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(54) **Title:** METHODS AND KITS FOR PREPARING RADIONUCLIDE COMPLEXES

(57) **Abstract:** A method for preparing a complex comprising a radioisotope of gallium for use in radiotherapy or in a medical imaging procedure, said method comprising adding a gallium radioisotope solution obtained directly from a gallium radionuclide generator to a composition comprising a pharmaceutically acceptable buffer and optionally also a pharmaceutically acceptable basic reagent, in amounts sufficient to increase the pH to a level in the range of 3 to 8, wherein the composition further comprises a chelator that is able to chelate radioactive gallium within said pH range and at moderate temperature, said chelator being optionally linked to a biological targeting agent.

### Methods and Kits for Preparing Radionuclide Complexes

The present invention relates to methods for preparing radioactive gallium complexes for use in therapy or diagnosis, for example in molecular imaging procedures, to kits for use in  
5 these methods, and to novel compositions used in them as well as to methods for molecular imaging and therapy carried out using the compositions or the kits.

### Background to the Invention

Molecular imaging is a well-known and useful technique for  
10 *in vivo* diagnostics. It may be used in a wide variety of methods including the three-dimensional mapping of molecular processes, such as gene expression, blood flow, physiological changes (pH, etc.), immune responses and cell trafficking. It can be used to detect and diagnose disease, select optimal  
15 treatments, and to monitor the effects of treatments to obtain an early readout of efficacy.

A number of distinct technologies can in principle be used for molecular imaging, including positron emission tomography (PET), single photon emission tomography (SPET), optical (O1)  
20 magnetic resonance imaging (MRI), X-ray Computed Tomography (CT) and Cerenkov luminescence imaging (CLI). Combinations of these modalities are emerging to provide improved clinical applications, e.g. PET/CT and SPET/CT ("multi-modal imaging").

Radionuclide imaging with PET and SPET has the advantage of  
25 extremely high sensitivity and small amounts of administered contrast agents (e.g. picomolar *in vivo*), which do not perturb the *in vivo* molecular processes. Moreover, the targeting principles for radionuclide imaging can be applied also in targeted delivery of radionuclide therapy. Typically the isotope  
30 that is used as a radionuclide in molecular imaging or therapy is incorporated into a molecule to produce a radiotracer that is pharmaceutically acceptable to the subject.

Most radiotracers have a relatively short half-life and so have to be produced *in situ*, for example in the radiopharmacy  
35 section of the relevant hospital, under sterile conditions. Some hospitals have difficulty with this if they do not have

specialist radiochemistry laboratories and therefore their ability to offer treatments such as PET may be restricted.

It may be difficult to prepare radiotracers with sensitive functional moieties. For example, incorporation of radioisotopes into the radiotracer may involve elevated temperatures that would disrupt protein structure and add undesirable complexity to the labelling process. It may be desirable to include sensitive functional moieties into radiotracers and so it is a need to provide radiotracers that may be prepared using mild conditions. Moreover it is desirable that labelling processes at the point of use are as simple as possible, with the minimum number of manipulations of radioactive materials, minimal need for costly equipment to perform the manipulations and the shortest possible time of preparation. As a result imaging conjugates with improved functionality and improved molecular imaging properties have been produced.

1,4,7, 10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) is a common chelator for gallium-68 (and other metallic radioisotopes such as Ga-67, In-111, Cu-64, Lu- 177, Y-90) used in molecular imaging and targeted radionuclide therapy. However, DOTA has a long radiolabelling time of around 30 to 60 minutes (relative to the half-life of <sup>68</sup>Ga ~ 68 minutes), which reduces the useful life of the tracer. In addition, chelation of gallium by DOTA derivatives often requires a high labelling temperature of around 95°C and acidic pH, which may be damaging to any biological targeting agent associated with the biotracer and adds complexity to the process.

WO2012/063028 describes a range of bifunctional molecules that are able to quickly chelate radionuclides at room temperature, whilst retaining stability towards dissociation in the biological milieu. In addition to the metal chelating portion, the bifunctional molecules have a reactive portion to couple the bifunctional molecule to a functional moiety, such as targeting group which can target, for example, cells, tissues or biological molecules in the body. They chelate at neutral pHs. Kits comprising these bifunctional molecules and radionuclides are also described.

However, a residual problem arises in relation to the radionuclides themselves. These are generally obtained by elution from generators. Many of these isotopes, such as  $^{68}\text{Ga}$  will only elute at low pH, for example at a pH of less than 2, such as about 1. At present, they require complex pretreatment procedures to raise the pH prior to or after addition to the chelator to produce a radiotracer. In particular, gallium is liable to precipitate out of solution at neutral to high pH and so requires particular handling. Typically, an eluate from a  $^{68}\text{Ga}$  generator for instance, is first subject to a purification step by passage through a cation exchange cartridge before it may be contacted with the chelator. In many cases, the labelling procedure is also complex. For example, it may be necessary to add buffer and acid with the chelating compound and then heat the mixture to relatively high temperatures, for example of  $100^{\circ}\text{C}$ , to achieve labelling. Then the product may require passing through further purification cartridges such as a SEP-Pak C-18 cartridge before being diluted in phosphate buffered saline (PBS) solution and passed through a sterile filter. All this requires complex and dedicated apparatus and the time taken erodes the useful life of the radionuclide.

WO2012/063028 describes that  $^{68}\text{Ga}$  eluate must be further acidified, and passed down an anion exchange column to concentrate it, before it is buffered and added to the bifunctional molecule to form the radiotracer. Such procedures require skilled staff and complex equipment which is not always available. They must be carried out in a strictly sterile environment. In addition,  $^{67}\text{Ga}$  radiolabelling was carried out by first reacting  $^{67}\text{Ga}$  citrate (which is of acidic pH), with the chelator complex followed by a subsequent buffering step, which again involves two steps.

So-called 'cold kits' have been produced previously for use with Technetium radiolabels. These are relatively simple to use and do not require significant handling of the radionuclide. However, in contrast to  $^{68}\text{Ga}$ , technetium is obtainable directly from a generator at close to neutral pH, typically of the order of from 4 to 8, and usually about 7.

The applicants have developed a method in which certain types of radionuclide chelator groups which may optionally be attached to targeting groups, can be formulated in a manner that allows them to be utilised directly with gallium solutions such as radionuclide eluates, in particular either those at low pH or neutral pH. As a result, the compositions can be used to provide robust, versatile and easy to use 'kits' that may be employed in clinical situations such as in hospitals.

#### 10 Summary of the Invention

According to a first aspect of the invention there is provided a method for preparing a complex comprising a radioisotope of gallium for use in radiotherapy or in a medical imaging procedure, said method comprising adding a gallium radioisotope solution obtained directly from a gallium generator to a composition comprising a pharmaceutically acceptable buffer and optionally also a pharmaceutically acceptable basic reagent, in amounts sufficient to increase the pH to a level in the range of 3 to 8, wherein the composition further comprises a chelator that is able to chelate radioactive gallium within said pH range and at moderate temperature, said chelator being optionally linked to a biological targeting agent.

The applicants have found that effective gallium radiolabelling may be achieved directly by contact with gallium solutions, in particular acidic solutions including the highly acidic eluates obtainable from  $^{68}\text{Ga}$  radionuclide generators which are generally at a pH of less than 2, for example at a pH of 1. No undue gallium precipitation occurs. As a result, gallium labelling procedures may be simplified by avoiding additional steps such as purification or concentration steps using ion exchange columns or membranes for example. In a particular embodiment, when the gallium radioisotope solution is  $^{68}\text{Ga}$  solution from a generator, there will be no need to subject it to an initial concentration step and no need to pass the solution through an ion exchange medium.

Suitable gallium-68 generators that may be used to supply the gallium radioisotope solution include Eckert & Ziegler's GalliaPharm 9, IRE-Elite Galli Eo™ and Parsisotope GalluGEN.

