(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
05 December 2024 (05.12.2024)

WIPO | PCT

(10) International Publication Number
WO 2024/250006 A2

(51) International Patent Classification:
A61K 45/06 (2006.01) *A61P 25/00* (2006.01)

(21) International Application Number:
PCT/US2024/032262

(22) International Filing Date:
03 June 2024 (03.06.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/505,874 02 June 2023 (02.06.2023) US

(71) Applicant: **THE JOHNS HOPKINS UNIVERSITY** [US/US]; 3400 N. Charles Street, Baltimore, Maryland 21218 (US).

(72) Inventors: **POMPER, Martin Gilbert**; c/o The Johns Hopkins University, 3400 North Charles Street, Baltimore, Maryland 21218 (US). **FOSS, Catherine**; c/o The Johns Hopkins University, 3400 North Charles Street, Baltimore, Maryland 21218 (US). **TUFFAHA, Sami**; c/o The Johns Hopkins University, 3400 North Charles Street, Baltimore, Maryland 21218 (US). **PADOVANO, William Michael**; c/o The Johns Hopkins University, 3400 North Charles Street, Baltimore, Maryland 21218 (US).

(74) Agent: **CHILDERS, Jeffrey W.**; 2275 Deming Way, Suite 310, Middleton, Wisconsin 53562 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2024/250006 A2

(54) Title: USES OF PSMA-TARGETING AND TSPO-TARGETING COMPOUNDS FOR EVALUATION OF INJURIES IN THE PERIPHERAL NERVOUS SYSTEM

(57) Abstract: Methods for diagnosing a peripheral nervous system (PNS) neuropathy comprising administering to a subject in need of treatment thereof, at least one of a translocator protein (TSPO)-targeting compound or a PSMA-targeting compound and taking an image, are disclosed.

USES OF PSMA-TARGETING AND TSPO-TARGETING COMPOUNDS FOR EVALUATION OF INJURIES IN THE PERIPHERAL NERVOUS SYSTEM

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 63/505,874, filed June 2, 2023, which is incorporated herein by reference in its entirety.

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with Government support under grant numbers CA134675, EB009367, EB024495, HL116316, HL131829 and OD006492, awarded by the National Institutes of Health and grant number 1397119 awarded by the Department of Defense. The government has certain rights in the invention.

BACKGROUND

Peripheral nerve injuries (PNIs) are a common cause of permanent disability, pain, and reduced quality of life. Bailey et al., 2009. These injuries occur in an estimated 1% to 3% of extremity traumas in the United States, resulting in an estimated 70,000 to 150,000 nerve injuries per year. Padovano et al., 2022; Taylor et al., 2008. PNIs are even more prevalent among military service members and veterans, comprising 8% of all combat-related injuries. Birch et al., 2012(a). Despite increased awareness of these injuries and advances in nerve surgical techniques, functional recovery is generally poor. Indeed, 41% of patients with median or ulnar nerve injuries do not return to work within one year of injury, Bruyns et al., 2003, and patients with nerve injuries experience disproportionate disability relative to those with non-nerve extremity traumas. Birch et al., 2012(b).

Poor outcomes after appropriately treated PNIs are generally due to irreversible denervation-induced muscle atrophy rather than a failure of nerve regeneration. Sarhane et al., 2021. This degenerative process completes after around 18-24 months and nerve fibers reaching the muscle after this point are generally unable to animate the atrophic muscle. MacDonald et al., 2014; Ehmsen et al., 20202. Unfortunately, because no imaging modality can reliably characterize internal architecture, closed nerve injuries (or open injuries without overt epineurial discontinuity), are usually managed with months of "watchful waiting" to

monitor for signs of spontaneous recovery. Months can be squandered, and permanent function lost, monitoring injuries that will never spontaneously recover.

To this end, assessment of nerve injuries generally involves physical examination and electrodiagnostic studies (EDX), which include electromyography (EMG) and nerve conduction studies (NCS). While EDX can often identify that a nerve pathology is present, it has limited utility for predicting outcomes or selecting surgical management. Robinson, 2015. This limitation arises because electrodiagnostic studies do not provide structural information on the nerve and therefore cannot distinguish between, for example, an axonotmetic injury (Sunderland Grade II) with a favorable prognosis and a neurotmetic injury (Sunderland Grade V) with a poor prognosis. Moreover, EDX provides only a rough estimate of an injury's location and no information on the zone of injury. Diagnostic high-resolution ultrasound can be a useful adjunct for evaluating structural compressive injuries, such as in carpal tunnel syndrome, but its poor spatial resolution also prevents assessment of internal nerve structure and zone of injury. Toros et al., 2009; Cartwright et al., 2007.

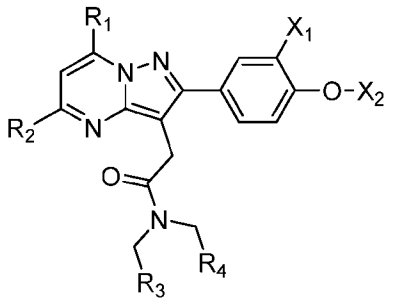
Recently, there has been academic interest in magnetic resonance diffusion tensor imaging (MR DTI) to characterize peripheral nerves. Pridmore et al., 2021. MR DTI can theoretically identify axonal injuries by pinpointing disruptions in axoplasmic flow along a nerve. Unfortunately, several practical factors limit its widespread clinical utility. Jeon et al., 2018. These factors include low signal-to-noise ratio, Widjaja et al., 2009, a lack of normative values and high variability in DTI values between patients, Hiltunen et al., 2005; Zhou et al., 2014, challenges imaging around orthopaedic hardware, Hargreaves et al., 2011, and very high susceptibility to motion artifacts including from pulsating arteries near nerves. Jones and Pierpaoli, 2005.

SUMMARY

In some aspects, the presently disclosed subject matter provides a method for diagnosing a peripheral nervous system (PNS) neuropathy, wherein PNS pathology encompasses PNS insults and/or neuropathies, recovery of PNS insults and/or neuropathies, muscle denervation including muscle denervation-induced muscle atrophy, and/or muscle re-innervation. In particular aspects, the method comprises administering to a subject in need of treatment thereof, at least one of a translocator protein (TSPO)-targeting compound

or a prostate-specific membrane antigen (PSMA)-targeting compound and taking an image. The imaging can include optical imaging, single-photon emission computerized tomography (SPECT) imaging, positron emission tomography (PET) imaging and/or magnetic resonance imaging (MRI).

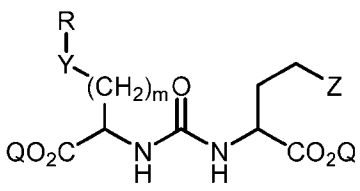
In certain aspects, the TSPO-targeting compound comprises a compound of formula (I):



(I);

wherein: X_1 can be present or absent and when present is selected from a radioisotope of fluorine, a radioisotope of iodine, a radioisotope of bromine, and a radioisotope of astatine; under the proviso that when X_1 is present, X_2 is H or C_1-C_4 alkyl and when X_1 is absent, X_2 is -L-I, wherein L is a linker and I is an imaging agent; and R_1, R_2, R_3 and R_4 are each independently selected from hydroxyl, C_1 to C_{10} alkyl, cycloalkyl, aryl, alkylamino, alkylamino, alkenyl, alkynyl, hydroxyalkyl, alkoxyl, dialkylamino thioalkyl, thioalkenyl, thioalkynyl, aryloxy, acyloxy, thioacyl, amido, and sulphonamido; wherein each of alkyl, or aryl moiety may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, hydroxyl, carboxyl, phosphoryl, phosphonyl, phosphono C_1-C_6 alkyl, carboxy C_1-C_6 alkyl, dicarboxy C_1-C_6 alkyl, dicarboxy halo C_1-C_6 alkyl, sulfonyl, cyano, nitro, alkoxy, alkylthio, acyl, acyloxy, thioacyl, acylthio, aryloxy, amino, alkylamino, dialkylamino, trialkylamino, arylalkylamino, guanidino, aldehydo, ureido, and aminocarbonyl, an amino acid residue, and a substituted amino acid residue; and pharmaceutically acceptable salts thereof.

In some aspects, the PSMA-targeting compound is a compound of formula (II):

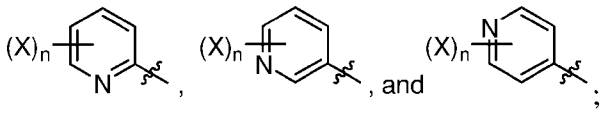


(II);

wherein: Z is tetrazole or CO_2Q; each Q is independently selected from hydrogen or a protecting group; and wherein:

(A) m is 0, 1, 2, 3, 4, 5, or 6;

R is a pyridine ring selected from:



, , and ;

wherein:

X is fluorine, iodine, a radioisotope of fluorine, a radioisotope of iodine, chlorine, bromine, a radioisotope of bromine, a radioisotope of astatine, NO_2, NH_2, $N^+(R^2)_3$, $Sn(R^2)_3$, $Si(R^2)_3$, $Hg(R^2)$, $B(OH)_2$, $–NHNH_2$, $–NHN=CHR^3$, $–NHNH–CH_2R^3$;

n is 1, 2, 3, or 4;

Y is O, S, N(R'), C(O), NR'C(O), C(O)N(R'), OC(O), C(O)O, NR'C(O)NR', NR'C(S)NR', $NR'S(O)_2$, $S(CH_2)_p$, $NR'(CH_2)_p$, $O(CH_2)_p$, $OC(O)CHR^8NHC(O)$, $NHC(O)CHR^8NHC(O)$, or a covalent bond; wherein p is 1, 2, or 3, R' is H or C_1-C_6 alkyl, and R^8 is hydrogen, alkyl, aryl or heteroaryl, each of which may be substituted;

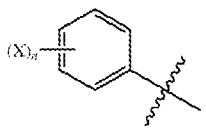
R^2 is C_1-C_6 alkyl; and

R^3 is alkyl, alkenyl, alkynyl, aryl, or heteroaryl each of which is substituted by fluorine, iodine, a radioisotope of fluorine, a radioisotope of iodine, chlorine, bromine, a radioisotope of bromine, or a radioisotope of astatine, NO_2, NH_2, $N^+(R^2)_3$, $Sn(R^2)_3$, $Si(R^2)_3$, $Hg(R^2)$, or $B(OH)_2$; or

(B) m is 0, 1, 2, 3, 4, 5, or 6;

Y is O, S, N(R'), C(O), NR'C(O), C(O)N(R'), OC(O), C(O)O, NR'C(O)NR', NR'C(S)NR', $NR'S(O)_2$, $S(CH_2)_p$, $NR'(CH_2)_p$, $O(CH_2)_p$, $OC(O)CHR^8NHC(O)$, $NHC(O)CHR^8NHC(O)$, or a covalent bond; wherein p is 1, 2, or 3, R' is H or C_1-C_6 alkyl, and R^8 is hydrogen alkyl, aryl or heteroaryl, each of which may be substituted;

R is



wherein

X' is selected from the group consisting of $NHNH_2$, $–NHN=CHR^3$, and $–NHNH–CH_2R^3$; wherein R^3 is alkyl, alkenyl, alkynyl, aryl, or heteroaryl each of which is substituted by fluorine, iodine, a radioisotope of fluorine, a radioisotope of iodine, bromine, a radioisotope of bromine, or a radioisotope of astatine; NO_2, NH_2, $N^+(R^2)_3$, $Sn(R^2)_3$, $Si(R^2)_3$, $Hg(R^2)$, or $B(OH)_2$;

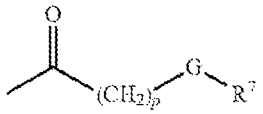
R^2 is C_1-C_6 alkyl;

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

(C) m is 4,

Y is NR', and

R is

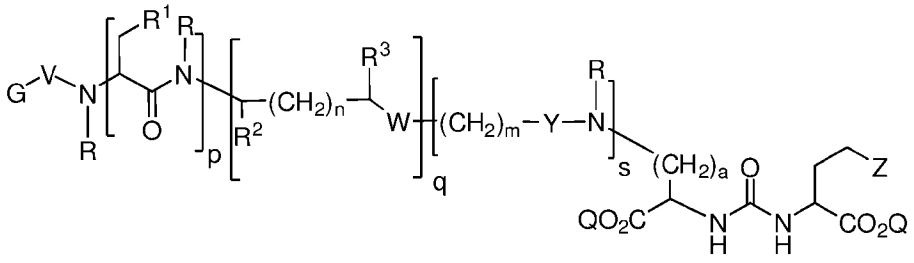


wherein G is O, NR' or a covalent bond;

R is H or C_1-C_6 alkyl; p is 1, 2, 3, or 4, and

R^7 is selected from the group consisting of NH_2, $N=CHR^3$, $NH–CH_2R^3$, wherein R^3 is alkyl, alkenyl, alkynyl, aryl, or heteroaryl each of which is substituted by fluorine, iodine, a radioisotope of fluorine, a radioisotope of iodine, chlorine, bromine, a radioisotope of bromine, or a radioisotope of astatine, NO_2, NH_2, $N^+(R^2)_3$, $Sn(R^2)_3$, $Si(R^2)_3$, $Hg(R^2)$, $B(OH)_2$; and R^2 is C_1-C_6 alkyl.

In other aspects, the PSMA-targeting compound comprises a compound of formula (III):



(III);

wherein:

q and s are each independently 0 or 1;

p is 0, 1, 2, or 3,

a is 1, 2, 3, or 4;

m is 1, 2, 3, 4, 5, or 6;

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

Z is tetrazole or CO_2Q;

each Q is independently selected from hydrogen or a protecting group;

V can be present or absent and when is present is selected from –C(O)-, –NRC(O)-, and –NRC(S)-;

W is selected from -NRC(O)-, -NRC(O)NR-, NRC(S)NR-, -NRC(O)O-, -OC(O)NR-, -OC(O)-, –C(O)NR-, or -C(O)O-;

Y is selected from -C(O)-, -NRC(O)-, -NRC(S)-, and -OC(O).

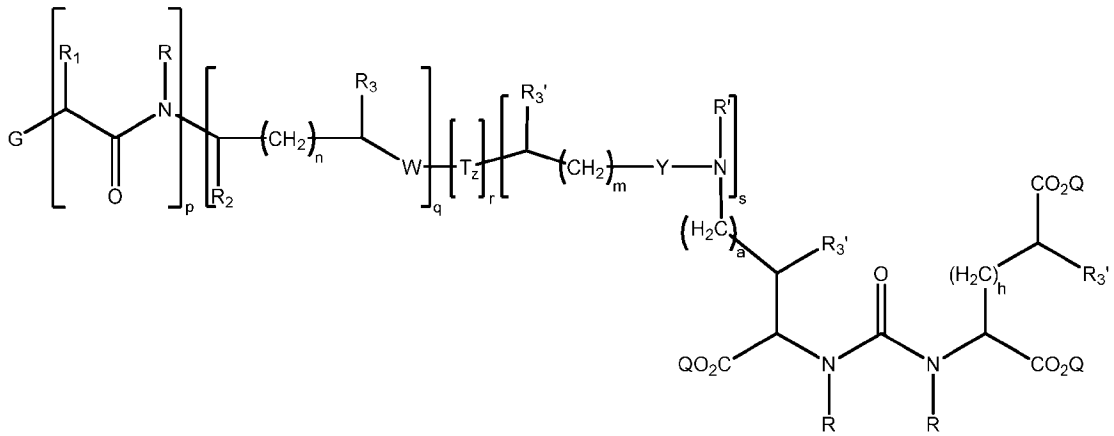
each R is independently H or C_1-C_4 alkyl;

each R^1 is independently H, C_1-C_6 alkyl, C_2-C_{12} aryl, or C_4-C_{16} alkylaryl, whereas when p is 2 or 3, each R^1 may be the same or different;

R^2 and R^3 are independently H, CO_2H, or CO_2R^4, where R^4 is a C_1-C_6 alkyl, C_2-C_{12} aryl, or C_4-C_{16} alkylaryl, wherein when one of R^2 and R^3 is CO_2H or CO_2R^4, the other is H; and

G is a metal chelating moiety optionally including a chelated metal or a dye moiety that emits in the visible or near infrared spectrum, wherein G can include any additional atoms or linkers necessary to attach the metal chelating moiety or dye moiety to the rest of the compound.

In other aspects, the PSMA-targeting compound is a compound of formula (IV):



(IV);

wherein:

each Q is independently hydrogen, a metal ion, a negative charge, or a protecting group;

a, h, m, and n are each independently an integer selected from the group consisting of 1, 2, 3, 4, 5, and 6;

s is 0 or 1;

r is 0 or 1;

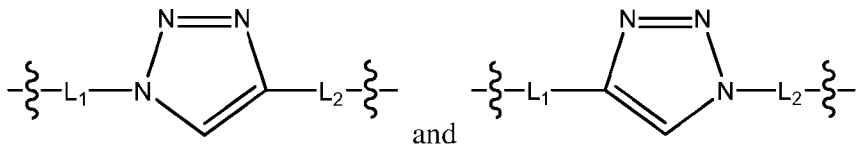
q is 0 or 1;

p is an integer selected from the group consisting of 0, 1, 2, and 3, and when p is 2 or 3, each R and R_1 can be the same or different;

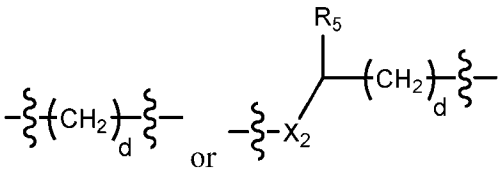
each R, R', and R_1 is independently hydrogen, C_1-C_6 substituted or unsubstituted alkyl, C_6-C_{12} substituted or unsubstituted aryl, C_6-C_{12} substituted or unsubstituted heteroaryl, or C_6-C_{16} alkyaryl;

R_2, R_3, and R_3' are each independently hydrogen, C_1-C_4 substituted or unsubstituted alkyl, $-CO_2H$, $-CO_2Q$, or $-CO_2R_4$, wherein R_4 is a C_1-C_6 substituted or unsubstituted alkyl, C_6-C_{12} substituted or unsubstituted aryl, C_6-C_{12} substituted or unsubstituted heteroaryl, or C_6-C_{16} alkyaryl, wherein if one of R_2 and R_3 is $-CO_2H$, or $-CO_2R_4$, then the other is H;

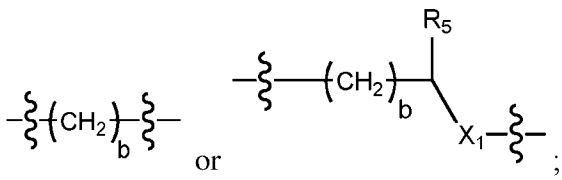
Tz is a triazole containing moiety selected from the group consisting of:



;

wherein L_1 is 

;

and L_2 is 

;

wherein:

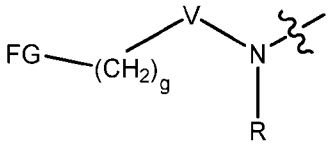
X_1 is $-NRC(O)-$, $-NRC(O)NR-$, $-NRC(S)NR$, or $-NRC(O)O-$;

X_2 is $-C(O)NR-$, $-NRC(O)NR-$, $-NRC(S)NR-$, or $-OC(O)NR-$;

R_5 is H, $-CO_2H$, or $-CO_2R_6$, wherein R_6 is C_1-C_6 alkyl, C_6-C_{12} aryl, or C_6-C_{16} alkyaryl; b is 1, 2, 3, or 4; and d is 1, 2, 3, or 4;

Y is –C(O) –, –NRC(O)–, –NRC(S)–, –OC(O)–;

W is a bond, $-(CH_2\text{-}O)_t-$, –NRC(O)–, –NRC(O)NR–, –NRC(S)NR–, –NRC(O)O–, –OC(O)NR–, –OC(O)–, –C(O)NR–, or –C(O)O–, wherein t is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8;

G is 

; FG is a fluorescent dye moiety that emits in the near-infrared spectrum; V is –C(O)-, -NRC(O)-, -NRC(S)-, or –OC(O)-, and g is an integer selected from the group consisting of 1, 2, 3, 4, 5, and 6;

under the condition that when r is 0, then q and s are both 0 or both 1;

or a pharmaceutically acceptable salt thereof; under the proviso that if R' is hydrogen.

Certain aspects of the presently disclosed subject matter having been stated hereinabove, which are addressed in whole or in part by the presently disclosed subject matter, other aspects will become evident as the description proceeds when taken in connection with the accompanying Examples and Drawings as best described herein below.

BRIEF DESCRIPTION OF THE DRAWINGS

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawings will be provided by the Office upon request and payment of the necessary fee.

Having thus described the presently disclosed subject matter in general terms, reference will now be made to the accompanying drawings, which are not necessarily drawn to scale, and wherein:

FIG. 1A, FIG. 1B, FIG. 1C, and FIG. 1D show fluorescently labeled DPA-713 (DPA-713-IRDye 680RD) uptake four weeks after sciatic nerve transection. FIG. 1A and FIG. 1B were taken from Animal 1 and FIG. 1C and FIG. 1D were taken from Animal 2 to allow for direct side-by-side comparisons. (FIG. 1A) control, non-operated leg Animal 1; (FIG. 1B) four weeks after sciatic nerve transection. Note DPA-713-dye uptake (red) in the

distal sciatic nerve stump and common peroneal nerve; (FIG. 1C) control, non-operated leg Animal 2; and (FIG. 1D) four weeks after sciatic nerve transection; lateral gastrocnemius muscle is cut and reflected to expose the tibial nerve. Note increased DPA-713-dye uptake in the common peroneal, tibial, and sural nerves;

FIG. 2A, FIG. 2B, FIG. 2C, and FIG. 2D show fluorescently labeled DPA-713 (DPA-713-IRDye 680RD) uptake after sciatic nerve repair. FIG. 2A and FIG. 2B were taken from Animal 3 and FIG. 4C and FIG. 4D were taken from Animal 4 to allow for direct side-by-side comparisons. (FIG. 2A) two weeks after common peroneal nerve crush. Note increased uptake of DPA-713-dye in the common peroneal nerve relative to the sciatic and sural nerves; (FIG. 2B) two weeks after sciatic nerve transection and repair; lateral gastrocnemius muscle is cut and reflected to expose the tibial nerve. Note DPA-713-dye uptake distal to the nerve coaptation (repair) site; (FIG. 2C) control, non-operated leg Animal 4; and (FIG. 2D) four weeks after sciatic nerve transection and repair. Note increased DPA-713-dye uptake in the distal portion of the tibial nerve, consistent with the expected progress of nerve regeneration at this timepoint;

FIG. 3 shows rodent *ex vivo* biodistribution results: 49 adult Lewis rats after ^{124}I-iodo-DPA713 administration. Sciatic nerve uptake of ^{124}I-iodo-DPA713 over time is represented as percent injected dose per segment (%ID/segment) for sham, repaired nerve, and unrepaired nerve at 2, 4, and 16 weeks post-injury. In this example, the sciatic nerve was divided into 4 approximately equal segments: two proximal to the site of injury and two distal to the site of injury. These segments are numbered 1 through 4 in this figure. Uptake was calculated for each segment using an automated gamma counter. In the figure, surgical groups are represented as bars, which are overlapped. Purple color represents the overlap of red (i.e., unrepaired) and blue (i.e., repaired) groups;

FIG. 4 shows an axial slice of a reconstructed pig PET-CT: Yorkshire pig underwent left median nerve transection without repair and right median nerve with repair. At 16 weeks post-op, at a timepoint when no substantial muscle reinnervation is expected, the animal underwent ^{124}I-iodo-DPA713 PET-CT. Note increased uptake in distal forearm corresponding to anticipated location of median nerve;

FIG. 5 shows pig histology: Note elevated TSPO expression that co-localizes with CD68 at the site of nerve injury and distal in the unrepaired median nerve. CD68 is a common macrophage marker;

FIG. 6 shows human histology: Note elevated TSPO expression that co-localizes with CD68 in the distal portion of nerves after several months after nerve injury;

FIG. 7A, FIG. 7B, and FIG. 7C show 2-weeks post-operative YC27 uptake. Images taken after tail vein injection. Areas of interest circled in white. (FIG. 7A) Sciatic transection with repair (arrowhead). Note increased uptake in the gastrocnemius and anterior compartment muscles. (FIG. 7B) Common peroneal nerve crush. Note uptake in the anterior compartment muscles, which are innervated by the common peroneal nerve, and sparing of the gastrocnemius muscle, which is innervated by the uninjured tibial nerve. (FIG. 7C) Selective transection without repair of the nerve branch to the medial head of the gastrocnemius muscle. The gastrocnemius muscle is split to reveal the tibial nerve. Note uptake in the medial head with sparing of the uninjured lateral head of the gastrocnemius muscle. *Images and colorbar enhanced to improve visibility for reproduction using Microsoft PowerPoint V16.71 (brightness 35%, contrast 35%);

FIG. 8A, FIG. 8B, and FIG. 8C show 4-weeks post-operative YC27 uptake. Images taken after tail vein injection. Areas of interest circled in white. (FIG. 8A) Sciatic transection without repair (asterisk). Note increased uptake in the gastrocnemius and anterior compartment muscles. (FIG. 8B) Sciatic transection with repair (arrowhead). Note similar uptake in gastrocnemius and anterior compartment muscles as in FIG. 8A. (FIG. 8C) Common peroneal nerve crush. Note near-complete resolution of uptake at this timepoint, consistent with the expected course of muscle reinnervation after crush injury. *Images and colorbar enhanced to improve visibility for reproduction using Microsoft PowerPoint V16.71 (brightness 35%, contrast 35%);

FIG. 9A, FIG. 9B, and FIG. 9C show 16-weeks post-operative YC27 uptake. Images taken after tail vein injection. Areas of interest circled in white. (FIG. 9A) Sciatic transection without repair (asterisk). Note increased uptake in the gastrocnemius and anterior compartment muscles. There also is slight uptake in the proximal stump of the cut sciatic nerve, which by this timepoint has formed a mature neuroma. (FIG. 9B) Sciatic transection with repair (arrowhead). Note absence of elevated muscle uptake at this

timepoint, consistent with the expected course of muscle reinnervation. (FIG. 9C) Common peroneal nerve crush. Note absence of elevated muscle uptake at this timepoint. *Images and colorbar enhanced to improve visibility for reproduction using Microsoft PowerPoint V16.71 (brightness 35%, contrast 35%);

FIG. 10 shows rodent *ex vivo* biodistribution results: 48 adult Lewis rats after ^{18}F-DCFPyL administration. Groups consisted of sciatic nerve transection with repair, transection without repair, and sham surgery (uninjured nerve). Animals underwent injection and harvest at 2, 4, and 16 weeks;

FIG. 11 shows a rodent ZJ-43 blocking study: 4 adult Lewis rats underwent sciatic transection without repair. At 4 weeks post-injury, animals received co-injection of ^{18}F-DCFPyL and ZJ-43, a potent competitive inhibitor of DCFPyL binding to GCPII. Green and dark blue bars represent animals that underwent sham surgery and sciatic transection, all 3 timepoints (2 weeks, 4 weeks, and 16 weeks combined) and are pooled for comparison. Note reduction in ^{18}F-DCFPyL activity in all tested tissues, including denervated gastrocnemius muscles;

FIG. 12 shows an axial slice of a reconstructed rodent PET-MRI. 6 adult Lewis rats underwent serial ^{68}Ga-PSMA-11 PET-MRI at 4 and 16 weeks post-operative. Animals underwent sciatic transection with repair (n=3) or transection without repair (n=3). Example axial slice of animal 4 weeks after transection without repair. Note increased uptake in the atrophic denervated muscle;

FIG. 13 shows a summary of rodent PET-MRI results. Difference in ^{68}Ga-PSMA-11 uptake standardized uptake value (SUV) between rodent leg muscles on the operated side and non-operated side. For each animal, leg SUV was calculated as average uptake in kBq/cc and normalized by average testes uptake in kBq/cc. Note the same group of 6 animals underwent imaging at 4 and 16 weeks;

FIG. 14 shows axial, coronal, and sagittal slices of a reconstructive pig PET CT: Yorkshire pig underwent left median nerve transection without repair and right median nerve with repair. At 16 weeks post-operative, at a timepoint when no substantial muscle reinnervation is expected, the animal underwent ^{68}Ga-PSMA-11 PET-CT. Note increased uptake in median nerve innervated flexor muscles; and

FIG. 15 shows pig histology: Note elevated GCPII expression that co-localizes with CD68 in denervated flexor carpi radialis muscle relative to innervated pectoralis major muscle. Alpha-BTX (alpha-bungarotoxin) antibody targets neuromuscular junctions. Beta-Tubulin antibody targets neurofilaments. CD68 is a common macrophage marker.

DETAILED DESCRIPTION

The presently disclosed subject matter now will be described more fully hereinafter with reference to the accompanying Drawings, in which some, but not all embodiments of the presently disclosed subject matter are shown. Like numbers refer to like elements throughout. The presently disclosed subject matter may be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will satisfy applicable legal requirements. Indeed, many modifications and other embodiments of the presently disclosed subject matter set forth herein will come to mind to one skilled in the art to which the presently disclosed subject matter pertains having the benefit of the teachings presented in the foregoing descriptions and the associated drawings. Therefore, it is to be understood that the presently disclosed subject matter is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims.

The presently disclosed subject matter represents the first clinically viable way to non-invasively evaluate peripheral nerve demyelination and recovery. In some embodiments, the presently disclosed subject matter provides for the use of translocator protein (TSPO)-targeting compounds and/or PSMA-targeting compounds to characterize peripheral nerve injuries (PNIs) and nerve regeneration via, for example, optical imaging, single-photon emission computerized tomography (SPECT) imaging, positron emission tomography (PET) imaging, and/or magnetic resonance imaging (MRI).

Following PNI, a well-described process of cellular and structural changes termed Wallerian degeneration occurs in the nerve downstream from the site of injury. This process is marked by a robust influx of activated macrophages around 3-5 days after injury, myelin degradation, and conversion of Schwann cells from a myelinating to a non-myelinating regenerative phenotype. The infiltrated macrophages largely remain within the denervated

distal nerve segment until they are progressively pushed out by a regenerating front of axons, provided that regeneration occurs. Therefore, visualizing macrophage content along an injured nerve may provide an inverse image of nerve regeneration.

TSPO is highly expressed in activated macrophages and microglia in neuroinflammatory conditions. Because TSPO is expressed in high concentrations on macrophages and non-myelinating regenerative phenotype Schwann cells, TSPO-targeting compounds may be used to characterize nerve injuries. Non-invasive evaluation of PNIs could fundamentally change management of these devastating injuries by allowing for earlier and more accurate diagnoses, better-informed care discussions, and improved monitoring of recovery.

Considering the severe consequences of peripheral nerve injury, the lack of alternative diagnostic modalities, and the morbidity associated with delayed or inadequate surgical management, the presently disclosed subject matter represents a ground-breaking improvement over current products and many issues associated with diagnosing PNIs may be overcome by augmenting, for example, extremity MRI with PET imaging.

In other embodiments, the presently disclosed subject matter provides for the use of PSMA-targeting compounds to characterize muscle denervation and reinnervation, such as via positron emission tomography (PET). This embodiment represents a novel use for these compounds and a potential breakthrough for the diagnosis and management of conditions associated with peripheral nervous system (PNS) neuropathy, including peripheral nerve injury (PNI), brachial plexus injury (BPI), and spinal cord injury (SCI).

PSMA, also referred to as glutamate carboxypeptidase II (GCPII) or N-acetyl-L-aspartyl-L-aspartyl-L-glutamate peptidase I (NAALADase 1), converts N-acetylaspartyl-glutamate (NAAG) to N-acetyl-aspartate (NAA) and glutamate. PSMA is typically expressed in very low levels in the muscle. A recent rodent study on amyotrophic lateral sclerosis (ALS), however, identified increased PSMA expression in affected muscles, Szabo et al, 2015, which was attributed to an influx of a specific population of inflammatory macrophages. Tallon et al., 2022. While macrophages infiltrate denervated muscle within 3-5 days of injury and are thought to modulate denervated neuromuscular junctions (NMJs), the purpose for this increased PSMA expression is not currently known. Glutamate appears to play a critical role in NMJ maturation during development, and blocking PSMA delays

synaptic pruning. A similar role, however, has not been explored in adult animals. The presently disclosed subject matter is the first to demonstrate increased uptake of PSMA-targeting ligands in denervated muscle after nerve injury, as well as resolution of uptake with muscle reinnervation. To this end, imaging with PSMA-targeting ligands may be used to diagnose PNS neuropathy and monitor recovery after treatment.

More particularly, in some embodiments, the presently disclosed subject matter provides a method for diagnosing a peripheral nervous system (PNS) neuropathy, the method comprising administering to a subject in need of treatment thereof, at least one of a translocator protein (TSPO)-targeting compound or a PSMA-targeting compound and taking an image. The imaging can include optical imaging, single-photon emission computerized tomography (SPECT) imaging, positron emission tomography (PET) imaging and/or magnetic resonance imaging (MRI). In certain embodiments, the imaging is *in vitro*, *in vivo*, or *ex vivo*. In some embodiments, the method further comprises diagnosing based on the image a disease or condition in a subject. In some embodiments, the method further comprises monitoring, based on the image, progression or regression of a disease or condition in a subject.

As used herein the term "PNS pathology" encompasses PNS insults and/or neuropathies, recovery of PNS insults and/or neuropathies, muscle denervation including muscle denervation-induced muscle atrophy, and/or muscle re-innervation. In certain embodiments, the peripheral nervous system (PNS) neuropathy is selected from a peripheral nerve injury (PNI), a brachial plexus injury (BPI), and a spinal cord injury (SCI).

Generally, a peripheral nerve fiber contains an axon (or long dendrite), myelin sheath, their Schwann cells, and the endoneurium. Peripheral nerve injury can be classified as: neurapraxia, in which the nerve remains intact but signaling ability is damaged; axonotmesis, in which the axon is damaged but the surrounding connecting tissue remains intact; and neurotmesis, in which both the axon and connective tissue are damaged. Neurapraxia is a temporary interruption of conduction without loss of axonal continuity. In neurapraxia, there is a physiologic block of nerve conduction in the affected axons. The endoneurium, perineurium, and the epineurium are intact and there is no Wallerian degeneration. Conduction is intact in the distal segment and proximal segment, but no conduction occurs across the area of injury. Axonotmesis involves loss of the relative

continuity of the axon and its covering of myelin, but preservation of the connective tissue framework of the nerve (the encapsulating tissue, the epineurium and perineurium, are preserved). Wallerian degeneration occurs distal to the site of injury and there are sensory and motor deficits distal to the site of lesion and there is no nerve conduction distal to the site of injury (up to 3 to 4 days after injury). Neurotmesis is a total severance or disruption of an entire nerve fiber. Neurotmesis may be partial or complete. Wallerian degeneration occurs distal to the site of injury. In neurotmesis, sensory-motor problems and autonomic function defect are severe. There is no nerve conduction distal to the site of injury (3 to 4 days after lesion). Surgical intervention typically is necessary.

More particularly, PNIs can be classified under two systems, the Seddon Classification and the Sunderland Classification. The Seddon Classification classifies peripheral nerve injuries into neuropraxia, axonotmesis, and neurotmesis. The Sunderland Classification further classifies PNIs into different degrees or levels of injury.

Neurapraxia is usually secondary to compression pathology and is the mildest form of peripheral nerve injury with minimal structural damage. Neurapraxia typically allows for a complete recovery with a relatively short recovery period. In a neuropraxic injury, a focal segment of the nerve is demyelinated at the site of injury with no injury or disruption to the axon or its surroundings. This type of PNI is usually due to prolonged ischemia from excess pressure or stretching of the nerve with no Wallerian degeneration. Symptoms associated with neurapraxia include pain, little to no muscle wasting, muscle weakness, numbness, and proprioception issues. Neurapraxia falls under a first degree Sunderland Classification.

Axonotmesis involves damage to the axon and its myelin sheath. The endoneurium, perineurium, and epineurium, however, remain intact. Although the internal structure is preserved, the damage of the axons does lead to Wallerian degeneration. This type of nerve injury also results in a complete recovery although it does take longer than a neuropraxic injury. Symptoms associated with axonotmesis is manifested with pain, muscle wasting, complete motor, sensory, and sympathetic function loss. Axonotmesis falls under the second and third degree Sunderland Classification.

Neurotmesis can occur at different levels and can be characterized using the Sunderland classification system. A 3rd-degree neurotmesis injury involves the disruption of the axon and endoneurium, in which the perineurium and epineurium remain intact.

Disruption of the axon and perineurium is considered a 4th-degree injury. A complete disruption of the entire nerve trunk is classified as a 5th-degree injury.

In some embodiments, the peripheral nerve injury (PNI) is selected from a stretch-related PNI, a laceration, a compression PNI, and a PNI related to one or more conditions selected from radiation, electricity, injection, crush, cold, and an intra-neural or extra-neural pathology.

Representative PSMA-targeting compounds and TSPO-targeting compounds are provided in:

International PCT Patent Application Publication No. WO2010/108125 for PSMA-Targeting Compounds and Uses Thereof, to Pomper et al., published September 23, 2010.

U.S. Patent No. 9,056,841 for PSMA-Targeting Compounds and Uses Thereof, to Pomper et al., issued June 16, 2015;

U.S. Patent No. 9,776,977 for PSMA-Targeting Compounds and Uses Thereof, to Pomper et al., issued October 3, 2017;

U.S. Patent No. 10,717,750 for ^{68}Ga-labeled NOTA-chelated PSMA-targeted Imaging and Therapeutic Agents, to Pomper et al., issued July 21, 2020;

U.S. Patent No. 11,021,450 for PSMA Targeted Fluorescent Agents for Image Guided Surgery, to Pomper et al., issued June 1, 2021;

U.S. Patent No. 11,661,402 for PSMA Targeted Fluorescent Agents for Image Guided Surgery, to Pomper et al., issued March 30, 2023;

U.S. Patent Application Publication No. 2022/0048872 for PSMA Targeted Fluorescent Agents for Image Guided Surgery, to Pomper et al., published February 17, 2022;

International PCT Patent Application Publication No. WO2010/014933 for PSMA-Binding Agents and Uses Thereof, to Pomper et al., published February 4, 2010;

U.S. Patent No. 9,226,981 for PSMA-Binding Agents and Uses Thereof, to Pomper et al., issued January 5, 2016;

U.S. Patent No. 9,861,713 for PSMA-Binding Agents and Uses Thereof, to Pomper et al., issued January 9, 2018;

U.S. Patent No. 10,500,292 for PSMA-Binding Agents and Uses Thereof, to Pomper et al., December 10, 2019;

U.S. Patent Application Publication No. 2011/0212025 for TSPO-targeting compounds and uses thereof, Pomper et al., published September 1, 2011.

U.S. Patent No. 8,778,304 for TSPO-targeting compounds and uses thereof, Pomper et al., issued July 15, 2014;

U.S. Patent No. 9,233,178 for TSPO-targeting compounds and uses thereof, Pomper et al., issued January 12, 2016;

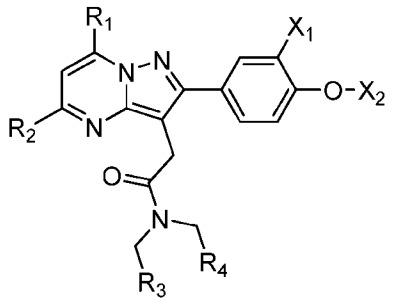
International PCT Patent Application Publication No. WO2013/138612 for Synthesis and Application of Novel Imaging Agents Conjugated to DPA 713 Analogs for Imaging Inflammation, to Pomper et al., published September 19, 2013.

U.S. Patent No. 9,498,546 for Synthesis and Application of Novel Imaging Agents Conjugated to DPA 713 Analogs for Imaging Inflammation, to Pomper et al., issued November 22, 2016;

International PCT Patent Application Publication No. WO2018232280 for PSMA Targeted Fluorescent Agents for Image Guided Surgery, to Pomper et al., published December 20, 2018; and

U.S. Published Patent Application No. 2020/0283412 for PSMA Targeted Fluorescent Agents for Image Guided Surgery, to Pomper et al., published September 10, 2020, each of which is incorporated herein by reference in its entirety.

In certain embodiments, the TSPO-targeting compound comprises a compound of formula (I):

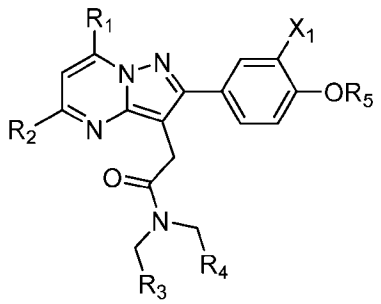


(I);

wherein: X_1 can be present or absent and when present is selected from a radioisotope of fluorine, a radioisotope of iodine, a radioisotope of bromine, and a radioisotope of astatine; under the proviso that when X_1 is present, X_2 is H or C_1-C_4 alkyl and when X_1 is absent, X_2 is -L-I, wherein L is a linker and I is an imaging agent; and R_1, R_2, R_3 and R_4 are each independently selected from hydroxyl, C_1 to C_{10} alkyl, cycloalkyl, aryl, alkylamino,

alkylamino, alkenyl, alkynyl, hydroxyalkyl, alkoxyl, dialkylamino thioalkyl, thioalkenyl, thioalkynyl, aryloxy, acyloxy, thioacyl, amido, and sulphonamido; wherein each of alkyl, or aryl moiety may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, hydroxyl, carboxyl, phosphoryl, phosphonyl, phosphono C_1-C_6 alkyl, carboxy C_1-C_6 alkyl, dicarboxy C_1-C_6 alkyl, dicarboxy halo C_1-C_6 alkyl, sulfonyl, cyano, nitro, alkoxy, alkylthio, acyl, acyloxy, thioacyl, acylthio, aryloxy, amino, alkylamino, dialkylamino, trialkylamino, arylalkylamino, guanidino, aldehydo, ureido, and aminocarbonyl, an amino acid residue, and a substituted amino acid residue; and pharmaceutically acceptable salts thereof.

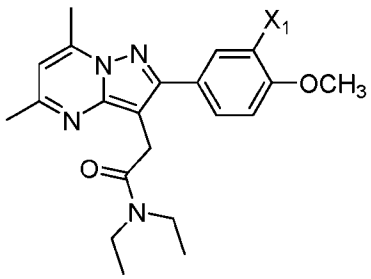
In particular embodiments, the compound of formula (I) is a compound of formula (Ia):



(Ia);

wherein R_5 is H or C_1-C_4 alkyl.

In more particular embodiments, the compound of formula (Ia) is:

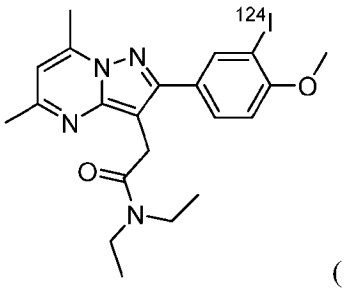


.

In certain embodiments, X_1 is selected from ^{18}F, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br, ^{80}Br, ^{80m}Br, ^{82}Br, ^{83}Br and ^{211}At.

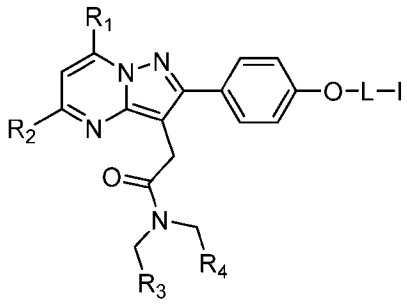
In particular embodiments, (a) X_1 is ^{123}I or ^{125}I and the imaging is single photon emission computed tomography (SPECT); or (b) X_1 is ^{18}F or ^{124}I and the imaging is positron emission tomography (PET).

