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(54) Title: NON-PEPTIDE TARGETED THERAPEUTICS AND USES THEREOF

(57) Abstract: Described herein are non-peptide drug conjugates (NPDCs) that target tumor cells expressing cell surface peptide and protein G protein-coupled receptors and their use in the treatment and/or diagnosis of cancer.

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NON-PEPTIDE TARGETED THERAPEUTICS AND USES THEREOF

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Patent Application No. 63/208,923 filed on June 09, 2021, which is incoporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] Described herein are non-peptide drug conjugates (NPDCs) and methods of using such drug conjugates as cancer therapeutics, diagnostics, or both.

BACKGROUND OF THE INVENTION

[0003] Neoplasms are abnormal growth of cells and cause enormous medical burdens, including morbidity and mortality, in humans. Neoplasms include benign or noncancerous neoplasms which do not display malignant features and are generally unlikely to become dangerous (e.g., adenomas); malignant neoplasms display features such as genetic mutations, loss of normal function, rapid division, and ability metastasize (invade) to other tissues; and neoplasms of uncertain or unknown behavior. Malignant neoplasms (i.e., cancerous solid tumors) are the leading cause of death in industrialized countries. Noncancerous neoplasms including benign adenomas can also cause significant morbidity and mortality. Although standard treatments can achieve significant effects in tumor growth inhibition and even tumor elimination, the applied drugs exhibit only minor selectivity for the malignant tissue over healthy tissue and their severe side effects limit their efficacy and use. Specific targeting of neoplastic cells without affecting healthy tissue is a major desire for effective solid tumor therapy. As one of 3 main classes of cell surface receptors, G protein-coupled receptors (GPCRs) are frequently overexpressed in tumor cells and are considered promising targets for selective tumor therapy. Despite the advances achieved with peptide-drug conjugate (PDC) therapeutics that target cell surface receptors, there is a significant need for therapeutics and diagnostics that overcome limitations imposed by peptide- and protein-based targeted therapeutics, such as inability to penetrate large solid tumors, instability to proteases and peptidases; unfavorable absorption, distribution, metabolism, and excretion (ADME) properties; and manufacturing challenges. Non-peptide ligands conjugated to suitable drug cargos or payloads represent a novel class of selective cancer therapeutics or diagnostics.

SUMMARY OF THE INVENTION

[0004] Described herein are non-peptide drug conjugates and their use in the treatment of tumors. The present disclosure provides an alternative and improved method for the treatment of tumors. In some embodiments, the non-peptide drug conjugates disclosed herein provide an improved method for targeting tumor cells over traditional therapies that have narrow therapeutic indexes.

[0005] In one aspect, described herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof:

NP – L - Q

Formula (I)

wherein:

NP is a nonpeptide ligand that binds to a G protein-coupled receptor (GPCR) expressed in tumor cells;

Q is a payload moiety comprising a chelating moiety or a radionuclide (**Z**) complex thereof; and

L is a linker that covalently connects the non-peptide ligand **NP** and the payload moiety **Q**; wherein the linker **L** is attached to **NP** at a position that permits binding of **NP** to the peptide or protein GPCR; and wherein upon administration to a mammal, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, targets tumor cells expressing the GPCR.

[0006] In some embodiments, the GPCR is a receptor for an endogenous peptide or protein ligand. In some embodiments, the GPCR is a receptor for an endogenous peptide or protein hormone or a chemokine.

[0007] In some embodiments, **NP** is a small molecule that binds to a GPCR that recognizes an endogenous peptide or protein hormone that is: adrenocorticotropic hormone (ACTH), amylin, angiotensin, atrial natriuretic peptide (ANP), calcitonin, cholecystokinin (CCK), gastrin, ghrelin, glucagon, growth hormone (GH), follicle-stimulating hormone (FSH), insulin, leptin, melanocyte-stimulating hormone (MSH), oxytocin, parathyroid hormone (PTH), prolactin, renin, somatostatin, thyroid-stimulating hormone (TSH), thyrotropin-releasing hormone (TRH), vasopressin, or vasoactive intestinal peptide (VIP). In some embodiments, **NP** binds to a GPCR that recognizes an endogenous peptide or protein hormone, provided that the GPCR does not bind neurotensin.

[0008] In some embodiments, the GPCR is a chemoattractant GPCR. In some embodiments, the chemoattractant GPCR that is: a classical GPCR that is formyl peptide receptor (FPR1, FPR2, or FPR3), platelet activating factor receptor (PAFR), activated complement component 5a

receptor (C5aR); or a chemokine GPCR that is binds to a CC chemokine (β-chemokine), CXC chemokine (α-chemokine), C chemokine (γ chemokine), or CX3C chemokine (d-chemokine).

[0009] In some embodiments, the GPCR is: an angiotensin receptor; apelin receptor; bombesin receptor; bradykinin receptor; calcitonin receptor; chemokine receptor; cholecytokinin receptor; corticotropic-releasing factor receptor; galanin receptor; ghrelin receptor; glucagon receptor; glycoprotein hormone receptor; gonadotropin-releasing hormone receptor; kisspeptin receptor; melanocortin receptor; motilin receptor; neuromedin U receptor; neuropeptide FF/AF receptor; neuropeptide S receptor; neuropeptide W/B receptor; neuropeptide Y receptor; opioid receptor; orexin receptor; parathyroid hormone receptor; prokineticin receptor; prolactin-releasing peptide receptor; QRFP receptor; relaxin family peptide receptor; somatostatin receptor; tachykinin receptor; thyrotropin-releasing hormone receptor; urotensin receptor; vasopressin and oxytocin receptor; VIP; or PACAP receptor.

[0010] In another aspect, described herein is a method for the treatment of tumors in a mammal comprising administering to the mammal a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the tumors comprise tumor cells expressing a GPCR. In some embodiments, the tissue(s) comprising the tumor cells also comprise non-tumor cells that do not express the GPCR or express the GPCR are lower expression levels than the tumor cells. In some embodiments, the the tumor cells overexpress the GPCR. In some embodiments, the GPCR expressed in the tumor cells of the tumor are targeted by the compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the tumor cells are cells of a solid tumor, adenoma, sarcoma, carcinoma, or lymphoma. In some embodiments, the tumor cells are cells of a neoplasm.

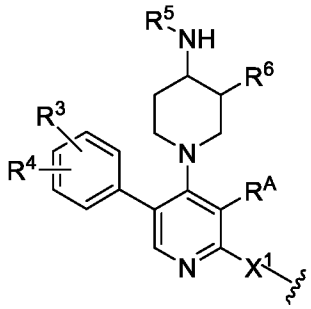
[0011] In some embodiments, neoplasms, benign or malignant, are based on the type of cell origin and comprise solid tumors, adenomas, sarcomas, carcinomas, or lymphomas. In some embodiments, mammals with malignant neoplasms have anal cancer, bladder cancer, bowel cancer, brain cancer, breast cancer, colon cancer, colorectal cancer, endometrial cancer, esophageal cancer, gallbladder cancer, gastric cancer, heart cancer, kidney cancer, lung cancer, liver cancer, melanoma, uterine cancer, lymphoma, ovarian cancer, pancreatic cancer, or prostate cancer.

[0012] In some embodiments, the solid tumor is an endocrine tumor (i.e., endocrine in origin). In some embodiments, the endocrine tumor is an adrenal tumor, neuroendocrine tumor, parathyroid tumor, pituitary tumor, or thyroid cancer. In some embodiments, the tumor comprises neuroendocrine tumors. In some embodiments, the tumor comprises somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

[0013] In some embodiments, mammals with benign neoplasms have adenomas of the colon, kidney, adrenal gland, thyroid, pituitary, parathyroid, liver, breast, appendix, bronchial tube, prostate, sebaceous gland, or salivary gland.

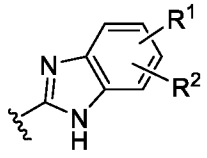
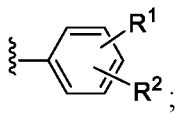
[0014] In some embodiments, **NP** is a non-peptide ligand that binds to somatostatin receptors expressed in tumor cells, and wherein **NP** is a non-peptide ligand comprising a 4-(4-aminopiperidin-1-yl)-5-(phenyl)pyridine structural motif or a 4-[(4αS,8αS)-octahydro-1H-pyrido[3,4-b][1,4]oxazin-6-yl]-5-(phenyl)pyridine structural motif; wherein -**L-Q** is attached to **NP** at the 2-position of the pyridine.

[0015] In some embodiments, **NP** has a structure of Formula (II), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof:



Formula (II)

wherein:

R^A is  or ;

each R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4heteroalkyl, -CN, -$N(R^7)_2$, or -OR^7;

R^5 is hydrogen, or substituted or unsubstituted C_1-C_6alkyl;

R^6 is hydrogen, -OR^7, -$N(R^7)_2$, -CN, halogen, C_1-C_6 alkyl, or C_1-C_6fluoroalkyl;

or R^5 and R^6 are taken together with the intervening atoms to which they are attached to form a morpholine;

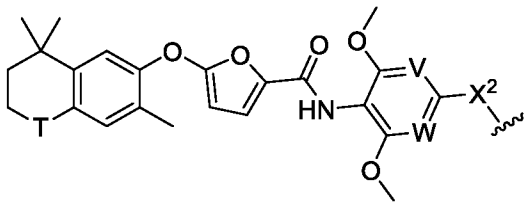
X^1 is absent, -O-, -S-, -$N(R^7)$-, -C(=O)-, -C(=O)$N(R^7)$-, -C(=O)O-, -$N(R^7)$C(=O)-, or a heterocycle; and

each R^7 is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl.

[0016] In some embodiments, **NP** is a non-peptide ligand that binds to gonadotropin-releasing hormone receptor (GnRHR) expressed in tumor cells; and wherein **NP** is a non-peptide ligand

comprising a N-{4,6-dimethoxy-pyrimidin-5-yl}-5-[3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furamide structural motif; a N-(4,6-dimethoxypyrimidin-5-yl)-5-(3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-2-furamide structural motif; or a N-(4,6-dimethoxypyrimidin-5-yl)-5-((3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy)furan-2-carboxamide structural motif.

[0017] In some embodiments, **NP** has a structure of Formula (X), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof:



Formula (X)

wherein:

T is absent, $-CH_2-$, $-CH(CH_3)-$or $-C(CH_3)_2-$;

X^2 is absent, -O-, or $-N(R^7)-$;

V is CH or N; and W is CH or N; and

R^7 is hydrogen or substituted or unsubstituted C_1-C_6alkyl.

[0018] In yet another aspect, described herein is a method of targeting delivery of a radionuclide to tumor cells in a mammal comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, to a mammal with tumors:

NP – L - Q

Formula (I)

wherein:

NP is a non-peptide ligand that binds to a G protein-coupled receptor (GPCR) expressed in tumor cells;

Q is a payload moiety comprising: a radionuclide (**Z**) and a chelator configured to bind the radionuclide (**Z**); and

L is a linker that covalently connects the non-peptide ligand **NP** and the payload moiety **Q**.

[0019] In some embodiments, the tumor cells are present in tissues and/or organs that comprise non-tumor cells that do not express the targeted GPCR or express the targeted GPCR at levels that are less than the level of expression in the tumor cells. In some embodiments, the tumor cells overexpress a GPCR. In some embodiments, the tumor cells overexpress the GPCR targeted by the compound of Formula (I).

[0020] In some embodiments, **L** is a non-cleavable linker or a cleavable linker.

[0021] In some embodiments, **NP** is a non-peptide ligand that binds to a GPCR that recognizes an endogenous peptide or protein hormone. In some embodiments, the GPCR is expressed in tumor cells of a solid tumor, adenoma, sarcoma, carcinoma, or lymphoma; **Q** comprises a radionuclide (**Z**) and a chelator configured to bind the radionuclide (**Z**); and **L** is an optional non-cleavable linker.

[0022] In some embodiments, **Z** is a diagnostic or therapeutic radionuclide. In some embodiments, **Z** is an Auger electron-emitting radionuclide, α-emitting radionuclide, β-emitting radionuclide, or γ-emitting radionuclide. In some embodiments, **Q** comprises a radionuclide (**Z**) and a chelator configured to bind the radionuclide (**Z**), wherein the radionuclide is suitable for positron emission tomography (PET) analysis, single-photon emission computerized tomography (SPECT), or magnetic resonance imaging (MRI).

[0023] In a further aspect, described herein is a method for identifying tissues or organs in a mammal comprising tumor cells expressing a G protein-coupled receptor (GPCR) comprising:

(i) administering to the mammal with a tumor a compound of Formula (I), or a pharmaceutically acceptable salt thereof:

NP – L - Q

Formula (I)

wherein:

NP is a non-peptide ligand that binds to a G protein-coupled receptor (GPCR) expressed in tumor cells;

Q is a payload moiety (**Q**) comprising: a radionuclide (**Z**) and a chelator configured to bind the radionuclide (**Z**);

L is a linker that covalently connects the non-peptide ligand **NP** and the payload moiety **Q**; wherein the linker **L** is attached to **NP** at a position that permits binding of **NP** to the GPCR;

(ii) performing positron emission tomography (PET) analysis, single-photon emission computerized tomography (SPECT), or magnetic resonance imaging (MRI).

[0024] In some embodiments, the tumor cells overexpress a GPCR. In some embodiments, the tumor cells overexpress the GPCR targeted by the compound of Formula (I).

[0025] In another aspect, described herein is a method for the in vivo imaging of tissues or organs in a mammal comprising tumor cells expressing a G protein-coupled receptor (GPCR) comprising:

(i) administering to the mammal a compound of Formula (I), or a pharmaceutically acceptable salt thereof:

NP – L - Q

Formula (I)

wherein:

NP is a non-peptide ligand that binds to a G protein-coupled receptor (GPCR) expressed in tumor cells;

Q is a payload moiety (**Q**) comprising: a radionuclide (**Z**) and a chelator configured to bind the radionuclide (**Z**);

L is a linker that covalently connects the non-peptide ligand **NP** and the payload moiety **Q**;

wherein the linker **L** is attached to **NP** at a position that permits binding of **NP** to the GPCR;

(ii) performing positron emission tomography (PET) analysis, single-photon emission computerized tomography (SPECT), or magnetic resonance imaging (MRI).

[0026] In some embodiments, the tumor cells are present in tissues and/or organs that comprise non-tumor cells that do not express the targeted GPCR or express the targeted GPCR at levels that are less than the level of expression in the tumor cells. In some embodiments, the tumor cells overexpress a GPCR. In some embodiments, the tumor cells overexpress the GPCR targeted by the compound of Formula (I).

[0027] In yet another aspect, described herein is a method for identifying tissues or organs in a mammal that overexpress a G protein-coupled receptor (GPCR) comprising:

(i) administering to the mammal a compound of Formula (I), or a pharmaceutically acceptable salt thereof:

NP – L - Q

Formula (I)

wherein:

NP is a nonpeptide ligand that binds to a G protein-coupled receptor (GPCR) expressed in tumor cells;

Q is a payload moiety comprising: a radionuclide (**Z**) and a chelator configured to bind the radionuclide (**Z**);

L is a linker that covalently connects the non-peptide ligand **NP** and the payload moiety **Q**;

wherein the linker **L** is attached to **NP** at a position that permits binding of **NP** to the GPCR;

(ii) performing positron emission tomography (PET) analysis, single-photon emission computerized tomography (SPECT), or magnetic resonance imaging (MRI).

[0028] In some embodiments, **Z** comprises a diagnostic radionuclide. In some embodiments, wherein: step (ii) is initiated after an amount of time following step (i) sufficient for interaction between the compound of Formula (I) and tumor cells in the mammal that express the GPCR.

[0029] Also described herein is a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt, or solvate thereof, and at least one pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is formulated for administration to a mammal by intravenous administration, subcutaneous administration, or oral administration.

[0030] In another aspect, described herein is a method for the treatment of cancer comprising administering to a mammal with cancer an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or an effective amount of pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0031] In another aspect, described herein is a method for treating tumors with a radionuclide comprising administering to a mammal with tumors an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or an effective amount of pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0032] In some embodiments, the mammal has anal cancer, bladder cancer, bowel cancer, brain cancer, breast cancer, colon cancer, colorectal cancer, endometrial cancer, esophageal cancer, gallbladder cancer, gastric cancer, heart cancer, kidney cancer, lung cancer, liver cancer, melanoma, uterine cancer, lymphoma, ovarian cancer, pancreatic cancer, or prostate cancer.

[0033] In some embodiments, the mammal has an endocrine cancer. In some embodiments, the endocrine cancer is adrenal tumors, neuroendocrine tumors, parathyroid tumors, pituitary tumors, or thyroid tumors.

[0034] In some embodiments, the mammal has neuroendocrine tumors. In some embodiments, the mammal has somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

[0035] In some embodiments, the tumors comprise an adenoma. In some embodiments, the adenoma is an adenoma of the colon, kidney, adrenal gland, thyroid, pituitary, parathyroid, liver, breast, appendix, bronchial tube, prostate, sebaceous gland, or salivary gland.

[0036] In any of the embodiments disclosed herein, the mammal is a human.

[0037] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

[0038] Cancer, a disease in which some cells undergo a genetic change in the control of their growth and replication that results in uncontroled growth and spreading, is one of the leading causes of death worldwide. General types of cancers include solid tumors (cancers that typically originate in organs), carcinomas (cancers that originate in skin or tissues that line organs), sarcomas (cancers of connective tissues such as bones), leukemias (cancers of bone marrow), and lymphomas and myelomas (cancers of the immune system). Neoplasms are abnormal growth of cells that result in solid tumors which may be benign (i.e. do not display malignant features and are generally unlikely to become dangerous such as adenomas), malignant (i.e. display features such as genetic mutations, loss of normal function, rapid division, and ability metastasize (invade) to other tissues), and of uncertain or unknown behavior. State-of-the-art treatment of neoplasms is accomplished by a combination of surgical procedures, chemotherapy, and radiation therapy. Surgical procedures can be curative under some conditions, but often requires multiple interventions as well as combination with radiation and chemotherapy. Chemotherapy proves to be a potent weapon in the fight against cancer in many cases, further optimization is required. Chemotherapy is typically performed by systemic administration of potent cytotoxic drugs, but these compounds lack tumor selectivity and therefore also kill healthy cells in the body. The resulting non-specific toxicity is the cause of severe side effects of chemotherapy which does not target the cancerous cells specifically over other cells. Radiotherapy is the use of high-energy radiation to kill cells. The source of radiation may be external-beam radiation (applied using an external source), internal radiation (placement of a radioactive material near the target cells), or radiotherapy from the systemic administration of a radioactive material. Similar to chemotherapy, many radiation therapy options also lack tumor cell identification properties needed to achieve the ultimate goal of targeted tumor therapy with drug molecules or radionuclides.

[0039] Described herein is the design of NPDCs that exploit characteristics that selectively identify neoplasms, such as significantly overexpressed cell surface receptors, different from healthy cells to achieve a therapeutic effect only in the selected cells. Neoplasms overexpressing a variety of cell surface GPCRs are actively targeted with the NPDCs described herein, thereby selectively delivering anti-cancer drugs or radionucliudes to the malignant cells.

[0040] GPCRs are a large and diverse group of integral membrane receptors and as a consequence are expressed in every cell type in the body. The function of GPCRs is to detect a host of signals outside the cell including but not limited to light, peptides, lipids, sugars and proteins and transmit the signal across the membrane to convert into intracellular responses.

Because of these critical actions, the GPCR superfamily is the largest and most important family of drug targets as highlighted by the large number of approved therapeutics targeting this class. GPCRs are generally poorly antigenic making them difficult targets for antibody-based strategies. For many GPCRs, a large proportion of the protein population resides in intracellular compartments at any given time reducing the total number of cell surface binding sites accessible to antibodies or peptides.

[0041] Many GPCRs, especially those that recognize endogenous peptides and endogenous proteins, such as chemokines, are ideal for NPDCs with suitable drug cargos or payloads because of their restricted physiologic expression and frequent overexpression in particularly intractable cancers (Reubi et al, The Journal Of Nuclear Medicine, Vol. 58, No. 9 (Suppl. 2), 10S-15S). Many human tumors overexpress different GPCRs, often times at significantly higher density than other tissues. For example, gastroenteropancreatic (GEP) neuroendocrine tumors (NETs) overexpress somatostatin receptors, namely SSTR2, SSTR3, and SSTR5. Other peptide receptors are overexpressed in NETs, such as the incretin receptor glucagonlike peptide 1 (GLP-1), the glucose-dependent insulinotropic polypeptide (GIP) receptor, and cholecystokinin (CCK) receptors (CCK1 and CCK2 subtypes). Medullary thyroid carcinomas (MTC) overexpress the CCK2 receptor and GIP receptors. Breast cancers overexpress gastrin-releasing peptide (GRP) receptors, Y1 subtype of neuropeptide Y (NPY) receptors, SSTR2, and CXCR4. Due to the complicated GPCR overexpression profiles in neoplasms, targeting multiple receptors simultaneously may address issues such as heterogeneity, resistance, and change of phenotype during disease progression that have hampered many current treatment options.

[0042] Most currently available GPCR-targeting drugs act at receptors for which the native ligands are small molecules, such as histamine, adrenaline, and neurotransmitters. Drugs targeting GPCR for which the native ligands are peptides or proteins, are typically also peptides or proteins.

[0043] Peptides are intrinsically sensitive to proteolytic enzymes and peptidases present in most tissues, and are rapidly degraded into multiple fragments which no longer have significant affinity to the intended receptors. There are ways to stabilize peptides (e.g. incorporating peptidomimetic structures or using more stable D amino acids in the peptide backbone) but such variations may lead to loss of affinity and/or selectivity, and negtively impact physicochemical properties (e.g. poor solubility and tendency to aggregate). In addition, peptides may cause unwanted immunogenic responses complicating later stages of development by masking the therapeutic effect and impacting the safety assessment.

[0044] When peptide ligands are linked to radionuclide payloads, the resulting conjugates often degrade apart rapidly in blood plasma and produce radioactive peptide fragments which may nonspecifically bind to both tumor and normal tissue. Such premature breakdown of peptide drug conjugates (PDCs) and antibody drug conjugates (ADCs) reduce the amount of radionuclide payloads distributed to targeted tumors, lowering treatment efficacy, and possibly increasing toxicity. In addition, peptides are most likely exclusively excreted via kidney, which may limit their applications. Marked kidney uptake of some peptide-based therapeutics has limited their routine use.

[0045] High affinity, small molecule ligands that bind peptide GPCRs and protein GPCRs, such as chemokine GPCRs, have been described and are cell permeable and can access populations of receptors in endoplasmic reticulum and endosomes. Owing to the low molecular weight of non-peptide small molecules, vascular permeability and tumor penetration should be improved compared to high molecular weight conjugates based on peptides and antibodies. The binding affinity of small molecule nonpeptide ligands in many cases surpasses that of FDA approved antibodies by orders of magnitude.

[0046] Provided herein are non-peptide drug conjugates (NPDCs). When the non-peptide ligand of a NPDC, which is a small molecule, binds to a GPCR, it embeds in the extracellular loops of the GPCR, leaving the conjugated drug cargo or payload moiety of the NPDC pointing to extracellular space. The conjugated drug cargo or payload moiety is linked to the non-peptide ligand in a manner that does not affect the binding affinity of the nonpeptide ligand to the GPCR. The conjugated drug cargos or payload moieties include chelated radionuclides, which are linked to the nonpeptide ligand using a stable linker or cleavable linker.

[0047] In some embodiments, slowly dissociating nonpeptide ligands for a GPCR can maintain therapeutically effective concentrations in a target tissue long after they have been cleared from the systemic circulation resulting in improved therapeutic windows and prolonged duration of action compared to their circulating plasma concentrations. In some embodiments, similar optimization of receptor residence time may be used as a selective tumor targeting mechanism to increase local concentrations or prolong tumor residence times of radionuclide conjugates in tumors, without relying on tumor specific intracellular trafficking. This same principle of concentration of GPCR ligands in target tissues enables PET labeling or radioligand imaging studies to visualize defined regions of receptor expression. If the conjugates are stably linked, release of nonselective free toxin can be avoided and conjugates that initially “miss” their cytotoxic target can be retained in the tumor for additional attempts. In some embodiments,

coupling of suitable payloads (e.g., radionuclides) to nonpeptide small molecule GPCR ligands provides an improved method for targeting of radionuclide conjugates to cancerous tissues.

[0048] In some embodiments, nonpeptide ligands for a GPCR that are internalized are optimized to increase internalization and improve intracellular retention.

Nonpeptide Small Molecule Drug Conjugates (NPDCs)

[0049] In one aspect, described herein is a non-peptide drug conjugate (NPDC). In some embodiments, the NPDC is a compound of Formula (I), or a pharmaceutically acceptable salt thereof:

NP – L - Q

Formula (I)

wherein:

NP is a nonpeptide ligand that binds to a G protein-coupled receptor (GPCR) expressed in tumor cells;

Q is a payload moiety comprising a chelating moiety or a radionuclide (**Z**) complex thereof; and

L is a linker that covalently connects the non-peptide ligand **NP** and the payload moiety **Q**; wherein the linker **L** is attached to **NP** at a position that permits binding of **NP** to the peptide or protein GPCR; and wherein upon administration to a mammal, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, targets tumor cells expressing the GPCR.

[0050] In some embodiments, the NPDC is a compound having the structure of Formula (I), or a pharmaceutically acceptable salt thereof:

NP – L - Q

Formula (I)

wherein:

NP is a non-peptide ligand that binds to a G protein-coupled receptor (GPCR) expressed in tumor cells;

Q is a payload moiety comprising a radionuclide (**Z**) and a chelator configured to bind the radionuclide (**Z**); and

L is a linker that covalently connects the non-peptide small molecule ligand **NP** and the payload moiety **Q**; wherein the linker **L** is attached to **NP** at a position that permits binding of **NP** to the peptide or protein GPCR; and wherein upon administration to a mammal with cancer, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is targeted to the tissues comprising tumor cells expressing the GPCR.

Targeted Tissues and Receptors

[0051] In some embodiments, the compound of Formula (I) demonstrates activity for the targeted GPCR receptor. In some embodiments, the activity is functional activity. In some embodiments, the activity is binding affinity. In some embodiments, the compound of Formula (I) demonstrates functional activity for the targeted GPCR receptor. In some embodiments, the compound of Formula (I) demonstrates binding affinity for the targeted GPCR receptor. In some embodiments, the compound of Formula (I) demonstrates binding affinity or functional activity to the targeted GPCR receptor with a binding affinity or functional activity that is less than 100 nM as measured in a suitable in vitro assay that measures such binding activity or functional activity. In some embodiments, the compound of Formula (I) demonstrates binding affinity or functional activity to the targeted GPCR receptor with a binding affinity or functional activity that is less than 100 nM as measured in a suitable in vitro assay that measures such binding activity or functional activity. In some embodiments, the compound of Formula (I) demonstrates binding affinity or functional activity to the targeted GPCR receptor with a binding affinity that is less than 10 nM as measured in a suitable in vitro assay that measures such binding activity. In some embodiments, the compound of Formula (I) demonstrates binding affinity or functional activity to the targeted GPCR receptor with a binding affinity or functional activity that is less than 5 nM as measured in a suitable in vitro assay that measures such binding activity. In some embodiments, the compound of Formula (I) demonstrates binding affinity or functional activity to the targeted GPCR receptor with a binding affinity or functional activity that is less than 1 nM as measured in a suitable in vitro assay that measures such binding activity or functional activity.

[0052] In some embodiments, the compound of Formula (I) has a binding affinity or functional activity to the targeted GPCR receptor that is at least 10-fold, at least 50-fold, at least 100-fold, at least 200-fold, at least 500-fold, or at least 1000-fold greater than the binding affinity or functional activity for non-target receptors. In some embodiments, the compound of Formula (I) is selective for one GPCR. In some embodiments, the compound of Formula (I) is selective for one family of GPCRs (e.g., the somatostatin family of receptors, which include SSTR1, SSTR2, SSTR3, SSTR4, SSTR5). In some embodiments, the compound of Formula (I) is selective for one GPCR within a family of GPCRs. In some embodiments, the compound of Formula (I) has a binding affinity or functional activity for a GPCR that is at least 10-fold greater than its binding affinity or functional activity for any other GPCR. In some embodiments, the compound of Formula (I) has a binding affinity or functional activity for one or more GPCRs.

[0053] In some embodiments, the compound of Formula (I) is stable in the presence of liver microsomal enzymes. In some embodiments, the compound of Formula (I) is stable in the

presence of proteases. In some embodiments, the compound of Formula (I) is stable in blood plasma. In some embodiments, the compound of Formula (I) is stable in blood plasma and optionally internalized into tumor cells after binding to the GPCR expressed in tumor cells. In some embodiments, the compound of Formula (I) comprises an optional linker **L**, is stable in blood plasma, and is optionally internalized into tumor cells after binding to the cancer cell surface peptide GPCR or protein GPCR.

[0054] In some embodiments, the compound of Formula (I) preferentially accumulates in tumor tissues that express the targetted GPCR. In some embodiments, the compound of Formula (I) preferentially accumulates in tissues or organs comprising tumor cells that express the GPCR(s) as compared to tissues or organ(s) lacking tumor cells that express the GPCR(s). In some embodiments, the compound of Formula (I) preferentially accumulates at least 1-fold, at least 2-fold, 3-fold, at least 4-fold, at least 5-fold, or greater than 5-fold more in tissues or organ(s) comprising tumor cells that express the GPCR(s) as compared to tissues or organs lacking tumor cells that express the GPCR(s). It is understood that the compound may accumulate in certain tissues and organs involved in the metabolism and/or excretion of therapeutics, including but not limited to the kidneys, liver and interstines.

[0055] In some embodiments, the GPCR targeted by the compound of Formula (I) is expressed at higher levels and/or at higher concentrations in or by tumor cells and at substantially lower levels in or by non-tumor cells.

[0056] In some embodiments, the GPCR targeted by the compound of Formula (I) is expressed in tumor cells in tissues and/or organs that normally do not express the GPCR.

[0057] In some embodiments, **NP** binds to a GPCR expressed in a tumor cell, provided that **NP** does not comprise an unnatural amino acid residue that is 2-amino-2-adamantane carboxylic acid, cyclohexylglycine, or 9-amino-bicyclo[3.3.1]nonane-9-carboxylic acid.

[0058] In some embodiments, the GPCR is a receptor for an endogenous peptide or an endogenous protein ligand, wherein endogenous peptide or endogenous protein ligand is a peptide or protein hormone or a chemokine.

Peptide GPCRs

[0059] Peptide hormones play regulatory functions mainly in the brain, gut, and endocrine system. These peptides are important in biology, but their receptors have become increasingly relevant clinically because they are often overexpressed in malignant tumors. In many instances, these peptide receptors are overexpressed in cancer cells, in comparison to their expression in normal tissue adjacent to the neoplasm and/or in its normal tissue of origin. The different level of receptor expression allows high uptake of peptide hormone receptor ligand conjugates in tumor

cells, while none or low uptake of such conjugates in cells do not express receptors. This feature allows peptide hormone ligand radionuclide conjugate to perform receptor-targeted imaging and therapy.

[0060] Numerous hormone-activated GPCRs are overexpressed in hormone-dependent and independent tumors and trigger multiple transduction pathways, which mediate relevant biological effects in diverse cancer cells. For example, bradykinin (BK) receptors are overexpressed in prostate cancer and mediate cell growth through Gαq and/or Gα13 which activate RhoA-dependent signaling.

[0061] Among the GPCR family members, the gonadotropin-releasing hormone (GnRH) receptor is a well-established target in the clinical practice of cancer treatment. GnRH receptors are expressed not only in the pituitary and in normal peripheral tissues, but also in various tumor cells like melanoma, prostate and endometrial carcinomas, leiomyomas, leiomyosarcomas, breast cancer, choriocarcinoma, epithelial and stromal tumors of the ovary. Several human tumor types, including ovarian, prostate, breast, endometrial, and lung cancer, overexpress or even uniquely express this receptor with respect to the surrounding nonmalignant cells.

[0062] The class of somatostatin receptors (SSTRs) consists of five members (SSTR1-5), which are widely expressed in different tissues in the body including nervous, pituitary, kidney, lung, and immune cells. Their natural ligand is the neuropeptide somatostatin (SST), which occurs in two active isoforms, the SST-14 and SST-28. In combination with their receptors, both isoforms act as inhibitory hormones. An important physiological function of the SSTR/SST axis is, for example, the inhibition of the release of growth hormones. SSTRs, particularly SSTR subtype 2, are found highly expressed in many neoplastic cells and in tumoral blood vessels. Overexpression of SSTRs, and in particular SSTR2, has been found in various neuroendocrine tumors, as well as other tumors such as breast, ovarian, and lung cancer. Targeting of the SSTR2 for drug delivery has been accomplished by using stabilized, cyclic somatostatin analogs such as octreotate, octreotide, and lanreotide. For example, covalently attaching a DOTA chelator to octreotide (DOTA-TATE, also known as DOTA-(Tyr^3)-octreotate) has made it possible to target delivery of radionuclides to tumor cells expressing somatostatin receptors. DOTA-TATE can be reacted with the radionuclides gallium-68, lutetium-177 and copper-64 to form radiopharmaceuticals for positron emission tomography (PET) imaging or radionuclide therapy. ^{177}Lu DOTA-TATE therapy is a form of peptide receptor radionuclide therapy (PRRT) which targets somatostatin receptors and is a form of targeted drug delivery.

[0063] The bombesin (Bn) receptor family consists of three members, namely the BB1, BB2, and BB3 receptor, which are expressed in the central nervous system (CNS), but also in the

periphery such as the gastrointestinal tract. They mediate a multitude of physiological functions, including an autocrine growth action on cells and potent CNS effects. The natural peptide ligand for the BB1 is the neuromedin B and for the BB2 the gastrin-releasing peptide, while the BB3 is considered an orphan receptor. Upregulation of Bn receptors was found in various cancer subtypes and especially the BB2 is highly overexpressed in tumors such as breast, prostate, small cell lung, and pancreatic cancer. Targeting the Bn receptors for drug delivery has typically centered on the use of Bn analogs, including for example the peptide [d-Tyr6,β-Ala11,Phe13,Nle14]-Bn(6-14).

[0064] The vasoactive intestinal peptide (VIP) receptors 1 and 2, which are overexpressed in various cancers such as colon, breast, and endocrine tumors. The natural ligand VIP and its analogs are investigated for the preparation of drug conjugates.

[0065] The cholecystokinin 2 receptor (CCK2R) is overexpressed in various cancers of the thyroid, lung, pancreas, liver, and the gastrointestinal tract. Targeting of this receptor for drug delivery has typically concerned the use of analogs of its natural peptide ligands cholecystokinin and gastrin.

[0066] The melanocortin receptor 1 (MC1R) was found to be upregulated in malignant melanoma. For the generation of drug conjugates for this system, shortened peptide analogs of the natural MC1R ligand α-MSH, for example, the agonist NAPamide, possess the potential as delivery agents.

[0067] The ghrelin receptor (GhrR), also named growth hormone secretagogue receptor 1a (GHSR1a), is a class A GPCR. It is widely expressed in the brain, especially in the hypothalamus, but also in the hippocampus and the pituitary. Furthermore, the GhrR was found to be expressed in a variety of peripheral tissues, including liver, heart, pancreas, thyroid, ovaries, testis, and more. The natural ligand of the GhrR is the peptide hormone ghrelin, a 28-amino acid peptide. Ligand binding to the GhrR occurs rather deep in the cavity created by the TM helices of the receptor. The ghrelin/GhrR axis plays a role for a multitude of physiological functions such as food intake, regulation of energy homeostasis, release of various hormones (e.g., growth hormone, prolactin, adrenocorticotropic hormone) and reward-seeking behavior. The GhrR is present in a vast number of different cancer subtypes. Expression of the GhrR was described in pituitary adenomas, thyroid, breast, lung, testis, ovarian, prostate, pancreatic, gastric, and colorectal cancer, as well as in astrocytoma.

[0068] The human Y1 receptor (hY1R) is a class A GPCR from the Y receptor family in human and is predominantly expressed in the CNS, for example, the hypothalamus, but also found in peripheral tissues including heart, lung, or smooth muscle. Besides the hY1R, three

other Y receptors are expressed in human, namely the Y2 receptor (hY2R), the Y4 receptor (hY4R), and the Y5 receptor (hY5R). These receptors are bound and activated by the neuropeptide Y family of peptide hormones, which consists of the neuropeptide Y (NPY), the peptide YY (PYY), and the human pancreatic polypeptide (hPP). NPY was found to be the most abundant peptide hormone in the mammalian CNS. Endogenous NPY is a 36-amino acid peptide and consists of a flexible N-terminus, a C-terminal amphipathic α-helix, and an amidated C-terminus. The presence in certain tumor tissues renders the hY1R a target for anti-cancer drug delivery. Expression of the hY1R together with the hY2R has been described in ovarian sex cord-stromal tumors, nephroblastomas, gastrointestinal stromal tumors, and testicular tumors. Sole expression of the hY1R was observed in adrenal cortical tumors and renal cell carcinomas. High expression of the hY1R was also determined in Ewing sarcoma tumors and breast cancer tumors and breast cancer-derived metastases. In contrast, in the surrounding non-neoplastic breast tissue expression of the hY2R was predominantly observed. This switch in the Y receptor expression pattern during neoplastic transformation of breast tissue therefore enables a specific drug shuttling into breast tumors when using a hY1R-preferring ligand as delivery agent.

[0069] Oprhan GPCRs have been linked to cancer development and progression on the basis of their overexpression and/or up-regulation by diverse factors. For instance, an elevated expression of the orphan G-protein-coupled receptor GPR49 was involved in the formation and proliferation of basal cell carcinoma, while GPR18 was found associated with melanoma metastases. In lung, cervix, skin, urinary bladder, testis, head and neck squamous cell carcinomas were detected high levels of GPR87.

[0070] As used herein, "peptide G protein-coupled receptor (GPCR)" means a GPCR that is the binding site for a peptide ligand. The native ligand for a peptide GPCR is a peptide ligand.

[0071] As used herein, "protein G protein-coupled receptor (GPCR)" means a GPCR that is the binding site for a protein ligand. The native ligand for a protein GPCR is a protein ligand.

[0072] In some embodiments, **NP** of the compound of Formula (I) binds to a GPCR that also binds to a peptide or protein hormone that is: adrenocorticotropic hormone (ACTH), amylin, angiotensin, atrial natriuretic peptide (ANP), calcitonin, cholecystokinin (CCK), gastrin, ghrelin, glucagon, growth hormone, follicle-stimulating hormone (FSH), insulin, leptin, melanocyte-stimulating hormone (MSH), oxytocin, parathyroid hormone (PTH), prolactin, renin, somatostatin, thyroid-stimulating hormone (TSH), thyrotropin-releasing hormone (TRH), vasopressin, or vasoactive intestinal peptide.

[0073] In some embodiments, **NP** binds to a GPCR, provided that the GPCR does not bind neurotensin.

[0074] In some embodiments, the GPCR is: angiotensin receptor; apelin receptor; bombesin receptor; bradykinin receptor; calcitonin receptor; chemokine receptor; cholecytokinin receptor; corticotropic-releasing factor receptor; galanin receptor; ghrelin receptor; glucagon receptor; glycoprotein hormone receptor; gonadotropin-releasing hormone receptor; kisspeptin receptor; melanocortin receptor; motilin receptor; neuromedin U receptor; neuropeptide FF/AF receptor; neuropeptide S receptor; neuropeptide W/B receptor; neuropeptide Y receptor; opioid receptor; orexin receptor; parathyroid hormone receptor; prokineticin receptor; prolactin-releasing peptide receptor; QRFP receptor; relaxin family peptide receptor; somatostatin receptor; tachykinin receptor; thyrotropin-releasing hormone receptor; urotensin receptor; vasopressin and oxytocin receptor; VIP and PACAP receptor; or combinations thereof.

[0075] In some embodiments, the GPCR is a member of one of the following families of receptors: angiotensin receptors (e.g. AGTR1, AGTR2); apelin receptor (APLNR); bombesin receptors (BB1/NMBR, BB2/GRPR, BRS3); bradykinin receptors (BDKRB1, BDKRB2); calcitonin receptor (e.g. CALCR, CALCRL); chemokine receptors (e.g. CCR1-10, CXCR1-6, etc); cholecytokinin receptors (CCKAR, CCKBR); corticotropic-releasing factor receptors (CRHR1, CRHR2); galanin receptors (GALR1-3); ghrelin receptor (GHSR); glucagon receptor family (e.g. GHRHR, GIPR, GLP1R, GLP2R, GCGR, SCTR); glycoprotein hormone receptors (FSHR, LHCGR, TSHR); gonadotropin-releasing hormone receptor (GNRHR, GNRHR2); kisspeptin receptor (KISS1R); melanocortin receptors (MC1-5R); motilin receptor (MLNR); neuromedin U receptors (NMUR1, NMUR1-2); neuropeptide FF/AF receptors (NPFFR1, NPFFR2); neuropeptide S receptors (NPSR1); neuropeptide W/B receptors (NPBWR1, NPBWR2); neuropeptide Y receptors (NPY1-6R); opioid receptors (OPRD1, OPRK1, OPRM1); orexin receptors (HCRTR1, HCRTR2); parathyroid hormone receptors (PTH1R, PTH2R); prokineticin receptors (PROKR1, PROKR2); prolactin-releasing peptide receptor (PRLHR); QRFP receptor (QRFPR); relaxin family peptide receptors (RXFP1-4); somatostatin receptors (SSTR1-5); tachykinin receptors (TACR1-3); thyrotropin-releasing hormone receptor (TRHR1, TRHR2); urotensin receptor (UTS2R); vasopressin and oxytocin receptors (AVPR1A, AVPR1B, AVPR2, OXTR); or VIP and PACAP receptors (ADCYAP1R1, VIPR1, VIPR2).

[0076] In some embodiments, the GPCR is a member of one of the following families of receptors: angiotensin receptors (e.g. AGTR1, AGTR2); apelin receptor (APLNR); bombesin receptors (BB1/NMBR, BB2/GRPR); bradykinin receptors (BDKRB1, BDKRB2); ghrelin receptor (GHSR); glycoprotein hormone receptors (FSHR, LHCGR); gonadotropin-releasing hormone receptor (GNRHR); kisspeptin receptor (KISS1R) melanocortin receptor family (MC1R, MC2R, MC3R, MC4R, MC5R); neuropeptide Y receptors (NPY1); neurotensin

receptors (NTSR1); parathyroid hormone receptors (PTH1R); prolactin-releasing peptide receptor (PRLHR); somatostatin receptor family (SSTR1, SSTR2, SSTR2, SSTR4, SSTR5); thyrotropin-releasing hormone receptor (TRHR1, TRHR2); or VIP and PACAP receptors (ADCYAP1R1, VIPR1, VIPR2).

Chemoattractant GPCRs

[0077] In some embodiments, the GPCR is a chemoattractant GPCR. In some embodiments, the GPCR is a chemoattractant GPCR that is: a classical GPCR that is formyl peptide receptor (FPR1, FPR2, or FPR3), platelet activating factor receptor (PAFR), activated complement component 5a receptor (C5aR); or a chemokine GPCR that is binds to a CC chemokine (β-chemokine), CXC chemokine (α-chemokine), C chemokine (γ chemokine), or CX3C chemokine (d-chemokine).

[0078] Tumor cells that metastasize preferentially to specific organs via the blood and lymphatic vessels present a great challenge in cancer eradication. One family of GPCRs that is closely linked to tumor metastasis is the chemokine receptors. Chemokines enhance the motility and survival of cancer cells in the vicinity and milieu of a tumor following their local release in either an autocrine or paracrine fashion into the microenvironment of tumor-surrounding regions. Among these are chemokines that are involved in metastatic cancer cell homing as well as cancer cell growth and survival, such as chemokine receptors CCR7 and CCR10. Local chemokine generation in the tumor milieu may recruit macrophages and leukocytes, which can then induce the release of matrix metalloproteases (MMPs) promoting tumor cell survival, growth, and invasion as well as improving the cytokine-rich microenvironment. CXCR4 is a well-documented chemokine receptor driving cancer metastasis. Moreover, cells in the most frequent sites of metastasis, including the lungs, bone marrow, lymph nodes, and liver, express the chemokine ligand CXCL12/SDF-1.

[0079] Tumor cells frequently express high levels of CXCR4, facilitating cell growth, survival, and migratory capability. For example, while CXCR4 is not found in normal breast tissues, it is rather overexpressed in breast cancer cells and a marked inhibition of breast cancer metastatic spread is achieved by inhibiting CXCR4. However, treatment with CXCR4 inhibitors requires caution, since CXCR4 inhibition induces progenitor/stem cell mobilization from the bone marrow. Hypoxia-inducible factor-1 (HIF-1α), which is activated by hypoxia, increases CXCR4 transcription. In highly aggressive basal-like breast cancer cells, CXCR4 may also couple to Gα12/13 when Gα13 protein is highly upregulated, and consequently drives spread via lymphatic vessels and site-specific metastasis in a Gα12/13-RhoA-dependent manner. This molecular

machinery is mediated similarly via PARs and LPA, all of which may serve as possible targets for metastasis prevention and treatment.

Chemokine GPCRs

Receptor	Expression	Function
CCR1	Monocytes, neutrophils, T lymphocytes, dendritic cells, tumor cells	Chemotaxis and activation Tumor growth, metastasis, angiogenesis
CCR2	Monocytes, basophils, T lymphocytes, dendritic cells, NK cells, endothelial cells, tumor cells	Chemotaxis and activation Tumor growth, metastasis, angiogenesis
CCR3	Eosinophils, basophils, Th2 lymphocytes, mast cells, tumor cells	Chemotaxis and activation Tumor growth, metastasis
CCR4	Macrophages, monocytes, basophils, T and B lymphocytes, dendritic cells, NK cells, mast cells, platelets, tumor cells	Chemotaxis and activation Tumor growth, metastasis, angiogenesis
CCR5	Macrophages, T lymphocytes, dendritic cells, NK cells, tumor cells	Chemotaxis and activation Tumor growth, metastasis, angiogenesis
CCR6	Neutrophils, T and B lymphocytes, dendritic cells, epithelial cells of some tissues, tumor cells	Chemotaxis and activation Tumor growth, metastasis
CCR7	T and B lymphocytes, dendritic cells Tumor cells	Lymphoid tissue chemotaxis and activation Tumor growth, metastasis
CCR8	Macrophages, Th2 lymphocytes, endothelial cells Tumor cells	Chemotaxis and activation Tumor metastasis
CCR9	T lymphocytes Tumor cells	Small intestinal specific chemotaxis and activation; tumor growth, metastasis; inhibiting tumor metastasis in some tumors
CCR10	T lymphocytes Tumor cells	Skin-specific chemotaxis and activation Tumor growth, metastasis, angiogenesis
CXCR1	Neutrophils, polymorphonuclear leukocytes, endothelial cells Tumor cells	Chemotaxis and activation Tumor growth, metastasis, angiogenesis
CXCR2	Neutrophils, basophils, T lymphocytes, oligodendrocytes, endothelial cells Tumor cells	Chemotaxis and activation Tumor growth, metastasis, angiogenesis
CXCR3	Macrophages, T lymphocytes, NK cells, NKT cells, endothelial cells Tumor cells	Chemotaxis and activation Two variants CXCR3-A and CXCR3-B have opposite function in tumor progression
CXCR4	Numerous cell types: hematopoietic cells and stem cells Tumor cells	Chemotaxis and activation Maintenance of stem phenotype Tumor growth, metastasis, angiogenesis
CXCR5	T and B lymphocytes Tumor cells	Chemotaxis and activation Tumor growth, metastasis; inhibiting tumor metastasis in some tumors
CXCR6	T and B lymphocytes, NK cells, NKT cells, plasma cells Tumor cells	Chemotaxis and activation Tumor growth, metastasis, angiogenesis; inhibiting tumor migration in some tumors

Receptor	Expression	Function
CXCR7	T and B lymphocytes, dendritic cells, endothelial cells, fetal hepatocytes Tumor cells	Chemotaxis and activation Tumor growth, metastasis, angiogenesis; assisting with CXCR4 to regulate tumor progression
CX3CR1	Monocytes, T and B lymphocytes, mast cells, dendritic cells, NK cells Tumor cells	Chemotaxis and activation Tumor growth, metastasis; inhibiting tumor invasion in some tumors
XCR1	Neutrophils, T lymphocytes, dendritic cells; tumor cells	Chemotaxis and activation

Solid tumors: benign and/or malignant neoplasms (cancer)

[0080] In one aspect, compounds of Formula (I) are used to treat benign and/or malignant neoplasms (solid tumors), wherein the neoplasm comprises cells that overexpress cell surface GPCRs.

[0081] The term "neoplasm" as used herein, refers to an abnormal growth of cells that may proliferate in an uncontrolled way and may have the ability to metastasize (spread).

[0082] Neoplasms include solid tumors, adenomas, carcinomas, sarcomas, leukemias and lymphomas, at any stage of the disease with or without metastases.

[0083] A solid tumor is an abnormal mass of tissue that usually does not contain cysts or liquid areas. Solid tumors may be benign (not cancer), or malignant (cancer). Different types of solid tumors are named for the type of cells that form them. Examples of solid tumors are sarcomas, carcinomas, and lymphomas. Leukemias (cancers of the blood) generally do not form solid tumors.

[0084] Solid tumors are cancers that typically originate in organs, such as the bladder, bowel, brain, breast, endometrium, heart, kidney, lung, liver, uterus, ovaries, pancreas or other endocrine organs (thyroid), and prostate.

[0085] An adenoma is a tumor that is not cancer. It starts in gland-like cells of the epithelial tissue (thin layer of tissue that covers organs, glands, and other structures within the body). An adenoma can grow from many glandular organs, including the adrenal glands, pituitary gland, thyroid, prostate, and others. Over time adenomas may transform to become malignant, at which point they are called adenocarcinomas. Even though benign, they have the potential to cause serious health complications by compressing other structures (mass effect) and by producing large amounts of hormones in an unregulated, non-feedback-dependent manner (causing paraneoplastic syndromes).

[0086] Adenomas typically are found in the colon (e.g. adenomatous polyps, which have a tendency to become malignant and to lead to colon cancer), kidneys (e.g. renal adenomas may be

precursor lesions to renal carcinomas), adrenal glands (e.g. adrenal adenomas; some secrete hormones such as cortisol, causing Cushing's syndrome, aldosterone causing Conn's syndrome, or androgens causing hyperandrogenism), thyroid (e.g. thyroid adenoma), pituitary (e.g. pituitary adenomas, such as prolactinoma), parathyroid (e.g. an adenoma of a parathyroid gland may secrete inappropriately high amounts of parathyroid hormone and thereby cause primary hyperparathyroidism), liver (e.g. hepatocellular adenoma), breast (e.g. fibroadenomas), appendix (e.g. cystadenoma), bronchial (e.g. bronchial adenomas may cause carcinoid syndrome, a type of paraneoplastic syndrome), prostate (e.g. prostate adenoma), sebaceous gland (e.g. sebaceous adenoma), and salivary glands.

[0087] Metastasis is the spread of malignant cells to new areas of the body, often by way of the lymph system or bloodstream. A metastatic tumor is one that has spread from the primary site of origin, or where it started, into different areas of the body. Metastatic tumors comprise malignant cells that express cell surface GPCRs.

[0088] Tumors formed from cells that have spread are called secondary tumors. Tumors may have spread to areas near the primary site, called regional metastasis, or to parts of the body that are farther away, called distant metastasis.

[0089] In some embodiments, the tumor to be treated comprises tumor cells expressing a GPCR, wherein the tumor is a primary or metastatic tumor. In some embodiments, the tumor to be treated comprises tumor cells expressing a GPCR, wherein the tumor is a primary or metastatic tumor of gastrointestinal origin, such as colorectal cancer, stomach cancer, small intestine cancer, or esophageal cancer. In some embodiments, the tumor to be treated comprises tumor cells expressing a GPCR, wherein the tumor is a primary or metastatic tumor of the pancreas. In some embodiments, the tumor to be treated comprises tumor cells expressing a GPCR, wherein the tumor is a primary or metastatic tumor of the lungs, such as squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma. In some embodiments, the tumor to be treated comprises tumor cells expressing a GPCR, wherein the tumor is a primary or metastatic neuroectodermal tumor, such as aphaechromotcytoma or a paraganglioma. In some embodiments, the tumor to be treated comprises tumor cells expressing a GPCR, wherein the tumor is a primary or metastatic bronchopulmonary or gastrointestinal neuroendocrine tumor. In some embodiments, the tumor to be treated comprises tumor cells expressing a GPCR, wherein the tumor is a primary or metastatic tumor of the rectum or colon.

[0090] In some embodiments, compounds of Formula (I) are used to treat a sarcoma, such as leiomyosarcoma or rhabdomyosarcoma.

[0091] In some embodiments, compounds of Formula (I) are used to treat an adenoma.

[0092] In another aspect, provided herein is a method for treating cancer in a mammal comprising administering to the mammal in need thereof, a non-peptide targeted therapeutic disclosed herein. In some embodiments, the cancer comprises tumor cells expressing one or more peptide hormone GPCRs. In some embodiments, the cancer comprises tumor cells that overexpress one or more GPCRs. In some embodiments, the cancer comprises a solid tumor. In some embodiments, the cancer comprises a sarcoma, carcinoma, or lymphoma. In some embodiments, the cancer comprises a neuroendocrine tumor. In some embodiments, the cancer comprises an insulinoma. In some embodiments, the cancer comprises peptide hormone GPCR-positive (e.g., somatostatin receptor-positive) gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

[0093] In some embodiments, the compound of Formula (I) is administered to an oncology patient. In some embodiments, the oncology patient has been diagnosed with a carcinoma, sarcoma, primary tumor, metastatic tumor, solid tumor, non-solid tumor, blood tumor, leukemia or lymphoma.

