Further studies on combination therapies, named peptide receptor chemoradionuclide therapy (PRCRT), have recently been published (Kong G, Callahan J, Hofman MS, et al. High clinical and morphologic response using 90Y-DOTA-octreotate sequenced with 177Lu-DOTA-octreotate induction peptide receptor chemoradionuclide therapy (PRCRT) for bulky neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2017;44:476–489). Similar "combined treatment approaches" will be carried out in the near future to improve the efficiency of PSMA-targeted radioligand therapies.

In a further example, the present disclosure provides one or more compounds or salts of the disclosure as disclosed herein above for use in medicine.

Preferred uses in medicine are in nuclear medicine such as nuclear diagnostic imaging, also named nuclear molecular imaging, and/or targeted radiotherapy of diseases associated with an overexpression, preferably of PSMA on the diseased tissue.

In a further example, the present disclosure provides a compound or salt of the disclosure as defined herein above for use in a method of diagnosing and/or staging cancer, preferably prostate cancer.

In another aspect, the present disclosure refers to a compound or salt thereof as disclosed herein for use in a method of diagnosing (a) cancer associated with overexpression of prostate-specific membrane antigen (PSMA) including prostate cancer associated with overexpression of PSMA; or (b) pathologic neoangiogenesis/angiogenesis associated with overexpression of PSMA.

In another aspect, the present disclosure refers to a compound or salt thereof as disclosed herein for use in treating (a) cancer associated with overexpression of PSMA including prostate cancer associated with overexpression of PSMA; or (b) pathologic neoangiogenesis/angiogenesis associated with overexpression of PSMA.

In another aspect, the present disclosure refers to use of a compound or salt thereof as disclosed herein in the manufacture of a medicament for diagnosing (a) cancer associated with overexpression of PSMA including prostate cancer associated with overexpression of PSMA; or (b) pathologic neoangiogenesis/angiogenesis associated with overexpression of PSMA.

In another aspect, the present disclosure refers to use of a compound or salt thereof as disclosed herein in the manufacture of a medicament for treating (a) cancer associated with overexpression of PSMA including prostate cancer associated with overexpression of PSMA; or (b) pathologic neoangiogenesis/angiogenesis associated with overexpression of PSMA.

Preferred indications are the detection or staging of cancer, such as, but not limited high grade gliomas, lung cancer and especially prostate cancer and metastasized prostate cancer, the detection of metastatic disease in patients with primary prostate cancer of intermediate-risk to high-risk, and the detection of metastatic sites, even at low serum PSA values in patients with biochemically recurrent prostate cancer. Another preferred indication is the imaging and visualization of neoangiogensis.

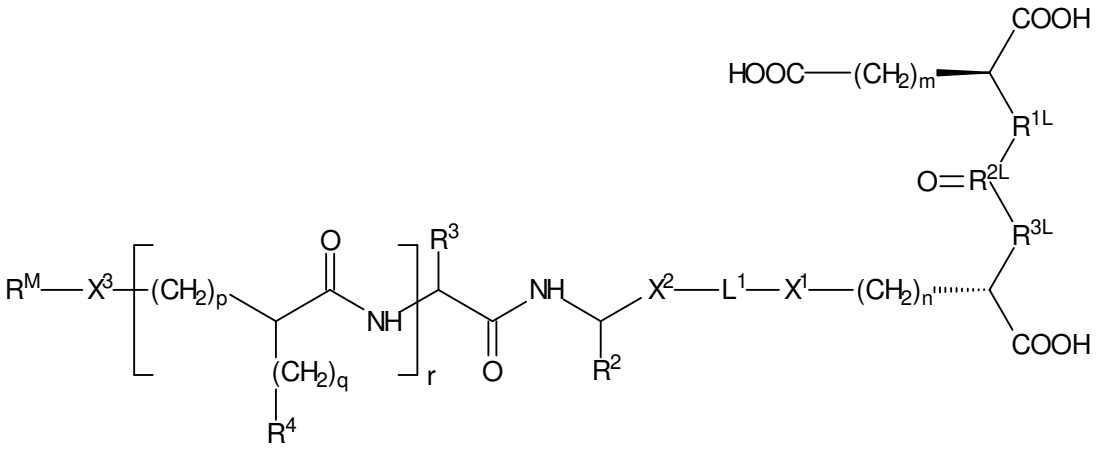
In terms of medical indications to be subjected to therapy, especially radiotherapy, cancer is a preferred indication. Prostate cancer is a particularly preferred indication.

In a further example, the present disclosure provides a compound or salt of the disclosure as defined herein above for use in a method of diagnosing and/or staging cancer, preferably prostate cancer.

