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Inorganic chemistry in nuclear imaging and radiotherapy: current and future directions

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Summary

Radiometals play an important role in diagnostic and therapeutic radiopharmaceuticals. This field of radiochemistry is multidisciplinary, involving radiometal production, separation of the radiometal from its target, chelate design for complexing the radiometal in a biologically stable environment, specific targeting of the radiometal to its in vivo site, and nuclear imaging and/or radiotherapy applications of the resultant radiopharmaceutical. The critical importance of inorganic chemistry in the design and application of radiometal-containing imaging and therapy agents is described from a historical perspective to future directions.

Keywords

Radiometals; Bifunctional chelates; Specific targeting; Nuclear imaging; Radiotherapy

Introduction

The application of radioisotopes of inorganic elements to nuclear medicine, both diagnostic and therapeutic, has been of interest almost since the discovery of radioactivity. The middle to late 1930s saw the development of radionuclides with potential medical applications with ^{32}P, ^{131}I, and ^{89}Sr and the first human studies for leukemia, thyroid and bone therapy, respectively, were initiated [1]. Since the early studies, many diagnostic and some therapeutic radiopharmaceuticals have been developed. Diagnostic nuclear imaging requires the use of penetrating radiations from radionuclides that emit either gamma rays or annihilation photons from positron emission. Radiotherapy requires particulate emission from alpha or beta decay (although there is some interest in Auger electrons) so that the energy of decay is deposited over a relatively short range (e.g., in the cancer cells). The development of the ^{99}Mo/^{99m}Tc generator in the late 1950s led to the predominance of ^{99m}Tc in diagnostic nuclear medicine and was the entry into the field of radiometal based imaging and therapeutic radiopharmaceuticals [2, 3]. Recent shortages of ^{99}Mo have brought to light the precarious position of the field of nuclear medicine because of its dependence on aging reactors for production of ^{99}Mo [4].

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Many excellent reviews (and the references therein) covering the production of radionuclides for medical applications[5–10] and the state of diagnostic and therapeutic radiopharmaceuticals[9, 11–25] have been published over the last 20 years. Here we describe the current status and trends in inorganic radiopharmaceutical chemistry and future directions. We have elected to not include those radiometals whose use is strictly as the aqua ions (e.g., $^{82}Rb^{+}$, $^{201}Tl^{+}$. $^{89}Sr^{2+}$) and to focus on those with reasonable half-lives for shipping or that are available in generator form.

Radiometals in radiopharmaceuticals

Radiometals have become an integral component of many radiopharmaceuticals because their nuclear properties (Table 1)[26] are more suitable for diagnostic and therapeutic nuclear medicine applications than those of their Main Group non-metal radionuclides. Not only are the nuclear emissions (α, β^{-}, β^{+}, γ) and their energies and half-lives important, but their availability and cost are more often the determining factors in their application for routine medical use. Additionally, there is a requirement for high specific activity (activity per unit mass) for many medical applications, particularly those involving receptor targeted radiopharmaceuticals. An excellent example illustrating these concepts is the advent of the $^{99}Mo/^{99m}Tc$ generator, which made the 6 h, high specific activity Tc-99m widely available at a reasonable cost.

Radiometals offer an advantage over radiolabeling organic molecules (e.g., with ^{18}F, ^{11}C, etc.) in that lyophilized “kit” formulations, which allow rapid radiolabeling, are often available. The radiopharmaceutical “kits” contain all ingredients except for the radiometal. To formulate the final radiopharmaceutical, the radiometal is added to the “kit” and the instructions (e.g., let stand at room temperature for 30 minutes, heat in a boiling water bath for 30 minutes, etc.) are followed, quality control is performed typically resulting in product yields greater than 90%, which are suitable for patient administration. An example of a “kit” formulation is that for Cardiolite® (Figure 1), which is clinically approved for myocardial imaging and requires the addition of ^{99m}Tc pertechnetate and heating.

The radiometals listed in Table 1 include some of the more widely used and potentially useful radionuclides for either diagnostic imaging or radiotherapy. There is no ideal diagnostic radiometal and no ideal therapeutic radiometal; each has its own unique benefits and associated problems. Technetium-99m was considered to be the ideal diagnostic radionuclide for many years because of its widespread availability, low cost, and relatively easy product formulations. The recent shortages of ^{99m}Tc have made the nuclear medicine field consider alternatives as it is not clear that the issues that led to the shortage will be solved. Not only are the aging reactors that make fission ^{99}Mo an issue, but so are concerns of non-proliferation shifting the field to consider conversion to low enriched ^{235}U or moving toward $^{98}Mo(n,\gamma)$ production of ^{99}Mo. Low enriched ^{235}U fuel will require irradiation of higher masses of uranium fuel to obtain the same activity (quantity) of ^{99}Mo, which will require modifications to the separation method and likely higher radioactive waste generation. The $^{98}Mo(n,\gamma)$ production of ^{99}Mo will result in lower specific activity ^{99}Mo (i.e., more mass because ^{98}Mo would not be separated from ^{99}Mo) and thus a larger or different generator system would be required.

The various radiometals listed in Table 1 have excellent nuclear properties for nuclear medicine applications. Their chemical properties (substitution rates (both on and off), redox chemistry, hydrolysis rates, etc.) on the radiotracer level, where the radiometal is often nM in concentration or lower, pose challenges. The availability of a matched pair of radionuclides, one for diagnosis and one for therapy, would be of value but is rarely available. True matched pairs would include different radioisotopes of the same element as with the diagnostic radionuclide ^{64}Cu and the therapeutic radionuclide ^{67}Cu. Pseudo-matched pairs would involve radioisotopes of similar but different elements as with the diagnostic radionuclide ^{99m} Tc and the therapeutic radionuclides $^{188/186}$Re. Indium-111 analogues have been used as an “ersatz” diagnostic matched pair for the radiotherapeutic ^{90}Y (which has no imageable γ emission), however the inorganic chemistry, in vivo chemistry, and in vivo pharmacokinetics of the ^{111}In product may be different from that of the analogous ^{90}Y product depending on the chelate and their relative kinetic stabilities. Thus, particular caution must be applied with “matched pairs” if the radiometals are not the same element.

Targeting strategies for radiometal conjugates

The current driving force behind the clinical application of radiopharmaceuticals in nuclear medicine is the ability to selectively direct, or target, radiolabeled molecules to active sites of human disease. In order to effectively accomplish this goal, a suitable diagnostic or therapeutic radiometal must be strategically attached to a biological targeting vector. Figure 2 illustrates a general schematic of the most common approach to a targeted radiopharmaceutical using a suitable bifunctional chelating agent (BFCA) directly linked to a biological targeting vector. Although direct labeling (with Tc and Re) has been reported, the labeling is generally non-specific and used primarily for antibody labeling. This discussion will be limited to the BFCA approach only.

The BFCA serves the dual purpose of providing a means to stably complex the radiometal and also allows for selective attachment directly to the selected biological targeting vector. A widely employed strategy for linking or conjugation of a BFCA to a biological targeting vector involves coupling a free primary amine (or activated carboxylic acid) located on the structure of the BFCA with an activated carboxylic acid (or primary amine) from the biological targeting vector to generate a stable amide bond linkage. In some cases, BFCA conjugation to a biological targeting vector requires the addition of an organic linking group in order to maximize in vivo targeting, or alter non-target tissue pharmacokinetics [27]. A variety of linking groups have been successfully employed including simple multi-amino acid linkages, aliphatic carbon chain linkages, and small organic heterocyclic compounds [27]. In all cases, the goal has been to generate a combination of radiometal, BFCA, and linking technology that results in a radiopharmaceutical to selectively target a human disease process while minimizing non-disease and non-target tissue background accumulation of radioactivity.

Numerous strategies for developing targeted radiopharmaceuticals have been employed over the past several decades, including the radiolabeling of small proteins, antibodies, antibody fragments, peptides, and small organic molecules [27–32]. For the purpose of this

discussion, we are limiting our scope to focus only on peptide targeting vectors, which have either recently shown clinical potential, or are currently being investigated pre-clinically for their future use as targeted radiopharmaceuticals [32–39]. Peptides, as a class in themselves, offer tremendous flexibility for modification when biological issues such as in vivo clearance kinetics and metabolic stability are taken into consideration. Further supporting the use of peptides as selective biological targeting vectors is the increasing evidence of the presence and up-regulation of various peptide receptors associated with human cancers. Table 2 provides an overview of various peptides and their respective receptor families currently under development for use as the biological targeting vector component of site directed radiopharmaceuticals. The list was selected based on current interest and use in the development of targeted radiopharmaceuticals where a significant body of literature is being assembled supporting the validity of these radiolabeled peptides including positive results upon in vitro evaluation, animal model biodistribution studies, animal model in vivo imaging, and in several cases human patient studies [32, 37]. Several of the peptide targeting vectors listed have undergone extensive evaluation as potential radiopharmaceuticals resulting in anywhere from thirty to several hundred unique peptide targeting vectors radiolabeled to obtain an optimum candidate for potential clinical evaluation [32, 37].

An example of a bioconjugate under current investigation is the bombesin peptide conjugated to 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA). These peptide targeting vectors have been conjugated with a variety of bifunctional chelating agents in order to complex and evaluate the spectrum of radiometals available for diagnostic and therapeutic radiopharmaceutical development [40].

Radiometal chelate considerations

Numerous chelates have been developed and evaluated for various radiometals as the basis of BFCAs that can be appended to biomolecules for targeting. It is clear that both thermodynamic and kinetic stability of the resultant radiometal complexes are important for the development of safe and efficacious radiopharmaceuticals, with kinetic stability being more important under the high dilution on injection in vivo [41, 42]. The dissociation rate (k_{off}) will determine in vivo stability ($K_s = k_{on}/k_{off}$) since equilibrium conditions are no longer applicable once the radiopharmaceutical has distributed throughout the blood volume. Any loss of the radiometal from its chelate in vivo leads to undesirable and higher non-target irradiation. Some radiometals additionally require the BFCA to provide redox stability to oxidation and/or reduction. Technetium and rhenium complexes are examples where the radiometal can be susceptible to in vivo oxidation to pertechnetate or perrhenate, while Cu(II) and Au(III) complexes are examples where the radiometals can be susceptible to reduction to either Cu(I) or Au(0); in all cases specific targeting is lost. There is no universal chelate that will function as the best BFCA for all radiometals. Each metal, in a given oxidation state, has its own unique and specific requirements for which donor atoms will yield sufficiently kinetically inert radiometal complexes for in vivo applications. Below we discuss the radiometals that we consider potentially the most useful for site directed radiopharmaceuticals in which peptides act as the targeting moiety.