The method is also applicable to solutions of <sup>67</sup>Ga salts, such as gallium citrate, which may be produced from a cyclotron. The resultant radiolabelled product may be of sufficiently high purity that it may be used directly in medical procedures such as radiotherapy or molecular imaging. In this instance, the product of the cyclotron is 'a gallium radioisotope solution obtained directly from a gallium generator' as required by the method of the invention.

The acidic solution such as the eluate is added to a composition comprising both the pharmaceutically acceptable buffer and the chelator and also a pharmaceutically acceptable basic reagent if required or necessary. As used herein, the term 'basic reagent' refers to a compound that will produce a neutralising effect when contacted with an acidic material.

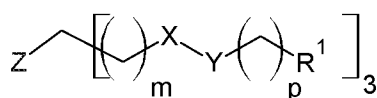
Thus, the chelator is present in the composition comprising the pharmaceutically acceptable buffer and the pharmaceutically acceptable basic reagent as a 'pre-mix'. This provides an efficient 'single step' procedure, in which the acidic gallium solution is added directly to the pre-mix composition so that the chelation and neutralisation occurs simultaneously.

The chelator for the radionuclide may be any chelator which is effective at moderate temperatures, for example from 10-30°C, and suitably at ambient temperature, and at moderate pHs, for example of from 3-8 and at low concentrations (for example from 1-10µM) and reaching acceptable yield in a short time (e.g. 1 - 5 minutes). In this instance, acceptable yields of complex would be at least 60%, for instance at least 70%, 80%, 90% or 95% of the administered radiolabel.

The chelation may be achieved at moderate temperatures and in particular at ambient temperature, so that heating steps or stages may be avoided, thus simplifying the procedure and ensuring that the radioactivity of the gallium remains at a good level. Versatile chelators of this type, which are effective at neutral pHs as well as at low pH, are known in the art.

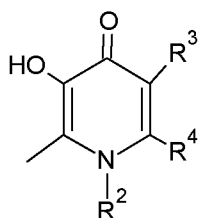
For example, suitable chelators include HBED, DFO, DTPA, DOTA, TRAP, NOTA, NOPO, NODAGA, MPO, 6SS, B6SS, PLED, TAME, NTP, and BAPEN.

In particular the radionuclide chelator is a compound of formula (I)

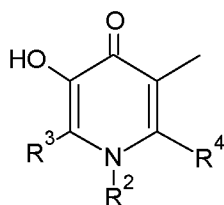


(I)

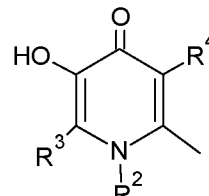
or a salt thereof; wherein one of X and Y is C=O and the other is NR; wherein each m and p are independently selected from 0 to 6; wherein R<sup>1</sup> is a chelating group capable of chelating a radionuclide and is selected from:



(i)

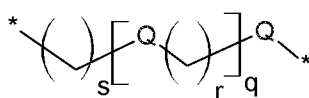


(ii)



(iii)

wherein R, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently hydrogen or an optionally substituted C<sub>1-7</sub>alkyl group; and where Z is hydrogen or a group of formula -B'-H, -B'-A, or a group -B'-A\*-T, where T is a targeting group capable of binding to a target of interest in a subject; A is a reactive group allowing coupling to the group T, A\* is a reacted reactive group A; B' is a linker group for linking the chelating group to a reactive group A, and is represented by the formula:



(iv)

wherein each Q is independently selected from a group consisting of -NR<sup>5</sup>-, -C(O)NR<sup>5</sup>-, -C(O)O-, -NR<sup>5</sup>C(O)NR<sup>5</sup>-, -NR<sup>5</sup>C(S)NR<sup>5</sup>- and -O-,

each R<sup>5</sup> is independently hydrogen or an optionally substituted C<sub>1-7</sub> alkyl group, each q and s are independently selected from 0 to 6 and each r is independently selected from 1 to 6.

Chelators of formula (I) are able to chelate radionuclides such as gallium radionuclides at a pH in the range of from 3 to 8 with a very high efficiency and at moderate temperature in a short time at low concentration. Chelators of this general type provide a useful advance over many of the previously known chelators, which only worked at low pH and therefore resulted in compositions which were not well suited to pharmaceutical application. By combining a chelator of this type with a neutralising alkaline salt and a buffer *ab initio*, in particular in a single unitary composition, the applicants have found that the composition may be used directly with gallium solutions having a range of acidic pHs, such as a solution of a <sup>67</sup>Ga salt, for instance <sup>67</sup>Ga citrate, obtainable from a cyclotron, as well as an eluate from a <sup>68</sup>Ga radionuclide generator, even when this is at low pH, for example of 2 or less, without requiring complex preparation or purification steps. This simplifies the production process and allows the possibility of forming 'cold kits' for use with specifically gallium radionuclides with minimal manipulation.

In a particular embodiment, the reagents used in the method (chelator, buffer and basic reagent) are in solid form, in particular in lyophilized or freeze-dried form. This allows them to form a stable mixture that may be stored or transported ready for use for generating radiotracers in situ. In one embodiment, the buffer and basic components are contained in one vessel or vial, to which an eluate from a gallium radionuclide generator may be added. The contents of this vial may then be simply added to a second vial or vessel containing the solid chelator. In another particular embodiment, all the reagents are combined in a single unitary composition. Suitably, the unitary composition is divided into units containing sufficient chelator for a single imaging operation. In this instance the generator may be eluted directly into the container such as the vial holding the unitary composition.



The amount of pharmaceutically acceptable buffer and, where necessary, any basic reagent, used in the method should be suitable for raising and maintaining the pH of the mixture formed on addition of the acidic gallium solution, such as the eluate from a  $^{68}\text{Ga}$  radionuclide generator to a pharmaceutically acceptable level, for example, in the range of from 3-8, for example from 4-7 such as from 5.5-7 and in particular from 6.5-7.5 or pH 6.0 to 7.0 on reconstitution, as well as maintaining a level at which the chelator will be effective to chelate a gallium radionuclide. The applicants have found that, under these circumstances, the activity of the chelator is not significantly reduced by direct exposure to low pHs. Furthermore, no unwanted precipitation of gallium occurs as a result of exposure to high pH, which is a problem that has been encountered previously in connection when handling specifically gallium solutions. Compositions in this pH range may be administered to patients directly without undue pain caused by high acidity.

The amount of chelator used in the method and so present in the composition will vary depending upon factors such as the precise nature of the chelator, the nature of the radionuclide to be chelated as well as the nature of the therapy or imaging process being undertaken. However, typically, the amount of chelator required in a composition for carrying out a single therapeutic treatment or imaging procedure is in the range of from 0.1-10 $\mu\text{moles}$ . In a liquid composition, for example, one produced for lyophilisation to form a solid composition or after reconstitution for administration, the concentration of the chelator is suitably in excess of 5 $\mu\text{M}$ , for example, from 10-100 $\mu\text{M}$ .

Suitable pharmaceutically acceptable buffers include inorganic and organic buffers. Examples of inorganic buffers include phosphate buffers, such as sodium phosphate, sodium phosphate dibasic, potassium phosphate and ammonium phosphate; bicarbonate or carbonate buffers; succinate buffers such as disodium succinate hexahydrate; borate buffers such as sodium borate; cacodylate buffers; citrate buffers such as sodium

citrate or potassium citrate; sodium chloride, zinc chloride or zwitterionic buffers. Examples of organic buffers include tris(hydroxymethyl)aminomethane (TRIS) buffers, such as Tris HCl, Tris EDTA, Tris Acetate, Tris phosphate or Tris glycine, 5 morpholine propanesulphonic acid (MOPS), and N-(2-hydroxyethyl) piperazine- N'(2-ethanesulfonic acid) (HEPES), dextrose, lactose, tartaric acid, arginine or acetate buffers such as ammonium, sodium or potassium acetate. In a particular embodiment, the buffer is other than an acetate buffer, and 10 other than a sodium acetate buffer.

