d-Glu-RGD. All of these peptides – already improved and derivatized with the aim to reduce the lipophilicity – showed a logD value in the range between +2 and -1.22.

In Niedermoser S. et al. (J Nucl Med. 2015 Jul;56(7):1100-5), newly developed ^{18}F-SIFA- and ^{18}F-SIFAlin- (SIFA = silicon-fluoride acceptor) modified TATE derivatives were compared with the current clinical gold standard ^{68}Ga-DOTATATE for high-quality imaging of somatostatin receptor-bearing tumors. For this purpose, ^{18}F-SIFA-TATE and two quite complex analogues, ^{18}F-SIFA-Glc-PEG1-TATE, ^{18}F-SIFAlin-Glc-Asp2-PEG1-TATE were developed. None of the agents showed a logD <-1.5.

In view of the above, the technical problem underlying the present invention can be seen in providing radio-diagnostics and radio-therapeutics which contain a silicone fluoride acceptor and which are, at the same time, characterized by favourable in-vivo properties.

Summary

In an aspect of the present disclosure, there is provided a ligand-SIFA-chelator conjugate, comprising, within in a single molecule three separate moieties:

(a) one or more ligands which are capable of binding to prostate-specific membrane antigen (PSMA),

(b) a silicon-fluoride acceptor (SIFA) moiety which comprises a covalent bond between a silicon and a fluorine atom, and

(c) one or more chelating groups, optionally containing a chelated nonradioactive or radioactive cation.

In another aspect of the present disclosure, there is provided a pharmaceutical or diagnostic composition comprising or consisting of one or more conjugates or compounds disclosed herein.

In a further aspect of the present disclosure, there is provided a conjugate or compound disclosed herein for use in the preparation of a medicament for use as a cancer diagnostic or imaging agent.

In another aspect of the present disclosure, there is provided a conjugate or compound disclosed herein for use in the preparation of a medicament for the treatment of cancer.

In a further aspect of the present disclosure, there is provided a conjugate or compound disclosed herein for use in the preparation of a medicament for the diagnosis, imaging or prevention of neoangiogenesis/angiogenesis.

In another aspect of the present disclosure, there is provided a conjugate or compound disclosed herein for use in the preparation of a medicament for use as a cancer diagnostic or imaging agent or for use in the treatment of cancer wherein the cancer is prostate, breast, lung, colorectal or renal cell carcinoma.

In a further aspect of the present disclosure, there is provided a conjugate or compound disclosed herein for use as a cancer diagnostic or imaging agent, for use in the treatment of cancer, for use in the diagnosis, imaging or prevention of neoangiogenesis/angiogenesis, for use as a cancer diagnostic or imaging agent, or for use in the treatment of cancer wherein the cancer is prostate, breast, lung, colorectal or renal cell carcinoma.

In another aspect of the present disclosure, there is provided a use of a conjugate or compound disclosed herein in the manufacture of a medicament for the treatment of cancer, in the manufacture of a medicament for the prevention of neoangiogenesis/angiogenesis, or in the manufacture of a medicament for the treatment of cancer wherein the cancer is prostate, breast, lung, colorectal or renal cell carcinoma.

Description

As will be become apparent in the following, the present invention established a proof-of-principle using specific conjugates which bind with high affinity to prostate-specific antigen (PSMA) as target. Accordingly, a further technical problem underlying the present invention can be seen in providing improved radio-therapeutics and –diagnostics for the medical indication which is cancer, preferably prostate cancer.

These technical problems are solved by the subject-matter of the claims. Accordingly, in the first aspect, the present invention relates to a ligand-SIFA-chelator conjugate, comprising, within in a single molecule: (a) one or more ligands which are capable of binding to a disease-relevant target molecule, (b) a silicon-fluoride acceptor (SIFA) moiety which comprises a covalent bond between a silicon and a fluorine atom and which can be labeled with ^{18}F by isotopic exchange of ^{19}F by ^{18}F or which is labeled with ^{18}F, and (c) one or more chelating groups, optionally containing a chelated nonradioactive or radioactive cation.

The ligand-SIFA-chelator conjugate comprises three separate moieties. The three separate moieties are a) one or more ligands which are capable of binding to a disease-relevant target molecule, (b) a silicon-fluoride acceptor (SIFA) moiety which comprises a covalent bond between a silicon and a fluorine atom, and (c) one or more chelating groups, optionally containing a chelated nonradioactive or radioactive cation.

