

# US Patent & Trademark Office

## Patent Public Search | Text View

---

United States Patent Application Publication	20250263393
Kind Code	A1
Publication Date	August 21, 2025
Inventor(s)	JIN; Yun

---

### FAP INHIBITORS

---

#### Abstract

Provided herein are a compound of Formula (I), a pharmaceutical composition comprising said compound, and method of use of the compound or pharmaceutical composition in the diagnosis or treatment of a disease characterized by overexpression of fibroblast activation protein (FAP).

---

<b>Inventors:</b>	JIN; Yun (Shanghai, CN)
<b>Applicant:</b>	SHANGHAI SINOTAU BIOTECH. CO., LTD (Shanghai, CN)
<b>Family ID:</b>	1000008628631
<b>Appl. No.:</b>	18/858234
<b>Filed (or PCT Filed):</b>	April 20, 2023
<b>PCT No.:</b>	PCT/CN2023/089429

#### Foreign Application Priority Data

WO	PCT/CN2022/088166	Apr. 21, 2022
----	-------------------	---------------

---

#### Publication Classification

**Int. Cl.:** C07D401/14 (20060101); A61K49/00 (20060101); A61K49/10 (20060101); A61K51/04 (20060101); C07D403/12 (20060101); C07D487/10 (20060101)

#### U.S. Cl.:

**CPC** C07D401/14 (20130101); A61K49/0052 (20130101); A61K49/106 (20130101); A61K51/0446 (20130101); C07D403/12 (20130101); C07D487/10 (20130101);

---

#### Background/Summary

CROSS-REFERENCE TO RELATED APPLICATIONS [0001] This application claims priority to International Patent Application No. PCT/CN2022/088166, filed on Apr. 21, 2022, the entirety of which is incorporated herein by reference.

## FIELD

[0002] Provided herein are certain compounds which demonstrate potent FAP enzymatic inhibition, great tumor uptake and/or retention, pharmaceutical compositions comprising said compounds, and method of use of the compounds or pharmaceutical compositions in the diagnosis or treatment of a disease characterized by overexpression of fibroblast activation protein (FAP).

## BACKGROUND

[0003] Fibroblast activation protein alpha (FAP, also named seprase, EC 3.4.21. B28), encoded by the FAP gene, also known as prolyl endopeptidase FAP, is a 760 amino acid type II transmembrane glycoprotein. It contains a short intracellular domain of 6 amino acids at the N-terminal, a transmembrane section of 22 amino acids and a large extracellular region at the C-terminal. The extracellular domain consists of a beta propeller domain, which functions as a substrate selectivity gatekeeper, and an alpha/beta hydrolase domain. FAP is not enzymatic active until it forms homodimer or heterodimer with DPP4.

[0004] FAP is a serine protease. It belongs to the propyl dipeptidyl peptidase family, which also includes DPP4, DPP7, DPP8, DPP9, prolyl carboxypeptidase, and prolyl endopeptidase (PREP). It mostly resembles DDP4, with which shares 84% amino acid homology and 51% identity. In addition to a post-proline exopeptidase, which is similar to DPP4, FAP is also an endopeptidase. It degrades denatured collagen I and III,  $\alpha$ 2-antiplasmin, FGF-21, LOX-L1, CXCL-5, CSF-1 and C1qT6 et al (Zhang et al, 2019) and regulates proteins that associated with ECM, ECM-cell interaction, coagulation, metabolism, tissue remodeling and wound healing.

[0005] FAP, albeit having a dozen of nature substrates, is rarely expressed in healthy tissues and has little impact on the normal physical activity. FAP knockout mice are normal, fertile and healthy (Niedermeyer et al 2000), suggesting that its function could be fully compensated by proteins with similar activity. Echoing with what is observed with FAP knockout mice, loss of function SNP variant in a Turkish family was not associated with any phenotype (Osborne et al 2014).

[0006] On the contrary, FAP is found upregulated in 90% of carcinoma. It promotes cancer cell proliferation, migration and invasion (An et al 2022). FAP is profoundly known as a marker of cancer associated fibroblast (CAF), which plays a pro-tumorigenic role in a broad spectrum of cancers, breast cancer, colorectal, pancreatic, lung, bladder, ovarian, head and neck, glioblastoma et al, just to name a few (Kratochwil et al 2019, Windisch et al 2020). As such, targeting FAP is a promising strategy for cancer therapy. Multiple approaches targeting FAP have been intensively exploited and developed as noted. Those could be clustered into: 1) FAP enzymatic inhibition and functional block by small molecular inhibitors, vaccination, antibody against FAP; 2) FAP protein depletion by PROTACs and oligonucleotide drugs of miRNA, shRNA, siRNA; 3) FAP (+) cell depletion, such as CAR-T and CAR-NK; 4) FAP directed prodrug and micelle (Chai et al 2018, Teng et al 2020); 5) FAP ligand mediated therapy, such as FAP ligand mediated radiotherapy or chemotoxicity and antibody-conjugated chemotherapy.

[0007] Besides cancers, FAP is involved in varying diseases, including but not limited to cardiovascular, infection, arthritis, inflammation, fibrosis, metabolic and autoimmune diseases (Tillmanns et al 2015, Croft et al 2019, Lay et al 2019, Schmidkonz et al 2020, Hoffmann et al 2021, Windisch et al 2021). FAP imaging is being exploited in delineating tumor volume, diagnosis and staging of FAP-associated diseases (Dendl et al 2021, Kratochwil et al 2019, Luo et al 2021).

[0008] FAP mediates tumor growth and FAP associated diseases in both enzymatic activity dependent and independent way. Breast cancer cell line that expressed enzymatic inactive FAP is more invasive and produces tumor that grow rapidly (Huang et al 2011), which is likely through activating PI3K and MMP2/9 pathways (Lv et al 2016).

[0009] Given the broad spectrum of FAP in oncology and multiple diseases, ligands binding/targeting FAP provides great potential of clinical value in therapy or diagnosis.

## SUMMARY

[0010] In one embodiment, provided herein are some chemical entities which demonstrate potent FAP enzymatic inhibition, great tumor uptake and/or retention. In one embodiment, without being limited by a particular theory, small animal PET/CT delineate the tumor volume with great tumor-to-blood, tumor-to-kidney ratio, and long-term tumor retention, and resulting in completely tumor inhibition in the in vivo efficacy study.

[0011] In one embodiment, provided herein is a compound of Formula (I):

##STR00001## [0012] or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof, wherein R<sup>sup.1</sup>, Q<sup>sup.1</sup> to Q<sup>sup.7</sup>, Ring C, R<sup>sup.2</sup>, n, X<sup>sup.1</sup>, G<sup>sup.1</sup>, X, Ring B, G, s, X<sup>sup.2</sup>, L, Ring A, R<sup>sup.3</sup>, m, R<sup>sup.4</sup>, p, and Z are as defined herein or elsewhere.

[0013] Also provided herein is a complex formed by a compound provided herein and a divalent or trivalent metal cation.

[0014] Also provided herein is a liposome comprising the compound provided herein. Also provided herein is a virus-like particle (VLP) comprising the compound provided herein.

[0015] Also provided herein is a pharmaceutical composition comprising a compound provided herein, a liposome provided herein, or a virus-like particle (VLP) provided herein, and a pharmaceutically acceptable excipient.

[0016] Also provided herein is a method for the diagnosis of a disease characterized by overexpression of fibroblast activation protein (FAP) in a subject, comprising administering to the subject a diagnostically effective amount of a compound provided herein, a complex provided herein, or a pharmaceutical composition provided herein.

[0017] Also provided herein is a method for the treatment of a disease characterized by overexpression of fibroblast activation protein (FAP) in a subject, comprising administering to the subject a therapeutically effective amount of a compound provided herein, a liposome provided herein, a virus-like particle (VLP) provided herein, or a pharmaceutical composition provided herein.

[0018] Also provided herein is a kit comprising a compound provided herein, a complex provided herein, a liposome provided herein, a virus-like particle (VLP) provided herein, or a pharmaceutical composition provided herein, and instructions for the diagnosis or treatment of a disease.

---

## Description

### BRIEF DESCRIPTION OF FIGURES

[0019] FIG. 1A, FIG. 1B, and FIG. 1C show organ distribution of <sup>sup.177</sup>Lu-FAPI-04 (n=2) and <sup>sup.177</sup>Lu-E1 (n=4) in HEK-FAPI tumor bearing nude mice at 3 hours, 24 hours, and 48 hours, respectively.

### DETAILED DESCRIPTION

[0020] It is to be understood that the invention provided herein is not limited to the particular methodology, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the invention provided herein. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

[0021] Several documents are cited throughout the text of this specification. Each of the documents cited herein (including all patents, patent applications, scientific publications, manufacturer's specifications, instructions etc.), whether supra or infra, is hereby incorporated by reference in its

entirety. In the event of a conflict between the definitions or teachings of such incorporated references and definitions or teachings recited in the present specification, the text of the present specification takes precedence.

## Definitions

[0022] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. In one embodiment, unless otherwise specified, the terms used herein are defined as described in “A multilingual glossary of biotechnological terms: (IUPAC Recommendations)”, Leuenberger, H. G. W, Nagel, B. and Klbl, H. eds. (1995), Helvetica Chimica Acta, CH-4010 Basel, Switzerland.

[0023] As used herein, and in the specification and the accompanying claims, the indefinite articles “a” and “an” and the definite article “the” include plural as well as single referents, unless the context clearly indicates otherwise.

[0024] As used herein, the terms “comprising” and “including” can be used interchangeably. The terms “comprising” and “including” are to be interpreted as specifying the presence of the stated features or components as referred to, but does not preclude the presence or addition of one or more features, or components, or groups thereof. Additionally, the terms “comprising” and “including” are intended to include examples encompassed by the term “consisting of”. Consequently, the term “consisting of” can be used in place of the terms “comprising” and “including” to provide for more specific embodiments of the invention.

[0025] As used herein, the term “or” is to be interpreted as an inclusive “or” meaning any one or any combination. Therefore, “A, B or C” means any of the following: “A; B; C; A and B; A and C; B and C; A, B and C”. An exception to this definition will occur only when a combination of elements, functions, steps or acts are in some way inherently mutually exclusive.

[0026] As used herein, the phrase “and/or” as used in a phrase such as “A and/or B” herein is intended to include both A and B; A or B; A (alone); and B (alone). Likewise, the phrase “and/or” as used in a phrase such as “A, B, and/or C” is intended to encompass each of the following embodiments: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0027] As used herein, and unless otherwise specified, the term “alkyl” refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, which is saturated. In one embodiment, the alkyl group has, for example, from one to twenty-four carbon atoms (C.sub.1-C.sub.24 alkyl), four to twenty carbon atoms (C.sub.4-C.sub.20 alkyl), six to sixteen carbon atoms (C.sub.6-C.sub.16 alkyl), six to nine carbon atoms (C.sub.6-C.sub.9 alkyl), one to fifteen carbon atoms (C.sub.1-C.sub.15 alkyl), one to twelve carbon atoms (C.sub.1-C.sub.12 alkyl), one to eight carbon atoms (C.sub.1-C.sub.8 alkyl) or one to six carbon atoms (C.sub.1-C.sub.6 alkyl) and which is attached to the rest of the molecule by a single bond.

Examples of alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, 1, 1-dimethylethyl (t-butyl), 3-methylhexyl, 2-methylhexyl, and the like. Unless otherwise specified, an alkyl group is optionally substituted.

[0028] As used herein, and unless otherwise specified, the term “alkenyl” refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, which contains one or more carbon-carbon double bonds. The term “alkenyl” also embraces radicals having “cis” and “trans” configurations, or alternatively, “E” and “Z” configurations, as appreciated by those of ordinary skill in the art. In one embodiment, the alkenyl group has, for example, from two to twenty-four carbon atoms (C.sub.2-C.sub.24 alkenyl), four to twenty carbon atoms (C.sub.4-C.sub.20 alkenyl), six to sixteen carbon atoms (C.sub.6-C.sub.16 alkenyl), six to nine carbon atoms (C.sub.6-C.sub.9 alkenyl), two to fifteen carbon atoms (C.sub.2-C.sub.15 alkenyl), two to twelve carbon atoms (C.sub.2-C.sub.12 alkenyl), two to eight carbon atoms (C.sub.2-C.sub.8 alkenyl) or two to six carbon atoms (C.sub.2-C.sub.6 alkenyl) and which is attached to the rest of the molecule by a single bond. Examples of alkenyl groups include, but are

not limited to, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1, 4-dienyl, and the like. Unless otherwise specified, an alkenyl group is optionally substituted.

[0029] As used herein, and unless otherwise specified, the term “alkynyl” refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, which contains one or more carbon-carbon triple bonds. In one embodiment, the alkynyl group has, for example, from two to twenty-four carbon atoms (C.sub.2-C.sub.24 alkynyl), four to twenty carbon atoms (C.sub.4-C.sub.20 alkynyl), six to sixteen carbon atoms (C.sub.6-C.sub.16 alkynyl), six to nine carbon atoms (C.sub.6-C.sub.9 alkynyl), two to fifteen carbon atoms (C.sub.2-C.sub.15 alkynyl), two to twelve carbon atoms (C.sub.2-C.sub.12 alkynyl), two to eight carbon atoms (C.sub.2-C.sub.8 alkynyl) or two to six carbon atoms (C.sub.2-C.sub.6 alkynyl) and which is attached to the rest of the molecule by a single bond. Examples of alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, and the like. Unless otherwise specified, an alkynyl group is optionally substituted.

[0030] As used herein, and unless otherwise specified, the term “cycloalkyl” refers to a non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, and which is saturated. Cycloalkyl group may include fused, bridged, or spiro ring systems. In one embodiment, the cycloalkyl has, for example, from 3 to 15 ring carbon atoms (C.sub.3-C.sub.15 cycloalkyl), from 3 to 10 ring carbon atoms (C.sub.3-C.sub.10 cycloalkyl), or from 3 to 8 ring carbon atoms (C.sub.3-C.sub.5 cycloalkyl). The cycloalkyl is attached to the rest of the molecule by a single bond. Examples of monocyclic cycloalkyl radicals include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Examples of polycyclic cycloalkyl radicals include, but are not limited to, adamantyl, norbornyl, decalinyl, 7, 7-dimethyl-bicyclo [2.2.1]heptanyl, spiro [3, 3]heptyl, spiro [3, 4]octyl, spiro [4, 3]octyl, spiro [3, 5]nonyl, spiro [5, 3]nonyl, spiro [3, 6]decyl, spiro [6, 3]decyl, spiro [4, 5]decyl, spiro [5, 4]decyl, bicyclo [2.2.1]heptyl, bicyclo [2.2.2]octyl, and the like. Unless otherwise specified, a cycloalkyl group is optionally substituted.

[0031] As used herein, and unless otherwise specified, the term “heteroalkyl” refers to a saturated straight or branched carbon chain that is interrupted one or more times with the same or different heteroatoms independently selected from nitrogen, oxygen, phosphorous, and sulfur. Examples of heteroalkyl include, but are not limited to, —O—CH.sub.3, —S—CH.sub.3, —CH.sub.2—O—CH.sub.3, —CH.sub.2—O—C.sub.2H.sub.5, —CH.sub.2—S—CH.sub.3, —CH.sub.2—S—C.sub.2H.sub.5, —C.sub.2H.sub.4—O—CH.sub.3, —C.sub.2H.sub.4—O—C.sub.2H.sub.5, —C.sub.2H.sub.4—S—CH.sub.3, —C.sub.2H.sub.4—S—C.sub.2H.sub.5, and the like. Unless otherwise specified, a heteroalkyl group is optionally substituted.

[0032] As used herein, and unless otherwise specified, the term “heterocyclyl” refers to a non-aromatic radical monocyclic or polycyclic moiety that contains one or more (e.g., one, one or two, one to three, or one to four) heteroatoms independently selected from nitrogen, oxygen, phosphorous, and sulfur. The heterocyclyl may be attached to the main structure at any heteroatom or carbon atom. A heterocyclyl group can be a monocyclic, bicyclic, tricyclic, tetracyclic, or other polycyclic ring system, wherein the polycyclic ring systems can be a fused, bridged or spiro ring system. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or more rings. A heterocyclyl group can be saturated or partially unsaturated. Saturated heterocycloalkyl groups can be termed “heterocycloalkyl”. Partially unsaturated heterocycloalkyl groups can be termed “heterocycloalkenyl” if the heterocyclyl contains at least one double bond, or “heterocycloalkynyl” if the heterocyclyl contains at least one triple bond. In one embodiment, the heterocyclyl has, for example, 3 to 18 ring atoms (3- to 18-membered heterocyclyl), 4 to 18 ring atoms (4- to 18-membered heterocyclyl), 5 to 18 ring atoms (3- to 18-membered heterocyclyl), 4 to 8 ring atoms (4- to 8-membered heterocyclyl), or 5 to 8 ring atoms (5- to 8-membered heterocyclyl). Whenever it appears herein, a numerical range such as “3 to 18” refers to each integer in the given range; e.g., “3 to 18 ring atoms” means that the heterocyclyl group can consist

of 3 ring atoms, 4 ring atoms, 5 ring atoms, 6 ring atoms, 7 ring atoms, 8 ring atoms, 9 ring atoms, 10 ring atoms, etc., up to and including 18 ring atoms. Examples of heterocyclyl groups include, but are not limited to, imidazolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, isoxazolidinyl, isothiazolidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuryl, and piperidinyl. Examples of heterocyclyl groups also include, but are not limited to, 1-(1, 2, 5, 6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, 1, 8 diazo-spiro-[4, 5] decyl, 1, 7 diazo-spiro-[4, 5] decyl, 1, 6 diazo-spiro-[4, 5] decyl, 2, 8 diazo-spiro [4, 5] decyl, 2, 7 diazo-spiro [4, 5] decyl, 2, 6 diazo-spiro [4, 5] decyl, 1, 8 diazo-spiro-[5, 4] decyl, 1, 7 diazo-spiro-[5, 4] decyl, 2, 8 diazo-spiro-[5, 4] decyl, 2, 7 diazo-spiro [5, 4] decyl, 3, 8 diazo-spiro [5, 4] decyl, 3, 7 diazo-spiro [5, 4] decyl, 1-azo-7, 11-dioxo-spiro [5, 5]undecyl, 1, 4-diazabicyclo [2.2.2]oct-2-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. Unless otherwise specified, a heterocyclyl group is optionally substituted.

[0033] As used herein, and unless otherwise specified, the term “aryl” refers to a monocyclic aromatic group and/or multicyclic monovalent aromatic group that contain at least one aromatic hydrocarbon ring. In certain embodiments, the aryl has from 6 to 18 ring carbon atoms (C.sub.6-C.sub.15 aryl), from 6 to 14 ring carbon atoms (C.sub.6-C.sub.14 aryl), or from 6 to 10 ring carbon atoms (C.sub.6-C.sub.10 aryl). Examples of aryl groups include, but are not limited to, phenyl, naphthyl, fluorenyl, azulenyl, anthryl, phenanthryl, pyrenyl, biphenyl, and terphenyl. The term “aryl” also refers to bicyclic, tricyclic, or other multicyclic hydrocarbon rings, where at least one of the rings is aromatic and the others of which may be saturated, partially unsaturated, or aromatic, for example, dihydronaphthyl, indenyl, indanyl, or tetrahydronaphthyl (tetralinyl). Unless otherwise specified, an aryl group is optionally substituted.

[0034] As used herein, and unless otherwise specified, the term “heteroaryl” refers to a monocyclic aromatic group and/or multicyclic aromatic group that contains at least one aromatic ring, wherein at least one aromatic ring contains one or more (e.g., one, one or two, one to three, or one to four) heteroatoms independently selected from O, S, and N. The heteroaryl may be attached to the main structure at any heteroatom or carbon atom. In certain embodiments, the heteroaryl has from 5 to 20, from 5 to 15, or from 5 to 10 ring atoms. The term “heteroaryl” also refers to bicyclic, tricyclic, or other multicyclic rings, where at least one of the rings is aromatic and the others of which may be saturated, partially unsaturated, or aromatic, wherein at least one aromatic ring contains one or more heteroatoms independently selected from O, S, and N. Examples of monocyclic heteroaryl groups include, but are not limited to, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, and triazinyl. Examples of bicyclic heteroaryl groups include, but are not limited to, indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indoliziny, benzofuranyl, isobenzofuranyl, chromonyl, coumarinyl, cinnolinyl, quinoxalinyl, indazolyl, purinyl, pyrrolopyridinyl, furopyridinyl, thienopyridinyl, dihydroisoindolyl, and tetrahydroquinolinyl. Examples of tricyclic heteroaryl groups include, but are not limited to, carbazolyl, benzindolyl, phenanthrolinyl, acridinyl, phenanthridinyl, and xanthenyl. Unless otherwise specified, a heteroaryl group is optionally substituted.

[0035] As used herein, and unless otherwise specified, the term “alkylene” or “alkylene chain” refers to a straight or branched multivalent (e.g., divalent or trivalent) hydrocarbon chain linking the rest of the molecule to a radical group (or groups), consisting solely of carbon and hydrogen, which is saturated. In one embodiment, the alkylene has, for example, from one to twenty-four carbon atoms (C.sub.1-C.sub.24 alkylene), one to fifteen carbon atoms (C.sub.1-C.sub.15 alkylene), one to twelve carbon atoms (C.sub.1-C.sub.12 alkylene), one to eight carbon atoms (C.sub.1-C.sub.8 alkylene), one to six carbon atoms (C.sub.1-C.sub.6 alkylene), two to four carbon atoms (C.sub.2-C.sub.4 alkylene), one to two carbon atoms (C.sub.1-C.sub.2 alkylene). Examples

of alkylene groups include, but are not limited to, methylene, ethylene, propylene, n-butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group (s) can be through one carbon or any two (or more) carbons within the chain. Unless otherwise specified, an alkylene chain is optionally substituted.

[0036] As used herein, and unless otherwise specified, the term “alkynylene” is a multivalent (e.g., divalent or trivalent) alkynyl group; the term “cycloalkylene” is a multivalent (e.g., divalent or trivalent) cycloalkyl group; the term “heterocyclylene” is a multivalent (e.g., divalent or trivalent) heterocyclyl group; the term “arylene” is a multivalent (e.g., divalent or trivalent) aryl group; and the term “heteroarylene” is a multivalent (e.g., divalent or trivalent) heteroaryl group. Other “ylene” terms can be constructed similarly from the corresponding “yl” terms.

[0037] It is to be understood that a “yl” term as used herein includes and can be replaced by the corresponding “ylene” term, if proper based on the valence of the group. For example, when a ring moiety of a compound provided herein is described as heterocyclyl, the ring moiety is also heterocyclylene if it is multivalent (e.g., divalent or trivalent), i.e., it is connected to multiple parts of the compound.

[0038] As used herein, and unless otherwise specified, the term “aralkyl” refers to an alkyl moiety, which is substituted by aryl. An example is the benzyl radical. As used herein, and unless otherwise specified, the term “heteroaralkyl” refers to an alkyl moiety, which is substituted by heteroaryl. Unless otherwise specified, the terms for other similar composite moieties can be constructed similarly.

[0039] When the groups described herein are said to be “substituted,” they may be substituted with any appropriate substituent or substituents. Illustrative examples of substituents include, but are not limited to, those found in the exemplary compounds and embodiments provided herein, as well as: a halogen atom such as F, Cl, Br, or I; cyano; oxo (=O); hydroxyl (—OH); alkyl; alkenyl; alkynyl; cycloalkyl; aryl; —(C=O)OR'; —O(C=O)R'; —C(=O)R'; —OR'; —S(O)XR'; —S—SR'; —C(=O)SR'; —SC(=O)R'; —NR'R'; —NR'C(=O)R'; —C(=O)NR'R'; —NR'C(=O)NR'R'; —OC(=O)NR'R'; —NR'C(=O)OR'; —NR'S(O).sub.xNR'R'; —NR'S(O).sub.xR'; and —S(O).sub.xNR'R', wherein: R' is, at each occurrence, independently H, C.sub.1-C.sub.15 alkyl or cycloalkyl, and x is 0, 1 or 2. In some embodiments the substituent is a C.sub.1-C.sub.12 alkyl group. In other embodiments, the substituent is a cycloalkyl group. In other embodiments, the substituent is a halo group, such as fluoro. In other embodiments, the substituent is an oxo group. In other embodiments, the substituent is a hydroxyl group. In other embodiments, the substituent is an alkoxy group (—OR'). In other embodiments, the substituent is a carboxyl group. In other embodiments, the substituent is an amino group (—NR'R').

[0040] As used herein, and unless otherwise specified, the term “optional” or “optionally” (e.g., optionally substituted) means that the subsequently described event or circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, “optionally substituted alkyl” means that the alkyl radical may or may not be substituted and that the description includes both substituted alkyl radicals and alkyl radicals having no substitution.

[0041] As used herein, and unless otherwise specified, the term “halo” or “halogen” refers to a halogen residue selected from the group consisting of F, Cl, Br, and I.

[0042] As used herein, and unless otherwise specified, the term “linker” refers to any chemically suitable linker. In one embodiment, a linker is not or only slowly cleaved under physiological conditions. In one embodiment, the linker does not comprise recognition sequences for proteases or recognition structures for other degrading enzymes. In one embodiment, when the compounds provided herein are administered systemically to allow broad access to all compartments of the body and subsequently enrichment of the compounds provided herein wherever in the body the tumor is located, the linker is chosen in such that it is not or only slowly cleaved in blood. In one

embodiment, the cleavage is considered slowly, if less than 50% of the linkers are cleaved 2 h after administration of the compound to a human patient. Suitable linkers include, but are not limited to, optionally substituted alkyl, heteroalkyl, cycloalkyl, cycloheteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, alkenyl, heteroalkenyl, cycloalkenyl, cycloheteroalkenyl, alkynyl, sulfonyl, amines, ethers, thioethers phosphines, phosphoramidates, carboxamides, esters, imidoesters, amidines, thioesters, sulfonamides, 3-thiopyrrolidine-2, 5-dione, carbamates, ureas, guanidines, thioureas, disulfides, oximes, hydrazines, hydrazides, hydrazones, diaza bonds, triazoles, triazolines, tetrazines, platinum complexes and amino acids, or combinations thereof. In one embodiment, the linker comprises 1, 4-piperazine, 1, 3-propane and a phenolic ether or combinations thereof.

[0043] The linker can also be a cleavable linker such as a peptide motif that is cleaved by cathepsin. Any suitable linker that is cleavable by cathepsin can be used. Certain suitable cleavable peptide linkers are described in Peterson et al., *Bioconjugate Chem.*, 1998. Suitable cleavable linkers, for example, comprises optionally substituted NO<sub>2</sub>-Tyr-Gln-Gly-Val-Gln-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Asn-Gly-Thr-Gly-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Ser-Val-Val-Phe-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Val-Gln-Ser-Ala-Phe, Multiple-Val-Gln-Phe-Val, NO<sub>2</sub>-Tyr-Gly-Val-Phe-Gln-Phe, NO<sub>2</sub>-Tyr-Gly-Thr-Val-Ala-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Ala-Thr-Ala-Phe-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gly-Ser-Val-Gln-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gly-Gly-Gln-Phe-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gln-Ser-Val-Gly-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gly-Ser-Thr-Phe-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gly-Thr-Val-Gln-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gly-Ser-Thr-Phe-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gly-Val-Ala-Gly-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gly-Ser-Thr-Phe-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Ala-Ala-Gly-Thr-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Val-Ala-Gln-Phe, NO<sub>2</sub>-Tyr-Gln-Gly-Val-Gly-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Val-Asn-Asn-Asn-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Ala-Ser-Ala-Asn-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Phe-Gln-Thr-Gln-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Ala-Ala-Ala-Ser-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gln-Tyr-Ser-Gly-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Ala-Ala-Thr-Ala-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Ala-Thr-Gln-Phe-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gln-Ser-Ala-Ser-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gly-Thr-Ser-Phe-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Thr-Ala-Gly-Ala-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Ala-Thr-Thr-Phe-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Ala-Ser-Gly-Ser-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gly-Thr-Thr-Phe-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gly-Ala-Ala-Gly-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gly-Thr-Gln-Phe-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Ala-Ala-Thr-Gly-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gly-Thr-Gln-Phe-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gln-Thr-Val-Gly-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gly-Thr-Gln-Phe-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Ala-Ser-Ala-Gly-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gly-Gln-Ser-Phe-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Thr-Ser-Ala-Thr-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gly-Thr-Val-Ala-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Thr-Ala-Gln-Ala-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gly-Val-Ala-Ala-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Val-Ala-Ser-Ala-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gln-Gly-Ser-Phe-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Thr-Ala-Thr-Asn-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Ala-Thr-Ser-Phe-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Thr-Gly-Val-Gly-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gly-Thr-Ala-Phe-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gln-Val-Ala-Gly-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gly-Ser-Ala-Gln-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Val-Ala-Ala-Gln-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Gln-Thr-Ala-Thr-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Thr-Gly-Tyr-Thr-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Ser-Ala-Gly-Thr-Phe-Lys (Aminobenzoyl), NO<sub>2</sub>-Tyr-Val-Tyr-Tyr-Val-Phe, NO<sub>2</sub>-Tyr-Ala-Ser-Tyr-Gly-Phe, Z-Phe-Lys-PABC, Z-Phe-Lys, Z-Val-Lys-PABC, Z-Ala-Lys-PABC, Phe-Phe-Lys-PABC, D-Phe-Phe-Lys-PABC, D-Ala-Phe-Lys-PABC, Gly-Phe-Lys-PABC, Ac-Phe-Lys-PABC, HCO-Phe-Lys-PABC, Phe-Lys-PABC, Z-Lys-PABC, Z-Val-Cit-PABC, Z-Val-Cit, Z-Phe-Cit-PABC, Z-Leu-Cit-PABC, Z-Ile-Cit-PABC, Z-Trp-Cit-PABC, Z-Phe-Arg (NO<sub>2</sub>)-PABC, and Z-Phe-Arg (Ts)-PABC.



[0044] As used herein, and unless otherwise specified, the term “amino acid” refers to any organic acid containing one or more amino substituents, e.g.,  $\alpha$ -,  $\beta$ - or  $\gamma$ -amino, derivatives of aliphatic carboxylic acids. In the polypeptide notation used herein, e.g., Xaa1Xaa2Xaa3Xaa4Xaa5, wherein Xaa1 to Xaa5 are each and independently selected from amino acids as defined, the left hand direction is the amino terminal direction and the right hand direction is the carboxy terminal direction, in accordance with standard usage and convention.

[0045] As used herein, and unless otherwise specified, the term “conventional amino acid” refers to the twenty naturally occurring amino acids, and encompasses all stereomeric isoforms, i.e., D, L-, D- and L-amino acids thereof. These conventional amino acids can herein also be referred to by their conventional three-letter or one-letter abbreviations and their abbreviations follow conventional usage (see, for example, Immunology-A Synthesis, 2nd Edition, E. S. Golub and D. R. Gren, Eds., Sinauer Associates, Sunderland Mass. (1991)).