In more particular embodiments, the compound of formula (Ia) is:



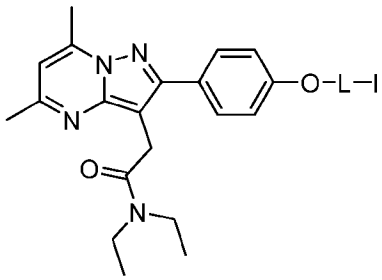
(^{124}I-iodo-DPA-713).

In other embodiments, the compound of formula (I) is a compound of formula (Ib):



(Ib).

In certain embodiments, the compound of formula (Ib) is:



.

In certain embodiments, L comprises an alkylene linker comprising between 1 to 10 carbon atoms. In certain embodiments, I comprises an imaging agent covalently linked to the linker, L, via an amide linkage.

In certain embodiments, the imaging agent comprises an optical dye. In particular embodiments, the optical dye comprises a fluorescent dye. In more particular embodiments, the fluorescent dye comprises a fluorescent dye that emits in the near infrared spectral region. In even more particular embodiments, the fluorescent dye is selected from a polymethine dye, a coumarin dye, a xanthene dye, and a boron-dipyrromethene (BODIPY) dye.

In certain embodiments, the polymethine dye is selected from a carbocyanine dye, an indocarbocyanine dye, an oxacarbocyanine dye, a thiacarbocyanine dye, and a merocyanine

dye. In certain embodiments, the xanthene dye is selected from a fluorescein dye and a coumarin dye.

In particular embodiments, the fluorescent dye is selected from:

BODIPY FL, BODIPY R6G, BODIPY TR, BODIPY TMR, BODIPY 493/503, BODIPY 530/550, BODIPY 558/568, BODIPY 564/570, BODIPY 576/589, BODIPY 581/591,BODIPY 630/650, and BODIPY 650/665;

VivoTag-645, VivoTag-680, VivoTag-S680, VivoTag-S750, VivoTag-800;

Alexa Fluor 488, Alexa Fluor 532, Alexa Fluor 546, Alexa Fluor 555, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 647, Alexa Fluor 660, Alexa Fluor 680, Alexa Fluor 700, Alexa Fluor 750, and AlexaFluor790;

Dy677, Dy676, Dy682, Dy752, Dy780;

DyLight 350, DyLight 405, DyLight 488, DyLight 547, DyLight 550, DyLight 594, DyLight 633, DyLight 647, DyLight 650, DyLight 680, DyLight 755, and DyLight 800;

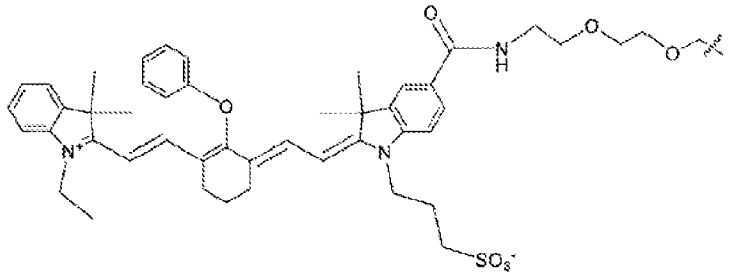
HiLyte Fluor 405, HiLyte Fluor 488, HiLyte Fluor 532, HiLyte Fluor 555, HiLyte™ Fluor 594, HiLyte Fluor 647, HiLyte Fluor 680, HiLyte Fluor 750;

IR800 (Dimethyl{4-[1,5,5-tris(4-dimethylaminophenyl)-2,4-pentadienylidene]-2,5-cyclohexadien-1-ylidene}ammonium perchlorate),

IRDye 650, IRDye 680RD, IRDye 680LT, IRDye 700, IRDye 700DX, IRDye 750, IRDye 800, IRDye 800CW, IRDye 800RS; and

ADS1065A, ADS1075A, ADS775MI, ADS775MP, ADS775PI, ADS775PP, ADS780HO, ADS780WS, ADS785WS, ADS790WS, ADS795WS, ADS798SM, ADS800AT, ADS815EI, ADS830AT, ADS830WS, ADS832WS, ADS845MC, and ADS920MC.

In particular embodiments, the optical dye is selected from: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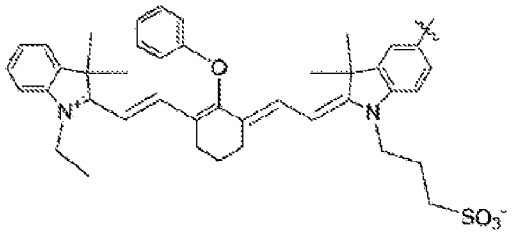
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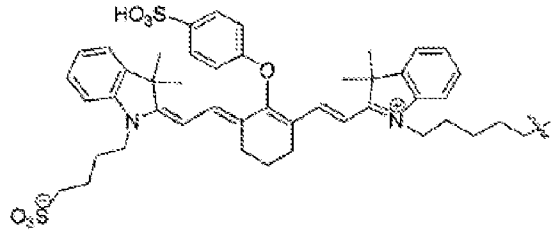
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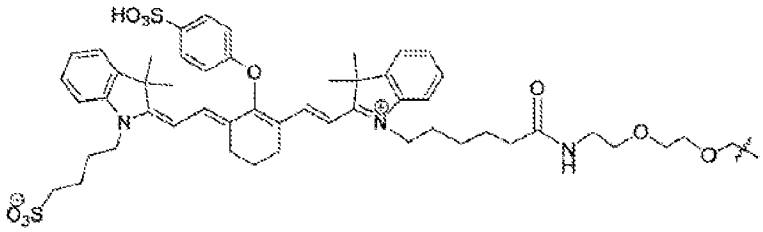
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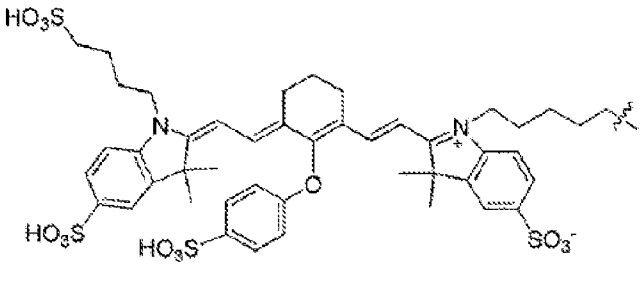
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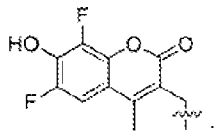
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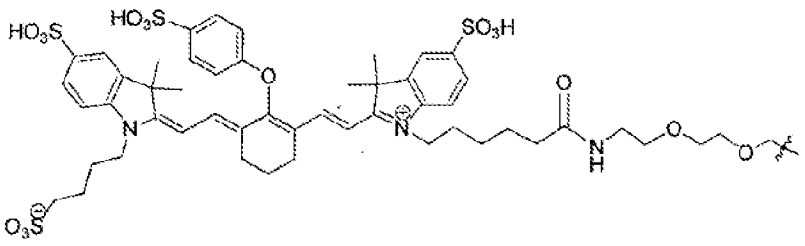
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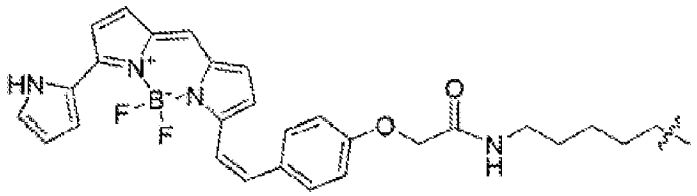
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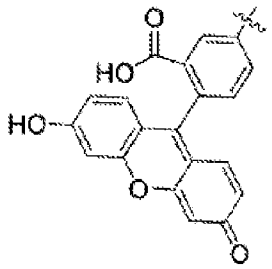
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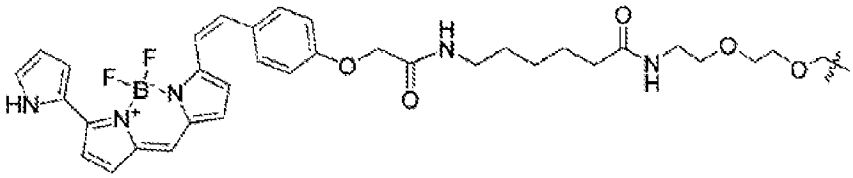
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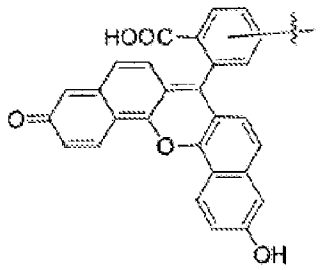
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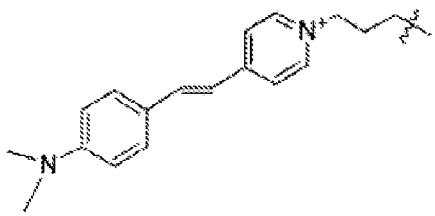
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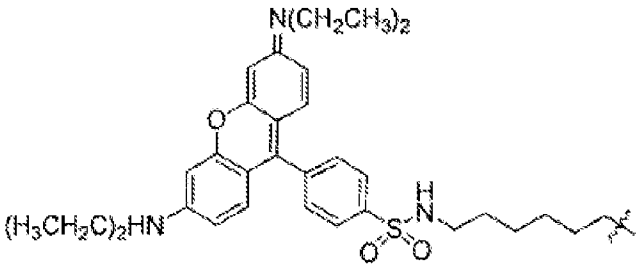
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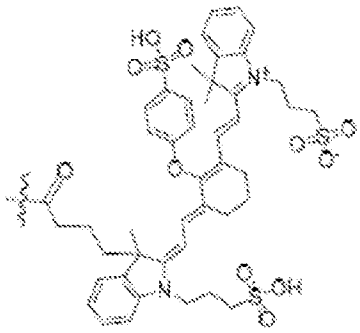
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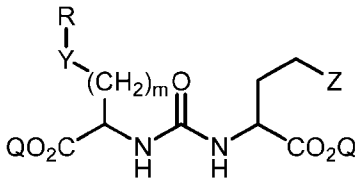
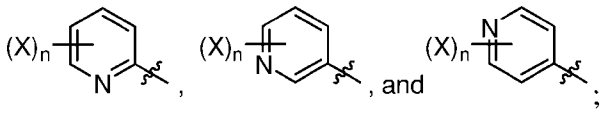
In some embodiments, the PSMA-targeting compound is a compound of formula (II):


(II);

wherein: Z is tetrazole or CO_2Q; each Q is independently selected from hydrogen or a protecting group; and wherein:

(A) m is 0, 1, 2, 3, 4, 5, or 6;

R is a pyridine ring selected from:



, , and ;

wherein:

X is fluorine, iodine, a radioisotope of fluorine, a radioisotope of iodine, chlorine, bromine, a radioisotope of bromine, a radioisotope of astatine, NO_2, NH_2, $N^+(R^2)_3$, $Sn(R^2)_3$, $Si(R^2)_3$, $Hg(R^2)$, $B(OH)_2$, $–NHNH_2$, $–NHN=CHR^3$, $–NHNH–CH_2R^3$;

n is 1, 2, 3, or 4;

Y is O, S, N(R'), C(O), NR'C(O), C(O)N(R'), OC(O), C(O)O, NR'C(O)NR', NR'C(S)NR', $NR'S(O)_2$, $S(CH_2)_p$, $NR'(CH_2)_p$, $O(CH_2)_p$, $OC(O)CHR^8NHC(O)$, $NHC(O)CHR^8NHC(O)$, or a covalent bond; wherein p is 1, 2, or 3, R' is H or C_1-C_6 alkyl, and R^8 is hydrogen, alkyl, aryl or heteroaryl, each of which may be substituted;

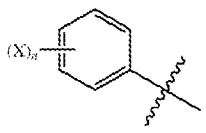
R^2 is C_1-C_6 alkyl; and

R^3 is alkyl, alkenyl, alkynyl, aryl, or heteroaryl each of which is substituted by fluorine, iodine, a radioisotope of fluorine, a radioisotope of iodine, chlorine, bromine, a radioisotope of bromine, or a radioisotope of astatine, NO_2, NH_2, $N^+(R^2)_3$, $Sn(R^2)_3$, $Si(R^2)_3$, $Hg(R^2)$, or $B(OH)_2$; or

(B) m is 0, 1, 2, 3, 4, 5, or 6;

Y is O, S, N(R'), C(O), NR'C(O), C(O)N(R'), OC(O), C(O)O, NR'C(O)NR', NR'C(S)NR', $NR'S(O)_2$, $S(CH_2)_p$, $NR'(CH_2)_p$, $O(CH_2)_p$, $OC(O)CHR^8NHC(O)$, $NHC(O)CHR^8NHC(O)$, or a covalent bond; wherein p is 1, 2, or 3, R' is H or C_1-C_6 alkyl, and R^8 is hydrogen alkyl, aryl or heteroaryl, each of which may be substituted;

R is



wherein

X' is selected from the group consisting of $NHNH_2$, $–NHN=CHR^3$, and $–NHNH–CH_2R^3$; wherein R^3 is alkyl, alkenyl, alkynyl, aryl, or heteroaryl each of which is substituted by fluorine, iodine, a radioisotope of fluorine, a radioisotope of iodine, bromine, a radioisotope of bromine, or a radioisotope of astatine; NO_2, NH_2, $N^+(R^2)_3$, $Sn(R^2)_3$, $Si(R^2)_3$, $Hg(R^2)$, or $B(OH)_2$;

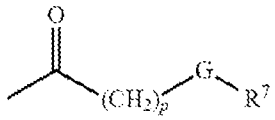
R^2 is C_1-C_6 alkyl;

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

(C) m is 4,

Y is NR', and

R is

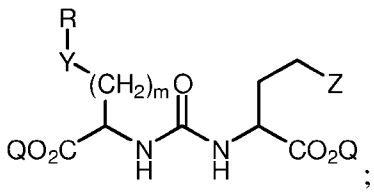


wherein G is O, NR' or a covalent bond;

R is H or C_1-C_6 alkyl; p is 1, 2, 3, or 4, and

R^7 is selected from the group consisting of NH_2, $N=CHR^3$, $NH–CH_2R^3$, wherein R^3 is alkyl, alkenyl, alkynyl, aryl, or heteroaryl each of which is substituted by fluorine, iodine, a radioisotope of fluorine, a radioisotope of iodine, chlorine, bromine, a radioisotope of bromine, or a radioisotope of astatine, NO_2, NH_2, $N^+(R^2)_3$, $Sn(R^2)_3$, $Si(R^2)_3$, $Hg(R^2)$, $B(OH)_2$; and R^2 is C_1-C_6 alkyl.

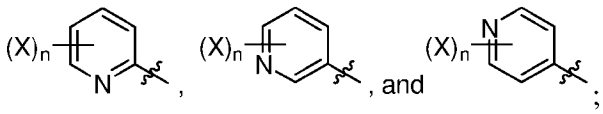
In certain embodiments, the compound of formula (II) has the structure:



;

wherein m is 0, 1, 2, 3, 4, 5, or 6;

R is a pyridine ring selected from the group consisting of:



;

wherein:

X is fluorine, iodine, a radioisotope of fluorine, a radioisotope of iodine, chlorine, bromine, a radioisotope of bromine, a radioisotope of astatine, NO_2, NH_2, $N^+(R^2)_3$, $Sn(R^2)_3$, $Si(R^2)_3$, $Hg(R^2)$, $B(OH)_2$, $–NHNH_2$, $–NHN=CHR^3$, and $–NHNH–CH_2R^3$;

each Q is independently selected from hydrogen or a protecting group;

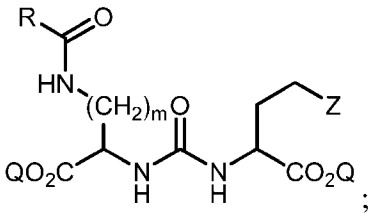
Y is O, S, N(R'), C(O), NR'C(O), C(O)N(R'), OC(O), C(O)O, NR'C(O)NR', NR'C(S)NR', $NR'S(O)_2$, $S(CH_2)_p$, $NR'(CH_2)_p$, $O(CH_2)_p$, $OC(O)CHR^8NHC(O)$, $NHC(O)CHR^8NHC(O)$, or a covalent bond; wherein p is 1, 2, or 3, R' is H or C_1-C_6 alkyl, and R^8 is hydrogen, alkyl, aryl or heteroaryl, each of which may be substituted;

Z is tetrazole or CO_2Q;

R^2 is C_1-C_6 alkyl; and

R^3 is alkyl, alkenyl, alkynyl, aryl, or heteroaryl, each of which is substituted by fluorine, iodine, a radioisotope of fluorine, a radioisotope of iodine, chlorine, bromine, a radioisotope of bromine, or a radioisotope of astatine; NO_2, NH_2, $N^+(R^2)_3$, $Sn(R^2)_3$, $Si(R^2)_3$, $Hg(R^2)$, or $B(OH)_2$.

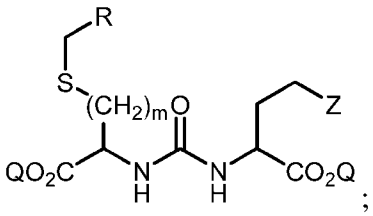
In certain embodiments, the compound of formula (II) has the structure:



;

wherein m is not 0.

In certain embodiments, the compound of formula (II) has the structure:



;

wherein m is not 0.

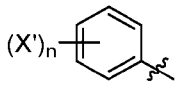
In certain embodiments, for the compound of formula (II):

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

Y is O, S, N(R'), C(O), NR'C(O), C(O)N(R'), OC(O), C(O)O, NR'C(O)NR', NR'C(S)NR', $NR'S(O)_2$, $S(CH_2)_p$, $NR'(CH_2)_p$, $O(CH_2)_p$, $OC(O)CHR^8NHC(O)$,

NHC(O)CHR^{8}NHC(O), or a covalent bond; wherein p is 1, 2, or 3, R' is H or C_1-C_6 alkyl, and R^8 is hydrogen, alkyl, aryl or heteroaryl, each of which may be substituted;

R is



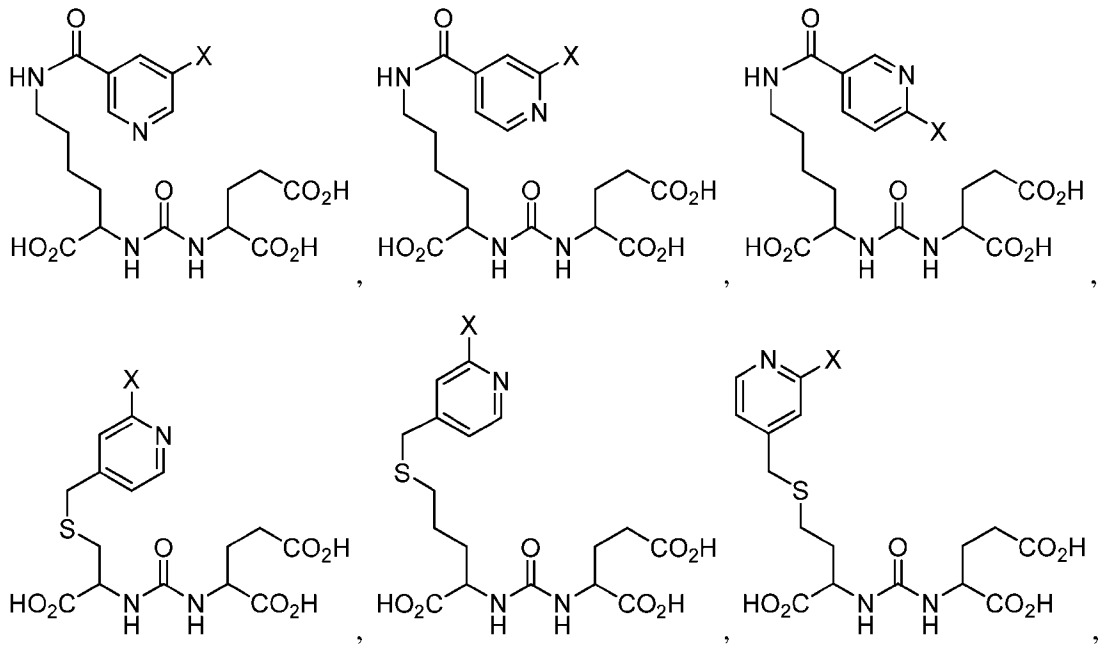
wherein

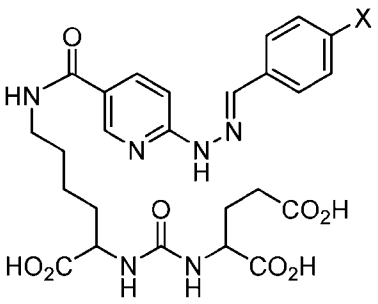
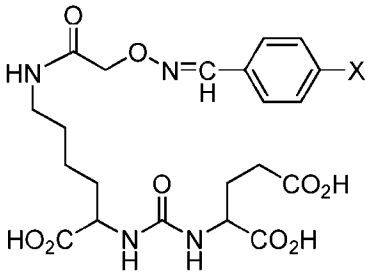
X' is selected from the group consisting of $NHNH_2$, –NHN=CHR^3, –NHNH–CH_2R^3; wherein R^3 is alkyl, alkenyl, alkynyl, aryl, or heteroaryl, each of which is substituted by fluorine, iodine, a radioisotope of fluorine, a radioisotope of iodine, bromine, a radioisotope of bromine, or a radioisotope of astatine; NO_2, NH_2, $N^+(R^2)_3$, $Sn(R^2)_3$, $Si(R^2)_3$, $Hg(R^2)$, and $B(OH)_2$, where R^2 is C_1-C_6 alkyl;

n is 1, 2, 3, 4, or 5.

In certain embodiments of the compound of formula (II), X or X' is fluorine, iodine, or a radioisotope of fluorine or iodine, bromine, a radioisotope of bromine, or a radioisotope of astatine. In particular embodiments of the compound of formula (II), X or X' is selected from ^{18}F, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br, ^{80}Br, ^{80m}Br, ^{82}Br, ^{83}Br and ^{211}At. In more particular embodiments of the compound of formula (II), X or X' is ^{18}F.

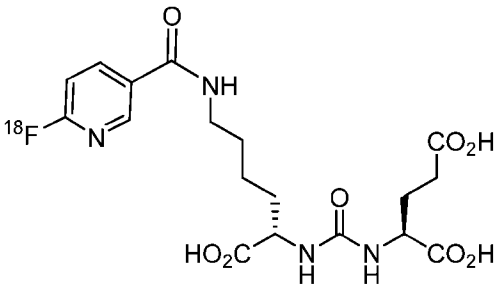
In particular embodiments, the compound of formula (II) is selected from:



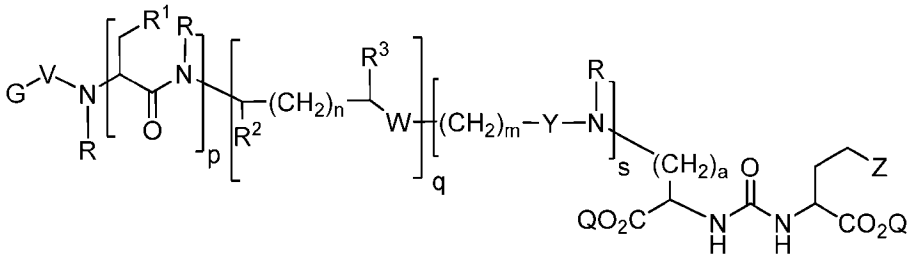
, and .

In more particular embodiments, the compound of formula (II) is:



(^{18}F-DCFPyL).

In other embodiments, the PSMA-targeting compound comprises a compound of formula (III):



(III);

wherein:

q and s are each independently 0 or 1;

p is 0, 1, 2, or 3,

a is 1, 2, 3, or 4;

m is 1, 2, 3, 4, 5, or 6;

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

Z is tetrazole or CO_2Q;

each Q is independently selected from hydrogen or a protecting group;

V can be present or absent and when is present is selected from –C(O)-, –NRC(O)-, and –NRC(S)-;

W is selected from -NRC(O)-, -NRC(O)NR-, NRC(S)NR-, -NRC(O)O-, -OC(O)NR-, -OC(O)-, –C(O)NR-, or -C(O)O-;

Y is selected from -C(O)-, -NRC(O)-, -NRC(S)-, and -OC(O).

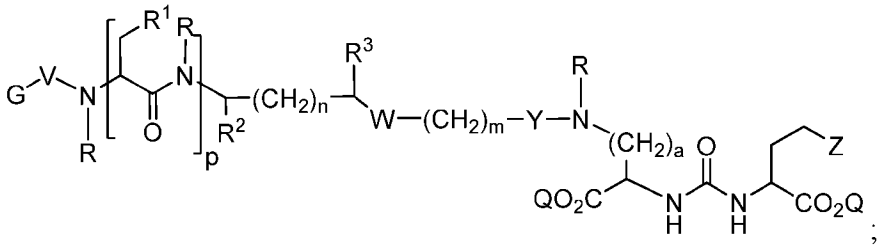
each R is independently H or C_1-C_4 alkyl;

each R^1 is independently H, C_1-C_6 alkyl, C_2-C_{12} aryl, or C_4-C_{16} alkylaryl, whereas when p is 2 or 3, each R^1 may be the same or different;

R^2 and R^3 are independently H, CO_2H, or CO_2R^4, where R^4 is a C_1-C_6 alkyl, C_2-C_{12} aryl, or C_4-C_{16} alkylaryl, wherein when one of R^2 and R^3 is CO_2H or CO_2R^4, the other is H; and

G is a metal chelating moiety optionally including a chelated metal or a dye moiety that emits in the visible or near infrared spectrum, wherein G can include any additional atoms or linkers necessary to attach the metal chelating moiety or dye moiety to the rest of the compound. For instance linking groups having alkyl, aryl, combination of alkyl and aryl, or alkyl and aryl groups having heteroatoms may be present in the chelating or dye moiety, so long as the linker does not interfere with the binding of the chelating moiety or the optical properties of the dye. In some embodiments, the linking group includes a poly(ethylene glycol) linker. The chelating moiety or dye moiety can include activated groups used to react with protein sidechains or other compounds. For example, such agents include, but are not limited to, N-hydroxysuccinimide (NHS), N-hydroxysulfosuccinimide (sulfo-NHS), anhydride, maleimide, N-benzyl, 4-isothiocyanatobenzyl (p-NCS-Bz), NH_2-MPAA, propargyl, TA, N-(2-aminoethyl)ethanamide, NH_2-PEG4, and hydrophilic dPEG spacer bound to a tetrafluorophenyl (TFP) ester. These agents can be bound to or form part of the linker which is bound to the chelating or dye moiety.

In certain embodiments, the compound of formula (III) has the following structure:



;

wherein:

Z is tetrazole or CO_2Q;

each Q is independently selected from hydrogen or a protecting group;

a is 1, 2, 3, or 4;

m is 1, 2, 3, 4, 5, or 6;

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

p is 0, 1, 2, or 3;

each R is independently H or C_1-C_4 alkyl;

V is selected from –C(O)-, -NRC(O)-, and -NRC(S)-;

W is selected from -NRC(O)-, -NRC(O)NR-, NRC(S)NR-, -NRC(O)O-, -OC(O)NR-, -OC(O)-, -C(O)NR-, and -C(O)O-;

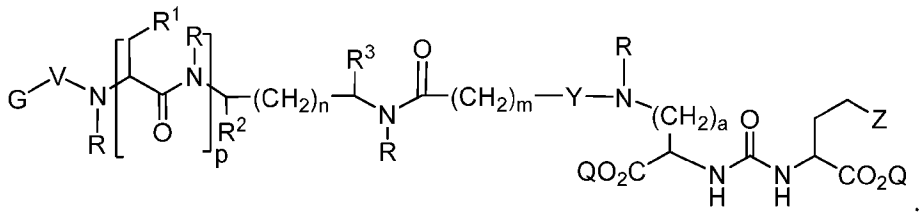
Y is selected from –C(O)-, -NRC(O)-, -NRC(S)-, and -OC(O)-;

R^1 is H, C_1-C_6 alkyl, C_2-C_{12} aryl, or C_4-C_{16} alkylaryl, whereas when p is 2 or 3, each R^1 may be the same or different;

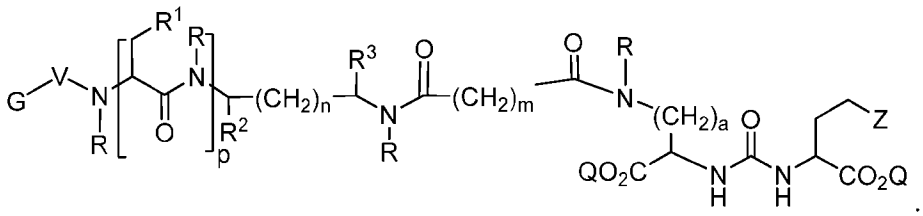
R^2 and R^3 are independently H, CO_2H, or CO_2R^4, where R^4 is a C_1-C_6 alkyl, C_2-C_{12} aryl, or C_4-C_{16} alkylaryl, wherein when one of R^2 and R^3 is CO_2H or CO_2R^4, the other is H; and

G a metal chelating moiety optionally including a chelated metal or a dye moiety that emits in the visible or near infrared spectrum.

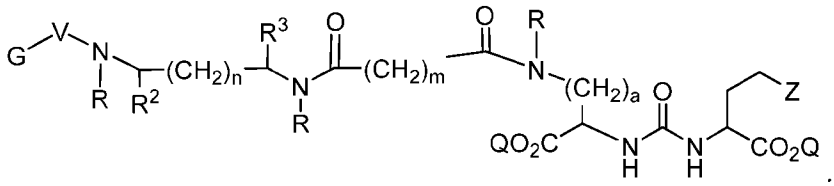
In certain embodiments, the compound of formula (III) has the following structure:



In certain embodiments, the compound of formula (III) has the following structure:



In certain embodiments, the compound of formula (III) has the following formula:



In certain embodiments, the compound of formula (III), R^1 is phenyl. In certain embodiments, for the compound of formula (III), R^4 is benzyl.

In certain embodiments, for the compound of formula (III): (a) R^2 is H, and R^3 is H; (b) R^3 is CO_2H and R^2 is H; (c) R^2 is CO_2H and R^3 is H; (d) R^2 is CO_2R^4 and R^3 is H; or (e) R^3 is CO_2R^4, and R^2 is H.

In some embodiments, G is an optical dye. In particular embodiments, the optical dye comprises a fluorescent dye. In more particular embodiments, the fluorescent dye comprises a fluorescent dye that emits in the near infrared spectral region. In even more particular embodiments, the fluorescent dye is selected from a polymethine dye, a coumarin dye, a xanthene dye, and a boron-dipyrromethene (BODIPY) dye.

In certain embodiments, the polymethine dye is selected from a carbocyanine dye, an indocarbocyanine dye, an oxacarbocyanine dye, a thiacarbocyanine dye, and a merocyanine dye. In certain embodiments, the xanthene dye is selected from a fluorescein dye and a coumarin dye.

In particular embodiments, the fluorescent dye is selected from:

BODIPY FL, BODIPY R6G, BODIPY TR, BODIPY TMR, BODIPY 493/503, BODIPY 530/550, BODIPY 558/568, BODIPY 564/570, BODIPY 576/589, BODIPY 581/591,BODIPY 630/650, and BODIPY 650/665;

VivoTag-645, VivoTag-680, VivoTag-S680, VivoTag-S750, VivoTag-800;

Alexa Fluor 488, Alexa Fluor 532, Alexa Fluor 546, Alexa Fluor 555, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 647, Alexa Fluor 660, Alexa Fluor 680, Alexa Fluor 700, Alexa Fluor 750, and AlexaFluor790;

Dy677, Dy676, Dy682, Dy752, Dy780;

DyLight 350, DyLight 405, DyLight 488, DyLight 547, DyLight 550, DyLight 594, DyLight 633, DyLight 647, DyLight 650, DyLight 680, DyLight 755, and DyLight 800;

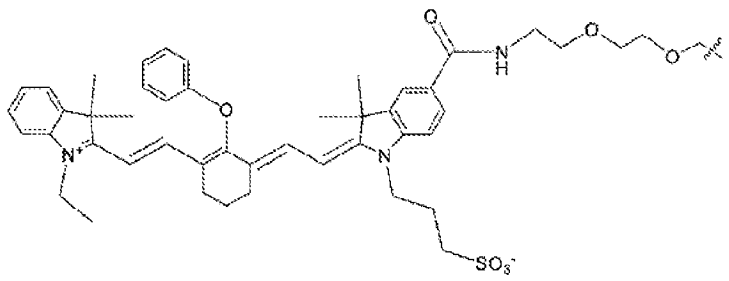
HiLyte Fluor 405, HiLyte Fluor 488, HiLyte Fluor 532, HiLyte Fluor 555, HiLyte™ Fluor 594, HiLyte Fluor 647, HiLyte Fluor 680, HiLyte Fluor 750;

IR800 (Dimethyl{4-[1,5,5-tris(4-dimethylaminophenyl)-2,4-pentadienylidene]-2,5-cyclohexadien-1-ylidene}ammonium perchlorate),

IRDye 650, IRDye 680RD, IRDye 680LT, IRDye 700, IRDye 700DX, IRDye 750, IRDye 800, IRDye 800CW, IRDye 800RS; and

ADS1065A, ADS1075A, ADS775MI, ADS775MP, ADS775PI, ADS775PP, ADS780HO, ADS780WS, ADS785WS, ADS790WS, ADS795WS, ADS798SM, ADS800AT, ADS815EI, ADS830AT, ADS830WS, ADS832WS, ADS845MC, and ADS920MC.

In particular embodiments, the optical dye is selected from:



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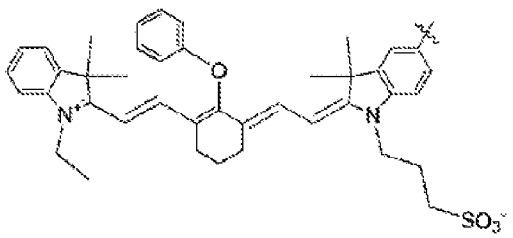

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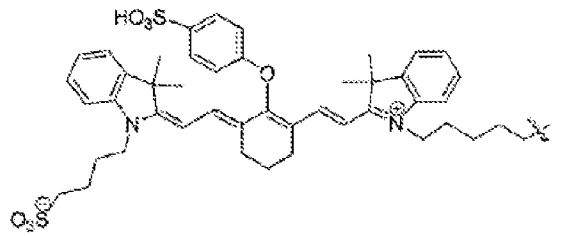

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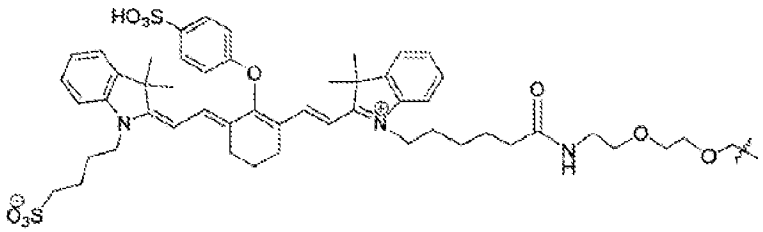

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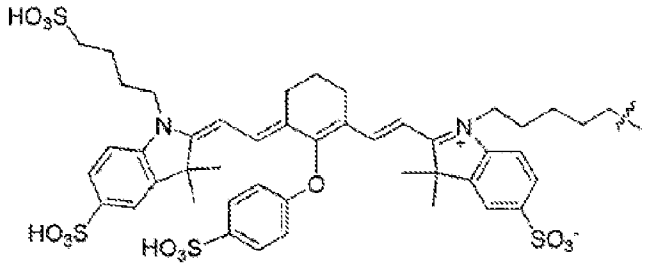
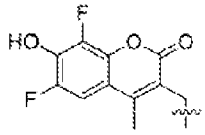
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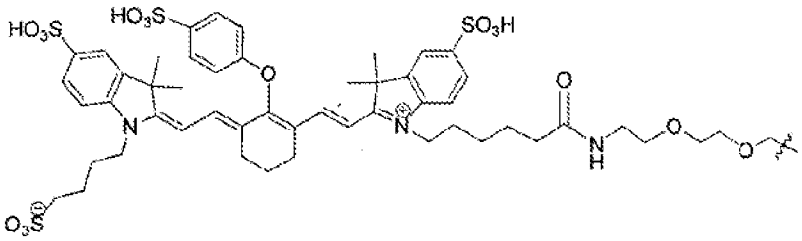
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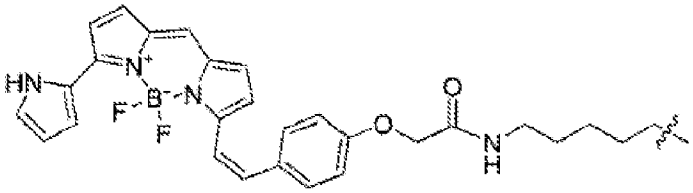
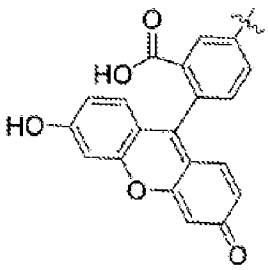
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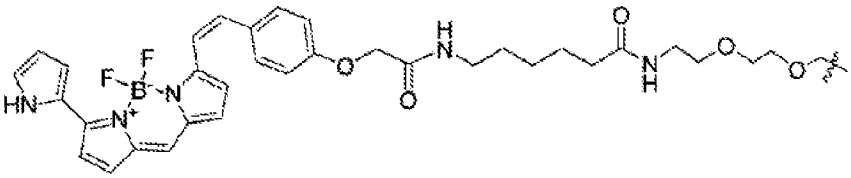
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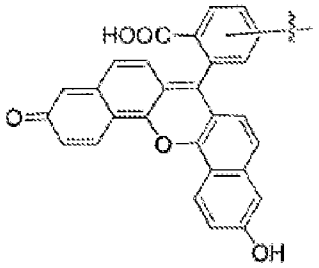

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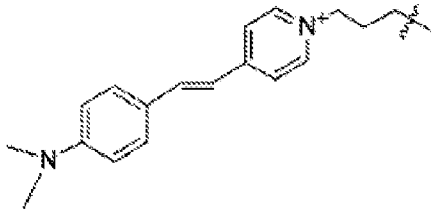

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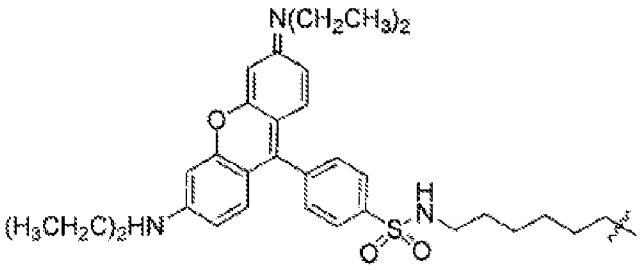

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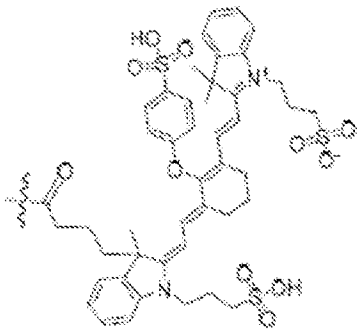

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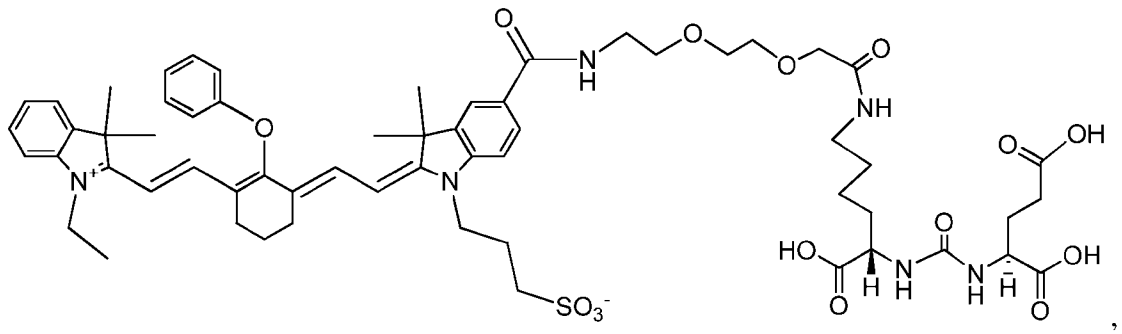
In particular embodiments of the compound of formula (III), G is an optical dye and the compound of formula (III) is selected from:



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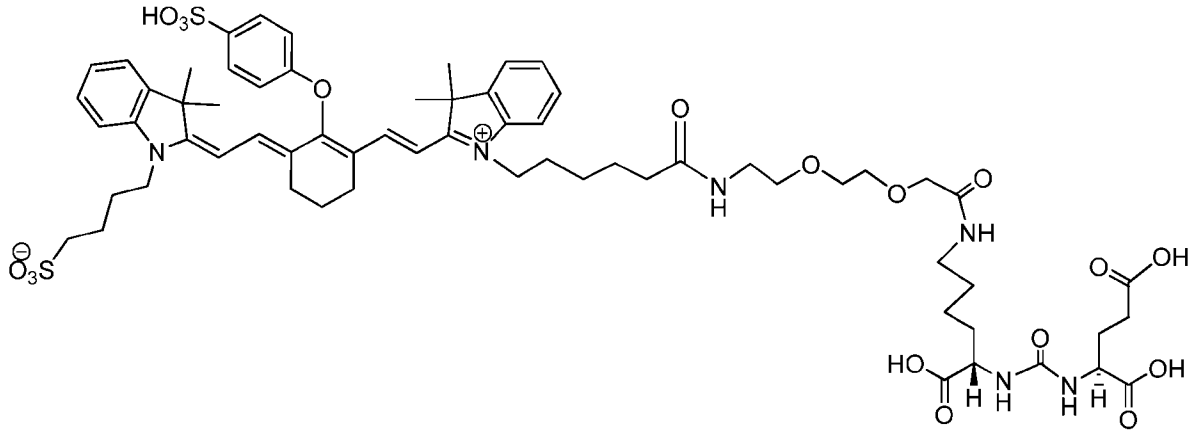

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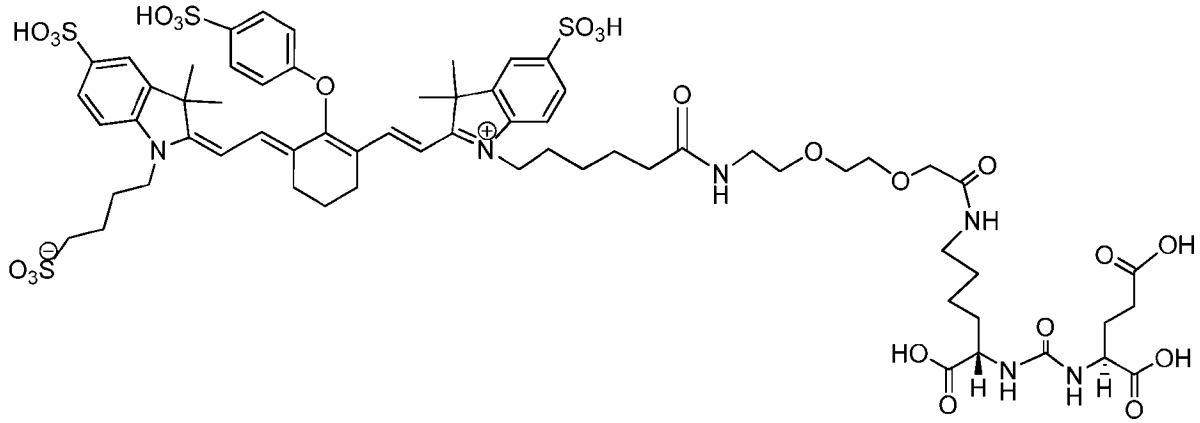