Technetium

The availability of technetium (as pertechnetate, TcO_4^{1-}) from a relatively inexpensive $^{99}Mo/^{99m}Tc$ generator, together with its nuclear properties, which are ideal for SPECT imaging, has made ^{99m}Tc the workhorse of the nuclear imaging community. Technetium is situated in the middle of the d-block transition elements in Group 7 between manganese and rhenium, and this position gives the metals in this triad one of the wider ranges of available oxidation states. Compounds of Tc have been reported in oxidation states ranging from +7 to −1, with Tc(V), Tc(III) and Tc(I) most commonly utilized in nuclear medicine applications. Over the years, many Tc complexes in a variety of oxidations states with a multitude of chelators have been synthesized and evaluated in vivo. The seminal work of Deutsch and Davison in the late 1970s and 1980s demonstrated the importance of Tc-99 inorganic chemistry to radiopharmaceutical development [43–48]. The chemistry of technetium labeled radiopharmaceuticals has been extensively reviewed and a few examples are shown in Figure 3 [27, 49, 50].

Currently there are numerous clinically approved radiopharmaceuticals based on ^{99m}Tc that are essentially small molecules and not based on the bifunctional chelate approach. Technetium(V) is the most accessible oxidation state from Tc(VII) as evidenced by the many approved Tc(V) radiopharmaceuticals such as Neurolite®, Ceretec®, Myoview® and MAG3® (Figure 3), which are approved for cerebral blood flow imaging, cerebral blood flow imaging and white blood cell labeling, myocardial perfusion, and renal filtration imaging, respectively. Current interest in small molecule ^{99m}Tc radiopharmaceutical development is in the area of potential myocardial perfusion imaging agents with faster liver clearance than the current agents (Cardiolite® and Myoview®). Duatti and co-workers developed the neutral ^{99m}TcN-NOET (Figure 4A), which contains the Tc-nitrido core and two N-ethyl-N-ethoxydithiocarbamates bound to the Tc(V) center[51, 52]. Evaluation in humans showed faster liver clearance [51]. Duatti, Tisato, Liu and Santos have all reported +1 cationic analogs in which one of the dithiocarbamate moieties is replaced with a tridentate PNP donor set (Figure 4B); addition of various ether groups were evaluated for the effect(s) on clearance [53–58].

Pertechnetate as eluted from the $^{99}Mo/^{99m}Tc$ generator behaves similarly to iodide, being taken up by the thyroid and excreted through the renal-urinary system. This rapid excretion of pertechnetate can be considered a benefit as this is the chemical species that will be generated by in vivo instability or metabolism of technetium complexes in lower oxidation states. As Tc(VII) in pertechnetate is coordinatively saturated, it is reduced during radiopharmaceutical preparations to generate stable radiometal complexes for in vivo applications.

Technetium(V) has a d^2 electronic configuration and is dominated by oxo chemistry in aqueous solution. These complexes tend to be either mono-oxo with square pyramidal or distorted octahedral geometries, or dioxo with octahedral geometry; examples of both are shown in Figure 3. Technetium(V) is easily accessible from pertechnetate (Tc(VII)), and radiopharmaceutical kit formulations often utilize Sn(II) as the reducing agent. Glucoheptonate or citrate are used in kit formulations when the chelate is slow to react compared to hydrolysis, which would result in the formation of colloidal TcO_2 if a suitable

chelate is not present. A range of donor atoms, including N, S, P and O, have been used to form Tc(V) complexes. Tetradentate chelates are generally used to make this somewhat labile system more kinetically inert, and the most commonly used BFCAs include mercaptoacetylglycylglycylglycine derivatives (N_3S MAG3 derivatives), diaminedithiol or amidoaminedithiol derivatives, the linear tetraamine 1, 4,8,11-tetraazaundecane (a 2-3-2 carbon backbone), and 6-hydrazinonicotinic acid (HYNIC) analogues [27, 59, 60]. The use of the HYNIC BFCA for ^{99m}Tc is attractive because it involves a simple labeling procedure for biomolecules without difficult chelate synthesis. However, HYNIC is generally a monodentate BFCA and thus requires the use of co-ligands to satisfy the coordination sphere of the Tc(V) center. Unfortunately, the co-ligands yielding the best pharmacokinetic properties tend to form multiple products while those that form single entities (e.g., thiol, phosphine donors) tend to be quite lipophilic with poor pharmacokinetics [61–64]. Two recent examples of Tc(V) complexes for targeting peptide receptors are ^{99m}Tc-depreotide (diamido amine thiol [N_3S] chelator linked to a somatostatin peptide)[65] and ^{99m}Tc-HYNIC-GRP [63], both shown in Figure 5.

The nitrido core has been evaluated as an alternative to the oxo core typically utilized with Tc(V) complexes. Duatti and Tisato utilized the PXP donor set along with bidentate (YZ) ligands as potential bifunctional chelates; only the $[TcN(PXP)(YZ)]^{0/+}$ (and no $[TcN(PXP)_2]^{2+}$ or $[TcN(YZ)_2]^{0/2-}$) formed at the ^{99m}Tc level making this a possible route to radiolabeling peptides [66].

Technetium(III) with its low-spin d^4electronic configuration is more kinetically inert than Tc(V); however, Tc(III) requires additional reducing agent for access from Tc(VII) pertechnetate and often higher temperatures. Technetium(III) has been shown to coordinate to soft and hard donors (N, O, P, and S) in both octahedral (paramagnetic) and 7-coordinate (diamagnetic) ligand environments. Teboroxime $[TcCl(CDO)_3BCH_3]$ is an example of a Tc(III) approved radiopharmaceutical for myocardial imaging (Figure 6). Very few Tc(III) complexes have been evaluated as bifunctional chelates, with the '4+1' NS_3/P system showing some promise [67, 68]. The challenges with this system include the harsher reducing conditions and controlling the higher lipophilicity associated with the sulfur and phosphorus donor ligands.

The low-spin d^6 electronic configuration of Tc(I) is kinetically inert and makes this oxidation state desirable as the basis of new Tc radiopharmaceutical development. The report by Alberto and co-workers demonstrating the accessibility of $[Tc(CO)_3(OH_2)_3]^+$ from pertechnetate in aqueous solution accelerated interest in potential Tc(I) radiopharmaceuticals [69–72]. The three carbon monoxide ligands are inert to substitution while the three coordinated water molecules offer an easy route for ligand exchange with a suitable tridentate chelate. The current availability of the commercial IsoLink® kit from Covidien makes this a desirable starting complex for radiolabeling with ^{99m}Tc. This allows for relatively fast exchange onto the Tc(I) center with a molecular targeting tridentate BFCA. Tc(I) is considered a "soft" metal center and as such prefers "soft" donors, which tend to make the resultant complex more lipophilic; however a balance must be achieved with clearance properties from non-target tissues in vivo. Thus, amine, imine and carboxylate donors are often used with the $[Tc(CO)_3]^+$ core to reduce lipophilicity and thus facilitate

clearance. Scorpionates [73], single amino acids (especially histadine analogues) [64], and other chelates were initially investigated as potential chelators for the bifunctional chelate approach for the $[Tc(CO)_3]^+$ core [74–79]. A representation of these binding moieties for the tricarbonyl core is given in Figure 7 [73, 75].

Benny and co-workers utilized “click” chemistry to improve radiolabeling efficiency of the tricarbonyl technetium(I) core at lower temperatures than reported by Schibli et al. [75, 80] to minimize potential damage to appended biological targeting vectors [81]. Two approaches were reported that differed primarily in the order of radiolabeling the $[Tc(CO)_3]^+$ core. One approach involved coupling the BFCA containing a pendant primary alkyne with an azido moiety containing the biological targeting group and subsequently radiolabeling it. The second approach involved radiolabeling the BFCA containing the primary alkyne and then reacting it with the azido targeting moiety [81]. Both approaches yielded the same product, but neither approach gave sufficient radiolabeling yields at 25°C at less than 10^{-5} M BFCA [81].

Although the availability of the Isolink kit has made this core easily accessible and the Tc(I) oxidation state offers high kinetic stability, an inherent issue with the $[Tc(CO)_3]^+$ core has been the resultant increased lipophilicity of its complexes. Increasing complex lipophilicity results in increased and often slow hepatobiliary clearance, which hinders imaging the pelvic/abdominal region.

Rhenium

Rhenium has been referred to as the radiotherapeutic matched pair for the diagnostic ^{99m}Tc. Its position as the 3rd row congener of Tc in Group 7 makes its chemistry similar to that of technetium in many ways, but there are differences which manifest themselves when redox chemistry or substitution kinetics are involved. Rhenium is more difficult to reduce than Tc and is slower to substitute. This leads to re-oxidation to perrhenate in vivo if the chelate systems are not carefully selected. Fortunately, perrhenate clears from the body quickly and thus does not accumulate in non-target organs/tissues. The slower substitution rates have led to lower lability in the site trans to the oxo group in Re(V) complexes, which has resulted in different products for Re(V) compared to Tc(V) [82]. The Re(V) complexes may have a ligand in the site trans to the oxo group whereas Tc(V) does not or substitution slows down reduction resulting in a completely different complex for Re(V) [82]. This may also be the reason that a Re(V) complex of propyleneamine oxime analogues has not been reported (i.e., the Re analogue of Ceretec®, Figure 3). Because reduction is more difficult for Re, the +5 oxidation state is the most accessible from perrhenate, although the ability to utilize the low spin d^6 tricarbonyl Re(I) core has received a lot of attention.

Rhenium(V) chemistry, like Tc(V), is dominated by oxo chemistry. Generally, chelators that are N_xS_{4-x} donors have been utilized to complex and stabilize the oxorhenium(V) core [83]. Diamine dithiols (DADT), monamine monoamide dithiols (MAMA), and diamide dithiols have all been shown to successfully chelate the oxorhenium (V) core and are most widely used as potential BFCAs for Re(V). The susceptibility of Re(V) complexes to oxidation to perrhenate on high dilution in vivo requires careful selection and testing of chelates for Re(V); thiolate and phosphine donors seem to be most suitable at stabilizing Re(V) to

oxidation, perhaps because both are themselves reducing in nature. The N_3S MAG3 type chelates do not function as well with Re(V) on the radiotracer level (especially in vivo) as they do with Tc(V) because oxidation is an issue. A second thiolate may add sufficient stability although the N_2S_2 chelates tend to generate more lipophilic complexes.