The fluorine atom on the SIFA moiety can be ^{19}F or ^{18}F.

Whilst certain ligands which are capable of binding to a disease-relevant target molecule

Claims

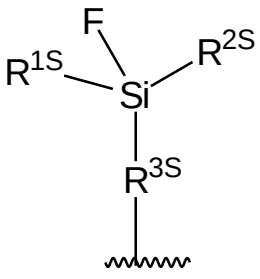
1. A ligand-SIFA-chelator conjugate, comprising, within in a single molecule three separate moieties:

(a) one or more ligands which are capable of binding to prostate-specific membrane antigen (PSMA),

(b) a silicon-fluoride acceptor (SIFA) moiety which comprises a covalent bond between a silicon and a fluorine atom, and

(c) one or more chelating groups, optionally containing a chelated nonradioactive or radioactive cation.

2. The conjugate in accordance with claim 1, wherein the silicon-fluoride acceptor (SIFA) moiety has the structure represented by formula (I):



(I),

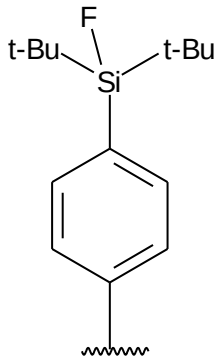
wherein

R^{1S} and R^{2S} are independently a linear or branched C3 to C10 alkyl group;

R^{3S} is a C1 to C20 hydrocarbon group comprising one or more aromatic and/or aliphatic units and/or up to 3 heteroatoms selected from O and S;

and wherein the SIFA moiety is attached to the remainder of the conjugate via the bond marked by ~~~~ .

3. The conjugate in accordance with claim 2, wherein the silicon-fluoride acceptor (SIFA) moiety has the structure represented by formula (Ia):



(Ia),

wherein t-Bu indicates a tert-butyl group.

4. The conjugate in accordance with claim 1, wherein the chelating group comprises at least one of

(i) a macrocyclic ring structure with 8 to 20 ring atoms of which 2 or more are heteroatoms selected from oxygen atoms and nitrogen atoms;

(ii) an acyclic, open chain chelating structure with 8 to 20 main chain atoms of which 2 or more are heteroatoms selected from oxygen atoms and nitrogen atoms; or

(iii) a branched chelating structure containing a quarternary carbon atom.

5. The conjugate in accordance with claim 4, wherein the chelating group is selected from bis(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (CBTE2a), cyclohexyl-1,2-diaminetetraacetic acid (CDTA), 4-(1,4,8,11-tetraazacyclotetradec-1-yl)-methylbenzoic acid (CPTA), N'-[5-[acetyl(hydroxy)amino]pentyl]-N-[5-[[4-[5-aminopentyl-(hydroxy)amino]-4-oxobutanoyl]amino]pentyl]-N-hydroxybutandiamide (DFO), 4,11-bis(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecan (DO2A) 1,4,7,10-tetracyclododecan-N,N',N'',N'''-tetraacetic acid (DOTA), α-(2-carboxyethyl)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTAGA), 1,4,7,10 tetraazacyclododecane N, N', N'', N''' 1,4,7,10-tetra(methylene) phosphonic acid (DOTMP), N,N'-dipyridoxylethylendiamine-N,N'-diacetate-5,5'-bis(phosphat) (DPDP), diethylene triamine N,N',N'' penta(methylene) phosphonic acid (DTMP), diethylenetriaminepentaacetic acid (DTPA), ethylenediamine-N,N'-tetraacetic acid (EDTA), ethyleneglykol-O,O-bis(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA), N,N-bis(hydroxybenzyl)-ethylenediamine-N,N'-diacetic acid (HBED), hydroxyethyldiaminetriacetic acid (HEDTA), 1-(p-nitrobenzyl)-1,4,7,10-tetraazacyclodecan-4,7,10-triacetate (HP-DOA3), 6-hydrazinyl-N-methylpyridine-3-carboxamide (HYNIC), tetra 3-hydroxy-N-methyl-2-pyridinone chelators (4-((4-(3-(bis(2-(3-hydroxy-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxamido)ethyl)amino)-2-((bis(2-(3-hydroxy-1-methyl-2-oxo-1,2-dihydropyridine-4-carboxamido)ethyl)amino)methyl)propyl)phenyl)amino)-4-oxobutanoic acid), abbreviated as