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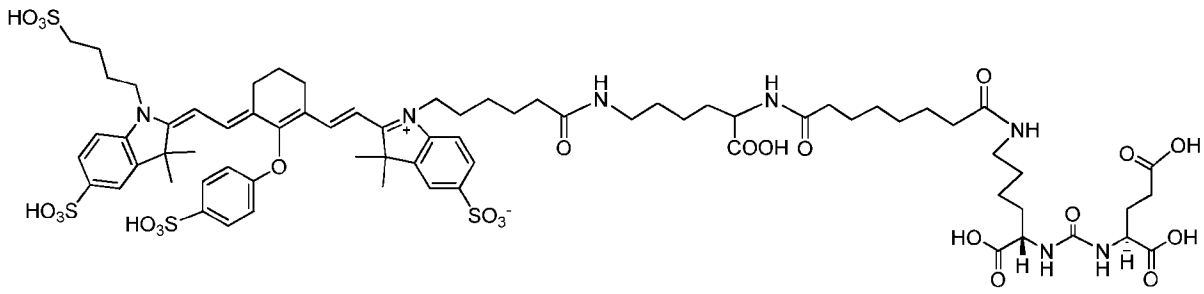

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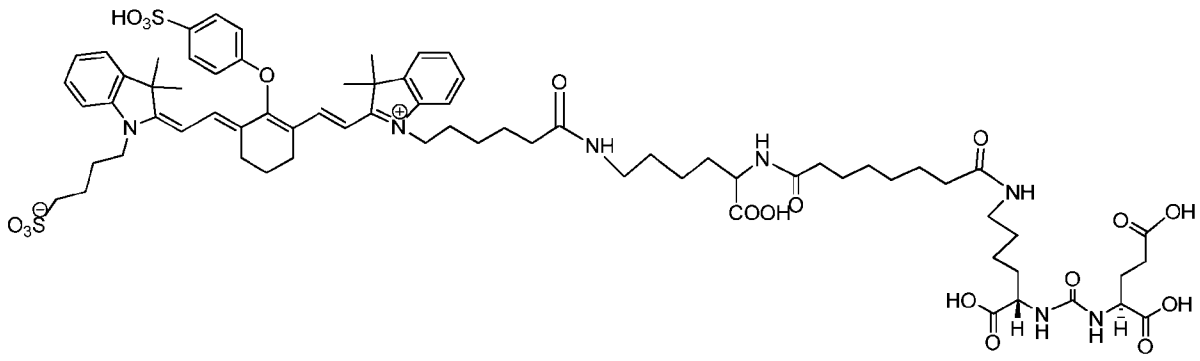

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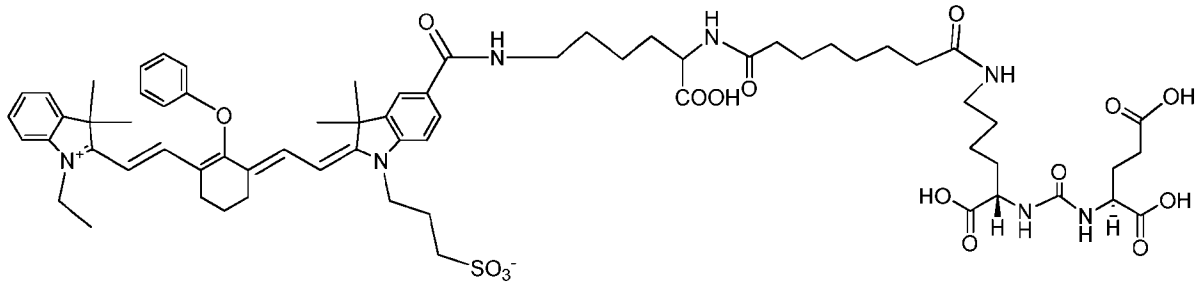

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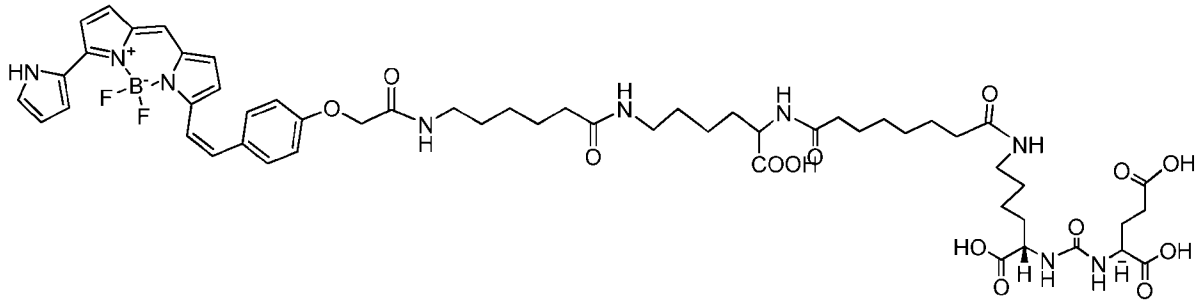

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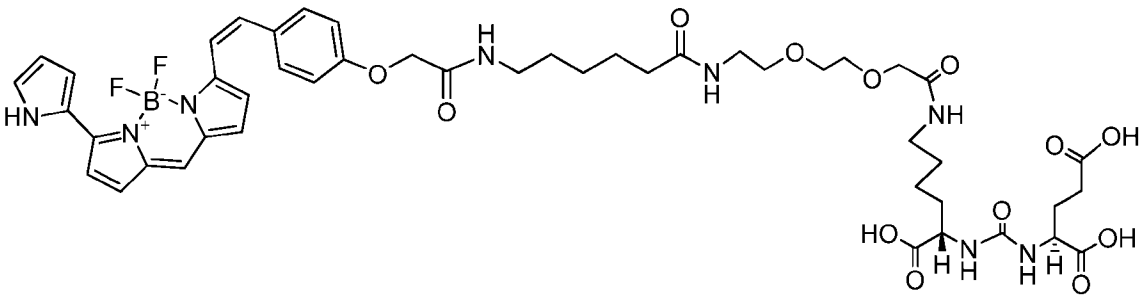

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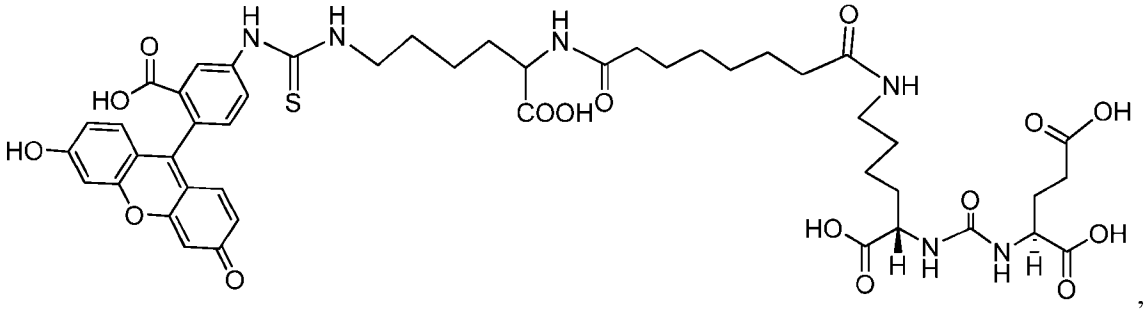

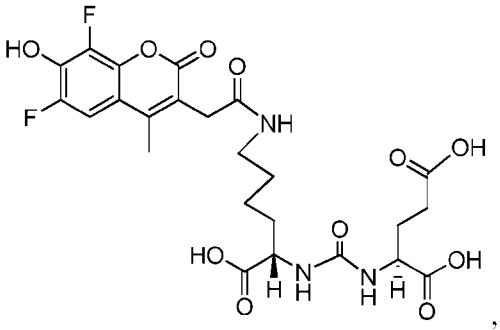

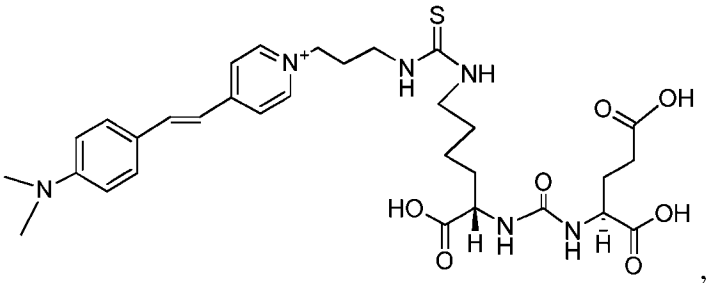

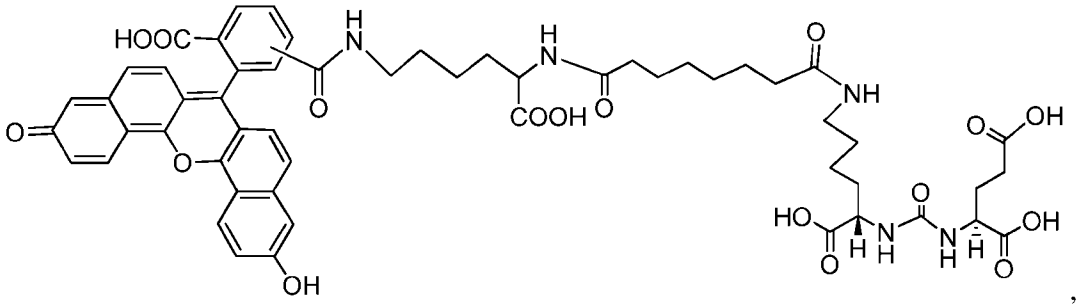

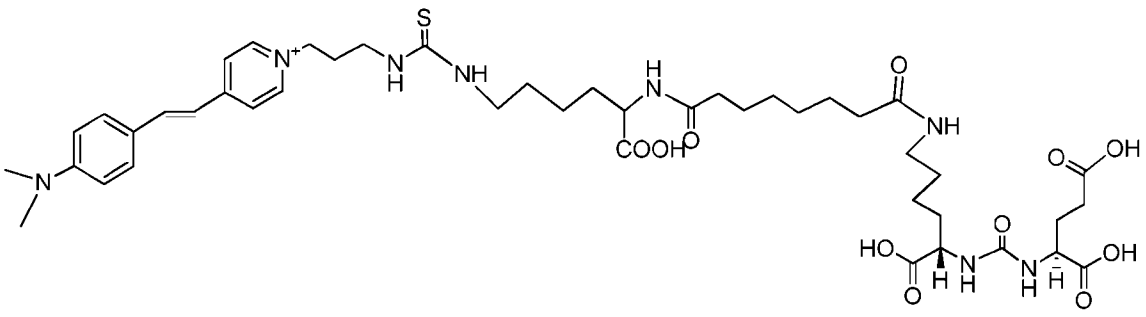

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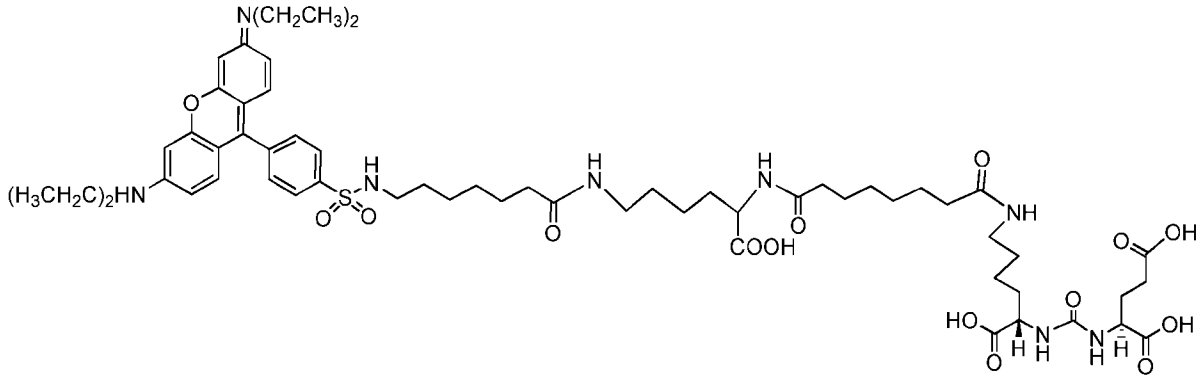

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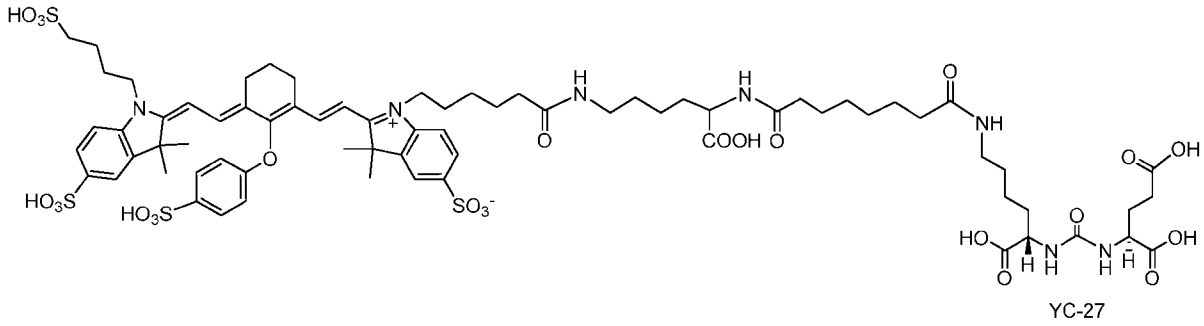
In more particular embodiments, the compound of formula (III) is:



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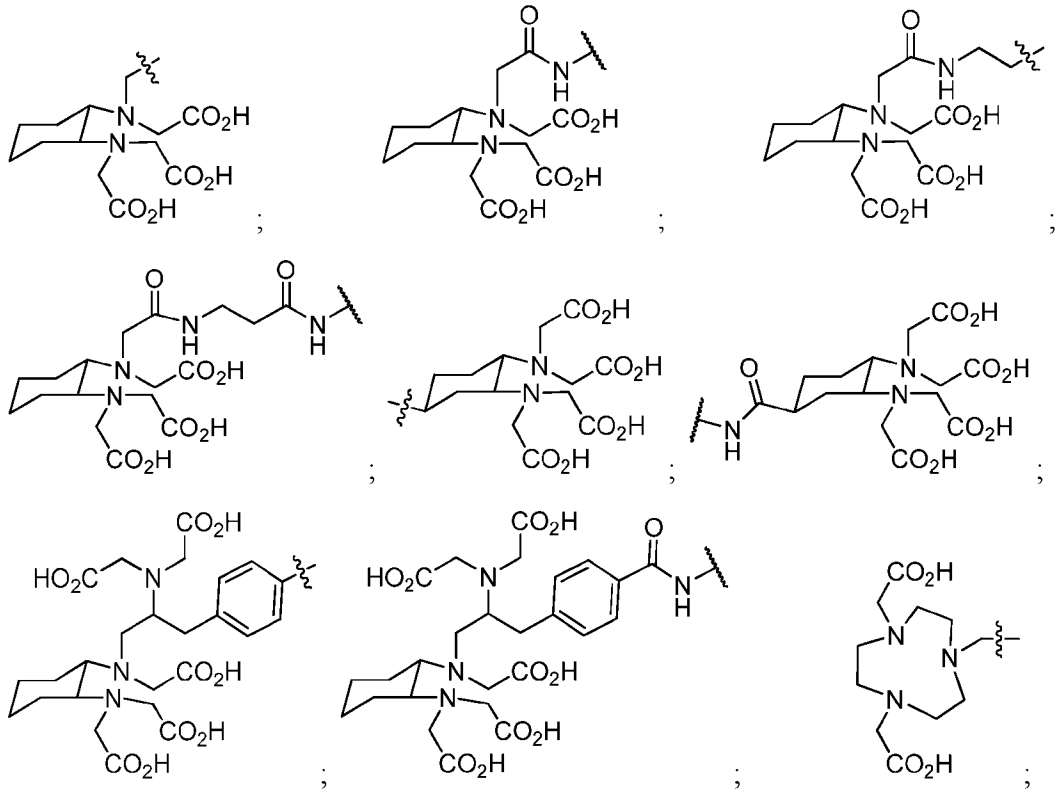
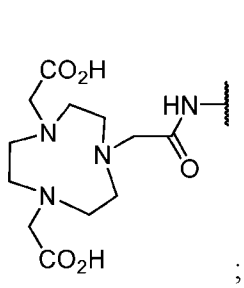
In other embodiments, for the compound of formula (III), the metal chelating moiety is selected from DOTAGA (1,4,7,10-tetraazacyclododececane,1-(glutaric acid)-4,7,10-triacetic acid), DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DOTASA (1,4,7,10-tetraazacyclododecane-1-(2-succinic acid)-4,7,10-triacetic acid), CB-DO2A (10-bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane), DEPA (7-[2-(Bis-carboxymethylamino)-ethyl]-4,10-bis-carboxymethyl-1,4,7,10-tetraaza-cyclododec-1-yl-acetic acid)), 3p-C-DEPA (2-[(carboxymethyl)][5-(4-nitrophenyl-1-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl]pentan-2-yl)amino]acetic acid)), TCMC (2-(4-isothiocyanotobenzyl)-1,4,7,10-tetraaza-1,4,7,10-tetra-(2-carbamonyl methyl)-cyclododecane), oxo-DO3A (1-oxa-4,7,10-triazacyclododecane-5-S-(4-isothiocyanatobenzyl)-4,7,10-triacetic acid), p-NH_2-Bn-Oxo-DO3A (1-Oxa-4,7,10-tetraazacyclododecane-5-S-(4-aminobenzyl)-4,7,10-triacetic acid), TE2A ((1,8-*N*,*N'*-bis-(carboxymethyl)-1,4,8,11-tetraazacyclotetradecane), MM-TE2A, DM-TE2A, CB-TE2A (4,11-bis(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane), CB-TE1A1P (4,8,11-

tetraazacyclotetradecane-1-(methanephosphonic acid)-8-(methanecarboxylic acid)), CB-TE2P (1,4,8,11-tetraazacyclotetradecane-1,8-bis(methanephosphonic acid), TETA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid), NOTA (1,4,7-triazacyclononane-N,N′,N″-triacetic acid), NODA (1,4,7-triazacyclononane-1,4-diacetate); NODAGA (1,4,7-triazacyclononane,1-glutaric acid-4,7-acetic acid), (NOTAGA) 1,4,7-triazonane-1,4-diyl)diacetic acid, DFO (Deferoxamine), NETA ([4-[2-(bis-carboxymethylamino)-ethyl]-7-carboxymethl-[1,4,7]triazonan-1-yl}-acetic acid), TACN-TM (N,N',N", tris(2-mercaptoethyl)-1,4,7-triazacyclononane), Diamsar (1,8-Diamino-3,6,10,13,16,19-hexaazabicyclo(6,6,6)eicosane, 3,6,10,13,16,19-Hexaazabicyclo[6.6.6]eicosane-1,8-diamine), Sarar (1-*N*-(4-aminobenzyl)-3, 6,10,13,16,19-hexaazabicyclo[6.6.6] eicosane-1,8-diamine), AmBaSar (4-((8-amino-3,6,10,13,16,19-hexaazabicyclo [6.6.6] icosane-1-ylamino) methyl) benzoic acid), and BaBaSar.

In particular embodiments, the compound of formula (III), the chelating agent is selected from:

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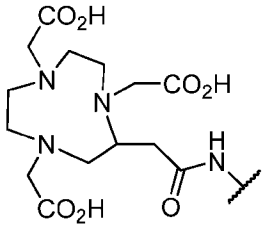
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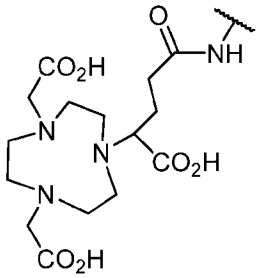
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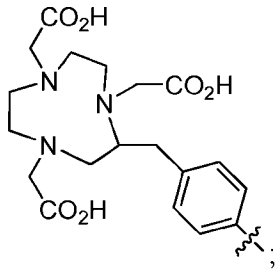
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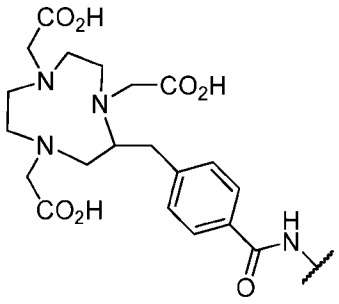
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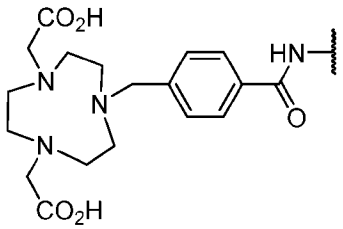
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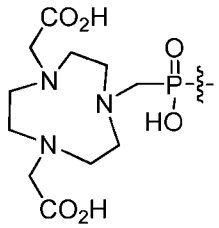
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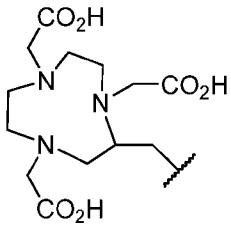
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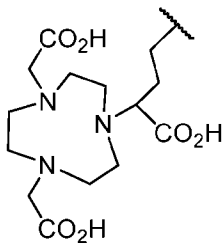
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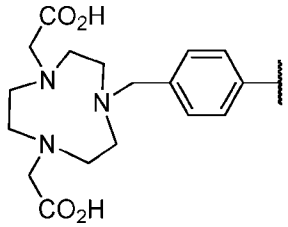
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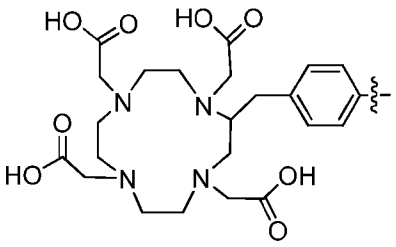
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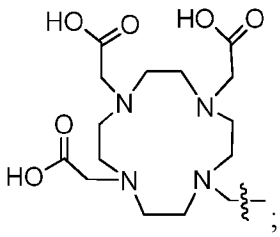
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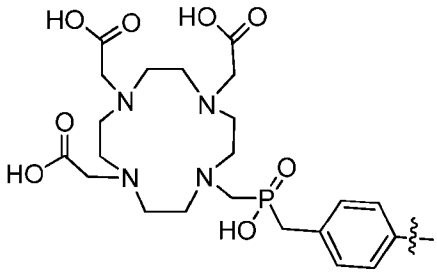
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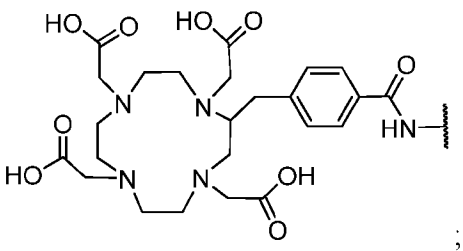
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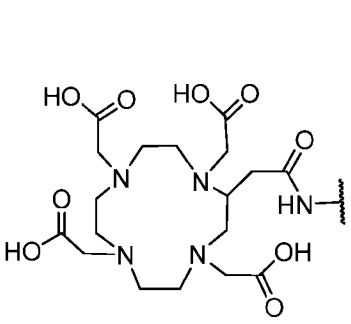
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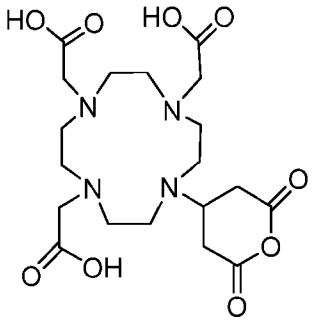
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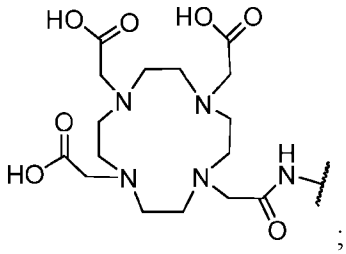
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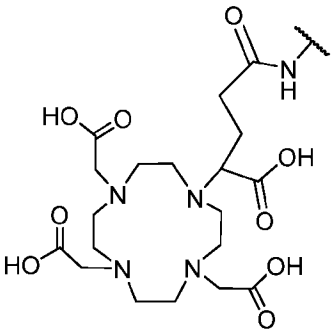
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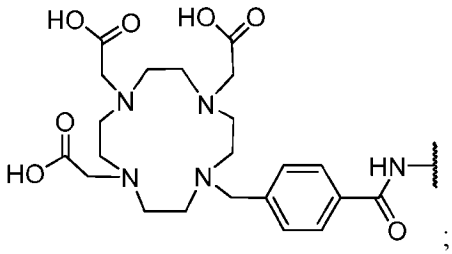
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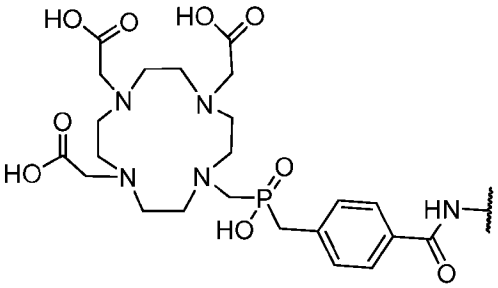
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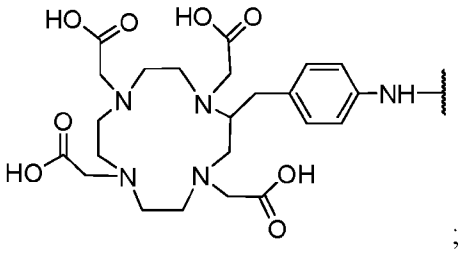
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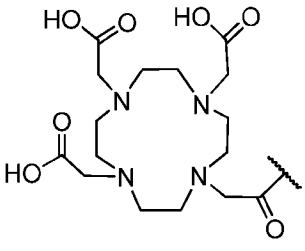
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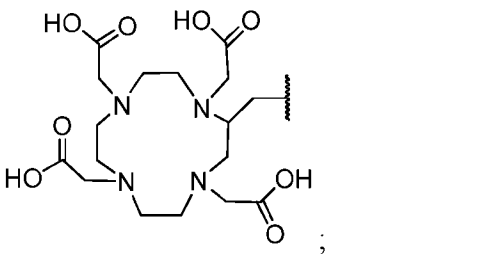
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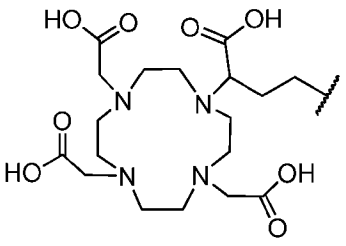
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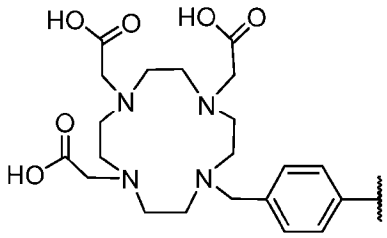
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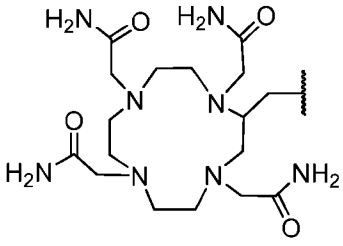
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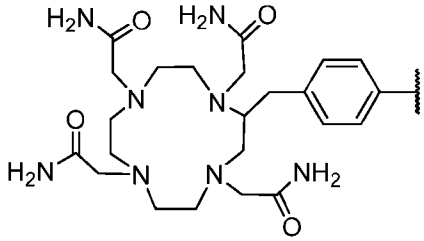
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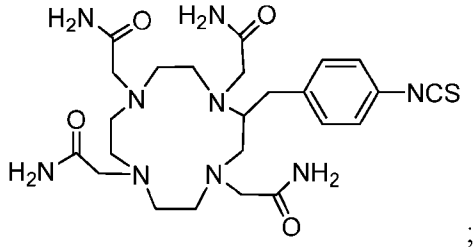
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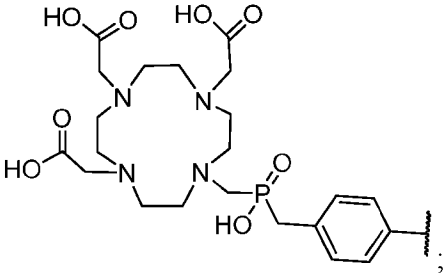
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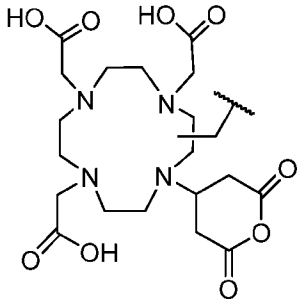
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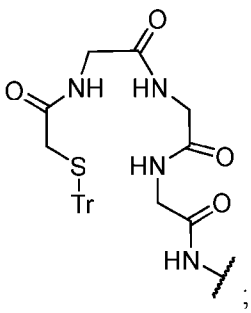
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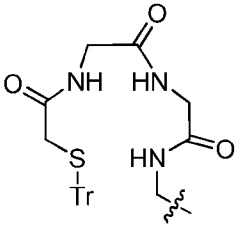
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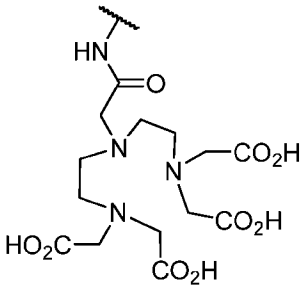
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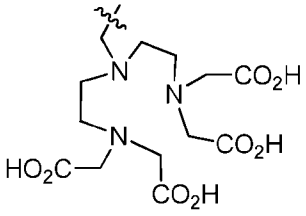
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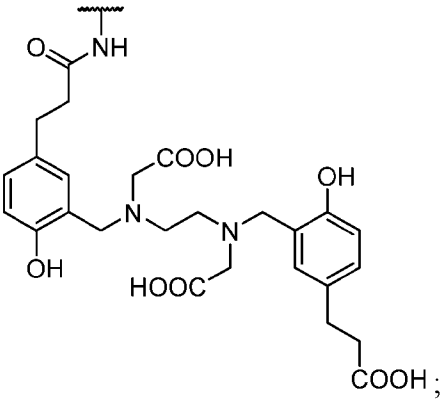
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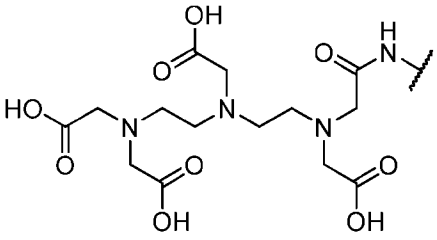
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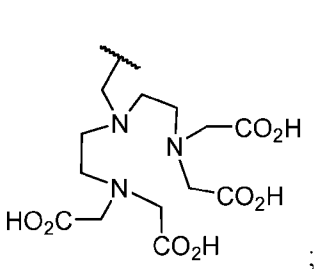

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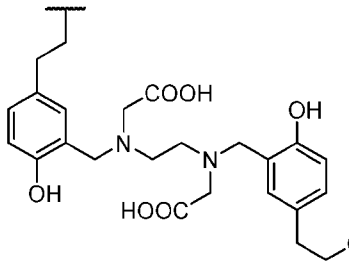
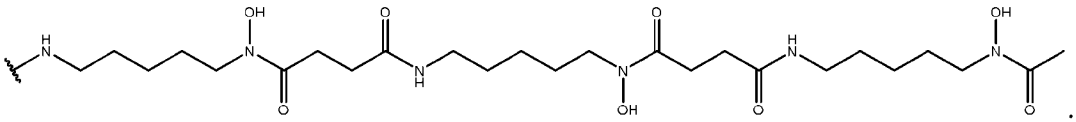
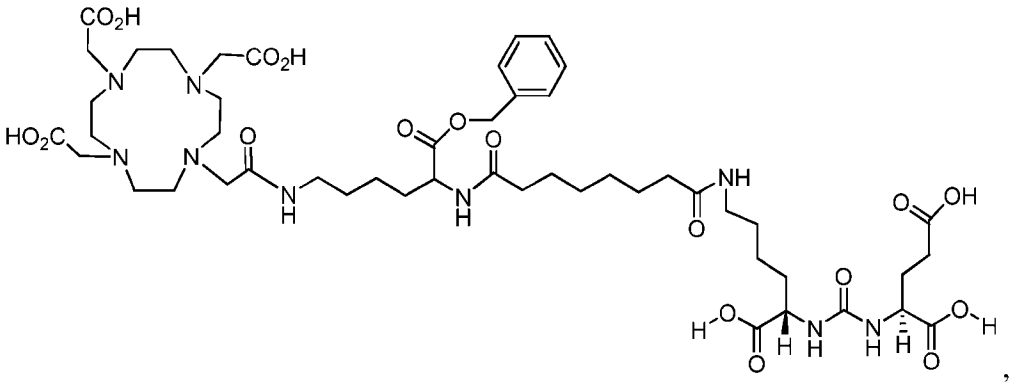


; and



.

In more particular embodiments, the compound of formula (III) is selected from:



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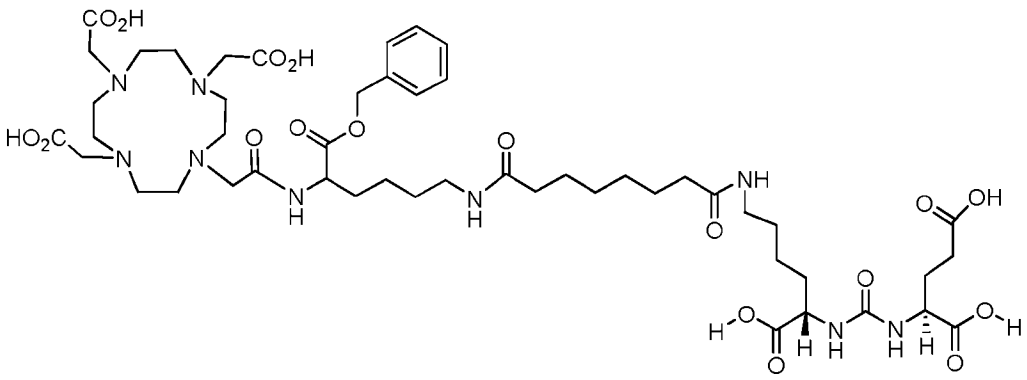
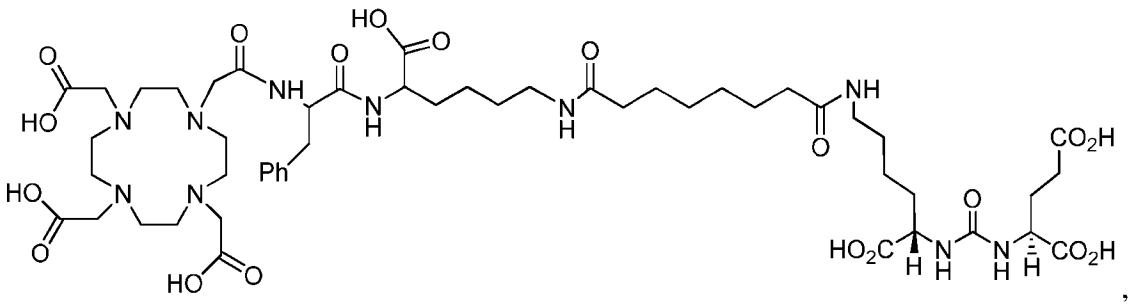


,



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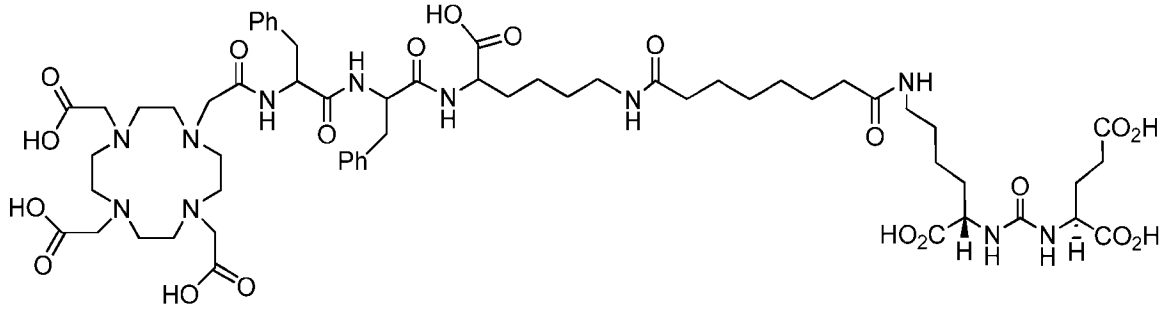

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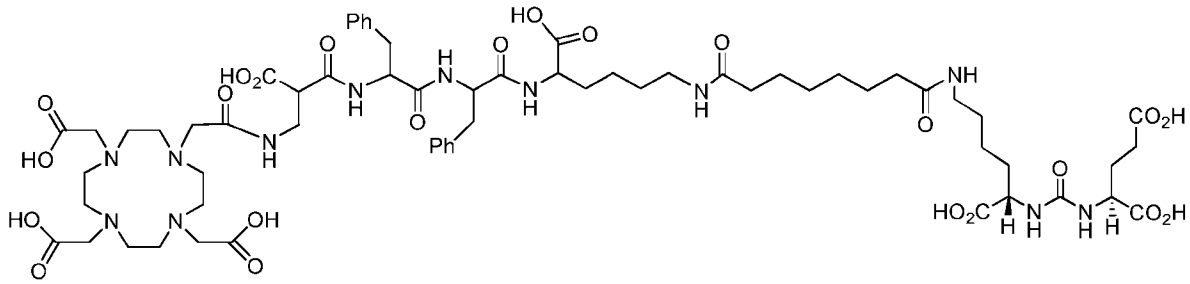

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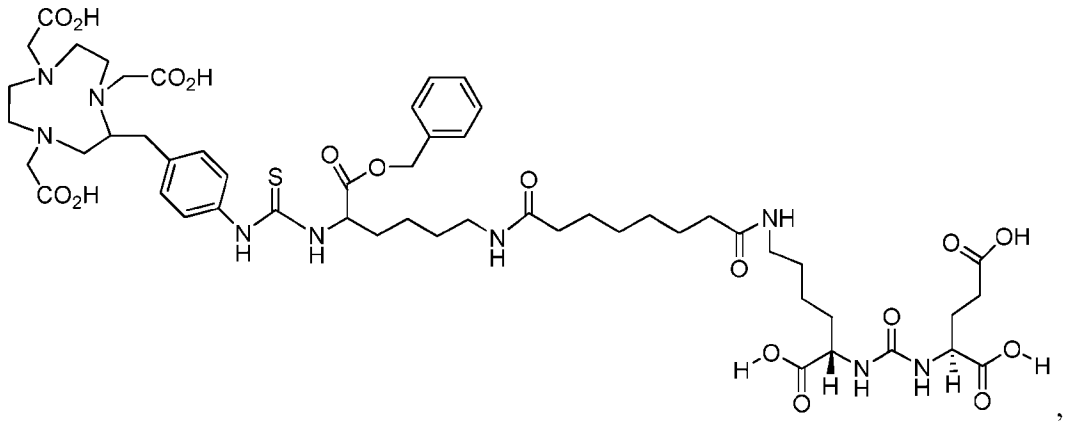
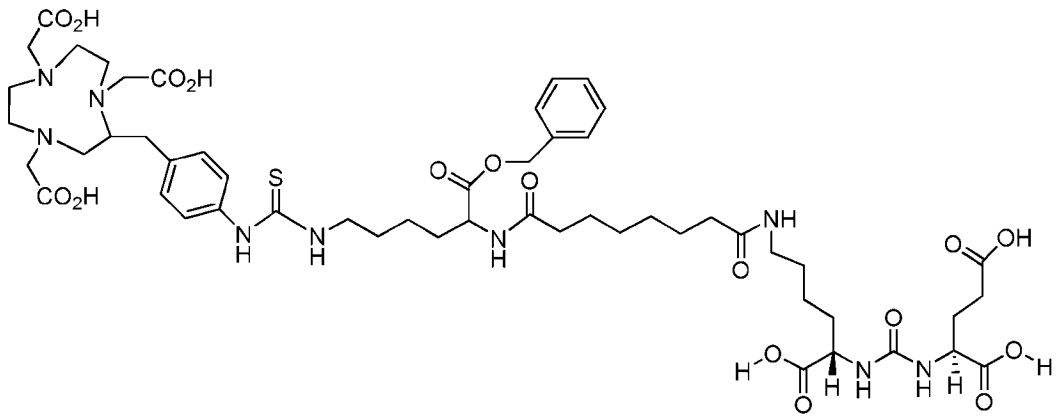


,



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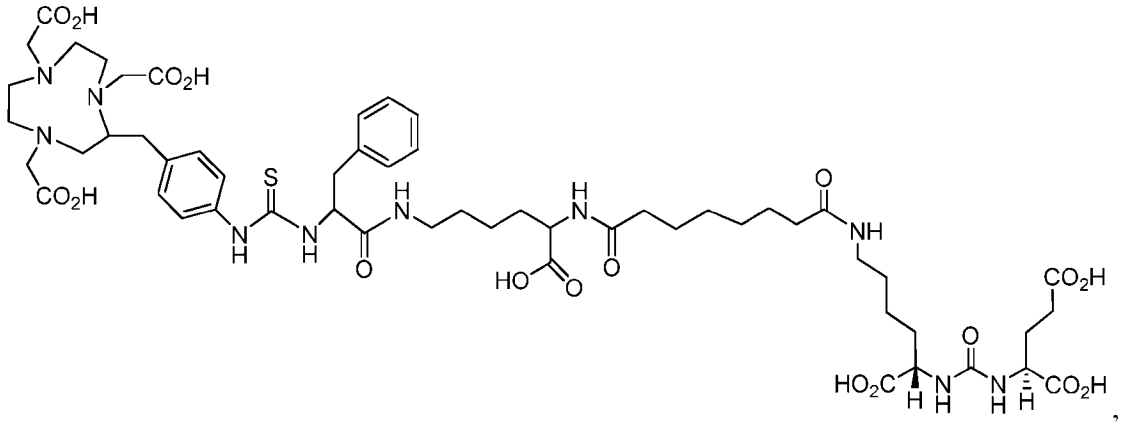

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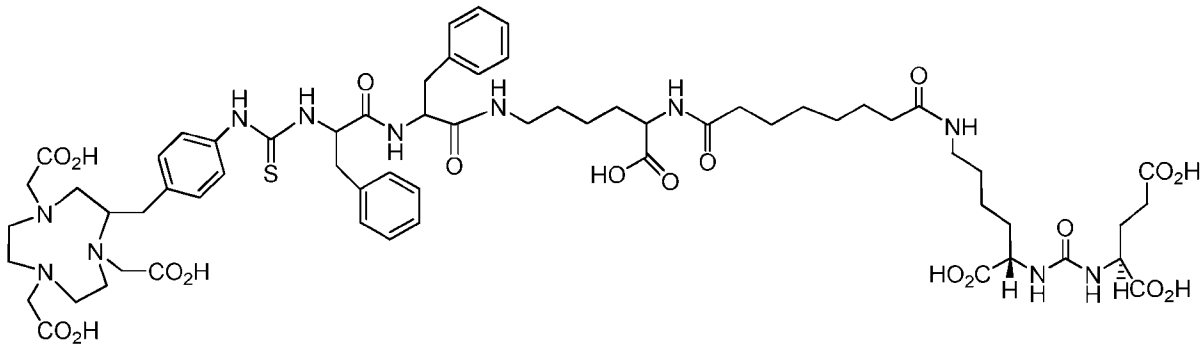
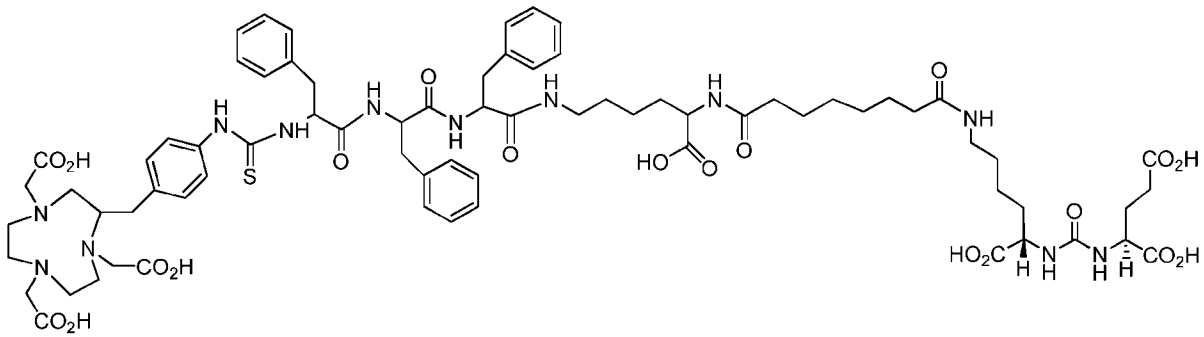


,



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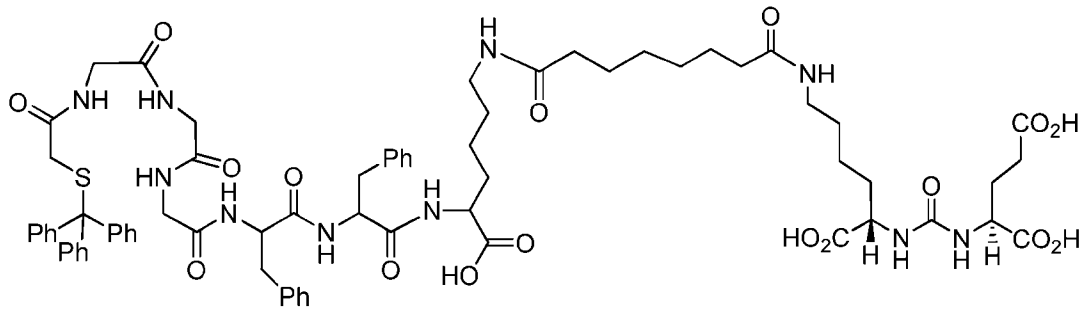
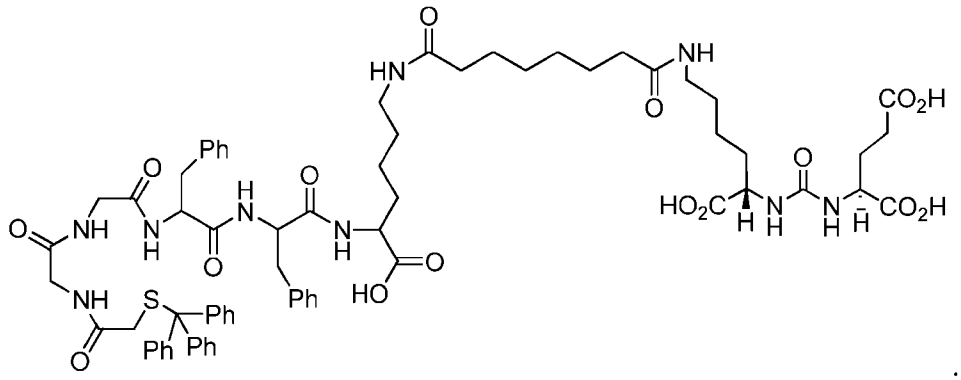
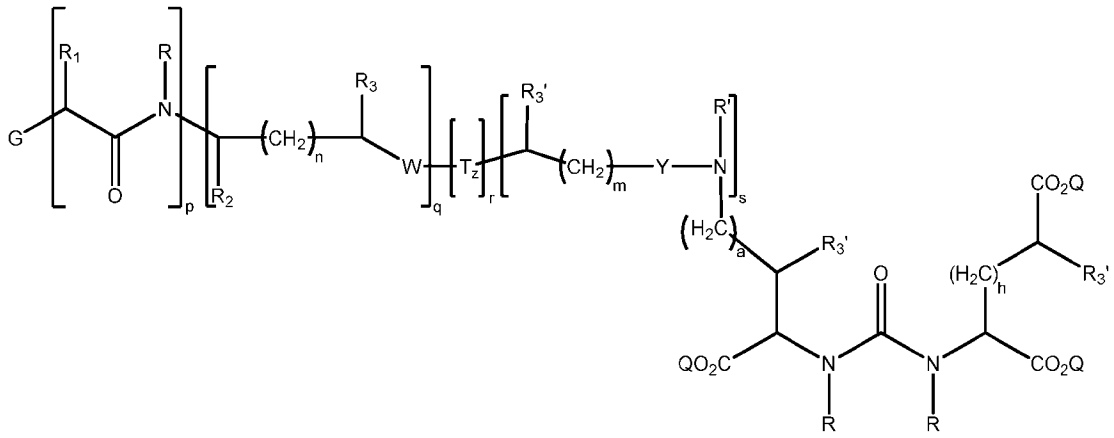


, and



In certain embodiments, for the compound of formula (III), the chelated metal is selected from ^{60}Cu, ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{55}Co, ^{57}Co, ^{203}Pb, ^{212}Pb, ^{225}Ac, ^{177}Lu, ^{99m}Tc, ^{67}Ga, ^{68}Ga, ^{149}Tb, ^{86}Y, ^{90}Y, ^{111}In, ^{186}Re, ^{188}Re, ^{153}Sm, ^{89}Zr, ^{213}Bi, ^{212}Bi, ^{212}Pb, ^{67}Ga, ^{47}Sc, ^{166}Dy, $Al^{18}F$, ^{166}Ho, and ^{177}Lu.

