Potential Technetium Small Molecule Radiopharmaceuticals

Silvia S. Jurisson* and John D. Lydon

Chemistry Department, University of Missouri, Columbia, Missouri 65211

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Contents

I. Introduction

The element technetium ($Z = 43$) is situated in the middle of the second-row transition series and has no stable isotopes. The chemistry of this element has been developed significantly since 1970 because one of its isotopes, ^{99m}Tc, has become the mainstay of diagnostic nuclear medicine. Technetium-99m in some chemical form is used in more than 85% of the diagnostic scans done each year in hospitals. The nuclear properties of ^{99m}Tc are virtually ideal for diagnostic imaging. Technetium-99m emits a 140 keV γ-ray with 89% abundance which is close to optimum for imaging with gamma cameras found in most hospitals. Its 6 h half-life is sufficiently long to synthesize the ^{99m}Tc-labeled radiopharmaceuticals, assay them for purity, inject them into the patient, and perform the imaging studies yet short enough to minimize the radiation dose to the patient. The inconvenience of purchasing a short half-life radionuclide was overcome by the development of the ^{99}Mo−^{99m}Tc generator, which takes advantage of the transient equilibrium between the parent radionuclide ^{99}Mo (66 h half-life) and the daughter radionuclide ^{99m}Tc (6 h half-life).

$$^{99}\mathrm{Mo} \xrightarrow{66\ \mathrm{hrs}} {}^{99m}\mathrm{Tc} \xrightarrow{6\ \mathrm{hrs}} {}^{99}\mathrm{Tc} \xrightarrow{2.12\times10^5\ \mathrm{yrs}} {}^{99}\mathrm{Ru\ (stable)}$$

The separation of ^{99m}Tc from ^{99}Mo is accomplished by the selective elution of $^{99m}TcO_4^-$ with sterile saline from an alumina column containing $^{99}MoO_4^{2-}$. The transient equilibrium results in optimum isolation of maximum ^{99m}Tc activity with minimal ^{99}Tc buildup every 23−24 h, which is ideal for hospitals. Nuclear medicine departments purchase a new generator every week and elute the $^{99m}TcO_4^-$ to be used in formulating ^{99m}Tc radiopharmaceuticals from the generators daily. The development of the ^{99}Mo−^{99m}Tc generator allowed this radionuclide to become both routinely available and economical.

^{99m}Tc radiopharmaceuticals can be divided into two classes of drugs: "technetium essential" and "technetium tagged". Technetium-essential radiopharmaceuticals are those in which the Tc is an integral part and for which the molecule would not be delivered to its target in the absence of the Tc. Technetium-tagged radiopharmaceuticals are those for which the targeting moiety (e.g., antibody, peptide, hormone) has been labeled with ^{99m}Tc, either directly or by means of a bifunctional chelate, and the ^{99m}Tc essentially reaches the target site as a passenger. A bifunctional chelate is a multidentate ligand, which has appropriate ligating groups for coordination to the metal and also contains a functional group for covalent attachment to the targeting moiety. Most Federal Drug Administration (FDA) approved radiopharmaceuticals fall into the class of technetium-essential drugs, although most of the future agents will likely be members of the class of technetium-tagged radiopharmaceuticals because of the rapid and continuous advances in molecular biology and genetic engineering and their impact on biochemical targeting.

A variety of ^{99m}Tc-based radiopharmaceuticals have been developed and approved by the FDA for determining organ function or assessing disease status by imaging methods. Bone imaging agents were among the first ^{99m}Tc-based radiopharmaceuticals developed, and these involve the coordination of ^{99m}Tc, believed to be in the +4 oxidation state, generally to alkyl diphosphonates such as hydroxymethylenediphosphonate (HMDP) and methylenediphosphonate (MDP). The ^{99m}Tc−diphosphonate radiopharmaceuticals ac-

* To whom correspondence should be addressed. Phone: 573-882-2107. Fax: 573-882-2754. E-mail: JurissonS@missouri.edu.

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Silvia Jurisson received her B.S. degree in Chemistry at the University of Delaware in 1978. She earned her Ph.D. degree with Professor Edward Deutsch at the University of Cincinnati in 1982, studying the inorganic chemistry of technetium radiopharmaceuticals. She then spent 2 years in Canberra, Australia, on postdoctoral fellowships with Professor W. G. Jackson at the University of New South Wales, Duntroon, and with Professor Alan Sargeson at the Australian National University. In 1984 she returned to the United States to work with Professor David Troutner at the University of Missouri, investigating the inorganic and radiochemistry of technetium amine oxime brain imaging agents. She then spent 5 years working as a Senior Research Scientist in the Radiopharmaceutical Research Department at Bristol-Myers Squibb in New Jersey developing potential radiopharmaceuticals based on technetium. In the fall of 1991, she joined the faculty in the Chemistry Department at the University of Missouri, Columbia, where she is now an Associate Professor. Her research interests include radiopharmaceutical chemistry (diagnostic and therapeutic) involving receptor targeting and radioenvironmental chemistry.

After receiving his Ph.D. in Chemistry at the University of Cincinnati (with Professor Edward Deutsch) and completing postdoctoral fellowships at the Australian National University (with Professor Alan Sargeson) and the University of Missouri (with Professor Richard Thompson), Jack Lydon was employed by Sun Chemical in Carlstadt, NJ. In 1993 he returned to the University of Missouri where he carries out research in coordination chemistry related to the development of radiopharmaceuticals.

cumulate in sites of actively growing bone, such as bone metastases or fractures. For more information on this subject, the reader is directed to an excellent review on bone agents.[1] Additional approved small molecule technetium radiopharmaceuticals include ^{99m}Tc−D,L-HM-PAO (Ceretec) and ^{99m}Tc−LL-ECD (Neurolite) for cerebral blood flow imaging, ^{99m}Tc−MAG3 (Technescan) for imaging renal function, and ^{99m}Tc−sestamibi (Cardiolite), ^{99m}Tc−tetrofosmin (Myoview), and ^{99m}Tc−furifosmin (TechneScan Q12; only approved in Europe) for myocardial perfusion imaging (Figure 1). In addition, ^{99m}Tc−sestamibi has also been approved for breast cancer imaging.[2] There are several excellent reviews detailing the structures and functions of these agents.[3−7] Another review by Liu in this issue of *Chemical Reviews* describes small peptide-based radiopharmaceuticals, and this area will therefore not be discussed in this review.

