composition is characterized by radiolabeling yield of greater than 90%. In

some embodiments, the composition is characterized by radiolabeling yield of greater than 92%. In some embodiments, the composition is characterized by radiolabeling yield of greater than 95%.

5. EXAMPLES

5.1. Example 1: [^{61}Cu]$CuCl_2$ Production

[0325] The production of the radionuclide was performed by irradiating a solid target of highly pure ^{61}Ni (purity > 99.42%) plated on a niobium coin backing with a proton beam.

[0326] Due to the relatively short half-lives ($t_{1/2}$ ^{68}Ga = 68 min; ^{18}F = 110 min) and physical properties of the radionuclides, the key challenges in the PET tracer industry remain a) the imaging quality, b) reliability of supply and distribution of the radiopharmaceutical at low cost and c) low radiation burden to the patient. The distinctive advantage of using ^{61}Cu as a positron emitter, e.g., in a PET tracer, will not only ensure a) good imaging quality due to its physical properties (low mean positron energy) but also the possibility of delayed imaging, expected to improve the diagnostic sensitivity due to the washout of radioactivity from the background, thus improved image contrast, b) a large distribution radius due to its relatively long half-life ($t_{1/2}$ ^{61}Cu = 205.5 min) while c) still keeping the radiation burden to the patient at a minimum. Provided herewith is an enabling description of new processes to produce highly pure ^{61}Cu, in the form of [^{61}Cu]$CuCl_2$, to be used in radiopharmaceutical applications, e.g., as a positron emitter in a PET tracer, in high activity concentration and volumes.

[0327] Trace metals and cold copper compete with ^{61}Cu to bind a chelator (for example, NODAGA) in this order: cold Cu(II) (i.e., stable isotopes) > Zn(II) > Fe(III) > Sn(IV) > Ti(IV) > Al(III.). The competition from these trace metals and cold copper decreases the tracer's radiolabeling yield and radiochemical purity significantly. Frequent sources of trace metals are the raw nickel metal powder itself, especially isotopically enriched nickel, reagents, and any metals in instruments used, such as iron. The purification process (ion-exchange columns) removes much of the trace metals except for cold (of particular relevance are stable isotopes ^{69}Cu and ^{65}Cu), which passes through into the product fraction by being the same element as the desired ^{61}Cu. One way of preventing cold copper contamination and the associated reduction in chemical purity is to pass the dissolved nickel raw material (stable isotopes) through the process and separate the cold copper from the nickel before plating (see FIG. 8 for ICP-MS analysis). Table 1 displays the chemical

purity of the [^{61}Cu]$CuCl_2$ by either bombardment of ^{nat}Ni or ^{61}Ni on a niobium backing and the resulting impurity profile.

Table 1. Chemical Purity of ^{61}Cu transmuted from ^{nat}Ni vs. ^{61}Ni.

	ng / MBq	
	Cu-61 from nat-Ni	Cu-61 from Ni-61
Aluminum (Al)	1.1	0.3
Cobalt (Co)	N/D	0.2
Copper (Cu)	0.3	0.6
Iron (Fe)	1.6	1.5
Lead (Pb)	0.4	0.7
Nickel (Ni)	3.4	0.1
Zinc (Zn)	0.7	0.1

5.1.1. Preparation of Plating Solution

5.1.1.1 Preparation of Buffer Solution

[0328] Ammonium Chloride (4.6 g, Aldrich: 326372, Trace Select) was weighed into a clean (no metal) Falcon Tube (50 mL), and the previously cleaned magnetic stirring bar was added. 6 mL of Trace Select water (Honeywell 95305) was added in one aliquot to flush walls of the Falcon in case any salt sticks to the Falcon tube walls. 1 mL of ammonium hydroxide 28% (Sigma 338818) was added with a 1000 µL pipette with a respective pipette tip, 8x times. The lid of the Falcon was closed, and the Falcon is, in turns, vortexed (1-2 minutes) (immersion in an ultra-sonic bath was a possible alternative for 1-2 minutes) and shaken, until all salt was dissolved. The Falcon tube can also be warmed (e.g., by rolling between hands) to improve solubility, temperature (e.g., around 23°C, preferably between 23-25°C). After complete dissolution of the salt, the pH acceptance criteria, pH range 9.28 – 9.62, needs to be verified by pH measurement of the solution at RT, e.g., with and electronic pH meter. The Falcon tube was closed with parafilm and stored at room temperature. Prior to use, any solid salt formation was redissolved.

5.1.1.2 Preparation of Nickel Nitrate Plating Solution

[0329] A 50 mL glass beaker was washed with nitric acid (Trace Select) followed by water (Trace Select). In a fume hood, the beaker was dried by placing it on a heating plate set to 150 °C. To the beaker was added 210 µg of natural (isotopic distribution) nickel (powder, Sigma-Aldrich <50 µm, 99.7% trace metals basis, essentially free from any impurities, except iron. The copper impurity amounts to < 0.3 ppm.) were weighed into the beaker and 4 mL of 65 % nitric acid were added

using a pipette. The beaker was placed back on the active heating plate and the stirring was set to 300 rpm. Ensure the ventilation of the fume hood was functioning properly (evolution of NO_2). During the dissolution, the solution turns green. The solution was reduced by evaporation to a volume of ≈ 600 µL and taken from the heating plate to cool down to room temperature. The remaining solution was transferred to a 50 mL metal-free Falcon tube. The glass beaker was rinsed with a total of 2.8 mL of Trace Select water, in steps of 0.8 mL, 1 mL, and 1 mL, where each step was transferred to the Falcon tube before the adding the next washing fraction. Buffer solution (4 mL), 11 mL of Trace Select water, and 3 mL of ammonium hydroxide 28% (Sigma 338818) were added to the Falcon tube. The pH of the solution was measured and adjusted to the required pH by adding ammonium hydroxide 28% (Aldrich 338818) using sterile B-Braun syringes.

[0330] The following are example lots of ^{60}Ni and ^{61}Ni (certificate as provided by Isoflex, USA, March 2018):

Table 2.

Isotope	^{61}Ni										
Enrichment	86.20%										
Form	Metal ingot/powder										
Certificate	6275										
Isotopic distribution	Isotope	Ni-58	Ni-60	Ni-61	Ni-62	Ni-64					
	Content (%)	1.17	0.8	86.2	11.7	0.14					
Chemical admixtures	Element	Al	Bi	Ca	Cd	Co	Cr	Cu	Fe	K	µg
	Content (ppm)	10	<10	20	10	<10	<10	20	40	<10	<50
	Element	Mo	Mn	Na	Pb	Si	Sn	Zn			
	Content (ppm)	<8	<50	<10	<10	20	30	50			

Table 3.

Isotope	^{61}Ni
Enrichment	99.39%
Form	Metal powder

Certificate	TBD/not specified										
Isotopic distribution	Isotope	Ni-58	Ni-60	Ni-61	Ni-62	Ni-64					
	Content (%)	0.01	0.29	99.39	0.29	0.02					
Chemical admixtures	Element	Al	Co	Cr	Cu	Fe	µg	Mn	Pb	Si	Ti
	Content (ppm)	12	<10	<10	14	<10	<10	<10	<10	<10	<10
	Element	Zn	C	S							
	Content (ppm)	<10	157	<10							

Table 4.

Isotope	^{60}Ni										
Enrichment	99.31%										
Form	metal powder										
Certificate	TBD/not specified										
Isotopic distribution	Isotope	Ni-58	Ni-60	Ni-61	Ni-62	Ni-64					
	Content (%)	0.21	99.31	0.46	0.015	0.005					
Chemical admixtures	Element	Al	Co	Cr	Cu	Fe	µg	Mn	Pb	Si	Ti
	Content (ppm)	<10	70	20	25	<10	<10	<10	<10	15	<10
	Element	Zn	C	S	P						
	Content (ppm)	15	114	20	30						

[0331] The samples of natural nickel from Sigma-Aldrich were essentially free from any impurities, except iron. The copper impurity amounts to < 0.3 ppm. Additional suitable sources of natural Ni include:

Nickel powder, <50 µm, 99.7% trace metals basis

Nickel rod, diam. 6.35 mm, =99.99% trace metals basis

Nickel foil, thickness 0.5 mm, 99.98% trace metals

5.1.2. Electroplating the Backing Surface

[0332] A disc shaped niobium backing was obtained from high purity Nb as described herein and (28 mm x 1.0 mm) was cleaned with ethanol (high-purity) and inserted in a Comecer Electroplating

Unit V21204. A platinum wire anode was positioned so that the distance relative to the coin surface was between about 1 and 3 mm, adjusted by a polymer spacer. The coin mass was determined to be 5.25 grams. Niobium backing (22 mm x 1.0 mm weighs 3.3 g). The plating solution was charged to the electrolyte container and attached to the apparatus. The voltage was set to 4.5V. The current reading after 5 min stabilization was 180 μA. The duty cycle for pump was set to 45%. The plating liquid turned from blue to transparent, slow decrease of current to 160 μA was observed over the period of 120 minutes. The plating process was stopped. The coin was taken out of the electrolytic cell and its weight was measured. The coin also underwent microscopic evaluation, FIGs. 1 and 2 using a DINOLite digital microscope to observe the crystal structure and homogeneity of the surface. The coin (FIG. 2) was stored in a metal-free Falcon tube under a nitrogen atmosphere.

5.1.3. Results of the Electroplating

[0333] Upon completion of electroplating, the coin underwent a microscopic evaluation using a DINOLite digital microscope to observe the crystal structure and homogeneity of the surface. As can be seen in FIG. 1 (panels A-C), a homogenous target coating having durable adhesion was obtained, see also FIG. 2.

5.1.4. General Guidelines for High-purity [^{61}Cu]Cl_2 Production

[0334] The purpose of this example was to enable the bulk production of ^{61}Cu from the deuteron irradiation of natural nickel and/or enriched ^{60}Ni. This effort was a proof of concept, and, therefore, there were no benchmarked specifications for ^{61}Cu. However, we optimized target performance, target geometry/material use, irradiation parameters, and chemical processing methods to produce [^{61}Cu]$CuCl_2$ following enriched ^{60}Ni irradiation, or, scaled accordingly for ^{nat}Ni irradiation. There were no pharmacopoeia specifications for radio-copper explicitly, however, test QC methods include assessment of radionuclidic purity and apparent molar activity (to demonstrate usability of the extracted [^{61}Cu]$CuCl_2$).

[0335] This example considers use of two different types of targets, natural nickel (^{nat}Ni) targets and highly enriched Nickel-60 (^{60}Ni) targets both of which were suitable for deuteron bombardment. However, ^{nat}Ni was cheap and available in high-purity while ^{60}Ni was still costly and required efficiency measures. If even higher yields were desired, target preparation efforts may be directly translated into the proton-based ^{61}Ni(p,n)^{61}Cu route, however, given the cost of enriched ^{61}Ni (c.a. $25 USD/μg), such an approach imposes the need for target recycling.

[0336] The set of guidelines below enable all types of targets in the production of ^{61}Cu, including the production of high-purity [^{61}Cu]$CuCl_2$ from the Nb coins with a Zn or Ni (any isotopic enrichment) coating electroplated thereon as provided herein. Specific details are also provided for deuteron, and proton irradiations, respectively. This protocol was followed to generate the ^{61}Cu-compositions evaluated in the following examples.

<table>
<tr><td>Target Backing Geometry</td><td>Flat coin - disc-shaped. The dimensions of the target backing form are:
Coin backing:
• Diameter Ø = 20 - 30 ± 0.1 mm
• Thickness H = 1.5 mm
Target Ni layer or coating
a. Diameter 13mm (deuteron) or 10 mm ± 10%(proton)
b. Mass 70-100 mg, e.g., around 100 ± 40 mg (deuteron) or around 50 ± 20 mg (proton)
c. Thickness (H) full density (d=8.9)
i. H_{min} = 0.1 mm; H_{max} = 0.14 mm corresponding to 70-100 mg deposited
Tolerances/finishes unless otherwise stated are as follows:
Surface finish: Ra 1.6
General tolerance: ISO 2768-m
Sharp edges and corners according to ISO 13 715</td></tr>
<tr><td>Target Backing Surface</td><td>Optional - Surface treated with abrasion by pink corundum grindstone – free of impurities</td></tr>
<tr><td>Target Backing Material</td><td>Niobium foil, 99.8% (metals basis), 1.0 mm (0.04 in) thick, annealed,
Stock No.: 10257
Lot No.: C15P07
<table><tr><th>Element</th><th>ppm</th></tr><tr><td>Carbon</td><td>24</td></tr><tr><td>Hydrogen</td><td>1</td></tr><tr><td>Molybdenum</td><td>2</td></tr><tr><td>Nickel</td><td>4</td></tr><tr><td>Silicon</td><td>1</td></tr><tr><td>Titanium</td><td>2</td></tr><tr><td>Zirconium</td><td>3</td></tr></table></td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>Iron</td><td>1</td></tr>
<tr><td>Hafnium</td><td>2</td></tr>
<tr><td>Nitrogen</td><td>14</td></tr>
<tr><td>Oxygen</td><td>56</td></tr>
<tr><td>Tantalum</td><td>785</td></tr>
<tr><td>Tungsten</td><td>4</td></tr>
</table>
</td></tr>
<tr><td>Target Backing Material</td><td>Niobium 99.9% typical certificate of analysis results, Goodfellows Product nr. 931-627-20
<table>
<tr><th>Element</th><th>ppm</th></tr>
<tr><td>B</td><td><10 ppm</td></tr>
<tr><td>Ni</td><td><5 ppm</td></tr>
<tr><td>O</td><td>100 ppm</td></tr>
<tr><td>Si</td><td>100 ppm</td></tr>
<tr><td>Zr</td><td><10 ppm</td></tr>
<tr><td>Ta</td><td>500 ppm</td></tr>
<tr><td>H</td><td><10 ppm</td></tr>
<tr><td>W</td><td><100 ppm</td></tr>
<tr><td>C</td><td>25 ppm</td></tr>
<tr><td>N</td><td>20 ppm</td></tr>
<tr><td>Fe</td><td>30 ppm</td></tr>
<tr><td>Cu</td><td><5 ppm</td></tr>
<tr><td>Mo</td><td>10 ppm</td></tr>
<tr><td>Ti</td><td><10 ppm</td></tr>
</table>
</td></tr>
<tr><td>Transfer system compatibility</td><td>As the target can be automatically transferred to/from the cyclotron by means of a pneumatic target transfer system, it was critical that the deposited Ni was robust to direct air flow and abrupt mechanical movements.
In certain embodiments, the target coating remains adhered to the backing during pneumatic transfer both to and from the cyclotron. Such a pneumatic system was typically fed by a compressed air connection of ~6-7 bar, and at minimum, 360 SLPM flow. Such a system was “push-push”, and therefore, compressed air was typically blown on both the front and rear sides of the</td></tr>
</table>

	coin, respectively, depending on the direction of transfer. The coin will also come to an abrupt stop as it reaches the target station or hot cell. In certain embodiments, suitable tests that indicate target durability include the following, whereby the total mass loss for all tests combined should be negligible (e.g. <1 μg): Visual inspection, gentle knocking/tapping on a countertop on top of white paper to check for loosening of target coating grains, gently rubbing an acid-washed Teflon spatula against the deposited target coating and checking for loosening of target coating grains, and/or placing and gently pressing down on a piece of Scotch tape against the target coating. If there was access to the cyclotron apparatus, it was recommended to transfer the coin back/forth multiple times and ensure target coating stability (i.e., no mass loss). Such a test may be performed with a degrader in place.
Method of Production	Electrodeposition from bath with a significantly high pH (e.g., 9.9-10.8)
Target Metal Form	To withstand the deposited beam power, the target metal was preferably metallic nickel (not, e.g., nickel oxide). Depending on the means of target preparation (e.g. electroplating), the raw nickel starting material need not necessarily be metallic. However, methods used for preparing ^{nat}Ni targets should ultimately be directly translatable to preparation of ^{60}Ni or ^{61}Ni targets. At present, it was understood that enriched Ni was typically in the form of a salt.
Target Additives	The use of binders must not necessary be avoided if they are absent of the final metallic coin and if an assessment on a case-by-case basis to understand potential impact to product quality has been done (e.g. ICP-MS on the binder material. Any reagents used for target preparation (e.g. electroplating reagents) must be of the highest quality, in particular, with regards to trace metals.
Metal Content	Preferably, the highest grades of reagents should be used, to avoid trace metals contamination of the target coating, as more than a tenth of a

	microgram per 100 µg of target metal (that is, 1 ppm of the target metal) is already a significant contamination that may render the coin unusable for production of high-purity radionuclides. In the case of the production of radiocopper it is not accepted to add more than 0.1 ppm of cold Cu as this would reduce the purity of the prepared radionuclide composition. Preferably, max level of impurities allowed to be added by the process to the initial nickel: • Copper (Cu): 0.1 ppm • High affinity metals (Ga, Lu, Pb, Y): 0.1 ppm • Zinc and cobalt (Zn, Co): 0.3 ppm • Transition and other metals (Cd, Cr, Al, Mn, Mo, Sn, Ti, V....): 1 ppm on a case by case • Iron (Fe): 10 ppm • Family I and II (K, Ba, µg, Be...): 1000 ppm The metal coins were analyzed on a batch per batch basis by dissolution in nitric acid to assess the metal contamination within the coin that were not found in the starting nickel metal and thus originate from the process. The amount suggested above were a good, albeit not strict, guide since chemical purification following irradiation will, in turn, further remove some of these impurities. The ultimate specification on this front will therefore be an iterative process as the Cu/Ni separation chemistry is refined. However, the process shall not significantly add impurities that were not in the originating pure nickel material. It is preferable that cold Cu should be minimized in the deposited Ni since this will follow the chemistry of any ^{61}Cu and cannot be separated post-irradiation. Any such cold Cu will directly compete with ^{61}Cu during radiolabeling of the pharmaceutical. Methods of removing Cu from the dissolved target metal are well known.

Density of Target	To withstand the deposited beam power, the Ni target should preferably be of reasonably high volumetric density (e.g. approximately ≥90% or, ≥8.0 g/cm^3).
Power Rating	The power rating for the target, including the combined deposited Ni and plate should preferably be: • ≥ 420 W (deuterons) • ≥ 820 W (protons)
Loading Mass of Target	The loading mass vs. the deposited mass of Ni (i.e. deposition efficiency) relates not to technical specifications, but rather, to cost. In the case of ^{nat}Ni deposition, loading efficiency will not have a significant impact on the cost of ^{61}Cu. However, losses should be minimized in considering the translation to enriched ^{6x}Ni. For ^{60}Ni, losses should be maintained below ~10%, and for ^{61}Ni, below ~1%. Some techniques such as magnetron sputtering are thus not possible for enriched nickel but are satisfactory for ^{nat}Ni.
Mass/thickness of Nickel	For deuterons (i.e. ^{nat}Ni or ^{60}Ni), the thickness should be appropriate for stopping the deuterons, with a maximum 10% variability in material deposition. Such thicknesses equate to: • ≥100 µm (assuming 100 % density) • ≥70 mg or ≥89 mg/cm^2 (assuming 10 mm diameter) For protons (i.e. ^{61}Ni), one may wish to selectively limit the deposited material to optimize the balance between material cost, yield, and backing material activation. With a maximum 10% variability in material deposition, four examples are noted below. ^{61}Ni Scenario #1 (11→9 MeV) • 78 µm (assuming 100 % density) • 55 mg or 69 mg/cm^2 (assuming 10 mm diameter well) ^{61}Ni Scenario #1 (12→8 MeV) • 155 µm (assuming 100 % density) • 108 mg or 138 mg/cm^2 (assuming 10 mm diameter well) ^{61}Ni Scenario #1 (13→7 MeV)

	• 233 µm (assuming 100 % density) • 163 mg or 208 mg/cm^2 (assuming 10 mm diameter well) ^{61}Ni Scenario #1 (13→4 MeV) • 309 µm (assuming 100 % density) • 216 mg or 275 mg/cm^2 (assuming 10 mm diameter well)
Isotopic enrichment	The ^{6x}Cu radioisotopes which will be coproduced during production of ^{61}Cu (t ½ = 3.339 h) include: • ^{57}Cu (t ½ = 0.196 s) ^{58}Cu (t ½ = 3.204 s) • ^{59}Cu (t ½ = 81.5 s) ^{60}Cu (t ½ = 23.7 m) • ^{62}Cu (t ½ = 9.673 m) ^{64}Cu (t ½ = 12.701 h) From a practical handling point of view, all but ^{60}Cu and ^{64}Cu are likely to have decayed prior to use. Only ^{64}Cu will have any impact on the possible shelf-life of ^{61}Cu. In addition to the production of Cu radioisotopes, other radionuclides (e.g. Co and Ni) will also be produced, the ratio of which will depend on the isotopic composition, and whether undergoing deuteron or proton irradiation. As these byproducts are chemically different from copper, such radionuclides may be removed during ^{61}Cu purification/processing. For example, The Cu-61 was purified from metal and radiometal impurities via a GE Healthcare FASTlab 2 module through a tributyl phosphate resin cartridge and a tertiary-amine-based weak ionic exchange resin containing long-chained alcohols.
Any other requirements	Niobium is preferred over silver for its better resistance to corrosion, its low amount of activation on irradiation and for its high melting temperature that permits the deposit of nickel by other processes such as melting or heat sintering. However, silver possesses a higher thermal conductivity and may be suitable for certain embodiments. For target backing manufacture, the following sheet of niobium is suitable for laser cutting: http:// www. Goodfellow .com

	NB000400 Niobium Foil, Size: 150x150 mm Thickness:1.5mm, Purity:99.9%, Temper:Annealed, Quality:LT From one sheet up to 25 target backings can be manufactured.

5.1.5. Purification and Characterization of [^{61}Cu]$CuCl_2$ and waste streams

[0337] The solid target irradiated material was dissolved in a total volume of 7 mL of 6 M HCl with the addition of 30% hydrogen peroxide via a dissolution chamber.