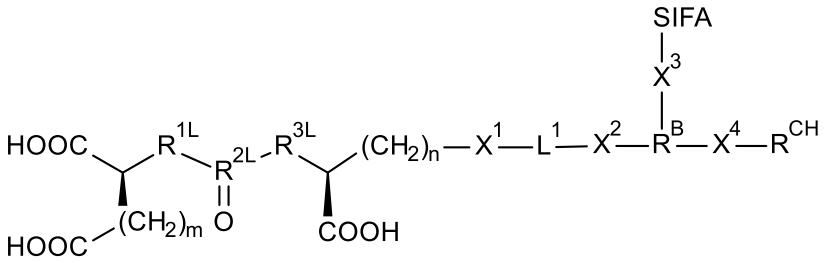
Me-3,2-HOPO, 1,4,7-triazacyclononan-1-succinic acid-4,7-diacetic acid (NODASA), 1-(1-carboxy-3-carboxypropyl)-4,7-(carbooxy)-1,4,7-triazacyclononane (NODAGA), 1,4,7-triazacyclononanetriacetic acid (NOTA), 4,11-bis(carboxymethyl)-1,4,8,11-tetraazabicyclo[6.6.2]hexadecane (TE2A), 1,4,8,11-tetraazacyclododecane-1,4,8,11-tetraacetic acid (TETA), tris(hydroxypyridinone) (THP), terpyridin-bis(methyleneamintetraacetic acid (TMT), 1,4,7-triazacyclononane-1,4,7-tris[methylene(2-carboxyethyl)phosphinic acid] (TRAP), 1,4,7,10-tetraazacyclotridecan-N,N',N'',N'''-tetraacetic acid (TRITA), 3-[[4,7-bis[[2-carboxyethyl(hydroxy)phosphoryl]methyl]-1,4,7-triazonan-1-yl]methyl-hydroxy-phosphoryl]propanoic acid, and triethylenetetraaminehexaacetic acid (TTHA).

6. The conjugate in accordance with claim 4, wherein the chelating group is 1,4,7,10-tetracyclododecan-N,N',N'',N'''-tetraacetic acid (DOTA), α-(2-carboxyethyl)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTAGA) or 1,4,7-triazacyclononane-1,4,7-tris[methylene(2-carboxyethyl)phosphinic acid] (TRAP).

7. The conjugate in accordance with claim 4 wherein the chelator contains a chelated cation selected from the cations of ^{43}Sc, ^{44}Sc, ^{47}Sc, ^{64}Cu, ^{67}Cu, ^{67}Ga, ^{68}Ga, ^{90}Y, ^{111}In, ^{149}Tb, ^{152}Tb, ^{155}Tb, ^{161}Tb, ^{166}Ho, ^{177}Lu, ^{186}Re, ^{188}Re,^{212}Pb, ^{212}Bi, ^{213}Bi, ^{225}Ac, and ^{227}Th or a cationic molecule comprising ^{18}F.

8. The conjugate in accordance with claim 1 wherein the SIFA fluorine atom is ^{18}F.

9. The conjugate in accordance with claim 1, which is a compound of formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein:

SIFA is a silicon-fluoride acceptor (SIFA) moiety which comprises a covalent bond between a silicon and a fluorine atom;

m is an integer of 2 to 6;

n is an integer of 2 to 6;

R^{1L} is CH_2, NH or O;

R^{3L} is CH_2, NH or O;

R^{2L} is C or P(OH);

X^1 is selected from an amide bond, an ether bond, a thioether bond, an ester bond, a thioester bond, an urea bridge, and an amine bond;

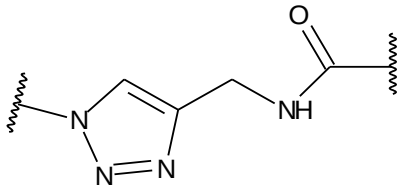
X^2 is selected from an amide bond, an ether bond, a thioether bond, an ester bond, a thioester bond, an urea bridge, and an amine bond;

L^1 is a divalent linking group with a structure selected from an oligoamide, an oligoether, an oligothioether, an oligoester, an oligothioester, an oligourea, an oligo(ether-amide), an oligo(thioether-amide), an oligo(ester-amide), an oligo(thioester-amide), oligo(urea-amide), an oligo(ether-thioether), an oligo(ether-ester), an oligo(ether-thioester), an oligo ether-urea), an oligo(thioether-ester), an oligo(thioether-thioester), an oligo(thioether-urea), an oligo(ester-thioester), an oligo(ester-urea), and an oligo(thioester-urea), wherein L^1 is optionally substituted with one or more substitutents independently selected from –OH, -OCH_3, -COOH, –$COOCH_3$, -NH_2, and -NHC(NH)NH_2;

