expression is correlated with regions of tumorigenic tissues, particularly the tumor stroma and therefore presents an excellent molecular target for the diagnosis and treatment of various cancers. Its expression has been confirmed in numerous cancers, such as pancreatic, liver, gall bladder, neuroblastoma, breast, ovarian, esophageal, kidney, melanoma and many other deadly and aggressive tumors and cancer types. FAP expression is also detected in fibrotic tissues and can also be a marker for a wide spectrum of clinical conditions including systemic fibrotic diseases such as systemic sclerosis (SSc), sclerodermatous graft vs. host disease, and nephrogenic systemic fibrosis, as well as numerous organ-specific disorders including radiation-induced fibrosis and cardiac, pulmonary, liver (such as NAFLD: non-alcoholic fatty liver disease and NASH: non-alcoholic steatohepatitis), and kidney fibrosis.

While several researchers have explored FAP as a cancer target, the development of agents that can serve as diagnostics or even therapeutics have proven only marginally useful, due to their pharmacokinetic limitations. To date FAP has proven to be a difficult target due to the low and limited expression of the target and the limited residence time the prior art compounds display *in vivo*. What is needed are improved FAP-binding agents that demonstrate better binding kinetics and biodistribution, thereby providing the basis for improved FAP-targeted diagnostic and therapeutic agents, i.e., compounds that can accumulate to a greater degree in tumors without unacceptable uptake in normal non-target tissues and organs.

SUMMARY

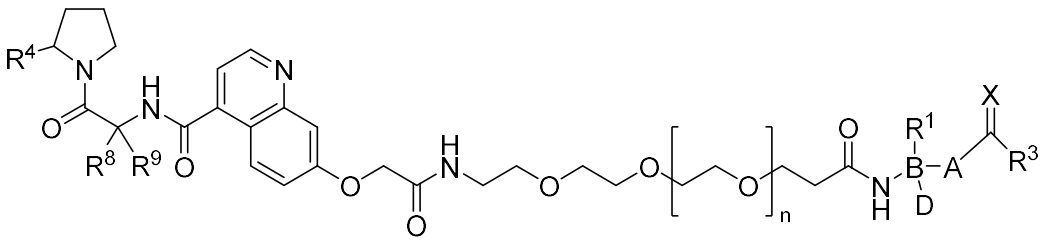
FAP-targeted therapeutics are emerging as a potential methodology for treating a wide variety of cancers that express FAP in the microenvironment and/or tumor cells themselves. Several FAP-targeted molecules, such as FAPI-04, FAPI-46, FAP-2286, PNT6555 have been studied preclinically and in early clinical trials. FAP-targeted therapies have shown some initial promise in humans; however relatively short tumor retention is a significant limitation. Current FAP-targeted compounds clear relatively rapidly from tumor tissue, limiting the radioactive absorbed dose to the tumor. Efforts have been made to improve tumor retention of FAP-targeted radiotracers with limited success.

Disclosed herein are a series of novel compounds that bind to the extracellular domain of FAP. Unlike existing compounds, the disclosed compounds exhibit a unique chemical

structure that allows for significantly higher affinity to FAP (see Example 2 & 3), leading to improved tumor retention.

The compounds disclosed herein can be attached to chelating groups for radionuclide binding and are therefore suitable for radioimaging and/or radiotherapy applications, for example the disclosed compounds can be radiolabeled with a positron emitter such as ^{18}F, ^{68}Ga or ^{64}Cu, and used for positron emission tomography (PET) (see Example 4). Alternatively, the compounds can be radiolabeled with an alpha particle emitter such as ^{225}Ac, a beta particle emitter such as ^{67}Cu or ^{177}Lu, or an Auger electron emitter (e.g. ^{111}In, ^{67}Ga, ^{99}mTc, ^{195}mPt, ^{125}I and ^{123}I). The compounds can also be attached to a cytotoxic agent for targeted delivery of the cytotoxic agent to tumors, for example conjugated to gemcitabine or doxycycline, or a venom. Likewise, the compounds can be conjugated to compounds having physiological effects, such as TLR agonists to stimulate the immune response of a recipient. The disclosed compounds have the advantage of surprisingly high affinity to FAP. Many of these compounds also have albumin binding/increased circulatory residence time but it is the potency/affinity to FAP that is believed to result in the significant tumor residence time. The increased circulatory residence time has the effects of increasing target loading while reducing accumulation of the compound in non-target tissues (see Example 6). Accordingly, the favorable binding kinetics of the compounds disclosed herein reduce the "wash-out" effect (i.e., low residence time) seen with prior art FAP-targeted compounds.

One example of the disclosure is a compound represented by the following structural formula (I):



(I);

or a pharmaceutically acceptable salt thereof, wherein:

n is 0 or 1;

A is NH, O, S or CR^6R^7;

B comprises or is a branched, unbranched or cyclic aliphatic group of up to 30 carbon atoms optionally interrupted by up to 10 heteroatoms or a peptidyl chain of up to 20 amino acid residues (for example, 3-20 or 3-15 carbon atoms optionally interrupted by up to 6

heteroatoms or up to 5 amino acid residues), wherein B is optionally substituted with 1-5 groups selected from F, Cl, Br, I, =O, OR^6, $OCOR^6$, $COOR^6$, CN, $=NR^6$, NR^6R^7, =S, and SR^6, provided that B comprises at least 3 atoms in a chain between group D and the group A;

D is selected from the group consisting of OPO_3H_2, PO_3H_2, OSO_3H, SO_3H and COOH or a C_1-C_4 alkyl ester thereof;

X is O or S;

R^1 is a chelating group, an optical dye or fluorophore, a cytotoxic agent, an immune stimulant, or a benzoyl group optionally substituted by one or more groups represented by R^5;

R^3 is C_1-C_8 alkyl or C_1-C_4 aralkyl, wherein:

the alkyl and aryl portions of the aralkyl are each optionally and independently substituted with F, Cl, Br, I, branched, unbranched or cyclic C_1-C_6 aliphatic group, OR^6, $OCOR^6$, $COOR^6$, CHO, COR^6, CH_2OR^6, NR^6R^7, $CH_2NR^6R^7$, SR^6, =O, =S and =NH;