Potential small molecule technetium radiopharmaceuticals will include both potential new technetium-essential agents such as [^{99m}Tc]TRODAT-1 for imaging dopamine receptors and ^{99m}Tc−BnAO for imaging hypoxia, as well as the new bifunctional chelating agents which when coupled with appropriate targeting moieties, such as peptides or antibodies, form the basis of technetium-tagged agents. Although a plethora of basic technetium inorganic chemistry has been reported, only that relevant to the topics of this review are covered. This review is subdivided into three categories: (1) receptor-specific molecules which encompasses neuroreceptor-, hormone/steroid receptor-, and multidrug resistance (MRD1) targeting molecules; (2) hypoxia targeting molecules; and (3) new potential bifunctional chelating agents. We have limited this review to cover the literature from 1995 to 1998. Although we have attempted to be comprehensive, we apologize in advance for any inadvertent omissions.

II. Receptor-Specific Molecules

Receptor-specific molecules may be either technetium-essential or technetium-tagged moieties. Radiolabeled peptides and antibodies for targeting specific tumor surface antigens or receptors will, in general, be technetium-tagged radiotracers in which a bifunctional chelate (vide infra) is appended to the biomolecule for radiolabeling with ^{99m}Tc. Radiolabeled peptides/antibodies are covered by Liu in another article in this issue of *Chemical Reviews*. Small molecule ^{99m}Tc receptor targeting molecules may by necessity become technetium-essential molecules, since the ^{99m}Tc chelate moiety will be a large portion of the molecule. Many of the small molecule receptors have natural ligands as targets with molecular weights on the order of a few hundred Daltons. A ^{99m}Tc chelate moiety results in a minimum molecular weight increase of 300 Da, thus at least doubling the size of the resultant receptor binding molecule. Both the bifunctional chelate approach (appending a ^{99m}Tc chelate to the biomolecule) and an integrated approach (incorporating the ^{99m}Tc binding site into the biomolecule itself) have been used with varying degrees of success. This section is subdivided into neuroreceptor targeting molecules, steroid/hormone receptor targeting molecules, multidrug resistance targeting molecules, and other receptor targeting molecules.

A. Neuroreceptor Targeting Molecules

Neuroreceptors have been the target of many potential radiopharmaceuticals radiolabeled with ^{99m}Tc because of their implication in a wide range of disorders, such as Parkinson's disease, schizophrenia, Alzheimer's disease, epileptic seizures, and drug addiction. Targeting neuroreceptors with ^{99m}Tc complexes requires a balance between size, lipophilicity,

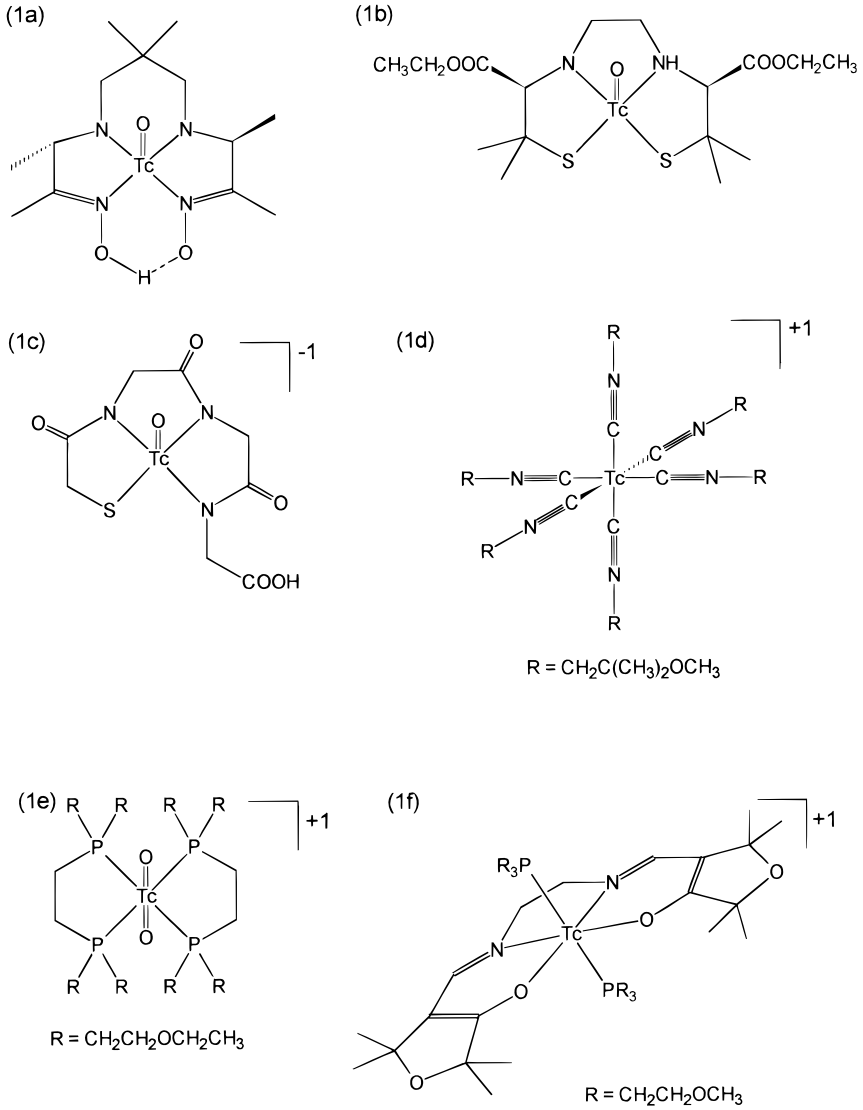


Figure 1. Some currently approved ^{99m}Tc radiopharmaceuticals: (a) ^{99m}Tc−D,L-HM-PAO (Ceretec); (b) ^{99m}Tc−LL-ECD (Neurolite); (c) ^{99m}Tc−MAG_3 (Technescan); (d) ^{99m}Tc−sestamibi (Cardiolite); (e) ^{99m}Tc−tetrofosmin (Myoview); (f) ^{99m}Tc−furifosmin (TechneScan Q12).

and receptor binding. The molecules must be neutral to cross the blood brain barrier by diffusion. The molecules must not be too large (MW < 600), must have an appropriate lipophilicity (log $P = 1.5-3$), and must have a high selectivity and specificity for the particular receptor.[8] Meeting these requirements and incorporating a ^{99m}Tc chelate into the molecule has been very difficult to achieve. The greatest obstacle to a successful ^{99m}Tc-based neuroreceptor imaging agent remains the low overall brain uptake of the ^{99m}Tc complexes.