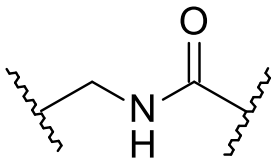
X^3 is selected from an amide bond, an ester bond, an ether, and an amine;

R^B is a trivalent coupling group;

X^4 is selected from an amide bond, an ether bond, a thioether bond, an ester bond, a thioester bond, a urea bridge, an amine bond, a linking group of the formula:



wherein the amide bond marked by ~~~ is formed with the chelating group, and the other bond marked by ~~~ is bound to R^B, and a linking group of the formula:



wherein the bond marked by ~~~ at the carbonyl end is formed with the chelating group, and the other bond marked by ~~~ is bound to R^B;

R^{CH} is chelating group optionally containing a chelated radioactive or nonradioactive cation.

10. The conjugate in accordance with claim 9, wherein –X^1-L^1-X^2- represents one of the following structures (L-1) and (L-2):

-NH-C(O)-R^6-C(O)-NH-R^7-NH-C(O)- (L-1)

-C(O)-NH-R^8-NH-C(O)-R^9-C(O)-NH-R^{10}-NH-C(O)- (L-2)

wherein

R^6 to R^{10} are independently selected from C2 to C10 alkylene, which alkylene groups may each be substituted by one or more substitutents independently selected from –OH, -OCH_3, -COOH, –$COOCH_3$, -NH_2, and -NHC(NH)NH_2

or wherein –X^1-L^1-X^2- represents one of the following structures (L-3) and (L-4):

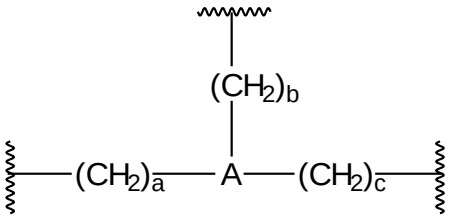
-NH-C(O)-R^{11}-C(O)-NH-R^{12}-CH(COOH)-NH-C(O)- (L-3)

-C(O)-NH-CH(COOH)-R^{13}-NH-C(O)-R^{14}-C(O)-NH-R^{15}-CH(COOH)-NH-C(O)- (L-4)

wherein

R^{11} to R^{15} are independently selected from C2 to C8 alkylene.

11. The conjugate in accordance with claim 9, wherein R^B has the structure represented by formula (IV):



(IV)

wherein:

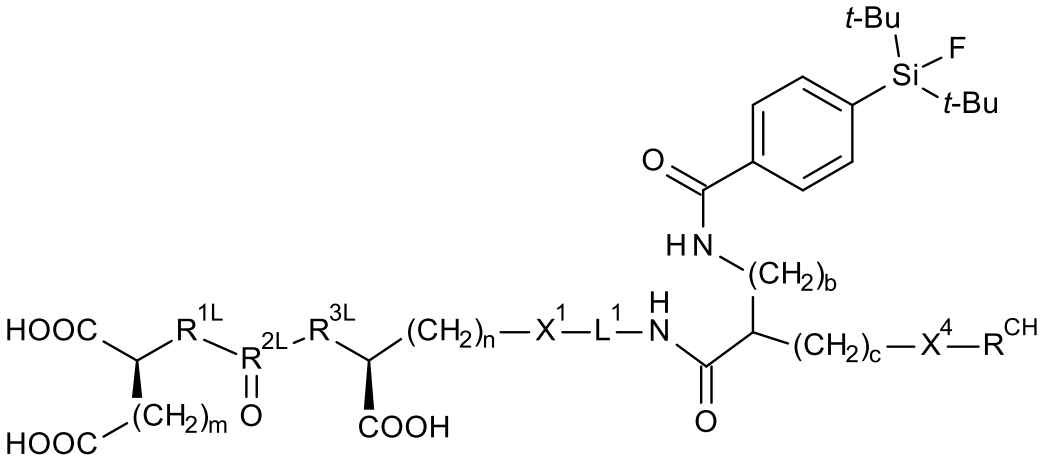
A is selected from N, CR^{16}, wherein R^{16} is H or C1-C6 alkyl, and a 5 to 7 membered carbocyclic or heterocyclic group;

the bond marked by ~~~ at $(CH_2)_a$ is formed with X^2, and a is an integer of 0 to 4;

the bond marked by ~~~ at $(CH_2)_b$ is formed with X^3, and b is an integer of 0 to 4; and

the bond marked by ~~~ at $(CH_2)_c$ is formed with X^4, and c is an integer of 0 to 4.