[0338] Separation and purification was accomplished using a cassette-based FASTlab platform using a TBP (tributylphosphate-based) resin (1 mL) (particle size 50-100 μm; pre-packed, Triskem) then a weakly basic (tertiary amine; TK201) resin (2 mL) (particle size 50-100 μm; pre-packed, Triskem) each of which were pre-conditioned with H_2O (7 mL) and HCl (10M, 7 mL). The cassette reagent vials were prepared using concentrated HCl (Optima Grade, Fischer Scientific), NaCl (ACS, Fischer Scientific) and milli-Q water (Millipore system, 18 MΩ-cm resistivity). 6M HCl (2 x 4.2 mL), 5M NaCl in 0.05 M HCl (4.2 mL). The subsequent ^{61}Cu was then purified with two subsequent ion exchange resins in a FASTlab synthesis unit.

1) The acid-adjusted dissolution solution (approx. 7 mL) was loaded over both columns in series and directed into a "Ni collection fraction". The TBP resin acted as a guard column as it quantitatively retained Fe^{3+} ions, while the Cu^{2+} and Co^{2+} complexes were quantitatively retained on the tertiary amine (TK201) resin.

2) Both columns were washed with 6M HCl (4 mL) to maximize Ni recovery for future recycling.

3) The TK201 column was washed with 4.5M HCl (5.5 mL) to elute the majority of cobalt salts.

4) The TK201 column was washed with 5M NaCl in 0.05M HCl (4 mL) to decrease residual acid on the resin and further remove any residual cobalt salts.

5) The TK201 column was washed with of 0.05M HCl (3 mL) to quantitatively elute the [^{61}Cu]$CuCl_2$.

[0339] The resulting [^{61}Cu]$CuCl_2$ solution of the plated material has an average activity of 1.0 – 4.5 GBq. This activity was measured using a dose calibrator from Comecer and its radionuclidic purity by a gamma spectrometer at PSI in Switzerland.

[0340] Gamma spectrometry measurements were performed to identify any radionuclidic impurities, particularly long-lived radionuclides. These results indicate a 89.3% and 94% reduction in impurities for ^{nat}Ni and ^{61}Ni on niobium backing materials with respect to silver backing materials when utilizing the methods disclosed herein. ICP-MS measurements were performed on the product of cold dissolutions by Labor Veritas in Switzerland to monitor elemental impurities present in product according to ICH-Q3D. All detected impurities were within regulated ICH-Q3D concentrations (see ICH-Q3D Guidelines, page 25).

[0341] The plating of highly enriched ^{61}Ni was also enabled with the same plating parameters as described above, for a higher yield and industrial production using proton irradiation (typically at 80 μA to 100 μA, 13 MeV protons for 1 hour to 2 hours and up to one half-life of ^{61}Cu).

5.1.6. Purity and activity evaluations of [^{61}Cu]$CuCl_2$ compositions prepared from ^{nat}Ni(d,n)^{61}Cu and ^{60}Ni(d,n)^{61}Cu using Nb-backed coins.

[0342] This example presents information on the activity of the produced ^{61}Cu generated using the Nb backing, Ni electrodeposited coins of the present disclosure; alongside cobalt radioisotopes, that were produced with deuteron irradiation using the coin comprising a natural nickel target and the coin comprising enriched ^{60}Ni as target, i.e., ^{nat}Ni(d,n)^{61}Cu and ^{60}Ni(d,n)^{61}Cu, respectively. The irradiated materials were dissolved and purified as described above.

[0343] The obtained and purified ^{61}Cu product and waste generated during purification from the products of deuteron irradiation of natural nickel/Nb coin and ^{60}Ni/Nb coin, respectively, was processed and analyzed by gamma-spectrometry and presented below.

[0344] TENDL-2019 is based on thick target yield calculations using isotopic abundancy of natural nickel/Nb coin and enriched ^{60}Ni/Nb coin, respectively.

5.1.7. Radiocobalt Content

[0345] Table 5 contains activities of cobalt radioisotopes in the different fractions post FASTlab purification as a mean of three measurements (n=3 irradiations) using ^{nat}Ni/Nb target coin. The activities were extrapolated to a 3 h and 50 μA beam at EoB (end of bombardment) +2 h. The

activity of [^{61}Cu]$CuCl_2$ in these irradiations was determined experimentally and confirmed to be ~80% of TENDL-2019 based estimates.

[0346] Activity of produced ^{61}Cu for irradiation with deuteron at 8.4 MeV, 3 h at 50 μA at 80% efficiency (EoB+2 h): 3052 MBq. Also see FIG. 3 for the change in cobalt radioisotopes with time along with the corresponding change in ^{61}Cu purity.

Table 5: Cobalt isotopes: natNi/Nb target coin

Radionuclide	Cu fraction [Bq]	Ni fraction [Bq]	Co-waste I+II [Bq]	Half-life [days]
^{56}Co	118345	2696	2458071	77
^{57}Co	0	0	474	272
^{58}Co	95395	2145	1940192	71
^{60}Co	124	3	2602	1925

[0347] Table 6 contains calculated activities of cobalt radioisotopes that would be obtained by using 99% enriched ^{60}Ni as target metal. The activities were extrapolated to a 3 h and 50 μA beam at EoB (end of bombardment) +2 h. The activity of ^{61}Cu was calculated accordingly.

[0348] The activity of produced ^{61}Cu with deuteron irradiation at 8.4 MeV, 3 h at 50 μA at 80% efficiency (EoB+2 h) was 11.552 MBq. Also see FIG. 4 for the change in cobalt radioisotopes with time and the corresponding change in ^{61}Cu purity.

Table 6: Cobalt isotopes: enriched ^{60}Ni/Nb target coin.

Radionuclide	^{61}Cu fraction [Bq]	Separated Ni [Bq]	Separated Co-waste I+II [Bq]	Half-life [days]
^{56}Co	365	8	7583	77
^{57}Co	0	0	1793	272
^{58}Co	242909	5463	4940424	71
^{60}Co	0.5	0	11	1925

5.1.8. Activity and Chemical Purity

[0349] Based on measured activities (MBq) at different beam currents (μA) and timescales (5 – 60 minutes), the measured activity resulting from deuteron bombardment of ^{nat}Ni, ^{60}Ni and proton bombardment of ^{61}Ni using the process described herein was found to be approximately > 80% of the theoretical activity calculated using the TENDL-19 cross section database.

[0350] The activity of radiocobalt and other long-lived radionuclides was measured post-release (> 3 weeks after bombardment). The EOB activity of the long-lived impurities was then extrapolated.

[0351] In Table 7, the extrapolated radiocobalt activity content and ^{61}Cu purity of [^{61}Cu]$CuCl_2$ solution produced by ^{nat}Ni as target metal for a 50 μA, 3 h deuteron irradiation after FASTlab purification were presented.

Table 7: Natural Ni/Nb Target Coin – Extrapolation of ^{61}Cu activity and purity in produced [^{61}Cu]$CuCl_2$ solution.

Hours post EoB	Co species activity in Cu fraction [Bq]	^{61}Cu activity [MBq]	^{64}Cu activity [MBq]	% Purity ^{61}Cu	% Purity PET nuclides ^{61}Cu + ^{64}Cu	% non-Cu radionuclides
0	213864	4622	70		99.995%	0.00456%
1	213784	3756	66	98.261%	99.994%	0.00559%
2	213704	3052	63	97.979%	99.993%	0.00686%
3	213624	2479	59	97.652%	99.992%	0.00841%
4	213544	2015	56	97.274%	99.990%	0.01031%
5	213465	1637	53	96.837%	99.987%	0.01263%
6	213385	1330	50	96.332%	99.985%	0.01545%
7	213305	1081	48	95.750%	99.981%	0.01890%
8	213225	878	45	95.081%	99.977%	0.02309%
9	213145	714	43	94.312%	99.972%	0.02817%
10	213066	580	41	93.432%	99.966%	0.03434%

[0352] Less than 0.03% non-Cu radioisotopes (^{56}Co and ^{58}Co) will be left in the copper fraction, assuming a product expiry time, e.g., >3 weeks post EoB. This value was lower than the limit allowed for Ga-68 cyclotron-produced as found in the Pharmacopeia (*0.1% at expiry for non-Ga radioisotopes):

[0353] The ^{64}Cu originating from ^{nat}Ni irradiation (content ~ 5% at expiry) will be the main impurity, reducing the radioisotopic purity of ^{61}Cu product at longer irradiation times or shelf-life (illustrated as the grey curve in FIG. 3).

[0354] Table 8 and FIG. 4 show the extrapolated radiocobalt activity content and ^{61}Cu purity of the produced [^{61}Cu]$CuCl_2$ solution after FASTlab purification.

Table 8: ^{60}Ni/Nb Target coin – Extrapolation of ^{61}Cu activity and purity in produced [^{61}Cu]$CuCl_2$ solution.

Hours post EoB	Co species activity in Cu fraction [Bq]	^{61}Cu activity [MBq]	^{64}Cu activity [MBq]	% Purity ^{61}Cu	% Purity PET nuclides ^{61}Cu + ^{64}Cu	% non-Cu radionuclides
0	243275	17498	0.378		99.999%	0.00139%
1	243176	14217	0.358	99.996%	99.998%	0.00171%
2	242977	11552	0.339	99.995%	99.998%	0.00210%
3	242680	9386	0.321	99.994%	99.997%	0.00259%
4	242285	7627	0.304	99.993%	99.997%	0.00318%
5	241792	6197	0.288	99.991%	99.996%	0.00390%
6	241201	5035	0.272	99.990%	99.995%	0.00479%
7	240514	4091	0.258	99.988%	99.994%	0.00588%
8	239731	3324	0.244	99.985%	99.993%	0.00721%
9	238853	2701	0.231	99.983%	99.991%	0.00884%
10	237882	2195	0.219	99.979%	99.989%	0.01084%

[0355] Less than 0.01% non-Cu radioisotopes (^{56}Co and ^{58}Co) were left in the Cu fraction, assuming a product expiry time of 8 h post EoB. This value was ten times lower than the allowed limit for ^{68}Ga cyclotron-produced as found in the Pharmacopeia (0.1% at expiry for non-Ga radioisotopes*).

[0356] Less than 0.02% ^{64}Cu was left in the copper fraction at an expiry time of 8 h post EoB, one hundred times lower than the specification required for ^{68}Ga (2% Ga radioisotopes were allowed for ^{68}Ga).

5.1.9. Purity of produced [^{61}Cu]$CuCl_2$ from Ni/Nb target coins: Comparison with Commercially Available Radionuclides

[0357] In Table 9, a comparison of the regulatory specifications on the purity of commercially available radionuclides are given along with the characteristics of the high purity [^{61}Cu]$CuCl_2$ produced from deuteron irradiation of natNi/Nb and enriched ^{60}Ni/Nb target coin (50 μA, 3 h) and after FASTlab purification described herein.

Table 9: Comparison between commercially available radionuclides and [^{61}Cu]$CuCl_2$ solution produced from irradiation of ^{nat}Ni/Nb coins and enriched ^{60}Ni/Nb coins.

Radionuclide	% Purity at EoB + 2 hours	% Max radioisotopes of same element at EoB + 2 hours	% Max other radioisotopes at EoB + 2 hours	Dominant impurities	% Purity at expiry	% Max other radioisotopes at expiry
^{111}In	99.93%	0.075%		^{65}Zn, ^{114m}In	99.85%	0.15%
^{18}F				^{56}Co	99.90%	0.10%
^{18}F				^{56}Co	99.99%	0.01%
^{68}Ga cyclotron	98%	2%	0.10%			
^{68}Ga generator	99.90%		0.001%	^{68}Ge		
^{177}Lu	99.90%	0.05%				
^{61}Cu from ^{nat}Ni	97.27% (EoB+ 4 h)	3.16%	0.013%	^{56}Co, ^{58}Co	95.08% (EoB+ 8 h)	5%
^{61}Cu from ^{60}Ni	99.99% (EoB+ 4 h)	0.009%	0.004%	^{56}Co, ^{58}Co	99.98% (EoB+ 8 h)	0.02%

[0358] As the first notable comparison, cyclotron production of ^{68}Ga from proton irradiation also produces long lived radionuclides, (see, e.g., Applied Radiation and Isotopes, 65(10), 1101–1107, IAEA-TECDOC-1863 Gallium-68 Cyclotron Production) notably ^{65}Zn (half-life=244 days) from the ^{66}Zn(p,pn)^{65}Zn decay. With a roughly 0.365% of ^{66}Zn in an enriched ^{68}Zn starting target metal, about 770 Bq of ^{65}Zn will be produced from a 50 µA, 3 h beam with an energy of 13 MeV in a thick target (TENDL-2019 based calculations). Using natural Zn with 27.7% abundancy in ^{66}Zn, 58 kBq of ^{65}Zn will be produced in one run of 50 µA for 3 h beam.

[0359] Similar with [^{61}Cu]$CuCl_2$ production, cyclotron production of [^{64}Cu]$CuCl_2$ from proton irradiation also produces long-lived cobalt radionuclides, namely, ^{55}Co, ^{57}Co, ^{58}Co, and ^{60}Co. (See, e.g., Nuclear Medicine & Biology, Vol. 24, pp. 35-43, 1997; Applied Radiation and Isotopes 68 (2010) 5–13). By operating with a degraded beam of below 13 MeV, ^{60}Co (from ^{64}Ni(p,na)^{60}Co) was reduced to 1 Bq per run of 50 µA, 3 h. With beam energies below 13 MeV, ^{55}Co, formed from the ^{58}Ni(p,a)^{55}Co reaction, will remain the main impurity (half-life=17.53 hours). The 170 Bq of the long-lived ^{57}Co was formed in about 170 Bq in these conditions mostly from ^{60}Ni(p,a)^{57}Co.

[0360] Note: These estimates were computed from thick target yields using TENDL-2019 cross section data and isotopic abundancy of enriched ^{64}Ni as follows: 0.00376% ^{58}Ni, 0.00298% ^{60}Ni, 0.0058% ^{61}Ni, 0.135% ^{62}Ni, 99.858% ^{64}Ni.

5.1.10. Enriched ^{61}Ni as Target Metal on Nb backed coins

[0361] ^{61}Cu was produced through the proton bombardment of ^{61}Ni electroplated Nb backed coin via cyclotron equipped with a solid target system irradiating a highly pure Niobium coin plated with highly pure ^{61}Ni (purity 99.42%). The proton beam currents used were up to 100 μA, and beam energy of 13 MeV. An aluminum beam degrader was used.

[0362] The solid target irradiated material was dissolved in a total volume of 7 mL of 6M HCl with the addition of 30% H_2O_2 in a heated dissolution chamber. The ^{61}Cu was purified from metal and radiometal impurities via a GE Healthcare FASTlab 2 module through a tributyl phosphate resin cartridge and a tertiary-amine-based weak ionic exchange resin containing long-chained alcohols. The product was finally eluted in an ISO class 5 environment in 3 mL 0.05 M HCl through a sterile filter Millex 4 mm Durapore PVDF 0.22 μm into a sterile evacuated vial. The vial was handled with care using the appropriate shielding and can be stored at room temperature until use using appropriate shielding for transport and handling. The properties of the [^{61}Cu]$CuCl_2$ solution were determined and are displayed below in Table 10.

Table 10. [^{61}Cu]$CuCl_2$ produced from ^{61}Ni.

Parameter	Test Method	Specification
Appearance	Visual inspection	Clear, colorless solution, free from particulate matter
Volume	Weight measurement	3 ± 0.3 mL
Activity concentration (EoP)	Dose calibrator	0.20 - 2 GBq/mL
pH value	pH paper strips	1-1.6
Radiochemical purity	Radio-TLC	≥ 99% (as [^{61}Cu]$CuCl_2$)
Radionuclidic identity	γ-Spectrometry (multichannel analyzer in lab at EoB+90 minutes)	γ-photons with energy peaks at: 283 keV ± 20 keV 511 ± 20 keV (eventually sum peak at 1022 keV ± 20 keV) 656 keV ± 20 keV
	Half-life via dose calibrator	200 ± 20 min
Radionuclidic purity	γ-Spectrometry (sent out, evaluated >3weeks, values extrapolated to in lab at EoB+90 minutes)	≥ 99.9%

Bacterial endotoxin content	LAL test (Endosafe)	≤ 17.5 EU/mL
Chemical purity	ICP-MS (sent out, evaluated >3weeks, values relevant to in lab at EoB+90 minutes as these do not change with time)	Sum of impurities ≤ 15 µg/GBq Cu ≤ 0.5 µg/GBq Al ≤ 2 µg/GBq Co ≤ 1 µg/GBq Fe ≤ 3 µg/GBq Pb ≤ 1 µg/GBq Ni ≤ 2 µg/GBq Zn ≤ 1 µg/GBq

*post-release (≥ 3 weeks)
#measured periodically

[0363] As shown in Table 11 and FIG. 5, commercially available [^{61}Cu]$CuCl_2$ contains radionuclidic impurities, particularly high levels of ^{56}Co and ^{58}Co, in addition to ^{110m}Ag and ^{109}Cd. Elimination of Ag and Cd isotopes from the Cu-61 product by replacing silver with niobium as backing material. There was a nine-fold reduction of ^{56}Co isotopes for natNi and >2000x reduction for Ni-61 (less shielding of radioactive waste is required). 50% reduction of long-lived cobalt isotopes (earlier final disposal of the produced waste) was also observed. It was clear from the data below, that the radionuclidic purity of [^{61}Cu]$CuCl_2$ produced by the methods described above to be superior to previously known methods and products. The high levels of long-lived Co, Ag, and Cd radionuclides pose a radiation burden for the patient and a radioactive waste issue for consumables that have come in contact with the [^{61}Cu]$CuCl_2$ product during radiopharmaceutical manufacturing and radiolabeling.

Table 11. Detailed radionuclidic impurities present in commercially available ^{61}Cu compared to high-purity [^{61}Cu]Cl_2 of the present disclosure, expressed in Bq/g.

		Ext. Coins	Present Coins	
Coin		nat-Ni on Ag	nat-Ni on Nb	^{61}Ni on Nb
Elements	**$T_{1/2}$**	**Bq/g**		
Co-56	77.23 days	5269.2	539.5	2.3
Co-57	271.74 days	1.8	1.5	1.2
Co-58	70.86 days	4586.8	503.8	588.5
Co-60	5.27 years	5.9	2.8	0.9
Ag-108m	439 years	0.9	N/D	N/D
Ag-110m	249.86 days	1.5	N/D	N/D
Cd-109	462.6 days.	10	N/D	N/D

[0364] The total radionuclidic impurity profile was summed (Table 12 and FIG. 6). There was an 83% decrease in radionuclidic impurities. When present in the [^{61}Cu]$CuCl_2$ product, these impurities can cause a radiation burden for the patient, waste issues, and degrade the quality of, e.g., a radiotracer or radiopharmaceutical. They can also interfere with the chelation process by competing with ^{61}Cu, which affects the accurate radiolabeling of the tracer. An 89.3% reduction of impurities was observed upon changing the backing material from silver to the niobium backing provided herein and using the Ni plating methods described herein. And Additional reduction of 46% was observed when using Ni-61 as starting material.

Table 12. Radionuclidic impurities in the produced [^{61}Cu]$CuCl_2$.

	Ext. Coins	**Present Coins**	
Coin	natNi on Ag.	nat-Ni on Nb	^{61}Ni on Nb
Bq/g	9876±1.5	1057±1.8	593±0.2

[0365] Consequent to the purity of the ^{61}Cu at EoB and End of Production (EoP, EoB + 2 hours), long-lived radionuclidic impurities decay slower and, thus, increase in concentration in relation to ^{61}Cu at longer timescales. Thus, the impurity profile may vary greatly based on the isotopic enrichment of the raw material, purity, method, and process of producing a coin, which influences the type and amount of radionuclidic impurities in the finished [^{61}Cu]$CuCl_2$ product.

[0366] FIG. 7. contrasts the radionuclidic purity of [^{61}Cu]$CuCl_2$ solution produced with commercially available natNi target metal on a Ag backing compared to the radionuclidic purity of [^{61}Cu]$CuCl_2$ solution produced by irradiation of Ni target metal electroplated according to the present disclosure on high purity Nb backing when assessed by gamma spectrometry in Bq/g (summed radionuclidic impurities) at t = 0h and at t = 12h. The presented data highlight the superior quality of the [^{61}Cu]$CuCl_2$ solution when produced by irradiation of Ni target coatings electroplated according to the present disclosure on high purity Nb backing, where the purity after 12 hours is still well above the purity limits set by pharmacopeia for similar radionuclides for medical use.

Table 13. Radionuclidic purity of commercially available ^{61}Cu compared to high-purity $[^{61}Cu]CuCl_2$ of the present disclosure as measured at EoP and EoP + 12 hours.

	Ext. Coins	Present Coins	
Coin	nat-Ni on Ag	nat-Ni on Nb	^{61}Ni on Nb
Purity% t = 0h	99.998	99.999	99.9999
Purity% t = 12h	99.978	99.993	99.999

5.1.11. Conclusion

[0367] The experimental activities of ^{61}Cu produced after deuteron irradiation were about 80% of the theoretical yield as calculated from TENDL-2019 cross section data.

[0368] The main long-lived nuclides in the radioactive waste fraction from cyclotron production of ^{61}Cu were radiocobalt species of ^{56}Co, ^{57}Co, ^{58}Co, and ^{60}Co. It was calculated that, after four years, ^{56}Co, ^{57}Co, and ^{58}Co will have decayed below regulatory clearance limits, LL*, leaving only ^{60}Co. *Clearance limits (LL) means the value corresponding to the activity concentration level of a material below which handling of this material is no longer subject to mandatory licensing or supervision.

[0369] The yield and purity of $[^{61}Cu]CuCl_2$ prepared with niobium coins was improved by plating the niobium coins with 99% enriched ^{60}Ni or ^{61}Ni. The purity of $[^{61}Cu]CuCl_2$ product was higher as ^{64}Cu was be formed as a radioisotopic impurity. Additionally, the ^{56}Co and ^{60}Co contents were reduced by a factor of 100. ^{57}Co amounts increased (but were low activity) and ^{58}Co amounts doubled (but decay below LL before $^{56}Co/^{58}Co$).

5.1.12. Batch Control of $[^{61}Cu]CuCl_2$

[0370] Three representative batches of $[^{61}Cu]CuCl_2$ solution were manufactured as described above (by irradiating a solid target consisting of highly pure ^{61}Ni (purity > 99.42%) plated on a niobium coin backing with a proton beam) and tested. The results of these analyses are presented in Table 14. "End of Production" or "EoP" refers to the end of the preparation of $[^{61}Cu]CuCl_2$.