The dopamine transporter (DAT) is the neuroreceptor which has received the most recent attention and has shown the most promise for a successful ^{99m}Tc-labeled neuroreceptor targeting moiety. The DAT is located on the presynaptic dopamine neurons concentrated in the striatum of the brain and has been implicated in Parkinson's disease and schizophrenia. Several groups have targeted the DAT using tropane analogues that are derivatives of well-known DAT antagonists (β-CIT or β-CFT; Figure 2a). Kung et al.[9−11] developed [^{99m}Tc]TRODAT-1 (Figure 2b) in which a diaminodithiol ligand is complexed with ^{99m}Tc and a tropane analogue is derivatized from one nitrogen. This led to the formation of two diastereomers on coordination to the TcO^{3+} core, both syn relative to the Tc−oxo group. The diastereomers both show nanomolar binding affinities (K_i values) for DAT in rat striatal homogenate (13.87 and 8.42 nM for the two diastereomers; 14.1 nM for the mixture; determined with the nonradioactive Re analogues).[9] Imaging with [^{99m}Tc]TRODAT-1 in humans demonstrated localization in the basal ganglia consistent with DAT binding, and the dosimetry studies showed this agent to be safe for administration.[12] Madras et al.[13,14] developed [^{99m}Tc]Technepine (Figure 2c), also a tropane analogue which is conjugated to the amine nitrogen of a dithiol−amide−amine ligand coordinated to the TcO^{3+} core. Again, two diastereomers, both syn relative to the Tc−oxo group, were observed. Both diastereomers showed nanomolar IC50 values for the DAT in cynomologous monkey brain homogenate (7.38 and 4.04 nM for the two diastereomers; 5.99 nM for the mixture; determined with the nonradioactive Re analogues).[13] Imaging with [^{99m}Tc]-Technepine in the female rhesus monkey showed

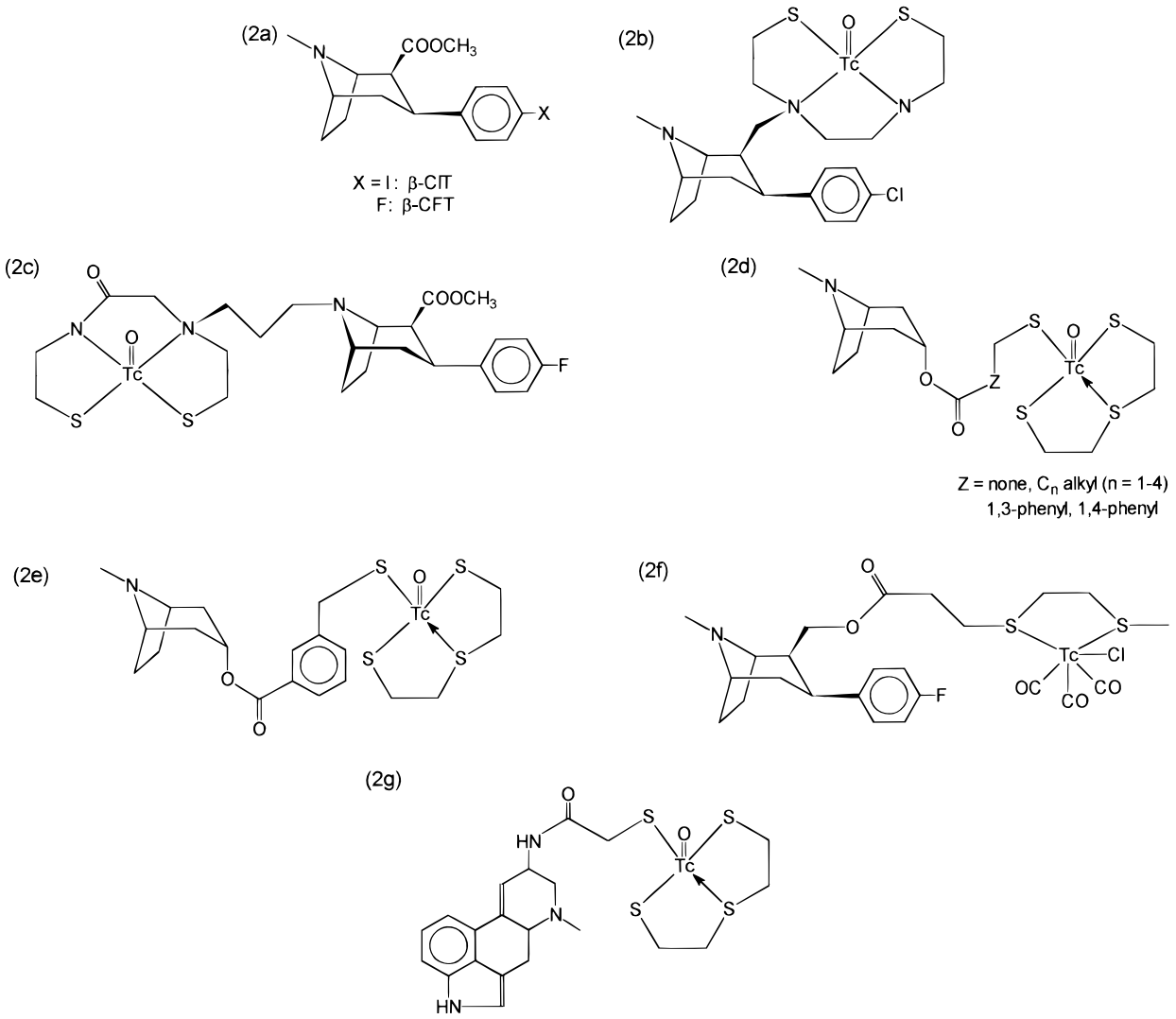


Figure 2. Dopamine transporter-selective molecules: (a) β-CIT or β-CFT; (b) [^{99m}Tc]TRODAT-1; (c) [^{99m}Tc]Technepine; (d) [^{99m}Tc]-3 + 1-α-tropanol; (e) [^{99m}Tc]-3 + 1-α-tropanol, Z = 1,3-phenyl; (f) [^{99m}Tc]TROTEC-1; (g) [^{99m}Tc]-3 + 1-ergoline.

striatal uptake within minutes of intravenous injection, and activity was observed in the striatum for up to 3 h.[13] Johannsen et al.[15] used the 3 + 1 ligand system for TcO^{3+} to derivatize with a tropane analogue for targeting the DAT (Figure 2d). This particular 3 + 1 system uses the dithiolthioether tridentate ligand and a monodentate thiol with an appended α-tropanol moiety. The α-tropanol analogue in which the Z group was a 1,3-phenyl moiety (Figure 2e) demonstrated the highest observed IC50 value of 2.4 μM in cloned human dopamine transporter cells.[15] Alberto et al.[16] synthesized [^{99m}Tc]-TROTEC-1 using their new Tc(I) synthon, $Tc(CO)_3(H_2O)_2Cl$, and a dithioether-derivatized tropane analogue which forms only one diastereomer and is less polar than the TcO^{3+} molecules described above (Figure 2f). The IC50 value of TROTEC-1 for human cloned DAT was found to be 1.4 nM (using the nonradioactive Re analog).[16] Johannsen et al.[17] also used the 3 + 1 ligand system with the TcO^{3+} core to target the dopamine transporter with a functionalized ergot alkaloid (Figure 2g). The monodentate 2-mercaptoacetyl group was derivatized with an 8-α-amino-6-methyl-ergoline moiety.