As regards the examples characterized in this specification, in particular in the claims, it is intended that each example mentioned in a dependent claim is combined with each example of each claim (independent or dependent) said dependent claim depends from. For example, in case of an independent claim 1 reciting 3 alternatives A, B and C, a

Claims

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



(I)

wherein:

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

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

X^1 is selected from an amide bond, an ether bond, a thioether bond, an ester bond, a thioester bond, a 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), which linking group may carry a group electron dense substituent (EDS);

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

R^2 is an optionally substituted aryl group or an optionally substituted aralkyl group, which aryl group or aralkyl group may be substituted on its aromatic ring with one or more substituents selected from halogen and –OH;

R^3 is an optionally substituted aryl group or an optionally substituted aralkyl group, which aryl group or aralkyl group may be substituted on its aromatic ring with one or more substituents selected from halogen and –OH;

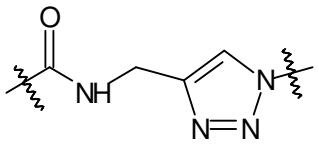
r is 0 or 1;

p is 0 or 1;

q is 0 or 1;

R^4 is selected from an optionally substituted aryl group and a group EDS, which aryl group may be substituted on its aromatic ring with one or more substituents selected from halogen,–OH and $–NH_2$;

X^3 is selected from an amide bond, an ether bond, a thioether bond, an ester bond, a thioester bond, a urea bridge, an amine bond, and a group of the formula

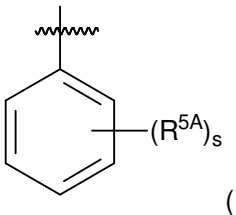


, wherein the marked bond at the carbonyl group attaches X^3 to R^M and the other marked bond attaches X^3 to the remainder of the compound of formula (I);

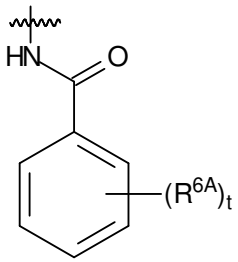
R^M is a marker group which comprises a chelating group optionally containing a chelated non-radioactive or radioactive cation;

and wherein the group EDS is contained at least once in the compound of formula (I) and has a structure selected from

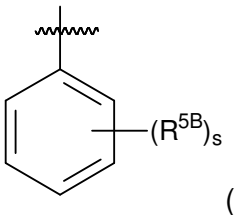
(E-1A), (E-1B), (E-2A) and (E-2B):



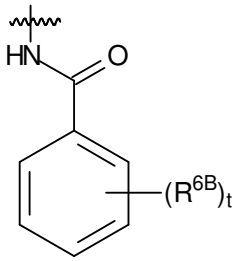
(E-1A)



(E-2A)



(E-1B)



(E-2B)

wherein

~~~ marks the bond which attaches the group EDS, to the remainder of the compound of formula (I);

s is 1, 2 or 3, preferably 1 or 2, and more preferably 1;

t is 1, 2 or 3, preferably 1 or 2, and more preferably 2;

R^{5A} is, independently for each occurrence for s > 1, an electron withdrawing substituent, which is preferably selected from $–NO_2$ and –COOH, and which is more preferably –COOH, and wherein the bond between R^{5A} and the phenyl ring indicates that the s groups R^{5A} replace s hydrogen atoms at any position on the phenyl ring;

R^{5B} is, independently for each occurrence for s > 1, a substituent carrying an electron lone pair at the atom directly attached to the phenyl ring shown in formula (E-1B), which substituent is preferably selected from –OH and $–NH_2$, and which is more preferably $–NH_2$, and wherein the bond between R^{5B} and the phenyl ring indicates that the s groups R^{5B} replace s hydrogen atoms at any position on the phenyl ring;

R^{6A} is, independently for each occurrence for t > 1, an electron withdrawing substituent, which is preferably selected from $–NO_2$ and –COOH, and which is more preferably –COOH, and wherein the bond between R^{6A} and the phenyl ring indicates that the t groups R^{6A} replace t hydrogen atoms at any position on the phenyl ring; and

R^{6B} is, independently for each occurrence for t > 1, a substituent carrying an electron lone pair at the atom directly attached to the phenyl ring shown in formula (E-1B), which substituent is preferably selected from –OH and $–NH_2$, and which is more preferably –OH, and wherein the bond between R^{6B} and the phenyl ring indicates that the t groups R^{6B} replace t hydrogen atoms at any position on the phenyl ring.

2. The compound or salt of claim 1, wherein m is 2, n is 2 or 4, R^{1L} is NH, R^{2L} is C, and R^{3L} is NH.

3. The compound or salt of claim 1 or 2, wherein L^1 is a divalent linking group with a structure selected from an oligoamide which comprises a total of 1 to 5, more preferably a total of 1 to 3, and most preferably a total of 1 or 2 amide bonds within its backbone, and an oligo(ester-amide) which comprises a total of 2 to 5, more preferably a total of 2 to 3, and most preferably a total of 2 amide and ester bonds within its backbone, which linking group may carry a group EDS.
~~~

4. The compound or salt of any of claims 1 to 3, wherein the moiety $–X^2-L^1-X^1-$ in formula (I) has a structure selected from:

*-C(O)-NH-R^7-NH-C(O)-R^8-C(O)-NH- (L-1),

*-C(O)-NH-R^{9A}-NH-C(O)-R^{10A}-C(O)-NH-R^{11A}-NH-C(O)- (L-2A) , and

*-C(O)-NH-R^{9B}-C(O)-NH-R^{10B}-C(O)-NH-R^{11B}-NH-C(O)- (L-2B);

wherein the amide bond marked with * is attached to the carbon atom carrying R^2 in formula (I), and wherein
R^7, R^8, R^{9A}, R^{9B}, R^{11A} and R^{11B} are independently selected from optionally substituted C2 to C10 alkanediyl, which alkanediyl groups may each be substituted by one or more substitutents independently selected from -OH, $-OCH_3$, -COOH, $-COOCH_3$, $-NH_2$, $-NHC(NH)NH_2$, and a group EDS, and
R^{10A} and R^{10B} are selected from optionally substituted C2 to C10 alkanediyl, and optionally substituted C6 to C10 arenediyl, which alkanediyl and arenediyl group may each be substituted by one or more substitutents independently selected from -OH, $-OCH_3$, -COOH, $-COOCH_3$, $-NH_2$, $-NHC(NH)NH_2$, and a group EDS.