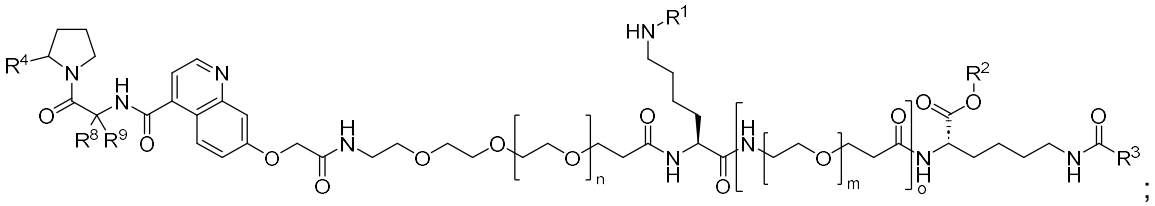
R^4 is CN or $B(OH)_2$;

each R^5 is independently selected from halo, cyano, halomethyl, $N^+(CH_3)_3W^-$ wherein W^- is a pharmaceutically acceptable anion;

R^6 and R^7 are independently selected from the group consisting of H or a C_1-C_6 alkyl; and

R^8 is $C_{1\text{-}4}$alkyl and R^9 is selected from H and C_1-C_4 alkyl or R^8 and R^9 taken together with their intervening carbon atom form a C_3-C_6 cycloalkyl.

In one aspect, there is provided a compound represented by the following structural formula:



;

or a pharmaceutically acceptable salt thereof, wherein

R^1 is a chelating group, an optical dye or fluorophore, a cytotoxic agent, or an immune stimulant, or a benzoyl group optionally substituted by one or more groups represented by R^5;

R^2 is H or C_1-C_4 alkyl;

R^3 is $C_{1\text{-}8}$ alkyl or $C_{1\text{-}4}$ aralkyl optionally substituted with F, Cl, Br, I, or $C_{1\text{-}4}$ alkyl;

R^4 is CN or $B(OH)_2$;

each R^5 is independently selected from halo, cyano, halomethyl, $N^+(CH_3)_3W^-$ wherein W^- is a pharmaceutically acceptable anion;

R^6 and R^7 are independently selected from the group consisting of H or a C_1-C_6 alkyl;

R^8 is C_1-C_4 alkyl and R^9 is selected from H and C_1-C_4 alkyl or R^8 and R^9 taken together with their intervening carbon atom form a C_3-C_6 cycloalkyl;

n is 0 or 1;

m is an integer from 0 to 12; and

o is 0 or 1;

optionally wherein the chelating group is chelated with a radionuclide.

Another aspect of the disclosure is a pharmaceutical composition comprising: i) a compound disclosed herein or a pharmaceutically acceptable salt thereof; and ii) a pharmaceutically acceptable carrier or diluent. For compounds comprising a chelating group, the chelating group is preferably chelated with a radionuclide.

Another example of the disclosure is a method of treating a subject with diseased tissue that expresses fibroblast activation protein alpha. The diseased tissue in one example can be a cancer or a fibrotic tissue. The method comprises administering an effective amount of the compound disclosed herein or pharmaceutically acceptable salt to the subject. Preferably, the compound used for therapy comprises a cytotoxic agent, such as a chelating group having a radionuclide that emits beta, alpha, Auger or other cytotoxic radiation which can kill the diseased tissue.

Thus, in another aspect, there is provided use of the compound, or pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating a diseased tissue, wherein the diseased tissue expresses fibroblast activation protein alpha, and wherein the radionuclide is a therapeutic radionuclide; preferably wherein the diseased tissue is:

(i) a cancer, such as a cancer selected from pancreatic cancer, liver cancer, gall bladder cancer, neuroblastoma, breast cancer, ovarian cancer, esophageal cancer, kidney cancer, prostate cancer, colorectal cancer, soft tissue sarcoma, bone sarcoma and melanoma; or

(ii) fibrotic.

Yet another example of the disclosure is a method of imaging a region in a subject having or suspected of having a cancer or a fibrotic tissue disease which expresses fibroblast activation protein alpha or fibrotic tissue, comprising:

a. administering to the subject a diagnostically effective amount of a compound disclosed herein or pharmaceutically acceptable salt thereof or a pharmaceutical composition disclosed herein;
b. exposing a region in the subject to an imaging device, the region suspected of having diseased tissue; and
c. obtaining an image of diseased tissue in the region.

Preferably, the compound used for imaging comprises a chelating group having a radionuclide that emits gamma-rays or positrons or other detectible radiation. In another example, the compound comprises an optical dye or a fluorophore, the emissions of which can be detected.

Hence, in another aspect, there is provided use of a compound, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for imaging a region in a subject having or suspected of having diseased tissue which expresses fibroblast activation protein alpha or fibrotic tissue, wherein the radionuclide is a diagnostic radionuclide; preferably wherein the region has or is suspected of having the diseased tissue includes:

(i) a primary cancer or a metastasis of the cancer; or
(ii) fibrotic tissue.

Yet another example of the disclosure is a method of imaging tumors. The method comprises:

a. administering to a subject, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, in an amount effective to contact and bind to the tumor and/or surrounding tissue;
b. irradiating the tumor and/or surrounding tissue at a wavelength absorbed by the bound compound;
c. and detecting a signal from the irradiated bound compound, thereby imaging the tumor and/or surrounding tissue.

Preferably, the compound used for imaging comprises a chelating group having a radionuclide that emits gamma-rays or positrons, or an optical dye or a fluorophore, or other detectible radiation.

In yet another aspect, there is provided use of a compound, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for imaging tumors, wherein:

a. the compound or the pharmaceutically acceptable salt thereof is to be contacted with the tumor and/or surrounding tissue in an amount sufficient to bind to the tumor;

b. the tumor and/or surrounding tissue is to be irradiated at a wavelength absorbed by the compound; and

c. a signal from the compound is to be detected, thereby imaging the tumor and/or surrounding tissue.

Still another embodiment of the disclosure is a method of treating diseased tissue. The method comprises:

a. administering to a subject, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, in an amount effective to contact and bind to the diseased tissue;

b. using the compound as a fiducial, irradiating the region of the bound compound with one or more doses of external beam radiation,

thereby treating the diseased tissue with radiation.

Preferably, the compound used for the fiducial comprises a chelating group having a radionuclide that emits gamma-rays or positrons, or an optical dye or a fluorophore, or other detectible radiation.

Thus, still another aspect, there is provided use of the compound, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for use in treating diseased tissue, wherein:

a. the compound, or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof, is to be contacted and bound to the diseased tissue; and

b. the compound is to be used as a fiducial, and the region of the bound compound is to be irradiated with one or more doses of external beam radiation, thereby treating the diseased tissue with radiation;

preferably, wherein the compound comprises a chelating group having a radionuclide that emits gamma-rays or positrons, or an optical dye or a fluorophore, or other detectible radiation.