Previous clinical trials have focused on the use of rhenium radiopharmaceuticals for the palliation of metastatic bone cancer [84–87], advanced lung cancer [88], and inoperable hepatocellular carcinoma [89]. The majority of current research with Re(V) includes potential use in bifunctional chelators, for example Re-N_2S_2-IMP 192 (Figure 8) [83, 90].

Since Re is more difficult to reduce than Tc, very few lower oxidation state complexes have been evaluated on the radiotracer level. The '4+1' NS_3/P type system for Re(III) has been reported, however challenges exist in the reduction of $^{188}ReO_4^-$ directly to Re(III) and a two step formulation involving ^{188}Re(EDTA) or ^{188}Re(thiourea) complexes as the intermediate has been investigated to minimize formation of colloidal reduced, hydrolyzed $^{188}ReO_2$, which arises from the amount of reducing agent necessary and the pH conditions required for its synthesis [91].

As with Tc, the low spin d^6 Re(I) oxidation state is kinetically inert and is currently being investigated predominantly as a surrogate to Tc(I) tricarbonyl complexes on the macroscopic level. Although reduction of perrhenate in aqueous solution to the +1 oxidation state is difficult, it may be useful in the future for radiotherapeutic applications similar to those imaging applications discovered for the technetium (I) tricarbonyl analogues [49, 73, 92, 93]. Valliant and co-workers have shown that the chemistry of tricarbonyl complexes with Re(I) and Tc(I) carborane complexes may be different for some carboranes due to differences in redox potentials of the two metals and perhaps to their differing substitution rates [94].

The availability of high specific activity radiorhenium (186 or 188) is essential for the development and approval of Re-based radiopharmaceuticals for radiotherapy. Although a $^{188}W/^{188}$Re generator is available, its routine availability is of question. The availability of high specific activity ^{186}Re would have a major impact for the field because the half-life and beta energy of ^{186}Re are more suitable for radiotherapeutic applications than those of ^{188}Re. Although production of ^{186}Re from an accelerator is possible, it is currently not being exploited [95–99]. The longer half-life of ^{186}Re would make it suitable for radiolabeling antibodies or other longer circulating biomolecules.

Copper

Development of copper radiopharmaceuticals has received much attention due the availability of multiple isotopes with radiopharmaceutical relevance [100]. The Cu isotopes of most interest include ^{64}Cu (imaging and therapy), ^{62}Cu (imaging) and ^{67}Cu (therapy) (see Table 1). The Cu (II) oxidation state is preferred for radiopharmaceutical use as it is more kinetically inert than the more common, yet labile Cu(I) oxidation state. Copper(II) complexes tend to be Jahn-Teller distorted and kinetic lability remains an issue [101–105]. Thus much research in this area addresses suitable chelates for kinetically inert, "in vivo" stable Cu(II) complexes. Copper(II) is considered a borderline soft metal, favoring nitrogen

and oxygen donor groups; thiolates and phosphines tend to reduce Cu(II) to the more labile Cu(I) unless care is taken. Early work in the development of a chelate system for Cu(II) focused on DOTA and 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid, TETA; however these complexes have demonstrated limited in vivo stability. Cross-bridged derivatives of DOTA and TETA, CB-DO2A and CB-TE2A, as well as the sarcophagine cage have proven more useful for chelation of Cu(II) for in vivo applications. BFCAs based on cross-bridged derivatives of DOTA and TETA and the sarcophagine cage have proven difficult to synthesize or easily modify and thus many investigators prefer to use the commercially available DOTA analogues even though they are not sufficiently stable under in vivo conditions. Brechbiel and co-workers have described a functionalized CB-TE2A analog with a reported 13% yield from cross-bridged cyclam, which was subsequently conjugated to RDG peptide analogs and labeled with ^{64}Cu showing excellent in vitro stability [106]. Additionally, these particular analogues are quite hydrophobic and hepatobiliary clearance is often observed, leading to less than desirable pharmacokinetics. Anderson and co-workers and references therein provide an excellent and comprehensive recent review of copper radiopharmaceutical research [100].

Since last reviewed, two NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid) Cu-64 conjugates[107–110] have been reported. The ^{64}Cu- NO2A-8-AOC-BBN(7–14)NH_2 conjugate[110] and the ^{64}Cu-NOTA-RGD-BBN conjugate[108, 109] were synthesized and showed nM affinities for GRP and both $\alpha_v\beta_3$ and GRP receptors, respectively. Both showed favorable biodistribution results and PET imaging in tumor bearing mice. A subsequent head-to-head study comparing ^{64}Cu- NO2A-8-AOC-BBN(7–14)NH_2, ^{64}Cu-DOTA-8-AOC-BBN(7–14)NH_2, and ^{64}Cu-CB-TE2A-8-AOC-BBN(7–14)NH_2 was also reported; while ^{64}Cu-CB-TE2A-8-AOC-BBN(7–14)NH_2 exhibited more favorable stability in vivo; a reduced uptake and retention was observed in the tumor tissue compared to ^{64}Cu- NO2A-8-AOC-BBN(7–14)NH_2 [107].

The NOTA chelate system may prove to be more suitable for Cu(II) than the analogous DOTA or TETA systems, as the coordination number of Cu(II) is better matched. This chelate system seems to form significantly more hydrophilic complexes with Cu(II) based on the reports of Smith and Liu [107–110]. Copper-64 is available to researchers on a regular basis from a few sources; however ^{62}Cu and especially ^{67}Cu are not readily available and it is questionable whether ^{67}Cu will be available in sufficient quantities for radiotherapy.

Recent studies with the small molecule ^{64}CuATSM, which is taken up and retained in hypoxic tissue [111], have focused on understanding the mechanism of uptake and retention under reducing conditions. Fujibayashi et al. [111] reported that ^{64}CuATSM not only is retained in hypoxic cells but also cells having mitochondrial dysfunction with higher levels of NADH and NADPH (reductases), even under normoxic conditions. Their findings indicate that ^{64}CuATSM may be more broadly applicable than other hypoxia imaging compounds such as ^{18}F-misonitroimidazole [111].

Gallium, indium, radiolanthanides, bismuth and actinium

Gallium, indium, the radiolanthanides, bismuth, and actinium have been grouped together because the aminocarboxylate chelates have been utilized to stabilize these radiometals for in vivo applications. These metals all form +3 cations and thus show some similarities in their chemistries, although they differ in their coordination numbers and thus the optimal chelate for in vivo stability. Gallium(III) is generally 6-coordinate, In(III) 6- to 8-coordinate (usually 7-coordinate), Y(III) 6- to 12-coordinate (8- and 9-coordinate most common), Ln(III) 6- to 12-coordinate (9-coordinate most common, but depends on the size of the metal ion), and Bi(III) 6- to 8-coordinate. The primary criterion for in vivo stability of these metal ions is to completely surround (saturate) their coordination sphere with donor atoms from the appropriate chelator. DTPA (diethylenetriaminepentaacetic acid), DOTA, NOTA, and various other amine carboxylate donor ligands have been used to complex these metal ions. Too many or too few donor atoms within a chelate to fully saturate the coordination sphere of the particular metal ion or a poor cavity fit between the chelate and the metal ion result in an unstable complex in vivo.

Approved radiopharmaceuticals incorporating these radiometals include Quadramet® (^{153}Sm-EDTMP) for bone pain palliation associated with metastatic disease (Figure 9A), Octreoscan® (^{111}In-DTPA-octreotide) for imaging somatostatin receptor positive cancers (Figure 9B), ^{67}Ga-citrate for tumor imaging, ^{111}In(oxine)$_3$ for platelet imaging, ^{111}In-Prostascint® for prostate cancer imaging, ^{111}In-Oncoscint® for colorectal and ovarian cancer imaging, and ^{90}Y-Zevalin® for treating non-Hodgkin's lymphoma, the last three all incorporating monoclonal antibody targeting vectors.

Both DTPA and DOTA conjugated to antibodies or peptides have proven to be suitable chelates for In(III) for in vivo applications. Conjugation of the peptide or antibody to DTPA or DOTA through one of the carboxylate arms leaves the required 7-coordination sites available for complexation to In(III). Indium-111 is readily available in high specific activity and both DTPA and DOTA analogs are suitable for use as BFCAs [112]. The DTPA is often the chelate of choice for In^{3+} because of its faster complex formation kinetics compared with DOTA. Various aminecarboxylates (DTPA, DOTA, NOTA) have been evaluated along with tris(2-mercaptobenzyl)amine and tris(2-hydroxybenzyl)amine chelates for Ga(III) [21, 40, 113]. Although studies utilizing DTPA and DOTA have been carried out for Ga(III), neither is optimal for the smaller metal ion. The cavity size of DTPA and DOTA are somewhat large for Ga(III) and its strong preference for forming 6-coordinate complexes leaves dangling carboxylate arms. NOTA may have a better size and coordination number for Ga(III) [114, 115]. The stability of the resultant radiometal complexes is important for minimizing non-target tissue radiation doses and for obtaining suitable diagnostic images. Gallium and indium, if lost from their chelator, will behave similarly in vivo to Fe(III) and will be complexed by transferrin in the blood and localized to the liver. Much of the current research for gallium and indium relies on the bifunctional chelate approach where the metal is stably complexed to a chelator that is ligated to a biological molecule or biological targeting vector, for example Octreoscan® (^{111}In- DTPA complexed to peptide) shown in Figure 9B [34].

Several radiolanthanides have nuclear properties suitable for radiotherapy applications including ^{153}Sm, ^{177}Lu, ^{149}Pm, ^{166}Dy, ^{166}Ho and ^{161}Tb (Table 1). The lanthanides are hard Lewis acids and form primarily ionic bonds in aqueous solution. Thus, in order to form complexes that are kinetically inert in vivo, they must be complexed with octadentate macrocyclic chelates such as DOTA although some hindered DTPA analogues (e.g., CHX-DTPA) have shown in vivo stability with radiolanthanides [116–120]. Use of DOTA as a BFCA may require either carbon backbone or aminocarboxylate arm derivatization to retain the octadenticity of the DOTA analogue, although there are many studies using one of the carboxylate arms for conjugation to the targeting agent [27, 116]. This derivatization is necessary as the radiolanthanides show significant uptake in the skeleton (as a calcium mimic) and the liver (where they are found as hydroxide colloids) in vivo if their complexes are not sufficiently stable [27, 116, 117]. The aminophosphonate chelate ethylenediaminetetramethylenephosphonic acid (EDTMP) was used to develop ^{153}Sm-EDTMP (Quadramet®) as a bone pain palliation agent; 1,4,7,10-tetraazacyclododecane-1,4,7,10-methylenephosphonic acid (DOTMP) has been investigated more recently to form a more kinetically inert complex with ^{166}Ho [116, 118]. Several excellent reviews on the lanthanide chemistry of radiopharmaceuticals have been published [27, 116, 117, 121].