5. The compound or salt of claim 4, wherein the moiety $–X^2-L^1-X^1-$ has a structure selected from:

*-C(O)-NH-CH(COOH)-R^{12}-NH-C(O)-R^{13}-C(O)-NH- (L-3),

*-C(O)-NH-CH(COOH)-R^{14}-NH-C(O)-R^{15}-C(O)-NH-R^{16}-CH(COOH)-NH-C(O)- (L-4), and

*-C(O)-NH-CH(COOH)-R^{17}-C(O)-NH-R^{18}-C(O)-NH-R^{19}-CH(COOH)-NH-C(O)- (L-5);

wherein the bond marked with * is attached to the carbon atom carrying R^2 in formula (I),
R^{12} and R^{14} are independently selected from linear C2 to C6 alkanediyl,
R^{13} is a linear C2 to C10 alkanediyl,
R^{15} and R^{16} are independently selected from linear C2 to C6 alkanediyl,
and wherein each of R^{13} and R^{15} may carry one group EDS as a substituent,
R^{17} is a linear C2 to C6 alkanediyl,

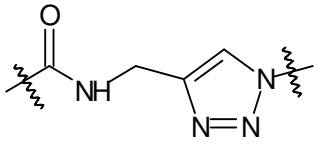
R^{18} is a phenylene group, and
R^{19} is a linear C2 to C6 alkanediyl.

6. The compound or salt of any of claims 1 to 5, wherein R^2 is an optionally substituted aralkyl group selected from optionally substituted -CH_2-phenyl and optionally substituted –CH_2-naphtyl, wherein the phenyl and the naphtyl group are optionally substituted with a substituent selected from halogen, preferably I, and -OH.

7. The compound or salt of any of claims 1 to 6, wherein R^3 is an optionally substituted aralkyl group selected from optionally substituted -CH_2-phenyl and optionally substituted –CH_2-naphtyl, wherein the phenyl and the naphtyl group are optionally substituted with a substituent selected from halogen and -OH.

8. The compound or salt of any of claims 1 to 7, wherein r is 1, and wherein R^4 is selected from optionally substituted phenyl, optionally substituted naphtyl, and a group EDS, which phenyl group and naphthyl group are optionally substituted with a substituent selected from halogen, –OH and –NH_2.

9. The compound or salt of any of claims 1 to 8, wherein X^3 is an amide bond or a group of the formula

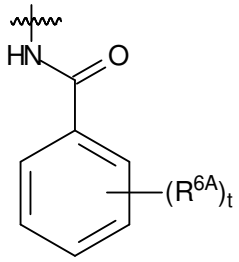


, wherein the marked bond at the carbonyl group attaches X^3 to R^M and the other marked bond attaches X^3 to the remainder of the molecule.

10. The compound or salt of any of claims 1 to 9, wherein R^M is a chelating group optionally containing a chelated non-radioactive or radioactive cation.

11. The compound or salt of any of claims 1 to 10 , wherein the compound of formula (I) either contains one group EDS which is carried by the linking group L^1, or contains two groups EDS, one being represented by R^4 and one being carried by L^1.

12. The compound or salt of any of claims 1 to 11, which contains a group EDS which has the formula (E-2A):

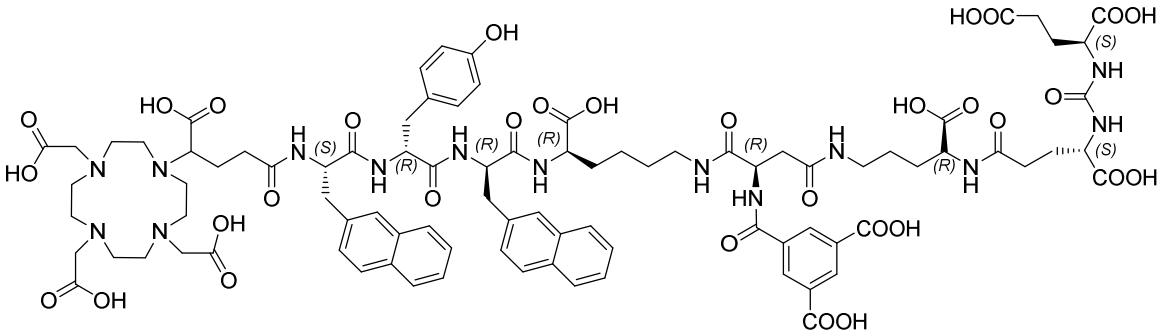


(E-2A)