[0094] Carcinomas include, but are not limited to, esophageal carcinoma, hepatocellular carcinoma, basal cell carcinoma (a form of skin cancer), squamous cell carcinoma (various tissues), bladder carcinoma, including transitional cell carcinoma (a malignant neoplasm of the bladder), bronchogenic carcinoma, colon carcinoma, colorectal carcinoma, gastric carcinoma, lung carcinoma, including small cell carcinoma and non-small cell carcinoma of the lung, adrenocortical carcinoma, thyroid carcinoma, pancreatic carcinoma, breast carcinoma, ovarian carcinoma, prostate carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinoma, cystadenocarcinoma, medullary carcinoma, renal cell carcinoma, ductal carcinoma in situ or bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical carcinoma, uterine carcinoma, testicular carcinoma, osteogenic carcinoma, epithelial carcinoma, and nasopharyngeal carcinoma, etc.

[0095] Sarcomas include, but are not limited to, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, chordoma, osteogenic sarcoma, osteosarcoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's sarcoma, leiomyosarcoma, rhabdomyosarcoma, and other soft tissue sarcomas.

[0096] Solid tumors include, but are not limited to, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma,

oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma. Benign solid tumors include adenomas.

[0097] Leukemias include, but are not limited to, a) chronic myeloproliferative syndromes (neoplastic disorders of multipotential hematopoietic stem cells); b) acute myelogenous leukemias (neoplastic transformation of a multipotential hematopoietic stem cell or a hematopoietic cell of restricted lineage potential; c) chronic lymphocytic leukemias (CLL; clonal proliferation of immunologically immature and functionally incompetent small lymphocytes), including B-cell CLL, T-cell CLL prolymphocyte leukemia, and hairy cell leukemia; and d) acute lymphoblastic leukemias (characterized by accumulation of lymphoblasts). Lymphomas include, but are not limited to, B-cell lymphomas (e.g., Burkitt's lymphoma); Hodgkin's lymphoma; and the like.

[0098] Primary and metastatic tumors include, e.g., lung cancer (including, but not limited to, lung adenocarcinoma, squamous cell carcinoma, large cell carcinoma, bronchioloalveolar carcinoma, non-small-cell carcinoma, small cell carcinoma, mesothelioma); breast cancer (including, but not limited to, ductal carcinoma, lobular carcinoma, inflammatory breast cancer, clear cell carcinoma, mucinous carcinoma); colorectal cancer (including, but not limited to, colon cancer, rectal cancer); anal cancer; pancreatic cancer (including, but not limited to, pancreatic adenocarcinoma, islet cell carcinoma, neuroendocrine tumors); prostate cancer; ovarian carcinoma (including, but not limited to, ovarian epithelial carcinoma or surface epithelial-stromal tumor including serous tumor, endometrioid tumor and mucinous cystadenocarcinoma, sex-cord-stromal tumor); liver and bile duct carcinoma (including, but not limited to, hepatocellular carcinoma, cholangiocarcinoma, hemangioma); esophageal carcinoma (including, but not limited to, esophageal adenocarcinoma and squamous cell carcinoma); non- Hodgkin's lymphoma; bladder carcinoma; carcinoma of the uterus (including, but not limited to, endometrial adenocarcinoma, uterine papillary serous carcinoma, uterine clear-cell carcinoma, uterine sarcomas and leiomyosarcomas, mixed mullerian tumors); glioma, glioblastoma, medulloblastoma, and other tumors of the brain; kidney cancers (including, but not limited to, renal cell carcinoma, clear cell carcinoma, Wilm's tumor); cancer of the head and neck (including, but not limited to, squamous cell carcinomas); cancer of the stomach (including, but not limited to, stomach adenocarcinoma, gastrointestinal stromal tumor); multiple myeloma; testicular cancer; germ cell tumor; neuroendocrine tumor; cervical cancer; carcinoids of the gastrointestinal tract, breast, and other organs; and signet ring cell carcinoma.

Payload Moieties (Q) Comprising Chelated Radionuclides

[0099] Radiopharmaceuticals have increasingly become very useful tools for physicians to diagnose, stage, treat, and monitor the progression of several diseases, especially cancer. The primary difference between radiopharmaceuticals and other pharmaceutical drugs is that radiopharmaceuticals contain a radionuclide. The nuclear decay properties of the radionuclide determine whether a radiopharmaceutical will be used clinically as a diagnostic agent or as a therapeutic agent. Diagnostic radiopharmaceuticals require radionuclides that emit either gamma (γ) rays or positrons ($\beta+$), which subsequently annihilate with nearby electrons to produce two 511 keV annihilation photons emitted approximately 180° away from each other. Gamma ray-emitting radionuclides (e. g. ^{99m}Tc, ^{111}In, ^{201}Tl, etc.) are useful for single photon emission computed tomography (SPECT), while positron-emitting radionuclides (e. g. ^{18}F, ^{89}Zr, ^{68}Ga, etc.) are useful for positron emission tomography (PET).

[00100] In contrast, therapeutic radiopharmaceuticals require radionuclides that emit particulate radiation, such as alpha (α) particles, beta ($\beta-$) particles, or Auger electrons. These particles, which strongly interact with target tissues (e. g. cancerous tumor) and lead to extensive localized ionization, can damage chemical bonds in DNA molecules and potentially induce cytotoxicity.

[00101] For most nuclear medicine applications, it is desired that a diagnostic radiopharmaceutical is paired with a therapeutic radiopharmaceutical. This concept is commonly known as “theranostics”. As a first step in the theranostic concept, a target molecule labeled with a diagnostic radionuclide is used for quantitative imaging of a tumor imaging biomarker, using positron emission tomography (PET) or single photon emission computed tomography (SPECT). When it is demonstrated that, with this targeted molecule, a tumoricidal radiation absorbed dose can be delivered to tumor and metastases, as a second step, the administration of the same or a similar target molecule labeled with a therapeutic radionuclide will be conducted.

[00102] In some embodiments, the chemical and pharmacokinetic behaviors of both the diagnostic and therapeutic radiopharmaceuticals match. In some embodiments, the diagnostic and therapeutic radionuclides are a chemically identical radioisotope pair (also known as a “matched pair”). One exmaples of a matched pair for theranostic radiopharmaceutical applications is the ^{123}I/^{131}I pair, where ^{123}I-labeled compounds are used for diagnosis, while ^{131}I-labeled compounds are used for therapy. Other theranostic matched pairs include ^{44}Sc/^{47}Sc, ^{64}Cu/^{67}Cu, ^{72}As/^{77}As, ^{86}Y/^{90}Y, and ^{203}Pb/^{212}Pb, among others. Alternatively, radionuclide pairs from different elements can be utilized for theranostic radiopharmaceutical development when their chemistry is very similar (e. g. ^{99m}Tc/$^{186/188}$Re) and there is no significant difference in the pharmacokinetic behavior between the diagnostic and therapeutic analogues. Another example is

the $^{68}Ga/^{177}Lu$ pair, where ^{68}Ga is used for diagnosis and ^{177}Lu is used for therapy. For example, gastroenteropancreatic endocrine tumors express high amounts of sst2 receptor that can be targeted with somatostatin receptor scintigraphy for diagnostic purposes with a ^{68}Ga sst2 ligand conjugate ([^{68}Ga]Ga-DOTA-TATE (NETSPOT™) or [^{68}Ga]Ga-DOTA-TOC (DOTA-(D-Phe1,Tyr3)-octreotide, SomaKit TOC®)), followed by treatment with a ^{177}Lu sst2 ligand conjugate ([^{177}Lu]Lu-DOTA-TATE) for endoradiotherapy.

[00103] In some embodiments, **NP** is a nonpeptide ligand that binds to a GPCR expressed in tumor cells of a solid tumor, adenoma, sarcoma, carcinoma, or lymphoma; **Q** comprises a radionuclide (**Z**) and a chelator configured to bind the radionuclide (**Z**); and **L** is a non-cleavable linker.

Chelators for Radionuclides

[00104] In some embodiments, **Q** is a payload moiety comprising a chelating moiety or a radionuclide (**Z**) complex thereof. In some embodiments, **Q** comprises a radionuclide (**Z**) and a chelator configured to bind the radionuclide (**Z**). In some embodiments, the chelator is attached to a non-peptide ligand through any suitable group or atom of the chelator. In some embodiments, the chelator is attached to a linker through any suitable group or atom of the chelator.

[00105] As used herein, "chelator" and "chelating moiety" are used interchangeably.

[00106] In some embodiments, the chelator is capable of binding a radioactive atom. In some embodiments, the binding is direct, e.g., the chelator makes hydrogen bonds or electrostatic interactions with a radioactive atom. In some embodiments, the binding is indirect, e.g., the chelator binds to a molecule that comprises a radioactive atom. In some embodiments, the chelator is or comprises a macrocycle.

[00107] In some embodiments, the chelator comprises one or more amine groups. In some embodiments, the metal chelator comprises two or more amine groups. In some embodiments, the chelator comprises three or more amine groups. In some embodiments, the chelator comprises four or more amine groups. In some embodiments, the chelator includes 4 or more N atoms, 4 or more carboxylic acid groups, or a combination thereof. In some embodiments, the chelator does not comprise S. In some embodiments, the chelator comprises a ring. In some embodiments, the ring comprises an O and/or a N atom. In some embodiments, the chelator is a ring that includes 3 or more N atoms, 3 or more carboxylic acid groups, or a combination thereof. In some embodiments, the chelator is polydentate ligand, bidentate ligand, or monodentate ligand. Polydentate ligands range in the number of atoms used to bond to a metal atom or ion. EDTA, a hexadentate ligand, is an example of a polydentate ligand that has six donor atoms with

electron pairs that can be used to bond to a central metal atom or ion. Bidentate ligands have two donor atoms which allow them to bind to a central metal atom or ion at two points. Ethylenediamine (en) and the oxalate ion (ox) are examples of bidentate ligands.

[00108] In some embodiments, a chelator described herein comprises a cyclic chelating agent or an acyclic chelating agent. In some embodiments, a chelator described herein comprises a cyclic chelating agent. In some embodiments, a chelator described herein comprises an acyclic chelating agent.

[00109] In some embodiments, a chelator described herein comprises DOTA, DOTAGA, DOTA(GA)2, NOTA, NODAGA, TRITA, TETA, DOTA-MA, DO3A-HP, DOTMA, DOTA-pNB, DOTP, DOTMP, DOTEP, DOTMPE, F-DOTPME, DOTPP, DOTBzP, DOTA-monoamide, p-NCS-DOTA, p-NCS-PADOTA, BAT, DO3TMP-Monoamide, p-NCS-TRITA, and CHX-A″-DTPA. In some embodiments, a chelator described herein comprises DTA, CyEDTA, EDTMP, DTPMP, DTPA, CyDTPA, Cy2DTPA, DTPA-MA, DTPA-BA, and BOPA.

[00110] In some embodiments, a chelator described herein comprises DOTA, DOTAGA, DOTA(GA)2, DOTP, DOTMA, DOTAM, DTPA, NTA, EDTA, DO3A, DO2A, NOC, NOTA, TETA, TACN, DiAmSar, CB-Cyclam, CB-TE2A, DOTA-4AMP, or NOTP.

[00111] In some embodiments, a chelator described herein comprises HP-DO3A, BT-DO3A, DO3A-Nprop, DO3AP, DO2A2P, DOA3P, DOTP, DOTPMB, DOTAMAE, DOTAMAP, $DO3AM^{Bu}$, DOTMA, TCE-DOTA, DEPA, PCTA, p-NO_2-Bn-PCTA, p-NO_2-Bn-DOTA, symPC2APA, symPCA2PA, asymPC2APA, asymPCA2PA, TRAP, AAZTA, $DATA^{m}$, THP, HEHA, HBED, or HBED-CC TFP.

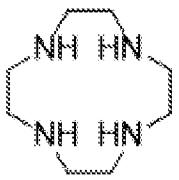
[00112] In some embodiments, a chelator described herein comprises DOTA, NOTA, NODAGA, DOTAGA, HBED, HBED-CC TFP, H2DEPDPA, DFO-B, Deferiprone, CP256, YM103, TETA, CB-TE2A, TE2A, Sar, DiAmSar, TRAPH, TRAP-Pr, TRAP-OH, TRAP-Ph, NOPO, DEADPA, PCTA, EDTA, PEPA, HEHA, DTPA, EDTMP, AAZTA, DO3AP, $DO3AP^{PrA}$, $DO3AP^{ABn}$, or DOTAM.

[00113] In some embodiments, the chelator is or comprises DOTA, HBED-CC, DOTAGA, DOTA(GA)2, NOTA, and DOTAM. In some embodiments, the chelator is or comprises NODAGA, NOTA, DOTAGA, DOTA(GA)2, TRAP, NOPO, NCTA, DFO, DTPA, and HYNIC.

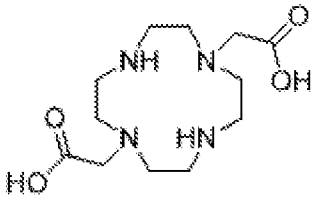
[00114] In some embodiments, the chelator comprises a macrocycle, e.g., a macrocycle comprising an O and/or a N atom, DOTA, HBED-CC, DOTAGA, DOTA(GA)2, NOTA, DOTAM, one or more amines, one or more ethers, one or more carboxylic acids, EDTA, DTPA, TETA, DO3A, PCTA, or desferrioxamine.

[00115] In some embodiments, **Q** comprises a chelating moiety or a radionuclide (**Z**) complex thereof, wherein the chelating moiety is: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA); 1,4,7,10-tetraazacyclododecane-1,4,7 -triacetic acid (DO3A); 1,4,7,10-tetraazacyclododecane-1,7-diacetic acid (DO2A); α,α',α'',α'''-tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTMA); 1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane (DOTAM); 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrapropionic acid (DOTPA); 2,2',2''-(10-(2-amino-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid; benzyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (Bn-DOTA); 6,6'-(((pyridine-2,6-diylbis(methylene))bis((carboxymethyl)azanediyl))-bis(methylene))dipicolinic acid (H_4pypa); H_4pypa-benzyl; 6,6',6'',6'''-(((pyridine-2,6-diylbis(methylene))bis(azanetriyl))tetrakis(methylene))-tetrapicolinic acid (H_4py4pa); H_4py4pa-benzyl; 6,6'-((ethane-1,2-diylbis((carboxymethyl)azanediyl))bis(methylene))dipicolinic acid (H_4octapa); H_4octapa-benzyl; or 3,6,9,12-tetrakis(carboxymethyl)-3,6,9,12-tetraazatetradecanedioic acid (TTHA).

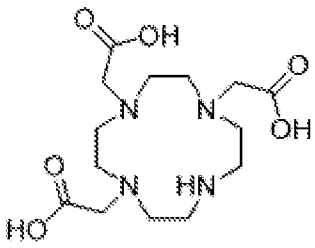
[00116] In some embodiments, a metal chelator described herein comprises one of the following structures:



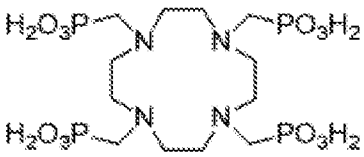
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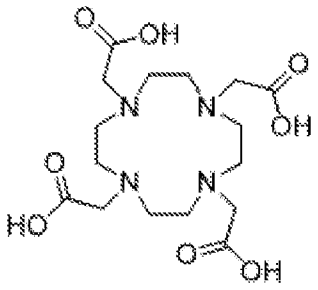
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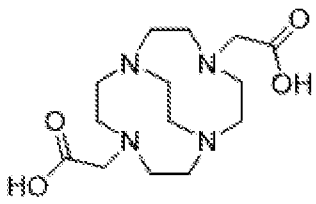
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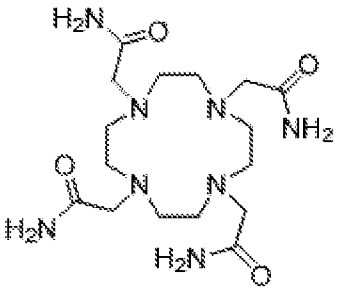
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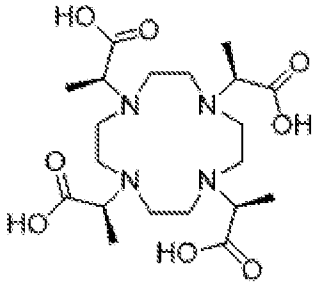
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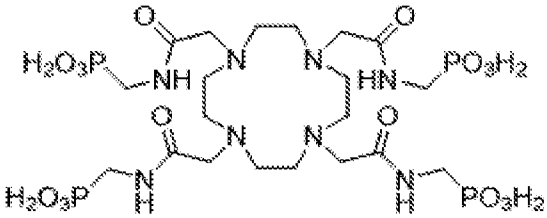
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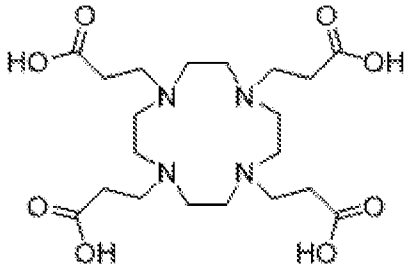
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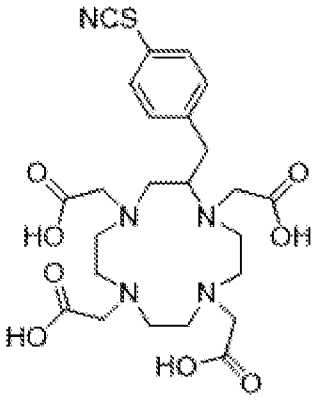
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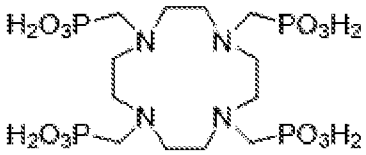
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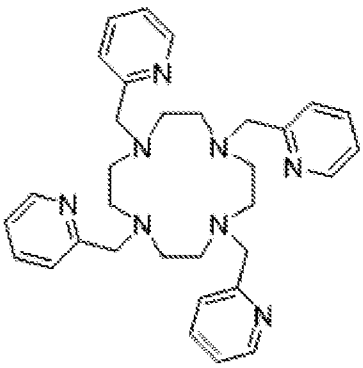
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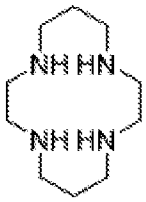
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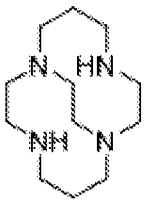
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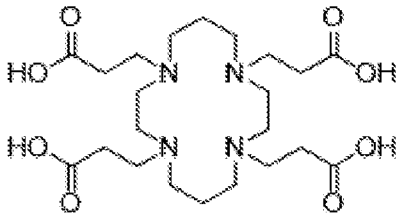
(L^{py}),



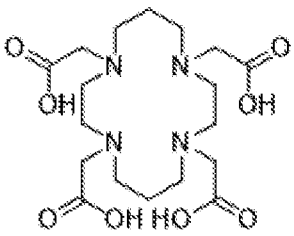
,



(CB-Cyclam),



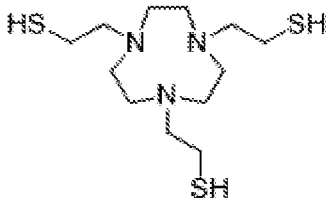
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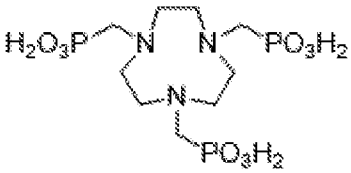
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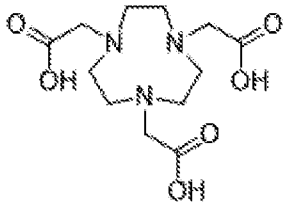
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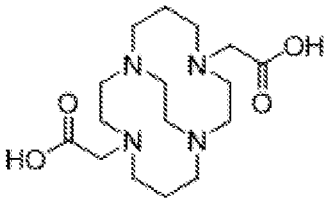
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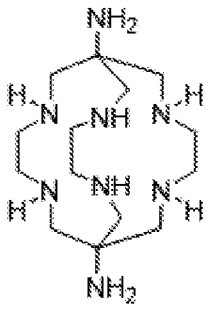
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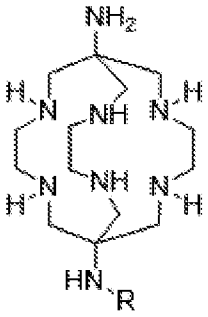
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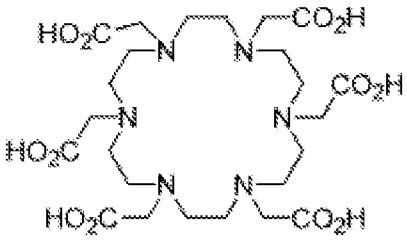
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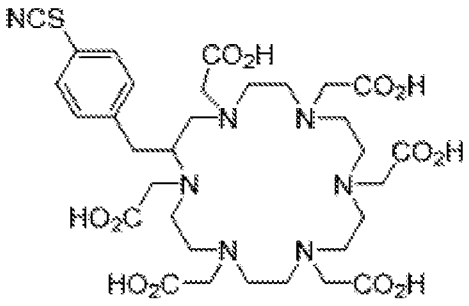
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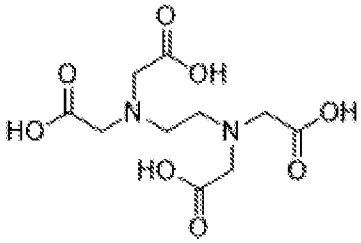
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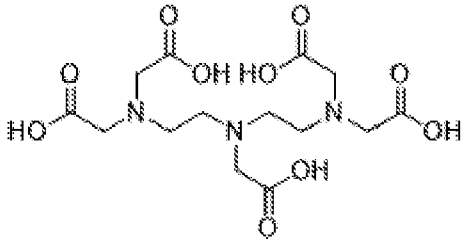
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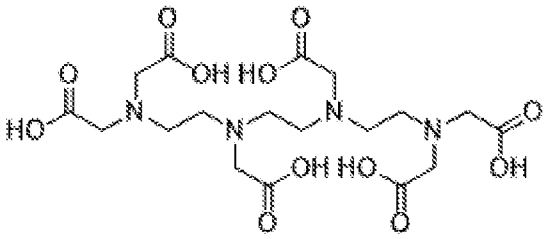
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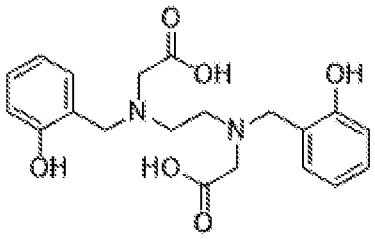
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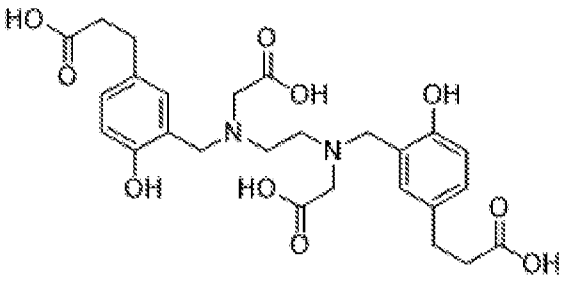
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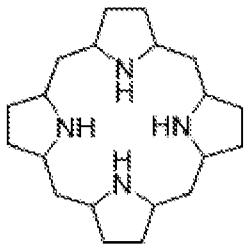
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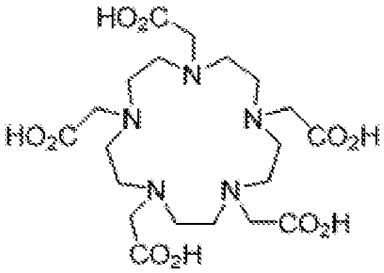
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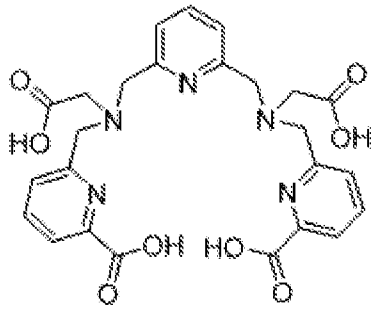
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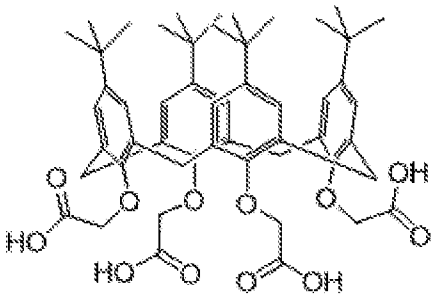
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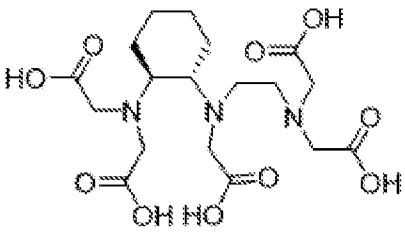
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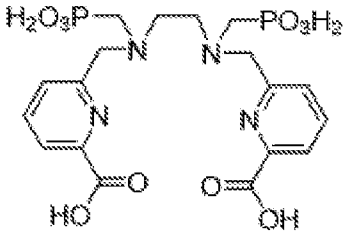
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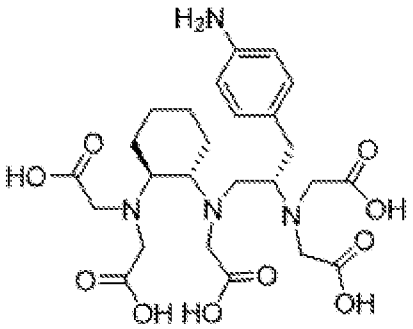
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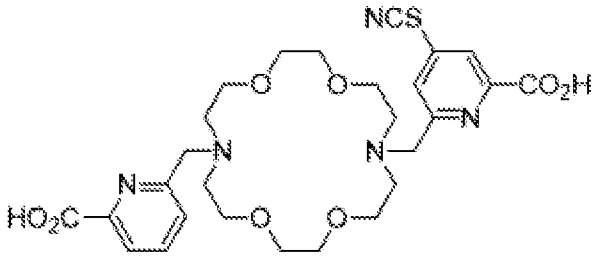
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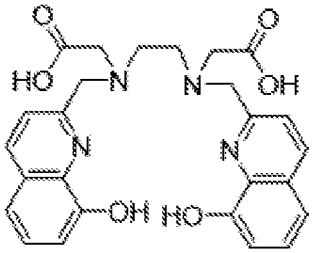
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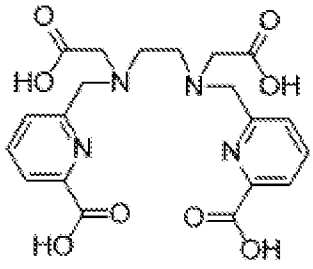
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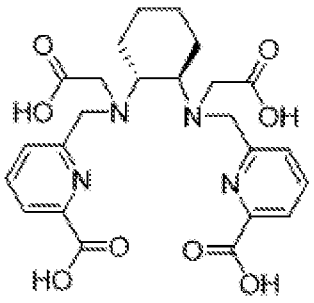
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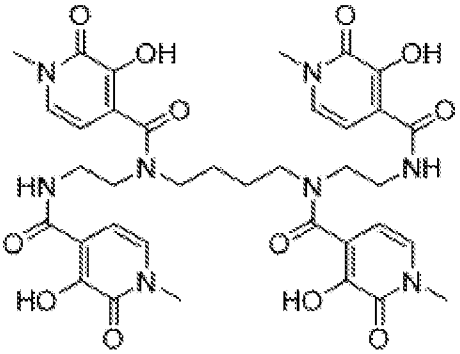
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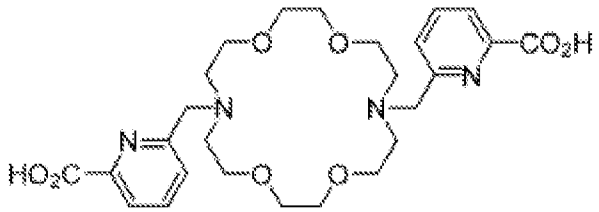
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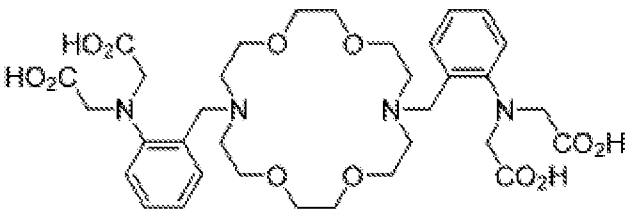
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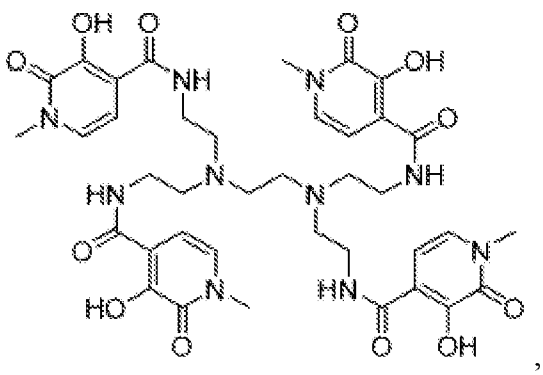
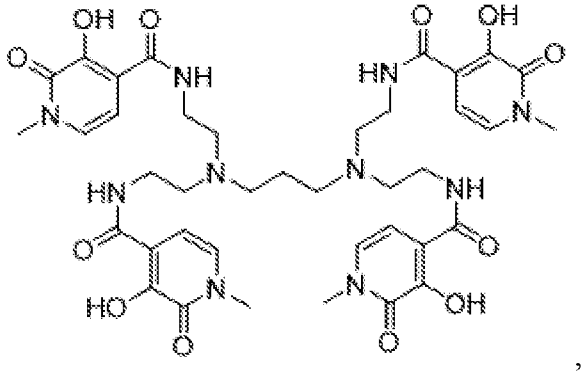
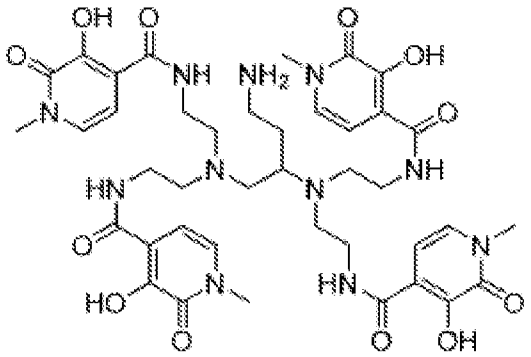
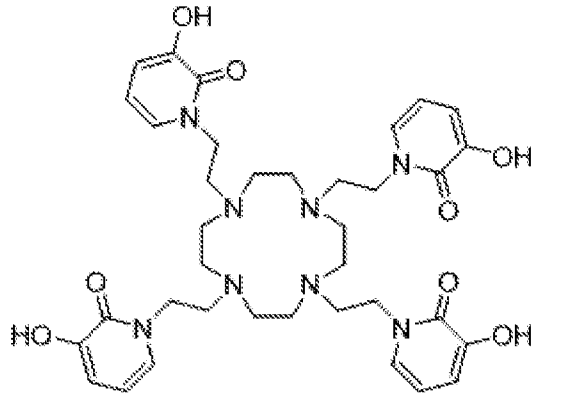
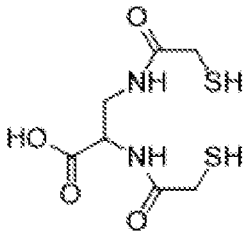
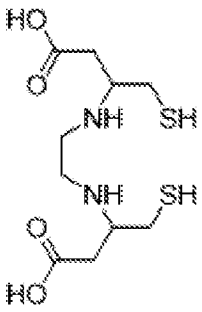
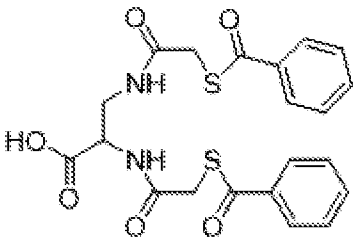
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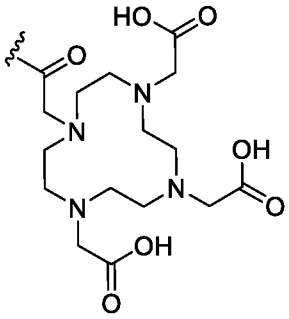
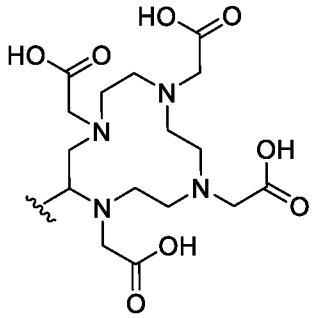
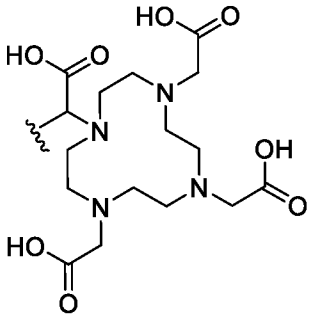
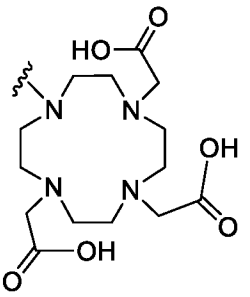


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(Bis(aminothiolate)), or

($SBTG_2DAP$).

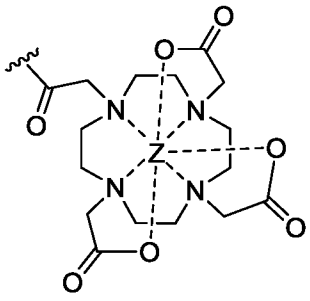
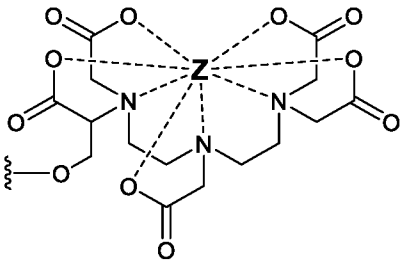
[00117] In some embodiments, **Q** comprises a chelating moiety or a radionuclide (**Z**) complex thereof, wherein the chelating moiety is: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA); or 1,4,7,10-tetraazacyclododecane-1,4,7 -triacetic acid (DO3A).

[00118] In some embodiments, **Q** comprises a chelating moiety or a radionuclide (**Z**) complex thereof, wherein the chelating moiety is:

[00119] In some embodiments, **Q** comprises a radionuclide (**Z**) and DOTA. In some embodiments, **Q** comprises a radionuclide (**Z**) and a DOTA derivative such as p-SCN-Bn-DOTA and MeO-DOTA-NCS. In some embodiments, **Q** comprises two independent chelators, and at least one or both are DOTA.

[00120] In some embodiments, **Q** comprises a radionuclide (**Z**) and a chelator configured to bind the radionuclide (**Z**), wherein the chelator comprises DOTA, DOTP, DOTMA, DOTAM, DTPA, NOTA, NTA, NODAGA, EDTA, DO3A, DO2A, NOC, TETA, CB-TE2A, DiAmSar, CB-Cyclam, DOTA-4AMP, H_4pypa, H_4octox, H_4octapa, p-NO_2-Bn-neunpa, or NOTP.

[00121] In some embodiments, **Q** is  or ; wherein **Z** is a diagnostic or therapeutic radionuclide.

[00122] In some embodiments, **Z** is an Auger electron-emitting radionuclide, α-emitting radionuclide, β-emitting radionuclide, or γ-emitting radionuclide. In some embodiments, **Z** is an Auger electron-emitting radionuclide that is 111-indium (^{111}In), 67-gallium (^{67}Ga), 68gallium (^{68}Ga), 99m-technetium (^{99m}Tc), or 195m-platinum (^{195m}Pt). In some embodiments, **Z** is an α-emitting radionuclide that is 225-actinium (^{225}Ac), 213-bismuth (^{213}Bi), 223-Radium (^{223}Ra), or 212-lead (^{212}Pb). In some embodiments, **Z** is a β-emitting radionuclide that is 90-yttrium (^{90}Y), 177-lutetium (^{177}Lu), iodine-131 (^{131}I), 186-rhenium (^{186}Re), 188-rhenium (^{188}Re), 64-copper (^{64}Cu), 67-copper (^{67}Cu), 153-samarium (^{153}Sm), 89-strontium (^{89}Sr), 198-gold (^{198}Au), 169-Erbium (^{169}Er), 165-dysprosium (^{165}Dy), 99m-technetium (^{99m}Tc), 89-zirconium (^{89}Zr), or 52-manganese (^{52}Mn). In some embodiments, **Z** is a γ-emitting radionuclide that is 60-cobalt (^{60}Co), 103-palldium (^{103}Pd), 137-cesium (^{137}Cs), 169-ytterbium (^{169}Yb), 192-iridium (^{192}Ir), or 226-radium (^{226}Ra).

[00123] In some embodiments, **Q** omprises a radionuclide (**Z**) and a chelator configured to bind the radionuclide (**Z**), wherein the radionuclide is suitable for positron emission tomography (PET) analysis, single-photon emission computerized tomography (SPECT), or magnetic resonance imaging (MRI). In some embodiments, the radionuclide is copper-64 (^{64}Cu), gallium-68 (^{68}Ga), 111-indium (^{111}In), or technetium-99m (^{99m}Tc).

Radionuclides

[00124] In some embodiments, **Z** is an Auger electron-emitting radionuclide. In some embodiments, **Z** is an α-emitting radionuclide. In some embodiments, **Z** is a β-emitting radionuclide. In some embodiments, **Z** is a γ-emitting radionuclide. In some embodiments, the type of radionuclide used in a non-peptide targeted therapeutic compound can be tailored to the specific type of cancer, the type of targeting moiety (e.g., non-peptide ligand), etc. Radionuclides that undergo α-decay emit α-particles (helium ions with a +2 charge) from their nuclei. As a result of α-decay the daughter nuclide has 2 protons less and 2 neutrons less than the parent nuclide. This means that in α-decay, the proton number is reduced by 2 while the nucleon number is reduced by 4. Radionuclides that undergo β-decay emit β-particles (electrons) from their nuclei. During β-decay, one of the neutrons changes into a proton and an electron. The proton remains in the nucleus while the electron is emitted as a β-particle. This means that in β-decay, the nucleus loses a neutron but gains a proton. In γ-decay, a nucleus in an excited state (higher energy state) emits a γ-ray photon to change to a lower energy state. There is no change in the proton number and nucleon number during the γ-decay. The emission of γ-rays often accompanies the emission of α-particles and β-particles.

[00125] Auger electrons (AEs) are very low energy electrons that are emitted by radionuclides that decay by electron capture (EC) (e.g., ^{111}In, ^{67}Ga, ^{99m}Tc, ^{195m}Pt, ^{125}I and ^{123}I). This energy is deposited over nanometre-micrometre distances, resulting in high linear energy transfer that is potent for causing lethal damage in cancer cells. Thus, AE-emitting radiotherapeutic agents have great potential for treatment of cancer.

[00126] β-Particles are electrons emitted from the nucleus. They typically have a longer range in tissue (of the order of 1–5 mm) and are the most frequently used.

[00127] α-Particles are helium nuclei (two protons and two neutrons) that are emitted from the nucleus of a radioactive atom. Depending on their emission energy, they can travel 50–100 μm in tissue. They are positively charged and are orders of magnitude larger than electrons. The amount of energy deposited per path length travelled (designated 'linear energy transfer') of α-particles is approximately 400 times greater than that of electrons. This leads to substantially more damage along their path than that caused by electrons. An α-particle track leads to a preponderance of

complex and largely irreparable DNA double-strand breaks. The absorbed dose required to achieve cytotoxicity relates to the number of α-particles traversing the cell nucleus. With use of this as a measure, cytotoxicity may be achieved with a range of 1 to 20 α-particle traversals of the cell nucleus. The resulting high potency, combined with the short range of α-particles (which reduces normal organ toxicity), has led to substantial interest in developing α-particle-emitting agents. The α-particle emitters typically used include bismuth-212, lead-212, bismuth-213, actinium-225, radium-223 and thorium-227.

[00128] In some embodiments, **Z** is a diagnostic or therapeutic radionuclide.

Representative Radionuclides

Isotope	Radionuclide $t_{1/2}$ (h)	Decay mode
^{60}Cu	0.4	β+ (93%), EC (7%)
^{61}Cu	3.3	β+ (62%), EC (38%)
^{62}Cu	0.16	β+ (98%), EC (2%)
^{64}Cu	12.7	β+ (19%), EC (41%), β- (40%)
^{66}Ga	9.5	β+ (56%), EC (44%)
^{67}Ga	78.2	EC (100%)
^{68}Ga	1.1	β+ (90%), EC (10%)
^{44}Sc	3.9	β+ (94%), EC (6%)
^{47}Sc	80.2	β- (100%)
^{111}In	67.2	EC (100%)
^{114m}In	49.5 d	EC (100%)
^{114}In (daughter)	73 s	β- (100%)
^{177}Lu	159.4	β- (100%)
^{86}Y	14.7	β+ (33%), EC (66%)
^{90}Y	64.1	β- (100%)
^{89}Zr	78.5	β+ (23%), EC (77%)
^{212}Bi	1.1	α (36%), β- (64%)
^{213}Bi	0.76	α (2.2%), β- (97.8%)
^{212}Pb (daughter is ^{212}Bi)	10.6	β- (100%)
^{225}Ac	240	α (100%)

[00129] In some embodiments, **Z** is an Auger electron-emitting radionuclide. In some embodiments, **Z** is an Auger electron-emitting radionuclide that is 111-indium (^{111}In), 67-gallium (^{67}Ga), 68gallium (^{68}Ga), 99m-technetium (^{99m}Tc), or 195m-platinum (^{195m}Pt).

[00130] In some embodiments, **Z** is an α-emitting radionuclide. In some embodiments, **Z** is an α-emitting radionuclide that is 225-actinium (^{225}Ac), 213-bismuth (^{213}Bi), 223-Radium (^{223}Ra), or 212-lead (^{212}Pb).

[00131] In some embodiments, **Z** is an β-emitting radionuclide. In some embodiments, **Z** is a β-emitting radionuclide that is 90-yttrium (^{90}Y), 177-lutetium (^{177}Lu), 186-rhenium (^{186}Re), 188-rhenium (^{188}Re), 64-copper (^{64}Cu), 67-copper (^{67}Cu), 153-samarium (^{153}Sm), 89-strontium (^{89}Sr), 198-gold (^{198}Au), 169-Erbium (^{169}Er), 165-dysprosium (^{165}Dy), 99m-technetium (^{99m}Tc), 89-zirconium (^{89}Zr), or 52-manganese (^{52}Mn).

[00132] In some embodiments, **Z** is a γ-emitting radionuclide. In some embodiments, **Z** is a γ-emitting radionuclide that is 60-cobalt (^{60}Co), 103-palldium (^{103}Pd), 137-cesium (^{137}Cs), 169-ytterbium (^{169}Yb), 192-iridium (^{192}Ir), or 226-radium (^{226}Ra).

[00133] In some embodiments, **Z** is an Auger electron-emitting radionuclide that is 111-indium (^{111}In), 67-gallium (^{67}Ga), 68gallium (^{68}Ga), 99m-technetium (^{99m}Tc), or 195m-platinum (^{195m}Pt); or **Z** is an α-emitting radionuclide that is 225-actinium (^{225}Ac), 213-bismuth (^{213}Bi), 223-Radium (^{223}Ra), or 212-lead (^{212}Pb); or **Z** is a β-emitting radionuclide that is 90-yttrium (^{90}Y), 177-lutetium (^{177}Lu), 186-rhenium (^{186}Re), 188-rhenium (^{188}Re), 64-copper (^{64}Cu), 67-copper (^{67}Cu), 153-samarium (^{153}Sm), 89-strontium (^{89}Sr), 198-gold (^{198}Au), 169-Erbium (^{169}Er), 165-dysprosium (^{165}Dy), 99m-technetium (^{99m}Tc), 89-zirconium (^{89}Zr), or 52-manganese (^{52}Mn); **Z** is a γ-emitting radionuclide that is 60-cobalt (^{60}Co), 103-palldium (^{103}Pd), 137-cesium (^{137}Cs), 169-ytterbium (^{169}Yb), 192-iridium (^{192}Ir), or 226-radium (^{226}Ra).

[00134] In some embodiments, **Z** is 90-yttrium (^{90}Y), 177-lutetium (^{177}Lu), 186-rhenium (^{186}Re), 188-rhenium (^{188}Re), 67-copper (^{67}Cu), 153-samarium (^{153}Sm), 89-strontium (^{89}Sr), 198-gold (^{198}Au), 169-Erbium (^{169}Er), 165-dysprosium (^{165}Dy), or technetium-99m (^{99m}Tc).

[00135] In some embodiments, **Z** is ^{94}Tc, ^{90}In, ^{111}In, ^{67}Ga, ^{68}Ga, ^{86}Y, ^{90}Y, ^{177}Lu, ^{161}Tb, ^{186}Re, ^{188}Re, ^{64}Cu, ^{67}Cu, ^{55}Co, ^{57}Co, ^{43}Sc, ^{44}Sc, ^{47}Sc, ^{225}Ac, ^{213}Bi, ^{212}Bi, ^{212}Pb, ^{227}Th, ^{153}Sm, ^{166}Ho, ^{152}Gd, ^{153}Gd, ^{157}Gd, and ^{166}Dy.

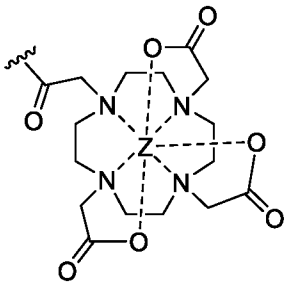
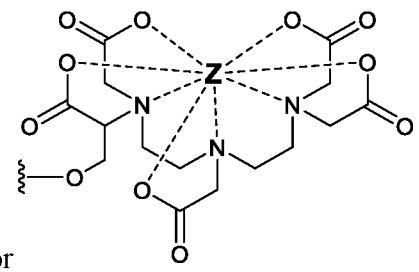
[00136] In some embodiments, **Z** is ^{67}Cu, ^{64}Cu, ^{90}Y, ^{109}Pd, ^{111}Ag, ^{149}Pm, ^{153}Sm, ^{166}Ho, ^{99m}Tc, ^{67}Ga, ^{68}Ga, ^{111}In, ^{90}Y, ^{177}Lu, ^{186}Re, ^{188}Re, ^{197}Au, ^{198}Au, ^{199}Au, ^{105}Rh, ^{165}Ho, ^{161}Tb, ^{149}Pm, ^{44}Sc, ^{47}Sc, ^{70}As, ^{71}As, ^{72}As, ^{73}As, ^{74}As, ^{76}As, ^{77}As, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{225}Ac, ^{117m}Sn, ^{67}Ga, ^{201}Tl, ^{160}Gd, ^{148}Nd, and ^{89}Sr.

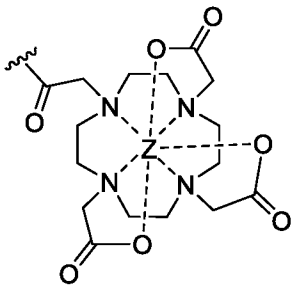
[00137] In some embodiments, **Z** is ^{68}Ga, ^{43}Sc, ^{44}Sc, ^{47}Sc, ^{177}Lu, ^{161}Tb, ^{225}Ac, ^{213}Bi, ^{212}Bi, or ^{212}Pb. In some embodiments, **Z** is ^{67}Ga, ^{99m}Tc, ^{111}In, or ^{201}Tl.

Exemplary Chelator and Radionuclide Complexes

[00138] Radionuclides have useful emission properties that can be used for diagnostic imaging techniques, such as single photon emission computed tomography (SPECT, e.g. ^{67}Ga, ^{99m}Tc, ^{111}In, ^{177}Lu) and positron emission tomography (PET, e.g. ^{68}Ga, ^{64}Cu, ^{44}Sc, ^{86}Y, ^{89}Zr), as well as therapeutic applications (e.g. ^{47}Sc, ^{114}mIn, ^{177}Lu, ^{90}Y, $^{212/213}$Bi, ^{212}Pb, ^{225}Ac, $^{186/188}$Re). A fundamental component of a radiometal-based radiopharmaceutical is the chelator, the ligand system that binds the radiometal ion in a tight stable coordination complex so that it can be properly directed to a desirable molecular target in vivo. Guidance for selecting the optimal match between chelator and radiometal for a particular use is provided in the art (e.g. see Price et al., "Matching chelators to radiometals for radiopharmaceuticals", *Chem. Soc. Rev.*, 2014, 43, 260-290).

[00139] In some embodiments, **Q** comprises a chelated or macrocyclic complex of a radionuclide. In some embodiments, **Q** comprises a diethylenetriaminepentaacetic acid (DTPA) chelate, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) chelate, or 1,4,7-triazacyclononane-1,4,7-trisacetic acid (NOTA) chelate or 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethyl-1,4,7,10-tetraacetic acid (DOTMA) chelate of a radionuclide.

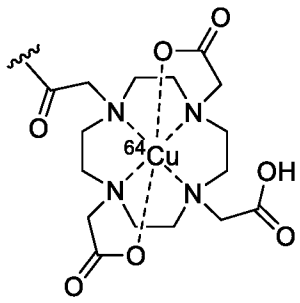
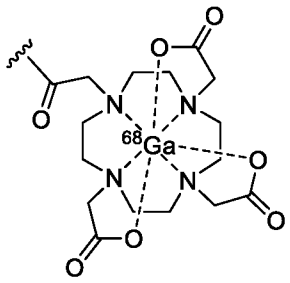
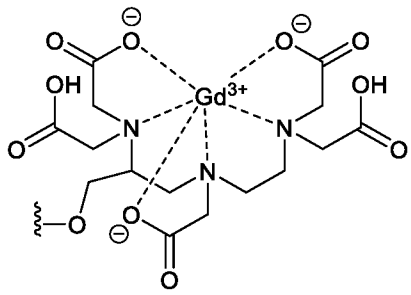
[00140] In some embodiments, **Q** is  or , where Z is a radionuclide.

[00141] In some embodiments, **Q** is , where **Z** is a radionuclide that is 90-yttrium (^{90}Y), 177-lutetium (^{177}Lu), 186-rhenium (^{186}Re), 188-rhenium (^{188}Re), 67-copper (^{67}Cu), 153-samarium (^{153}Sm), 89-strontium (^{89}Sr), 198-gold (^{198}Au), 169-Erbium (^{169}Er), 165-dysprosium (^{165}Dy), or technetium-99m (^{99m}Tc).

Emission Tomography

[00142] In some embodiments, **Q** comprises a chelated radionuclide that is suitable for positron emission tomography (PET) analysis or single-photon emission computerized tomography (SPECT). In some embodiments, **Q** comprises a chelated radionuclide that is suitable for single-photon emission computerized tomography (SPECT). In some embodiments, **Q** comprises a chelated radionuclide that is suitable for positron emission tomography (PET) analysis. In some embodiments, **Q** comprises a chelated radionuclide that is suitable for positron emission tomography imaging, positron emission tomography with computed tomography imaging, or positron emission tomography with magnetic resonance imaging.

[00143] In some embodiments, **Q** comprises a diethylenetriaminepentaacetic acid (DTPA) chelate, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) chelate, or 1,4,7-triazacyclononane-1,4,7-trisacetic acid (NOTA) chelate or 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethyl-1,4,7,10-tetraacetic acid (DOTMA) chelate of a radionuclide. In some embodiments, **Q** comprises a chelated radionuclide, wherein the radionuclide is copper-64 (^{64}Cu), gallium-68 (^{68}Ga), or technetium-99m (^{99m}Tc).

[00144] In some embodiments, **Q** is , , or .

[00145] In some embodiments, a conjugate described herein is designed to have a prescribed elimination profile. The elimination profile can be designed by adjusting the sequence and length of the non-peptide ligand, the property of the linker, the type of radionuclide, etc. In some embodiments, the conjugate has an elimination half-life of about 5 minutes to about 12 hours. In some embodiments, the conjugate has an elimination half-life of about 10 minutes to about 8 hours. In some embodiments, the conjugate has an elimination half-life of at least about 15 minutes, at least about 30 minutes, at least about 1 hour, at least about 2 hours, at least about 3

hours, at least about 4 hours, at least about 5 hours, at least about 6 hours, at least about 8 hours. In some embodiments, the conjugate has an elimination half-life of at most about 15 minutes, at most about 30 minutes, at most about 1 hour, at most about 2 hours, at most about 3 hours, at most about 4 hours, at most about 5 hours, at most about 6 hours, or at most about 8 hours. In some embodiments, the elimination half-life is determined in rats. In some embodiments, the elimination half-life is determined in humans.