In other embodiments, the PSMA-targeting compound is a compound of formula (IV):



(IV);

wherein:

each Q is independently hydrogen, a metal ion, a negative charge, or a protecting group;

a, h, m, and n are each independently an integer selected from the group consisting of 1, 2, 3, 4, 5, and 6;

s is 0 or 1;

r is 0 or 1;

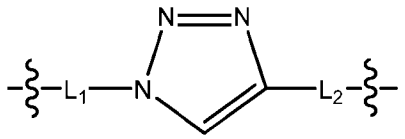
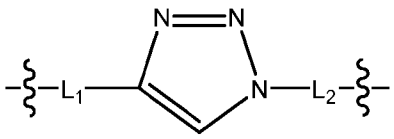
q is 0 or 1;

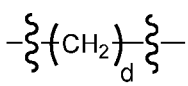
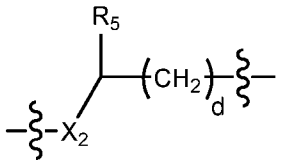
p is an integer selected from the group consisting of 0, 1, 2, and 3, and when p is 2 or 3, each R and R_1 can be the same or different;

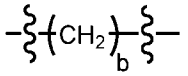
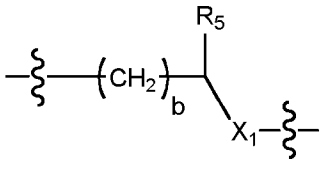
each R, R', and R_1 is independently hydrogen, C_1-C_6 substituted or unsubstituted alkyl, C_6-C_{12} substituted or unsubstituted aryl, C_6-C_{12} substituted or unsubstituted heteroaryl, or C_6-C_{16} alkyaryl;

R_2, R_3, and R_3' are each independently hydrogen, C_1-C_4 substituted or unsubstituted alkyl, $-CO_2H$, $-CO_2Q$, or $-CO_2R_4$, wherein R_4 is a C_1-C_6 substituted or unsubstituted alkyl, C_6-C_{12} substituted or unsubstituted aryl, C_6-C_{12} substituted or unsubstituted heteroaryl, or C_6-C_{16} alkyaryl, wherein if one of R_2 and R_3 is $-CO_2H$, or $-CO_2R_4$, then the other is H;

Tz is a triazole containing moiety selected from the group consisting of:


and

;

wherein L_1 is

or

;

and L_2 is

or

;

wherein:

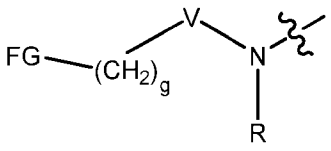
X_1 is $-NRC(O)-$, $-NRC(O)NR-$, $-NRC(S)NR$, or $-NRC(O)O-$;

X_2 is $-C(O)NR-$, $-NRC(O)NR-$, $-NRC(S)NR-$, or $-OC(O)NR-$;

R_5 is H, $-CO_2H$, or $-CO_2R_6$, wherein R_6 is C_1-C_6 alkyl, C_6-C_{12} aryl, or C_6-C_{16} alkyaryl; b is 1, 2, 3, or 4; and d is 1, 2, 3, or 4;

Y is $-C(O)-$, $-NRC(O)-$, $-NRC(S)-$, $-OC(O)-$;

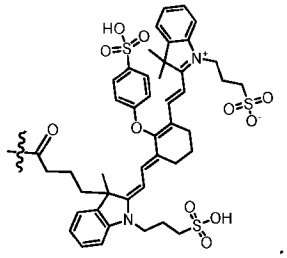
W is a bond, $-(CH_2\text{-}O)_t-$, $-NRC(O)-$, $-NRC(O)NR-$, $-NRC(S)NR-$, $-NRC(O)O-$, $-OC(O)NR-$, $-OC(O)-$, $-C(O)NR-$, or $-C(O)O-$, wherein t is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8;

G is  ; FG is a fluorescent dye moiety that emits in the near-infrared spectrum; V is –C(O)-, -NRC(O)-, -NRC(S)-, or –OC(O)-, and g is an integer selected from the group consisting of 1, 2, 3, 4, 5, and 6;

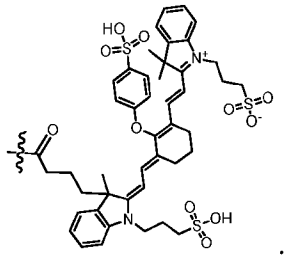
under the condition that when r is 0, then q and s are both 0 or both 1;

or a pharmaceutically acceptable salt thereof; under the proviso that if R' is hydrogen.

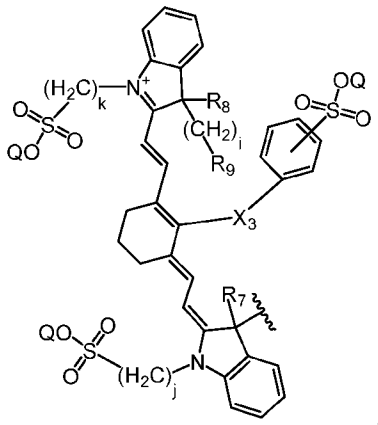
In certain embodiments, the fluorescent dye moiety is:



In certain embodiments, the fluorescent dye moiety cannot be:



In particular embodiments, the compound of formula (IV), the fluorescent dye moiety is:



wherein:

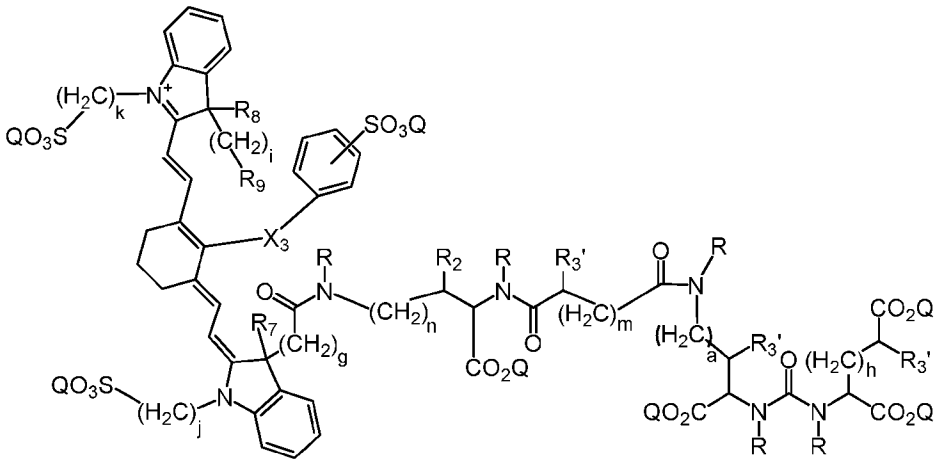
i, j, and k are each an integer selected from the group consisting of 1, 2, 3, 4, 5, and 6;

X_3 is a single bond, –O–, or –S–;

R_7, R_8, and R_9 are each independently hydrogen, C_1-C_4 unsubstituted or substituted alkyl, or $–CO_2Q$;

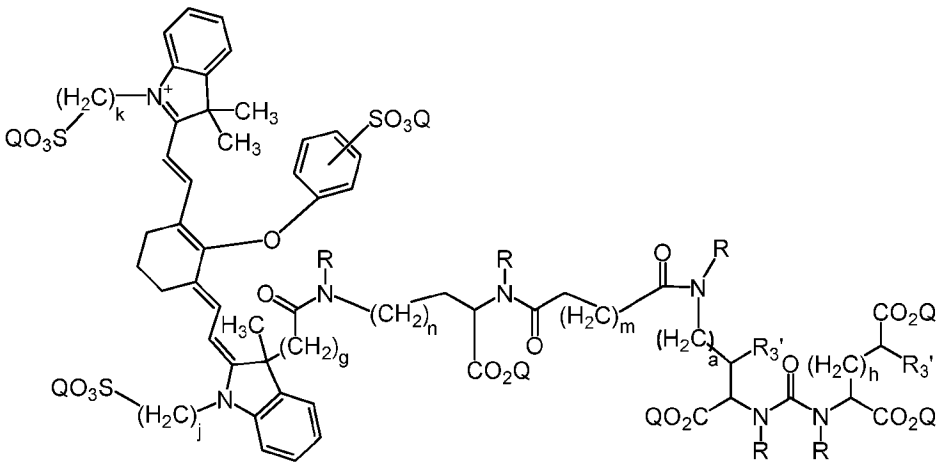
each Q is independently hydrogen, a metal ion, a negative charge, or a protecting group.

In certain embodiments, the compound of formula (IV) is:



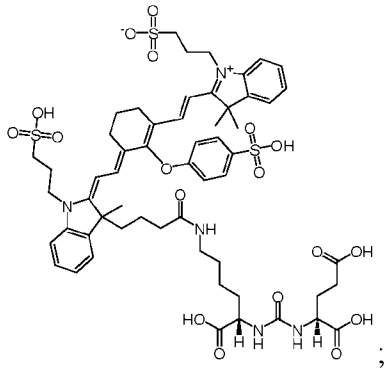
(IVa).

In certain embodiments, the compound of formula (IV) is:



(IVb).

In particular embodiments, the compound of formula (IV) is selected from: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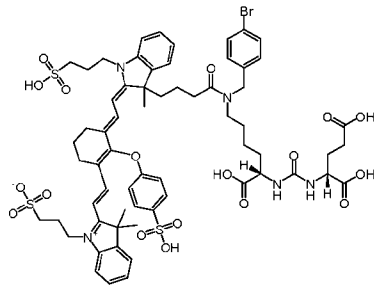
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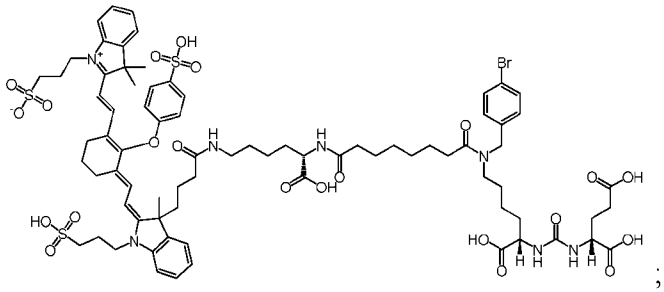
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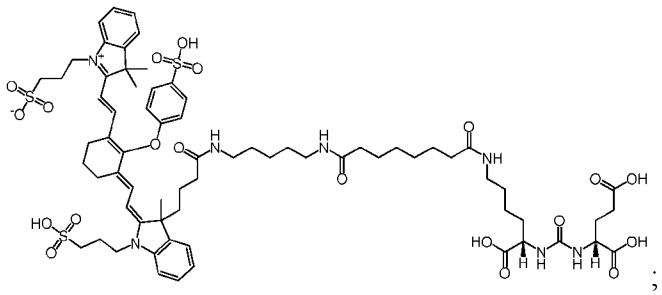
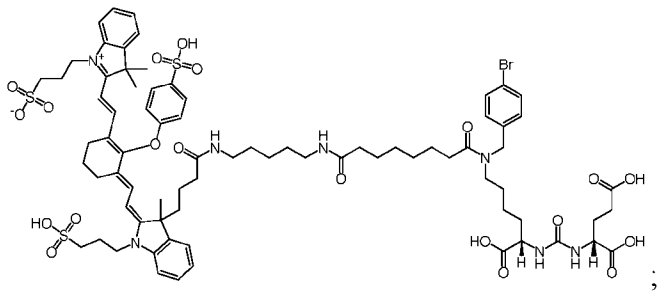

;

5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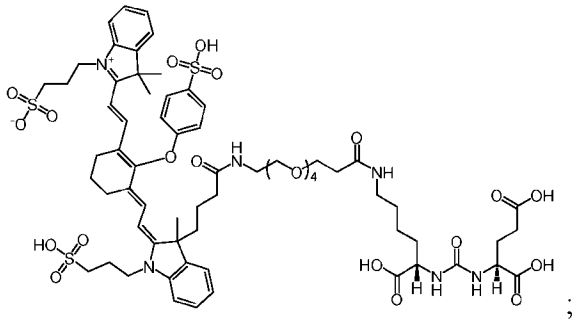
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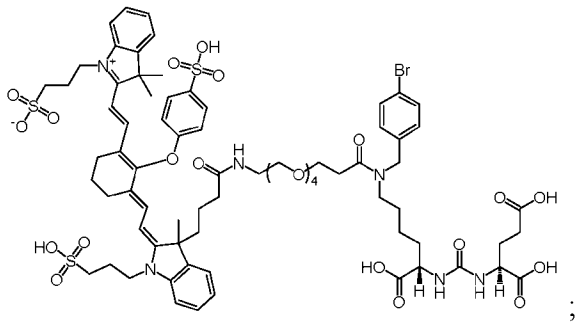
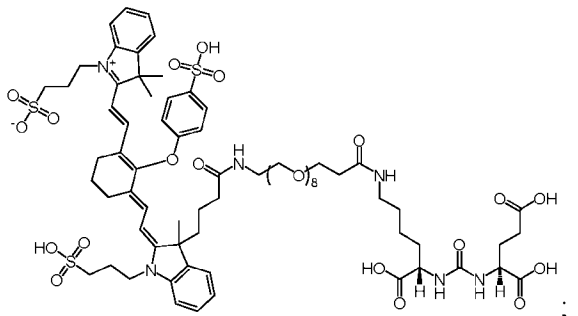
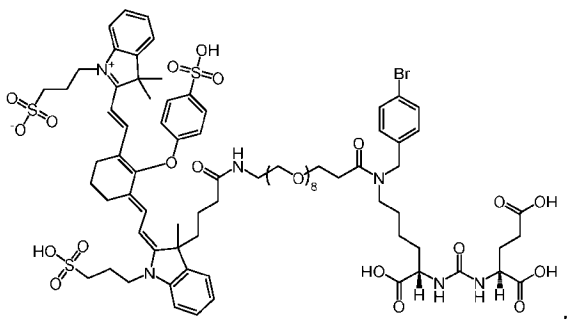
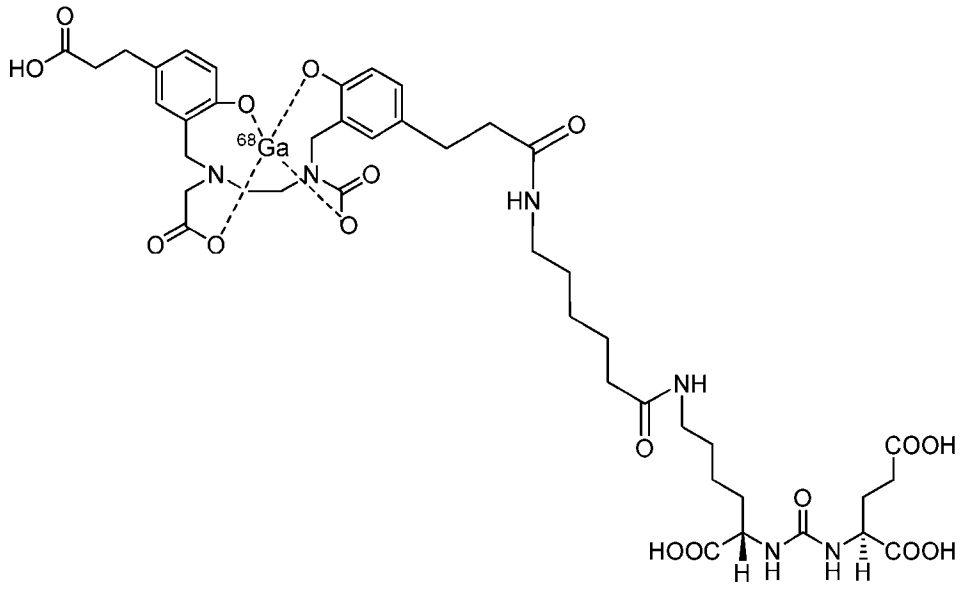

;


; and


.

In other embodiments, the PSMA-targeting compound is:



(^{68}GA-PSMA-11).

In general, the "effective amount" of an active agent refers to the amount necessary to elicit the desired biological response. As will be appreciated by those of ordinary skill in this art, the effective amount of an agent may vary depending on such factors as the desired biological endpoint, the agent to be delivered, the makeup of the pharmaceutical composition, the target tissue, and the like.

In certain embodiments, the presently disclosed method can be practiced *in vitro* or *ex vivo* by introducing, and preferably mixing, the compound and cell(s) or tumor(s) in a controlled environment, such as a culture dish or tube. The method can be practiced *in vivo*, in which case contacting means exposing the target in a subject to at least one compound of the presently disclosed subject matter, such as administering the compound to a subject via any suitable route. According to the presently disclosed subject matter, contacting may comprise introducing, exposing, and the like, the compound at a site distant to the cells to be contacted, and allowing the bodily functions of the subject, or natural (e.g., diffusion) or man-induced (e.g., swirling) movements of fluids to result in contact of the compound and the target.

The subject treated by the presently disclosed methods in their many embodiments is desirably a human subject, although it is to be understood that the methods described herein are effective with respect to all vertebrate species, which are intended to be included in the term "subject." Accordingly, a "subject" can include a human subject for medical purposes,

such as for the treatment of an existing condition or disease or the prophylactic treatment for preventing the onset of a condition or disease, or an animal (non-human) subject for medical, veterinary purposes, or developmental purposes. Suitable animal subjects include mammals including, but not limited to, primates, e.g., humans, monkeys, apes, and the like; bovines, e.g., cattle, oxen, and the like; ovines, e.g., sheep and the like; caprines, e.g., goats and the like; porcines, e.g., pigs, hogs, and the like; equines, e.g., horses, donkeys, zebras, and the like; felines, including wild and domestic cats; canines, including dogs; lagomorphs, including rabbits, hares, and the like; and rodents, including mice, rats, and the like. An animal may be a transgenic animal. In some embodiments, the subject is a human including, but not limited to, fetal, neonatal, infant, juvenile, and adult subjects. Further, a "subject" can include a patient afflicted with or suspected of being afflicted with a condition or disease. Thus, the terms "subject" and "patient" are used interchangeably herein. In some embodiments, the subject is human. In other embodiments, the subject is non-human.

The present disclosure provides a pharmaceutical composition including one compound of formula (I-IV) alone or in combination with one or more additional therapeutic agents in admixture with a pharmaceutically acceptable excipient. One of skill in the art will recognize that the pharmaceutical compositions include the pharmaceutically acceptable salts of the compounds described above. Pharmaceutically acceptable salts are generally well known to those of ordinary skill in the art, and include salts of active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituent moieties found on the compounds described herein. When compounds of the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent or by ion exchange, whereby one basic counterion (base) in an ionic complex is substituted for another. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt.

When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent or by ion exchange, whereby one acidic counterion (acid) in an ionic complex is substituted for

another. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-toluenesulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al, "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

Accordingly, pharmaceutically acceptable salts suitable for use with the presently disclosed subject matter include, by way of example but not limitation, acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, or teoclate. Other pharmaceutically acceptable salts may be found in, for example, Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000). In therapeutic and/or diagnostic applications, the compounds of the disclosure can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000).

Depending on the specific conditions being treated, such agents may be formulated into liquid or solid dosage forms and administered systemically or locally. The agents may be delivered, for example, in a timed- or sustained-slow release form as is known to those skilled in the art. Techniques for formulation and administration may be found in

Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000). Suitable routes may include oral, buccal, by inhalation spray, sublingual, rectal, transdermal, vaginal, transmucosal, nasal or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intra-articullar, intra -sternal, intra-synovial, intra-hepatic, intralesional, intracranial, intraperitoneal, intranasal, or intraocular injections or other modes of delivery.

For injection, the agents of the disclosure may be formulated and diluted in aqueous solutions, such as in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

Use of pharmaceutically acceptable inert carriers to formulate the compounds herein disclosed for the practice of the disclosure into dosages suitable for systemic administration is within the scope of the disclosure. With proper choice of carrier and suitable manufacturing practice, the compositions of the present disclosure, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the disclosure to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for oral ingestion by a subject (e.g., patient) to be treated.

For nasal or inhalation delivery, the agents of the disclosure also may be formulated by methods known to those of skill in the art, and may include, for example, but not limited to, examples of solubilizing, diluting, or dispersing substances, such as saline; preservatives, such as benzyl alcohol; absorption promoters; and fluorocarbons.

Pharmaceutical compositions suitable for use in the present disclosure include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. Generally, the compounds according to the disclosure are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from 0.01 to 1000 mg, from

0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. A non-limiting dosage is 10 to 30 mg per day. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, the bioavailability of the compound(s), the adsorption, distribution, metabolism, and excretion (ADME) toxicity of the compound(s), and the preference and experience of the attending physician.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions.

Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethyl-cellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium

stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers may be added.

The term "combination" is used in its broadest sense and means that a subject is administered at least two agents, more particularly a compound described herein and at least one other therapeutic agent. More particularly, the term "in combination" refers to the concomitant administration of two (or more) active agents for the treatment of a, e.g., single disease state. As used herein, the active agents may be combined and administered in a single dosage form, may be administered as separate dosage forms at the same time, or may be administered as separate dosage forms that are administered alternately or sequentially on the same or separate days. In one embodiment of the presently disclosed subject matter, the active agents are combined and administered in a single dosage form. In another embodiment, the active agents are administered in separate dosage forms (e.g., wherein it is desirable to vary the amount of one but not the other). The single dosage form may include additional active agents for the treatment of the disease state.

Further, the compounds described herein can be administered alone or in combination with adjuvants that enhance stability of the compounds, alone or in combination with one or more therapeutic agents, facilitate administration of pharmaceutical compositions containing them in certain embodiments, provide increased dissolution or dispersion, increase inhibitory activity, provide adjunct therapy, and the like, including other active ingredients. Advantageously, such combination therapies utilize lower dosages of the conventional therapeutics, thus avoiding possible toxicity and adverse side effects incurred when those agents are used as monotherapies.

The timing of administration of a compound described herein and at least one additional therapeutic agent can be varied so long as the beneficial effects of the combination of these agents are achieved. Accordingly, the phrase "in combination with" refers to the administration of a compound described herein and at least one additional therapeutic agent either simultaneously, sequentially, or a combination thereof. Therefore, a subject administered a combination of a compound described herein and at least one additional therapeutic agent can receive a compound and at least one additional therapeutic agent at the same time (i.e., simultaneously) or at different times (i.e., sequentially, in either

order, on the same day or on different days), so long as the effect of the combination of both agents is achieved in the subject.

When administered sequentially, the agents can be administered within 1, 5, 10, 30, 60, 120, 180, 240 minutes or longer of one another. In other embodiments, agents administered sequentially, can be administered within 1, 5, 10, 15, 20 or more days of one another. Where the compound described herein and at least one additional therapeutic agent are administered simultaneously, they can be administered to the subject as separate pharmaceutical compositions, each comprising either a compound or at least one additional therapeutic agent, or they can be administered to a subject as a single pharmaceutical composition comprising both agents.

When administered in combination, the effective concentration of each of the agents to elicit a particular biological response may be less than the effective concentration of each agent when administered alone, thereby allowing a reduction in the dose of one or more of the agents relative to the dose that would be needed if the agent was administered as a single agent. The effects of multiple agents may, but need not be, additive or synergistic. The agents may be administered multiple times.

In some embodiments, when administered in combination, the two or more agents can have a synergistic effect. As used herein, the terms "synergy," "synergistic," "synergistically" and derivations thereof, such as in a "synergistic effect" or a "synergistic combination" or a "synergistic composition" refer to circumstances under which the biological activity of a combination of a compound described herein and at least one additional therapeutic agent is greater than the sum of the biological activities of the respective agents when administered individually.

Synergy can be expressed in terms of a "Synergy Index (SI)," which generally can be determined by the method described by F. C. Kull et al., Applied Microbiology 9, 538 (1961), from the ratio determined by:

$$Q_a/Q_A + Q_b/Q_B = \text{Synergy Index (SI)}$$

wherein:

Q_A is the concentration of a component A, acting alone, which produced an end point in relation to component A;

Q_a is the concentration of component A, in a mixture, which produced an end point;

Q_B is the concentration of a component B, acting alone, which produced an end point in relation to component B; and

Q_b is the concentration of component B, in a mixture, which produced an end point.

Generally, when the sum of Q_a/Q_A and Q_b/Q_B is greater than one, antagonism is indicated. When the sum is equal to one, additivity is indicated. When the sum is less than one, synergism is demonstrated. The lower the SI, the greater the synergy shown by that particular mixture. Thus, a "synergistic combination" has an activity higher that what can be expected based on the observed activities of the individual components when used alone. Further, a "synergistically effective amount" of a component refers to the amount of the component necessary to elicit a synergistic effect in, for example, another therapeutic agent present in the composition.

Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this presently described subject matter belongs.

While the following terms in relation to compounds of formula (I-IV) are believed to be well understood by one of ordinary skill in the art, the following definitions are set forth to facilitate explanation of the presently disclosed subject matter. These definitions are intended to supplement and illustrate, not preclude, the definitions that would be apparent to one of ordinary skill in the art upon review of the present disclosure.

The terms substituted, whether preceded by the term "optionally" or not, and substituent, as used herein, refer to the ability, as appreciated by one skilled in this art, to change one functional group for another functional group on a molecule, provided that the valency of all atoms is maintained. When more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. The substituents also may be further substituted (e.g., an aryl group substituent may have another substituent off it, such as another aryl group, which is further substituted at one or more positions).

Where substituent groups or linking groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., -

CH_2O- is equivalent to -OCH_2-; -C(=O)O- is equivalent to -OC(=O)-; -OC(=O)NR- is equivalent to -NRC(=O)O-, and the like.

When the term "independently selected" is used, the substituents being referred to (e.g., R groups, such as groups R_1, R_2, and the like, or variables, such as "m" and "n"), can be identical or different. For example, both R_1 and R_2 can be substituted alkyls, or R_1 can be hydrogen and R_2 can be a substituted alkyl, and the like.

The terms "a," "an," or "a(n)," when used in reference to a group of substituents herein, mean at least one. For example, where a compound is substituted with "an" alkyl or aryl, the compound is optionally substituted with at least one alkyl and/or at least one aryl. Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different.

A named "R" or group will generally have the structure that is recognized in the art as corresponding to a group having that name, unless specified otherwise herein. For the purposes of illustration, certain representative "R" groups as set forth above are defined below.

Descriptions of compounds of the present disclosure are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

Unless otherwise explicitly defined, a "substituent group," as used herein, includes a functional group selected from one or more of the following moieties, which are defined herein:

The term hydrocarbon, as used herein, refers to any chemical group comprising hydrogen and carbon. The hydrocarbon may be substituted or unsubstituted. As would be known to one skilled in this art, all valencies must be satisfied in making any substitutions.

The hydrocarbon may be unsaturated, saturated, branched, unbranched, cyclic, polycyclic, or heterocyclic. Illustrative hydrocarbons are further defined herein below and include, for example, methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, allyl, vinyl, *n*-butyl, *tert*-butyl, ethynyl, cyclohexyl, and the like.

The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched chain, acyclic or cyclic hydrocarbon group, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent groups, having the number of carbon atoms designated (i.e., C_{1-10} means one to ten carbons, including 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbons). In particular embodiments, the term "alkyl" refers to C_{1-20} inclusive, including 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20 carbons, linear (i.e., "straight-chain"), branched, or cyclic, saturated or at least partially and in some cases fully unsaturated (i.e., alkenyl and alkynyl) hydrocarbon radicals derived from a hydrocarbon moiety containing between one and twenty carbon atoms by removal of a single hydrogen atom.

Representative saturated hydrocarbon groups include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *sec*-pentyl, isopentyl, neopentyl, *n*-hexyl, *sec*-hexyl, *n*-heptyl, *n*-octyl, *n*-decyl, *n*-undecyl, dodecyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, and homologs and isomers thereof.

"Branched" refers to an alkyl group in which a lower alkyl group, such as methyl, ethyl, or propyl, is attached to a linear alkyl chain. "Lower alkyl" refers to an alkyl group having 1 to about 8 carbon atoms (i.e., a C_{1-8} alkyl), e.g., 1, 2, 3, 4, 5, 6, 7, or 8 carbon atoms. "Higher alkyl" refers to an alkyl group having about 10 to about 20 carbon atoms, e.g., 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbon atoms. In certain embodiments, "alkyl" refers, in particular, to C_{1-8} straight-chain alkyls. In other embodiments, "alkyl" refers, in particular, to C_{1-8} branched-chain alkyls.

Alkyl groups can optionally be substituted (a "substituted alkyl") with one or more alkyl group substituents, which can be the same or different. The term "alkyl group substituent" includes but is not limited to alkyl, substituted alkyl, halo, arylamino, acyl, hydroxyl, aryloxyl, alkoxyl, alkylthio, arylthio, aralkyloxyl, aralkylthio, carboxyl, alkoxycarbonyl, oxo, and cycloalkyl. There can be optionally inserted along the alkyl chain one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms, wherein the

nitrogen substituent is hydrogen, lower alkyl (also referred to herein as "alkylaminoalkyl"), or aryl.

Thus, as used herein, the term "substituted alkyl" includes alkyl groups, as defined herein, in which one or more atoms or functional groups of the alkyl group are replaced with another atom or functional group, including for example, alkyl, substituted alkyl, halogen, aryl, substituted aryl, alkoxyl, hydroxyl, nitro, amino, alkylamino, dialkylamino, sulfate, cyano, and mercapto.

The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain having from 1 to 20 carbon atoms or heteroatoms or a cyclic hydrocarbon group having from 3 to 10 carbon atoms or heteroatoms, or combinations thereof, consisting of at least one carbon atom and at least one heteroatom selected from O, N, P, Si and S, and wherein the nitrogen, phosphorus, and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P and S and Si may be placed at any interior position of the heteroalkyl group or at the position at which alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)- CH_3$, $O-CH_3$, $-O-CH_2-CH_3$, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$.

As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)NR', -NR'R", -OR', -SR, -S(O)R, and/or $-S(O_2)R'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

"Cyclic" and "cycloalkyl" refer to a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, e.g., 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms. The

cycloalkyl group can be optionally partially unsaturated. The cycloalkyl group also can be optionally substituted with an alkyl group substituent as defined herein, oxo, and/or alkylene. There can be optionally inserted along the cyclic alkyl chain one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms, wherein the nitrogen substituent is hydrogen, unsubstituted alkyl, substituted alkyl, aryl, or substituted aryl, thus providing a heterocyclic group. Representative monocyclic cycloalkyl rings include cyclopentyl, cyclohexyl, and cycloheptyl. Multicyclic cycloalkyl rings include adamantyl, octahydronaphthyl, decalin, camphor, camphane, and noradamantyl, and fused ring systems, such as dihydro- and tetrahydronaphthalene, and the like.

The term "cycloalkylalkyl," as used herein, refers to a cycloalkyl group as defined hereinabove, which is attached to the parent molecular moiety through an alkylene moiety, also as defined above, e.g., a C_{1-20} alkylene moiety. Examples of cycloalkylalkyl groups include cyclopropylmethyl and cyclopentylethyl.

The terms "cycloheteroalkyl" or "heterocycloalkyl" refer to a non-aromatic ring system, unsaturated or partially unsaturated ring system, such as a 3- to 10-member substituted or unsubstituted cycloalkyl ring system, including one or more heteroatoms, which can be the same or different, and are selected from nitrogen (N), oxygen (O), sulfur (S), phosphorus (P), and silicon (Si), and optionally can include one or more double bonds.

The cycloheteroalkyl ring can be optionally fused to or otherwise attached to other cycloheteroalkyl rings and/or non-aromatic hydrocarbon rings. Heterocyclic rings include those having from one to three heteroatoms independently selected from oxygen, sulfur, and nitrogen, in which the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. In certain embodiments, the term heterocylic refers to a non-aromatic 5-, 6-, or 7-membered ring or a polycyclic group wherein at least one ring atom is a heteroatom selected from O, S, and N (wherein the nitrogen and sulfur heteroatoms may be optionally oxidized), including, but not limited to, a bi- or tri-cyclic group, comprising fused six-membered rings having between one and three heteroatoms independently selected from the oxygen, sulfur, and nitrogen, wherein (i) each 5-membered ring has 0 to 2 double bonds, each 6-membered ring has 0 to 2 double bonds, and each 7-membered ring has 0 to 3 double bonds, (ii) the nitrogen and sulfur heteroatoms may be optionally oxidized, (iii) the nitrogen heteroatom may optionally be quaternized, and

(iv) any of the above heterocyclic rings may be fused to an aryl or heteroaryl ring. Representative cycloheteroalkyl ring systems include, but are not limited to pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidinyl, piperazinyl, indolinyl, quinuclidinyl, morpholinyl, thiomorpholinyl, thiadiazinanyl, tetrahydrofuranyl, and the like.

The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1 -piperazinyl, 2-piperazinyl, and the like. The terms "cycloalkylene" and "heterocycloalkylene" refer to the divalent derivatives of cycloalkyl and heterocycloalkyl, respectively.

An unsaturated hydrocarbon has one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(l,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. Alkyl groups which are limited to hydrocarbon groups are termed "homoalkyl."

More particularly, the term "alkenyl" as used herein refers to a monovalent group derived from a C_{2-20} inclusive straight or branched hydrocarbon moiety having at least one carbon-carbon double bond by the removal of a single hydrogen molecule. Alkenyl groups include, for example, ethenyl (i.e., vinyl), propenyl, butenyl, 1-methyl-2-buten-1-yl, pentenyl, hexenyl, octenyl, allenyl, and butadienyl.

The term "cycloalkenyl" as used herein refers to a cyclic hydrocarbon containing at least one carbon-carbon double bond. Examples of cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadiene, cyclohexenyl, 1,3-cyclohexadiene, cycloheptenyl, cycloheptatrienyl, and cyclooctenyl.

The term "alkynyl" as used herein refers to a monovalent group derived from a straight or branched C_{2-20} hydrocarbon of a designed number of carbon atoms containing at least one carbon-carbon triple bond. Examples of "alkynyl" include ethynyl, 2-propynyl (propargyl), 1-propynyl, pentynyl, hexynyl, and heptynyl groups, and the like.

The term "alkylene" by itself or a part of another substituent refers to a straight or branched bivalent aliphatic hydrocarbon group derived from an alkyl group having from 1 to about 20 carbon atoms, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbon atoms. The alkylene group can be straight, branched, or cyclic. The alkylene group also can be optionally unsaturated and/or substituted with one or more "alkyl group substituents." There can be optionally inserted along the alkylene group one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms (also referred to herein as "alkylaminoalkyl"), wherein the nitrogen substituent is alkyl as previously described. Exemplary alkylene groups include methylene ($–CH_2–$); ethylene ($–CH_2–CH_2–$); propylene ($–(CH_2)_3–$); cyclohexylene ($–C_6H_{10}–$); $–CH=CH–CH=CH–$; $–CH=CH–CH_2–$; -$CH_2CH_2CH_2CH_2$-, -$CH_2CH=CHCH_2$-, -CH_2CsCCH_2-, -$CH_2CH_2CH(CH_2CH_2CH_3)CH_2$-, -$(CH_2)_q$-N(R)-$(CH_2)_r$–, wherein each of q and r is independently an integer from 0 to about 20, e.g., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, and R is hydrogen or lower alkyl; methylenedioxyl ($–O–CH_2–O–$); and ethylenedioxyl (-O-$(CH_2)_2$–O–). An alkylene group can have about 2 to about 3 carbon atoms and can further have 6-20 carbons. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being some embodiments of the present disclosure. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

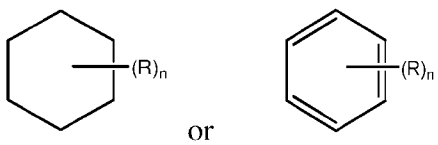
The term "heteroalkylene" by itself or as part of another substituent means a divalent group derived from heteroalkyl, as exemplified, but not limited by, -CH_2-CH_2-S-CH_2-CH_2- and -CH_2-S-CH_2-CH_2-NH-CH_2-. For heteroalkylene groups, heteroatoms also can occupy either or both of the chain termini (e.g., alkyleneoxo, alkylenedioxo, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula -C(O)OR'- represents both -C(O)OR'- and –R'OC(O)-.

The term "aryl" means, unless otherwise stated, an aromatic hydrocarbon substituent that can be a single ring or multiple rings (such as from 1 to 3 rings), which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms (in each separate ring in the case of multiple rings) selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5- thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4- pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5- isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. The terms "arylene" and "heteroarylene" refer to the divalent forms of aryl and heteroaryl, respectively.

For brevity, the term "aryl" when used in combination with other terms (e.g., aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the terms "arylalkyl" and "heteroarylalkyl" are meant to include those groups in which an aryl or heteroaryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl, furylmethyl, and the like) including those alkyl groups in which a carbon atom (e.g., a methylene group) has been replaced by, for example, an oxygen atom (e.g., phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like). The term "haloaryl," however, as used herein is meant to cover only aryls substituted with one or more halogens.

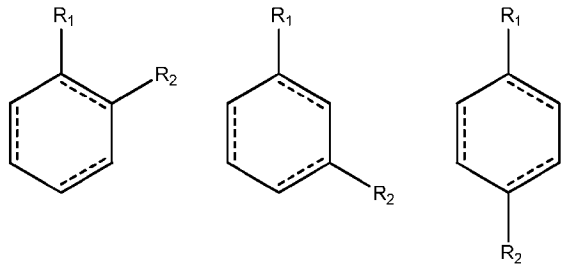
Where a heteroalkyl, heterocycloalkyl, or heteroaryl includes a specific number of members (e.g., "3 to 7 membered"), the term "member" refers to a carbon or heteroatom.

Further, a structure represented generally by the formula:



or

as used herein refers to a ring structure, for example, but not limited to a 3-carbon, a 4-carbon, a 5-carbon, a 6-carbon, a 7-carbon, and the like, aliphatic and/or aromatic cyclic compound, including a saturated ring structure, a partially saturated ring structure, and an unsaturated ring structure, comprising a substituent R group, wherein the R group can be present or absent, and when present, one or more R groups can each be substituted on one or more available carbon atoms of the ring structure. The presence or absence of the R group and number of R groups is determined by the value of the variable "n," which is an integer generally having a value ranging from 0 to the number of carbon atoms on the ring available for substitution. Each R group, if more than one, is substituted on an available carbon of the ring structure rather than on another R group. For example, the structure above where n is 0 to 2 would comprise compound groups including, but not limited to:



and the like.

A dashed line representing a bond in a cyclic ring structure indicates that the bond can be either present or absent in the ring. That is, a dashed line representing a bond in a cyclic ring structure indicates that the ring structure is selected from a saturated ring structure, a partially saturated ring structure, and an unsaturated ring structure.

