Cancer. Molecular Imaging and Biology, 2016: p. 1-9; Delker, A., et al., *Dosimetry for 177Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer.* European journal of nuclear medicine and molecular imaging, 2016. **43**(1): p. 42-51; Kabasakal, L., et al., *Pre-therapeutic dosimetry of normal organs and tissues of 177Lu-PSMA-617 prostate-specific membrane antigen (PSMA) inhibitor in patients with castration-resistant prostate cancer.* European journal of nuclear medicine and molecular imaging, 2015. **42**(13): p. 1976-1983; Yadav, M.P., et al., *177Lu-DKFZ-PSMA-617 therapy in metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment.* European Journal of Nuclear Medicine and Molecular Imaging, 2016: p. 1-11). These elevated numbers are explainable by the physiologic expression of PSMA (Silver, D.A., et al., *Prostate-specific membrane antigen expression in normal and malignant human tissues.* Clinical Cancer Research, 1997. **3**(1): p. 81-85) and the renal excretion of the radiolabeled compound. The occasional occurring renal and hematological toxicities after administration are usually reversible, although is legitimate concern about chronic toxicity especially in patients with overall long survival rates, like in PCa patients. Therefore, a suitable concept is needed to reduce the unwanted radiation and simultaneously to increase the tumor uptake.

In view of the above, the technical problem underlying the present invention can be seen in the provision of means and methods of alleviating radiation-induced side effects of PSMA-targeting radiolabeled diagnostics and therapeutics. A further technical problem can be seen in the provision of means and methods to increase tumor uptake of such diagnostics and therapeutics. More generally speaking, the technical problem can be seen in the provision of improved PSMA binding agents.

The technical problem is solved by the subject-matter summarized in the attached claims and explained in further detail below.

In particular, the present disclosure provides, in a first example, a compound of formula (I), or a pharmaceutically acceptable salt thereof,

〰 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;

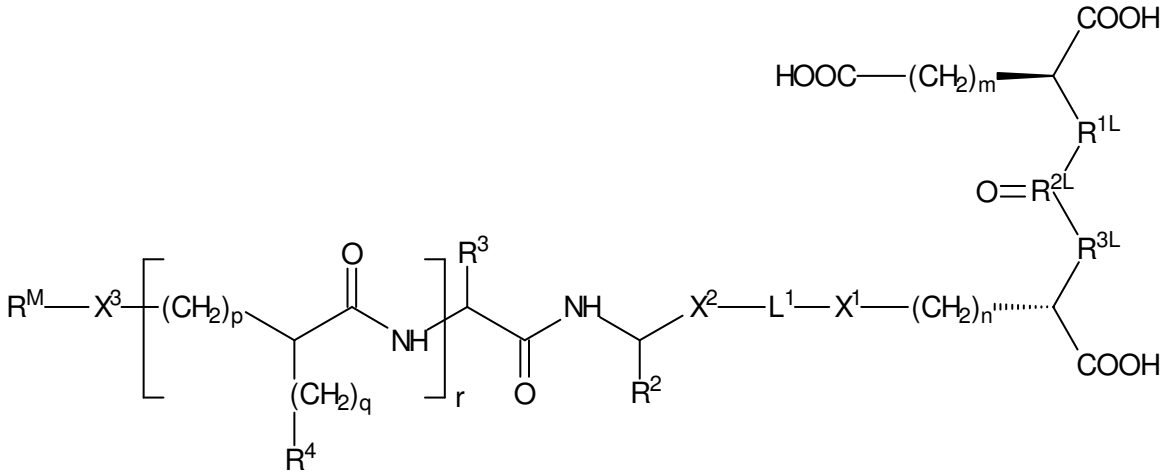
R^{5A} is, independently for each occurrence for s > 1, an electron withdrawing substituent, which is preferably selected from $–NO_2$ and –COOH, and which is more preferably –COOH, and wherein the bond between R^{5A} and the phenyl ring indicates that the s groups R^{5A} replace s hydrogen atoms at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

In one aspect, the present disclosure refers to 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 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;

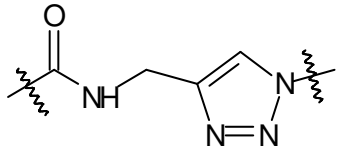
r is 0 or 1;

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

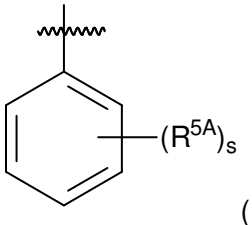


, wherein the marked bond at the carbonyl group attaches X^3 to R^M and the other marked bond attaches X^3 to the remainder of the compound of formula (I);

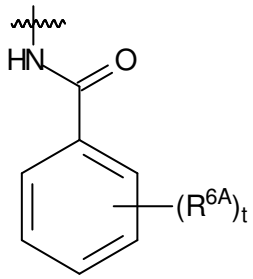
R^M is a marker group which comprises a chelating group optionally containing a chelated non-radioactive or radioactive cation;

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

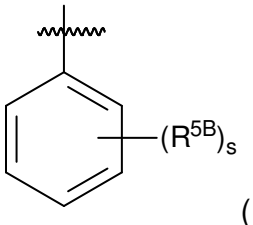
(E-1A), (E-1B), (E-2A) and (E-2B):



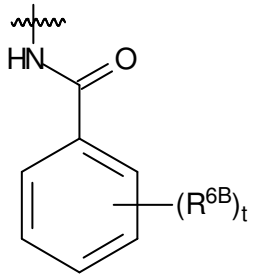
(E-1A)



(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.

The introduction of an EDS substituent as shown above, wherein an aromatic ring carries one or more substituents with a high electron density selected from an electron withdrawing substituent and a substituent carrying an electron lone pair leads to several unexpected advantages. These advantages include increased affinity, improved internalization, elevated tumor cell retention, lower unspecific binding, reduced renal accumulation and an increased tumor uptake.

Especially the reduced unspecific uptake in organs other than prostate leads to less unwanted radiation and reduces radiation-induced side effects.

To exemplify these advantages, we refer to the properties of the particularly preferred compounds herein designated PSMA-71 and PSMA-66 which is discussed in more detail below.

In particular, nanomolar affinity (5.3 ± 2.0 nM vs. 7.9 ± 2.4 nM), drastically improved internalization (206.8 ± 1.7% vs. 75.5 ± 1.6%) demonstrate the superiority of [^{177}Lu]PSMA-71 when compared to [^{177}Lu]PSMA I&T. The biodistribution data revealed that [^{177}Lu]PSMA-71 exhibited markedly higher tumor (14.29 ± 0.89 vs. 4.06 ± 1.12 %ID/g, respectively) uptake compared to [^{177}Lu]PSMA I&T while the renal accumulation was similar (32.36 ± 2.49 vs. 34.66 ± 17.20 %ID/g, respectively).

Similarly, lower nanomolar affinity (3.8 ± 0.3 nM vs. 7.9 ± 2.4 nM), drastically improved internalization (297.8 ± 2.0% vs. 75.5 ± 1.6%), elevated *in vitro* tumor cell retention (90.1 ± 3.5% vs. 62.8 ± 0.4%, 60 min incubation) together with lower unspecific binding *in vivo*, reduced renal accumulation (117.5 ± 6.9% ID/g vs. 128.9 ± 10.7% ID/g) and a more than twofold increase in tumor uptake (10.0 ± 0.4% vs. 4.7 ± 1.0% ID/g), demonstrate the superiority of [^{177}Lu]PSMA-66 in direct comparison to [^{177}Lu]PSMA I&T.

As noted above, salts of the compounds of the disclosure including compounds of formula (I) (and including their preferred examples) are also suitable for use in the context of the disclosure. It will be understood that these salts are generally pharmaceutically acceptable salt forms of these compounds which may be formed, e.g., by protonation of an atom carrying an electron lone pair which is susceptible to protonation, such as an amino group, with an inorganic or organic acid, or as a salt of a carboxylic acid group with a physiologically acceptable cation as they are well known in the art. Exemplary base addition salts comprise, for example, alkali metal salts such as sodium or potassium salts; alkaline-earth metal salts such as calcium or magnesium salts; ammonium salts; aliphatic amine salts such as trimethylamine, triethylamine, dicyclohexylamine, ethanolamine, diethanolamine, triethanolamine, procaine salts, meglumine salts, diethanol amine salts or ethylenediamine salts; aralkyl amine salts such as N,N-dibenzylethylenediamine salts, benetamine salts; heterocyclic aromatic amine salts such as pyridine salts, picoline salts, quinoline salts or isoquinoline salts; quaternary ammonium salts such as tetramethylammonium salts, tetraethylammonium salts, benzyltrimethylammonium salts, benzyltriethylammonium salts, benzyltributylammonium salts, methyltrioctylammonium salts or tetrabutylammonium salts; and basic amino acid salts such as arginine salts or lysine salts. Exemplary acid addition salts comprise, for example, mineral acid salts such as hydrochloride, hydrobromide, hydroiodide, sulfate salts, nitrate salts, phosphate salts (such as, e.g., phosphate, hydrogenphosphate, or dihydrogenphosphate salts), carbonate salts, hydrogencarbonate salts or perchlorate salts; organic acid salts such as acetate, propionate, butyrate, pentanoate, hexanoate, heptanoate, octanoate, cyclopentanepropionate, undecanoate,

lactate, maleate, oxalate, fumarate, tartrate, malate, citrate, nicotinate, benzoate, salicylate or ascorbate salts; sulfonate salts such as methanesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, benzenesulfonate, p-toluenesulfonate (tosylate), 2-naphthalenesulfonate, 3-phenylsulfonate, or camphorsulfonate salts; and acidic amino acid salts such as aspartate or glutamate salts.