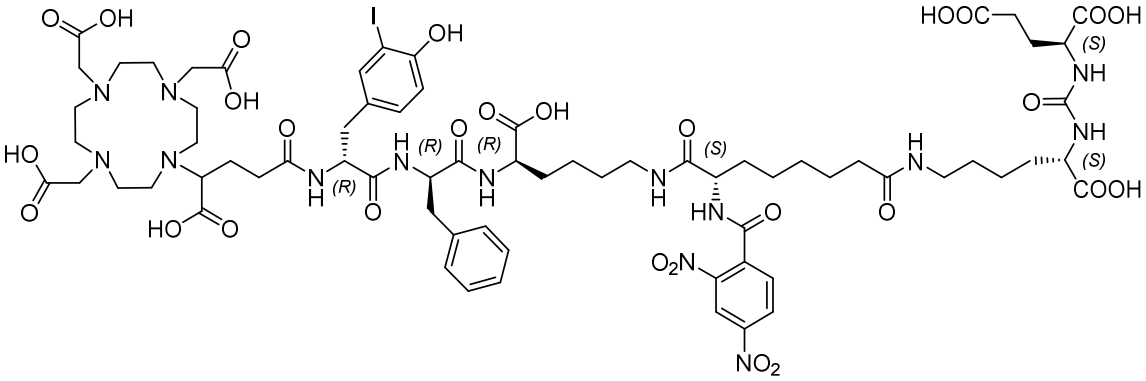
wherein ~~~ marks the bond which attaches the group EDS to the remainder of the compound of formula (I); and

t is 1 or 2, and R^{6A} is selected from $–NO_2$ and –COOH.

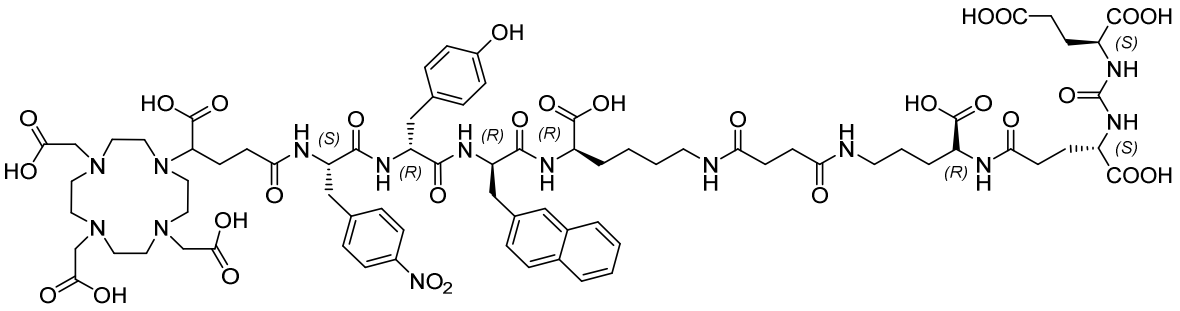
13. The compound or salt thereof of any one of claims 1 to 12, wherein said compound or salt has one of the following formulae:



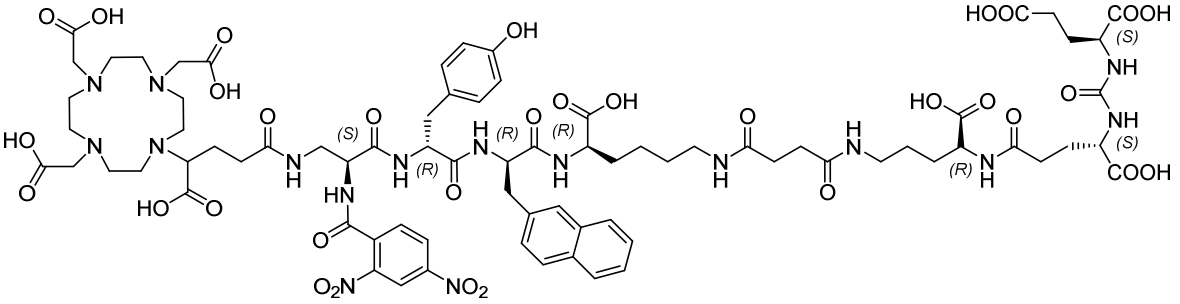
(Ih)



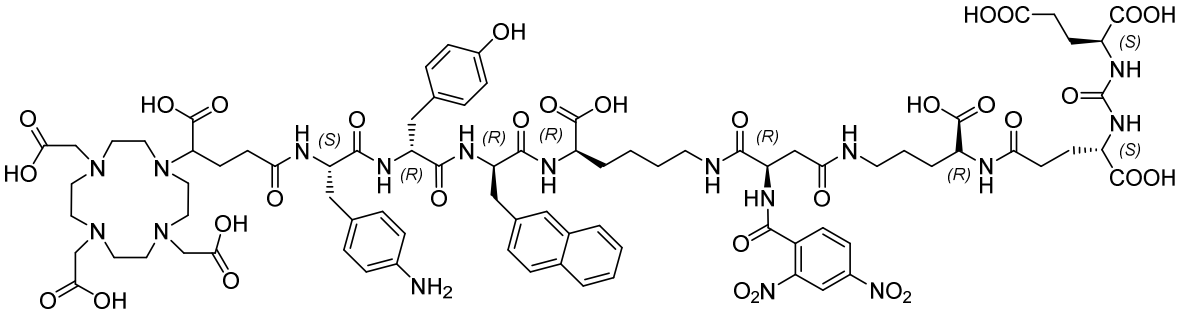
(Ii)