The symbol (~~~~) denotes the point of attachment of a moiety to the remainder of the molecule.

When a named atom of an aromatic ring or a heterocyclic aromatic ring is defined as being "absent," the named atom is replaced by a direct bond.

Each of above terms (e.g. , "alkyl," "heteroalkyl," "cycloalkyl, and "heterocycloalkyl", "aryl," "heteroaryl," "phosphonate," and "sulfonate" as well as their divalent derivatives) are meant to include both substituted and unsubstituted forms of the indicated group. Optional substituents for each type of group are provided below.

Substituents for alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl monovalent and divalent derivative groups (including those groups often referred to as alkylene, alkenyl,

heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to: -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R'", -OC(O)R', -C(O)R', -CO_2R',-C(O)NR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R'", -NR"C(O)OR', -NR-C(NR'R")=NR'", -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN, CF_3, fluorinated C_{1-4} alkyl, and -NO_2 in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such groups. R', R", R'" and R"" each may independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. As used herein, an "alkoxy" group is an alkyl attached to the remainder of the molecule through a divalent oxygen. When a compound of the disclosure includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'" and R"" groups when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7- membered ring. For example, -NR'R" is meant to include, but not be limited to, 1- pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., -CF_3 and -CH_2CF_3) and acyl (e.g., -$C(O)CH_3$, -$C(O)CF_3$, -$C(O)CH_2OCH_3$, and the like).

Similar to the substituents described for alkyl groups above, exemplary substituents for aryl and heteroaryl groups (as well as their divalent derivatives) are varied and are selected from, for example: halogen, -OR', -NR'R", -SR', -SiR'R"R'", -OC(O)R', -C(O)R', -CO_2R', -C(O)NR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R'", -NR"C(O)OR', -NR-C(NR'R"R'")=NR"", -NR-C(NR'R")=NR'" -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN and -NO_2, -R', -N_3, -$CH(Ph)_2$, fluoro(C_{1-4})alkoxo, and fluoro(C_{1-4})alkyl, in a number ranging from zero to the total number of open valences on aromatic ring system; and where R', R", R'" and R"" may be independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,

substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. When a compound of the disclosure includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R'" and R"" groups when more than one of these groups is present.

Two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)-$(CRR')_q$-U-, wherein T and U are independently -NR-, -O-, -CRR'- or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$NR'- or a single bond, and r is an integer of from 1 to 4.

One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CRR')_s$-X'- $(C"R'")_d$-, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituents R, R', R" and R'" may be independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

As used herein, the term "acyl" refers to an organic acid group wherein the -OH of the carboxyl group has been replaced with another substituent and has the general formula RC(=O)-, wherein R is an alkyl, alkenyl, alkynyl, aryl, carbocylic, heterocyclic, or aromatic heterocyclic group as defined herein). As such, the term "acyl" specifically includes arylacyl groups, such as a 2-(furan-2-yl)acetyl)- and a 2-phenylacetyl group. Specific examples of acyl groups include acetyl and benzoyl. Acyl groups also are intended to include amides, -RC(=O)NR', esters, -RC(=O)OR', ketones, -RC(=O)R', and aldehydes, -RC(=O)H.

The terms "alkoxyl" or "alkoxy" are used interchangeably herein and refer to a saturated (i.e., alkyl–O–) or unsaturated (i.e., alkenyl–O– and alkynyl–O–) group attached to the parent molecular moiety through an oxygen atom, wherein the terms "alkyl," "alkenyl," and "alkynyl" are as previously described and can include C_{1-20} inclusive, linear, branched, or cyclic, saturated or unsaturated oxo-hydrocarbon chains, including, for example,

methoxyl, ethoxyl, propoxyl, isopropoxyl, *n*-butoxyl, *sec*-butoxyl, *tert*-butoxyl, and *n*-pentoxyl, neopentoxyl, *n*-hexoxyl, and the like.

The term "alkoxyalkyl" as used herein refers to an alkyl-O-alkyl ether, for example, a methoxyethyl or an ethoxymethyl group.

"Aryloxyl" refers to an aryl-O- group wherein the aryl group is as previously described, including a substituted aryl. The term "aryloxyl" as used herein can refer to phenyloxyl or hexyloxyl, and alkyl, substituted alkyl, halo, or alkoxyl substituted phenyloxyl or hexyloxyl.

"Aralkyl" refers to an aryl-alkyl-group wherein aryl and alkyl are as previously described, and included substituted aryl and substituted alkyl. Exemplary aralkyl groups include benzyl, phenylethyl, and naphthylmethyl.

"Aralkyloxyl" refers to an aralkyl-O– group wherein the aralkyl group is as previously described. An exemplary aralkyloxyl group is benzyloxyl, i.e., C_6H_5-CH_2-O-. An aralkyloxyl group can optionally be substituted.

"Alkoxycarbonyl" refers to an alkyl-O-C(=O)– group. Exemplary alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, butyloxycarbonyl, and *tert*-butyloxycarbonyl.

"Aryloxycarbonyl" refers to an aryl-O-C(=O)– group. Exemplary aryloxycarbonyl groups include phenoxy- and naphthoxy-carbonyl.

"Aralkoxycarbonyl" refers to an aralkyl-O-C(=O)– group. An exemplary aralkoxycarbonyl group is benzyloxycarbonyl.

"Carbamoyl" refers to an amide group of the formula –C(=O)NH_2. "Alkylcarbamoyl" refers to a R'RN–C(=O)– group wherein one of R and R' is hydrogen and the other of R and R' is alkyl and/or substituted alkyl as previously described.

"Dialkylcarbamoyl" refers to a R'RN–C(=O)– group wherein each of R and R' is independently alkyl and/or substituted alkyl as previously described.

The term carbonyldioxyl, as used herein, refers to a carbonate group of the formula -O-C(=O)-OR.

"Acyloxyl" refers to an acyl-O- group wherein acyl is as previously described.

The term "amino" refers to the –NH_2 group and also refers to a nitrogen containing group as is known in the art derived from ammonia by the replacement of one or more

hydrogen radicals by organic radicals. For example, the terms "acylamino" and "alkylamino" refer to specific N-substituted organic radicals with acyl and alkyl substituent groups, respectively.

An "aminoalkyl" as used herein refers to an amino group covalently bound to an alkylene linker. More particularly, the terms alkylamino, dialkylamino, and trialkylamino as used herein refer to one, two, or three, respectively, alkyl groups, as previously defined, attached to the parent molecular moiety through a nitrogen atom. The term alkylamino refers to a group having the structure –NHR' wherein R' is an alkyl group, as previously defined; whereas the term dialkylamino refers to a group having the structure –NR'R", wherein R' and R" are each independently selected from alkyl groups. The term trialkylamino refers to a group having the structure –NR'R"R"', wherein R', R", and R"' are each independently selected from alkyl groups. Additionally, R', R", and/or R"' taken together may optionally be $-(CH_2)_k-$ where k is an integer from 2 to 6. Examples include, but are not limited to, methylamino, dimethylamino, ethylamino, diethylamino, diethylaminocarbonyl, methylethylamino, isopropylamino, piperidino, trimethylamino, and propylamino.

The amino group is -NR'R", wherein R' and R" are typically selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

The terms alkylthioether and thioalkoxyl refer to a saturated (i.e., alkyl–S–) or unsaturated (i.e., alkenyl–S– and alkynyl–S–) group attached to the parent molecular moiety through a sulfur atom. Examples of thioalkoxyl moieties include, but are not limited to, methylthio, ethylthio, propylthio, isopropylthio, *n*-butylthio, and the like.

"Acylamino" refers to an acyl-NH– group wherein acyl is as previously described. "Aroylamino" refers to an aroyl-NH– group wherein aroyl is as previously described.

The term "carbonyl" refers to the –C(=O)– group, and can include an aldehyde group represented by the general formula R-C(=O)H.

The term "carboxyl" refers to the –COOH group. Such groups also are referred to herein as a "carboxylic acid" moiety.

The term "cyano" refers to the -C≡N group.

The terms "halo," "halide," or "halogen" as used herein refer to fluoro, chloro, bromo, and iodo groups. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_{1-4})alkyl" is mean to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

The term "hydroxyl" refers to the –OH group.

The term "hydroxyalkyl" refers to an alkyl group substituted with an –OH group.

The term "mercapto" refers to the –SH group.

The term "oxo" as used herein means an oxygen atom that is double bonded to a carbon atom or to another element.

The term "nitro" refers to the $–NO_2$ group.

The term "thio" refers to a compound described previously herein wherein a carbon or oxygen atom is replaced by a sulfur atom.

The term "sulfate" refers to the $–SO_4$ group.

The term thiohydroxyl or thiol, as used herein, refers to a group of the formula –SH.

More particularly, the term "sulfide" refers to compound having a group of the formula –SR.

The term "sulfone" refers to compound having a sulfonyl group $–S(O_2)R$.

The term "sulfoxide" refers to a compound having a sulfinyl group –S(O)R

The term ureido refers to a urea group of the formula $–NH—CO—NH_2$.

Throughout the specification and claims, a given chemical formula or name shall encompass all tautomers, congeners, and optical- and stereoisomers, as well as racemic mixtures where such isomers and mixtures exist.

Certain compounds of the present disclosure may possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)-or (S)- or, as D- or L- for amino acids, and individual isomers are encompassed within the scope of the present disclosure. The compounds of the present disclosure do not include those which are known in art to be too unstable to synthesize and/or isolate. The present disclosure is meant to include compounds in racemic, scalemic, and optically pure forms. Optically active (R)- and (S)-, or D- and L-isomers may

be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefenic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the disclosure.

It will be apparent to one skilled in the art that certain compounds of this disclosure may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the disclosure. The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures with the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this disclosure.

The compounds of the present disclosure may also contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are encompassed within the scope of the present disclosure.

The compounds of the present disclosure may exist as salts. The present disclosure includes such salts. Examples of applicable salt forms include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (e.g. (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures, succinates, benzoates, and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in art. Also included are base addition salts such as sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a

similar salt. When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent or by ion exchange. Examples of acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like. Certain specific compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

Certain compounds of the present disclosure can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present disclosure. Certain compounds of the present disclosure may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present disclosure and are intended to be within the scope of the present disclosure.

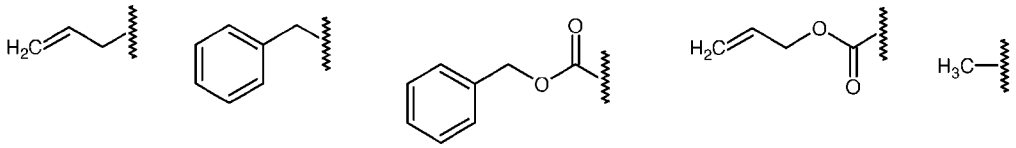
In addition to salt forms, the present disclosure provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present disclosure. Additionally, prodrugs can be converted to the compounds of the present disclosure by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present disclosure when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

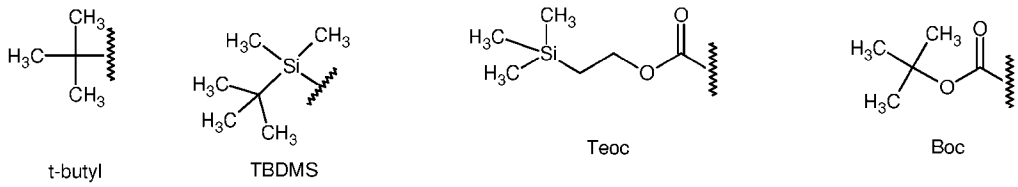
The term "protecting group" refers to chemical moieties that block some or all reactive moieties of a compound and prevent such moieties from participating in chemical reactions until the protective group is removed, for example, those moieties listed and described in T. W. Greene, P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd ed. John Wiley & Sons (1999). It may be advantageous, where different protecting groups are employed, that each (different) protective group be removable by a different means. Protective groups that are cleaved under totally disparate reaction conditions allow differential removal of such protecting groups. For example, protective groups can be removed by acid, base, and hydrogenolysis. Groups such as trityl, dimethoxytrityl, acetal and tert-butyldimethylsilyl are acid labile and may be used to protect carboxy and hydroxy reactive moieties in the presence of amino groups protected with Cbz groups, which are removable by hydrogenolysis, and Fmoc groups, which are base labile. Carboxylic acid and hydroxy reactive moieties may be blocked with base labile groups such as, without limitation, methyl, ethyl, and acetyl in the presence of amines blocked with acid labile groups such as tert-butyl carbamate or with carbamates that are both acid and base stable but hydrolytically removable.

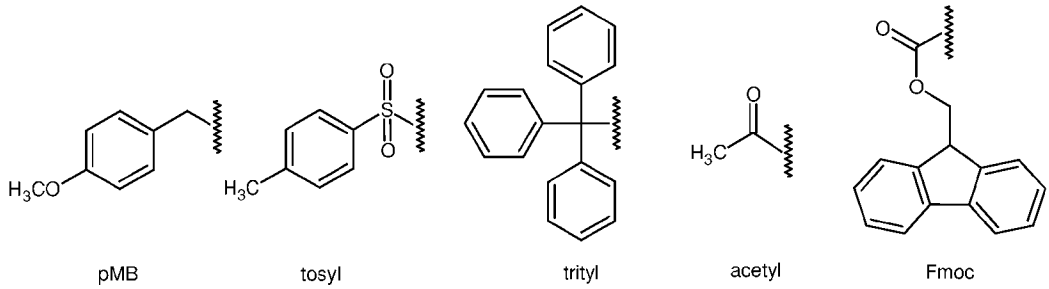
Carboxylic acid and hydroxy reactive moieties may also be blocked with hydrolytically removable protective groups, such as the benzyl group, while amine groups capable of hydrogen bonding with acids may be blocked with base labile groups such as Fmoc. Carboxylic acid reactive moieties may be blocked with oxidatively-removable protective groups such as 2,4-dimethoxybenzyl, while co-existing amino groups may be blocked with fluoride labile silyl carbamates.

Allyl blocking groups are useful in the presence of acid- and base- protecting groups since the former are stable and can be subsequently removed by metal or pi-acid catalysts. For example, an allyl-blocked carboxylic acid can be deprotected with a palladium(O)-catalyzed reaction in the presence of acid labile t-butyl carbamate or base-labile acetate amine protecting groups. Yet another form of protecting group is a resin to which a compound or intermediate may be attached. As long as the residue is attached to the resin, that functional group is blocked and cannot react. Once released from the resin, the functional group is available to react.

Representative protecting groups include, but are not limited to, benzyl, p-methoxybenzyl (PMB), tertiary butyl (t-Bu), methoxymethyl (MOM), methoxyethoxymethyl (MEM), methylthiomethyl (MTM), tetrahydropyranyl (THP), tetrahydrofuranyl (THF), benzyloxymethyl (BOM), trimethylsilyl (TMS), triethylsilyl (TES), t-butyldimethylsilyl (TBDMS), and triphenylmethyl (trityl, Tr), and include moieties having the following chemical structures:







Following long-standing patent law convention, the terms "a," "an," and "the" refer to "one or more" when used in this application, including the claims. Thus, for example, reference to "a subject" includes a plurality of subjects, unless the context clearly is to the contrary (e.g., a plurality of subjects), and so forth.

Throughout this specification and the claims, the terms "comprise," "comprises," and "comprising" are used in a non-exclusive sense, except where the context requires otherwise. Likewise, the term "include" and its grammatical variants are intended to be non-limiting, such that recitation of items in a list is not to the exclusion of other like items that can be substituted or added to the listed items.

For the purposes of this specification and appended claims, unless otherwise indicated, all numbers expressing amounts, sizes, dimensions, proportions, shapes, formulations, parameters, percentages, quantities, characteristics, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term "about" even though the term "about" may not expressly appear with the value, amount, or range. Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are not and need not be exact, but may be approximate and/or larger or smaller as desired, reflecting tolerances, conversion factors, rounding off, measurement error and the like, and other factors known to those of skill in the art depending on the desired properties sought to be obtained by the presently disclosed subject matter. For example, the term "about," when referring to a value can be meant to encompass variations of, in some embodiments, ± 100% in some embodiments ± 50%, in some embodiments ± 20%, in some embodiments ± 10%, in some embodiments ± 5%, in some embodiments ±1%, in some embodiments ± 0.5%, and in some embodiments ± 0.1% from the specified amount, as such variations are appropriate to perform the disclosed methods or employ the disclosed compositions.

Further, the term "about" when used in connection with one or more numbers or numerical ranges, should be understood to refer to all such numbers, including all numbers in a range and modifies that range by extending the boundaries above and below the numerical values set forth. The recitation of numerical ranges by endpoints includes all numbers, e.g., whole integers, including fractions thereof, subsumed within that range (for example, the recitation of 1 to 5 includes 1, 2, 3, 4, and 5, as well as fractions thereof, e.g., 1.5, 2.25, 3.75, 4.1, and the like) and any range within that range.

EXAMPLES

The following Examples have been included to provide guidance to one of ordinary skill in the art for practicing representative embodiments of the presently disclosed subject matter. In light of the present disclosure and the general level of skill in the art, those of skill can appreciate that the following Examples are intended to be exemplary only and that numerous changes, modifications, and alterations can be employed without departing from the scope of the presently disclosed subject matter. The synthetic descriptions and specific

examples that follow are only intended for the purposes of illustration, and are not to be construed as limiting in any manner to make compounds of the disclosure by other methods.

EXAMPLE 1

Representative TSPO-Targeting Compounds for Evaluation of Injuries in the Peripheral Nervous System

1.1 Near-infrared imaging

Ex-vivo near-infrared (NIR) imaging of different nerve injuries was performed using NIR-labeled DPA-713. Lewis rats received 10-nmol doses of DPA-713-dye via tail vein injection prior to sacrifice, hip disarticulation, and hindlimb imaging using a LI-COR Pearl Impulse Small Animal Imaging System (LI-COR Biosciences). Hindlimb groups included: 4-weeks after sciatic nerve transection; 4-weeks after sciatic nerve transection with epineurial suture repair; 2-weeks after sciatic nerve transection with epineurial suture repair; 2-weeks after common peroneal nerve crush; and uninjured control.

We demonstrated low baseline DPA-713-dye uptake in uninjured sciatic nerves (FIG. 1A, 1C), and a consistent increase in DPA-713-dye uptake within denervation portions of nerve after sciatic transection without repair (FIG. 1B, 1D).

At 2 weeks post-injury, we also demonstrated increase DPAY-713-dye uptake distal to the site of common perineal nerve crush (FIG. 2A) and distal to the site of sciatic nerve transection with repair (FIG. 2B). At 4 weeks following nerve repair, we demonstrated resolution of DPA-713-dye uptake in regeneration portions of nerve (FIG. 2D) toward baseline of the uninjured limb (FIG. 2C).

1.2 Biodistribution

We next evaluated the biodistribution of ^{124}I-iodo-DPA713 after sciatic nerve injury. Forty-nine Lewis rats received unilateral sciatic nerve transection without repair, transection with repair, or sham surgery and underwent biodistribution evaluations at 2 weeks, 4 weeks, or 16 weeks post-injury (n=16 per timepoint). Animals received 109+/- 50 μCi of ^{124}I-Iodo-DPA713 intravenously prior to euthanasia and harvest of the sciatic nerve. The nerve was harvested in 4 segments to measure uptake along the nerve: 2 segments proximal to the injury site and 2 segments distal to the injury site. Activity in each segment was calculated using an automated gamma counter (LKB Compugamma CS 1282) and expressed as percent

injected dose per gram (%ID/segment). Similar to the NIR imaging finding, uptake was elevated just proximal to the injury site and distal to the injury site at 2 weeks post-injury in nerves that had undergone either transection without repair or transection with repair (FIG. 3). By 4 weeks post-injury, nerve uptake resolved toward sham surgery in repaired nerves but remained elevated in unrepaired nerves (FIG. 3). This trend persisted at 16 weeks post-injury (FIG. 3).

1.3 Large animal ^{124}I-iodo-DPA713 PET-CT

A female Yorkshire pig at age 5 months underwent proximal right median nerve transection with repair and left median nerve transection without repair at the proximal humerus, 12 cm from the olecranon. The median nerve size, regenerative capacity, and regenerative distance between injury and forearm flexor muscles are analogous to humans. Scholz et al., 2010; Smith et al., 2022.

At 16-weeks post-injury and a weight of 68.8 kg, the animal received intravenous injection of 3 mCi of ^{124}I-iodo-DPA713 prior to whole-body imaging on a clinical PET-CT scanner (Siemens Biography mCT PET-CT). Increased uptake ^{124}I-iodo-DPA713 localized to the bilateral distal forearms in regions corresponding the expected location of the median nerves (FIG. 4).

1.4 Large animal histology

The Yorkshire pig was sacrificed following PET-CT and the median nerves were harvested for histology. Immunohistochemical analysis identified co-localization between the macrophage marker CD68 and TSPO at the neuroma stump, as well as in the distal denervated median nerve (FIG. 5).

1.5 Human Histology

TSPO expression was also evaluated in human major peripheral nerve biopsies collected from patients with nerve injuries at the time of nerve reconstruction. As in the pig histology, TSPO+/CD68+ macrophages were identified in degenerated nerves several months after injury (FIG. 6).

EXAMPLE 2

Representative PSMA-Targeting Compounds for Evaluation of Injuries in the Peripheral Nervous System

2.1 Background

In this Example, we sought to investigate the clinical GCPII-binding PET agents to evaluate muscle denervation. We demonstrate sustained uptake of ^{18}F-DCFPyL and ^{68}Ga-PSMA-11 in both rodent and pig nerve injury models at least 16 weeks after muscle denervation. Given its established safety and clinical availability, GCPII-based PET has high translational potential in the care of patients with complex PNS injuries.

2.1 Near-infrared imaging

Lewis rats received diverse injuries to the sciatic nerve and its branches. At various timepoints after injury, animals rats received 10 nanomole doses of the fluorescent PSMA-targeting ligand YC27 via tail vein injection prior to sacrifice and hindlimb harvest. The skin was removed and biceps femoris dissected away to expose the sciatic nerve for evaluation using a Pearl Impulse Near-Infrared (NIR) Imager.

At 2 weeks post-injury, sciatic nerve transection with repair resulted in elevated YC27 uptake in anterior and posterior leg compartment musculature (FIG. 7A). A complete crush injury of the proximal common peroneal nerve resulted in YC27 uptake in the denervated anterior compartment muscles only (FIG. 7B). Selective transection of the medial gastrocnemius muscle branch resulted in specific YC27 uptake to the denervated medial head with sparing of the uninjured lateral head (FIG. 7C).

At 4 weeks post-injury, YC27 uptake remained elevated in affected muscles after transection without repair (FIG. 8A) and transection with repair (FIG. 8B). Uptake resolved 4 weeks after common peroneal crush, consistent with the expected course of re-innervation (FIG. 8C). Similarly, YC27 uptake remained high 16 weeks after sciatic nerve transection without repair (FIG. 9A but resolved in the limb after sciatic transection with repair (FIG. 9B). Muscle uptake also resolves towards baseline 16 weeks after common perineal nerve crush (FIG. 9C).

2.3 Biodistribution

Forty-eight rats (24 Male, 24 Female) received unilateral sciatic nerve transection without repair, transection with repair, or sham surgery and underwent biodistribution evaluations at 2 weeks, 4 weeks, or 16 weeks post-injury (n=16 per timepoint). Animals received 140+/- 45 μCi of ^{18}F-DCFPyL intravenously prior to euthanasia and harvest of gastrocnemius muscles (FIG. 10). Activity in each muscle was calculated using an

automated gamma counter (LKB Compugamma CS 1282) and expressed as percent injected dose per gram (%ID/g).

2.4 Blocking Studies

Four additional animals received co-injection of 100 ± 2 μCi of ^{18}F-DCFPyL and 100 mg/kg of ZJ-43, a potent competitive inhibitor of GCPII binding, 4 weeks after sciatic nerve transection without repair. ZJ-43 eliminated differences in ^{18}F-DCFPyL activity between denervated and non-denervated muscles, consistent with ^{18}F-DCFPyL specificity for muscle GCPII (FIG. 11).

2.5 Serial small-animal PET-MRI

Six adult Lewis rats underwent serial ^{68}Ga-PSMA-11 PET-MRI (right sciatic transection with or without repair; n=3 each) at 4 weeks and 16 weeks post-injury. Animals received ^{68}Ga-PSMA-11 intravenously 1 hour prior to 7T PET-MRI (Bruker BioSpec 70/30). An example axial slice taken from an animal 4 weeks after unilateral sciatic transection without repair is demonstrated in FIG. 12. At 4 weeks post-injury, the injured limbs in both operative groups had approximately 2 times greater uptake than the uninjured contralateral side (FIG. 13). At 16 weeks post-injury, uptake remained elevated in unrepaired animals at 1.99 ± 0.42 times greater than contralateral limbs, but decreased in repaired animals to 1.33 ± 0.29 times greater than contralateral (FIG. 13).

2.6 Large animal ^{68}Ga-PSMA-11 PET-CT

A female Yorkshire pig at age 5 months underwent proximal right median nerve transection with repair and left median nerve transection without repair at the proximal humerus, 12 cm from the olecranon. At 16-weeks post-injury, the animal received intravenous injection of 2.41 mCi of ^{68}Ga-PSMA-11 prior to whole-body imaging on a clinical PET-CT scanner (Siemens Biography mCT PET-CT). SUV_{max} (maximum standardized uptake value) was elevated in all median-nerve innervated muscle groups relative to uninjured muscle references (Table 1, FIG. 14). When pooled across muscle groups, denervated muscles had 70% greater SUV_{max} than uninjured, non-denervated muscles (1.39 kBq/cc versus 0.82 kBq/cc).

Table 1: Tissue ^{68}Ga-PSMA-11 PET-CT uptake in a swine model for nerve injury

Tissue	Averaged (kBq/cc)	SD (kB/cc)
Right deep flexor compartment	0.684119	0.148651
Left deep flexor comparmtent	0.767523	0.162857
Right superficial flexor compartment	0.510268	0.154572
Left superficial flexor compartment	0.591223	0.149287
Forearm Extensor compartments	0.388471	0.098278
Biceps Muscles	0.416186	0.075396
Pectoralis Major muscles	0.36479	0.115247
Latissimus muscles	0.204879	0.075032
Liver	0.676448	0.219343

2.7 GCPII expression is attributable to muscle macrophages

Immunohistochemical analyses were performed on muscles harvested after pig ^{68}Ga-PSMA-11 PET-CT . Increased GCPII expression in denervated muscles, such as the flexor carpi radialis, muscle was noted to co-localize with CD68, which is a common marker for macrophages (FIG. 15). Note absence of GCPII/CD68 co-localization in the uninjured, non-denervated pectoralis major muscle. The innervation status of both muscles was confirmed by staining for beta tubulin, a common marker for axons, and alpha bungarotoxin, a common marker for neuromuscular junctions.

REFERENCES

All publications, patent applications, patents, and other references mentioned in the specification are indicative of the level of those skilled in the art to which the presently disclosed subject matter pertains. All publications, patent applications, patents, and other references are herein incorporated by reference to the same extent as if each individual publication, patent application, patent, and other reference was specifically and individually

indicated to be incorporated by reference. It will be understood that, although a number of patent applications, patents, and other references are referred to herein, such reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art.

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Although the foregoing subject matter has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be understood by those skilled in the art that certain changes and modifications can be practiced within the scope of the appended claims.

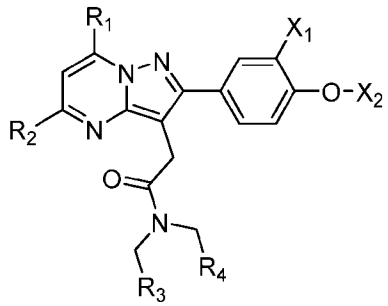
THAT WHICH IS CLAIMED:

1. A method for diagnosing a peripheral nervous system (PNS) neuropathy, the method comprising administering to a subject in need of treatment thereof, at least one of a translocator protein (TSPO)-targeting compound or a PSMA-targeting compound and taking an image.

2. The method of claim 1, wherein the peripheral nervous system (PNS) neuropathy includes a PNS insult and/or neuropathy, a recovery of a PNS insult and/or neuropathy, and muscle denervation, including muscle denervation-induced muscle atrophy, and/or muscle re-innervation.

3. The method of claim 1 or claim 2, wherein the PNS neuropathy is selected from a peripheral nerve injury (PNI), a brachial plexus injury (BPI), and a spinal cord injury (SCI), including a stretch-related PNI, a laceration, a compression PNI, and a PNI related to one or more conditions selected from radiation, electricity, injection, crush, cold, and an intra-neural or extra-neural pathology.

4. The method of claim 1, wherein the TSPO-targeting compound comprises a compound of formula (I):



(I);

wherein:

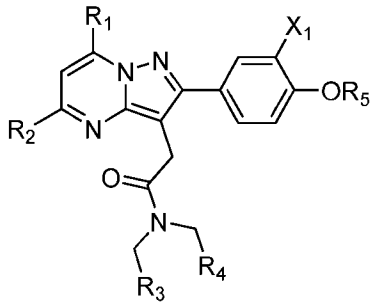
X_1 can be present or absent and when present is selected from a radioisotope of fluorine, a radioisotope of iodine, a radioisotope of bromine, and a radioisotope of astatine;

under the proviso that when X_1 is present, X_2 is H or C_1-C_4 alkyl and when X_1 is absent, X_2 is -L-I, wherein L is a linker and I is an imaging agent; and

R_1, R_2, R_3 and R_4 are each independently selected from hydroxyl, C_1 to C_{10} alkyl, cycloalkyl, aryl, alkylamino, alkylamino, alkenyl, alkynyl, hydroxyalkyl, alkoxyl, dialkylamino thioalkyl, thioalkenyl, thioalkynyl, aryloxy, acyloxy, thioacyl, amido, and sulphonamido; wherein each of alkyl, or aryl moiety may be unsubstituted or substituted with one or more substituents selected from the group consisting of halo, hydroxyl, carboxyl, phosphoryl, phosphonyl, phosphono C_1-C_6 alkyl, carboxy C_1-C_6 alkyl, dicarboxy C_1-C_6 alkyl, dicarboxy halo C_1-C_6 alkyl, sulfonyl, cyano, nitro, alkoxy, alkylthio, acyl, acyloxy, thioacyl, acylthio, aryloxy, amino, alkylamino, dialkylamino, trialkylamino, arylalkylamino, guanidino, aldehydo, ureido, and aminocarbonyl, an amino acid residue, and a substituted amino acid residue; and

pharmaceutically acceptable salts thereof.

5. The method of claim 4, wherein the compound of formula (I) is a compound of formula (Ia):

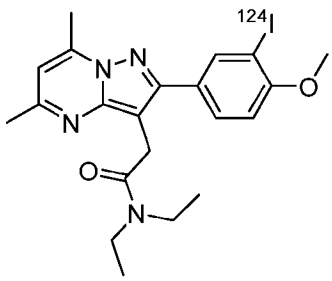


(Ia);

wherein R_5 is H or C_1-C_4 alkyl.

6. The method of claim 4 or claim 5, wherein X_1 is selected from ^{18}F, $^{123}1$, $^{124}1$, $^{125}1$, $^{131}1$, ^{75}Br, ^{76}Br, ^{77}Br, ^{80}Br, ^{80m}Br, ^{82}Br, ^{83}Br and ^{211}At.

7. The method of claim 5, wherein the compound of formula (Ia) is:



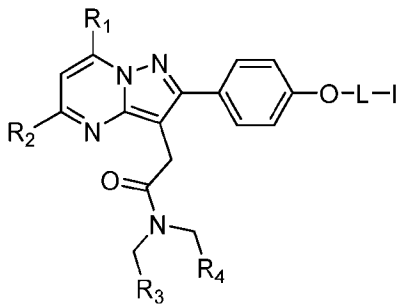
. (^{124}I-iodo-DPA-713).

8. The method of any one of claim 4 to claim 7, wherein:

(a) X_1 is ^{123}I or ^{125}I and the imaging is single photon emission computed tomography (SPECT); or

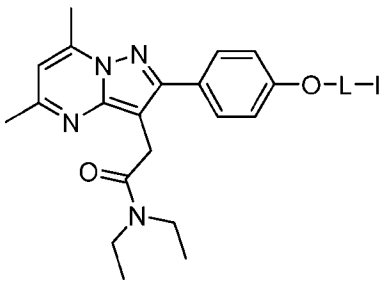
(b) X_1 is ^{18}F or ^{124}I and the imaging is positron emission tomography (PET).

9. The method of claim 4, wherein the compound of formula (I) is a compound of formula (Ib):



(Ib).

10. The method of claim 9, wherein the compound of formula (Ib) is:



.

11. The method of claim 4, claim 9, or claim 10, wherein L comprises an alkylene linker comprising between 1 to 10 carbon atoms.

12. The method of claim 4 or claim 9-11, wherein I comprises an imaging agent covalently linked to the linker, L, via an amide linkage.

13. The method of claim 4 or claim 9-12, wherein the imaging agent comprises an optical dye.

14. The method of claim 13, wherein the optical dye comprises a fluorescent dye.

15. The method of claim 14, wherein the fluorescent dye comprises a fluorescent dye that emits in the near infrared spectral region.

16. The method of claim 14, wherein the fluorescent dye is selected from a polymethine dye, a coumarin dye, a xanthene dye, and a boron-dipyrromethene (BODIPY) dye.

17. The method of claim 16, wherein the polymethine dye is selected from a carbocyanine dye, an indocarbocyanine dye, an oxacarbocyanine dye, a thiacarbocyanine dye, and a merocyanine dye.

18. The method of claim 16, wherein the xanthene dye is selected from a fluorescein dye and a coumarin dye.

19. The method of claim 14, wherein the fluorescent dye is selected from:

BODIPY FL, BODIPY R6G, BODIPY TR, BODIPY TMR, BODIPY 493/503, BODIPY 530/550, BODIPY 558/568, BODIPY 564/570, BODIPY 576/589, BODIPY 581/591,BODIPY 630/650, and BODIPY 650/665;

VivoTag-645, VivoTag-680, VivoTag-S680, VivoTag-S750, VivoTag-800;

Alexa Fluor 488, Alexa Fluor 532, Alexa Fluor 546, Alexa Fluor 555, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 647, Alexa Fluor 660, Alexa Fluor 680, Alexa Fluor 700, Alexa Fluor 750, and AlexaFluor790;

Dy677, Dy676, Dy682, Dy752, Dy780;

DyLight 350, DyLight 405, DyLight 488, DyLight 547, DyLight 550, DyLight 594, DyLight 633, DyLight 647, DyLight 650, DyLight 680, DyLight 755, and DyLight 800;

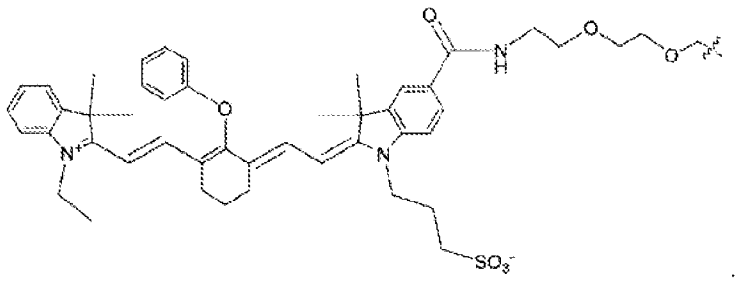
HiLyte Fluor 405, HiLyte Fluor 488, HiLyte Fluor 532, HiLyte Fluor 555, HiLyte™ Fluor 594, HiLyte Fluor 647, HiLyte Fluor 680, HiLyte Fluor 750;

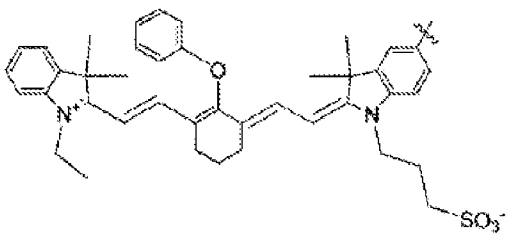
IR800 (Dimethyl{4-[1,5,5-tris(4-dimethylaminophenyl)-2,4-pentadienylidene]-2,5-cyclohexadien-1-ylidene}ammonium perchlorate);

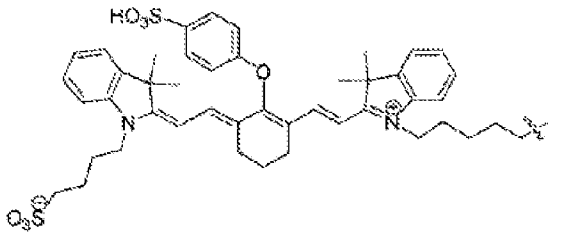
IRDye 650, IRDye 680RD, IRDye 680LT, IRDye 700, IRDye 700DX, IRDye 750, IRDye 800, IRDye 800CW, IRDye 800RS; and

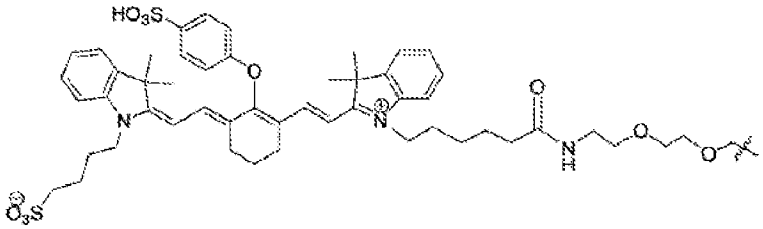
ADS1065A, ADS1075A, ADS775MI, ADS775MP, ADS775PI, ADS775PP, ADS780HO, ADS780WS, ADS785WS, ADS790WS, ADS795WS, ADS798SM, ADS800AT, ADS815EI, ADS830AT, ADS830WS, ADS832WS, ADS845MC, and ADS920MC.

20. The method of claim 13, wherein the optical dye is selected from:


;


;


;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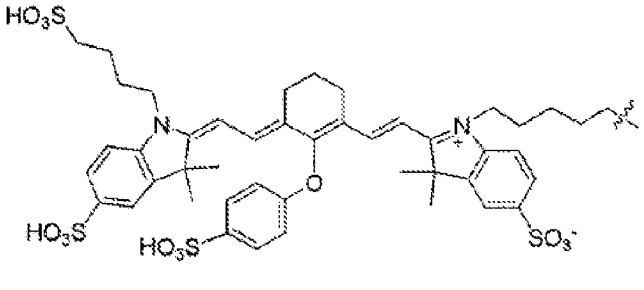
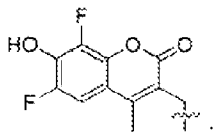
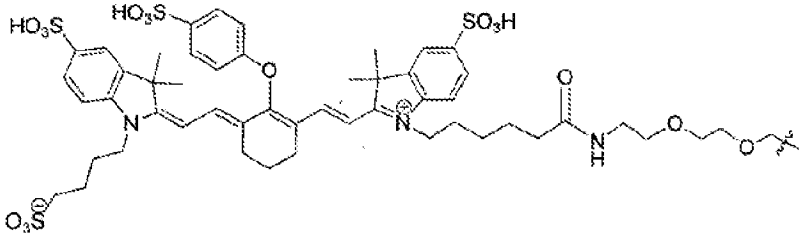
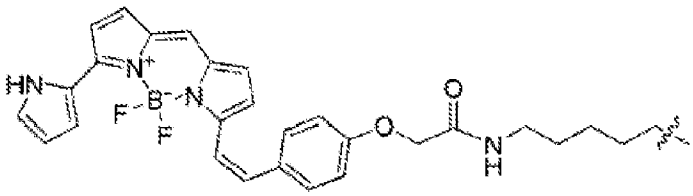

;

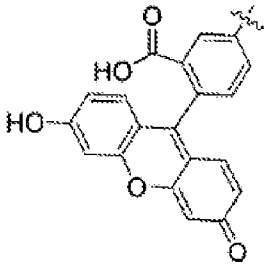

;



;



;



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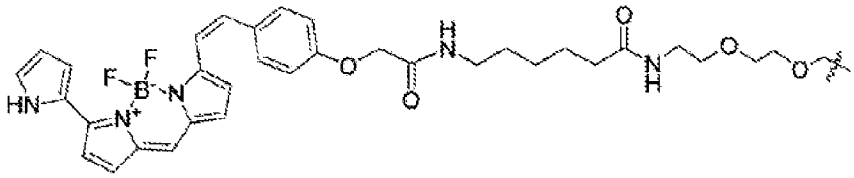

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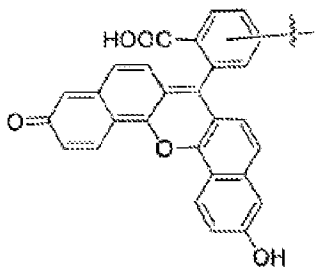

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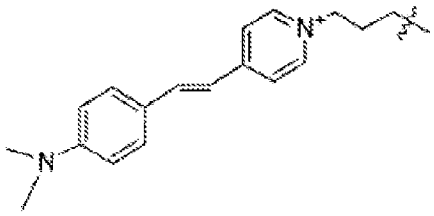
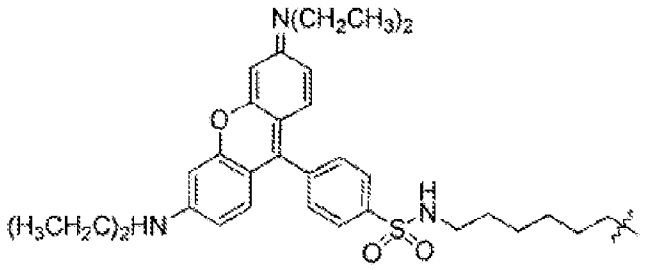
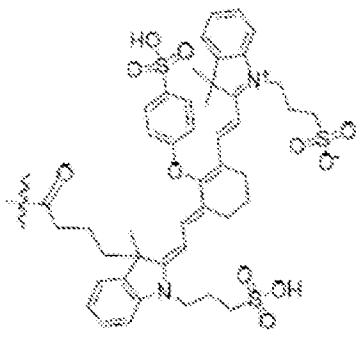


;



; and



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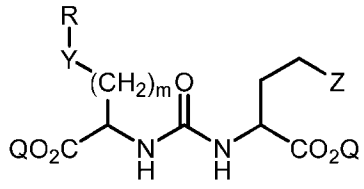
21. The method of claim 1, wherein the PSMA-targeting compound is a compound of formula (II):


(II);

wherein:

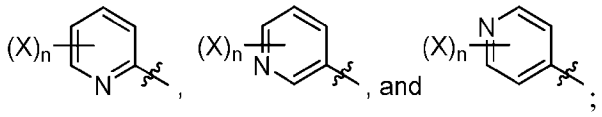
Z is tetrazole or CO_2Q;

each Q is independently selected from hydrogen or a protecting group;

and wherein:

(A) m is 0, 1, 2, 3, 4, 5, or 6;

R is a pyridine ring selected from:



wherein:

X is fluorine, iodine, a radioisotope of fluorine, a radioisotope of iodine, chlorine, bromine, a radioisotope of bromine, a radioisotope of astatine, NO_2, NH_2, $N^+(R^2)_3$, $Sn(R^2)_3$, $Si(R^2)_3$, $Hg(R^2)$, $B(OH)_2$, –$NHNH_2$, –$NHN{=}CHR^3$, –$NHNH{-}CH_2R^3$;

n is 1, 2, 3, or 4;

Y is O, S, N(R'), C(O), NR'C(O), C(O)N(R'), OC(O), C(O)O, NR'C(O)NR', NR'C(S)NR', $NR'S(O)_2$, $S(CH_2)_p$, $NR'(CH_2)_p$, $O(CH_2)_p$, $OC(O)CHR^8NHC(O)$, $NHC(O)CHR^8NHC(O)$, or a covalent bond; wherein p is 1, 2, or 3, R' is H or C_1-C_6 alkyl, and R^8 is hydrogen, alkyl, aryl or heteroaryl, each of which may be substituted;

R^2 is C_1-C_6 alkyl; and

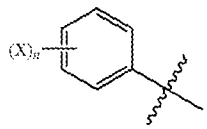
R^3 is alkyl, alkenyl, alkynyl, aryl, or heteroaryl each of which is substituted by fluorine, iodine, a radioisotope of fluorine, a radioisotope of iodine, chlorine, bromine, a radioisotope of bromine, or a radioisotope of astatine, NO_2, NH_2, $N^+(R^2)_3$, $Sn(R^2)_3$, $Si(R^2)_3$, $Hg(R^2)$, or $B(OH)_2$; or

(B) m is 0, 1, 2, 3, 4, 5, or 6;

Y is O, S, N(R'), C(O), NR'C(O), C(O)N(R'), OC(O), C(O)O, NR'C(O)NR', NR'C(S)NR', $NR'S(O)_2$, $S(CH_2)_p$, $NR'(CH_2)_p$, $O(CH_2)_p$, $OC(O)CHR^8NHC(O)$, $NHC(O)CHR^8NHC(O)$, or a

covalent bond; wherein p is 1, 2, or 3, R' is H or C_1-C_6 alkyl, and R^8 is hydrogen alkyl, aryl or heteroaryl, each of which may be substituted;

R is



wherein

X' is selected from the group consisting of $NHNH_2$, $–NHN=CHR^3$, and $–NHNH–CH_2R^3$; wherein R^3 is alkyl, alkenyl, alkynyl, aryl, or heteroaryl each of which is substituted by fluorine, iodine, a radioisotope of fluorine, a radioisotope of iodine, bromine, a radioisotope of bromine, or a radioisotope of astatine; NO_2, NH_2, $N^+(R^2)_3$, $Sn(R^2)_3$, $Si(R^2)_3$, $Hg(R^2)$, or $B(OH)_2$;

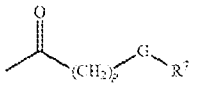
R^2 is C_1-C_6 alkyl;

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

(C) m is 4,

Y is NR', and

R is

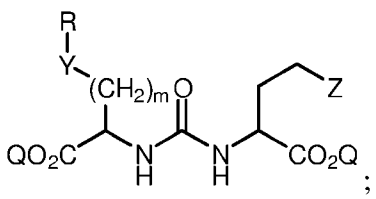


wherein G is O, NR' or a covalent bond;

R is H or C_1-C_6 alkyl; p is 1, 2, 3, or 4, and

R^7 is selected from the group consisting of NH_2, $N=CHR^3$, $NH–CH_2R^3$, wherein R^3 is alkyl, alkenyl, alkynyl, aryl, or heteroaryl each of which is substituted by fluorine, iodine, a radioisotope of fluorine, a radioisotope of iodine, chlorine, bromine, a radioisotope of bromine, or a radioisotope of astatine, NO_2, NH_2, $N^+(R^2)_3$, $Sn(R^2)_3$, $Si(R^2)_3$, $Hg(R^2)$, $B(OH)_2$; and R^2 is C_1-C_6 alkyl.