[00146] A herein described conjugate can have an elimination half-life in a tumor and non-tumor tissue of the subject. The elimination half-life in a tumor can be the same as or different from (either longer or shorter than) the elimination half-life in a non-tumor issue. In some embodiments, the elimination half-life of the conjugate in a tumor is about 15 minutes to about 1 day. In some embodiments, the elimination half-life of the conjugate in a tumor is at least 1.1, at least 1.2, at least 1.3, at least 1.4, at least 1.5, at least 2.0, at least 2.5, at least 3.0, at least 4.0, or at least 5.0-fold of the elimination half-life of the conjugate in a non-tumor tissue of the subject.

[00147] As used herein, the "elimination half-life" can refer to the time it takes from the maximum concentration after administration to half maximum concentration. In some embodiments, the elimination half-life is determined after intravenous administration. In some embodiments, the elimination half-life is measured as biological half-life, which is the half-life of the pharmaceutical in the living system. In some embodiments, the elimination half-life is measured as effective half-life, which is the half-life of a radiopharmaceutical in a living system taking into account the half-life of the radionuclide.

[00148] Response and toxicity prediction is essential for the rational implementation of cancer therapy. The biological effects of radionuclide therapy are mediated by a well-defined physical quantity, the absorbed dose (D), which is defined as the energy absorbed per unit mass of tissue.

[00149] Radiation dosimetry is the measurement, calculation and assessment of the ionizing radiation dose absorbed by an object, usually the human body, and may be thought of as the ability to perform the equivalent of a pharmacodynamic study in treated patients in real time. This applies both internally, due to ingested or inhaled radioactive substances, or externally due to irradiation by sources of radiation. Dosimetry analysis may be performed as part of patient treatment to calculate tumour versus normal organ absorbed dose and therefore the likelihood of treatment successs.

[00150] A conjugate described herein can have a prescribed time-integrated activity coefficient (i.e., ã) in a tumor or non-tumor tissues of a subject. As used herein, ã represents the cumulative number of nuclear transformations occurring in a source tissue over a dose-integration period per unit administered activity. The ã value of a conjugate can be tuned by modifications of the

NPDC. The ã value can be determined using a method known in the art. In some embodiments, the ã value of the conjugate in a tumor is from about 10 minutes to about 1 day. The ã value of the conjugate in a tumor can be the same as the ã value of the conjugate in a non-tumor tissue of the subject. The ã value of the conjugate in a tumor can be longer or shorter than the ã value of the conjugate in a non-tumor tissue of the subject. In some embodiments, the ã value of the conjugate in a tumor is at least 1.1, at least 1.2, at least 1.3, at least 1.4, at least 1.5, at least 2.0, at least 2.5, at least 3.0, at least 4.0, or at least 5.0-fold of the ã value of the conjugate in a non-tumor tissue of the subject.

[00151] A conjugate described herein can have an ã value in an organ of a subject. In some embodiments, the conjugate has an ã value in a kidney of the subject of at most 24 hours. In some embodiments, the ã value of the conjugate in a kidney of the subject is at most 18 hours, 15 hours, 12 hours, 10 hours, 8 hours, 6 hours, or 5 hours. In some embodiments, the ã value of the conjugate in a kidney of the subject is about 30 minutes to about 24 hours. In some embodiments, the ã value of the conjugate in a kidney of the subject is about 2 to 24 hours. In some embodiments, the ã value of the conjugate in a kidney of the subject is more than 24 hours. In some embodiments, the ã value of the conjugate in a liver of the subject is at most 24 hours. In some embodiments, the ã value of the conjugate in a liver of the subject is at most 18 hours, 15 hours, 12 hours, 10 hours, 8 hours, 6 hours, or 5 hours. In some embodiments, the ã value of the conjugate in a liver of the subject is about 30 minutes to about 24 hours. In some embodiments, the ã value of the conjugate in a liver of the subject is about 2 to 24 hours. In some embodiments, the ã value of the conjugate in a liver of the subject is more than 24 hours.

Linkers

[00152] In some embodiments, the linker has a prescribed length thereby linking **NP** and **Q** while allowing an appropriate distance therebetween.

[00153] In some embodiments, the linker is flexible. In some embodiments, the linker is rigid.

[00154] In some embodiments, the linker comprises a linear structure. In some embodiments, the linker comprises a non-linear structure. In some embodiments, the linker comprises a branched structure. In some embodiments, the linker comprises a cyclic structure.

[00155] In some embodiments, the linker comprises one or more linear structures, one or more non-linear structures, one or more branched structures, one or more cyclic structures, one or more flexible moieties, one or more rigid moieties, or combinations thereof.

[00156] In some embodiments, a linker comprises one or more amino acid residues. In some embodiments, the linker comprises 1 to 3, 1 to 5, 1 to 10, 5 to 10, or 5 to 20 amino acid residues. In some embodiments, one or more amino acids of the linker are unnatural amino acids.

[00157] In some embodiments, the linker comprises a peptide linkage. The peptide linkage comprises L-amino acids and/or D-amino acids. In some embodiments, D-amino acids are preferred in order to minimize immunogenicity and nonspecific cleavage by background peptidases or proteases. Cellular uptake of oligo-D-arginine sequences is known to be as good as or better than that of oligo-L-arginines.

[00158] In some embodiments, a linker has 1 to 100 atoms, 1 to 50 atoms, 1 to 30 atoms, 1 to 20 atoms, 1 to 15 atoms, 1 to 10 atoms, or 1 to 5 atoms in length. In some embodiments, the linker has 1 to 10 atoms in length. In some embodiments, the linker has 1 to 20 atoms in length.

[00159] In some embodiments, a linker can comprise flexible and/or rigid regions. Exemplary flexible linker regions include those comprising Gly and Ser residues ("GS" linker), glycine residues, alkylene chain, PEG chain, etc. Exemplary rigid linker regions include those comprising alpha helix-forming sequences, proline-rich sequences, and regions rich in double and/or triple bonds.

[00160] In some embodiments, a linker is cleavable. In some embodiments, a linker is designed to be cleavable to aid in eleimiantion of the conujugate from the mammal. In some embodiments, a linker is designed for cleavage in the presence of particular conditions or in a particular environment, such conditions or environments near such targeted cells, tissues, or regions. Such linkers mainly include chemically cleavable linkers that respond to low pH (acid-labile linkers) or reducing environment (disulfide linkers), and enzymatically cleavable linkers that are susceptible to the action of certain lysosomal enzymes (peptide linkers or β-glucuronide linkers).

[00161] In some embodiments, a linker is cleavable under physiological conditions. In some embodiments, a linker is cleavable under intracellular conditions. In some embodiments, the linker is chemically cleavable. In some embodiments, the linker is enzymatically cleavable. In some embodiments, the linker is pH-sensitive, i.e., sensitive to hydrolysis at certain pH values. For example, the pH-sensitive linker can be hydrolyzable under acidic conditions. For example, a linker can be an acid-labile linker that is hydrolyzable in the lysosome (e.g., a hydrazone, semicarbazone, thiosemicarbazone, cis-aconitic amide, orthoester, acetal, ketal, or the like). Such linkers can be relatively stable under neutral pH conditions, such as those in the blood, but are unstable below pH 7.0, such as pH 6.5 to 4.5, the approximate pH of the lysosome and/or endosome.

[00162] In some embodiments, the linker comprises one or more of di-sulfide bonds.

[00163] In some embodiments, the linker is cleaved in or near tissues suffering from hypoxia, such as cancer cells and cancerous tissues. In some embodiments, the linker comprises a disulfide bond. In some embodiments, a linker comprising a disulfide bond is preferentially cleaved in

hypoxic regions. Hypoxia is thought to cause cancer cells to become more resistant to radiation and chemotherapy, and also to initiate angiogenesis. In a hypoxic environment in the presence of, for example, leaky or necrotic cells, free thiols and other reducing agents become available extracellularly, while the O_2 that normally keeps the extracellular environment oxidizing is by definition depleted. In some embodiments, this shift in the redox balance promotes reduction and cleavage of a disulfide bond within a linker. In addition to disulfide linkages which take advantage of thiol-disulfide equilibria, linkages including quinones that fall apart when reduced to hydroquinones are used in a linker designed to be cleaved in a hypoxic environment.

[00164] In some embodiments, the linker is is cleaved by an intracellular peptidase or protease enzyme, including, but not limited to, a lysosomal or endosomal protease. In some embodiments, the linker is is cleaved by a glycosidase, e.g., glucuronidase. Small peptide sequences such as Val-Cit and Phe-Lys have been developed as linkers for ADCs. These bi-peptide linkers show good stability in serum, yet can be recognized and rapidly hydrolyzed by certain lysosomal proteases, such as cathepsin B, following internalization. β-glucuronide linkers can be readily cleaved by the abundant lysosomal enzyme β-glucuronidase, facilitating facile and selective release of the active drug. In other embodiments, the linker is not cleavable.

[00165] In some embodiments, the linker is cleaved by a protease, a matrix metalloproteinase, a serine protease, or a combination thereof. In some embodiments, the linker is cleaved by a reducing agent. In some embodiments, the linker is cleaved by an oxidizing agent or oxidative stress. In some embodiments, the linker is cleaved by an MMP. The hydrolytic activity of matrix metalloproteinases (MMPs) has been implicated in the invasive migration of metastatic tumor cells. In some embodiments, a linker includes the amino-acid sequences PLG-C(Me)-AG, PLGLAG which are cleaved by the metalloproteinase enzymes MMP-2, MMP-9, or MMP-7 (MMPs involved in cancer and inflammation).

[00166] In some embodiments, the linker is cleaved by proteolytic enzymes or reducing environment, as may be found near cancerous cells. Such an environment, or such enzymes, are typically not found near normal cells.

[00167] In some embodiments, the linker is cleaved by serine proteases including but not limited to thrombin and cathepsins. In some embodiments, the linker is cleaved by cathepsin K, cathepsin S, cathepsin D, cathepsin E, cathepsin W, cathepsin F, cathepsin A, cathepsin C, cathepsin H, cathepsin Z, or any combinations thereof. In some embodiments, the linker is cleaved by cathepsin K and/or cathepsin S.

[00168] In some embodiments, the linker is cleaved in a necrotic environment. Necrosis often leads to the release of enzymes or other cell contents that may be used to trigger cleavage of a

linker. In some embodiments, cleavage of the linker occurs by necrotic enzymes (e.g., by calpains).

[00169] For additional details regarding linkers and their use in the compounds described herein, see: Wu, A.M.; Senter, P.D. Arming antibodies: prospects and challenges for immunoconjugates. *Nat. Biotechnol.* 2005, 23(9): 1137-1146; Beck, A.; *et al.* The next generation of antibody-drug conjugates comes of age. *Discov. Med.* 2010, 10(53): 329-339; Nolting, B.; et al. Linker technologies for antibody-drug conjugates. Methods. Mol. Biol. 2013, 1045: 71-100; Jain, N.; *et al.* Current ADC linker chemistry. *Pharm. Res.* 2015, 32: 3526-3540; McCombs, J.R.; Owen, S.C. Antibody drug conjugates: design and selection of linker, payload and conjugation chemistry. *AAPS J.* 2015, 17(2): 339-351; Jun Lu, *et al.*, Linkers Having a Crucial Role in Antibody–Drug Conjugates, *Int J Mol Sci.* 2016 Apr; 17(4): 561; each of which is incoproated by reference for such linker disclosures.

[00170] In some embodiments, the linker comprises one or more of unsubstituted or substituted alkylene, unsubstituted or substituted cycloalkylene, unsubstituted or substituted heterocycloalkylene, unsubstituted or substituted arylene, and unsubstituted or substituted heteroarylene.

[00171] In some embodiments, L is absent or a non-cleavable linker. In some embodiments, when L is absent then the chelate is directly linked to the NP (e.g., one of the acetic acid groups of DOTA or DOTAGA are used to join the chelate to NP). In some embodiments, L is absent or comprises one or more amino acids, PEG groups, $-L^1-$, $-L^1-L^2-$, $-L^1-L^2-L^3-$, $-L^1-L^2-L^3-L^4-$, $-L^1-L^2-L^3-L^4-L^5-$, $-L^2-$, $-L^2-L^3-$, $-L^2-L^3-L^4-$, $-L^2-L^3-L^4-L^5-$, $-L^3-$, $-L^3-L^4-$, $-L^3-L^4-L^5-$, $-L^4-$, $-L^4-L^5-$, $-L^5-$, $-L^1-L^2-L^3-L^4-L^5-$, or a combination thereof.

[00172] In some embodiments, L is absent or comprises one or more amino acids, PEG groups, $-L^1-$, $-L^2-$, $-L^3-$, $-L^4-$, $-L^5-$, $-L^1-L^2-L^3-L^4-L^5-$, or a combination thereof.

[00173] In some embodiments, each L^1 is independently absent, unsubstituted or substituted alkylene, unsubstituted or substituted heteroalkylene, unsubstituted or substituted alkenylene, unsubstituted or substituted alkynylene, unsubstituted or substituted cycloalkylene, unsubstituted or substituted heterocycloalkylene, unsubstituted or substituted arylene, unsubstituted or substituted heteroarylene, one or more amino acids, $-(CH_2)_p-$, $-C(=O)-$, $-C(=O)-(CH_2)_p-$, $-(CH_2)_p-C(=O)-$, $-(CH_2)_p-C(=O)-(CH_2)_p-$, $-C(=O)NH-$, $-C(=O)NH-(CH_2)_p-$, $-(CH_2)_p-C(=O)NH-$, $-(CH_2)_p-C(=O)NH-(CH_2)_p-$, $-NHC(=O)-$, $-NHC(=O)-(CH_2)_p-$, $-(CH_2)_p-NHC(=O)-$, $-(CH_2)_p-NHC(=O)-(CH_2)_p-$, $-NHC(=O)NH-$, $-NHC(=O)NH-(CH_2)_p-$, $-(CH_2)_p-NHC(=O)NH-$, $-(CH_2)_p-NHC(=O)NH-(CH_2)_p-$, each p is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12. In some embodiments, each L^1 is independently absent, unsubstituted or substituted alkylene, unsubstituted or

substituted heteroalkylene, unsubstituted or substituted monocyclic cycloalkylene, unsubstituted or substituted monocyclic heterocycloalkylene, unsubstituted or substituted phenylene, unsubstituted or substituted monocyclic heteroarylene, one or more amino acids, $-(CH_2)_p-$, -C(=O)-, -C(=O)-$(CH_2)_p-$, $-(CH_2)_p$-C(=O)-, $-(CH_2)_p$-C(=O)-$(CH_2)_p-$, -C(=O)NH-, -C(=O)NH-$(CH_2)_p-$, $-(CH_2)_p$-C(=O)NH-, $-(CH_2)_p$-C(=O)NH-$(CH_2)_p-$, each p is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12.

[00174] In some embodiments, each L^2 is independently absent, -O-, -S-, -S(=O)-, $-S(=O)_2-$, -NH-, -CH(OH)-, -NHC(=O)-, -C(=O)O-, -OC(=O)-, -CH(=N)-, -CH(=N-NH)-, $-CCH_3(=N)-$, $-CCH_3(=N-NH)-$, -OC(=O)NH-, -NHC(=O)NH-, -NHC(=O)O-, $-(CH_2)_p-$, -C(=O)-$(CH_2CH_2X)_p-$, or $-(CH_2CH_2X)_p-$, each p is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12; each X is independently selected from O, S, and NR^X; and R^X is hydrogen or C_1-C_4alkyl. In some embodiments, each L^2 is independently -C(=O)-, -C(=O)NH-, -C(=O)O-, $-(CH_2)_p-$, -C(=O)-$(CH_2CH_2O)_p-$, or $-(OCH_2CH_2)_p-$, each p is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12.

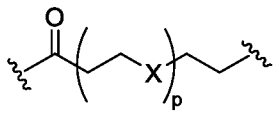
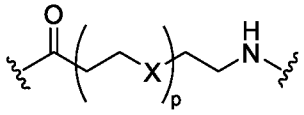
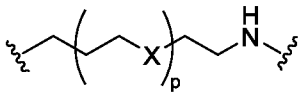
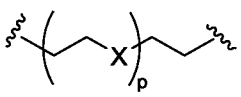
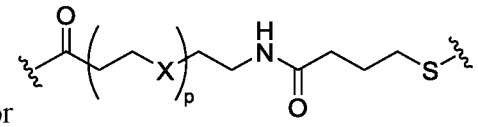
[00175] In some embodiments, each L^3 is independently absent, unsubstituted or substituted alkylene, unsubstituted or substituted heteroalkylene, unsubstituted or substituted alkenylene, unsubstituted or substituted alkynylene, unsubstituted or substituted cycloalkylene, unsubstituted or substituted heterocycloalkylene, unsubstituted or substituted arylene, unsubstituted or substituted heteroarylene, one or more amino acids, $-(CH_2)_q-$, $-(CH_2CH_2X)_q-$, or $-(XCH_2CH_2)_q-$, each q is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12; each X is independently selected from O, S, and NR^X; and R^X is hydrogen or C_1-C_4alkyl. In some embodiments, each L^3 is independently unsubstituted or substituted alkylene, unsubstituted or substituted heteroalkylene, $-(CH_2)_q-$, each q is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12.

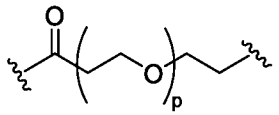
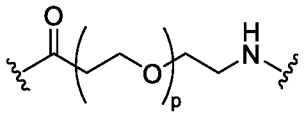
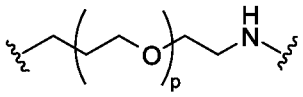
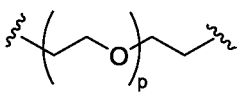
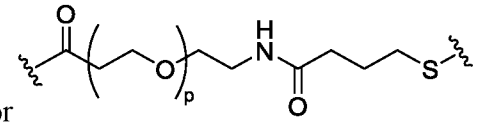
[00176] In some embodiments, each L^4 is independently absent, -O-, -S-, -S(O)-, $-S(O)_2-$, -NH-, -CH(OH)-, -C(=O)-, -C(=O)NH-, -NHC(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)NH-, -NHC(=O)NH-, or -NHC(=O)O-. In some embodiments, each L^4 is independently absent, -NH-.

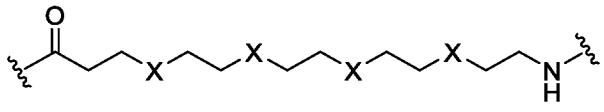
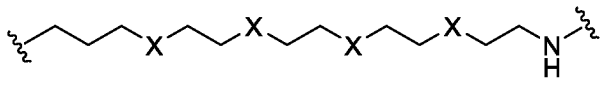
[00177] In some embodiments, each L^5 is independently absent, unsubstituted or substituted alkylene, or unsubstituted or substituted heteroalkylene. In some embodiments, each L^5 is independently absent or unsubstituted or substituted alkylene.

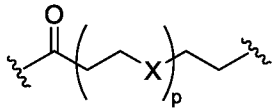
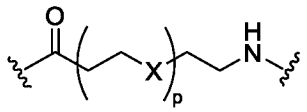
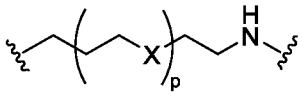
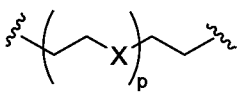
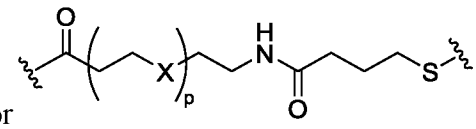
[00178] In some embodiments, L is absent or a linker that is $-L^1-$, $-L^2-$, $-L^3-$, $-L^4-$, $-L^5-$, $-L^1-L^2-L^3-L^4-L^5-$, or a combination thereof. In some embodiments, L is absent or a linker that is $-L^1-$, $-L^2-$, $-L^3-$, $-L^4-$, $-L^5-$, $-L^1-L^2-L^3-L^4-L^5-$, or a combination thereof; each L^1 is independently absent, unsubstituted or substituted alkylene, unsubstituted or substituted heteroalkylene, unsubstituted or substituted alkenylene, unsubstituted or substituted alkynylene, unsubstituted or substituted monocyclic cycloalkylene, unsubstituted or substituted monocyclic heterocycloalkylene,

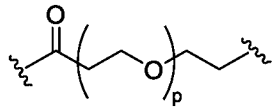
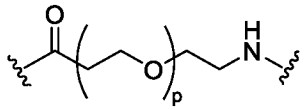
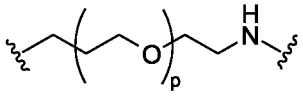
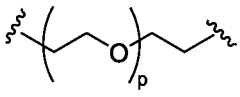
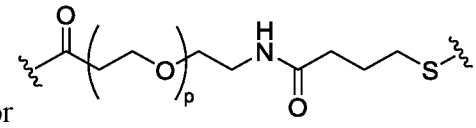
unsubstituted or substituted phenylene, unsubstituted or substituted monocyclic heteroarylene, one or more amino acids, -$(CH_2)_p$-, -$(CH_2)_p$-,-C(=O)-, -C(=O)-$(CH_2)_p$-, -C(=O)NH-,-C(=O)NH-$(CH_2)_p$-, each p is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12; each L^2 is independently -C(=O)-, -C(=O)NH-, -C(=O)O-, -$(CH_2)_p$-, -C(=O)-$(CH_2CH_2O)_p$-, or -$(CH_2CH_2O)_p$-, each p is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12; each L^3 is independently unsubstituted or substituted alkylene, unsubstituted or substituted heteroalkylene, -$(CH_2)_q$-, each q is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12; each L^4 is independently absent, -NH-; each L^5 is independently absent, unsubstituted or substituted alkylene, or unsubstituted or substituted heteroalkylene.

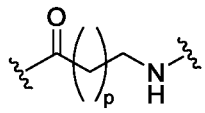
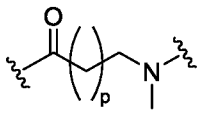
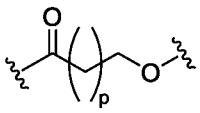
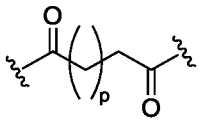
[00179] In some embodiments, -L^2-L^3-L^4-L^5- is , , , , or ; each p is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12; wherein each X is independently O or NR^X; and R^X is hydrogen or C_1-C_4alkyl.

[00180] In some embodiments, -L^2-L^3-L^4-L^5- is , , , , or ; each p is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12.

[00181] In some embodiments, -L^2-L^3-L^4-L^5- is  or , wherein each X is independently O or NR^X; and R^X is hydrogen or C_1-C_4alkyl.

[00182] In some embodiments, L is , , , , or ; each p is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12; and each X is independently O or NR^X; and R^X is hydrogen or C_1-C_4alkyl.

[00183] In some embodiments, **L** is , , , , or ; each p is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12.

[00184] In some embodiments, **L** is , , , or ; each p is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12.

[00185] In some embodiments, **L** is absent or comprises one or more amino acids, PEG groups, -L^1-, -L^2-, -L^3-, -L^4-, -L^5-, -L^1-L^2-, -L^1-L^2-L^3-, -L^1-L^2-L^3-L^4-, -L^2-L^3-L^4-L^5-, -L^2-L^3-L^4-, -L^3-L^4-L^5-, -L^1-L^2-L^3-L^4-L^5-, or a combination thereof;

each L^1 is independently absent, unsubstituted or substituted alkylene, unsubstituted or substituted heteroalkylene, unsubstituted or substituted alkenylene, unsubstituted or substituted alkynylene, unsubstituted or substituted cycloalkylene, unsubstituted or substituted heterocycloalkylene, unsubstituted or substituted arylene, unsubstituted or substituted heteroarylene, one or more amino acids, -$(CH_2)_p$-, -C(=O)-, -$(CH_2)_p$-C(=O)-, -C(=O)-$(CH_2)_p$-, -$(CH_2)_p$-C(=O)-$(CH_2)_p$-, -C(=O)NH-, -C(=O)NH-$(CH_2)_p$-, -$(CH_2)_q$-C(=O)NH-, -$(CH_2)_p$C(=O)NH-$(CH_2)_p$-, -NHC(=O)-, -NHC(=O)-$(CH_2)_p$-, -$(CH_2)_q$-NHC(=O)-, -$(CH_2)_p$NHC(=O)-$(CH_2)_p$-, -NHC(=O)NH-, -NHC(=O)NH-$(CH_2)_p$-, -$(CH_2)_q$-NHC(=O)NH-, -$(CH_2)_p$NHC(=O)NH-$(CH_2)_p$-, each p is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

each L^2 is independently absent, -O-, -S-, -S(=O)-, -$S(=O)_2$-, -NH-, -CH(OH)-, -NHC(=O)-, -C(=O)O-, -OC(=O)-, -CH(=N)-, -CH(=N-NH)-, -CCH_3(=N)-, -CCH_3(=N-NH)-, -

OC(=O)NH-, -NHC(=O)NH-, -NHC(=O)O-, -$(CH_2)_p$-, -C(=O)-$(CH_2CH_2X)_p$-, or -$(CH_2CH_2X)_p$-, each p is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

each L^3 is independently absent, unsubstituted or substituted alkylene, unsubstituted or substituted heteroalkylene, unsubstituted or substituted alkenylene, unsubstituted or substituted alkynylene, unsubstituted or substituted cycloalkylene, unsubstituted or substituted heterocycloalkylene, unsubstituted or substituted arylene, unsubstituted or substituted heteroarylene, one or more amino acids, -$(CH_2)_q$-, -$(CH_2CH_2X)_q$-, or -$(XCH_2CH_2)_q$-, each q is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

each L^4 is independently absent, -O-, -S-, -S(=O)-, -$S(=O)_2$-, -NH-, -CH(OH)-, -C(=O)-, -C(=O)NH-, -NHC(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)NH-, -OC(=S)NH-, -NHC(=O)NH-, -NHC(=S)NH-, -NHC(=O)O- or -NHC(=S)O-;

each L^5 is independently absent, unsubstituted or substituted alkylene, unsubstituted or substituted heteroalkylene, or unsubstituted or substituted benzylene;

each X is independently selected from O, S, and NR^X; and each R^X is independently selected from hydrogen, C_1-C_4alkyl and -CH_2CO_2H.

[00186] In some embodiments, each L^1 is independently absent, unsubstituted or substituted alkylene, unsubstituted or substituted heteroalkylene, unsubstituted or substituted alkenylene, unsubstituted or substituted alkynylene, unsubstituted or substituted cycloalkylene, unsubstituted or substituted heterocycloalkylene, unsubstituted or substituted arylene, unsubstituted or substituted heteroarylene, one or more amino acids, -$(CH_2)_p$-, -C(=O)-, -C(=O)-$(CH_2)_p$-, -C(=O)NH-, -C(=O)NH-$(CH_2)_p$-, each p is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12.

[00187] In some embodiments, **L** is absent or a linker that is -L^1-L^2-L^3-L^4-L^5-;

L^1 is absent, unsubstituted or substituted alkylene, unsubstituted or substituted heteroalkylene, unsubstituted or substituted alkenylene, unsubstituted or substituted alkynylene, unsubstituted or substituted monocyclic cycloalkylene, unsubstituted or substituted monocyclic heterocycloalkylene, unsubstituted or substituted phenylene, unsubstituted or substituted monocyclic heteroarylene, one or more amino acids, -$(CH_2)_p$-, -C(=O)-, -C(=O)-$(CH_2)_p$-, -C(=O)NH-, -C(=O)NH-$(CH_2)_p$-, each p is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

L^2 is -C(=O)-, -C(=O)NH-, -C(=O)O-, -$(CH_2)_p$-, -C(=O)-$(CH_2CH_2O)_p$-, or -$(CH_2CH_2O)_p$-, each p is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

L^3 is unsubstituted or substituted alkylene, unsubstituted or substituted heteroalkylene, -$(CH_2)_q$-, each q is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

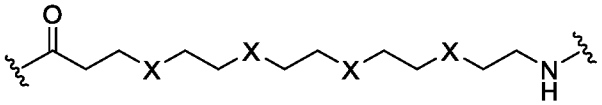
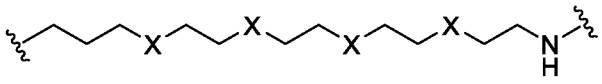
L^4 is absent or -NH-;

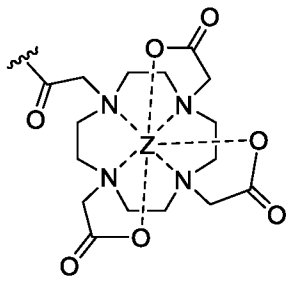
L^5 is absent, unsubstituted or substituted alkylene, or unsubstituted or substituted heteroalkylene.

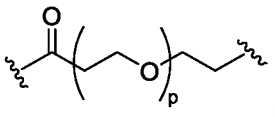
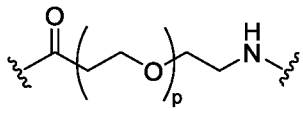
[00188] In some embodiments, **L** comprises -L^4-L^5-; L^4 is absent, -O-, -NH-, -C(=O)-, -NHC(=O)-, -NHC(=O)NH-, or -NHC(=S)NH-; and L^5 is absent, C_1-C_2alkylene or benzylene. In some embodiments, **L** comprises -L^4-L^5-; L^4 is absent, -O-, -NH-, -C(=O)-, -NHC(=O)-, -NHC(=O)NH-, or -NHC(=S)NH-; and L^5 is absent, C_1-C_2alkylene or -CH_2-(phen-1,4-ylene). In some embodiments, **L** comprises -L^4-L^5-; L^4 is absent, -O-, -NH-, -C(=O)-, or -NHC(=O)-; and L^5 is absent or C_1-C_2alkylene. In some embodiments, **L** comprises -L^4-L^5-; L^4 is absent, -O-, -NH-, -C(=O)-, or -NHC(=O)-; and L^5 is absent -CH_2- or -CH_2CH_2-.

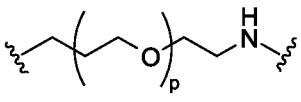
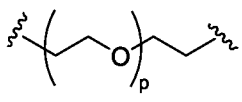
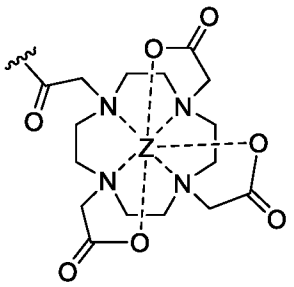
[00189] In some embodiments, the linker comprises a click chemistry residue. In some embodiments, the linker is attached to a non-peptide ligand, to a metal chelator or both via click chemistry. For example, in some embodiments, a non-peptide ligand comprises an azide group that reacts with an alkyne moiety of the linker. For another example, in some embodiments, a non-peptide ligand comprises an alkyne group that reacts with an azide of the linker. The metal chelator and the linker can be attached similarly. In some embodiments, the linker comprises an azide moiety, an alkyne moiety, or both. In some embodiments, the linker comprises a triazole moiety.

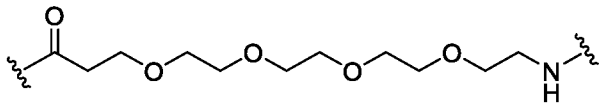
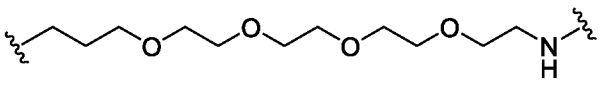
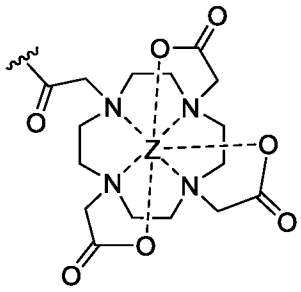
Representative Linker and Payload Moieties

[00190] In some embodiments, **L** is  or , wherein each X is independently O or NR^X; and R^X is hydrogen or C_1-C_4alkyl; and

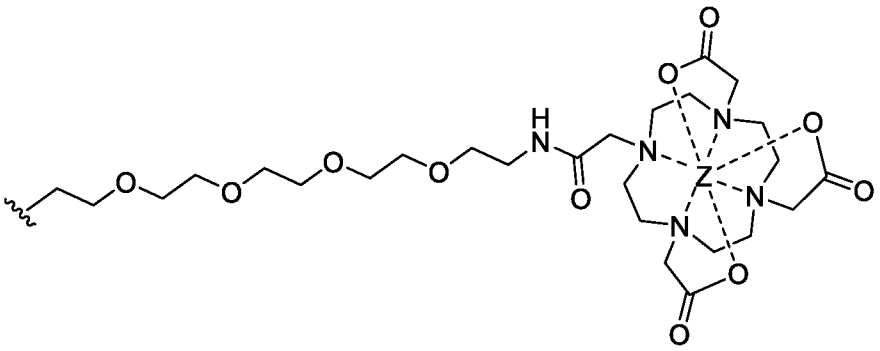
Q is .

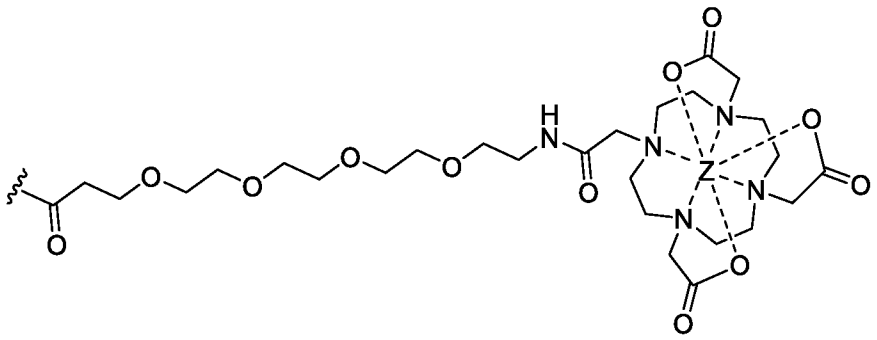
[00191] In some embodiments, **L** is , ,

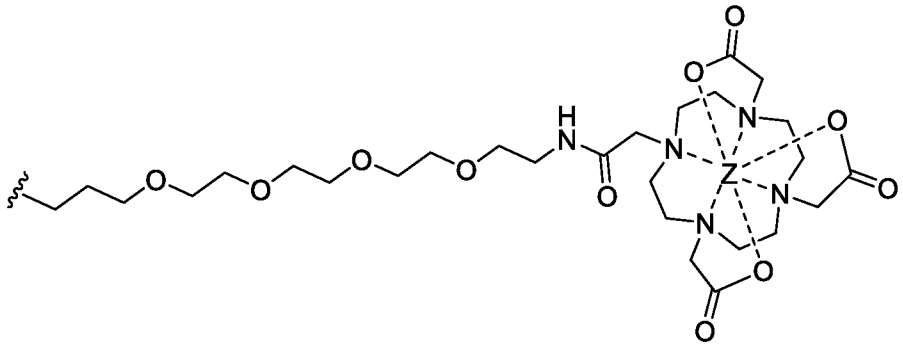

, or 
; and **Q** is 
.

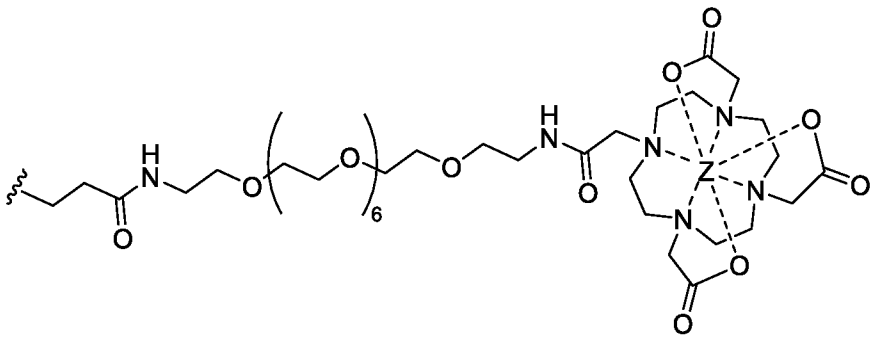
[00192] In some embodiments, **L** is 
or 
; and **Q** is 
.

[00193] In some embodiments, -**L**-**Q** is

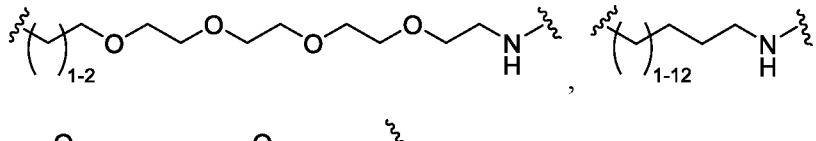

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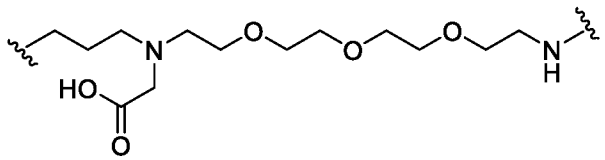

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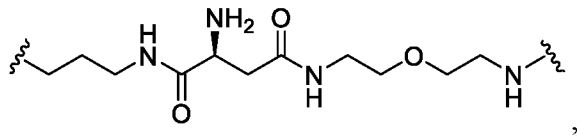

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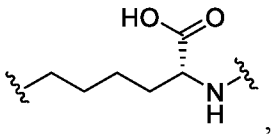
[00194] In some embodiments, linker **L** is:

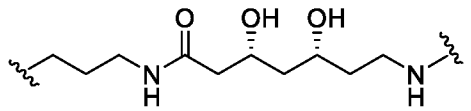

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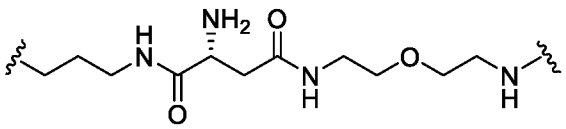
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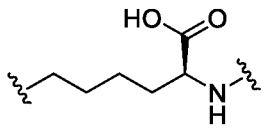

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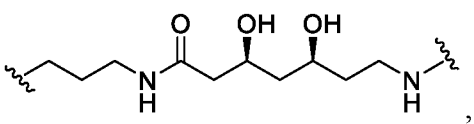

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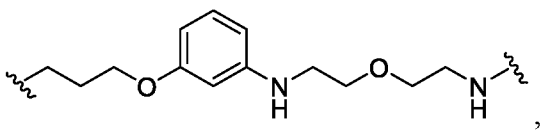

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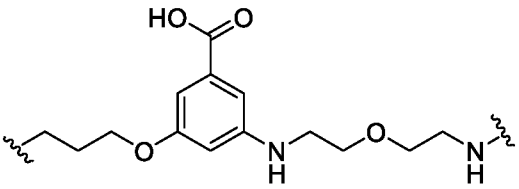

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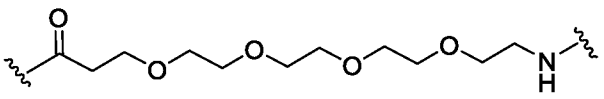

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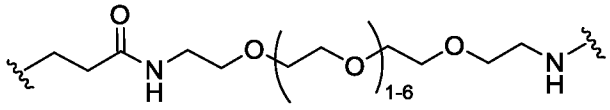

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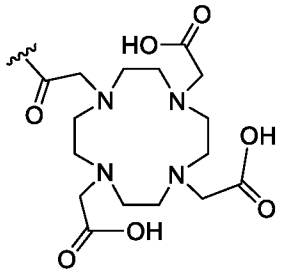

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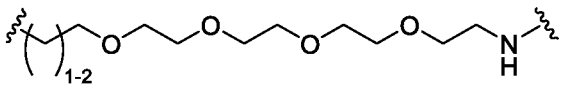
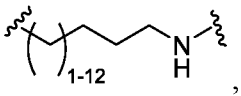
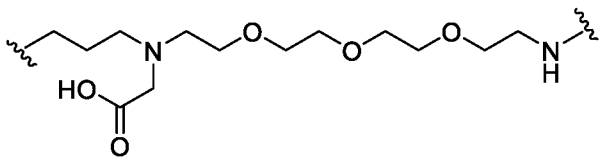
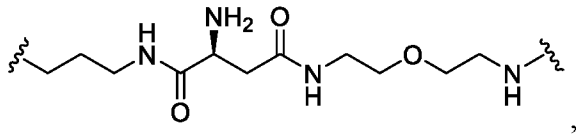
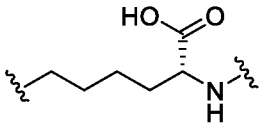
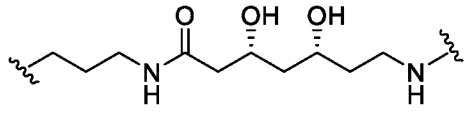
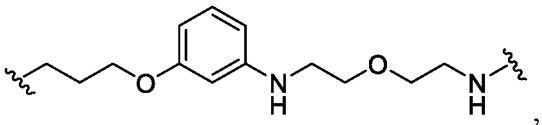
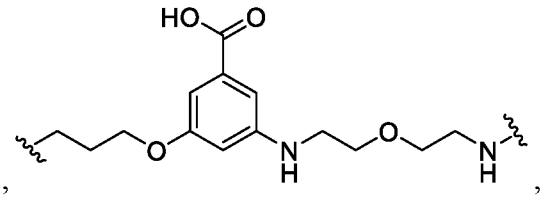
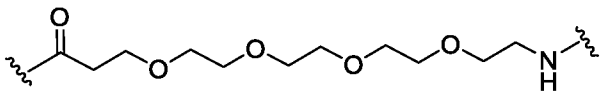
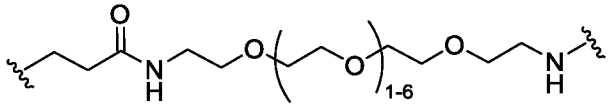

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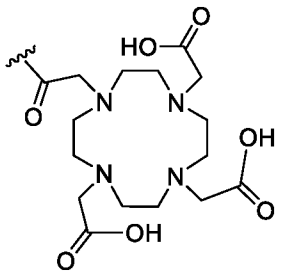
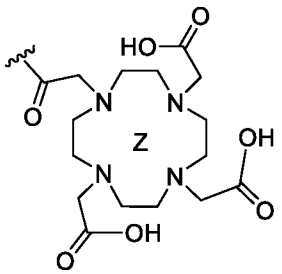

, or


; and

Q is: , or a radionuclide (**Z**) complex thereof.

[00195] In some embodiments, **L** is:

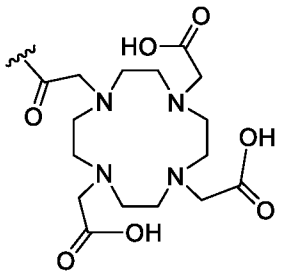

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, or

; and

Q is  or .

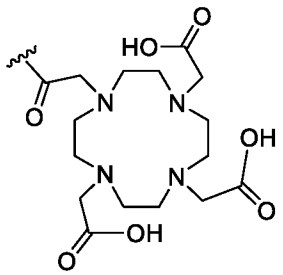
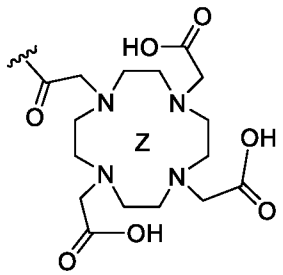
[00196] In some embodiments, **-L-Q** is: $-(CH_2)_p(CH_2)_qNH-Q$, $-(CH_2)_p(OCH_2CH_2)_pNH-Q$, $-C(=O)(CH_2)_p(CH_2)_qNH-Q$, $-C(=O)(CH_2)_p(OCH_2CH_2)_pNH-Q$,

-C(=O)CH(NH_2)CH_2C(=O)NH$CH_2CH_2OCH_2CH_2$NH-Q, or

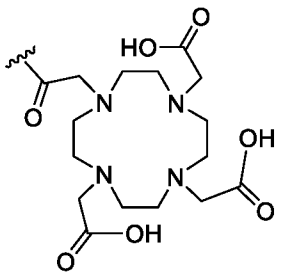
-(C_2-C_4alkylene)($NR^X CH_2CH_2)_p(OCH_2CH_2)_q$NH-Q; and

Q is:  , or a radionuclide (**Z**) complex thereof.

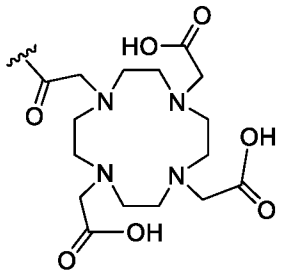
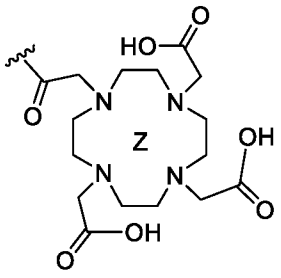
[00197] In some embodiments, -**L**-**Q** is: -$(CH_2)_p(CH_2)_q$NH-Q, -$(CH_2)_p(OCH_2CH_2)_p$NH-Q, -C(=O)$(CH_2)_p(CH_2)_q$NH-Q, -C(=O)$(CH_2)_p(OCH_2CH_2)_p$NH-Q, -C(=O)CH(NH_2)CH_2C(=O)NH$CH_2CH_2OCH_2CH_2$NH-Q, or -(C_2-C_4alkylene)($NR^X CH_2CH_2)_p(OCH_2CH_2)_q$NH-Q; and

Q is  or  .

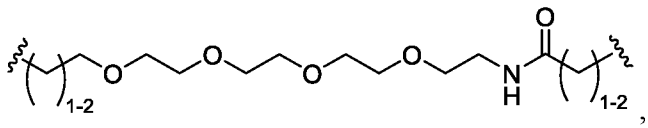
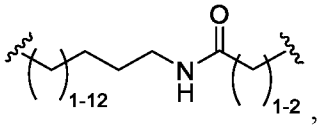
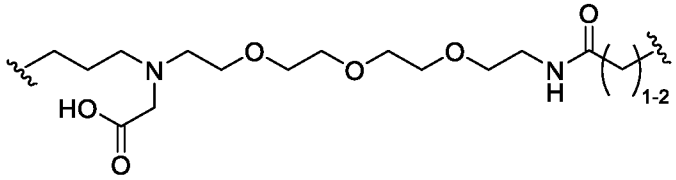
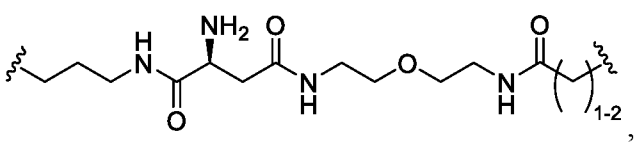
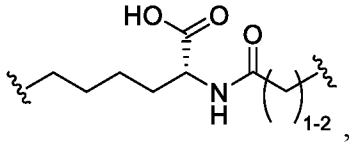
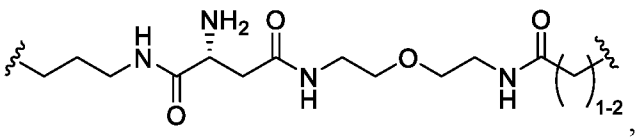
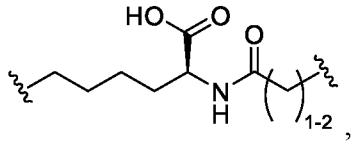
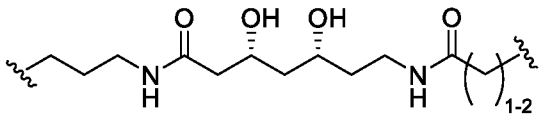
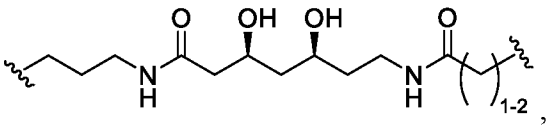
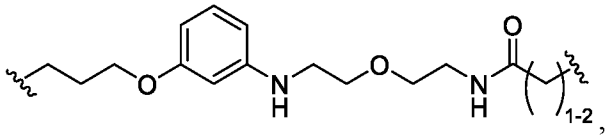
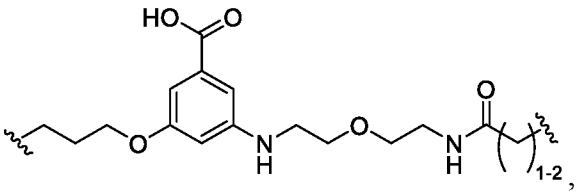
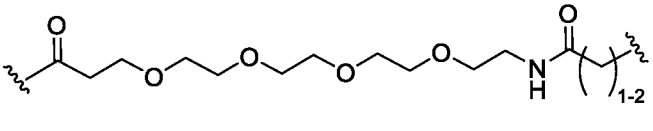
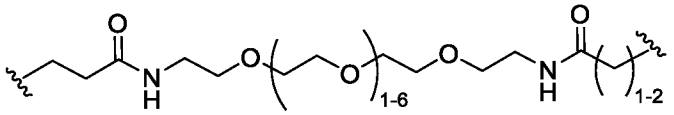
[00198] In some embodiments, -**L**-**Q** is: -$(CH_2)_p(CH_2)_6$NH-Q, -$CH_2CH_2(OCH_2CH_2)_4$NH-Q, -$CH_2CH_2CH_2(OCH_2CH_2)_4$NH-Q, -C(=O)$(CH_2)_p(CH_2)_6$NH-Q, -C(=O)$CH_2CH_2(OCH_2CH_2)_4$NH-Q, -C(=O)CH($NH_2$)$CH_2$C(=O)NH$CH_2CH_2OCH_2CH_2$NH-Q, or -($C_2$-$C_4$alkylene)N($CH_2CO_2H$)$CH_2CH_2(OCH_2CH_2)_3$NH-Q; and

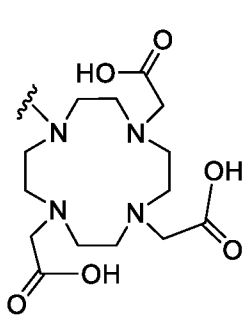
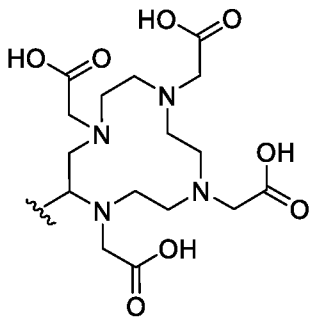
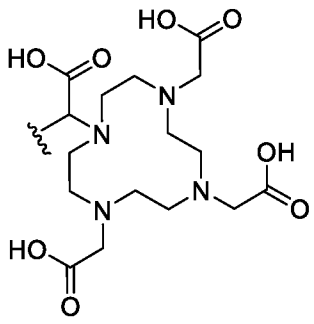
Q is:  , or a radionuclide (**Z**) complex thereof.

[00199] In some embodiments, -**L**-**Q** is: -$(CH_2)_p(CH_2)_6$NH-Q, -$CH_2CH_2(OCH_2CH_2)_4$NH-Q, -$CH_2CH_2CH_2(OCH_2CH_2)_4$NH-Q, -C(=O)$(CH_2)_p(CH_2)_6$NH-Q, -C(=O)$CH_2CH_2(OCH_2CH_2)_4$NH-Q, -C(=O)CH($NH_2$)$CH_2$C(=O)NH$CH_2CH_2OCH_2CH_2$NH-Q, or -($C_2$-$C_4$alkylene)N($CH_2CO_2H$)$CH_2CH_2(OCH_2CH_2)_3$NH-Q; and

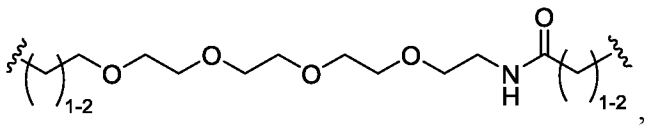
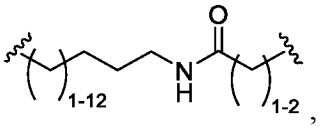
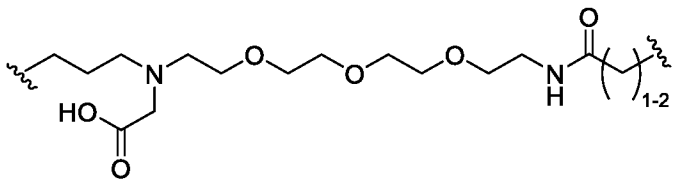
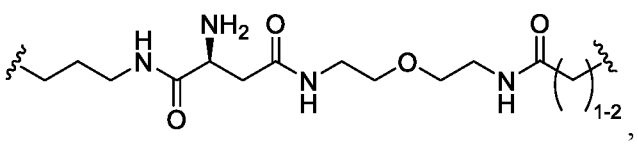
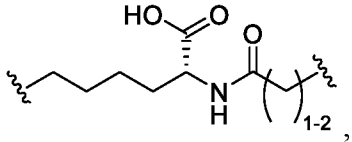
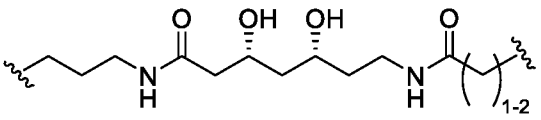
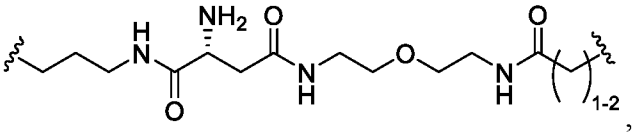
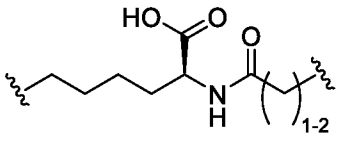
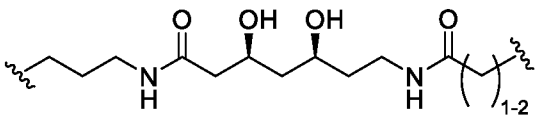
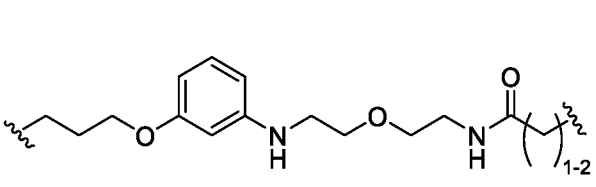
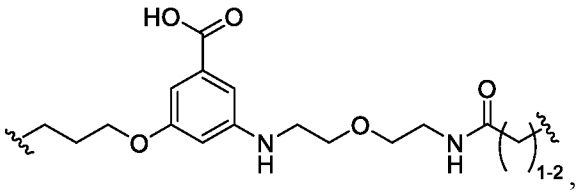
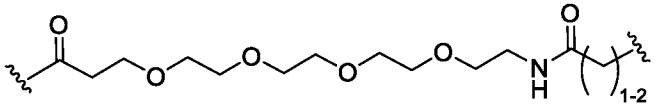
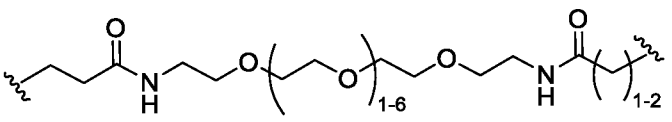
Q is  or .