[0046] As used herein, and unless otherwise specified, the term “non-conventional amino acid” refers to unnatural amino acids or chemical amino acid analogues, e.g.  $\alpha$ ,  $\alpha$ -disubstituted amino acids, N-alkyl amino acids, homo-amino acids, dehydroamino acids, aromatic amino acids (other than phenylalanine, tyrosine and tryptophan), and ortho-, meta- or para-aminobenzoic acid. Non-conventional amino acids also include compounds which have an amine and carboxyl functional group separated in a 1, 3 or larger substitution pattern, such as  $\beta$ -alanine,  $\gamma$ -amino butyric acid, Freidinger lactam, the bicyclic dipeptide (BTD), amino-methyl benzoic acid and others known in the art. Statine-like isosteres, hydroxyethylene isosteres, reduced amide bond isosteres, thioamide isosteres, urea isosteres, carbamate isosteres, thioether isosteres, vinyl isosteres and other amide bond isosteres known to the art may also be used. The use of analogues or non-conventional amino acids may improve the stability and biological half-life of the added peptide since they are more resistant to breakdown under physiological conditions. The person skilled in the art will be aware of similar types of substitution which may be made. A non-limiting list of non-conventional amino acids which may be used as suitable building blocks for a peptide and their standard abbreviations (in brackets) is as follows:  $\alpha$ -aminobutyric acid (Abu), L-N-methylalanine (Nmala),  $\alpha$ -amino- $\alpha$ -methylbutyrate (Mgabu), L-N-methylarginine (Nmarg), aminocyclopropane (Cpro), L-N-methylasparagine (Nmasn), carboxylate L-N-methylaspartic acid (Nmasp), aninoisobutyric acid (Aib), L-N-methylcysteine (Nmcsys), aminonorbornyl (Norb), L-N-methylglutamine (Nmglu), carboxylate L-N-methylglutamic acid (Nmglu), cyclohexylalanine (Chexa), L-N-methylhistidine (Nmhis), cyclopentylalanine (Cpen), L-N-methylisoleucine (Nmile), L-N-methylleucine (Nmleu), L-N-methyllysine (Nmlys), L-N-methylmethionine (Nmmt), L-N-methylnorleucine (Nmnl), L-N-methylnorvaline (Nmna), L-N-methylornithine (Nmorn), L-N-methylphenylalanine (Nmpe), L-N-methylproline (Nmpro), L-N-methylserine (Nmser), L-N-methylthreonine (Nmthr), L-N-methyltryptophan (Nmtrp), D-ornithine (Dorn), L-N-methyltyrosine (Nmtyr), L-N-methylvaline (Nmval), L-N-methylethylglycine (Nmetg), L-N-methyl-t-butylglycine (Nmbug), L-norleucine (Nle), L-norvaline (Nva),  $\alpha$ -methyl-aminoisobutyrate (Maib),  $\alpha$ -methyl- $\gamma$ -aminobutyrate (Mgabu), D- $\alpha$ -methylalanine (Dmala),  $\alpha$ -methylcyclohexylalanine (Mchexa), D- $\alpha$ -methylarginine (Dmarg),  $\alpha$ -methylcyclopentylalanine (Mcpen), D- $\alpha$ -methylasparagine (Dmasn),  $\alpha$ -methyl- $\alpha$ -naphthylalanine (Manap), D- $\alpha$ -methylaspartate (Dmasp),  $\alpha$ -methylpenicillamine (Mpen), D- $\alpha$ -methylcysteine (Dmcsys), N-(4-aminobutyl) glycine (Nglu), D- $\alpha$ -methylglutamine (Dmgln), N-(2-aminoethyl) glycine (Naeg), D- $\alpha$ -methylhistidine (Dmhis), N-(3-aminopropyl) glycine (Norn), D- $\alpha$ -methylisoleucine (Dmile), N-amino- $\alpha$ -methylbutyrate (Nmaabu), D- $\alpha$ -methylleucine (Dmleu),  $\alpha$ -naphthylalanine (Anap), D- $\alpha$ -methyllysine (Dmlys), N-benzylglycine (Nphe), D- $\alpha$ -methylmethionine (Dmmet), N-(2-carbamylethyl) glycine (Ngjn), D- $\alpha$ -methylornithine (Dmorn), N-(carbamylmethyl) glycine (Nasn), D- $\alpha$ -methylphenylalanine (Dmphe), N-(2-carboxyethyl) glycine (Nglu), D- $\alpha$ -methylproline (Dmpro), N-(carboxymethyl) glycine (Nasp), D- $\alpha$ -methylserine (Dmser), N-cyclobutylglycine (Ncbut), D- $\alpha$ -methylthreonine (Dmthr), N-cycloheptylglycine (Nchep), D- $\alpha$ -methyltryptophan (Dmtrp), N-cyclohexylglycine (Nchex), D- $\alpha$ -methyltyrosine

(Dmty), N-cyclodecylglycine (Ncdec), D- $\alpha$ -methylvaline (Dmval), N-cyclododecylglycine (Ncdod), D-N-methylalanine (Dnmala), N-cyclooctylglycine (Ncoct), D-N-methylarginine (Dnmarg), N-cyclopropylglycine (Nepro), D-N-methylasparagine (Dnmasn), N-cycloundecylglycine (Ncund), D-N-methylaspartate (Dnmasp), N-(2, 2-diphenylethyl) glycine (Nbhm), D-N-methylcysteine (Dnmcys), N-(3, 3-diphenylpropyl) glycine (Nbhe), D-N-methylglutamine (Dnmglu), N-(3-guanidinopropyl) glycine (Narg), D-N-methylglutamate (Dnmglu), N-(1-hydroxyethyl) glycine (Ntbx), D-N-methylhistidine (Dnmhis), N-(hydroxyethyl) glycine (Nser), D-N-methylisoleucine (Dnmile), N-(imidazolylethyl) glycine (Nhis), D-N-methylleucine (Dnmleu), N-(3-indolylethyl) glycine (Nhtrp), D-N-methyllysine (Dnnilys), N-methyl- $\gamma$ -aminobutyrate (Nmgabu), N-methylcyclohexylalanine (Nmchexa), D-N-methylmethionine (Dnmmet), D-N-methylornithine (Dnmorn), N-methylcyclopentylalanine (Nmcpen), N-methylglycine (Nala), D-N-methylphenylalanine (Dnmphe), N-methylaminoisobutyrate (Nmaib), D-N-methylproline (Dnmpro), N-(1-methylpropyl) glycine (Nile), D-N-methylserine (Dnmser), N-(2-methylpropyl) glycine (Nleu), D-N-methylthreonine (Dnmthr), D-N-methyltryptophan (Dnmtrp), N-(1-methylethyl) glycine (Nval), D-N-methyltyrosine (Dnmtyr), N-methyl- $\alpha$ -naphthylalanine (Nmanap), D-N-methylvaline (Dnmval), N-methylpenicillamine (Nmpen),  $\gamma$ -aminobutyric acid (Gabu), N-(p-hydroxyphenyl) glycine (Nhtrp), L-/butylglycine (Tbug), N-(thiomethyl) glycine (Ncys), L-ethylglycine (Etg), penicillamine (Pen), L-homophenylalanine (Hphe), L- $\alpha$ -methylalanine (Mala), L- $\alpha$ -methylarginine (Marg), L- $\alpha$ -methylasparagine (Masn), L- $\alpha$ -methylaspartate (Masp), L- $\alpha$ -methyl-t-butylglycine (Mtbug), L- $\alpha$ -methylcysteine (Mcys), L-methylethylglycine (Metg), L- $\alpha$ -methylglutamine (Mglu), L- $\alpha$ -methylglutamate (Mglu), L- $\alpha$ -methylhistidine (Mhis), L- $\alpha$ -methylhomophenylalanine (Mhphe), L- $\alpha$ -methylisoleucine (Mile), N-(2-methylthioethyl) glycine (Nmet), L- $\alpha$ -methylleucine (Mleu), L- $\alpha$ -methyllysine (Mlys), L- $\alpha$ -methylmethionine (Mmet), L- $\alpha$ -methylnorleucine (Mnle), L- $\alpha$ -methylnorvaline (Mnva), L- $\alpha$ -methylornithine (Mom), L- $\alpha$ -methylphenylalanine (Mphe), L- $\alpha$ -methylproline (Mpro), L- $\alpha$ -methylserine (Mser), L- $\alpha$ -methylthreonine (Mthr), L- $\alpha$ -methyltryptophan (Mtrp), L- $\alpha$ -methyltyrosine (Mtyr), L- $\alpha$ -methylvaline (Mval), L-N-methylhomophenylalanine (Nmhphe), N—(N-(2, 2-diphenylethyl) carbamylmethyl) glycine (Nnbhm), N—(N-(3, 3-diphenylpropyl)-carbamylmethyl) glycine (Nnbhe), 1-carboxy-1-(2, 2-diphenyl-ethylamino) cyclopropane (Nmhc), L-O-methyl serine (Omser), L-O-methyl homoserine (Omhsr).

[0047] As used herein, and unless otherwise specified, the term “radioactive moiety” refers to a molecular assembly which carries a radioactive nuclide. The nuclide is bound either by covalent or coordinate bonds which remain stable under physiological conditions. Examples are [<sup>113</sup>I]-3-iodobenzoic acid or <sup>68</sup>Ga-DOTA.

[0048] As used herein, and unless otherwise specified, the term “fluorescent isotope” refers to an isotope that emits electromagnetic radiation after excitation by electromagnetic radiation of a shorter wavelength.

[0049] As used herein, and unless otherwise specified, the term “radioisotope” is a radioactive isotope of an element (included by the term “radionuclide”) emitting  $\alpha$ -,  $\beta$ -, and/or  $\gamma$ -radiation.

[0050] As used herein, and unless otherwise specified, the term “radioactive drug” refers to a biologic active compound which is modified by a radioisotope. Especially, intercalating substances can be used to deliver the radioactivity to direct proximity of DNA (e.g. a <sup>131</sup>I-carrying derivative of Hoechst-33258).

[0051] As used herein, and unless otherwise specified, the terms “chelating agent” or “chelator” are used interchangeably and refer to a molecule, often an organic one, and often a Lewis base, having two or more unshared electron pairs available for donation to a metal ion. The metal ion is usually coordinated by two or more electron pairs to the chelating agent. The terms “bidentate chelating agent”, “tridentate chelating agent”, and “tetradentate chelating agent” refer to chelating agents having, respectively, two, three, and four electron pairs readily available for simultaneous donation

to a metal ion coordinated by the chelating agent. Usually, the electron pairs of a chelating agent forms coordinate bonds with a single metal ion; however, in certain examples, a chelating agent may form coordinate bonds with more than one metal ion, with a variety of binding modes being possible.

[0052] As used herein, and unless otherwise specified, the term “fluorescent dye” refers to a compound that emits visible or infrared light after excitation by electromagnetic radiation of a shorter and suitable wavelength. It is understood by the skilled person that each fluorescent dye has a predetermined excitation wavelength.

[0053] As used herein, and unless otherwise specified, the term “contrast agent” refers to a compound which increases the contrast of structures or fluids in medical imaging. The enhancement is achieved by absorbing electromagnetic radiation or altering electromagnetic fields.

[0054] As used herein, and unless otherwise specified, the term “paramagnetic” refers to paramagnetism induced by unpaired electrons in a medium. A paramagnetic substance induces a magnetic field if an external magnetic field is applied. Unlike diamagnetism the direction of the induced field is the same as the external field and unlike ferromagnetism the field is not maintained in absence of an external field.

[0055] As used herein, and unless otherwise specified, the term “nanoparticle” as used herein refers to particles, such as particles of spheric shape, with diameters of sizes between 1 and 100 nanometers. Depending on the composition, nanoparticles can possess magnetical, optical or physico-chemical qualities that can be assessed. Additionally surface modification is achievable for many types of nanoparticles.

[0056] As used herein, and unless otherwise specified, a “pharmaceutically acceptable salt” includes both acid and base addition salts. Suitable pharmaceutically acceptable salts of the compound provided herein include acid addition salts which may, for example, be formed by mixing a solution of choline or derivative thereof with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compound provided herein carries an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts (e.g., sodium or potassium salts); alkaline earth metal salts (e.g., calcium or magnesium salts); and salts formed with suitable organic ligands (e.g., ammonium, quaternary ammonium and amine cations formed using counter anions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl sulfonate and aryl sulfonate). Illustrative examples of pharmaceutically acceptable salts include but are not limited to: acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium edetate, camphorate, camphor sulfonate, camsylate, carbonate, chloride, citrate, clavulanate, cyclopentane propionate, digluconate, dihydrochloride, dodecylsulfate, edetate, edisylate, estolate, esylate, ethanesulfonate, formate, fumarate, gluceptate, glucoheptonate, gluconate, glutamate, glycerophosphate, glycolylarsanilate, hemisulfate, heptanoate, hexanoate, hexylresorcinolate, hydrabamine, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, lauryl sulfate, malate, maleate, malonate, mandelate, mesylate, methanesulfonate, methylsulfate, mucate, 2-naphthalenesulfonate, napsylate, nicotinate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, pectinate, persulfate, 3-phenylpropionate, phosphate/diphosphate, picrate, pivalate, polygalacturonate, propionate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, undecanoate, valerate, and the like (see, for example, Berge, S. M., et al, “Pharmaceutical Salts”, Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds provided herein contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0057] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the

compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes provided herein.

[0058] In addition to salt forms, also provided herein are compounds that are in a prodrug form. Prodrugs of a compound readily undergoes chemical changes under physiological conditions to provide the compound. A prodrug is an active or inactive compound that is modified chemically through in vivo physiological action, such as hydrolysis, metabolism and the like, into a compound provided herein following administration of the prodrug to a patient. Additionally, prodrugs can be converted to the compounds provided herein by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compounds provided herein when placed in a transdermal patch reservoir with a suitable enzyme. The suitability and techniques involved in making and using prodrugs are known by those skilled in the art. For a general discussion of prodrugs involving esters see Svensson and Tunek *Drug Metabolism Reviews* 16.5 (1988) and Bundgaard *Design of Prodrugs*, Elsevier (1985). Examples of a masked carboxylate anion include a variety of esters, such as alkyl (for example, methyl, ethyl), cycloalkyl (for example, cyclohexyl), aralkyl (for example, benzyl, p-methoxybenzyl), and alkylcarbonyloxyalkyl (for example, pivaloyloxymethyl). Amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases in vivo releasing the free drug and formaldehyde (Bundgaard *J. Med. Chem.* 2503 (1989)). Also, drugs containing an acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard *Design of Prodrugs*, Elsevier (1985)). Hydroxyl groups have been masked as esters and ethers. EP 0 039 051 (Sloan and Little, Apr. 11, 1981) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

[0059] Compounds provided herein can be synthesized according to one or more of the methods/examples provided herein. It should be noted that the general procedures may be shown as it relates to preparation of compounds having unspecified stereochemistry. However, such procedures are generally applicable to those compounds of a specific stereochemistry, e.g., where the stereochemistry about a group is (S) or (R). In addition, the compounds having one stereochemistry (e.g., (R)) can often be utilized to produce those having opposite stereochemistry (i.e., (S)) using well-known methods, for example, by inversion.

[0060] Certain compounds provided herein possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are intended to be encompassed within the scope of this application.

[0061] The compounds provided herein may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (<sup>3</sup>H), iodine-125 (<sup>sup</sup>.125I) or carbon-14 (<sup>sup</sup>.14C). All isotopic variations of the compounds provided herein, whether radioactive or not, are intended to be encompassed within the scope of this application.

[0062] As used herein, and unless otherwise specified, the term “pharmaceutical composition” refers to a substance and/or a combination of substances being used for the identification, prevention or treatment of a tissue status or disease. The pharmaceutical composition is formulated to be suitable for administration to a patient in order to prevent and/or treat disease. Further a pharmaceutical composition refers to the combination of an active agent with a carrier, inert or active, making the composition suitable for therapeutic use. Pharmaceutical compositions can be formulated for oral, parenteral, topical, inhalative, rectal, sublingual, transdermal, subcutaneous or vaginal application routes according to their chemical and physical properties. Pharmaceutical compositions comprise solid, semisolid, liquid, transdermal therapeutic systems (TTS). Solid compositions are selected from the group consisting of tablets, coated tablets, powder, granulate, pellets, capsules, effervescent tablets or transdermal therapeutic systems. Also comprised are liquid compositions, selected from the group consisting of solutions, syrups, infusions, extracts, solutions

for intravenous application, solutions for infusion or solutions of the carrier systems provided herein. Semisolid compositions provided herein comprise emulsion, suspension, creams, lotions, gels, globules, buccal tablets and suppositories.

[0063] As used herein, and unless otherwise specified, the term “pharmaceutically acceptable” means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

[0064] As used herein, and unless otherwise specified, the term “carrier” or “excipient”, as used herein, refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic agent is administered. Such pharmaceutical carriers can be sterile liquids, such as saline solutions in water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. A saline solution is a carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. Examples of suitable pharmaceutical carriers are described in “Remington's Pharmaceutical Sciences” by E. W. Martin.

[0065] As used herein, and unless otherwise specified, the term “cytotoxic effect” refers to the depletion, elimination and/or the killing of a target cell (s). As used herein, and unless otherwise specified, the term “cytotoxic agent” refers to an agent that has a cytotoxic and/or cytostatic effect on a cell. The term is intended to include chemotherapeutic agents, and toxins such as enzymatically active toxins of bacterial, fungal, plant, or animal origin, and fragments thereof. As used herein, and unless otherwise specified, the term “cytostatic effect” refers to the inhibition of cell proliferation. As used herein, and unless otherwise specified, the term “cytostatic agent” refers to an agent that has a cytostatic effect on a cell, thereby inhibiting the growth and/or expansion of a specific subset of cells.

[0066] As used herein, and unless otherwise specified, the term “cytokine” refers to small proteins (~5-20 kDa) that are involved in autocrine signaling, paracrine signaling and endocrine signaling as immunomodulating agents. Cytokines include chemokines, interferons, interleukins, lymphokines, and tumor necrosis factors but generally not hormones or growth factors.

[0067] As used herein, and unless otherwise specified, the term “immunomodulatory molecule” refers to substance that stimulates or suppresses the immune system and may help the body fight cancer, infection, or other diseases. Specific immunomodulating molecules can be monoclonal antibodies, cytokines, and vaccines, which affect specific parts of the immune system.

[0068] As used herein, and unless otherwise specified, the term “amphiphilic substance” refers to compounds with both hydrophilic and lipophilic properties. Common amphiphilic substances are phospholipids, cholesterol, glycolipids, fatty acids, bile acids, saponins, pediocins, local anesthetics, Ab proteins and antimicrobial peptides.

[0069] As used herein, and unless otherwise specified, the term “protein” and “polypeptide” are used interchangeably herein and refer to any peptide-bond-linked chain of amino acids, regardless of length or post-translational modification. In one embodiment, the amino acid is any of the amino acids provided herein. Proteins provided herein (including protein derivatives, protein variants, protein fragments, protein segments, protein epitopes and protein domains) can be further modified by chemical modification. This means such a chemically modified polypeptide comprises other chemical groups than the 20 naturally occurring amino acids. Examples of such other chemical groups include without limitation glycosylated amino acids and phosphorylated amino acids. Chemical modifications of a polypeptide may provide advantageous properties as compared to the

parent polypeptide, e.g., one or more of enhanced stability, increased biological half-life, or increased water solubility.

[0070] As used herein, and unless otherwise specified, the terms “nucleic acid” and “polynucleotide” are used interchangeably herein and refer to polymeric or oligomeric macromolecules, or large biological molecules, essential for all known forms of life. Nucleic acids, which include DNA (deoxyribonucleic acid) and RNA (ribonucleic acid), are made from monomers known as nucleotides. Most naturally occurring DNA molecules consist of two complementary biopolymer strands coiled around each other to form a double helix. The DNA strand is also known as polynucleotides consisting of nucleotides. Each nucleotide is composed of a nitrogen-containing nucleobase as well as a monosaccharide sugar called deoxyribose or ribose and a phosphate group. Naturally occurring nucleobases comprise guanine (G), adenine (A), thymine (T), uracil (U) or cytosine (C). The nucleotides are joined to one another in a chain by covalent bonds between the sugar of one nucleotide and the phosphate of the next, resulting in an alternating sugar-phosphate backbone. If the sugar is desoxyribose, the polymer is DNA. If the sugar is ribose, the polymer is RNA. Typically, a polynucleotide is formed through phosphodiester bonds between the individual nucleotide monomers. As used herein, and unless otherwise specified, the term “nucleic acid” includes but is not limited to ribonucleic acid (RNA), deoxyribonucleic acid (DNA), and mixtures thereof such as RNA-DNA hybrids (within one strand), as well as cDNA, genomic DNA, recombinant DNA, crRNA and mRNA. A nucleic acid may consist of an entire gene, or a portion thereof, the nucleic acid may also be a miRNA, siRNA, piRNA or shRNA. miRNAs are short ribonucleic acid (RNA) molecules, which are on average 22 nucleotides long but may be longer and which are found in all eukaryotic cells, i.e., in plants, animals, and some viruses, which functions in transcriptional and post-transcriptional regulation of gene expression. miRNAs are post-transcriptional regulators that bind to complementary sequences on target messenger RNA transcripts (mRNAs), usually resulting in translational repression and gene silencing. Small interfering RNAs (siRNAs), sometimes known as short interfering RNA or silencing RNA, are short ribonucleic acid (RNA molecules), between 20-25 nucleotides in length. They are involved in the RNA interference (RNAi) pathway, where they interfere with the expression of specific genes. A short hairpin RNA (shRNA) or small hairpin RNA (shRNA) is an artificial RNA molecule with a tight hairpin turn that can be used to silence target gene expression via RNA interference (RNAi). Expression of shRNA in cells is typically accomplished by delivery of plasmids or through viral or bacterial vectors. piRNAs are also short RNAs which usually comprise 26-31 nucleotides and derive their name from so-called piwi proteins they are binding to. The nucleic acid can also be an artificial nucleic acid. Artificial nucleic acids include polyamide or peptide nucleic acid (PNA), morpholino and locked nucleic acid (LNA), as well as glycol nucleic acid (GNA) and threose nucleic acid (TNA). Each of these is distinguished from naturally-occurring DNA or RNA by changes to the backbone of the molecule. The nucleic acids, can, e.g., be synthesized chemically, e.g., in accordance with the phosphotriester method (see, for example, Uhlmann, E. & Peyman, A. (1990) Chemical Reviews, 90, 543-584).

[0071] As used herein, and unless otherwise specified, the term “viral structural protein” (VSP) refers to viral coat proteins (VCP) or viral envelope glycoproteins (VEG). As used herein, and unless otherwise specified, the term “viral coat protein” (VCP) refers to a structural virus capsid protein of a virus. In one embodiment, the virus is a double-stranded DNA virus, single-stranded DNA virus, double-stranded RNA virus, single-stranded RNA virus, negative-sense single-stranded RNA virus, single-stranded RNA reverse transcribing virus, double-stranded RNA reverse transcribing virus. The VCP can comprise major capsid proteins of adeno-associated virus (AAV).

[0072] As used herein, and unless otherwise specified, the term “viral envelope glycoproteins” (VEG) refers to viral proteins that are part of the viral envelope. The viral envelope is typically derived from portions of the host cell membrane, e.g., comprises phospholipids, and additionally comprise viral glycoproteins that, e.g., help the virus to avoid the immune system. Enveloped

viruses comprise DNA viruses, such as Herpesviruses, Poxviruses, and Hepadnaviruses; RNA viruses, such as Flavivirus, Togavirus, Coronavirus, Hepatitis D, Orthomyxovirus, Paramyxovirus, Rhabdovirus, Bunyavirus, Filovirus and Retroviruses. In one embodiment, the viral envelop glycoprotein is derived from any of these viruses.

[0073] As used herein, and unless otherwise specified, the term “liposome” refers to uni- or multilamellar (e.g., 2, 3, 4, 5, 6, 7, 8, 9, and 10 lamellar) lipid structures enclosing an aqueous interior, depending on the number of lipid membranes formed. Lipids, which are capable of forming a liposomes include all substances having fatty or fat-like properties. Such lipids comprise an extended apolar residue (X) and usually a water soluble, polar, hydrophilic residue (Y), which can be characterized by the basic formula

$X-Y_n$  [0074] wherein n equals or is greater than zero. Lipids with  $n=0$  are termed “apolar lipids”, while lipids with  $n>1$  are referred to as “polar lipids”. In one embodiment, lipids, which can make up the lipids in the liposomes provided herein are selected from the group consisting of glycerides, glycerophospholipids, sulfolipids, sphingolipids, phospholipids, isoprenolides, steroids, stearines, sterols and carbohydrate containing lipids.

[0075] A virus like particle (VLP) is a multimer of VSP, such as VCPs and/or VEPs that does not comprise polynucleotides but which otherwise has properties of a virus, e.g., binds to cell surface receptors, is internalized with the receptor, is stable in blood, and/or comprises glycoproteins etc. VLPs are typically assembled of multimers of VCPs and/or VEPs, in particular of VCPs. VLPs are known in the art and have been produced from a number of viruses including Parvoviridae (e.g., adeno-associated virus), Retroviridae (e.g., HIV), Flaviviridae (e.g., Hepatitis C virus) and bacteriophages (e.g., QP, AP205).

[0076] As used herein, and unless otherwise specified, the term “fibroblast activation protein (FAP)” “as used herein is also known under the term “seprase”. Both terms can be used interchangeably herein. Fibroblast activation protein is a homodimeric integral protein with dipeptidyl peptidase IV (DPPIV)-like fold, featuring an alpha/beta-hydrolase domain and an eight-bladed beta-propeller domain.

[0077] It should be noted that if there is a discrepancy between a depicted structure and a name for that structure, the depicted structure is to be accorded more weight.

## COMPOUNDS

[0078] In one embodiment, provided herein is a compound of Formula (I):

##STR00002## [0079] wherein: [0080] R<sup>sup.1</sup> is —H, —CN, —B(OH)<sub>sub.2</sub>, —(C=O)-alkyl, —(C=O)-aryl-, —C=C—(C=O)-aryl, —C=C—S(O)<sub>sub.2</sub>-aryl, —CO<sub>sub.2</sub>H, —SO<sub>sub.3</sub>H, —SO<sub>sub.2</sub>NH<sub>sub.2</sub>, —SO<sub>sub.2</sub>F, —PO<sub>sub.3</sub>H<sub>sub.2</sub>, or 5-tetrazolyl; [0081] each of Q<sup>sup.1</sup> to Q<sup>sup.7</sup> is independently absent, O, C(R<sup>sup.5</sup>)<sub>sub.2</sub>, NR<sup>sup.5</sup>, C=O, C=S, or 3- to 10-membered N-containing heterocyclyl, provided that (i) two O are not directly adjacent to each other, and (ii) at least three of Q<sup>sup.1</sup> to Q<sup>sup.7</sup> are present; [0082] Ring C is 1-naphthyl, 5- to 10-membered N-containing heteroaryl, or 5- to 10-membered N-containing heterocyclyl; [0083] each instance of R<sup>sup.2</sup>, R<sup>sup.3</sup>, or R<sup>sup.4</sup> is independently —OH, halo, C<sub>sub.1</sub>-C<sub>sub.6</sub> alkyl, —O—(C<sub>sub.1</sub>-C<sub>sub.6</sub> alkyl), —N(R<sup>sup.5</sup>)<sub>sub.2</sub>, or —S—(C<sub>sub.1</sub>-C<sub>sub.6</sub> alkyl), each of said C<sub>sub.1</sub>-C<sub>sub.6</sub> alkyl being independently and optionally substituted with one or more substituents independently selected from —OH, oxo, and halo; [0084] X<sup>sup.1</sup> is absent, O, NR<sup>sup.5</sup>, S, C=O, C=S, —(C=O)—NR<sup>sup.5</sup>—\*, —(C=S)—NR<sup>sup.5</sup>—\*, —O-aryl—\*, —NR<sup>sup.5</sup>-aryl—\*, —(C=O)—NR<sup>sup.5</sup>-aryl—\*, —(C=S)—NR<sup>sup.5</sup>-aryl—\*, wherein \* refers to the direction toward Ring C; [0085] G<sup>sup.1</sup> is absent, C<sub>sub.1</sub>-C<sub>sub.5</sub> alkylene, or C<sub>sub.2</sub>-C<sub>sub.5</sub> alkynylene, wherein said C<sub>sub.1</sub>-C<sub>sub.5</sub> alkylene and C<sub>sub.2</sub>-C<sub>sub.5</sub> alkynylene are optionally substituted with one or more substituents independently selected from —OH, oxo, halo, C<sub>sub.1</sub>-C<sub>sub.3</sub> alkyl optionally substituted with one or more halo, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl; [0086] each instance of X is independently absent, O, NR<sup>sup.5</sup>, C=O, C=S, —

(C=O)—NR.sup.5—\*, —NR.sup.5—(C=O)—\*, —(C=S)—NR.sup.5—\*, or —NR.sup.5—(C=S)—\*, wherein \* refers to the direction toward Ring C; [0087] each instance of G is independently absent, C.sub.1-C.sub.5 alkylene, or C.sub.2-C.sub.5 alkynylene, wherein said C.sub.1-C.sub.5 alkylene and C.sub.2-C.sub.5 alkynylene are optionally substituted with one or more substituents independently selected from —OH, oxo, halo, C.sub.1-C.sub.3 alkyl optionally substituted with one or more halo, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl; [0088] each instance of Ring B is absent, C.sub.3-C.sub.10 cycloalkyl, C.sub.6-C.sub.10 aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl; [0089] X.sup.2 is absent, O, NR.sup.5, C=O, C=S, —(C=O)—NR.sup.5—\*, —NR.sup.5—(C=O)—\*, —(C=S)—NR.sup.5—\*, or —NR.sup.5—(C=S)—\*, wherein \* refers to the direction toward Ring C; [0090] L is absent or a linker; [0091] Ring A is absent, 5 to 10-membered N-containing heteroaryl or 5 to 10-membered N-containing heterocyclyl; [0092] provided that G.sup.1, at least one G, at least one Ring B, Ring A, or L is present; [0093] n is 0, 1, 2, or 3; [0094] m is 0, 1, 2, or 3; [0095] p is 0, 1, 2, or 3; [0096] s is 0, 1, 2, or 3; [0097] each instance of R.sup.5 is independently —H or C.sub.1-C.sub.6 alkyl optionally substituted with one or more substituents independently selected from —OH, oxo, and halo; and [0098] Z is a radioactive moiety, a chelating agent, a fluorescent dye, or a contrast agent; or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

[0099] In one embodiment, at least three of Q.sup.1 to Q.sup.7 are present. In one embodiment, exactly three of Q.sup.1 to Q.sup.7 are present. In one embodiment, at least four of Q.sup.1 to Q.sup.7 are present. In one embodiment, exactly four of Q.sup.1 to Q.sup.7 are present. In one embodiment, at least five of Q.sup.1 to Q.sup.7 are present. In one embodiment, exactly five of Q.sup.1 to Q.sup.7 are present. In one embodiment, at least six of Q.sup.1 to Q.sup.7 are present. In one embodiment, exactly six of Q.sup.1 to Q.sup.7 are present. In one embodiment, all of Q.sup.1 to Q.sup.7 are present.

[0100] In one embodiment, Q.sup.1 is absent. In one embodiment, Q.sup.1 is O. In one embodiment, Q.sup.1 is C(R.sup.5).sub.2. In one embodiment, Q.sup.1 is CH.sub.2. In one embodiment, Q.sup.1 is NR.sup.5. In one embodiment, Q.sup.1 is NH. In one embodiment, Q.sup.1 is C=O. In one embodiment, Q.sup.1 is C=S. In one embodiment, Q.sup.1 is 3- to 10-membered N-containing heterocyclyl. In one embodiment, Q.sup.1 is 5- to 6-membered N-containing heterocyclyl. In one embodiment, the heterocyclyl is heterocycloalkyl. In one embodiment, Q.sup.1 is azetidin-1-yl. In one embodiment, Q.sup.1 is pyrrolidin-1-yl. In one embodiment, Q.sup.1 is piperidin-1-yl. In one embodiment, Q.sup.1 is azepan-1-yl. In one embodiment, Q.sup.1 is azocan-1-yl. The point of attachment for these groups is toward the direction of the fused pyrrolidine ring bearing R.sup.1.