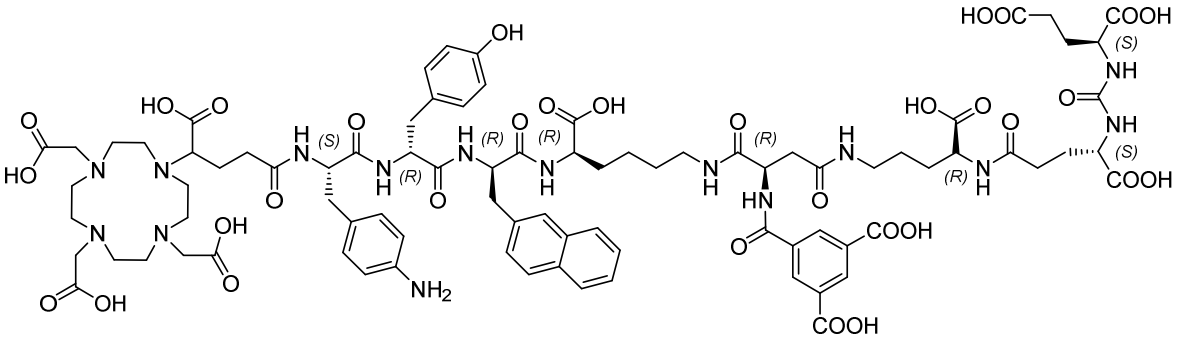
(Ij)



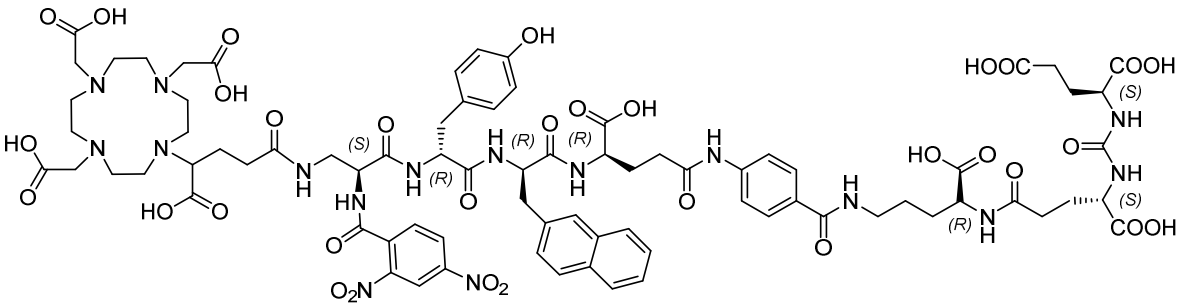
(Ik)



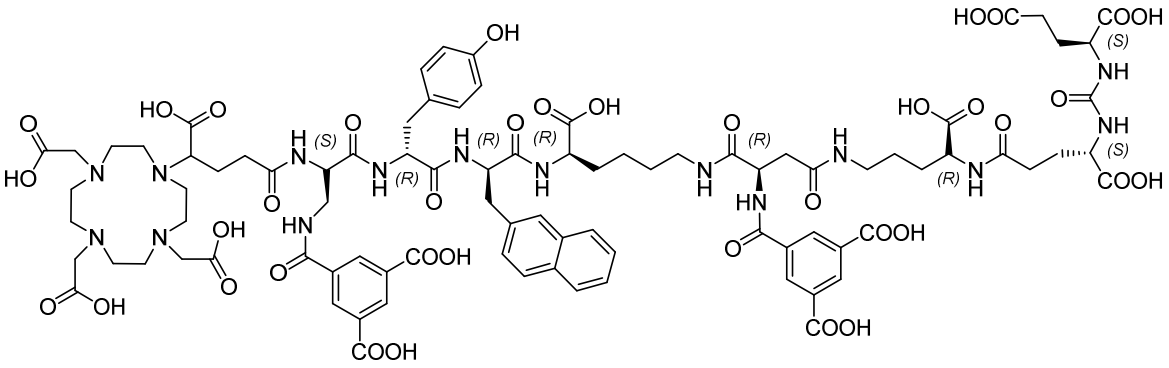
(Im)



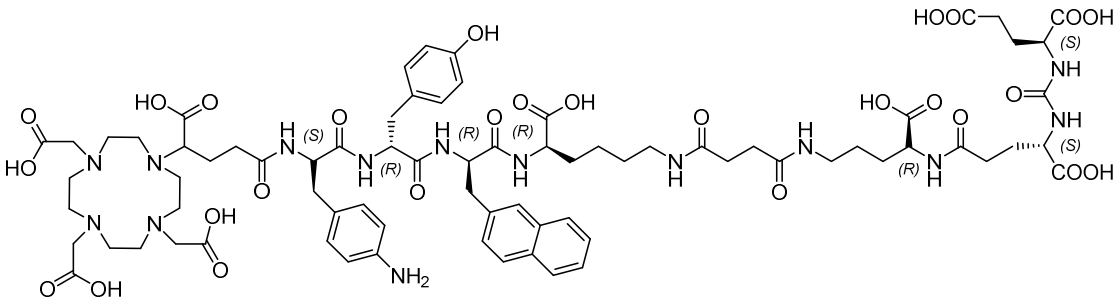
(In)