Suitably the buffer is a phosphate buffer, such as sodium phosphate buffer. The buffer may comprise one or more phosphate salt, and in particular comprise a monobasic and dibasic sodium phosphate salt. For example, a suitable buffer comprises 15 sodium phosphate monobasic anhydrous and sodium phosphate dibasic heptahydrate in a ratio of about 1.5:1 to 2.5:1.

The total amount of buffer present will depend upon factors such as the particular nature of the buffer and the nature of the complex as well as the particular molecular imaging 20 procedure which is to be carried out. Typically however, the buffer is present in the dried composition in an amount of from 5 to 95 mole percent. Thus, in a liquid composition, for example, one produced for lyophilisation to form a solid composition or after reconstitution for administration, the concentration of 25 the buffer reagent is suitably in the range of from 0.01 to 0.6M, for example from 0.1 to 0.5M, for example at about 0.2M (20mM).

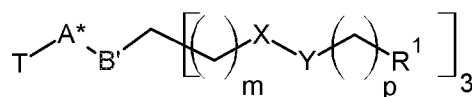
In some embodiments, it may not be necessary to include a pharmaceutically acceptable basic reagent, in particular where 30 the buffer is a particularly 'strong' buffer such as ammonium acetate. However, in a particular embodiment, a pharmaceutically acceptable basic reagent is added to the buffer to facilitate neutralisation of the eluate. Suitable pharmaceutically acceptable basic reagents include alkaline 35 salts such as hydroxides, carbonates, bicarbonates or oxides of alkali or alkaline earth metals, such as sodium, potassium, calcium or magnesium, or ammonium salts or basic organic

reagents. For example, suitable reagents may be selected from sodium hydroxide, potassium hydroxide, ammonium hydroxide, magnesium oxide, calcium carbonate, magnesium carbonate, magnesium aluminum silicates, sodium carbonate, sodium bicarbonate, triethanolamine, or any combination thereof. In particular, the pharmaceutically acceptable basic reagent is an alkali metal salt, such as an alkali metal hydroxide, in particular sodium or potassium hydroxide. In an alternative embodiment, the basic reagent is sodium bicarbonate.

The amount of pharmaceutically acceptable basic reagent present in the composition will vary depending upon factors such as the precise nature of the reagent, the intended use of the kit and thus the pH of the eluate of the particular radionuclide generator intended to be used with it. Typically however, the amount of such reagent in a composition for use in a single therapy or imaging operation is from 0.5-0.75mmoles. Thus, in a liquid composition, for example, one produced for lyophilisation to form a solid composition or after reconstitution for administration, the concentration of the basic reagent is suitably in the range of from 0.01 to 0.6M, for example from 0.1 to 0.15M.

In a particular embodiment, the chelator of formula (I) is, or has the capability of becoming linked to a targeting moiety T as defined above.

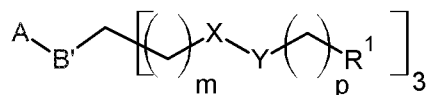
The complexes used in the compositions of the invention will suitably comprise a biological targeting agent that is bound to the chelator, in particular covalently as described above where the compound of formula (I) includes a group 'T', but otherwise, a biological targeting agent may be associated with the compound of formula (I) by other means, for example by conjugation. In particular the biological targeting agent is covalently bonded to the chelator and the chelator is a compound of formula (II) where Z is a group -B'-A\*-T:



(II)

or a salt thereof; wherein T, A\*, B', X, Y, R<sup>1</sup>, m and p are as defined above.

In another embodiment, the chelator is a compound which is capable of reacting a targeting group, and therefore is a  
5 compound of formula (III)



(III)

or a salt thereof; wherein T, A, B', X, Y, R<sup>1</sup>, m and p are as defined above.

10 Particularly preferred examples of compounds of formula (I) are described in WO2012/063028.

In a particular embodiment, R<sup>1</sup> is a group of sub-formula (i) or (ii) as described above, such as a group of sub-formula (i).

15 Suitably R<sup>3</sup> and R<sup>4</sup> are selected from hydrogen or lower C<sub>1-4</sub>alkyl groups such as methyl. In a particular embodiment R<sup>3</sup> is hydrogen. In another particular embodiment, R<sup>4</sup> is methyl.

In a particular embodiment, each X, Y, m, p, Q, s, r and q are similar.

20 In a particular embodiment, X is C(O) and Y is NR. Suitably R is hydrogen or C<sub>1-4</sub>alkyl and in particular is hydrogen.

In a particular embodiment, p is 1. In another particular embodiment, m is 2.

25 In a particular embodiment, q is 0.

Suitably, within the group B, Q is a group -C(O)NR<sup>5</sup>. In particular R<sup>5</sup> is selected from hydrogen and C<sub>1-4</sub>alkyl group, such as hydrogen.

Suitable biological targeting moieties T in formula (I) for  
30 use in the compositions of the invention will be groups which are capable of directing the molecules to different targets of interest in the biological system in question. Generally, these will therefore form a 'specific binding pair' with the target of interest, such that the targeting moiety T and the target of  
35 interest will have particular specificity for each other and

which in normal conditions bind to each other in preference to binding to other molecules. Examples of specific binding pairs are well known in the art and include for example receptors and ligands, enzymes and substrates, and immunoglobulins such as antibodies and antigens. Thus, targeting moieties T may be peptides, proteins or other biological molecules, such as aptamers, or small molecule ligands, that bind to specific in vivo molecular targets. Classes of targets of interest include ligands or receptors or transporters expressed on diseased cells or tissue, cell surface antigen associated with disease states, or tumour markers, e.g. cancer specific markers or tissue specific markers.

In a particular embodiment, the targeting moiety T is a ligand that targets a cancer specific marker such as prostate specific membrane antigen (PSMA). Such ligands include DKFZ-PSMA-11 (Eder M. et al., *Bioconjugate Chem.* 2012, 688).

Alternatively, the targeting moiety T may comprise an antibody such as an anti-CD33 antibody, or binding fragment thereof, for imaging cancer cells expressing CD33 such as cells of myelomonocytic lineage and leukaemic cells, (see Emberson et al., *J. Immunol. Methods.* 305 (2 ): 135-51, 2005) or antibodies capable of binding to the glycoprotein carcinoembryonic antigen (CEA) as members of this family of glycoproteins are expressed on colorectal cancer cells, gastric cancer cells, pancreatic cancer cells, lung cancer cells, medullary thyroid cancer cells and breast cancer cells, as well as anti-PSMA antibodies and binding fragments thereof. Other suitable antibodies may show affinity to cell adhesion molecules. These include the monoclonal antibody, SER 4, which binds to the macrophage adhesion molecule, sialoadhesin. Sialoadhesin is found on the surface of macrophages, and, for example, in high amounts on macrophages of the spleen, liver, lymph node, bone marrow colon and lungs.

A further example of the suitable T groups are tissue inhibitors of metalloproteinases (TIMPs) , such as TIMP-2, which allow for imaging matrix metalloproteinase expression, as expression of metalloproteinases has been implicated in

metastatic processes, (see Giersing et al., Bioconjug Chem. 12(6): 964-71, 2001). In yet a further embodiment, the targeting moiety T may be a polypeptide such as complement receptor 2 (CR2). Yet a further example may exploit the  
5 affinity or the peptide sequence arginine-glycine-aspartic acid (RGD) for the  $[\alpha][\nu][\beta]3$  integrin expressed highly in the endothelium of tissues undergoing angiogenesis as is commonly seen in tumours, atherosclerotic plaque and repairing diseased tissue such as infarcted myocardium, by linking an RGD  
10 peptide derivative to the bifunctional compound by means of a suitable reactive group A. Other T groups may comprise the peptide octreotide or related analogues of somatostatin that have affinity to the somatostatin receptor expressed highly at the surface of cancer cells e.g. in carcinoid, medullary thyroid  
15 carcinoma and other neuroendocrine tumours.