[0101] In one embodiment, Q.sup.2 is absent. In one embodiment, Q.sup.2 is O. In one embodiment, Q.sup.2 is C(R.sup.5).sub.2. In one embodiment, Q.sup.2 is CH.sub.2. In one embodiment, Q.sup.2 is NR.sup.5. In one embodiment, Q.sup.2 is NH. In one embodiment, Q.sup.2 is C=O. In one embodiment, Q.sup.2 is C=S. In one embodiment, Q.sup.2 is 3- to 10-membered N-containing heterocyclyl. In one embodiment, Q.sup.2 is 5- to 6-membered N-containing heterocyclyl. In one embodiment, the heterocyclyl is heterocycloalkyl. In one embodiment, Q.sup.2 is azetidin-1-yl. In one embodiment, Q.sup.2 is pyrrolidin-1-yl. In one embodiment, Q.sup.2 is piperidin-1-yl. In one embodiment, Q.sup.2 is azepan-1-yl. In one embodiment, Q.sup.2 is azocan-1-yl. The point of attachment for these groups is toward the direction of the fused pyrrolidine ring bearing R.sup.1.

[0102] In one embodiment, Q.sup.3 is absent. In one embodiment, Q.sup.3 is O. In one embodiment, Q.sup.3 is C(R.sup.5).sub.2. In one embodiment, Q.sup.3 is CH.sub.2. In one embodiment, Q.sup.3 is NR.sup.5. In one embodiment, Q.sup.3 is NH. In one embodiment, Q.sup.3 is C=O. In one embodiment, Q.sup.3 is C=S. In one embodiment, Q.sup.3 is 3- to 10-membered N-containing heterocyclyl. In one embodiment, Q.sup.3 is 5- to 6-membered N-



containing heterocyclyl. In one embodiment, the heterocyclyl is heterocycloalkyl. In one embodiment, Q.sup.3 is azetidin-1-yl. In one embodiment, Q.sup.3 is pyrrolidin-1-yl. In one embodiment, Q.sup.3 is piperidin-1-yl. In one embodiment, Q.sup.3 is azepan-1-yl. In one embodiment, Q.sup.3 is azocan-1-yl. The point of attachment for these groups is toward the direction of the fused pyrrolidine ring bearing R.sup.1.

[0103] In one embodiment, Q.sup.4 is absent. In one embodiment, Q.sup.4 is O. In one embodiment, Q.sup.4 is C(R.sup.5).sub.2. In one embodiment, Q.sup.4 is CH.sub.2. In one embodiment, Q.sup.4 is NR.sup.5. In one embodiment, Q.sup.4 is NH. In one embodiment, Q.sup.4 is C=O. In one embodiment, Q.sup.4 is C=S. In one embodiment, Q.sup.4 is 3- to 10-membered N-containing heterocyclyl. In one embodiment, Q.sup.4 is 5- to 6-membered N-containing heterocyclyl. In one embodiment, the heterocyclyl is heterocycloalkyl. In one embodiment, Q.sup.4 is azetidin-1-yl. In one embodiment, Q.sup.4 is pyrrolidin-1-yl. In one embodiment, Q.sup.4 is piperidin-1-yl. In one embodiment, Q.sup.4 is azepan-1-yl. In one embodiment, Q.sup.4 is azocan-1-yl. The point of attachment for these groups is toward the direction of the fused pyrrolidine ring bearing R.sup.1.

[0104] In one embodiment, Q.sup.5 is absent. In one embodiment, Q.sup.5 is O. In one embodiment, Q.sup.5 is C(R.sup.5).sub.2. In one embodiment, Q.sup.5 is CH.sub.2. In one embodiment, Q.sup.5 is NR.sup.5. In one embodiment, Q.sup.5 is NH. In one embodiment, Q.sup.5 is C=O. In one embodiment, Q.sup.5 is C=S. In one embodiment, Q.sup.5 is 3- to 10-membered N-containing heterocyclyl. In one embodiment, Q.sup.5 is 5- to 6-membered N-containing heterocyclyl. In one embodiment, the heterocyclyl is heterocycloalkyl. In one embodiment, Q.sup.5 is azetidin-1-yl. In one embodiment, Q.sup.5 is pyrrolidin-1-yl. In one embodiment, Q.sup.5 is piperidin-1-yl. In one embodiment, Q.sup.5 is azepan-1-yl. In one embodiment, Q.sup.5 is azocan-1-yl. The point of attachment for these groups is toward the direction of the fused pyrrolidine ring bearing R.sup.1.

[0105] In one embodiment, Q.sup.6 is absent. In one embodiment, Q.sup.6 is O. In one embodiment, Q.sup.6 is C(R.sup.5).sub.2. In one embodiment, Q.sup.6 is CH.sub.2. In one embodiment, Q.sup.6 is NR.sup.5. In one embodiment, Q.sup.6 is NH. In one embodiment, Q.sup.6 is C=O. In one embodiment, Q.sup.6 is C=S. In one embodiment, Q.sup.6 is 3- to 10-membered N-containing heterocyclyl. In one embodiment, Q.sup.6 is 5- to 6-membered N-containing heterocyclyl. In one embodiment, the heterocyclyl is heterocycloalkyl. In one embodiment, Q.sup.6 is azetidin-1-yl. In one embodiment, Q.sup.6 is pyrrolidin-1-yl. In one embodiment, Q.sup.6 is piperidin-1-yl. In one embodiment, Q.sup.6 is azepan-1-yl. In one embodiment, Q.sup.6 is azocan-1-yl. The point of attachment for these groups is toward the direction of the fused pyrrolidine ring bearing R.sup.1.

[0106] In one embodiment, Q.sup.7 is absent. In one embodiment, Q.sup.7 is O. In one embodiment, Q.sup.7 is C(R.sup.5).sub.2. In one embodiment, Q.sup.7 is CH.sub.2. In one embodiment, Q.sup.7 is NR.sup.5. In one embodiment, Q.sup.7 is NH. In one embodiment, Q.sup.7 is C=O. In one embodiment, Q.sup.7 is C=S. In one embodiment, Q.sup.7 is 3- to 10-membered N-containing heterocyclyl. In one embodiment, Q.sup.7 is 5- to 6-membered N-containing heterocyclyl. In one embodiment, the heterocyclyl is heterocycloalkyl. In one embodiment, Q.sup.7 is azetidin-1-yl. In one embodiment, Q.sup.7 is pyrrolidin-1-yl. In one embodiment, Q.sup.7 is piperidin-1-yl. In one embodiment, Q.sup.7 is azepan-1-yl. In one embodiment, Q.sup.7 is azocan-1-yl. The point of attachment for these groups is toward the direction of the fused pyrrolidine ring bearing R.sup.1.

[0107] In one embodiment, at least four of Q.sup.1 to Q.sup.7 are present, wherein two are C=O, one is CH.sub.2 and one is NH. In one embodiment, exactly four of Q.sup.1 to Q.sup.7 are present, wherein two are C=O, one is CH.sub.2, and one is NH. In one embodiment, Q.sup.4 to Q.sup.7 are present, wherein Q.sup.4 and Q.sup.7 are C=O, and Q.sup.1 and Q.sup.6 are independently CH.sub.2 or NH.

[0108] In one embodiment, Q.sup.1, Q.sup.2, and Q.sup.3 are each independently absent or CH.sub.2; Q.sup.4 is CH.sub.2, C=O, or C=S; Q.sup.1 is NR.sup.5; Q.sup.6 is CHR.sup.5; and Q.sup.7 is C=O, or C=S. In one embodiment, -Q.sup.4-Q.sup.5-Q.sup.6-Q.sup.7- (in the same direction) is —(C=O)—NH—CH.sub.2—(C=O)—. In one embodiment, -Q.sup.1-Q.sup.2-Q.sup.3-Q.sup.4-Q.sup.5-Q.sup.6-Q.sup.7- (in the same direction) is —(C=O)—NH—CH.sub.2—(C=O)—.

[0109] In one embodiment, Q.sup.1, Q.sup.2, Q.sup.3, and Q.sup.4 are each independently absent or CH.sub.2; Q.sup.5 is 5- to 6-membered N-containing heterocyclyl; Q.sup.6 is CHR.sup.5; and Q.sup.7 is C=O or C=S. In one embodiment, Q.sup.1 is O or NR.sup.5, and -Q.sup.2-Q.sup.3-Q.sup.4-Q.sup.5-Q.sup.6-Q.sup.7- is

##STR00003##

wherein \* refers to the direction toward Ring C. In one embodiment, Q.sup.1 is O, and -Q.sup.2-Q.sup.3-Q.sup.4-Q.sup.5-Q.sup.6-Q.sup.7- is

##STR00004##

In one embodiment, Q.sup.1 is O, and -Q.sup.2-Q.sup.3-Q.sup.4-Q.sup.5-Q.sup.6-Q.sup.7- is

##STR00005##

In one embodiment, Q.sup.1 is NH and -Q.sup.2-Q.sup.3-Q.sup.4-Q.sup.5-Q.sup.6-Q.sup.7- is

##STR00006##

In one embodiment, Q.sup.1 is NH and -Q.sup.2-Q.sup.3-Q.sup.4-Q.sup.5-Q.sup.6-Q.sup.7- is

##STR00007##

[0110] In one embodiment, Ring C is 1-naphthyl.

[0111] In one embodiment, Ring C is 5- to 10-membered N-containing heteroaryl. In one embodiment, Ring C is 5-membered N-containing heteroaryl. In one embodiment, Ring C is pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, 1, 2, 3-triazolyl, or 1, 2, 4-triazolyl. In one embodiment, Ring C is 6-membered N-containing heteroaryl. In one embodiment, Ring C is pyridyl, pyrimidinyl, pyridazinyl, or triazinyl. In one embodiment, the 5- or 6-membered N-containing heteroaryl is fused to a phenyl or another 5- or 6-membered N-containing heteroaryl. In one embodiment, Ring C is quinolinyl, 1, 8-naphthyridinyl, pyrido [2, 3-b] pyrazinyl, or quinazolinyl. In one embodiment, Ring C is quinolinyl.

[0112] In one embodiment, Ring C is 5- to 10-membered N-containing heterocyclyl. In one embodiment, Ring C is 5-membered N-containing heterocyclyl. In one embodiment, Ring C is pyrrolidinyl. In one embodiment, Ring C is 6-membered N-containing heterocyclyl. In one embodiment, Ring C is piperidinyl. In one embodiment, the 5- or 6-membered N-containing heterocyclyl is fused to a phenyl or another 5- or 6-membered N-containing heteroaryl. In one embodiment, Ring C is 1, 2, 3, 4-tetrahydroquinolinyl.

[0113] In one embodiment, there are two ring atoms between the ring atom of Ring C two which Q.sup.1 is attached and a nitrogen atom of Ring C.

[0114] In one embodiment, Ring C is N

##STR00008##

[0115] In one embodiment, Ring C is

##STR00009##

wherein the shown point of attachment is toward Q.sup.1.

[0116] In one embodiment, Ring C is

##STR00010##

wherein the shown point of attachment is toward Q.sup.1.

[0117] In one embodiment, X.sup.1 is absent, O, NRS, S, C=O, C=S, —(C=O)—NR.sup.5—\*, —(C=S)—NR.sup.5—\*, —O-aryl—\*, —NR.sup.5-aryl—\*, —(C=O)—NR.sup.5-aryl—\*, —(C=S)—NR.sup.5-aryl—\*, wherein \* refers to the direction toward Ring C. In one embodiment, X.sup.1 is absent. In one embodiment, X.sup.1 is O. In one embodiment, X.sup.1 is NR.sup.5. In one embodiment, X.sup.1 is NH. In one embodiment, X.sup.1 is N(CH.sub.3). In one embodiment,

X.sup.1 is  $\text{---}(\text{C}=\text{O})\text{NR.sup.5---}^*$ . In one embodiment, X.sup.1 is  $\text{---}(\text{C}=\text{O})\text{NH---}^*$ .

[0118] In one embodiment, G.sup.1 is absent. In one embodiment, G.sup.1 is C.sub.1-C.sub.5 alkylene. In one embodiment, G.sup.1 is C.sub.2-C.sub.5 alkylene. In one embodiment, G.sup.1 is C.sub.1 alkylene. In one embodiment, G.sup.1 is C.sub.2 alkylene. In one embodiment, G.sup.1 is C.sub.3 alkylene. In one embodiment, G.sup.1 is C.sub.4 alkylene. In one embodiment, G.sup.1 is C.sub.5 alkylene. In one embodiment, G.sup.1 is C.sub.2-C.sub.5 alkynylene. In one embodiment, G.sup.1 is C.sub.2 alkynylene. In one embodiment, G.sup.1 is C.sub.3 alkynylene. In one embodiment, G.sup.1 is C.sub.4 alkynylene. In one embodiment, G.sup.1 is C.sub.5 alkynylene. In one embodiment, G.sup.1 is unsubstituted. In one embodiment, G.sup.1 is substituted with one or more substituents independently selected from  $\text{---OH}$ , oxo, halo, C.sub.1-C.sub.3 alkyl optionally substituted with one or more halo, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl. In one embodiment, G.sup.1 is substituted with one or more halo (e.g., one or more fluoro).

[0119] In one embodiment, s is 0. In one embodiment, s is 1. In one embodiment, s is 2. In one embodiment, s is 3.

[0120] In one embodiment, X.sup.2 is absent, O, NR.sup.5, C=O, C=S,  $\text{---}(\text{C}=\text{O})\text{---NR.sup.5---}^*$ ,  $\text{---NR.sup.5---}(\text{C}=\text{O})\text{---}^*$ ,  $\text{---}(\text{C}=\text{S})\text{---NR.sup.5---}^*$ , or  $\text{---NR.sup.5---}(\text{C}=\text{S})\text{---}^*$ , wherein \* refers to the direction toward Ring C. In one embodiment, X.sup.2 is absent. In one embodiment, X.sup.2 is O. In one embodiment, X.sup.2 is NR.sup.5. In one embodiment, X.sup.2 is NH. In one embodiment, X.sup.2 is N(CH.sub.3). In one embodiment, X.sup.2 is  $\text{---}(\text{C}=\text{O})\text{NR.sup.5---}^*$ . In one embodiment, X.sup.2 is  $\text{---}(\text{C}=\text{O})\text{NH---}^*$ .

[0121] In one embodiment, each instance of X is independently absent, O, NR.sup.5, C=O, C=S,  $\text{---}(\text{C}=\text{O})\text{---NR.sup.5---}^*$ ,  $\text{---NR.sup.5---}(\text{C}=\text{O})\text{---}^*$ ,  $\text{---}(\text{C}=\text{S})\text{---NR.sup.5---}^*$ , or  $\text{---NR.sup.5---}(\text{C}=\text{S})\text{---}^*$ , wherein \* refers to the direction toward Ring C. In one embodiment, each instance of X is independently absent, O, NH, N(CH.sub.3), C=O,  $\text{---}(\text{C}=\text{O})\text{---NH---}^*$ , or  $\text{---NH---}(\text{C}=\text{O})\text{---}^*$ . In one embodiment, each instance of X is independently absent. In one embodiment, each instance of X is independently absent when each instance of Ring B is absent.

[0122] In one embodiment, each instance of G is independently absent. In one embodiment, each instance of G is independently C.sub.1-C.sub.5 alkylene. In one embodiment, each instance of G is independently C.sub.1-C.sub.3 alkylene. In one embodiment, each instance of G is independently C.sub.1 alkylene. In one embodiment, each instance of G is independently C.sub.2 alkylene. In one embodiment, each instance of G is independently C.sub.3 alkylene. In one embodiment, each instance of G is independently C.sub.4 alkylene. In one embodiment, each instance of G is independently C.sub.5 alkylene. In one embodiment, each instance of G is independently C.sub.2-C.sub.5 alkynylene. In one embodiment, each instance of G is independently C.sub.2 alkynylene. In one embodiment, each instance of G is independently C.sub.3 alkynylene. In one embodiment, each instance of G is independently C.sub.4 alkynylene. In one embodiment, each instance of G is independently C.sub.5 alkynylene. In one embodiment, an instance of G is present when an instance of Ring B is present. In one embodiment, G is unsubstituted. In one embodiment, G is substituted with one or more substituents independently selected from  $\text{---OH}$ , oxo, halo, C.sub.1-C.sub.3 alkyl optionally substituted with one or more halo, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl. In one embodiment, G is substituted with one or more halo (e.g., one or more fluoro).

[0123] In one embodiment, G.sup.1, at least one G, at least one Ring B, Ring A, or L is present. In one embodiment, at least Ring A and G.sup.1 are present. In one embodiment, at least Ring A, G.sup.1, and X.sup.1 are present. In one embodiment, at least G.sup.1 and X.sup.1 are present. In one embodiment, at least one Ring B and one G are present. In one embodiment, at least one G and one X are present.

[0124] In one embodiment,  $\text{---X.sup.2-[G-X---(Ring B)---X].sub.s-G.sup.1-X.sup.1---}$  is  $\text{---G.sup.1-X.sup.1---}$ , wherein G.sup.1 is C.sub.2-C.sub.5 alkylene, and X.sup.1 is O, NR.sup.5, or

—(C=O)NR<sup>sup.5</sup>—\*. In one embodiment, G<sup>sup.1</sup> is C<sub>sub.2</sub>-C<sub>sub.5</sub> alkylene, and X<sup>sup.1</sup> is O. In one embodiment, G<sup>sup.1</sup> is C<sub>sub.2</sub>-C<sub>sub.5</sub> alkylene, and X<sup>sup.1</sup> is NH. In one embodiment, G<sup>sup.1</sup> is C<sub>sub.2</sub>-C<sub>sub.5</sub> alkylene, and X<sup>sup.1</sup> is N(CH<sub>sub.3</sub>). In one embodiment, G<sup>sup.1</sup> is C<sub>sub.2</sub>-C<sub>sub.5</sub> alkylene, and X<sup>sup.1</sup> is —(C=O)NH—\*.

[0125] In one embodiment, —X<sup>sup.2</sup>-[G-X— (Ring B) —X]<sub>sub.s</sub>-G<sup>sup.1</sup>-X<sup>sup.1</sup>— is -G- (Ring B) -G<sup>sup.1</sup>-X<sup>sup.1</sup>—, wherein G is C<sub>sub.1</sub>-C<sub>sub.2</sub> alkylene, G<sup>sup.1</sup> is C<sub>sub.1</sub>-C<sub>sub.2</sub> alkylene, and X<sup>sup.1</sup> is O, NR<sup>sup.5</sup>, or —(C=O)NR<sup>sup.5</sup>—\*. In one embodiment, G is C<sub>sub.1</sub>-C<sub>sub.2</sub> alkylene, G<sup>sup.1</sup> is C<sub>sub.1</sub>-C<sub>sub.2</sub> alkylene, and X<sup>sup.1</sup> is O. In one embodiment, G is C<sub>sub.1</sub>-C<sub>sub.2</sub> alkylene, G<sup>sup.1</sup> is C<sub>sub.1</sub>-C<sub>sub.2</sub> alkylene, and X<sup>sup.1</sup> is NH. In one embodiment, G is C<sub>sub.1</sub>-C<sub>sub.2</sub> alkylene, G<sup>sup.1</sup> is C<sub>sub.1</sub>-C<sub>sub.2</sub> alkylene, and X<sup>sup.1</sup> is N(CH<sub>sub.3</sub>).

[0126] In one embodiment, —X<sup>sup.2</sup>-[G-X— (Ring B) —X]<sub>sub.s</sub>-G<sup>sup.1</sup>-X<sup>sup.1</sup>— is -G- (Ring B) —X<sup>sup.1</sup>—, wherein G is C<sub>sub.1</sub>-C<sub>sub.2</sub> alkylene, and X<sup>sup.1</sup> is O, NR<sup>sup.5</sup>, or —(C=O)NR<sup>sup.5</sup>—\*. In one embodiment, G is C<sub>sub.1</sub>-C<sub>sub.2</sub> alkylene, and X<sup>sup.1</sup> is O. In one embodiment, G is C<sub>sub.1</sub>-C<sub>sub.2</sub> alkylene, and X<sup>sup.1</sup> is —(C=O)NH—\*.

[0127] In one embodiment, —X<sup>sup.2</sup>-[G-X— (Ring B) —X]<sub>sub.s</sub>-G<sup>sup.1</sup>-X<sup>sup.1</sup>— is —X<sup>sup.2</sup>-G-X-G<sup>sup.1</sup>-X<sup>sup.1</sup>—, wherein X<sup>sup.2</sup> is NR<sup>sup.5</sup>, G is C<sub>sub.1</sub>-C<sub>sub.3</sub> alkylene, X is O, NR<sup>sup.5</sup>, —(C=O)—NR<sup>sup.5</sup>—\*, or —NR<sup>sup.5</sup>—(C=O)—\*, G<sup>sup.1</sup> is C<sub>sub.1</sub>-C<sub>sub.3</sub> alkylene, and X<sup>sup.1</sup> is O, NR<sup>sup.5</sup>, or —(C=O)NR<sup>sup.5</sup>—\*. In one embodiment, X<sup>sup.2</sup> is NH, G is C<sub>sub.1</sub>-C<sub>sub.3</sub> alkylene, X is —NH—(C=O)—\*, G<sup>sup.1</sup> is C<sub>sub.1</sub>-C<sub>sub.3</sub> alkylene, and X<sup>sup.1</sup> is —(C=O)NH—\*. In one embodiment, X<sup>sup.2</sup> is NH, G is C<sub>sub.1</sub>-C<sub>sub.3</sub> alkylene, X is N(CH<sub>sub.3</sub>), G<sup>sup.1</sup> is C<sub>sub.1</sub>-C<sub>sub.3</sub> alkylene, and X<sup>sup.1</sup> is —(C=O)NH—\*.

[0128] In one embodiment, each instance of -[G-X— (Ring B) —X]— is independently ##STR00011##

[0129] In one embodiment, L is absent. In one embodiment, L is a linker. In one embodiment, the linker is a peptide comprising 2 to 5 amino acids. In one embodiment, the linker is or comprises a functional group selected from the group consisting of amine, amide, thioamide, ether, thioether, phosphine, phosphoramidate, carboxamide, ester, imidoester, amidine, thioester, sulfonyl, sulfonamide, carbamate, urea, guanidine, thiourea, disulfide, oxime, hydrazine, hydrazide, hydrazone, triazole, triazoline, and tetrazine. In one embodiment, the linker is or comprises an amide. In one embodiment, the linker is or comprises a thioamide. In one embodiment, the linker is or comprises a thiourea. In one embodiment, L is or comprises —NH—. In one embodiment, L is or comprises —C(=S)—. In one embodiment, L is or comprises —C(=S)NH—\*. In one embodiment, L is or comprises —NHC(=S)—\*. In one embodiment, L is or comprises —C(=O)—. As used herein and unless otherwise specified, \* in a L group refers to the direction toward Ring A.

[0130] In one embodiment, L is a C<sub>sub.1</sub>-C<sub>sub.24</sub> alkylene, wherein one or more —CH<sub>sub.2</sub>— in the alkylene is optionally replaced by —O—, —C(=O)O—\*, —OC(=O)—\*, —NH—, —NHC(=O)—\*, —C(=O)NH—\*, —C(=S)—, —C(=S)NH—\*, —NHC(=S)—\*, or —C(=O)—\*, wherein \* refers to the direction toward Ring A. In one embodiment, the terminal —CH<sub>sub.2</sub>— to the direction toward Z is replaced. In one embodiment, the terminal —CH<sub>sub.2</sub>— to the direction of toward Ring A is replaced. In one embodiment, both terminal —CH<sub>sub.2</sub>— are replaced. In one embodiment, L is —NH—(C<sub>sub.1</sub>-C<sub>sub.12</sub> alkylene)-\*. In one embodiment, L is —O—(C<sub>sub.1</sub>-C<sub>sub.12</sub> alkylene)-\*. In one embodiment, L is —NHC(=O)—(C<sub>sub.1</sub>-C<sub>sub.12</sub> alkylene)-\*. In one embodiment, L is —(C<sub>sub.1</sub>-C<sub>sub.12</sub> alkylene)-NHC(=O)—\*. In one embodiment, L is —C(=O)—(C<sub>sub.1</sub>-C<sub>sub.12</sub> alkylene)-\*. In one embodiment, L is —C(=S)NH—(C<sub>sub.1</sub>-C<sub>sub.12</sub> alkylene)-\*. In one embodiment, L is —NHC(=S)—(C<sub>sub.1</sub>-C<sub>sub.12</sub> alkylene)-\*. In one embodiment, L is —(C<sub>sub.1</sub>-C<sub>sub.12</sub> alkylene)-NHC(=S)—\*. In one embodiment, L is —NH—(C<sub>sub.1</sub>-C<sub>sub.12</sub> alkylene)-NHC(=S)—\*. In one embodiment, L is —C(=O)—(C<sub>sub.1</sub>-C<sub>sub.12</sub> alkylene)-NHC(=S)—\*. In one embodiment, L is —NHC(=O)—(C<sub>sub.1</sub>-C<sub>sub.12</sub> alkylene)-

NHC(=S)—\*. In one embodiment, L is —NH—(C.sub.1-C.sub.12 alkylene)-C(=O)—\*. In one embodiment, L is —C(=O)—(C.sub.1-C.sub.12 alkylene)-C(=O)—\*. In one embodiment, L is —O—(C.sub.1-C.sub.12 alkylene)-C(=O)—\*. In one embodiment, L is —C(=S)—(C.sub.1-C.sub.12 alkylene)-\*. In one embodiment, L is —NHC(=S)NH—(C.sub.1-C.sub.12 alkylene)-\*. In one embodiment, L is —NH—CH.sub.2—\*. In one embodiment, L is —O—CH.sub.2—C(=O)\*.

[0131] In one embodiment, L is

##STR00012##  
In one embodiment, L is

##STR00013##  
[0132] In one embodiment, the compound is a compound of Formula (II-A):  
##STR00014## [0133] or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

[0134] In one embodiment, the compound is a compound of Formula (II-A'):  
##STR00015## [0135] or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

[0136] In one embodiment of Formula (II-A), n is 1. In one embodiment, the one R.sup.2 is attached to 5-position of quinolinyl. In one embodiment, the one R.sup.2 is attached to 7-position of quinolinyl. In one embodiment, the one R.sup.2 is attached to 8-position of quinolinyl.

[0137] In one embodiment of Formula (II-A'), n is 1. In one embodiment, the one R.sup.2 is attached to 5-position of quinolinyl. In one embodiment, the one R.sup.2 is attached to 7-position of quinolinyl. In one embodiment, the one R.sup.2 is attached to 8-position of quinolinyl.

[0138] In one embodiment, the compound is a compound of Formula (III-A):  
##STR00016## [0139] or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

[0140] In one embodiment, the compound is a compound of Formula (III-A'):  
##STR00017## [0141] or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

[0142] In one embodiment, the compound is a compound of Formula (IV-A):  
##STR00018## [0143] or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

[0144] In one embodiment, the compound is a compound of Formula (IV-A'):  
##STR00019## [0145] or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

[0146] In one embodiment, the compound is a compound of Formula (IV-B):  
##STR00020## [0147] or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

[0148] In one embodiment, the compound is a compound of Formula (IV-B'):  
##STR00021## [0149] or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

[0150] In one embodiment, the compound is a compound of Formula (II-B):  
##STR00022## [0151] or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

[0152] In one embodiment, the compound is a compound of Formula (II-B'):  
##STR00023## [0153] or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

[0154] In one embodiment of Formula (II-B), n is 1. In one embodiment, the one R.sup.2 is attached to 5-position of quinolinyl. In one embodiment, the one R.sup.2 is attached to 6-position of quinolinyl. In one embodiment, the one R.sup.2 is attached to 7-position of quinolinyl.

[0155] In one embodiment of Formula (II-B'), n is 1. In one embodiment, the one R.sup.2 is attached to 5-position of quinolinyl. In one embodiment, the one R.sup.2 is attached to 6-position

of quinolinyl. In one embodiment, the one R<sup>sup.2</sup> is attached to 7-position of quinolinyl.

[0156] In one embodiment, the compound is a compound of Formula (III-B):

##STR00024## [0157] or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

[0158] In one embodiment, the compound is a compound of Formula (ITT-B'):

##STR00025## [0159] or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

[0160] In one embodiment, the compound is a compound of Formula (IV-C):

##STR00026## [0161] or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

[0162] In one embodiment, the compound is a compound of Formula (IV-C'):

##STR00027## [0163] or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

[0164] In one embodiment, the compound is a compound of Formula (IV-D):

##STR00028## [0165] or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

[0166] In one embodiment, the compound is a compound of Formula (IV-D'):

##STR00029## [0167] or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

[0168] In one embodiment, the compound is a compound of Formula (II-A) (including sub-formulas such as (III-A), (IV-A), and (IV-B)), except that X<sup>sup.1</sup> is attached to the 5-position of quinolinyl. In one embodiment, the compound is a compound of Formula (II-A) (including sub-formulas such as (III-A), (IV-A), and (IV-B)), except that X<sup>sup.1</sup> is attached to the 7-position of quinolinyl.

[0169] In one embodiment, the compound is a compound of Formula (II-A') (including sub-formulas such as (III-A'), (IV-A'), and (IV-B')), except that X<sup>sup.1</sup> is attached to the 5-position of quinolinyl. In one embodiment, the compound is a compound of Formula (II-A') (including sub-formulas such as (III-A'), (IV-A'), and (IV-B')), except that X<sup>sup.1</sup> is attached to the 7-position of quinolinyl.

[0170] In one embodiment, each instance of Ring B is absent, C<sub>sub.3</sub>-C<sub>sub.10</sub> cycloalkyl, C<sub>sub.6</sub>-C<sub>sub.10</sub> aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl.

[0171] In one embodiment, Ring B is absent.

[0172] In one embodiment, Ring B is C<sub>sub.3</sub>-C<sub>sub.10</sub> cycloalkyl. In one embodiment, Ring B is C<sub>sub.3</sub>-C<sub>sub.8</sub> cycloalkyl. In one embodiment, the cycloalkyl is a monocyclic cycloalkyl. In one embodiment, the cycloalkyl is a bridged cycloalkyl. In one embodiment, the cycloalkyl is a spiro cycloalkyl. In one embodiment, the cycloalkyl is cyclopropyl. In one embodiment, the cycloalkyl is cyclobutyl. In one embodiment, the cycloalkyl is cyclopentyl. In one embodiment, the cycloalkyl is cyclohexyl. In one embodiment, the cycloalkyl is

##STR00030##

In one embodiment, the cycloalkyl is

##STR00031##

In one embodiment, the cycloalkyl is

##STR00032##

In one embodiment, the cycloalkyl is

##STR00033##

In one embodiment, the cycloalkyl is

##STR00034##

[0173] In one embodiment, Ring B is 5 to 10-membered heteroaryl. In one embodiment, Ring B is 5 to 6-membered heteroaryl. In one embodiment, the heteroaryl is pyridyl. In one embodiment, the heteroaryl is

##STR00035##

In one embodiment, the right side point of attachment of these groups (as shown here) is toward Ring C.

[0174] In one embodiment, Ring B is 5 to 10-membered heterocyclyl. In one embodiment, Ring B is 3 to 8-membered heterocyclyl. In one embodiment, the heterocyclyl is a monocyclic heterocyclyl. In one embodiment, the heterocyclyl is a bridged heterocyclyl. In one embodiment, the heterocyclyl is a spiro heterocyclyl. In one embodiment, the heterocyclyl is azetidiny. In one embodiment, the heterocyclyl is pyrrolidiny. In one embodiment, the heterocyclyl is piperidiny. In one embodiment, the heterocyclyl is

##STR00036##

In one embodiment, the heterocyclyl is

##STR00037##

In one embodiment, the heterocyclyl is

##STR00038##

In one embodiment, the right side point of attachment of these groups (as shown here) is toward Ring C.

[0175] In one embodiment, Ring A is absent. In one embodiment, Ring A is 5 to 10-membered N-containing heteroaryl. In one embodiment, Ring A is 5 to 6-membered N-containing heteroaryl.