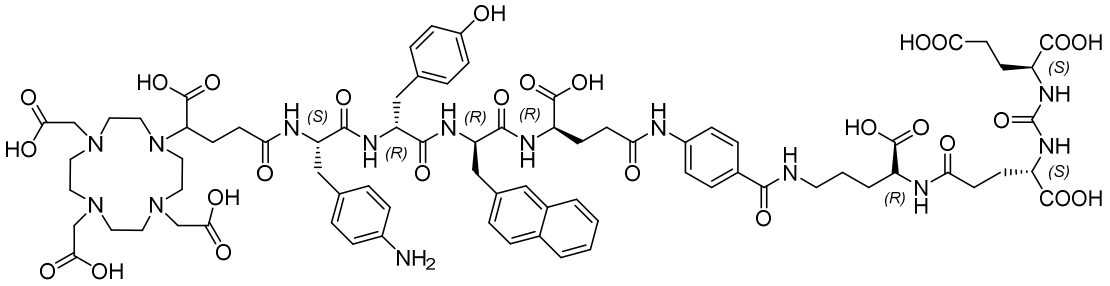
(Io)



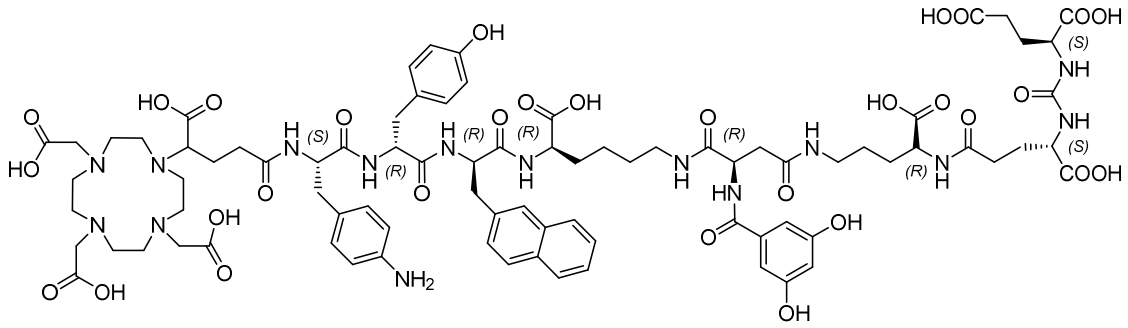
(Ip)



(Iq)

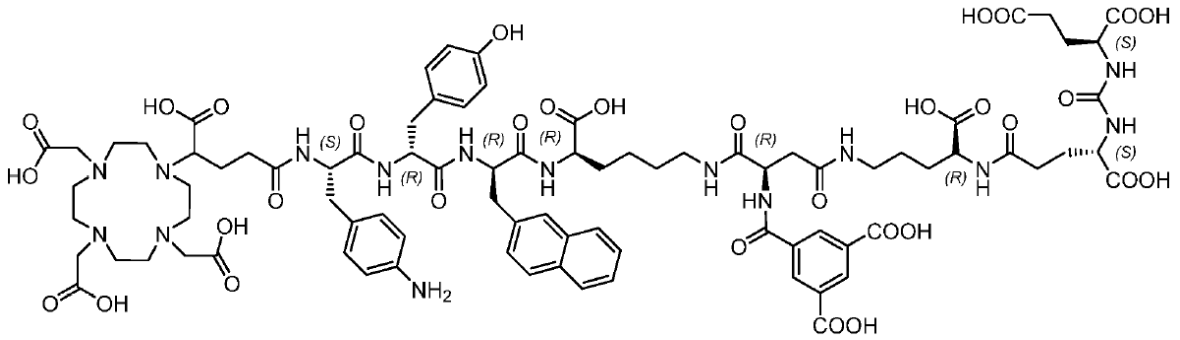


(Ir)



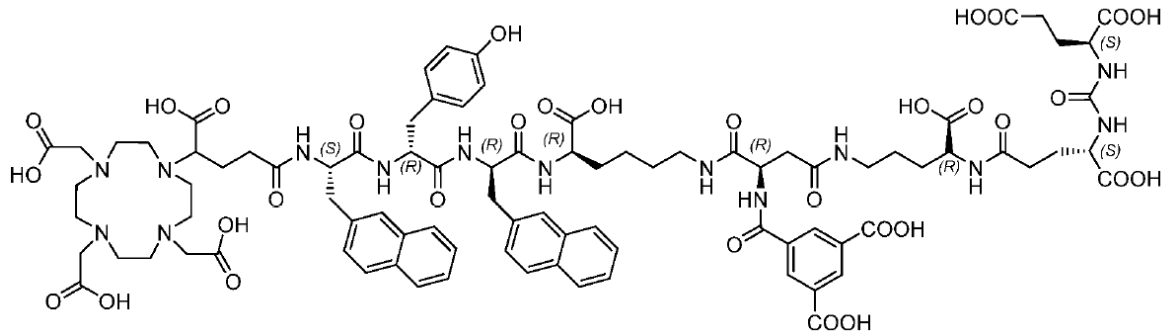
(Is).