Further examples of pharmaceutically acceptable salts include, but are not limited to, acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium edetate, camphorate, camphor-sulfonate, camsylate, carbonate, chloride, citrate, clavulanate, cyclopentanepropionate, digluconate, dihydrochloride, dodecylsulfate, edetate, edisylate, estolate, esylate, ethanesulfonate, formate, fumarate, gluceptate, glucoheptonate, gluconate, glutamate, glycerophosphate, glycolylarsanilate, hemisulfate, heptanoate, hexanoate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, lauryl sulfate, malate, maleate, malonate, mandelate, mesylate, methanesulfonate, methylsulfate, mucate, 2-naphthalenesulfonate, napsylate, nicotinate, nitrate, N-methylglucamine ammonium salt, oleate, oxalate, pamoate (embonate), palmitate, pantothenate, pectinate, persulfate, 3-phenylpropionate, phosphate/diphosphate, picrate, pivalate, polygalacturonate, propionate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, undecanoate, valerate, and the like (see, for example, S. M. Berge et al., "Pharmaceutical Salts", J. Pharm. Sci., 66, pp. 1-19 (1977)).

It is understood that throughout the present specification the term "compound" encompasses solvates, polymorphs, prodrugs, codrugs, cocrystals, tautomers, racemates, enantiomers, or diastereomers or mixtures thereof unless mentioned otherwise.

When the compounds of the present disclosure are provided in crystalline form, the structure can contain solvent molecules. The solvents are typically pharmaceutically acceptable solvents and include, among others, water (hydrates) or organic solvents. Examples of possible solvates include ethanolates and iso-propanolates.

The term "codrug" refers to two or more therapeutic compounds bonded via a covalent chemical bond. A detailed definition can be found, e.g., in N. Das et al., European Journal of Pharmaceutical Sciences, 41, 2010, 571–588.

The term "cocrystal" refers to a multiple component crystal in which all components are solid under ambient conditions when in their pure form. These components co-exist as a stoichiometric or non-stoichometric ratio of a target molecule or ion (i.e., compound of the present disclosure) and one or more neutral molecular cocrystal formers. A detailed discussion can be found, for example, in Ning Shan et al., Drug Discovery Today, 13(9/10), 2008, 440-446 and in D. J. Good et al., Cryst. Growth Des., 9(5), 2009, 2252–2264.

The compounds of the present disclosure can also be provided in the form of a prodrug, namely a compound which is metabolized in vivo to the active metabolite. Suitable prodrugs are, for instance, esters. Specific examples of suitable groups are given, among others, in US 2007/0072831 in paragraphs [0082] to [0118] under the headings prodrugs and protecting groups.

To the extent compounds of the disclosure exhibit a pH-dependent charged state, it is understood that all possible charged states are embraced. A preferred pH range in this regard is from 0 to 14.

To the extent a compound according to the disclosure bears a net charge, it is understood that the compound is provided in electroneutral form. This is achieved by one or more counterions, preferred counterions being defined in relation to the term “salt” herein above.

In formula (I), m is an integer of 2 to 6. Preferably, m is 2 to 4, more preferably 2. R^{1L} is CH_2, NH or O, preferably NH. R^{2L} is C or P(OH), preferably C. R^{3L} is CH_2, NH or O, preferably NH. Thus, compounds of formula (I) or their salts are also preferred wherein m is 2, R^{1L} is NH, R^{2L} is C, and R^{3L} is NH.

n is an integer of 2 to 6, preferably 2 to 4, more preferably 2 or 4, and most preferably 2.

Thus, compounds of formula (I) or their salts are particularly preferred wherein m is 2, n is 2 or 4, R^{1L} is NH, R^{2L} is C, and R^{3L} is NH. More preferred are compounds of formula (I) or their salts wherein m is 2, n is 2, R^{1L} is NH, R^{2L} is C, and R^{3L} is NH.

X^1 in formula (I) is selected from an amide bond (i.e. -C(O)-NH-), an ether bond (i.e. –O-), a thioether bond (i.e. –S-), an ester bond (i.e. -C(O)-O-, a thioester bond (i.e. -C(S)-O- or -C(O)-S-), a urea bridge (i.e. –NH-C(O)-NH-), and an amine bond (i.e. –NH-). Preferred as X^1 is the amide bond.

Moreover, it is further preferred in formula (I) that either n is 2 and X^1 is the amide bond with the carbon atom of the amide bond –C(O)-NH- being attached to the group -$(CH_2)_n$-, or that n is 4 and X^1 is the amide bond with the carbon atom of the amide bond –C(O)-NH- being attached to the group -$(CH_2)_n$-. Among these, more preferred is the option that n is 2 and X^1 is the amide bond with the carbon atom of the amide bond –C(O)-NH- being attached to the group -$(CH_2)_n$-.

Thus, particularly preferred are compounds of formula (I) and their salts wherein, in formula (I), m is 2, n is 2, R^{1L} is NH, R^{2L} is C, R^{3L} is NH, and X^1 is an amide bond with the carbon atom of the amide bond –C(O)-NH- being attached to the group -$(CH_2)_n$-.

L^1 in formula (I) 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), preferably with a structure selected from an oligoamide and an oligo(ester-amide), and more preferably with an oligoamide structure, which linking group may carry a group EDS.

The term “oligo” as used in the definition of L^1 in the terms oligoamide, oligoether, oligothioether, oligoester, oligothioester, oligourea, oligo(ether-amide), oligo(thioether-amide), oligo(ester-amide), oligo(thioester-amide), oligo(urea-amide), oligo(ether-thioether), oligo(ether-ester), oligo(ether-thioester), oligo (ether-urea), oligo(thioether-ester), oligo(thioether-thioester), oligo(thioether-urea), oligo(ester-thioester), oligo(ester-urea), and oligo(thioester-urea) is preferably to be understood as referring to a group wherein 2 to 20, more preferably wherein 2 to 10 subunits are linked by the type of bonds specified in the same terms. As will be understood by the skilled reader, where two different types of bonds are indicated in brackets, both types of bonds are contained in the concerned group (e.g. in “oligo (ester-amide)”, ester bonds and amide bonds are contained).
It is more preferred that L^1 has 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. In a particularly preferred example, L^1 represents a divalent linking group with an oligoamide structure which comprises 1 or 2 amide bonds within its backbone.

Furthermore, L^1 may carry a group EDS (i.e. a group carrying a substituent with a high electron density or "electron dense substituent") as defined herein, i.e. a group EDS which is covalently attached to L^1. Preferably, the optional group EDS is attached as a substituent to the backbone of the divalent linking group L^1, L^1 having a structure as defined above 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), preferably a structure selected from an oligoamide and an oligo(ester-amide), and most preferably an oligoamide structure, which backbone extends between X^1 and X^2 in the compound of formula (I). Also in this regard, the further preferred definitions for L^1 apply, i.e. it is more preferred that L^1 has 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. In a particularly preferred example, L^1 represents a divalent linking group with an oligoamide structure which comprises 1 or 2 amide bonds within its backbone.

In accordance with the above, L^1 may carry one or more, e.g. 2 or 3, groups EDS. However, it is preferred that L^1 does not carry a group EDS, or that L^1 carries one group EDS, and it is more preferred that L^1 carries one group EDS.

If L^1 carries a group EDS (including the more preferred case that EDS carries one group EDS), it is preferred that the group EDS has a structure selected from (E-1A), (E-2A) and (E-2B). It is more preferred that the group EDS has a structure selected from (E-2A) and (E-2B), and most preferably it has the structure (E-2A).

As will be understood by the skilled reader, the indication that L^1 may carry a group EDS serves as information on a possible position of this group in the compounds in accordance with the disclosure. The fact that L^1 may carry a group EDS does not impose a restriction on the presence of other groups that may be present e.g. as alternative or additional substituents on the backbone of L^1. For example, it is preferred that the linking group L^1 contains one or more, such as two, groups which are independently selected from -OH, $-OCH_3$, -COOH, $-COOCH_3$, $-NH_2$, and $-NHC(NH)NH_2$ attached as substitutents to its

and wherein each of R^{13} and R^{15} may carry one group EDS as a substituent and preferably each of R^{13} and R^{15} carries one group EDS as a substituent,
R^{17} is a linear C2 to C6 alkanediyl, preferably a linear C2 to C4 alkanediyl,
R^{18} is a phenylene group, e.g. a *para*-phenylene group, and
R^{19} is a linear C2 to C6 alkanediyl, preferably a linear C2 to C4 alkanediyl.