In another embodiment, the targeting groups T are polypeptides capable of binding to phosphatidylserine (PS) so that the resultant complex can be employed in apoptosis or cell death imaging studies. Examples of such polypeptides include  
20 Annexin V and the C2 domain of a synaptotagmin. Polypeptides that comprise one or more C2 domains are well known in the art. While some polypeptides have only one C2 domain, others have two or more C2 domains, and the domains are generally described by attaching a letter (in alphabetical order) to the end of the  
25 name (e.g., C2A, C2B, and so on). For a protein that contains only one C2 domain, the domain is simply referred to as C2 domain. Particular examples include the C2A domain of rat synaptotagmin I or a C2A domain of a synaptotagmin of another species. Further examples of proteins that contain a C2 domain  
30 include but are not limited to synaptotagmin 1-13, protein kinase C family members of serine/threonine kinases, phospholipase A2, phospholipase 51, cofactors in the coagulation cascade including factors V and VIII, and members of the copine family. Human synaptotagmins include synaptotagmin 1-7, 12 and  
35 13.

Other suitable targeting moieties T are bombesin, gastrin, or VCAM targeting peptide.

The targeting moieties T are linked to a chelator molecule to form the compound of formula (I) by means of a suitable linker group A\*. The nature of the linker group A\* will depend upon the nature of the targeting moiety T and will be determined using conventional chemistry.

Alternatively, they may comprise calcium chelating groups such as bisphosphonate derivatives, which target bones and in particular bone cancers.

In an alternative embodiment, the chelator may not include a targeting group, but act simply as a metal chelator, for general radiochemical monitoring, such as in monitoring of renal function.

Typically the linker group A\* is formed from a reactive group A which, in a particular embodiment is a protein-reactive functional group. The protein reactive group may react with proteins or modified proteins or peptides or other vehicles derivatised for the purpose. Preferably the protein-reactive group A is or comprises a maleimide group, an isothiocyanate group such as an alkyl or arylisothiocyanate, an aldehyde, an ester, or "click" reagent such as an alkyne, azide, alkene, hydrazine, hydrazine derivative, alkoxyamine, alkoxyamine derivative, aminoxy, thiol group. Maleimide, isothiocyanate, aldehyde and ester groups efficiently react with peptide thiol- or amine-containing residues (cysteine, lysine) and so a conjugate can easily form. Other bioorthogonal functional groups can be engineered into peptides and proteins for the purpose of conjugating them with alkyne, azide, alkene, hydrazine, aminoxy or thiol groups.

As used herein, the term 'alkyl' refers to straight or branched groups, which unless otherwise specified, contain from 1-10 and suitably from 1-7 carbon atoms. The term 'aryl' refers to aromatic groups which comprise for example phenyl groups, optionally linked to alkyl groups.

Compounds of formula (I) may be prepared using methods described in WO2012/063028.

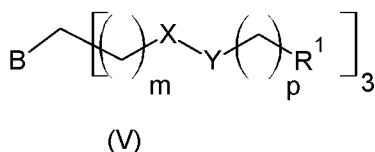
For example, a compound of formula (II) above is, in general terms, obtainable by linking a group A to either a

targeting moiety T or a chelator molecule, and then connected to the other of these. Thus for example, they may be obtained by reacting a compound of formula (III) above, which is reacted with a compound of formula (IV)



Where T is as defined above. Suitable reaction conditions will depend upon factors such as the precise nature of the groups A, T etc. and will be determinable to a skilled chemist.

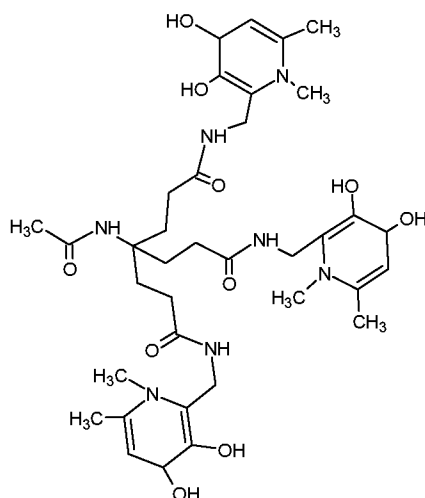
10 Compounds of formula (III) will themselves be produced by coupling a compound of formula (V)



with a reactive group such as a maleimide group, for example as shown in Example 5 of WO2012/063028.

15 A particular compound of formula (V) where B is a group  $\text{H}_2\text{N}(\text{CH}_2)_2\text{C}(\text{O})\text{NH}$  is shown in Zhou T et al. J. Med Chem. 2006, 49, 4171-4182 (see compound (1) in scheme below). The compound is a derivative of the tris(hydroxypyridinone chelator CP256 (which may also be known as THP) which is of formula

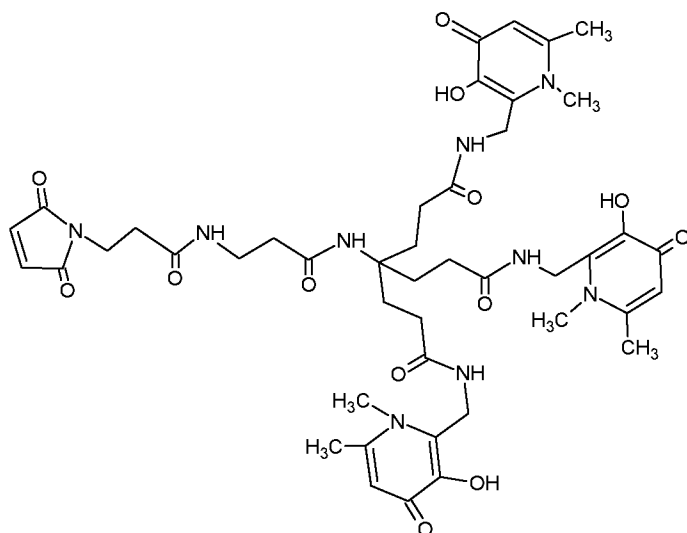
20



CP256.

This may be derivatised as described in WO2012/063028 to form a compound of formula (III) above where A is a maleimide group. Thus a particular compound of formula (III) is of  
 25 formula YM103 as follows:

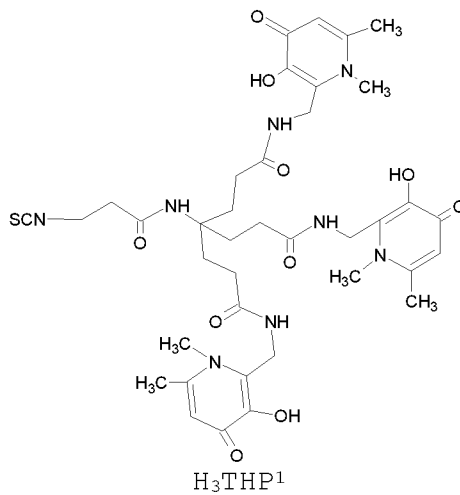


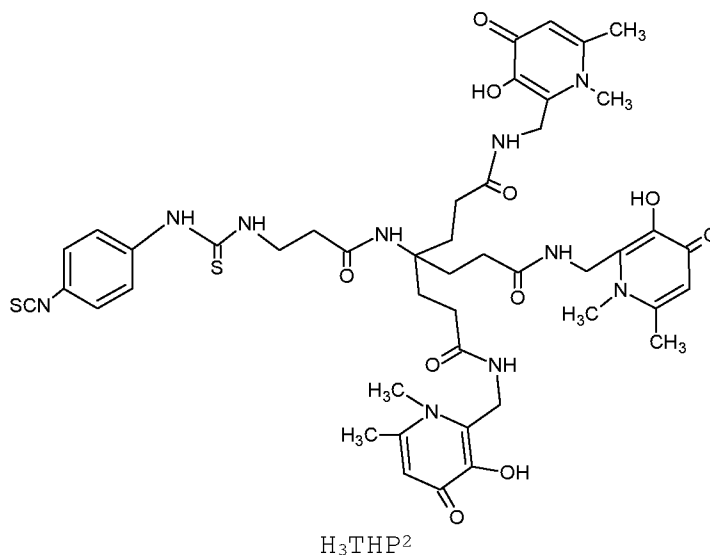


of a salt thereof.