[0176] In one embodiment, Ring A is 5 to 10-membered N-containing heterocyclyl. In one embodiment, Ring A is 5 to 8-membered N-containing heterocyclyl. In one embodiment, the heterocyclyl is a monocyclic heterocyclyl. In one embodiment, the heterocyclyl is a bridged heterocyclyl. In one embodiment, the heterocyclyl is a spiro heterocyclyl. In one embodiment, the heterocyclyl is azetidiny. In one embodiment, the heterocyclyl is pyrrolidiny. In one embodiment, the heterocyclyl is piperidiny. In one embodiment, the heterocyclyl is azepany. In one embodiment, the heterocyclyl is azocany. In one embodiment, the heterocyclyl is piperaziny. In one embodiment, the heterocyclyl is

##STR00039##

In one embodiment, the heterocyclyl is

##STR00040##

In one embodiment, the heterocyclyl is

##STR00041##

In one embodiment, the heterocyclyl is

##STR00042##

In one embodiment, the heterocyclyl is

##STR00043##

In one embodiment, the heterocyclyl is

##STR00044##

In one embodiment, the right point of attachment of these groups (as shown here) is toward Ring B.

[0177] In one embodiment, n is 0. In one embodiment, n is 1. In one embodiment, n is 2. In one embodiment, n is 3.

[0178] In one embodiment, each instance of R<sup>sup.2</sup> is independently —OH, halo, C<sub>sub.1</sub>-C<sub>sub.6</sub> alkyl, —O—(C<sub>sub.1</sub>-C<sub>sub.6</sub> alkyl), —N(R<sup>sup.5</sup>).sub.2, or —S—(C<sub>sub.1</sub>-C<sub>sub.6</sub> alkyl), each of said C<sub>sub.1</sub>-C<sub>sub.6</sub> alkyl being independently and optionally substituted with one or more substituents independently selected from —OH, oxo, and halo. In one embodiment, each instance of R<sup>sup.2</sup> is independently halo, C<sub>sub.1</sub>-C<sub>sub.6</sub> alkyl, —O—(C<sub>sub.1</sub>-C<sub>sub.6</sub> alkyl), or —N(R<sup>sup.5</sup>).sub.2.

[0179] In one embodiment, m is 0. In one embodiment, m is 1. In one embodiment, m is 2. In one embodiment, m is 3.

[0180] In one embodiment, each instance of R<sup>sup.3</sup> is independently —OH, halo, C<sub>sub.1</sub>-C<sub>sub.6</sub> alkyl, —O—(C<sub>sub.1</sub>-C<sub>sub.6</sub> alkyl), —N(R<sup>sup.5</sup>).sub.2, or —S—(C<sub>sub.1</sub>-C<sub>sub.6</sub> alkyl), each of

said C.sub.1-C.sub.6 alkyl being independently and optionally substituted with one or more substituents independently selected from —OH, oxo, and halo. In one embodiment, each instance of R.sup.3 is independently halo, C.sub.1-C.sub.6 alkyl, —O—(C.sub.1-C.sub.6 alkyl), or —N(R.sup.5).sub.2.

[0181] In one embodiment, p is 0. In one embodiment, p is 1. In one embodiment, p is 2. In one embodiment, p is 3.

[0182] In one embodiment, each instance of R.sup.4 is independently —OH, halo, C.sub.1-C.sub.6 alkyl, —O—(C.sub.1-C.sub.6 alkyl), —N(R.sup.5).sub.2, or —S—(C.sub.1-C.sub.6 alkyl), each of said C.sub.1-C.sub.6 alkyl being independently and optionally substituted with one or more substituents independently selected from —OH, oxo, and halo. In one embodiment, each instance of R.sup.4 is independently halo, C.sub.1-C.sub.6 alkyl, —O—(C.sub.1-C.sub.6 alkyl), or —N(R.sup.5).sub.2.

[0183] In one embodiment,

##STR00045##

is

##STR00046##

In one embodiment,

##STR00047##

is a mixture of enantiomers (e.g., a racemic) or a mixture of diastereomers.

[0184] In one embodiment, R.sup.1 is —H, —CN, —B(OH).sub.2, —(C=O)-alkyl, —(C=O)-aryl-, —C=C—(C=O)-aryl, —C=C—S(O).sub.2-aryl, —CO.sub.2H, —SO.sub.3H, —SO.sub.2NH.sub.2, —SO.sub.2F, —PO.sub.3H.sub.2, or 5-tetrazolyl. In one embodiment, R.sup.1 is —CN. In one embodiment, R.sup.1 is —B(OH).sub.2.

[0185] In one embodiment, Z is a radioactive moiety. In one embodiment, the radioactive moiety is a fluorescent isotope, a radioisotope, or a radioactive drug. In one embodiment, the radioactive moiety is a radioactive isotope suitable for diagnostic use. In one embodiment, the radioactive moiety is a radioactive isotope suitable for therapeutic use. In one embodiment, the radioactive moiety is a radioactive isotope suitable for medical imaging or radiotherapy. In one embodiment, the radioactive moiety is selected from the group consisting of alpha radiation emitting isotopes, beta radiation emitting isotopes, gamma radiation emitting isotopes, Auger electron emitting isotopes, X-ray emitting isotopes, and fluorescence emitting isotopes.

[0186] In one embodiment, the radioactive moiety is .sup.177Lu-DOTA, .sup.177Lu-DOTAGA, .sup.68Ga-DOTA, .sup.90Y-DOTA, Al.sup.18F-NOTA, .sup.203Pb-TCMC, .sup.212Pb-TCMC, .sup.64Cu-DOTA, or .sup.225Ac-DOTA. In one embodiment, the radioactive moiety is .sup.177Lu-DOTA. In one embodiment, the radioactive moiety is .sup.177Lu-DOTAGA. In one embodiment, the radioactive moiety is .sup.68Ga-DOTA.

[0187] In one embodiment, the radioactive moiety is .sup.11C, .sup.18F, .sup.72As, .sup.72Se, .sup.123I, .sup.124I, .sup.131I, or .sup.211At.

[0188] In one embodiment, Z is a fluorescent dye. In one embodiment, the fluorescent dye is an Xanthene, an Acridine, an Oxazine, an Cyanine, a Styryl dye, a Coumarin, a Porphine, a Metal-Ligand-Complex, a Fluorescent protein, a Nanocrystals, a Perylene, a Boron-dipyrromethene, or a Phthalocyanine, or a conjugate or combination thereof.

[0189] In one embodiment, Z is a chelating agent. A wide variety of chelating agents have been reported, e.g., by Banerjee et al. (Banerjee, et al., Dalton Trans, 2005, 24: 3886), by Price, et al. (Chem Soc Rev, 2014, 43: 260), by Wadas, et al. (Chem Rev, 2010, 110: 2858), as well as in U.S. Pat. Nos. 5,367,080, 5,367,080, 5,364,613, 5,021,556, 5,075,099, and 5,886,142, the entirety of each of which is incorporated herein by reference. In one embodiment, the chelating agent is a linear chelating agent. In one embodiment, the chelating agent is a cyclic agent. In one embodiment, the chelating agent is a macrocyclic chelating agent. In one embodiment, the chelating agent is a nitrogen-containing macrocyclic chelating agent. In one embodiment, the



chelating agent is a tetrapyrroline chelating agent, N3S chelating agent, N2S2 chelating agent, or N4 chelating agent.

[0190] In one embodiment, the chelating agent is capable of binding with a radioactive moiety. In one embodiment, the binding is through ionic, covalent, dipolar, or ion-dipole interactions. In one embodiment, the chelating agent binds directly to the radioactive moiety. In one embodiment, the chelating agent binds indirectly to the radioactive moiety (e.g., through a linker).

[0191] In one embodiment, the chelating agent comprises one or more amines (e.g., primary amine, secondary amine, or tertiary amine). In one embodiment, the chelating agent comprises one or more ring oxygen atoms. In one embodiment, the chelating agent comprises one or more ring nitrogen atoms. In one embodiment, the chelating agent comprises two ring nitrogen atoms. In one embodiment, the chelating agent comprises three ring nitrogen atoms. In one embodiment, the chelating agent comprises four ring nitrogen atoms. In one embodiment, the chelating agent comprises one or more carboxylic acids. In one embodiment, the chelating agent comprises two carboxylic acids. In one embodiment, the chelating agent comprises three carboxylic acids. In one embodiment, the chelating agent comprises four carboxylic acids. In one embodiment, the chelating agent comprises two or more ring nitrogen atoms, and two or more carboxylic acids.

[0192] In one embodiment, the chelating agent is a chelating agent that forms a complex with a divalent or trivalent metal cation. In one embodiment, the chelating agent is 1, 4, 7, 10-tetraazacyclododecane-N, N', N, N'-tetra acetic acid (DOTA), ethylenediaminetetraacetic acid (EDTA), 1, 4, 7-triazacyclononane-1, 4, 7-triacetic acid (NOTA), 1, 4, 7, 10-tetraazacyclododecane-1-(glutaric acid)-4, 7, 10-triacetic acid (DOTAGA), 2-[4, 7, 10-tris (2-amino-2-oxoethyl)-1, 4, 7, 10-tetrazacyclododec-1-yl]acetamide (TCMC), triethylenetetramine (TETA), iminodiacetic acid, diethylenetriamine-N, N, N', N', N''-penta acetic acid (DTPA), bis-(carboxymethyl imidazole) glycine, or 6-hydrazinopyridine-3-carboxylic acid (HYNIC). In one embodiment, the chelating agent is DOTA, NOTA, EDTA, DTPA, TETA, DO3A, PCTA, or desferrioxamine.

[0193] In one embodiment, the chelating agent is AAZTA, BAT, CDTA, DTA, CyEDTA, EDTMP, DTPMP, CyDTPA, Cy2DTPA, DTPA-MA, DTPA-BA, BOPA, NTA, NOC, NOTP, CY-DTA, DTCBP, CTA, cyclam, CB-Cyclam, cyclen, TETA, sarcophagine, CPTA, TEAMA, Cyclen, DATA, DFO, DATA (M), DATA (P), DATA (Ph), DATA (PPh), DEDPA, H.sub.4octapa, H.sub.2dedpa, H.sub.5decapa, H.sub.2azapa, H2CHX-DEDPA, DFO, DFO-Chx-MAL, DFO-p-SCN, DFO-1AC, DFO-BAC, p-SCN-Bn-DFO, DFO-pPhe-NCS, DFO-HOPO, DFC, diphosphine, DOTAGA, DOTA-MFCO, DOTAM, DOTAM-mono-acid, DOTA-MA, DOTA-pNB, DOTA-4AMP, nitro-DOTA, nitro-PA-DOTA, p-NCS-Bz-DOTA, PA-DOTA, DOTA-NCS, DOTA-NHS, CB-DO2A, PCTA, p-NH.sub.2-Bn-PCTA, p-SCN-Bn-PCTA, p-SCN-Bn-DOTA, DOTMA, NB-DOTA, H4NB-DOTA, H4TCE-DOTA, HOPO, 3,4,3-(Li-1, 2-HOPO), TREN (Me-3, 2-HOPO), TCE-DOTA, DOTP, DOTMP, DOTE, DOTMPE, F-DOTPMPE, DOTPP, DOTBzP, DOTA-monoamide, DOXP, p-NCS-DOTA, p-NCS-PADOTA, p-NCS-TRITA, TRITA, TETA, 3p-C-DEPA, 3p-C-DEPA-NCS, p-NH.sub.2—BN-OXO-DO3A, p-SCN-BN-TCMC, TCMC, 4-aminobutyl-DOTA, azido-mono-amide-DOTA, BCN-DOTA, butyne-DOTA, BCN-DOTA-GA, DOA3P, DO2a2p, DO2A (trans-H2do2a), DO3A, DO3A-thiol, DO3AtBu-N-(2-aminoethyl) ethanamide, DO3TMP-monoamide, DO2AP, CB-DO2A, C3B-DO2A, HP-DO3A, DOTA-NHS-ester, maleimide-DOTA-GA, maleimido-mono-amide-DOTA, maleimide-DOTA, NH2-DOTA-GA, NH2-PEG4-DOTA-GA, GA, p-NH2-Bn-DOTA, p-NO2-Bn-DOTA, p-SCN-Bn-DOTA, p-SCN-Bz-DOTA, TA-DOTA, TA-DOTA-GA, OTTA, DOXP, TSC, FSC, DTC, DTCBP, PTSM, ATSM, H2ATSM, H2PTSM, Dp44mT, DpC, Bp44mT, QT, hybrid thiosemicarbazone-benzothiazole, thiosemicarbazone-styrylpyridine tetradentate ligands H2L2-4, HBED, HBED-CC, dmHBED, dmEHGP, HBED-nn, SHBED, Br-Me2HBED, BPCA, HEHA, BF-HEHA, deferiprone, THP, HYNIC (2-hydrazino nicotinamide), NHS-HYNIC, HYNIC-Kp-DPPB, HYNIC-Ko-DPPB, (HYNIC) (tricine) 2, (HYNIC) (EDDA) Cl, p-EDDHA, AIM, AIMA, IAMB, MAMA, MAMA-DGal, MAMA-MGal,

MAMA-DA, MAMA-HAD, PSC, macropa, macropaquin, macroquin-S03, Crown, MAG3B, NODAGA, SCN-Bz-NOTA-R, NOT-P (NOTMP), NOTAM, p-NCS-NOTA, TACN, TACN-TM, NETA, NETA-monoamine, p-SCN-PhPr-NE3TA, C-NE3TA-NCS, C-NETA-NCS, 3p-C-NETA, NODASA, NOPO, NODA, NODA-MPAA, NO2A, N-benzyl-NODA, C-NOTA, BCNOT-monoamine, maleimido-mono-amide-NOTA, NO2A-azide, NO2A-butyne, NO2AP, NO3AP, N-NOTA, oxo-DO3A, p-NH2-Bn-NOTA, p-NH.sub.2-Bn-oxo-DO3A, p-NO.sub.2-Bn-cyclen, p-SCN-Bn-NOTA, p-SCN-Bn-oxo-DO3A, TRAP, PEPA, BF-PEPA, pycup, pycup2A, pycup1AlBn, pycup2Bn, SarAr-R, DiAmSar, AmBaSar-R, siamSar, Sar, Tachpyr, tachpyr- (6-Me), TAM A, TAM B, TAME, TAME-Hex, THP-Ph-NCS, THP-NCS, THP-TATE, NTP, H3THP, THPN, CB-TE2A, PCB-TE1A1P, \_TETA-NHS, CPTA, CPTA-NHS, CB-TE1K1P, CB-TE2A, TE2A, H2CB-TE2A, TE2P, CB-TE2P, MM-TE2A, DM-TE2A, 2C-TETA, 6C-TETA, BAT, BAT-6, NHS-BAT ester, SSBAT, CHX-A"-DTPA, SCN-CHX-A-DTPA-P, SCN-TETA, TMT-amine, p-BZ-HTCPP, H4pypa, H4octox, p-NO.sub.2-Bn-neunpa, p-SCN-Bn-H4neunpa, TTHA, tBu4pypa-C7-NHS, H4neunpa, H2macropa, BT-DO3A, DO3A-Nprop, DO3AP, DOTPMB, DOTAMAE, DOTAMAP, DO3AMBu, DEPA, p-NO.sub.2-Bn-PCTA, symPC2APA, symPCA2PA, asymPC2APA, asymPCA2PA, .sup.99mTc(CO).sub.3—Chelators, N.sub.xS.sub.4-x(N.sub.4, N.sub.2 S.sub.2, N.sub.3S), or MeO-DOTA-NCS. In one embodiment, the chelating agent is DOTA, DOTAGA, NOPO, PCTA, NOTA, NODAGA, NODA-MPAA, HBED, TETA, CB-TE2A, DTPA, CHX-A"-DTPA, DFO, Macropa, Crown, DOTAM (also called TCMC), PSC, HOPO, HEHA, TRAP, THP, DATA, NOTP, sarcophagine, FSC, NETA, H4octapa, Pycup, N.sub.xS.sub.4-x(N.sub.4, N.sub.2S.sub.2, N.sub.3S), Hynic, .sup.99mTc(CO).sub.3-chelators, or their analogs. In one embodiment, the chelating agent is DOTA, DOTAGA, NOPO, PCTA, DOTAM, PSC, Macropa, Crown, NOTA, NODAGA, NODA-MPAA, HBED, CB-TE2A, DFO, THP, or N.sub.4. In one embodiment, the chelating agent is DOTA, DOTAGA, NOPO, PCTA, DOTAM, PSC, Macropa, Crown, NOTA, or NODAGA. In one embodiment, the chelating agent is DOTA, NOPO, PCTA, Macropa or Crown. The structures of the chelating agents are known in the art and have been reported, e.g., in U.S. Pat. Nos. 4,885,363, 5,720,934, 5,367,080, 5,364,613, 5,021,556, 5,075,099, and 5,886,142; Li, et al., Nucl Med Biol, 2001, 28: 145; Eisenwiener, et al., Bioconjug Chem, 2002, 13: 530; Brechbiel, et al., Bioconjug Chem, 1991, 2: 187; Price, et al., Chem Soc Rev, 2014, 43: 260; Schwartz, et al., Bioconjug Chem, 1991, 2: 333; Nock, et al., J Nucl Med, 2005, 46: 1727; McAuley, et al., Canadian J Chem, 1989, 67: 1657; Doulias et al., Free Radic Biol Med, 2003, 35: 719; Pfister, et al., EJNMMI Res, 2015, 5: 74; Cusnir, et al., Int J Mol Sci, 2017, 18; Demoin, et al., Nucl Med Biol, 2016, 43: 802; Thiele, et al., Angew Chem Int Ed, 2017, 56: 14712; Price, et al., Chem Soc Rev, 2014, 43: 260; Allott, et al., Chem Commun (Camb), 2017, 53: 8529; Tomesello, et al., Molecules, 2017, 22: 1282; Ma, et al., Dalton Trans, 2015, 44: 4884; Babich, et al., J Nucl Med, 1993, 34: 1964; Babich, et al., Nucl Med Biol, 1995, 22: 25; and WO 2022/123462, the entirety of each of which is incorporated herein by reference.

[0194] In one embodiment, the chelating agent is a chelating agent in Table 1.







TABLE-US-00001 TABLE 1 [00048]

[0195] In one embodiment, the chelating agent is a chelating agent in Table 1A.

TABLE-US-00002 TABLE 1A [00081] [00082] [00083]  
 [00084] [00085] [00086]  
 [00087] [00088] [00089]  
 [00090] [00091] [00092]  
 [00093] [00094] [00095]  
 [00096] [00097] [00098]  
 [00099] [00100] [00101]  
 [00102] [00103] [00104]  
 [00105] [00106] [00107]  
 [00108] [00109] [00110]  
 [00111] [00112]

[0196] In one embodiment, the chelating agent with a linker (Z-L) is a structure in Table 1B.

TABLE-US-00003 TABLE 1B [00113] [00114] [00115]  
 [00116] [00117] [00118]  


[0197] As used herein and unless otherwise specified, when a chelating agent is described or shown herein as a radical group, Z is the radical group itself; when a chelating agent is described or shown herein as a complete molecule, Z is a radical group resulted from removal of hydrogen, hydroxy or other reactive group of the molecule. In one embodiment, when the molecule has a —COOH group, Z is a radical group resulted from removal of the —OH group from the —COOH group. In one embodiment, when the molecule has a —PO.sub.3H.sub.2 group, Z is a radical group resulted from removal of the —OH group from the —PO.sub.3H.sub.2 group. In one embodiment, when the molecule has a —NH.sub.2 group, Z is a radical group resulted from removal of an H from the —NH.sub.2 group.

[0198] In one embodiment, Z is a contrast agent. In one embodiment, the contrast agent comprises a paramagnetic agent. In one embodiment, the paramagnetic agent comprises paramagnetic nanoparticles.

[0199] In one embodiment, Z is a cytostatic and/or cytotoxic agent. In one embodiment, the cytostatic and/or cytotoxic agent is selected from the group consisting of alkylating substances, anti-metabolites, antibiotics, epothilones, nuclear receptor agonists and antagonists, anti-androgens, anti-estrogens, platinum compounds, hormones and antihormones, interferons and inhibitors of cell cycle-dependent protein kinases (CDKs), inhibitors of cyclooxygenases and/or lipoxygenases, biogenic fatty acids and fatty acid derivatives, including prostanoids and leukotrienes, inhibitors of protein kinases, inhibitors of protein phosphatases, inhibitors of lipid kinases, platinum coordination complexes, ethyleneimines, methylmelamines, trazines, vinca alkaloids, pyrimidine analogs, purine analogs, alkylsulfonates, folic acid analogs, anthracendiones, substituted urea, methylhydrazin derivatives, such as acediasulfone, aclarubicin, a-amanitin, ambazone, aminoglutethimide, L-asparaginase, monomethyl auristatin E, azathioprine, bleomycin, busulfan, calcium folinate, carboplatin, capecitabine, carmustine, celecoxib, chlorambucil, cis-platin, cladribine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, dapsone, daunorubicin, dibrompropamide, diethylstilbestrol, docetaxel, dolastatin 10 and 15, doxorubicin, enediynes, epirubicin, epothilone B, epothilone D, estramucin phosphate, estrogen, ethinylestradiol, etoposide, flavopiridol, floxuridine, fludarabine, fluorouracil, fluoxymesterone, flutamide, fosfestrol, furazolidone, gemcitabine, gonadotropin releasing hormone analog, hexamethylmelamine, hydroxycarbamide, hydroxymethylnitrofurantoin, hydroxyprogesterone caproate, hydroxyurea, idarubicin, idoxuridine, ifosfamide, interferon  $\alpha$ , irinotecan, leuprolide, lomustine, lurtotecan, mafenide sulfate, olamide, mechlorethamine, medroxyprogesterone acetate, megastrolacetate, melphalan, mepacrine, mercaptopurine, methotrexate, metronidazole, mitomycin C, mitopodizide, mitotane, mitoxantrone, mithramycin,

nalidixic acid, nifuratel, nifuroxazide, nifuralazine, nifurtimox, nimustine, ninorazole, nitrofurantoin, nitrogen mustards, oleomucin, oxolinic acid, pentamidine, pentostatin, phenazopyridine, phthalylsulfathiazole, pipobroman, prednimustine, prednisone, preussin, procarbazine, pyrimethamine, raltitrexed, rapamycin, rofecoxib, rosiglitazone, salazosulfapyridine, scriflavinium chloride, semustine streptozocine, sulfacarbamide, sulfacetamide, sulfachlopyridazine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfaethidole, sulfafurazole, sulfaguanidine, sulfaguanole, sulfamethizole, sulfamethoxazole, co-trimoxazole, sulfamethoxydiazine, sulfamethoxypyridazine, sulfamoxole, sulfanilamide, sulfaperin, sulfaphenazole, sulfathiazole, sulfisomidine, staurosporin, tamoxifen, taxol, teniposide, tertiposide, testolactone, testosteronepropionate, thioguanine, thiotepa, tinidazole, topotecan, triaziquone, treosulfan, trimethoprim, trofosfamide, UCN-01, vinblastine, vincristine, vindesine, vinblastine, vinorelbine, zorubicin, or their respective derivatives or analogs thereof and combinations thereof.

[0200] In one embodiment, the cytostatic and/or cytotoxic agent is selected from the group consisting of doxorubicin,  $\alpha$ -amanitin and monomethyl auristatin E. In one embodiment, Z is doxorubicin.

[0201] In one embodiment, Z is a cytokine. In one embodiment, the cytokine is a chemokine molecule. In one embodiment, the chemokine molecule is selected from the group consisting of CXCL9, CXCL10 and CX3CL1. In one embodiment, Z is CXCL9. In one embodiment, Z is CXCL10. In one embodiment, Z is CX3CL1.

[0202] In one embodiment, Z is an immunomodulatory molecule. In one embodiment, the immunomodulatory molecule is selected from the group consisting of CXCL1, CXCL2, CXCL3, CXCL4, CXCL5, CXCL6, CXCL7, CXCL8, CXCL11, CXCL12, CXCL13, CXCL14, CXCL15, CXCL16, CXCL17, CX3CL1, CCL1, CCL2, CCL3, CCL4, CCL5, CCL6, CCL7, CCL8, CCL9, CCL10, CCL11, CCL12, CCL13, CCL14, CCL15, CCL16, CCL17, CCL18, CCL19, CCL20, CCL21, CCL22, CCL23, CCL24, CCL25, CCL26, CCL27, CCL28, interleukin-2, interferon alpha and interferon gamma. In one embodiment, the immunomodulatory molecule is selected from the group consisting of CXCL3, interleukin-2 and CCL8. In one embodiment, Z is interleukin-2.

[0203] In one embodiment, Z is an amphiphilic substance. In one embodiment, the amphiphilic substance is selected from the group consisting of a lipid, a phospholipid and other highly lipophilic moiety conjugated to a polar group such as an ammonium ion or inositol triphosphate. In one embodiment, the lipid is selected from the group consisting of saccharolipids, prenol lipids, sterol lipids, glycerolipids, polyketides and fatty acids and the phospholipid is selected from the group consisting of plasmalogens, sphingo lipids, phosphatidates and phosphoinositides. In one embodiment, the amphiphilic substance is a lipid or a phospholipid. In one embodiment, the amphiphilic substance is N-PEGylated 1, 2-disteaorylglycero-3-phosphoethanolamine. In one embodiment, Z is a lipid. In one embodiment, Z is a phospholipid. In one embodiment, Z is N-PEGylated 1, 2-disteaorylglycero-3-phosphoethanolamine.

[0204] In one embodiment, Z is a nucleic acid. In one embodiment, the nucleic acid is selected from the group consisting of DNA, RNA, siRNA, mRNA, PNA and cDNA. In one embodiment, the nucleic acid encodes a cytokine and/or an immunomodulatory molecule provided herein. In one embodiment, the nucleic acid is a siRNA or PNA.

[0205] In one embodiment, Z is a viral structural protein. In one embodiment, the viral structural protein is of a virus selected from the group consisting of [0206] (i) double-stranded DNA virus, such as Myoviridae, Siphoviridae, Podoviridae, Herpesviridae, Adenoviridae, Baculoviridae, Papillomaviridae, Polydnviridae, Polyomaviridae, Poxviridae; [0207] (ii) single-stranded DNA virus, such as Anelloviridae, Inoviridae, Parvoviridae; [0208] (iii) double-stranded RNA virus, such as Reoviridae; [0209] (iv) single-stranded RNA virus, such as Coronaviridae, Picomaviridae, Caliciviridae, Togaviridae, Flaviviridae, Astroviridae, Arteriviridae, Hepeviridae; [0210] (v) negative-sense single-stranded RNA virus, such as Arenaviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Bunyaviridae, Orthomyxoviridae, Bomaviridae; [0211] (vi) single-stranded RNA

reverse transcribing virus, such as Retroviridae; [0212] (vii) double-stranded DNA reverse transcribing virus, such as Caulimoviridae, Hepadnaviridae.

[0213] In one embodiment, the viral structural protein, such as VCP is derived from a virus selected from the group consisting of double-stranded DNA virus, such as Myoviridae, Siphoviridae, Podoviridae, Herpesviridae, Adenoviridae, Baculoviridae, Papillomaviridae, Polydnaviridae, Polyomaviridae, Poxviridae; single-stranded DNA virus, such as Anelloviridae, Inoviridae, Parvoviridae; double-stranded RNA virus, such as Reoviridae; single-stranded RNA virus, such as Coronaviridae, Picomaviridae, Caliciviridae, Togaviridae, Flaviviridae, Astroviridae, Arteriviridae, Hepeviridae; negative-sense single-stranded RNA vims, such as Arenaviridae, Filoviridae, Paramyxoviridae, Rhabdoviridae, Bunyaviridae, Orthomyxoviridae, Bomaviridae; single-stranded RNA reverse transcribing vims, such as Retroviridae; double-stranded DNA reverse transcribing vims, such as Caulimoviridae, Hepadnaviridae. In one embodiment, the VCP is from a family of the Parvoviridae, such as from adeno-associated vims. In one embodiment, the VCP is human AAV, bovine AAV, caprine AAV, avian AAV, canine parvovirus (CPV), mouse parvovirus; minute vims of mice (MVM); parvovirus B19 (B19); parvovirus HI (HI); human bocavims (HBoV); feline panleukopenia vims (FPV); or goose parvovirus (GPV). In one embodiment, the VCP is from a certain AAV-serotype, such as AAV-1, AAV-2, AAV-2-AAV-3 hybrid, AAV-3a, AAV-3b, AAV-4, AAV-5, AAV-6, AAV-6.2, AAV-7, AAV-8, AAV-9, AAV-10, AAVrh. 10, AAV-11, AAV-12, AAV-13 or AAVrh32.33. In one embodiment, the VCP is from AAV-2 or a variant thereof that is capable of assembling into a VLP.

[0214] In one embodiment, Z is protein. In one embodiment, the protein is selected from the group consisting of a membrane bound protein and unbound protein. Examples of the protein include but are not limited to CEA, CA19-9, Macrophage Migration Inhibition Factor (MIF), IL-8 (interleukin 8), AXL, MER and c-MET.

[0215] In one embodiment, Z is biotin. In one embodiment, provided herein is a liposome comprising a compound provided herein, wherein Z is an amphiphilic substance.

[0216] The liposomes provided herein can be various types of liposomes, for example, as described in Alavi et al., Adv Pharm Bull, 2017. In one embodiment, the liposomes provided herein is a stealth liposome. Stealth liposomes are known in the art and are for example reviewed by Immordino et al., Int J Nanomedicine, 2006.

[0217] The liposome provided herein can be positively charged, negatively charged or neutral liposomes. The charge of a liposome is determined by the lipid composition and is the average of all charges of the lipids comprised in the liposome. For example, a mixture of a negatively charged phospholipid and cholesterol will yield a negatively charged liposome.

[0218] In one embodiment, lipids/phospholipids to be used in liposomes include but are not limited to glycerides, glycerophospholipides, glycerophosphinolipids, glycerophosphonolipids, sulfolipids, sphingolipids, phospholipids, isoprenolides, steroids, stearines, sterols and carbohydrate containing lipids.

[0219] In one embodiment, the negatively charged lipid/phospholipid is selected from the group consisting of phosphatidylserine (PS), phosphatidylglycerol (PG) and phosphatidic acid (PA). PS and PG are collective terms for lipids sharing a similar phosphatidylserine and phosphatidylglycerol, respectively, head group. However, many different apolar residues can be attached to these head groups. Thus, PSs and PGs isolated from different natural sources vary substantially in the length, composition and/or chemical structure of the attached apolar residues and naturally occurring PS and PG usually is a mixture of PSs and PGs with different apolar residues.

[0220] In one embodiment, the PS employed in the liposomes provided herein is selected from the group consisting of palmitoylloeoylephosphatidylserine, palmitoyllinoeoylephosphatidylserine, palmitoylarachidonoylphosphatidylserine, palmitoyldocosahenoylephosphatidylserine, stearoylloeoylephosphatidylserine, stearoyllinoeoylephosphatidylserine, stearoyl-

arachidonoylphosphatidylserine, stearoyldocosahexaenoylphosphatidylserine, dicaprylphosphatidylserine, dilauroylphosphatidylserine, dimyristoylphosphatidylserine, diphytanoylphosphatidylserine, diheptadecanoylphosphatidylserine, dioleoylphosphatidylserine, dipalmitoylphosphatidylserine, distearoylphosphatidylserine, dilinoleoylphosphatidylserine, diarachidonoylphosphatidylserine, didocosahexaenoylphosphatidylserine, PS from brain, and PS from soy bean; in one embodiment, dioleoylphosphatidylserine.

[0221] In one embodiment, the PG employed in the liposome provided herein is selected from the group consisting of palmitoyloleoylphosphatidylglycerol, palmitoyllinoleoylphosphatidylglycerol, palmitoylarachidonoylphosphatidylglycerol, palmitoyl-docosahexaenoylphosphatidylglycerol, stearoyloleoylphosphatidylglycerol, stearoyl-linoleoylphosphatidylglycerol, stearoylarachidonoylphosphatidylglycerol, stearoyldocosa-hexaenoylphosphatidylglycerol, dicaprylphosphatidylglycerol, dilauroylphosphatidylglycerol, diheptadecanoylphosphatidylglycerol, diphytanoylphosphatidylglycerol, dimyristoylphosphatidylglycerol, dipalmitoylphosphatidylglycerol, dielaidoylphosphatidylglycerol, distearoylphosphatidylglycerol, dioleoylphosphatidylglycerol, dilinoleoylphosphatidylglycerol, diarachidonoylphosphatidylglycerol, docosahexaenoylphosphatidylglycerol, and PG from egg; in one embodiment, dioleoylphosphatidylglycerol.