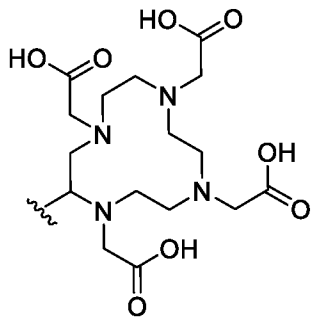
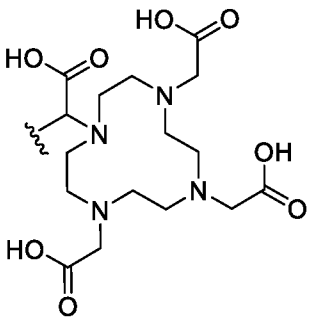
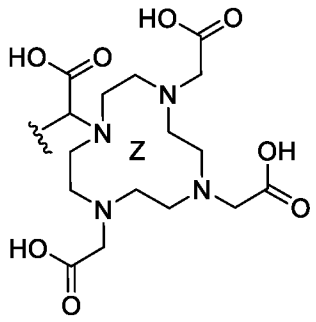
[00200] In some embodiments, linker **L** is:

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; and

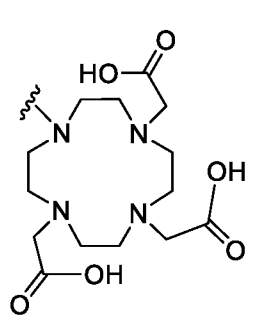
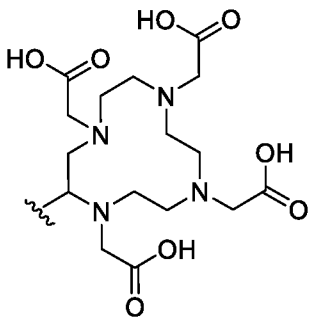
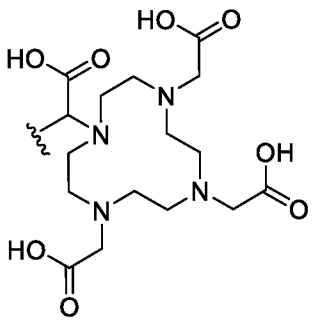
Q is: ,  or , or a radionuclide (**Z**) complex thereof.

[00201] In some embodiments, linker **L** is:

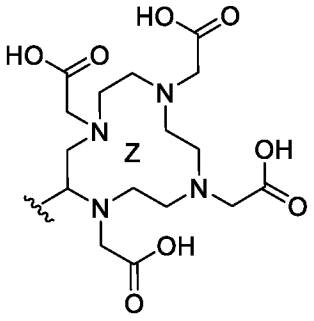
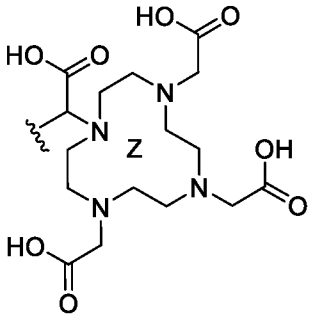
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Q is:  ,  ,  or  .

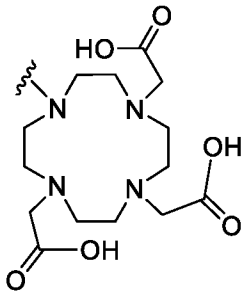
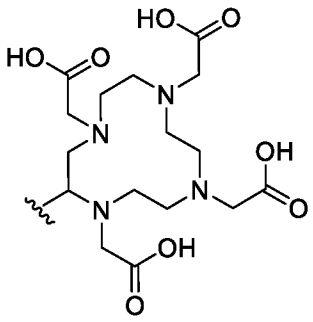
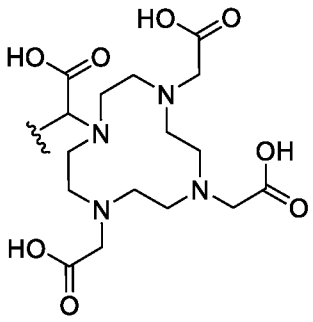
[00202] In some embodiments, **-L-Q** is: $-(CH_2)_p(CH_2)_qNHC(=O)CH_2Q$, $-(CH_2)_p(CH_2)_qNHC(=O)CH_2CH_2Q$, $-(CH_2)_p(OCH_2CH_2)_pNHC(=O)CH_2Q$, $-(CH_2)_p(OCH_2CH_2)_pNHC(=O)CH_2CH_2Q$, $-C(=O)(CH_2)_p(CH_2)_qNH\ C(=O)CH_2Q$, $-C(=O)(CH_2)_p(CH_2)_qNH\ C(=O)CH_2CH_2Q$, $-C(=O)(CH_2)_p(OCH_2CH_2)_pNHC(=O)CH_2Q$, $-C(=O)(CH_2)_p(OCH_2CH_2)_pNHC(=O)CH_2CH_2Q$, $-C(=O)CH(NH_2)CH_2C(=O)NHCH_2CH_2OCH_2CH_2NHC(=O)CH_2Q$, $-C(=O)CH(NH_2)CH_2C(=O)NHCH_2CH_2OCH_2CH_2NHC(=O)CH_2CH_2Q$, $-(C_2\text{-}C_4alkylene)(NR^XCH_2CH_2)_p(OCH_2CH_2)_qNHC(=O)CH_2Q$ or $-(C_2\text{-}C_4alkylene)(NR^XCH_2CH_2)_p(OCH_2CH_2)_qNHC(=O)CH_2CH_2Q$; and

Q is:  ,  or  , or a radionuclide (**Z**) complex thereof.

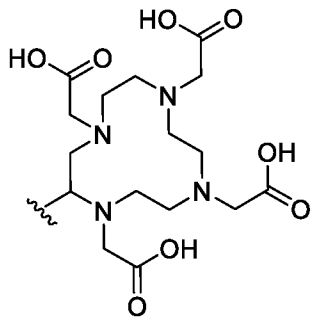
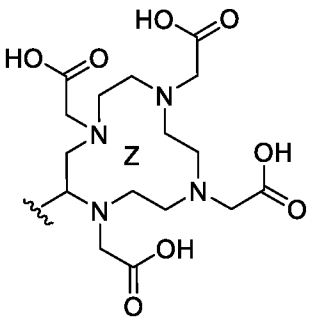
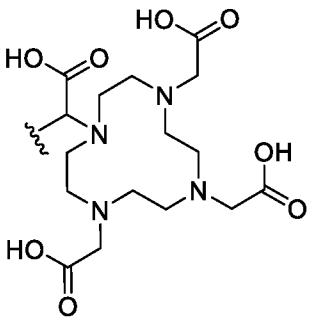
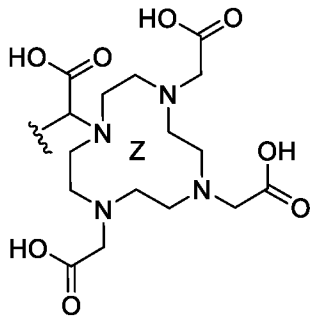
[00203] In some embodiments, **-L-Q** is: $-(CH_2)_p(CH_2)_qNHC(=O)CH_2CH_2Q$, $-(CH_2)_p(OCH_2CH_2)_pNHC(=O)CH_2CH_2Q$, $-C(=O)(CH_2)_p(CH_2)_qNH\ C(=O)CH_2CH_2Q$, $-C(=O)(CH_2)_p(OCH_2CH_2)_pNHC(=O)CH_2CH_2Q$, $-C(=O)CH(NH_2)CH_2C(=O)NHCH_2CH_2OCH_2CH_2NHC(=O)CH_2CH_2Q$, or $-(C_2\text{-}C_4alkylene)(NR^XCH_2CH_2)_p(OCH_2CH_2)_qNHC(=O)CH_2CH_2Q$; and

Q is:  or .

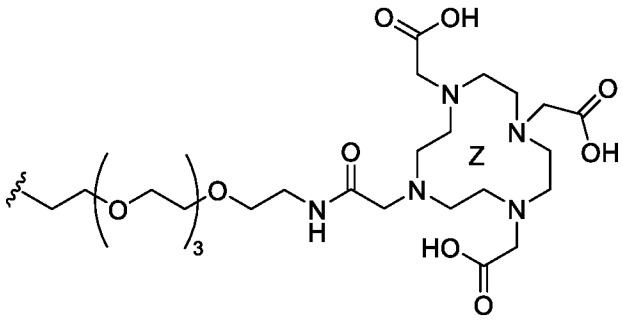
[00204] In some embodiments, -**L**-**Q** is: $-(CH_2)_p(CH_2)_6NHC(=O)CH_2Q$, $-(CH_2)_p(CH_2)_6NHC(=O)CH_2CH_2Q$, $-CH_2CH_2(OCH_2CH_2)_4NHC(=O)CH_2Q$, $-CH_2CH_2(OCH_2CH_2)_4NHC(=O)CH_2CH_2Q$, $-CH_2CH_2CH_2(OCH_2CH_2)_4NHC(=O)CH_2Q$, $-CH_2CH_2CH_2(OCH_2CH_2)_4NHC(=O)CH_2CH_2Q$, $-C(=O)(CH_2)_p(CH_2)_6NHC(=O)CH_2Q$, $-C(=O)(CH_2)_p(CH_2)_6NHC(=O)CH_2CH_2Q$, $-C(=O)CH_2CH_2(OCH_2CH_2)_4NHC(=O)CH_2Q$, $-C(=O)CH_2CH_2(OCH_2CH_2)_4NHC(=O)CH_2CH_2Q$, $-C(=O)CH(NH_2)CH_2C(=O)NHCH_2CH_2OCH_2CH_2NHC(=O)CH_2Q$, $-C(=O)CH(NH_2)CH_2C(=O)NHCH_2CH_2OCH_2CH_2NHC(=O)CH_2CH_2Q$, $-(C_2\text{-}C_4\text{alkylene})N(CH_2CO_2H)CH_2CH_2(OCH_2CH_2)_3NHC(=O)CH_2Q$, or $-(C_2\text{-}C_4\text{alkylene})N(CH_2CO_2H)CH_2CH_2(OCH_2CH_2)_3NHC(=O)CH_2CH_2Q$; and

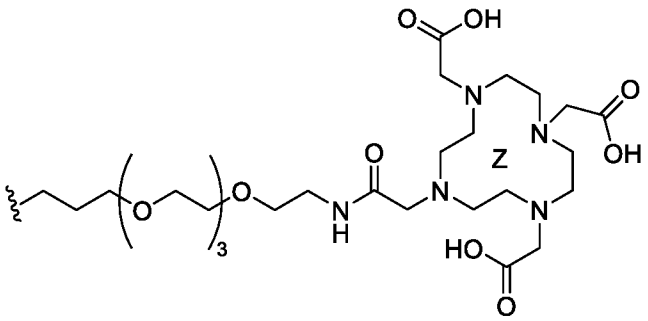
Q is: ,  or , or a radionuclide (**Z**) complex thereof.

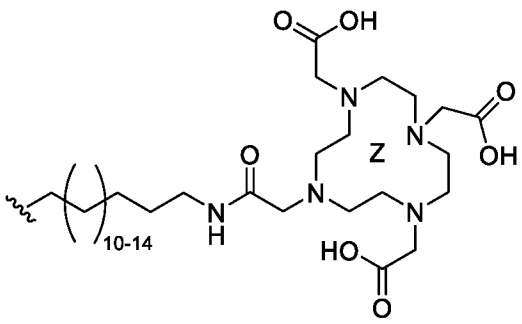
[00205] In some embodiments, -**L**-**Q** is: $-(CH_2)_p(CH_2)_6NHC(=O)CH_2CH_2Q$, $-CH_2CH_2(OCH_2CH_2)_4NHC(=O)CH_2CH_2Q$, $-CH_2CH_2CH_2(OCH_2CH_2)_4NHC(=O)CH_2CH_2Q$, $-C(=O)(CH_2)_p(CH_2)_6NHC(=O)CH_2CH_2Q$, $-C(=O)CH_2CH_2(OCH_2CH_2)_4NHC(=O)CH_2CH_2Q$, $-C(=O)CH(NH_2)CH_2C(=O)NHCH_2CH_2OCH_2CH_2NHC(=O)CH_2CH_2Q$, or $-(C_2\text{-}C_4\text{alkylene})N(CH_2CO_2H)CH_2CH_2(OCH_2CH_2)_3NHC(=O)CH_2CH_2Q$; and

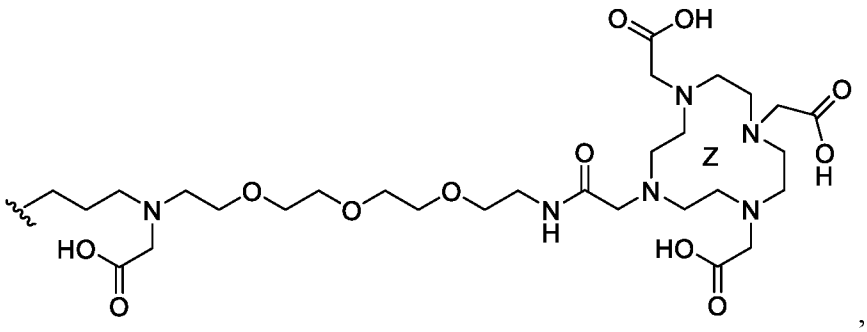
Q is: , ,  or .

[00206] In some embodiments, **-L-Q** is:

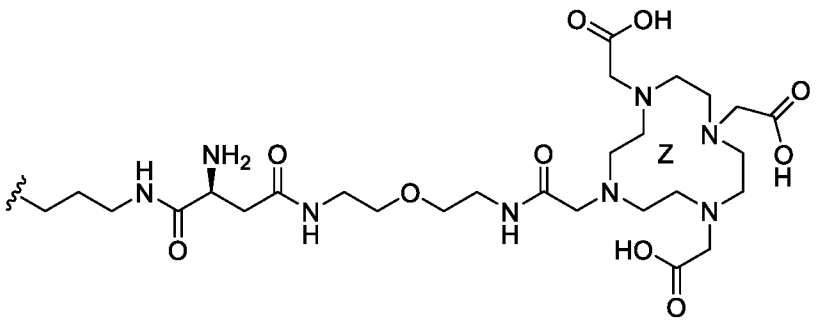
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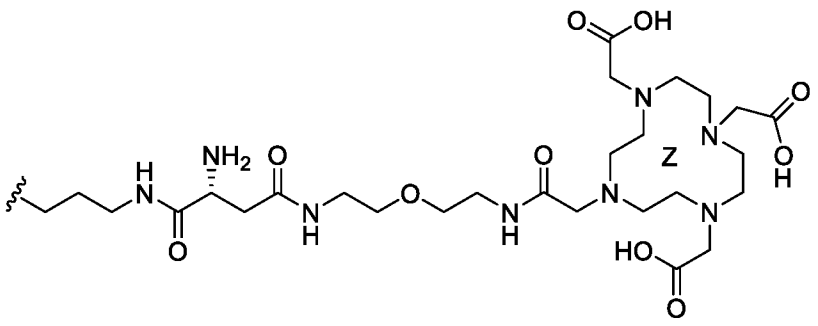
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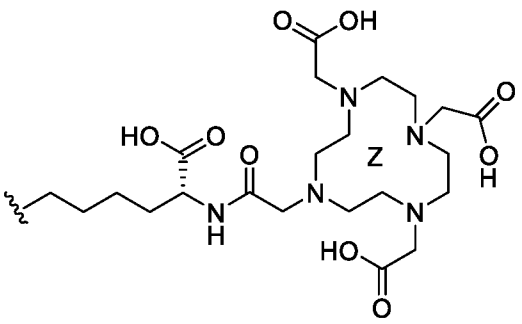
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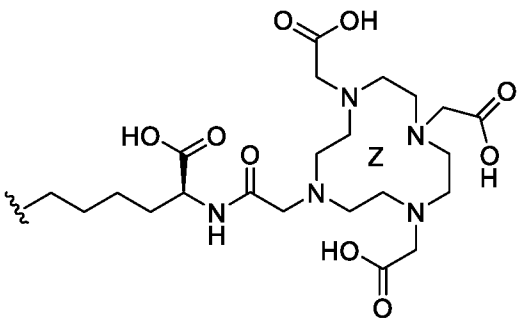
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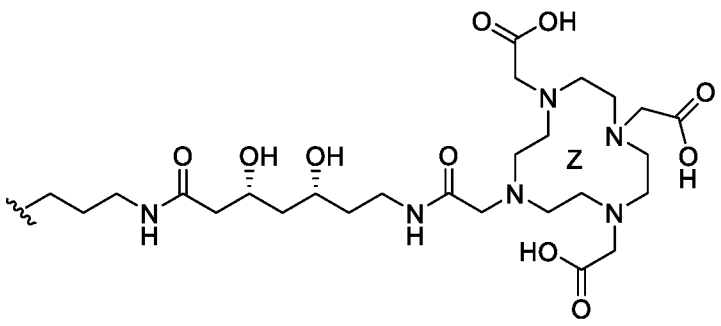
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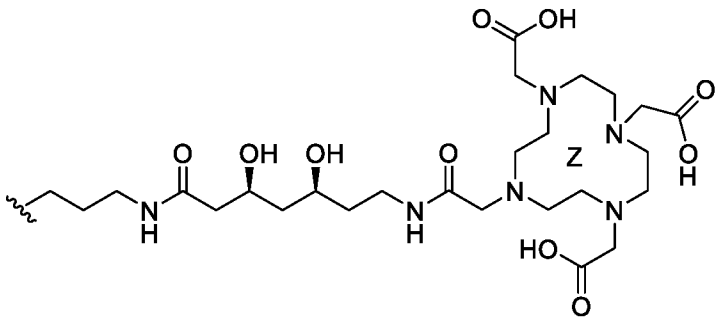
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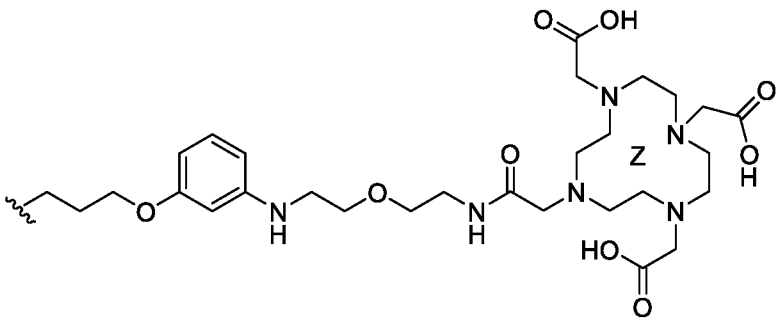
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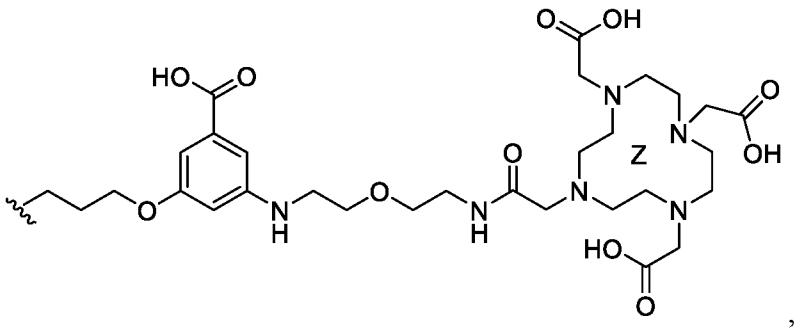
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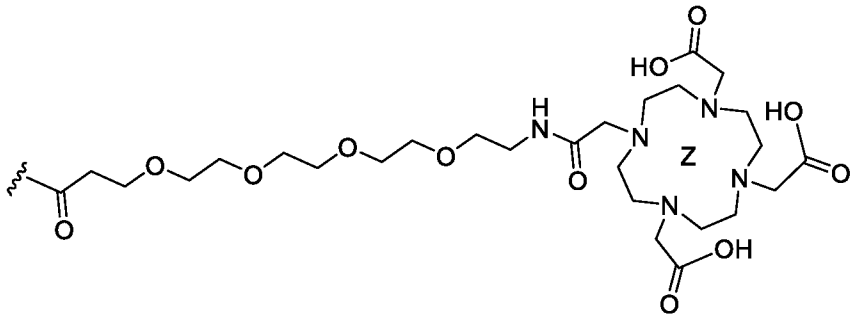
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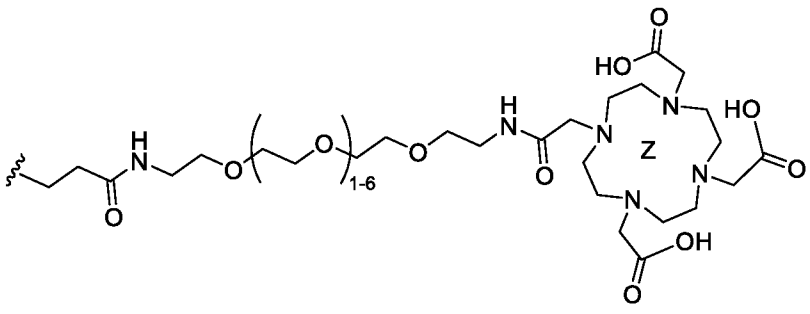
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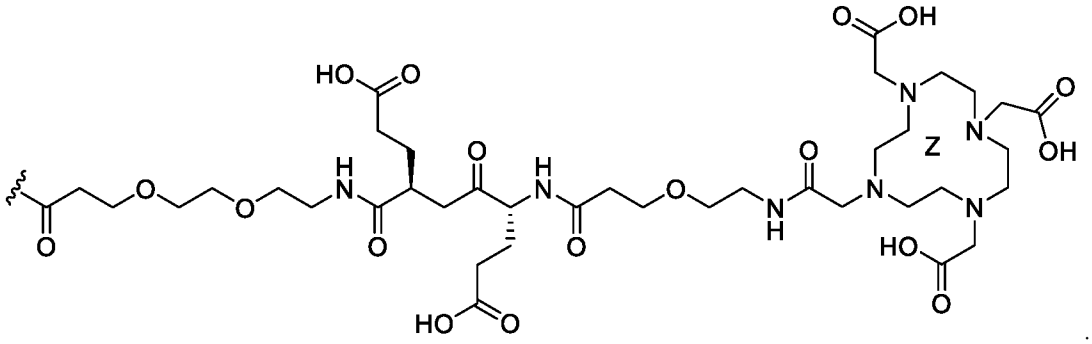
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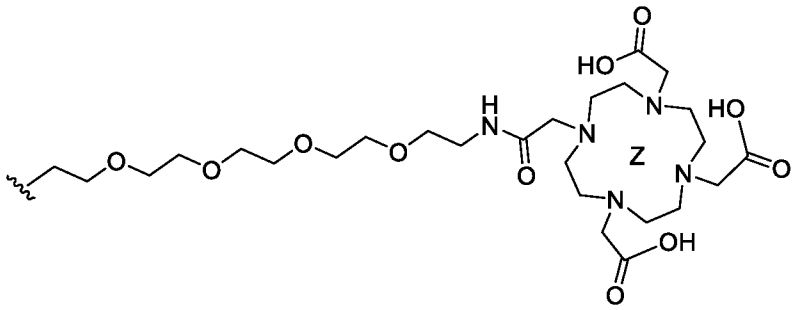
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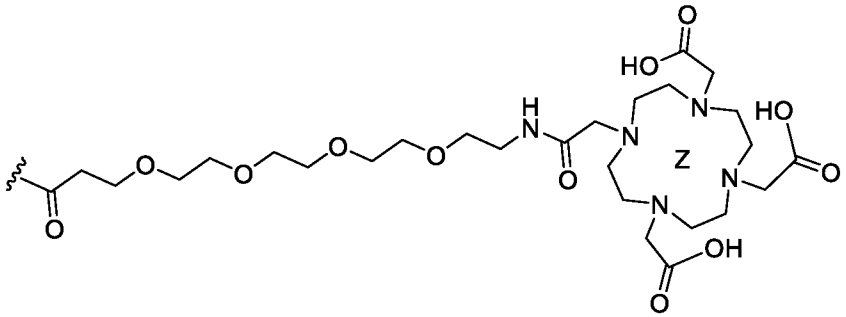
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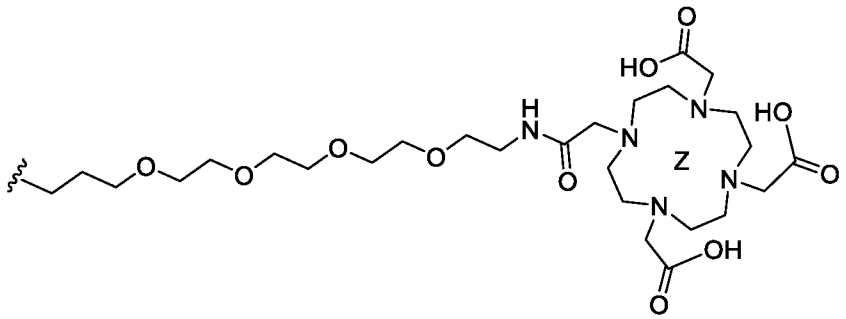
[00207] In some embodiments, -**L**-**Q** is:



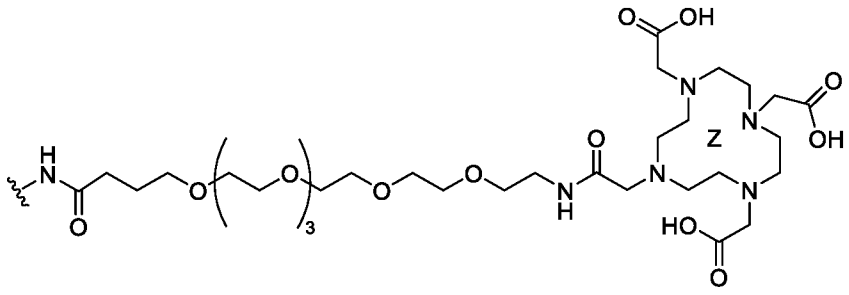
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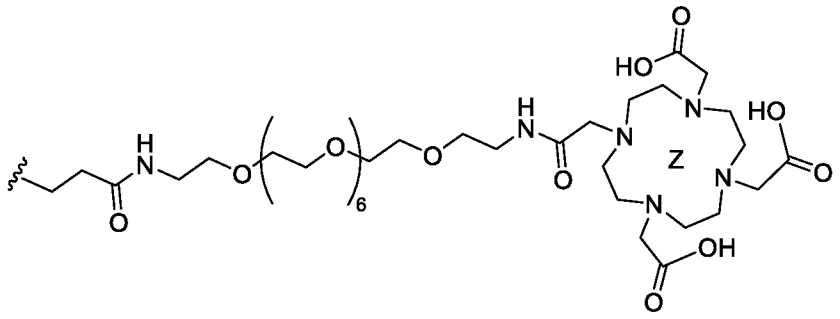
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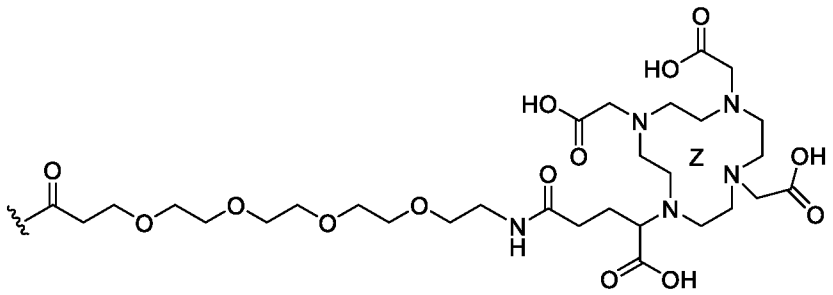
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Representative Non-Peptide Small Molecule Drug Conjugates (NPDCs)

[00208] As used herein, "non-peptide ligand" means a compound that is a small molecule. As used herein, "non-peptide ligand" means a compound that is a small molecule with a molecular weight < 900 Daltons. A non-peptide ligand is not derived from chains of amino acids linked by peptide bonds. A non-peptide ligand is not an oligopeptide (e.g. dipeptide, tripeptide, tetrapeptide). Larger structures such as nucleic acids, proteins, and polysaccharides are not small molecules.

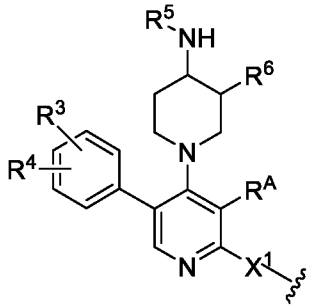
[00209] In some embodiments, **NP** is a non-peptide ligand that binds to tumor cells expressing somatostatin receptors.

[00210] In some embodiments, **NP** is a non-peptide ligand for the somatostatin receptor, wherein **NP** is a compound described in US Patent Number 10,696,689, US Patent Publication Number US20200010453, each of which is herein incorporated by reference for such compounds. In some embodiments, the non-peptide ligand is a compound described in any one of Formulas (I), (Ia), (Ib), (Ic), (Id), (II), (IIa), (IIb), (IIc), (IId), (III), (IIIa), (IIIb), (IIIc), or (IIId), of US Patent Number 10,696,689. In some embodiments, the non-peptide ligand is a compound described in Table 1, Table 2, or Table 3 of US10,696,689. In some embodiments, the non-peptide ligand is a compound described in Formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), or (XI) of US20200010453. In some embodiments, the non-peptide ligand is a compound described in Table 1, Table 2, Table 3, or Table 4 of International Patent Application Publication Number WO 2018/170284.

[00211] In some embodiments, the non-peptide ligand is a compound described in US9643951, US9630976, US20200000816, each of which is herein incorporated for such compounds.

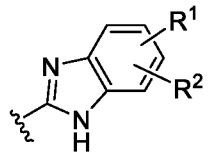
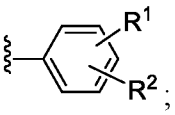
[00212] In some embodiments, **NP** is a non-peptide ligand comprising a 4-(4-aminopiperidin-1-yl)-5-(phenyl)pyridine structural motif or a 4-[(4αS,8αS)-octahydro-1H-pyrido[3,4-b][1,4]oxazin-6-yl]-5-(phenyl)pyridine structural motif. In some embodiments, **NP** is a non-peptide ligand comprising a 4-(4-aminopiperidin-1-yl)-5-(phenyl)pyridine structural motif or a 4-[(4αS,8αS)-octahydro-1H-pyrido[3,4-b][1,4]oxazin-6-yl]-5-(phenyl)pyridine structural motif; wherein -**L**-**Q** is attached to **NP** at the 2-position of the pyridine.

[00213] In some embodiments, **NP** has a structure of Formula (II), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof:



Formula (II)

wherein:

R^A is  or ;

each R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4heteroalkyl, -CN, -$N(R^7)_2$, or -OR^7;

R^5 is hydrogen, or substituted or unsubstituted C_1-C_6alkyl;

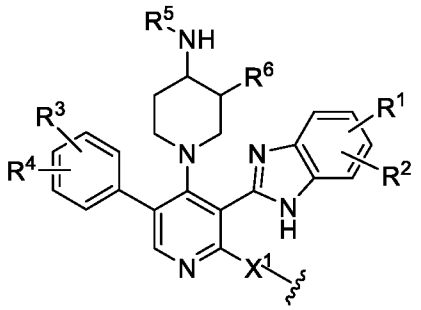
R^6 is hydrogen, -OR^7, -$N(R^7)_2$, -CN, halogen, C_1-C_6 alkyl, or C_1-C_6fluoroalkyl;

or R^5 and R^6 are taken together with the intervening atoms to which they are attached to form a morpholine;

X^1 is absent, -O-, -S-, -$N(R^7)$-, -C(=O)-, -C(=O)$N(R^7)$-, -C(=O)O-, -$N(R^7)$C(=O)-, or a heterocycle; and

each R^7 is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl.

[00214] In some embodiments, **NP** has a structure of Formula (III), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof:



Formula (III)

wherein:

each R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4heteroalkyl, -CN, -$N(R^7)_2$, or -OR^7;

R^5 is hydrogen, or substituted or unsubstituted C_1-C_6alkyl;

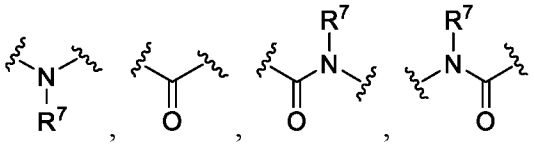
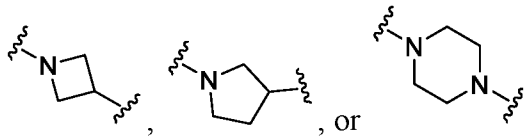
R^6 is hydrogen, -OR^7, -$N(R^7)_2$, -CN, halogen, C_1-C_6 alkyl, or C_1-C_6fluoroalkyl;

or R^5 and R^6 are taken together with the intervening atoms to which they are attached to form a morpholine;

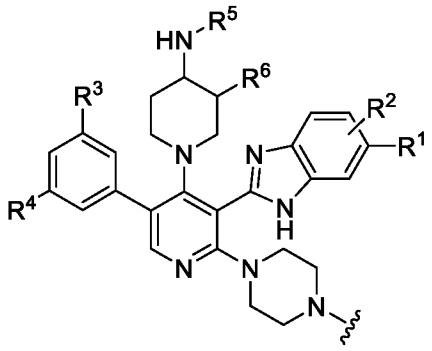
X^1 is absent, -O-, -S-, -$N(R^7)$-, -C(=O)-, -C(=O)$N(R^7)$-, -C(=O)O-, -$N(R^7)$C(=O)-, or a heterocycle;

each R^7 is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl.

[00215] In some embodiments, X^1 is absent, -O-, -S-, -$N(R^7)$-, -C(=O)-, -C(=O)$N(R^7)$-, -C(=O)O-, -$N(R^7)$C(=O)-, azetidine, pyrrolidine, piperidine, or piperazine.

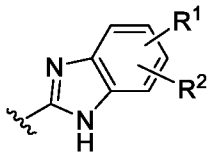
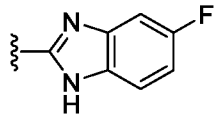
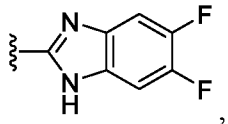
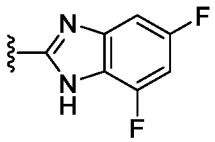
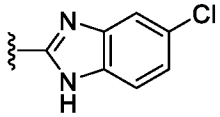
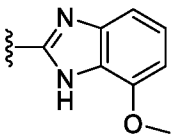
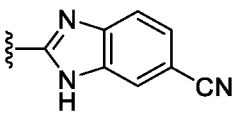
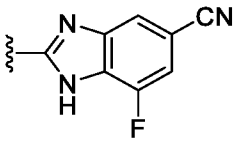
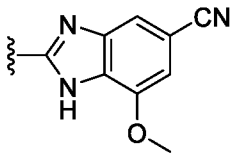
[00216] In some embodiments, X^1 is absent, -O-, -S-, , , or .

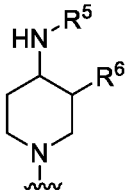
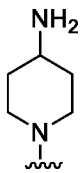
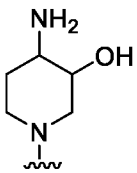
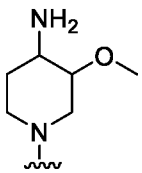
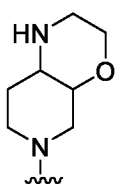
[00217] In some embodiments, **NP** has a structure of Formula (III), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof:

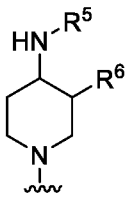
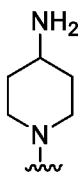
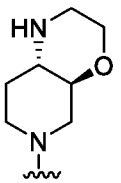


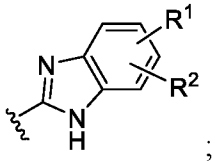
Formula (III).

[00218] In some embodiments, each R^1, R^2, R^3 and R^4 is independently hydrogen, F, Cl, Br, -CN, -$N(R^7)_2$, or C_1-C_4alkyl. In some embodiments, each each R^1, R^2, R^3 and R^4 is independently hydrogen, F, Cl, -CH_3, -CH_2CH_3, or -OCH_3. In some embodiments, R^5 is hydrogen; R^6 is hydrogen, -OH, or -OCH_3; or R^5 and R^6 are taken together with the intervening atoms to which they are attached to form a morpholine. In some embodiments, R^7 is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl. In some embodiments, R^7 is independently hydrogen or C_1-C_6alkyl. In some embodiments, R^7 is hydrogen, -CH_3, or -CH_2CH_3.

[00219] In some embodiments,  is , , , , , , , or .

[00220] In some embodiments,  is , , , or .

[00221] In some embodiments,  is  or .

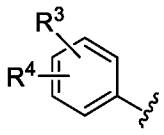
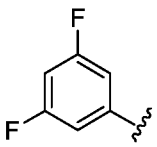
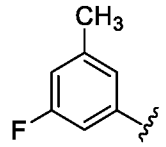
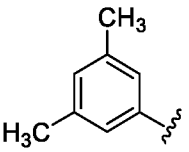
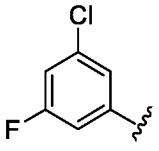
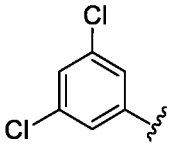
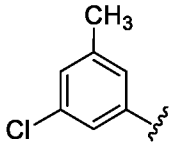
[00222] In some embodiments, R^A is ;

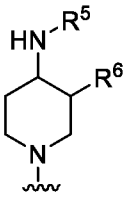
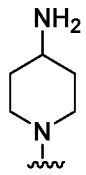
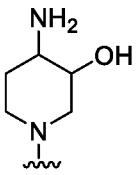
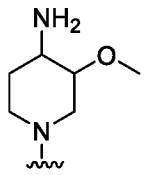
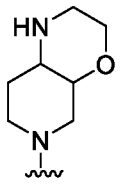
each R^1, R^2, R^3 and R^4 is independently hydrogen, F, Cl, Br, C_1-C_4alkyl, -CN, -$N(R^7)_2$, or -OR^7;

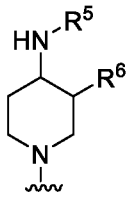
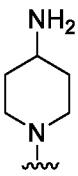
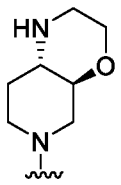
R^5 is hydrogen; R^6 is hydrogen or -OR^7; or

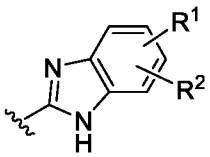
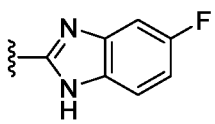
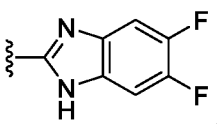
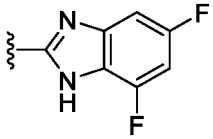
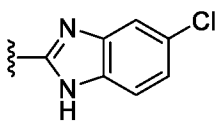
R^5 and R^6 are taken together with the intervening atoms to which they are attached to form a morpholine; and

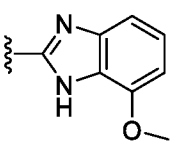
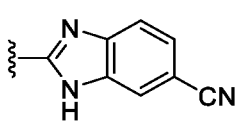
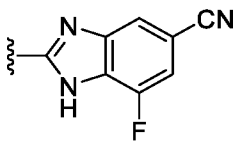
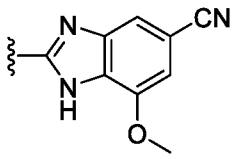
each R^7 is independently hydrogen, -CH_3, or -CH_2CH_3.

[00223] In some embodiments,  is , , , , , or ; and

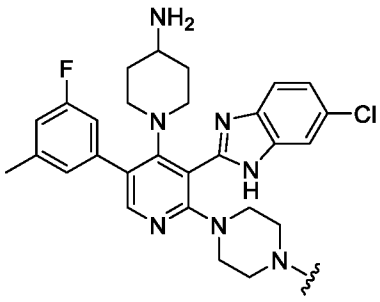
 is , , , or .

[00224] In some embodiments,  is  or ; and

 is , , , ,

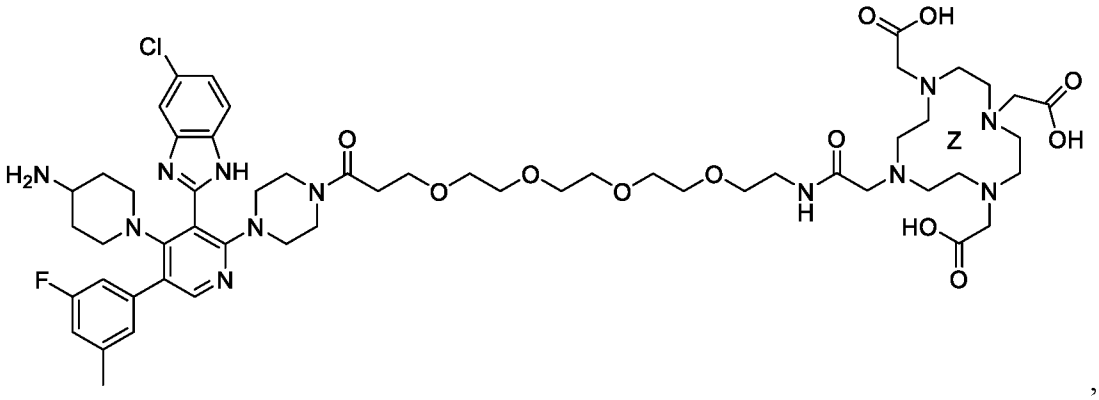
, , , or .

[00225] In some embodiments, the GPCR is the Somatostatin type 2 receptor (SSTR2); and **NP** has the following structure:

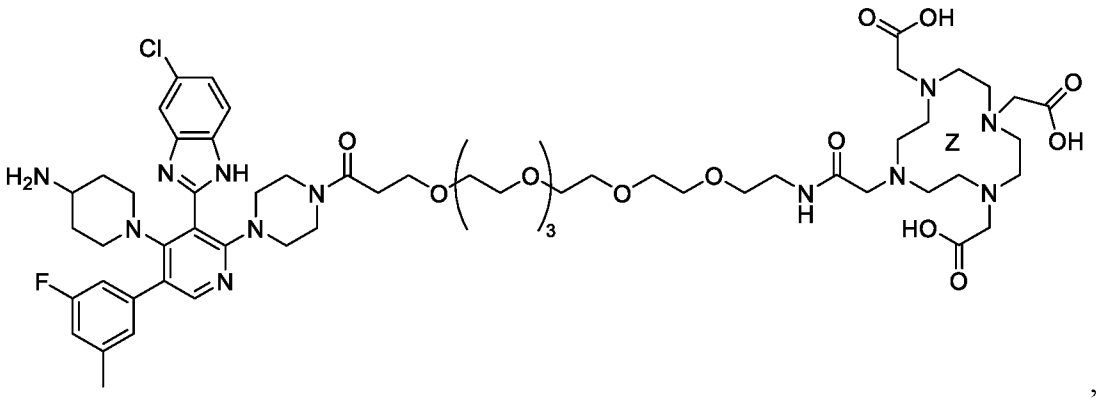


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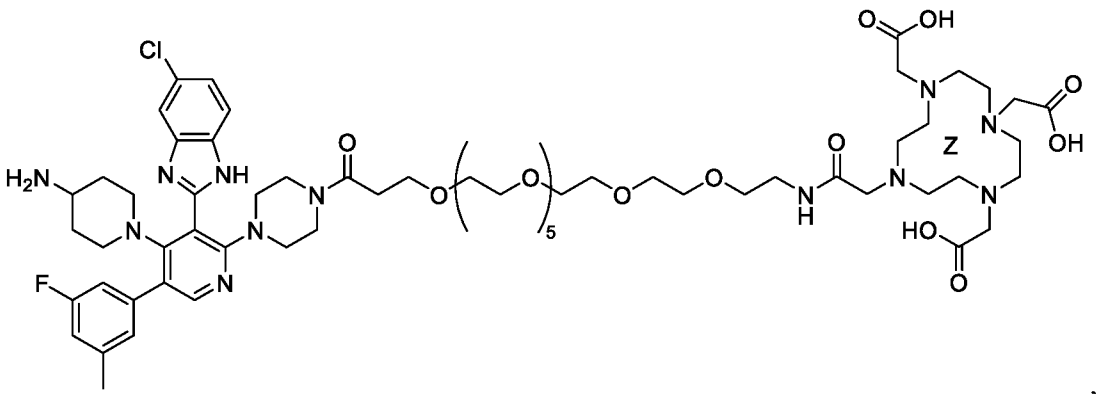
[00226] In some embodiments, the compound has the following structure:



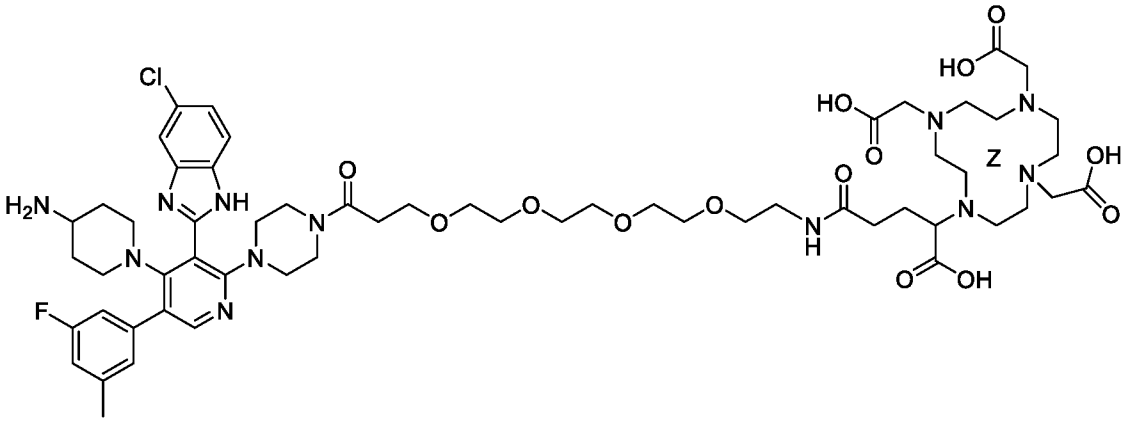
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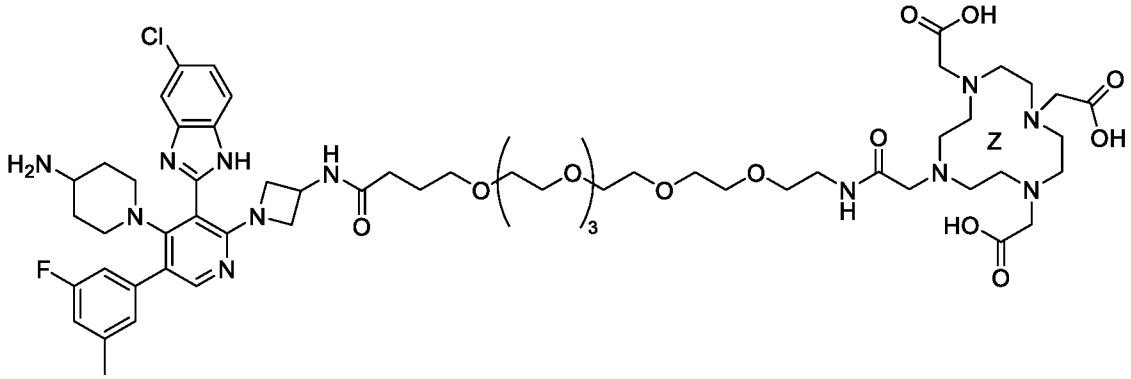
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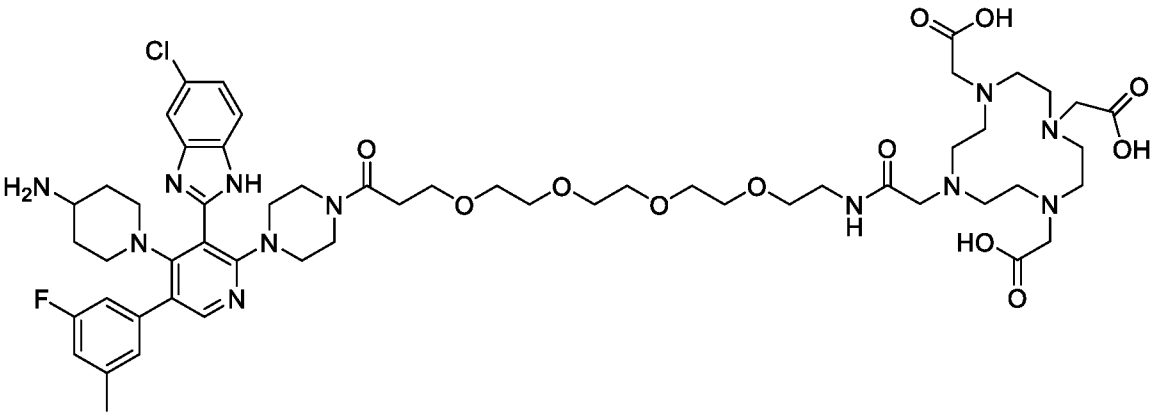


, or

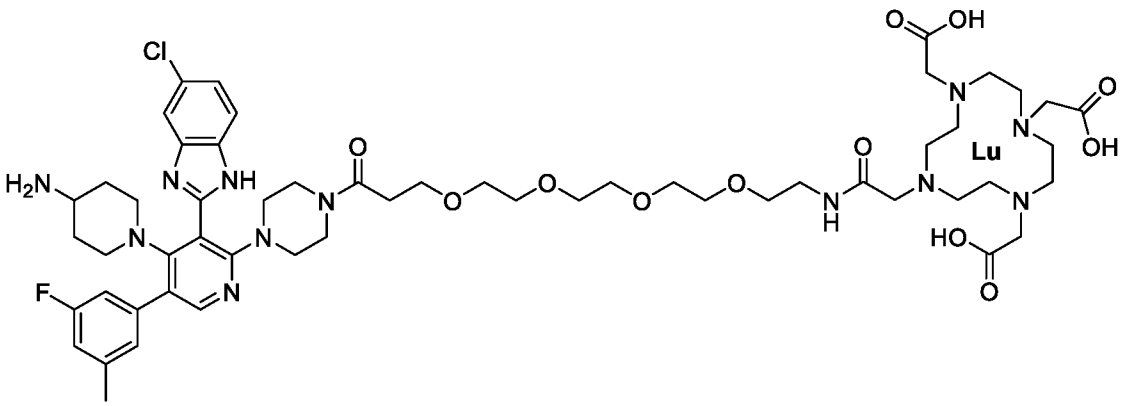


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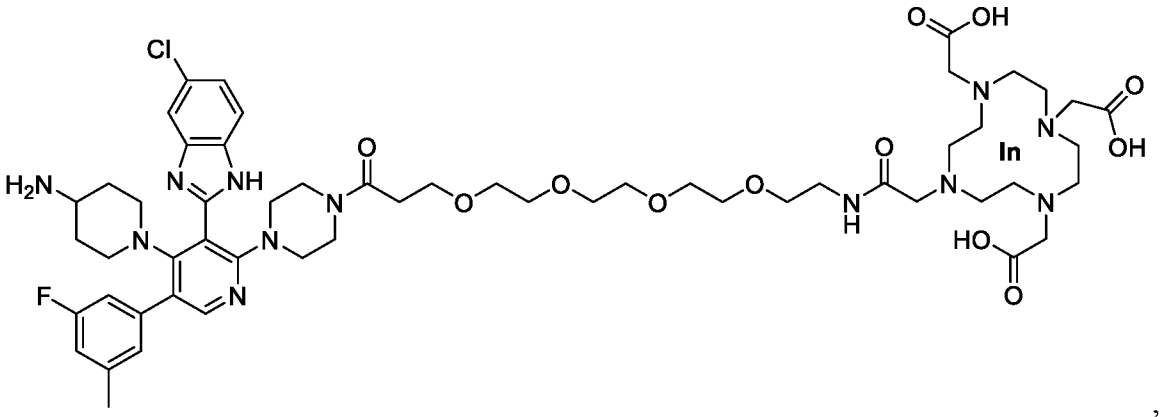
[00227] In some embodiments, the compound has the following structure:



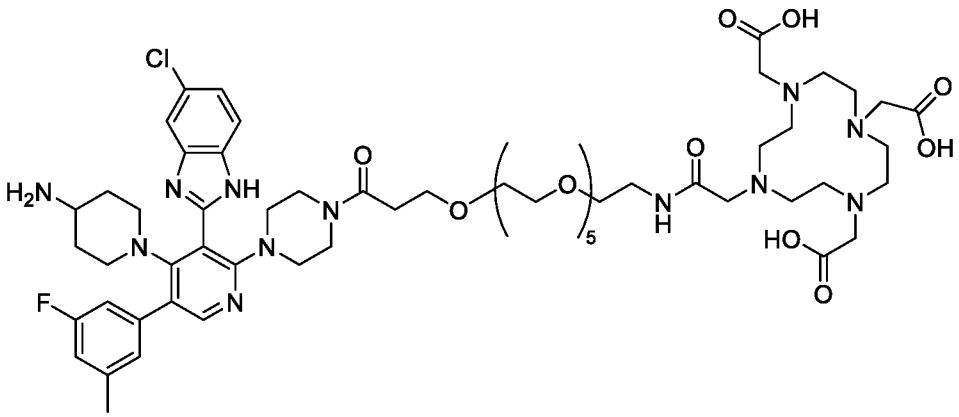
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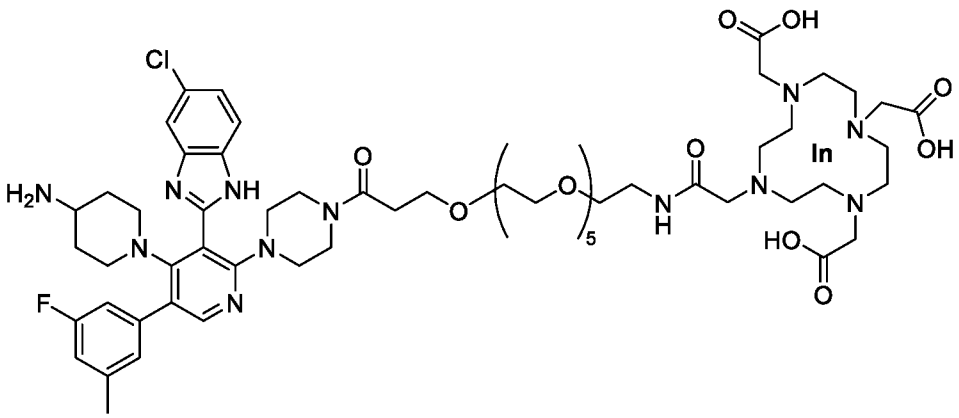
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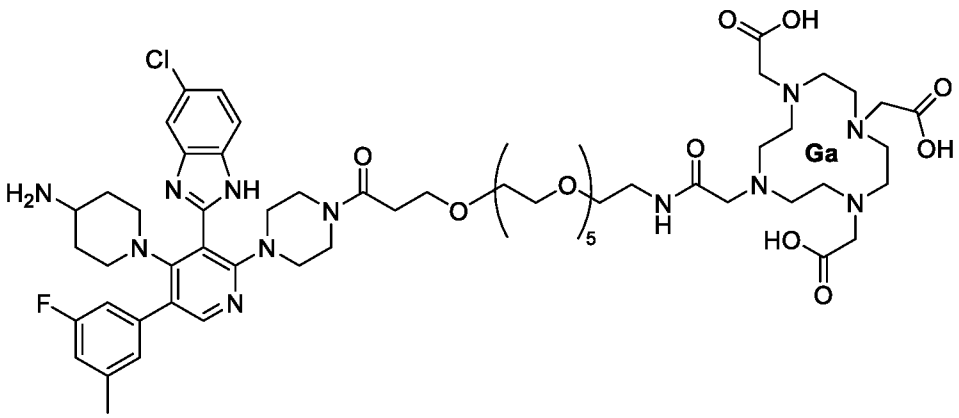
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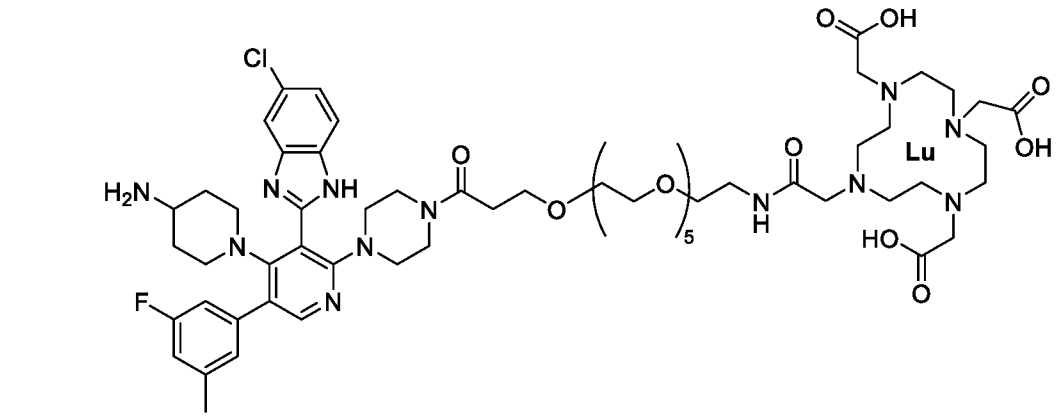
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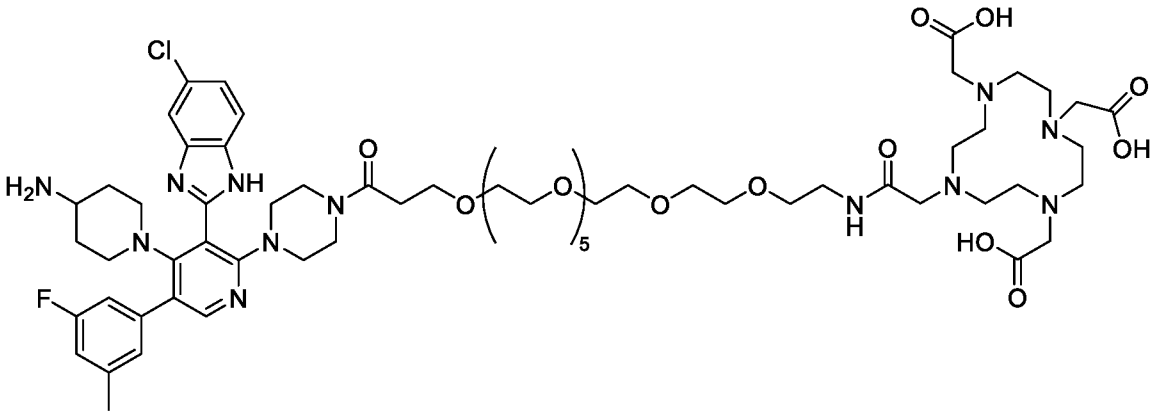
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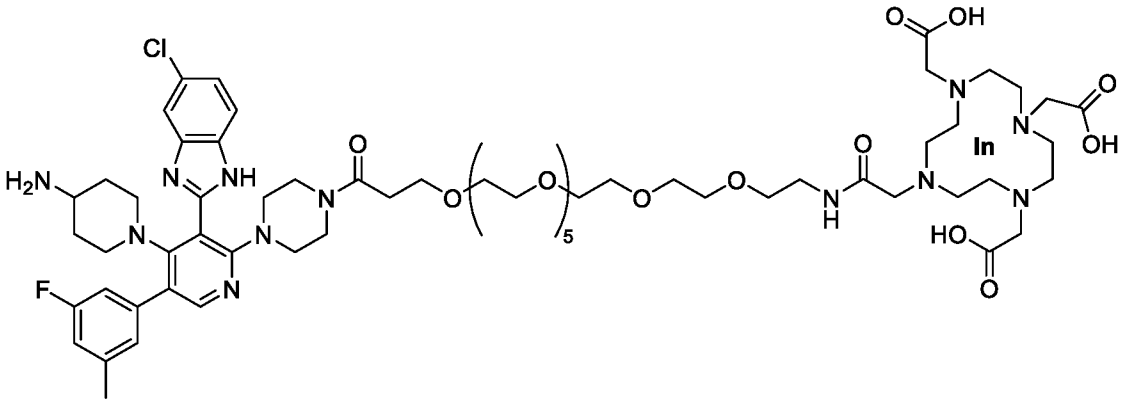
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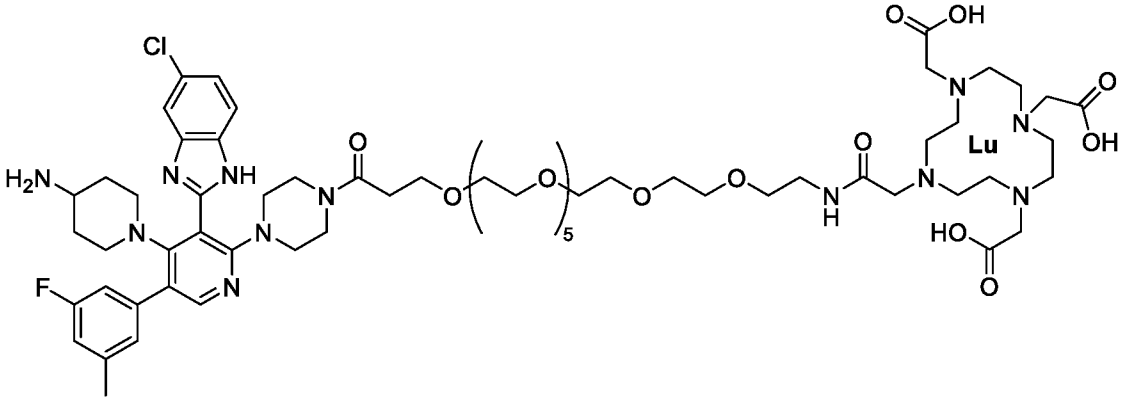
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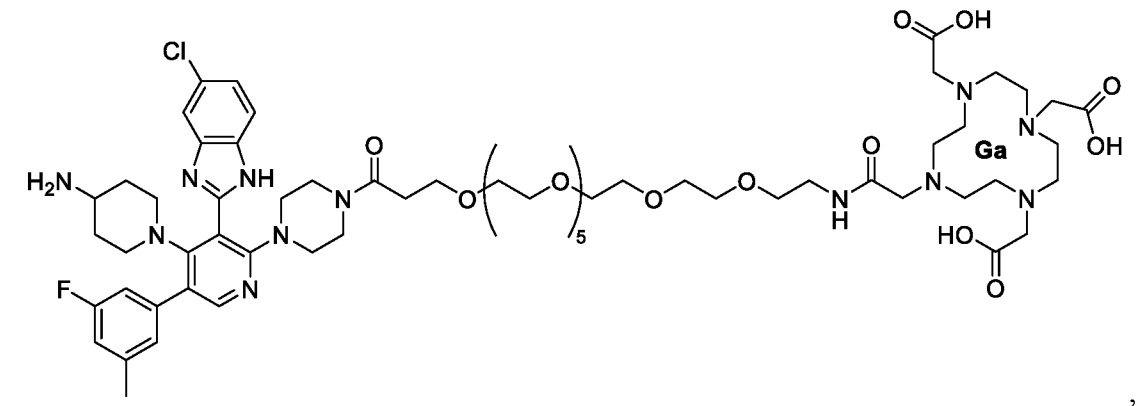
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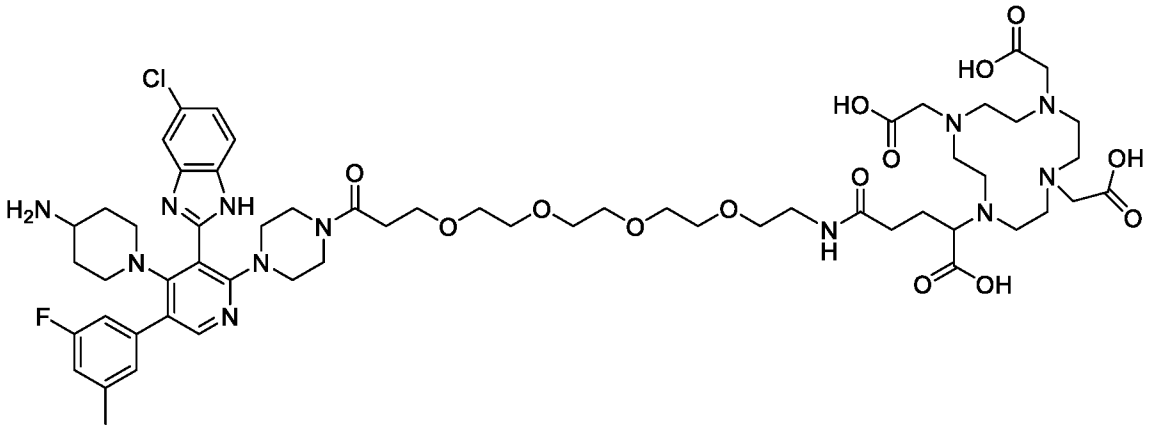
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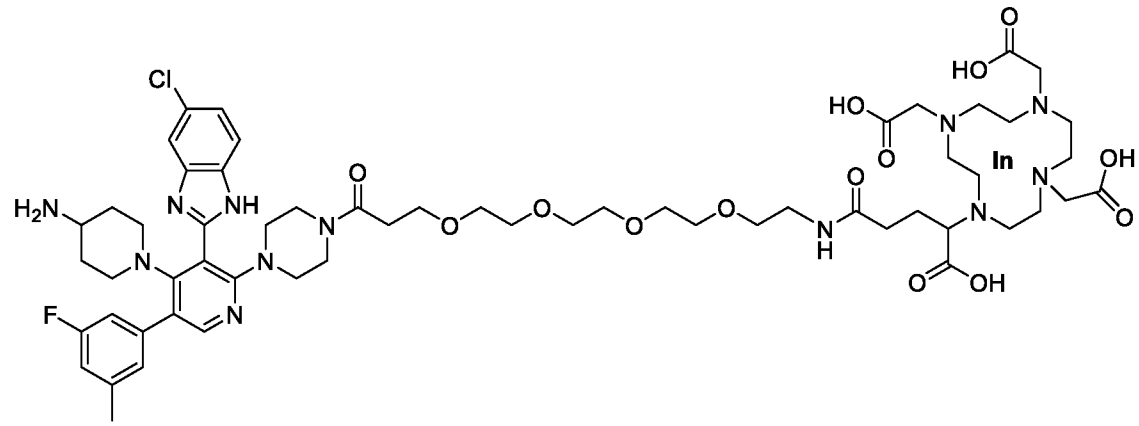
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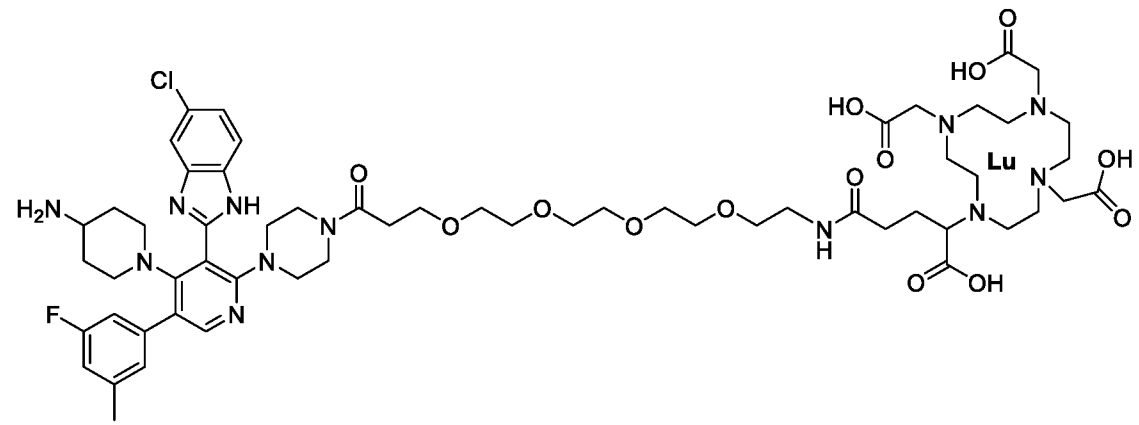
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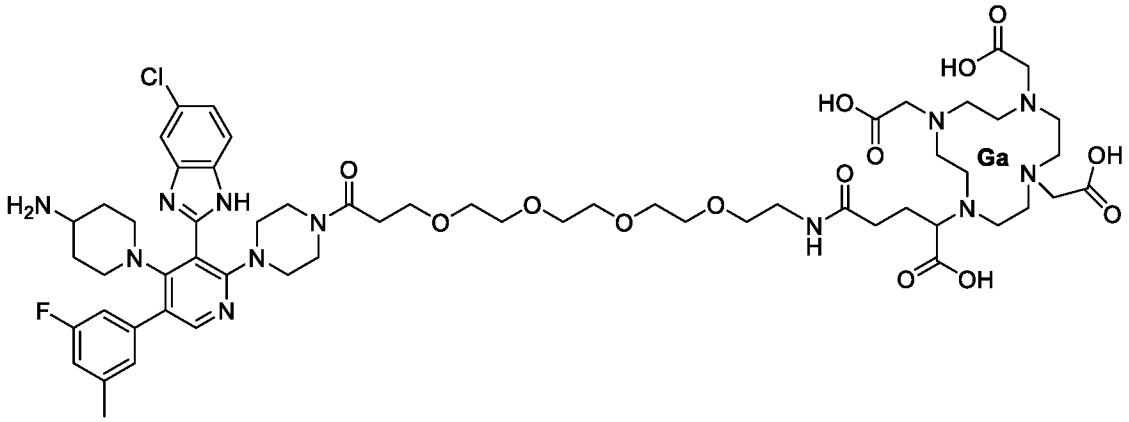
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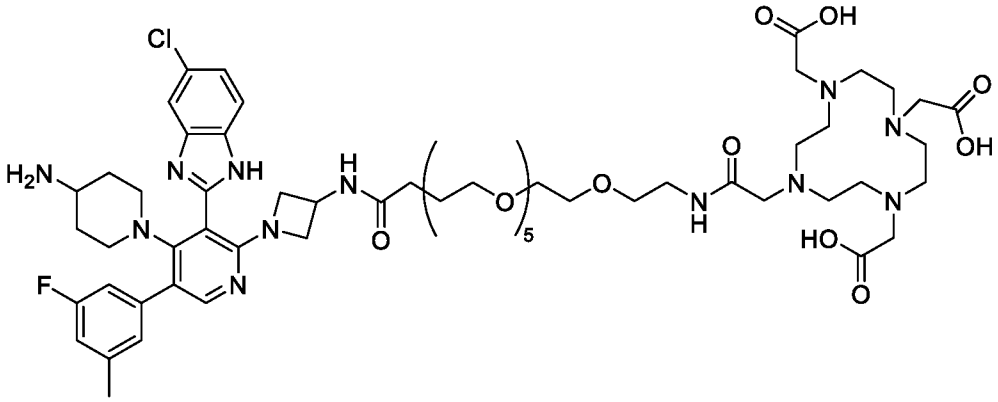
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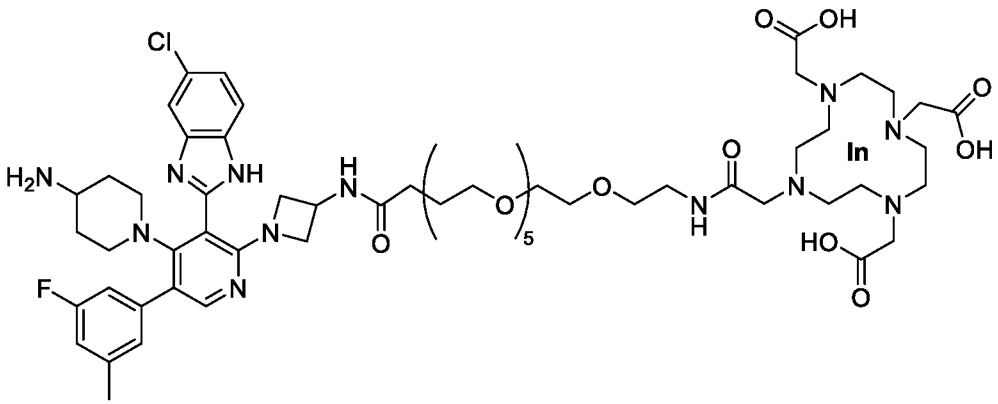
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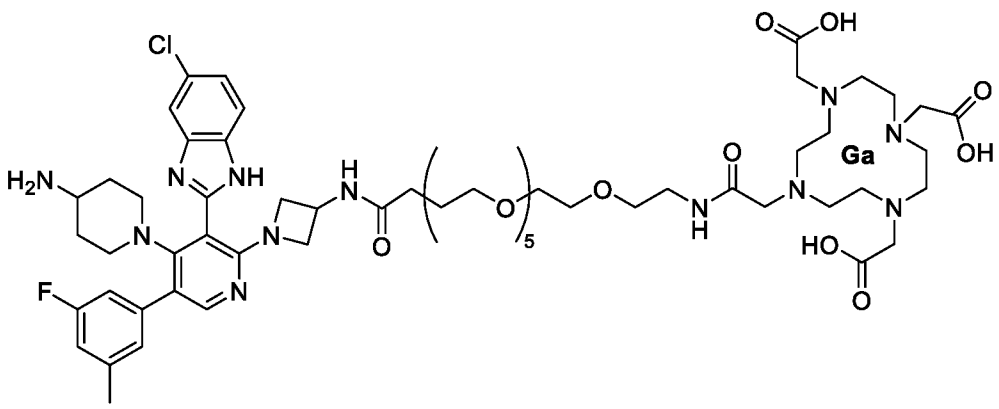
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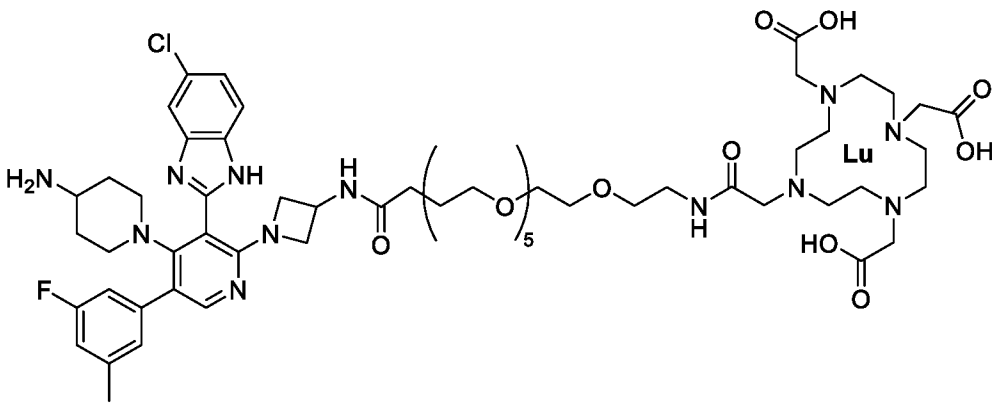
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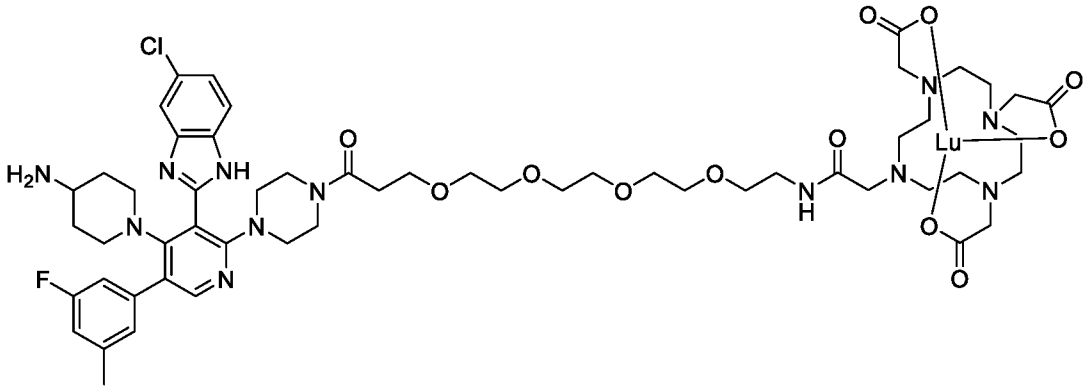
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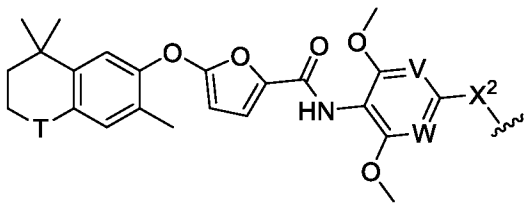
[00228] In some embodiments, the compound has the following structure:



[00229] In some embodiments, **NP** is a non-peptide ligand that binds to tumor cells expressing the gonadotropin-releasing hormone receptor (GnRHR).

[00230] In some embodiments, **NP** is a non-peptide ligand comprising a N-{4,6-dimethoxy-2-aminopyrimidin-5-yl}-5-[3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furamide structural motif; a N-(4,6-dimethoxypyrimidin-5-yl)-5-(3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-2-furamide structural motif; or a N-(4,6-dimethoxypyrimidin-5-yl)-5-((3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy)furan-2-carboxamide structural motif.

[00231] In some embodiments, the GPCR is GnRHR; and **NP** has a structure of Formula (X), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof:



Formula (X)

wherein:

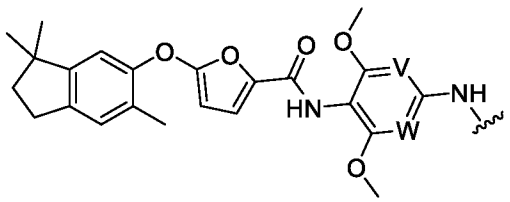
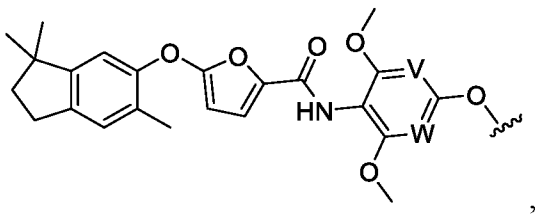
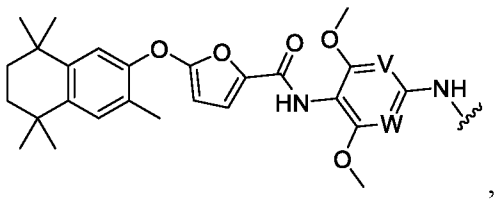
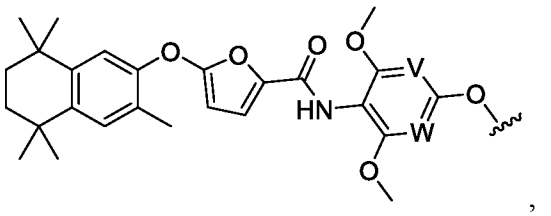
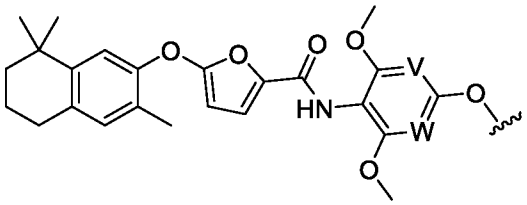
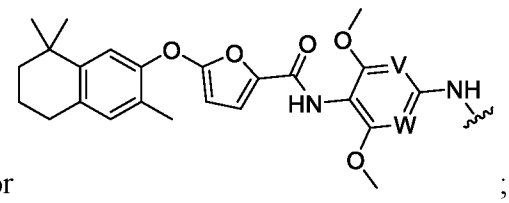
T is absent, $-CH_2-$, $-CH(CH_3)-$or $-C(CH_3)_2-$;

X^2 is absent, -O-, or $-N(R^7)-$;

V is CH or N; and W is CH or N;

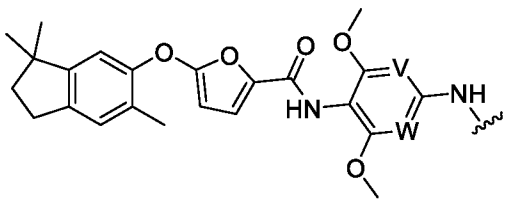
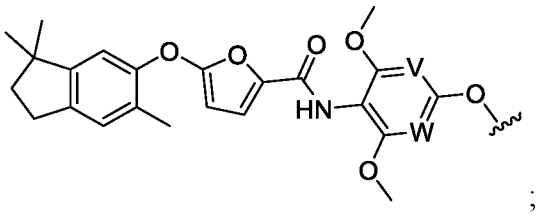
R^7 is hydrogen or substituted or unsubstituted C_1-C_6alkyl.

[00232] In some embodiments, the GPCR is GnRHR; and **NP** has one of the following structures:


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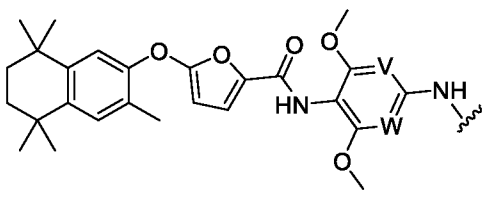
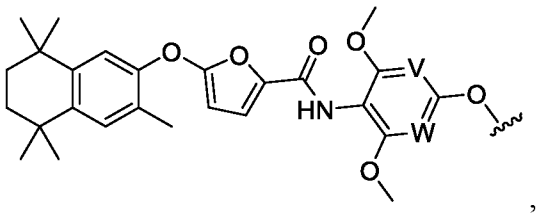
wherein, V is CH or N; and W is CH or N.

[00233] In some embodiments, the GPCR is GnRHR; and **NP** has one of the following structures:


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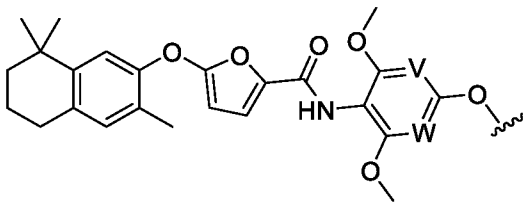
wherein, V is CH or N; and W is CH or N.

[00234] In some embodiments, the GPCR is GnRHR; and **NP** has one of the following structures:

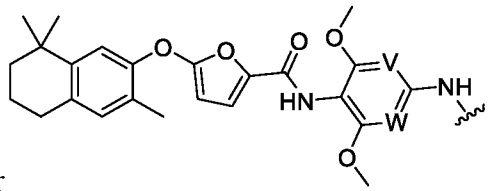

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wherein, V is CH or N; and W is CH or N.

[00235] In some embodiments, the GPCR is GnRHR; and **NP** has one of the following structures:



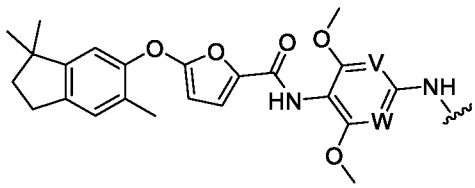
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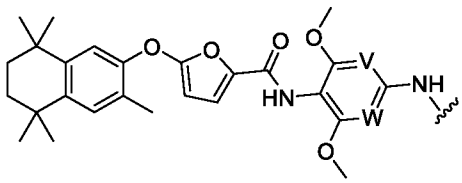
wherein, V is CH or N; and W is CH or N.

[00236] In some embodiments, the GPCR is GnRHR; and **NP** has the following structure:



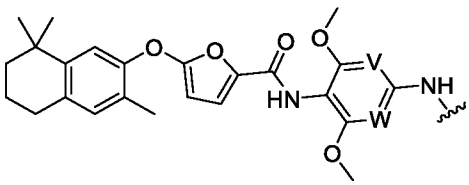
wherein, V is CH or N; and W is CH or N.

[00237] In some embodiments, the GPCR is GnRHR; and **NP** has the following structure:



wherein, V is CH or N; and W is CH or N.

[00238] In some embodiments, the GPCR is GnRHR; and **NP** has the following structure:



wherein, V is CH or N; and W is CH or N.

[00239] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

Synthesis of Compounds

[00240] Compounds described herein are synthesized using standard synthetic techniques or using methods known in the art in combination with methods described herein.

[00241] Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC are employed.

[00242] Compounds are prepared using standard organic chemistry techniques such as those described in, for example, March's Advanced Organic Chemistry, 6th Edition, John Wiley and Sons, Inc. Alternative reaction conditions for the synthetic transformations described herein may

be employed such as variation of solvent, reaction temperature, reaction time, as well as different chemical reagents and other reaction conditions.

[00243] In one aspect, compounds described herein are in the form of pharmaceutically acceptable salts. In addition, the compounds described herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00244] The term "pharmaceutically acceptable salt" refers to a form of a therapeutically active agent that consists of a cationic form of the therapeutically active agent in combination with a suitable anion, or in alternative embodiments, an anionic form of the therapeutically active agent in combination with a suitable cation. Handbook of Pharmaceutical Salts: Properties, Selection and Use. International Union of Pure and Applied Chemistry, Wiley-VCH 2002. S.M. Berge, L.D. Bighley, D.C. Monkhouse, J. Pharm. Sci. 1977, 66, 1-19. P. H. Stahl and C. G. Wermuth, editors, *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, Weinheim/Zürich:Wiley-VCH/VHCA, 2002. Pharmaceutical salts typically are more soluble and more rapidly soluble in stomach and intestinal juices than non-ionic species and so are useful in solid dosage forms. Furthermore, because their solubility often is a function of pH, selective dissolution in one or another part of the digestive tract is possible and this capability can be manipulated as one aspect of delayed and sustained release behaviors. Also, because the salt-forming molecule can be in equilibrium with a neutral form, passage through biological membranes can be adjusted.

[00245] In some embodiments, pharmaceutically acceptable salts are obtained by reacting a compound of Formula (I) with an acid. In some embodiments, the compound of Formula (I) (i.e. free base form) is basic and is reacted with an organic acid or an inorganic acid. Inorganic acids include, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and metaphosphoric acid. Organic acids include, but are not limited to, 1-hydroxy-2-naphthoic acid; 2,2-dichloroacetic acid; 2-hydroxyethanesulfonic acid; 2-oxoglutaric acid; 4-acetamidobenzoic acid; 4-aminosalicylic acid; acetic acid; adipic acid; ascorbic acid (L); aspartic acid (L); benzenesulfonic acid; benzoic acid; camphoric acid (+); camphor-10-sulfonic acid (+); capric acid (decanoic acid); caproic acid (hexanoic acid); caprylic acid (octanoic acid); carbonic acid; cinnamic acid; citric acid; cyclamic acid; dodecylsulfuric acid; ethane-1,2-disulfonic acid; ethanesulfonic acid; formic acid; fumaric acid; galactaric acid; gentisic acid; glucoheptonic acid (D); gluconic acid (D); glucuronic acid (D); glutamic acid; glutaric acid; glycerophosphoric acid; glycolic acid; hippuric acid; isobutyric acid; lactic acid (DL); lactobionic acid; lauric acid; maleic acid; malic acid (- L); malonic acid; mandelic acid (DL);

methanesulfonic acid; naphthalene-1,5-disulfonic acid; naphthalene-2-sulfonic acid; nicotinic acid; oleic acid; oxalic acid; palmitic acid; pamoic acid; phosphoric acid; proprionic acid; pyroglutamic acid (- L); salicylic acid; sebacic acid; stearic acid; succinic acid; sulfuric acid; tartaric acid (+ L); thiocyanic acid; toluenesulfonic acid (*p*); and undecylenic acid.

[00246] In some embodiments, a compound of Formula (I) is prepared as a chloride salt, sulfate salt, bromide salt, mesylate salt, maleate salt, citrate salt or phosphate salt.

[00247] In some embodiments, pharmaceutically acceptable salts are obtained by reacting a compound of Formula (I) with a base. In some embodiments, the compound of Formula (I) is acidic and is reacted with a base. In such situations, an acidic proton of the compound of Formula (I) is replaced by a metal ion, e.g., lithium, sodium, potassium, magnesium, calcium, or an aluminum ion. In some cases, compounds described herein coordinate with an organic base, such as, but not limited to, ethanolamine, diethanolamine, triethanolamine, tromethamine, meglumine, N-methylglucamine, dicyclohexylamine, tris(hydroxymethyl)methylamine. In other cases, compounds described herein form salts with amino acids such as, but not limited to, arginine, lysine, and the like. Acceptable inorganic bases used to form salts with compounds that include an acidic proton, include, but are not limited to, aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydroxide, lithium hydroxide, and the like. In some embodiments, the compounds provided herein are prepared as a sodium salt, calcium salt, potassium salt, magnesium salt, meglumine salt, N-methylglucamine salt or ammonium salt.

[00248] It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms. In some embodiments, solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of compounds described herein are conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein optionally exist in unsolvated as well as solvated forms.

[00249] In some embodiments, sites on the organic radicals (e.g., alkyl groups, aromatic rings) of compounds of Formula (I) are deuterated.

[00250] In some embodiments, the compounds of Formula (I) possess one or more stereocenters and each stereocenter exists independently in either the R or S configuration. In some embodiments, the compound of Formula (I) exists in the R configuration. In some embodiments, the compound of Formula (I) exists in the S configuration. The compounds presented herein

include all diastereomeric, individual enantiomers, atropisomers, and epimeric forms as well as the appropriate mixtures thereof. The compounds and methods provided herein include all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof.

[00251] Individual stereoisomers are obtained, if desired, by methods such as, stereoselective synthesis and/or the separation of stereoisomers by chiral chromatographic columns or the separation of diastereomers by either non-chiral or chiral chromatographic columns or crystallization and recrystallization in a proper solvent or a mixture of solvents. In certain embodiments, compounds of Formula (I) are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds/salts, separating the diastereomers and recovering the optically pure individual enantiomers. In some embodiments, resolution of individual enantiomers is carried out using covalent diastereomeric derivatives of the compounds described herein. In another embodiment, diastereomers are separated by separation/resolution techniques based upon differences in solubility. In other embodiments, separation of stereoisomers is performed by chromatography or by the forming diastereomeric salts and separation by recrystallization, or chromatography, or any combination thereof. Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley And Sons, Inc., 1981. In some embodiments, stereoisomers are obtained by stereoselective synthesis.

[00252] In some embodiments, compounds described herein are prepared as prodrugs. A "prodrug" refers to an agent that is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they are easier to administer than the parent drug. They are, for instance, bioavailable by oral administration whereas the parent is not. Further or alternatively, the prodrug also has improved solubility in pharmaceutical compositions over the parent drug. In some embodiments, the design of a prodrug increases the effective water solubility. See for example Design of Prodrugs, Bundgaard, A. Ed., Elseview, 1985 and Method in Enzymology, Widder, K. *et al.*, Ed.; Academic, 1985, vol. 42, p. 309-396; Bundgaard, H. "Design and Application of Prodrugs" in A Textbook of Drug Design and Development, Krosgaard-Larsen and H. Bundgaard, Ed., 1991, Chapter 5, p. 113-191; and Bundgaard, H., Advanced Drug Delivery Review, 1992, 8, 1-38, each of which is incorporated herein by reference.

[00253] A "metabolite" of a compound disclosed herein is a derivative of that compound that is formed when the compound is metabolized. The term "metabolized," as used herein, refers to the sum of the processes (including, but not limited to, hydrolysis reactions and reactions catalyzed

by enzymes) by which a particular substance is changed by an organism. Thus, enzymes may produce specific structural alterations to a compound. For example, cytochrome P450 catalyzes a variety of oxidative and reductive reactions while uridine diphosphate glucuronyltransferases catalyze the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulfhydryl groups. Metabolites of the compounds disclosed herein are optionally identified either by administration of compounds to a host and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells in vitro and analysis of the resulting compounds.

Pharmaceutical compositions

[00254] In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable inactive ingredients that facilitate processing of the active compounds into preparations that are used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein is found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), herein incorporated by reference for such disclosure.

[00255] In some embodiments, the compounds described herein are administered either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition. Administration of the compounds and compositions described herein can be effected by any method that enables delivery of the compounds to the site of action. These methods include, though are not limited to delivery via enteral routes (including oral), and parenteral routes (including injection or infusion, and subcutaneous).

[00256] In some embodiments, pharmaceutical compositions suitable for oral administration are presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion.

[00257] In some embodiments, pharmaceutical compositions are formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers,

with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use.

Methods of Treatment

[00258] In some embodiments, the methods comprise administering to a subject a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula (I) or pharmaceutically acceptable salt or solvate thereof is administered in a pharmaceutical composition. In some embodiments, the subject has cancer. In some embodiments, the cancer is a solid tumor or hematological cancer. In some embodiments, the subject has a noncancerous tumor. In some embodiments, the subject has an adenoma.

[00259] In embodiments, the treatment is sufficient to reduce or inhibit the growth of the subject's tumor, reduce the number or size of metastatic lesions, reduce tumor load, reduce primary tumor load, reduce invasiveness, prolong survival time, or maintain or improve the quality of life, or combinations thereof.

[00260] In some embodiments, provided herein are methods for killing a tumor cell comprising contacting the tumor cell with a compound of Formula (I) or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula (I) or pharmaceutically acceptable salt or solvate thereof releases a number of alpha particles by natural radioactive decay. In some embodiments, the released alpha particles are sufficient to kill the tumor cell. In some embodiments, the released alpha particles are sufficient to stop cell growth. In some embodiments, the tumor cell is a malignant tumor cell. In some embodiments, the tumor cell is a benign tumor cell. In some embodiments, the method comprises killing a tumor cell with a beta-particle emitting radionuclide. In some embodiments, the method comprises killing a tumor cell with an alpha-particle emitting radionuclide. In some embodiments, the method comprises killing a tumor cell with a gamma-particle emitting radionuclide.

[00261] In one aspect, provided herein are methods and compositions for treating cancers. Cancer includes tissue and organ carcinogenesis including metastases such as for example gastrointestinal cancer, (e.g., gastric cancer, esophageal cancer, pancreatic cancer colorectal cancer, intestinal cancer, anal cancer, liver cancer, gallbladder cancer, or colon cancer; lung cancer; thyroid cancer; skin cancer (e.g., melanoma); oral cancer; urinary tract cancer (e.g.

bladder cancer or kidney cancer); blood cancer (e.g. myeloma or leukemia) or prostate cancer. In some embodiments, the present disclosure provides methods and compositions for treating gastrointestinal cancer in a subject in need thereof by administering an effective amount of a non-peptide targeted therapeutic compound disclosed herein to the subject. Non-limiting examples of gastrointestinal cancers that can be treated according to the methods of the present disclosure include gastric cancer, esophageal cancer, pancreatic cancer, lung cancer (small cell lung cancer and/or non small-cell lung cancer), colorectal cancer, intestinal cancer, anal cancer, liver cancer, gallbladder cancer, or colon cancer. In some embodiments, the cancer is Hodkin's lymphoma or B-cell lymphoma.

[00262] In one aspect, provided herein are methods and compositions for treating an adenoma.

[00263] In one aspect, provided herein are methods and compositions for treating a peptide hormone G protein-coupled receptor expressing cancer. In some embodiments, the peptide hormone G protein-coupled receptor-expressing cancer to be treated is a primary or metastatic cancer of gastrointestinal origin, such as colorectal cancer, stomach cancer, small intestine cancer, or esophageal cancer. In some embodiments, the peptide hormone G protein-coupled receptor-expressing cancer to be treated is primary or metastatic pancreatic cancer. In some embodiments, the peptide hormone G protein-coupled receptor-expressing cancer to be treated is primary or metastatic lung cancer, such as squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma. In some embodiments, the peptide hormone G protein-coupled receptor-expressing cancer to be treated is a sarcoma, such as leiomyosarcoma or rhabdomyosarcoma. In some embodiments, the peptide hormone G protein-coupled receptor-expressing cancer to be treated is a primary or metastasized neuroectodermal tumor, such as aphaechromotcytoma or a paraganglioma. In some embodiments, the peptide hormone G protein-coupled receptor-expressing cancer is a primary or a metastasized bronchopulmonary or a gastrointestinal neuroendocrine tumor. In some embodiments, the cancer is colorectal cancer.

[00264] In one aspect, provided herein is a method for identifying tissues or organs in a mammal that overexpress one or more peptide hormone G protein-coupled receptors comprising:

(i) administering to the mammal a non-peptide targeted therapeutic compound disclosed herein; and

(ii) performing positron emission tomography (PET) analysis on the mammal.

[00265] In some embodiments, the mammal was diagnosed with cancer.

[00266] In another aspect, provided herein is a method for treating cancer in a mammal comprising administering to the mammal in need thereof, a non-peptide targeted therapeutic compound disclosed herein. In some embodiments, the cancer expresses one or more peptide

hormone G protein-coupled receptors. In some embodiments, the cancer comprises a peptide hormone G protein-coupled receptor-positive cancer. In some embodiments, the cancer comprises a solid tumor. In some embodiments, the cancer comprises a sarcoma, carcinoma, or lymphoma. In some embodiments, the cancer comprises a neuroendocrine tumor. In some embodiments, the cancer comprises an insulinoma. In some embodiments, the cancer comprises peptide hormone G protein-coupled receptor-positive (e.g., somatostatin receptor-positive) gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

[00267] In some embodiments, compounds of Formula (I) disclosed herein are used in a method for in vivo imaging of a subject. In some embodiments, the method includes the steps of:

(i) administering to the mammal a compound of Formula (I);

(ii) waiting a time sufficient to allow the compound to accumulate at a tissue or cell site to be imaged; and

(iii) imaging the cells or tissues with a non-invasive imaging technique.

[00268] In some embodiments, the non-invasive imaging technique is positron emission tomography (PET) analysis. In some embodiments, the non-invasive imaging technique is selected from positron emission tomography imaging, or positron emission tomography with computed tomography imaging, and positron emission tomography with magnetic resonance imaging.

Methods of Dosing and Treatment Regimens

[00269] In one embodiment, compounds of Formula (I), or a pharmaceutically acceptable salt thereof, are used in the preparation of medicaments for the treatment of tumors in a mammal. Methods for treating any of the diseases or conditions described herein in a mammal in need of such treatment, involves administration of pharmaceutical compositions that include at least one compound of Formula (I) or a pharmaceutically acceptable salt, active metabolite, prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said mammal.

[00270] In certain embodiments, the compositions containing the compound(s) described herein are administered for diagnostic and/or therapeutic treatments.

[00271] The amount of a given agent that corresponds to such an amount varies depending upon factors such as the particular conjuate, specific cancer or tumor to be treated (and its severity), the identity (*e.g.*, weight, sex) of the subject or host in need of treatment, but nevertheless is determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific conjugate being administered, the route of administration, the condition being treated, and the subject or host being treated. Optimal doses are generally determined using experimental

models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the subject.

[00272] Toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD_{50} and the ED_{50}. The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD_{50} and ED_{50}. In certain embodiments, the data obtained from cell culture assays and animal studies are used in formulating the therapeutically effective daily dosage range and/or the therapeutically effective unit dosage amount for use in mammals, including humans.

[00273] The amount of conjugates or pharmaceutically acceptable salts or solvates thereof and/or pharmaceutical compositions administered can be sufficient to deliver a therapeutically effective dose of the particular subject. In some embodiments, conjugate dosages are between about 0.1 pg and about 50 mg per kilogram of body weight, 1 μg and about 50 mg per kilogram of body weight, or between about 0.1 and about 10 mg/kg of body weight. Therapeutically effective dosages can also be determined at the discretion of a physician. By way of example only, the dose of the conjugate or a pharmaceutically acceptable salt or solvate thereof described herein for methods of treating a disease as described herein is about 0.001 mg/kg to about 1 mg/kg body weight of the subject per dose. In some embodiments, the dose of conjugate or a pharmaceutically acceptable salt or solvate thereof described herein for the described methods is about 0.001 mg to about 1000 mg per dose for the subject being treated. In some embodiments, a conjugate or a pharmaceutically acceptable salt or solvate thereof described herein is administered to a subject at a dosage of from about 0.01 mg to about 500 mg, from about 0.01 mg to about 100 mg, or from about 0.01mg to about 50 mg.

[00274] In some embodiments, a conjugate or a pharmaceutically acceptable salt or solvate thereof described herein is administered to a subject at a dosage of about 0.01 picomole to about 1 mole, about 0.1 picomole to about 0.1 mole, about 1 nanomole to about 0.1 mole, or about 0.01 micromole to about 0.1 millimole.

[00275] In some embodiments, a conjugate or a pharmaceutically acceptable salt or solvate thereof described herein is administered to a subject at a dosage of about 0.01 Gbq to about 1000 Gbq, about 0.5 Gbq to about 100 Gbq, or about 1 Gbq to about 50 Gbq.

[00276] In some embodiments, the dose is administered once a day, 1 to 3 times a week, 1 to 4 times a month, or 1 to 12 times a year.

[00277] In any of the aforementioned aspects are further embodiments in which the effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is: (a)

systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by injection to the mammal.

Combination Treatments

[00278] In certain instances, it is appropriate to administer at least one compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with one or more other therapeutic agents.

[00279] In one embodiment, the therapeutic effectiveness of one of the compounds described herein is enhanced by administration of an adjuvant (*i.e.*, by itself the adjuvant has minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, in some embodiments, the benefit experienced by a patient is increased by administering one of the compounds described herein with another agent (which also includes a therapeutic regimen) that also has therapeutic benefit.

[00280] In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient is simply be additive of the two therapeutic agents or the patient experiences a synergistic benefit.

Certain Terminology

[00281] Unless otherwise stated, the following terms used in this application have the definitions given below. The use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[00282] As used herein, C_1-C_x includes C_1-C_2, C_1-C_3 . . . C_1-C_x. By way of example only, a group designated as "C_1-C_6" indicates that there are one to six carbon atoms in the moiety, i.e. groups containing 1 carbon atom, 2 carbon atoms, 3 carbon atoms or 4 carbon atoms. Thus, by way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl group, *i.e.*, the alkyl group is selected from among methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *t*-butyl.

[00283] An "alkyl" group refers to an aliphatic hydrocarbon group. The alkyl group is branched or straight chain. In some embodiments, the "alkyl" group has 1 to 10 carbon atoms, i.e. a C_1-C_{10}alkyl. Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range; *e.g.*, "1 to 10 carbon atoms" means that the alkyl group consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated. In some embodiments, an alkyl is a C_1-C_6alkyl. In one aspect the alkyl is methyl,

ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tertiary butyl, pentyl, neopentyl, or hexyl.

[00284] An "alkylene" group refers to a divalent alkyl radical. Any of the above mentioned monovalent alkyl groups may be an alkylene by abstraction of a second hydrogen atom from the alkyl. In some embodiments, an alkylene is a C_1-C_6alkylene. In other embodiments, an alkylene is a C_1-C_4alkylene. Typical alkylene groups include, but are not limited to, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, and the like. In some embodiments, an alkylene is -CH_2-.

[00285] An "alkoxy" group refers to a (alkyl)O- group, where alkyl is as defined herein.

[00286] The term "alkenyl" refers to a type of alkyl group in which at least one carbon-carbon double bond is present. In one embodiment, an alkenyl group has the formula –C(R)=CR_2, wherein R refers to the remaining portions of the alkenyl group, which may be the same or different. In some embodiments, R is H or an alkyl. In some embodiments, an alkenyl is selected from ethenyl (*i.e.*, vinyl), propenyl (*i.e.*, allyl), butenyl, pentenyl, pentadienyl, and the like. Non-limiting examples of an alkenyl group include -CH=CH_2, -C(CH_3)=CH_2, -CH=$CHCH_3$, -C(CH_3)=$CHCH_3$, and –CH_2CH=CH_2.

[00287] The term "alkynyl" refers to a type of alkyl group in which at least one carbon-carbon triple bond is present. In one embodiment, an alkenyl group has the formula -C≡C-R, wherein R refers to the remaining portions of the alkynyl group. In some embodiments, R is H or an alkyl. In some embodiments, an alkynyl is selected from ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Non-limiting examples of an alkynyl group include -C≡CH, -C≡CCH_3 -C≡CCH_2CH_3, and -CH_2C≡CH.

[00288] The term "heteroalkyl" refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen (e.g. –NH-, -N(alkyl)-, sulfur, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C_1-C_6heteroalkyl.

[00289] The term "carbocyclic" or "carbocycle" refers to a ring or ring system where the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from "heterocyclic" rings or "heterocycles" in which the ring backbone contains at least one atom which is different from carbon. In some embodiments, at least one of the two rings of a bicyclic carbocycle is aromatic. In some embodiments, both rings of a bicyclic carbocycle are aromatic. Carbocycles include aryls and cycloalkyls.

[00290] As used herein, the term "aryl" refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. In one aspect, aryl is phenyl or a naphthyl. In some

embodiments, an aryl is a phenyl. In some embodiments, an aryl is a phenyl, naphthyl, indanyl, indenyl, or tetrahydronaphthyl. In some embodiments, an aryl is a C_6-C_{10}aryl. Depending on the structure, an aryl group is a monoradical or a diradical (i.e., an arylene group).

[00291] The term "cycloalkyl" refers to a monocyclic or polycyclic aliphatic, non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. In some embodiments, cycloalkyls are spirocyclic or bridged compounds. In some embodiments, cycloalkyls are optionally fused with an aromatic ring, and the point of attachment is at a carbon that is not an aromatic ring carbon atom. Cycloalkyl groups include groups having from 3 to 10 ring atoms. In some embodiments, cycloalkyl groups are selected from among cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, spiro[2.2]pentyl, norbornyl and bicycle[1.1.1]pentyl. In some embodiments, a cycloalkyl is a C_3-C_6cycloalkyl. In some embodiments, a cycloalkyl is a C_3-C_4cycloalkyl.