Also in this context, it is preferred that the group EDS which may be attached to R^{13} and R^{15} has a structure selected from (E-1A), (E-2A) and (E-2B). It is more preferred that the group EDS has a structure selected from (E-2A) and (E-2B), and most preferably it has the structure (E-2A).

Furthermore, it is preferred that the total number of carbon atoms in R^{12} and R^{13} in formula (L-3), without carbon atoms contained in the group EDS as substituent, is 6 to 16, more preferably 6 to 14, and the total number of carbon atoms in R^{14}, R^{15} and R^{16} in formula (L-4), without carbon atoms contained in the group EDS as substituent, is 6 to 16, more preferably 6 to 14.

It will be understood from the information provided with respect to preferred meanings of n and X^1 above that it is particularly preferred that $–X^2\text{-}L^1\text{-}X^1–$ in formula (I) has a structure (L-3) if n is 4, and that $–X^2\text{-}L^1\text{-}X^1–$ in formula (I) has a structure (L-4) or (L-5) if n is 2.

It is specifically preferred that, in formula (I), n is 2 and the moiety $–X^2\text{-}L^1\text{-}X^1–$ has one of the following structures:

*-C(O)-NH-CH(COOH)-$(CH_2)_4$-NH-C(O)-CH(EDS)-CH_2-C(O)-NH-$(CH_2)_3$-CH(COOH)-NH-C(O)-
(L-6)

*-C(O)-NH-CH(COOH)-$(CH_2)_2$-C(O)-NH-Ph-C(O)-NH-$(CH_2)_3$-CH(COOH)-NH-C(O)-
(L-7)

wherein the bond marked with * is attached to the carbon atom carrying R^2 in formula (I), EDS is a group EDS as defined herein, including its preferred examples, and Ph is a *para*-phenylene group.

Also in this context, it is preferred that the group EDS has a structure selected from (E-1A), (E-2A) and (E-2B). It is more preferred that the group EDS has a structure selected from (E-2A) and (E-2B), and most preferably it has the structure (E-2A).

In formula (I), R^2 is an optionally substituted aryl group or an optionally substituted aralkyl group, preferably an optionally substituted aralkyl group. As will be understood, the term "aralkyl group" as used herein refers to an alkyl group wherein a hydrogen atom is replaced by an aryl group as a substituent. Preferably, the aralkyl group is a group wherein one aryl group is bound to an alkanediyl group. The aryl group or aralkyl group represented by R^2 may be substituted on its aromatic ring with one or more substituents selected from halogen, preferably I, and –OH. The aryl and the aryl portion of the aralkyl group are preferably selected from phenyl and naphthyl, such as 2-naphthyl. The alkanediyl portion of the aralkyl group is preferably a C1-C4 alkanediyl group, more preferably a $–CH_2-$ group. Thus, R^2 is more preferably selected from optionally substituted $-CH_2$-phenyl, and optionally substituted $–CH_2$-naphtyl, in particular optionally substituted $–CH_2$-(2-naphtyl). Optionally substituted $-CH_2$-(2-naphtyl) is a particularly preferred option for R^2.

The optionally substituted aryl group and the aryl portion of the optionally substituted aralkyl group, including their preferred examples, may be substituted with one or more substituents selected from halogen, preferably I, and –OH. Thus, one or more than one, e.g. 2 or 3, substituent(s) selected from halogen, preferably I, and –OH can be present. However, it is preferred that R^2 is non-substituted.

In view of the above, it will be understood that, R^2 is most preferably non-substituted $-CH_2$-(naphtyl), and that the naphthyl group is most preferably a 2-naphtyl group to provide R^2 as $–CH_2$-(2-naphthyl).

In formula (I), R^3 is an optionally substituted aryl group or an optionally substituted aralkyl group, preferably an optionally substituted aralkyl group. The aryl group or aralkyl group may be substituted on its aromatic ring with one or more substituents selected from halogen, preferably I, and –OH. The aryl and the aryl portion of the aralkyl group are preferably selected from phenyl and naphthyl, such as 2-naphthyl. It is more preferred that the aryl and the aryl portion of the aralkyl are phenyl. The alkanediyl portion of the aralkyl group is preferably a C1-C4 alkanediyl group, more preferably a $–CH_2-$ group. Thus, R^3 is more preferably optionally substituted $-CH_2$-phenyl.

The optionally substituted aryl group and the aryl portion of the optionally substituted aralkyl group, including their preferred examples, may be substituted with one or more substituents selected from halogen, preferably I, and –OH. Thus, one or more than one, e.g. 2 or 3, substituent(s) selected from halogen, preferably I, and –OH can be present.

In a more preferred example, X^3 is an amide bond -C(O)-NH- with the carbon atom attached to R^M.

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

As will be understood by the skilled reader, the above definition according to which R^M comprises a chelating group encompasses the case that R^M is a chelating group; in this case the chelating group is typically directly bound to X^3;
and the case that R^M comprises, together with the chelating group, e.g. a further linker moiety; in this case the chelating group can be indirectly bound via this further linker moiety to X^3.

The chelating group provided by R^M is suitable to form a chelate with a radioactive or non-radioactive cation. Suitable chelating groups for diverse cations are well known in the art, and can be used in the context of the present disclosure.

The chelating group optionally containing a chelated non-radioactive or radioactive cation is preferably selected from a chelating group comprising at least one of

(i) a macrocyclic ring structure with 8 to 20 ring atoms of which 2 or more, preferably 3 or more, are selected from oxygen atoms, sulfur atoms and nitrogen atoms; and

(ii) an acyclic, open chain chelating structure with 8 to 20 main chain atoms of which 2 or more, preferably 3 or more are heteroatoms selected from oxygen atoms, sulfur atoms and nitrogen atoms.

An exemplary chelating group, and thus also an exemplary group R^M, is a residue of a chelating agent 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-tetraazacyclododecan-N,N',N'',N'''-tetraacetic acid (DOTA), 2-[1,4,7,10-tetraazacyclododecane-4,7,10-triacetic acid]-pentanedioic acid (DOTAGA), N,N'-dipyridoxylethylendiamine-N,N'-diacetate-5,5'-bis(phosphat) (DPDP), 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

wherein the bond marked with ~~~ is attached to the remainder of the compound of formula (I), and wherein the chelating group may contain a chelated non-radioactive or radioactive cation.

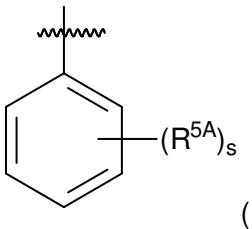
Exemplary radioactive cations that are optionally chelated by the chelating group are selected from the cations of ^{44}Sc, ^{47}Sc, ^{51}Cr, ^{52m}Mn, ^{58}Co, ^{52}Fe, ^{56}Ni, ^{57}Ni, ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{66}Ga, ^{68}Ga, ^{67}Ga, ^{89}Zr, ^{90}Y, ^{89}Y, ^{94m}Tc, ^{99m}Tc, ^{97}Ru, ^{105}Rh, ^{109}Pd, ^{111}Ag,^{110m}In, ^{111}In, ^{113m}In, ^{114m}In, ^{117m}Sn, ^{121}Sn, ^{127}Te, ^{142}Pr, ^{143}Pr, ^{149}Pm, ^{151}Pm, ^{149}Tb, ^{153}Sm, ^{157}Gd, ^{161}Tb, ^{166}Ho, ^{165}Dy, ^{169}Er, ^{169}Yb, ^{175}Yb, ^{172}Tm, ^{177}Lu, ^{186}Re, ^{188}Re, ^{191}Pt, ^{197}Hg, ^{198}Au, ^{199}Au, ^{212}Pb, ^{203}Pb, ^{211}At, ^{212}Bi, ^{213}Bi, ^{223}Ra, ^{225}Ac, and ^{227}Th, or a cationic molecule comprising ^{18}F, such as ^{18}F-$[AlF]^{2+}$.

Preferred chelated cations are selected from the cations of ^{44}Sc, ^{47}Sc, ^{64}Cu, ^{67}Cu, ^{68}Ga, ^{90}Y, ^{111}In, ^{161}Tb, ^{166}Ho, ^{177}Lu, ^{188}Re, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{225}Ac, and ^{227}Th, or a cationic molecule comprising ^{18}F.

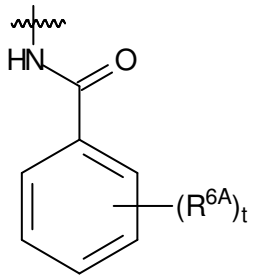
In formula (I), the group EDS is contained at least once, such that e.g. one, two or three groups EDS may be contained. Preferably, the compounds or salts in accordance with the disclosure contain one group or two groups EDS. As explained above, the group(s) EDS may be carried by L^1, and/or may be represented by R^4.

The most preferred compounds of formula (I) or their salts are those which contain one group EDS which is carried by the linking group L^1, including its preferred examples as set forth above, and those which contain two groups EDS, one being represented by R^4 (i.e. r is 1) and one being carried by L^1, including its preferred examples as set forth above.