[0222] Similar to PS and PG, PE is also a generic term for lipids sharing a phosphatidylethanolamine head group. In one embodiment, the PE is selected from the group consisting of palmitoyloleoylphosphatidylethanolamine, palmitoyllinoleoylphosphatidylethanolamine, palmitoylarachidonoylphosphatidylethanolamine, palmitoyldocosahexaenoylphosphatidylethanolamine, stearoyloleoylphosphatidylethanolamine, stearoyllinoleoylphosphatidylethanolamine, stearoylarachidonoylphosphatidylethanolamine, stearoyldocosahexaenoylphosphatidylethanolamine, dilauroylphosphatidylethanolamine, dimyristoylphosphatidylethanolamine, diphytanoylphosphatidylethanolamine, dipalmitoylphosphatidylethanolamine, diheptadecanoylphosphatidylethanolamine, distearoylphosphatidylethanolamine, dielaidoylphosphatidylethanolamine, diarachidonoylphosphatidylethanolamine, docosahexaenoylphosphatidylethanolamine, PE from bacteria, PE from heart, PE from brain, PE from liver, PE from egg, and PE from soybean, in one embodiment, 1, 2-diacyl-sn-glycero-3-PE, 1-acyl-2-acyl-sn-glycero-3-PE, 1, 2-dipalmitoyl-PE and/or 1, 2-dilauroyl-sn-glycero-3-PE (DLPE).

[0223] The liposome provided herein can comprise at least one further component selected from the group consisting of an adjuvant, additive, and auxiliary substance. In one embodiment, adjuvants are selected from the group consisting of unmethylated DNA, such as unmethylated DNA comprising CpG dinucleotides (CpG motif), such as CpG ODN with phosphorothioate (PTO) backbone (CpG PTO ODN) or phosphodiester (PO) backbone (CpG PO ODN); bacterial products from the outer membrane of Gram-negative bacteria, such as monophosphoryl lipid A (MPLA), lipopolysaccharides (LPS), muramyl dipeptides and derivatives thereof; synthetic lipopeptide derivatives, such as ParmCys; lipoarabinomannan; peptidoglycan; zymosan; heat shock proteins (HSP), such as HSP 70; dsRNA and synthetic derivatives thereof, such as Poly Epol C; polycationic peptides, such as poly-L-arginine; taxol; fibronectin; flagellin; imidazoquinoline; cytokines with adjuvant activity, such as GM-CSF, interleukin-(IL-) 2, IL-6, IL-7, IL-18, type I and II, interferons, such as interferon-gamma, TNF-alpha; 25-dihydroxyvitamin D3 (calcitriol); synthetic oligopeptides, such as MHCII-presented peptides; gel-like precipitates of aluminum hydroxide (alum). In one embodiment, adjuvants, which can be comprised in the liposome provided herein are selected from the group unmethylated DNA, such as unmethylated DNA comprising CpG dinucleotides (CpG motif), such as CpG ODN with phosphorothioate (PTO) backbone (CpG PTO ODN) or phosphodiester (PO) backbone (CpG PO ODN), bacterial products from the outer membrane of Gram-negative bacteria, such as monophosphoryl lipid A (MPLA) and synthetic lipopeptide derivatives, such as ParmCys.



[0224] As used herein, and unless otherwise specified, the term “additive” comprises substances, which stabilize any component of the liposome or of the liquid medium like, for example, antioxidants, radical scavengers or the like. In one embodiment, stabilizers are selected from the group consisting of a-tocopherol or carbohydrates, such as glucose, sorbitol, sucrose, maltose, trehalose, lactose, cellubiose, raffinose, maltotriose, or dextran. The stabilizers can be comprised in the lipid membranes of the liposomes, the interior of the liposomes and/or within the liquid medium surrounding the liposomes.































[0225] Liposomes provided herein can have a diameter between 10 and 1000 nm. In one embodiment, they have a diameter of between 30 and 800 nm, between 40 and 500 nm, between 50 and 300 nm, or between 100 and 200 nm. The diameter of the liposomes can be affected, for example, by extrusion of the liposomal composition through sieves or meshes with a known pore size. This and further methods of controlling the size of liposomes are known in the art and are described, for example, in Mayhew et al. (1984) *Biochim. Biophys. Acta* 775: 169-174 or Olson et al. (1979) *Biochim. Biophys. Acta* 557: 9-23.

[0226] In one embodiment, the liposome or the mixture of liposomes provided herein are comprised in a liquid medium. As used herein, and unless otherwise specified, the term “liquid medium” comprises all biocompatible, physiological acceptable liquids and liquid compositions such as FLO, aqueous salt solutions, and buffer solutions like, for example, PBS, Ringer solution and the like.

[0227] In one embodiment, the liposome is loaded with a substance selected from the group consisting of an agent and a nucleic acid.

[0228] In one embodiment, the agent that the liposome is loaded with is a cytostatic and/or cytotoxic agent provided herein. In one embodiment, the nucleic acid that the liposome is loaded with is a nucleic acid provided herein. A variety of methods are available in the art to “load” a liposome with a given therapeutic agent. In one embodiment, the therapeutic agent (s) is (are) admixed with the lipid components during formation of the liposomes. Other passive loading methods include dehydration-rehydration (Kirby & Gregoriadis (1984) *Biotechnology* 2: 979), reverse-phase evaporation (Szoka & Papahadjopoulos (1978) *Proc. Natl. Acad. Sci. USA* 75: 4194), or detergent-depletion (Milschmann et al. (1978) *Biochim. Biophys. Acta* 512: 147-155). Other methodologies for encapsulating therapeutic agents include so called “remote loading” or “active loading” in which due to a gradient, for example, a pH or salt gradient between the exterior and the interior of a preformed liposome the therapeutic agent is transported into the liposome along the gradient (see, for example, Cheung et al. (1998) *Biochim. Biophys. Acta* 1414: 205-216; Cullis et al. (1991) *Trends Biotechnol.* 9: 268-272; Mayer et al. (1986) *Chem. Phys. Lipids* 40: 333-345).

[0229] In one embodiment, the compound is a compound in Table 2, or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

TABLE-US-00004 TABLE 2 [00119] [00120]  
[00121] [00122] [00123]  
[00124] [00125] [00126]  
[00127] [00128] [00129]  
[00130] [00131] [00132]  
[00133] [00134] [00135]  
[00136] [00137] [00138]  
[00139] [00140] [00141]  
[00142] [00143] [00144]  
[00145] [00146] [00147]  
[00148]

[0230] In one embodiment, provided herein is a complex formed by a compound provided herein and a divalent or trivalent metal cation. In one embodiment, the complex is formed when Z is a chelating agent.

[0231] In one embodiment, the metal cation is a cation of Cr, Ga, In, Tc, Re, La, Yb, Sm, Ho, Y, Pm, Dy, Er, Lu, Sc, Pr, Gd, Bi, Ru, Pd, Rh, Sb, Ba, Hg, Eu, Tl, Pb, Cu, Re, Au, Ac, Th, or Ag. In one embodiment, the metal cation is a cation of Ga. In one embodiment, the metal cation is a cation of Lu.

[0232] In one embodiment, the metal cation is a cation of <sup>51</sup>Cr, <sup>67</sup>Ga, <sup>68</sup>Ga, <sup>111</sup>In, <sup>99m</sup>Tc, <sup>186</sup>Re, <sup>188</sup>Re, <sup>139</sup>La, <sup>140</sup>La, <sup>175</sup>Yb, <sup>153</sup>Sm, <sup>166</sup>Ho, <sup>88</sup>Y, <sup>90</sup>Y, <sup>149</sup>Pm, <sup>165</sup>Dy, <sup>169</sup>Er, <sup>177</sup>Lu, <sup>47</sup>Sc, <sup>142</sup>Pr, <sup>159</sup>Gd, <sup>212</sup>Bi, <sup>213</sup>Bi, <sup>97</sup>Ru, <sup>109</sup>Pd, <sup>105</sup>Rh, <sup>101</sup>mRh, <sup>119</sup>Sb, <sup>128</sup>Ba, <sup>197</sup>Hg, <sup>151</sup>Eu, <sup>153</sup>Eu, <sup>169</sup>Eu, <sup>201</sup>Tl, <sup>203</sup>Pb, <sup>212</sup>Pb, <sup>64</sup>Cu, <sup>67</sup>Cu, <sup>188</sup>Re, <sup>186</sup>Re, <sup>198</sup>Au, <sup>225</sup>Ac, <sup>227</sup>Th, or <sup>199</sup>Ag. In one embodiment, the metal cation is a cation of <sup>68</sup>Ga. In one embodiment, the metal cation is a cation of <sup>177</sup>Lu.

[0233] In one embodiment, without being limited by a particular theory, a compound or complex provided herein exhibit suitable cellular uptake in FAP transfected cells, as well as tumor uptake in FAP-positive tumors.

#### PHARMACEUTICAL COMPOSITION AND METHOD OF USE

[0234] In one embodiment, provided herein is a pharmaceutical composition comprising a compound provided herein or a complex provided herein and a pharmaceutically acceptable excipient.

[0235] In one embodiment, provided herein is a virus-like particle (VLP) comprising a compound provided herein, wherein Z is a viral structural protein. In one embodiment, the virus-like particle is loaded with a substance selected from the group consisting of an agent and a nucleic acid. In one embodiment, the agent that the virus-like particle is loaded with is a cytostatic and/or cytotoxic agent provided herein. In one embodiment, the nucleic acid that the virus-like particle is loaded with is a nucleic acid provided herein.

[0236] In one embodiment, provided herein is a pharmaceutical composition comprising a compound provided herein, a liposome provided herein, or a virus-like particle provided herein, and a pharmaceutically acceptable excipient.

[0237] In one embodiment, provided herein is a method for the diagnosis of a disease characterized by overexpression of fibroblast activation protein (FAP) in a subject, comprising administering to the subject a diagnostically effective amount of a compound provided herein, a complex provided herein, or a pharmaceutical composition provided herein. In one embodiment, a compound provided herein, a complex provided herein, or a pharmaceutical composition provided herein is for use in the diagnosis of a disease characterized by overexpression of fibroblast activation protein (FAP) in a subject.

[0238] In one embodiment, provided herein is a method for the treatment of a disease characterized by overexpression of fibroblast activation protein (FAP) in a subject, comprising administering to the subject a therapeutically effective amount of a compound provided herein or a pharmaceutical composition provided herein. In one embodiment, a compound provided herein or a pharmaceutical composition provided herein is for use in the treatment of a disease characterized by overexpression of fibroblast activation protein (FAP) in a subject.

[0239] In one embodiment, provided herein is a method for the treatment of a disease characterized by overexpression of fibroblast activation protein (FAP) in a subject, comprising administering to the subject a therapeutically effective amount of a compound provided herein, a liposome provided herein, a virus-like particle (VLP) provided herein, or a pharmaceutical composition provided herein. In one embodiment, a compound provided herein, a liposome provided herein, a virus-like particle (VLP) provided herein, or a pharmaceutical composition provided herein is for use in the treatment of a disease characterized by overexpression of fibroblast activation protein (FAP) in a subject.

[0240] In one embodiment, the disease characterized by overexpression of fibroblast activation



protein (FAP) is cancer, chronic inflammation, atherosclerosis, fibrosis, tissue remodeling, or keloid disorder.

[0241] In one embodiment, the disease is cancer. In one embodiment, the cancer is breast cancer, pancreatic cancer, small intestine cancer, colon cancer, rectal cancer, lung cancer, head and neck cancer, ovarian cancer, hepatocellular carcinoma, 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, or prostate cancer. In one embodiment, the cancer is glioma, breast cancer, colon cancer, lung cancer, head and neck cancer, liver cancer, or pancreatic cancer. In one embodiment, the cancer is glioma. In one embodiment, the cancer is colon cancer.

[0242] In one embodiment, the disease is chronic inflammation. In one embodiment, the chronic inflammation is rheumatoid arthritis, osteoarthritis, or Crohn's disease. In one embodiment, the chronic inflammation is rheumatoid arthritis.

[0243] In one embodiment, the disease is fibrosis. In one embodiment, the fibrosis is pulmonary fibrosis, such as idiopathic pulmonary fibrosis, or liver cirrhosis.

[0244] In one embodiment, the disease is tissue remodeling. In one embodiment, the tissue remodeling occurs after myocardial infarction.

[0245] In one embodiment, the disease is a keloid disorder. In one embodiment, the keloid disorder is scar formation, keloid tumors, or keloid scar.

[0246] In one embodiment, the subject is an animal. In one embodiment, the subject is a mammal. In one embodiment, the subject is a human.

[0247] In one embodiment, provided herein is a kit comprising a compound provided herein, a complex provided herein, or a pharmaceutical composition provided herein and instructions for the diagnosis or treatment of a disease provided herein. In one embodiment, provided herein is a kit comprising a compound provided herein, a complex provided herein, a liposome provided herein, a virus-like particle (VLP) provided herein, or a pharmaceutical composition provided herein, and instructions for the treatment of a disease.

[0248] It is understood that any embodiment of the compounds provided herein, as set forth above, and any specific substituent and/or variable in the compounds provided herein, as set forth above, may be independently combined with other embodiments and/or substituents and/or variables of the compounds to form embodiments not specifically set forth above. In addition, in the event that a list of substituents and/or variables is listed for any particular group or variable, it is understood that each individual substituent and/or variable may be deleted from the particular embodiment and/or claim and that the remaining list of substituents and/or variables will be considered to be within the scope of embodiments provided herein.

[0249] It is understood that in the present description, combinations of substituents and/or variables of the depicted formulae are permissible only if such contributions result in stable compounds.

## EXAMPLES

[0250] Certain embodiments of the invention are illustrated by the following non-limiting examples.

### Methods of Preparation

[0251] Compounds provided herein may be prepared using reactions and techniques known in the art and those described herein.

### Preparation of Intermediate Compounds

D1: Tert-butyl-6-hydroxyquinoline-4-carboxylate

##STR00149##

[0252] Step 1: To a solution of D1-1 (20.00 g, 79.34 mmol) in t-BuOH (2-methylpropan-2-ol) (200 mL) was added di-tert-butyl dicarbonate (20.75 g, 95.21 mmol) and DMAP (N, N-dimethylpyridin-4-amine) (96.51 mg, 0.79 mmol). The mixture was stirred at 30° C. overnight. The reaction mixture

was quenched by water (100 mL) and extracted with EtOAc (ethyl acetate) (100 mL×3). The combined organic layer was dried and concentrated to give a crude product, which was purified by flash chromatography to afford the compound D1-2 (23.00 g, 74.63 mmol, yield: 94.06%) as a white solid. LC-MS (ESI): 308 [M+H].sup.+.

[0253] Step 2: To a solution of D1-2 (23.00 g, 74.63 mmol) in 1, 4-dioxane (230 mL) was added 4, 4, 5, 5-tetramethyl-2-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 3, 2-dioxaborolane (22.74 g, 89.56 mmol), potassium acetate (21.97 g, 223.89 mmol) and Pd (dppf) Cl.sub.2 (6.05 g, 7.46 mmol) at r.t., and the reaction mixture was stirred at 100° C. under nitrogen overnight. The resulting suspension was filtered through a celite and the filter cake was washed with EtOAc (100 mL×3). The combined organic layer was concentrated to give crude product, which was purified by flash chromatography to afford the compound D1-3 (25.00 g, 70.37 mol, yield: 94.30%) as white solid. LC-MS (ESI): 356 [M+H].sup.+.

[0254] Step 3: To a solution of D1-3 (25.00 g, 70.37 mmol) in DMSO (50 mL) and EtOH (200 mL) was added 2.0 mol/L NaOH in water (106 mL) at 0° C. under nitrogen. The reaction mixture was stirred at 0° C. for 0.5 h, then 30% H.sub.2O.sub.2(23.93 mL, 211.11 mmol) was added dropwise at 0° C. The solution was stirred at r.t. for 2 h. The reaction was quenched by addition of water (100 mL) and extracted with EtOAc (50 mL×3). The combined organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the title compound D1 (14.00 g, 57.08 mmol, yield: 81.11%) as a white solid. LC-MS (ESI): 246 [M+H].sup.+.

D2: (1S, 3S, 5S)-2-glycyl-2-azabicyclo [3.1.0]hexane-3-carbonitrile

##STR00150##

[0255] Step 1: To a solution of D2-1 (15.00 g, 66.29 mmol) in DCM (Dichloromethane) (100 mL) was added TFA (trifluoroacetic acid) (100 mL). The reaction mixture was stirred at r.t. for 3 h and evaporated under reduced pressure to give a crude (13.00 g), which was dissolved in DCM (130 mL), followed by addition of (tert-butoxycarbonyl) glycine (13.94 g, 79.55 mmol), HATU (O-(7-azabenzotriazol-1-yl)-N, N, N, N-tetramethyl uronium hexafluorophosphate) (37.79 g, 99.44 mmol) and DIEA (N-ethyl-N-isopropylpropan-2-amine) (32.81 mL, 198.87 mmol). The reaction mixture was stirred at r.t. for 3 h. Then the resulting solution was quenched by addition of water (100 mL) and extracted with DCM (100 mL×2), dried and concentrated to give a crude, which was purified by flash chromatography to afford the compound D2-2 (16.00 g, 56.47 mmol, two steps yield: 85.19%) as a white solid. LC-MS (ESI): 284 [M+H].sup.+.

[0256] Step 2: To a solution of D2-2 (16.00 g, 56.47 mmol) in DCM (160 mL) was added trifluoroacetic anhydride (17.79 g, 84.71 mmol) and DIEA (27.95 mL, 169.41 mmol). The mixture was stirred at r.t. for 3 h, and then concentrated to give a residue, to which was added DCM (100 mL), adjust the reaction solution to alkaline with saturated sodium bicarbonate aqueous solution, extracted with DCM (50 mL×2) and washed with brine (10 mL). The combined organic layer was dried and concentrated to give a crude product, which was purified by flash chromatography to afford the compound D2-3 (3.70 g, 13.95 mmol, yield: 24.70%) as a white solid. LC-MS (ESI): 266 [M+H].sup.+.

[0257] Step 3: To a solution of D2-3 (250.00 mg, 0.94 mmol) in DCM (3 mL) was added TFA (2 mL), and was stirred at r.t. for 3 h. The resulting mixture was evaporated under reduced pressure to give crude D2 (240.00 mg, crude) as white solid. LC-MS (ESI): 166 [M+H].sup.+.

D3: Methyl-6-hydroxyquinoline-4-carboxylate

##STR00151##

[0258] Step 1: To a solution of D3-1 (30.00 g, 119.01 mmol) in MeOH (300 mL) was added thionyl chloride (25.90 mL, 357.04 mmol). The mixture was stirred at 60° C. for 24 h and then concentrated to give a residue, to which was added DCM (300 mL). Adjust the reaction solution to alkaline with saturated sodium bicarbonate aqueous solution, extracted with DCM (50 mL×2) and washed with brine (300 mL). The combined organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound D3-2 (37.80 g, crude)

as a white solid. LC-MS (ESI): 266 [M+H].sup.+.

[0259] Step 2: To a solution of D3-2 (37.8 g, crude) in 1, 4-dioxane (400 mL) was added 4, 4, 5, 5-tetramethyl-2-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)-1, 3, 2-dioxaborolane (36.27 g, 142.81 mmol), potassium acetate (34.99 g, 357.03 mmol) and Pd (dppf) Cl.sub.2 (9.67 g, 11.90 mmol) at r.t. and the reaction mixture was stirred at 100° C. for 16 h. The reaction mixture was quenched by water (150 mL) and extracted with EtOAc (200 mL×2). The organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound D3-3 (40.10 g, crude) as white solid. LC-MS (ESI): 314 [M+H].sup.+.

[0260] Step 3: To a solution of D3-3 (40.10 g, crude) in EtOH: DMSO=4: 1 (400 mL) was added aq. NaOH (2 N, 179 mL) at 0° C. and the reaction mixture was stirred at 0° C. for 0.5 h, then 30% H.sub.2O.sub.2 (40.46 mL, 357.03 mmol) was added dropwise at 0° C. The reaction mixture was stirred at 0° C. for 2 h. Then, the reaction was quenched by addition of saturated aqueous NH.sub.4Cl and extracted with EtOAc (200 mL×3). The combined organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound D3 (20.10 g, 98.92 mmol, yield: three steps 83.12%) as a white solid. LC-MS (ESI) m/z: 204 [M+H].sup.+.

D4: Tert-butyl-4-((3-(hydroxymethyl) bicyclo [1.1.1]pentan-1-yl) methyl) piperazine-1-carboxylate  
##STR00152##

[0261] Step 1: To a solution of D4-1 (2.00 g, 11.75 mmol) in DMF (20 mL) was added tert-butyl piperazine-1-carboxylate (2.63 g, 14.10 mmol), HATU (6.70 g, 17.63 mmol) and DIEA (5.81 mL, 35.25 mmol) under nitrogen. The reaction mixture was stirred at r.t. overnight. Then the resulting solution was quenched by addition of water (30 mL) and extracted with EtOAc (20 mL×2). The combined organic layer was washed with brine (50 mL), dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound D4-2 (3.78 g, 11.17 mmol, yield: 95.04%) as a white solid. LC-MS (ESI) m/z: 339 [M+H].sup.+.

[0262] Step 2: To a solution of D4-2 (3.78 g, 11.17 mmol) in THF (tetrahydrofuran) (40 mL) under nitrogen was added lithium aluminum hydride (1.27 g, 33.51 mmol) at 0° C., and the reaction mixture was stirred at r.t. overnight. The reaction mixture was quenched by Na.sub.2SO.sub.4.Math.10H.sub.2O (7.30 g), filtered and washed with EtOAc (50 mL). The organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the title compound D4 (1.05 g, 3.54 mmol, yield: 31.71%) as a white solid. LC-MS (ESI): 297 [M+H].sup.+.

Example 1 (Method A): E1: 2, 2', 2''-(10-(2-(4-(3-((4-((2-((1S, 3S, 5S)-3-cyano-2-azabicyclo [3.1.0]hexan-2-yl)-2-oxoethyl) carbamoyl) quinolin-6-yl) oxy) propyl) piperazin-1-yl)-2-oxoethyl)-1, 4, 7, 10-tetraazacyclododecane-1, 4, 7-triyl) triacetic acid

##STR00153##

[0263] Step 1: To a solution of E1-1 (1.00 g, 4.09 mmol) in DCM (10 mL) was added MsCl (methanesulfonyl chloride) (703.03 mg, 6.14 mmol) and triethylamine (1.70 mL, 12.27 mmol). The mixture was stirred at r.t. for 24 h. The resulting mixture was quenched by water (10 mL) and extracted with DCM (30 mL×3). The combined organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound E1-2 (1.20 g, 3.72 mmol, yield: 91.00%) as a colorless oil. LC-MS (ESI): 323 [M+H].sup.+.

[0264] Step 2: To a solution of E1-2 (1.20 g, 3.72 mmol) in DMF (12 mL) was added K.sub.2CO.sub.3 (potassium carbonate) (1.03 g, 7.44 mmol) and D3 (755.90 mg, 3.72 mmol). The reaction mixture was stirred at 60° C. for 16 h. The resulting mixture was concentrated to give a residue, which was purified by flash chromatography to afford the compound E1-3 (460.00 mg, 1.07 mmol, yield: 28.79%) as a white solid. LC-MS (ESI): 430 [M+H].sup.+.

[0265] Step 3: To a solution of E1-3 (460.00 mg, 1.07 mmol) in MeOH (5 mL) was added aq. NaOH (1.07 mL, 2N) at r.t. and the reaction mixture was stirred at r.t. for 2 h. Then the reaction mixture was concentrated, quenched by addition of water (5 mL), adjust the pH to 4 with 6 N

aqueous hydrochloride, extracted with EtOAc (ethyl acetate) (10 mL×2). The combined organic layer was dried and concentrated to give compound E1-4 (405.00 mg, 0.98 mmol, yield: 91.10%) as a colorless oil. LC-MS (ESI): 416 [M+H].sup.+.

[0266] Step 4: To a solution of E1-4 (202.00 mg, 0.49 mmol) in DMF (3 mL) under nitrogen was added D2 (80.95 mg, 0.49 mmol), HATU (277.40 mg, 0.73 mmol) and DIEA (0.24 mL, 1.46 mmol). The reaction mixture was stirred at r.t. overnight. The resulting mixture was quenched by water (10 mL) and extracted with EtOAc (10 mL×2). The combined organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound E1-5 (172.00 mg, 0.31 mmol, yield: 62.38%) as a colorless oil. LC-MS (ESI): 563 [M+H].sup.+.

[0267] Step 5: To a solution of E1-5 (172.00 mg, 0.31 mmol) in ACN (acetonitrile) (3 mL) was added TsOH (4-methylbenzenesulfonic acid) (158.42 mg, 0.92 mmol), and the reaction mixture was stirred at 60° C. for 2 h. The mixture was then evaporated under reduced pressure to give crude, which was dissolved in DMF (3 mL), followed by addition of DOTA-PNP (2, 2', 2''-(10-(2-(4-nitrophenoxy)-2-oxoethyl)-1, 4, 7, 10-tetraazacyclododecane-1, 4, 7-triyl) triacetic acid) (178.51 mg, 0.34 mmol) and DIEA (0.50 mL, 3.06 mmol). The reaction mixture was stirred at r.t. for 2 h. The resulting mixture was then concentrated to give a crude, which was purified by prep-HPLC to afford the title compound E1 (10.0 mg, 0.01 mmol, yield: 3.85%) as a white solid. LC-MS (ESI): 849.4 [M+H].sup.+.

[0268] .sup.1H NMR (400 MHz, D.sub.2O) δ 8.90 (d, J=5.6 Hz, 1H), 8.10 (d, J=9.6 Hz, 1H), 7.99 (d, J=5.6 Hz, 1H), 7.75 (d, J=2.8 Hz, 1H), 7.73-7.68 (m, 1H), 5.03-4.95 (m, 1H), 4.57-4.40 (m, 3H), 4.29-4.19 (m, 2H), 3.96-3.50 (m, 11H), 3.47-2.74 (m, 23H), 2.66-2.54 (m, 1H), 2.32-2.18 (m, 3H), 1.97-1.78 (m, 1H), 1.07-0.96 (m, 1H), 0.89-0.81 (m, 1H).

Example 2 (Method B): E2: 2, 2', 2''-(10-(2-(4-(3-((4-((2-((1S, 3S, 5S)-3-cyano-2-azabicyclo [3.1.0]hexan-2-yl)-2-oxoethyl) carbamoyl) quinolin-6-yl) (methyl) amino) propyl) piperazin-1-yl)-2-oxoethyl)-1, 4, 7, 10-tetraazacyclododecane-1, 4, 7-triyl) triacetic acid

##STR00154##

[0269] Step 1: To a solution of E2-1 (4.00 g, 12.98 mmol) in toluene (40 mL) was added 3-(methylamino) propan-1-ol (1.39 g, 15.59 mmol), Pd.sub.2 (dba).sub.3 (1.19 g, 1.30 mmol) and BINAP (Diacetato [(R)-(+)-2, 2-bis(diphenylphosphino)-1, 1-binaphthyl]ruthenium (II)) (1.62 g, 2.60 mmol). The reaction mixture was stirred at 100° C. for 3 h. The suspension was then filtered through a celite and the filter cake was washed with DCM (40 mL×2), to which was added water (20 mL) and separated. The organic layer was dried over and concentrated to give a residue, which was purified by flash chromatography to afford the compound E2-2 (2.20 g, 6.95 mmol, yield: 53.57%) as a yellow solid. LC-MS (ESI): 317 [M+H].sup.+.

[0270] Step 2: To a solution of E2-2 (2.20 g, 6.95 mmol) in DCM (20 mL) was added MsCl (1.19 g, 10.44 mmol) and triethylamine (2.89 mL, 20.85 mmol). The mixture was stirred at r.t. for 24 h. The reaction mixture was quenched by water (20 mL) and extracted with DCM (30 mL×3). The combined organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound E2-3 (2.00 g, 5.07 mmol, yield: 72.95%) as a yellow oil. LC-MS (ESI): 395 [M+H].sup.+.

[0271] Step 3: To a solution of E2-3 (2.00 g, 5.07 mmol) in DMF (20 mL) was added tert-butyl piperazine-1-carboxylate (944.34 mg, 5.07 mmol), KI (841.62 mg, 5.07 mmol) and K.sub.2CO.sub.3 (2.10 g, 15.21 mmol). The reaction mixture was stirred at 60° C. for 16 h. The resulting suspension was then filtered through a celite and the filter cake was washed with EtOAc (10 mL×3), to which was added water (30 mL) and separated. The organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound E2-4 (1.30 g, 2.68 mmol, yield: 52.91%) as a yellow solid. LC-MS (ESI): 485 [M+H].sup.+.

[0272] Step 4: To a solution of E2-4 (1.30 g, 2.68 mmol) in TFA (1.17 mL) was added TfOH

(trifluoromethanesulfonic acid) (0.07 mL), TES (triethylsilane) (0.03 mL) and H.sub.2O (0.07 mL). The reaction mixture was stirred at r.t. for 2 h and evaporated under reduced pressure to give crude, which was dissolved in DCM (10 mL), followed by addition of di-tert-butyl dicarbonate (876.36 mg, 4.02 mmol) and TEA (triethylamine) (1.12 mL, 8.04 mmol). The reaction mixture was stirred at r.t. for 24 h. Then the resulting solution was quenched by addition of water (15 mL) and extracted with DCM (10 mL×3). The organic layer was washed with brine (10 mL), dried and concentrated to give a crude, which was purified by flash chromatography to afford the compound E2-5 (1.10 g, 2.57 mmol, yield: 95.78%) as a yellow oil. LC-MS (ESI) 429 [M+H].sup.+.

[0273] Step 5: To a solution of E2-5 (840.00 mg, 1.96 mmol) in DMF (9 mL) under nitrogen was added D2 (500.00 mg, crude), HATU (1.12 g, 2.94 mmol) and DIEA (0.97 mL, 5.88 mmol). The reaction mixture was stirred at r.t. overnight. Then, the resulting reaction mixture was quenched by addition of water (10 mL) and extracted with EA (10 mL×2). The combined organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound E2-6 (240.00 mg, 0.42 mmol, yield: 21.27%) as a yellow oil. LC-MS (ESI): 576 [M+H].sup.+.

[0274] Step 6: To a solution of E2-6 (240 mg, 0.42 mmol) in ACN (3 mL) was added TsOH (215.25 mg, 1.25 mmol). The reaction mixture was stirred at 60° C. for 2 h and then evaporated under reduced pressure to give crude, which was dissolved in DMF (3 mL), followed by addition of DOTA-PNP (241.00 mg, 0.46 mmol) and DIEA (0.69 mL, 4.17 mmol). The reaction mixture was stirred at r.t. for 2 h and concentrated to give a crude product, which was purified by prep-HPLC to afford the title compound E2 (40.00 mg, 0.05 mmol, yield: 11.05%) as a yellow solid. LC-MS (ESI): 862.3 [M+H].sup.+.

[0275] .sup.1H NMR (400 MHz, D.sub.2O) δ 8.43 (d, J=4.4 Hz, 1H), 7.76 (d, J=9.6 Hz, 1H), 7.43-7.33 (m, 2H), 7.06 (d, J=2.8 Hz, 1H), 5.00-4.92 (m, 1H), 4.38 (s, 2H), 3.86-3.15 (m, 23H), 3.11-2.53 (m, 18H), 2.35-2.24 (m, 1H), 1.92-1.70 (m, 3H), 1.05-0.95 (m, 1H), 0.89-0.79 (m, 1H).