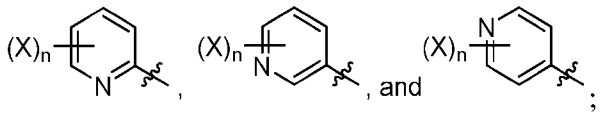
22. The method of claim 21, wherein the compound of formula (III) has the structure:



;

wherein m is 0, 1, 2, 3, 4, 5, or 6;

R is a pyridine ring selected from the group consisting of:



wherein:

X is fluorine, iodine, a radioisotope of fluorine, a radioisotope of iodine, chlorine, bromine, a radioisotope of bromine, a radioisotope of astatine, NO_2, NH_2, $N^+(R^2)_3$, $Sn(R^2)_3$, $Si(R^2)_3$, $Hg(R^2)$, $B(OH)_2$, $–NHNH_2$, $–NHN=CHR^3$, and $–NHNH–CH_2R^3$;

each Q is independently selected from hydrogen or a protecting group;

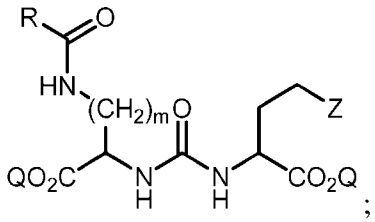
Y is O, S, N(R'), C(O), NR'C(O), C(O)N(R'), OC(O), C(O)O, NR'C(O)NR', NR'C(S)NR', $NR'S(O)_2$, $S(CH_2)_p$, $NR'(CH_2)_p$, $O(CH_2)_p$, $OC(O)CHR^8NHC(O)$, $NHC(O)CHR^8NHC(O)$, or a covalent bond; wherein p is 1, 2, or 3, R' is H or C_1-C_6 alkyl, and R^8 is hydrogen, alkyl, aryl or heteroaryl, each of which may be substituted;

Z is tetrazole or CO_2Q;

R^2 is C_1-C_6 alkyl; and

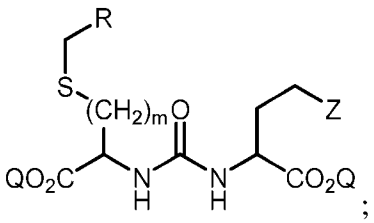
R^3 is alkyl, alkenyl, alkynyl, aryl, or heteroaryl, each of which is substituted by fluorine, iodine, a radioisotope of fluorine, a radioisotope of iodine, chlorine, bromine, a radioisotope of bromine, or a radioisotope of astatine; NO_2, NH_2, $N^+(R^2)_3$, $Sn(R^2)_3$, $Si(R^2)_3$, $Hg(R^2)$, or $B(OH)_2$.

23. The method of claim 22, wherein the compound of formula (II) has the structure:



wherein m is not 0.

24. The method of claim 22, wherein the compound of formula (II) has the structure:



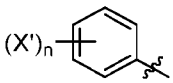
wherein m is not 0.

25. The method of claim 21, wherein for the compound of formula (II):

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

Y is O, S, N(R'), C(O), NR'C(O), C(O)N(R'), OC(O), C(O)O, NR'C(O)NR', NR'C(S)NR', $NR'S(O)_2$, $S(CH_2)_p$, $NR'(CH_2)_p$, $O(CH_2)_p$, $OC(O)CHR^8NHC(O)$, $NHC(O)CHR^8NHC(O)$, or a covalent bond; wherein p is 1, 2, or 3, R' is H or C_1-C_6 alkyl, and R^8 is hydrogen, alkyl, aryl or heteroaryl, each of which may be substituted;

R is



wherein

X' is selected from the group consisting of $NHNH_2$, $–NHN=CHR^3$, $–NHNH–CH_2R^3$; wherein R^3 is alkyl, alkenyl, alkynyl, aryl, or heteroaryl, each of which is substituted by fluorine, iodine, a radioisotope of fluorine, a radioisotope of iodine, bromine, a radioisotope of bromine, or a radioisotope of astatine; NO_2, NH_2, $N^+(R^2)_3$, $Sn(R^2)_3$, $Si(R^2)_3$, $Hg(R^2)$, and $B(OH)_2$, where R^2 is C_1-C_6 alkyl;

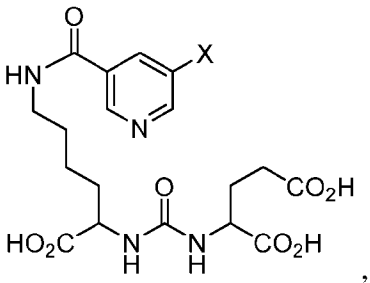
n is 1, 2, 3, 4, or 5.

26. The method of claim 21, wherein for the compound of formula (II), X or X' is fluorine, iodine, or a radioisotope of fluorine or iodine, bromine, a radioisotope of bromine, or a radioisotope of astatine.

27. The method of claim 26, wherein for the compound of formula (II), X or X' is selected from ^{18}F, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br, ^{80}Br, ^{80m}Br, ^{82}Br, ^{83}Br and ^{211}At.

28. The method of claim 27, wherein for the compound of formula (II), X or X' is ^{18}F.

29. The method of claim 21, wherein the compound of formula (II) is selected from: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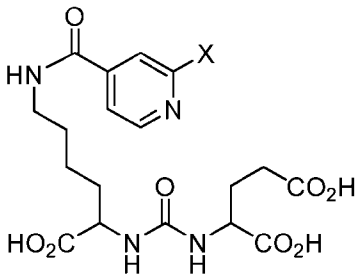
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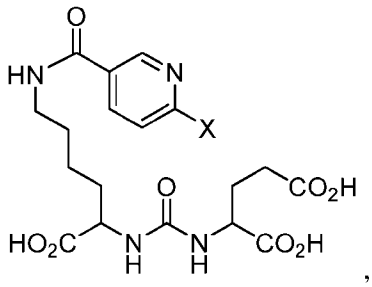
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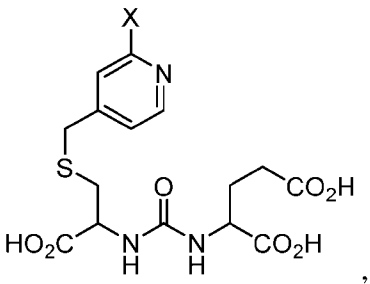
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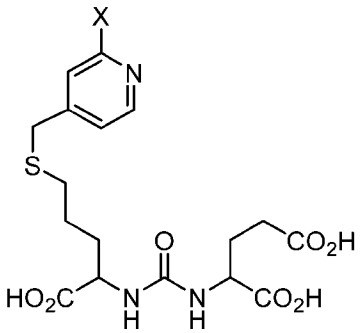
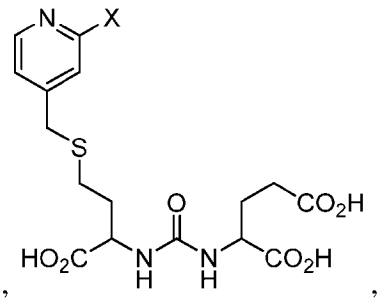

,

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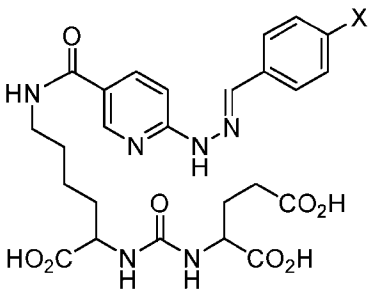
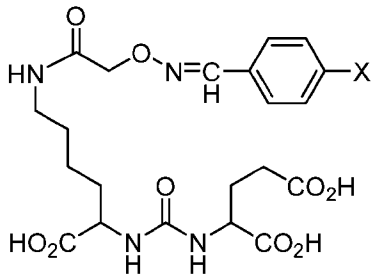

, and

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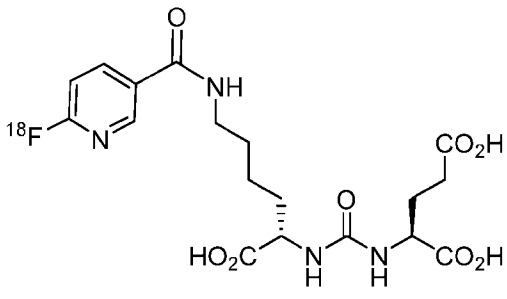
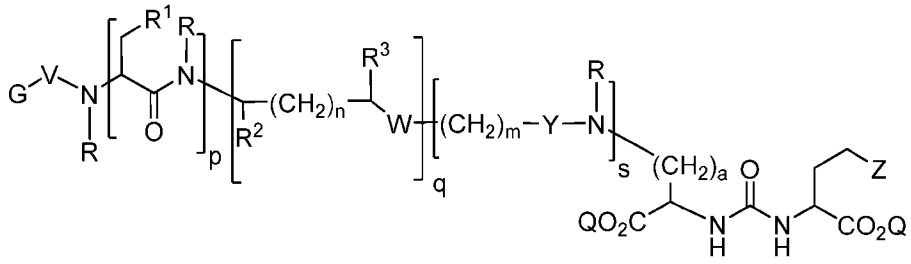
30. The method of claim 21, wherein the compound of formula (II) is:


(^{18}F-DCFPyL).

31. The method of claim 1, wherein the PSMA-targeting compound comprises a compound of formula (III):



(III);

wherein:

q and s are each independently 0 or 1;

p is 0, 1, 2, or 3,

a is 1, 2, 3, or 4;

m is 1, 2, 3, 4, 5, or 6;

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

Z is tetrazole or CO_2Q;

each Q is independently selected from hydrogen or a protecting group;

V can be present or absent and when is present is selected from –C(O)-, –NRC(O)-, and –NRC(S)-;

W is selected from -NRC(O)-, -NRC(O)NR-, NRC(S)NR-, -NRC(O)O-, -OC(O)NR-, -OC(O)-, –C(O)NR-, or -C(O)O-;

Y is selected from -C(O)-, -NRC(O)-, -NRC(S)-, and -OC(O).

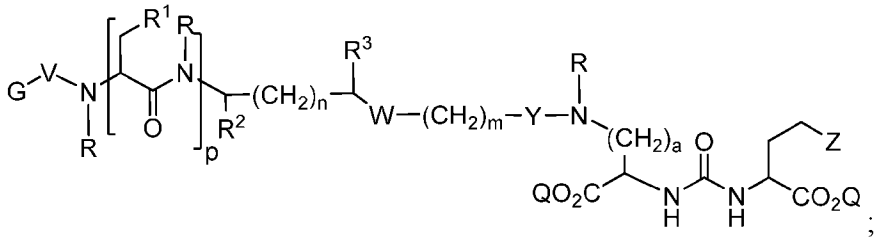
each R is independently H or C_1-C_4 alkyl;

each R^1 is independently H, C_1-C_6 alkyl, C_2-C_{12} aryl, or C_4-C_{16} alkylaryl, whereas when p is 2 or 3, each R^1 may be the same or different;

R^2 and R^3 are independently H, CO_2H, or CO_2R^4, where R^4 is a C_1-C_6 alkyl, C_2-C_{12} aryl, or C_4-C_{16} alkylaryl, wherein when one of R^2 and R^3 is CO_2H or CO_2R^4, the other is H; and

G is a metal chelating moiety optionally including a chelated metal or a fluorescent dye moiety that emits in the visible or near infrared spectrum, wherein G can include any additional atoms or linkers necessary to attach the metal chelating moiety or fluorescent dye moiety to the rest of the compound.

32. The method of claim 31, wherein the compound of formula (III) has the following structure:



;

wherein:

Z is tetrazole or CO_2Q;

each Q is independently selected from hydrogen or a protecting group;

a is 1, 2, 3, or 4;

m is 1, 2, 3, 4, 5, or 6;

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

p is 0, 1, 2, or 3;

each R is independently H or C_1-C_4 alkyl;

V is selected from –C(O)-, -NRC(O)-, and -NRC(S)-;

W is selected from -NRC(O)-, -NRC(O)NR-, NRC(S)NR-, -NRC(O)O-, -OC(O)NR-, -OC(O)-, -C(O)NR-, and -C(O)O-;

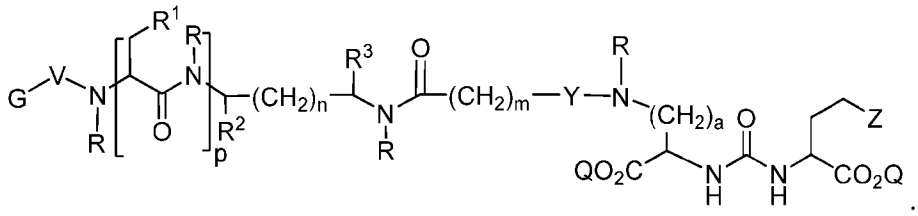
Y is selected from –C(O)-, -NRC(O)-, -NRC(S)-, and -OC(O)-;

R^1 is H, C_1-C_6 alkyl, C_2-C_{12} aryl, or C_4-C_{16} alkylaryl, whereas when p is 2 or 3, each R^1 may be the same or different;

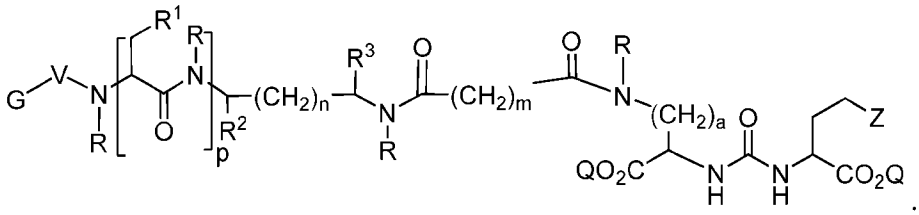
R^2 and R^3 are independently H, CO_2H, or CO_2R^4, where R^4 is a C_1-C_6 alkyl, C_2-C_{12} aryl, or C_4-C_{16} alkylaryl, wherein when one of R^2 and R^3 is CO_2H or CO_2R^4, the other is H; and

G a metal chelating moiety optionally including a chelated metal or a fluorescent dye moiety that emits in the visible or near infrared spectrum.

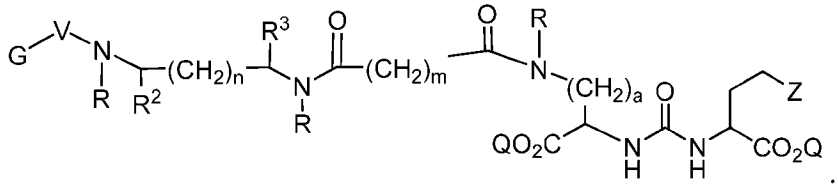
33. The method of claim 31, wherein the compound of formula (III) has the following structure:



34. The method of claim 31, wherein the compound of formula (III) has the following structure:



35. The method of claim 31, wherein the compound of formula (III) has the following formula:



36. The method of claim 31, wherein for the compound of formula (III), R^1 is phenyl.

37. The method of claim 31, wherein for the compound of formula (III):

(a) R^2 is H, and R^3 is H;

(b) R^3 is CO_2H and R^2 is H;

(c) R^2 is CO_2H and R^3 is H;

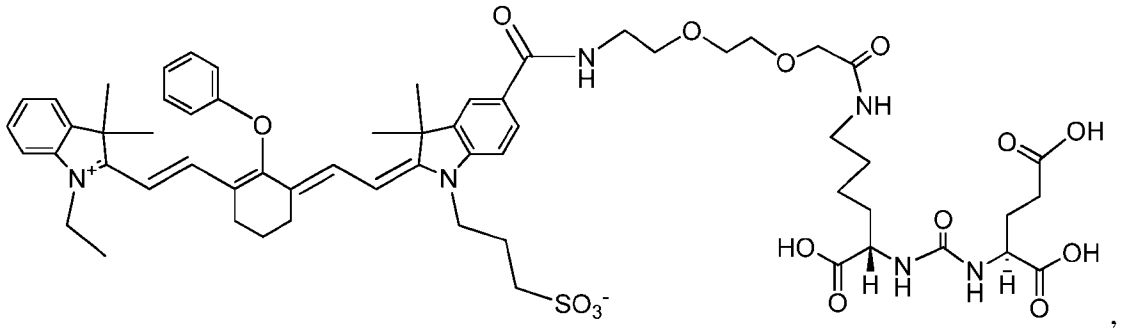
(d) R^2 is CO_2R^4 and R^3 is H; or

(e) R^3 is CO_2R^4, and R^2 is H.

38. The method of claim 31, wherein for the compound of formula (III), R^4 is benzyl.

39. The method of claim 31, wherein G is an optical dye selected from a dye of any one of claims 14-20.

40. The method of claim 31, wherein G is an optical dye and the compound of formula (III) is selected from:



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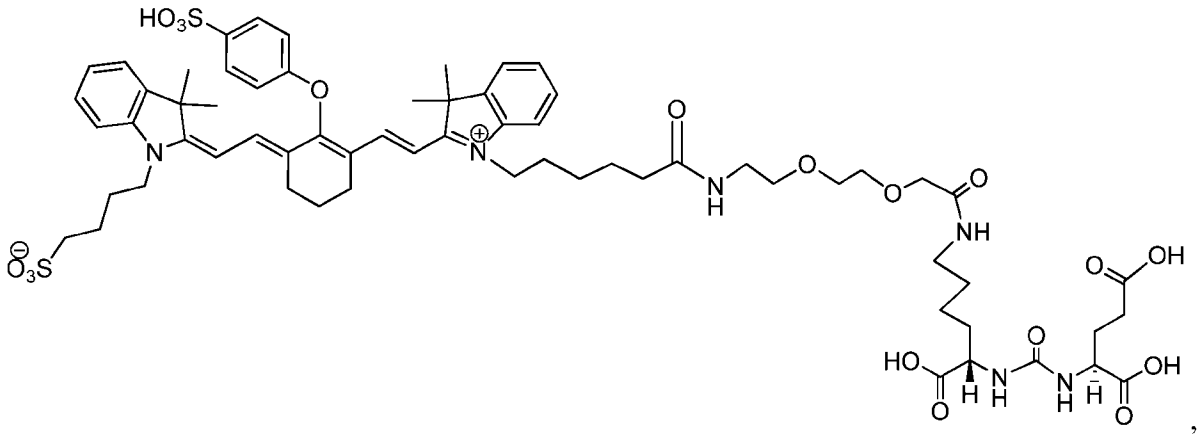

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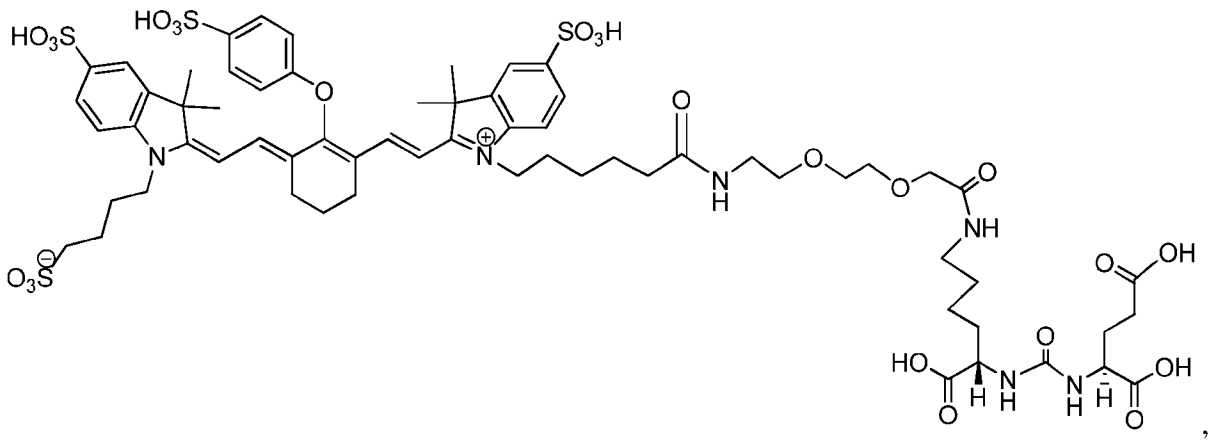

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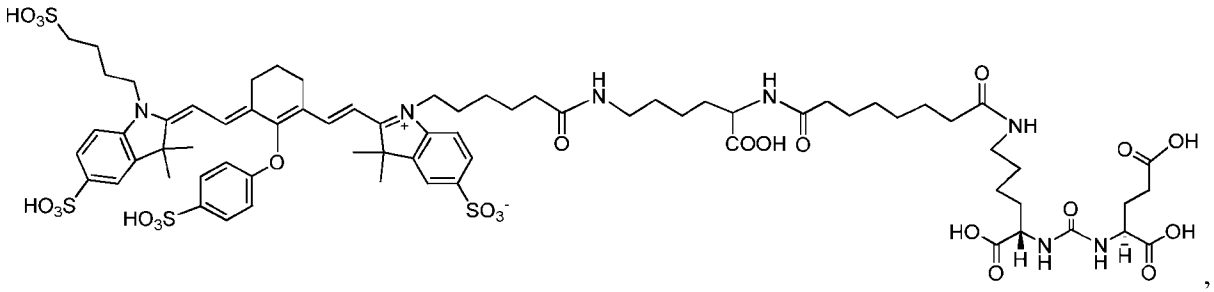

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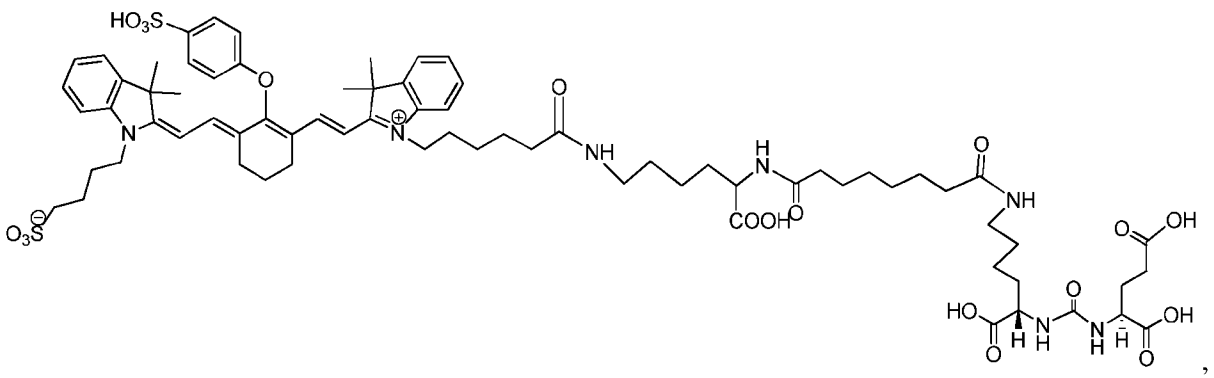

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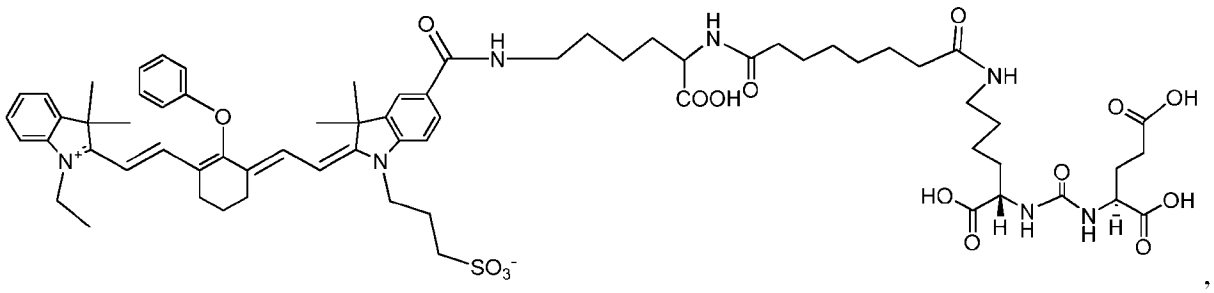

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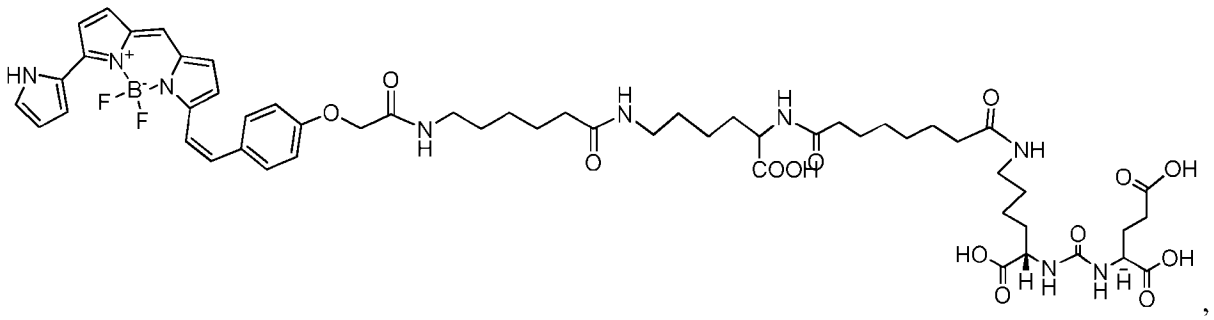

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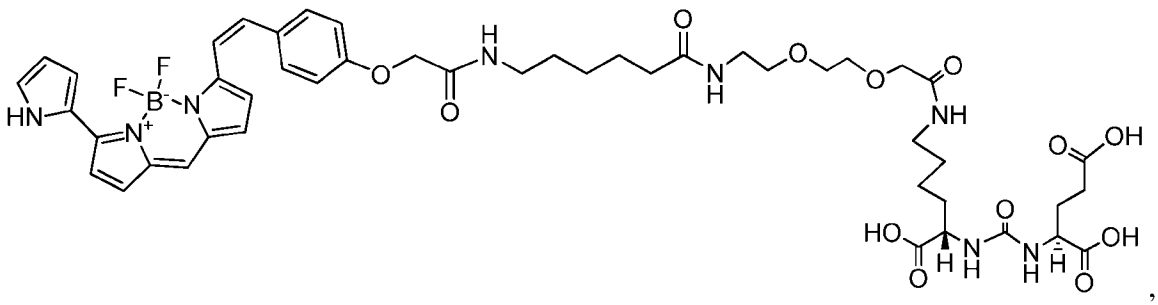

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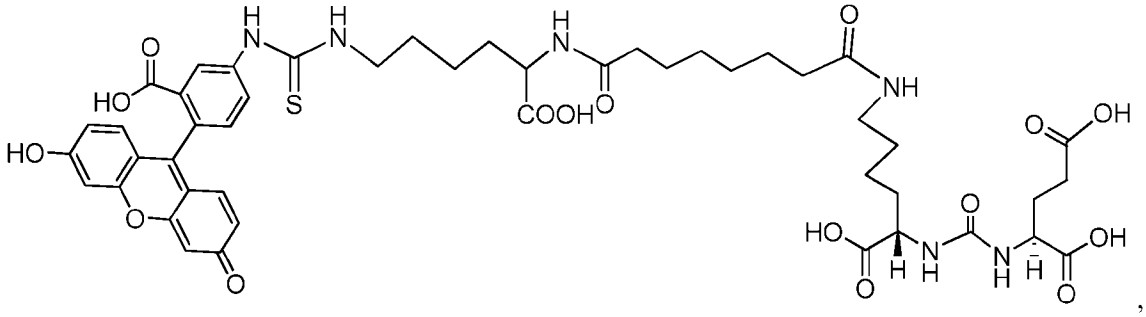

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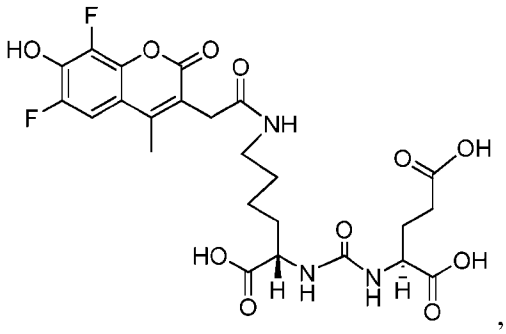

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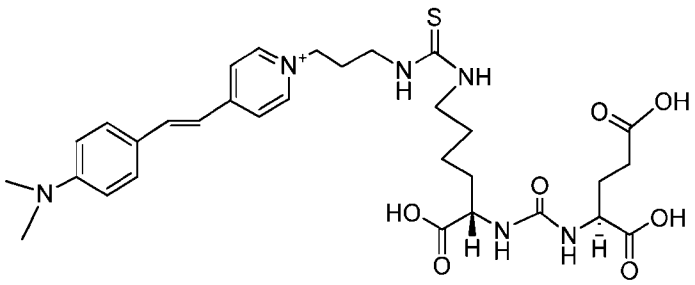

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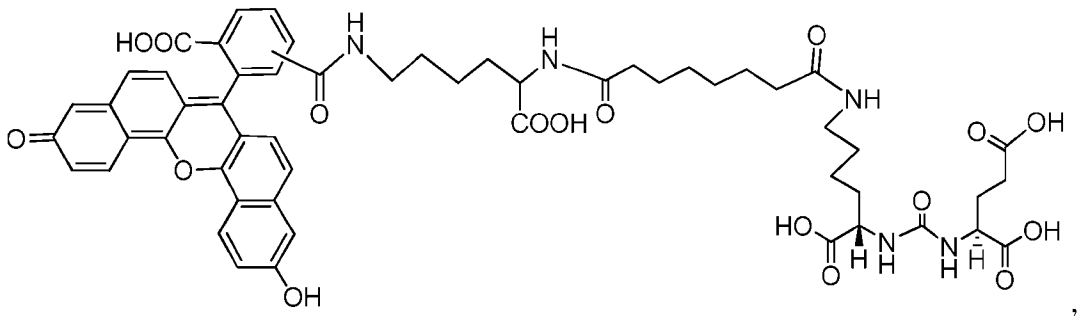

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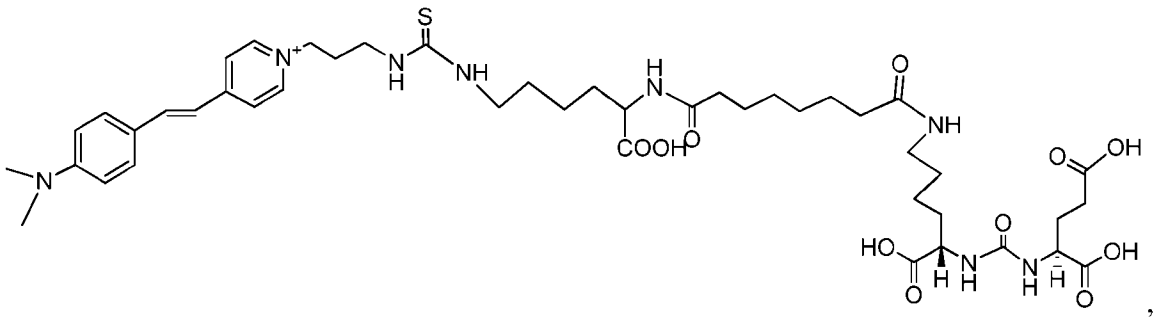

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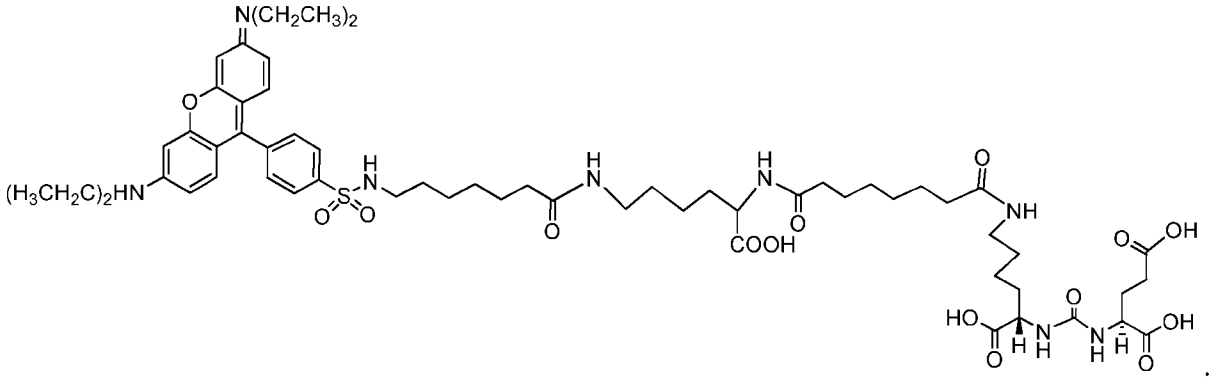
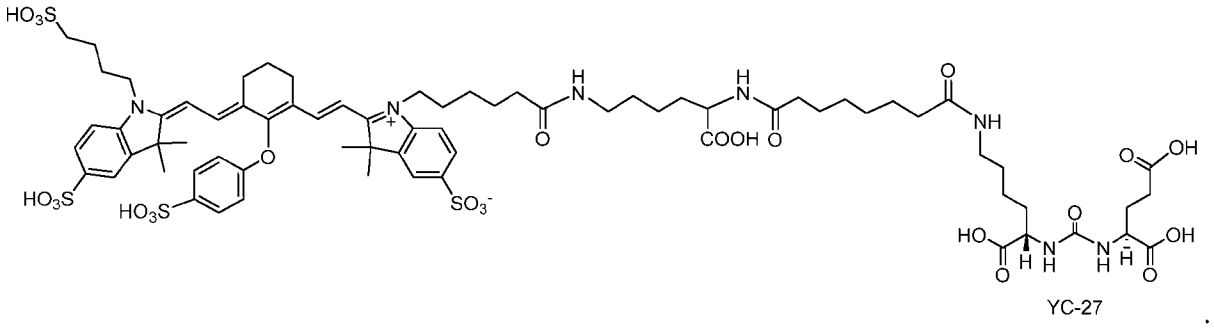


41. The method of claim 31, wherein the compound of formula (III) is:

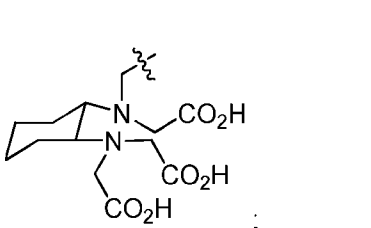


YC-27

42. The method of claim 31, wherein for the compound of formula (III), wherein the metal chelating moiety is selected from DOTAGA (1,4,7,10-tetraazacyclododececane,1-(glutaric acid)-4,7,10-triacetic acid), DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DOTASA (1,4,7,10-tetraazacyclododecane-1-(2-succinic acid)-4,7,10-triacetic acid), CB-DO2A (10-bis(carboxymethyl)-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane), DEPA (7-[2-(Bis-carboxymethylamino)-ethyl]-4,10-bis-carboxymethyl-1,4,7,10-tetraaza-cyclododec-1-yl-acetic acid)), 3p-C-DEPA (2-[(carboxymethyl)][5-(4-nitrophenyl-1-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecan-1-yl]pentan-2-yl)amino]acetic acid)), TCMC (2-(4-isothiocyanotobenzyl)-1,4,7,10-tetraaza-1,4,7,10-tetra-(2-carbamonyl methyl)-cyclododecane), oxo-DO3A (1-oxa-4,7,10-triazacyclododecane-5-S-(4-isothiocyanatobenzyl)-4,7,10-triacetic acid), p-NH_2-Bn-Oxo-DO3A (1-Oxa-4,7,10-tetraazacyclododecane-5-S-(4-aminobenzyl)-4,7,10-triacetic acid), TE2A ((1,8-*N*,*N'*-bis-(carboxymethyl)-1,4,8,11-tetraazacyclotetradecane), MM-TE2A, DM-TE2A, CB-TE2A (4,11-bis(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane), CB-TE1A1P (4,8,11-tetraazacyclotetradecane-1-

(methanephosphonic acid)-8-(methanecarboxylic acid)), CB-TE2P (1,4,8,11-tetraazacyclotetradecane-1,8-bis(methanephosphonic acid), TETA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid), NOTA (1,4,7-triazacyclononane-N,N′,N″-triacetic acid), NODA (1,4,7-triazacyclononane-1,4-diacetate); NODAGA (1,4,7-triazacyclononane,1-glutaric acid-4,7-acetic acid), (NOTAGA) 1,4,7-triazonane-1,4-diyl)diacetic acid, DFO (Deferoxamine), NETA ([4-[2-(bis-carboxymethylamino)-ethyl]-7-carboxymethl-[1,4,7]triazonan-1-yl}-acetic acid), TACN-TM (N,N',N", tris(2-mercaptoethyl)-1,4,7-triazacyclononane), Diamsar (1,8-Diamino-3,6,10,13,16,19-hexaazabicyclo(6,6,6)eicosane, 3,6,10,13,16,19-Hexaazabicyclo[6.6.6]eicosane-1,8-diamine), Sarar (1-*N*-(4-aminobenzyl)-3, 6,10,13,16,19-hexaazabicyclo[6.6.6] eicosane-1,8-diamine), AmBaSar (4-((8-amino-3,6,10,13,16,19-hexaazabicyclo [6.6.6] icosane-1-ylamino) methyl) benzoic acid), and BaBaSar.