Seratonin receptors have shown involvement in Alzheimer's disease, schizophrenia, anxiety, depression, and suicide. Johannsen et al.[18,19] targeted the 5-HT_2 seratonin receptors using the 3 + 1 ligand system and the TcO^{3+} core. The monodentate thiol was derivatized to include models of the nitrogen and phenylalkyl portions or the quinazoline portion of ketanserin (Figure 3a), the prototypic 5-HT_2 receptor antagonist. The ^{99m}Tc molecule showing the highest 5-HT_2 receptor affinity was that in which the monodentate thiol contained a methylamine and a phenylalkyl moiety (Figure 3b) and the ^{99m}Tc chelate replaced the quinazoline portion of ketanserin. This molecule was found to have an IC50 value of 7 nM in rat brain homogenate against [^{3}H]-ketanserin. Only 0.4% of the injected dose was observed in the brain at 10 min. In subsequent work,[18] the same group endeavored to improve the brain uptake by modifying the lipophilicity. They demonstrated in a series of five variations of the monothiolate ligand that the pK_a of the amine group could be lowered by the addition of an ether functionality, thus increasing the effective lipophilicity and the resultant brain uptake. The best candidate, as judged by a brain

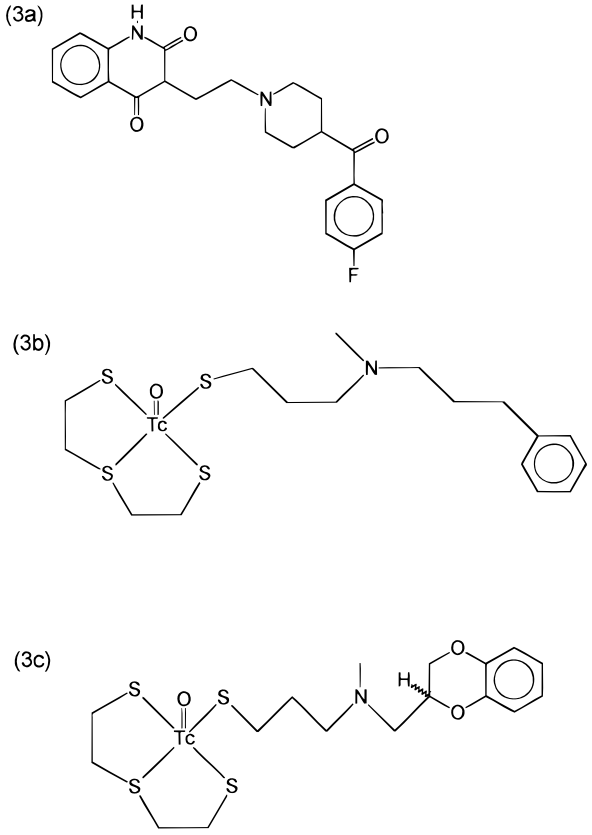


Figure 3. Seratonin 5-HT_2 selective molecules: (a) Ketanserin; (b) [^{99m}Tc]-3 + 1-containing methylamine and phenylalkyl groups of ketanserin; (c) [^{99m}Tc]-3 + 1-containing methylamine and ether-containing phenylalkyl groups of ketanserin.

uptake of 1.3% at 5 min, is shown in Figure 3c.

Alzheimer's disease is characterized by the development of neuritic amyloid plaques.[20−22] It is not clear at this time whether the amyloid plaque causes or results from Alzheimer's disease. Congo Red and Chrysamine G (Figure 4a and 4b) are aromatic dyes which are used for staining amyloid plaque in tissue sections of Alzheimer's patients postmortem.[20−22] Han et al.[23] synthesized and evaluated a Tc(I)−tetrakis-(*tert*-butylisonitrile) complex containing a bidentate Congo Red or a bidentate Chrysamine G analogue for binding amyloid plaque in vitro. They replaced the biphenyl moiety in Congo Red or Chrysamine G with a bipyridyl unit capable of binding to metals (Figure 4c). The resultant Tc(I) complexes (Figure 4d) were evaluated in vitro for binding to β1−40 amyloid fibrils and the minor brain amyloid peptide NAC. Both complexes showed affinity for both types of amyloid in the submicromolar range, values comparable to Congo Red and Chrysamine G binding to amyloid fibrils.[23] Although they show affinity for amyloid plaque similar to Congo Red and Chrysamine G, they are charged monocationic complexes and would not be able to cross the intact blood brain barrier by diffusion.

B. Hormone/Steroid Receptor Targeting Molecules

The estrogen, progesterone, and androgen receptors may be useful for targeting breast and prostate

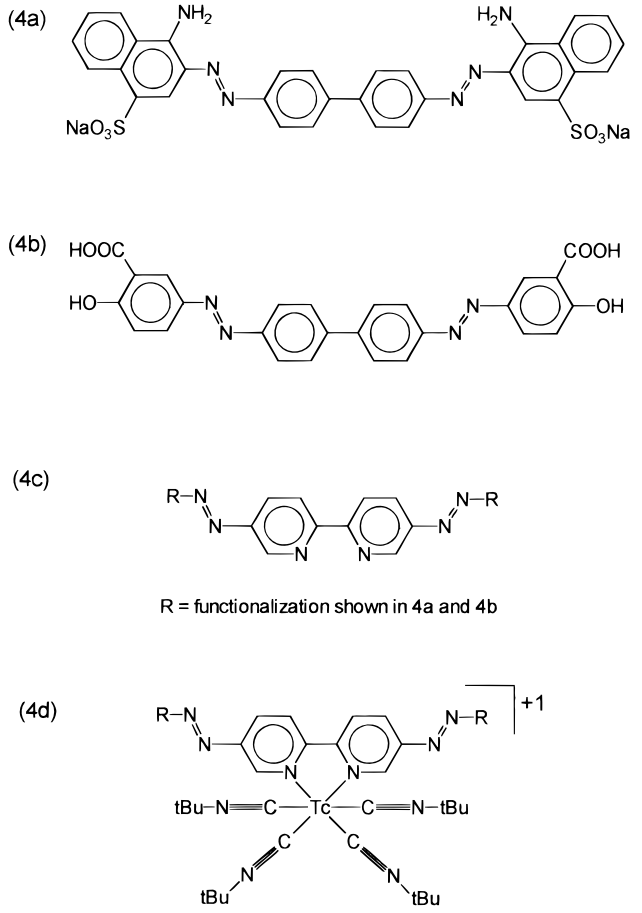


Figure 4. Amyloid plaque targeting molecules: (a) Congo Red; (b) Chrysamine G; (c) Metal binding analogues; (d) Tc(I)−*t*Bu−isonitrile analogues.