12. The conjugate in accordance with claim 1, which is a compound of formula (IIIa):



(IIIa)

or a pharmaceutically acceptable salt thereof, wherein:

m is an integer of 2 to 6;

n is an integer of 2 to 6;

b is an integer of 0 to 4;

c is an integer of 0 to 4;

R^{1L} is CH_2, NH or O;

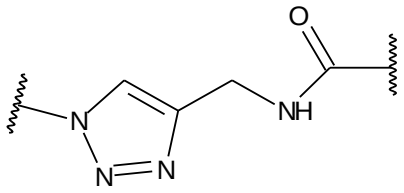
R^{3L} is CH_2, NH or O;

R^{2L} is C or P(OH);

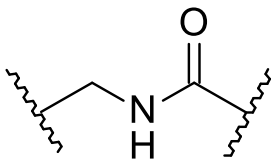
X^1 is selected from an amide bond, an ether bond, a thioether bond, an ester bond, a thioester bond, an urea bridge, and an amine bond;

L^1 is a divalent linking group with a structure selected from an oligoamide, an oligoether, an oligothioether, an oligoester, an oligothioester, an oligourea, an oligo(ether-amide), an oligo(thioether-amide), an oligo(ester-amide), an oligo(thioester-amide), oligo(urea-amide), an oligo(ether-thioether), an oligo(ether-ester), an oligo(ether-thioester), an oligo ether-urea), an oligo(thioether-ester), an oligo(thioether-thioester), an oligo(thioether-urea), an oligo(ester-thioester), an oligo(ester-urea), and an oligo(thioester-urea), wherein L^1 is optionally substituted with one or more substitutents independently selected from –OH, -OCH_3, -COOH, –$COOCH_3$, -NH_2, and -NHC(NH)NH_2;

X^4 is selected from an amide bond, an ether bond, a thioether bond, an ester bond, a thioester bond, a urea bridge, an amine bond, a linking group of the formula:



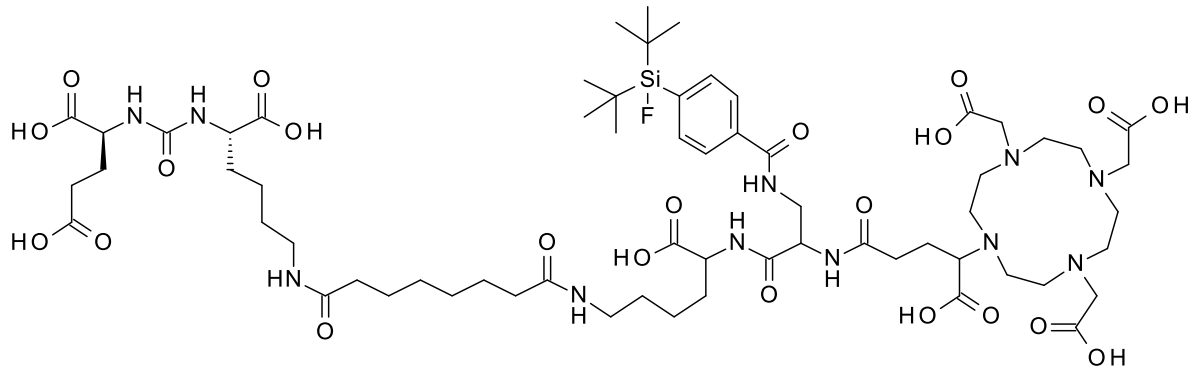
wherein the amide bond marked by ~~~~ is formed with the chelating group, and a linking group of the formula:

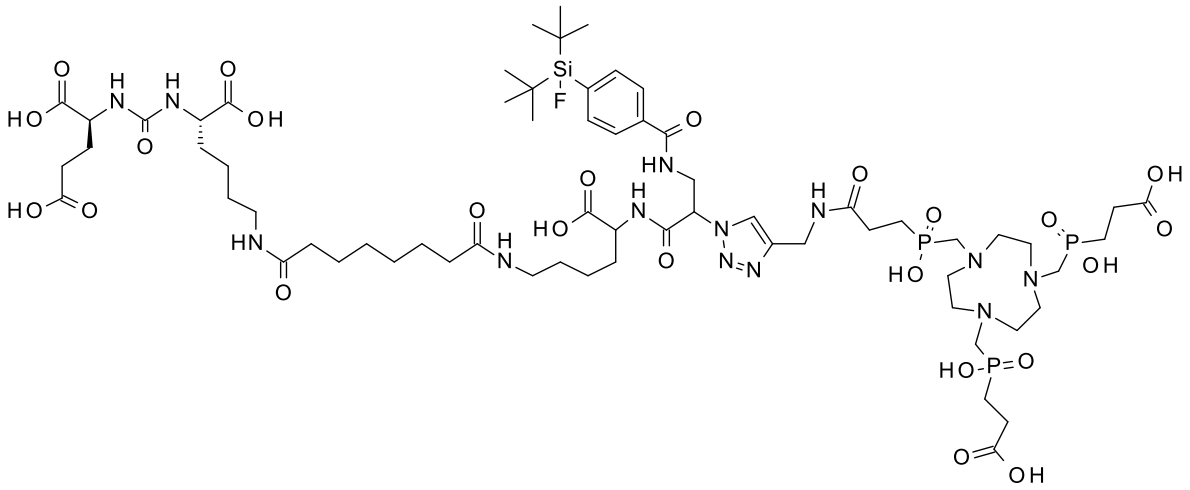


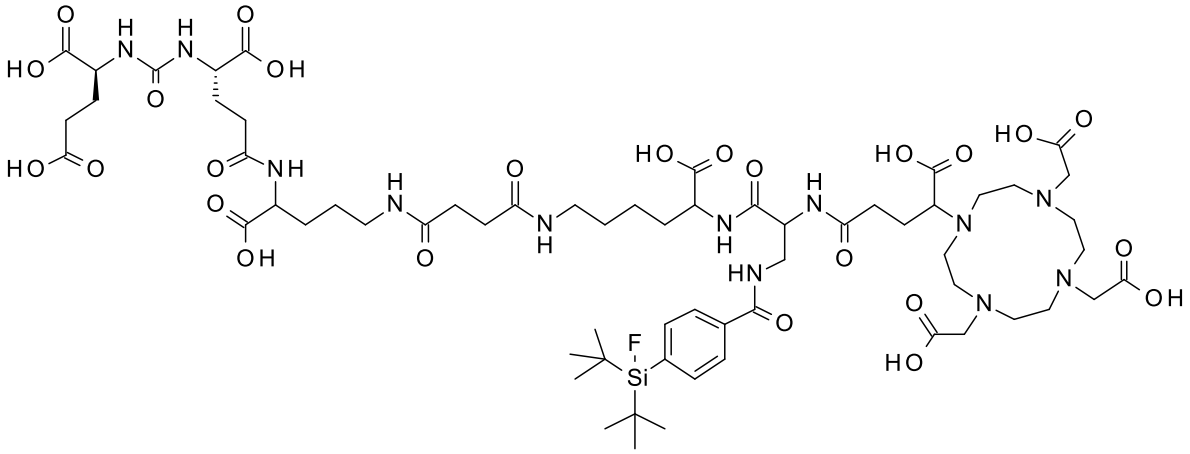
wherein the bond marked by ~~~~ at the carbonyl end is formed with the chelating group; and