As set out above, the group EDS has a structure selected from (E-1A), (E-1B), (E-2A) and (E-2B):



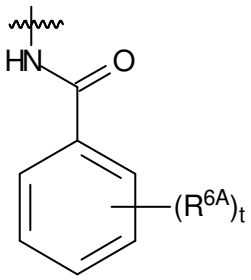
(E-1A)



(E-2A)

It is likewise generally preferred that, in the group EDS (E-1B), the substituents R^{5B} are the same for s > 1 and are selected from –OH and $–NH_2$, and are more preferably $–NH_2$, and that, in the group EDS (E-2B), the substituents R^{6B} are the same for t > 1 and are selected from -OH and $–NH_2$, and are more preferably –OH.

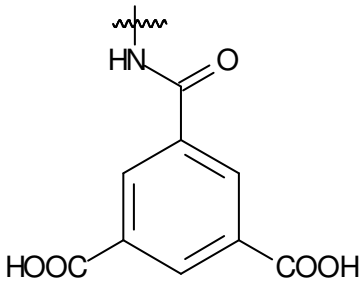
Thus, it is further preferred that the compound of formula (I) contains a group EDS which has the formula (E-2A):



(E-2A)

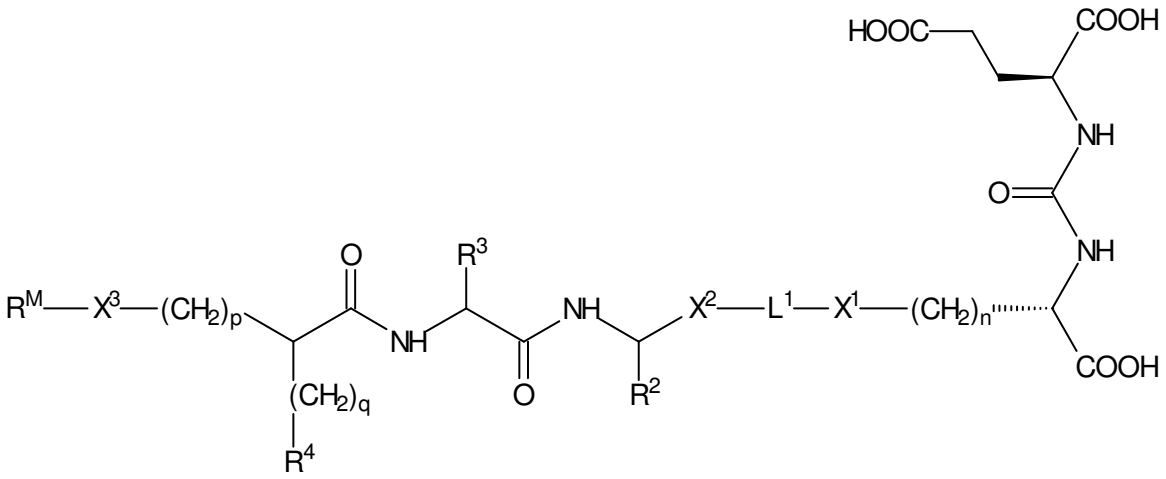
wherein ~~~ marks the bond which attaches the group EDS to the remainder of the compound of formula (I); and
t is 1 or 2, and R^{6A} is $-NO_2$ or –COOH.

Most preferred as group EDS in the context of the present disclosure is the group



(E-3).

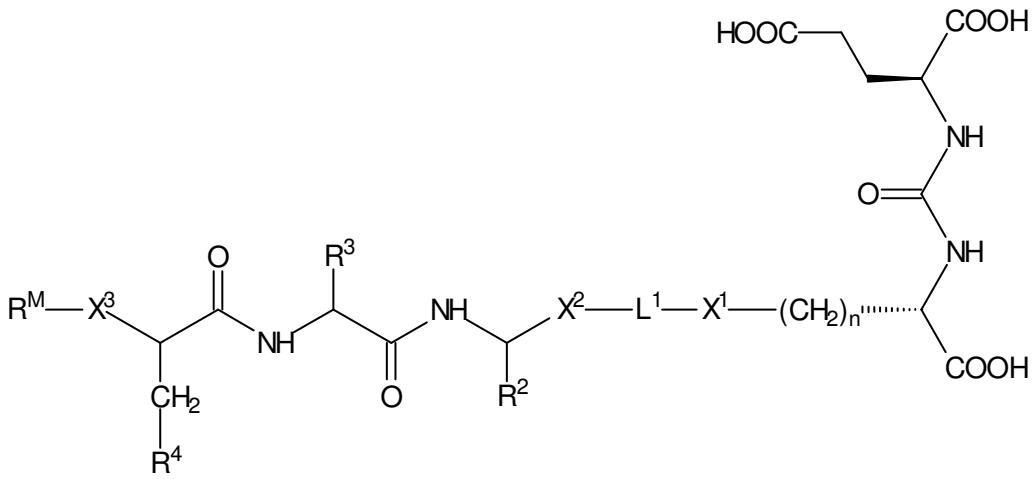
In line with the above, preferred compounds of formula (I) are illustrated by the following formula (Ia)



(Ia),

wherein n, X^1, L^1, X^2, R^2, R^3, R^4, q, p, X^3 and R^M are defined as above, including their preferred examples, and wherein the group EDS is contained at least once and has a structure as defined above, including the preferred examples.

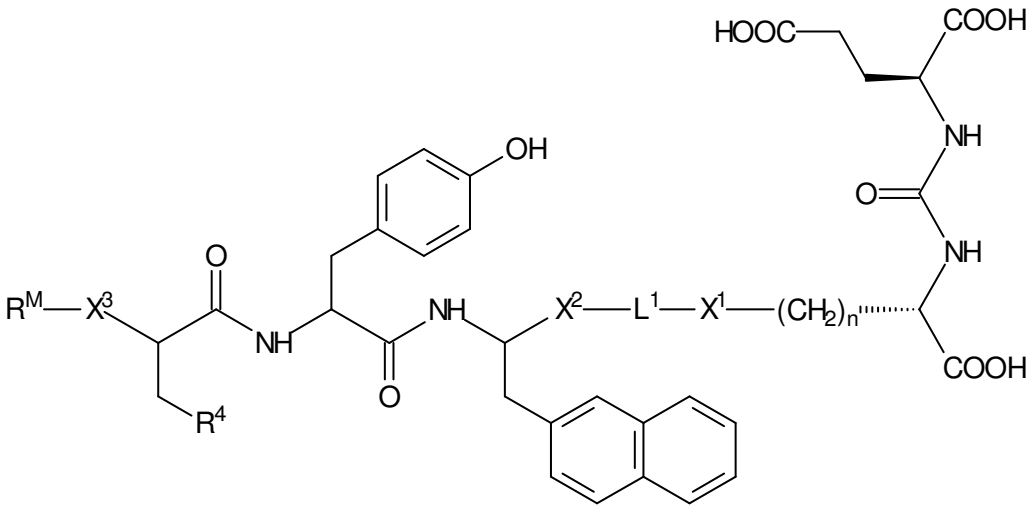
More preferred compounds of formula (I) are illustrated by the following formula (Ib)



(Ib)

wherein n, X^1, L^1, X^2, R^2, R^3, R^4, X^3 and R^M are defined as above, including their preferred examples, and wherein the group EDS is contained at least once and has a structure as defined above, including the preferred examples.

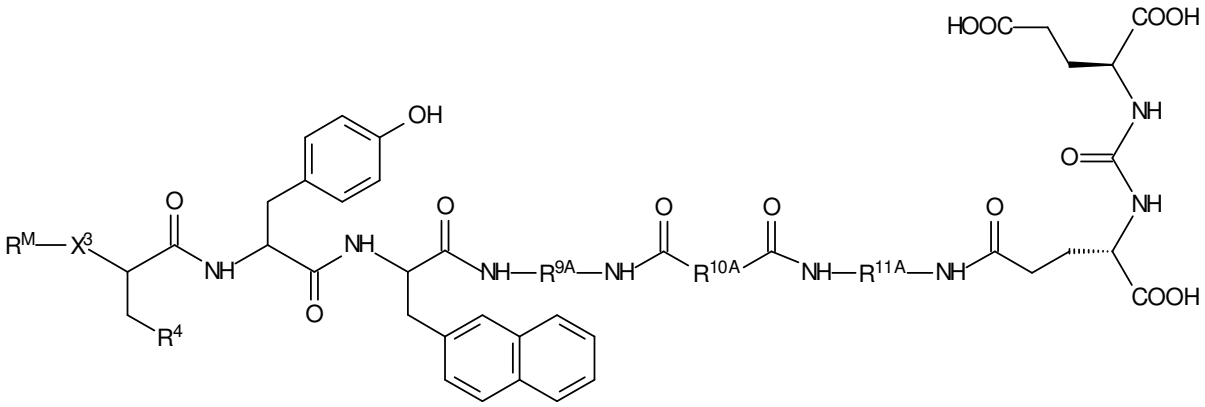
Still more preferred compounds of formula (I) are illustrated by the following formula (Ic)



(Ic)