Even still another example of the disclosure is a method of treating diseased tissue. The method comprises:

a. administering to a subject, a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, in an amount effective to contact and bind to the diseased tissue;

b. using the compound as a fiducial for guided surgery applications, to resect the region of the diseased tissue

thereby excising the diseased tissue.

Preferably, the compound used for the fiducial comprises a chelating group having a radionuclide that emits gamma-rays or positrons, or an optical dye or a fluorophore, or other detectible radiation.

Therefore, in yet another aspect, there is provided use of the compound, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition in the manufacture of a medicament for use in treating diseased tissue, wherein:

a. the compound, or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof, is to be contacted and bound to the diseased tissue; and

b. the compound is to be used as a fiducial for guided surgery applications, to resect the region of the diseased tissue thereby excising the diseased tissue;

preferably, wherein the compound comprises a chelating group having a radionuclide that emits gamma-rays or positrons, or an optical dye or a fluorophore, or other detectible radiation.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1. Show the organ biodistribution of [Lu-177]RTX-1371R in BALB/C nude mice previously transplanted with U-87/MG cells.

FIG. 2. Show the organ biodistribution of [Lu-177]RTX-1391R in BALB/C nude mice previously transplanted with U-87/MG cells.

FIG. 3. Show the organ biodistribution of [Lu-177]RTX-1392R in BALB/C nude mice previously transplanted with U-87/MG cells.

FIG. 4. shows the organ biodistribution of [Lu-177]RTX-1356R and [Lu-177]RTX-1391R in BALB/C nude mice previously transplanted with U-87/MG cells.

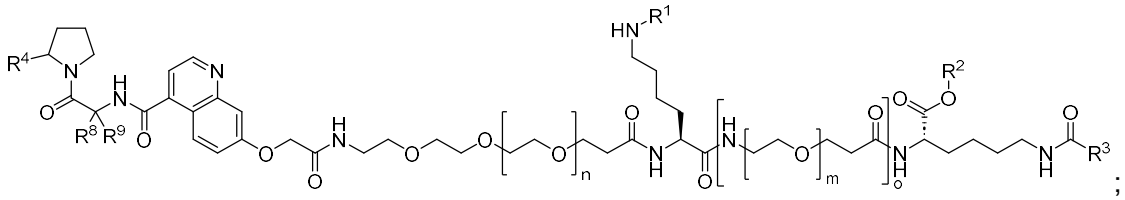
FIG. 5. shows the organ biodistribution of [Lu-177]RTX-1357R and [Lu-177]RTX-1392R in BALB/C nude mice previously transplanted with U-87/MG cells.

FIG. 6. shows the organ biodistribution of [Lu-177]RTX-1359R and [Lu-177]RTX-1371R in BALB/C nude mice previously transplanted with U-87/MG cells.

CLAIMS

We claim:

1. A compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein

R^1 is a chelating group, an optical dye or fluorophore, a cytotoxic agent, or an immune stimulant, or a benzoyl group optionally substituted by one or more groups represented by R^5;

R^2 is H or C_1-C_4 alkyl;

R^3 is C_{1-8} alkyl or C_{1-4} aralkyl optionally substituted with F, Cl, Br, I, or C_{1-4} alkyl;

R^4 is CN or $B(OH)_2$;

each R^5 is independently selected from halo, cyano, halomethyl, $N^+(CH_3)_3W^-$ wherein W^- is a pharmaceutically acceptable anion;

R^6 and R^7 are independently selected from the group consisting of H or a C_1-C_6 alkyl;

R^8 is C_1-C_4 alkyl and R^9 is selected from H and C_1-C_4 alkyl or R^8 and R^9 taken together with their intervening carbon atom form a C_3-C_6 cycloalkyl;

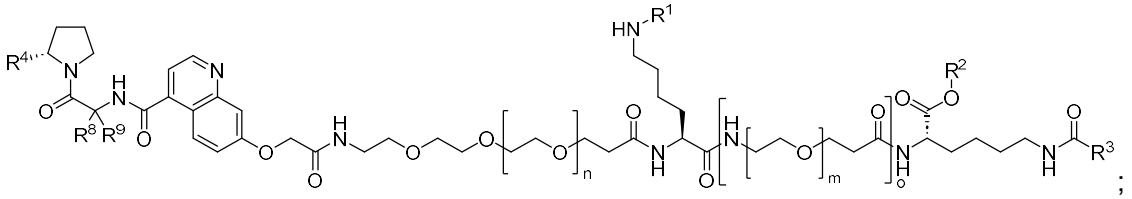
n is 0 or 1;

m is an integer from 0 to 12; and

o is 0 or 1;

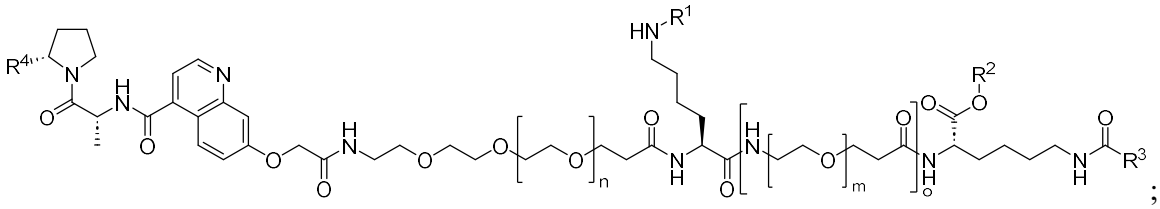
optionally wherein the chelating group is chelated with a radionuclide.

2. The compound of claim 1, wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

3. The compound of claims 1 or 2, wherein the compound is represented by the following structural formula


; or a pharmaceutically acceptable salt thereof.

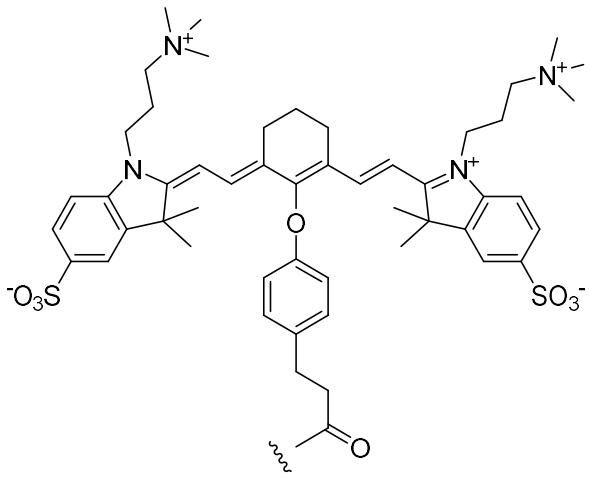
4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein R^3 methyl, (4-isobutylphenyl)methyl, (4-isobutylphenyl)propyl, (4-iodophenyl)methyl, or (4-iodophenyl)propyl.