Yttrium(III) is often considered a pseudo-lanthanide as it is situated above La(III) in Group 3. As ^{90}Y has no gamma emissions (Table 1), researchers have often used ^{111}In to assess its in vivo biodistribution even though this is not ideal; when ^{90}Y is lost from its chelate it localizes primarily to bone, liver and other organs similar to the radiolanthanides [3], while ^{111}In localizes with transferrin to the liver. Yttrium and the radiolanthanides undergo hydrolysis if they are lost from their chelate in the body resulting in colloidal $M(OH)_3$, which will accumulate in the liver and other blood rich organs; some of the radiometal will localize in the bone if hydrolysis occurs more slowly [118]. Sterically hindered DTPA analogs (CHX-DTPA and CyDTPA) have been determined to be suitable for ^{90}Y labeling with faster formation kinetics than DOTA [122–126]. Yttrium-90-Zevalin® (an antibody-CHX-DTPA bifunctional chelator) is an example of a ^{90}Y radiopharmaceutical currently in clinical use [127, 128].

Bismuth(III) is of interest because two of its radioisotopes, ^{212}Bi and ^{213}Bi (Table 1), are alpha emitters with tremendous potential for targeted radiotherapy [129–131]. For convenience, DTPA and DOTA analogues have been evaluated as chelators for Bi(III); Brechbiel et al. recently reported on a decadentate DOTA analog, namely 3p–*C*-DEPA, which showed very good labeling yields with $^{205/206}$Bi at room temperature (~94% in 1 h) and very good in vivo stability in mice [132]. Clinical studies of patients with advanced myeloid leukemia showed the difficulties (loss of radiometal from chelate; short half-life) and small successes (selected destruction of leukemia cells with few side effects) of targeted alpha therapy from [^{213}Bi]-HuM195 (a DTPA conjugated antibody) [129, 133, 134]. Because of the limited success of these initial studies, further clinical studies were extended to [^{225}Ac]-HuM195 to yield more dose per injected radiopharmaceutical from the cumulative effects of all daughter product emissions [129, 133]. Any loss of bismuth from its chelate would result in localization and predominant increased radiation exposure to the

kidneys [129]. Recently, Maecke and co-workers demonstrated the therapeutic potential of a ^{213}Bi labeled peptide, ^{213}Bi-DOTA-PESIN as compared directly to the analogous ^{177}Lu labeled peptide, ^{177}Lu-DOTA-PESIN [135]. The results from this preclinical study conducted in a mouse model of prostate cancer clearly confirmed that α therapy using ^{213}Bi was much more efficacious than β therapy employing ^{177}Lu in controlling tumor growth while at the same time also confirming previous findings of marked kidney damage associated with ^{213}Bi therapy.

Actinium-225 has been suggested for use as an in vivo generator system for a decay chain that would result in a therapeutic dose from 4 alphas and 2 betas, and includes ^{213}Bi [129]. This additional therapeutic dose would be beneficial for treatment, but there is a risk that the recoiling daughter nucleus would be lost from the chelator and result in undesirable non-target irradiation in vivo unless the decay occurs inside the targeted cancer cell [136]. The DOTA and DTPA chelates have been evaluated for ^{225}Ac; if lost from its chelate, ^{225}Ac generally localizes in the liver or skeletal system in vivo, but proper chelation can reduce the localization in non-target tissue [129, 136]. Several reviews have reported the benefits, usefulness and challenges of actinium as a potential nanogenerator [129–131, 133, 136–138].

The +3 radiometals have similarities in the BFCAs that are used with them; however there are issues that need to be addressed for each in order for them to become clinically useful. All of these radiometals are susceptible to hydrolysis and thus the reaction pH is critical for their formation, especially at the radiotracer level; hydrolysis becomes an issue at least two pH units earlier than at the macroscopic level and thus radiolabeling must be accomplished under acidic conditions even though protons are released on complexation. The commercially available ^{68}Ge/^{68}Ga generator makes ^{68}Ga, a 68 minute positron emitter readily available to the diagnostic nuclear medicine community. Although currently available ^{68}Ge/^{68}Ga generator systems have ^{68}Ge breakthrough issues, using suitable solid phase ion exchange technology it is possible to further purify the eluted ^{68}Ga [139, 140]. Gallium-67, a SPECT radionuclide, is available in high specific activity from accelerator production on a routine basis although the gamma emission is not optimum for SPECT image acquisition. There is no ideal chelator that has been identified for $^{67/68}Ga^{3+}$ to date. Recent reports with various nitrogen (amine and imine) and oxygen (carboxylate, phenolate, hydroxamate) donor chelates suggest that perhaps the NOTA analogs will prove to be ideal, however there has been no effort to determine the best donor atoms for Ga^{3+} [141, 142].

The radiolanthanides (and there are several of them with suitable nuclear properties; see Table 1) have the advantage that a BFCA that is suitable for one of them should work for all of them. Because their bonding is ionic in nature, octadentate macrocyclic DOTA analogs are the ideal BFCA [116, 118, 143]. The issue of high specific activity production of radiolanthanides must be addressed in order to promote routine use.

Bismuth radioisotopes suffer from availability, as does ^{225}Ac. Although the alpha particles emitted by these radionuclides have high cell killing potential, their routine availability remains an issue for clinical use. Additionally, there has been very little, if any, chelate

design specifically for these two radiometals. DOTA has been the BFCA of choice without consideration of other potential chelates (i.e., donors).

Zirconium

Zirconium has become of interest in the radiopharmaceutical arena because one of its radioisotopes, ^{89}Zr (Table 1), has nuclear properties suitable for use in PET imaging. Zirconium is considered a labile, +4 metal ion with chemistry somewhat similar to that of lutetium in that it is a hard metal center preferring hard, anionic oxygen donors [144]. Zirconium forms 8-coordinate complexes; however unlike the lanthanides that favor DOTA and DTPA chelates, zirconium has been shown to be lost in vivo from these complexes [145]. In fact, the stability constant (log K_{ML}) for Zr-DTPA is ~36 [40]; once again kinetics is the dominant factor for in vivo stability. In vivo studies of ^{89}Zr-$ZrCl_4$ showed high liver uptake, while $^{89}Zr(C_2O_4)_4^{4-}$ showed uptake in the skeletal system [145]. ^{89}Zr can be produced at a cyclotron and has been utilized as a PET radionuclide for labeling antibodies and peptides (some using desferrioxamine as the chelator) [133, 146–149]. A recent study showed that ^{89}Zr-desferrioxamine B-J591 can be used to successfully diagnose prostate specific membrane antigen positive prostate tumors in vivo [145]. Although the availability of a longer-lived positron emitter (3.26 days for ^{89}Zr) would be beneficial by allowing delayed PET imaging, the 100% abundance emission of a 909 keV gamma is not desirable; and may be a significant deterrent.

Gold

Two radioisotopes of Au are of interest for radiotherapeutic applications, namely ^{198}Au and ^{199}Au (Table 1). Gold-199 has more suitable beta and gamma emissions for nuclear medicine applications and is available in high specific activity from an enriched Pt target. The high abundance, higher energy gamma of ^{198}Au (412 keV) makes it less favorable for in vivo applications but it is more readily available for development. These two radionuclides are readily available (both are reactor produced) to interested researchers. Unfortunately, the chemistry of Au(III) is not straight-forward and both hydrolysis and reduction to Au(0) are problems that need to be overcome. At the radiotracer level, hydrolysis becomes an issue for Au(III) above pH 4; extracting (t-Bu_4N)[$^{198/199}AuCl_4$] into an organic solvent such as $CHCl_3$ prior to reaction with the chelate addresses this issue [150].

Recently, Bottenus and co-workers investigated a series of gold(III) bis-thiosemicarbazone complexes [150]. Although one of the complexes reported, Au(3,4-HxTSE) (Figure 10), showed favorable in vitro stability, biodistribution studies in CF-1 normal mice showed >50% ID/g remaining in the bloodstream at 4 h p.i. with high lung uptake possibly resulting from complex binding to serum albumin [150]. Stabilizing Au(III) to reduction under in vivo conditions continues to be an issue that must be overcome to generate a potential ^{199}Au radiotherapeutic agent.

Gold-198 nanoparticles have received recent attention for potential radiotherapeutic applications as in vivo reduction is not an issue. Gum Arabic coated nanoparticles (GA-^{198}AuNP) were formed by addition of an alanine based phosphine reducing agent

$P(CH_2NHCH(CH_3)COOH)_3$ (THPAL) to a mixture of $^{198}AuCl_4^-$ and Gum Arabic under acidic conditions. Nanoparticle formation was accompanied by a color change from yellow to purple, and TEM images indicated gold particle diameters in the range of 12 – 18 nm [151–153]. Animal studies in PC-3 tumor bearing SCID mice where GA-^{198}AuNPs were administered via intratumoral injection demonstrated slowed tumor growth when compared to the non-radioactive treated control group [151].

Because of the difficulties encountered with Au(III) chemistry, the availability of suitable chelates is limited. Design of a chelate to essentially encapsulate the Au(III) center so that its axial sites are not available for attack and reduction may be what is needed. The chelate itself must be stable to oxidation or Au(0) will form through internal redox chemistry.

Rhodium

Rhodium-105 is an interesting isotope for radiopharmaceutical use. Its moderate β^- emission is useful for therapeutic applications, while low abundance γ emissions are available for in vivo mapping of the Rh-105 containing radiopharmaceutical as well as for dosimetry determinations (Table 1). The low spin d^6 electronic configuration of Rh(III) makes its complexes kinetically inert. In fact, Rh(III) undergoes extremely slow water exchange ($T_{1/2}$ ~ 30 years), second only to its 3rd row congener Ir(III) [154]. This allows for formation of metal chelate complexes with favorable in vivo stability. This high kinetic inertness is overcome in substitution reactions by using refluxing alcohol (ethanol for biological applications) to reduce Rh(III) to the more labile Rh(I) in situ to facilitate substitution; carrying out the reactions in a normoxic atmosphere results in oxidation back to Rh(III) following substitution [155].