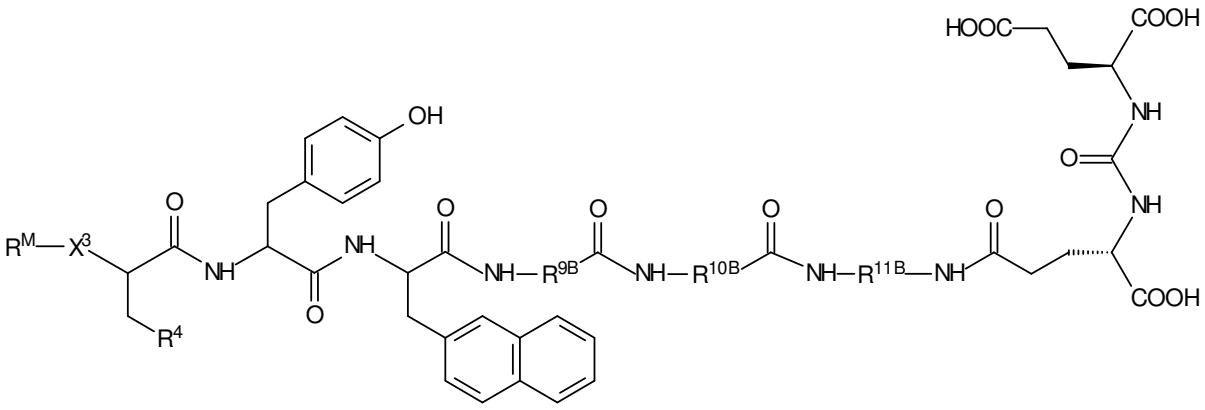
wherein n, X^1, L^1, X^2, R^4, X^3 and R^M are defined as above, including their preferred examples, and wherein the group EDS is contained at least once and has a structure as defined above, including its preferred examples.

Still more preferred compounds of formula (I) are illustrated by the following formulae (Id) and (Ie):



(Id)

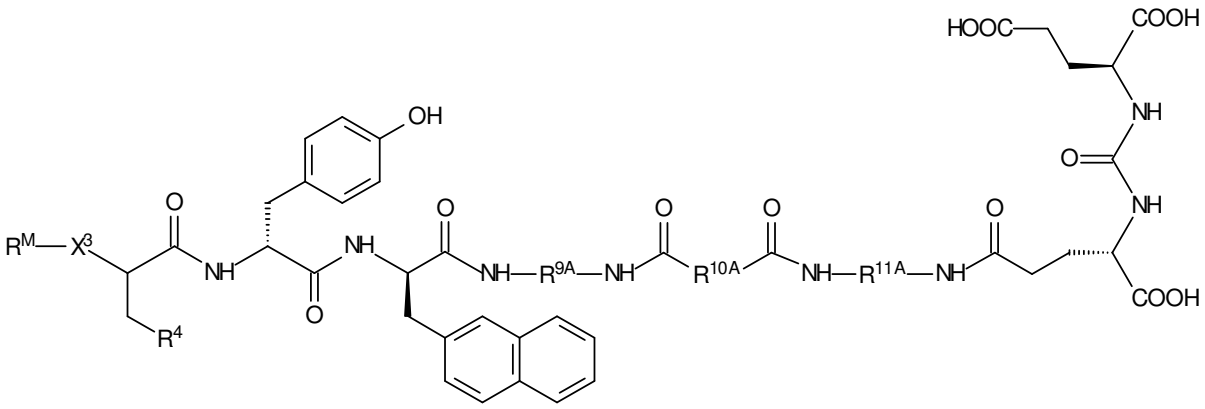
wherein R^{9A}, R^{10A}, R^{11A}, R^4, X^3 and R^M are defined as above, including their preferred examples, and wherein either (i) R4 is a group EDS with a structure as defined above, including its preferred examples, or (ii) R^{10A} carries one group EDS with a structure as defined above, including its preferred examples, or both (i) and (ii) apply;



(Ie)

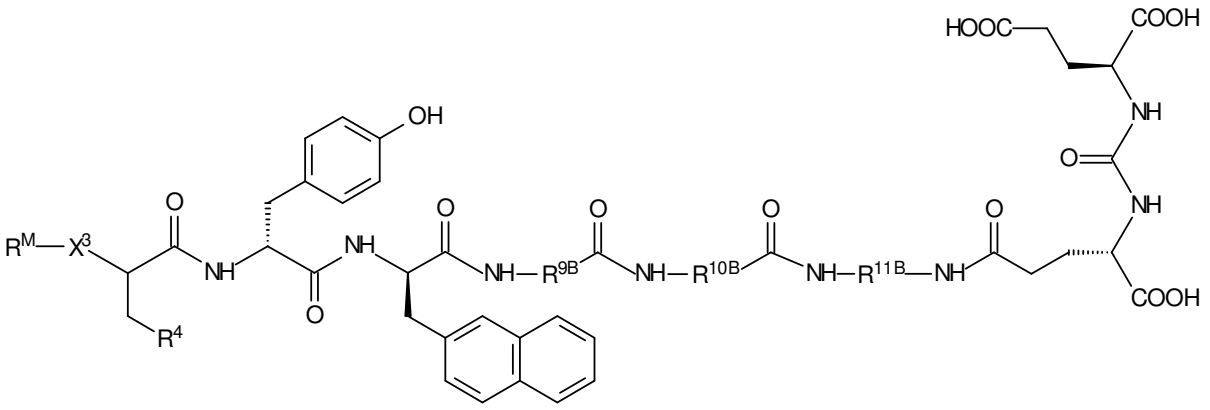
wherein R^{9B}, R^{10B}, R^{11B}, R^4, X^3 and R^M are defined as above, including their preferred examples, and wherein R^4 is a group EDS with a structure as defined above, including its preferred examples.

Particularly preferred compounds of formula (I) are illustrated by the following formulae (If) and (Ig)



(If)

wherein R^{9A}, R^{10A}, R^{11A}, R^4, X^3 and R^M are defined as above, including their preferred examples, and wherein either (i) R4 is a group EDS with a structure as defined above, including its preferred examples, or (ii) R^{10A} carries one group EDS with a structure as defined above, including its preferred examples, or both (i) and (ii) apply;



(Ig)

wherein R^{9B}, R^{10B}, R^{11B}, R^4, X^3 and R^M are defined as above, including their preferred examples, and wherein R^4 is a group EDS with a structure as defined above, including its preferred examples.

In a preferred example, said chelating group has a radionuclide bound which radionuclide emits α-radioation. Radionuclides emitting α-radioation include ^{212}Bi, ^{213}Bi, and ^{225}Ac.

As noted above, the introduction of the electron deficient substituents drastically increased the internalization capacities. This feature results in higher tumor uptake and especially longer retention in the tumor tissue as demonstrated by the *in vitro* experiments (see examples). Since the complex of the chelator and alpha-particle emitting radionuclide is prone to decomplexation via physical recoil effect, the feature of elongated intracellular retention will reduce the probability of freely circulating radionuclides *in vivo* and thus increase safety and reduce unwanted radiation.

Particularly preferred compounds of the disclosure are the following:

[$^{nat/177}$Lu]PSMA-52	**-F(4-NO_2)-y-2-nal-k(Suc-N^5-orn-C^4-EuE)**	3.4 ± 0.2	229.9 ± 8.0	-4.11 ± 0.07	95.4
[$^{nat/177}$Lu]PSMA-53	**2,4-DNBA-Dap(DOTAGA)-y-2-nal-k(Suc-N^5-orn-C^4-EuE)**	3.2 ± 0.5	293.6 ± 10.0	-4.08 ± 0.04	95.9
[$^{nat/177}$Lu]PSMA-61	**-F(4-NH_2)y-2-nal-k(d[N^5-orn-C^4-EuE]-2,4-DNBA)**	4.5 ± 0.4	359.5 ± 22.6	-4.07 ± 0.05	63.3
[$^{nat/177}$Lu]PSMA-62	**-F(4-NH_2)y-2-nal-k(d[N^5-orn-C^4-EuE]-TMA)**	4.0 ± 0.2	343.9 ± 6.0	-4.12 ± 0.05	> 91.0
[$^{nat/177}$Lu]PSMA-66	**-Dap(TMA)y-2-nal-k(d[N^5-orn-C^4-EuE]-TMA)**	3.8 ± 0.3	297.8 ± 2.0	-4.25 ± 0.14	64.4
[$^{nat/177}$Lu]PSMA-71	**-2-Nal-y-2-nal-k(d[N^5-orn-C^4-EuE]-TMA)**	5.3 ± 2.0	206.8 ± 1.7	-4.13 ± 0.09	98.2
[$^{nat/177}$Lu]PSMA-49	**-F(4-NH_2)y-2-nal-k(Suc-N^5-orn-C^4-EuE)**	2.5 ± 0.6	245.0 ± 4.2	-4.01 ± 0.11.	74.2.
[$^{nat/177}$Lu]PSMA-60	**-F(4-NH_2)y-2-nal-e(Abz-N^5-orn-C^4-EuE)**	6.6 ± 1.5	267.4 ± 7.9	-3.85 ± 0.13 n.d.	98.5 n.d.
[$^{nat/177}$Lu]PSMA-78	**-F(4-NH_2)y-2-nal-k(d[N^5-orn-C^4-EuE]-3,5-DHBA)**	3.9 ± 0.6.	289.0 ± 6.2	n.d.	n.d.
[$^{nat/177}$Lu]PSMA-65	**2,4-DNBA-Dap(DOTAGA)y-2-nal-e(Abz-N^5-orn-C^4-EuE)**	3.5 ± 0.3n.d.	340.2 ± 19.9	-4.15 ± 0.08n.d.	98.7 n.d.