Table 14: Analyses of three batches of [^{61}Cu]$CuCl_2$.

	Specification	**Results**		
Batch	-	1	2	3
Volume	3 ± 0.3 mL	3.02 mL	3.00 mL	3.19 mL
Activity concentration (EoP; end of production; 1 hour after bombardment)	0.50 - 2.00 GBq/mL	1.30 GBq/mL	1.29 GBq/mL	1.47 GBq/mL
Apparent molar activity	35 – 580 MBq/nmol	144.44 MBq/nmol	144.44 MBq/nmol	163.33 MBq/nmol
pH value	1-1.6	1.3	1.2	1.3
Radiochemical purity	≥ 99% (as [^{61}Cu]$CuCl_2$)	100%	100%	100%
Radionuclidic identity	γ-photons with energy peaks at: 283 keV ± 20 keV 511 ± 20 keV (eventually sum peak at 1022 keV ± 20 keV) 656 keV ± 20 keV	290 keV 506 keV 654 keV	286 keV 510 keV 652 keV	286 keV 510 keV 656 keV
Half-life	200 ± 20 min	195.6 min	196.2 min	195.6 min
Radionuclidic purity*	≥ 99.9%	99.99%	99.99%	99.99%
Bacterial endotoxin content	≤ 17.5 EU/mL	≤ 3.75 EU/mL	≤ 3.75 EU/mL	≤ 3.75 EU/mL
Chemical purity*	Sum of impurities ≤ 20 µg/GBq	Sum of impurities 2.40 µg/GBq	Sum of impurities 2.11 µg/GBq	Sum of impurities 2.72 µg/GBq

*post-release.

5.1.13. Radionuclidic Purity

[0371] Radionuclidic purity is important in radiopharmacy since any radionuclidic impurities increase the radiation dose received by the patient and may also degrade the quality of any imaging procedure performed. For example, if significant levels of other radionuclides are present then biological distribution may be altered. Radionuclide samples contain some contaminants arising

the production process or the decay of the primary radioisotope. Radionuclide impurities can occur as a result of the manufacturing process, for example, for nuclides produced by cyclotron there can be contaminants due to impurities in the target or by the energy of the reaction. In order to control the effects of these contaminants on the radiation dose received by the patient, limits are set on the maximum levels of contamination allowed. These limits are defined by governmental agencies, e.g., in pharmacopoeia monographs, and vary depending upon the radionuclide concerned and the physical decay characteristics of the likely contaminants. Measurement of radionuclidic purity may be performed high resolution using gamma-ray spectroscopy on samples well after bombardment. The activity of the long lived isotopes is then extrapolated back to EoB, EoP, or EoS or even at expiration. High activity emitted from long lived radionuclidic impurities greatly increases the cost and complexity of managing the disposal of all consumables that come into contact with the nuclide composition.

[0372] Through the deuteron irradiation of natural nickel and ^{60}Ni, and proton irradiation of ^{61}Ni, long-lived isotopes of cobalt are produced: ^{56}Co, ^{57}Co, ^{58}Co and ^{60}Co. Other long-lived radionuclides such as ^{110m}Ag, ^{108m}Ag and ^{109}Cd are produced through the irradiation of commonly used silver backing material, which are dissolved along with starting material during the purification process. Due to their long half-lives, the proportion of these radionuclides increases with time compared to the ^{61}Cu, decreasing the radionuclidic purity of the product, especially at later time points when using ^{nat}Ni as a starting material. Though most cobalt isotopes can be separated in the purification process, the ^{110m}Ag, ^{108m}Ag and ^{109}Cd end up in the ^{61}Cu fraction and nickel solution that is further used in recycling of irradiated target coating. The long-lived radionuclides become problematic when considering the radiation burden to the patient and the accumulation of radioactive waste. Third-party coin manufacturers did not publish the contamination from the non-niobium coin backings (e.g., silver). As provided by the present disclosure, the method of making and using coins comprising niobium represents an advantage, e.g., in view of the radionuclidic and chemical purity of samples produced following subatomic particle bombardment, isolation, and purification. A detailed comparison of the known ^{61}Cu products (prepared via Ag backings and prior art methods of plating the target) to ^{61}Cu as provided by the present disclosure is provided below.

[0373] With these factors in mind, a niobium backing material was chosen due to its inert nature to acids at room temperature and at elevated temperatures. This characteristic allows the niobium

backing material to resist the acid medium used during the dissolution and purification process. By doing so, higher radionuclidic and chemical purity can be achieved in the radiometal aqueous solution, eventually resulting in higher purity for the radiopharmaceutical prepared from the desired ^{61}Cu isotope. Although plating methods of niobium exist, the element has not yet been used for radionuclide production due to the poor adhesion of the plated Ni material (as discussed above). The Ni (or ^{68}Zn for the production of ^{68}Ga) requires sufficient adhesion for the coin to survive thermal loads (1200 W) during irradiation and pneumatic shuttle acceleration at 5 bar to 7 bar of pressure and abrupt stop at the head. On the other hand, however, the plated Ni (or Zn) must dissolve sufficiently during the dissolution and purification process. Attempts were made to plasma-coat niobium backings for plating nickel (Ni). However, this process resulted in losses and incomplete dissolution of Ni from the niobium backing. The thermal processes involved in plasma coating altered the grain structure of the niobium backing material, leading to a strong bond between the plated nickel and niobium. This strong bond made it difficult for the nickel to fully dissolve, causing losses. The plasma coating process itself resulted in very high losses in target coating, rendering the process not viable for use, especially with very expensive highly enriched target metals. The main reference to this summary is the IAEA documentation regarding cyclotron radionuclide production, *IAEA RADIOISOTOPES AND RADIOPHARMACEUTICALS, REPORTS, No. 1.* (INTERNATIONAL ATOMIC ENERGY AGENCY VIENNA, 2016) Additionally, a monetary evaluation regarding the procurement costs of niobium utilized as a backing material displays a 40% lower cost in comparison to commonly used backing materials such as gold, silver, and platinum where costs range from €80 to €120 per backing material (single coin).

[0374] Parallel to this, elements pertaining to the radiochemical purity of the labelling process are controlled by manufacturing the plating solution under controlled conditions described herein. By procuring the plating solution from a raw base material of, e.g., nickel, the possibility of contamination is now independent from outside sources and suppliers. Such material and equipment used in these cases are inert glass beakers and falcon tubes (ensured to not contain any undesirable substances), TraceSelect pure water, pure reagents (trace-metal grade), inert coin adapter and electrolytic cell (on the electroplating unit), etc. Through this, the contaminants of trace metals can be minimized reduced or avoided all together. This difference between 99.9% purity and 99.99% purity plays a role in the resulting chemical purity of a radionuclide and

therefore in the radiochemical purity of, e.g., a radiotracer or radiopharmaceutical prepared from the radionuclide, where the presence of cold Cu, Zn, Fe, Sn, Ti, or Al or any salt thereof are an issue as they will compete for binding to the chelator in the tracer along with the desired radionuclide (^{61}Cu).

[0375] Robustness of plating was tested through a drop and scratch test. This assessment ensures that the electrodeposited substrate on the backing will survive mechanical impacts of the shuttling system and established an increased probability of survivability under the cyclotron beam.

[0376] In certain embodiments, coins were irradiated with 8.4 MeV deuterons for an average duration of 120 mins at a range of 40 μA to 45 μA or with 13.2 MeV deuterons at 40 μA to 45 μA using an ARTMS or GE shuttling system on a GE PET Trace cyclotron.

[0377] In certain embodiments, the coins were irradiated with 8.4 MeV deuterons for an average duration of 120 mins at a range of 40 μA to 45 μA or with 10 μA to 100 μA 13 MeV protons using an ARTMS or GE shuttling system on a GE PET Trace cyclotron.

[0378] Dissolution of Ni from the niobium backing was accomplished via the utilization of a dissolution system in 10 M HCl. The subsequent ^{61}Cu was then purified with two subsequent ion exchange resins in a FASTlab synthesis unit. The processing time for these purifications can reach up to 60 minutes.

[0379] The resulting [^{61}Cu]$CuCl_2$ solution of the plated material has an average activity of 1.7 – 4.5 GBq. This activity was measured using a dose calibrator and its radionuclidic purity by a calibrated gamma spectrometer e.g., at PSI in Switzerland.

[0380] Gamma spectrometry measurements were performed to identify any radionuclidic impurities, particularly long-lived radionuclides. These results indicate an 89.3% and 94% reduction in impurities for ^{nat}Ni and ^{61}Ni on niobium backing materials with respect to silver backing materials when utilizing the methods disclosed herein. ICP-MS measurements are performed on the product of cold dissolutions by Labor Veritas in Switzerland to monitor elemental impurities present in the product according to ICH-Q3D. All detected impurities are within regulated ICH-Q3D concentrations (see ICH-Q3D Guidelines, pg 25).

[0381] The plating of highly enriched ^{61}Ni was also enabled with the same plating parameters as described above, for a higher yield and industrial production using proton irradiation (typically at 10 μA to 100 μA, 13 MeV protons for 20 minutes to 2 hours and up to one half-life of ^{61}Cu).

[0382] Following automated transportation of the irradiated coin from the cyclotron to the hot cell docking station, the capsule was transferred to a QIS dissolution unit with tongs. The transmuted target metal was dissolved from the niobium backing material using 1:1 7M HCl: 30% H_2O_2 (ultratrace analysis, Merck) (4 mL). The acid-peroxide mixture is circulated, immersing the coin and target metal surface to dissolve all irradiated elements at 2 mL/min for about 23 minutes at about 60 °C. When the target metal was fully dissolved, acidic solution containing the dissolved metal was withdrawn and the QIS system was flushed with 10M HCl (3 mL). The combined acidic solutions were then fed forward to the FASTlab purification unit.

[0383] For this reason, gamma spectrometry analyses were carried out on decayed samples (at least 10 half-lives of ^{61}Cu, corresponding at the earliest to 1.4 d after EoP). The analysis was performed using a high-purity germanium (HPGe) detector GEM30-70 from Ortec.

5.1.14. Activity concentration

[0384] The activity of the $[^{61}Cu]CuCl_2$ solution was quantified using a dose calibrator following *Ph. Eur. 2.2.66* guidelines. The test was carried out at the end of the radionuclide production (EoP; end of production; end of bombardment plus 1 hour) using a certified dose calibrator, selecting the ^{61}Cu measuring channel. The weight of the $[^{61}Cu]CuCl_2$ solution was measured using an analytical scale. Assuming a density of the aqueous solution of 1.0 g/mL, the weight is converted into a volume. The activity concentration, expressed in GBq/mL, is then calculated by dividing the activity by the volume.

5.1.15. Apparent molar activity

[0385] The suitability of the $[^{61}Cu]CuCl_2$ solution for radiolabeling was ensured by determining the apparent molar activity. This test assessed the impact of competing trace metals on ^{61}Cu chelation by quantifying the minimum amount of a given chelator required for efficient radiolabeling. The test can be performed with various chelators that can complex copper (e.g., NOTA, DOTA, NODAGA). Among them, NODAGA has been assessed for ^{61}Cu molar activity. The test measures the percentage of complexation by radio-TLC after reacting a fixed amount of

[^{61}Cu]$CuCl_2$ solution with different amounts of chelator (titration). The results are then plotted (x axis (logarithmic): nmol of chelator; y axis: % of complexation), and a sigmoidal curve is obtained. The EC_{50} point is extrapolated, corresponding to the amount of chelator needed to achieve the 50% of complexation. The apparent molar activity is calculated by dividing the ^{61}Cu activity used extrapolated at the end of production (EoP) by 2 times the EC_{50} value.

[0386] This test was not performed as a routine analysis, but when changes occur in 1) the grade of a chemical employed for the manufacturing of the [^{61}Cu]$CuCl_2$ solution, 2) the quality of a consumable employed for the manufacturing of the [^{61}Cu]$CuCl_2$ solution, 3) the target coin manufacturing process, and 4) if poor radiolabeling yields were observed. The AMA test is specific to a chelator and labelling conditions (e.g., buffer concentration and pH) and has thus to be repeated when these parameters are modified.

5.1.16. pH

[0387] The pH value was determined by colorimetric evaluation using pH paper strips with a narrow range (pH interval 0 – 2.5) exposed to a 10 µL of the [^{61}Cu]$CuCl_2$ solution. The color of the paper strips was compared to the reference color scale displayed on the strips container.

5.1.17. Radiochemical Purity (Radio-TLC)

[0388] The radiochemical purity of a [^{61}Cu]$CuCl_2$ solution prepared as described herein was determined by radio-TLC following *Ph. Eur. 2.2.66* guidelines. The test determined the percentage of ^{61}Cu present in the desired ionic form, namely as free Cu^{2+}. The retention factor (R_f) was determined as the distance from the origin to the peak divided by the distance from the origin to the solvent front. Ionic [^{61}Cu]Cu^{2+} migrated to the solvent front (R_f = 0.8-1.0), while colloidal [^{61}Cu]$Cu(OH)_2$ remained at the point of application (R_f = 0.0-0.2). The specification required that ≥ 99% of the whole radioactivity detected was present in the ionic form [^{61}Cu]Cu^{2+}.

[0389] For the test, 2 µL of the radioactive solution was applied at 1 cm away from the lower end of an iTLC paper plate (8 x 1 cm), consisting of glass microfiber chromatography paper impregnated with silica gel. After drying, the iTLC plate was placed in a glass chamber where it was run in a 0.1 M citrate buffer solution (pH 5). When the solvent front had reached a distance of approximately 1 cm from the top of the iTLC plate, the plate was removed from the chamber and

scanned using a PET miniGita Star from Elysia-Raytest, equipped with a β-sensitive detector and controlled by the software Gina Star from Elysia-Raytest.

5.1.18. Gamma spectrometry (Radionuclidic identity)

[0390] The radionuclidic identity of a [^{61}Cu]$CuCl_2$ solution prepared as described herein was confirmed by gamma spectrometry following *Ph. Eur. 2.2.66* guidelines. The presence of the main γ-photons with energy peaks characteristic of ^{61}Cu (listed in Table 15) was assessed. The table also lists the energy peak of the γ-photons belonging to ^{58}Co, which represents the main impurity detected in the test. The test was carried out at EoP using a Mucha Star multichannel analyser from Elysia-Raytest, equipped with a NaI detector, and controlled by the Gina Star from Elysia-Raytest software.

Table 15: Energy peaks characteristic of ^{61}Cu and of its main impurity ^{58}Co.

Peak	Energy (keV)
Cu-61	67
Cu-61	283
Beta peak	511
Cu-61	656
Co-58	811
Sum peak	1022
Cu-61	1185

5.1.19. Half-life (Radionuclidic identity)

[0391] The radionuclidic identity of a [^{61}Cu]$CuCl_2$ solution prepared as described herein was further confirmed by half-life determination following *Ph. Eur. 2.2.66* guidelines. The test was carried out at the end of the radionuclide production (EoP) using a certified dose calibrator from Comecer (model VDC-505), selecting the ^{61}Cu measuring channel. The specification required the measured half-life value to be within a predefined range of the accepted half-life value (20%).

5.1.20. LAL test (Bacterial endotoxin content)

[0392] The bacterial endotoxins were determined in a [^{61}Cu]$CuCl_2$ solution prepared as described herein by limulus amoebocyte lysate (LAL) test following *Ph. Eur. 2.6.14* guidelines. This system applies LAL kinetic chromogenic methodology that measures color intensity directly proportional to the endotoxin concentration in the sample. Each cartridge contained predefined amounts of LAL reagent, chromogenic substrate, and control standard endotoxin (CSE). The LAL reagent was

mixed automatically by the device with the sample or the positive product control. The mixtures were incubated and then combined with the chromogenic substrate. For quantification, the optical density of the substrate was measured and analyzed against an internally archived standard curve. The analysis was performed in duplicate for the sample as well as for the positive product control. The system contained an internal printer to generate a report.

5.1.21. Bioburden

[0393] The bioburden of the aqueous [^{61}Cu]$CuCl_2$ manufacturing process described hereinn was evaluated following *Ph. Eur. 2.6.12* guidelines. This test enables the detection and quantification of the viable microorganisms present in the system prior to terminal sterilization and represents a good reference point for evaluating the degree of safety of the process. The manufacturing process was performed in completeness but used non-irradiated target coins for radiation protection. The collected non-radioactive solution was analyzed by the Membrane-Filtration Method. Half of the sample was passed through a membrane filter with a pore size of 0.45 µm. The filter was placed onto Soybean-Casein Digest Agar and incubated to determine the total aerobic microbial count (TAMC). The other half of the sample was passed through a membrane filter with a pore size of 0.45 µm. The filter was then placed onto Sabouraud Dextrose Agar and incubated to determine the total yeast and mold count (TYMC). The bioburden was expressed in colony-forming units (CFU).

5.1.22. Control of Starting Material

[0394] Reagents and starting materials used to manufacture the radionuclide ^{61}Cu are provided in Table 16. The reagents employed in production were of TraceSelect grade to minimize the trace metal impurities. These impurities could impact radiolabeling, which may result in a poor complexation of ^{61}Cu with the chelator.

Table 16: Materials used to purify and formulate [^{61}Cu]$CuCl_2$.

Material	Quality
^{61}Ni	99.42% enrichment
Niobium coin backing	99.9% purity
Hydrochloric acid	30%, Ultrapure
Hydrogen peroxide	30%, Suprapure
Sodium chloride	99.99%, Suprapure
Water	Ultrapure

FASTlab cassette	Cassette's plastic components either sterile or tested for low bioburden
Solid Target Valve Box (STVB) cassette	Cassette's plastic components either sterile or tested for low bioburden
TBP and TK201 cartridges	Ion-exchange cartridge for purification
FASTlab water bag	Sterile WFI USP/Ph. Eur.
Vials	20 mL sterile evacuated
Syringe needles	Sterile
Sterile filter Millex GV	0.22 µm pore size, sterile

[0395] At the end of the electroplating process, the target coin was examined using an optical microscope (20x, 50x and 250x magnification). All the steps of the coin manufacturing were performed using TraceSelect grade chemicals and metal-free consumables. The target coins were stored in a cool, dark environment in metal-free sealed containers.

5.1.23. Impurities

[0396] The impurities present in the irradiated starting material can undergo a nuclear reaction, leading to the formation of undesired radioactive species, as summarized in Table 17. Due to the high isotopic purity of the ^{61}Ni (99.42% enrichment), these contaminations were limited.

Table 17: Composition of the ^{61}Ni target coin plating and main nuclear reactions.

^{61}Ni composition	^{58}Ni (0.004%), ^{60}Ni (0.3%), ^{61}Ni (99.42%), ^{62}Ni (0.3%), ^{64}Ni (0.004%)
Desired nuclear reaction	^{61}Ni(p,n)^{61}Cu
Contamination reactions (selection of the main contributions)	^{60}Ni(p,α)^{57}Co (half-life: 271.74 d) ^{61}Ni(p,α)^{58}Co (half-life: 70.86 d) ^{61}Ni(p,n)^{60}Co (half-life: 1925 d)

[0397] The presence of "cold" trace metal ions in the target coin material and reagents used during the dissolution and purification stages are to be limited. These trace metal ions can impact the subsequent radiolabeling processes by interfering with the complexation of ^{61}Cu with the chelator. TraceSelect grade reagents and metal-free consumables are used with the aim of minimizing trace metal contamination.

[0398] The concentration of the trace metal ions in the [^{61}Cu]$CuCl_2$ solution is determined by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) (Table 18). ICP-AES can be used as alternative technique.

5.2. Example 2: Preparation of Compounds

[0399] The examples and preparations provided below further illustrate and exemplify the compounds as disclosed herein and methods of preparing such compounds. It is to be understood that the scope of the present disclosure is not limited in any way by the scope of the following examples and preparations.

[0400] The chemical entities described herein can be synthesized according to one or more illustrative schemes herein and/or techniques well known in the art. Unless specified to the contrary, the reactions described herein take place at atmospheric pressure, generally within a temperature range from -10° C to 200° C. Further, except as otherwise specified, reaction times and conditions are intended to be approximate, e.g., taking place at atmospheric pressure within a temperature range of -10° C to 200° C over a period that can be, for example, 1 to 24 hours; reactions left to run overnight in some embodiments can average a period of 16 hours.

[0401] Isolation and purification of the chemical entities and intermediates described herein can be affected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography or thick-layer chromatography, or a combination of these procedures. See, e.g., Carey et al. Advanced Organic Chemistry, 3rd Ed., 1990 New York: Plenum Press; Mundy et al., Name Reaction and Reagents in Organic Synthesis, 2nd Ed., 2005 Hoboken, NJ: J. Wiley & Sons. Specific illustrations of suitable separation and isolation procedures are given by reference to the examples hereinbelow. However, other equivalent separation or isolation procedures can also be used.

[0402] In all of the methods, it is well understood that protecting groups for sensitive or reactive groups may be employed where necessary, in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T.W. Greene and P.G.M. Wuts (1999) Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons). These groups may be removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art.

[0403] When desired, the (R)- and (S)-isomers of the nonlimiting exemplary compounds, if present, can be resolved by methods known to those skilled in the art, for example, by formation of diastereoisomeric salts or complexes which can be separated, e.g., by crystallization; via formation of diastereoisomeric derivatives which can be separated, e.g., by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, e.g., enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, e.g., on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. Alternatively, a specific enantiomer can be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts, or solvents, or by converting one enantiomer to the other by asymmetric transformation.

[0404] The compounds described herein can be optionally contacted with a pharmaceutically acceptable acid to form the corresponding acid addition salts. Also, the compounds described herein can be optionally contacted with a pharmaceutically acceptable base to form the corresponding basic addition salts.

[0405] In some embodiments, disclosed compounds can generally be synthesized by an appropriate combination of generally well-known synthetic methods. Techniques useful in synthesizing these chemical entities are both readily apparent and accessible to those of skill in the relevant art, based on the instant disclosure. Many of the optionally substituted starting compounds and other reactants are commercially available, e.g., from Millipore Sigma or can be readily prepared by those skilled in the art using commonly employed synthetic methodology.