Example 3 (Method C): E3: 2, 2', 2''-(10-(2-(4-((4-((2-((1S, 3S, 5S)-3-cyano-2-azabicyclo [3.1.0]hexan-2-yl)-2-oxoethyl) carbamoyl) quinolin-6-yl) oxy) piperidin-1-yl) methyl) piperidin-1-yl)-2-oxoethyl)-1, 4, 7, 10-tetraazacyclododecane-1, 4, 7-triyl) triacetic acid

##STR00155## ##STR00156##

[0276] Step 1: To a solution of E3-1 (1.00 g, 4.97 mmol) in DCM (10 mL) was added MsCl (854.00 mg, 7.46 mmol) and triethylamine (2.07 mL, 14.90 mmol). The mixture was stirred at r.t. for 24 h. The reaction mixture was quenched by water (10 mL) and extracted with DCM (10 mL×3). The combined organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound d E3-2 (1.12 g, crude) as a colorless oil. LC-MS (ESI): 280 [M+H].sup.+.

[0277] Step 2: To a solution of D1 (1.21 g, 4.97 mmol) in DMF (15 mL) was added E3-2 (1.12 g, crude) and Cs.sub.2CO.sub.3 (Cesium carbonate) (3.26 g, 9.94 mmol). The reaction mixture was stirred at 60° C. overnight. The reaction mixture was quenched by water (20 mL) and extracted with DCM (30 mL×3). The organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound E3-3 (763.00 mg, 1.78 mmol, yield: 35.83%) as a white solid. LC-MS (ESI): 429 [M+H].sup.+.

[0278] Step 3: To a solution of E3-3 (663.00 mg, 1.78 mmol) in TFA (0.6 mL) was added TfOH (0.03 mL), TES (0.02 mL) and H.sub.2O (0.03 mL). The reaction mixture was stirred at r.t. for 2 h. The resulting mixture was evaporated under reduced pressure to give crude, which was dissolved in DCM (5 mL), followed by addition of di-tert-butyl dicarbonate (543.00 mg, 2.49 mmol) and TEA (0.69 mL, 4.98 mmol). The mixture was stirred at r.t. for 24 h. The reaction mixture was quenched by water (10 mL) and extracted with DCM (10 mL×3). The combined organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound E3-4 (350.00 mg, 0.94 mmol, yield: 52.80%) as a colorless oil. LC-MS (ESI): 373 [M+H].sup.+.

[0279] Step 4: To a solution of E3-4 (200.00 mg, 0.54 mmol) in DMF (3 mL) under nitrogen was added D2 (89.21 mg, 0.54 mmol), HATU (307.80 mg, 0.81 mmol) and DIEA (0.27 mL, 1.61 mmol). The reaction mixture was stirred at r.t. overnight. The resulting mixture was quenched by water (10 mL) and extracted with EtOAc (10 mL×2). The combined organic layer was washed with brine (10 mL), dried and concentrated to give a crude product, which was purified by prep-HPLC to afford the compound E3-5 (146.00 mg, 0.28 mmol, yield: 52.03%) as a colorless oil. LC-MS (ESI): 520 [M+H].sup.+.

[0280] Step 5: To a solution of E3-5 (146.00 mg, 0.28 mmol) in DCM (2 mL) was added TFA (1 mL), and stirred at r.t. for 2 h. The resulting mixture was evaporated under reduced pressure to give crude compound, which was dissolved in ACN (2 mL), followed by addition of tert-butyl-4-(bromomethyl) piperidine-1-carboxylate (77.89 mg, 0.28 mmol) and DIEA (0.19 mL, 1.12 mmol). The reaction mixture was stirred at 80° C. for 12 h. The resulting reaction mixture was quenched by water (5 mL) and extracted with EtOAc (5 mL×3). The combined organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound E3-6 (81.00 mg, 0.13 mmol, yield: 46.90%) as a colorless oil. LC-MS (ESI): 617 [M+H].sup.+.

[0281] Step 6: To a solution of E3-6 (81.00 mg, 0.13 mmol) in ACN (2 mL) was added TsOH (68.00 mg, 0.39 mmol) and the reaction mixture was stirred at 60° C. for 2 h. The solution was evaporated under reduced pressure to give crude, which was dissolved in DMF (2 mL), followed by addition of DOTA-PNP (76.00 mg, 0.144 mmol) and DIEA (0.22 mL, 1.31 mmol). The reaction mixture was stirred at r.t. for 2 h. Then, the reaction mixture was concentrated to give a crude, which was purified by prep-HPLC to afford the title compound E3 (20.00 mg, 0.02 mmol, yield: 17.04%) as a white solid. LC-MS (ESI): 903.5 [M+H].sup.+.

[0282] .sup.1H NMR (400 MHz, D.sub.2O) δ 8.94 (d, J=5.2 Hz, 1H), 8.19-8.10 (m, 1H), 8.05-7.98 (m, 1H), 7.89 (s, 1H), 7.84-7.69 (m, 1H), 5.08-4.98 (m, 1H), 4.95-4.79 (m, 1H), 4.52 (s, 2H), 4.35-4.20 (m, 2H), 4.04-3.81 (m, 2H), 3.72-3.20 (m, 17H), 3.20-2.88 (m, 12H), 2.77-2.57 (m, 2H), 2.50-1.67 (m, 10H), 1.30-1.10 (m, 2H), 1.10-0.97 (m, 1H), 0.88 (s, 1H).

Example 4 (Method D): E4: 2, 2', 2''-(10-(2-(7-(3-((4-((2-((1S, 3S, 5S)-3-cyano-2-azabicyclo [3.1.0]hexan-2-yl)-2-oxoethyl) carbamoyl) quinolin-6-yl) oxy) propyl)-2, 7-diazaspiro [4.4]nonan-2-yl)-2-oxoethyl)-1, 4, 7, 10-tetraazacyclododecane-1, 4, 7-triyl) triacetic acid

##STR00157##

[0283] Step 1: To a solution of D3 (1.00 g, 4.92 mmol) in DM M (10 mL) was added 3-bromopropan-1-ol (820.60 mg, 5.90 mmol) and Cs.sub.2CO.sub.3 (3.23 g, 9.84 mmol). The reaction mixture was stirred at 60° C. overnight. The reaction mixture was quenched by water (10 mL) and extracted with DCM (10 mL×3). The organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound E4-1 (872.00 mg, 3.34 mmol, yield: 67.82%) as a colorless oil. LC-MS (ESI): 262 [M+H].sup.+.

[0284] Step 2: To a solution of E4-1 (872.00 mg, 3.34 mmol) in DCM (10 mL) was added MsCl (573.85 mg, 5.01 mmol) and triethylamine (1.39 mL, 10.02 mmol). The mixture was stirred at r.t. for 24 h. The reaction mixture was quenched by water (10 mL) and extracted with DCM (10 mL×3). The combined organic layer was dried and concentrated to give crude, which was dissolved in DMf (10 mL), followed by addition of tert-butyl 2, 7-diazaspiro [4.4]nonane-2-carboxylate (830.86 mg, 3.67 mmol), K.sub.2CO.sub.3 (1.38 g, 10.02 mmol) and KI (554.44 mg, 3.34 mmol). The reaction mixture was stirred at 60° C. overnight. The reaction mixture was quenched by water (10 mL) and extracted with DCM (10 mL×3). The organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound E4-2 (452.00 mg, 0.96 mmol, yield: 28.84%) as a white solid. LC-MS (ESI): 470 [M+H].sup.+.

[0285] Step 3: To a solution of E4-2 (452.00 mg, 0.96 mmol) in MeOH (5 mL) was added aq. NaOH (1.92 mL, 2N) at r.t. and the reaction mixture was stirred at r.t. for 2 h. Then the reaction mixture was concentrated to remove most of methanol, followed by addition of water (5 mL),

adjust the pH to 4 with 6 N aqueous hydrochloride, extracted with EtOAc (10 mL×2). The combined organic layer was dried and concentrated to give crude (390 mg, crude). The crude (100 mg) was dissolved in DMF (2 mL) under nitrogen, followed by addition of D2 (36.26 mg, 0.22 mmol), HATU (125.40 mg, 0.33 mmol) and DIEA (0.11 mL, 0.66 mmol). The reaction mixture was stirred at r.t. overnight. The resulting mixture was quenched by water (5 mL) and extracted with EtOAc (10 mL×2). The combined organic layer was washed with brine (10 mL), dried and concentrated to give a crude product, which was purified by prep-HPLC to afford the compound E4-3 (60.00 mg, 0.10 mmol, yield: 45.35%) as a white solid. LC-MS (ESI): 603 [M+H].sup.+.

[0286] Step 4: To a solution of E4-3 (60.00 mg, 0.10 mmol) in ACN (2 mL) was added TsOH (51.66 mg, 0.30 mmol) and the reaction mixture was stirred at 60° C. for 3 h. The solution was evaporated under reduced pressure to give crude, which was dissolved in DMF (2 mL), followed by addition of DOTA-PNP (57.81 mg, 0.11 mmol) and DIEA (0.18 mL, 1.10 mmol). The reaction mixture was stirred at r.t. for 2 h. Then, the reaction mixture was concentrated to give a crude, which was purified by prep-HPLC to afford the title compound E4 (8.00 mg, 0.009 mmol, yield: 9.04%) as a white solid. LC-MS (ESI): 889.5 [M+H].sup.+.

[0287] .sup.1H NMR (400 MHz, D.sub.2O) δ 8.92 (d, J=5.6 Hz, 1H), 8.11 (d, J=9.6 Hz, 1H), 7.99 (d, J=5.6 Hz, 1H), 7.83-7.74 (m, 1H), 7.76-7.68 (m, 1H), 5.07-4.99 (m, 1H), 4.60-4.44 (m, 2H), 4.26 (s, 2H), 3.83-3.56 (m, 10H), 3.53-3.34 (m, 8H), 3.32-2.97 (m, 16H), 2.75-2.54 (m, 1H), 2.37-2.28 (m, 1H), 2.28-1.77 (m, 8H), 1.09-0.98 (m, 1H), 0.88 (s, 1H).

Example 5: E5: 2, 2', 2''-(10-(2-(4-((3-(((4-((2-((1S, 3S, 5S)-3-cyano-2-azabicyclo [3.1.0]hexan-2-yl)-2-oxoethyl) carbamoyl) quinolin-6-yl) oxy) methyl) bicyclo [1.1.1]pentan-1-yl) methyl) piperazin-1-yl)-2-oxoethyl)-1, 4, 7, 10-tetraazacyclododecane-1, 4, 7-triyl) triacetic acid

##STR00158## ##STR00159##

[0288] Step 1: To a solution of D4 (1.05 g, 3.54 mmol) in THF (10 mL) was added MsCl (608.26 mg, 5.31 mmol) and triethylamine (1.47 mL, 10.62 mmol). The mixture was stirred at r.t. for 24 h. The reaction mixture was quenched by water (10 mL) and extracted with DCM (10 mL×3). The combined organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound d E5-1 (1.20 g, 3.20 mmol, yield: 90.46%) as a colorless oil. LC-MS (ESI): 375 [M+H].sup.+.

[0289] Step 2: To a solution of E5-1 (1.20 g, 3.20 mmol) in DMF (15 mL) was added D1 (784.90 mg, 3.20 mmol) and Cs.sub.2CO.sub.3 (3.15 g, 9.60 mmol). The reaction mixture was stirred at 60° C. overnight. The reaction mixture was quenched by water (20 mL) and extracted with EtOAc (20 mL×3). The organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound E5-2 (602.00 mg, 1.15 mmol, yield: 35.88%) as a white solid. LC-MS (ESI): 524 [M+H].sup.+.

[0290] Step 3: To a solution of E5-2 (602.00 mg, 1.15 mmol) in TFA (6 mL) was added TfOH (0.3 mL), TES (0.2 mL) and H.sub.2O (0.3 mL). The reaction mixture was stirred at r.t. for 2 h. The resulting mixture was evaporated under reduced pressure to give crude, which was dissolved in DCM (5 mL), followed by addition of di-tert-butyl dicarbonate (376.05 mg, 1.73 mmol) and TEA (0.48 mL, 3.45 mmol). The mixture was stirred at r.t. for 24 h. The reaction mixture was quenched by water (10 mL) and extracted with DCM (10 mL×3). The combined organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound E5-3 (92.00 mg, 0.20 mmol, yield: 17.12%) as a colorless oil. LC-MS (ESI): 468 [M+H].sup.+.

[0291] Step 4: To a solution of E5-3 (92.00 mg, 0.20 mmol) in DMF (2 mL) under nitrogen was added D2 (33.04 mg, 0.2 mmol), HATU (152.00 mg, 0.40 mmol) and DIEA (0.20 mL, 1.20 mmol). The reaction mixture was stirred at r.t. overnight. The resulting mixture was quenched by water (5 mL) and extracted with EtOAc (5 mL×2). The combined organic layer was washed with brine (5 mL), dried and concentrated to give a crude product, which was purified by prep-HPLC to afford the compound E5-4 (86.00 mg, 0.14 mmol, yield: 71.10%) as a colorless oil. LC-MS (ESI): 615

[M+H].sup.+.

[0292] Step 5: To a solution of E5-4 (86.00 mg, 0.14 mmol) in ACN (2 mL) was added TsOH (72.32 mg, 0.42 mmol) and the reaction mixture was stirred at 60° C. for 2 h. The solution was evaporated under reduced pressure to give crude, which was dissolved in DMF (2 mL), followed by addition of DOTA-PNP (80.93 mg, 0.15 mmol) and DIEA (0.23 mL, 1.40 mmol). The reaction mixture was stirred at r.t. for 2 h. Then, the reaction mixture was concentrated to give a crude, which was purified by prep-HPLC to afford the title compound E5 (26.00 mg, 0.03 mmol, yield: 20.63%) as a white solid. LC-MS (ESI): 901.4 [M+H].sup.+.

[0293] .sup.1H NMR (400 MHz, D.sub.2O)  $\delta$  8.89 (d, J=5.6 Hz, 1H), 8.09 (d, J=9.2 Hz, 1H), 7.98 (d, J=5.6 Hz, 1H), 7.78-7.66 (m, 2H), 5.04-4.96 (m, 1H), 4.57-4.32 (m, 4H), 4.24 (s, 2H), 3.87-2.94 (m, 33H), 2.67-2.55 (m, 1H), 2.36-2.27 (m, 1H), 1.89 (s, 7H), 1.07-0.96 (m, 1H), 0.91-0.82 (m, 1H).

Example 6: E6: 2, 2', 2''-(10-(2-(4-((3-(((4-((2-((1S, 3S, 5S)-3-cyano-2-azabicyclo [3.1.0]hexan-2-yl)-2-oxoethyl) carbamoyl) quinolin-6-yl) oxy) methyl) azetidin-1-yl) methyl) piperidin-1-yl)-2-oxoethyl)-1, 4, 7, 10-tetraazacyclododecane-1, 4, 7-triyl) triacetic acid

##STR00160##

[0294] Step 1: To a solution of D1 (1.00 g, 4.08 mmol) in DMF (15 mL) was added tert-butyl 3-(bromomethyl) azetidine-1-carboxylate (1.22 g, 4.90 mmol) and Cs.sub.2CO.sub.3 (4.01 g, 12.24 mmol). The reaction mixture was stirred at 60° C. overnight. The reaction mixture was quenched by water (20 mL) and extracted with DCM (30 mL×3). The organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound E6-1 (1.20 g, 2.90 mmol, yield: 71.01%) as a colorless oil. LC-MS (ESI): 415 [M+H].sup.+.

[0295] Step 2: To a solution of E6-1 (1.20 g, 2.90 mmol) in TFA (12 mL) was added TfOH (0.6 mL), TES (0.4 mL) and H.sub.2O (0.6 mL). The reaction mixture was stirred at r.t. for 2 h. The resulting mixture was evaporated under reduced pressure to give crude, which was dissolved in DCM (10 mL), followed by addition of di-tert-butyl dicarbonate (948.30 mg, 4.35 mmol) and TEA (1.21 mL, 8.70 mmol). The mixture was stirred at r.t. for 24 h. The reaction mixture was quenched by water (10 mL) and extracted with DCM (10 mL×3). The combined organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound E6-2 (480.00 mg, 1.34 mmol, yield: 46.26%) as a colorless oil. LC-MS (ESI): 359 [M+H].sup.+.

[0296] Step 3: To a solution of E6-2 (807.03 mg, 2.25 mmol) in DMF (10 mL) under nitrogen was added D2 (372 mg, 2.25 mmol), HATU (1.71 g, 4.50 mmol) and DIEA (2.23 mL, 13.50 mmol). The reaction mixture was stirred at r.t. overnight. The resulting mixture was quenched by water (10 mL) and extracted with EtOAc (10 mL×2). The combined organic layer was washed with brine (10 mL), dried and concentrated to give a crude product, which was purified by prep-HPLC to afford the compound E6-3 (322.00 mg, 0.28 mmol, yield: 28.28%) as a white solid. LC-MS (ESI): 506 [M+H].sup.+.

[0297] Step 4: To a solution of E6-3 (322.00 mg, 0.28 mmol) in DCM (5 mL) was added TFA (2 mL), and stirred at r.t. for 2 h. The resulting mixture was evaporated under reduced pressure to give crude compound, which was dissolved in ACN (2 mL), followed by addition of tert-butyl 4-(bromomethyl) piperidine-1-carboxylate (94.58 mg, 0.34 mmol) and DIEA (0.18 mL, 1.12 mmol). The reaction mixture was stirred at 80° C. for 12 h. The resulting reaction mixture was quenched by water (5 mL) and extracted with EtOAc (5 mL×3). The combined organic layer was dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound E6-4 (102.00 mg, 0.17 mmol, yield: 26.57%) as a colorless oil. LC-MS (ESI): 603 [M+H].sup.+.

[0298] Step 5: To a solution of E6-4 (102.00 mg, 0.17 mmol) in ACN (1 mL) was added TsOH (87.82 mg, 0.51 mmol) and the reaction mixture was stirred at 60° C. for 2 h. The solution was



evaporated under reduced pressure to give crude, which was dissolved in DMF (1 mL), followed by addition of DOTA-PNP (99.85 mg, 0.19 mmol) and DIEA (0.28 mL, 1.70 mmol). The reaction mixture was stirred at r.t. for 2 h. Then, the reaction mixture was concentrated to give a crude, which was purified by prep-HPLC to afford the title compound E6 (20.00 mg, 0.02 mmol, yield: 13.29%) as a white solid. LC-MS (ESI): 889.5 [M+H].sup.+.

[0299] .sup.1H NMR (400 MHz, D.sub.2O)  $\delta$  8.95-8.88 (m, 1H), 8.11 (d, J=10.0 Hz, 1H), 8.03-7.94 (m, 1H), 7.82-7.73 (m, 2H), 5.04-4.92 (m, 1H), 4.56-4.42 (m, 2H), 4.40-3.97 (m, 9H), 3.94-2.73 (m, 28H), 2.68-2.54 (m, 2H), 2.36-2.25 (m, 1H), 1.94-1.84 (m, 2H), 1.66 (d, J=12.8 Hz, 2H), 1.26-1.09 (m, 2H), 1.06-0.95 (m, 1H), 0.90-0.78 (m, 1H).

Example 7 (Method E): E7: 2, 2', 2''-(10-(1-carboxy-5-((2-(4-((2-((1S, 3S, 5S)-3-cyano-2-azabicyclo [3.1.0]hexan-2-yl)-2-oxoethyl) carbamoyl) quinolin-8-yl) amino)-4-oxobutanamido) ethyl) amino)-5-oxopentyl)-1, 4, 7, 10-tetraazacyclododecane-1, 4, 7-triyl) triacetic acid

##STR00161## ##STR00162##

[0300] Step 1: To a solution of E7-1 (200.00 mg, 1.06 mmol) in DCM (2 mL) was added HATU (403.85 mg, 1.06 mmol), DIEA (0.70 mL, 4.24 mmol) and D2 (175.11 mg, 1.06 mmol). The mixture was stirred at r.t. overnight. The resulting mixture was evaporated under reduced pressure to give crude, which was purified by flash chromatography to afford the title compound E7-2 (266.00 mg, 0.79 mmol, yield: 70.61%) as a white solid. LC-MS (ESI): 336 [M+H].sup.+.

[0301] Step 2: To a solution of E7-2 (266 mg, 0.79 mmol) in THF (3 mL) was added DMAP (48 mg, 0.40 mmol) and dihydrofuran-2, 5-dione (79.06 mg, 0.79 mmol). The mixture was stirred at 60° C. overnight. The reaction mixture was quenched by water (5 ml) and extracted with EtOAc (5 mL×3). The combined organic layer was dried and concentrated to give a crude product, which was purified by flash chromatography to afford the title compound E7-3 (231 mg, 0.53 mmol, yield: 67.15%) as a white solid. LC-MS (ESI): 436 [M+H].sup.+.

[0302] Step 3: To a solution of E7-3 (231 mg, 0.53 mmol) in DMSO (2 mL) was added 1-hydroxypyrrolidine-2, 5-dione (61.00 mg, 0.53 mmol) and DCC (Dicyclohexylcarbodiimide) (546.77 mg, 2.65 mmol). The mixture was stirred at r.t. overnight under dark. The reaction mixture was quenched by water (5 ml) and extracted with EtOAc (5 mL×3). The combined organic layer was dried and concentrated to give a crude product E7-4 (175 mg, crude) as a colorless oil. LC-MS (ESI): 533 [M+H].sup.+.

[0303] Step 4: To a solution of E7-4 (175 mg, crude) in DMF (2 mL) was added tert-butyl (2-aminoethyl) carbamate (84.92 mg, 0.53 mmol) and DIEA (0.44 mL, 2.65 mmol). The mixture was stirred at r.t. for 2 h. The resulting mixture was evaporated under reduced pressure to give crude compound, which was dissolved in ACN (2 mL), followed by addition of TsOH (273.80 mg, 1.59 mmol) and DIEA (0.19 mL, 1.12 mmol). The reaction mixture was stirred at 50° C. overnight. The resulting reaction mixture was concentrated to give a residue, which was purified by flash chromatography to afford the title compound E7-5 (95.00 mg, 0.20 mmol, yield of two steps: 37.54%) as a yellow solid. LC-MS (ESI): 478 [M+H].sup.+.

[0304] Step 5: To a solution of E7-5 (50.00 mg, 0.10 mmol) in DMF (1 mL) was added DIC (N, N'-Diisopropylcarbodiimide) (25.24 mg, 0.20 mmol), HOBT (1-Hydroxybenzotriazole) (27.02 mg, 0.20 mmol), 5-(tert-butoxy)-5-oxo-4-(4, 7, 10-tris (2-(tert-butoxy)-2-oxoethyl)-1, 4, 7, 10-tetraazacyclododecan-1-yl) pentanoic acid (63.08 mg, 0.09 mmol) (preparation see Organic Process Research & Development 2009, 13, 535-542) and DIEA (0.06 mL, 0.40 mmol). The reaction mixture was stirred at r.t. overnight. The reaction mixture was quenched by water (5 ml) and extracted with EtOAc (5 mL×3). The combined organic layer was dried and concentrated to give a crude product (77 mg), which was dissolved in TFA (1 mL). The reaction mixture was stirred at 40° C. for 1 h. Then the resulting solution was concentrated to give a crude, which was purified by Prep-HPLC to afford the title compound E7 (2.00 mg, 0.002 mmol, yield of two steps: 2.01%) as a white solid. LC-MS (ESI): 937 [M+H].sup.+.

Example 8 (Method F): E8: 2, 2', 2''-(10-(1-carboxy-4-(4-((3-((4-((2-((1S, 3S, 5S)-3-cyano-2-

azabicyclo [3.1.0]hexan-2-yl)-2-oxoethyl) carbamoyl) quinolin-8-yl) carbamoyl) bicyclo [1.1.1]pentan-1-yl) methyl) piperazin-1-yl)-4-oxobutyl)-1, 4, 7, 10-tetraazacyclododecane-1, 4, 7-triyl) triacetic acid

##STR00163## ##STR00164##

[0305] Step 1: To a mixture D4-1 (5.00 g, 29.38 mmol) in anhydrous tetrahydrofuran (50 mL) was added a tetrahydrofuran solution of Borane-tetrahydrofuran complex (1 M, 35.26 mL) under nitrogen at 0° C. The reaction mixture was stirred at room temperature for 3 h. The mixture was quenched by water (50 mL) slowly at 0° C. The resulting solution was extracted with ethyl acetate (50 mL×3). The organic layer was dried and concentrated to give crude, which was purified by flash chromatography to afford the title compound E8-1 (3.00 g, 19.21 mmol, yield: 65.37%) as a colorless oil. LC-MS (ESI): 157 [M+H].sup.+.

[0306] Step 2: To a solution of E8-1 (500 mg, 3.18 mmol) in DCM (5 mL) was added MsCl (550.30 mg, 4.80 mmol) and triethylamine (1.33 mL, 9.61 mmol). The mixture was stirred at r.t. for 2 h. The resulting mixture was quenched by water (10 mL) and extracted with DCM (10 mL×3). The combined organic layer was dried and concentrated to give the title compound E8-2 (542.00 mg, crude) as a colorless oil. LC-MS (ESI): 235 [M+H].sup.+.

[0307] Step 3: To a solution of E8-2 (542.00 mg, crude) in MeOH (5 mL) was added tert-butyl piperazine-1-carboxylate (422.06 mg, 3.20 mmol), K<sub>2</sub>CO<sub>3</sub> (1.33 g, 9.61 mmol) and KI (584.93 mg, 3.52 mmol) at r.t. and the reaction mixture was stirred at 60° C. overnight. The resulting mixture was quenched by water (5 mL) and extracted with EtOAc (10 mL×2). The combined organic layer was washed with brine (10 mL), dried and concentrated to give a crude product. The crude was dissolved in MeOH (5 mL), followed by addition of aq. NaOH (2 N, 3.20 mL, 6.41 mmol), the reaction mixture was stirred at r.t. overnight. Then the reaction mixture was concentrated, quenched by addition of water (5 mL), adjust the pH to 4 with 6 N aqueous hydrochloride, extracted with EtOAc (ethyl acetate) (10 mL×2). The combined organic layer was dried and concentrated to give compound E8-3 (423.00 mg, crude) as a white solid. LC-MS (ESI): 309 [M-H].sup.-.

[0308] Step 4: To a solution of E8-3 (186.23 mg, crude) in DMF (2 mL) was added E7-2 (200.00 mg, 0.60 mmol), DIC (151.44 mg, 1.20 mmol), HOBT (162.14 mg, 1.20 mmol) and DIEA (0.40 mL, 2.40 mmol). The mixture was stirred at r.t. overnight. The resulting mixture was quenched by water (10 mL) and extracted with DCM (10 mL×3). The combined organic layer was dried and concentrated to give a crude, which was dissolved in ACN (2 mL), followed by addition of TsOH (309.96 mg, 1.80 mmol). The reaction mixture was stirred at 50° C. for 1 h. The resulting reaction mixture was concentrated to give E8-4 (205 mg, crude) as a yellow solid. LC-MS (ESI): 528 [M+H].sup.+.

[0309] Step 5: To a solution of E8-4 (205.00 mg, crude) in DMF (2 mL) was added DIC (151.44 mg, 1.20 mmol), HOBT (162.14 mg, 1.20 mmol), 5-(tert-butoxy)-5-oxo-4-(4, 7, 10-tris (2-(tert-butoxy)-2-oxoethyl)-1, 4, 7, 10-tetraazacyclododecan-1-yl) pentanoic acid (378.50 mg, 0.54 mmol) and DIEA (0.40 mL, 2.40 mmol). The reaction mixture was stirred at r.t. overnight. The reaction mixture was quenched by water (3 mL) and extracted with EtOAc (2 mL×3). The combined organic layer was dried and concentrated to give a crude product, which was dissolved in TFA (1 mL). The reaction mixture was stirred at 40° C. for 1 h. Then the resulting solution was concentrated to give a crude, which was purified by Prep-HPLC to afford the title compound E8 (3.00 mg, 0.003 mmol, yield of three steps: 0.51%) as a white solid. LC-MS (ESI): 986 [M+H].sup.+.

Example 9 (Method G): E18: 2, 2', 2''-(10-(2-(4-(((4-(((4-((2-((1S, 3S, 5S)-3-cyano-2-azabicyclo [3.1.0]hexan-2-yl)-2-oxoethyl) carbamoyl) quinolin-6-yl) oxy) methyl) piperidin-1-yl) methyl) piperidin-1-yl)-2-oxoethyl)-1, 4, 7, 10-tetraazacyclododecane-1, 4, 7-triyl) triacetic acid

##STR00165##

[0310] Step 1: To a solution of E18-1 (1.50 g, 7.38 mmol) in DMF (15 mL) was added D3 (4.11 g, 14.76 mmol) and potassium carbonate (3.06 g, 22.15 mmol). The mixture was stirred at 50° C.

under nitrogen overnight. The resulting mixture was quenched by addition of water (100 mL) and extracted with EtOAc (100 mL×2). The combined organic layers were dried and concentrated to give a crude product E18-2 (1.89 g, 4.72 mmol, yield: 63.90%) as a white solid.

[0311] LC-MS (ESI): 401 [M+H].sup.+.

[0312] Step 2: To a solution of E18-2 (1.89 g, 4.72 mmol) in DCM (16 mL) was added trifluoroacetic acid (4 mL). The reaction mixture was stirred at 20° C. for 3 h. The resulting mixture was evaporated under reduced pressure to give crude compound, which was dissolved in DMF (15 mL), followed by addition of E18-1 (2.59 g, 9.32 mmol) and potassium carbonate (1.93 g, 13.9 mmol). The reaction mixture was stirred at 50° C. overnight. The resulting mixture was quenched by addition of water (100 mL) and extracted with EtOAc (100 mL×2). The combined organic layers were dried and concentrated to give a crude product, which was purified by flash chromatography to afford the compound E18-3 (701.00 mg, 1.41 mmol, yield: 30.20%) as a white solid. LC-MS (ESI): 498 [M+H].sup.+.

[0313] Step 3: To a solution of E18-3 (701.00 mg, 1.41 mmol) in THF (4 mL) was added H.sub.2O (2 mL), MeOH (1 mL) and sodium hydroxide (158.00 mg, 2.82 mmol) under nitrogen. The reaction mixture was stirred at 20° C. for 2 h. Then the reaction mixture was concentrated to remove most of methanol and tetrahydrofuran, followed by addition of water (20 mL), adjust the pH to 4 with 6 N aqueous hydrochloride, extracted with EtOAc (20 mL×2). The combined organic layers were dried and concentrated to give crude (650.00 mg, crude), which was dissolved in DMF (7 mL). To this solution were added D2 (244.00 mg, 1.48 mmol), HATU (1.02 g, 2.69 mmol) and N, N-diisopropylethylamine (0.94 mL, 5.38 mmol) at 20° C. under nitrogen. After addition, the mixture was stirred at 20° C. 16 h. The resulting solution was quenched by addition of water (50 mL) and extracted with EtOAc (30 mL×2). The combined organic layers were dried and concentrated to give a crude product, which was purified by flash chromatography to afford the compound E18-4 (310.00 mg, 0.49 mmol, yield: 36.60%) as a white solid. LC-MS (ESI): 631 [M+H].sup.+.