Much of the early work towards development of a Rh-105 chelate system focused on nitrogen and oxygen donor atoms such as cyclam and cyclen derivatives, amine oximes, amine phenols, and amine porphyrin ligands [156, 157]. A variety of tetrathioether chelates (macrocyclic and acyclic) have been evaluated and were shown to give ^{105}Rh-S_4 complexes in >90% yield with high stability [157–163]. Additionally, NS_3, N_2S_2 and N_4 macrocyclic and N_2S_2 acyclic ligands were evaluated; although the complexes formed were very stable, their yields dropped with increasing N donor atoms [161, 164–167]. More recently, the acyclic N_2P_2 and S_2P_2 chelates were evaluated for ^{105}Rh complexation and again stabilities were very high [168]. The macrocyclic S_4 and acyclic N_2S_2 chelates conjugated to the bombesin peptide BBN(7–14)NH_2 with various linkers showed good binding to GRP receptors, indicating promise for targeting prostate cancer [162, 164, 166]. Radiochemical yields of >90% were achieved with many of the chelate systems that have been reported. Overall, the presence of amine donor atoms increased the pH necessary for complexation and resulted in lower yields at the radiotracer level due to the competing hydrolysis reaction; the more amine N donors present, the higher the pH needed and the lower the yield [161, 164–167]. The presence of phosphine donors allowed reduced temperatures and lower concentrations of ethanol to be used at the radiotracer level (phosphine acts as both a reducing agent and chelate) but at the expense of significantly higher ligand concentrations (~1000 fold increase needed) [168]. Although higher temperatures and ethanol concentrations are required for the tetrathioether chelate systems, they may prove to be more

suitable BFCAs due to ligand stability and the use of lower ligand concentrations for generating the ^{105}Rh bioconjugate. Based on literature reports to date, either the 222-S_4 or 333-S_4 acyclic ligand systems will be most useful as they each only generate one isomer on complexation with Rh(III) (*cis*- and *trans*-dichloro, respectively) [159, 162].

Rhodium-105 is available in high specific activity. Its radiotracer complexes are kinetically inert in vivo and thus transchelation will not be an issue. Its slow substitution kinetics can be a hurdle in radiolabeling as higher temperatures are needed (e.g., refluxing ethanol) to generate Rh(I) in situ to allow faster substitution [160, 163, 168]. The higher temperatures required may be a problem for some biotargeting groups. As with many metals, hydrolysis is an issue above pH 6–7 and this must be considered during any radiosyntheses.

Future directions

Inorganic chemistry will continue to play an important role in diagnostic and therapeutic radiopharmaceuticals. There is no single radionuclide or BFCA that is optimal for all applications in either imaging or treatment. The recent worldwide shortages experienced with the ^{99}Mo/^{99m}Tc generator may show their after effects through development of additional isotope production facilities or alternative methods to the production of ^{99}Mo. These shortages will likely also show their effects through the development of other radionuclides and radiopharmaceuticals as alternatives to ^{99m}Tc based diagnostic imaging agents. There is much recent interest in ^{18}F and ^{68}Ga based agents as PET alternatives to ^{99m}Tc. The development of multimodality imaging agents (MRI and PET/SPECT)[169, 170] and radiolabeled nanoparticle imaging agents[171] were not included in this paper, however these are two of the new up and coming areas about which we will likely see much more in the future.

Radiotherapeutic agents hold hope as alternatives to chemotherapeutic drugs in that the side effects can be significantly less due to the very low concentrations of actual drug administered (nM versus mM concentrations). However, delivery of sufficient radiation dose to tumors without overburdening the non-target tissues continues to be an issue that needs to be overcome.

All of the radiometals discussed have both advantages and disadvantages regarding their routine use. The nuclear properties (Table 1) of the radiometals make them useful for radiopharmaceutical applications. Their availability in high specific activity (high activity/unit mass) and their chemistry at the radiotracer level (often nM or less) have made their routine use challenging. The interest in using a commercially available BFCA (i.e., DOTA or DTPA analogs) rather than synthesizing an appropriate BFCA has increased interest in the radiometals for which these BFCAs may be useful (e.g., radiolanthanides, ^{90}Y, ^{111}In, $^{67/68}$Ga, ^{64}Cu) even when the resultant radiometal complex is less than optimal (e.g., DOTA for Cu) in vivo. Suitable chelates as the basis of BFCAs are lacking for the less used radiometals for which DOTA or DTPA will not serve as a useful BFCA (e.g., ^{199}Au, ^{105}Rh, ^{89}Zr, $^{67/68}$Ga). Addressing the issues of isotope availability, high specific activity, and appropriate BFCA technology in this field for the various radiometals

will be critical for the development of the next generation of radiopharmaceuticals for use in nuclear medicine.

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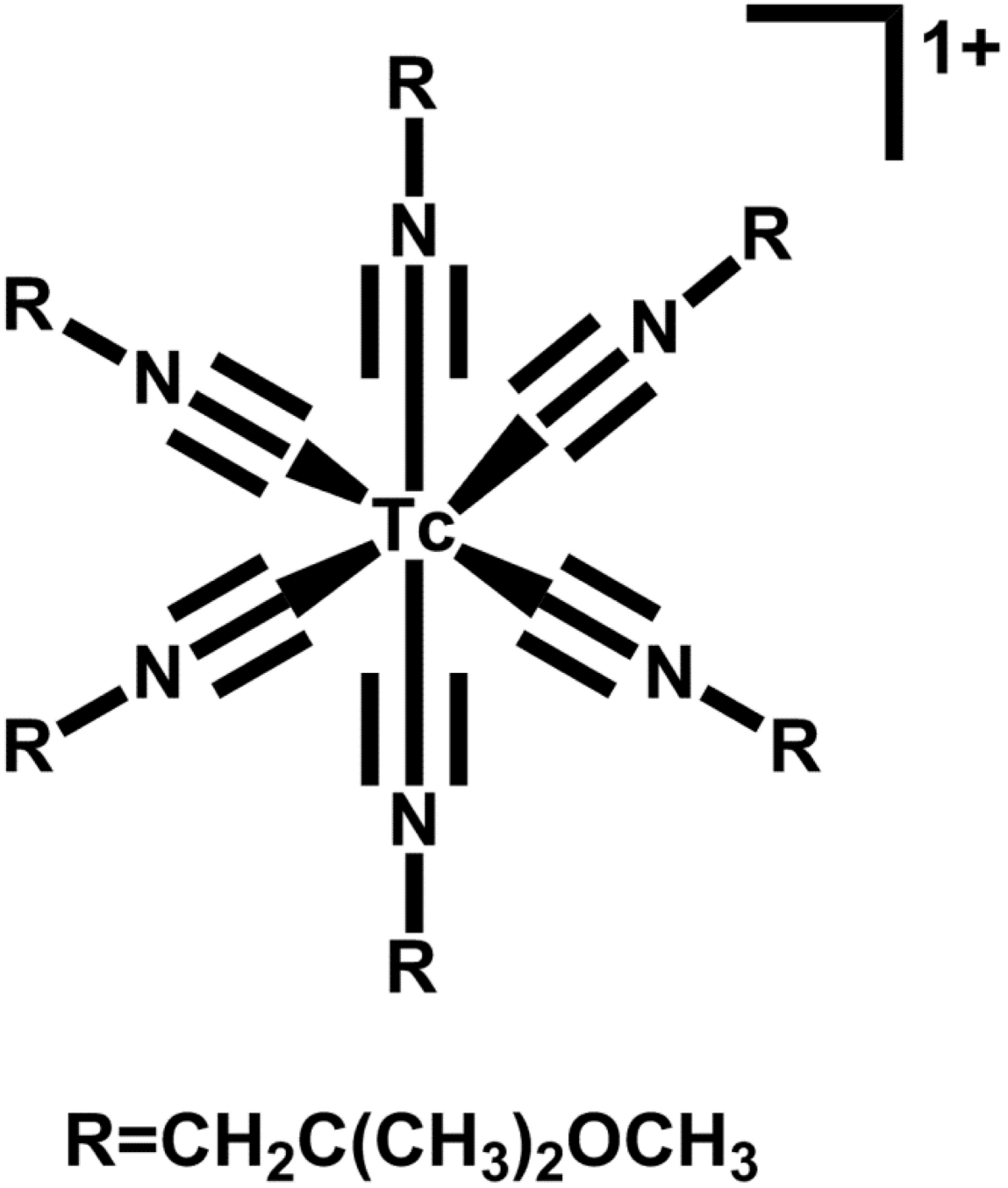

Figure 1.
Structure of Cardiolite.