[0406] The discussion below is offered to illustrate certain of the diverse methods available for use in making the disclosed compounds and is not intended to limit the scope of reactions or reaction sequences that can be used in preparing the compounds provided herein. The skilled artisan will understand that standard atom valences apply to all compounds disclosed herein in genus or named compound for unless otherwise specified.

[0407] HPLC spectra for all compounds were acquired using an Shimadzu LC-20A Prominence system with an Elysia-Raytest Gabi Star radioactivity-HPLC-flow-monitor γ detector and an UV detector Shimadzu SPD-20A. Chromatography was performed on a Macherey-Nagel Nucleosil 100-5-C18 AB, 125 x 4.6 mm, dp: 5 µm column with water containing 0.1% formic acid as

solvent A and acetonitrile containing 0.1% formic acid as solvent B at a flow rate of 2.0 mL/min. The gradient program was as follows: 10% B (0−2 min), 10-55% B (2−12 min), 55-99% B (12−17 min), 99% B (17 – 19.1 min), 99 -10% B (19.1 – 19.2 min), and 10% (19.2 – 22 min). High-resolution mass spectra (HRMS) data were acquired in positive ion mode using an Agilent G1969A API-TOF with an electrospray ionization (ESI) source. Nuclear Magnetic Resonance (NMR) spectra were acquired on a Bruker spectrometer with 600 MHz or 400 MHz for proton (^{1}H NMR) and 150 MHz for carbon (^{13}C NMR); chemical shifts are reported in (δ). Preparative HPLC was performed on Agilent Prep 1200 series with UV detector set to 254 nm and 220 nm. Samples were injected onto a Phenomenex Luna 75 x 30 mm, 5 µm, C_{18} column at room temperature. The flow rate was 40 mL/min. A linear gradient was used with 10% (or 50%) of MeOH (A) in H_2O (with 0.1 % TFA) (B) to 100% of MeOH (A). HPLC was used to establish the purity of target compounds. All final compounds were determined to be > 95% purity when analyzed according to the HPLC methods described above.

5.3. Example 3: General Synthetic Schemes

[0408] The disclosed compounds can be prepared according to the following schemes. The following schemes represent the general methods used in preparing these compounds. However, the synthesis of these compounds is not limited to these representative methods, as they can also be prepared through various other methods by those skilled in the art of synthetic chemistry.

5.3.1. General procedure (a)

[0409] Imidazole-2-carboxyaldehyde (1.0 eq.), methyl-2-bromovalerate (1.14 eq.), and potassium carbonate (2.0 eq.) were mixed in 30 mL acetonitrile (9.06 mL/mmol). The reaction was stirred for 24 h at 45 °C. Insoluble salts were filtered off, and the brown liquid was concentrated by rotary evaporation to a volume of ~ 5 ml for the subsequent flash chromatography. Automated normal-phase flash chromatography was applied for purification. The product was obtained as a colorless oil.

5.3.2. General procedure (b)

[0410] The amine (1.0 eq.) and the aldehyde (5.0 eq.) were dissolved in THF (6.45 mL/mmol), and the reactants heated at 70 °C for 24 h during the reaction solution became yellowish. After cooling to room temperature, sodium triacetoxyborohydride (6.0 eq.) was added stepwise (300 mg every 30 min). After 5 h, MeOH (32 mL/mmol) was added, and the solvents were removed

under reduced pressure, generating a yellow oil. This was dissolved in H_2O/ACN (6.45 mL/mmol, 2:1, v/v), and the pH of the solution was carefully adjusted with TFA to pH 2–3. The crude mixture was purified by reversed-phase automated flash chromatography. Fractions containing the product were combined, and the solvents were removed by rotary evaporation.

5.3.3. General procedure (c)

[0411] The methyl esters were heated at 95 °C for 24 h in 5 ml H_2O/TFA (35 mL/mmol, 1:1, v/v). Solvents were removed under reduced pressure, and the product was lyophilized.

5.3.4. General procedure (d)

[0412] Dissolve the carboxylic acid in a dry solvent (e.g., DCM). Add the chosen coupling reagent (CDI, DCC, EDC), thionyl chloride, or phosgene for acid chloride formation, or HATU, TBTU, HOAt, HOBt, etc., for active ester formation. Stir the reaction mixture at an appropriate temperature until activation is complete. Add the amine to the pre-activated carboxylic acid. Adjust the pH of the reaction mixture to primary conditions by adding an appropriate base such as triethylamine (TEA, DIPEA, *sym*-collidine, or similar). Stir the reaction mixture at room temperature or a suitable temperature for the amidation reaction to proceed. Monitor the progress of the reaction using analytical techniques such as TLC (Thin Layer Chromatography) or other suitable methods (e.g., HPLC-MS). Workup: Quench the reaction by adding a suitable acid or base to neutralise excess reagents. Extract the desired product into an organic solvent. Wash the organic layer with water and brine to remove impurities. Isolate the product by evaporating the solvent under reduced pressure. Purify the crude product using chromatographic methods if necessary.

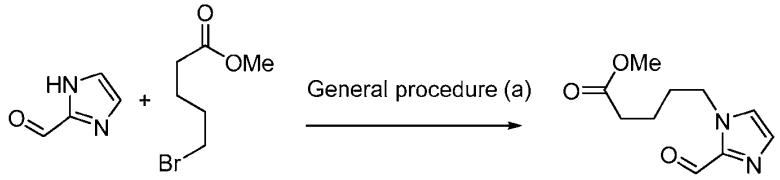
5.3.5. General procedure (e)

[0413] The amine (1.00 eq.) was dissolved in 10% Na_2CO_3(aq.) (2.4 mL/mmol) and 1,4-dioxane (1.5 mL/mmol) and cooled to 0 °C. Boc_2O (1.20 eq.) was added dropwise, and the mixture was left stirring at rt for 16 h. The solution was washed with Et_2O, and the aqueous phase was acidified with 2 m HCl. After extraction with EtOAc, the combined organic phases were dried over $MgSO_4$, filtered and concentrated. The residue was dried *in vacuo*. To achieve selective single protection of the triazacyclononane, it is important to pay attention to the temperature and the equivalents of Boc.

5.3.6. General procedure (f)

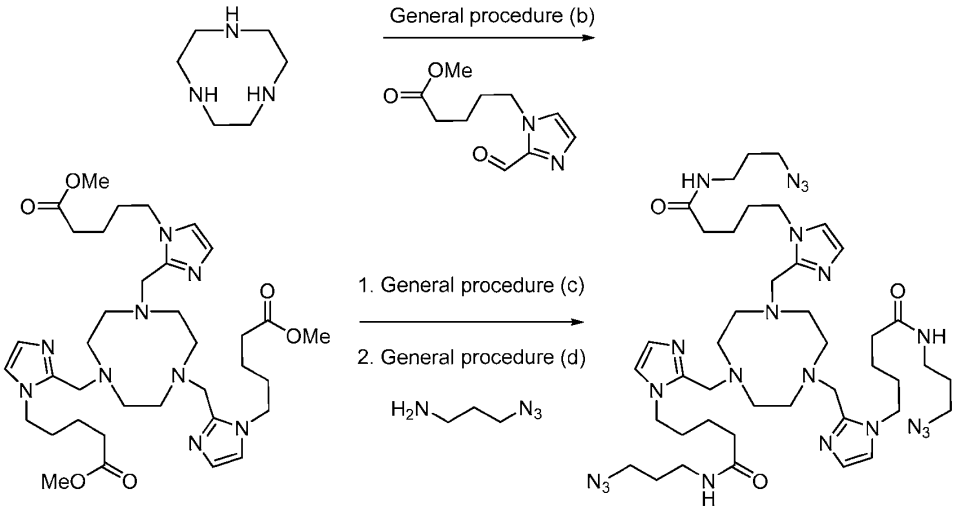
[0414] A solution of the Boc-protected amine (1.00 eq.) in CH_2Cl_2 (31.5 mL/mmol) was treated dropwise with TFA (21.0 eq.) and stirred for 4 h at rt. The solvent was evaporated, and the residue was dissolved in toluene and evaporated three times to remove any residual TFA.

[0415] Synthesis of methyl 5-(2-formyl-1H-imidazol-1-yl)pentanoate

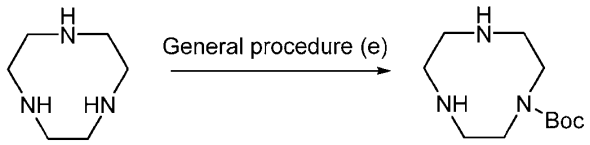


[0416] ^{1}H-NMR ($CDCl_3$): δ = 9.76 (s, 1H), 7.24 (d, J = 1.88 Hz, 1H), 7.14 (d, J = 1.9 Hz, 1H), 4.36 (t, J=7.4 Hz, 2H), 3.62 (s, 3H), 2.31 (t, J=7.0 Hz, 2H), 1.78 (m, 2H), 1.61 (m, 2H). HR-ESI-MS: calc. for $C_{10}H_{15}N_2O_3$ ([M + H]+): 211.1083, found: 211.1075. RP- HPLC (analytical): tR = 9.2 min, purity > 99 %.

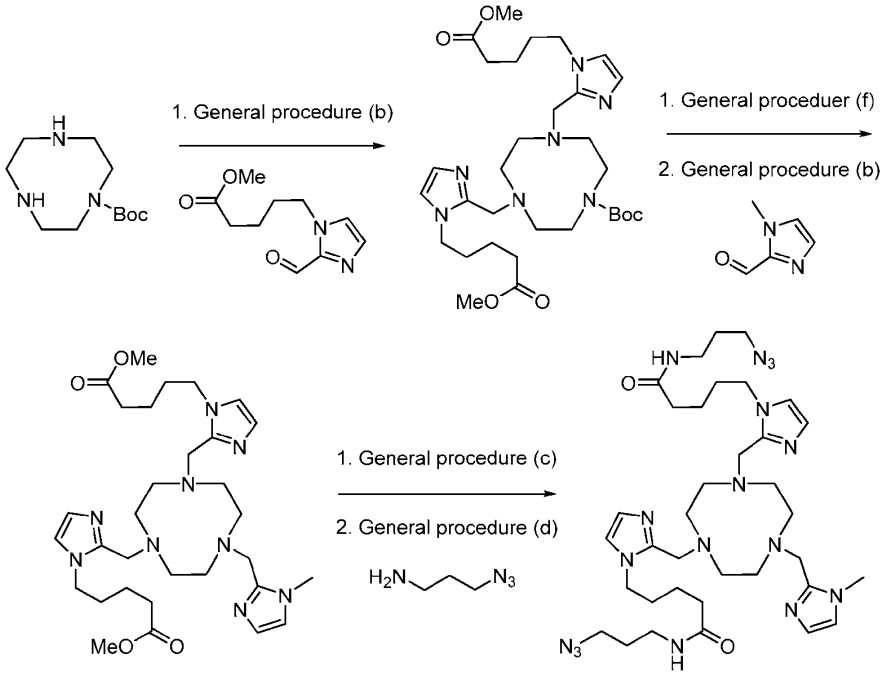
[0417] Synthesis of 5,5',5''-(((1,4,7-triazonane-1,4,7-triyl)tris(methylene))tris(1H-imidazole-2,1-diyl))tris(N-(3-azidopropyl)pentanamide)



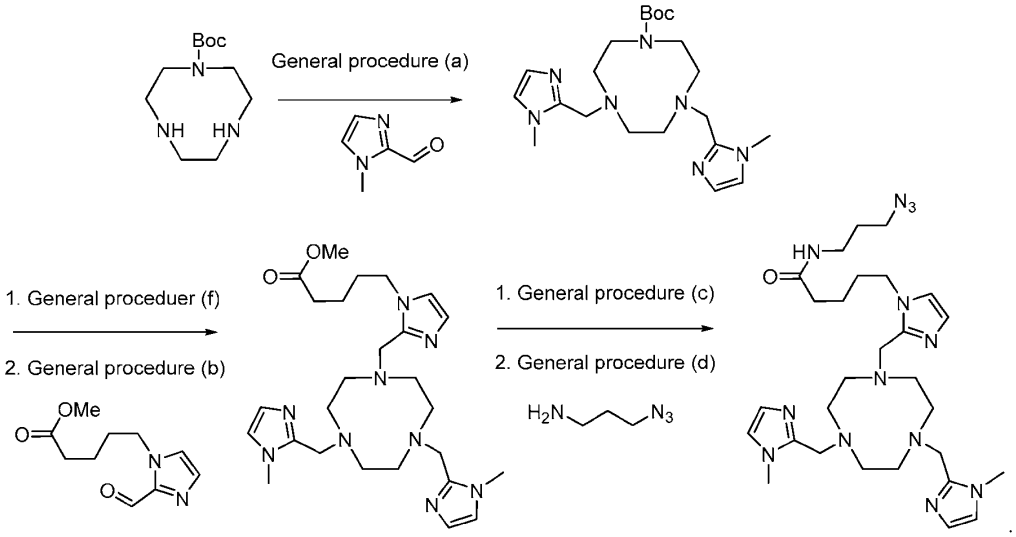
[0418] Synthesis of tert-butyl 1,4,7-triazonane-1-carboxylate



[0419] Synthesis of 5,5'-(((7-((1-methyl-1H-imidazol-2-yl)methyl)-1,4,7-triazonane-1,4-diyl)bis(methylene))bis(1H-imidazole-2,1-diyl))bis(N-(3-azidopropyl)pentanamide)



[0420] Synthesis of N-(3-azidopropyl)-5-(2-((4,7-bis((1-methyl-1H-imidazol-2-yl)methyl)-1,4,7-triazonan-1-yl)methyl)-1H-imidazol-1-yl)pentanamide

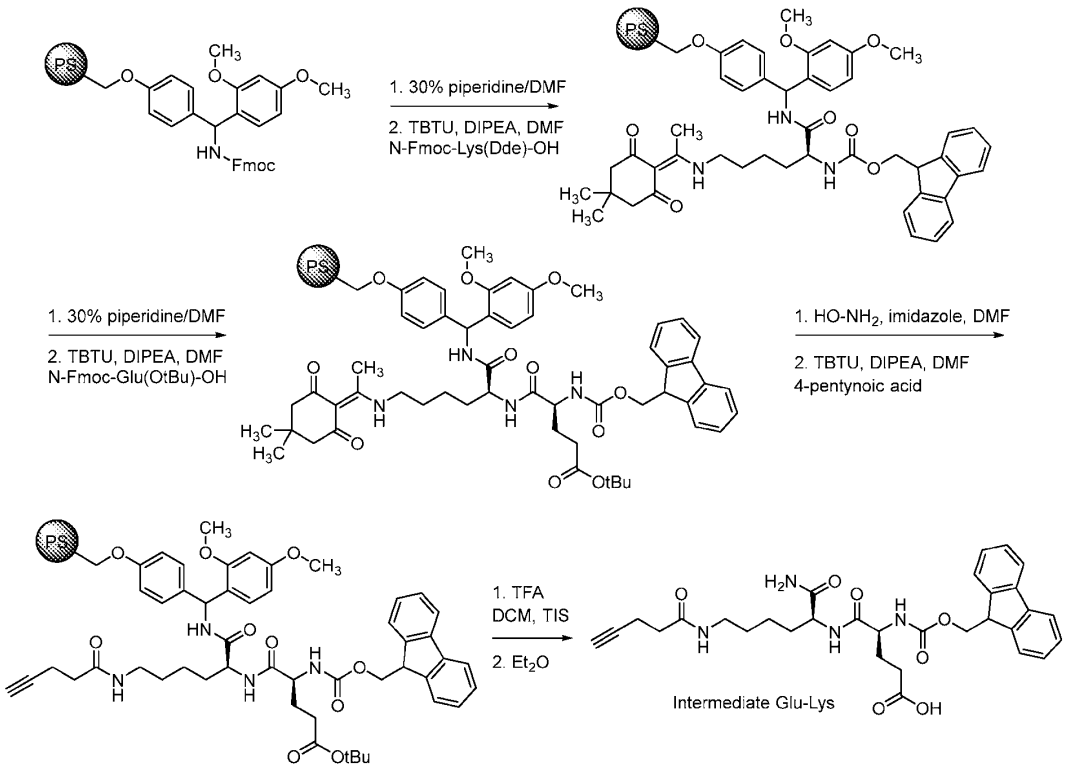


[0421] The synthesis of cyclo C^{γ}-N^{α} [-Arg-Gly-Asp-Chg-Glu]-Lys(pentyl)-NH_2

[0422] Peptides were synthesized from the carboxyl terminus to the amino terminus by repeated "coupling-cycles" using solid phase peptide synthesis SPPS conditions. Briefly, the carboxyl group of each incoming amino acid was activated by in situ active ester formation using O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) and coupled to the amino group of the growing peptide chain. For this reaction, amino acids, and TBTU were dissolved in DMF, mixed with DIPEA, and added to the resin after a short activation period of time.

[0423] Completion of the reaction was confirmed by ninhydrin-assay after each elongation step. After removal of excess of amino acid and reagents by multiple wash steps with DMF and isopropanol, the Fmoc protecting group was removed from the N-terminus using a mixture of 30% piperidine/DMF followed by washing steps.

[0424] Synthesis of Fmoc-L-Glu-L-Lys(pentynoate)-NH_2; (S)-4-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-5-(((S)-1-amino-1-oxo-6-(pent-4-ynamido)hexan-2-yl)amino)-5-oxopentanoic acid.



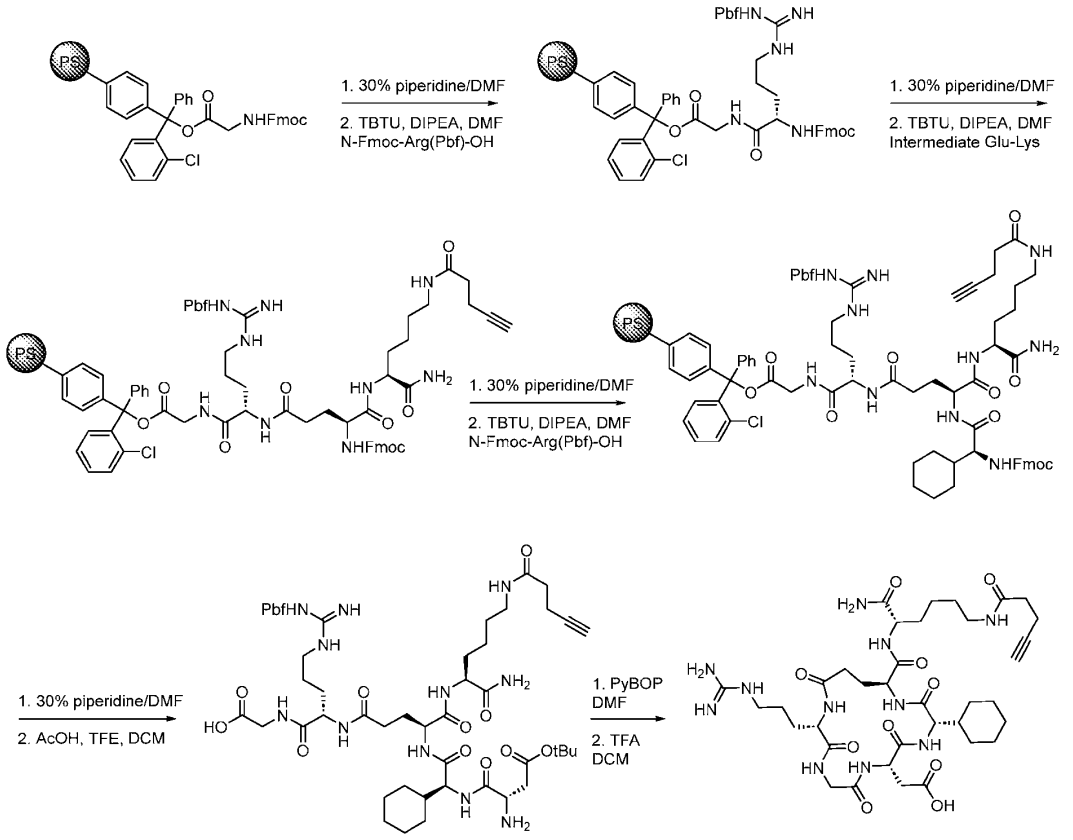
[0425] The production of the building block was performed by SPPS using a Fmoc-Rink-Amide resin. After Fmoc removal, the building block was prepared by coupling Fmoc-L-Lys(Dde)-OH followed by Fmoc-L-Glu(OtBu)-OH.

[0426] The Dde-protecting group of Lys was removed by a mixture of hydroxylamine and imidazole in DMF. The reaction progress was confirmed by HPLC and mass spectrometry. After successful side chain deprotection, 4-pentynoic acid was coupled to the *N*-ε amine as described above.

[0427] Cleavage from the resin was performed in one step using a mixture of trifluoroacetic acid in H_2O and triisoproylsilane (TIPS) as a scavenger. After cleavage, the mixture was filtered through a sintered glass funnel and the filtrate was precipitated by dropping the cleavage solution into ice cooled diethyl ether. Repeated washing of the precipitate with cold ether, followed by dissolving the building block in aqueous solution and freeze-drying gave the crude peptide as an off-white lyophilate. Purity and identity of the crude product was checked by RP-HPLC and mass spectrometry. Purification of this building block was done by using preparative RP-HPLC

with appropriate gradient systems containing water/acetonitrile mixtures using TFA as ion pairing agent. All fractions were analyzed, and pure fractions were pooled and freeze-dried. Elemental Analysis: C, 64.57; H, 6.29; N, 9.72; O, 19.42.

[0428] Synthesis of cyclo C^{γ}-N^{α} [-Arg(Pbf)-Gly-Asp(OtBu)-Chg-Glu]-Lys(pentynoate)-NH_2; 2-((3S,6S,12S,17S)-17-(((S)-1-amino-1-oxo-6-(pent-4-ynamido)hexan-2-yl)carbamoyl)-3-cyclohexyl-12-(3-guanidinopropyl)-2,5,8,11,14-pentaoxo-1,4,7,10,13-pentaazacycloheptadecan-6-yl)acetic acid



[0429] For the SPPS, H-Gly-2Cl-Trityl-PS resin was used as a preloaded resin.