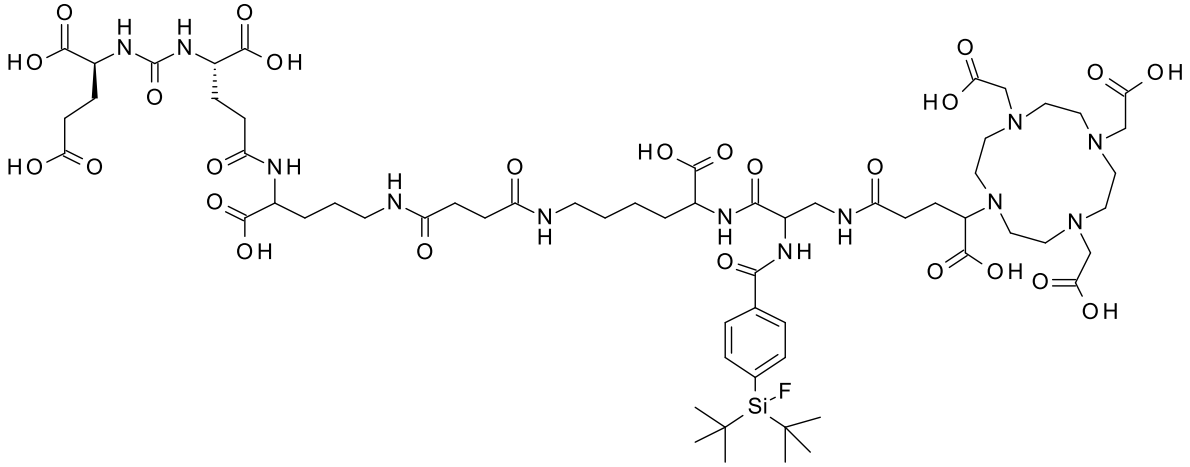
R^{CH} is chelating group optionally containing a chelated radioactive or nonradioactive cation.

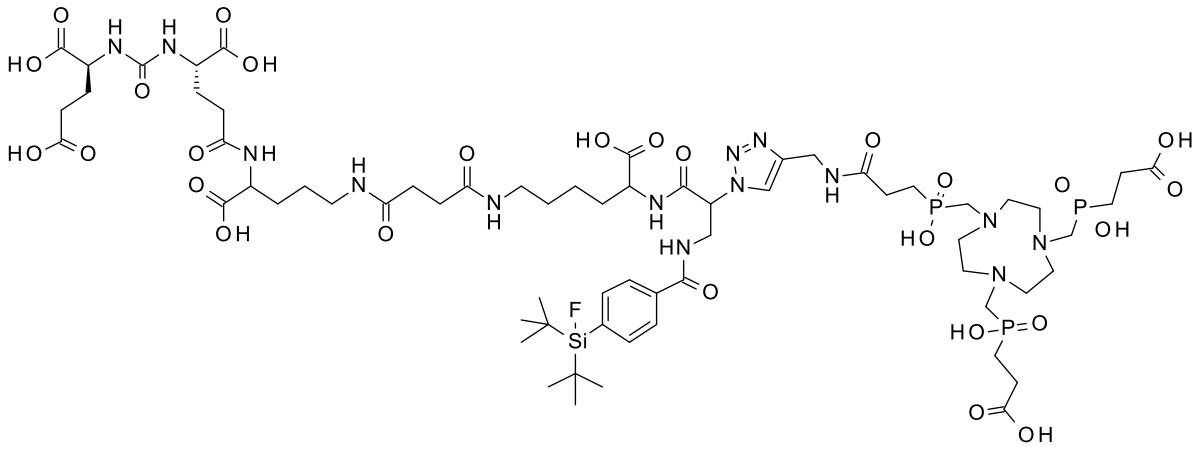
13. The conjugate in accordance with claim 1 wherein the conjugate is a compound selected from the group consisting of:

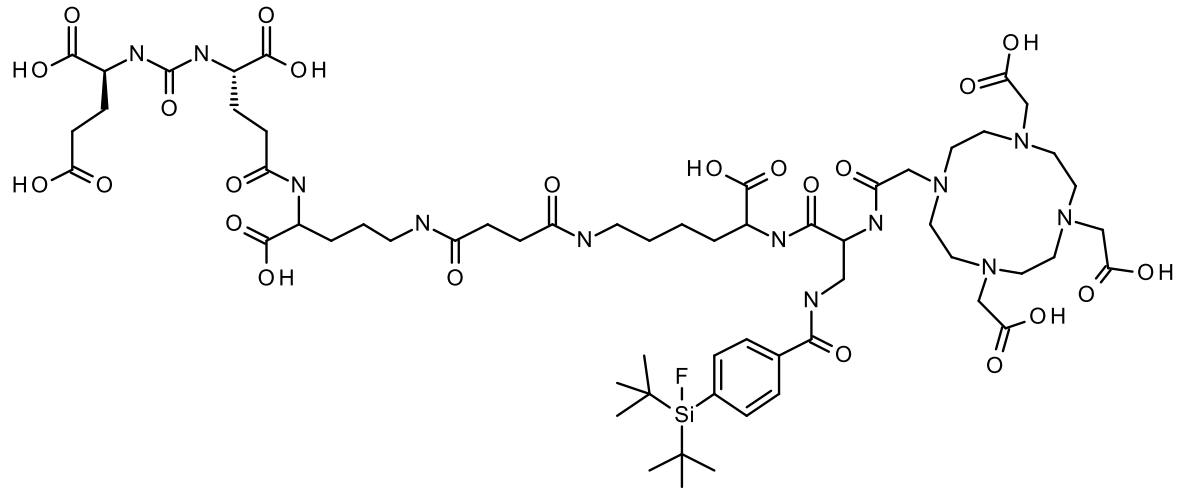


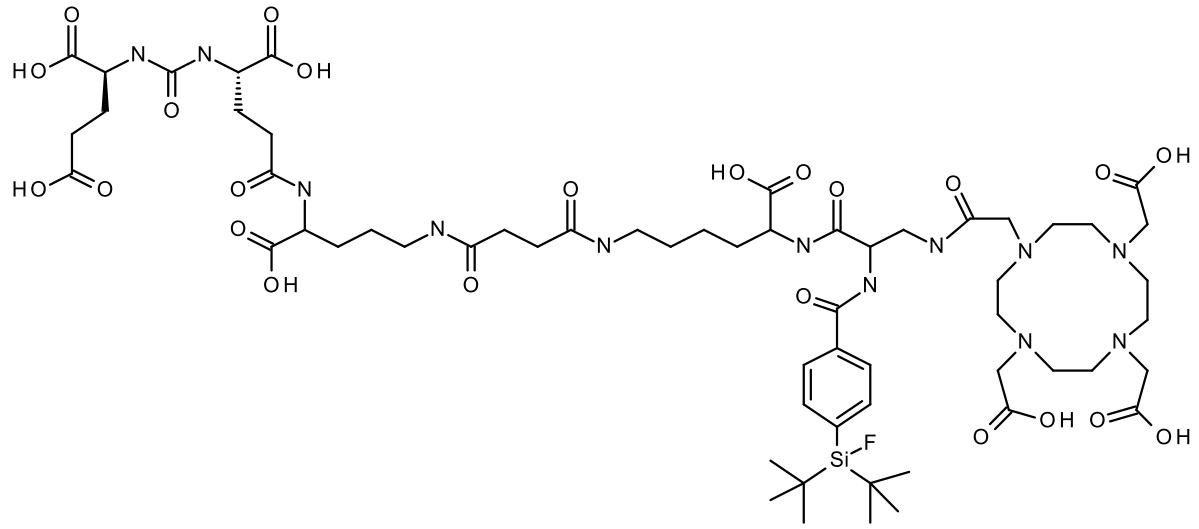












and pharmaceutically acceptable salts and individual isomers thereof, optionally containing a chelated nonradioactive or radioactive cation and wherein the fluorine atom is optionally ^{18}F.

14. A pharmaceutical or diagnostic composition comprising or consisting of one or more conjugates or compounds in accordance with any one of claims 1 to 13.

15. A conjugate or compound in accordance with any one of claims 1 to 13 for use in the preparation of a medicament for use as a cancer diagnostic or imaging agent.

16. A conjugate or compound in accordance with any one of claims 1 to 13 for use in the preparation of a medicament for the treatment of cancer.

17. A conjugate or compound in accordance with any one of claims 1 to 13 for use in the preparation of a medicament for the diagnosis, imaging or prevention of neoangiogenesis/angiogenesis.

18. A conjugate or compound in accordance with any one of claims 1 to 13 for use in the preparation of a medicament for use as a cancer diagnostic or imaging agent or for use in the treatment of cancer wherein the cancer is prostate, breast, lung, colorectal or renal cell carcinoma.

19. A conjugate or compound in accordance with any one of claims 1 to 13 for use as a cancer diagnostic or imaging agent, for use in the treatment of cancer, for use in the diagnosis, imaging or prevention of neoangiogenesis/angiogenesis, for use as a cancer diagnostic or imaging agent, or for use in the treatment of cancer wherein the cancer is prostate, breast, lung, colorectal or renal cell carcinoma.

20. Use of a conjugate or compound in accordance with any one of claims 1 to 13 in the manufacture of a medicament for the treatment of cancer, in the manufacture of a medicament for preventing neoangiogenesis/angiogenesis, or in the manufacture of a medicament for the treatment of cancer wherein the cancer is prostate, breast, lung, colorectal or renal cell carcinoma.