Preferred labeling schemes for these most preferred compounds are as defined herein above.

In a further example, the present disclosure provides a pharmaceutical composition comprising or consisting of one or more compounds or salts of the disclosure as disclosed herein above.

In a further example, the present disclosure provides a diagnostic composition comprising or consisting of one or more compounds or salts of the disclosure as disclosed herein above.

In another aspect, the present disclosure refers to a pharmaceutical or diagnostic composition comprising or consisting of one or more compounds or salts as disclosed herein.

In a further example, the present disclosure provides a therapeutic composition comprising or consisting of one or more compounds or salts of the disclosure as disclosed herein above.

The pharmaceutical composition may further comprise pharmaceutically acceptable carriers,

excipients and/or diluents. Examples of suitable pharmaceutical carriers, excipients and/or diluents are well known in the art and include phosphate buffered saline solutions, water, emulsions, such as oil/water emulsions, various types of wetting agents, sterile solutions etc. Compositions comprising such carriers can be formulated by well known conventional methods. These pharmaceutical compositions can be administered to the subject at a suitable dose. Administration of the suitable compositions may be effected by different ways, e.g., by intravenous, intraperitoneal, subcutaneous, intramuscular, topical, intradermal, intranasal or intrabronchial administration. It is particularly preferred that said administration is carried out by injection and/or delivery, e.g., to a site in the pancreas or into a brain artery or directly into brain tissue. The compositions may also be administered directly to the target site, e.g., by biolistic delivery to an external or internal target site, like the pancreas or brain. The dosage regimen will be determined by the attending physician and clinical factors. As is well known in the medical arts, dosages for any one patient depends upon many factors, including the patient's size, body surface area, age, the particular compound to be administered, sex, time and route of administration, general health, and other drugs being administered concurrently. Pharmaceutically active matter may be present in amounts between 0,1 ng and 10 mg/kg body weight per dose; however, doses below or above this exemplary range are envisioned, especially considering the aforementioned factors.

To the extent the above disclosed pharmaceutical composition, diagnostic composition and therapeutic composition comprises one or more compounds of the disclosure, it is preferred that no further pharmaceutically active compounds, diagnostically active compounds or therapeutically active compounds are present. In the alternative, further therapeutically active, diagnostically active or pharmaceutically active compounds may be present, for example, anticancer agents.

Combination of a therapeutic treatment with the compounds of the present disclosure might have a synergistic or cumulative treatment effect, similar to the treatment of neuroendocrine tumors with [^{177}Lu]DOTATATE radiotherapy in combination with chemotherapy or immunotherapies. A first phase 3 study comparing the combination of ^{177}Lu PRRT and capecitabine (Xeloda; Genentech), an oral chemotherapy agent, with [^{177}Lu]DOTATATE alone has been started at Erasmus MC, Rotterdam in 2017 (van Essen M, Krenning EP, Kam BL, de Herder WW, van Aken MO, Kwekkeboom DJ. Report on short-term side effects of treatments with 177Lu-octreotate in combination with capecitabine in seven patients with gastroenteropancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2008;35:743–748).

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 and/or treating (a) cancer including prostate cancer; or (b) neoangiogenesis/angiogenesis.

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 and/or treating (a) cancer including prostate cancer; or (b) neoangiogenesis/angiogenesis.

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.

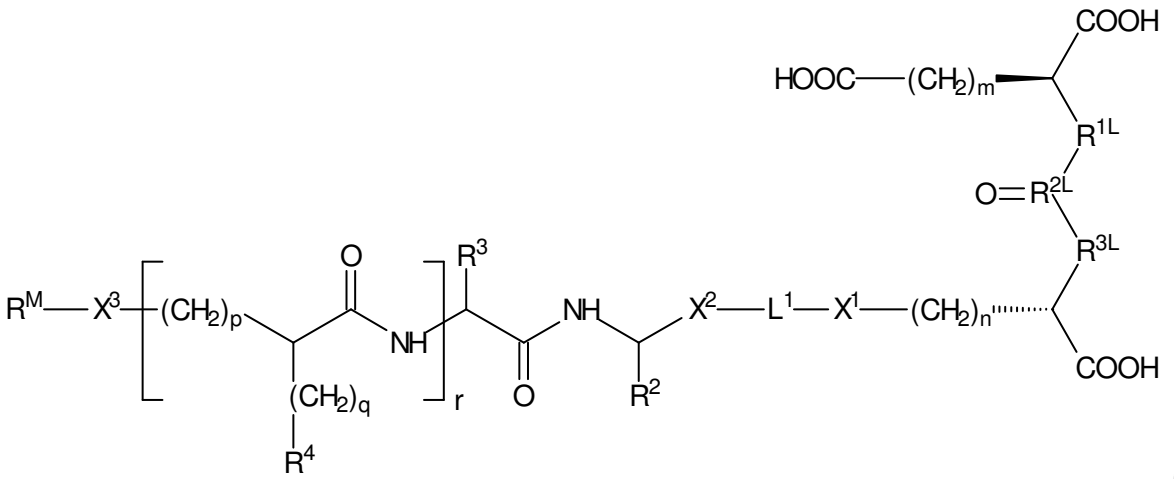
As regards the examples characterized in this specification, in particular in the claims, it is intended that each example mentioned in a dependent claim is combined with each example of each claim (independent or dependent) said dependent claim depends from. For example, in case of an independent claim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

dependent claim 2 reciting 3 alternatives D, E and F and a claim 3 depending from claims 1 and 2 and reciting 3 alternatives G, H and I, it is to be understood that the specification unambiguously discloses examples corresponding to combinations A, D, G; A, D, H; A, D, I; A, E, G; A, E, H; A, E, I; A, F, G; A, F, H; A, F, I; B, D, G; B, D, H; B, D, I; B, E, G; B, E, H; B, E, I; B, F, G; B, F, H; B, F, I; C, D, G; C, D, H; C, D, I; C, E, G; C, E, H; C, E, I; C, F, G; C, F, H; C, F, I, unless specifically mentioned otherwise.

Similarly, and also in those cases where independent and/or dependent claims do not recite alternatives, it is understood that if dependent claims refer back to a plurality of preceding claims, any combination of subject-matter covered thereby is considered to be explicitly disclosed. For example, in case of an independent claim 1, a dependent claim 2 referring back to claim 1, and a dependent claim 3 referring back to both claims 2 and 1, it follows that the combination of the subject-matter of claims 3 and 1 is clearly and unambiguously disclosed as is the combination of the subject-matter of claims 3, 2 and 1. In case a further dependent claim 4 is present which refers to any one of claims 1 to 3, it follows that the combination of the subject-matter of claims 4 and 1, of claims 4, 2 and 1, of claims 4, 3 and 1, as well as of claims 4, 3, 2 and 1 is clearly and unambiguously disclosed.

In particular, the disclosure provides the subject matter summarized in the following items.

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



(I)

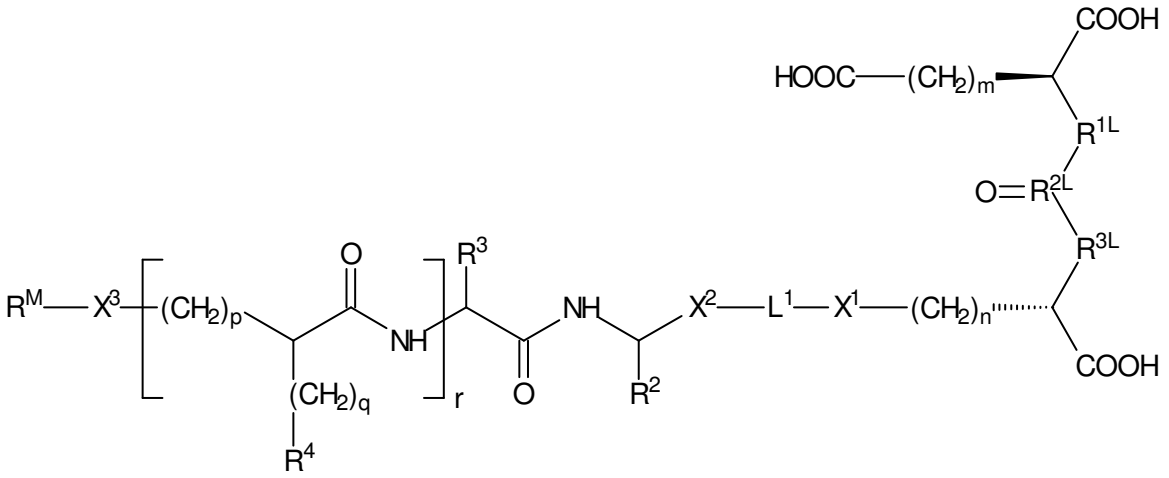
wherein:

m is an integer of 2 to 6, preferably 2 to 4, more preferably 2;

n is an integer of 2 to 6, preferably 2 to 4, more preferably 2 or 4;