[0430] The order of incoming amino acid derivatives during synthesis was: 1. Fmoc-L-Arg(Pbf)-OH; 2. Fmoc-L-Glu-L-Lys(pentynoate)-NH_2; 3. Fmoc-L-Chg-OH; and 5. Fmoc-L-Asp(OtBu)-OH.

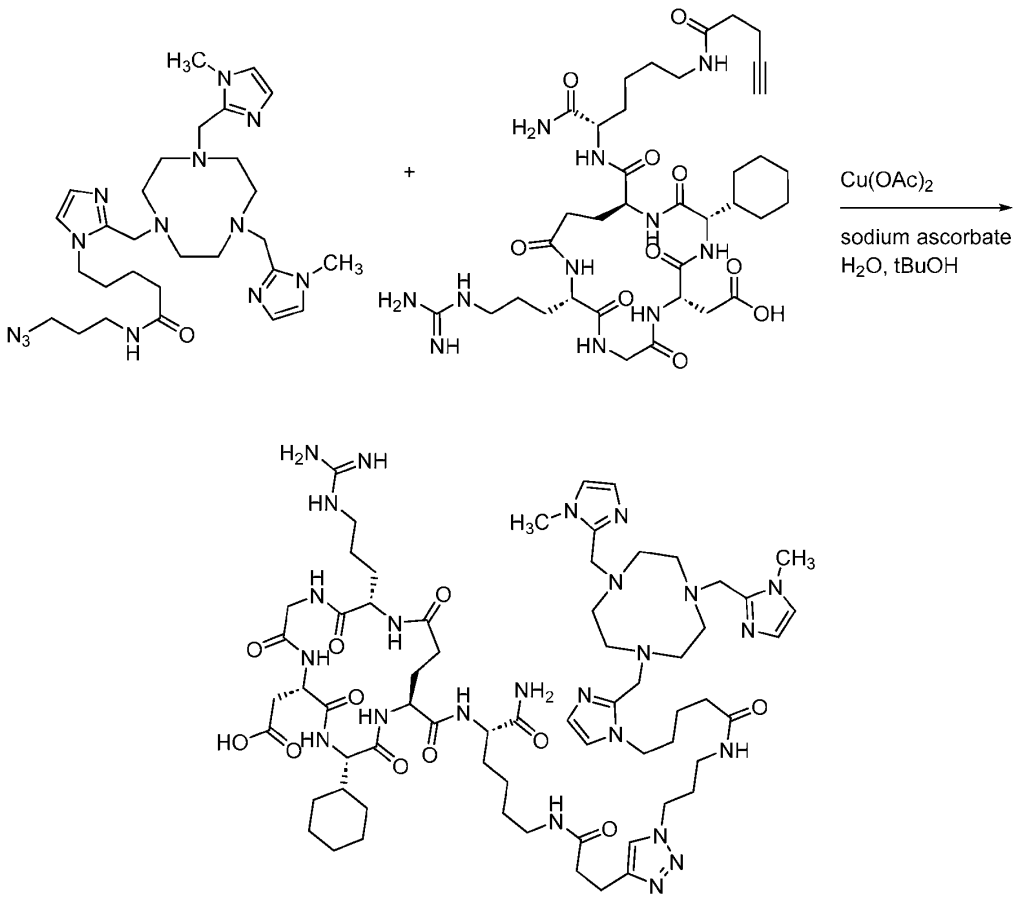
[0431] The protected peptide chain was cleaved from the solid support using a mixture of 2,2,2 trifluoroethanol, dichloromethane and acetic acid. After cleavage, the mixture was filtered through a sintered glass funnel and the filtrate was concentrated under reduced pressure. The solid was reconstituted in water/acetonitrile and freeze-dried to give the crude fully protected peptide.

[0432] C-N-cyclisation of the linear peptide was performed using PyBOP in DMF and progress was monitored by HPLC and MS. After successful cyclisation, the solvent was removed with a rotary evaporator. The residue was dissolved in water/acetonitrile and freeze-dried to obtain the crude material as a white powder.

[0433] Removal of all side-chains protecting groups was performed by a mixture of trifluoroacetic acid in dichloromethane. After completed deprotection, the volume was reduced under reduced pressure before the peptide was precipitated by dropping the cleavage mixture into ice-cooled diethyl ether. After centrifugation, the precipitate was washed twice with diethyl ether, dried and dissolved in water/acetonitrile and freeze-dried.

[0434] The crude peptide was purified using preparative RP-HPLC with appropriate gradient systems containing water/acetonitrile mixtures using TFA as ion pairing agent. All fractions that met specifications for HPLC-purity were pooled and freeze-dried.

[0435] Synthesis of NOTI-MVA-SDM17; NOTI-Me_2-TVA-NR-$(CH_2)_3$-triazolylene-$(CH_2)_2$-C(O)-Lys-SDM17.



[0436] A stirred solution of peptide (cyclo C^{γ}-N^{α} [-Arg-Gly-Asp-Chg-Glu]-Lys(pentynoate)-NH_2) (1.1 eq.), NOTI-MVA-azide (1 eq.) and sodium ascorbate in H_2O/tert-butanol was heated to 45 °C under an atmosphere of nitrogen. The reaction mixture was treated with $Cu(OAc)_2$ dissolved in H_2O and stirred for 30 minutes. Completion of the reaction was monitored by HPLC and MS. NODAGA was added and the reaction solution was stirred for 15 minutes to remove chelated copper from the complex. This de-metallization process was repeated twice. After confirmation by HPLC and MS, the reaction mixture was centrifuged; supernatant fluid was decanted and freeze-dried.

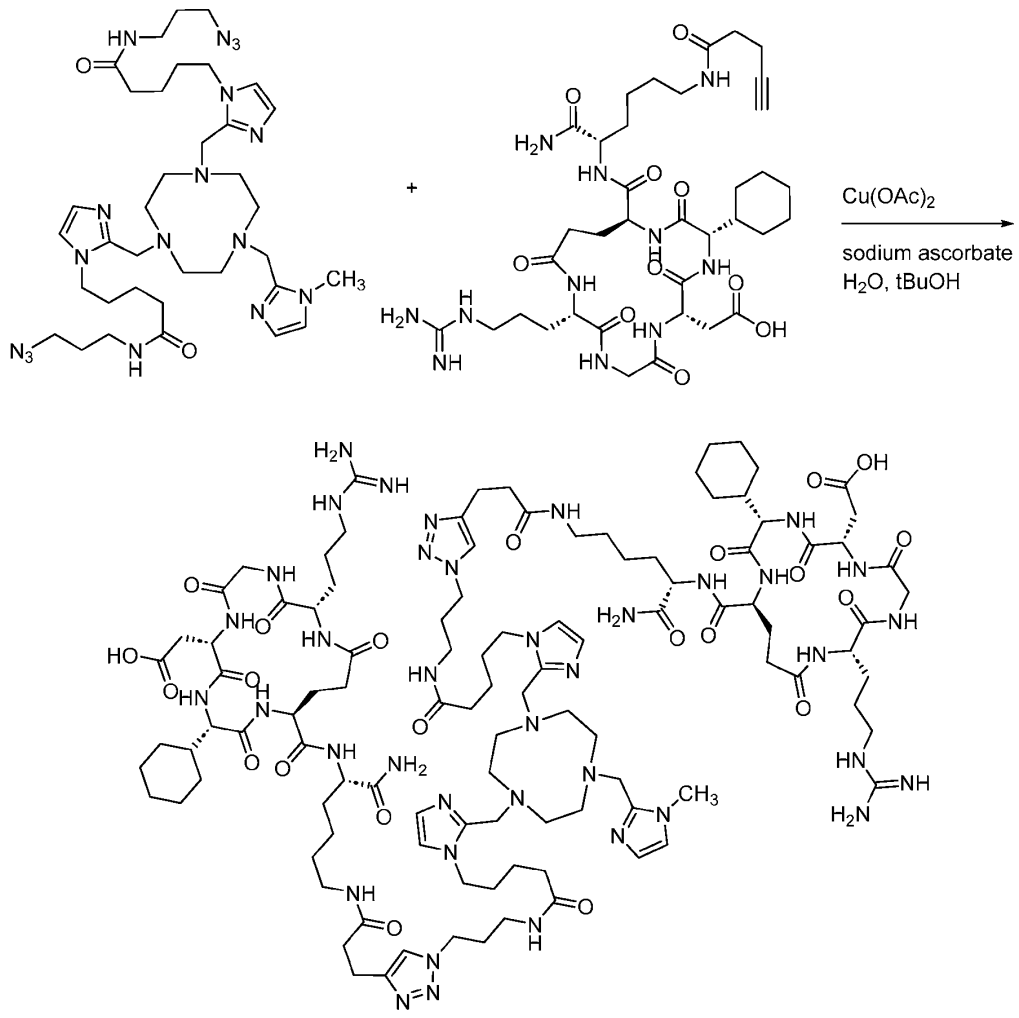
[0437] The crude peptide was purified using preparative RP-HPLC with appropriate gradient systems containing water/acetonitrile mixtures using TFA as ion pairing agent. All fractions that met specifications for HPLC-purity were pooled and freeze-dried. Molecular formula $C_{64}H_{102}N_{24}O_{11}$. Calc. molecular weight: 1383.7. Found 1384.4 $[M+H]^+$.

[0438] Copper complexation and radiochemical yield of compound NOTI-Me_2-TVA-NR-$(CH_2)_3$-triazolylene-$(CH_2)_2$-C(O)-Lys-SDM17; NOTI-MVA-SDM17.

	NOTI-MVA-SDM17 (nmol)	$^{61}CuCl_2$ in 0.05 M HCl (µL)	Sodium acetate 0.5 M + 20 µg/mL ascorbic acid (µL)	Time (min)	RCY (%)
A	0.5	50	100	5	>99
B	0.5	50	100	10	>99
C	0.5	50	100	15	>99
D	0.25	50	100	5	>99
E	0.25	50	100	10	>99
F	0.25	50	100	15	>99
G	0.10	50	100	5	>99
H	0.10	50	100	10	>99
I	0.10	50	100	15	>99
J	0.05	50	100	5	>99

pH = 5.5; RT

[0439] Synthesis of NOTI-DVA-$(SDM17)_2$; 2,2'-((3S,3'S,6S,6'S,12S,12'S,17S,17'S)-((((2S,2'S)-((3,3'-((((5,5'-(((7-((1-methyl-1H-imidazol-2-yl)methyl)-1,4,7-triazonane-1,4-diyl)bis(methylene))bis(1H-imidazole-2,1-diyl))bis(pentanoyl))bis(azanediyl))bis(propane-3,1-diyl))bis(1H-1,2,3-triazole-1,4-diyl))bis(propanoyl))bis(azanediyl))bis(1-amino-1-oxohexane-6,2-diyl))bis(azanediyl))bis(carbonyl))bis(3-cyclohexyl-12-(3-guanidinopropyl)-2,5,8,11,14-pentaoxo-1,4,7,10,13-pentaazacycloheptadecane-17,6-diyl))diacetic acid



[0440] A stirred solution of peptide (cyclo C^{γ}-N^{α} [-Arg-Gly-Asp-Chg-Glu]-Lys(pentynamide)-NH_2) (2.2 eq.), NOTI-DVA-diazide (1 eq.) and sodium ascorbate in H_2O/tert-butanol was heated to 45 °C under an atmosphere of nitrogen. The reaction mixture was treated with $Cu(OAc)_2$ dissolved in H_2O and stirred for 30 minutes. Completion of the reaction was monitored by HPLC and MS. NODAGA was added and the reaction solution was stirred for 15 minutes to remove chelated copper from the complex. This de-metallization process was repeated twice. After confirmation by HPLC and MS, the reaction mixture was centrifuged; supernatant fluid was decanted and freeze-dried.

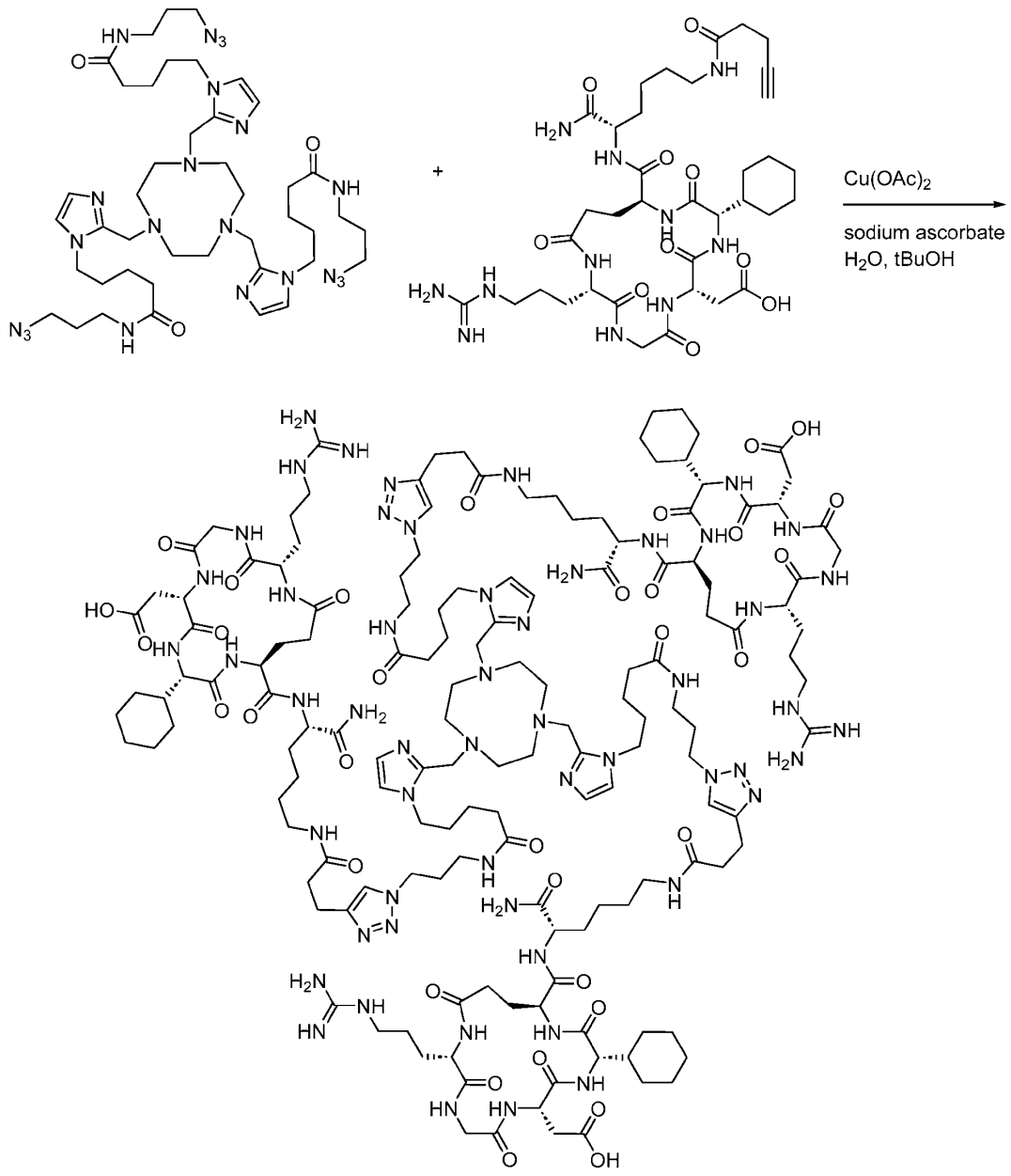
[0441] The crude peptide was purified using preparative RP-HPLC with appropriate gradient systems containing water/acetonitrile mixtures using TFA as ion pairing agent. All fractions that met specifications for HPLC-purity were pooled and freeze-dried. Molecular formula $C_{107}H_{171}N_{39}O_{22}$. Calc. molecular weight: 2355.8. Found 2356.4 $[M+H]^+$.

	NOTI-MVA-$(SDM17)_2$ (nmol)	$^{61}CuCl_2$ in 0.05 M HCl (µL)	Sodium acetate 0.5 M + 20 µg/mL ascorbic acid (µL)	Time (min)	RCY (%)
A	0.25	50	100	5	>99
B	0.25	50	100	10	>99
C	0.10	50	100	5	>99
D	0.10	50	100	10	>99

pH = 5.5, RT

[0442] Synthesis of NOTI-TVA-$(SDM17)_3$; 2,2',2''-((3S,3'S,3''S,6S,6'S,6''S,12S,12'S,12''S,17S,17'S,17''S)-((((2S,2'S,2''S)-((3,3',3''-((((5,5',5''-(((1,4,7-triazonane-1,4,7-triyl)tris(methylene))tris(1H-imidazole-2,1-diyl))tris(pentanoyl))tris(azanediyl))tris(propane-3,1-diyl))tris(1H-1,2,3-triazole-1,4-diyl))tris(propanoyl))tris(azanediyl))tris(1-amino-1-oxohexane-6,2-diyl))tris(azanediyl))tris(formyl))tris(3-cyclohexyl-12-(3-guanidinopropyl)-2,5,8,11,14-pentaoxo-1,4,7,10,13-pentaazacycloheptadecane-17,6-diyl))triacetic acid

[0443] The synthesis of NOTI-{cyclo C^{γ}-N^{α} [-Arg-Gly-Asp-Cpg-Glu]-Lys(pentyl)-NH_2}$_3$ was performed as follows:

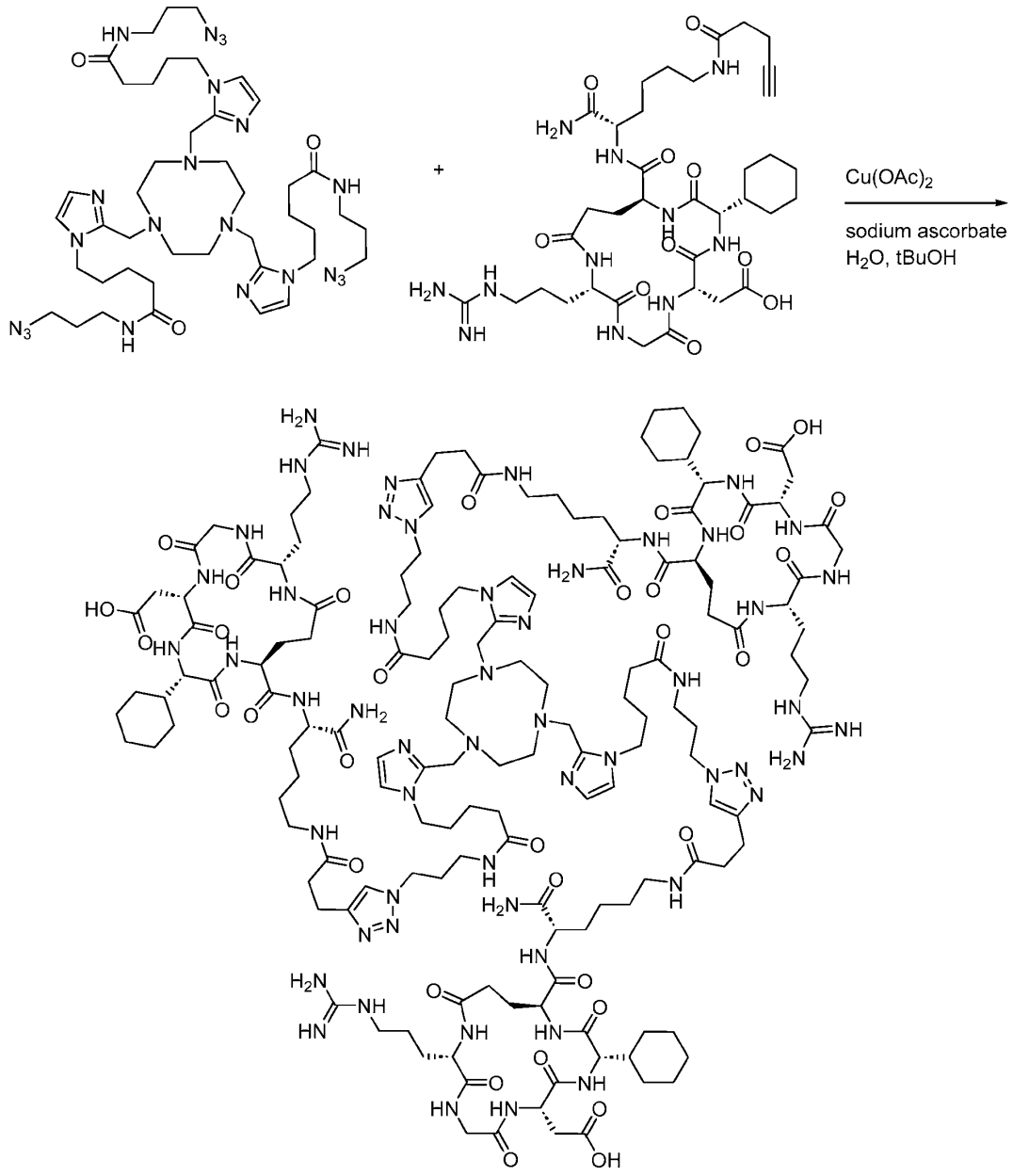


[0444] A stirred solution of peptide (cyclo C^{γ}-N^{α} [-Arg-Gly-Asp-Chg-Glu]-Lys(pentynoate)-NH_2) (3.3 eq.), NOTI-TVA-triazide (1 eq.) and sodium ascorbate in H_2O/tert-butanol was heated to 45 °C under an atmosphere of nitrogen. The reaction mixture was treated with $Cu(OAc)_2$ dissolved in H_2O and stirred for 30 minutes. Completion of the reaction was monitored by HPLC

and MS. NODAGA was added and the reaction solution was stirred for 15 minutes to remove chelated copper from the complex. This de-metallization process was repeated twice. After confirmation by HPLC and MS, the reaction mixture was centrifuged; supernatant fluid was decanted and freeze-dried.

[0445] The crude peptide was purified using preparative RP-HPLC with appropriate gradient systems containing water/acetonitrile mixtures using TFA as ion pairing agent. All fractions that met specifications for HPLC-purity were pooled and freeze-dried. Molecular formula $C_{150}H_{240}N_{54}O_{33}$. Calc. molecular weight: 3327.9. Found 3328.7 $[M+H]^+$.