[00292] The term "halo" or, alternatively, "halogen" or "halide" means fluoro, chloro, bromo or iodo. In some embodiments, halo is fluoro, chloro, or bromo.

[00293] The term "fluoroalkyl" refers to an alkyl in which one or more hydrogen atoms are replaced by a fluorine atom. In one aspect, a fluoroalkyl is a C_1-C_6fluoroalkyl.

[00294] The term "heterocycle" or "heterocyclic" refers to heteroaromatic rings (also known as heteroaryls) and heterocycloalkyl rings containing one to four heteroatoms in the ring(s), where each heteroatom in the ring(s) is selected from O, S and N, wherein each heterocyclic group has from 3 to 10 atoms in its ring system, and with the proviso that any ring does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups (also known as heterocycloalkyls) include rings having 3 to 10 atoms in its ring system and aromatic heterocyclic groups include rings having 5 to 10 atoms in its ring system. The heterocyclic groups include benzo-fused ring systems. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl, indolin-2-onyl, isoindolin-1-onyl, isoindoline-1,3-dionyl, 3,4-dihydroisoquinolin-1(2H)-onyl, 3,4-dihydroquinolin-2(1H)-onyl, isoindoline-1,3-dithionyl, benzo[d]oxazol-2(3H)-onyl, 1H-benzo[d]imidazol-2(3H)-onyl, benzo[d]thiazol-2(3H)-onyl, and quinolizinyl. Examples of aromatic heterocyclic groups are

pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups are either C-attached (or C-linked) or *N*-attached where such is possible. For instance, a group derived from pyrrole includes both pyrrol-1-yl (*N*-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole includes imidazol-1-yl or imidazol-3-yl (both *N*-attached) or imidazol-2-yl, imidazol-4-yl or imidazol-5-yl (all C-attached). The heterocyclic groups include benzo-fused ring systems. Non-aromatic heterocycles are optionally substituted with one or two oxo (=O) moieties, such as pyrrolidin-2-one. In some embodiments, at least one of the two rings of a bicyclic heterocycle is aromatic. In some embodiments, both rings of a bicyclic heterocycle are aromatic.

[00295] The terms "heteroaryl" or, alternatively, "heteroaromatic" refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. Illustrative examples of heteroaryl groups include monocyclic heteroaryls and bicyclic heteroaryls. Monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. Monocyclic heteroaryls include indolizine, indole, benzofuran, benzothiophene, indazole, benzimidazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine. In some embodiments, a heteroaryl contains 0-4 N atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms in the ring. In some embodiments, a heteroaryl contains 0-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, heteroaryl is a C_1-C_9heteroaryl. In some embodiments, monocyclic heteroaryl is a C_1-C_5heteroaryl. In some embodiments, monocyclic heteroaryl is a 5-membered or 6-membered heteroaryl. In some embodiments, bicyclic heteroaryl is a C_6-C_9heteroaryl.

[00296] A "heterocycloalkyl" group refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. In some embodiments, a heterocycloalkyl is fused with an aryl or heteroaryl. In some embodiments, the heterocycloalkyl is oxazolidinonyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidin-2-onyl, pyrrolidine-2,5-dithionyl, pyrrolidine-2,5-dionyl, pyrrolidinonyl, imidazolidinyl, imidazolidin-2-onyl, or

thiazolidin-2-onyl. In one aspect, a heterocycloalkyl is a C_2-C_{10}heterocycloalkyl. In another aspect, a heterocycloalkyl is a C_4-C_{10}heterocycloalkyl. In some embodiments, a heterocycloalkyl is monocyclic or bicyclic. In some embodiments, a heterocycloalkyl is monocyclic and is a 3, 4, 5, 6, 7, or 8-membered ring. In some embodiments, a heterocycloalkyl is monocyclic and is a 3, 4, 5, or 6-membered ring. In some embodiments, a heterocycloalkyl is monocyclic and is a 3 or 4-membered ring. In some embodiments, a heterocycloalkyl contains 0-2 N atoms in the ring. In some embodiments, a heterocycloalkyl contains 0-2 N atoms, 0-2 O atoms and 0-1 S atoms in the ring.

[00297] The term "bond" or "single bond" refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. In one aspect, when a group described herein is a bond, the referenced group is absent thereby allowing a bond to be formed between the remaining identified groups.

[00298] The term "moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[00299] The term "optionally substituted" or "substituted" means that the referenced group is optionally substituted with one or more additional group(s) individually and independently selected from halogen, -CN, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -OH, $-CO_2H$, $-CO_2$alkyl, $-C(=O)NH_2$, -C(=O)NH(alkyl), $-C(=O)N(alkyl)_2$, $-S(=O)_2NH_2$, $-S(=O)_2NH(alkyl)$, $-S(=O)_2N(alkyl)_2$, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some other embodiments, optional substituents are independently selected from halogen, -CN, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, -OH, $-CO_2H$, $-CO_2(C_1$-C_4alkyl), $-C(=O)NH_2$, $-C(=O)NH(C_1$-C_4alkyl), $-C(=O)N(C_1$-C_4alkyl$)_2$, $-S(=O)_2NH_2$, $-S(=O)_2NH(C_1$-C_4alkyl), $-S(=O)_2N(C_1$-C_4alkyl$)_2$, C_1-C_4alkyl, C_3-C_6cycloalkyl, C_1-C_4fluoroalkyl, C_1-C_4heteroalkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkoxy, $-SC_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl, and $-S(=O)_2C_1$-C_4alkyl. In some embodiments, optional substituents are independently selected from halogen, -CN, $-NH_2$, -OH, $-NH(CH_3)$, $-N(CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-CHF_2$, $-CF_3$, $-OCH_3$, $-OCHF_2$, and $-OCF_3$. In some embodiments, substituted groups are substituted with one or two of the preceding groups. In some embodiments, an optional substituent on an aliphatic carbon atom (acyclic or cyclic) includes oxo (=O).

[00300] The term "modulate" as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[00301] The term "modulator" as used herein, refers to a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, the interactions of an agonist, partial agonist, an inverse agonist, antagonist, degrader, or combinations thereof. In some embodiments, a modulator is an agonist.

[00302] The terms "administer," "administering", "administration," and the like, as used herein, refer to the methods that may be used to enable delivery of compounds or compositions to the desired site of biological action. These methods include, but are not limited to oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular or infusion). Those of skill in the art are familiar with administration techniques that can be employed with the compounds and methods described herein.

[00303] The terms "co-administration" or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[00304] The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of an agent or a compound being administered, which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case is optionally determined using techniques, such as a dose escalation study.

[00305] The terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[00306] The term "pharmaceutical combination" as used herein, means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of

Formula (I), or a pharmaceutically acceptable salt thereof, and a co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

[00307] The terms "article of manufacture" and "kit" are used as synonyms.

[00308] The term "subject" or "patient" encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one aspect, the mammal is a human.

[00309] The terms "treat," "treating" or "treatment," as used herein, include alleviating, abating or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

Abbreviations:

$Pd(DTBPF)Cl_2$: [1,1′-Bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II);

HATU: 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate;

TFA: trifluoroacetic acid;

TEA: triethylamine;

DIEA or DIPEA: N,N-diisopropylethylamine;

Prep-HPLC: preparative high-performance liquid chromatography;

LCMS: Liquid chromatography–mass spectrometry;

MS: mass spectrometry;

HCl : hydrochloric acid or hydrochloride;

MeCN or CH_3CN or ACN: acetonitrile;

H_2O: water;

DMSO: dimethyl sulfoxide;

DMF : dimethylformamide;

DCM : dichloromethane;

PE: petroleum ether;

rt: room temperature;

hrs: hours;

h or hr: hour;

min : minute

mg: milligrams;

mL: milliliter;

Eq: equivalents;

mmol: millimole;

mol: moles;

Na_2CO_3: sodium carbonate;

K_2CO_3: potassium carbonate;

Na_2SO_4: sodium sulfate;

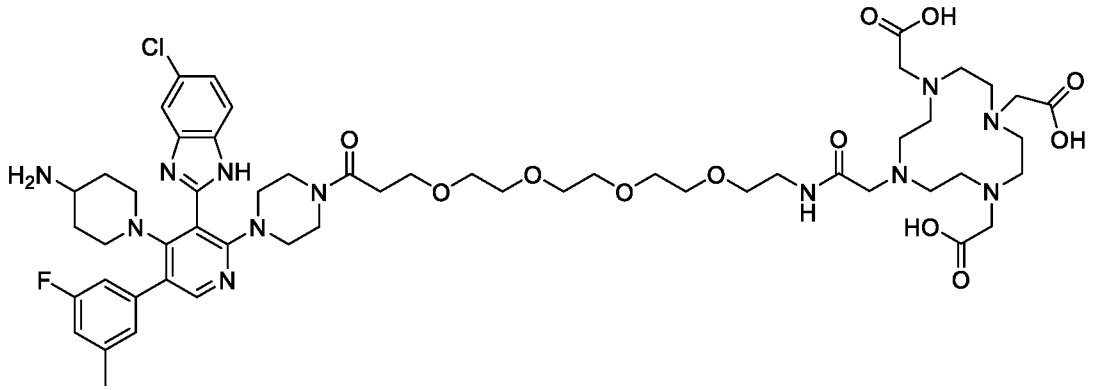
Brine: saturated NaCl solution.

EXAMPLES

[00310] The following examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Synthesis of Compounds

Example 1: 2-(4-{[(15-{4-[4-(4-Aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl]piperazin-1-yl}-15-oxo-3,6,9,12-tetraoxapentadecan-1-yl)carbamoyl]methyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid (Compound 1)



[00311] **Step-1**: To a DMF (2 mL) solution of 2,2-dimethyl-4-oxo-3,8,11,14,17-pentaoxa-5-azaicosan-20-oic acid (91 mg, 1 Eq, 0.25 mmol) was added HATU (0.14 g, 1.5 Eq, 0.38 mmol), DIPEA (97 mg, 0.13 mL, 3 Eq, 0.75 mmol) and benzyl (1-(3-(5-chloro-1H-benzo[d]imidazol-2-

yl)-5-(3-fluoro-5-methylphenyl)-2-(piperazin-1-yl)pyridin-4-yl)piperidin-4-yl)carbamate (0.16 g, 1 Eq, 0.25 mmol). The resulting mixture was stirred at ambient temperature for 0.5 h. The reaction crude was purified by C18 reverse phase chromatography eluting with MeCN (0.1% TFA)/water (0.1% TFA) (5-75%). Pure fractions were combined, concentrated, neutralized with saturated $NaHCO_3$ (3 mL), added solid NaCl (5 g), and extracted with ethyl acetate (2 x 20 mL). Organic layer was dried with $MgSO_4$, filtered, and concentrated to give benzyl (1-(3-(5-chloro-1H-benzo[d]imidazol-2-yl)-2-(4-(2,2-dimethyl-4-oxo-3,8,11,14,17-pentaoxa-5-azaicosan-20-oyl)piperazin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl)piperidin-4-yl)carbamate as a clear oil (202 mg). MS (M+H) = 1001.7.

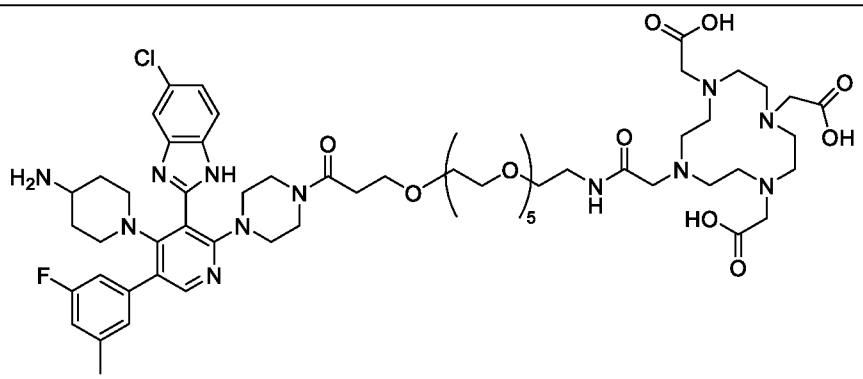
[00312] **Step-2**: To a DCM (1.0 mL) solution of benzyl (1-(3-(5-chloro-1H-benzo[d]imidazol-2-yl)-2-(4-(2,2-dimethyl-4-oxo-3,8,11,14,17-pentaoxa-5-azaicosan-20-oyl)piperazin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl)piperidin-4-yl)carbamate (202 mg, 1 Eq, 0.202 mmol) was added TFA (921 mg, 622 µL, 40 Eq, 8.08 mmol). The resulting mixture was stirred at ambient temperature for 1 h. The reaction crude was concentrated, MTBE (0.4 mL) and hexane (3 mL) were added to oil out the desired product. The top layer was decanted and remaining residue was dried under vacuum to give the crude TFA salt of 2-(4,7,10-tris(2-(tert-butoxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid. MS (M+H) =901.5.

[00313] **Step-3**: To a DMF (1.0 mL) solution of 2-(4,7,10-tris(2-(tert-butoxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid (0.11 g, 1 Eq, 0.20 mmol) was added 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (0.11 g, 1.5 Eq, 0.30 mmol), DIPEA (0.21 g, 0.28 mL, 8 Eq, 1.6 mmol) and benzyl (1-(2-(4-(1-amino-3,6,9,12-tetraoxapentadecan-15-oyl)piperazin-1-yl)-3-(5-chloro-1Hbenzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl)piperidin-4-yl)carbamate--2,2,2-trifluoroacetaldehyde (1/1) (0.27 g, 73% Wt, 0.99 Eq, 0.20 mmol). The resulting mixture was stirred at ambient temperature for 0.5 h. The reaction crude was purified by C18 reverse phase chromatography eluting with MeCN (0.1% TFA)/water (0.1% TFA) (5-55%). Pure fractions were combined, neutralized with saturated $NaHCO_3$ (3 mL), added solid NaCl (5 g), and extracted with ethyl acetate (20 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated to give crude 2-(4-{[(15-{4-[4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl]piperazin-1-yl}-15-oxo-3,6,9,12-tetraoxapentadecan-1-yl)carbamoyl]methyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid. MS (M+H) = 1456.3. Half MS (M+H) = 729.0.

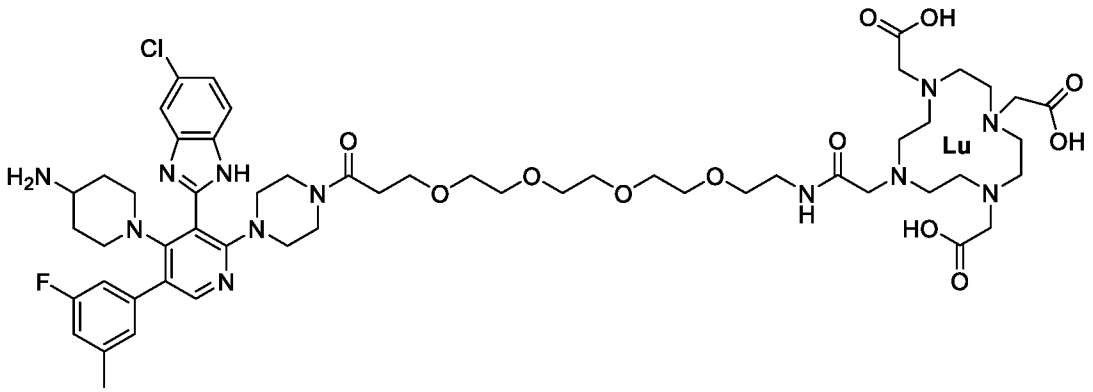
[00314] **Step-4:** To a TFA (4 g, 3 mL, 4e+2 Eq, 4e+1 mmol) solution of tri-tert-butyl 2,2',2''-(10-(18-(4-(4-(4-(((benzyloxy)carbonyl)amino)piperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-

2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-2,18-dioxo-6,9,12,15-tetraoxa-3-azaoctadecyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (145 mg, 1 Eq, 99.6 μmol) was added thioanisole (0.2 g, 0.2 mL, 2e+1 Eq, 2 mmol). The resulting mixture was heated at 50 °C for 1 h. The reaction mixture was concentrated under vacuum to remove most TFA. Hexane (4 mL) was added, and the top layer was decanted. The remaining residue was concentrated to remove hexane and purified by C18 reverse phase chromatography eluting with MeCN (0.1% TFA)/water (0.1% TFA) (5-35%). Pure fractions were dried with under vacuum to give the TFA salt of 2-(4-{[(15-{4-[4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl]piperazin-1-yl}-15-oxo-3,6,9,12-tetraoxapentadecan-1-yl)carbamoyl]methyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid (85 mg). MS (M+H) = 1154.0.

[00315] The following compound were prepared similarly to **Example 1** with appropriate substituting reagents and substrates at different steps and they may require additional functional group modifications via well-known chemistry with appropriate reagents.

Compound #		MS
4	 2-(4-{[(21-{4-[4-(4-Aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl]piperazin-1-yl}-21-oxo-3,6,9,12,15,18-hexaoxaheneicosan-1-yl)carbamoyl]methyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid	(M+H) = 1241.7

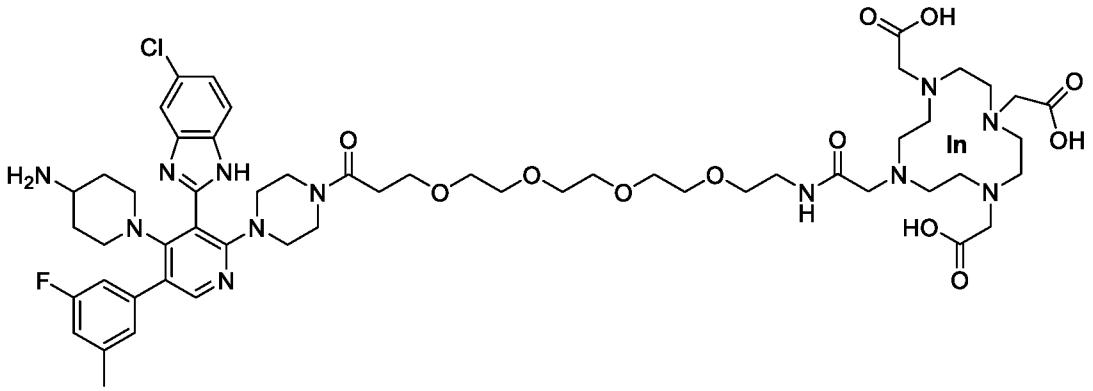
Example 2: 2-(4-{[(15-{4-[4-(4-Aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl]piperazin-1-yl}-15-oxo-3,6,9,12-tetraoxapentadecan-1-yl)carbamoyl]methyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid Lutetium complex (Compound 2)



Step-1: To a MeCN (0.9 mL) solution of 1. 2,2',2''-(10-(18-(4-(4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-

[00316] yl)-2,18-dioxo-6,9,12,15-tetraoxa-3-azaoctadecyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid-2,2,2-trifluoroacetaldehyde (1/2) (35 mg, 1 Eq, 51 µmol) was added water (0.5 mL), $LuCl_3$ (15 mg), and saturated $NaHCO_3$ solution (0.05 mL). The resulting mixture was heated at 80 °C for 1 h. LCMS showed complete conversion to desired product. This reaction was repeated on the same scale and the reaction mixture was combined with previous batch. The resulting mixture was purified by C18 reverse phase. Pure fractions were combined and dried under vacuum to give the title lutetium complex as a white solid (42 mg, 54%). MS (M+H) = 1325.9. Half MS (M+H) = 663.7.

Example 3: 2-(4-{[(15-{4-[4-(4-Aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl]piperazin-1-yl}-15-oxo-3,6,9,12-tetraoxapentadecan-1-yl)carbamoyl]methyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid Indium complex (Compound 3)



[00317] **Step-1**: To a DMF (1.5 mL) solution of 2,2-dimethyl-4-oxo-3,8,11,14,17-pentaoxa-5-azaicosan-20-oic acid (115.2 mg, 97% Wt, 1 Eq, 305.8 µmol) was added HATU (174.4 mg, 1.5 Eq, 458.7 µmol) and DIPEA (316.2 mg, 0.43 mL, 8.0 Eq, 2.446 mmol). The resulting mixture was stirred at room temperature for 10 minutes, followed by the addition of benzyl (1-(3-(5-

chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-(piperazin-1-yl)pyridin-4-yl)piperidin-4-yl)carbamate--2,2,2-trifluoroacetaldehyde (1/2) (260.0 mg, 1 Eq, 305.8 µmol). The reaction mixture was stirred at 20 °C for 2 hrs. The resulting mixture was diluted with ethyl acetate, washed with water and brine, separated, and concentrated to give crude benzyl (1-(3-(5-chloro-1H-benzo[d]imidazol-2-yl)-2-(4-(2,2-dimethyl-4-oxo-3,8,11,14,17-pentaoxa-5-azaicosan-20-oyl)piperazin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl)piperidin-4-yl)carbamate as a light brown solid. This material was used for next step without further purification. MS (M+H)=1001.9.

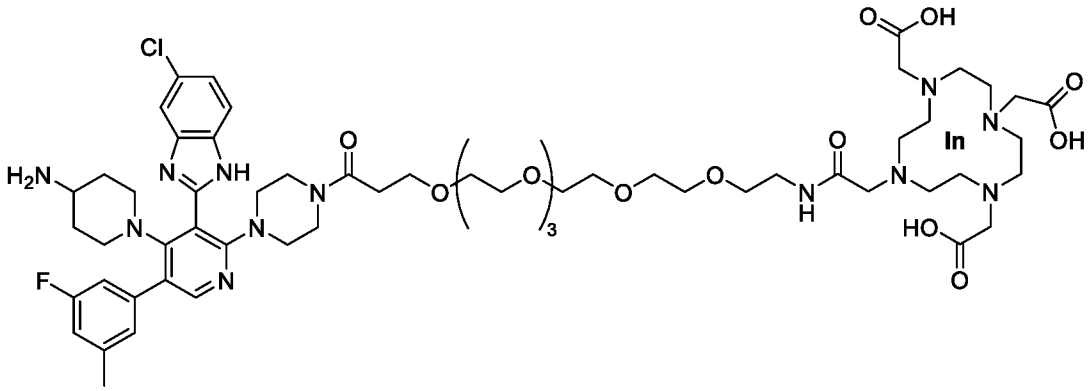
[00318] **Step-2**: To a DCM (1 mL) solution of benzyl (1-(3-(5-chloro-1H-benzo[d]imidazol-2-yl)-2-(4-(2,2-dimethyl-4-oxo-3,8,11,14,17-pentaoxa-5-azaicosan-20-oyl)piperazin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl)piperidin-4-yl)carbamate (306 mg, 1 Eq, 306 µmol) was added TFA (1.39 g, 941 µL, 40 Eq, 12.2 mmol). The resulting mixture was stirred at ambient temperature for 0.5 h. The reaction crude was concentrated, and the remaining residue was purified by C18 reverse phase chromatography eluting with MeCN (0.1% TFA)/water (0.1% TFA). Pure fractions were combined and dried under vacuum to give crude benzyl (1-(2-(4-(1-amino-3,6,9,12-tetraoxapentadecan-15-oyl)piperazin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl)piperidin-4-yl)carbamate (205 mg, 227 µmol, 74.4%) as a TFA salt. This material was used for next step without further purification. MS (M+H)=901.7.

[00319] **Step-3**: To a DMF (1.5 mL) solution of 2-(4,7,10-tris(2-(tert-butoxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid (116.3 mg, 1.0 Eq, 203.1 µmol) was added 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (115.8 mg, 1.5 Eq, 304.7 µmol) and DIPEA (210.0 mg, 0.28 mL, 8 Eq, 1.625 mmol). The resulting mixture was stirred at room temperature for 10 minutes, followed by the addition of benzyl (1-(2-(4-(1-amino-3,6,9,12-tetraoxapentadecan-15-oyl)piperazin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl)piperidin-4-yl)carbamate--2,2,2-trifluoroacetaldehyde (1/1) (203.0 mg, 1.0 Eq, 203.1 µmol). The reaction mixture was stirred at 25 °C for 2 hrs. The reaction crude was diluted with ethyl acetate, washed with water and brine, and concentrated to give crude tri-tert-butyl 2,2',2''-(10-(18-(4-(4-(4-(((benzyloxy)carbonyl)amino)piperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-2,18-dioxo-6,9,12,15-tetraoxa-3-azaoctadecyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate as a light brown solid. MS (M+H)=1457.5.

[00320] **Step-4**: To a TFA (2.2 g, 1.5 mL, 97 Eq, 20 mmol) solution was added crude tri-tert-butyl 2,2',2''-(10-(18-(4-(4-(4-(((benzyloxy)carbonyl)amino)piperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-2,18-dioxo-6,9,12,15-tetraoxa-3-azaoctadecyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (295.0 mg, 1 Eq, 202.6 µmol) and the resulting mixture was heated at 60 °C for 1 hour. The reaction crude was concentrated and purified by C18 reverse phase chromatography eluting with MeCN (0.1% TFA)/water (0.1% TFA). Pure fractions were combined and dried under vacuum to give the TFA salt of 2,2',2''-(10-(18-(4-(4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-2,18-dioxo-6,9,12,15-tetraoxa-3-azaoctadecyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (160 mg, 139 µmol, 68.5%). MS (M+H) =1154.4.

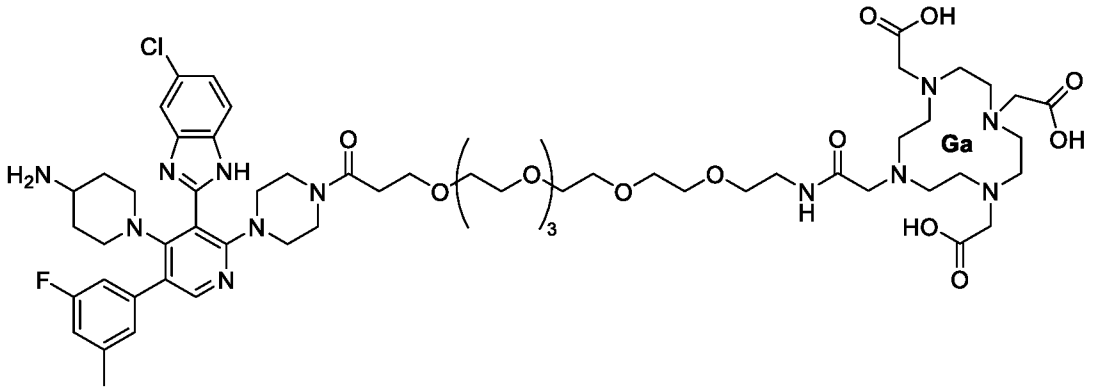
[00321] **Step-5**: The TFA salt of 2,2',2''-(10-(18-(4-(4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-2,18-dioxo-6,9,12,15-tetraoxa-3-azaoctadecyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (45 mg, 1 Eq, 33 µmol) was combined with sodium bicarbonate(28 mg, 10 Eq, 0.33 mmol), indium(III) chloride (22 mg, 3 Eq, 0.10 mmol), MeCN (0.3 mL) and Water (0.3 mL). The resulting mixture was stirred at 40 °C for 3 hrs. The reaction crude was purified by C18 reverse phase chromatography eluting with MeCN (0.1% TFA)/water (0.1% TFA). Pure fractions were combined and dried and to give the title indium complex (38.3 mg, 26.2 µmol, 79%) as a TFA salt. MS (M+H)=1265.9.

Example 4: 2-(4-{[(21-{4-[4-(4-Aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl]piperazin-1-yl}-21-oxo-3,6,9,12,15,18-hexaoxaheneicosan-1-yl)carbamoyl]methyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid Indium complex (Compound 5)



[00322] **Step-1**: To an 8-mL flask were added 2,2',2''-(10-(24-(4-(4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-2,24-dioxo-6,9,12,15,18,21-hexaoxa-3-azatetracosyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (40 mg, 1 Eq, 32 μmol), Indium trichloride (20 mg, 5.8 μL, 2.8 Eq, 90 μmol), Sodium bicarbonate (15 mg, 6.9 μL, 5.5 Eq, 0.18 mmol), Water (0.25 mL) and Acetonitrile (0.5 mL). The resulting mixture was stirred at 80 °C for 1 hour. The reaction mixture was diluted with DMSO (4 mL) and filtered. The filtrate was purified by Prep-HPLC using the following conditions: Column, SunFire Prep C18 OBD Column, 19*150 mm 5 um 10 nm; mobile phase, Water (0.05% TFA) and ACN (30% ACN up to 75% in 15 min); Total flow rate, 20 mL/min; Detector, UV 220 nm. This resulted in the TFA salt of title indium complex (24.6 mg, 15.6 μmol, 48%) as a white solid. MS (M+H) =1354.7,1356.7.

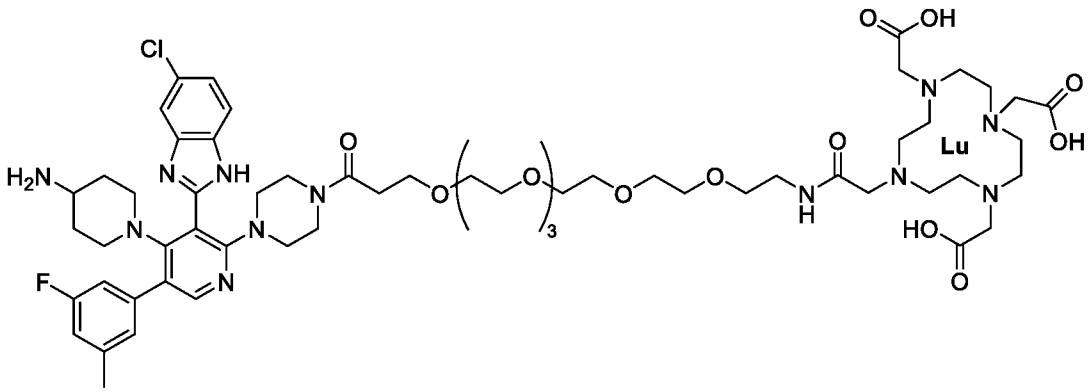
Example 5: 2-(4-{[(21-{4-[4-(4-Aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl]piperazin-1-yl}-21-oxo-3,6,9,12,15,18-hexaoxaheneicosan-1-yl)carbamoyl]methyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid Gallium complex (Compound 6)



[00323] **Step-1**: Into an 8-mL flask were added 2,2',2''-(10-(24-(4-(4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-2,24-dioxo-6,9,12,15,18,21-hexaoxa-3-azatetracosyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (10 mg, 1 Eq, 8.1 μmol), Gallium chloride (4 mg, 2 μL, 3 Eq, 0.02 mmol), sodium bicarbonate (4 mg, 6 Eq, 0.05 mmol), Water (0.15 mL) and Acetonitrile (0.3 mL). The resulting mixture was stirred at 80 °C for 2 hrs. The reaction mixture was diluted with DMSO (4 mL) and filtered. The filtrate was purified by Prep-HPLC using the following conditions: Column, SunFire Prep C18 OBD Column, 19*150 mm 5 um 10 nm; mobile phase, Water (0.05% TFA) and ACN (30% ACN up to 75% in 15 min); Total flow rate, 20mL/min;

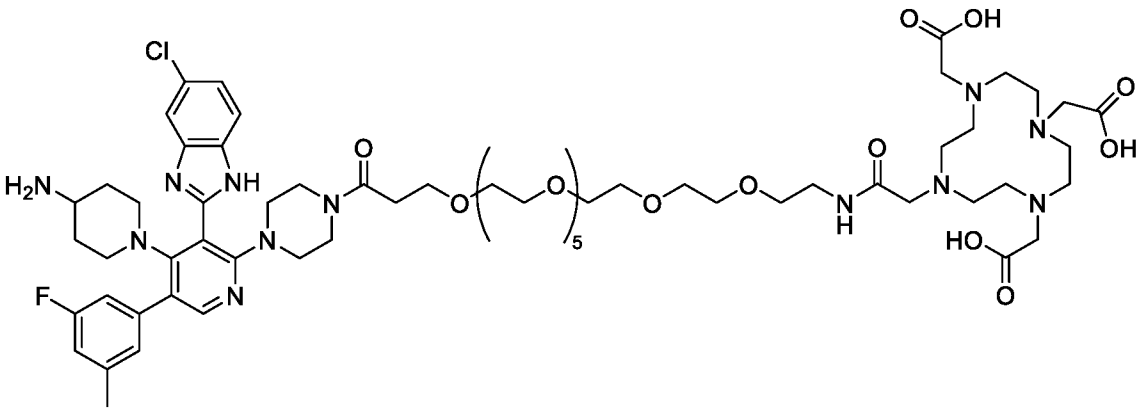
Detector, UV 220 nm. This resulted in the TFA salt of title gallium complex (6 mg, 4 µmol, 50%) as a white solid. MS (M+H)=1309.3, 1311.3.

Example 6: 2-(4-{[(21-{4-[4-(4-Aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl]piperazin-1-yl}-21-oxo-3,6,9,12,15,18-hexaoxaheneicosan-1-yl)carbamoyl]methyl}-7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid Lutetium complex (Compound 7)



[00324] **Step-1**: Into an 8-mL flask was added a mixture of 2,2',2''-(10-(24-(4-(4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-2,24-dioxo-6,9,12,15,18,21-hexaoxa-3-azatetracosyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (10 mg, 1 Eq, 8.1 µmol), Lutetium (III) chloride (7 mg, 3 Eq, 0.02 mmol), sodium bicarbonate (5 mg, 7 Eq, 0.06 mmol), Acetonitrile (0.3 mL) and Water (0.15 mL). The mixture was stirred at 80 °C for 2 hrs. The reaction mixture was diluted with DMSO (4 mL), filtered and the filtrate was purified by Prep-HPLC using the following conditions: Column, SunFire Prep C18 OBD Column, 19*150 mm 5 um 10 nm; mobile phase, Water (0.05% TFA) and ACN (30% ACN up to 75% in 15 min); Total flow rate, 20 mL/min; Detector, UV 220 nm. This resulted in the title lutetium complex (2.5 mg, 1.5 µmol, 19%) as a white solid. MS (M+H)=1414.8, 1416.8.

Example 7: 2-(7-{[(27-{4-[4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl]piperazin-1-yl}-27-oxo-3,6,9,12,15,18,21,24-octaoxaheptacosan-1-yl)carbamoyl]methyl}-4,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid (Compound 8)



[00325] **Step-1**: Into a 500-mL round-bottom flask, was placed 2,4-dichloronicotinaldehyde (19 g, 1 Eq, 0.11 mol), tert-butyl piperidin-4-ylcarbamate (22 g, 1.0 Eq, 0.11 mol), DIEA (14 g, 19 mL, 1.0 Eq, 0.11 mol) and MeCN (200 mL). The resulting mixture was stirred at 25 °C for 1 hour. The reaction crude was diluted with water (100 mL) and extracted with ethyl acetate (3x100 mL). Organic layers were combined, washed with brine (2x100 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The remaining residue was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (1:2). This resulted in tert-butyl (1-(2-chloro-3-formylpyridin-4-yl)piperidin-4-yl)carbamate (20 g, 59 mmol, 55%) as a yellow solid. MS (M+H)=340.1, 342.1.

[00326] **Step-2**: Into a 100-mL round-bottom flask, was placed tert-butyl (1-(5-bromo-2-chloro-3-formylpyridin-4-yl)piperidin-4-yl)carbamate (4 g, 1 Eq, 0.01 mol) and HCl in dioxane (45 g, 30 mL, 4 M, 1e+2 Eq, 1.2 mol). The resulting reaction mixture was stirred at 25 °C for 2 hrs. The reaction mixture was concentrated under vacuum to afford crude 4-(4-aminopiperidin-1-yl)-5-bromo-2-chloronicotinaldehyde hydrochloride (2.8 g, 7.9 mmol, 80%) as a light-yellow solid. This material was used for next step without further purification. MS (M+H)=318.0, 320.0.

[00327] **Step-3**: Into a 100-mL round-bottom flask, was placed 4-(4-aminopiperidin-1-yl)-5-bromo-2-chloronicotinaldehyde hydrochloride (2.8 g, 1 Eq, 7.9 mmol), K_2CO_3 (5.4 g, 5.0 Eq, 39 mmol), and THF (30 mL). The resulting mixture was stirred at 25 °C, followed by the addition of Cbz-Cl (2.0 g, 1.7 mL, 1.5 Eq, 12 mmol). The reaction solution was stirred at 25 °C for additional 2 hrs. The resulting mixture was extracted with ethyl acetate (3x50 mL). Organic layers were combined, washed with brine (1x50 mL), dried over anhydrous sodium sulfate and concentrated. The remaining residue was purified by silica gel chromatography eluting with PE/EA (1:1). This resulted in benzyl (1-(5-bromo-2-chloro-3-formylpyridin-4-yl)piperidin-4-yl)carbamate (3.5 g, 7.0 mmol, 88%, 90% Purity) as a yellow solid. MS (M+H)=452.1, 454.1.

[00328] **Step-4**: Into a 100-mL round-bottom flask was placed a mixture of benzyl (1-(5-bromo-2-chloro-3-formylpyridin-4-yl)piperidin-4-yl)carbamate (3.5 g, 1 Eq, 7.7 mmol), (3-fluoro-5-

methylphenyl)boronic acid (1.1 g, 0.92 Eq, 7.1 mmol), 1,1'-Bis(diphenylphosphino)ferrocene-palladium(II) dichloride (280 mg, 0.049 Eq, 383 μmol), K_3PO_4 (4.9 g, 3.0 Eq, 23 mmol), Toluene (175 mL) and Water (17.5 mL). The resulting mixture was stirred at 50 °C for 2.5 hrs under N_2. The reaction mixture was concentrated, extracted with ethyl acetate (3x50 mL). Organic layers were combined, washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The remaining residue was purified by silica gel chromatography eluting with PE/EA (1:1). This resulted in benzyl (1-(2-chloro-5-(3-fluoro-5-methylphenyl)-3-formylpyridin-4-yl)piperidin-4-yl)carbamate (2.8 g, 4.6 mmol, 60%, 80% Purity) as a yellow solid. MS (M+H)=482.4, 484.4.

[00329] **Step-5**: Into a 40-mL vial, were placed benzyl (1-(2-chloro-5-(3-fluoro-5-methylphenyl)-3-formylpyridin-4-yl)piperidin-4-yl)carbamate (600 mg, 1 Eq, 1.24 mmol), tert-butyl piperazine-1-carboxylate (350 mg, 1.51 Eq, 1.88 mmol), DIEA (483 mg, 651 μL, 3.00 Eq, 3.74 mmol), and DMSO (6 mL). The resulting mixture was stirred at 100 °C for 3 hrs. The reaction crude was extracted with ethyl acetate (3x50 mL). Organic layers were combined, washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated. The remaining residue was purified by silica gel chromatography eluting with PE/EA (1:1). This resulted in tert-butyl 4-(4-(4-(((benzyloxy)carbonyl)amino)piperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-formylpyridin-2-yl)piperazine-1-carboxylate (400 mg, 0.57 mmol, 46%, 90% Purity) as a yellow solid. MS (M+H)=632.4.

[00330] **Step-6**: Into a 40-mL vial, were placed tert-butyl 4-(4-(4-(((benzyloxy)carbonyl)amino)piperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-formylpyridin-2-yl)piperazine-1-carboxylate (400 mg, 1 Eq, 633 μmol), 4-chlorobenzene-1,2-diamine (180 mg, 1.99 Eq, 1.26 mmol), $Na_2S_2O_5$ (360 mg, 2.99 Eq, 1.89 mmol) and DMSO (4 mL). The resulting mixture was stirred at 80 °C for 1 h. The reaction crude was extracted with ethyl acetate (3x50 mL). Organic layers were combined, washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated. The remaining residue was purified by silica gel chromatography eluting PE/EA (1:1). This resulted in tert-butyl 4-(4-(4-(((benzyloxy)carbonyl)amino)piperidin-1-yl)-3-(6-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazine-1-carboxylate (500 mg, 0.60 mmol, 94%, 90% Purity) as a yellow solid. MS (M+H)=754.5, 756.5.

[00331] **Step-7**: To a DCM (9 mL) solution of tert-butyl 4-(4-(4-(((benzyloxy)carbonyl)amino)piperidin-1-yl)-3-(6-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazine-1-carboxylate (500 mg, 1 Eq, 663 μmol) was added TFA (3 mL). The resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was

concentrated under vacuum. The remaining residue was diluted with ethyl acetate (10 mL) and saturated $NaHCO_3$ was added until pH=8. The resulting mixture was extracted with ethyl acetate (50 mL) and the organic layer was concentrated under vacuum. This resulted in crude benzyl (1-(3-(6-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-(piperazin-1-yl)pyridin-4-yl)piperidin-4-yl)carbamate (390 mg, 0.54 mmol, 81%, 90% Purity) as a yellow oil. MS (M+H)=654.2, 656.2.

[00332] **Step-8**: Into a 40-mL vial, were placed 2,2-dimethyl-4-oxo-3,8,11,14,17,20,23,26,29-nonaoxa-5-azadotriacontan-32-oic acid (323 mg, 1.00 Eq, 596 µmol), 4-methylmorpholine (181 mg, 3.00 Eq, 1.79 mmol), perfluorophenyl diphenylphosphinate (275 mg, 1.20 Eq, 716 µmol), and DMF (4 mL). Crude benzyl (1-(3-(6-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-(piperazin-1-yl)pyridin-4-yl)piperidin-4-yl)carbamate (390 mg, 1 Eq, 596 µmol) was added and the resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with water (20 mL), extracted with ethyl acetate (50 mL), separated, and concentrated under vacuum. The remaining residue was purified by Flash-Prep-HPLC using the following conditions: Column, C18 silica gel; mobile phase, Water (0.1% TFA) and CH_3CN (10% CH_3CN up to 90% in 10 min); Detector, UV 254 &220 nm. This resulted in benzyl (1-(3-(5-chloro-1H-benzo[d]imidazol-2-yl)-2-(4-(2,2-dimethyl-4-oxo-3,8,11,14,17,20,23,26,29-nonaoxa-5-azadotriacontan-32-oyl)piperazin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl)piperidin-4-yl)carbamate (500 mg, 0.40 mmol, 68%, 95% Purity) as light yellow oil. MS (M+H)=1177.9.

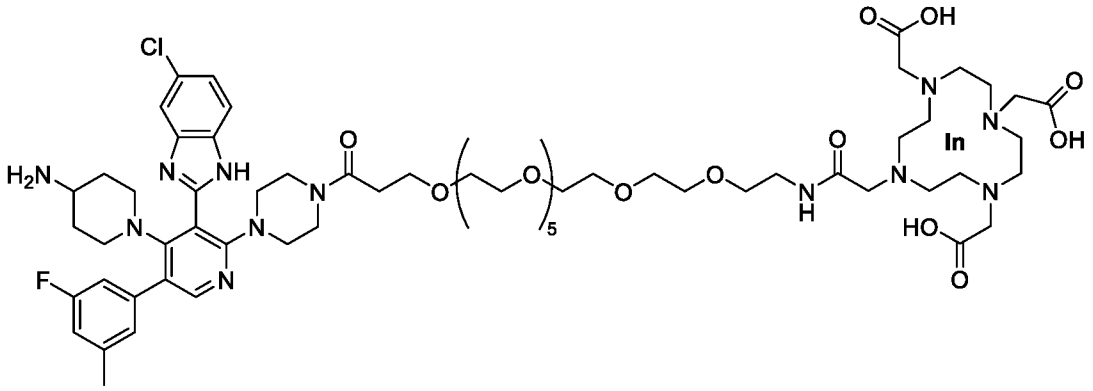
[00333] **Step-9**: To a DCM (15 mL) solution of benzyl (1-(3-(5-chloro-1H-benzo[d]imidazol-2-yl)-2-(4-(2,2-dimethyl-4-oxo-3,8,11,14,17,20,23,26,29-nonaoxa-5-azadotriacontan-32-oyl)piperazin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl)piperidin-4-yl)carbamate (500 mg, 1 Eq, 425 µmol) was added TFA (5 mL). The reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under vacuum to afford crude benzyl (1-(2-(4-(1-amino-3,6,9,12,15,18,21,24-octaoxaheptacosan-27-oyl)piperazin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl)piperidin-4-yl)carbamate 2,2,2-trifluoroacetate (500 mg, 420 µmol, 98.8%) as a yellow oil. This material was used for next step without further purification. MS (M+H)=1077.5.

[00334] **Step-10**: Into a 40-mL vial, were placed 2-(4,7,10-tris(2-(tert-butoxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid (240 mg, 0.999 Eq, 419 µmol), HATU (191 mg, 1.20 Eq, 502 µmol), DIEA (271 mg, 365 µL, 5.00 Eq, 2.10 mmol) and DMF (5 mL). Crude benzyl (1-(2-(4-(1-amino-3,6,9,12,15,18,21,24-octaoxaheptacosan-27-oyl)piperazin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl)piperidin-4-

yl)carbamate 2,2,2-trifluoroacetate (500 mg, 1 Eq, 420 µmol) was added and the resulting solution was stirred at 25 °C for 2 hrs. The reaction mixture was purified by Flash-Prep-HPLC using the following conditions: Column, C18 silica gel; mobile phase, Water (0.1% TFA) and CH_3CN (10% CH_3CN up to 90% in 10 min); Detector, UV 254 &220 nm. This resulted in tri-tert-butyl 2,2',2''-(10-(30-(4-(4-(4-(((benzyloxy)carbonyl)amino)piperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-2,30-dioxo-6,9,12,15,18,21,24,27-octaoxa-3-azatriacontyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (510 mg, 0.30 mmol, 71%, 95% Purity) as an off-white solid. MS (M+H)=1632.0.

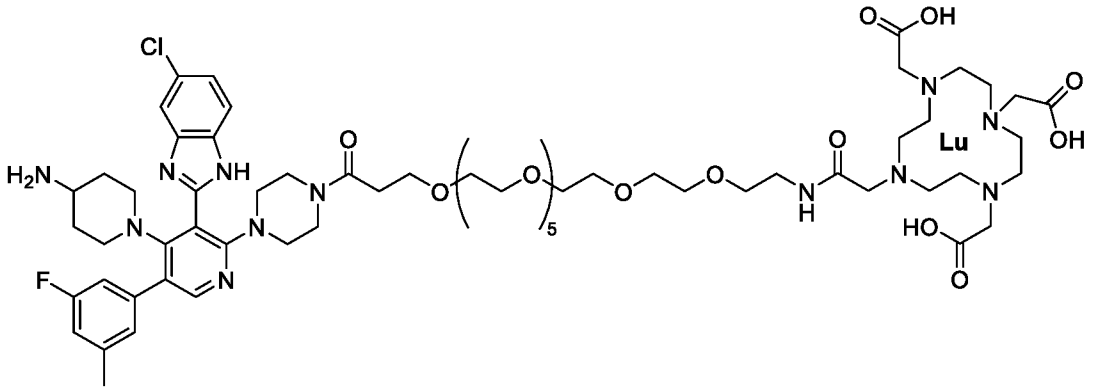
[00335] **Step-11**: Into a 40-mL vial, was place a mixture of tri-tert-butyl 2,2',2''-(10-(30-(4-(4-(4-(((benzyloxy)carbonyl)amino)piperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-2,30-dioxo-6,9,12,15,18,21,24,27-octaoxa-3-azatriacontyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (350 mg, 1 Eq, 214 µmol) and TFA (4 mL). The resulting mixture was stirred at 60 °C for 2 hrs. The reaction mixture was concentrated and the remaining residue was purified by Prep-HPLC using the following condition: Column, SunFire Prep C18 OBD Column, 19*150 mm 5 um; mobile phase, Water (0.05% TFA) and ACN (30.0% ACN up to 50.0% in 7 min); Total flow rate, 20 mL/min; Detector, UV 220 nm. This resulted in 2,2',2''-(10-(30-(4-(4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-2,30-dioxo-6,9,12,15,18,21,24,27-octaoxa-3-azatriacontyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid--2,2,2-trifluoroacetic acid (1/1) (170 mg, 117 µmol, 54.4%, 99.0% Purity) as an off-white solid. MS (M+H)=1329.6.

Example 8: 2-(7-{[(27-{4-[4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl]piperazin-1-yl}-27-oxo-3,6,9,12,15,18,21,24-octaoxaheptacosan-1-yl)carbamoyl]methyl}-4,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid Indium Complex (Compound 9)



[00336] **Step-1**: 2,2',2"-(10-(30-(4-(4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-2,30-dioxo-6,9,12,15,18,21,24,27-octaoxa-3-azatriacontyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (50 mg, 1 Eq, 38 µmol) was combined with sodium bicarbonate (30 mg, 9.5 Eq, 0.36 mmol), indium (III) chloride (25 mg, 3.0 Eq, 0.11 mmol), Water (0.25 mL) and Acetonitrile (0.5 mL). The resulting mixture was stirred at 80 °C for 2 hrs. The reaction mixture was concentrated under vacuum and the remaining residue was purified by Prep-HPLC using the following conditions: Column, SunFire Prep C18 OBD Column, 19*150 mm 5 um 10 nm; mobile phase, Water (0.1% FA) and ACN (30% ACN up to 80% in 16 min); Total flow rate, 20 mL/min; Detector, UV 220 nm. This resulted in the title indium complex (28.4 mg, 19.1 µmol, 51%) as a white solid. MS (M+H)=1441.7,1443.7.

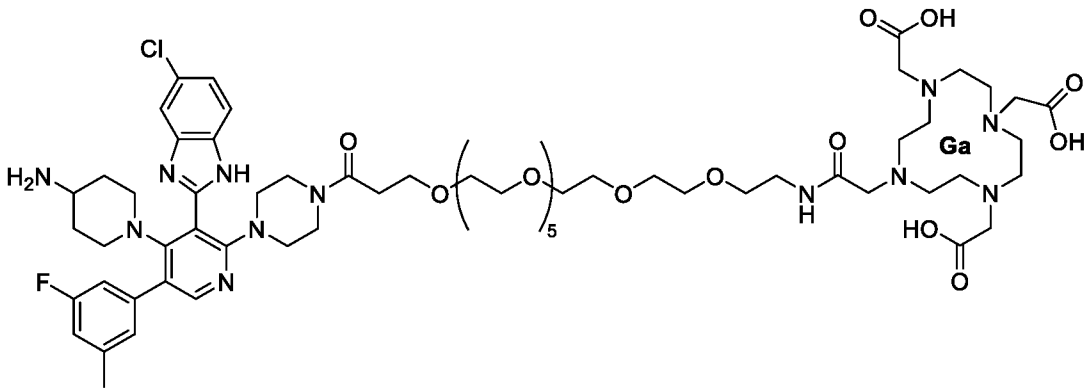
Example 9: 2-(7-{[(27-{4-[4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl]piperazin-1-yl}-27-oxo-3,6,9,12,15,18,21,24-octaoxaheptacosan-1-yl)carbamoyl]methyl}-4,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid Lutetium Complex (Compound 10)



[00337] **Step-1**: 2,2',2"-(10-(30-(4-(4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-2,30-dioxo-6,9,12,15,18,21,24,27-octaoxa-3-azatriacontyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (10 mg, 1 Eq, 7.5 µmol) was combined with sodium bicarbonate (6 mg, 9 Eq, 0.07 mmol), Lutetium (III) chloride (7 mg, 3 Eq, 0.02 mmol), Water (0.25 mL) and Acetonitrile (0.5 mL). The resulting mixture was stirred at 80 °C for 2 hrs. The reaction mixture was concentrated under vacuum and the remaining residue was purified by Prep-HPLC using the following conditions: Column, SunFire Prep C18 OBD Column, 19*150 mm 5 um 10 nm; mobile phase, Water (0.1% FA) and ACN (30% ACN up to 70% in 15 min); Total flow rate, 20

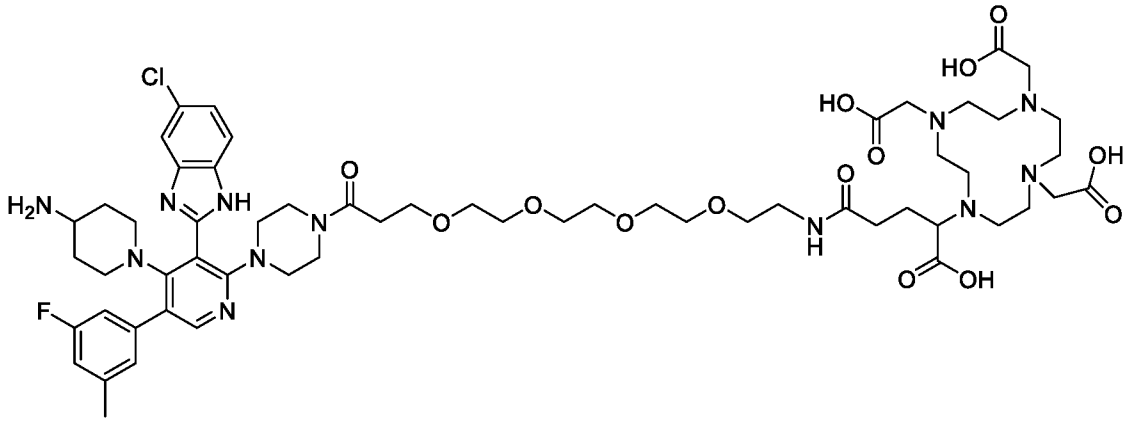
mL/min; Detector, UV 220 nm. This resulted in the title lutetium complex (7.2 mg, 4.7 µmol, 62%) as a white solid. MS (M+H)=1502.9,1504.9.