14. The compound or salt thereof of any one of claims 1 to 12, wherein said compound or salt has the following formula:



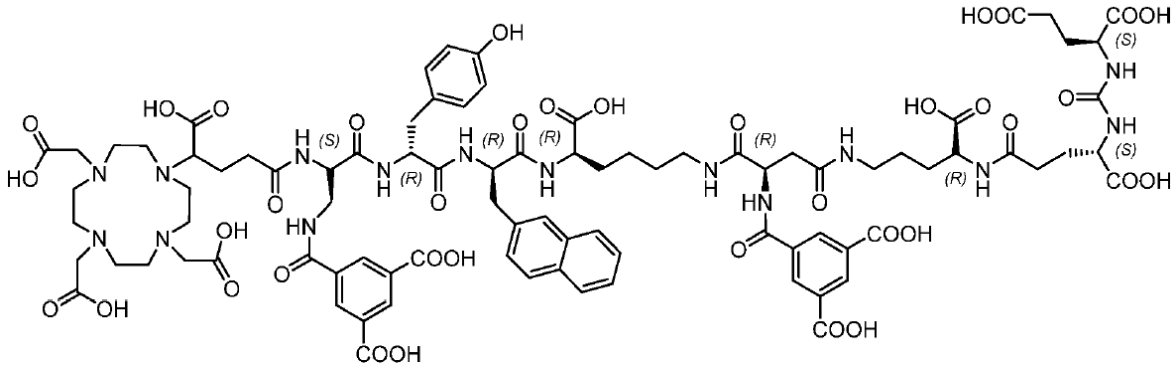
or salt thereof.

15. The compound or salt thereof of any one of claims 1 to 12, wherein said compound or salt has the following formula:



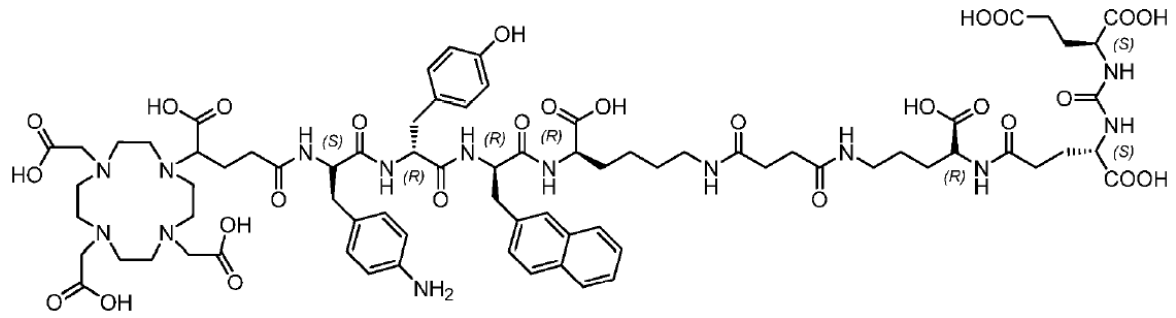
or salt thereof.

16. The compound or salt thereof of any one of claims 1 to 12, wherein said compound or salt has the following formula:



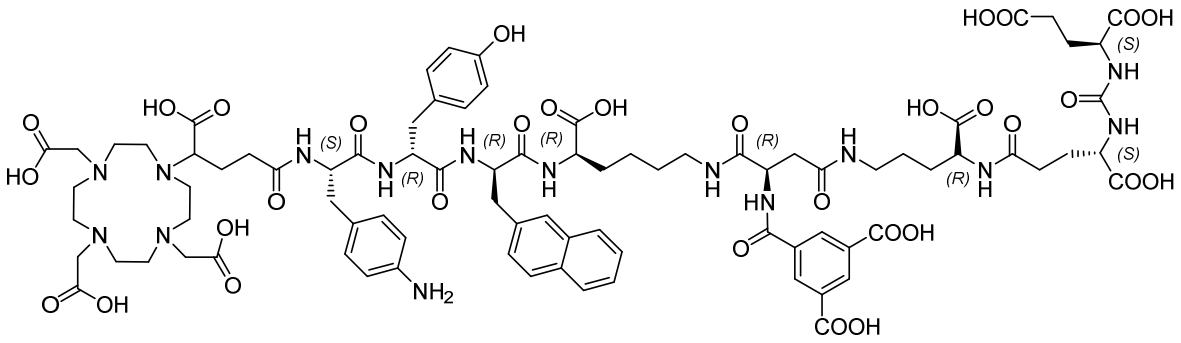
or salt thereof.

17. The compound or salt thereof of any one of claims 1 to 12, wherein said compound or salt has the following formula:



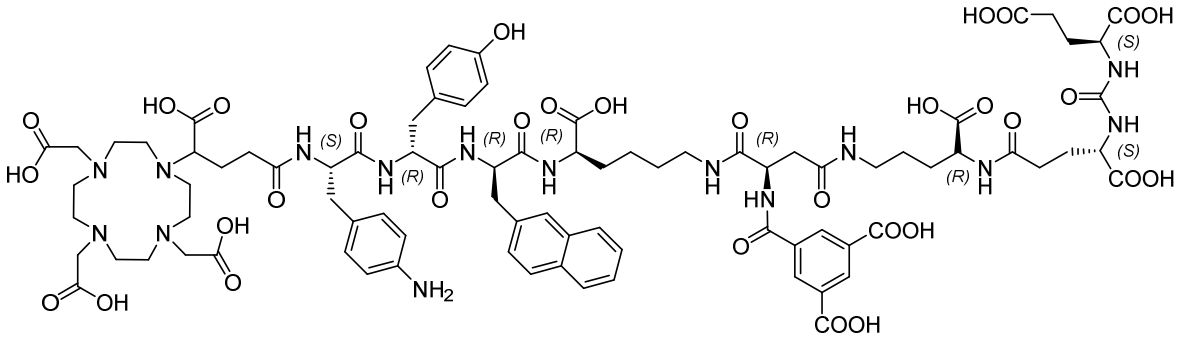
or salt thereof.