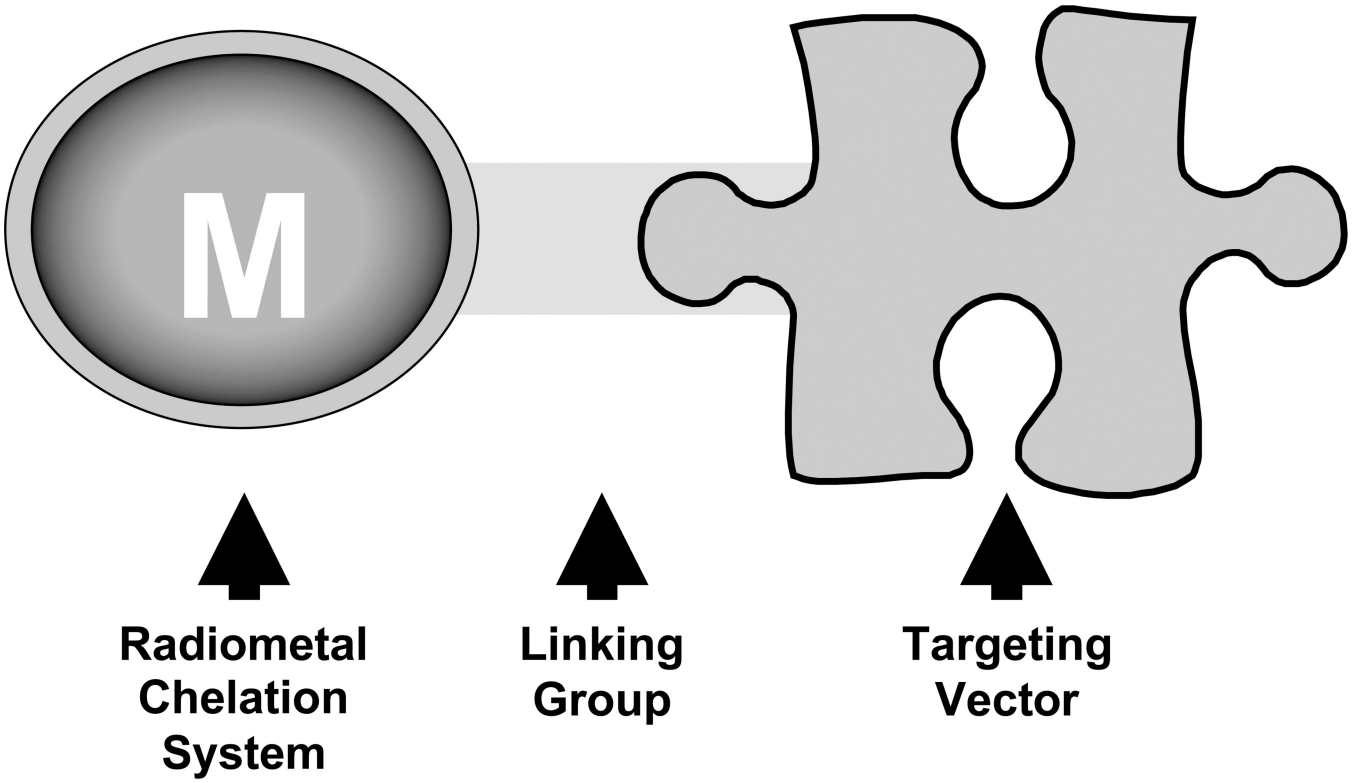

Figure 2.
Cartoon of a generic bifunctional chelating agent.

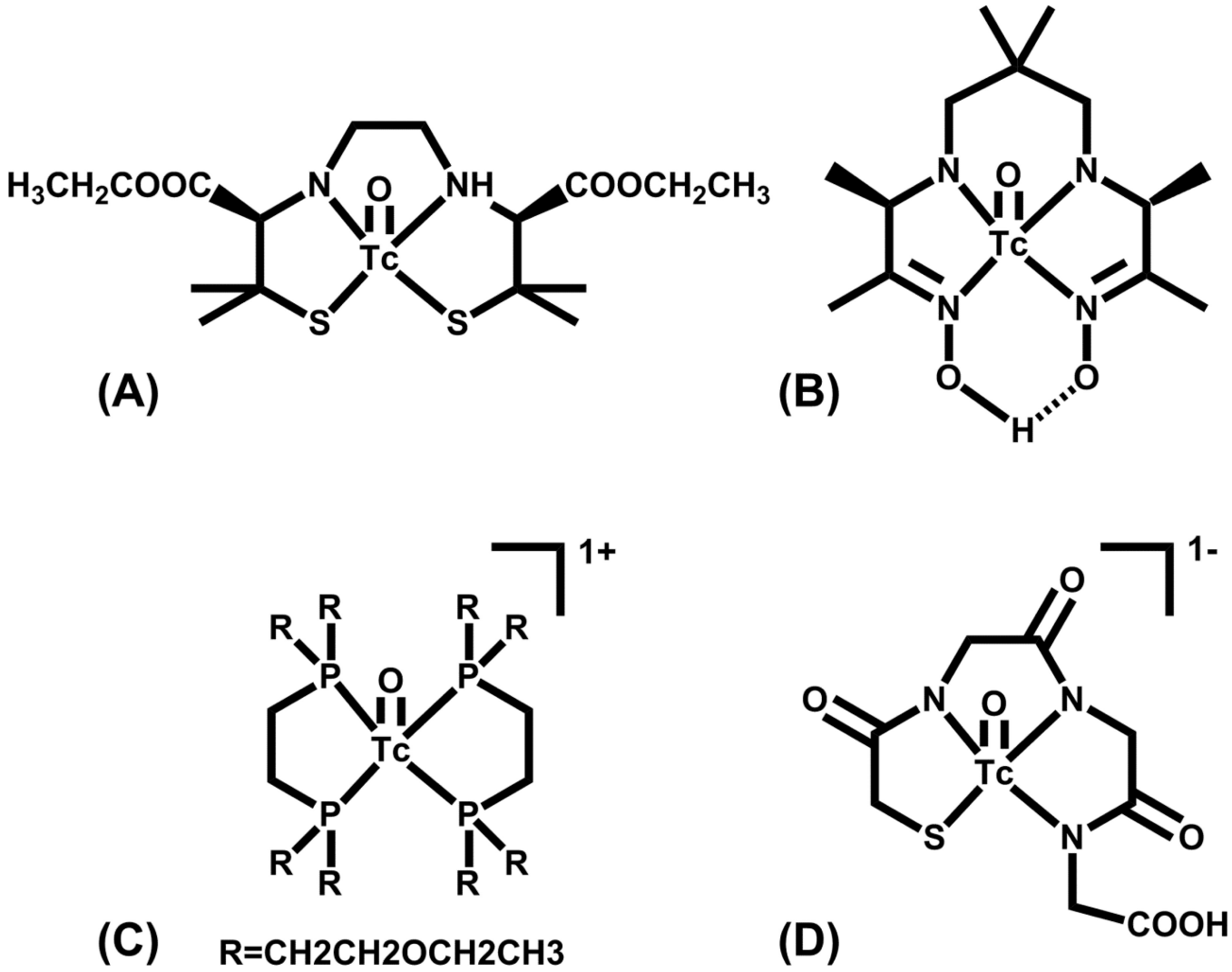

Figure 3.
Structures of (A) Neurolite®, (B) Ceretec®, (C) Myoview®, and (D) MAG3.

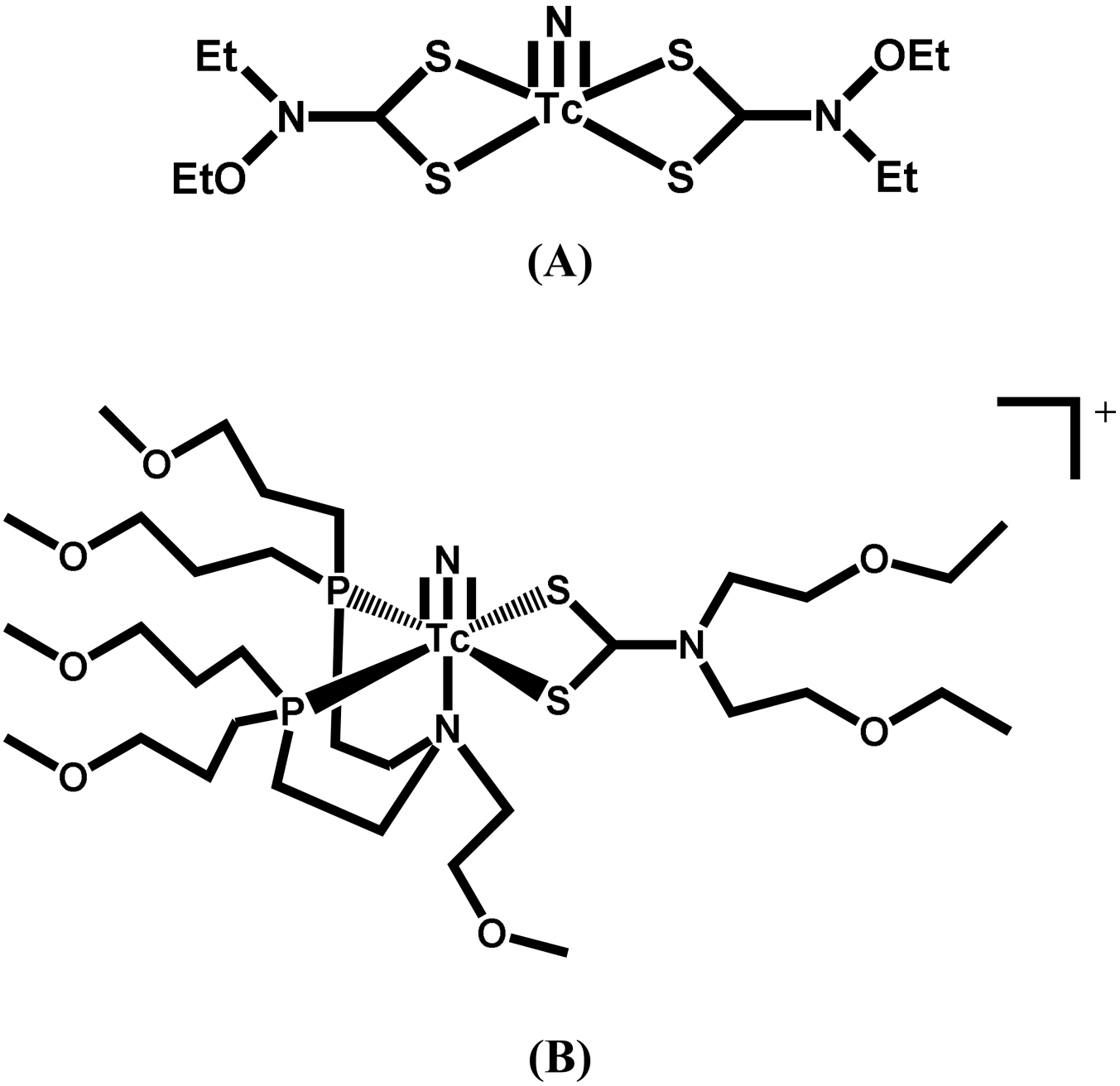

Figure 4.
Structures of (A) TcN-NOET and (B) $TcN(S_2)(PNP)^+$.