Example 10: 2-(7-{[(27-{4-[4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl]piperazin-1-yl}-27-oxo-3,6,9,12,15,18,21,24-octaoxaheptacosan-1-yl)carbamoyl]methyl}-4,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl)acetic acid Gallium Complex (Compound 11)



[00338] **Step-1**: 2,2',2''-(10-(30-(4-(4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-2,30-dioxo-6,9,12,15,18,21,24,27-octaoxa-3-azatriacontyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (10 mg, 1 Eq, 7.5 µmol) was combined with sodium bicarbonate (5 mg, 8 Eq, 0.06 mmol), gallium trichloride (5 mg, 4 Eq, 0.03 mmol), Water (0.25 mL) and Acetonitrile (0.5 mL). The resulting mixture was stirred at 80 °C for 2 hrs. The reaction mixture was diluted with DMSO (4 mL), filtered, and the filtrate was purified by Prep-HPLC using the following conditions: Column, SunFire Prep C18 OBD Column, 19*150 mm 5 um 10 nm; mobile phase, Water and ACN (30% ACN up to 80% in 15 min); Total flow rate, 20 mL/min; Detector, UV 220 nm. The resulting product partially decomposed to acid during lyophilization, thus this material was purified under neutral conditions and lyophilized. This resulted in the title gallium complex. MS (M+H)=1398.6,1440.6.

Example 11: 4-[(15-{4-[4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl]piperazin-1-yl}-15-oxo-3,6,9,12-tetraoxapentadecan-1-yl)carbamoyl]-2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl]butanoic acid (Compound 12)



[00339] **Step-1**: Benzyl (1-(2-chloro-5-(3-fluoro-5-methylphenyl)-3-formylpyridin-4-yl)piperidin-4-yl)carbamate (400 mg, 1 Eq, 830 µmol) was combined with tert-butyl piperazine-1-carboxylate (309 mg, 2.00 Eq, 1.66 mmol), N-ethyl-N-isopropylpropan-2-amine (322 mg, 3.00 Eq, 2.49 mmol) and DMSO (2 mL). The resulting mixture was stirred at 100 °C for 1 h. The reaction crude was diluted with water (20 mL) and extracted with ethyl acetate (2x30 mL). Organic layers were combined, washed by water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The remaining residue was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (1:3). This resulted in tert-butyl 4-(4-(4-(((benzyloxy)carbonyl)amino)piperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-formylpyridin-2-yl)piperazine-1-carboxylate (367 mg, 581 µmol, 70.0%) as a yellow solid. MS (M+H)=632.3.

[00340] **Step-2**: To a DMSO (2 mL) solution of tert-butyl 4-(4-(4-(((benzyloxy)carbonyl)amino)piperidin-1-yl)-5-(3-fluoro-5-methylphenyl)-3-formylpyridin-2-yl)piperazine-1-carboxylate (367 mg, 1 Eq, 581 µmol) was added 4-chlorobenzene-1,2-diamine (166 mg, 2.00 Eq, 1.16 mmol) and $Na_2S_2O_5$ (331 mg, 3.00 Eq, 1.74 mmol). The resulting mixture was stirred at 80 °C for 1 h. The reaction mixture was extracted with ethyl acetate (3x50 mL). Organic layers were combined, washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The remaining residue was purified by silica gel chromatography eluting with PE/EA (1:1). This resulted in tert-butyl 4-(4-(4-(((benzyloxy)carbonyl)amino)piperidin-1-yl)-3-(6-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazine-1-carboxylate (365 mg, 484 µmol, 83.3%) as a yellow solid. MS (M+H)=754.2.

[00341] **Step-3**: To a DCM (3 mL) solution of tert-butyl 4-(4-(4-(((benzyloxy)carbonyl)amino)piperidin-1-yl)-3-(6-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazine-1-carboxylate (249 mg, 1 Eq, 330 µmol) was added TFA (1 mL). The resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was

concentrated under vacuum. This resulted in crude benzyl (1-(3-(6-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-(piperazin-1-yl)pyridin-4-yl)piperidin-4-yl)carbamate (200 mg, 306 μmol, 92.6%) as a brown solid. This material was used for next step without further purification. MS (M+H)=654.2.

[00342] **Step-4**: 2,2-dimethyl-4-oxo-3,8,11,14,17-pentaoxa-5-azaicosan-20-oic acid (72.1 mg, 1.00 Eq, 197 μmol), 4-methylmorpholine (120 mg, 6.02 Eq, 1.19 mmol) was combined with perfluorophenyl diphenylphosphinate (182 mg, 2.40 Eq, 474 μmol) and DMF (1 mL). The resulting mixture was stirred at 25 °C for 10 min, followed by the addition of crude benzyl (1-(3-(6-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-(piperazin-1-yl)pyridin-4-yl)piperidin-4-yl)carbamate (258 mg, 2 Eq, 394 μmol). The reaction mixture was stirred at ambient temperature for additional 1 h. The reaction crude was purified by Prep-HPLC using the following conditions: Column, C18 silica gel; mobile phase, Water (0.1% TFA) and ACN (50.0% ACN up to 85.0% in 12 min); Total flow rate, 70 mL/min; Detector, UV 220 nm. This resulted in tert-butyl (15-(4-(4-(4-(((benzyloxy)carbonyl)amino)piperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-15-oxo-3,6,9,12-tetraoxapentadecyl)carbamate (300 mg, 300 μmol, 152%) as a white solid. MS (M+H)=1001.2.

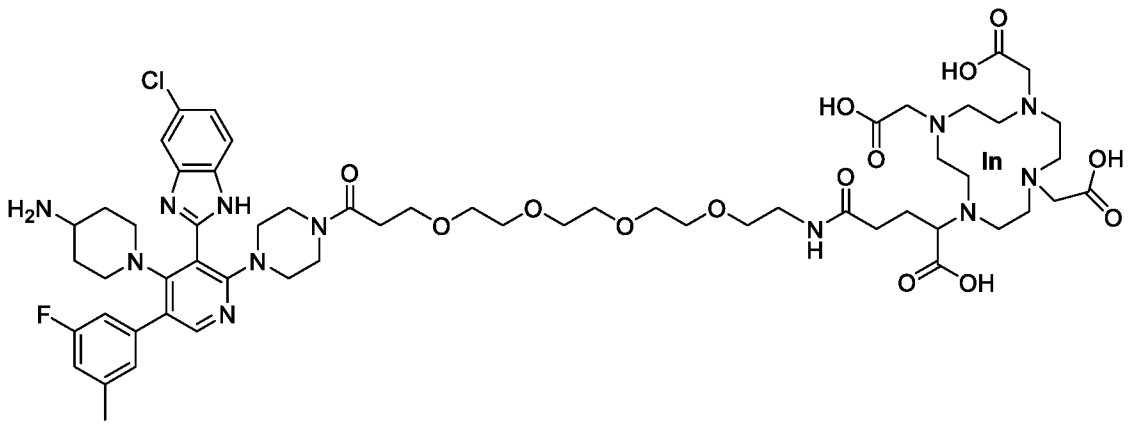
[00343] **Step-5**: To a DCM (3 mL) solution of tert-butyl (15-(4-(4-(4-(((benzyloxy)carbonyl)amino)piperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-15-oxo-3,6,9,12-tetraoxapentadecyl)carbamate (298 mg, 1 Eq, 298 μmol) was added TFA (1 mL). The resulting solution was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under vacuum and the remaining residue was purified by prep-HPLC using the following conditions: Column, SunFire Prep C18 OBD Column, 19*150 mm 5 um; mobile phase, Water (0.05% TFA) and ACN (30.0% ACN up to 50.0% in 7 min); Total flow rate, 20 mL/min; Detector, UV 220 nm. This resulted in benzyl (1-(2-(4-(1-amino-3,6,9,12-tetraoxapentadecan-15-oyl)piperazin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl)piperidin-4-yl)carbamate (250 mg, 277 μmol, 93.2%) as a yellow solid. MS (M+H)=901.4.

[00344] **Step-6**: Into a 8-mL vial, was placed a mixture of 5-(tert-butoxy)-5-oxo-4-(4,7,10-tris(2-(tert-butoxy)-2-oxoethyl)-1,4,7,10-tetraazacyclododecan-1-yl)pentanoic acid (97.2 mg, 1.00 Eq, 139 μmol), perfluorophenyl diphenylphosphinate (63.9 mg, 1.20 Eq, 166 μmol), 4-methylmorpholine (42.1 mg, 3.00 Eq, 416 μmol), and DMF (2 mL). The resulting mixture was stirred at 25 °C for 1 h, followed by the addition of benzyl (1-(3-(6-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-(piperazin-1-yl)pyridin-4-yl)piperidin-4-yl)carbamate (258

mg, 2 Eq, 394 μmol). The reaction mixture was stirred at 25 °C for 1 hour. The reaction crude was purified by Prep-HPLC using the following conditions: Column, C18 silica gel; mobile phase, Water (0.1% TFA) and ACN (50.0% ACN up to 85.0% in 12 min); Total flow rate, 70 mL/min; Detector, UV 220 nm. This resulted in tert-butyl (15-(4-(4-(4-(((benzyloxy)carbonyl)amino)piperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-15-oxo-3,6,9,12-tetraoxapentadecyl)carbamate (230 mg, 139 μmol, 105%) as a white solid. MS (M+H)=1585.0.

[00345] **Step-7**: tri-tert-butyl 2,2',2''-(10-(24-(4-(4-(4-(((benzyloxy)carbonyl)amino)piperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-2,2-dimethyl-4,8,24-trioxo-3,12,15,18,21-pentaoxa-9-azatetracosan-5-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (230 mg, 1 Eq, 145 μmol) was combined with TFA (1 mL). The resulting mixture was stirred at 60 °C for 2 hrs and lyophilized with water (5 mL) and ACN (1 mL) to afford 4-[(15-{4-[4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl]piperazin-1-yl}-15-oxo-3,6,9,12-tetraoxapentadecan-1-yl)carbamoyl]-2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl]butanoic acid (48 mg, 39 μmol, 27 %) as a white solid. MS (M+H)=1226.6.

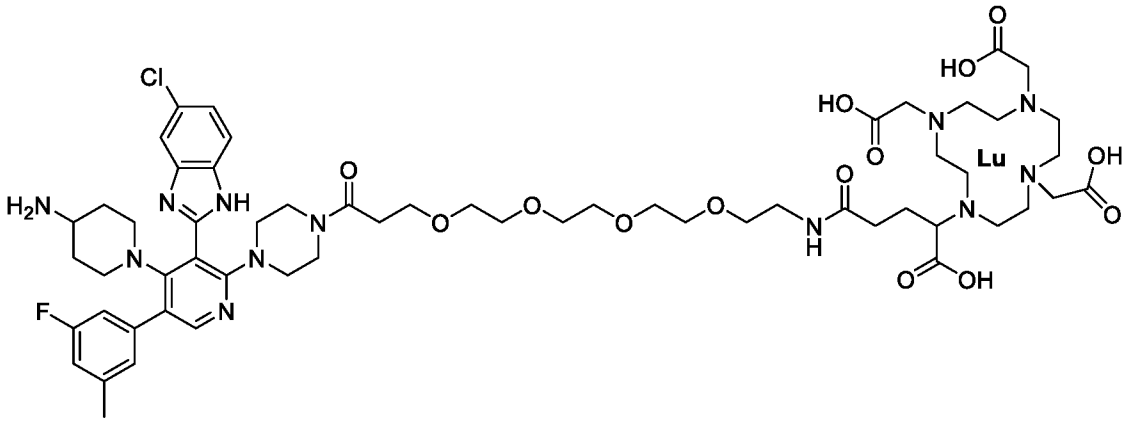
Example 12: 4-[(15-{4-[4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl]piperazin-1-yl}-15-oxo-3,6,9,12-tetraoxapentadecan-1-yl)carbamoyl]-2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl]butanoic acid Indium Complex (Compound 13)



[00346] **Step-1**: Into an 8-mL flask, was added a mixture of 2,2',2''-(10-(1-(4-(4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-20-carboxy-1,17-dioxo-4,7,10,13-tetraoxa-16-azaicosan-20-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (10 mg, 1 Eq, 8.2

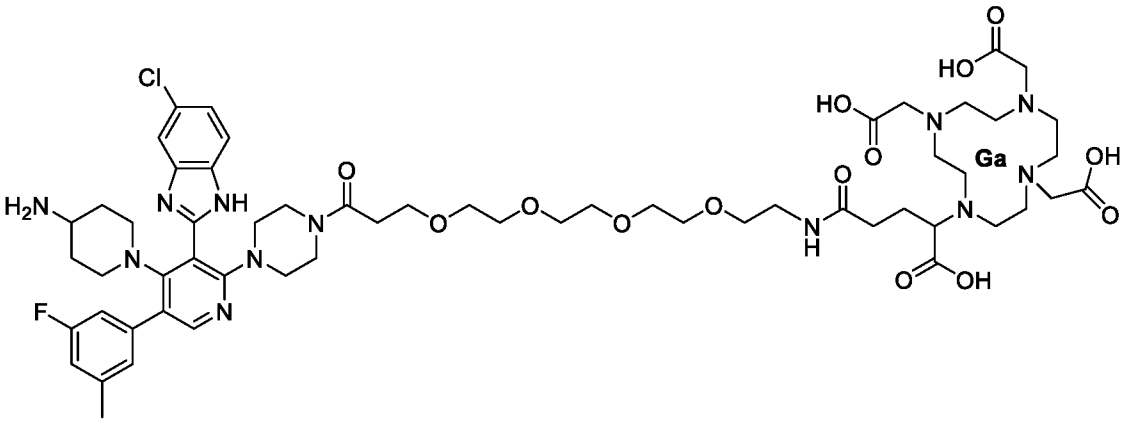
μmol), Indium trichloride (5 mg, 3 Eq, 0.02 mmol), Sodium bicarbonate (3 mg, 1 μL, 4 Eq, 0.04 mmol), Water (0.1 mL) and ACN (0.2 mL). The resulting mixture was stirred at 80 °C 2 hrs. The reaction crude was diluted with DMSO (4 mL), filtered, and the filtrate was purified by Prep-HPLC using the following conditions: Column, SunFire Prep C18 OBD Column, 19*150 mm 5 um 10 nm; mobile phase, Water (0.05% TFA) and ACN (30% ACN up to 75% in 15 min); Total flow rate, 20 mL/min; Detector, UV 220 nm. This resulted in the TFA salt of the title indium complex (6.6 mg, 4.2 μmol, 52 %) as a white solid. MS (M+H)=1337.3, 1339.3.

Example 13: 4-[(15-{4-[4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl]piperazin-1-yl}-15-oxo-3,6,9,12-tetraoxapentadecan-1-yl)carbamoyl]-2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl]butanoic acid Lutetium Complex (Compound 14)



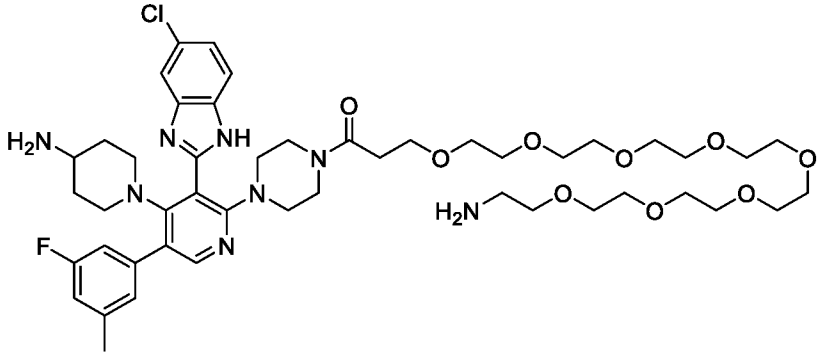
[00347] **Step-1**: Into an 8-mL flask was added a mixture of 2,2',2''-(10-(1-(4-(4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-20-carboxy-1,17-dioxo-4,7,10,13-tetraoxa-16-azaicosan-20-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (10 mg, 1 Eq, 8.2 μmol), Lutetium (III) chloride (7 mg, 3 Eq, 0.02 mmol), Sodium bicarbonate (4 mg, 2 μL, 6 Eq, 0.05 mmol), Water (0.1 mL) and ACN (0.2 mL). The resulting mixture was stirred at 80 °C for 2 hrs. The reaction crude was diluted with DMSO (4 mL), filtered, and the filtrate was purified by Prep-HPLC using the following conditions: Column, SunFire Prep C18 OBD Column, 19*150 mm 5 um 10 nm; mobile phase, Water (0.05% TFA) and ACN (30% ACN up to 75% in 15 min); Total flow rate, 20 mL/min; Detector, UV 220 nm. This resulted in the title lutetium complex (8.2 mg, 5.0 μmol, 62%) as a white solid. MS (M+H)=1398.0, 1400.0.

Example 14: 4-[(15-{4-[4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl]piperazin-1-yl}-15-oxo-3,6,9,12-tetraoxapentadecan-1-yl)carbamoyl]-2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl]butanoic acid Gallium Complex (Compound 15)



[00348] **Step-1**: Into an 8-mL flask was added a mixture of 2,2',2''-(10-(1-(4-(4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl)piperazin-1-yl)-20-carboxy-1,17-dioxo-4,7,10,13-tetraoxa-16-azaicosan-20-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (10 mg, 1 Eq, 8.2 μmol), Gallium chloride (5 mg, 3 Eq, 0.03 mmol), Sodium bicarbonate (4 mg, 2 μL, 6 Eq, 0.05 mmol), Water (0.1 mL) and ACN (0.2 mL). The reaction crude was diluted with DMSO (4 mL), filtered, and the filtrate was purified by Prep-HPLC using the following conditions: Column, SunFire Prep C18 OBD Column, 19*150 mm 5 um 10 nm; mobile phase, Water and ACN (30% ACN up to 80% in 15 min); Total flow rate, 20 mL/min; Detector, UV 220 nm. This resulted in the title gallium complex (7.2 mg, 5.6 μmol, 68%) as a white solid. MS (M+H)=1292.5, 1294.5.

Example 15: 1-amino-27-{4-[4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl]piperazin-1-yl}-3,6,9,12,15,18,21,24-octaoxaheptacosan-27-one (Compound 16)



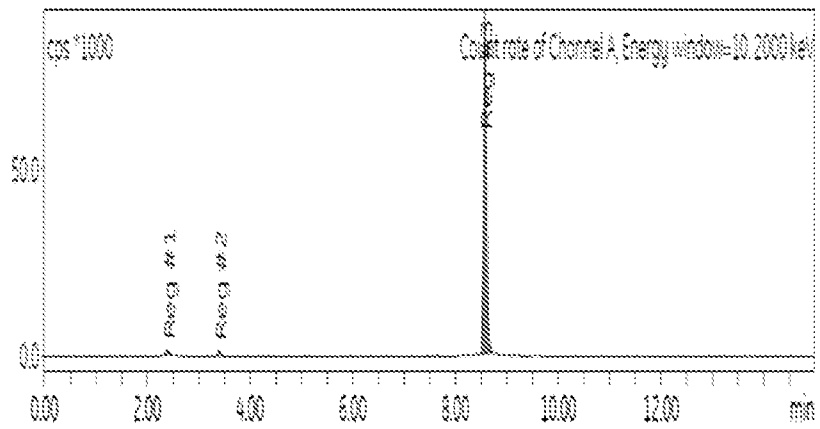
[00349] **Step-1**: To a DMF (1.5 mL) solution of 2,2-dimethyl-4-oxo-3,8,11,14,17,20,23,26,29-nonaoxa-5-azadotriacontan-32-oic acid (51 mg, 97% Wt, 1.5 Eq, 92 µmol) was added HATU (35 mg, 1.5 Eq, 92 µmol) and DIPEA (40 mg, 53 µL, 5 Eq, 0.31 mmol). The resulting mixture was stirred at room temperature for 10 minutes, followed by the addition of benzyl (1-(3-(5-chloro-1H-benzo[d]imidazol-2-yl)-5-(3-fluoro-5-methylphenyl)-2-(piperazin-1-yl)pyridin-4-yl)piperidin-4-yl)carbamate (46 mg, 1 Eq, 61 µmol). The reaction mixture was stirred at 20 °C for 2 hrs. The reaction mixture was diluted with ethyl acetate, washed with water and brine, and concentrated. The remaining residue was purified by C18 reverse phase chromatography eluting with MeCN (0.1% TFA)/water (0.1% TFA). Pure fractions were combined and dried to give benzyl (1-(3-(5-chloro-1H-benzo[d]imidazol-2-yl)-2-(4-(2,2-dimethyl-4-oxo-3,8,11,14,17,20,23,26,29-nonaoxa-5-azadotriacontan-32-oyl)piperazin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl)piperidin-4-yl)carbamate (31.3 mg, 26.6 µmol, 43%) as an off-white solid. MS (M+H)=1177.9.

[00350] **Step-2**: To a DCM (1 mL) solution of benzyl (1-(3-(5-chloro-1H-benzo[d]imidazol-2-yl)-2-(4-(2,2-dimethyl-4-oxo-3,8,11,14,17,20,23,26,29-nonaoxa-5-azadotriacontan-32-oyl)piperazin-1-yl)-5-(3-fluoro-5-methylphenyl)pyridin-4-yl)piperidin-4-yl)carbamate (31.3 mg, 1 Eq, 26.6 µmol) was added TFA (1 g, 1 mL, 5e+2 Eq, 0.01 mol). The resulting mixture was stirred at 60 °C for 2 hrs. The reaction crude was concentrated and purified by C18 reverse phase chromatography eluting with MeCN (0.1% TFA)/water (0.1% TFA). Pure fractions were combined and dried to give the TFA salt of 1-amino-27-{4-[4-(4-aminopiperidin-1-yl)-3-(5-chloro-1H-1,3-benzodiazol-2-yl)-5-(3-fluoro-5-methylphenyl)pyridin-2-yl]piperazin-1-yl}-3,6,9,12,15,18,21,24-octaoxaheptacosan-27-one (15.1 mg, 16.0 µmol, 60.2%). MS (M+H)=943.6.

Example 16: ***Radiochemical synthesis of the ^{111}In[In]-Complex of Compound 1***

[00351] [^{111}In]$InCl_3$ (20.7 MBq, 40.0 µL, 0.1 M HCl) and **Compound 1** (2.9 nmol, 2.9 µL, 1.0 mM in deionized (DI) water) were added to a NH_4OAc solution (4.0 µL, 1.0 M). The resulting mixture was heated at 85 °C in a thermal mixer for 30 min. At the end of labeling, Ca-DTPA (4.0 µL, 4 mM) was added. The radiochemical purity was 97.1% determined by RP-HPLC. The radiotracer solution for in vivo studies was prepared by dilution with 0.9% saline.

HPLC chromatogram of the ^{111}In[In]-Complex of Compound 1.



iTLC radiochromatogram of the ^{111}In[In]-Complex of Compound 1.



Example A-1: Parenteral Pharmaceutical Composition

[00352] To prepare a parenteral pharmaceutical composition suitable for administration by injection (subcutaneous, intravenous), 0.001-500 mg of a compound Formula (I), or a pharmaceutically acceptable salt or solvate thereof, is dissolved in sterile water and then mixed with 10 mL of 0.9% sterile saline. A suitable buffer is optionally added as well as optional acid or base to adjust the pH. The mixture is incorporated into a dosage unit form suitable for administration by injection

Biology Examples

Example B-1: SSTR assays

Functional assay for SSTR2 agonists

[00353] General overview: All five SSTR subtypes are Gi coupled G-protein coupled receptors (GPCRs) that lead to decreases in intracellular cyclic AMP (cAMP) when activated by an agonist. Therefore, measurement of intracellular cAMP levels can be used to assess whether compounds of the invention are agonists of SSTR subtypes (John Kelly, Troy Stevens,W. Joseph

Thompson, and Roland Seifert, *Current Protocols in Pharmacology,* 2005,2.2.1-2.2). One example of an intracellular cAMP assay is described below.

cAMP assay protocol

[00354] Four days prior to the assay, 5,000 Chinese hamster ovary cells (CHO-K1, ATCC #CCL-61) stably expressing the human somatostatin receptor subtype 2 are plated in each well of a 96-well tissue culture-treated plate in Ham's F12 growth media (ThermoFisher #10-080-CM) supplemented with 10% donor bovine serum (Gemini Bio-Products #100-506), 100 U/mL penicillin; 100 ug/mL streptomycin; 2 mM L-glutamine (Gemini Bio-Products #400-110) and 0.2 mg/mL hygromycin B (GoldBio #31282-04-9). The cells are cultured at 37 °C, 5% CO_2 and 95% humidity. On the day of the assay, the media is aspirated and the cells are treated with 50 µL of 1.6 µM NKH477 (Sigma #N3290) plus various dilutions of compounds of the invention in assay buffer [lx Hank's Balanced Salt Solution (ThermoFisher #SH3058802), 0.5 mM HEPES pH 7.4, 0.1% bovine serum albumin, 0.2 mM 3-Isobutyl-1-methylxanthine (IBMX, VWR #200002-790)]. The cells are incubated for 20 minutes at 37 °C (the final concentration of the compounds of the invention are typically 0 - 10,000 nM). The cells are treated with 50 µL of lysis buffer (HRTF cAMP kit, Cisbio). The lysate is transferred to 384-well plates and cAMP detection and visualization antibodies are added and incubated for 1-24 hours at room temperature. The time-resolved fluorescent signal is read with a Tecan M1000Pro multiplate reader. The intracellular cAMP concentrations are calculated by regression to a standard curve and are plotted vs. the concentration of the compounds of the invention and the EC_{50} of the compounds are calculated using standard methods. All data manipluations are in GraphPad Prism v8 (GraphPad, San Diego, CA).

Example B-2: GnRHR assays

Functional assay for GnRHR

[00355] General overview: GnRHR is a $G_{q/11}$-coupled receptor that mediates the action of the GnRH hoprmone by activating the phosphatidylinositol-calcium second messanger system. Activation of the GnRHR induces the accumulation of inositol monophosphate, a stable metabolite of IP-3, that can be characterized as a measure of agonistic activity (increase in IP-One) or antagonistic activity (blockade of IP-One accumulation) by compounds of the invention. One example of an intracellular IP-One assay used to characterize GnRHR antagonists is described below.

IP-One assay protocol

24 hours prior to the assay, 30,000 FlpIn T-Rex 293 Cells (ThermoFisher #R78007) stably expressing the functional human GnRH receptor upon induction with tetracycline were plated in

a 96-well tissue culture-treated plate in FlpIn T-Rex 293 Growth Medium [DMEM (Corning #10-013-CM) supplemented with 10% fetal bovine serum (Gemini Bio-Products #900-208), 100 U/mL penicillin; 100 µg/mL streptomycin; 2 mM L-glutamine (Gemini Bio-Products #400-110)] and 50 ng/mL tetracycline hydrocholoride (Sigma, T7660). Cells were cultured at 37°C, 5% CO_2 and 95% humidity. On the day of the assay, the growth media was discarded and the cells were treated with 50 µL of a dose response curve of GnRH (Bachem #4033013) in the presence of various concentrations of fixed compound in assay buffer [10 mM HEPES (Biopioneer Cat# C0113) pH 7.4, 1 mM $CaCl_2$ (Fisher Scientific BP510-100), 0.5 mM $MgCl_2$ (Sigma M8266-100G), 4.2 mM KCl (Fisher Scientific P330-500), 146 mM NaCl (Spectrum Chemical #SO155), 5.5 mM Glucose (Sigma G7528), 50 mM LiCl (Fisher Scientific L121-100), 0.1% bovine serum albumin (Fisher Scientific Cat# BP1600)] and incubated for 1 hour at 37°C (the final concentrations of GnRH ranged from 0-250 nM and the final concentrations of the compound ranged from 0 - 10,000 nM). 50 µL of lysis buffer (HRTF IP-one kit, Cisbio) was added on top of the treatment to lyse the cells. The lysate was transferred to 384-well plates and IP-one detection and visualization antibodies were added and incubated for 1-24 hours at room temperature. The time-resolved fluorescent signal was read with a Tecan M1000Pro (Tecan) multiplate reader. The intracellular IP-one concentrations were calculated by regression to a standard curve and were plotted vs. the concentration of the GnRH agonists in the presence of various concentrations of antagonist and the K_B of the compounds were calculated using standard curve-fitting methods. All data manipulations were performed using GraphPad Prism v8 (GraphPad, San Diego, CA).

[00356] Illustrative biological activity of compounds is demonstrated in the following Table.

Biological activity

Compound #	hSST2 EC50 (nM)
1	+
2	+
3	+
4	+
5	+
6	+
7	+
8	+
9	+
10	+

Compound #	hSST2 EC50 (nM)
11	+
12	+
13	+
14	+
15	+
16	+

+ = less than 10 nM

[00357] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof:

NP – L - Q

Formula (I)

wherein:

NP is a non-peptide ligand that binds to G protein-coupled receptor (GPCR) expressed in tumor cells;

Q is a payload moiety comprising a chelating moiety or a radionuclide (**Z**) complex thereof; and

L is a linker that covalently connects the non-peptide ligand **NP** and the payload moiety **Q**;

wherein the linker **L** is attached to **NP** at a position that permits binding of **NP** to the GPCR; wherein upon administration to a mammal, the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is targeted to tumor cells expressing the GPCR; and wherein the GPCR is a peptide GPCR and the native ligand for the peptide GPCR is a peptide ligand that is not neurotensin.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the GPCR is a peptide GPCR and the native ligand for the peptide GPCR is an endogenous peptide or protein hormone or a chemokine.

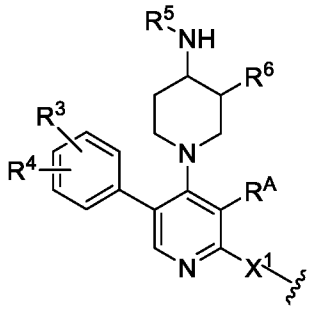
3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the GPCR is a peptide GPCR and the native ligand for the peptide GPCR is a peptide or protein hormone that is: adrenocorticotropic hormone (ACTH), amylin, angiotensin, atrial natriuretic peptide (ANP), calcitonin, cholecystokinin (CCK), gastrin, ghrelin, glucagon, growth hormone (GH), follicle-stimulating hormone (FSH), insulin, leptin, melanocyte-stimulating hormone (MSH), Neuropeptide Y, oxytocin, parathyroid hormone (PTH), prolactin, renin, somatostatin, thyroid-stimulating hormone (TSH), thyrotropin-releasing hormone (TRH), vasopressin, or vasoactive intestinal peptide (VIP).

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein the GPCR is: angiotensin receptor; apelin receptor; bombesin receptor; bradykinin receptor; calcitonin receptor; chemokine receptor; cholecytokinin receptor; corticotropic-releasing factor receptor; galanin receptor; ghrelin receptor; glucagon receptor; glycoprotein hormone receptor; gonadotropin-releasing hormone receptor; kisspeptin receptor; melanocortin receptor; motilin receptor; neuromedin U receptor;

neuropeptide FF/AF receptor; neuropeptide S receptor; neuropeptide W/B receptor; neuropeptide Y receptor; opioid receptor; orexin receptor; parathyroid hormone receptor; prokineticin receptor; prolactin-releasing peptide receptor; QRFP receptor; relaxin family peptide receptor; somatostatin receptor; tachykinin receptor; thyrotropin-releasing hormone receptor; urotensin receptor; a vasopressin and oxytocin receptor; or VIP and PACAP receptor.

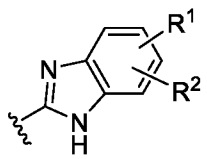
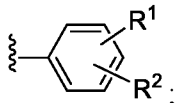
5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein: **NP** is a non-peptide ligand that binds to somatostatin receptors expressed in tumor cells, and wherein **NP** is a non-peptide ligand comprising a 4-(4-aminopiperidin-1-yl)-5-(phenyl)pyridine structural motif or a 4-[(4αS,8αS)-octahydro-1H-pyrido[3,4-b][1,4]oxazin-6-yl]-5-(phenyl)pyridine structural motif; wherein **-L-Q** is attached to **NP** at the 2-position of the pyridine.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein: **NP** has a structure of Formula (II), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof:



Formula (II)

wherein:

R^A is  or ;

each R^1, R^2, R^3 and R^4 is independently hydrogen, halogen, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4fluoroalkyl, substituted or unsubstituted C_1-C_4heteroalkyl, -CN, -N(R^7)$_2$, or -OR^7;

R^5 is hydrogen, or substituted or unsubstituted C_1-C_6alkyl;

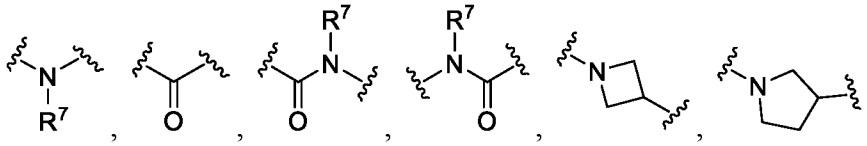
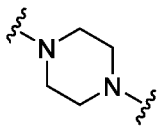
R^6 is hydrogen, -OR^7, -N(R^7)$_2$, -CN, halogen, C_1-C_6 alkyl, or C_1-C_6fluoroalkyl;

or R^5 and R^6 are taken together with the intervening atoms to which they are attached to form a morpholine; and

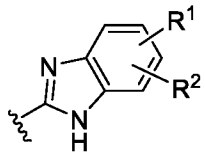
X^1 is absent, -O-, -S-, -N(R^7)-, -C(=O)-, -C(=O)N(R^7)-, -C(=O)O-, -N(R^7)C(=O)-, or a heterocycle;

each R^7 is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl.

7. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein:

X^1 is absent, -O-, -S-, , or 

8. The compound of claim 6 or 7, or a pharmaceutically acceptable salt thereof, wherein:

R^A is ;

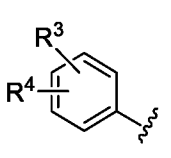
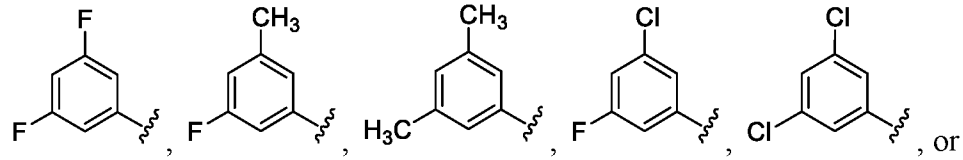
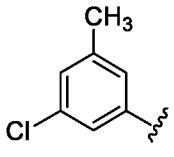
each R^1, R^2, R^3 and R^4 is independently hydrogen, F, Cl, Br, C_1-C_4alkyl, -CN, -N(R^7)$_2$, or -OR^7;

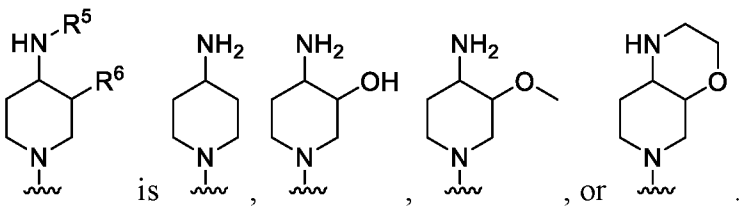
R^5 is hydrogen; R^6 is hydrogen or -OR^7; or

R^5 and R^6 are taken together with the intervening atoms to which they are attached to form a morpholine; and

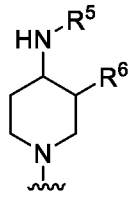
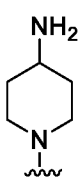
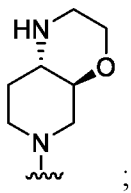
each R^7 is independently hydrogen, -CH_3, or -CH_2CH_3.

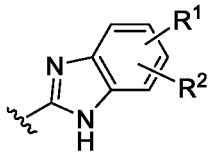
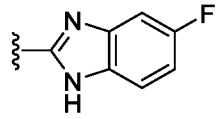
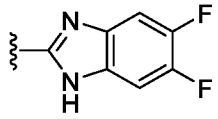
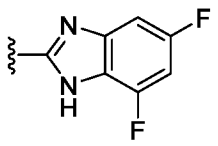
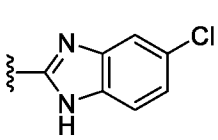
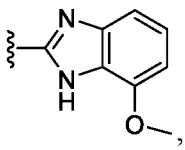
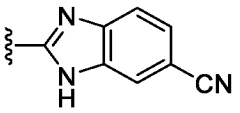
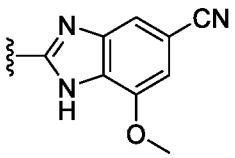
9. The compound of any one of claims 6-8, or a pharmaceutically acceptable salt thereof, wherein:

 is , or ; and

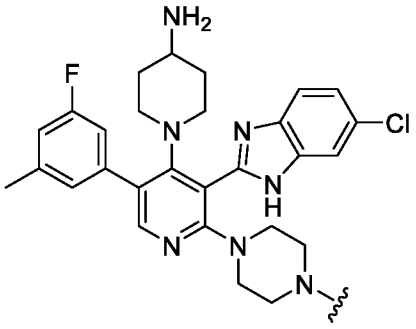
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10. The compound of any one of claims 6-9, or a pharmaceutically acceptable salt thereof,

wherein:  is  or  ; and

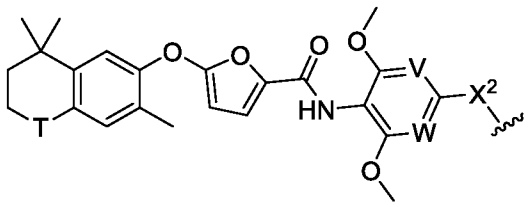
 is  ,  ,  ,  ,  ,  ,  , or  .

11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, wherein: the GPCR is the Somatostatin type 2 receptor (SSTR2); and **NP** has the following structure:

 .

12. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein: **NP** is a non-peptide ligand that binds to gonadotropin-releasing hormone receptor (GnRHR) expressed in tumor cells; and wherein **NP** is a non-peptide ligand comprising a N-{4,6-dimethoxy-pyrimidin-5-yl}-5-[3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy]-2-furamide structural motif; a N-(4,6-dimethoxypyrimidin-5-yl)-5-(3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy)-2-furamide structural motif; or a N-(4,6-dimethoxypyrimidin-5-yl)-5-((3,3,6-trimethyl-2,3-dihydro-1H-inden-5-yl)oxy)furan-2-carboxamide structural motif.

13. The compound of any one of claims 1-4 or 12, or a pharmaceutically acceptable salt thereof, wherein: **NP** has a structure of Formula (X), or a pharmaceutically acceptable salt or pharmaceutically acceptable solvate thereof:



Formula (X)

wherein:

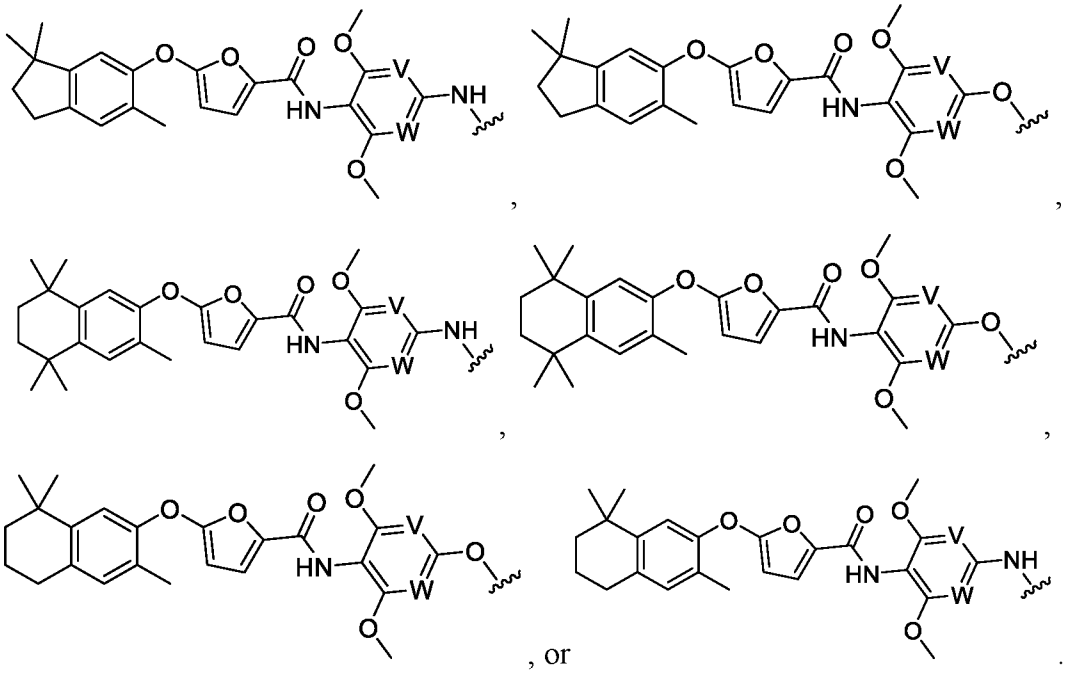
T is absent, $-CH_2-$, $-CH(CH_3)-$or $-C(CH_3)_2-$;

X^2 is absent, -O-, or $-N(R^7)-$;

V is CH or N; and W is CH or N; and

each R^7 is independently hydrogen or substituted or unsubstituted C_1-C_6alkyl.

14. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein: the GPCR is GnRHR; and **NP** has one of the following structures:



, or

15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein:

Q comprises a chelating moiety or a radionuclide (**Z**) complex thereof; and

L is a non-cleavable linker.

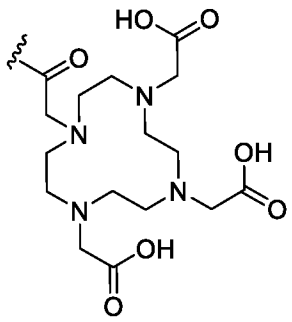
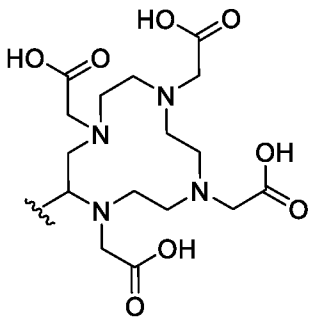
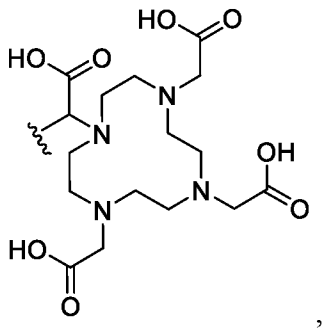
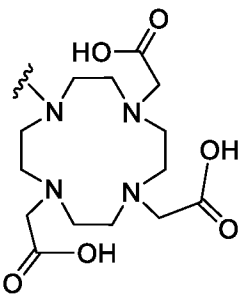
16. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein: **Q** comprises a chelating moiety or a radionuclide (**Z**) complex thereof, wherein the

chelating moiety comprises DOTA, DOTP, DOTMA, DOTAM, DTPA, NOTA, NTA, NODAGA, EDTA, DO3A, DO2A, NOC, TETA, CB-TE2A, DiAmSar, CB-Cyclam, DOTA-4AMP, H_4pypa, H_4octox, H_4octapa, p-NO_2-Bn-neunpa, or NOTP.

17. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein: **Q** comprises a chelating moiety or a radionuclide (**Z**) complex thereof, wherein the chelating moiety is:
1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA); 1,4,7,10-tetraazacyclododecane-1,4,7 -triacetic acid (DO3A); 1,4,7,10-tetraazacyclododecane-1,7-diacetic acid (DO2A); α,α',α",α'"-tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTMA); 1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane (DOTAM); 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrapropionic acid (DOTPA); 2,2',2"-(10-(2-amino-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid; benzyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (Bn-DOTA); p-hydroxy-benzyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (p-OH-Bn-DOTA); p-SCN-benzyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (p-SCN-Bn-DOTA); 6,6'-(((pyridine-2,6-diylbis(methylene))bis((carboxymethyl)azanediyl))bis(methylene))dipicolinic acid (H_4pypa); H_4pypa-benzyl; 6,6',6",6'"-(((pyridine-2,6-diylbis(methylene))bis(azanetriyl))tetrakis(methylene))-tetrapicolinic acid (H_4py4pa); H_4py4pa-benzyl; 6,6'-((ethane-1,2-diylbis((carboxymethyl)azanediyl))bis(methylene))dipicolinic acid (H_4octapa); H_4octapa-benzyl; or 3,6,9,12-tetrakis(carboxymethyl)-3,6,9,12-tetraazatetradecanedioic acid (TTHA).

18. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein **Q** comprises a chelating moiety or a radionuclide (**Z**) complex thereof, wherein the chelating moiety is: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA); or 1,4,7,10-tetraazacyclododecane-1,4,7 -triacetic acid (DO3A).

19. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein: **Q** comprises a chelating moiety or a radionuclide (**Z**) complex thereof, wherein the chelating moiety is:


,

,

,

.

20. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein:

L is absent or comprises one or more amino acids, PEG groups, -L^1-, -L^2-, -L^3-, -L^4-, -L^5-, -L^1-L^2-, -L^1-L^2-L^3-, -L^1-L^2-L^3-L^4-, -L^2-L^3-L^4-L^5-, -L^2-L^3-L^4-, -L^3-L^4-L^5-, -L^1-L^2-L^3-L^4-L^5-, or a combination thereof;

each L^1 is independently absent, unsubstituted or substituted alkylene, unsubstituted or substituted heteroalkylene, unsubstituted or substituted alkenylene, unsubstituted or substituted alkynylene, unsubstituted or substituted cycloalkylene, unsubstituted or substituted heterocycloalkylene, unsubstituted or substituted arylene, unsubstituted or substituted heteroarylene, one or more amino acids, -$(CH_2)_p$-, -C(=O)-, -$(CH_2)_p$-C(=O)-, -C(=O)-$(CH_2)_p$-, -$(CH_2)_p$-C(=O)-$(CH_2)_p$-, -C(=O)NH-, -C(=O)NH-$(CH_2)_p$-, -$(CH_2)_q$-C(=O)NH-, -$(CH_2)_p$C(=O)NH-$(CH_2)_p$-, -NHC(=O)-, -NHC(=O)-$(CH_2)_p$-, -$(CH_2)_q$-NHC(=O)-, -$(CH_2)_p$NHC(=O)-$(CH_2)_p$-, -NHC(=O)NH-, -NHC(=O)NH-$(CH_2)_p$-, -$(CH_2)_q$-NHC(=O)NH-, -$(CH_2)_p$NHC(=O)NH-$(CH_2)_p$-, each p is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

each L^2 is independently absent, -O-, -S-, -S(=O)-, -$S(=O)_2$-, -NH-, -CH(OH)-, -NHC(=O)-, -C(=O)O-, -OC(=O)-, -CH(=N)-, -CH(=N-NH)-, -CCH_3(=N)-, -CCH_3(=N-NH)-, -OC(=O)NH-, -NHC(=O)NH-, -NHC(=O)O-, -$(CH_2)_p$-, -C(=O)-$(CH_2CH_2X)_p$-, or -$(CH_2CH_2X)_p$-, each p is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

each L^3 is independently absent, unsubstituted or substituted alkylene, unsubstituted or substituted heteroalkylene, unsubstituted or substituted alkenylene, unsubstituted or substituted alkynylene, unsubstituted or substituted cycloalkylene, unsubstituted or substituted heterocycloalkylene, unsubstituted or substituted arylene, unsubstituted or substituted heteroarylene, one or more amino acids, $-(CH_2)_q-$, $-(CH_2CH_2X)_q-$, or $-(XCH_2CH_2)_q-$, each q is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

each L^4 is independently absent, -O-, -S-, -S(O)-, $-S(O)_2-$, -NH-, -CH(OH)-, -C(=O)-, -C(=O)NH-, -NHC(=O)-, -C(=O)O-, -OC(=O)-, -OC(=O)NH-, -OC(=S)NH-, -NHC(=O)NH-, -NHC(=S)NH-, -NHC(=O)O- or -NHC(=S)O-;

each L^5 is independently absent, unsubstituted or substituted alkylene, unsubstituted or substituted heteroalkylene, or unsubstituted or substituted benzylene;

each X is independently selected from O, S, and NR^X; and each R^X is independently selected from hydrogen, C_1-C_4alkyl and $-CH_2CO_2H$.

21. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, wherein: **L** is absent or a linker that is $-L^1-L^2-L^3-L^4-L^5-$;

L^1 is absent, unsubstituted or substituted alkylene, unsubstituted or substituted heteroalkylene, unsubstituted or substituted alkenylene, unsubstituted or substituted alkynylene, unsubstituted or substituted monocyclic cycloalkylene, unsubstituted or substituted monocyclic heterocycloalkylene, unsubstituted or substituted phenylene, unsubstituted or substituted monocyclic heteroarylene, one or more amino acids, $-(CH_2)_p-$, -C(=O)-, $-C(=O)-(CH_2)_p-$, -C(=O)NH-,$-C(=O)NH-(CH_2)_p-$, each p is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

L^2 is -C(=O)-, -C(=O)NH-, -C(=O)O-, $-(CH_2)_p-$, $-C(=O)-(CH_2CH_2O)_p-$, or $-(CH_2CH_2O)_p-$, each p is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

L^3 is unsubstituted or substituted alkylene, unsubstituted or substituted heteroalkylene, $-(CH_2)_q-$, each q is independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

L^4 is absent or -NH-;

L^5 is absent, unsubstituted or substituted alkylene, or unsubstituted or substituted heteroalkylene.

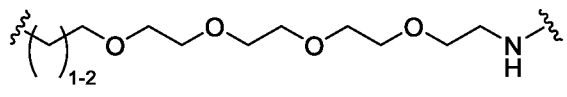
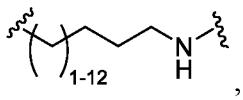
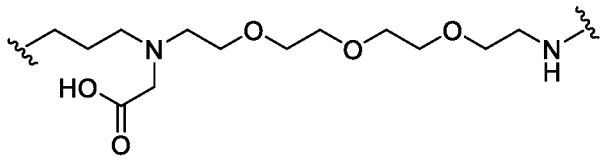
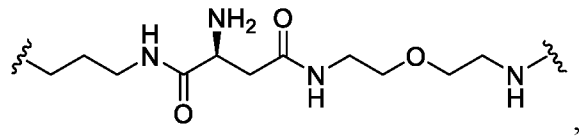
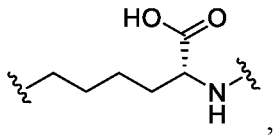
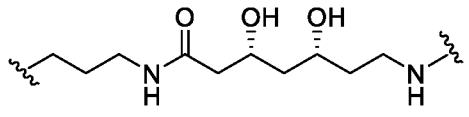
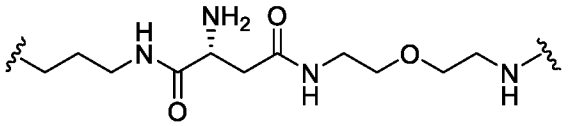
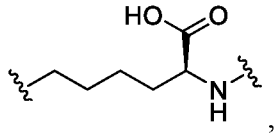
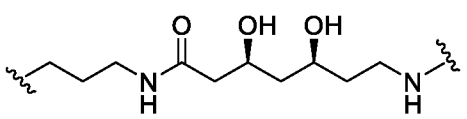
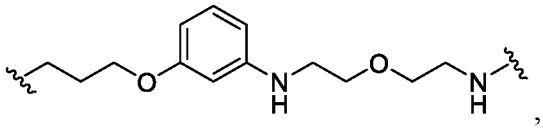
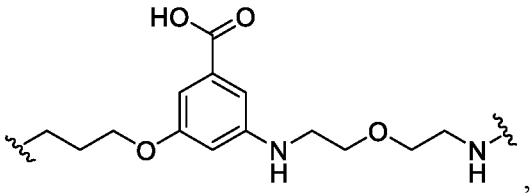
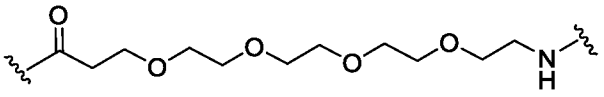
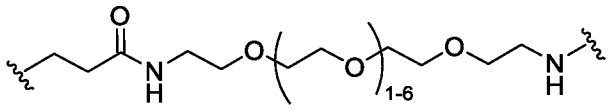
22. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein:

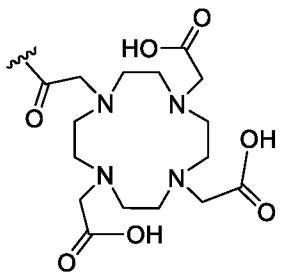
L comprises $-L^4-L^5-$;

L^4 is absent, -O-, -NH-, -C(=O)-, or -NHC(=O)-; and

L^5 is absent or C_1-C_2alkylene.

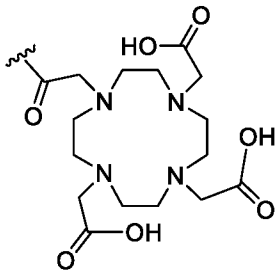
23. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein linker **L** is:












, or
; and

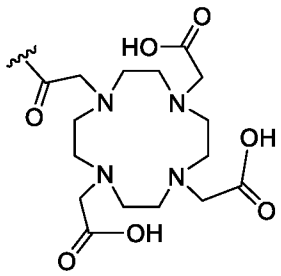
Q is: , or a radionuclide (**Z**) complex thereof.

24. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein **-L-Q** is:

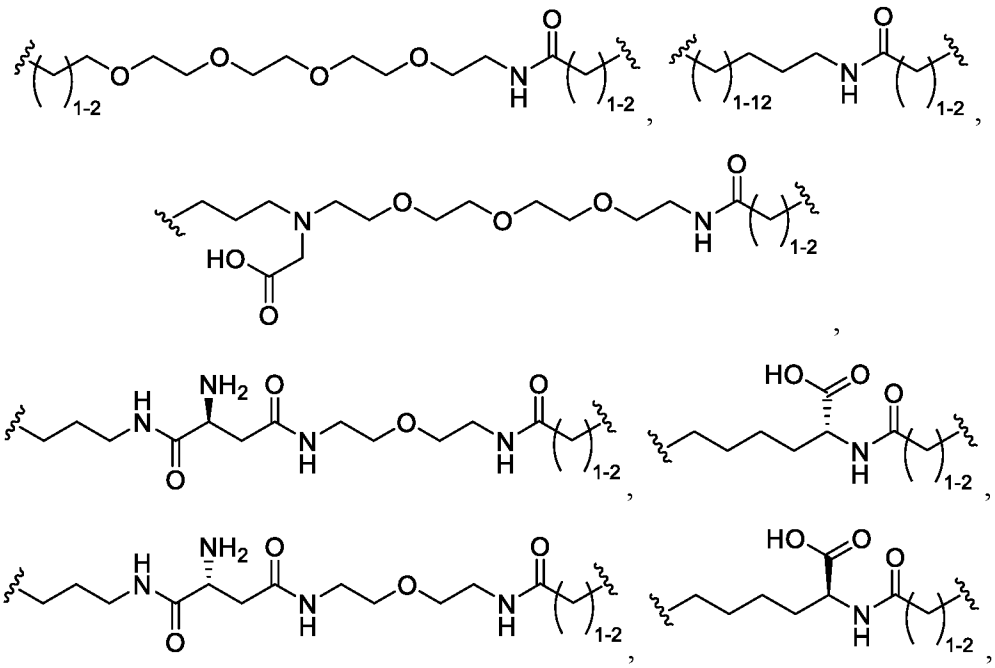
$-(CH_2)_p(CH_2)_qNH$-Q, $-(CH_2)_p(OCH_2CH_2)_pNH$-Q, $-C(=O)(CH_2)_p(CH_2)_qNH$-Q, $-C(=O)(CH_2)_p(OCH_2CH_2)_pNH$-Q, $-C(=O)CH(NH_2)CH_2C(=O)NHCH_2CH_2OCH_2CH_2NH$-Q, or $-(C_2$-C_4alkylene$)(NR^XCH_2CH_2)_p(OCH_2CH_2)_qNH$-Q; and

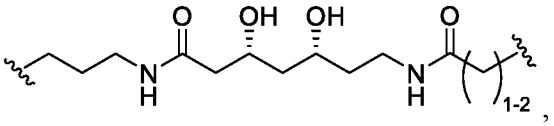
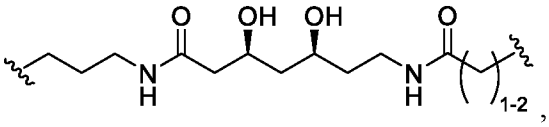
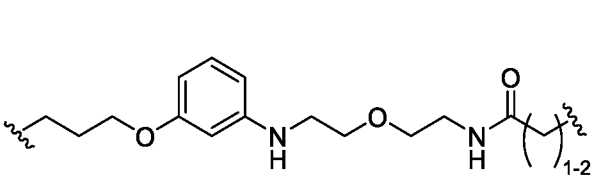
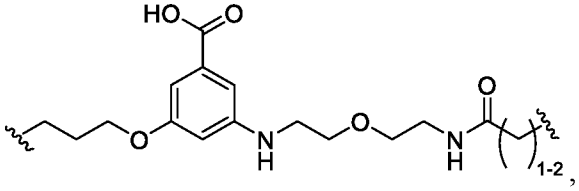
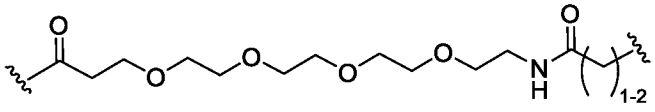
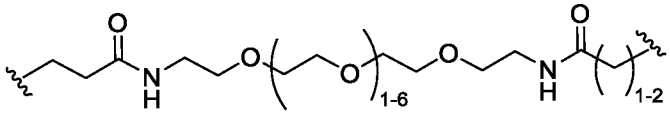
Q is:  , or a radionuclide (**Z**) complex thereof.

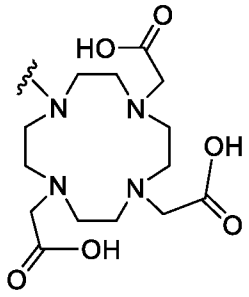
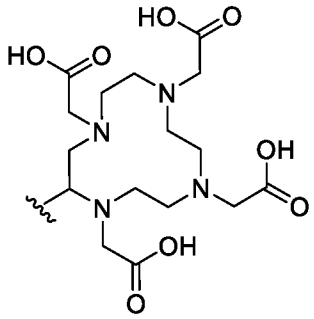
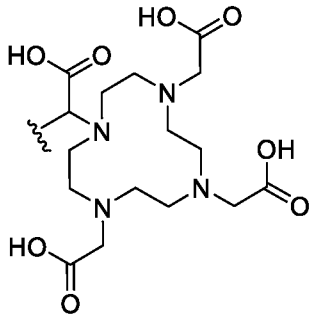
25. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein -**L**-**Q** is: -$(CH_2)_p(CH_2)_6NH$-Q, -$CH_2CH_2(OCH_2CH_2)_4NH$-Q, -$CH_2CH_2CH_2(OCH_2CH_2)_4NH$-Q, -$C(=O)(CH_2)_p(CH_2)_6NH$-Q, -$C(=O)CH_2CH_2(OCH_2CH_2)_4NH$-Q, -$C(=O)CH(NH_2)CH_2C(=O)NHCH_2CH_2OCH_2CH_2NH$-Q, or -($C_2$-$C_4$alkylene)$N(CH_2CO_2H)CH_2CH_2(OCH_2CH_2)_3NH$-Q; and

Q is:  , or a radionuclide (**Z**) complex thereof.

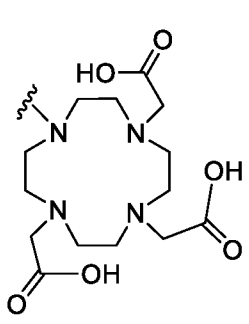
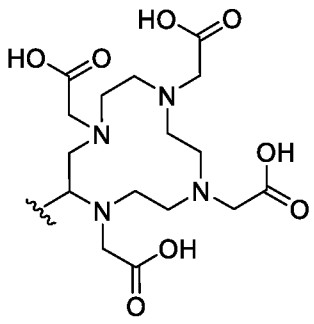
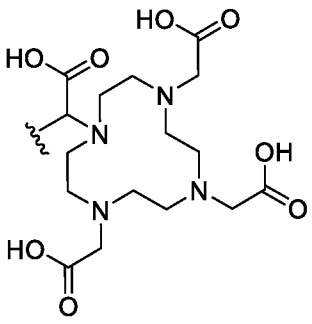
26. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein linker **L** is:



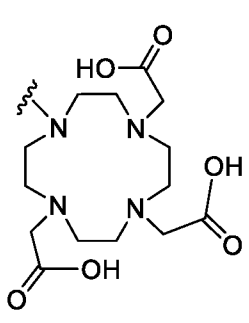
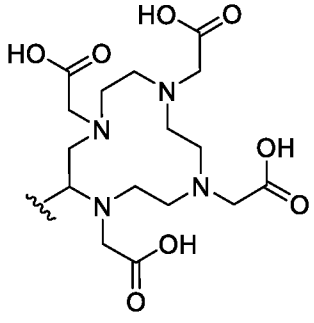
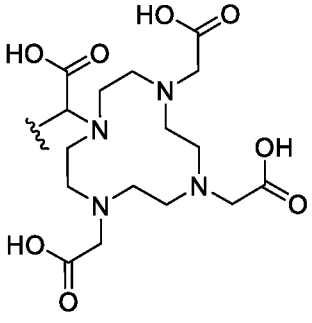

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, or

; and

Q is:

,

or

, or a radionuclide (**Z**) complex thereof.

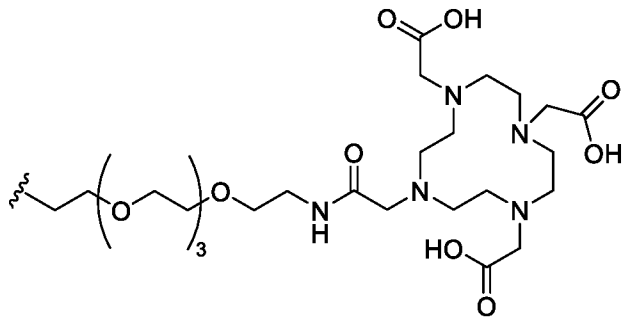
27. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein -**L**-**Q** is: $-(CH_2)_p(CH_2)_qNHC(=O)CH_2Q$, $-(CH_2)_p(CH_2)_qNHC(=O)CH_2CH_2Q$, $-(CH_2)_p(OCH_2CH_2)_pNHC(=O)CH_2Q$, $-(CH_2)_p(OCH_2CH_2)_pNHC(=O)CH_2CH_2Q$, $-C(=O)(CH_2)_p(CH_2)_qNH\ C(=O)CH_2Q$, $-C(=O)(CH_2)_p(CH_2)_qNH\ C(=O)CH_2CH_2Q$, $-C(=O)(CH_2)_p(OCH_2CH_2)_pNHC(=O)CH_2Q$, $-C(=O)(CH_2)_p(OCH_2CH_2)_pNHC(=O)CH_2CH_2Q$, $-C(=O)CH(NH_2)CH_2C(=O)NHCH_2CH_2OCH_2CH_2NHC(=O)CH_2Q$, $-C(=O)CH(NH_2)CH_2C(=O)NHCH_2CH_2OCH_2CH_2NHC(=O)CH_2CH_2Q$, $-(C_2\text{-}C_4\text{alkylene})(NR^XCH_2CH_2)_p(OCH_2CH_2)_qNHC(=O)CH_2Q$ or $-(C_2\text{-}C_4\text{alkylene})(NR^XCH_2CH_2)_p(OCH_2CH_2)_qNHC(=O)CH_2CH_2Q$; and

Q is: ,  or , or a radionuclide (**Z**) complex thereof.

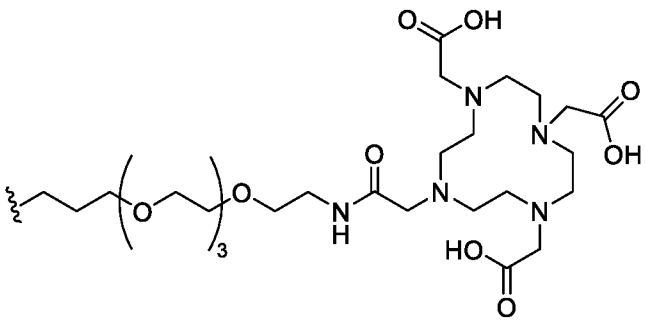
28. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein **-L-Q** is: $-(CH_2)_p(CH_2)_6NHC(=O)CH_2Q$, $-(CH_2)_p(CH_2)_6NHC(=O)CH_2CH_2Q$, $-CH_2CH_2(OCH_2CH_2)_4NHC(=O)CH_2Q$, $-CH_2CH_2(OCH_2CH_2)_4NHC(=O)CH_2CH_2Q$, $-CH_2CH_2CH_2(OCH_2CH_2)_4NHC(=O)CH_2Q$, $-CH_2CH_2CH_2(OCH_2CH_2)_4NHC(=O)CH_2CH_2Q$, $-C(=O)(CH_2)_p(CH_2)_6NHC(=O)CH_2Q$, $-C(=O)(CH_2)_p(CH_2)_6NHC(=O)CH_2CH_2Q$, $-C(=O)CH_2CH_2(OCH_2CH_2)_4NHC(=O)CH_2Q$, $-C(=O)CH_2CH_2(OCH_2CH_2)_4NHC(=O)CH_2CH_2Q$, $-C(=O)CH(NH_2)CH_2C(=O)NHCH_2CH_2OCH_2CH_2NHC(=O)CH_2Q$, $-C(=O)CH(NH_2)CH_2C(=O)NHCH_2CH_2OCH_2CH_2NHC(=O)CH_2CH_2Q$, $-(C_2\text{-}C_4\text{alkylene})N(CH_2CO_2H)CH_2CH_2(OCH_2CH_2)_3NHC(=O)CH_2Q$, or $-(C_2\text{-}C_4\text{alkylene})N(CH_2CO_2H)CH_2CH_2(OCH_2CH_2)_3NHC(=O)CH_2CH_2Q$; and

Q is: ,  or , or a radionuclide (**Z**) complex thereof.

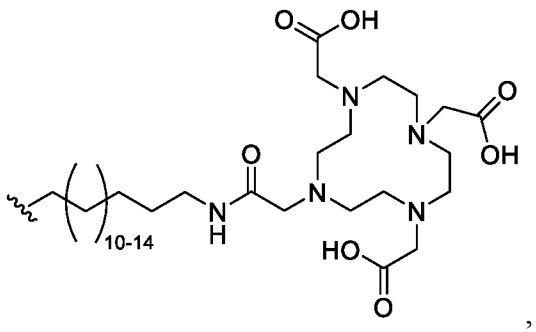
29. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein **-L-Q** is:



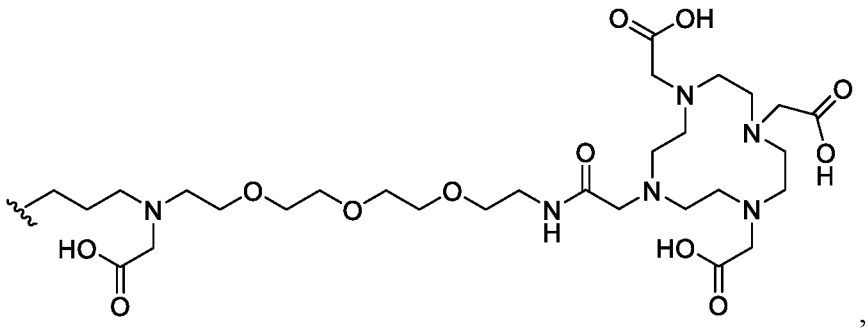
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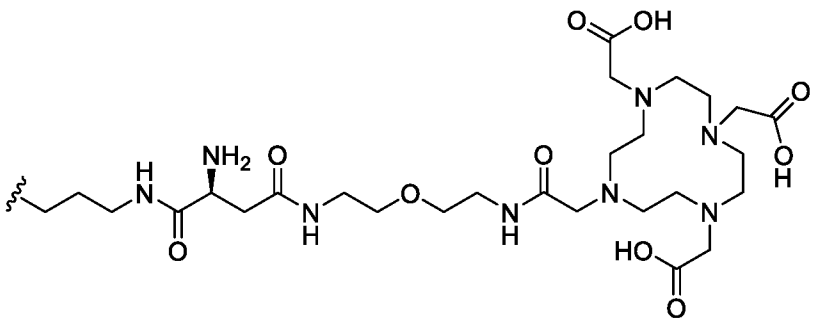
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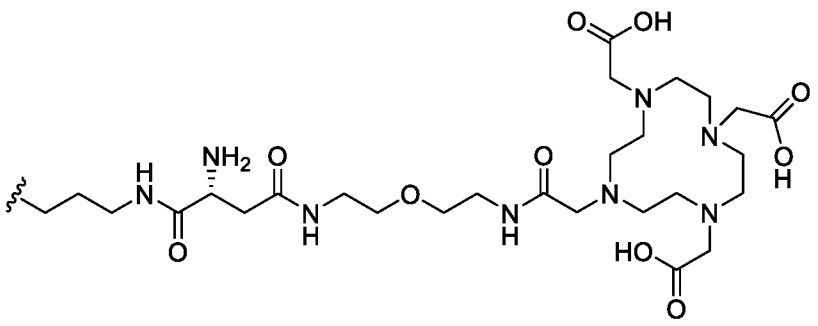
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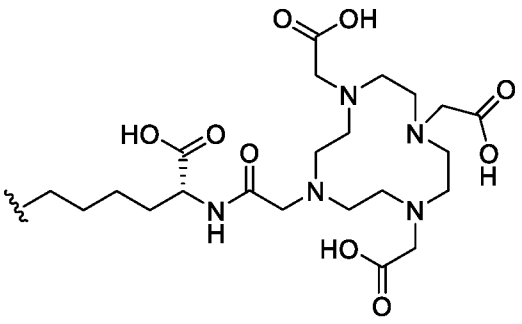
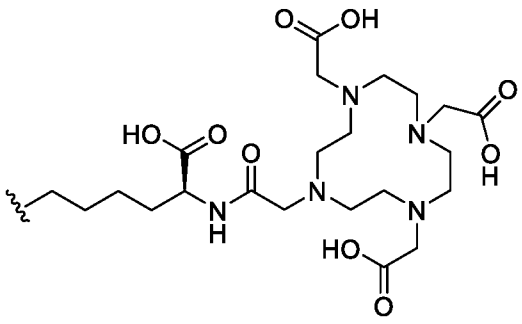
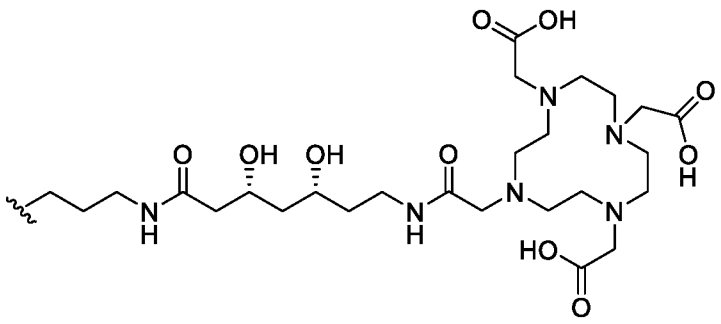
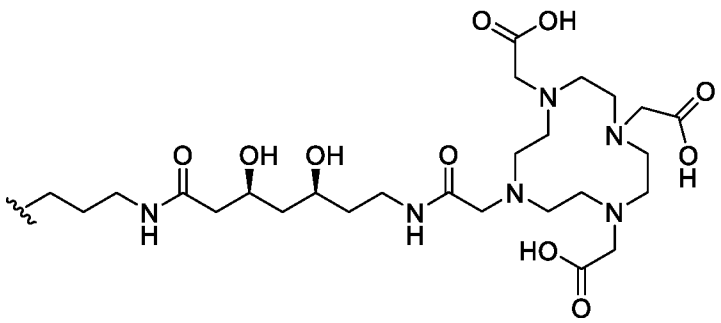
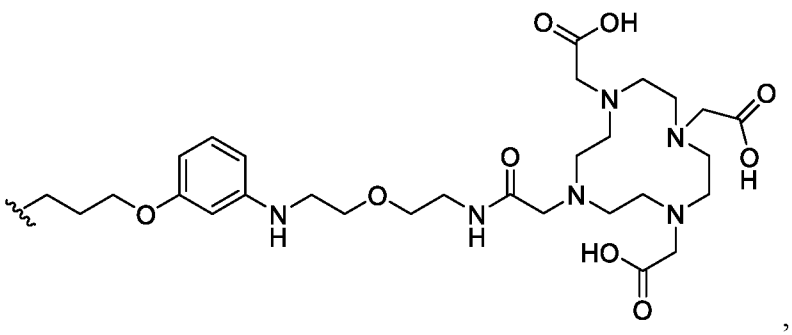
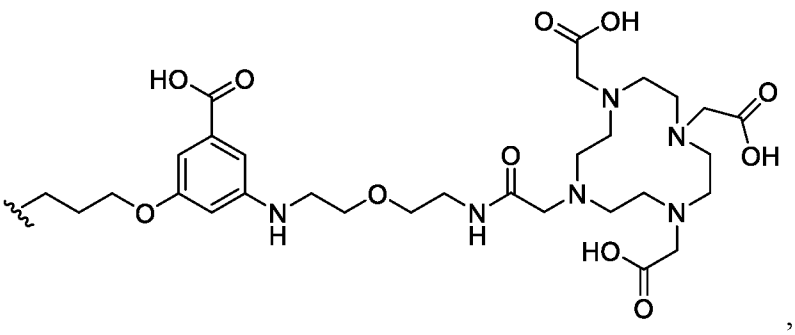
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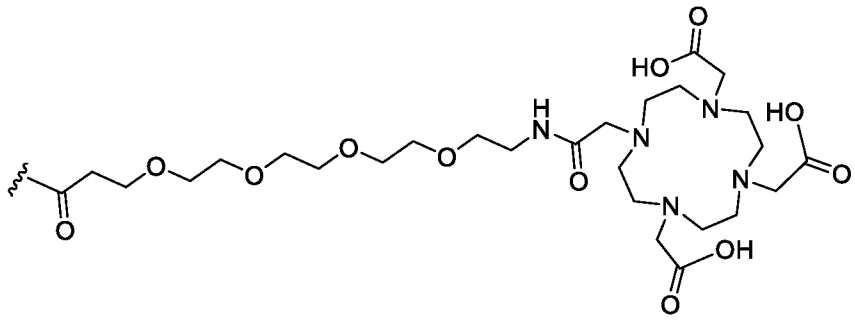


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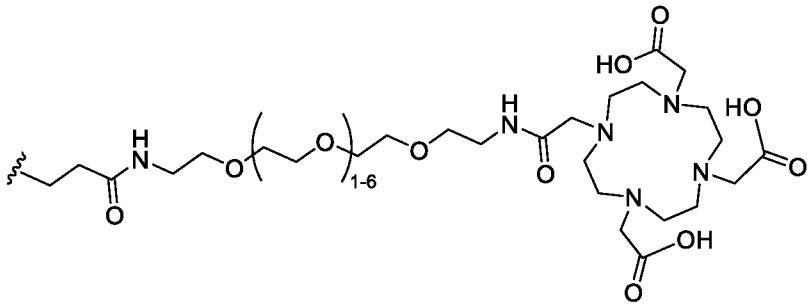


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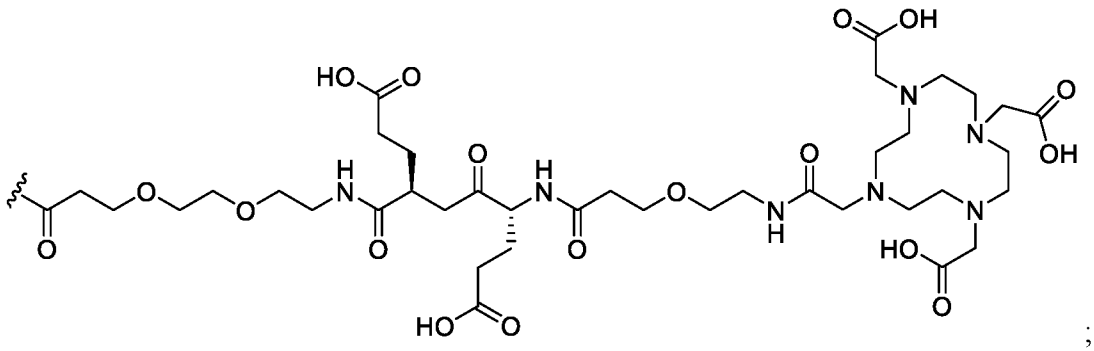

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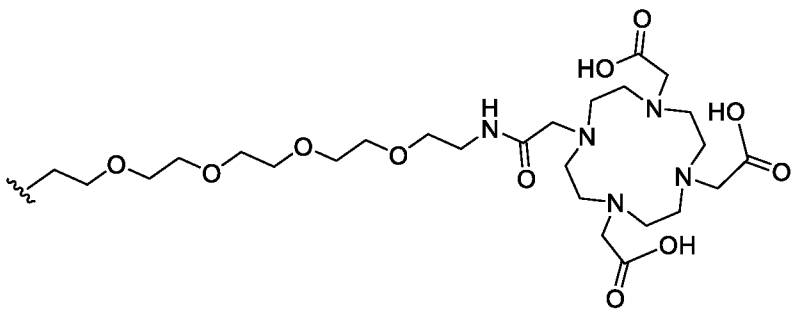
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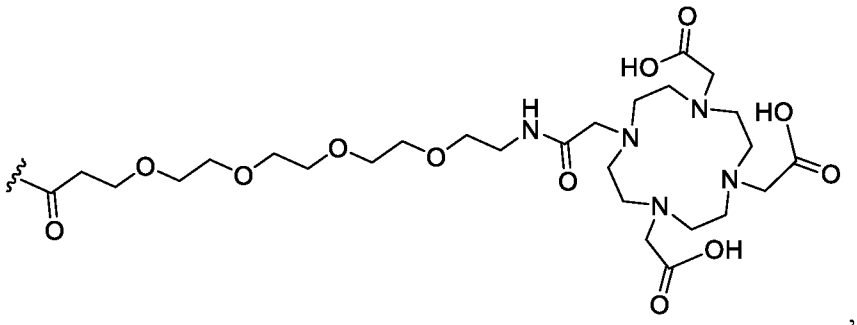
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or a radionuclide (**Z**) complex thereof.

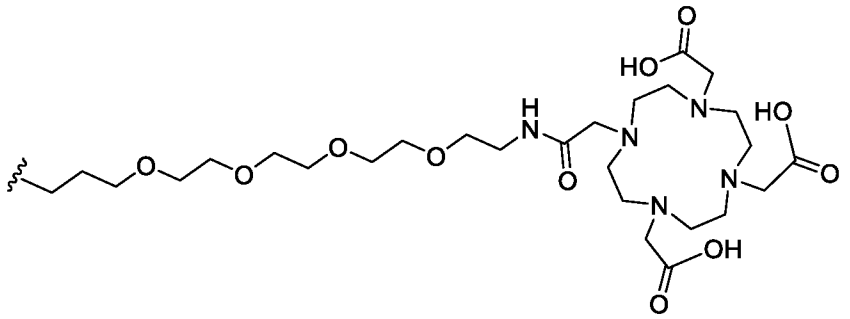
30. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt thereof, wherein **-L-Q** is:



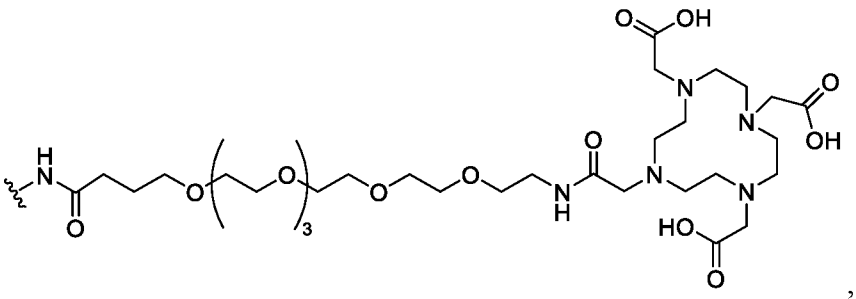
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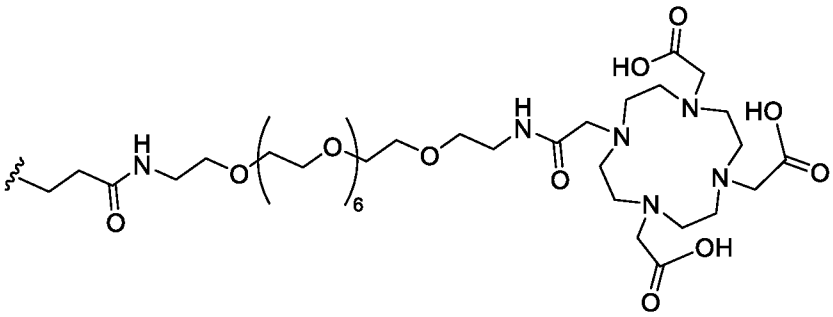
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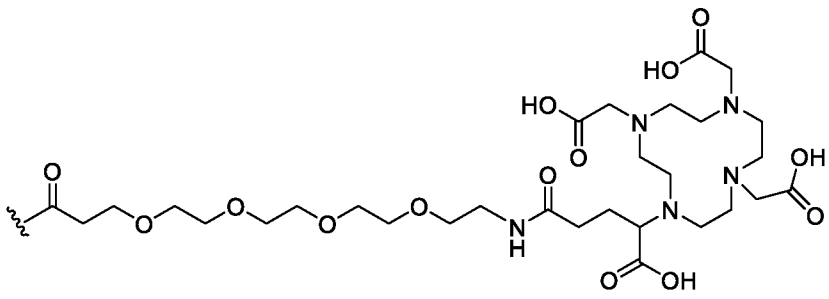
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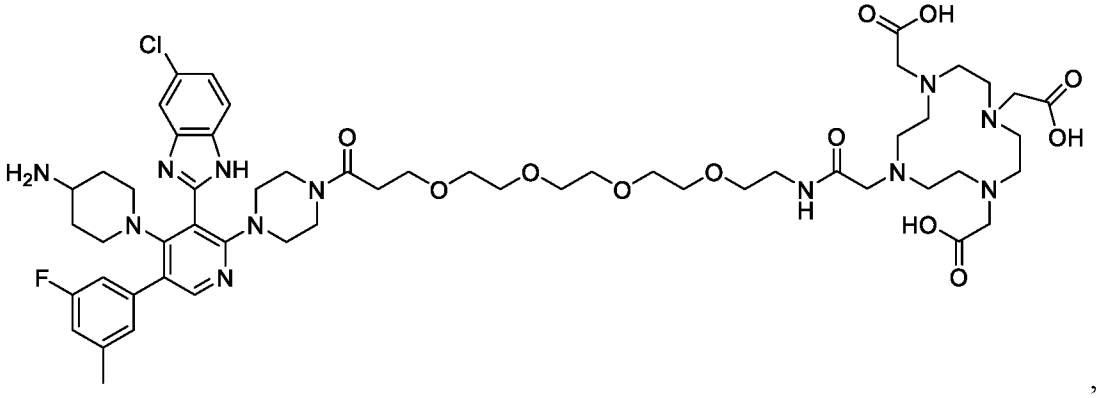
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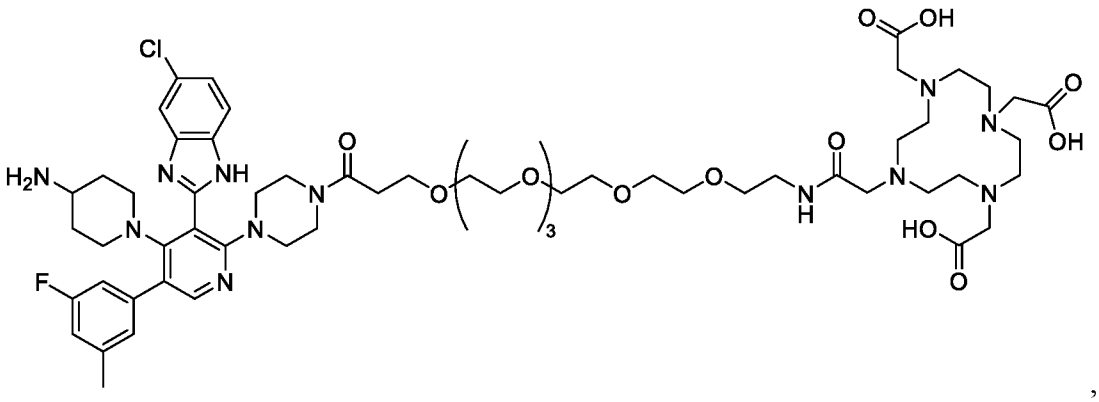
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or a radionuclide (**Z**) complex thereof

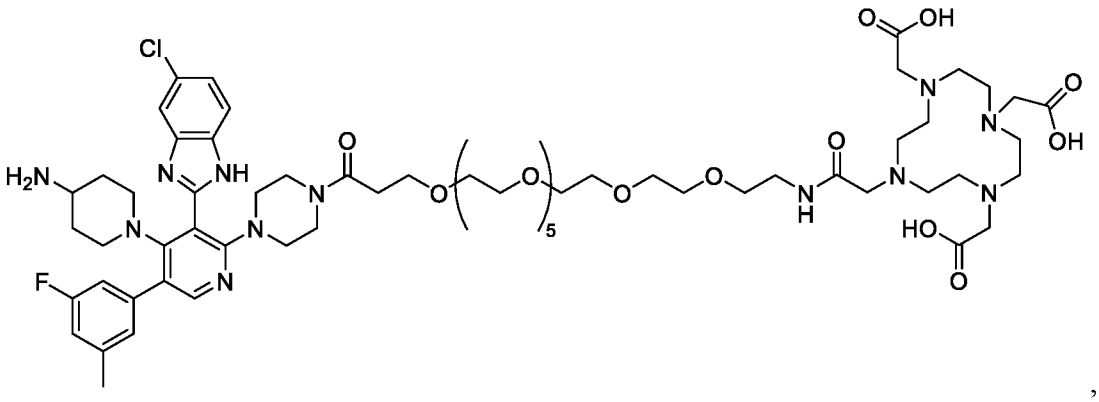
31. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, has one of the following structures:



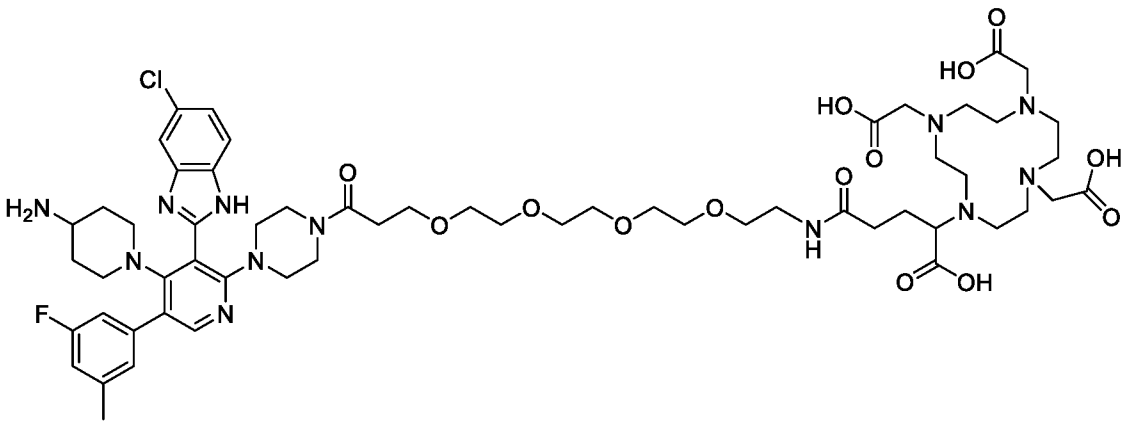
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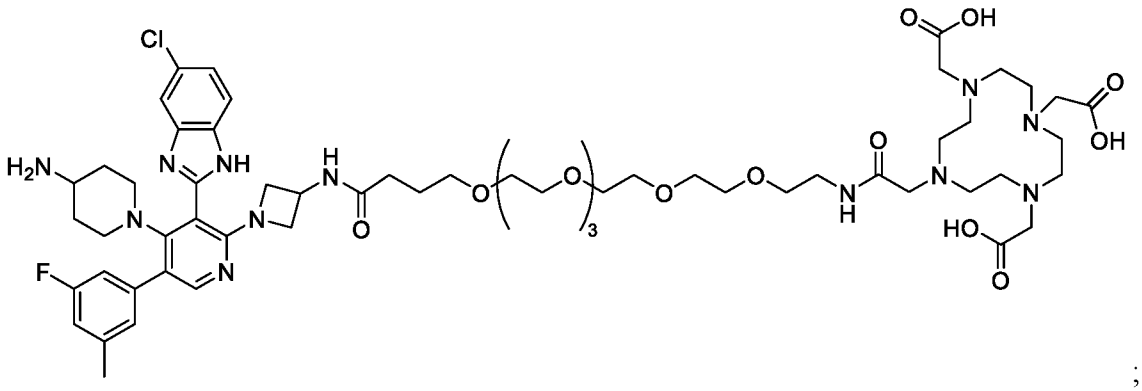
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;

or a radionuclide (**Z**) complex thereof.

32. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein: **Z** is a diagnostic or therapeutic radionuclide.

33. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein: **Z** is an Auger electron-emitting radionuclide, α-emitting radionuclide, β-emitting radionuclide, or γ-emitting radionuclide.

34. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein:

Z is an Auger electron-emitting radionuclide that is 111-indium (^{111}In), 67-gallium (^{67}Ga), 68gallium (^{68}Ga), 99m-technetium (^{99m}Tc), or 195m-platinum (^{195m}Pt); or

Z is an α-emitting radionuclide that is 225-actinium (^{225}Ac), 213-bismuth (^{213}Bi), 223-Radium (^{223}Ra), or 212-lead (^{212}Pb); or

Z is a β-emitting radionuclide that is 90-yttrium (^{90}Y), 177-lutetium (^{177}Lu), 186-rhenium (^{186}Re), 188-rhenium (^{188}Re), 64-copper (^{64}Cu), 67-copper (^{67}Cu), 153-samarium (^{153}Sm), 89-strontium (^{89}Sr), 198-gold (^{198}Au), 169-Erbium (^{169}Er), 165-dysprosium (^{165}Dy), 99m-technetium (^{99m}Tc), 89-zirconium (^{89}Zr), or 52-manganese (^{52}Mn); or

Z is a γ-emitting radionuclide that is 60-cobalt (^{60}Co), 103-palldium (^{103}Pd), 137-cesium (^{137}Cs), 169-ytterbium (^{169}Yb), 192-iridium (^{192}Ir), or 226-radium (^{226}Ra).

35. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein: **Z** is a radionuclide suitable for positron emission tomography (PET) analysis, single-photon emission computerized tomography (SPECT), or magnetic resonance imaging (MRI).

36. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein: **Z** is copper-64 (^{64}Cu), gallium-68 (^{68}Ga), 111-indium (^{111}In), or technetium-99m (^{99m}Tc).

37. The compound of any one of claims 1-31, or a pharmaceutically acceptable salt thereof, wherein: **Z** is 111-indium (^{111}In), 115-indium (^{115}In), 67-gallium (^{67}Ga), 68-gallium (^{68}Ga), 70-gallium (^{70}Ga), 225-actinium (^{225}Ac), 175-lutetium (^{175}Lu) or 177-lutetium (^{177}Lu).
38. A pharmaceutical composition comprising a compound of any one of claims 1-37, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.
39. The pharmaceutical composition of claim 38, wherein the pharmaceutical composition is formulated for administration to a mammal by intravenous administration.
40. A method for the treatment of cancer comprising administering to a mammal with cancer an effective amount of a compound of any one of claims 1-37, or a pharmaceutically acceptable salt thereof, or an effective amount of pharmaceutical composition of claim 38 or claim 39.
41. A method for treating tumors with a radionuclide comprising administering to a mammal with tumors an effective amount of a compound of any one of claims 1-37, or a pharmaceutically acceptable salt thereof, or an effective amount of pharmaceutical composition of claim 38 or claim 39.
42. The method of claim 40 or claim 41, wherein the mammal has anal cancer, bladder cancer, bowel cancer, brain cancer, breast cancer, colon cancer, colorectal cancer, endometrial cancer, esophageal cancer, gallbladder cancer, gastric cancer, heart cancer, kidney cancer, lung cancer, liver cancer, melanoma, uterine cancer, lymphoma, ovarian cancer, pancreatic cancer, or prostate cancer.
43. The method of claim 40 or claim 41, wherein the mammal has an endocrine cancer.
44. The method of claim 43, wherein the endocrine cancer is adrenal tumors, neuroendocrine tumors, parathyroid tumors, pituitary tumors, or thyroid tumors.
45. The method of claim 40 or claim 42, wherein the mammal has neuroendocrine tumors.
46. The method of claim 40 or claim 42, wherein the mammal has somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs).
47. The method of claim 42, wherein the tumors comprise an adenoma.
48. The method of claim 47, wherein the adenoma is an adenoma of the colon, kidney, adrenal gland, thyroid, pituitary, parathyroid, liver, breast, appendix, bronchial tube, prostate, sebaceous gland, or salivary gland.

49. A method of targeting delivery of a radionuclide to tumors in a mammal comprising administering to a mammal with tumors a compound of Formula (I), or a pharmaceutically acceptable salt thereof:

NP – L - Q

Formula (I)

wherein:

NP is a non-peptide ligand that binds to a G protein-coupled receptor (GPCR) expressed in tumor cells;

Q is a payload moiety comprising a radionuclide (**Z**) and a chelator configured to bind the radionuclide (**Z**); and

L is a linker that covalently connects the non-peptide small molecule ligand **NP** and the payload moiety **Q**.

50. The method of claim 49, wherein **Z** is a diagnostic or therapeutic radionuclide.

51. The method of claim 49, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of any one of claims 1-38, or a pharmaceutically acceptable salt thereof.

52. A method for identifying tissues or organs in a mammal with tumor cells expressing a G protein-coupled receptor (GPCR) comprising:

(i) administering to the mammal a compound of Formula (I), or a pharmaceutically acceptable salt thereof:

NP – L - Q

Formula (I)

wherein:

NP is a non-peptide ligand that binds to a G protein-coupled receptor (GPCR) expressed in tumor cells;

Q is a payload moiety comprising a chelating moiety or a radionuclide (**Z**) complex thereof;

L is a linker that covalently connects the non-peptide ligand **NP** and the payload moiety **Q**; wherein the linker **L** is attached to **NP** at a position that permits binding of **NP** to the GPCR;

(ii) performing positron emission tomography (PET) analysis, single-photon emission computerized tomography (SPECT), or magnetic resonance imaging (MRI).

53. A method for the in vivo imaging of tissues or organs in a mammal with tumors comprising:

(j) administering to the mammal a compound of Formula (I), or a pharmaceutically acceptable salt thereof:

NP – L - Q

Formula (I)

wherein:

NP is a non-peptide ligand that binds to a G protein-coupled receptor (GPCR) expressed in tumor cells

Q is a payload moiety comprising a chelating moiety or a radionuclide (**Z**) complex thereof;

L is a linker that covalently connects the non-peptide ligand **NP** and the payload moiety **Q**; wherein the linker **L** is attached to **NP** at a position that permits binding of **NP** to the GPCR;

(ii) performing positron emission tomography (PET) analysis, single-photon emission computerized tomography (SPECT), or magnetic resonance imaging (MRI).

54. A method for identifying tissues or organs in a mammal that overexpress a G protein-coupled receptor (GPCR) comprising:

(i) administering to the mammal a compound of Formula (I), or a pharmaceutically acceptable salt thereof:

NP – L - Q

Formula (I)

wherein:

NP is a non-peptide ligand that binds to a G protein-coupled receptor (GPCR) expressed in tumor cells;

Q is a payload moiety comprising a chelating moiety or a radionuclide (**Z**) complex thereof;

L is a linker that covalently connects the non-peptide ligand **NP** and the payload moiety **Q**; wherein the linker **L** is attached to **NP** at a position that permits binding of **NP** to the GPCR;

(ii) performing positron emission tomography (PET) analysis, single-photon emission computerized tomography (SPECT), or magnetic resonance imaging (MRI).

55. The method of any one of claims 52-54, wherein: **Z** is a diagnostic radionuclide.

56. The method of any one of claims 52-55, wherein: step (ii) is imitated after an amount of time following step (i) sufficient for interaction between the compound of Formula (I) and GPCR expressed in tumor cells in the mammal.

57. The method of any one of claims 52-56, wherein the compound of Formula (I), or a pharmaceutically acceptable salt thereof, is a compound of any one of claims 1-38, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/032691

A. CLASSIFICATION OF SUBJECT MATTER

A61K 47/54(2017.01)i; **A61K 51/04**(2006.01)i; **A61P 35/00**(2006.01)i; **C07D 401/14**(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 47/54(2017.01); A61K 31/395(2006.01); A61K 31/403(2006.01); A61K 31/4545(2006.01); A61K 38/12(2006.01); A61K 39/395(2006.01); C07D 277/56(2006.01); C07D 401/14(2006.01); C07K 16/00(2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal), STN (Registry, Caplus), google & keywords: non-peptide ligand, G protein-coupled receptor(GPCR), payload, linker, tumor cell, chelating moiety, radionuclide complex

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LI, G. et al., "Synthesis and evaluation of a ligand targeting the somatostatin-2 receptor for drug delivery to neuroendocrine cancers", Bioorganic & medicinal chemistry letters, 2015, Vol. 25, No. 8, pages 1792-1798 abstract; pages 1792, 1793; figure 1; schemes 1, 3, 4	1-4
A	US 2009-0324620 A1 (FUSELIER, J. A. et al.) 31 December 2009 (2009-12-31) claim 115; paragraphs [0007], [0012]-[0014], [0031], [0032], [0049], [0052], [0053], [0055], [0059], [0060], [0072], [0075], [0087], [0091], [0092]	1-4
A	US 2004-0058951 A1 (LANZA, G. M. et al.) 25 March 2004 (2004-03-25) claims 1-43	1-4
A	US 2010-0092496 A1 (BOYD, S. E. et al.) 15 April 2010 (2010-04-15) claim 1; paragraphs [0014], [0016]-[0036], [0205], [0366]	1-4
A	US 2009-0041791 A1 (FENG, B.) 12 February 2009 (2009-02-12) claims 1, 4; paragraphs [0014]-[0025], [0185]	1-4

☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 September 2022	**30 September 2022**

Name and mailing address of the ISA/KR	Authorized officer
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2018-170284 A1 (CRINETICS PHARMACEUTICALS, INC.) 20 September 2018 (2018-09-20) the whole document	1-4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/032691

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **40-57**
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 40-57 pertain to methods for treatment of the human body therapy; as well as diagnostic methods, and thus relate to a subject matter which this International Search Authority is not required to search, under PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv).

2. ☑ Claims Nos.: **7, 14, 16-19, 22, 39, 44, 47, 48**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 7, 14, 16-19, 22, 39, 44, 47 and 48 are regarded to be unclear because they refer to claims which do not comply with PCT Rule 6.4 (a).

3. ☑ Claims Nos.: **5, 6, 8-13, 15, 20, 21, 23-38, 40-43, 45, 46, 56, 57**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2022/032691

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
US 2009-0324620 A1	31 December 2009	AT 455561 T	15 February 2010
		AU 2003-220011 A1	16 September 2003
		AU 2003-220011 B2	29 May 2008
		BR 0308090 A	11 April 2006
		CA 2476182 A1	12 September 2003
		CN 102133407 A	27 July 2011
		CN 1649625 A	03 August 2005
		CO 5611160 A2	28 February 2006
		DK 1487493 T3	25 May 2010
		EP 1487493 A2	22 December 2004
		EP 1487493 A4	30 August 2006
		EP 1487493 B1	20 January 2010
		ES 2339934 T3	27 May 2010
		IS 7431 A	31 August 2004
		JP 2006-510571 A	30 March 2006
		JP 4477881 B2	09 June 2010
		KR 10-1003622 B1	24 December 2010
		KR 10-2004-0088568 A	16 October 2004
		MX PA04008419 A	26 November 2004
		NO 20044039 L	29 September 2004
		NZ 534719 A	29 February 2008
		PL 373567 A1	05 September 2005
		US 2006-0009622 A1	12 January 2006
		US 7771727 B2	10 August 2010
		WO 03-074551 A2	12 September 2003
		WO 03-074551 A3	25 March 2004
		WO 03-074551 A8	03 November 2005
		ZA 200406614 B	28 June 2006
US 2004-0058951 A1	25 March 2004	AU 2003-209392 B2	09 October 2008
		AU 2004-207824 A1	12 August 2004
		AU 2009-200095 A1	05 February 2009
		BR 0307206 A	21 December 2004
		CA 2474386 A1	31 July 2003
		CA 2474386 C	05 July 2011
		CA 2514201 A1	12 August 2004
		CN 100356984 C	26 December 2007
		CN 101249269 A	27 August 2008
		CN 1738815 A	22 February 2006
		CO 5601001 A2	31 January 2006
		EP 1572639 A1	14 September 2005
		EP 1572639 A4	09 August 2006
		EP 1594550 A2	16 November 2005
		EP 1594550 A4	11 July 2007
		EP 2269659 A1	05 January 2011
		JP 2005-525319 A	25 August 2005
		JP 2006-516993 A	13 July 2006
		JP 2010-248248 A	04 November 2010
		JP 4731117 B2	20 July 2011
		JP 5444154 B2	19 March 2014
		KR 10-0978126 B1	26 August 2010

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2022/032691

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
		KR 10-2004-0090986 A	27 October 2004
		MX PA04007188 A	18 October 2005
		NZ 534500 A	27 July 2007
		TR 200401834 T2	21 October 2005
		US 2004-0248856 A1	09 December 2004
		US 2006-0147380 A1	06 July 2006
		US 2008-0145311 A1	19 June 2008
		US 2008-0175792 A1	24 July 2008
		US 7255875 B2	14 August 2007
		US 7279150 B2	09 October 2007
		US 7344698 B2	18 March 2008
		US 7566442 B2	28 July 2009
		US 7727512 B2	01 June 2010
		WO 03-062198 A1	31 July 2003
		WO 03-062198 A8	06 November 2003
		WO 2003-06219 8	04 August 2005
		WO 2004-067483 A2	12 August 2004
		WO 2004-067483 A3	25 November 2004
		ZA 200406686 B	19 September 2005
US 2010-0092496 A1	15 April 2010	AT 524473 T	15 September 2011
		AU 2005-244980 A1	01 December 2005
		AU 2005-244980 B2	15 September 2011
		AU 2006-315252 A1	24 May 2007
		BR PI0510909 A2	16 December 2008
		CA 2564076 A1	01 December 2005
		CA 2564076 C	18 February 2014
		CA 2603860 A1	19 October 2006
		CA 2627190 A1	24 May 2007
		CN 1997402 A	11 July 2007
		CN 1997402 B	02 April 2014
		EP 1747021 A2	31 January 2007
		EP 1747021 B1	09 September 2015
		EP 1865991 A2	19 December 2007
		EP 1948242 A2	30 July 2008
		EP 1948242 B1	14 September 2011
		EP 1948242 B9	08 February 2012
		ES 2371191 T3	28 December 2011
		IL 179077 A	31 October 2011
		JP 2007-538099 A	27 December 2007
		JP 2008-535845 A	04 September 2008
		JP 4806680 B2	02 November 2011
		KR 10-1079023 B1	01 November 2011
		KR 10-2007-0048138 A	08 May 2007
		MX PA06013413 A	23 January 2007
		NO 20065881 L	13 February 2007
		NZ 550934 A	28 May 2010
		RU 2006144958 A	27 June 2008
		RU 2402548 C2	27 October 2010
		UA 85716 C2	25 February 2009
		US 2006-0004081 A1	05 January 2006

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2022/032691

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
		US 2006-0024317 A1	02 February 2006
		US 2006-0247295 A1	02 November 2006
		US 2008-0293800 A1	27 November 2008
		US 7517903 B2	14 April 2009
		US 7691962 B2	06 April 2010
		US 7714016 B2	11 May 2010
		US 7968586 B2	28 June 2011
		US 8399403 B2	19 March 2013
		WO 2005-112919 A2	01 December 2005
		WO 2005-112919 A3	01 February 2007
		WO 2005-112919 A8	07 December 2006
		WO 2006-110476 A2	19 October 2006
		WO 2006-110476 A3	07 September 2007
		WO 2007-059404 A2	24 May 2007
		WO 2007-059404 A3	09 August 2007
		ZA 200609483 B	30 January 2008
US 2009-0041791 A1	12 February 2009	AU 2005-216251 A1	09 September 2005
		AU 2005-216251 B2	10 March 2011
		CA 2556752 A1	09 September 2005
		CA 2556752 C	02 February 2016
		EP 1718667 A2	08 November 2006
		EP 1718667 A4	08 April 2009
		EP 1718667 B1	09 January 2013
		JP 2007-527421 A	27 September 2007
		JP 5064037 B2	31 October 2012
		US 2005-0256030 A1	17 November 2005
		US 2010-0273843 A1	28 October 2010
		US 7375078 B2	20 May 2008
		US 7754681 B2	13 July 2010
		US 7989434 B2	02 August 2011
		WO 2005-082023 A2	09 September 2005
		WO 2005-082023 A3	22 December 2005
WO 2018-170284 A1	20 September 2018	AU 2018-234806 A1	03 October 2019
		BR 112019019168 A2	14 April 2020
		CA 3056131 A1	20 September 2018
		CN 110650951 A	03 January 2020
		EA 201992083 A1	18 March 2020
		EP 3596062 A1	22 January 2020
		EP 3596062 A4	26 August 2020
		IL 269241 A	28 November 2019
		IL 269241 B	01 September 2022
		JP 2020-511452 A	16 April 2020
		JP 7106564 B2	26 July 2022
		KR 10-2019-0121404 A	25 October 2019
		MX 2019010949 A	24 October 2019
		SG 11201908512 YA	30 October 2019
		TW 201840550 A	16 November 2018
		US 11072598 B2	27 July 2021
		US 2020-0010453 A1	09 January 2020