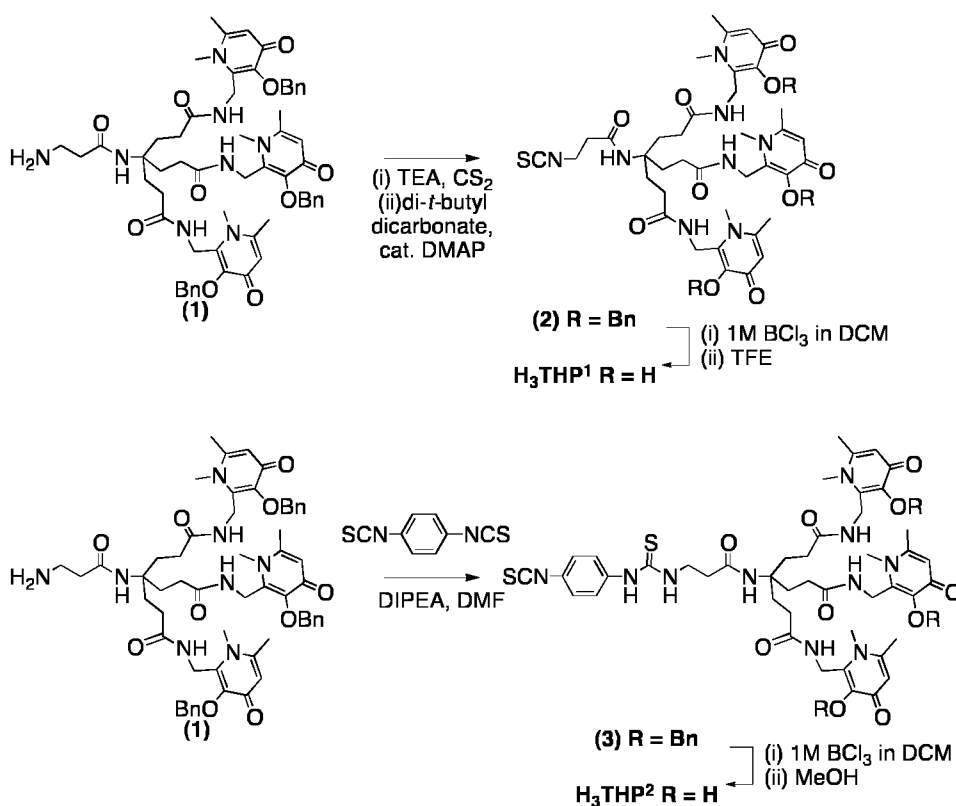
An alternative compound of formula III are compounds of formula (I) where A comprises an isothiocyanate group, which is  
5 able to conjugate to primary amines.

Examples of such compounds include compounds of formula designated H<sub>3</sub>THP<sup>1</sup> and H<sub>3</sub>THP<sup>2</sup> or salts thereof.





These compounds may be prepared using methods analogous to those described in WO2012/063028 for example as set out in the following reaction schemes:



In the above scheme, compound (1) as described in Zhou et al. (supra.) is reacted with triethylamine and carbon disulfide in ethanol, to give a precipitated dithiocarbamate intermediate upon addition of water (Munch et al. Tetrahedron Letters (2008), 49, 3117). The precipitated intermediate is re-suspended in a

solution of carbon disulfide/ethanol and addition of di-*tert*-butyl dicarbonate and a catalytic amount of 4-dimethylaminopyridine resulted in formation of (2). Subsequent removal of the benzyl groups with BCl<sub>3</sub> in DCM, followed by  
5 addition of trifluoroethanol results in H<sub>3</sub>THP<sup>1</sup>, which is purified using reverse phase semi-preparative HPLC to give the product as a trifluoroacetate salt.

To synthesize H<sub>3</sub>THP<sup>2</sup>, an excess of *p*-phenylene diisothiocyanate and diisopropylethylamine in DMF are added to a  
10 solution of (1), followed by isolation of (3) using reverse semi-preparative HPLC. Similar to (2), the benzyl groups of (3) are removed using BCl<sub>3</sub> in DCM, followed by addition of methanol, resulting in a chloride salt of bifunctional chelator H<sub>3</sub>THP<sup>2</sup>.

Suitable salts are pharmaceutically acceptable salts  
15 such as halide salts and in particular chlorides. Such compounds have been found to give rise fast radiolabelling (<5 minutes) with <sup>68</sup>Ga, at room temperature and physiological pH. Such pHs can be achieved in the compositions of the invention using material direct from the <sup>68</sup>Ga generator.

The compositions of the invention may comprise further  
20 excipients or pharmaceutically acceptable carriers or fillers as would be understood in the art, as well as reagents such as stabilisers, antimicrobial agents, cryoprotectants, antioxidants, free radical scavengers, solubilizing agents,  
25 tonicifying agents, surfactants and collapse temperature modifiers, used in lyophilisation.

Suitable fillers for use in the formulations include for  
example, sugars such as mannitol, lactose, sucrose, trehalose, sorbitol, glucose, or raffinose, or amino acids such as  
30 arginine, glycine or histidine, as well as polymers such as dextran or polyethylene glycol (PEG).

Suitable free radical scavengers are those which protect  
against autoradiolysis, such as ascorbic acid or gentisic acid. The amount of free radical scavenger which may be added to the  
35 composition will depend upon factors such as the nature of the scavenger used and the nature of the composition. In a typical

embodiment, a kit may contain from 1-4%w/w free radical scavenger.

Tonicifying agents may be selected for example from sodium chloride, sucrose, mannitol or dextrose.

5 Antimicrobial agents may be selected from benzyl alcohol, phenol, m-cresol, methyl paraben or ethyl paraben.

Surfactants may include polysorbate such as polysorbate 80.

Collapse temperature modifiers may be selected for example, from dextran, hydroxyethylstarch, Ficoll or Gelatin.

10 In a particular embodiment, the compositions do not include agents which may inhibit metals other than gallium as described in Belgium Patent No.1021191, WO2016030103 or WO2016030104. Such agents are sugars such as monosaccharides, disaccharides or polysaccharides as well as derivatives thereof. Particular  
15 examples are glucose, fructose,  $\beta$ -cyclodextrin, mannose and fucoidan. The applicants have found that such agents are not required in the compositions of the invention.

These compositions may be formed into kits for use in a medical imaging procedure and such kits form a further aspect of  
20 the invention. Thus the invention further provides a kit for use in a method as described above, said kit comprising a composition comprising a pharmaceutically acceptable buffer and optionally also a pharmaceutically acceptable basic reagent, and a chelator that is able to chelate radioactive gallium within a  
25 pH range of from 3 to 8 and at moderate temperature, said chelator being optionally linked to a biological targeting agent. The chelator is in admixture with the buffer composition in the kit. Although they may be provided in the form of solutions, in particular sterile solutions, the components of  
30 the kit are suitably in a solid form in particular in lyophilized or freeze-dried form. Each kit suitably comprises sufficient reagents to carry out one or more molecular imaging procedures held within a container. The container is a sterile sealed container and may be filled with an inert atmosphere such  
35 as nitrogen gas. Such kits may further comprise elements such as instructions and outer packaging and may be supplied to

hospitals or clinics for reconstitution in situ, using a supply of gallium radiolabels present in appropriate generators.