5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein n is 1; and wherein:

(i) o is 1 and m is 3 to 12, preferably wherein m is 8; or

(ii) o is 0.

6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein R^1 is a fluorophore or an optical dye, preferably wherein the fluorophore is


; and the optical dye is selected from the group consisting of: a carbocyanin, indocarbocyanin, oxacarbocyanin, thiacarbocyanin, merocyanin, polymethine, coumarin, rhodamine, xanthene, fluorescein, Borodipyrromethane (BODIPY), VivoTag-680, VivoTag-S750, AlexaFluor dyes (e.g., AlexaFluor660, AlexaFluor680, AlexaFluor700, AlexaFluor750, AlexaFluor790) and DylightFluor dyes.

7. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein R^1 is a chelating group that is the residue of a chelating agent, preferably wherein the chelating group is the residue of a chelating agent selected from 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), p-SCN-Bn-NOTA**,** , 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic

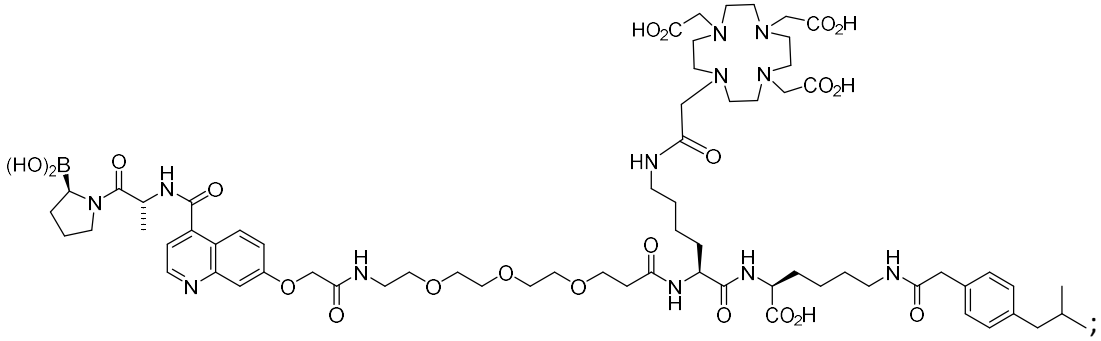
acid (DOTA), p-SCN-Bn-DOTA (also known as 2B-DOTA-NCS),PIP-DOTA, diethylenetriaminepentaacetic acid (DTPA), PIP-DTPA, AZEP-DTPA, ethylenediamine tetraacetic acid (EDTA), triethylenetetraamine-N,N,N',N'',N''',N'''-hexa-acetic acid (TTHA), 7-[2-(bis-carboxymethylamino)-ethyl]-4,10-bis-carboxymethyl-1,4,7,10-tetraaza-cyclododec-1-yl-acetic acid (DEPA), 2,2′,2″-(10-(2-(bis(carboxymethyl)amino)-5-(4-isothiocyanatophenyl) pentyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (3p-C-DEPA-NCS), NETA,{4-carboxymethyl-7-[2-(carboxymethylamino)-ethyl]-perhydro-1,4,7-triazonin-1-yl}-acetic acid (NPTA), diacetylpyridinebis(benzoylhydrazone), 1,4,7,10,13,16-hexaazacyclooctadecane N,N′,N″,N‴,N⁗,N⁗′-hexaaceticacid (HEHA), octadentate terephthalamide ligands, 2,2′-(4-(2-(bis(carboxymethyl)amino)-5-(4-isothiocyanatophenyl)pentyl)-10-(2-(bis(carboxymethyl)amino)ethyl)-1,4,7,10-tetraazacyclododecane-1,7-diyl)diacetic acid, N,N′-bis[(6-carboxy-2-pyridil)methyl]-4,13-diaza-18-crown-6 (H2macropa), 6-((16-((6-carboxypyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)-4-isocyanatopicolinic acid (macropa-NCO), 6-((16-((6-carboxypyridin-2-yl)methyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7-yl)methyl)-4-isothiocyanatopicolinic acid (macropa-NCS), 3,9-carboxymethyl-6-(2-methoxy-5-isothiocyanatophenyl)carboxymethyl-3,6,9,15-tetraazabicyclo-[9.3.1]pentadeca-1(15),11,13-triene and 2-[4,7,10-tris(2-amino-2-oxoethyl)-1,4,7,10-tetrazacyclododec-1-yl]acetamide (TCMC or DOTAM).

8. The compound of claim 7, or a pharmaceutically acceptable sat thereof, wherein the residue of the chelating agent is:

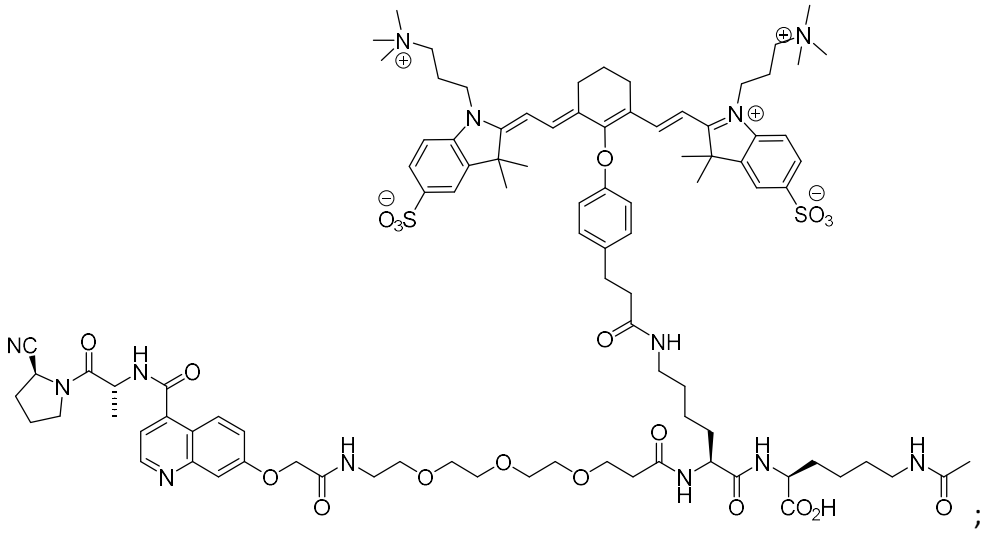
(i) the residue of macropa-NCS or macropa-NCO, preferably wherein the macropa-NCS or macropa-NCO is chelated with ^{225}Ac; or

(ii) the residue of p-SCN-Bn-NOTA, p-SCN-Bn-DOTA, NOTA or DOTA.