[0446] The crude peptide was purified using preparative RP-HPLC with appropriate gradient systems containing water/acetonitrile mixtures using TFA as ion pairing agent. All fractions that met specifications for HPLC-purity (IPC) were pooled and freeze-dried. Molecular Weight: 3333.963. Chemical Formula: C150H246N54O33. Elemental Analysis: C, 54.04; H, 7.44; N, 22.69; O, 15.84.


Cu(OAc)2
sodium ascorbate
H2O, tBuOH

Synthesis of trim compounds with $^{61}Cu[CuCl_2]$ (e.g., III-1)

	NOTI-MVA-$(SDM17)_3$ (nmol)	$^{61}CuCl_2$ in 0.05 M HCl (µL)	Sodium acetate 0.5 M + 20 µg/mL ascorbic acid (µL)	Time (min)	RCY (%)
A	0.25	50	100	5	>99
B	0.10	50	100	5	>99

pH = 5.5, RT

5.4. Example 4: Exemplary Method of Measuring Apparent Molar Activity

[0447] A $[^{61}Cu]CuCl_2$ solution may be characterized by apparent molar activity (AMA). Apparent molar activity assesses, for example, competing trace metal impurities of ^{61}Cu chelation by quantifying the minimum amount of a given chelator required for efficient radiolabeling.

[0448] An AMA test measures the percentage of complexation, by radio-TLC, after titrating a quantity of $[^{61}Cu]CuCl_2$ solution with different amounts of a chelator (e.g., DOTA, NODAGA, etc).

[0449] The results were then plotted (x-axis (logarithmic): nmol of chelator; y-axis: % of complexation). The lowest nmol value of chelator corresponding to ≥ 95% complexation achieved was recorded.

[0450] The experimental AMA value was then calculated according to the formula:

$$AMA\ value\ (experimental) = \frac{Activity\ [MBq]}{n_{NODAGA}\ [nmol]}$$

where:

- Activity: indicates the activity present in the fixed amount of $[^{61}Cu]CuCl_2$ solution used for the titration decay corrected at the EoP (end of production; end of bombardment plus 1 hour).
- n_{NODAGA}: indicates the lowest nmol value of chelator for which ≥ 95% complexation was achieved.

[0451] This test was performed to assess, for example:

1) the grade of a chemical employed for the manufacturing of the [^{61}Cu]$CuCl_2$ solution;
2) the quality of a consumable employed for the manufacturing of the [^{61}Cu]$CuCl_2$ solution;

3) the target coin manufacturing process; or

4) in case poor radiolabeling yields were observed.

[0452] AMA Test Procedure

- The mobile phase was prepared as (0.1M sodium citrate) as follows:
    - Weigh 5.882 g of trisodium citrate dihydrate.
    - Add Suprapur water up to a volume of 200 mL.
    - Adjust the pH by adding HCl dropwise until it reaches a pH of 5.
- Transfer an adequate amount of mobile phase into the TLC development chamber to cover a depth of 5 mm.
- Prepare the sodium acetate solution (0.5 M in Ultrapur water) as follows:
    - Weigh 2.051 g of sodium acetate.
    - Add Ultrapur water up to a volume of 50 mL.
    - Apply 10 µL of the solution on a pH strip and check if the pH was 8.
- A 5 mM stock solution of NODAGA was prepared in 0.5 M sodium acetate (Stock 1) as follows:
    - Weigh 3.1 mg of NODAGA.
    - Add Ultrapur water or equivalent up to a volume of 1.5 mL.
    - Store at -20°C after use.
- A 50 µM stock solution of NODAGA was prepared in 0.5 M sodium acetate (Stock 2) by mixing 10 µL of Stock 1 with 990 µL 0.5 M sodium acetate. Store at -20°C after use.

- NODAGA test solutions S1-S2 were prepared for chelator titration as displayed in Table T1 by diluting Stock 2 with the listed volumes of sodium acetate 0.5 M. The test solution S0 was a blank solution (without the addition of NODAGA) of 100 µL of 0.5 M sodium acetate.

Table T1: Preparation of solution 1 – 3 for chelator titration.

Solution name	c_{NODAGA} [nM]	Volume stock 2 [µL]	Volume sodium acetate [µL]
S0	0	0	100
S 1	3000	100	1567
S 2	1500	50	1617
S 3	900	30	1637

- The test solutions, S4-S10, 1:10 dilutions of the solutions S1-S7, were prepared with 0.5 M sodium acetate according to the dilution scheme shown in **Error! Reference source not found.**Table T2.

Table T2: Preparation of solution 4 - 10 for chelator titration.

Solution name	c_{NODAGA} [nM]	Volume Sx [µL]	Volume sodium acetate [µL]
S 4	300	100 of S1	900
S 5	150	100 of S2	900
S 6	90	100 of S3	900
S 7	30	100 of S4	900
S 8	15	100 of S5	900
S 9	9	100 of S6	900
S 10	3	100 of S7	900

- A solution of 0.05 M HCl was prepared as follows:
    - Add 5 mL of Ultrapur water in a 15 mL Falcon tube.
    - Add 53 µL of 30% HCl to the falcon using a micropipette.
    - Add Ultrapur water up to 10 mL.
    - Spot 10 µL of the solution on a pH strip and confirm the pH is between 1.0 and 1.6.
- The $[^{61}Cu]CuCl_2$ solution was diluted with 0.05 M hydrochloric acid to reach a total volume of 1 mL with an activity concentration of 0.2 MBq/µL (EoP) according to the following formula:

$$[^{61}\mathrm{Cu}]\mathrm{CuCl_2}\ \text{solution}\ [\mu\mathrm{L}] = \frac{0.2\ [\mathrm{MBq}/\mu\mathrm{L}]}{AC(EoP)[\mathrm{MBq}/\mu\mathrm{L}]} * 1000\ \mu L$$

0.05 M hydrochloric acid for dilution $= 1000\ \mu L - [^{61}\mathrm{Cu}]\mathrm{CuCl_2}$ solution to draw [µL]
where AC (EoP) is the activity concentration at EoP.

- The solutions were named "diluted Cu-61 solution". See the examples in **Error! Reference source not found.**Table T3.

Table T3: $[^{61}Cu]CuCl_2$ dilution examples.

Activity eluted at EoP [MBq]	Volume [mL]	Activity concentration at EoP [MBq/µL]	Dilution for AMA test
1000	3.0	0.33	600 µL of $[^{61}Cu]CuCl_2$ diluted with 400 µL of 0.05 M HCl
2000	3.0	0.67	300 µL of $[^{61}Cu]CuCl_2$ diluted with 700 µL of 0.05 M HCl
3500	3.0	1.17	233 µL of $[^{61}Cu]CuCl_2$ diluted with 767 µL of 0.05 M HCl

- Add in each solution for chelator titration 50 µL of diluted $[^{61}Cu]CuCl_2$ solution (as prepared in Table T3), obtaining the reaction solutions listed in **Error! Reference source not found.**Table T4.

Table T4: Reaction solutions.

Reaction solution name	NODAGA solution	Volume of NODAGA solution Sx [µL]	Volume of ^{61}Cu solution [µL]	Finale volume [µL]	n_{NODAGA} [nmol]	c_{NODAGA} [nM]
RS 1	S1	100	50	150	0.3	2000
RS 2	S2	100	50	150	0.15	1000
RS 3	S3	100	50	150	0.09	600
RS 4	S4	100	50	150	0.03	200
RS 5	S5	100	50	150	0.015	100
RS 6	S6	100	50	150	0.009	60
RS 7	S7	100	50	150	0.003	20
RS 8	S8	100	50	150	0.0015	10
RS 9	S9	100	50	150	0.0009	6
RS 10	S10	100	50	150	0.0003	2
RS 0	S0	100 (Only 100 µL of sodium acetate 0.5 M)	50	150	0	0

- The reaction solutions were incubated at room temperature for 5 minutes.
- After incubation, perform TLC measurement on all the reaction solutions as follows:
    - Using a micropipette, spot 2 μL of each [^{61}Cu]Cu-NODAGA reaction solution RS0-RS10 onto different pre-cut TLC paper.
    - Allow the TLC paper to dry for about 5 minutes or until there was no visible stain.
    - Place the TLC paper in the TLC chamber with the stained side on the bottom of the chamber. When the solvent front was about 1 cm from the top of the strip, remove the TLC paper from the TLC chamber with tweezers.
    - Mark the solvent front on the TLC paper strip with a pencil.
    - Measure the distance between the starting line and the solvent front with a ruler and let the strip dry completely.
- After scanning the TLC plate, the software (e.g., Biochrom) will generate an evaluation report. Print the evaluation report and record the results. All data (i.e., RF, % of total activity, % of ROI) of the peaks must be documented.
- Using the regions of interest (ROI) technique (drawing regions over distinct areas of activities), the % of complexation of [^{61}Cu]Cu-NODAGA was expressed as a percentage of the total detected activity, as follows:

$$Complexation_{[61Cu]Cu-NODAGA}(\%) = \frac{Activity_{[^{61}Cu]Cu-NODAGA}[counts]}{Total\ activity\ [counts]} * 100$$

[0453] The TLC scanner results were plotted (x-axis (logarithmic): nmol of NODAGA chelator; y-axis: % of complexation), and will follow a sigmoidal trend. An example of plot was given below in Figure T1.

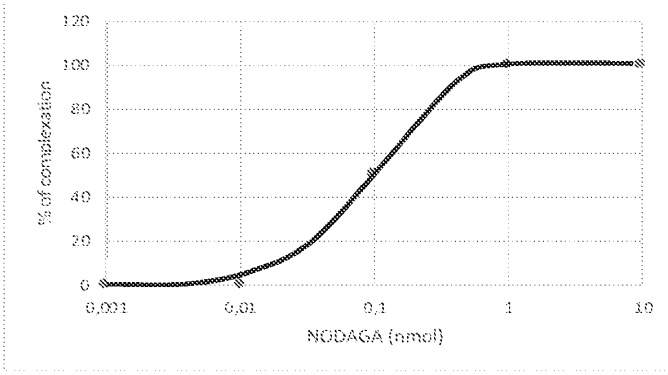


Figure T1: AMA test plot obtained plotting at x-axis (logarithmic) the nmol of titrating chelator and at y-axis the % of complexation obtained via radio-TLC.

- The lowest value of nmol of chelator in correspondence of which ≥ 95% complexation is identified on the plot. An example was reported in **Error! Reference source not found.**Figure T2.

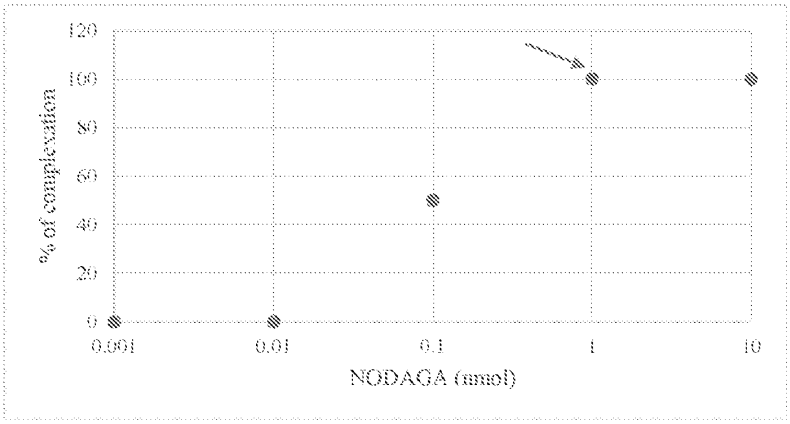


Figure T2: Experimental point corresponding to the lowest value of nmol of chelator in correspondence of which ≥ 95% complexation was achieved (red arrow).

[0454] The experimental AMA value was then calculated according to the formula:

$$AMA\ value\ (experimental) = \frac{Activity\ [MBq]}{n_{NODAGA}\ [nmol]}$$

where:

Activity: indicates the activity present in the fixed amount of $[^{61}Cu]CuCl_2$ solution used for the titration decay corrected at the EoP.

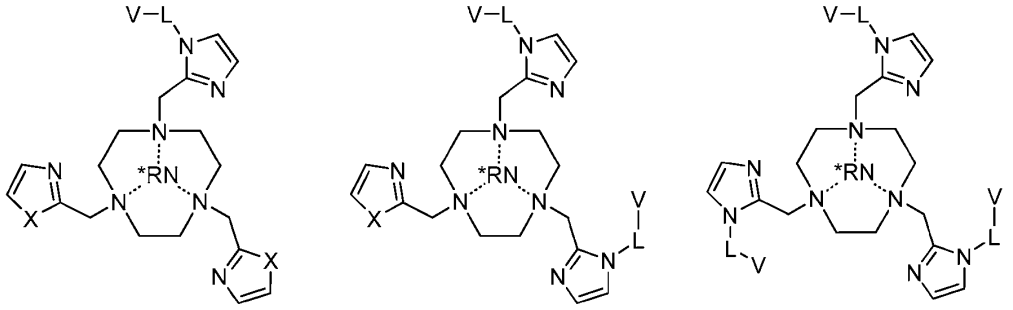
6. EQUIVALENTS AND INCORPORATION BY REFERENCE

[0455] While aspects of the present disclosure have been particularly shown and described with reference to certain embodiments and various alternate embodiments, it will be understood by persons skilled in the relevant art that various changes in form and details can be made therein without departing from the scope of the present disclosure.

[0456] All references, issued patents and patent applications cited within the body of the instant specification are hereby incorporated by reference in their entirety, for all purposes. In particular, U.S. Provisional Application No. 63/568,708 (filed Mar. 22, 2024) and International Application No. PCT/US2023/75064 (filed Sep. 25, 2023) are hereby incorporated by reference in their entirety.

WHAT IS CLAIMED IS:

1. A compound, wherein the compound is of Formula I, II, or III:



(I) (II) (III)

or is a pharmaceutically acceptable salt thereof;

wherein:

*RN is an optionally present radionuclide;

each X is independently -S- or -NR^{a1}-; and

each R^{a1} is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group;

each V is a targeting moiety that binds to an integrin, such as $\alpha_v\beta_6$ integrin;

each L is independently a bond or a linking moiety;

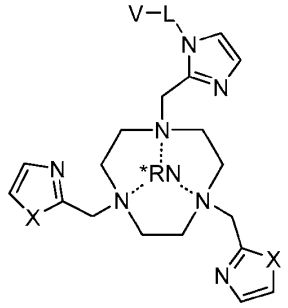
each linking moiety independently comprises a divalent PEG-containing moiety or an optionally substituted, saturated or partially unsaturated, straight or branched divalent aliphatic C_{1-50} hydrocarbon chain, wherein one or more carbon atoms in the chain are optionally replaced by a divalent group independently selected from -O-, -NR^{a2}-, -$N^+(R^{a2})_2$-, -S-, -S(O)-, -$S(NR^{a2})$-, -$S(O)_2$-, $S(O)(NR^{a2})$-, -$S(NR^a)_2$-, -C(O)-, -C(S)-, and -Cy^A-;

each Cy^A independently comprises an optionally substituted ring system selected from a 3- to 12-membered saturated or partially unsaturated carbocyclene; a phenylene; a 3- to 12-membered saturated or partially unsaturated heterocyclene having 1-3

heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 5- to 6-membered heteroarylene having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and a combination of any of these ring systems including fused variants thereof; and

each R^{a2} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group.

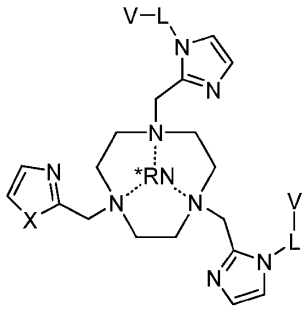
2. The compound according to claim 1, wherein the compound is of Formula I:



(I)

or is a pharmaceutically acceptable salt thereof.

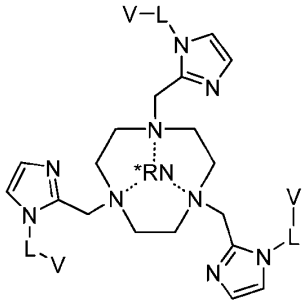
3. The compound according to claim 1, wherein the compound is of Formula II:



(II)

or is a pharmaceutically acceptable salt thereof.

4. The compound according to claim 1, wherein the compound is of Formula III:



(III)

or is a pharmaceutically acceptable salt thereof.

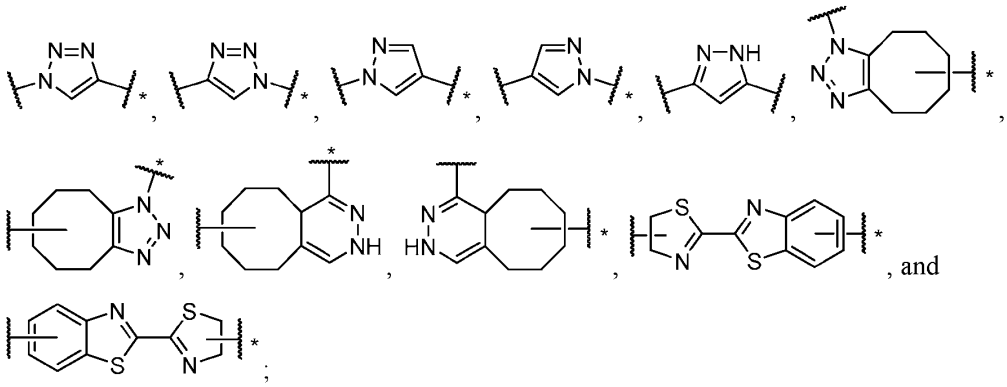
5. The compound according to any one of claims 1-3, wherein each X is -NR^{a1}-.

6. The compound according to claim 5, wherein R^{a1} is hydrogen.

7. The compound according to claim 5, wherein R^{a1} is an optionally substituted C_{1-6} aliphatic group.

8. The compound according to any one of the preceding claims, wherein each L is a linking moiety, optionally comprising a divalent PEG moiety.

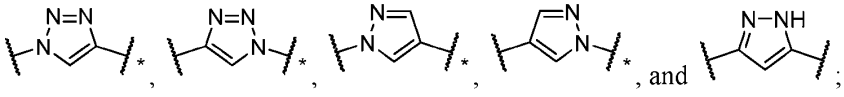
9. The compound according to claim 8, wherein at least one linking moiety comprises a Cy^A group selected from



wherein * represents the direction of connection toward V.

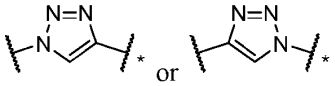
10. The compound according to claim 8, wherein at least one linking moiety comprises a Cy^A group that is a 5- or 6-membered heteroarylene having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

11. The compound according to claim 10, wherein the 5- or 6-membered heteroarylene is selected from



wherein * represents the direction of connection toward V.

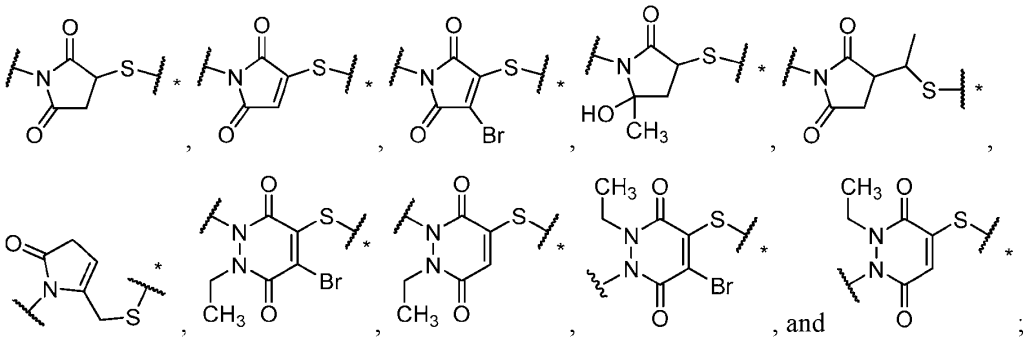
12. The compound according to claim 10, wherein the 5- or 6-membered heteroarylene is



13. The compound according to claim 10, wherein the 5- to 6-membered heteroarylene comprises a divalent form of 1,2,3-triazole.

14. The compound according to claim 8, wherein at least one linking moiety comprises a Cy^A group that is a 3- to 7-membered saturated or partially unsaturated heterocyclene having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

15. The compound according to claim 14, wherein the 3- to 7-membered heterocyclene is selected from



wherein * represents the direction of connection toward V.

16. The compound according to claim 14, wherein the 3- to 7-membered heterocyclene is a divalent form of succinimide, maleimide, or pyridazinedione.

17. The compound according to any one of claims 1-16, wherein at least one linking moiety comprises at least one occurrence of -C(O)NR^{a2}-*, such as -C(O)NH-*, wherein * represents the direction of connection toward V.

18. The compound according to claim 17, wherein at least one linking moiety comprises two occurrences of -C(O)NR^{a2}-*, such as -C(O)NH-*.

19. The compound according to claim 17, wherein at least one linking moiety comprises an optionally substituted -C$_{1-6}$alkyl-C(O)NR^{a2}-*, such as -C$_{1-6}$alkyl-C(O)NH-*.

20. The compound according to claim 19, wherein at least one linking moiety comprises an optionally substituted -C$_{1-6}$alkyl-C(O)NR^{a2}-C$_{1-6}$alkyl-*, such as -C$_{1-6}$alkyl-C(O)NH-C$_{1-6}$alkyl-*.

21. The compound according to any one of claima 1-20, wherein at least one linking moiety comprises an optionally substituted -C$_{1-6}$alkyl-HetAr-C$_{1-6}$alkyl-*, wherein HetAr is a divalent form of 1,2,3-triazole.

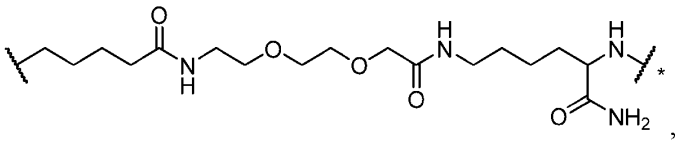
22. The compound according to claim 21, wherein at least one linking moiety comprises an optionally substituted -C(O)NR^{a2}-C$_{1-6}$alkyl-HetAr-C$_{1-6}$alkyl-C(O)NR^{a2}-*, such as -C(O)NH-C$_{1-6}$alkyl-HetAr-C$_{1-6}$alkyl-C(O)NH-*.