18. The compound or salt thereof of any one of claims 1 to 12, wherein said compound or salt has the following formula:



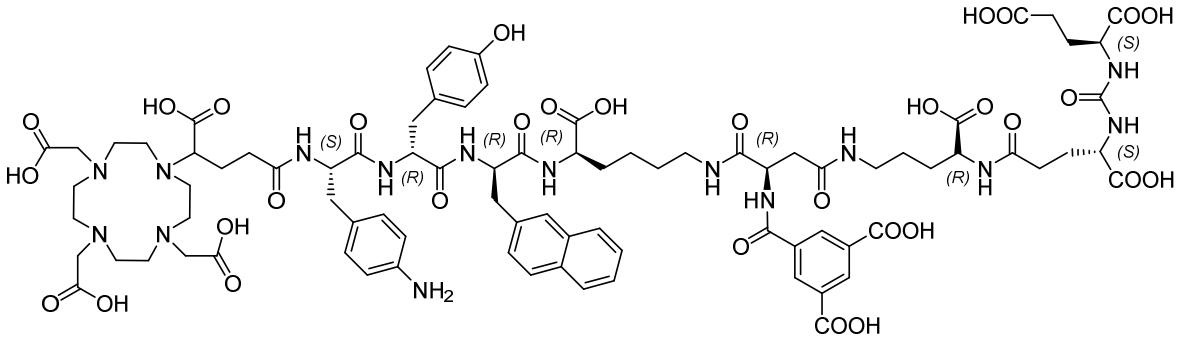
, or a pharmaceutically acceptable salt thereof, and wherein the compound is chelated with ^{225}Ac or cation thereof.

19. The compound or salt thereof of any one of claims 1 to 12, wherein said compound or salt has the following formula:



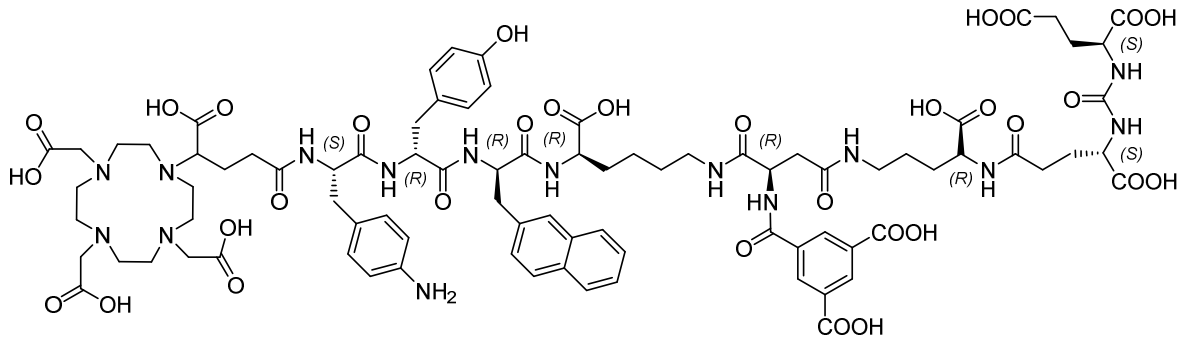
, or a salt thereof, and wherein the compound is chelated with ^{161}Tb or cation thereof.

20. The compound or salt thereof of any one of claims 1 to 12, wherein said compound or salt has the following formula:



, or a salt thereof and wherein the compound is chelated with ^{212}Pb or cation thereof.

21. The compound or salt thereof of any one of claims 1 to 12, wherein said compound or salt has the following formula:



, or a salt thereof and wherein the compound is chelated with ^{177}Lu or cation thereof.

2214. A pharmaceutical or diagnostic composition comprising or consisting of one or more compounds or salts in accordance with any one of claims 1 to 13.

2315. A compound or salt thereof in accordance with any one of claims 1 to 13 for use in a method of diagnosing

(a) cancer associated with overexpression of prostate-specific membrane antigen (PSMA) including prostate cancer associated with overexpression of PSMA; or

(b) pathologic neoangiogenesis/angiogenesis associated with overexpression of PSMA.

2416. A compound or salt thereof in accordance with any one of claims 1 to 13 for use in treating

(a) cancer associated with overexpression of PSMA including prostate cancer associated with overexpression of PSMA; or

(b) pathologic neoangiogenesis/angiogenesis associated with overexpression of PSMA.

2517. Use of a compound or salt thereof in accordance with any one of claims 1 to 13 in the manufacture of a medicament for diagnosing

(a) cancer associated with overexpression of PSMA including prostate cancer associated with overexpression of PSMA; or

(b) pathologic neoangiogenesis/angiogenesis associated with overexpression of PSMA.

2618. Use of a compound or salt thereof in accordance with any one of claims 1 to 13 in the manufacture of a medicament for treating

(a) cancer associated with overexpression of PSMA including prostate cancer associated with overexpression of PSMA; or

(b) pathologic neoangiogenesis/angiogenesis associated with overexpression of PSMA.