Certain compositions used in these kits are novel and these form a further aspect of the invention. Thus the invention  
5 further provides a unitary composition for use in a method described above, said composition comprising (i) a chelator which is able to chelate with a gallium radionuclide at pH 3 to 8 and at moderate temperature, optionally linked to a biological targeting agent, (ii) a pharmaceutically acceptable buffer and  
10 optionally also (iii) a pharmaceutically acceptable basic reagent, wherein (ii) and optionally (iii) are present in the composition in amounts sufficient to result in a pH of from 3 to 8 where eluate directly from a gallium generator is added to the composition.

15 In particular, the gallium radionuclide chelator is a compound of formula (I) as described above. The composition may be in solution, for example in sterile solution, but is suitably in solid form, for example in lyophilized or freeze-dried form.

The composition of the invention is one which, in solution,  
20 has pH in the range of from 3 to 8 after addition of acidic gallium solution obtained directly from a gallium generator. It suitably includes a pharmaceutically acceptable buffer as described above, and also a pharmaceutically acceptable basic reagent, also as described above.

25 In a further aspect, the invention provides a process for producing a composition of the invention as described above, said method comprising mixing a chelator as defined above with a suitable amount of a pharmaceutically acceptable basic buffer and optionally also a pharmaceutically acceptable basic reagent  
30 and optionally lyophilising the resultant mixture.

In a particular embodiment, the compositions are prepared by mixing together components as described above in aqueous solution. The solution will suitably comprise the chelator of formula (I) in a concentration in excess of 5 $\mu$ M for example from  
35 10-100 $\mu$ M, a base in a concentration from 0.1-0.6M and a buffer in a concentration of from 0.01-0.6M, together with fillers and other excipients as described above as required. Thereafter,

the composition is suitably subjected to a lyophilisation procedure as would be understood in the art, to produce a dried composition.

The amount of composition subjected to the lyophilisation procedure may be sufficient to produce sufficient for a one or two therapeutic or imaging operation. In such cases, it may be preferable to lyophilise the composition in vials, in particular glass vials. Alternatively, where larger volumes of composition are subjected to drying, the dried composition may be subsequently divided into individual dosage units.

Once produced in this way, the composition may be packaged and stored for distribution, ready for reconstitution with an acidic gallium solution, such as a  $^{68}\text{Ga}$  eluate from a radiolabel generator, in situ.

In such generators,  $^{68}\text{Ga}$  radionuclide is supplied on a column which is eluted with an acid, in particular an inorganic acid such as hydrochloric acid, at concentrations of from 0.05M-1M, for example from 0.05 to 0.6M HCl, in particular at about 0.1M HCl, to obtain the  $^{68}\text{Ga}$  radionuclide for use in an imaging procedure.

$^{67}\text{Ga}$  radionuclides, which may be used in molecular imaging or therapy, are generally prepared in a cyclotron procedure, and supplied in the form of an acid salt such as  $^{67}\text{Ga}$  citrate. Solutions produced may be used as the acidic gallium solution in the method of the invention.

In accordance with the invention, the product obtained is directly useable in a physiological procedure such as imaging procedure or therapy since the pH of the eluate is adjusted upwards by the presence of the base and buffer at the same time as the labelling process, in which the radionuclide becomes chelated. The process is rapid and easy to operate with few handling steps. This ensures that the reagent has a good useful life before the half-life of the radionuclide is eroded, with minimal radiation exposure to operators, minimal opportunity for microbial contamination, and minimal requirement for complex and costly equipment.

The amount of eluate that will be added to the reagents will vary depending upon factors such as the precise nature of the eluate and the composition, the required amount of reagent required for the imaging procedure, the size and nature of the patient to whom the composition is to be administered. However, typically, about 3-7ml for example about 5ml eluate will be added to produce a suitable dosage unit.

If required, a dried composition of the invention may be rehydrated with sterile water or saline, before addition of eluate, but in a particular embodiment, the eluate is added directly to the dried reagents.

In a further aspect, the invention provides a radiolabelled product obtained by a method as described above for use in a molecular imaging or radionuclide therapy procedure. Suitable molecular imaging procedures are well known in the art and include PET and SPECT procedures as well as X-ray Computed Tomography (CT) and Cerenkov luminescence imaging (CLI).

Thus in a further aspect, the invention provides a method for obtaining a molecular image of a patient, said method comprising carrying out a process to generate a radiolabelled product as described above, administering the product into patient in need thereof and monitoring the results using a molecular imaging technique.

Yet a further aspect provides a method for treating a patient with a radionuclide, said method comprising carrying out a process to generate a  $^{67}\text{Ga}$  radiolabelled product as described above, and administering the product into patient in need thereof.

The amount of radiolabelled product administered will vary depending upon factors such as the nature of the patient and the organ or tissue targeted by the targeting moiety in the composition, the nature of the radiolabel and the particular imaging technique or therapy employed. The precise amount administered will be determined in accordance with usual clinical practice.

Thus the invention provides effective 'cold kits' for use in a range of clinical situations where gallium and in

particular  $^{68}\text{Ga}$  is utilised. Physiologically acceptable products may be generated rapidly and easily at room temperature, and so the available half-life of the radiolabel is maximised. The level of labelling (radiochemical purity) using such chelators and in particular, compounds of formula (I) is particularly effective, typically in excess of 95% and therefore, significant purification procedures may be avoided.

The invention will now be particularly described by way of Example with reference to the accompanying figures in which:  
Figure 1 is a graph showing the results of a comparison of chelation efficiency of a range of chelators using the method of the invention.

However, it will be apparent to one skilled in the art that the specific details are not required in order to practice the invention. The following descriptions of specific embodiments of the present invention are presented for purposes of illustration and description. They are not intended to be exhaustive of or to limit the invention to the precise forms disclosed. Many modifications and variations are possible in view of the above teachings. The embodiments are shown and described in order to best explain the principles of the invention and its practical applications, to thereby enable others skilled in the art to best utilize the invention and various embodiments with various modifications as are suited to the particular use contemplated.

#### Example 1

##### Preparation of $^{68}\text{Ga}$ labelled reagent

A range of compositions comprising the chelator CP256 were prepared containing various concentrations of pharmaceutically acceptable buffer (sodium phosphate buffer) and pharmaceutically acceptable basic reagent (sodium hydroxide) as set out in Table 1 below. The mixtures were lyophilised under vacuum overnight.

An Eckert and Zeigler  $^{68}\text{Ga}$  generator was eluted with 0.1M HCl, to produce 5ml eluents of 300MBq per elution. Portions (1ml) of the eluent were added each of the compositions at room temperature.

The pH of the resultant solutions was measured. The %



radiolabelling of the CP256 (THP) was investigated using TLC. The results are also shown in Table 1 below.

Table 1

Reagent (amounts)			pH	Radiolabelling % TLC
CP256 (nmoles)	NaOH (mmoles)	Phosphate buffer (mmoles)		
13.5	0.15	0.10	7	>47
13.5	0.10	0.10	7	>74
13.5	0.15	0.25	7	>76
13.5	0.00	0.50	4	>85
13.5	0.10	0.25	7	>89
13.5	0.05	0.25	5-6	>90
13.5	0	0.25	4	>90
13.5	0.05	0.10	5-6	>90
13.5	0	0.10	3-4	>90

The results show that radiolabelled CP256 was obtained with high levels of efficiency in 2 minutes. The high level of purity in some instances would mean that there is no need to further purify the gallium before administration to patients.

#### Example 2

##### Preparation of <sup>68</sup>Ga labelled reagent

The methodology of Example 1 was repeated using a range of formulations comprising 0.13M sodium bicarbonate, 0.1M phosphate buffer (PBS) and a range of CP256 concentrations as listed in the following Table. Highly efficient labelling was achieved in relation to the concentration of the chelator as illustrated in Tables 2 and 2a.