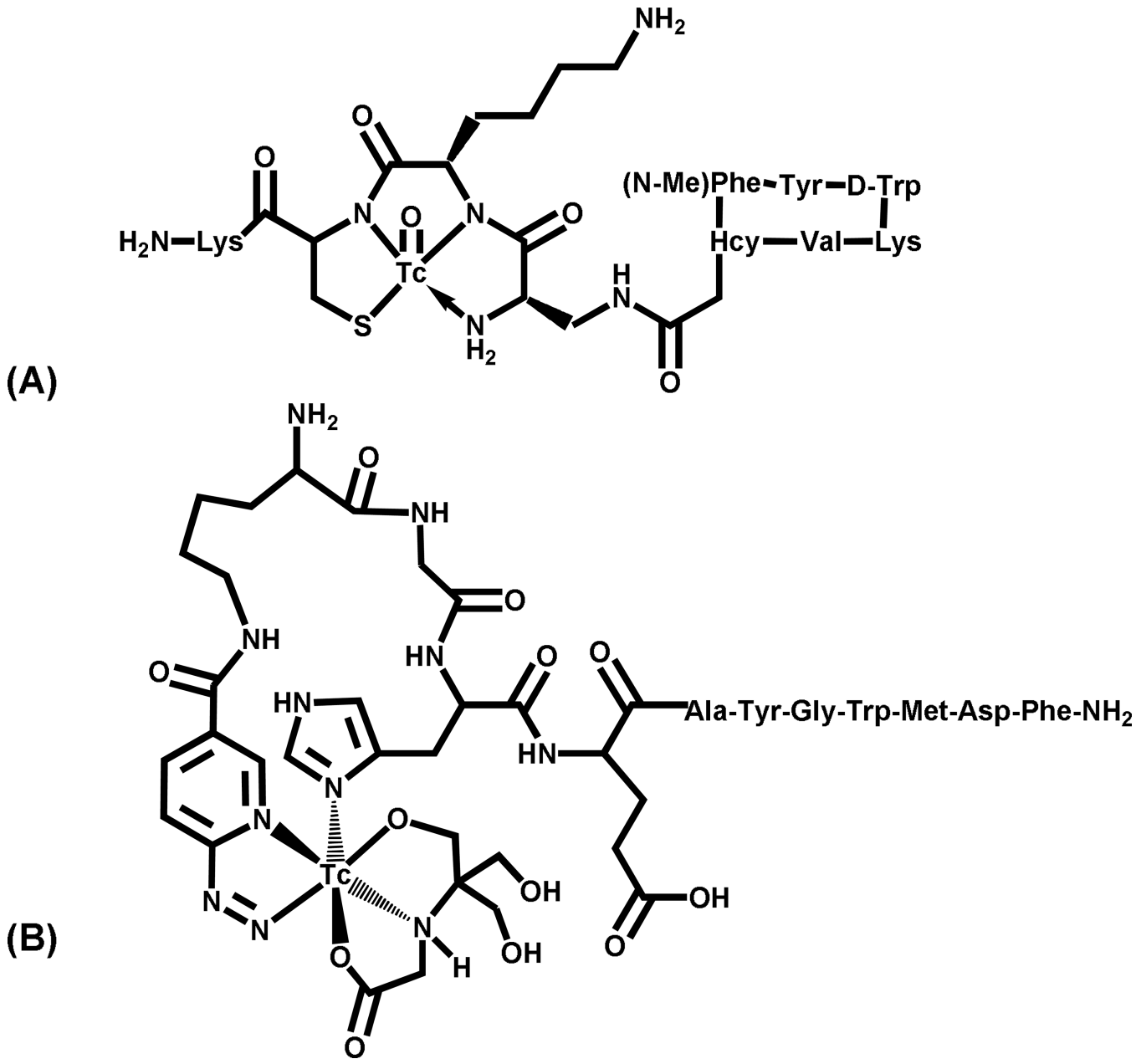

Figure 5.
Structures of (A) ^{99m}Tc-depreotide and (B) ^{99m}Tc-HYNIC-GRP peptide.

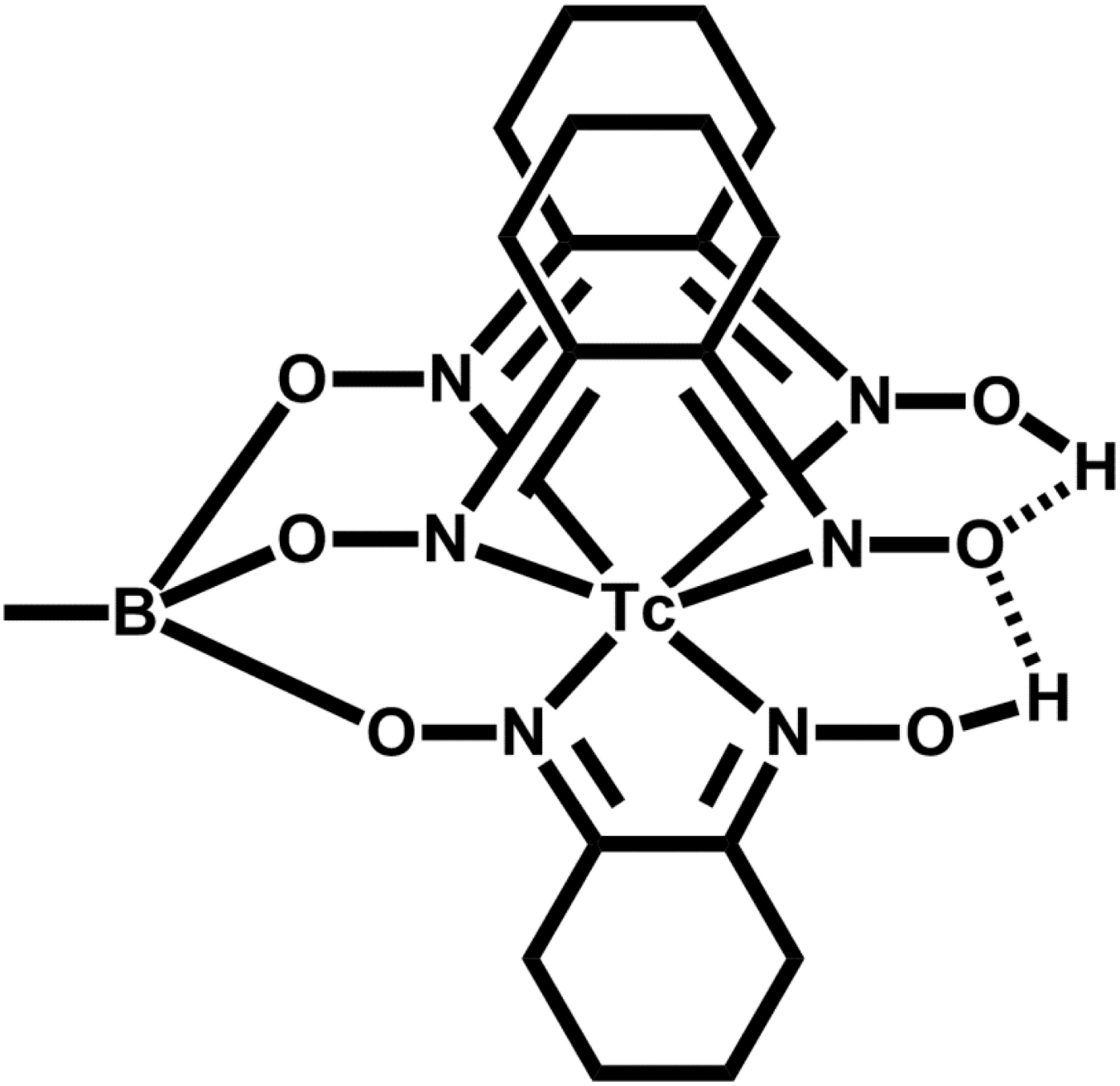

Figure 6.
Structure of Teboroxime.

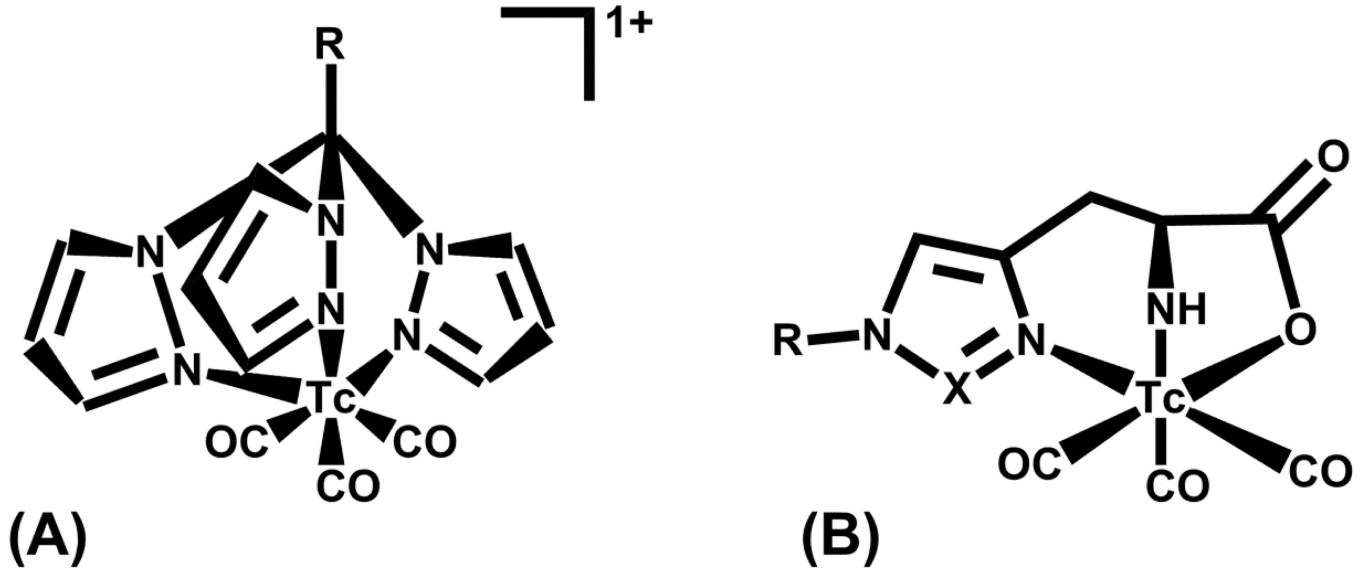

Figure 7.
^{99m}Tc(I) tricarbonyl complexes anchored by (A) tris(pyrazoyl)methane and (B) histadine (X = CH_2, N) functionalized tridentate chelates.