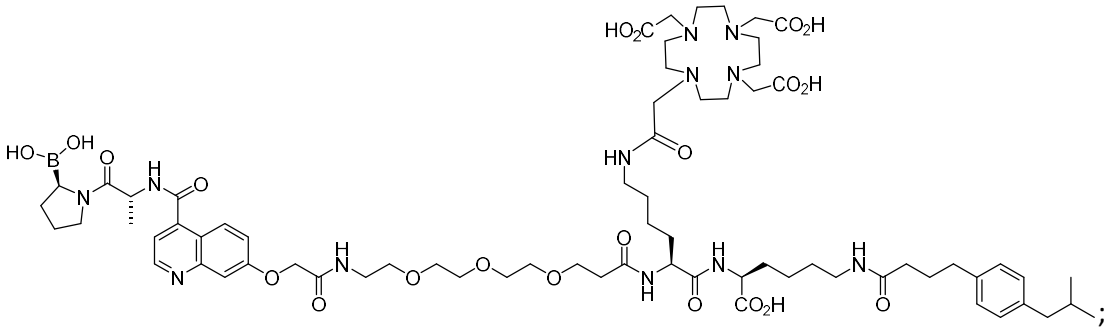
9. The compound of claim 1, or pharmaceutically acceptable salt thereof, wherein the compound is represented by a structural formula selected from:



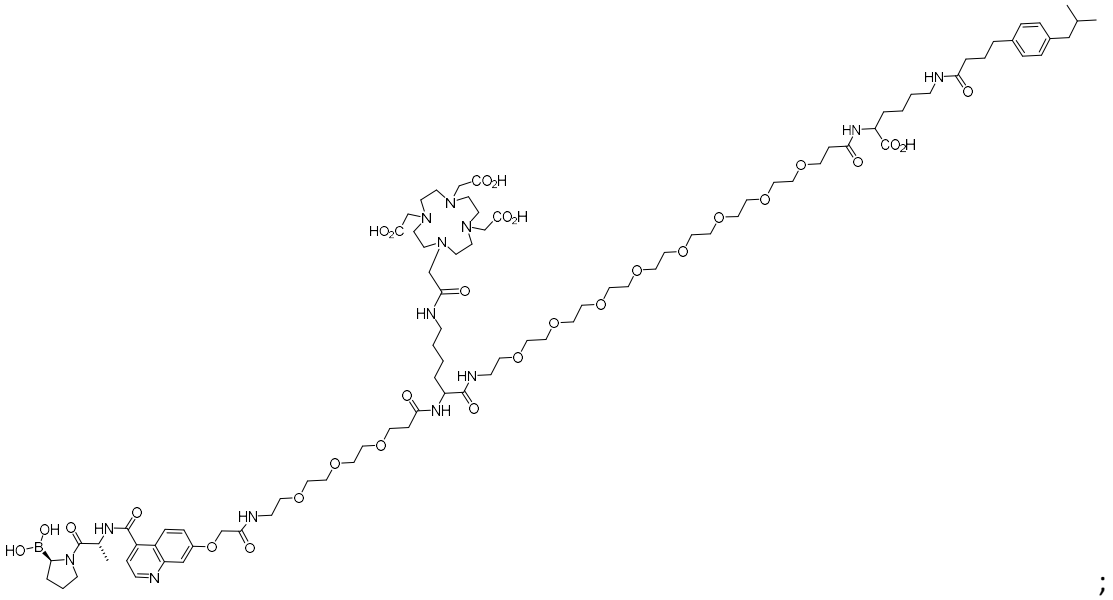
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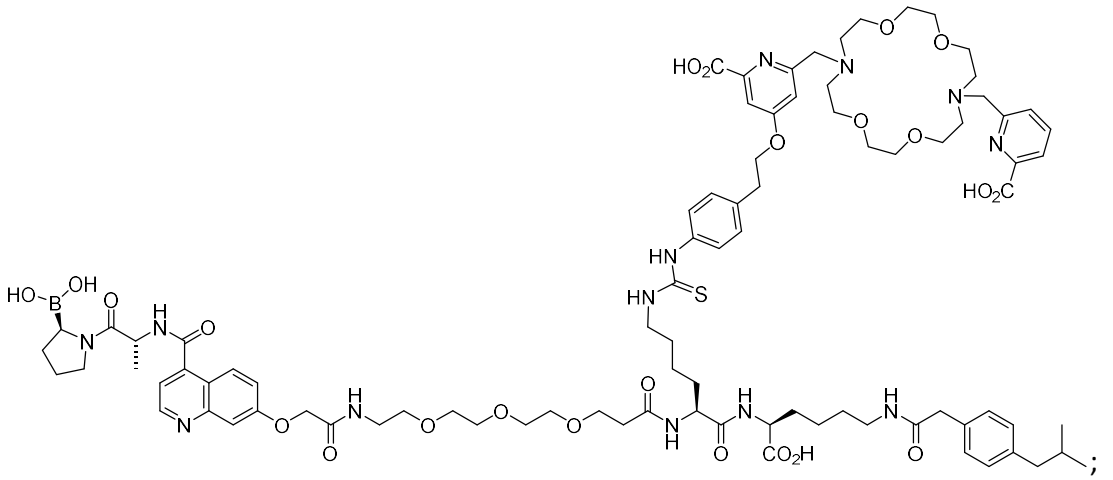
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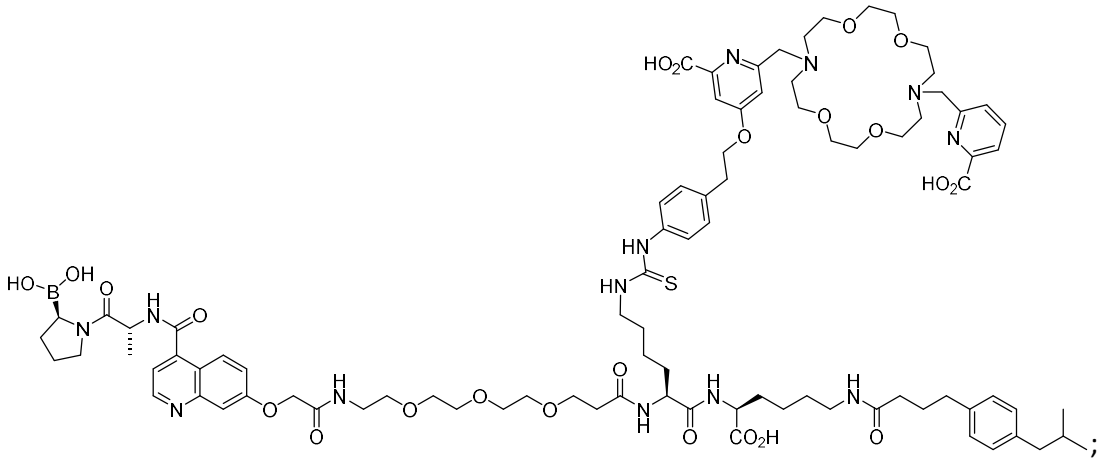
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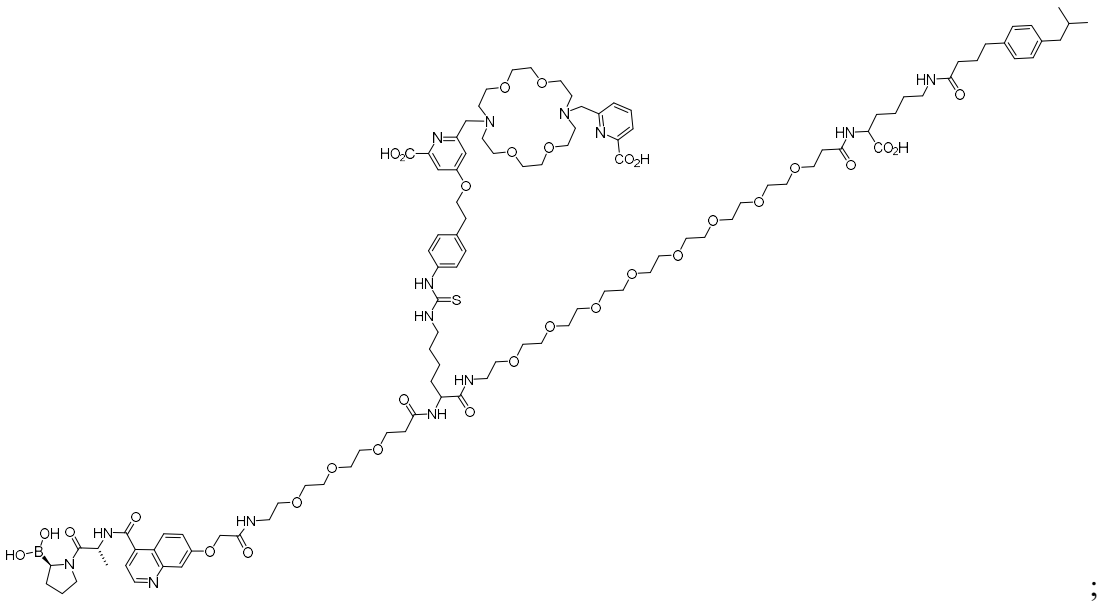
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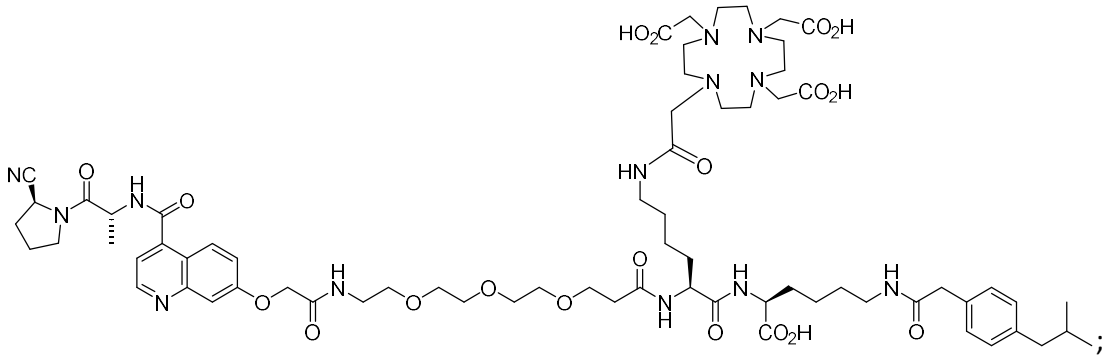
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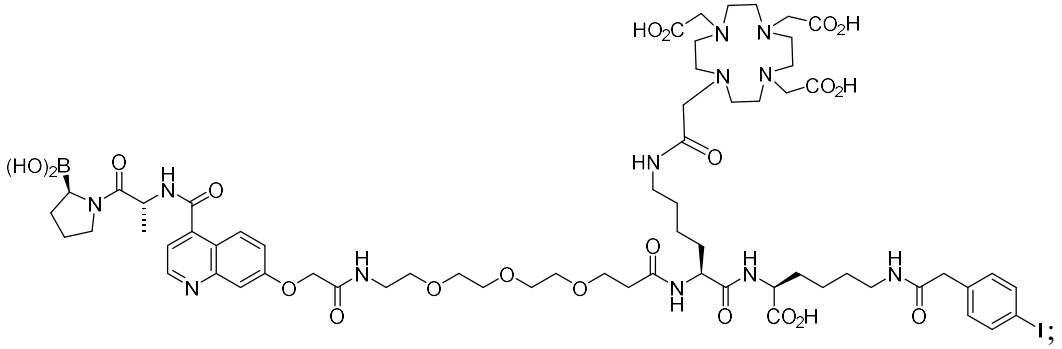
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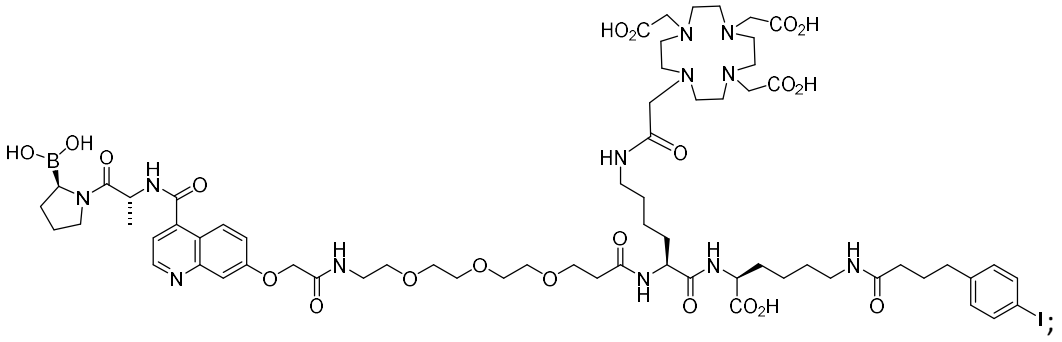