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 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;

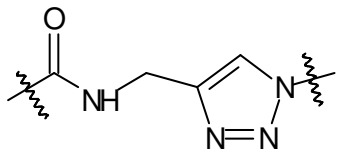
r is 0 or 1;

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

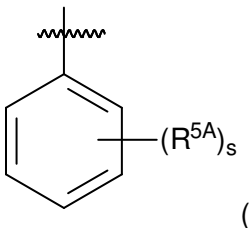


, wherein the marked bond at the carbonyl group attaches X^3 to R^M and the other marked bond attaches X^3 to the remainder of the compound of formula (I);

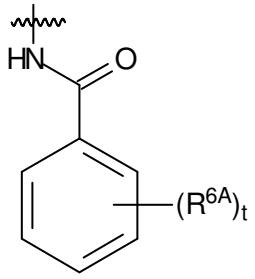
R^M is a marker group which comprises a chelating group optionally containing a chelated non-radioactive or radioactive cation;

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

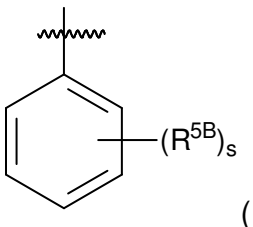
(E-1A), (E-1B), (E-2A) and (E-2B):



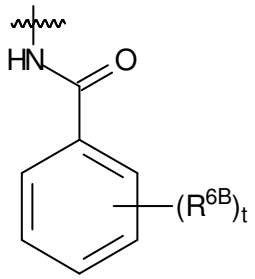
(E-1A)



(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) (L-2), 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,

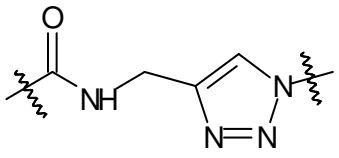
R^{18} is a phenylene group, and
R^{19} is a linear C2 to C6 alkanediyl.

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

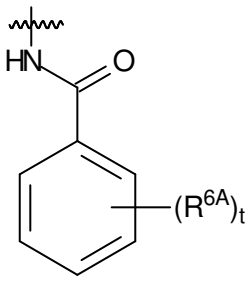


, wherein the marked bond at the carbonyl group attaches X^3 to R^M and the other marked bond attaches X^3 to the remainder of the molecule.

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):

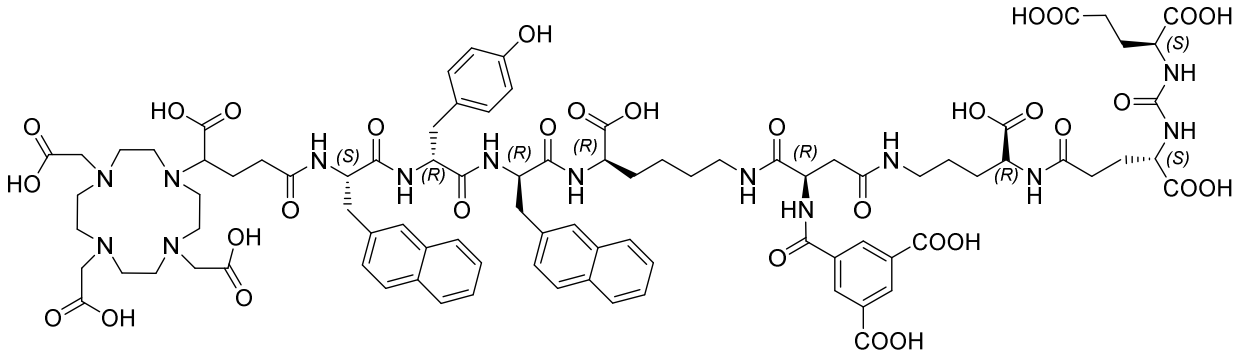


(E-2A)

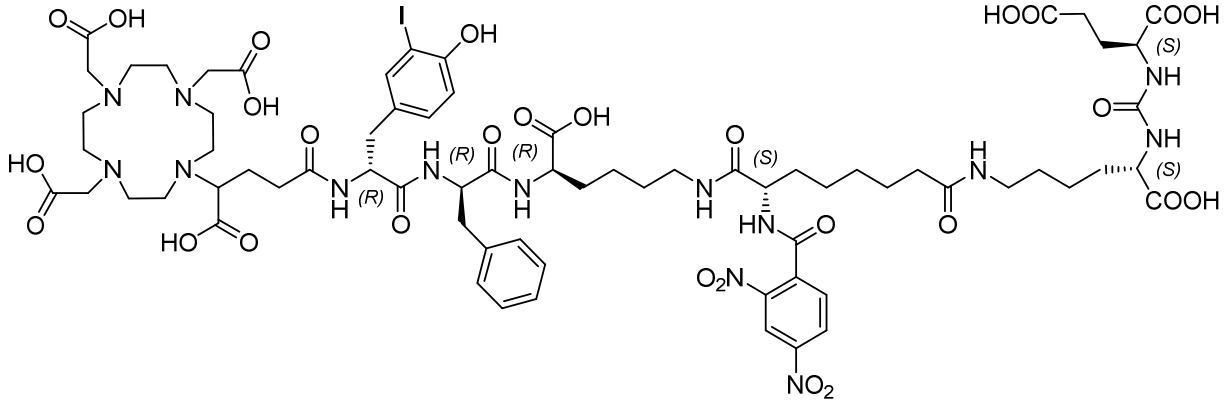
wherein ~~~ marks the bond which attaches the group EDS to the remainder of the compound of formula (I); and

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

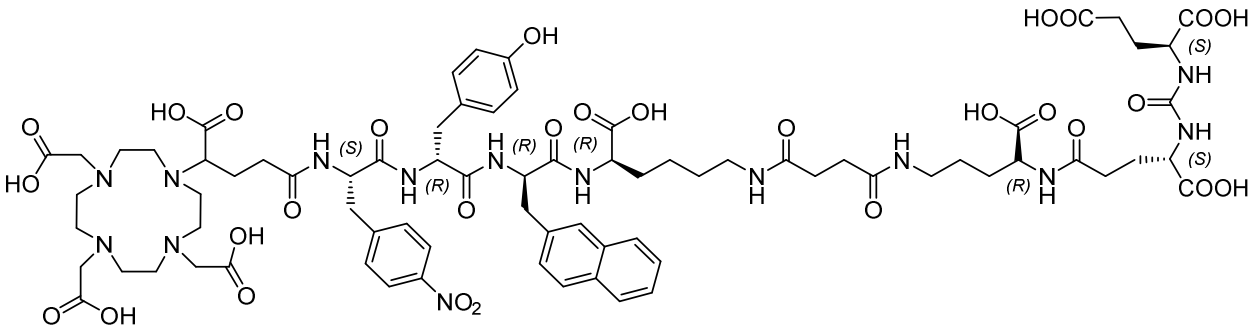
13. The compound or salt thereof of any one of claims 1 to 12, wherein said compound or salt has one of the following formulae:



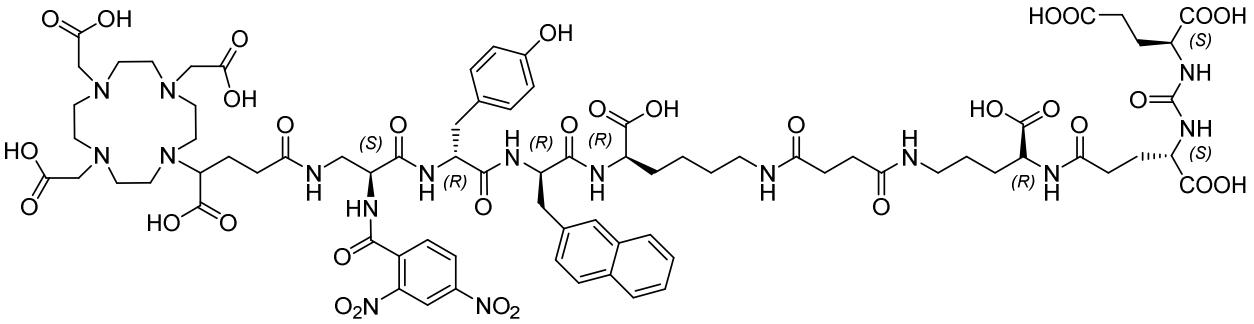
(Ih)



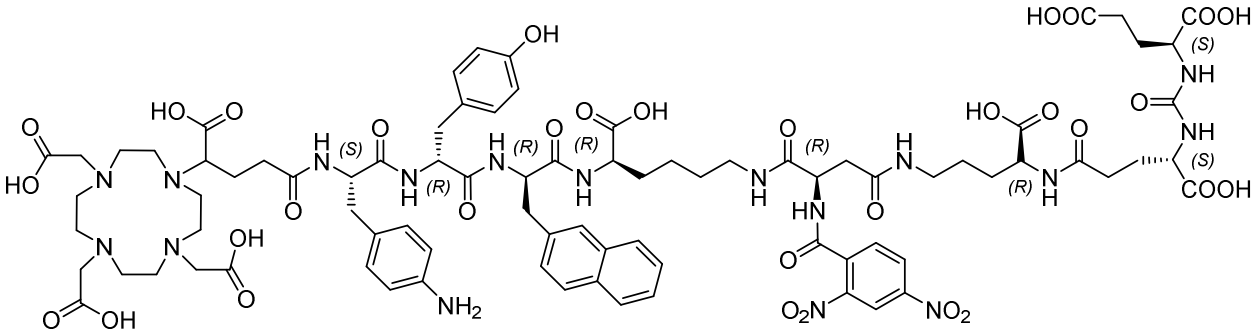
(Ii)