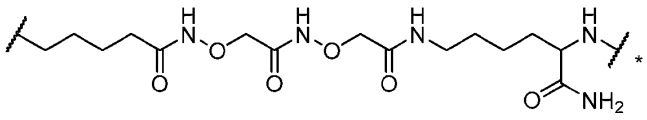
23. The compound according to claim 22, wherein at least one linking moiety comprises an optionally substituted -C$_{1-6}$alkyl-C(O)NR^{a2}-C$_{1-6}$alkyl-HetAr-C$_{1-6}$alkyl-C(O)NR^{a2}-C$_{1-6}$alkyl-*, such as -C$_{1-6}$alkyl-C(O)NH-C$_{1-6}$alkyl-HetAr-C$_{1-6}$alkyl-C(O)NH-C$_{1-6}$alkyl-*.

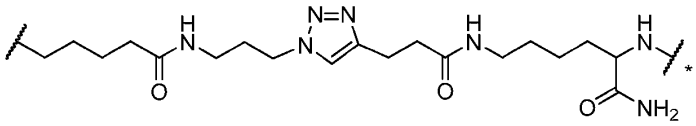
24. The compound according to claim 17, wherein at least one linking moiety comprises an optionally substituted -NH-PEG$_{(1-3)}$-C(O)-AA$_{(1-3)}$-, -NH-AA$_{(1-3)}$-C(O)-AA$_{(1-3)}$-, -NH-AA$_{(1-3)}$-PEG$_{(1-3)}$-C(O)-AA$_{(1-3)}$-, or -NH-AA$_{(1-3)}$-C(O)-AA$_{(1-3)}$- (written from the N-to-C direction);

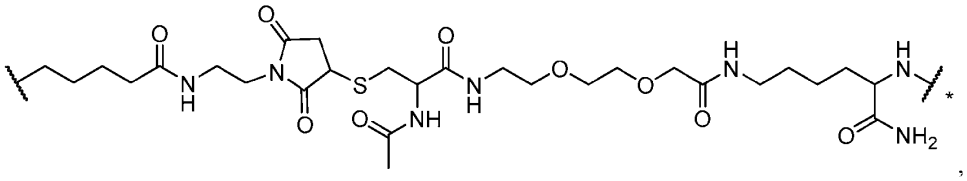
wherein each AA is independently selected from an optionally substituted -NH-PEG$_2$-C(O)-ε-Lys-NH-, -NH-Aoa-Aoa-C(O)-ε-Lys-NH-, -NH-Cys-PEG$_2$-(CH$_2$)C(O)-ε-Lys-NH-, and -NH-Cys-Aoa-Aoa-C(O)-ε-Lys-NH- (written from the N-to-C direction).

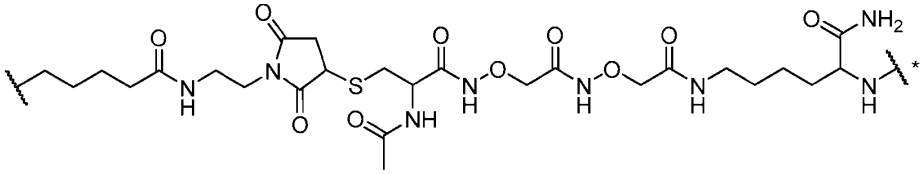
25. The compound according to claim 8, wherein at least one linking moiety is selected from the following, wherein * represents the direction of connection toward V:

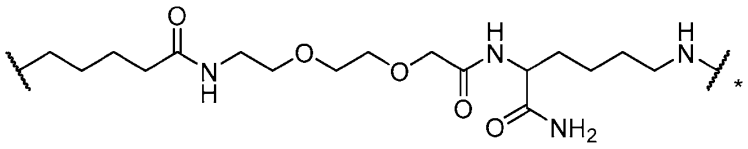


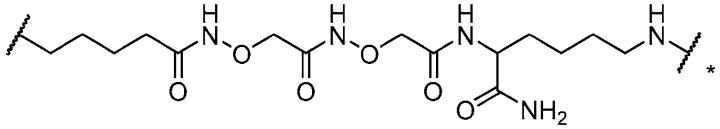


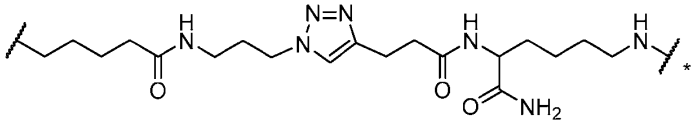


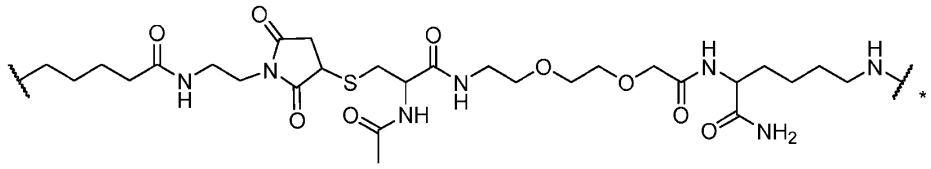




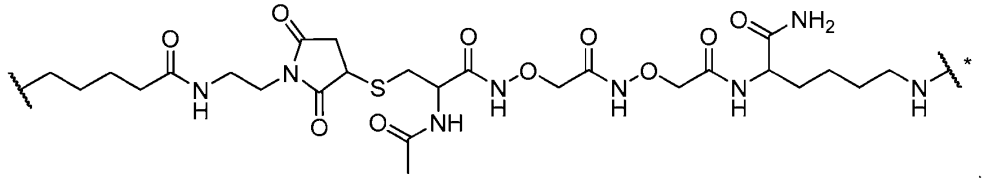








, and



26. The compound according to any one of the preceding claims, wherein the targeting moiety comprises means for binding an integrin receptor.

27. The compound according to any one of the preceding claims, wherein at least one targeting moiety is independently selected from an antibody, an RGD-peptide, a cysteine knot peptide, an integrin $\alpha_v\beta_6$ agonist, and an integrin $\alpha_v\beta_6$ antagonist.

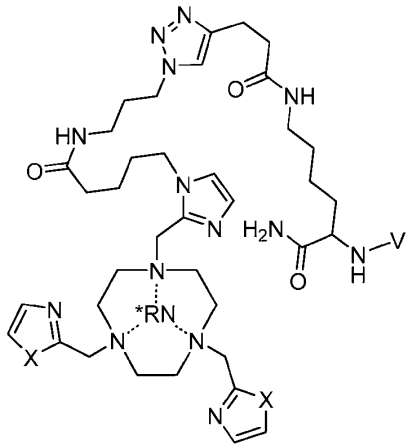
28. The compound according to any one of the preceding claims, wherein at least one targeting moiety comprises cilengitide, tirofiban, JSM-6427, risuteganib, GSK3008348, SDM17, GLPG0187, CWHM-12, nesvategrast, bexotegrast, EMD527040, MK-0429, or Tyr_2.

29. The compound according to any one of claims 1-27, wherein at least one targeting moiety comprises an RGD-peptide.

30. The compound according to claim 29, wherein the RGD peptide is selected from: cilengitide, SDM17, Tyr_2, A20FMDV2, SFITGv6, SFLAP3, $R_0$1-MG-F2, Echistatin, MK-0429, TDI-3761, TDI-4161, 29P, iRGD, c8, c[FRGDLAFp(NMe)K(Ac)], Tyr_{12}.

31. The compound according to claim 30, wherein the RGD peptide is SDM17.

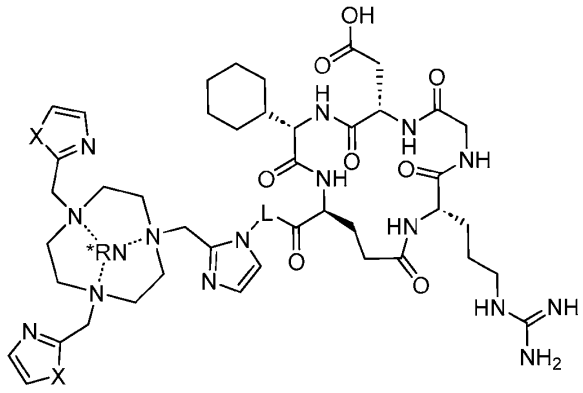
32. The compound according to any one of claims 1, 2, 5-7, or 27-31, wherein the compound is of Formula IA:



(IA)

or is a pharmaceutically acceptable salt thereof.

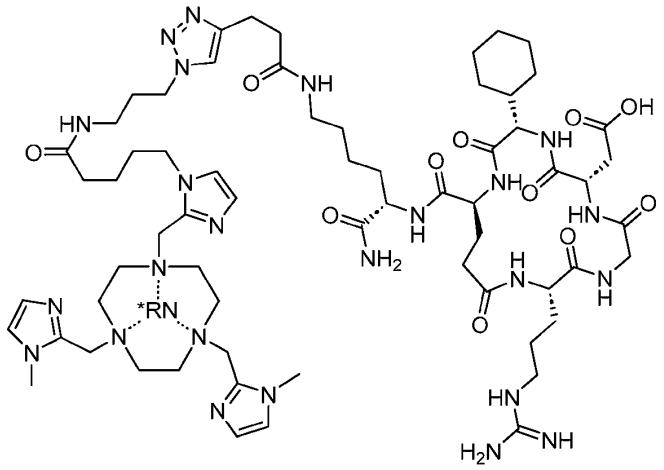
33. The compound according to any one of claims 1, 2, 5-7, or 8-25, wherein the compound is of Formula IB:



(IB)

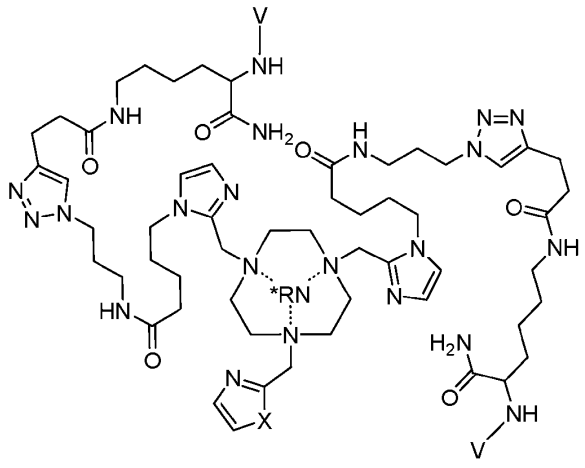
or is a pharmaceutically acceptable salt thereof.

34. The compound according to claim 32 or 33, wherein the compound is of the structure:



or is a pharmaceutically acceptable salt thereof.

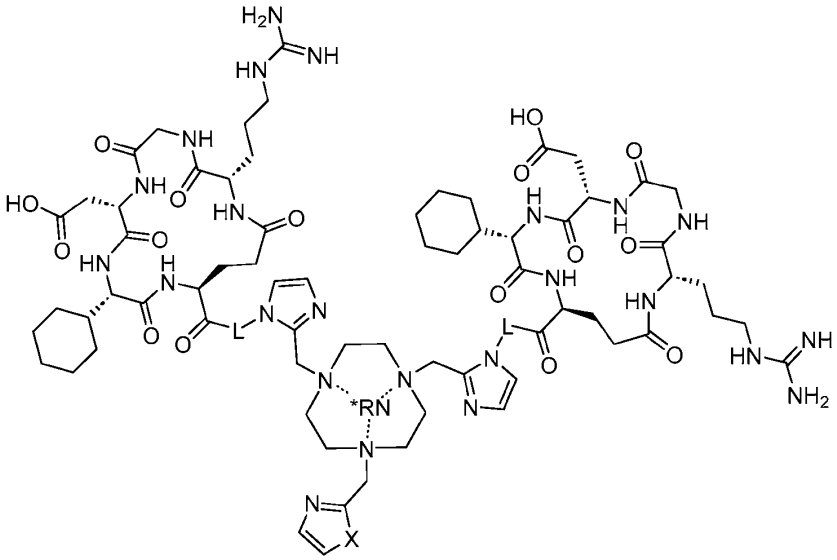
35. The compound according to any one of claims 1, 3, 5-7, or 26-31, wherein the compound is of Formula IIA:



(IIA)

or is a pharmaceutically acceptable salt thereof.

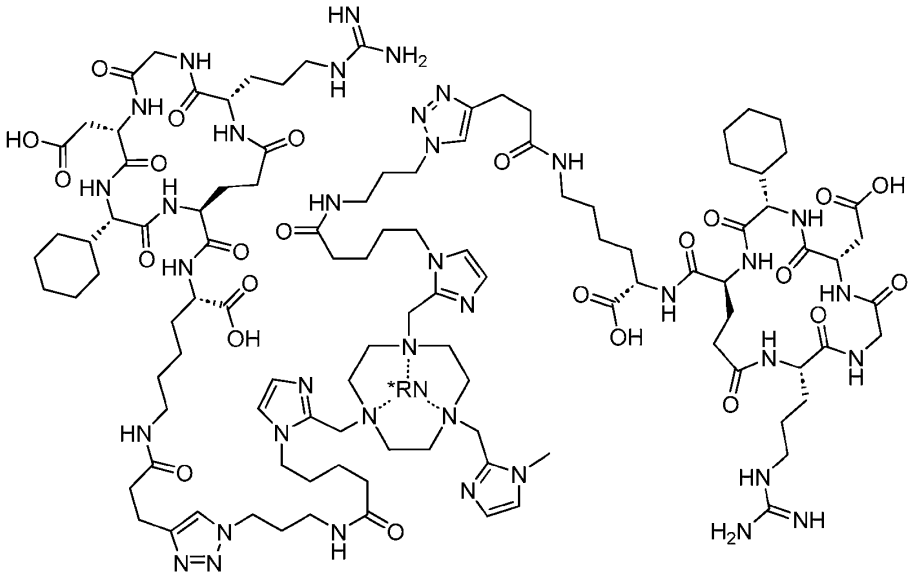
36. The compound according to any one of claims 1, 3, 5-7, or 8-25, wherein the compound is of Formula IIB:



(IIB)

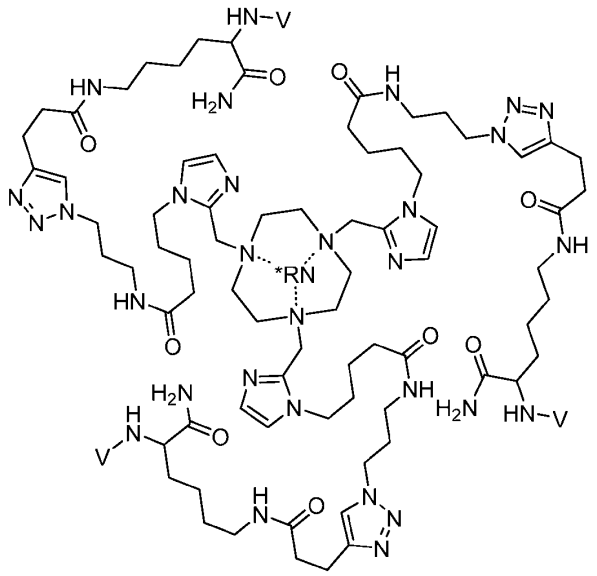
or is a pharmaceutically acceptable salt thereof.

37. The compound according to claim 35 or 36, wherein the compound is of the structure:



or is a pharmaceutically acceptable salt thereof.

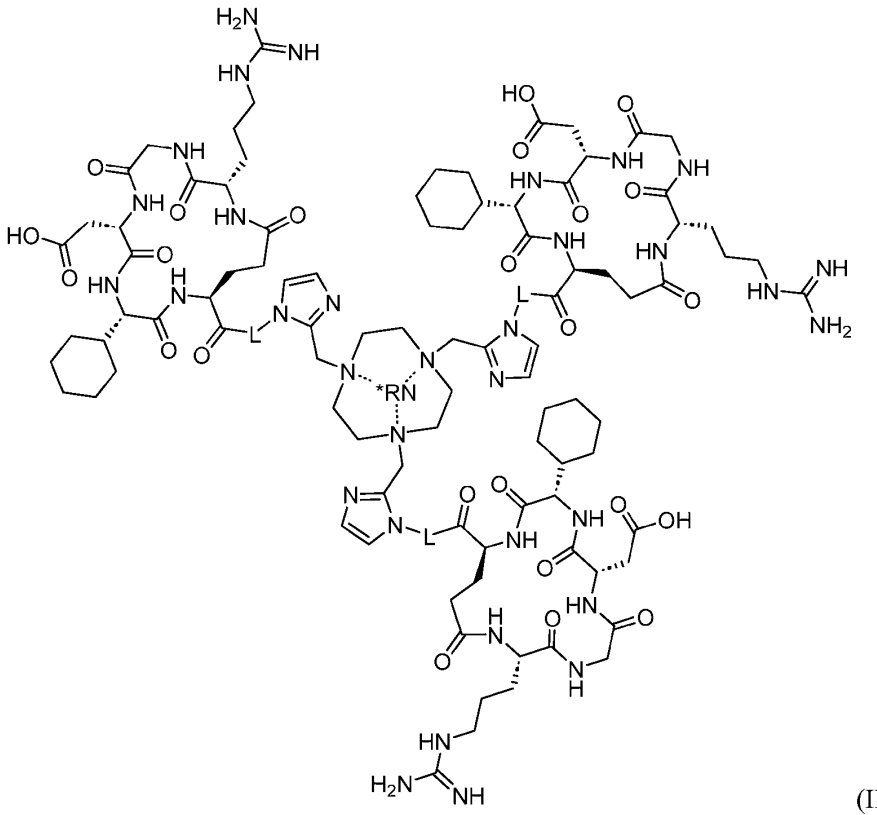
38. The compound according to any one of claims 1, 4, or 26-31, wherein the compound is of Formula IIIA:



(IIIA)

or is a pharmaceutically acceptable salt thereof.

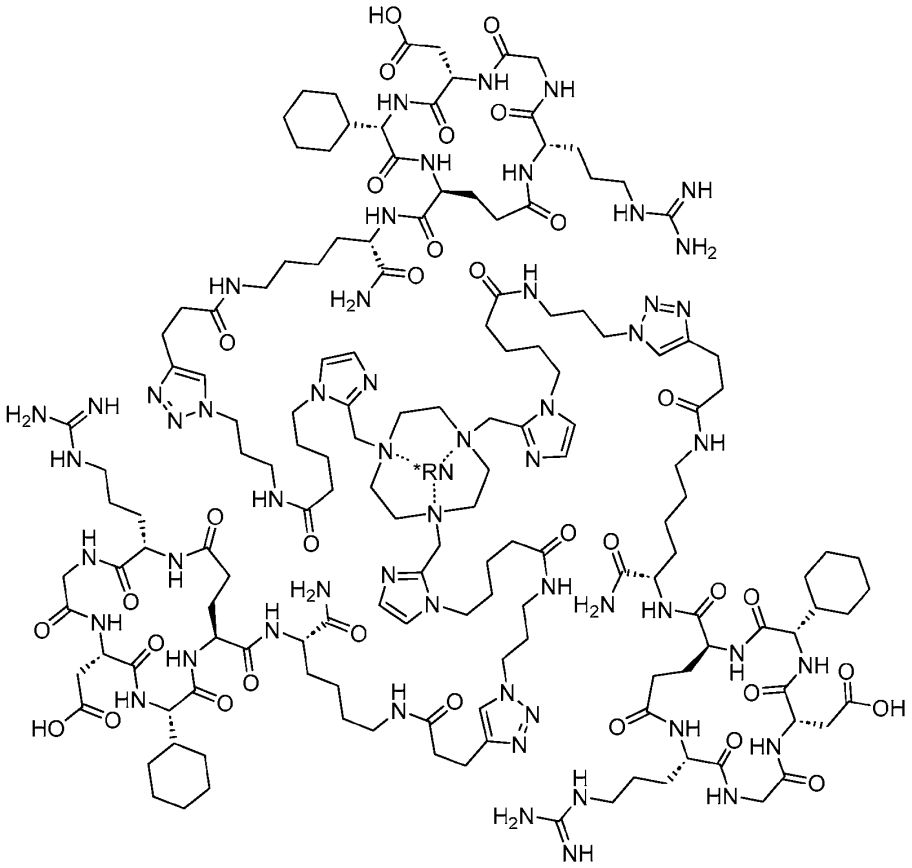
39. The compound according to any one of claims 1, 4, or 8-25, wherein the compound is of Formula IIIB:



(IIIB)

or is a pharmaceutically acceptable salt thereof.

40. The compound according to claim 38 or 39, wherein the compound has the structure:



or is a pharmaceutically acceptable salt thereof.

41. The compound according to any one of the preceding claims, wherein *RN is present.

42. The compound according to claim 41, wherein the radionuclide is selected from ^{51}Cr, ^{55}Co, ^{60}Cu, ^{61}Cu, ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{62}Zn, ^{66}Ga, ^{67}Ga, ^{68}Ga, [^{18}F]AlF, ^{111}In, ^{113m}In, ^{52m}Mn, ^{99m}Tc, ^{186}Re, ^{188}Re, ^{139}La, ^{140}La, ^{175}Yb, ^{179}Yb, ^{153}Sm, ^{177m}Sn, ^{166}Ho, ^{86}Y, ^{88}Y, ^{90}Y, ^{149}Pm, ^{165}Dy, ^{169}Er, ^{177}Lu, ^{52}Fe, ^{43}Sc, ^{44}Sc, ^{46}Sc, ^{47}Sc, ^{142}Pr, ^{157}Gd, ^{159}Gd, ^{212}Bi, ^{213}Bi, ^{72}As, ^{77}As, ^{97}Ru, ^{109}Pd, ^{105}Rh, ^{101m}Rh, ^{119}Sb, ^{197}Hg, ^{151}Eu, ^{153}Eu, ^{169}Eu, ^{201}Tl, ^{149}Tb, ^{152}Tb, ^{155}Tb, ^{161}Tb, ^{203}Pb, ^{212}Pb, ^{151}Pm, ^{153}Pm, ^{142}Pr, ^{143}Pr, ^{188}Re, ^{198}Au, ^{199}Au, ^{227}Th, ^{111}Ag, ^{199}Ag, ^{211}At, ^{223}Ra, ^{225}Ac, ^{88}Zr, and ^{89}Zr.

43. The compound according to claim 42, wherein the radionuclide is selected from ^{61}Cu, ^{62}Cu, ^{64}Cu, and ^{67}Cu.