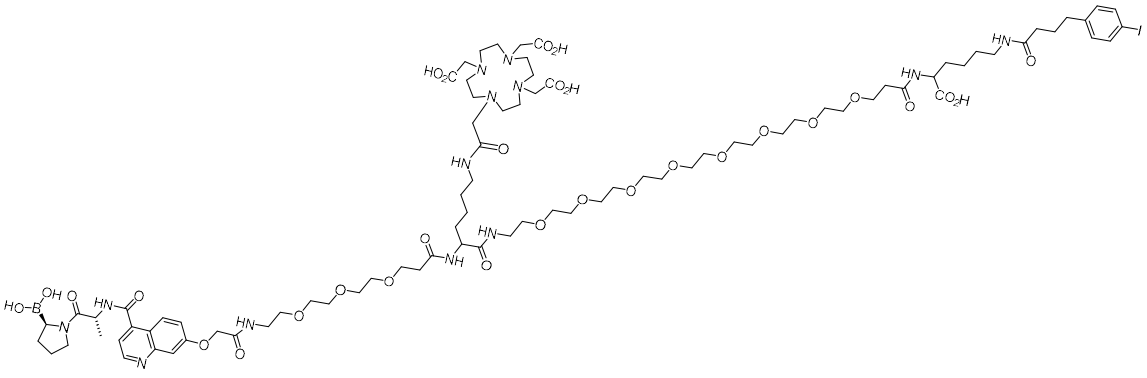
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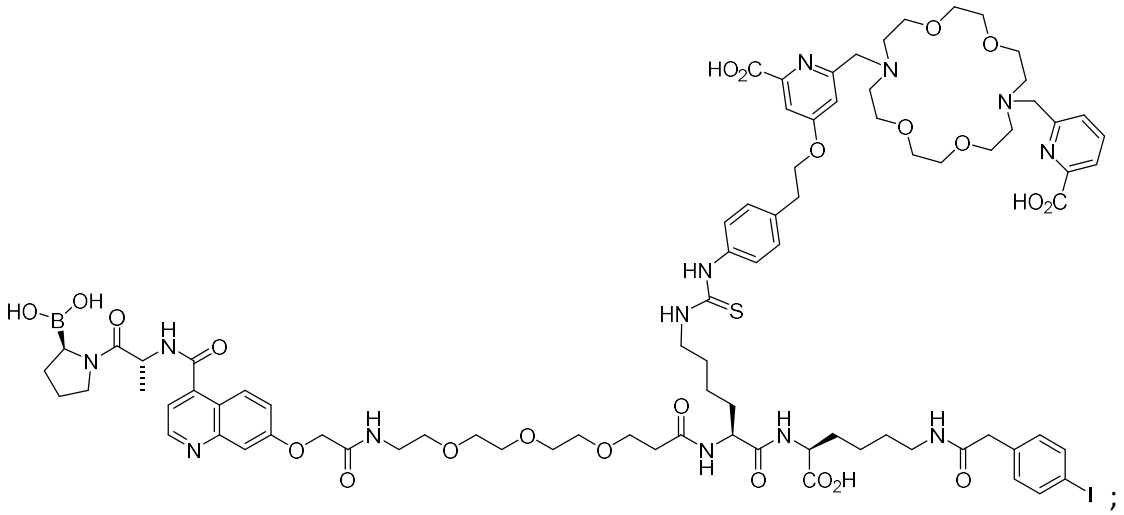
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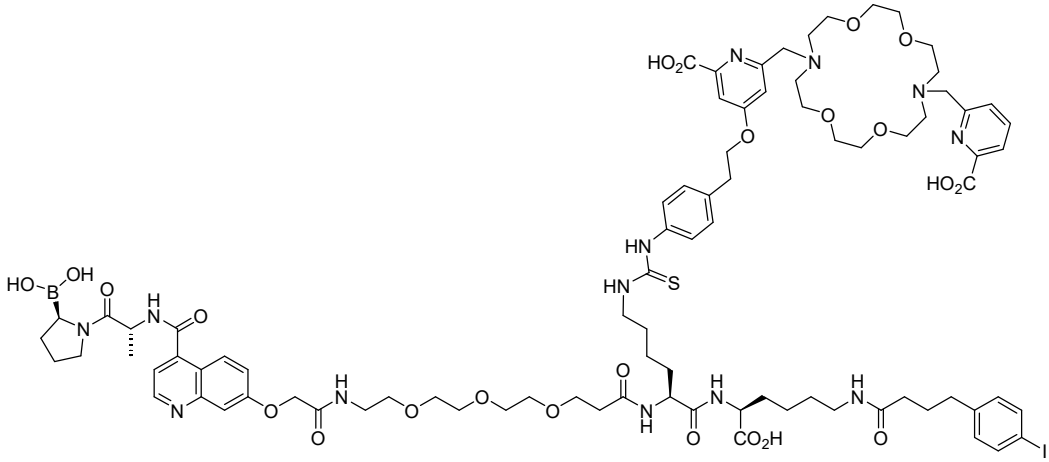