43. The method of claim 31, wherein for the compound of formula (III), the chelating agent is selected from: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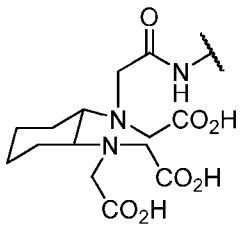
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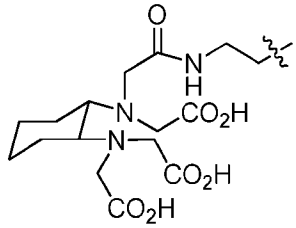
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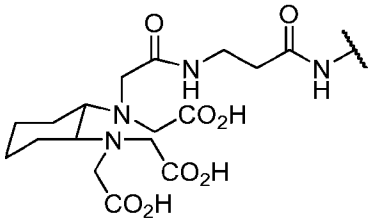
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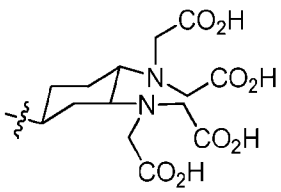
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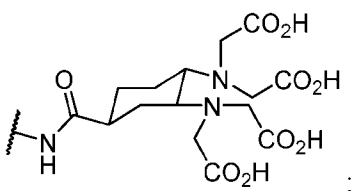
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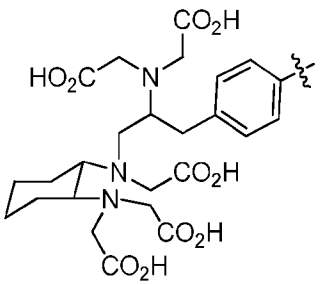
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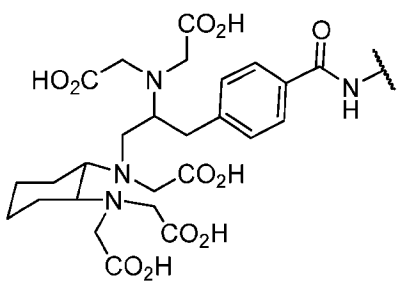
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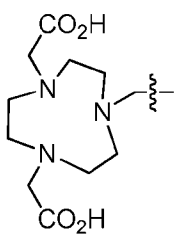
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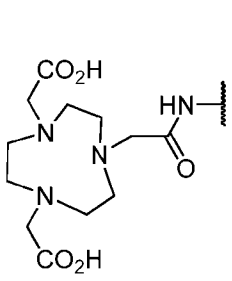
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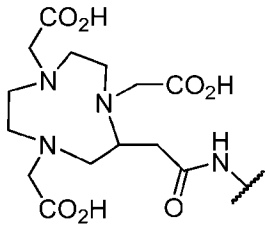
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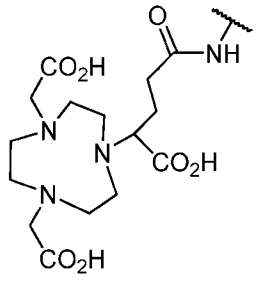
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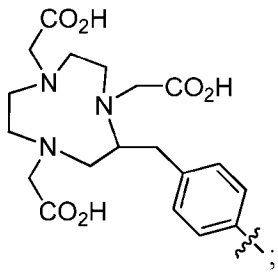
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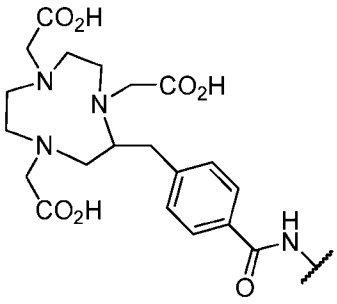
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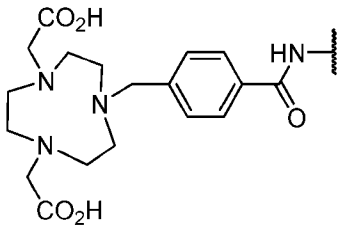
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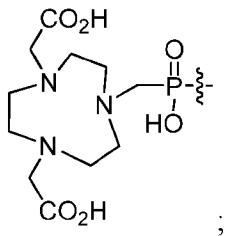
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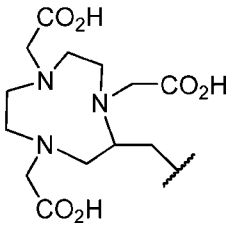
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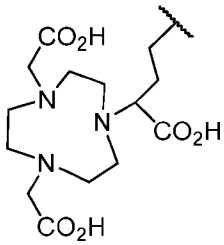
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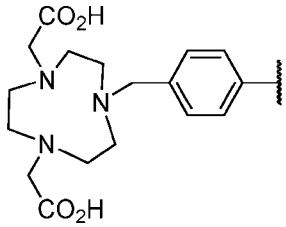
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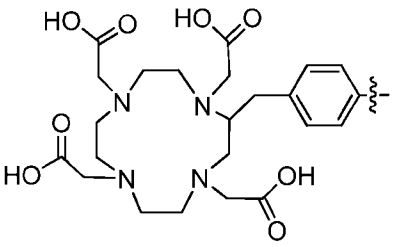
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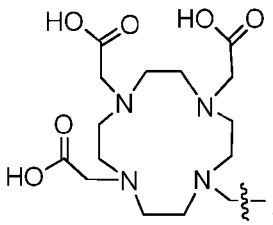
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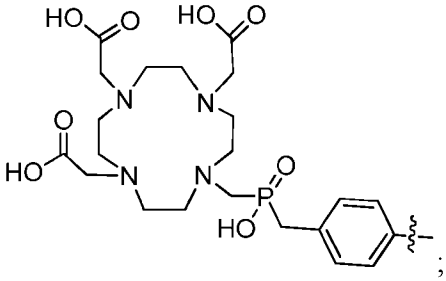
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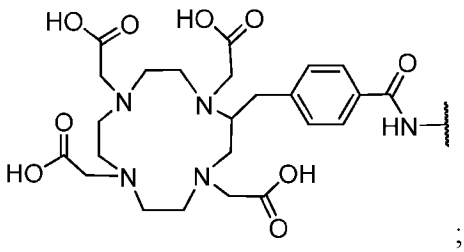

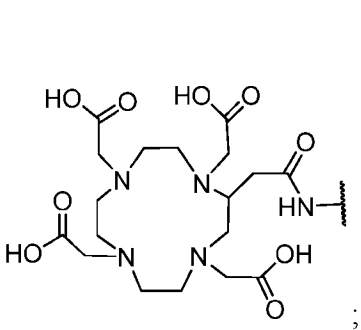
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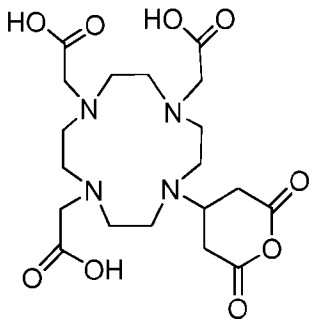
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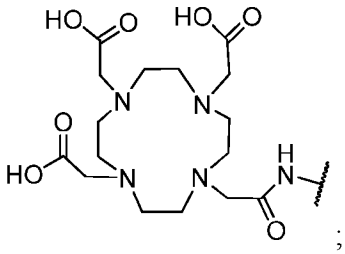
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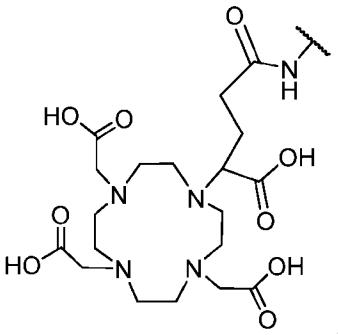
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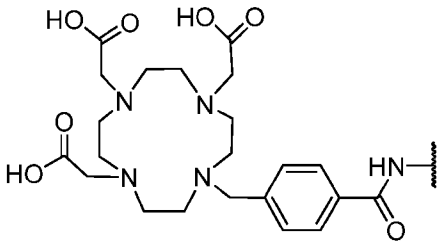
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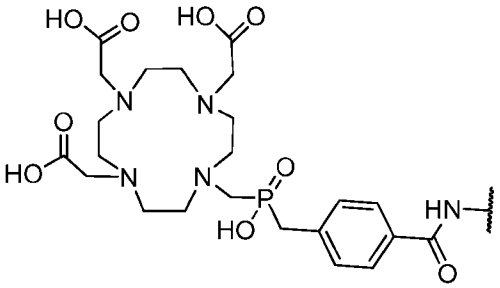
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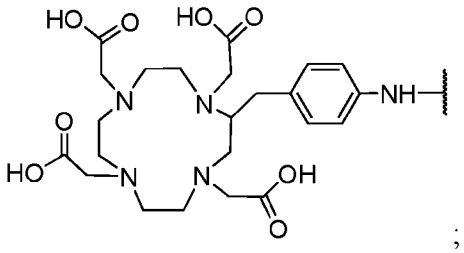
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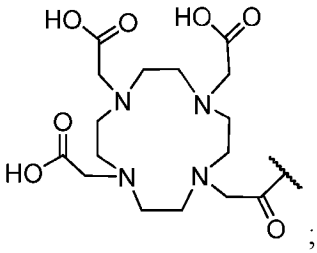
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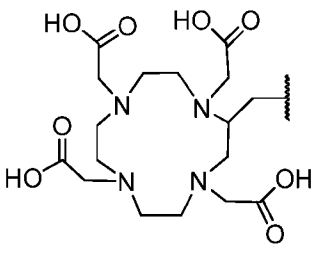
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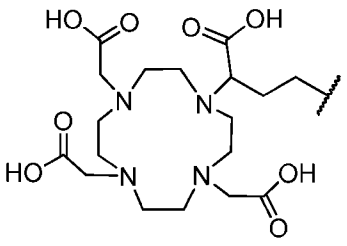
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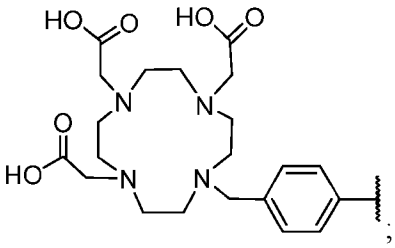
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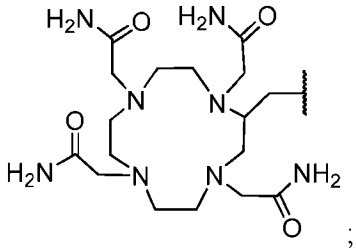
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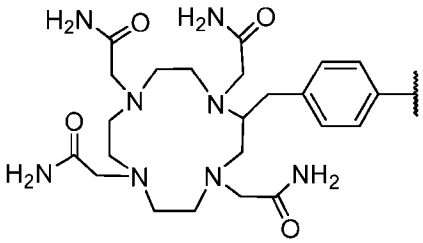
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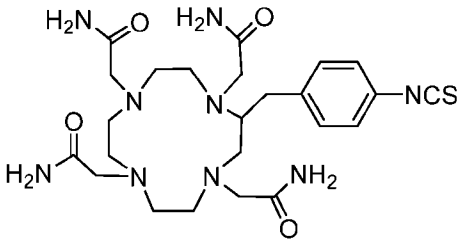
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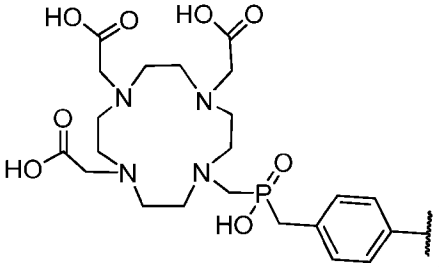
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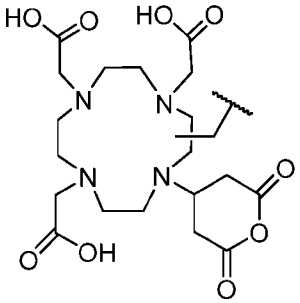
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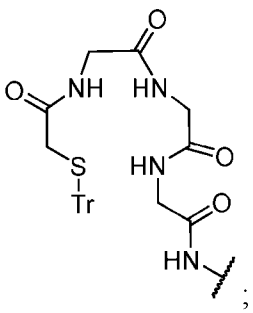
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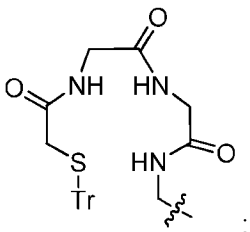
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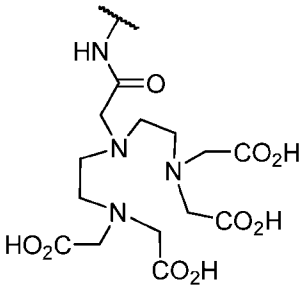
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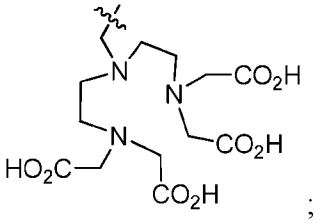
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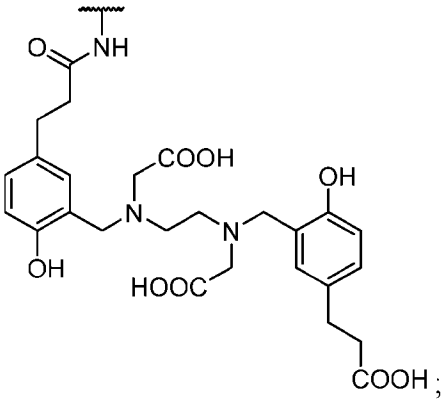
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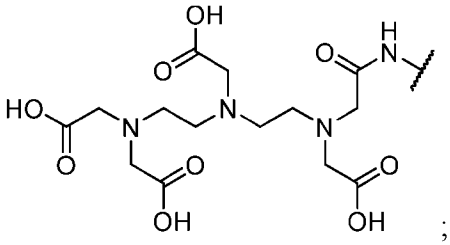
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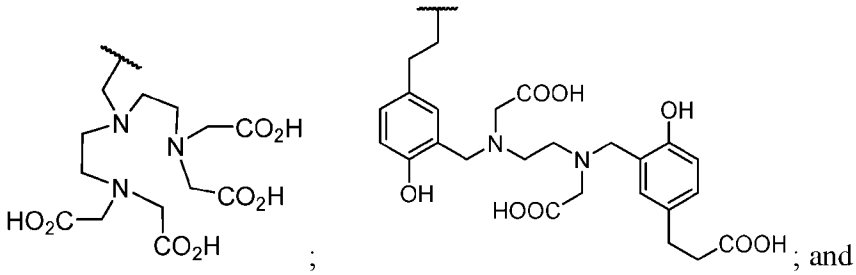
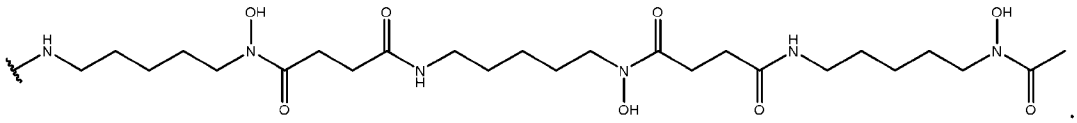


; and



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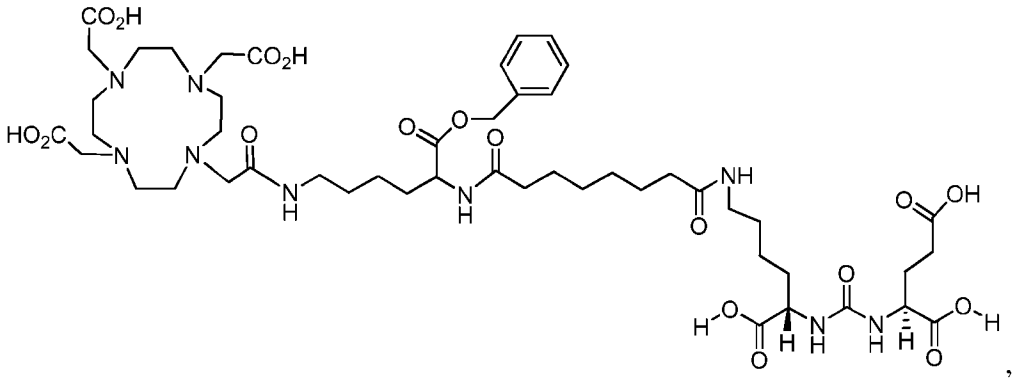
44. The method of claim 31, wherein the compound of formula (III) is selected from:



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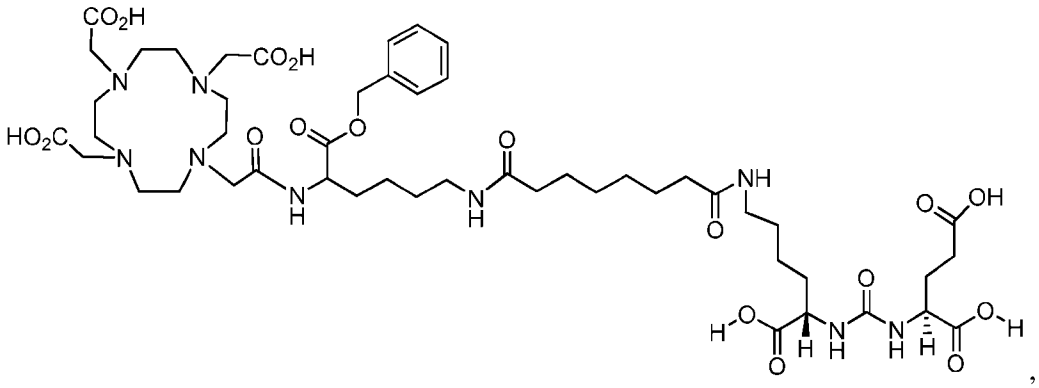

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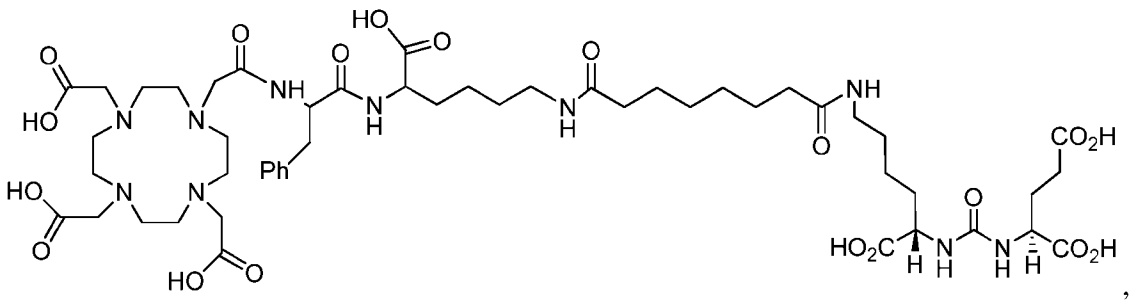

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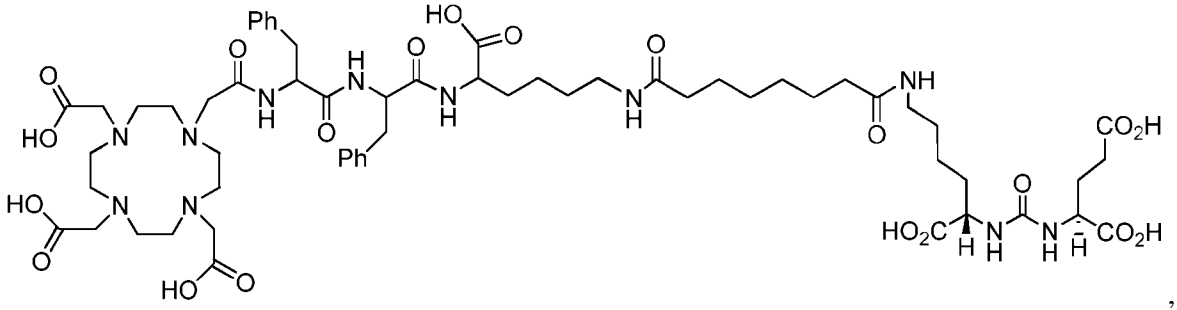

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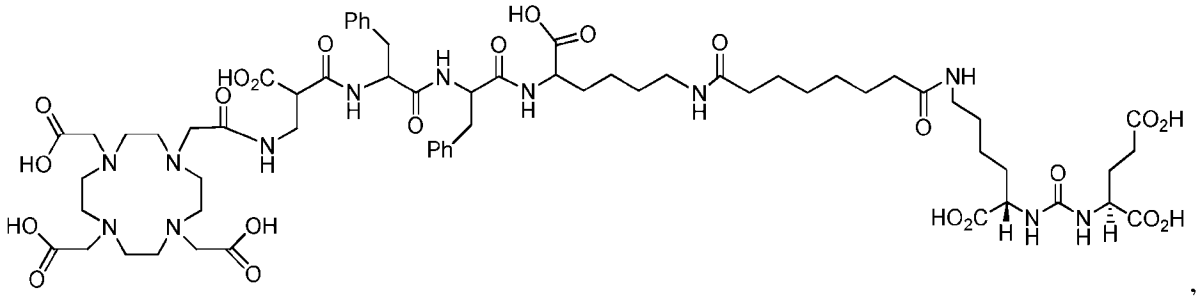

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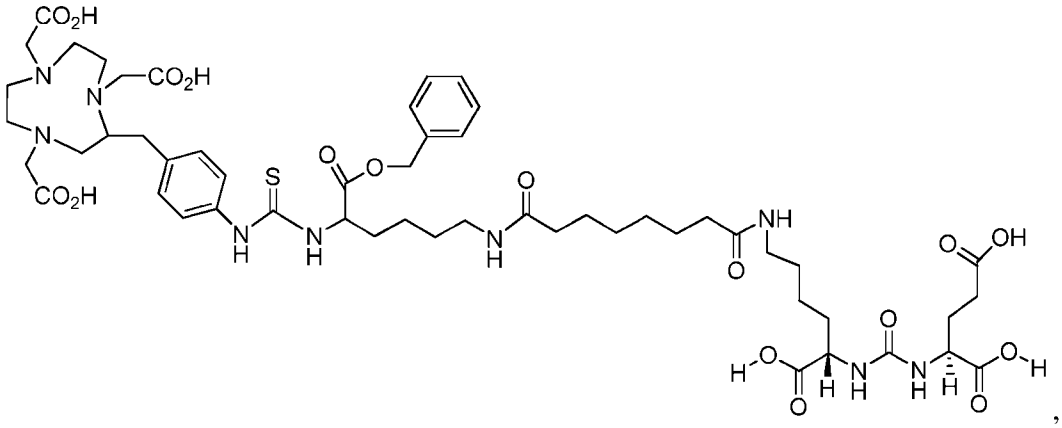

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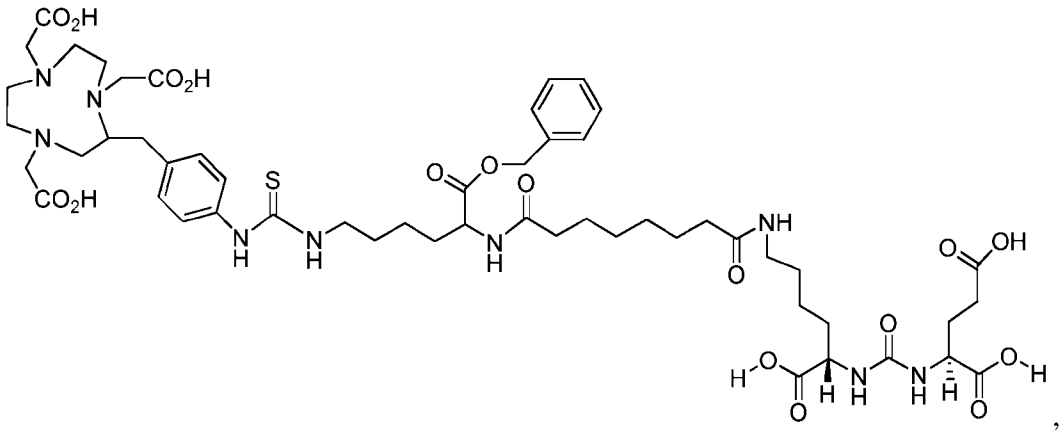

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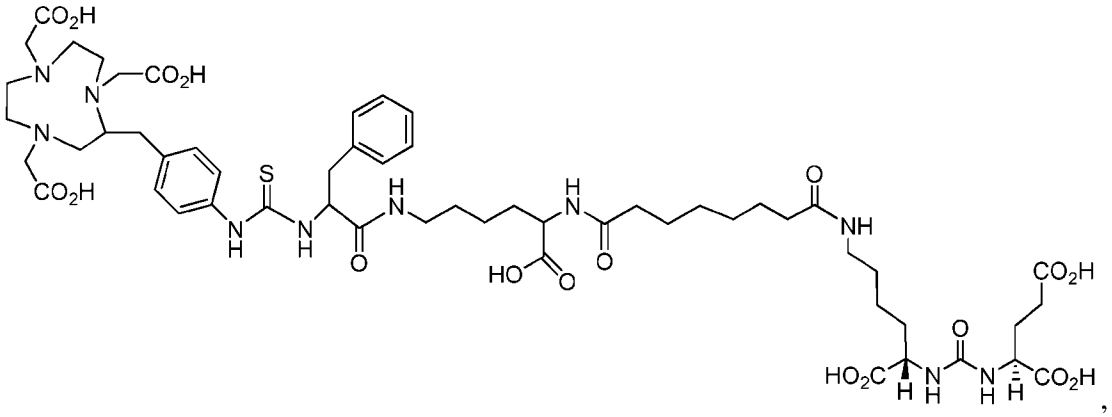

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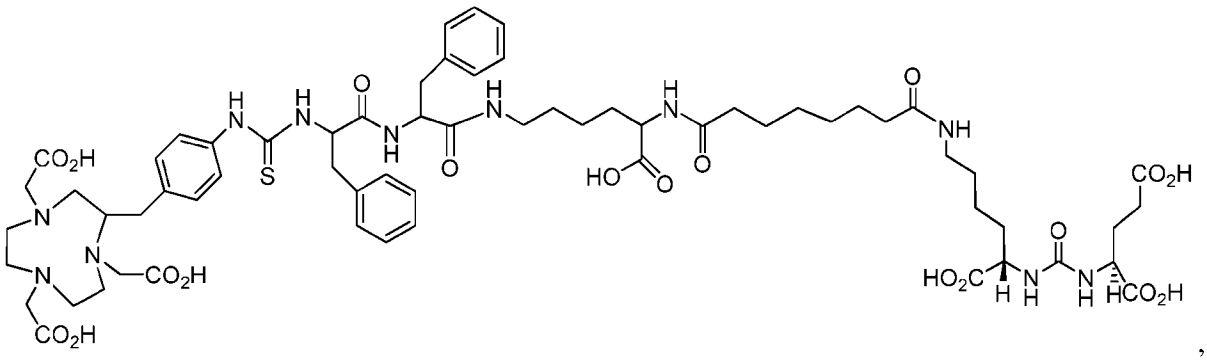

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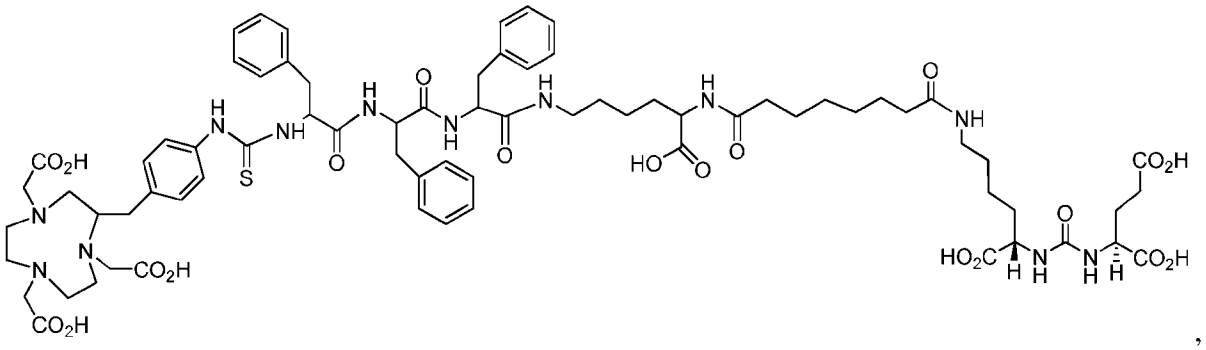

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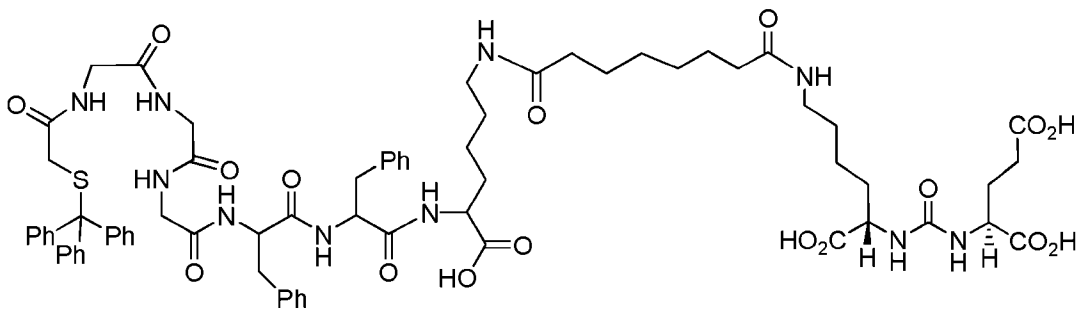

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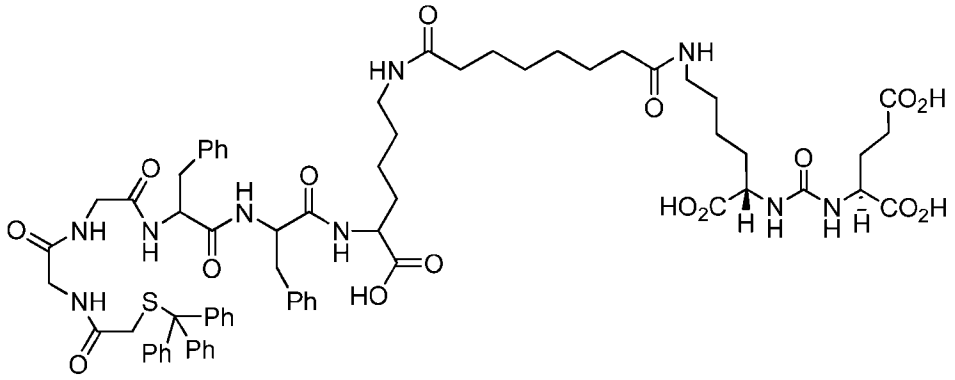
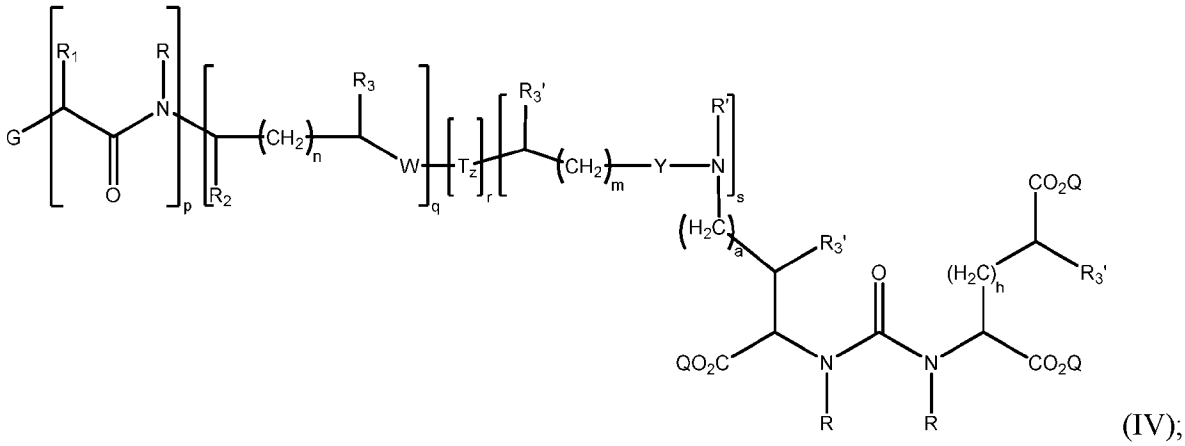


45. The method of claim 31, wherein for the compound of formula (III), the chelated metal is selected from ^{60}Cu, ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{55}Co, ^{57}Co, ^{203}Pb, ^{212}Pb, ^{225}Ac, ^{177}Lu, ^{99m}Tc, ^{67}Ga, ^{68}Ga, ^{149}Tb, ^{86}Y, ^{90}Y, ^{111}In, ^{186}Re, ^{188}Re, ^{153}Sm, ^{89}Zr, ^{213}Bi, ^{212}Bi, ^{212}Pb, ^{67}Ga, ^{47}Sc, ^{166}Dy, $Al^{18}F$, ^{166}Ho, and ^{177}Lu.

46. The method of claim 1, wherein the PSMA-targeting compound is a compound of formula (IV):



(IV);

wherein:

each Q is independently hydrogen, a metal ion, a negative charge, or a protecting group;

a, h, m, and n are each independently an integer selected from the group consisting of 1, 2, 3, 4, 5, and 6;

s is 0 or 1;

r is 0 or 1;

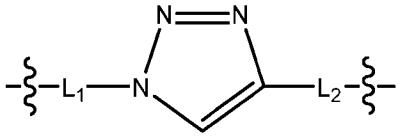
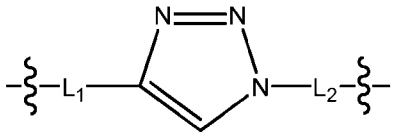
q is 0 or 1;

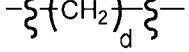
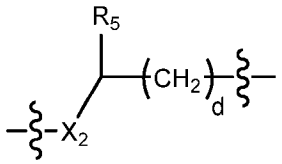
p is an integer selected from the group consisting of 0, 1, 2, and 3, and when p is 2 or 3, each R and R_1 can be the same or different;

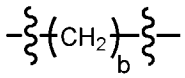
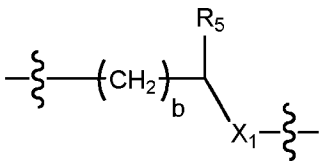
each R, R', and R_1 is independently hydrogen, C_1-C_6 substituted or unsubstituted alkyl, C_6-C_{12} substituted or unsubstituted aryl, C_6-C_{12} substituted or unsubstituted heteroaryl, or C_6-C_{16} alkyaryl;

R_2, R_3, and R_3' are each independently hydrogen, C_1-C_4 substituted or unsubstituted alkyl, $-CO_2H$, $-CO_2Q$, or $-CO_2R_4$, wherein R_4 is a C_1-C_6 substituted or unsubstituted alkyl, C_6-C_{12} substituted or unsubstituted aryl, C_6-C_{12} substituted or unsubstituted heteroaryl, or C_6-C_{16} alkyaryl, wherein if one of R_2 and R_3 is $-CO_2H$, or $-CO_2R_4$, then the other is H;

Tz is a triazole containing moiety selected from the group consisting of:


and

;

wherein L_1 is

or

;

and L_2 is

or

;

wherein:

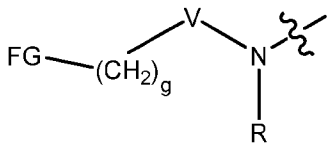
X_1 is $-NRC(O)-$, $-NRC(O)NR-$, $-NRC(S)NR$, or $-NRC(O)O-$;

X_2 is $-C(O)NR-$, $-NRC(O)NR-$, $-NRC(S)NR-$, or $-OC(O)NR-$;

R_5 is H, $-CO_2H$, or $-CO_2R_6$, wherein R_6 is C_1-C_6 alkyl, C_6-C_{12} aryl, or C_6-C_{16} alkyaryl; b is 1, 2, 3, or 4; and d is 1, 2, 3, or 4;

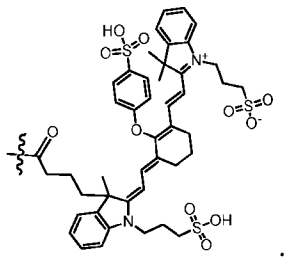
Y is $-C(O)-$, $-NRC(O)-$, $-NRC(S)-$, $-OC(O)-$;

W is a bond, $-(CH_2\text{-}O)_t-$, $-NRC(O)-$, $-NRC(O)NR-$, $-NRC(S)NR-$, $-NRC(O)O-$, $-OC(O)NR-$, $-OC(O)-$, $-C(O)NR-$, or $-C(O)O-$, wherein t is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8;

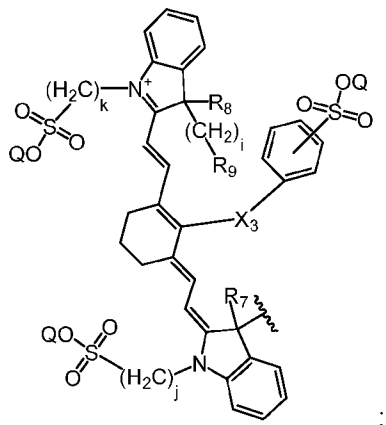
G is  ; FG is a fluorescent dye moiety that emits in the near-infrared spectrum; V is –C(O)-, -NRC(O)-, -NRC(S)-, or –OC(O)-, and g is an integer selected from the group consisting of 1, 2, 3, 4, 5, and 6;

under the condition that when r is 0, then q and s are both 0 or both 1;

or a pharmaceutically acceptable salt thereof; under the proviso that if R' is hydrogen, then the fluorescent dye moiety cannot be:



47. The method of claim 46, wherein for the compound of formula (IV), the fluorescent dye moiety is:

 ;

wherein:

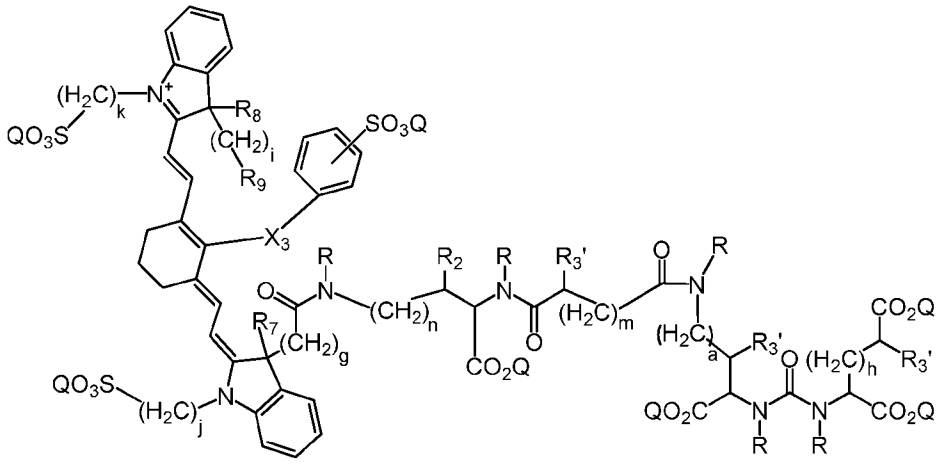
i, j, and k are each an integer selected from the group consisting of 1, 2, 3, 4, 5, and 6;

X_3 is a single bond, –O–, or –S–;

R_7, R_8, and R_9 are each independently hydrogen, C_1-C_4 unsubstituted or substituted alkyl, or $–CO_2Q$;

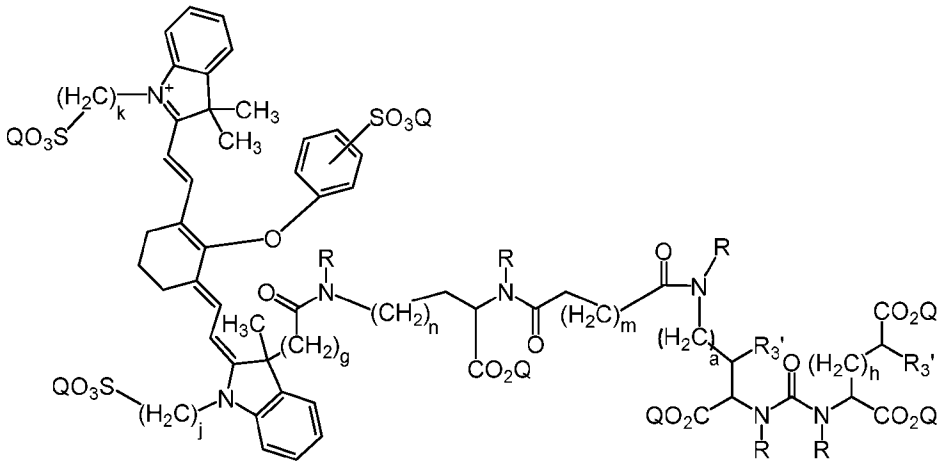
each Q is independently hydrogen, a metal ion, a negative charge, or a protecting group.

48. The method of claim 46, wherein the compound of formula (IV) is:



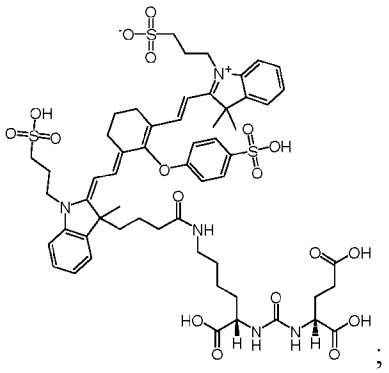
(IVa).

49. The method of claim 46, wherein the compound of formula (IV) is:

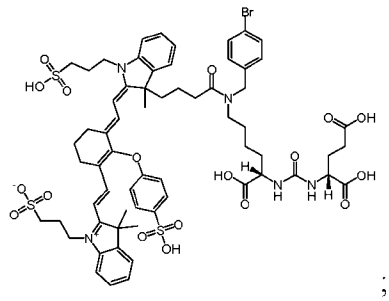


(IVb).

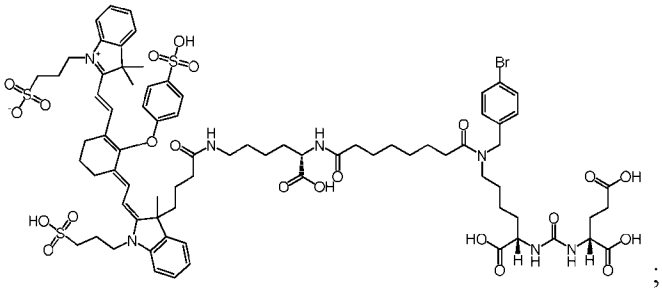
50. The method of claim 46, wherein the compound of formula (IV) is selected from:

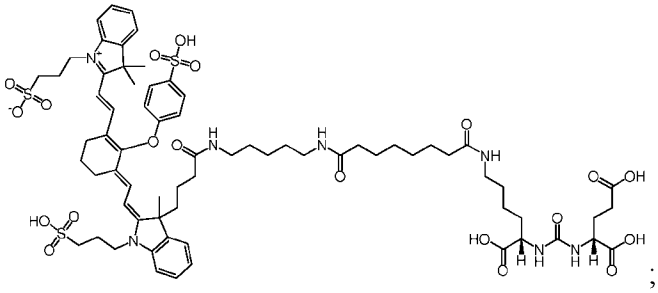


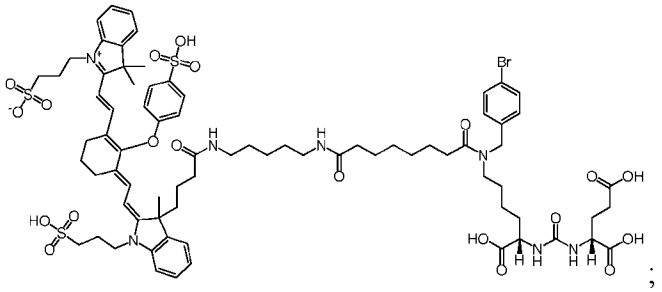
;

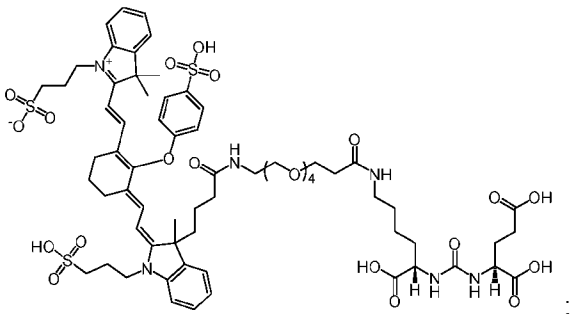


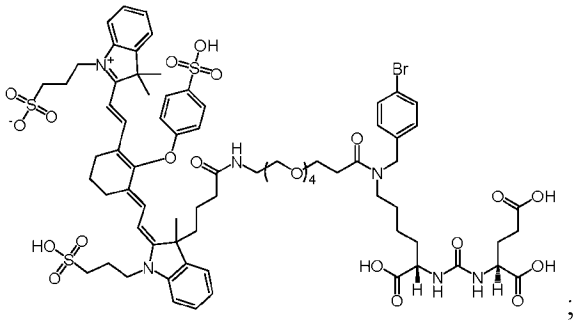
;

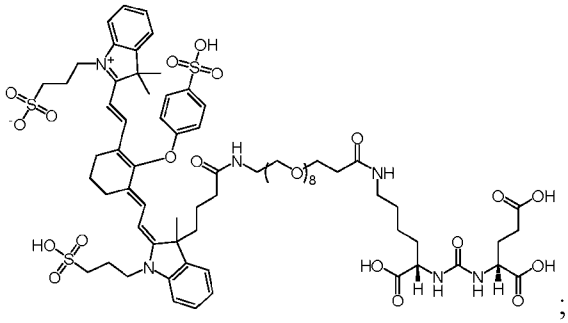

;


;

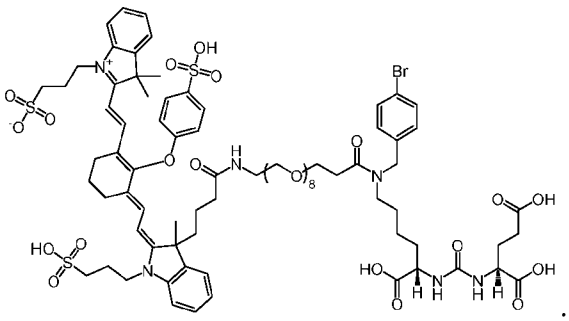

;


;


;

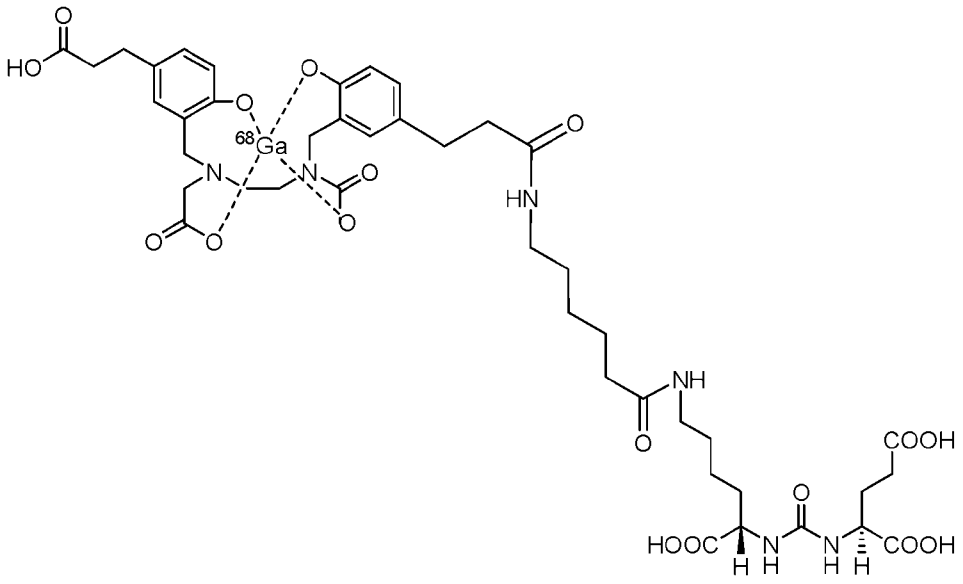


; and



.