Table 2

CP256 (THP)		
Concentration $\mu$ M	% Labelling	Standard Dev
1000	97.55	1.45
100	95.76	4.84
10	91.52	2.36
1	62.62	7.99
0.1	31.29	4.47
0.001	0.00	1.63

Table 2A

CP256 (THP)		
Concentration	% Labelling	Standard Dev
1 mM	97	0.15
500µM	9695.76	1.42
50 µM	9791.52	0.97
5 µM	9762.62	0.06
500nM	981.29	0.14
50nM	150.00	3.10

### Example 3

#### Comparison of radiolabelling using different chelators

5 The method of Example 1 was repeated using a range of different chelators (DOTA, NOTA, TRAP, NOTP, HBED, DFO and THP) at various concentrations. The amounts of phosphate buffer and sodium hydroxide was adjusted to provide a pH of either 4 or 7 on addition of the 0.1M eluate. Solutions were incubated at room  
10 temperature for 10 minutes.

The results at pH 7 are shown in Figure 1. Acceptable labelling efficiencies in excess of 95% were only found with with THP and DFO. All other chelators did not label >95% at pH 7.0. In addition the concentration of most the other chelators  
15 had to be quite high to achieve > 90% labelling

### Example 4

#### Lyophilised kit

A vial comprising a lyophilised reagent mixture, prepared  
20 as described above and comprising CP256(THP)(40µg) linked to a PSMA targeting agent (30 nmoles), sodium bicarbonate (42mg), sodium phosphate monobasic anhydrous (8.2mg) and sodium phosphate dibasic heptahydrate (8.5mg) is prepared. It could be reconstituted using a 0.1M HCl eluate (5ml) obtained from an  
25 Eckert and Zeigler <sup>68</sup>Ga generator to produce a solution of pH 6.5 to 7.0, which may be used in therapy or in molecular imaging.

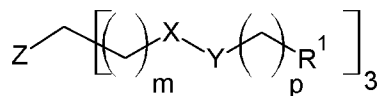
Example 5Alternative Lyophilised kit

A vial comprising a lyophilised reagent mixture as described in Example 4 but also containing from 1 to 2 mg  
5 ascorbic acid may also be prepared. This kit also can be reconstituted using a 0.1M HCl eluate (5ml) obtained from an Eckert and Zeigler <sup>68</sup>Ga generator to produce a solution of pH 6.5 to 7.0, which may be used in therapy or in molecular imaging.

## Claims

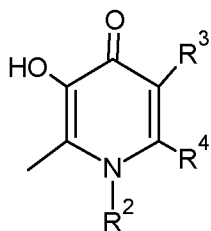
1. A method for preparing a complex comprising a radioisotope  
5 of gallium for use in radiotherapy or in a medical imaging  
procedure, said method comprising adding a gallium radioisotope  
solution obtained directly from a gallium radionuclide generator  
to a composition comprising a pharmaceutically acceptable buffer  
and optionally also a pharmaceutically acceptable basic reagent,  
10 in amounts sufficient to increase the pH to a level in the range  
of 3 to 8, wherein the composition further comprises a chelator  
that is able to chelate radioactive gallium within said pH range  
and at moderate temperature, said chelator being optionally  
linked to a biological targeting agent.
- 15
2. A method according to claim 1 wherein the gallium solution  
is an eluate obtained directly from a gallium-68 radionuclide  
generator.
- 20
3. A method according to claim 2 wherein the eluate is at a pH  
of less than 2.
4. A method according to any one of the preceding claims  
wherein the composition comprises a pharmaceutically acceptable  
25 basic reagent.
5. A method according to claim 4 wherein the pharmaceutically  
acceptable basic reagent is selected from an alkali metal  
hydroxide, carbonate or bicarbonate, in particular sodium or  
30 potassium hydroxide, carbonate or bicarbonate.
6. A method according to any one of the preceding claims  
wherein the chelator is linked to a biological targeting agent.

7. A method according to any one of the preceding claims wherein the chelator is a compound of formula (I)

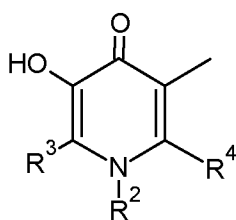


(I)

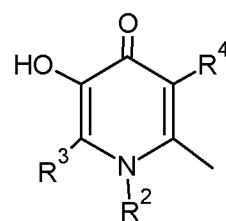
5 or a salt thereof; wherein one of X and Y is C=O and the other is NR; wherein each m and p are independently selected from 0 to 6; wherein R<sup>1</sup> is a chelating group capable of chelating a radionuclide and is selected from:



(i)



(ii)



(iii)

10

wherein R, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently hydrogen or an optionally substituted C<sub>1-7</sub>alkyl group; and where Z is hydrogen or a group of formula -B'-H, -B'-A, or a group -B'-A\*-T, where

15

T is a targeting group capable of binding to a target of interest in a subject;

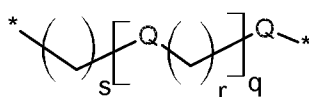
A is a reactive group allowing coupling to the group T,

A\* is a reacted reactive group A;

B' is a linker group for linking the chelating group to a

20

reactive group A, and is represented by the formula:



(iv)

25 wherein each Q is independently selected from a group consisting of -NR<sup>5</sup>-, -C(O)NR<sup>5</sup>-, -C(O)O-, -NR<sup>5</sup>C(O)NR<sup>5</sup>-, -NR<sup>5</sup>C(S)NR<sup>5</sup>- and -O-, each R<sup>5</sup> is independently hydrogen or an optionally substituted C<sub>1-7</sub> alkyl group, each q and s are independently selected from 0 to 6 and each r is independently selected from 1 to 6.

8. A method according to claim 7 wherein in the compound of formula (I), R<sup>1</sup> is a group (iii) as defined in claim 7.

5 9. A method according to claim 7 or claim 8 wherein the compound of formula (I) is a compound of formula (II) or a salt thereof



(I)

10 wherein T, A\*, B, X, Y, R<sup>1</sup>, m and p are as defined in claim 7.

10. A method according to claim 9 wherein the group A\* is a maleimide group or comprises an isothiocyanate group.

15 11. A method according to any one of the preceding claims wherein the pharmaceutically acceptable buffer is a phosphate buffer, bicarbonate or carbonate buffer, succinate buffer, borate buffer, cacodylate buffer, citrate buffer, sodium chloride, zinc chloride, a zwitterionic buffer, a  
 20 tris(hydroxymethyl)aminomethane (TRIS) buffer, morpholine propanesulphonic acid (MOPS), N-(2-hydroxyethyl) piperazine-N'(2-ethanesulfonic acid) (HEPES), dextrose, lactose, tartaric acid, arginine or an acetate buffer.

25 12. A method according to any one of the preceding claims wherein the chelator comprises a biological targeting agent, such as a ligand that targets a cancer specific marker.

30 13. A method according to claim 12 wherein the biological targeting agent is specific for prostate specific membrane antigen (PSMA).

35 14. A method according to any one of the preceding claims wherein the acidic gallium solution is obtained by eluting a <sup>68</sup>Ga radionuclide column with an inorganic acid.

15. A method according to claim 14 wherein the inorganic acid is hydrochloric acid.
- 5 16. A kit for use in a method according to any one of the preceding claims, said kit comprising a composition comprising a pharmaceutically acceptable buffer, a chelator that is able to chelate radioactive gallium within a pH range of from 3 to 8 and at moderate temperature, said chelator being optionally linked  
10 to a biological targeting agent and optionally also a pharmaceutically acceptable basic reagent, wherein the composition produces a solution having a pH in the range of from 3 to 8 when a solution obtained directly from a gallium radionuclide generator is added thereto.
- 15 17. A kit according to claim 16 wherein the composition is in liquid form.
18. A kit according to claim 16 wherein components of the kit  
20 are in lyophilized or freeze-dried form.
19. A kit according to any one of claims 16 to 18 wherein components are present in an amount sufficient to carry out a one or more therapeutic or molecular imaging procedures and are  
25 held within a container.
20. A kit according to any one of claims 16 to 19 wherein the chelator is a compound as defined in any one of claims 7 to 9.
- 30 21. A unitary composition for use in a method according to any one of claims 1 to 15, said composition comprising (i) a chelator which is able to chelate with a gallium radionuclide at pH 3 to 8 and at moderate temperature, optionally linked to a biological targeting agent, (ii) a pharmaceutically acceptable  
35 buffer and optionally also (iii) a pharmaceutically acceptable basic reagent, wherein (ii) and (iii) are present in the composition in amounts sufficient to result in a pH in the range

of from 3 to 8 when a solution obtained directly from a gallium radionuclide generator is added thereto.