[0314] Step 4: To a solution of E18-4 (310.00 mg, 0.49 mmol) in DCM (4 mL) was added trifluoroacetic acid (1 mL). The reaction mixture was stirred at 25° C. for 2 h. The resulting mixture was concentrated to give a crude compound, which was dissolved in DMF (1 mL). To the solution was added DOTA-PNP (284.00 mg, 0.54 mmol) and DIEA (0.52 mL, 2.95 mmol). The reaction mixture was stirred at 25° C. for 2 h. The crude product was purified by prep-HPLC to afford the E18 (40.00 mg, 0.04 mmol, yield: 8.87%) as a white solid. LC-MS (ESI): 918

[M+H].sup.+ .sup.1H NMR (400 MHz, D.sub.2O) δ 8.62 (d, J=4.4 Hz, 1H), 7.84 (d, J=9.2 Hz, 1H), 7.51-7.42 (m, 2H), 7.36 (d, J=9.2 Hz, 1H), 4.98 (d, J=10.4 Hz, 1H), 4.43-4.36 (m, 2H), 4.31-4.21 (m, 1H), 3.98-3.88 (m, 2H), 3.76-3.54 (m, 7H), 3.52-3.42 (m, 2H), 3.35-3.18 (m, 8H), 3.11-2.80 (m, 12H), 2.67-2.47 (m, 3H), 2.31 (d, J=14.0 Hz, 1H), 2.12-1.83 (m, 7H), 1.79-1.46 (m, 5H), 1.23-1.04 (m, 2H), 1.04-0.95 (m, 1H), 0.91-0.80 (m, 1H).

Example 10 (Method H): E19: 2, 2', 2''-(10-(2-(4-((4-(((4-((2-((1S, 3S, 5S)-3-cyano-2-azabicyclo [3.1.0]hexan-2-yl)-2-oxoethyl) carbamoyl) quinolin-6-yl) oxy) methyl) piperidin-1-yl) methyl) piperidin-1-yl)-2-oxoethyl)-1, 4, 7, 10-tetraazacyclododecane-1, 4, 7-triyl) triacetic acid

##STR00166## ##STR00167##

[0315] Step 1: To a solution of E19-1 (0.61 mL, 6.00 mmol) was added SOCl.sub.2 (5 mL, 68.50 mmol) at 20° C. The mixture was stirred at 70° C. for 3 h. The resulting mixture was concentrated to give a crude (1.30 g), which was dissolved in DCM (20 mL) at 0° C. To the solution was added DIEA (1.98 mL, 12.00 mmol) and E7-2 (2.01 g, 6.00 mmol) under nitrogen. The reaction solution was stirred at 25° C. for 2 h. The resulting mixture was quenched by addition of water (100 mL) and extracted with EtOAc (100 mL×2). The combined organic layers were dried and concentrated to give a crude product E19-2 (1.70 g, 3.52 mmol, yield: 58.62%) as a white solid. LC-MS (ESI): 484 [M+H].sup.+.

[0316] Step 2: To a solution of E19-2 (1.70 g, 3.52 mmol) in acetone (17 mL) was added tert-butyl

(2-(methylamino) ethyl) carbamate (732.54 mg, 4.21 mmol) and potassium carbonate (532.68 mg, 3.86 mmol) at 25° C. The mixture was stirred at 25° C. under N.sub.2 atmosphere for 3 h. The resulting mixture was quenched by addition of water (150 mL), extracted with EA (100 mL×2). The combined organic layers were dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound E19-3 (423.00 mg, 0.73 mmol, 20.86% yield) as a yellow solid. LC-MS (ESI): 578 [M+H].sup.+.

[0317] Step 3: A solution of E19-3 (105.80 mg, 0.18 mmol) in DCM (2 mL) and TFA (0.5 mL) was stirred at 25° C. under N.sub.2 atmosphere for 16 h. The resulting mixture was concentrated to give a crude product (98.00 mg, crude), which was dissolved in DMF (5 mL) to give a clear solution. To the solution was added DIEA (0.30 mL, 1.80 mmol) and E19-4 (149.83 mg, 0.18 mmol) (Mol. Pharmaceutics 2020, 17, 12, 4589-4602) under nitrogen. After addition, the mixture was stirred at 25° C. for 2 h. The resulting mixture was concentrated to give a residue, which was purified by prep-HPLC (method 1) to afford the title compound E19-5 (65.00 mg, 0.06 mmol, yield: 31.30%) as yellow oil. LC-MS (ESI): 1161 [M+H].sup.+.

[0318] Step 4: To a solution of E19-5 (57.00 mg, 0.05 mmol) in DCM (0.50 mL) was added TES (0.03 mL) and TFA (0.5 mL) at 25° C. The mixture was stirred at 25° C. under N.sub.2 atmosphere for 16 h. The resulting mixture was concentrated to give a residue, which was purified by prep-HPLC to afford the title compound E19 (7.00 mg, 7.10 µmol, yield: 14.46%) as a yellow solid. LC-MS (ESI): 936 [M+H].sup.+ .sup.1H NMR (400 MHz, D.sub.2O) δ 8.92-8.90 (m, 1H), 8.28-8.20 (m, 1H), 7.99 (d, J=8.0 Hz, 1H), 7.72-7.62 (m, 2H), 5.07 (d, J=10.8 Hz, 1H), 4.51 (d, J=5.2 Hz, 2H), 3.80 (d, J=16.4 Hz, 2H), 3.70-3.65 (m, 2H), 3.61-3.50 (m, 3H), 3.40-3.25 (m, 5H), 3.22-3.08 (m, 7H), 2.88-2.63 (m, 12H), 2.52-2.35 (m, 5H), 2.13-1.86 (m, 5H), 1.71-1.66 (m, 2H), 1.33-1.15 (m, 1H), 1.11-1.01 (m, 1H), 0.934-0.91 (m, 1H).

Example 11 (Method I): E20: 2, 2'- (4-(2-amino-2-oxoethyl)-10-(2-(4-((3-(((4-((2-((1S, 3S, 5S)-3-cyano-2-azabicyclo [3.1.0]hexan-2-yl)-2-oxoethyl) carbamoyl) quinolin-6-yl) oxy) methyl) azetidin-1-yl) methyl) piperidin-1-yl)-2-oxoethyl)-1, 4, 7, 10-tetraazacyclododecane-1, 7-diyl) diacetic acid

##STR00168## ##STR00169##

[0319] Step 1: To a solution of E6-4 (1.00 g, 1.66 mmol) in isopropyl alcohol (10 mL) was added HCl/EA (4M, 2.08 mL, 8.30 mmol) dropwise at 0° C. while keeping internal temperature between 0° C.-5° C. under N.sub.2. The mixture was stirred at 20° C. for 12 h. The reaction mixture was filtered and the filter cake was washed with heptane (20 mL), dried in vacuum to give a crude (580.00 mg). The crude (111.00 mg) was dissolved in DMF (1 mL), followed by addition of E20-1 (114.00 mg, 0.22 mmol) (U.S. Pat. No. 4,885,363A), DIEA (0.15 mL, 0.88 mmol) and HATU (125.00 mg, 0.33 mmol). The reaction mixture was stirred at 20° C. for 4 h and was concentrated to give a residue, which was purified by C18 reversed phase column eluting with MeOH in H.sub.2O (0.1% HCOOH) to afford the title compound E20-2 (112.00 mg, 0.11 mmol, yield: 50.60%) as yellow oil. LC-MS (ESI): 1000 [M+H].sup.+.

[0320] Step 2: To a solution of E20-2 (102.00 mg, 0.11 mmol) in DCM (0.5 mL) was added TFA (0.50 mL) and TES (0.03 mL). After addition, the mixture was stirred at 20° C. for 2 h. The resulting mixture was concentrated to give a crude product, which was purified by prep-HPLC to afford the title compound E20 (1.00 mg, 1.08 µmol, yield: 1.06%) as a white solid. LC-MS (ESI): 888 [M+H].sup.+ .sup.1H NMR (400 MHz, D<sub>2</sub>O) δ 8.72 (d, J=4.4 Hz, 1H), 7.97 (d, J=9.2 Hz, 1H), 7.65-7.41 (m, 3H), 5.05 (dd, J=10.8, 2.6 Hz, 1H), 4.57-4.46 (m, 2H), 4.41-3.92 (m, 7H), 3.87-2.46 (m, 30H), 2.40-2.12 (m, 3H), 2.00-1.80 (m, 2H), 1.78-1.60 (m, 2H), 1.30-1.00 (m, 3H), 0.99-0.85 (m, 1H).

Example 12 (Method J): E21: 2, 2'- (7-(2-(4-((3-(((4-((2-((1S, 3S, 5S)-3-cyano-2-azabicyclo [3.1.0]hexan-2-yl)-2-oxoethyl) carbamoyl) quinolin-6-yl) oxy) methyl) azetidin-1-yl) methyl) piperidin-1-yl)-2-oxoethyl)-1, 4, 7-triazonane-1, 4-diyl) diacetic acid

##STR00170##

[0321] Step 1: To a solution of E6-4 (100.00 mg, 0.17 mmol) in isopropyl alcohol (1.5 mL) was added HCl/EA solution (4M, 1 mL, 4 mmol) at 20° C. The reaction mixture was stirred at 20° C. under nitrogen for 12 h. The reaction mixture was concentrated to give a crude product, which was dissolved in DMSO (1 mL), followed by addition of DIEA (0.23 ml, 1.40 mmol), EDCI (212.00 mg, 1.11 mmol) and HOAt (151.00 mg, 1.11 mmol) under N.sub.2. The reaction mixture was stirred at 0° C. for 5 min. Then, to the mixture was added 2, 2', 2''-(1, 4, 7-triazonane-1, 4, 7-triyl) triacetic acid (NOTA) (463.59 mg, 1.53 mmol) in EtOH (1 ml) at 0° C. The reaction mixture was stirred at 0° C. for 1 h and then concentrated to give a crude product, which was purified by prep-HPLC to afford the title compound E21 (1.70 mg, 2.16 µmol, yield: 0.94%) as a white solid. LC-MS (ESI): 788 [M+H].sup.+ .sup.1H NMR (400 MHz, D.sub.2O) δ 8.74 (d, J=4.4 Hz, 1H), 8.38 (s, 1H), 7.98 (d, J=9.2 Hz, 1H), 7.59 (d, J=4.4 Hz, 1H), 7.53 (d, J=9.2 Hz, 1H), 5.06 (d, J=10.0 Hz, 1H), 4.58-4.05 (m, 9H), 3.89-3.79 (m, 1H), 3.77-3.52 (m, 7H), 3.42-3.37 (m, 1H), 3.24-2.80 (m, 15H), 2.71-2.59 (m, 2H), 2.44-2.30 (m, 1H), 2.02-1.87 (m, 2H), 1.80-1.67 (m, 2H), 1.32-1.11 (m, 2H), 1.11-1.03 (m, 1H), 0.95-0.85 (m, 1H).

Example 13 (Method K): E22: rac-2, 2', 2''-(10-(2-(4-(((1r, 4r)-4-(((4-((2-((1R, 3R, 5R)-3-cyano-2-azabicyclo [3.1.0]hexan-2-yl)-2-oxoethyl) carbamoyl) quinolin-6-yl) (methyl) amino) methyl) cyclohexyl) methoxy) piperidin-1-yl)-2-oxoethyl)-1, 4, 7, 10-tetraazacyclododecane-1, 4, 7-triyl) triacetic acid

##STR00171## ##STR00172##

[0322] Step 1: To a solution of E22-1 (5.00 g, 26.88 mmol) in THF (50 ml) was added BH.sub.3/THF (32.26 ml, 32.26 mmol) at 0° C. The mixture was stirred at 25° C. under N.sub.2 for 3 h. The resulting mixture was quenched by addition of methanol (20 mL) dropwise and concentrated to give a crude product, which was purified by flash chromatography to afford the compound E22-2 (3.63 g, 21.10 mmol, yield: 78.57%) as colorless oil. LC-MS (ESI): 173 [M+H].sup.+.

[0323] Step 2: To a solution of E22-2 (3.00 g, 17.42 mmol) and TEA (5.34 ml, 38.3 mmol) in THF (30 ml) was added TMS-Cl (4.68 ml, 36.6 mmol) at 0° C. The mixture was stirred at 25° C. under N.sub.2 atmosphere for 16 h. The resulting mixture was filtered through Celite and the filter cake was washed with petroleum ether (60 mL). The filtrate was concentrated to give a crude product (3.60 g), which was dissolved in triethylsilane (36 mL), followed by addition of benzyl 4-oxopiperidine-1-carboxylate (3.30 g, 14.14 mmol), trimethylsilyl trifluoromethanesulfonate (1.33 ml, 7.36 mmol) at -60° C. The mixture was stirred at 0° C. under N.sub.2 atmosphere for 1 h. Then the resulting solution was quenched by addition of water (100 mL) and extracted with EtOAc (100 mL×2). The combined organic layers were washed with brine (200 mL), dried and concentrated to give a residue, which was purified by flash chromatography to afford the title compound E22-3 (3.40 g, 6.98 mmol, yield: 47.40%) as colorless oil. LC-MS (ESI): 390 [M+H].sup.+.

[0324] Step 3: To a solution of E22-3 (3.40 g, 6.98 mmol) in MeOH (50 mL) was added wet Pd/C (340.00 mg, 10% in weight) and di-tert-butyl dicarbonate (3.15 ml, 13.55 mmol) at 0° C., The reaction mixture was stirred at 20° C. under H.sub.2 balloon for 16 h. Then the mixture was filtered and concentrated to give a residue, which was purified by flash chromatography to afford the compound E22-4 (1.50 g, 4.22 mmol, yield: 60.46%) as colorless oil. LC-MS (ESI): 356 [M+H].sup.+.

[0325] Step 4: To a solution of E22-4 (1.50 g, 4.22 mmol) in THF (8 ml), water (4 ml) and MeOH (2 ml) was added LiOH (202.00 mg, 8.44 mmol). The mixture was stirred at 25° C. under N.sub.2 atmosphere for 2 h. The reaction mixture was concentrated to give a crude product (2.00 g) as a yellow solid, which was dissolved in MeCN (20 mL), followed by addition of pyridine (0.55 ml, 6.85 mmol), di-tert-butyl dicarbonate (1.86 ml, 8.00 mmol) and methylamine (1.77 g, 57.10 mmol). The mixture was stirred at 25° C. under N.sub.2 atmosphere for 16 h. Then the resulting solution was quenched by addition of water (80 mL) and extracted with EtOAc (80 mL×2). The combined organic layers were washed with brine (150 mL), dried and concentrated to give a residue, which

was purified by flash chromatography to afford the compound E22-5 (506.00 mg, 1.43 mmol, yield: 24.99%) as a yellow solid. LC-MS (ESI): 355 [M+H].sup.+.

[0326] Step 5: To a solution of E22-5 (470.00 mg, 1.33 mmol) in THF (5 mL) was added BH.sub.3/Me.sub.2S (0.53 mL, 5.30 mmol) at 0° C. The reaction mixture was stirred at 70° C. under N.sub.2 for 1 h. Then the resulting solution was quenched by addition of MeOH (20 mL) and concentrated to give a residue, which was purified by flash chromatography to afford the title compound E22-6 (203.00 mg, 0.60 mmol, yield: 45.11%) as yellow oil. LC-MS (ESI): 341 [M+H].sup.+.

[0327] Step 6: To a solution of E22-6 (170.00 mg, 0.50 mmol) in toluene (3 mL) were added Cs.sub.2CO.sub.3 (651.00 mg, 1.99 mmol), D3-2 (186.00 mg, 0.70 mmol), XantPhos (57.80 mg, 0.10 mmol) and Pd.sub.2(dba).sub.3 (45.70 mg, 0.05 mmol). The mixture was stirred at 100° C. under nitrogen for 16 h. Then the mixture was filtered and the filtrate was concentrated to give a residue, which was purified by flash chromatography to afford the title compound E22-7 (87.00 mg, 0.16 mmol, yield: 33.10%) as yellow oil. LC-MS (ESI): 526 [M+H].sup.+.

[0328] Step 7: To a solution of E22-7 (87.00 mg, 0.16 mmol) in THF (2 mL), Water (1 mL) and MeOH (0.5 mL) was added 2M NaOH (0.25 mL, 0.50 mmol) at 0° C. The mixture was stirred at 20° C. under N.sub.2 atmosphere for 2 h. The reaction mixture was concentrated to give a crude product (88.00 mg), which was dissolved in DMF (2 mL), followed by addition of D2 (30.00 mg, 0.18 mmol), HATU (86.00 mg, 0.23 mmol) and DIEA (0.13 mL, 0.75 mmol) under nitrogen. The reaction mixture was stirred at 20° C. for 16 h. Then the resulting solution was quenched by addition of water (2 mL), extracted with EtOAc (10 mL×2), dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound E22-8 (65.00 mg, 0.10 mmol, yield: 65.60%) as yellow oil. LC-MS (ESI) m/z: 659 [M+H].sup.+.

[0329] Step 8: To a solution of E22-8 (65.00 mg, 0.10 mmol) in acetonitrile (3 mL) was added TsOH (58.00 mg, 0.31 mmol) under nitrogen. The reaction mixture was stirred at 40° C. for 2 h. Then the mixture was concentrated to give crude product (58.00 mg), which was dissolved in DMF (1 mL), followed by addition of DOTA-PNP (60.0 mg, 0.11 mmol) and DIEA (0.09 mL, 0.52 mmol). The reaction mixture was stirred at 20° C. for 16 h. The resulting mixture was concentrated to give a crude, which was purified by prep-HPLC to afford the title compound E22 (47.00 mg, 0.05 mmol, yield: 47.10%) as a yellow solid. LC-MS (ESI): 945 [M+H].sup.+ .sup.1H NMR (400 MHz, D.sub.2O) δ 8.42 (d, J=4.8 Hz, 1H), 7.77 (d, J=9.6 Hz, 1H), 7.50-7.35 (m, 2H), 7.01 (d, J=2.8 Hz, 1H), 4.97 (dd, J=10.6, 2.5 Hz, 1H), 4.48-4.29 (m, 2H), 3.93-3.77 (m, 1H), 3.73-3.54 (m, 7H), 3.52-3.43 (m, 2H), 3.39-3.24 (m, 9H), 3.21-2.87 (m, 18H), 2.67-2.51 (m, 1H), 2.36-2.26 (m, 1H), 1.92-1.84 (m, 1H), 1.83-1.70 (m, 2H), 1.67-1.50 (m, 5H), 1.40-1.21 (m, 3H), 1.05-0.94 (m, 1H), 0.95-0.80 (m, 3H), 0.75-0.61 (m, 2H).

Example 14 (Method L): E23: 2, 2', 2''-(10-(2-(4-(((1r, 4r)-4-(((4-((2-((1R, 3R, 5R)-3-cyano-2-azabicyclo [3.1.0]hexan-2-yl)-2-oxoethyl) carbamoyl) quinolin-6-yl) oxy) methyl) cyclohexyl) methoxy) piperidin-1-yl)-2-oxoethyl)-1, 4, 7, 10-tetraazacyclododecane-1, 4, 7-triyl) triacetic acid  
##STR00173## ##STR00174##

[0330] Step 1: To a solution of D2 (4.37 g, 26.46 mmol) in DMF (75 mL) was added DIEA (17.46 mL, 105.84 mmol), HOBt (3.57 g, 26.46 mmol), DIC (4.09 mL, 26.46 mmol) and E23-1 (5.00 g, 26.46 mmol) (WO2022/135326A1) at 0° C. After addition, the mixture was stirred at 25° C. under N.sub.2 for 2 h. The resulting mixture was quenched by addition of water (500 mL) and extracted with ethyl acetate (350 mL×2). The combined organic layers were dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound E23-2 (4.45 g, 13.24 mmol, yield: 50.11%) as a yellow solid. LC-MS (ESI): 337 [M+H].sup.+.






[0331] Step 2: To a solution of E22-4 (920.00 mg, 2.59 mmol) in THF (13 mL) was added Lithium borohydride (589.00 mg, 15.53 mmol) at 0° C. The mixture was stirred at 25° C. under nitrogen for 6 h. The reaction mixture was quenched by NH.sub.4Cl (50 mL) and extracted with EtOAc (50 mL×2). The combined organic layers were washed with brine (150 mL), dried and concentrated to

give a crude product, which was purified by flash chromatography to afford the compound E23-3 (550.00 mg, 1.68 mmol, yield: 64.90%) as a white solid. LC-MS (ESI): 328 [M+H].sup.+.










[0332] Step 3: To a solution of E23-3 (300.00 mg, 0.92 mmol) in THF (5 mL) were added E23-2 (308.00 mg, 0.92 mmol), triphenylphosphine (312.00 mg, 1.19 mmol), then diisopropyl azodicarboxylate (0.23 ml, 1.19 mmol) was added at 0° C. The reaction mixture was stirred at 25° C. for 3 h. Then the resulting solution was quenched by addition of water (40 mL) and extracted with EtOAc (40 mL×2). The combined organic layers were washed with brine (100 mL), dried and concentrated to give a residue, which was purified by flash chromatography to afford the compound E23-4 (240.00 mg, 0.37 mmol, yield: 40.60%) as a yellow solid. LC-MS (ESI) m/z: 646 [M+H].sup.+.

[0333] Step 4: To a solution of E23-4 (86.00 mg, 0.13 mmol) in CH.sub.3CN (3 mL) was added TsOH (76.00 mg, 0.40 mmol) under nitrogen. The reaction mixture was stirred at 40° C. for 2 h. Then the mixture was concentrated to give a crude product (80.00 mg), which was dissolved in DMF (1 mL), followed by addition of DOTA-PNP (85.00 mg, 0.16 mmol) and DIEA (0.13 mL, 0.73 mmol). The reaction mixture was stirred at 25° C. for 16 h. The crude product was purified by prep-HPLC to afford the title compound E23 (75.80 mg, 0.08 mmol, yield: 54.60%) as a white solid. LC-MS (ESI): 932 [M+H].sup.+ .sup.1H NMR (400 MHz, D.sub.2O) δ 8.60 (d, J=4.8 Hz, 1H), 7.78 (d, J=9.2 Hz, 1H), 7.47 (dd, J=20.8, 3.6 Hz, 2H), 7.30 (d, J=10.0 Hz, 1H), 4.96 (d, J=10.0 Hz, 1H), 4.40 (s, 2H), 3.92-3.77 (m, 3H), 3.77-3.61 (m, 6H), 3.59-3.49 (m, 2H), 3.51-3.23 (m, 11H), 3.19 (d, J=6.7 Hz, 2H), 3.14-2.83 (m, 10H), 2.70-2.50 (m, 1H), 2.30 (d, J=13.6 Hz, 1H), 1.94-1.70 (m, 5H), 1.67 (d, J=12.4 Hz, 3H), 1.50-1.19 (m, 3H), 1.10-0.88 (m, 3H), 0.90-0.69 (m, 3H).

[0334] The following compounds were prepared using procedures analogous to those described in Examples above. As is appreciated by those skilled in the art, these analogous examples may involve variations in general reaction conditions. The Method column indicates preparatory methods described above used in the preparation of the compounds.

TABLE-US-00005 LCMS (ESI) Meth- [M + Cpd od Structure H].sup.+ .sup.1H-NMR E9 C [00175]  embedded image 875.4 .sup.1H NMR (400 MHz, D.sub.2O) δ 8.92 (d, J = 5.6 Hz, 1H), 8.12 (d, J = 9.6 Hz, 1H), 7.99 (d, J = 5.6 Hz, 1H), 7.75-7.67 (m, 2H), 5.05-4.96 (m, 1H), 4.58-4.40 (m, 4H), 4.25-4.06 (m, 2H), 3.96-3.55 (m, 12H), 3.49-3.40 (m, 2H), 3.38-3.18 (m, 8H), 3.15-2.82 (m, 11H), 2.68- 2.55 (m, 1H), 2.40-2.25 (m, 1H), 1.95- 1.82 (m, 1H), 1.09-0.98 (m, 1H), 0.95- 0.85 (m, 3H), 0.82-0.71 (m, 2H). E10 C [00176]  embedded image 889.5 .sup.1H NMR (400 MHz, D.sub.2O) δ 8.97-8.90 (m, 1H), 8.19-8.10 (m, 1H), 8.00-7.92 (m, 1H), 7.80-7.67 (m, 1H), 7.57-7.46 (m, 1H), 5.38-5.21 (m, 1H), 5.11-4.97 (m, 1H), 4.91-4.78 (m, 1H), 4.57-4.45 (m, 3H), 4.44-4.08 (m, 5H), 3.80-3.67 (m, 2H), 3.64-3.47 (m, 6H), 3.36-2.87 (m, 19H), 2.74-2.48 (m, 2H), 2.39-2.26 (m, 1H), 1.94-1.82 (m, 1H), 1.70- 1.61 (m, 2H), 1.56-1.39 (m, 3H), 1.13- 0.97 (m, 3H), 0.93-0.83 (m, 1H). E11 C [00177]  embedded image 875.4 .sup.1H NMR (400 MHz, D.sub.2O) δ 8.96 (d, J = 5.6 Hz, 1H), 8.20-8.11 (m, 1H), 8.04- 7.97 (m, 1H), 7.83-7.71 (m, 1H), 7.58- 7.46 (m, 1H), 5.36-5.25 (m, 1H), 5.11- 5.01 (m, 1H), 4.99-4.82 (m, 1H), 4.53- 4.33 (m, 3H), 4.31-4.15 (m, 3H), 4.05- 3.75 (m, 3H), 3.68-2.73 (m, 26H), 2.69- 2.53 (m, 2H), 2.39-2.27 (m, 1H), 1.97- 1.82 (m, 2H), 1.71-1.60 (m, 2H), 1.23- 1.08 (m, 2H), 1.06-0.95 (m, 1H), 0.90- 0.82 (m, 1H). E12 A [00178]  embedded image 941.5 .sup.1H NMR (400 MHz, D.sub.2O) δ 8.94-8.85 (m, 1H), 8.08 (d, J = 9.2 Hz, 1H), 7.97 (d, J = 5.2 Hz, 1H), 7.75-7.65 (m, 2H), 4.99 (d, J = 10.8 Hz, 1H), 4.56-4.40 (m, 2H), 4.23 (s, 2H), 4.16-3.82 (m, 4H), 3.76- 3.55 (m, 6H), 3.54-3.46 (m, 2H), 3.45- 3.26 (m, 12H), 3.21-2.87 (m, 11H), 2.67- 2.53 (m, 1H), 2.30 (d, J = 14 Hz, 1H), 2.10-1.76 (m, 11H), 1.07-0.96 (m, 1H), 0.90-0.79 (m, 1H). E13 C [00179]  embedded image 929.5 .sup.1H NMR (400 MHz, D.sub.2O) δ 8.87 (d, J = 5.6 Hz, 1H), 8.07 (d, J = 9.2 Hz, 1H), 7.95 (d, J = 5.2 Hz, 1H), 7.75-7.62 (m, 2H), 5.02-4.96 (m, 1H), 4.50-4.45 (m, 2H), 4.32-4.21 (m, 2H), 4.21-4.14 (m, 2H), 4.12-4.04 (m, 2H), 4.04-3.94 (m, 2H), 3.79-3.45 (m, 9H), 3.39-2.89 (m, 18H), 2.72-2.51 (m, 4H), 2.53-2.40 (m, 1H), 2.38-2.26 (m, 2H), 2.23-2.04 (m, 2H), 1.94-1.78 (m, 2H), 1.66-1.55 (m, 2H), 1.20-1.05 (m, 2H), 1.04-



0.96 (m, 1H), 0.90-0.81 (m, 1H). E14 A [00180]  embedded image 943.5 .sup.1H NMR (400 MHz, D.sub.2O)  $\delta$  8.85 (d, J = 5.2 Hz, 1H), 8.05 (d, J = 9.6 Hz, 1H), 7.94 (d, J = 5.6 Hz, 1H), 7.76-7.63 (m, 2H), 5.06-4.92 (m, 1H), 4.47 (s, 2H), 4.24-2.69 (m, 37H), 2.63-2.53 (m, 1H), 2.34-2.25 (m, 1H), 1.91-1.81 (m, 1H), 1.60-1.44 (m, 12H), 1.05-0.94 (m, 1H), 0.90-0.81 (m, 1H). E15 D [00181]  embedded image 875.4 .sup.1H NMR (400 MHz, D.sub.2O)  $\delta$  8.89 (d, J = 5.6 Hz, 1H), 8.08 (d, J = 9.2 Hz, 1H), 7.97 (d, J = 5.4 Hz, 1H), 7.77-7.71 (m, 1H), 7.69 (d, J = 9.3 Hz, 1H), 4.98 (d, J = 8.7 Hz, 1H), 4.53-4.38 (m, 2H), 4.27-4.15 (m, 2H), 3.95-3.82 (m, 2H), 3.61-3.49 (m, 8H), 3.44-3.27 (m, 10H), 3.09-2.99 (m, 4H), 2.94-2.83 (m, 2H), 2.67-2.53 (m, 1H), 2.34-2.24 (m, 1H), 2.23-2.09 (m, 4H), 1.91-1.79 (m, 1H), 1.17 (d, J = 6.6 Hz, 9H), 1.06-0.92 (m, 1H), 0.88-0.81 (m, 1H). E16 D [00182]  embedded image 875.4 .sup.1H NMR (400 MHz, D.sub.2O)  $\delta$  8.91 (d, J = 4.5 Hz, 1H), 8.10 (d, J = 9.7 Hz, 1H), 7.99 (s, 1H), 7.75 (s, 1H), 7.71 (d, J = 9.0 Hz, 1H), 5.05-4.95 (m, 1H), 4.77-4.66 (m, 6H), 4.64-4.47 (m, 2H), 4.48-4.21 (m, 4H), 3.91-2.83 (m, 23H), 2.72-2.48 (m, 1H), 2.36-1.77 (m, 10H), 1.11-0.99 (m, 1H), 0.91-0.66 (m, 1H). E17 D [00183]  embedded image 917.5 .sup.1H NMR (400 MHz, D.sub.2O)  $\delta$  8.89 (d, J = 5.6 Hz, 1H), 8.09 (d, J = 9.2 Hz, 1H), 7.98 (d, J = 5.6 Hz, 1H), 7.75 (d, J = 2.8 Hz, 1H), 7.72-7.65 (m, 1H), 5.03-4.94 (m, 1H), 4.55-4.40 (m, 2H), 4.31-4.15 (m, 3H), 4.05-3.78 (m, 2H), 3.65-3.16 (m, 22H), 3.14-2.78 (m, 10H), 2.66-2.53 (m, 1H), 2.34-2.25 (m, 1H), 2.25-2.13 (m, 2H), 1.94-1.78 (m, 3H), 1.63-1.46 (m, 4H), 1.43-1.32 (m, 2H), 1.06-0.92 (m, 1H), 0.92-0.78 (m, 1H). E24 D [00184]  embedded image 912.4 .sup.1H NMR (400 MHz, D.sub.2O)  $\delta$  8.98 (d, J = 5.6 Hz, 1H), 8.84 (s, 1H), 8.50 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 9.3 Hz, 1H), 8.06 (dd, J = 16.0, 6.9 Hz, 2H), 7.99-7.85 (m, 2H), 5.65 (m, 2H), 5.03 (d, J = 10.6 Hz, 1H), 4.56-4.49 (m, 3H), 4.48-2.71 (m, 34H), 2.62 (td, J = 12.8, 11.4, 5.8 Hz, 1H), 2.31 (d, J = 13.6 Hz, 1H), 1.88 (d, J = 8.0 Hz, 1H), 1.04 (t, J = 7.6 Hz, 1H), 0.86 (m, 1H). E25 H [00185]  embedded image 864.4 .sup.1H NMR (400 MHz, D.sub.2O)  $\delta$  8.83 (d, J = 4.4 Hz, 1H), 8.13 (d, J = 7.6 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.66-7.47 (m, 2H), 5.00 (dd, J = 10.8, 2.5 Hz, 1H), 4.47-4.38 (m, 2H), 3.60-3.39 (m, 8H), 3.24-3.17 (m, 2H), 3.16-2.95 (m, 14H), 2.91-2.82 (m, 3H), 2.74-2.53 (m, 10H), 2.34-2.19 (m, 1H), 2.09-1.94 (m, 2H), 1.91-1.76 (m, 1H), 1.04-0.93 (m, 1H), 0.91-0.76 (m, 1H). E26 I [00186]  embedded image 886.5 .sup.1H NMR (400 MHz, D.sub.2O)  $\delta$  9.01 (d, J = 5.6, 1.2 Hz, 1H), 8.21 (d, J = 9.6 Hz, 1H), 8.09 (dd, J = 5.6, 1.6 Hz, 1H), 7.90-7.86 (m, 2H), 5.08 (m, 1H), 4.66-4.51 (m, 2H), 4.50-4.12 (m, 8H), 3.88-2.90 (m, 29H), 2.70 (m, 2H), 2.39 (m, 1H), 1.97 (m, 2H), 1.76 (m, 2H), 1.25 (m, 2H), 1.11 (m, 1H), 1.01-0.88 (m, 1H). E27 L [00187]  embedded image 916.4 .sup.1H NMR (400 MHz, D.sub.2O)  $\delta$  8.60 (d, J = 4.4 Hz, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.47 (d, J = 4.4 Hz, 1H), 7.42 (d, J = 2.8 Hz, 1H), 7.33 (dd, J = 9.2, 2.8 Hz, 1H), 5.10-4.93 (m, 1H), 4.49-4.37 (m, 2H), 4.16, 4.06 (m, 2H), 3.99-3.89 (m, 1H), 3.79-3.21 (m, 22H), 3.12-2.93 (m, 8H), 2.93-2.84 (m, 1H), 2.65-2.51 (m, 1H), 2.35-2.19 (m, 1H), 1.94-1.78 (m, 3H), 1.71-1.64 (m, 6H), 1.44-1.23 (m, 2H), 1.08-0.94 (m, 1H), 0.92-0.79 (m, 1H). E28 F [00188]  embedded image 976.4 .sup.1H NMR (400 MHz, D.sub.2O)  $\delta$  8.95 (t, J = 4.8 Hz, 1H), 8.20 (d, J = 7.2 Hz, 1H), 8.10-8.02 (m, 1H), 7.78-7.68 (m, 2H), 5.09 (d, J = 8.4 Hz, 1H), 4.58-4.52 (m, 2H), 4.52-4.39 (m, 2H), 4.25-4.09 (m, 2H), 4.00-3.91 (m, 1H), 3.88-2.87 (m, 30H), 2.82-2.61 (m, 4H), 2.58-2.48 (m, 1H), 2.39 (dd, J = 13.6, 2.4 Hz, 1H), 2.03-1.91 (m, 2H), 1.86-1.72 (m, 4H), 1.47 (s, 2H), 1.13-1.05 (m, 1H), 0.99-0.91 (m, 1H).