44. The compound according to claim 43, wherein the radionuclide is ^{61}Cu or ^{67}Cu.

45. The compound according to claim 44, wherein the radionuclide is ^{61}Cu.

46. The compound according to claim 45, wherein the radionuclide is ^{67}Cu.

47. The compound according to claim 1, wherein the compound is selected from:
NOTI-TVA-[NR-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_3$;

NOTI-Me-DVA-[NR-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_2$;

NOTI-Me_2-MVA-NR-$(PEG)_2$-CH_2-C(O)-Lys-SDM17;

NOTI-TVA-[NR-$(CH_2)_3$-triazolylene-$(CH_2)_2$-C(O)-Lys-SDM17]$_3$;

NOTI-Me-DVA-[NR-$(CH_2)_3$-triazolylene-$(CH_2)_2$-C(O)-Lys-SDM17]$_2$;

NOTI-Me_2-MVA-NR-$(CH_2)_3$-triazolylene-$(CH_2)_2$-C(O)-Lys-SDM17;

NOTI-TVA-[$(Aoa)_2$-Lys-SDM17]$_3$;

NOTI-Me-DVA-[$(Aoa)_2$-Lys-SDM17]$_2$;

NOTI-Me_2-MVA-$(Aoa)_2$-Lys-SDM17;

NOTI-TVA-[$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_3$;

NOTI-Me-DVA-[$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_2$;

NOTI-Me_2-MVA-$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(PEG)_2$-CH_2-C(O)-Lys-SDM17;

NOTI-TVA-[$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(Aoa)_2$-Lys-SDM17]$_3$;

NOTI-Me-DVA-[$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(Aoa)_2$-Lys-SDM17]$_2$; and

NOTI-Me_2-MVA-$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(Aoa)_2$-Lys-SDM17;

or is a pharmaceutically acceptable salt thereof.

48. The compound according to claim 1, wherein the compound is selected from;
*RN-NOTI-TVA-[NR-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_3$;

*RN-NOTI-Me-DVA-[NR-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_2$;

*RN-NOTI-Me_2-MVA-NR-$(PEG)_2$-CH_2-C(O)-Lys-SDM17;

*RN-NOTI-TVA-[NR-$(CH_2)_3$-triazolylene-$(CH_2)_2$-C(O)-Lys-SDM17]$_3$;

*RN-NOTI-Me-DVA-[NR-$(CH_2)_3$-triazolylene-$(CH_2)_2$-C(O)-Lys-SDM17]$_2$;

*RN-NOTI-Me_2-MVA-NR-$(CH_2)_3$-triazolylene-$(CH_2)_2$-C(O)-Lys-SDM17;

*RN-NOTI-TVA-[$(Aoa)_2$-Lys-SDM17]$_3$;

*RN-NOTI-Me-DVA-[$(Aoa)_2$-Lys-SDM17]$_2$;

*RN-NOTI-Me_2-MVA-$(Aoa)_2$-Lys-SDM17;

*RN-NOTI-TVA-[$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_3$;

*RN-NOTI-Me-DVA-[$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_2$;

*RN-NOTI-Me_2-MVA-S(NAc)Cys-$(PEG)_2$-CH_2-C(O)-Lys-SDM17;

*RN-NOTI-TVA-[$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(Aoa)_2$-Lys-SDM17]$_3$;

*RN-NOTI-Me-DVA-[$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(Aoa)_2$-Lys-SDM17]$_2$; and

*RN-NOTI-Me_2-MVA-$(CH_2)_2$-succinimidylene-S(NAc)Cys-$(Aoa)_2$-Lys-SDM17;

or is a pharmaceutically acceptable salt thereof.

49. The compound according to claim 1, wherein the compound is selected from:

[^{61}Cu]Cu-NOTI-TVA-[NR-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_3$;

[^{61}Cu]Cu-NOTI-Me-DVA-[NR-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_2$;

[^{61}Cu]Cu-NOTI-Me_2-MVA-NR-$(PEG)_2$-CH_2-C(O)-Lys-SDM17;

[^{67}Cu]Cu-NOTI-TVA-[NR-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_3$;

[^{67}Cu]Cu-NOTI-Me-DVA-[NR-$(PEG)_2$-CH_2-C(O)-Lys-SDM17]$_2$;

[^{67}Cu]Cu-NOTI-Me_2-MVA-NR-$(PEG)_2$-CH_2-C(O)-Lys-SDM17;

[^{61}Cu]Cu-NOTI-TVA-[NR-$(CH_2)_3$-triazolylene-$(CH_2)_2$-C(O)-Lys-SDM17]$_3$;

[^{61}Cu]Cu-NOTI-Me-DVA-[NR-$(CH_2)_3$-triazolylene-$(CH_2)_2$-C(O)-Lys-SDM17]$_2$;

[^{61}Cu]Cu-NOTI-Me_2-MVA-NR-$(CH_2)_3$-triazolylene-$(CH_2)_2$-C(O)-Lys-SDM17;

[^{67}Cu]Cu-NOTI-TVA-[NR-$(CH_2)_3$-triazolylene-$(CH_2)_2$-C(O)-Lys-SDM17]$_3$;

[^{67}Cu]Cu-NOTI-Me-DVA-[NR-$(CH_2)_3$-triazolylene-$(CH_2)_2$-C(O)-Lys-SDM17]$_2$;

[^{67}Cu]Cu-NOTI-Me$_2$-MVA-NR-(CH$_2$)$_3$-triazolylene-(CH$_2$)$_2$-C(O)-Lys-SDM17;

[^{61}Cu]Cu-NOTI-TVA-[(Aoa)$_2$-Lys-SDM17]$_3$;

[^{61}Cu]Cu-NOTI-Me-DVA-[(Aoa)$_2$-Lys-SDM17]$_2$;

[^{61}Cu]Cu-NOTI-Me$_2$-MVA-(Aoa)$_2$-Lys-SDM17;

[^{67}Cu]Cu-NOTI-TVA-[(Aoa)$_2$-Lys-SDM17]$_3$;

[^{67}Cu]Cu-NOTI-Me-DVA-[(Aoa)$_2$-Lys-SDM17]$_2$;

[^{67}Cu]Cu-NOTI-Me$_2$-MVA-(Aoa)$_2$-Lys-SDM17;

[^{61}Cu]Cu-NOTI-TVA-[(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(PEG)$_2$-CH$_2$-C(O)-Lys-SDM17]$_3$;

[^{61}Cu]Cu-NOTI-Me-DVA-[(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(PEG)$_2$-CH$_2$-C(O)-Lys-SDM17]$_2$;

[^{61}Cu]Cu-NOTI-Me$_2$-MVA-(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(PEG)$_2$-CH$_2$-C(O)-Lys-SDM17;

[^{67}Cu]Cu-NOTI-TVA-[(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(PEG)$_2$-CH$_2$-C(O)-Lys-SDM17]$_3$;

[^{67}Cu]Cu-NOTI-Me-DVA-[(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(PEG)$_2$-CH$_2$-C(O)-Lys-SDM17]$_2$;

[^{67}Cu]Cu-NOTI-Me$_2$-MVA-(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(PEG)$_2$-CH$_2$-C(O)-Lys-SDM17;

[^{61}Cu]Cu-NOTI-TVA-[(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(Aoa)$_2$-Lys-SDM17]$_3$;

[^{61}Cu]Cu-NOTI-Me-DVA-[(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(Aoa)$_2$-Lys-SDM17]$_2$;

[^{61}Cu]Cu-NOTI-Me$_2$-MVA-(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(Aoa)$_2$-Lys-SDM17;

[^{67}Cu]Cu-NOTI-TVA-[(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(Aoa)$_2$-Lys-SDM17]$_3$;

[^{67}Cu]Cu-NOTI-Me-DVA-[(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(Aoa)$_2$-Lys-SDM17]$_2$; and

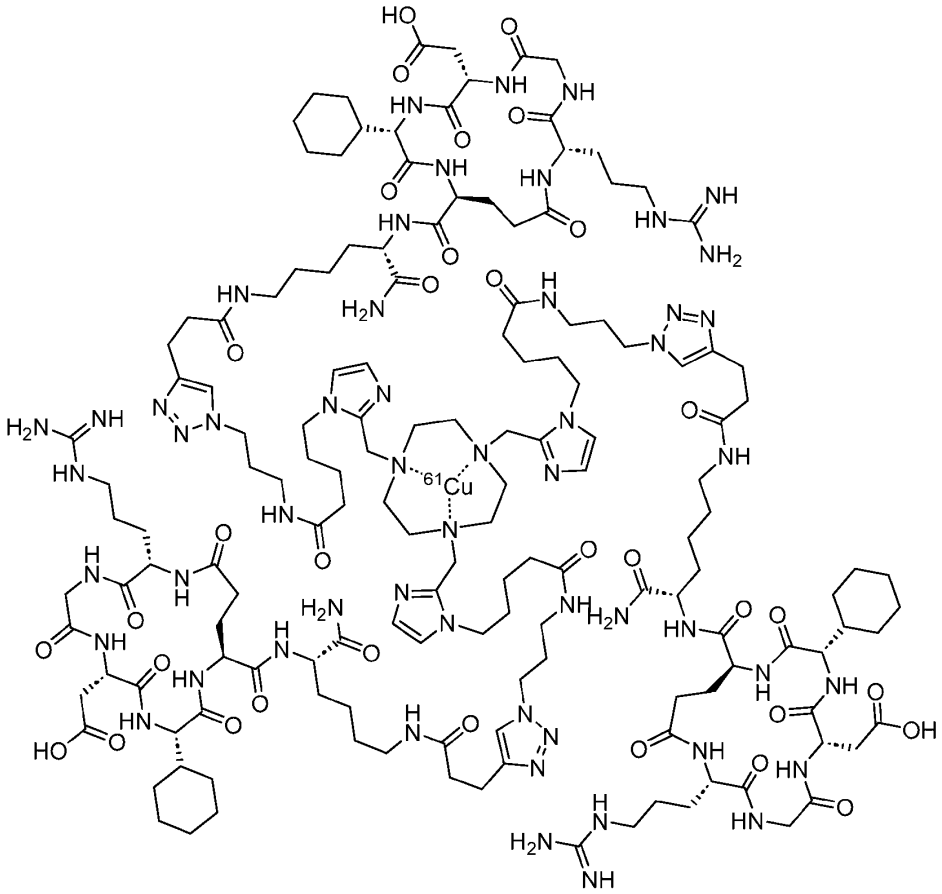
[^{67}Cu]Cu-NOTI-Me$_2$-MVA-(CH$_2$)$_2$-succinimidylene-S(NAc)Cys-(Aoa)$_2$-Lys-SDM17;

or is a pharmaceutically acceptable salt thereof.

50. A pharmaceutical composition comprising a compound according to any one of the preceding claims and one or more pharmaceutically acceptable excipients.

51. The pharmaceutical composition according to claim 50, wherein the compound is according to claim 45.

52. The pharmaceutical composition according to claim 51, wherein the compound has the structure:



or is a pharmaceutically acceptable salt thereof.

53. The composition according to claim 51 or 52, wherein the composition is characterized by one or more of:

a apparent molar activity of the compound of ≥ 3 MBq/nmol;

a radiochemical purity of ≥ 90%;

an activity concentration of ≥ 8 MBq/mL;

a radionuclidic purity at end of synthesis of ≥ 95%;

a radiocobalt radionuclidic purity at the end of synthesis of ≤ 0.05%; and

a radionuclidic purity at the end of synthesis characterized by having $^{110m}Ag \leq 0.1$ Bq/g, $^{108m}Ag \leq 0.1$ Bq/g, or $^{109}Cd \leq 0.1$ Bq/g.

54. The composition according to any one of claims claim 51-53, wherein the composition is characterized by a apparent molar activity of the compound of ≥ 5 MBq/nmol.

55. The composition according to any one of claims 51-54, wherein the composition is characterized by a radiochemical purity of ≥ 93%.

56. The composition according to any one of claims 51-55, wherein the composition is characterized by an activity concentration of ≥ 8 MBq/mL.

57. The composition according to any one of claims 51-56, wherein the composition is characterized by a radionuclidic purity of the compound at end of synthesis of ≥ 95%.

58. The composition according to any one of claims 51-57, wherein the composition is characterized by a radionuclidic purity at end of synthesis of characterized by a of the sum of radiocobalt ≤ 0.05%.

59. The composition according to any one of claims 51-58, wherein the composition is characterized by a apparent molar activity of the compound of 35-2 GBq/nmol.

60. The composition according to any one of claims 51-59, wherein the composition is characterized by radiochemical purity of ≥ 95%.

61. The composition according to any one of claims 51-60, wherein the composition is characterized by activity concentration of ≥ 12 MBq/mL.

62. The composition according to any one of claims 51-61, wherein the composition is characterized by radionuclidic purity at end of synthesis of ≥ 98%.

63. The composition according to any one of claims 51-62, wherein the composition is characterized by radionuclidic purity at end of synthesis of ≥ 99.99%.

64. The composition according to any one of claims 51-63, wherein the radionuclidic purity at end of synthesis is characterized by having a sum of radiocobalt of ≤ 0.01%.

65. The composition according to any one of claims 51-64, wherein the radionuclidic purity at end of synthesis is characterized by having ^{56}Co or ^{58}Co of ≤ 800 Bq/g.

66. The composition according to any one of claims 51-65, wherein the radionuclidic purity at the end of synthesis is characterized by having ^{56}Co of ≤ 8 Bq/g.

67. The composition according to any one of claims 51-66, wherein the chemical purity at end of synthesis is characterized by having Al ≤ 1.2 ng/MBq, Co ≤ 0.2 ng/MBq, Fe ≤ 1.7 ng/MBq, Pb ≤ 0.8 ng/MBq, or Zn ≤ 0.8 ng/MBq.

68. The composition according to any one of claims 51-67, wherein the radionuclidic impurities at end of synthesis sum to ≤ 1200 Bq/g.

69. The pharmaceutical composition according to any one of claims 51-67, wherein the 56[Co]Co specific activity is from 1 Bq/g to 100 Bq/g, e.g., from 1 Bq/g to 50 Bq/g, from 1 Bq/g to 25 Bq/g, from 1 Bq/g to 10 Bq/g, from 1 Bq/g to 8 Bq/g, or from 1 Bq/g to 4 Bq/g.

70. The pharmaceutical composition according to any one of claims 51-67, wherein the pharmaceutical composition is characterized by one or more of: a 110mAg specific activity ≤ 0.1 Bq/g, a 108mAg specific activity ≤ 0.1 Bq/g, or a 109Cd specific activity ≤ 0.1 Bq/g.

71. The pharmaceutical composition according to any one of claims 51-67, wherein the sum of the specific activities of the radionuclidic impurities in the pharmaceutical composition is ≤ 8,000 Bq/g, e.g., ≤ 5,000 Bq/g, ≤ 3,000 Bq/g, or ≤ 1,200 Bq/g.

72. The pharmaceutical composition according to any one of claims 51-67, wherein the pharmaceutical composition is characterized by one or more of: Al ≤ 1.2 ng/MBq, Co ≤ 0.2 ng/MBq, Fe ≤ 1.7 ng/MBq, Pb ≤ 0.8 ng/MBq, or Zn ≤ 0.8 ng/MBq.

73. The pharmaceutical composition according to any one of claims 51-67, wherein the activity concentration of the pharmaceutical composition is ≥ 10 MBq/mL, e.g., ≥ 20 MBq/mL, ≥ 30 MBq/mL, ≥ 40 MBq/mL, ≥ 50 MBq/mL, ≥ 60 MBq/mL, ≥ 70 MBq/mL, ≥ 80 MBq/mL, or ≥ 90 MBq/mL.

74. The pharmaceutical composition according to any one of claims 51-67, wherein the activity concentration of the pharmaceutical composition is from 10 MBq/mL to 100 MBq/mL, e.g., from 40 MBq/mL to 90 MBq/mL.

75. The pharmaceutical composition according to any one of claims 51-67, wherein the apparent molar activity of the radiotracer is ≥ 1 MBq/nmol, e.g., ≥ 10 MBq/nmol, ≥ 20 MBq/nmol, ≥ 30 MBq/nmol, or ≥ 50 MBq/nmol.

76. A method of generating one or more images of a subject, the method comprising:

administering to the subject an effective amount of a pharmaceutical composition according to any one of claims 50-75 and generating one or more images of at least a part of the subject's body.

77. The method of claim 76, wherein the composition according to claim 50 or 51 is administered to the subject.

78. The method of claim 77, wherein the image is generated using positron emission tomography (PET), PET- computer tomography (PET-CT), or single-photon emission computerized tomography (SPECT).

79. The method of any one of claims 76-78, further comprising determining the presence or absence of a disease in the subject based on the presence or absence of localization of the radionuclide in the one or more images of the subject's body.

80. The method of claim 79, wherein when the subject is determined to have a disease, the method further comprises administering to the subject a therapeutically effective amount of a composition of claim 50.

81. The method of claim 80, wherein the disease is selected from cancers, inflammatory diseases, infectious diseases, and immune diseases.

82. The method of claim 81, wherein the disease is cancer, and the cancer is selected from breast cancer (e.g., triple-negative breast cancer), pancreatic cancer, pancreatic adenocarcinoma, pancreatic ductal cancer (PDA), small intestine cancer, colon cancer, gastric cancer, rectal cancer, lung adenocarcinoma, lung cancer (e.g., non-small cell lung cancer), head and neck cancer, head and neck squamous cell carcinomas (HNSCCs), idiopathic pulmonary fibroma, ovarian cancer, hepatocellular carcinoma, epithelial cancer, esophageal cancer, hypopharynx cancer, nasopharynx cancer, larynx cancer, myeloma cells, bladder cancer, cholangiocellular carcinoma, clear cell renal carcinoma, neuroendocrine tumor, oncogenic osteomalacia, sarcoma, CUP (carcinoma of unknown primary), thymus carcinoma, desmoid tumors, glioma, astrocytoma, cervix carcinoma, and prostate cancer.

83. The method of claim 82, wherein the cancer is selected from pancreatic adenocarcinoma, pancreatic ductal cancer (PDA), lung adenocarcinoma, head and neck squamous cell carcinomas (HNSCCs), and idiopathic pulmonary fibroma.

84. A method of detecting a disease in a subject, comprising:

administering to a subject an effective amount of the pharmaceutical composition according to any one of claims 50-75;

detecting the localization of the radionuclide; and

determining the presence or absence of the disease based on the presence or absence of localization.

85. The method according to claim 84, wherein detecting is by positron emission tomography (PET), PET- computer tomography (PET-CT), or single-photon emission computerized tomography (SPECT).

86. The method according to any one of claims 84-85, wherein the disease is associated with increased expression of αvβ6-integrin and is selected from cancers, inflammatory diseases, infectious diseases, and immune diseases, preferably fibrosis or cancer.

87. The method of claim 84, wherein the disease is cancer, and the cancer is selected from breast cancer (e.g., triple-negative breast cancer), pancreatic cancer, small intestine

cancer, colon cancer, gastric cancer, rectal cancer, lung cancer (e.g., non-small cell lung cancer), head and neck cancer, ovarian cancer, hepatocellular carcinoma, epithelial cancer, esophageal cancer, hypopharynx cancer, nasopharynx cancer, larynx cancer, myeloma cells, bladder cancer, cholangiocellular carcinoma, clear cell renal carcinoma, neuroendocrine tumor, oncogenic osteomalacia, sarcoma, CUP (carcinoma of unknown primary), thymus carcinoma, desmoid tumors, glioma, astrocytoma, cervix carcinoma, and prostate cancer.

88. A method of determining the effect of cancer treatment on a subject afflicted with cancer comprising:

administering to the subject an effective amount of a compound comprising a radionuclide according to any one of claims 1-46, 48, and 49, or a pharmaceutical composition comprising an effective amount of a compound comprising a radionuclide according to any one of claims 50-75 at an earlier time point and at a later time point;

detecting the localization of the radionuclide at both the earlier time point and at a later time point; and

determining the effect of the cancer treatment by comparing the amount of localization at the later time point to the amount of localization at the earlier time point.

89. The method of claim 88, wherein the localization of the compound is detected using positron emission tomography (PET), PET- computer tomography (PET-CT), or single-photon emission computerized tomography (SPECT).

90. The method of claim 88 or 89, wherein the earlier time point is before commencing the cancer treatment and the later time point is at least two weeks after commencing the cancer treatment.

91. The method of any one of claims 88-90, wherein the cancer is selected from breast cancer (e.g., triple-negative breast cancer), pancreatic cancer, small intestine cancer, colon cancer, gastric cancer, rectal cancer, lung cancer (e.g., non-small cell lung cancer), head and neck cancer, ovarian cancer, hepatocellular carcinoma, epithelial cancer, esophageal cancer, hypopharynx cancer, nasopharynx cancer, larynx cancer, myeloma cells, bladder

cancer, cholangiocellular carcinoma, clear cell renal carcinoma, neuroendocrine tumor, oncogenic osteomalacia, sarcoma, CUP (carcinoma of unknown primary), thymus carcinoma, desmoid tumors, glioma, astrocytoma, cervix carcinoma, and prostate cancer.

92. A method of treating a disease in a patient in need thereof, comprising administering to the patient an effective amount of a compound according to any one of claims 1-46, 48 and 49, or a pharmaceutical composition comprising a compound of any one of claims 50-75.

93. The method of claim 92, wherein the disease is selected from cardiovascular diseases, liver fibrosis and cirrhosis, arthritic disorders (e.g., rheumatoid arthritis), IgG4-related disease, pulmonary fibrosis and interstitial lung disease, Crohn's disease, tuberculosis, sarcoidosis, and periprosthetic joint infections.

94. A theranostic method comprising:

(a) administering to a subject an effective amount of a first compound comprising a ^{61}Cu radionuclide or a pharmaceutical composition comprising an effective amount of a first compound comprising a ^{61}Cu radionuclide, wherein the first compound is a compound of claim 45;

(b) generating one or more images of the subject (e.g., of a certain region or part of the subject's body); and

(c) administering to the subject an effective amount of a second compound comprising a ^{67}Cu radionuclide or a pharmaceutical composition comprising an effective amount of a second compound comprising a ^{67}Cu radionuclide, wherein the second compound is a compound of claim 46.