cancers. Estrogen receptors and progesterone receptors are present in about 65% of human breast cancers.[24,25] The presence or absence of these receptors in cases of breast carcinoma is an important determinant for the therapeutic regimen (hormonal or chemical) that is likely to be most effective in treatment. Patients with estrogen/progesterone receptor positive breast cancer respond with a remission rate of ca. 50−65% to endocrine therapy. Prostate cancer has been found to be responsive to both androgens and estrogens and contains androgen receptors, although their levels are relatively low.[26,27] Targeting the steroid receptors with ^{99m}Tc complexes has been the focus of several research groups and has proven quite challenging. Steroids are relatively small molecules (MW ca. 300), and appending a ^{99m}Tc chelate will at least double its size and more than double its mass. In addition, the nonspecific binding of the resultant molecules to nonreceptor macromolecules and their metabolic and chemical stability must be considered. The nonspecific binding of the steroid-derivatized ^{99m}Tc chelates has been the greatest problem in going from in vitro cell binding studies to in vivo imaging studies.

Katzenellenbogen has been at the forefront of radiolabeling steroids for targeting breast cancer and prostate cancer.[6,24] He has synthesized and evaluated a number of estradiol and progestin derivatives appended to diaminedithiol technetium(V) and rhenium(V) oxo complexes for their affinity for the

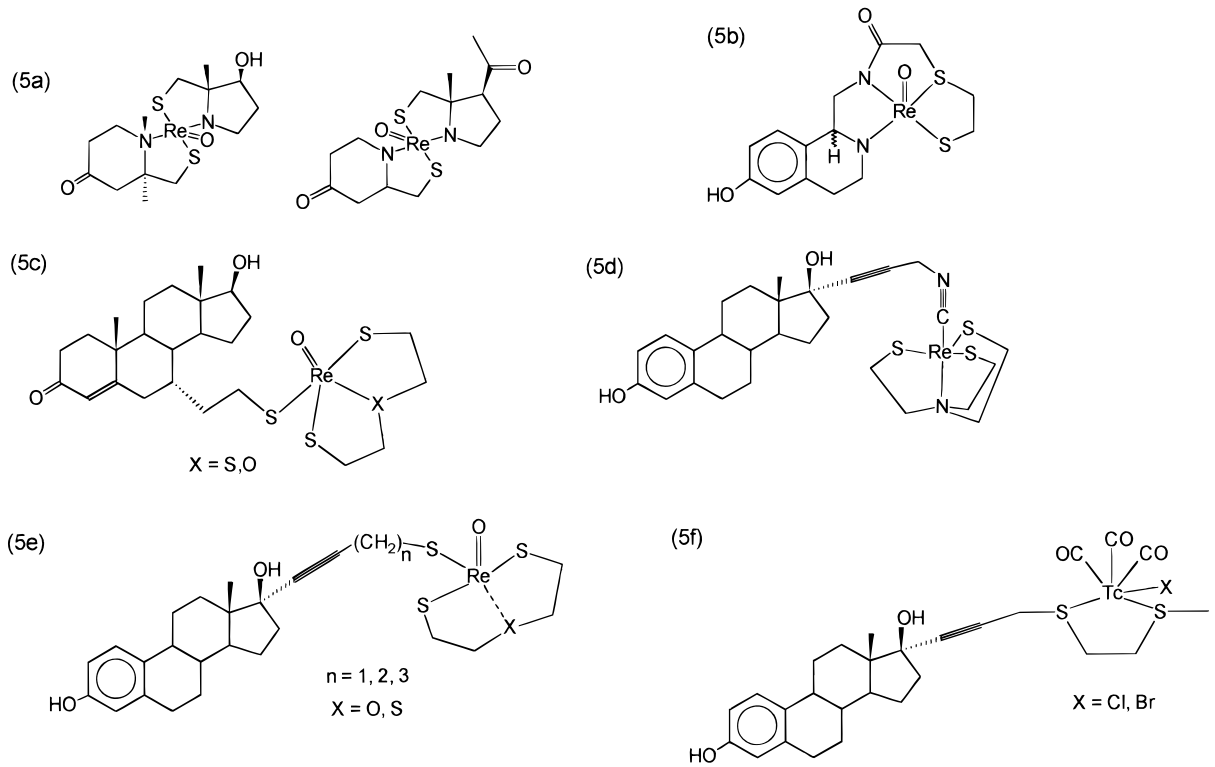


Figure 5. Hormone receptor targeting molecules: (a) two different double bidentate-N,S rhenium(V)oxo progesterone and androgen analogues, (b) integrated N_2S_2-rhenium(V)oxo estradiol analogue, (c) ReO(3 + 1)-progesterone analogue, (d) Re(III)(4 + 1) estradiol, (e) ReO(3 + 1) estradiol, (f) $TcX(CO)_3$(dithioether−estradiol) analogue.

estrogen or progesterone receptors.[6,24] Several of these molecules showed high binding affinity for the progesterone receptor; however, their nonspecific binding in vivo was very unsatisfactory.[28−30] Katzenellenbogen has recently applied an integrated approach to incorporate ^{99m}Tc and Re into a molecule that when complexed to the metal resembles an androgen or progesterone receptor binding steroid.[6,24,31] Thus, the ^{99m}Tc is not appended to the bioactive molecule in a bifunctional chelate approach but has become an integral and essential part of the molecule. Two systems have been developed to look like steroid molecules on coordination of the metal (Tc or Re) using either two different bidentate ligands or an integrated tetradentate ligand. The double bidentate ligand system was based on two different aminethiol chelates (Figure 5a), and surprisingly, only one predominant Re(V) and Tc(V) complex formed.[6,32,33] The specific receptor binding of these molecules for the progesterone and androgen receptors was found to be quite low, even though they resembled progesterone and 5α-dihydrotestosterone. In addition, the lipophilicities of these two integrated complexes were found to be significantly lower than the steroids, and their in vivo stability was found to be poor.[6,33] Most recently, Hom and Katzenellenbogen designed a tetradentate oxorhenium(V) complex mimic of a steroidal estrogen using the integrated approach.[31] A Tc/Re chelate was designed that mimics the steric properties of the steroid and has nearly the same molecular volume. A tetradentate amino−amido−thioether−thiol ligand system was designed for Tc(V) which forms a classic Re(V) oxo complex (Figure 5b). Two diastereomers resulted on metal complexation in which the chiral (unique) proton was either syn or anti to the Re−oxo group. Both diastereomers were found to have similar partition coefficients (2.62 and 2.69). The relative binding affinity for the estrogen receptor, however, was very low.[31] Differences in the dipole moments between the integrated Re complex and estradiol and differences in the specific functionalities present on the two molecules are used to rationalize the low binding affinity observed. It will be difficult to incorporate all the properties of a steroid receptor binding molecule into an integrated Tc-essential steroid mimic; however, this approach may yet prove to be the most successful.