#### Purification Method

[0335] Prep-HPLC Purification Method 1: The compound was purified on Shimadzu LC-20AP and UV detector. The column used was Shim-pack GIS C18 (250\*20) mm, m. Column flow was 20 ml/min. Mobile phase were used (A) 0.1% TFA in Water and (B) Acetonitrile. Purification were carried out employing a linear gradient from 5% to 35% of (B) Acetonitrile for 20 or 30 min. The UV spectra were recorded at 220 nm&254 nm.

[0336] Prep-HPLC Purification Method 2: The compound was purified on Shimadzu LC-20AP and UV detector. The column used was Shim-pack GIS C18 (250\*20) mm, m. Column flow was 20 ml/min. Mobile phase were used (A) 0.1% NH.sub.3 in Water and (B) Acetonitrile. Purification were carried out employing a linear gradient from 5% to 35% of (B) Acetonitrile for 20 or 30 min.



The UV spectra were recorded at 220 nm&254 nm.

[0337] Prep-HPLC Purification Method 3: The compound was purified on Shimadzu LC-20AP and UV detector. The column used was Shim-pack GIS C18 (250\*20) mm, 10 m. Column flow was 20 ml/min. Mobile phase were used (A) 0.1% NH<sub>4</sub>HCO<sub>3</sub> in Water and (B) Acetonitrile. Purification were carried out employing a linear gradient from 2% to 35% of (B) Acetonitrile for 25 min or 30 min. The UV spectra were recorded at 220 nm&254 nm.

[0338] The following compounds were purified by prep-HPLC using the methods described above.

TABLE-US-00006 Purification Compound Method E1 Method 1 E2 Method 2 E3 Method 1 E4 Method 1 E5 Method 2 E6 Method 1 E7 Method 1 E8 Method 1 E9 Method 2 E10 Method 1 E11 Method 1 E12 Method 1 E13 Method 1 E14 Method 1 E15 Method 1 E16 Method 1 E17 Method 1 E18 Method 2 E19 Method 3 E20 Method 3 E21 Method 3 E22 Method 3 E23 Method 3 E24 Method 1 E25 Method 3 E26 Method 3

#### Radiochemistry

[0339] <sup>177</sup>Lu label: <sup>177</sup>Lu-cpmd was prepared in sodium acetate buffer (1M, pH 4.75) after incubation of 30 µg of precursor with 5mCi <sup>177</sup>LuCl<sub>3</sub> (ITG) at 70° C. for 30 min. Quality control was performed by iTLC (Eckert&Ziegler). The hot compound was diluted with 0.9% NaCl solution for further utility.

[0340] <sup>68</sup>Ga label: <sup>68</sup>GaCl<sub>3</sub> solution (1.0 mL, 370 MBq), was eluted from the <sup>68</sup>Ge/<sup>68</sup>Ga generator (Isotope Technologies Garching) with 0.05M HCl. <sup>68</sup>Ga-cpmd was prepared in sodium acetate buffer (1M, pH 4.2) after incubation of 20 g of precursor with 20mCi <sup>68</sup>GaCl<sub>3</sub> at 95° C. for 20 min. Quality standard: RCP>98% (iTLC), specific activity >0.75mCi/ug, and activity >1mCi/ml.

#### Biological Assays and Data

[0341] The biological activities of the compounds provided herein can be determined by using any suitable assay for determining the in vitro binding affinity of a compound as a FAP or PREP competitive inhibitor.

[0342] The cell-based assay is conducted to determine the cell internalization capability of a compound over time, including the efflux property.

[0343] The biological activity data for each compound was either reported in at least one experiment or the average of multiple experiments. It is understood that the data described herein may have reasonable variations depending on the specific conditions and procedures used by the person conducting the experiments.

#### FAP and PREP Enzymatic Assay

[0344] Recombinant FAP (SinoBio, Cat. #10464-H07H), was diluted in FAP enzymatic buffer (50 mM Tris pH7.5, 140 mM NaCl) into 1 ng/ul. Compounds were diluted with the same buffer into varying concentrations. Z-GP-AMC (Biochem partner, Cat #. 68542-93-8) was regenerated into 8.3 mM/mL with FAP enzymatic buffer. 50 µl of compound and 20 µl of diluted FAP were mixed and incubated at RT for 15 min, followed with addition of 30 µl of diluted Z-GPAMC. The mixture was incubated at 37° C. for 30 minutes. Reaction was terminated with glacial acid. The released AMC was detected with fluorescence reader (Perkin Elmer Victor Nivo Plate reader) with excitation and emission wavelength at 360 nm and 460 nm, respectively.

[0345] For PREP enzymatic assay, PREP (R&D System, Cat. #4308-SE), cpmd and Z-GP-AMC were diluted with PREP enzymatic buffer (100 mM Tris pH7.5, 1 mM EDTA, 3 mM DTT). The procedure remained the same as FAP enzymatic assay.

[0346] Curve fitting, IC<sub>50</sub> calculation and QC analysis was conducted by Prism 6.0.

TABLE-US-00007 Ex FAP IC<sub>50</sub>(nM) PREP IC<sub>50</sub>(µM) FAPI-04 3.2 >10 E1 20.9 >10 E2 2.5 >10 E3 5.8 >10 E4 3.2 >10 E5 4.5 >10 E6 4.5 >10 E9 0.6 >10 E10 7.4 >10 E11 15.1 >10 E12 2.4 >10 E13 2.4 >10 E14 0.4 >10 E15 1.3 >10 E16 2.7 >10 E17 2.0 >10 E18 11.3 >10 E19 7.1 >10 E23 2.1 >10 E24 0.7 >10 E25 19.7 >10 E26 42.3 >10 E27 1.2 >10 E28 54.8 >10

#### Cell Based Assay

[0347] Cell uptake: HEK-FAP cells were cultured in 24-well plates. 20nCi of .sup.177Lu-labeled compound was added into each well, and then incubated in 37° C., 5% CO.sub.2 incubator for varying durations. At each time point, the supernatant, cell membrane fraction and intracellular fraction were collected. The cell membrane fraction was recovered by incubating cells with buffer containing 50 mM glycine and 100 mM NaCl, pH 2.7 for 10 minutes at 37° C., 5% CO.sub.2, while the intracellular fraction was collected by harvesting the cell pellets following trypsin digestion. .sup.177Lu-compound in each component was detected by gamma counter.

[0348] Efflux: 20nCi of .sup.177Lu-labeled compound was incubated with cells for 2 hours, and then cells was washed and replaced with fresh medium. At each time point, the supernatant, cell membrane fraction and intracellular fraction were collected. The cell membrane fraction was recovered by incubating cells with buffer containing 50 mM glycine and 100 mM NaCl, pH 2.7 for 10 minutes at 37° C., 5% CO.sub.2, while the intracellular fraction was collected by harvesting the cell pellets following trypsin digestion. .sup.177Lu-compound in each component was detected by gamma counter.

TABLE-US-00008 \*Internalization \*Efflux 1 hr 4 hr 24 hr \*\*0 hr 4 hr 24 hr Ex (%) (%) (%) (%) (%) (%) \*\*\*FAPI-04 14.6 16.5 8.0 16.0 8.2 4.1 E1 18.3 24.1 19.5 20.5 19.3 10.1 E2 16.5 24.2 16.2 21.5 15.7 8.9 E4 29.9 39.2 35.1 29.6 26.7 26.8 E5 21.6 34.8 39.5 23.1 19.4 25.2 E6 18.9 38.7 37.2 32.7 27.1 26.7 E7 31.3 42.5 32.7 21.6 18.5 19.6 E8 4.8 7.7 19.9 2.0 2.2 2.0 E9 22.8 24.7 33.4 22.1 9.9 15.3 E10 16.8 15.2 22.2 13.9 3.5 7.5 E11 13.1 22.7 21.0 9.1 2.9 5.8 E12 28.5 40.1 30.8 26.9 20.2 21.3 E13 15.9 21.2 29.3 9.7 8.2 9.1 E14 39.4 41.6 30.6 20.7 15.6 27.7 E16 39.6 42.5 27.6 31.6 21.0 23.7 E17 24.5 15.8 22.9 20.1 16.8 12.8 \*The percentage of intracellular fraction is presented. \*\*The cells were washed and replaced with fresh medium after 2-hour incubation with .sup.177Lu labeled compounds. \*\*\*Reference compound from WO2019154886A1

[0349] Compare to literature compound FAPI-04 (WO2019/154886A1) the presented examples demonstrated improved cell internalization capability and lower efflux profile in the assay.

#### Biodistribution

[0350] 5×10<sup>6</sup> HEK FAP cell/site was inoculated into nude mice (Vital River). Mice was used for biodistribution assay when the tumor size reached 200 mm<sup>3</sup>. Animals were housed according to IACUC guidance and had accessed to food and water ad libitum.

[0351] 20-30 μCi of .sup.177Lu-cpmd was injected each mouse. At each indicated time, blood, heart, lung, spleen, liver, kidney, muscle, bone et al were collected, weighted and proceeded to gamma counter to collect the radioactivity. Uptake in every organ was calculated and measured in percentage of injected dose/gram tissue.

[0352] Organ distribution of .sup.177Lu-FAPI-04 (n=2) and .sup.177Lu-E1 (n=4) in HEK-FAPI tumor bearing nude mice are shown in FIG. 1A (3 hours), FIG. 1B (24 hours), and FIG. 1C (48 hours). The radio labeled compounds are shown to accumulate within the FAP expressing tumor. Compound E1 demonstrated higher enrichment at any time point than reference compound FAPI-04.

[0353] The embodiments described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the invention and are encompassed by the appended claims.

#### REFERENCE

[0354] An J L., Hou D K., and Wang L., et al. Fibroblast activation protein-alpha knockdown suppresses prostate cancer cell invasion and proliferation Histol Histopathol. 2022 Feb. 7; 18430. [0355] Chai X P, Sun G L, and Fang Y F, et al. Tumor-targeting efficacy of a BF211 prodrug through hydrolysis by fibroblast activation protein-a. Acta Pharmacol Sin. 2018 March; 39 (3): 415-424. [0356] Croft A P., Campos J., and Jansen K., et al. Distinct fibroblast subsets drive inflammation and damage in arthritis. Nature. 2019 Jun. 1; 570 (7760): 246-251. [0357] Dendl, K., Koerber S A., and Kratochwil C., et al. FAP and FAPI-PET/CT in Malignant and Non-Malignant

Diseases: A Perfect Symbiosis? *Cancers* (Basel). 2021 October; 13 (19): 4946. [0358] Hoffmann D B, Fraccarollo D, Galuppo P, et al. Genetic ablation of fibroblast activation protein alpha attenuates left ventricular dilation after myocardial infarction. *PLoS One*. 2021 Mar. 5; 16 (3): e0248196. [0359] Huang Y., Simms A E., and Mazur A., et al. Fibroblast activation protein-ax promotes tumor growth and invasion of breast cancer cells through non-enzymatic functions. *Clin Exp Metastasis*. 2011 August; 28 (6): 567-79. [0360] Kratochwil, C., Flechsig, P., and Lindner T., et al. .sup.68Ga-FAPI PET/CT: Tracer Uptake in 28 Different Kinds of Cancer. *J Nucl Med*. 2019 June; 60 (6): 801-805. [0361] Lay, A J., Zhang H M., and McCaughan G W., et al. Fibroblast activation protein in liver fibrosis. *Front Biosci*. 2019 Jan. 1; 24: 1-17. [0362] Luo, Y P., Pan, Q Q., and Yang, H X., et al. Fibroblast Activation Protein-Targeted PET/CT with .sup.68Ga-FAPI for Imaging IgG4-Related Disease: Comparison to .sup.18F-FDG PET/CT. *J Nucl Med*. 2021 February; 62 (2): 266-271. [0363] Lv, B., Xie, F., and Zhao, P., et al. Promotion of cellular growth and motility is independent of enzymatic activity of fibroblast activation protein-a. *Cancer Genomics Proteomics*, 2016, 13: 201-208. [0364] Niedermeyer J., Hilberg, MK., and Garin-Chesa, P., et al. Targeted disruption of mouse fibroblast activation protein. *Mol Cell Biol*. 2000 February; 20 (3): 1089-94. [0365] Osborne B., Yao TW., and Wang XM., et al. A rare variant in human fibroblast activation protein associated with ER stress, loss of enzymatic function and loss of cell surface localization. *Biochim Biophys Acta*. 2014 July; 1844 (7): 1248-59. [0366] Teng C., Zhang B., and Yuan Z. et al. Fibroblast activation protein-ax-adaptive micelles deliver anti-cancer drugs and reprogram stroma fibrosis. *Nanoscale*. 2020 Dec. 8; 12 (46): 23756-23767. [0367] Tillmanns J, Hoffmann D, Habbaba Y, et al. Fibroblast activation protein alpha expression identifies activated fibroblasts after myocardial infarction. *J Mol Cell Cardiol*. 2015 October; 87: 194-203. [0368] Schmidkonz C., Rauber S., and Atzinger A. et al. Disentangling inflammatory from fibrotic disease activity by fibroblast activation protein imaging. *Ann Rheum Dis*. 2020 November; 79 (11): 1485-1491. [0369] Windisch P., Zwahlen D R., and Koerber S A. et al. Clinical Results of Fibroblast Activation Protein (FAP) Specific PET and Implications for Radiotherapy Planning: Systematic Review. *Cancer* 2020, 12: 2629-2649. [0370] Windisch P, Zwahlen D R., and Koerber S A et al. Clinical Results of Fibroblast Activation Protein (FAP) Specific PET for non-malignant indications: Systematic Review. *EJNMMI Research* 2021, 11: 18. [0371] Zhang H., Hanson E J., and Koczorowska M M et al. Identification of Novel Natural Substrates of Fibroblast Activation Protein-alpha by Differential Degradomics and Proteomics. *Mol Cell Proteomics*. 2019 January; 18 (1): 65-85.

## Claims

1. A compound of Formula (I): ##STR00189## wherein: R.sup.1 is —H, —CN, —B(OH).sub.2, —(C=O)-alkyl, —(C=O)-aryl-, —C=C—(C=O)— aryl, —C=C—S(O).sub.2-aryl, —CO.sub.2H, —SO.sub.3H, —SO.sub.2NH.sub.2, —SO.sub.2F, —PO.sub.3H.sub.2, or 5-tetrazolyl; each of Q.sup.1 to Q.sup.7 is independently absent, O, C(R.sup.5).sub.2, NR.sup.5, C=O, C=S, or 3- to 10-membered N-containing heterocyclyl, provided that (i) two O are not directly adjacent to each other, and (ii) at least three of Q.sup.1 to Q.sup.7 are present; Ring C is 1-naphthyl, 5- to 10-membered N-containing heteroaryl, or 5- to 10-membered N-containing heterocyclyl; each instance of R.sup.2, R.sup.3, or R.sup.4 is independently —OH, halo, C.sub.1-C.sub.6 alkyl, —O—(C.sub.1-C.sub.6 alkyl), —N(R.sup.5).sub.2, or —S—(C.sub.1-C.sub.6 alkyl), each of said C.sub.1-C.sub.6 alkyl being independently and optionally substituted with one or more substituents independently selected from —OH, oxo, and halo; X.sup.1 is absent, O, NR.sup.5, S, C=O, C=S, —(C=O)—NR.sup.5—\*, —(C=S)—NR.sup.5—\*, —O-aryl—\*, —NR.sup.5-aryl—\*, —(C=O)—NR.sup.5-aryl—\*, —(C=S)—NR.sup.5-aryl—\*, wherein \* refers to the direction toward Ring C; G.sup.1 is absent, C.sub.1-C.sub.5 alkylene, or C.sub.2-C.sub.5 alkynylene, wherein said C.sub.1-C.sub.5 alkylene and C.sub.2-C.sub.5 alkynylene are optionally substituted with one or more

substituents independently selected from —OH, oxo, halo, C.sub.1-C.sub.3 alkyl optionally substituted with one or more halo, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl; each instance of X is independently absent, O, NR.sup.5, C=O, C=S, —(C=O)—NR.sup.5—\*, —NR.sup.5—(C=O)—\*, —(C=S)—NR.sup.5—\*, or —NR.sup.5—(C=S)—\*, wherein \* refers to the direction toward Ring C; each instance of G is independently absent, C.sub.1-C.sub.5 alkylene, or C.sub.2-C.sub.5 alkynylene, wherein said C.sub.1-C.sub.5 alkylene and C.sub.2-C.sub.5 alkynylene are optionally substituted with one or more substituents independently selected from —OH, oxo, halo, C.sub.1-C.sub.3 alkyl optionally substituted with one or more halo, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl; each instance of Ring B is absent, C.sub.3-C.sub.10 cycloalkyl, C.sub.6-C.sub.10 aryl, 5- to 10-membered heteroaryl, or 3- to 10-membered heterocyclyl; X.sup.2 is absent, O, NR.sup.5, C=O, C=S, —(C=O)—NR.sup.5—\*, —NR.sup.5—(C=O)—\*, —(C=S)—NR.sup.5—\*, or —NR.sup.5—(C=S)—\*, wherein \* refers to the direction toward Ring C; L is absent or a linker; Ring A is absent, 5 to 10-membered N-containing heteroaryl or 5 to 10-membered N-containing heterocyclyl; provided that G.sup.1, at least one G, at least one Ring B, Ring A, or L is present; n is 0, 1, 2, or 3; m is 0, 1, 2, or 3; p is 0, 1, 2, or 3; s is 0, 1, 2, or 3; each instance of R.sup.5 is independently —H or C.sub.1-C.sub.6 alkyl optionally substituted with one or more substituents independently selected from —OH, oxo, and halo; and Z is a radioactive moiety, a chelating agent, a fluorescent dye, or a contrast agent; or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein Q.sup.1, Q.sup.2, and Q.sup.3 are each independently absent or CH.sub.2; Q.sup.4 is CH.sub.2, C=O, or C=S; Q.sup.5 is NR.sup.5; Q.sup.6 is CHR.sup.5; and Q.sup.7 is C=O, or C=S.
3. The compound of claim 2, wherein -Q.sup.1-Q.sup.2-Q.sup.3-Q.sup.4-Q.sup.5-Q.sup.6-Q.sup.7- is —(C=O)—NH—CH.sub.2—(C=O)—.
4. The compound of claim 1, wherein Q.sup.1, Q.sup.2, Q.sup.3, and Q.sup.4 are each independently absent or CH.sub.2; Q.sup.5 is 5- to 6-membered N-containing heterocyclyl; Q.sup.6 is CHR.sup.5; and Q.sup.7 is C=O or C=S.
5. The compound of claim 4, wherein Q.sup.1 is O or NR.sup.5, and -Q.sup.2-Q.sup.3-Q.sup.4-Q.sup.5-Q.sup.6-Q.sup.7- is ##STR00190## wherein \* refers to the direction toward Ring C.
6. The compound of any one of claims 1 to 5, wherein Ring C is 5 to 10-membered N-containing heteroaryl.
7. The compound of any one of claims 1 to 5, wherein Ring C is ##STR00191##
8. The compound of claim 7, wherein Ring C is ##STR00192## wherein the shown point of attachment is toward Q.sup.1.
9. The compound of any one of claims 1 to 8, wherein X.sup.1 is O, NR.sup.5, or —(C=O)NR.sup.5—\*.
10. The compound of any one of claims 1 to 9, wherein G.sup.1 is C.sub.2-C.sub.5 alkylene.
11. The compound of any one of claims 1 to 10, wherein s is 0.
12. The compound of any one of claims 1 to 10, wherein s is 1.
13. The compound of any one of claims 1 to 12, wherein X.sup.2 is absent, O, or NH.
14. The compound of any one of claims 1 to 13, wherein each instance of X is independently absent.
15. The compound of any one of claims 1 to 14, wherein each instance of G is independently C.sub.1-C.sub.3 alkylene.
16. The compound of any one of claims 1 to 8, wherein —X.sup.2-[G-X—(Ring B)—X].sub.s-G.sup.1-X.sup.1— is -G.sup.1-X.sup.1—, wherein G.sup.1 is C.sub.2-C.sub.5 alkylene, and X.sup.1 is O, NR.sup.5, or —(C=O)NR.sup.5—\*.
17. The compound of any one of claims 1 to 8, wherein —X.sup.2-[G-X—(Ring B)—X].sub.s-G.sup.1-X.sup.1— is -G- (Ring B) -G.sup.1-X.sup.1—, wherein G is C.sub.1-C.sub.2 alkylene,

- G.sup.1 is C.sub.1-C.sub.2 alkylene, and X.sup.1 is O, NR.sup.5, or  $-(C=O)NR.sup.5-$ .\*.
18. The compound of any one of claims 1 to 8, wherein  $-X.sup.2-[G-X- (Ring B) -X].sub.s-G.sup.1-X.sup.1-$  is  $-G- (Ring B) -X.sup.1-$ , wherein G is C.sub.1-C.sub.2 alkylene, and X.sup.1 is O, NR.sup.5, or  $-(C=O)NR.sup.5-$ .\*.
19. The compound of any one of claims 1 to 8, wherein  $-X.sup.2-[G-X- (Ring B) -X].sub.s-G.sup.1-X.sup.1-$  is  $-X.sup.2-G-X-G.sup.1-X.sup.1-$ , wherein X.sup.2 is NR.sup.5, G is C.sub.1-C.sub.3 alkylene, X is O, NR.sup.5,  $-(C=O)-NR.sup.5-$ \*, or  $-NR.sup.5-(C=O)-$ \*, G.sup.1 is C.sub.1-C.sub.3 alkylene, and X.sup.1 is O, NR.sup.5, or  $-(C=O)NR.sup.5-$ .\*.
20. The compound of any one of claims 1 to 19, wherein L is absent.
21. The compound of any one of claims 1 to 19, wherein L is a linker.
22. The compound of claim 21, wherein the linker is a peptide comprising 2 to 5 amino acids.
23. The compound of any one of claims 1 to 19, wherein L is ##STR00193## wherein \* refers to the direction toward Ring A.
24. The compound of any one of claims 1 to 23, which is a compound of Formula (II-A): ##STR00194## or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.
25. The compound of claim 24, which is a compound of Formula (III-A): ##STR00195## or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.
26. The compound of claim 24, which is a compound of Formula (IV-A) or (IV-B): ##STR00196## or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.
27. The compound of any one of claims 1 to 23, which is a compound of Formula (II-B) ##STR00197## or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.
28. The compound of claim 27, which is a compound of Formula (III-B): ##STR00198## or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.
29. The compound of claim 28, which is a compound of Formula (IV-C) or (IV-D): ##STR00199## or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.
30. The compound of any one of claims 1 to 29, wherein Ring B is C.sub.3-C.sub.10 cycloalkyl.
31. The compound of claim 30, wherein the cycloalkyl is a monocyclic cycloalkyl, a bridged cycloalkyl, or a spiro cycloalkyl.
32. The compound of claim 31, wherein the cycloalkyl is ##STR00200##
33. The compound of any one of claims 1 to 29, wherein Ring B is 5 to 10-membered heteroaryl.
34. The compound of claim 33, wherein the heteroaryl is ##STR00201##
35. The compound of any one of claims 1 to 29, wherein Ring B is 5 to 10-membered heterocyclyl.
36. The compound of claim 35, wherein the heterocyclyl is ##STR00202##
37. The compound of any one of claims 1 to 36, wherein Ring A is 5 to 10-membered N-containing heterocyclyl.
38. The compound of claim 37, wherein the heterocyclyl is a monocyclic heterocyclyl.
39. The compound of claim 38, wherein the heterocyclyl is ##STR00203##
40. The compound of claim 37, wherein the heterocyclyl is a bridged heterocyclyl, a spiro heterocyclyl, or a fused heterocyclyl.
41. The compound of claim 40, wherein the heterocyclyl is ##STR00204##
42. The compound of any one of claims 1 to 41, wherein n is 1.
43. The compound of any one of claims 1 to 42, wherein each instance of R.sup.2 is independently halo, C.sub.1-C.sub.6 alkyl,  $-O-(C.sub.1-C.sub.6 \text{ alkyl})$ , or  $-N(R.sup.5).sub.2$ .
44. The compound of any one of claims 1 to 41, wherein n is 0.
45. The compound of any one of claims 1 to 44, wherein m is 0.
46. The compound of any one of claims 1 to 45, wherein p is 0.

47. The compound of any one of claims 1 to 46, wherein ##STR00205## is ##STR00206##
48. The compound of any one of claims 1 to 47, wherein R.sup.1 is —CN.
49. The compound of any one of claims 1 to 48, wherein Z is a radioactive moiety.
50. The compound of claim 49, wherein the radioactive moiety is a fluorescent isotope, a radioisotope, or a radioactive drug.
51. The compound of claim 49, wherein the radioactive moiety is selected from the group consisting of alpha radiation emitting isotopes, beta radiation emitting isotopes, gamma radiation emitting isotopes, Auger electron emitting isotopes, X-ray emitting isotopes, and fluorescence emitting isotopes.
52. The compound of claim 49, wherein the radioactive moiety is .sup.177Lu-DOTA, .sup.177Lu-DOTAGA, .sup.68Ga-DOTA, .sup.90Y-DOTA, Al.sup.18F-NOTA, .sup.203Pb-TCMC, .sup.212Pb-TCMC, .sup.64Cu-DOTA, or .sup.225Ac-DOTA.
53. The compound of claim 49, wherein the radioactive moiety is .sup.11C, .sup.18F, .sup.72As, .sup.72Se, .sup.123I, .sup.124I, .sup.131I or .sup.211At.
54. The compound of any one of claims 1 to 48, wherein Z is a fluorescent dye.
55. The compound of claim 54, wherein the fluorescent dye is an Xanthene, an Acridine, an Oxazine, an Cyanine, a Styryl dye, a Coumarin, a Porphine, a Metal-Ligand-Complex, a Fluorescent protein, a Nanocrystals, a Perylene, a Boron-dipyrromethene, or a Phthalocyanine, or a conjugate or combination thereof.
56. The compound of any one of claims 1 to 48, wherein Z is a chelating agent.
57. The compound of claim 56, wherein the chelating agent is a chelating agent that forms a complex with a divalent or trivalent metal cation.
58. The compound of claim 56, wherein the chelating agent is 1, 4, 7, 10-tetraazacyclododecane-N, N', N, N'-tetra acetic acid (DOTA), ethylenediaminetetraacetic acid (EDTA), 1, 4, 7-triazacyclononane-1, 4, 7-triacetic acid (NOTA), 1, 4, 7, 10-tetraazacyclododecane-1-(glutaric acid)-4, 7, 10-triacetic acid (DOTAGA), 2-[4, 7, 10-tris (2-amino-2-oxoethyl)-1, 4, 7, 10-tetrazacyclododec-1-yl]acetamide (TCMC), triethylenetetramine (TETA), iminodiacetic acid, diethylenetriamine-N, N, N', N', N''-penta acetic acid (DTPA), bis- (carboxymethyl imidazole) glycine, or 6-hydrazinopyridine-3-carboxylic acid (HYNIC).
59. The compound of claim 56, wherein the chelating agent or the chelating agent with a linker (Z-L) is a structure in Table 1, Table 1A, or Table 1B.
60. The compound of any one of claims 1 to 48, wherein Z is a contrast agent.
61. The compound of claim 60, wherein the contrast agent comprises a paramagnetic agent.
62. A compound in Table 2, or a stereoisomer, or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.
63. A complex formed by a compound of any one of claims 1 to 62 and a divalent or trivalent metal cation.
64. The complex of claim 63, wherein the metal cation is a cation of Cr, Ga, In, Tc, Re, La, Yb, Sm, Ho, Y, Pm, Dy, Er, Lu, Sc, Pr, Gd, Bi, Ru, Pd, Rh, Sb, Ba, Hg, Eu, Tl, Pb, Cu, Re, Au, Ac, Th, or Ag.
65. The complex of claim 63, wherein the metal cation is a cation of .sup.51Cr, .sup.67Ga, .sup.68Ga, .sup.111In, .sup.99mTc, .sup.186Re, .sup.188Re, .sup.139La, .sup.140La, .sup.175Yb, .sup.153Sm, .sup.166Ho, .sup.88Y, .sup.90Y, .sup.149Pm, .sup.165Dy, .sup.169Er, .sup.177Lu, .sup.47Sc, .sup.142Pr, .sup.159Gd, .sup.212Bi, .sup.213Bi, .sup.97Ru, .sup.109Pd, .sup.105Rh, .sup.101mRh, .sup.119Sb, .sup.128Ba, .sup.197Hg, .sup.151Eu, .sup.153Eu, .sup.169Eu, .sup.201Tl, .sup.203Pb, .sup.212Pb, .sup.64Cu, .sup.67Cu, .sup.188Re, .sup.186Re, .sup.198Au, .sup.225Ac, .sup.227Th, or .sup.199Ag.
66. A pharmaceutical composition comprising a compound of any one of claims 1 to 62 or a complex of any one of claims 63 to 65, and a pharmaceutically acceptable excipient.
67. A method for the diagnosis or treatment of a disease characterized by overexpression of

fibroblast activation protein (FAP) in a subject, comprising administering to the subject a diagnostically or therapeutically effective amount of a compound of any one of claims 1 to 62, a complex of any one of claims 63 to 65, or a pharmaceutical composition of claim 66.

**68.** The method of claim 67, wherein the disease is cancer, chronic inflammation, atherosclerosis, fibrosis, tissue remodeling, or keloid disorder.

**69.** The method of claim 68, wherein the disease is cancer, and the cancer is breast cancer, pancreatic cancer, small intestine cancer, colon cancer, rectal cancer, lung cancer, head and neck cancer, ovarian cancer, hepatocellular carcinoma, 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, or prostate cancer.

**70.** A kit comprising a compound of any one of claims 1 to 62, a complex of any one of claims 63 to 65, or a pharmaceutical composition of claim 66, and instructions for the diagnosis or treatment of a disease.

---