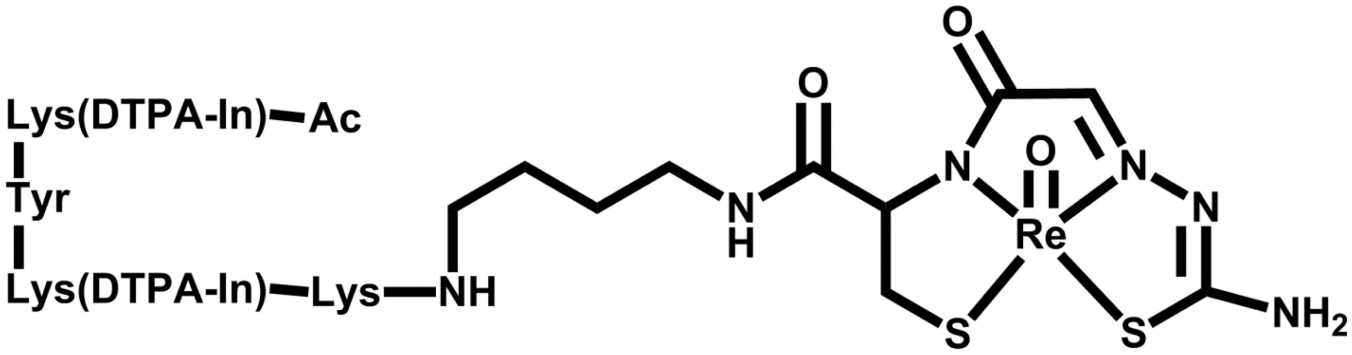

Figure 8.
Structure of Re-N_2S_2-IMP 1.

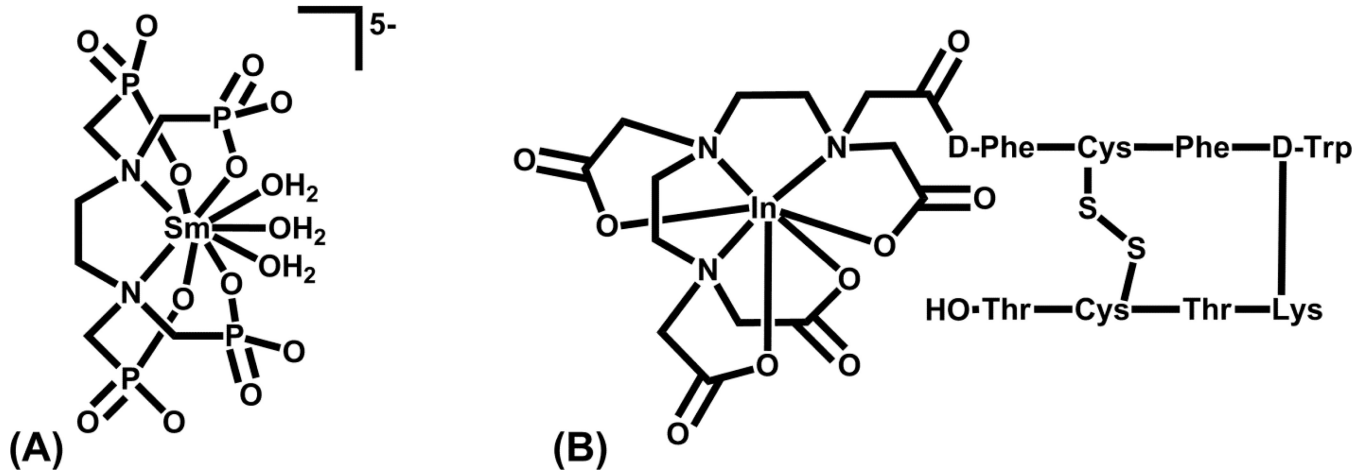

Figure 9.
Structures of (A) Quadramet® and (B) Octreoscan®.

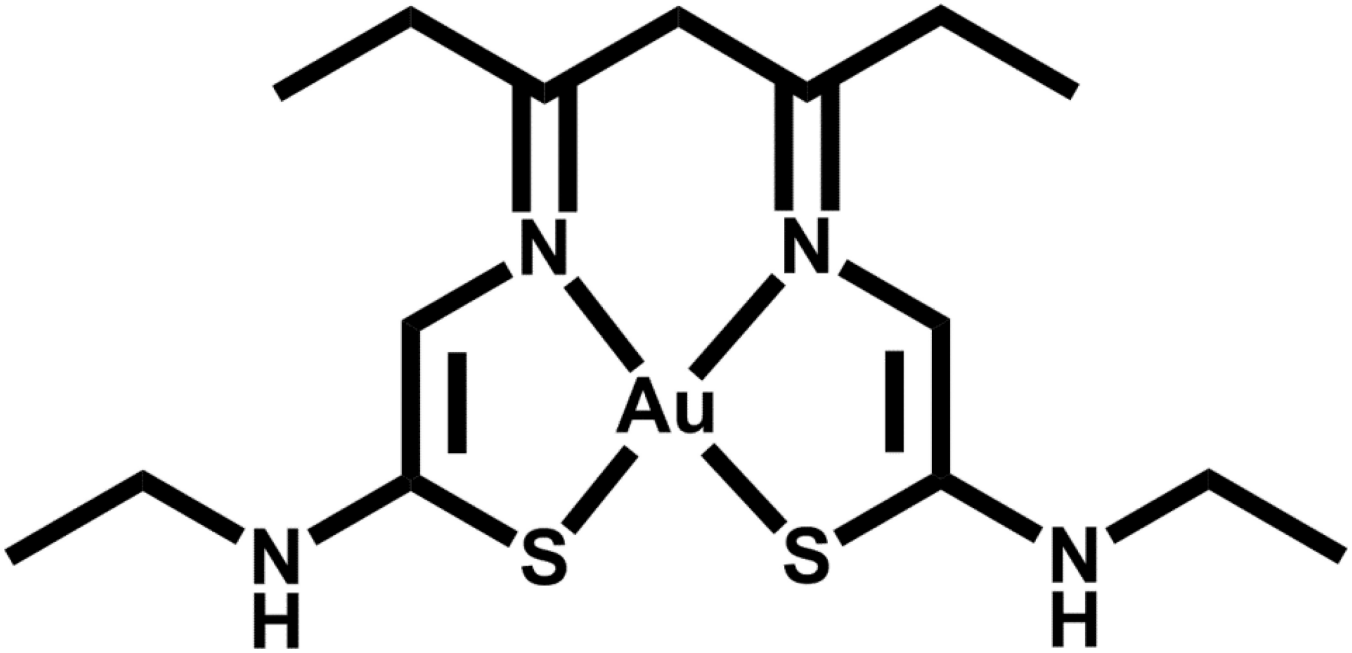

Figure 10.
Structure of [Au(3,4-HxTSE)]

Table 1

Radionuclide properties (National Nuclear Data Center, http://www.nndc.bnl.gov)

Radionuclide	Decay path and maximum particle emission (%)	Gamma emission (%)	Half-life
Cu-62	2.926 MeV β^+ (97.4%) EC decay (2.6%)	511 keV (194.9)	9.74 min
Cu-64	0.653 MeV β^+ (17.6%) EC decay (43.9%) 0.579 MeV β^- (38.5%)	511 keV (35.2)	12.7 h
Cu-67	0.562 MeV β^-	184.6 keV (48.7) 93.3 keV (16.1) 91.3 keV (7)	2.58 d
Ga-67	EC decay	393.5 keV (4.6) 300 keV (16.6) 184.6 keV (21.4) 93.3 keV (38.8)	3.2617 d
Ga-68	0.836 MeV β^+ (90%) EC decay (10%)	1077 keV (3 %) 511 keV (178.3%)	67.71 min
Zr-89	0.902 MeV β^+ (22.74%) EC Decay (77.26%)	511 keV (45.5) 909 keV (99)	3.27 d
Y-90	2.28 MeV β^-		64.053 h
Tc-99m	IT	140 keV (89)	6.0067 h
Rh-105	0.5672 MeV β^-	318.9 keV (19.1)	35.36 h
In-111	EC decay	245 keV (94.1) 171 keV (90.7)	2.8047 d
Pm-149	1.072 MeV β^- (95.9%)	286 keV (3.1)	53.08 h
Sm-153	0.8076 MeV β^-	103 keV (29.25)	46.50 h
Tb-161	0.593 MeV β^-	74.6 keV (10.2)	6.89 d
Dy-166	0.4868 MeV β^-	82.5 keV (13)	81.6 h
Ho-166	1.8547 MeV β^-	80.57 keV (6.56)	26.824 h
Lu-177	0.498 MeV β^-	208.4 keV (10.36) 112.95 keV (6.17)	6.647 d
Re-186	1.07 MeV β^-	137.2 keV (9.47)	3.7186 d
Re-188	2.12 MeV β^-	155 keV (15.6)	17.003 h
Au-198	1.372 MeV β^-	411.8 keV (95.62)	2.695 d
Au-199	0.452 MeV β^-	208.2 keV (8.72) 158.4 keV (40)	3.139 d
Bi-212	2.252 MeV β^- (64.06%) 6.09 MeV α (35.94%) 8.78 MeV α (Po-212)	727.3 keV (6.67)	60.55 min
Bi-213	1.423 MeV β^- (97.8%) 5.87 MeV α (2.1%) 8.375 MeV α (Po-213)	440.5 keV (25.94)	45.59 min
Ac-225	5.83 MeV α 6.34 MeV α (Fr-221) 7.07 MeV α (At-217) 1.423 MeV β^- (Bi-213)	99 keV (5.8)	10 d

Table 2

Peptides and peptide receptors currently under evaluation as biological targeting vectors in diagnostic and therapeutic radiopharmaceuticals

Peptide	Receptor	Tumor expression
Somatostatin (SST)	Somatostatin receptor subtype – 2 (SST2)	Neuroendocrine including gastroenteropancretic, carcinoids, pituitary, breast, brain, small cell lung cancer
Bombesin (BBN) / Gastrin Releasing Peptide (GRP)	Bombesin receptor subtype – 2 (BB2)	Prostate, breast, pancreas, small cell lung, colorectal
α-Melanotropin (α−MSH)	Melanocortin-1 receptor (MC1R)	Melanomas
Neurotensin (NT)	Nuerotensin receptor (NTR1)	Colon, Ewing's sarcoma, breast, exocrine pancreatic cancer
Neuropeptide Y (NPY)	Neuropeptide receptor Y1 (Y-1)	Breast cancer, ovary, adrenal, brain, kidney, Ewing's sarcoma
Cholecystokinin (CCK)	Cholecystokinin-B (CCK-B)	Small cell lung cancer, medullary thyroid cancer, astrocytomas
Arg-Gly-Asp (RGD)	$\alpha_V\beta_3$ integrin	Tumor angiogenesis in melanoma, ovarian, lung carcinoma, neuroblastomas, glioblastomas, breast cancer