Johannsen and co-workers have extended their 3 + 1 ligand system for Tc and Re to target the estrogen and androgen receptors.[26,34] Dithiol−thioether and dithiol tridentate ligands and monodentate thiol-derivatized estradiols (on the A ring) were used to prepare model Re(V) oxo complexes for targeting the estrogen receptor (Figure 5c).[34] No stability data, in vitro receptor binding data, or in vivo biodistribution data are reported. The same 3 + 1 ligand system described above was used to prepare Re(V) oxo complexes targeting the androgen receptor except that the monodentate thiol was derivatized with a testosterone (on the B ring).[26] Again, no biological data are reported.

The preparation of a new 17α-substituted estradiol rhenium(III) model complex based on a (4 + 1) mixed-ligand system was recently reported (Figure 5d).[35] In the same paper, the binding affinities of eight rhenium 17α-substituted estradiol conjugates were presented. These include six Re(V) (3 + 1) complexes varying in the estradiol alkyl linker group and the tridentate SSS or SOS coligand (Figure 5e), the Re-

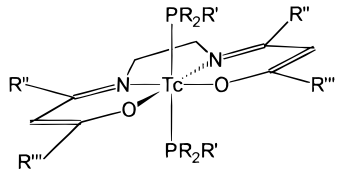
(III) (4 +1) example, and a Re(I) dithioether tricarbonyl (Re analogue of Figure 5f, X = Br). The best relative binding affinity (RBA), where 3,17β-estradiol RBA = 100%, was found for the Re(V) (SSS + 1) complex (RBA of 10.5 at 25 °C), with the longest linker (propyl).

The tricarbonyltechnetium(I) and rhenium(I) chemistry of Alberto was used to synthesize neutral chlorotricarbonyldithioether complexes of Tc(I) and Re(I) in which an estradiol analogue was incorporated into the dithioether ligand (Figure 5e, X = Cl).[36] The Re and ^{99}Tc complexes were prepared and fully characterized in this study. No stability or biological data are reported.

C. Multidrug Resistance (MRD1) Targeting Molecules

Multidrug resistance (MDR) is a pathological state indicating the development of resistance by tumors to chemotherapeutic agents. This is believed to be one of the primary reasons for treatment failure in cancer patients. MDR is best characterized by the overexpression of P-glycoprotein (Pgp), a transmembrane pump that transports cytotoxic materials out of the cells.[37−39] Multidrug resistance has been shown to affect a wide range of compounds which are lipophilic and monocationic at physiologic pH. The development of agents which can block the action of Pgp, known as MDR modulators, is a target of pharmaceutical development since they may reestablish the cytotoxic effects of chemotherapeutic agents in tumor cells when administered simultaneously.

A number of research groups have been interested in developing diagnostic agents for assessing MDR. The three ^{99m}Tc myocardial perfusion agents (^{99m}Tc−sestamibi, ^{99m}Tc−tetrofosmin, ^{99m}Tc−furifosmin (^{99m}Tc-Q12)) are all lipophilic monocations and have been evaluated for potential utility in diagnosing and monitoring multidrug resistance (Figure 1d, 1e, 1f).[37−39] Technetium-99m−sestamibi is a monocationic hexakis-isonitrile ((2-methoxy-2-methyl-1-propyl)isonitrile) complex of Tc(I) which is an approved myocardial imaging agent. This agent has also shown uptake in a variety of tumors.[40−42] Technetium-99m−sestamibi was shown to be transported out of tumor cells expressing MDR by the Pgp glycoprotein.[38,43] Technetium-99m−tetrofosmin is a monocationic Tc(V) dioxo complex containing two bidentate phosphines (1,2-bis((bis-ethoxyethyl)phosphino)ethane) in the equatorial plane of the octahedral complex.[44] Tech-



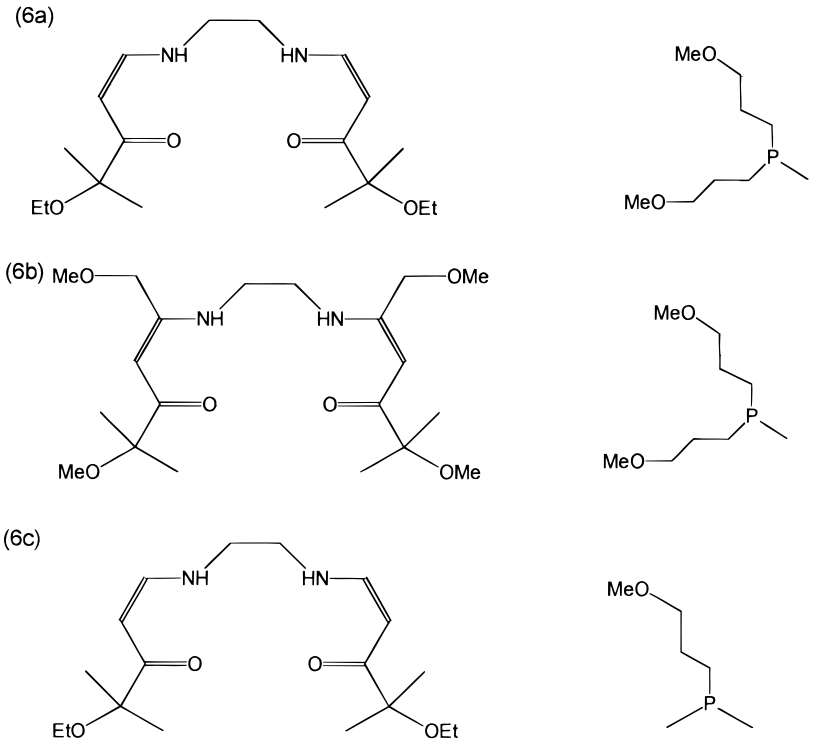


Figure 6. General structure of the ^{99m}Tc−Q compounds of the type *trans*-[^{99m}Tc(phosphine)$_2$(Schiff base)]$^+$ and then the Schiff base and phosphine ligands for (a) Q57, (b) Q58, (c) Q63.