51. The method of claim 1, wherein the PSMA-targeting compound is:



(^{68}GA-PSMA-11).

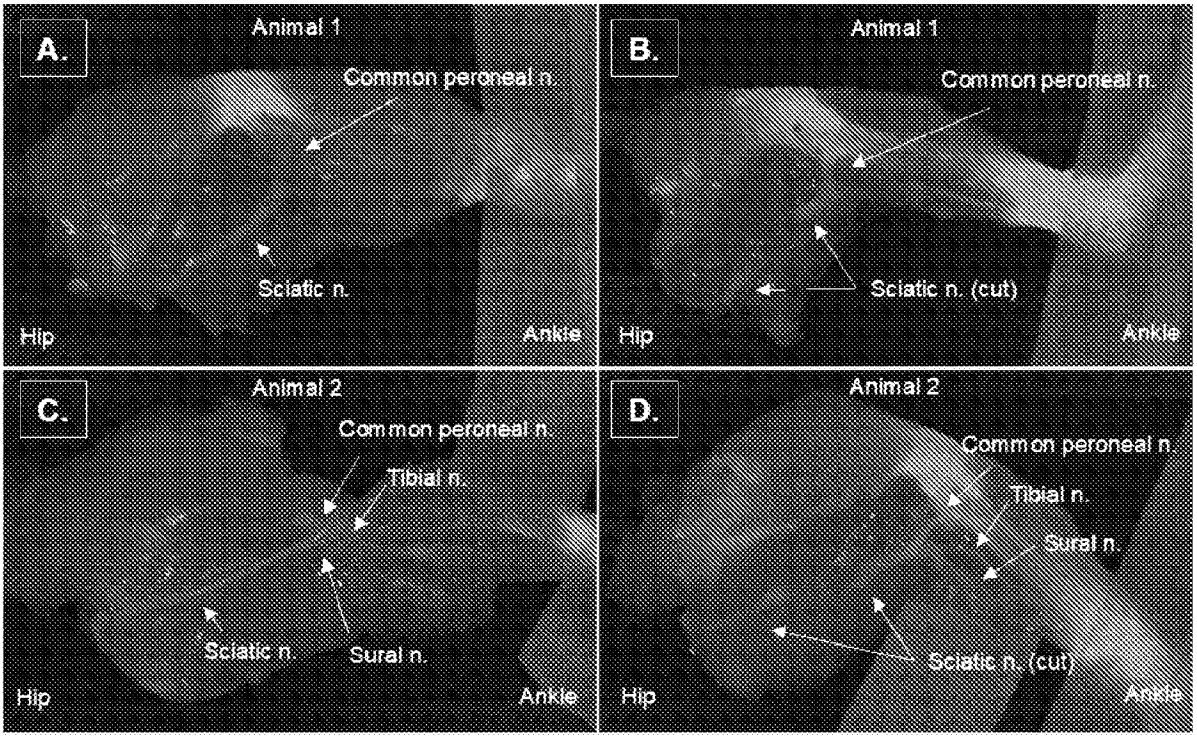

A.
Animal 1
Common peroneal n.
Sciatic n.
Hip
Ankle
B.
Animal 1
Common peroneal n.
Sciatic n. (cut)
Hip
Ankle
C.
Animal 2
Common peroneal n.
Tibial n.
Sciatic n.
Sural n.
Hip
Ankle
D.
Animal 2
Common peroneal n.
Tibial n.
Sural n.
Sciatic n. (cut)
Hip
Ankle

Fig. 1

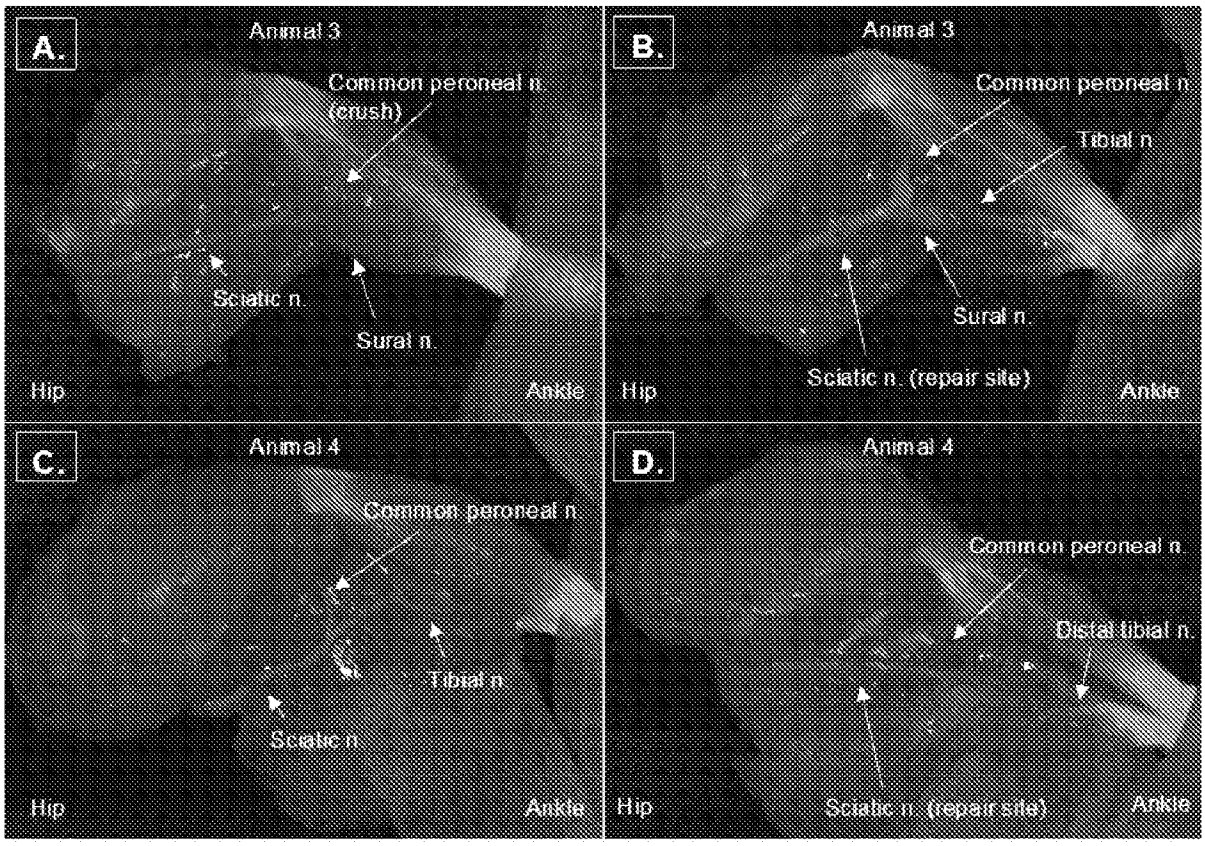

A.
Animal 3
Common peroneal n. (crush)
Sciatic n.
Sural n.
Hip
Ankle
B.
Animal 3
Common peroneal n.
Tibial n.
Sural n.
Sciatic n. (repair site)
Hip
Ankle
C.
Animal 4
Common peroneal n.
Tibial n.
Sciatic n.
Hip
Ankle
D.
Animal 4
Common peroneal n.
Distal tibial n.
Sciatic n. (repair site)
Hip
Ankle

Fig. 2

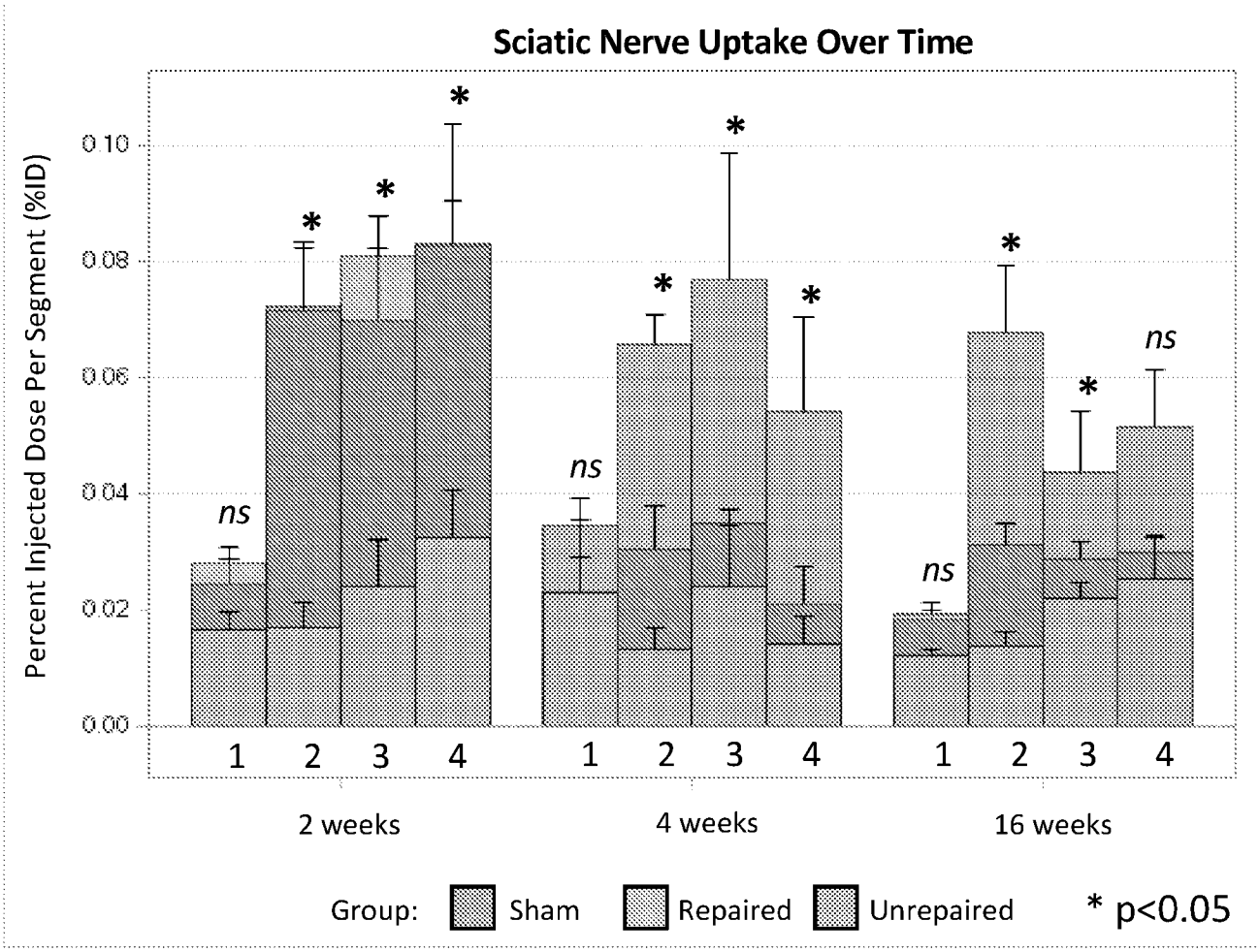

Sciatic Nerve Uptake Over Time
Percent Injected Dose Per Segment (%ID)
0.10
0.08
0.06
0.04
0.02
0.00
ns
*
1
2
3
4
2 weeks
4 weeks
16 weeks
Group:
Sham
Repaired
Unrepaired
* p<0.05

Fig. 3

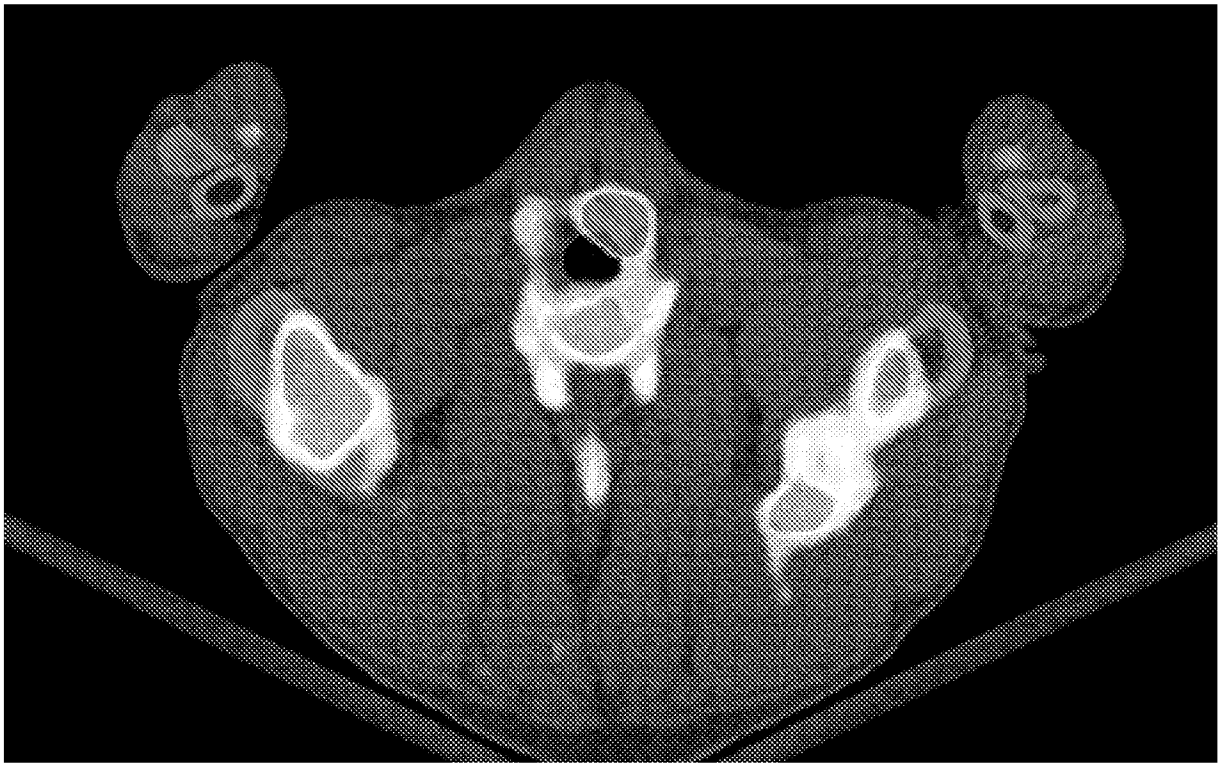


Fig. 4

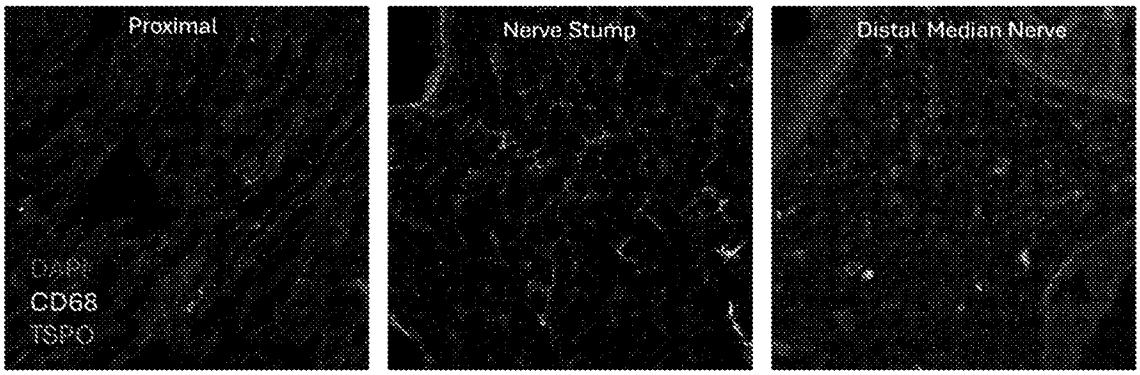


Fig. 5

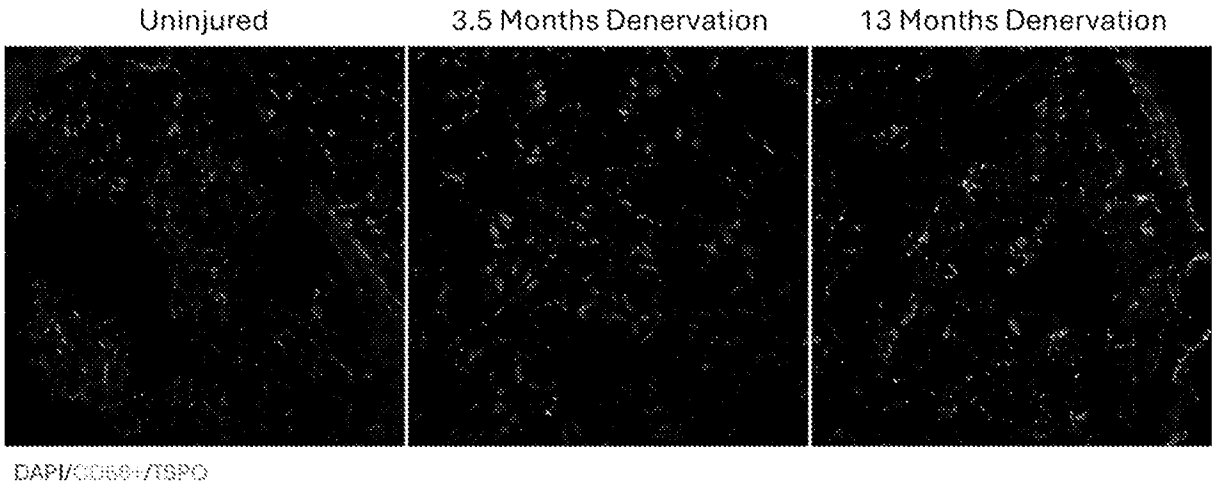

Uninjured
3.5 Months Denervation
13 Months Denervation
DAPI/CD68+/TSPO

Fig. 6

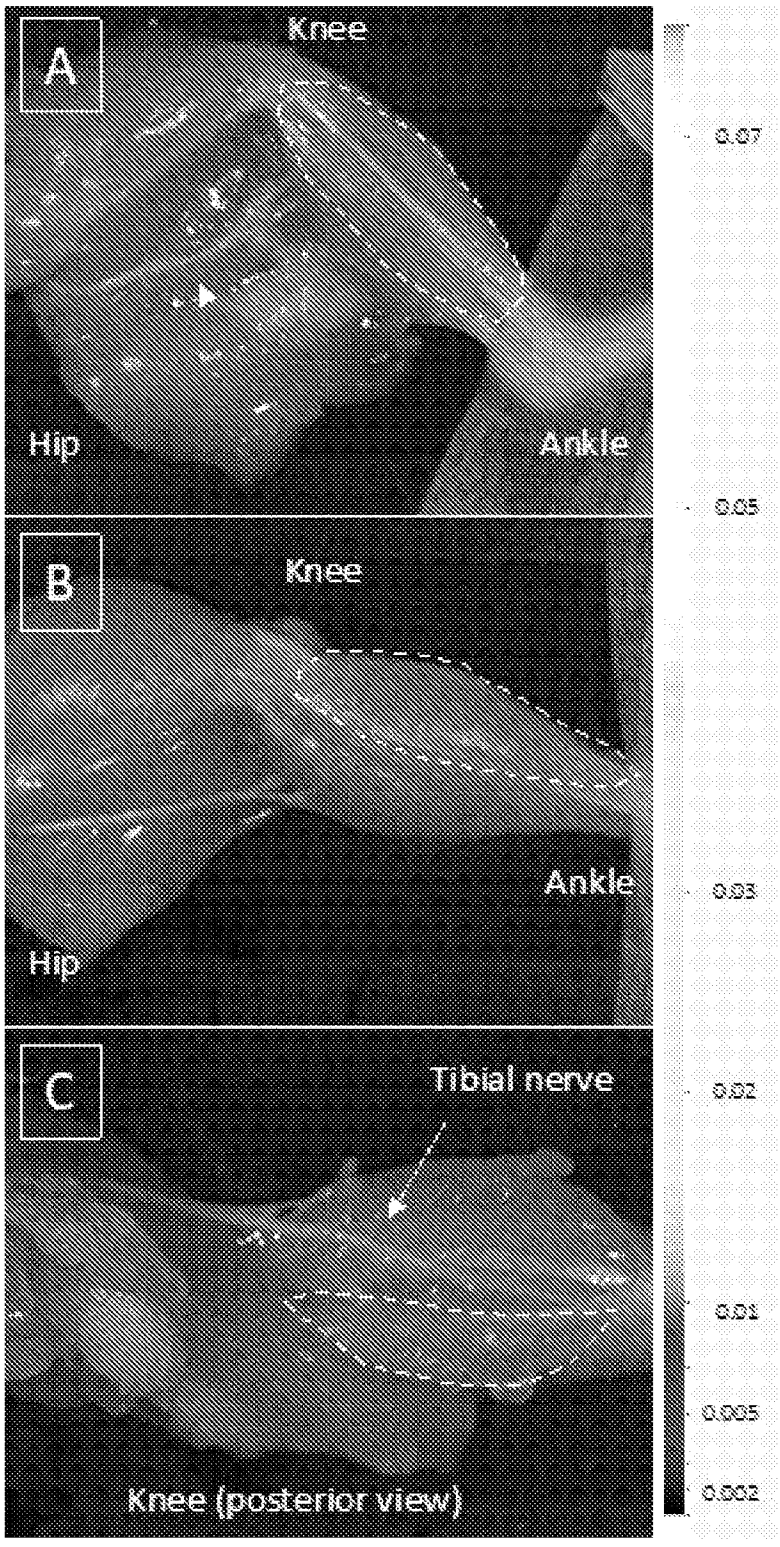

A
Knee
Hip
Ankle
B
Knee
Ankle
Hip
C
Tibial nerve
Knee (posterior view)
0.07
0.05
0.03
0.02
0.01
0.005
0.002

Fig. 7

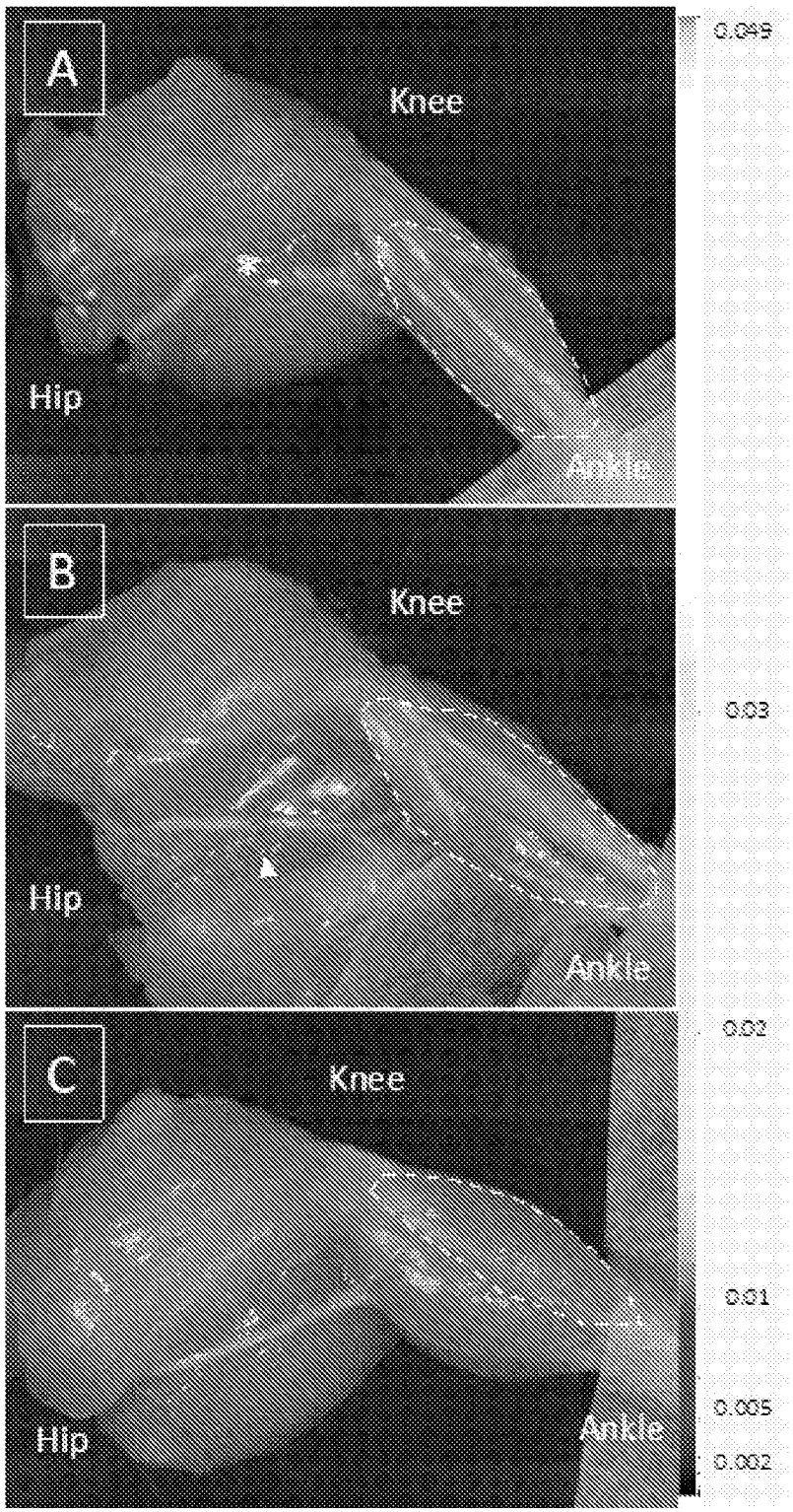

A
Knee
Hip
Ankle
0.049
B
Knee
Hip
Ankle
0.03
C
Knee
Hip
Ankle
0.02
0.01
0.005
0.002

Fig. 8

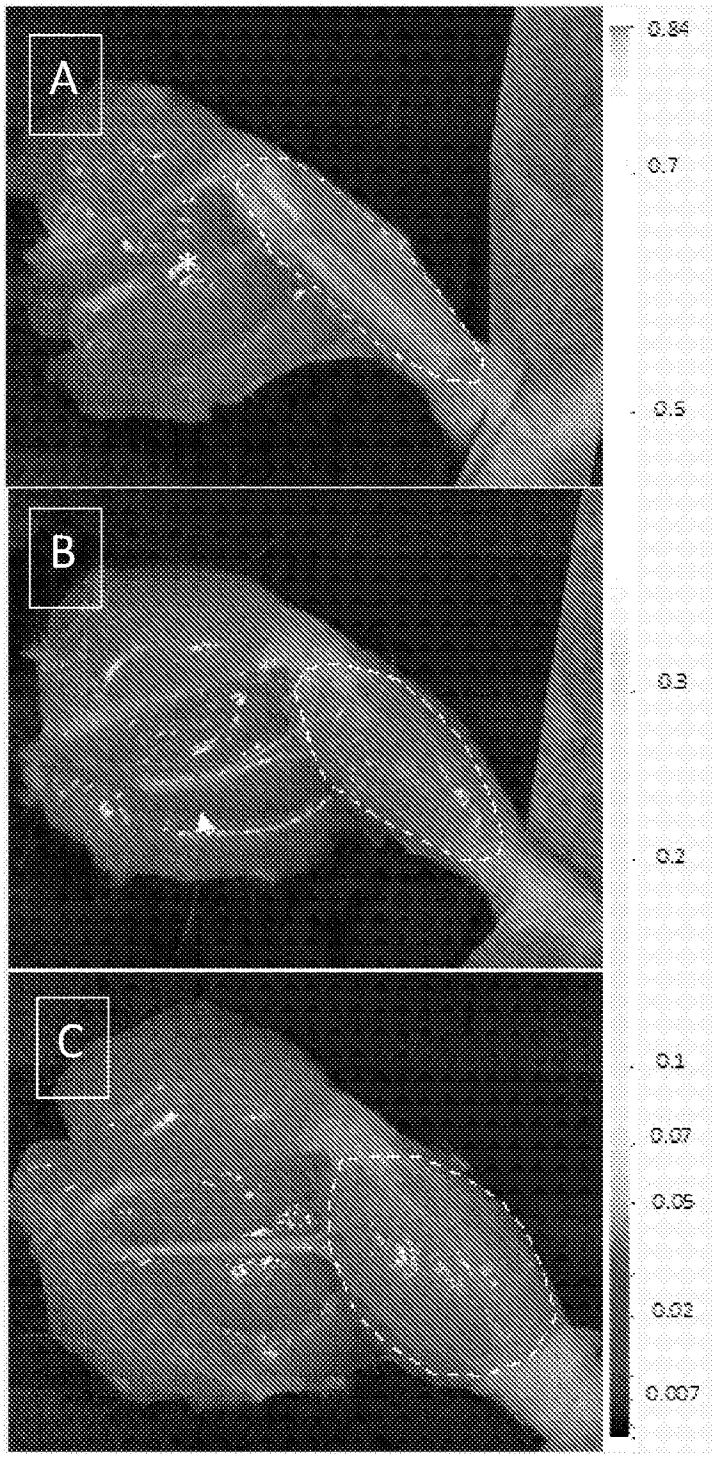


Fig. 9

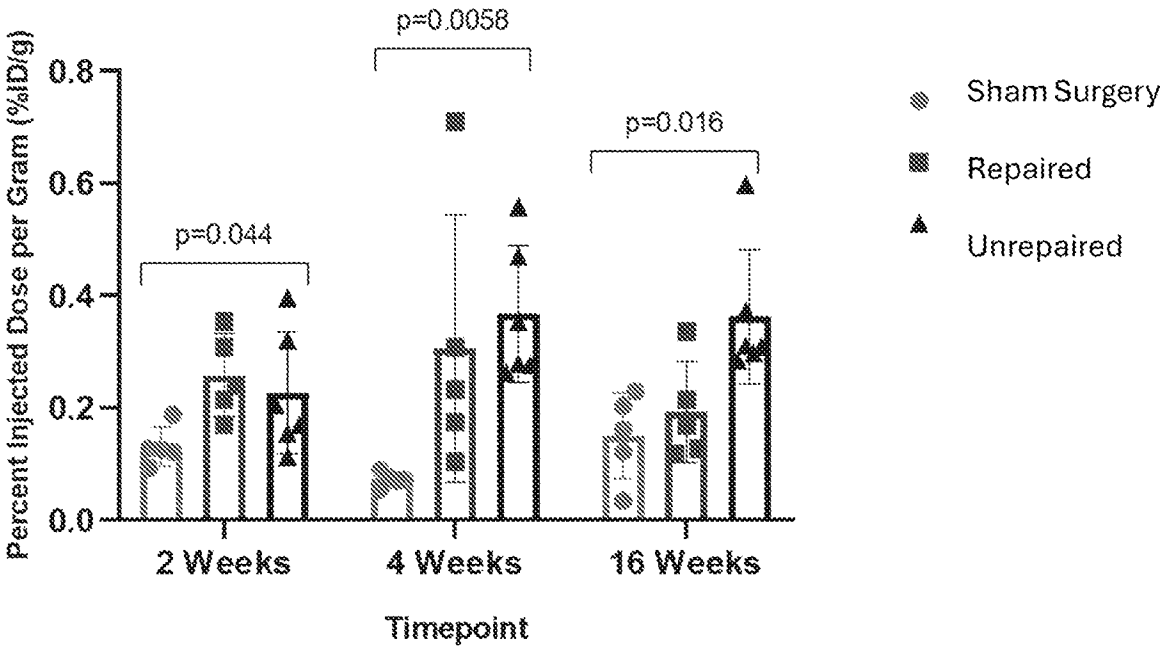

p=0.0058
p=0.016
p=0.044
Percent Injected Dose per Gram (%ID/g)
0.8
0.6
0.4
0.2
0.0
2 Weeks
4 Weeks
16 Weeks
Timepoint
Sham Surgery
Repaired
Unrepaired

Fig. 10

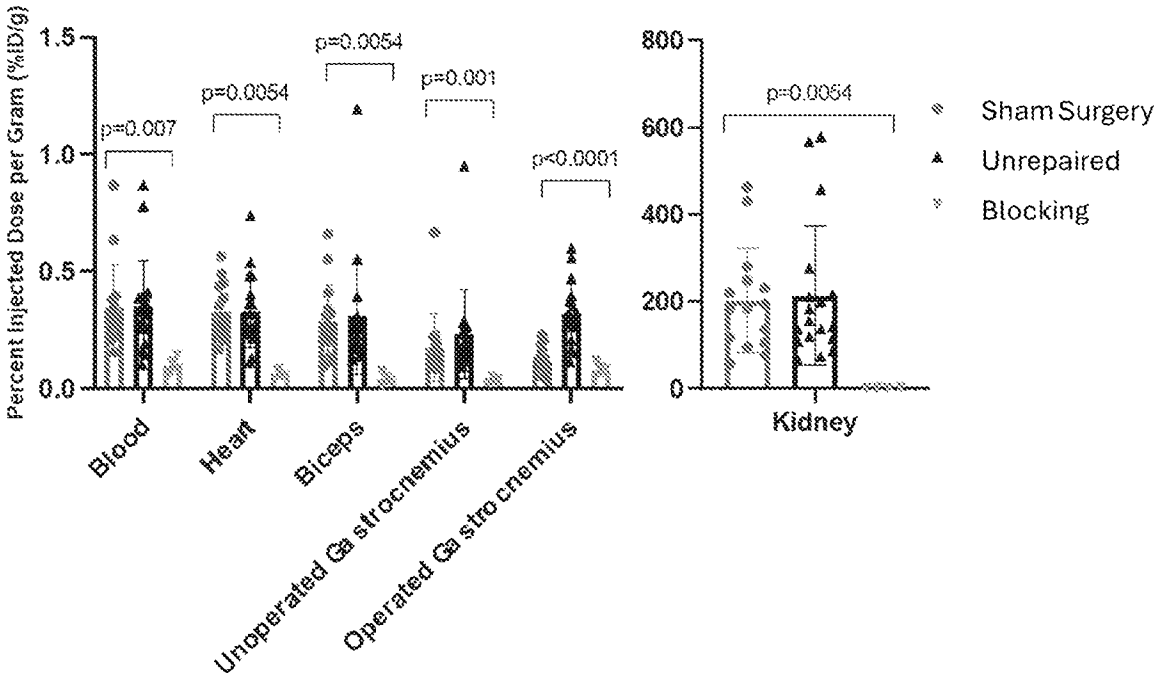

Percent Injected Dose per Gram (%ID/g)
1.5
1.0
0.5
0.0
800
600
400
200
0
p=0.007
p=0.0054
p=0.0054
p=0.001
p<0.0001
p=0.0054
Blood
Heart
Biceps
Unoperated Gastrocnemius
Operated Gastrocnemius
Kidney
Sham Surgery
Unrepaired
Blocking

Fig. 11

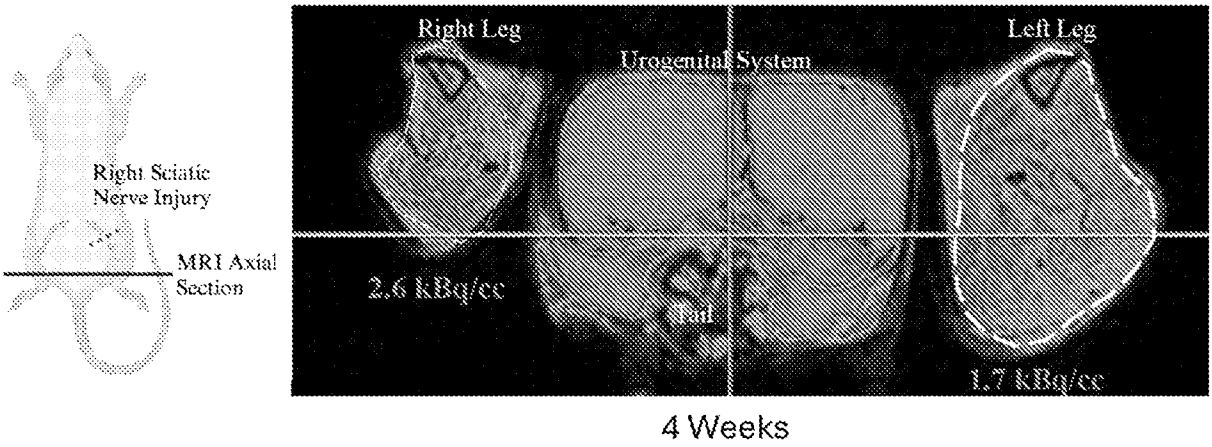

Right Sciatic
Nerve Injury
MRI Axial
Section
Right Leg
Urogenital System
Left Leg
2.6 kBq/cc
Tail
1.7 kBq/cc
4 Weeks

Fig. 12

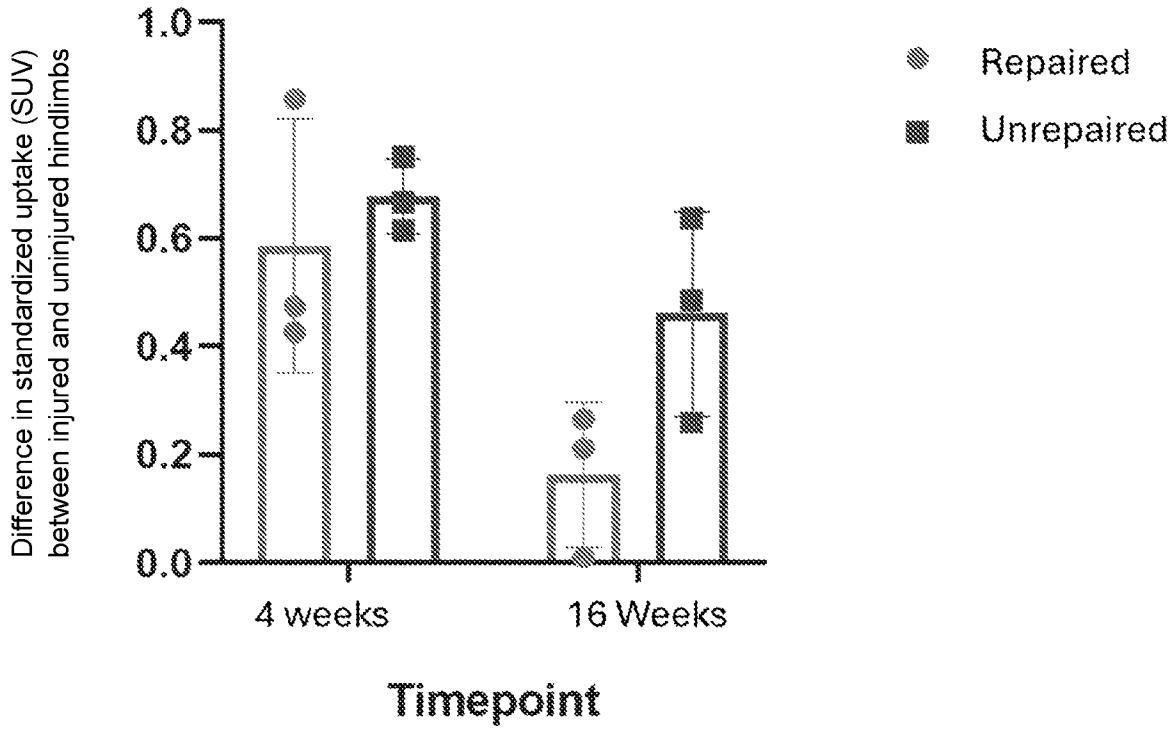

Difference in standardized uptake (SUV) between injured and uninjured hindlimbs
1.0
0.8
0.6
0.4
0.2
0.0
4 weeks
16 Weeks
Timepoint
Repaired
Unrepaired

Fig. 13

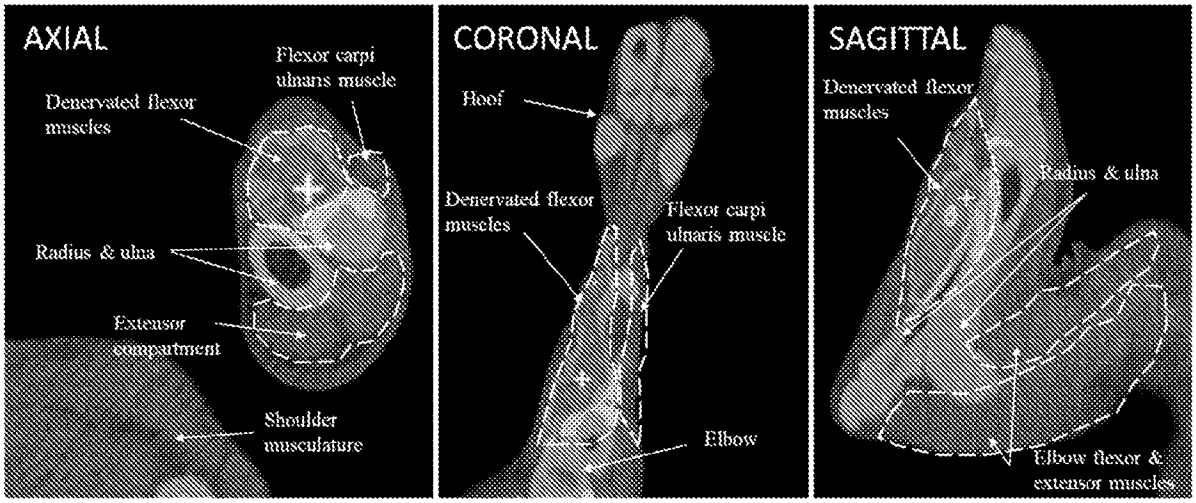

AXIAL
Flexor carpi ulnaris muscle
Denervated flexor muscles
Radius & ulna
Extensor compartment
Shoulder musculature
CORONAL
Hoof
Denervated flexor muscles
Flexor carpi ulnaris muscle
Elbow
SAGITTAL
Denervated flexor muscles
Radius & ulna
Elbow flexor & extensor muscles
16 Weeks

Fig. 14

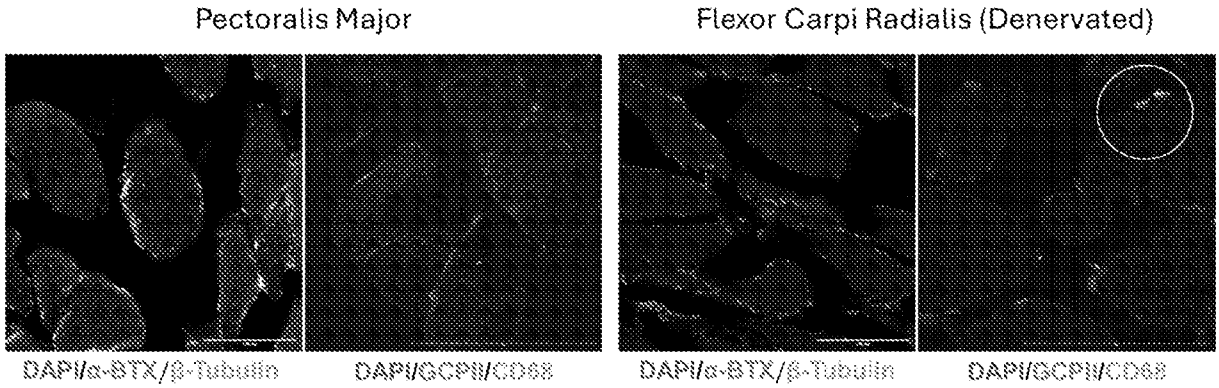

Pectoralis Major
Flexor Carpi Radialis (Denervated)
DAPI/α-BTX/β-Tubulin
DAPI/GCPII/CD68
DAPI/α-BTX/β-Tubulin
DAPI/GCPII/CD68

Fig. 15