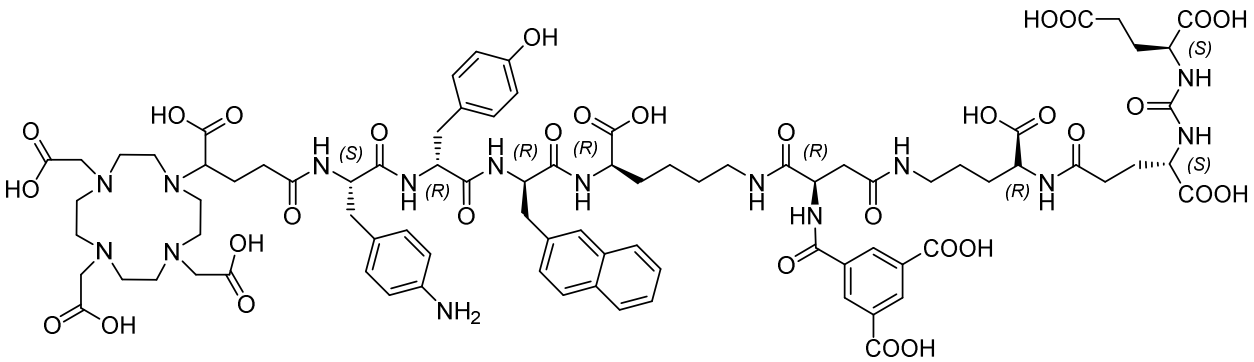
(Ij)



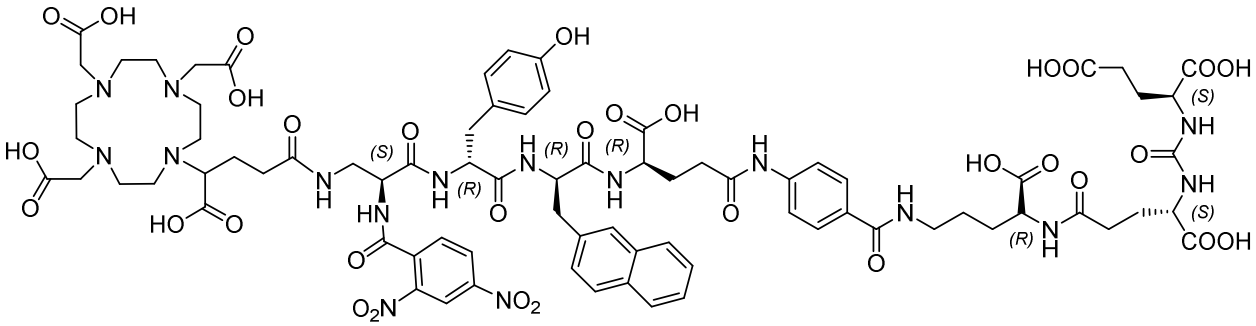
(Ik)



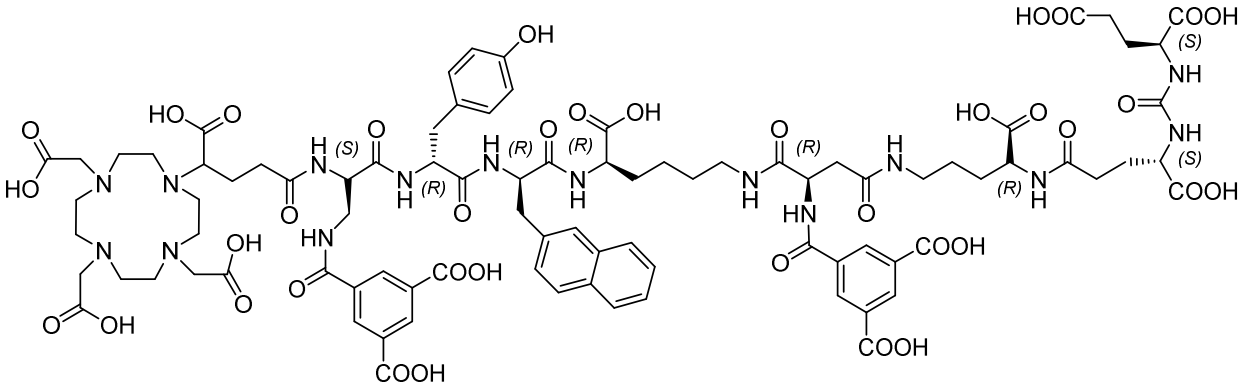
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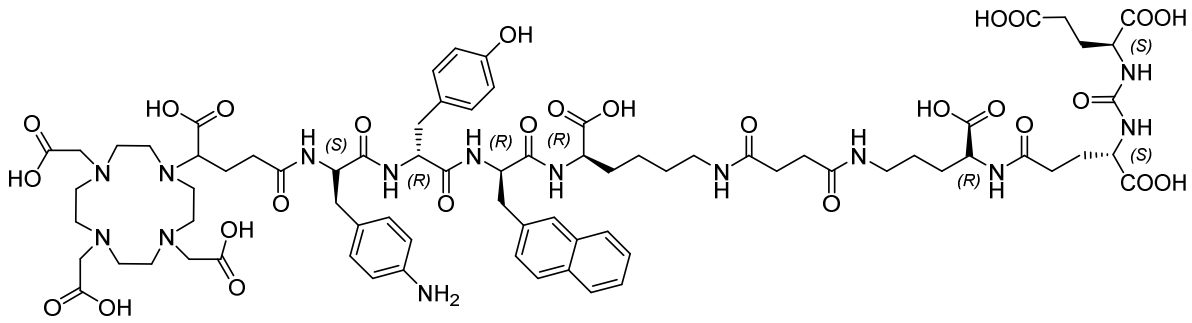
(In)



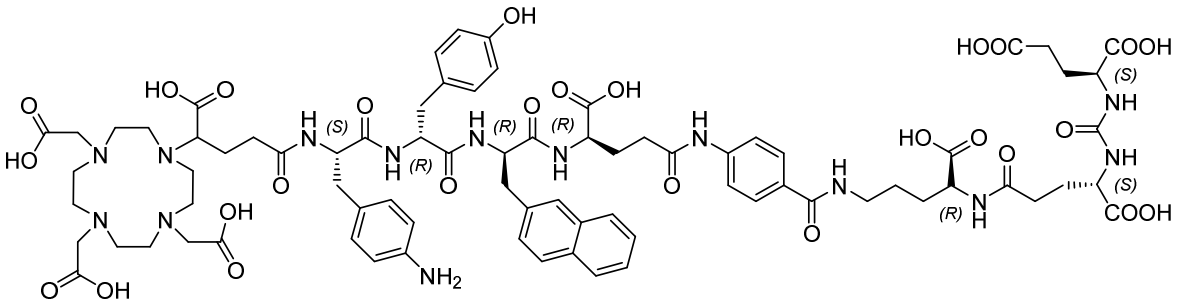
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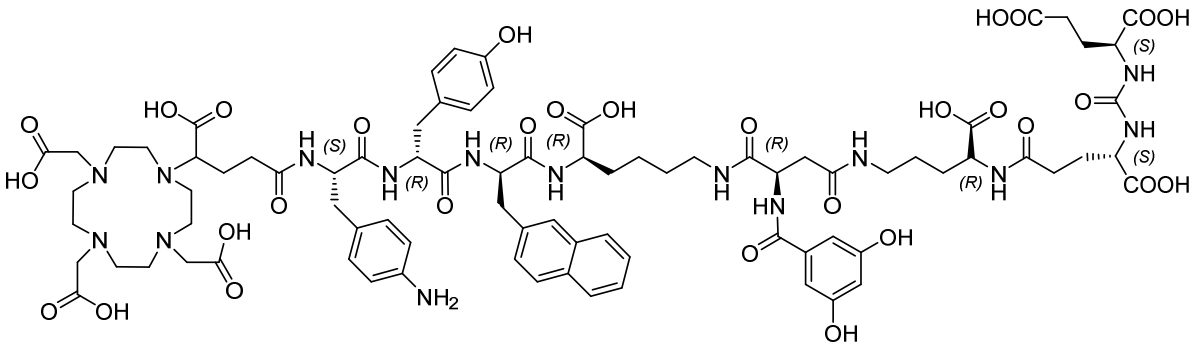
(Ip)



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(Is).

14. 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.

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

(a) cancer including prostate cancer; or

(b) neoangiogenesis/angiogenesis.

16. 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 and/or treating

(a) cancer including prostate cancer; or

(b) neoangiogenesis/angiogenesis.