netium-99m−furifosmin is a monocationic Tc(III) complex with a tetradentate Schiff base (1,2-bis-[[(dihydro-2,2,5,5-tetramethyl-3(2*H*)-furanonato)-methylene]amino]ethane) occupying the equatorial plane and phosphine ligands (tris(3-methoxy-1-propyl)phosphine) occupying the two remaining trans sites in the octahedron.[45] Technetium-99m−sestamibi and ^{99m}Tc−tetrofosmin display similar MDR behavior in multidrug resistant human KB-8−5 carcinoma cells and in human KB3−1 nonmultidrug resistant cells.[37] Both showed enhanced uptake in the MDR cells in the presence of a modulator (cyclosporin A) and demonstrated significant uptake in non-MDR cells, which could be vastly reduced in the presence of valinomycin. Technetium-99m−furifosmin was not nearly as effective in differentiating MDR from non-MDR cells or in demonstrating Pgp involvement. A large number of Tc−Q compounds related to ^{99m}Tc−furifosmin were also evaluated in this study.[37] Three of the Q series of compounds (^{99m}Tc−Q57, ^{99m}Tc−Q58, ^{99m}Tc−Q63; Figure 6a, 6b, and 6c) demonstrated similar or somewhat higher effectiveness as MDR transport substrates compared to ^{99m}Tc−sestamibi and ^{99m}Tc−tetrofosmin.[37] Development of an agent for noninvasively imaging the Pgp transporter in vivo will aid in the understanding of multidrug resistance in cancer patients. The ultimate goal of a successful MDR imaging agent would be the determination of chemotherapeutic regimens before and during treatment to potentially give cancer patients the best opportunity for a successful outcome.

D. Other Receptor Binding Molecules

Sigma receptors have been shown to be expressed on a variety of human tumors including melanoma, breast cancer, nonsmall cell lung carcinoma, and prostate cancer.[46] John et al. prepared and evaluated a ^{99m}Tc complex with a diaminodithiol ligand containing a nitrogen-appended alkylaminopiperidine moiety for targeting sigma receptors, [^{99m}Tc]BAT-EN6 (Figure 7a).[46] The TcO(N_2S_2) group was substituted for the haloaryl portion of 4-IPEMP (Figure 7b), a known sigma binding ligand. [^{99m}Tc]BAT-EN6 showed high specific binding (K_i = 42.7 nM in human breast ductal carcinoma). Two isomers were observed in which the pendant alkylaminopiperdine moiety is syn or anti to the Tc−oxo group. The specificity of the two isomers has not yet been determined. Not surprisingly, the primary clearance route of this neutral molecule is through the hepatobiliary system.

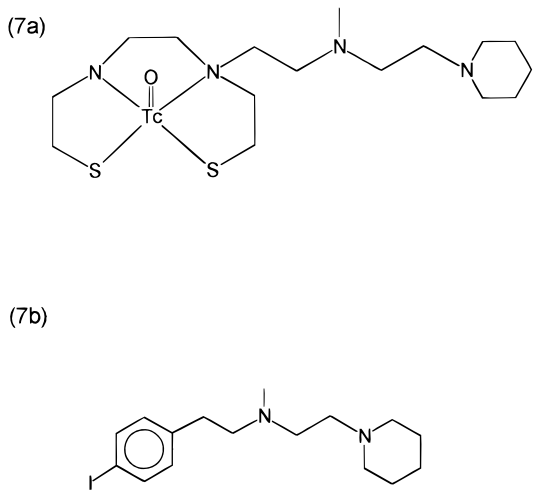


Figure 7. Sigma receptor targeting molecules: (a) [^{99m}Tc]-BAT-EN6, (b) 4-IPEMP.

III. Hypoxia Targeting Molecules

Identifying viable versus necrotic tissue following myocardial infarction and strokes and determining the oxygen status of solid human tumors remain important challenges for the physician in determining the treatment regime. Tumors which are hypoxic (low oxygen content) appear to fare worse in response to radiotherapy, some chemotherapy, and even some surgery.[47,48] Hypoxic tissue can be differentiated from oxic tissue (normal oxygen concentrations) and necrotic tissue (dead or nonviable tissue) based on differences in the reduction potential within the cells. To function as a hypoxic tissue marker, a radiopharmaceutical must be able to traverse and enter the cell and it must have a reduction potential accessible to the hypoxic tissue but not the normal tissue. Once the compound has entered the hypoxic cells, it should be reduced and trapped, leading to "hot spot" imaging rather than defect (lack of uptake) imaging. Hypoxic markers will be unaffected in normal oxygenated tissues and thereby not retained because they will diffuse back out of the cells. Because necrotic tissue receives no blood flow, these agents will not be delivered to nonviable tissue.

Misonidazole is considered the gold standard hypoxia marker to which all other compounds are compared.[49] An agent based on ^{99m}Tc would be optimal because of the ready availability and lower cost of this radionuclide compared to the cyclotron-produced F-18, which has been used to radiolabel misonidazole.[50−53] Currently there are two basic types of ^{99m}Tc compounds under investigation as hypoxic tissue markers: BMS 181321[49] and BMS 194796 (also known as BRU 59−2) (nitroimidazole-derivatized TcO^{3+} amine oxime complexes) and ^{99m}Tc−HL-91[55] (a TcO^{3+} amine oxime complex) (Figure 8a and 8b). DiRocco et al.[54] showed BMS 181321, TcO(PnAO-2-(2-nitroimidazole)), to localize in hypoxic regions in an ischemic rabbit myocardium analogously to C-14-labeled misonidazole, and the ischemic/nonischemic ratio for the two compounds was nearly identical. The second-generation ^{99m}Tc hypoxia imaging agent from the Bracco group is BMS 194796 (or BRU 59−2), ^{99m}-Tc−5-oxa-6-(2-nitroimidazole)propyleneamine oxime (Figure 8c).[49] Substitution of an oxygen for a methylene group in the propylene backbone and a shift of the 2-nitroimidazole functionality from the 2-position in BMS 181321 to the 6-position yields the second-generation agent BMS 194796 (now BRU 59−2). Moving the 2-nitroimidazole group to the 6-position and 5-oxa substitution of the propyleneamine oxime backbone gave a mixture of four isomers (two sets of diastereomeric pairs of enantiomers). Although separation of the two diastereomeric pairs was possible, they were found to interconvert.[49] Fortunately, no difference was observed in the performance of the two diastereomers in ischemic tissue. BMS 194796 (or