22. A composition according to claim 21 wherein the gallium  
5 radionuclide chelator is a compound of formula (I) as defined in any one of claims 7 to 10.

23. A composition according to claim 21 or claim 22 which is lyophilized or freeze-dried form.

10

24. A composition according to any one of claims 21 to 23 which, in solution, has pH the range of from 3.0 to 8.

25. A composition according to any one of claims 21 to 24 which  
15 includes a pharmaceutically acceptable basic reagent.

26. A composition according to claim 25 wherein the pharmaceutically acceptable basic reagent is selected from an alkali metal hydroxide, in particular sodium or potassium  
20 hydroxide.

27. A composition according to any one of claims 21 to 26 wherein the pharmaceutically acceptable buffer is a phosphate buffer, bicarbonate or carbonate buffer, succinate buffer,  
25 borate buffer, cacodylate buffer, citrate buffer, sodium chloride, zinc chloride, a zwitterionic buffer, a tris(hydroxymethyl)aminomethane (TRIS) buffer, morpholine propanesulphonic acid (MOPS), N-(2-hydroxyethyl) piperazine-N'(2-ethanesulfonic acid) (HEPES), dextrose, lactose, tartaric  
30 acid, arginine or an acetate buffer.

28. A composition according to any one of claims 21 to 27 wherein the biological targeting agent is a ligand that targets a cancer specific marker.

35



29. A composition according to claim 28 wherein the biological targeting agent is specific for prostate specific membrane antigen (PSMA).

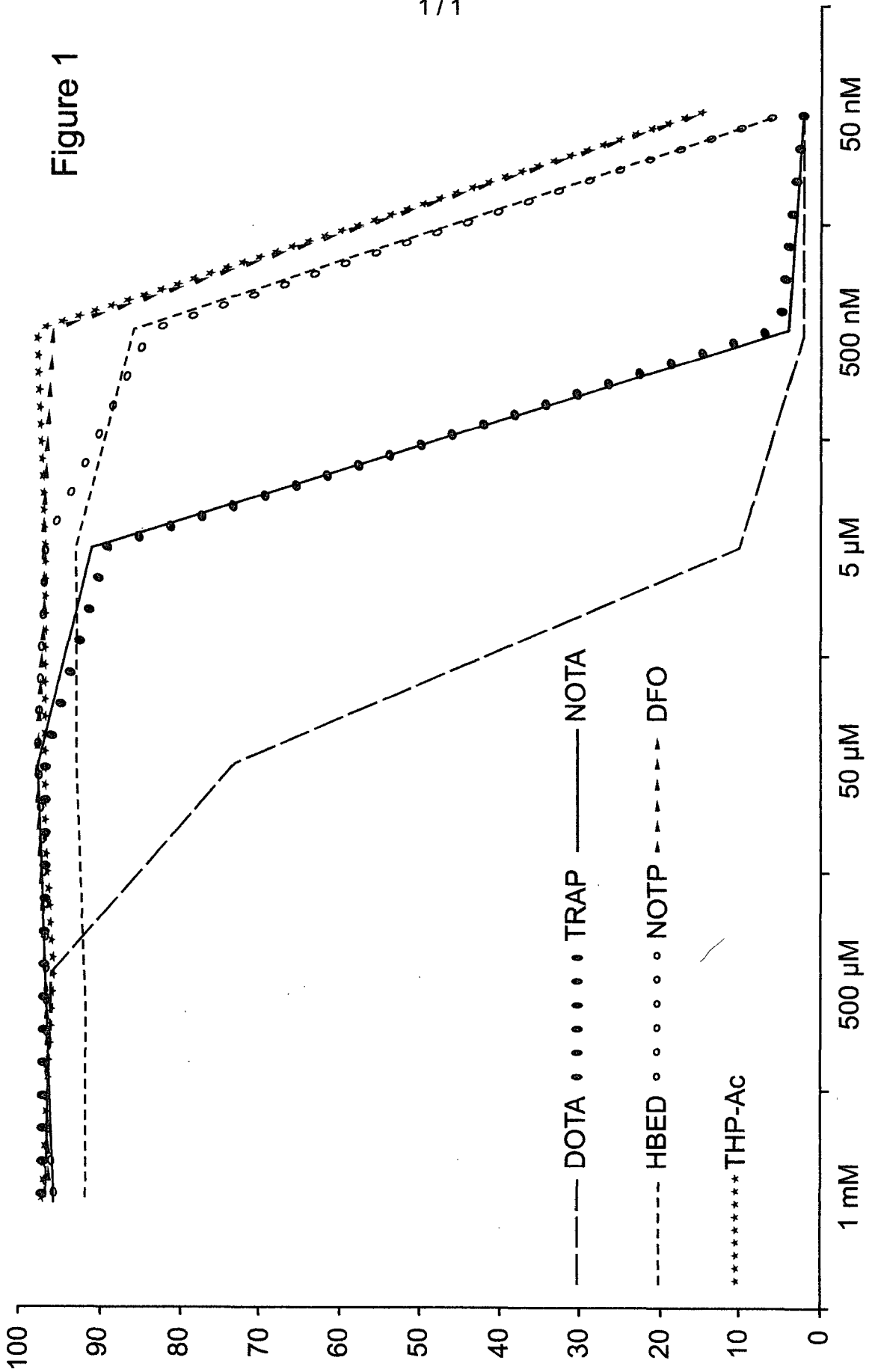
5 30. A composition according to any one of claims 21 to 28 which further comprises a free-radical scavenger.

10 31. A process for producing a composition according to any one of claims 21 to 30, said method comprising mixing a chelator as defined in claim 21 with a suitable amount of a pharmaceutically acceptable basic buffer and optionally also a pharmaceutically acceptable basic reagent and optionally lyophilising the resultant mixture.

15 32. A product obtained by a method according to any one of claims 1 to 15 for use in a molecular imaging procedure or in therapy.

20 33. A method for obtaining a molecular image of a patient, said method comprising administering to a patient a product according to claim 32 and monitoring the results using a molecular imaging technique.

25 34. A method for treating a patient with  $^{67}\text{Ga}$  radionuclide, said method comprising administering to a patient in need thereof, an effective amount of a product obtained used a method according to claim 31 wherein the gallium radionuclide is  $^{67}\text{Ga}$ .



INTERNATIONAL SEARCH REPORT

International application No  
PCT/GB2016/050637

A. CLASSIFICATION OF SUBJECT MATTER  
INV. C07B59/00  
ADD.  
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED  
Minimum documentation searched (classification system followed by classification symbols)  
C07B  
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/024013 A2 (ADVANCED ACCELERATOR APPLIC S A [FR]; FUGAZZA LORENZA [IT]; FILANNINO) 21 February 2013 (2013-02-21) the whole document	1-34
A	WO 2012/063028 A1 (KING S COLLEGE LONDON [GB]; BALLINGER JAMES RUSSELL [GB]; BERRY DAVID) 18 May 2012 (2012-05-18) cited in the application page 54 - page 54	1-34
X,P	WO 2016/030103 A1 (ANMI S A [BE]) 3 March 2016 (2016-03-03) the whole document	1-34

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
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Date of the actual completion of the international search <b>19 May 2016</b>	Date of mailing of the international search report <b>27/05/2016</b>
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