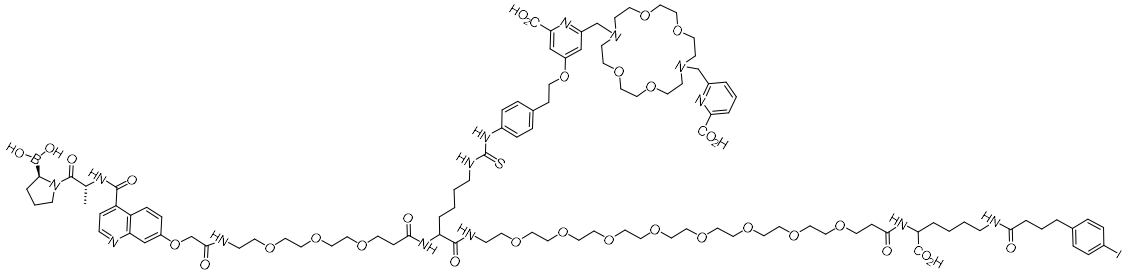
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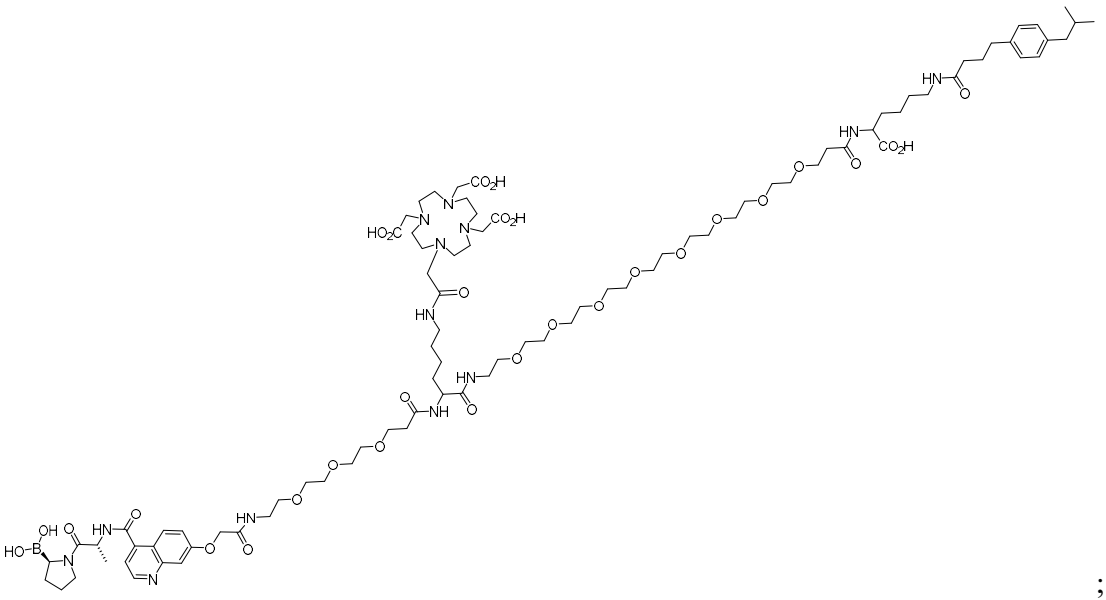


; and



.

10. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is represented by the following structural formula:



;

optionally wherein the compound is chelated with a radionuclide.

11. The compound of any one of claims 1 to 5 and 7 to 10, or a pharmaceutically acceptable salt thereof, wherein the residue of the chelating agent is chelated with a radionuclide, wherein the radionuclide is selected from ^{177}Lu, ^{175}Lu, ^{45}Sc, ^{64}Cu, ^{67}Cu, ^{68}Cu, ^{66}Ga, ^{67}Ga, ^{68}Ga, ^{69}Ga, ^{71}Ga, ^{90}Y, ^{89}Y, ^{86}Y, ^{89}Zr, ^{90}Y, ^{99m}Tc, ^{111}In, ^{113}In, ^{115}In, ^{139}La, ^{134}Ce, ^{136}Ce, ^{138}Ce, ^{140}Ce, ^{142}Ce, ^{151}Eu, ^{153}Eu, ^{152}Dy, ^{149}Tb, ^{159}Tb, ^{154}Gd, ^{155}Gd, ^{156}Gd, ^{157}Gd, ^{158}Gd, ^{160}Gd, ^{188}Re, ^{186}Re, ^{211}At, ^{217}At, ^{227}Th, ^{226}Th, ^{225}Ac, ^{233}Ra, ^{152}Dy, ^{213}Bi, ^{212}Bi, ^{211}Bi, ^{203}Pb, ^{212}Pb, ^{255}Fm, and uranium-230; preferably wherein the radionuclide is:

(i) an alpha-emitting radionuclide such as ^{225}Ac, ^{233}Ra, and ^{212}Pb; or

(ii) an Auger electron emitting radionuclide or a beta-emitting radionuclide such as ^{177}Lu, ^{90}Y, and ^{67}Cu.

12. A pharmaceutical composition comprising:

a. the compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof; and

b. a pharmaceutically acceptable carrier or diluent.

13. Use of the compound of claim 11, or pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 12 in the manufacture of a medicament for treating a diseased tissue, wherein the diseased tissue expresses fibroblast activation protein alpha, and wherein the radionuclide is a therapeutic radionuclide; preferably wherein the diseased tissue is:

(i) a cancer, such as a cancer selected from pancreatic cancer, liver cancer, gall bladder cancer, neuroblastoma, breast cancer, ovarian cancer, esophageal cancer, kidney cancer, prostate cancer, colorectal cancer, soft tissue sarcoma, bone sarcoma and melanoma; or

(ii) fibrotic.

14. Use of a compound of any one of claims 6, 7 and 9 to 11, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 12 in the manufacture of a medicament for imaging a region in a subject having or suspected of having diseased tissue which expresses fibroblast activation protein alpha or fibrotic tissue, wherein the radionuclide is a diagnostic radionuclide; preferably wherein the region has or is suspected of having the diseased tissue includes:

(i) a primary cancer or a metastasis of the cancer; or

(ii) fibrotic tissue.

15. Use of a compound of claim 6, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for imaging tumors, wherein:

a. the compound or the pharmaceutically acceptable salt thereof is to be contacted with the tumor and/or surrounding tissue in an amount sufficient to bind to the tumor;

b. the tumor and/or surrounding tissue is to be irradiated at a wavelength absorbed by the compound; and

c. a signal from the compound is to be detected, thereby imaging the tumor and/or surrounding tissue.

16. Use of the compound of any one of claims 6, 7 and 9 to 11, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 12 in the manufacture of a medicament for use in treating diseased tissue, wherein:

a. the compound, or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof, is to be contacted and bound to the diseased tissue; and

b. the compound is to be used as a fiducial, and the region of the bound compound is to be irradiated with one or more doses of external beam radiation, thereby treating the diseased tissue with radiation;

preferably, wherein the compound comprises a chelating group having a radionuclide that emits gamma-rays or positrons, or an optical dye or a fluorophore, or other detectible radiation.

17. Use of the compound of any one of claims 6, 7 and 9 to 11, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 12 in the manufacture of a medicament for use in treating diseased tissue, wherein:

a. the compound, or the pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof, is to be contacted and bound to the diseased tissue; and

b. the compound is to be used as a fiducial for guided surgery applications, to resect the region of the diseased tissue thereby excising the diseased tissue;

preferably, wherein the compound comprises a chelating group having a radionuclide that emits gamma-rays or positrons, or an optical dye or a fluorophore, or other detectible radiation.