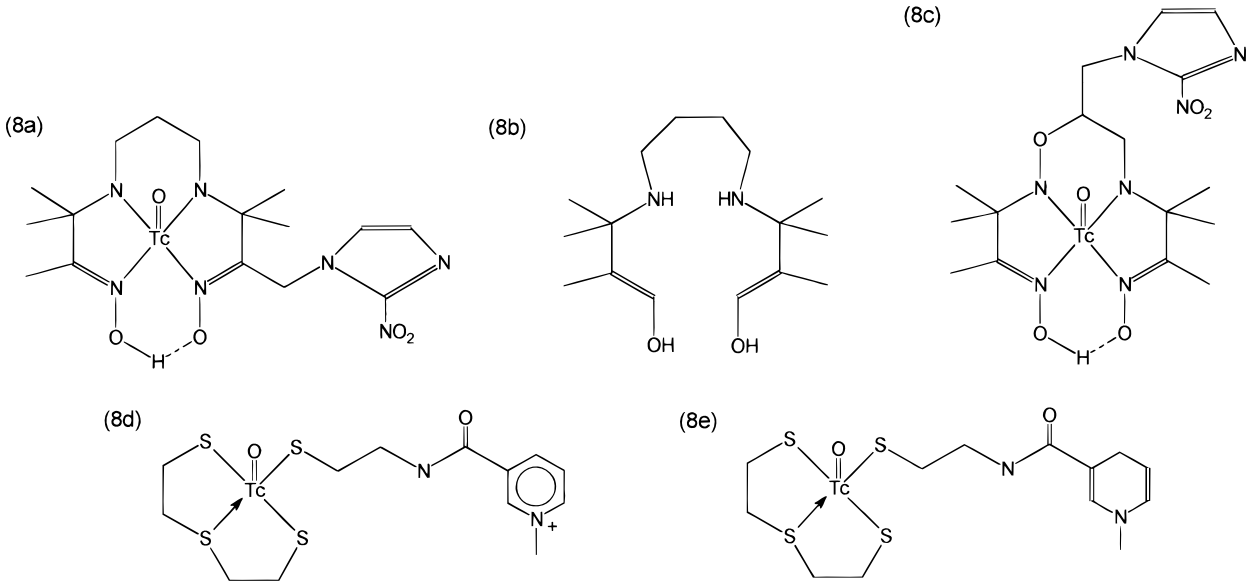


Figure 8. Hypoxia tissue markers: (a) [^{99m}Tc]-BMS-181321, (b) HL-91 (BnAO), (c) [^{99m}Tc]-BMS-194796 (now [^{99m}Tc]-BRU-59-2), (d) [^{99m}Tc]-3 + 1-pyridinium analogue, (e) [^{99m}Tc]-3 + 1-dihydropyridine analogue.

BRU 59−2) shows higher target-to-nontarget ratios and improved uptake in ischemic regions compared to BMS 181321 in a rabbit model.[54] Ischemic myocardium was readily visualized by gamma camera imaging in an in vivo pig model.[56]

Technetium-99m−HL-91 is a non-imidazole-containing Tc(V) oxo complex whose structure remains uncertain. HL-91 is 4,9-diaza-3,3,10,10-tetramethyldodecan-2,11-dione dioxime (BnAO), which is a tetradentate amine oxime ligand containing a butane moiety between the two coordinating amine nitrogens capable of forming a seven-membered chelate ring on coordination with a metal. Propylene and ethylene groups between the two amine nitrogens are known to lead to Tc(V) monooxo complexes on coordination of the tetradentate amine oxime ligands, while the analogous pentylene moiety leads to a Tc(V) dioxo complex.[57] The Tc(V) oxo complex with the butylene analogue, HL-91, has never been structurally characterized. Kanni et al.[58] very recently reported the crystal structures of the Tc(V) nitrido complexes with the propylene, butylene, and pentylene tetradentate amine oxime ligands, and all three are analogous, forming distorted octahedra with water molecules coordinated in the position trans to the nitrido group. In all cases, the Tc(V) sits above the plane of the four amine oxime nitrogens toward the bulky nitrido group. Obviously the Tc(V) nitrido complexes with these ligands are somewhat different from that observed with the Tc(V) oxo complexes, in that different cores were observed for the Tc(V) oxo complexes as the chelate ring size became larger.[57] Although the structure of ^{99m}Tc−HL-91 remains uncertain, its uptake and retention in ischemic and hypoxic tissue was clearly demonstrated in the isolated perfused rat heart.[55] The greatest uptake was observed in low flow ischemic myocardium. Regional myocardial ischemia was demonstrated in vivo in dogs by gamma camera imaging.[59]

Kneiss et al.[60] reported preliminary studies on nicotinamide- and pyridinium-derivatized monodentate thiols for preparing ^{99m}Tc complexes as potential redox markers. A tridentate dithiolthioether chelate and the nicotinamide and methylpyridinium-substituted monodentate thiol were used to prepare $Tc^{(V)}O$ and $Re^{(V)}O$ 3 + 1 complexes. Reduction of the pyridinium complexes (Figure 8d) of Tc and Re with dithionate yielded the 1,4-dihydropyridine analogues (Figure 8e). The reduced analogues were only characterized in solution by the characteristic dihydropyridine absorbance at ca. 360 nm because of their sensitivity to reoxidation by air.[60] Further research with these type of compounds may lead to redox-active ^{99m}Tc radiotracers.

IV. New Potential Bifunctional Chelates (BFC) For Tc-99m

The development of schemes for bifunctional chelation of the ^{99m}Tc center to biomolecules (or receptor avid molecules) continues to be a very active endeavor. Refinement of the previously demonstrated Tc(V) oxo tetradentate amino and/or amido $N_xS_{(4-x)}$ systems (e.g., BAT, MAMA, etc.) and the TcO(3 + 1) systems using a combination of linear tridentate and monodentate thiolate ligands occupies much of the BFC effort. Expansions on the functionalized peptide (e.g., MAG_3) approach also continues to be a fertile area. Likewise, the use of Tc-labeled hydrazine (e.g., HYNIC) derivatives which were earlier applied for the development of BFC agents continues to undergo further development. Relatively new approaches to bifunctional chelation of technetium include the use of Tc(I) complexes incorporating the $Tc(CO)_3^+$ core. These include two subtypes, namely, the $CpTc(CO)_3$ category in which the bioactive molecule is appended to the cyclopentadienyl ring and the group of compounds which maintain the *fac*-$Tc(CO)_3$ feature while completing the octahedral sphere with a variety of appropriate ligands. A relatively new and novel class of water-soluble phosphines has recently been utilized to develop new bifunctional chelation systems.

A. HYNIC-Containing Chelates

Although HYNIC (2-hydrazinonicotinamide) has previously been used for labeling bioactive molecules (e.g., chemotactic peptides, IgG, somatostatin analogues, and oligonucleotides), its mode of coordination was not well understood. Recent work on bifunctional chelation of ^{99m}Tc using the HYNIC motif has been dominated by the groups of Davison and Edwards.

Davison has devoted a substantial effort to characterize the basic coordination chemistry of organic hydrazines using the HYNIC surrogates 2-hydrazinopyridine,[61−63] 2-hydrazino-imidazoline,[62] and 2-hydrazino-4-(trifluoromethyl)pyrimidine.[64] Three basic modes of coordination have been found, including a monodentate diazenido and the two bidentate modes involving the hydrazino and heterocyclic nitrogens. The ^{99}Tc and Re model compounds were synthesized and fully characterized. This work was subsequently applied to the development of a ^{99m}Tc-labeled chemotactic peptide−HYNIC conjugate using pyrimidine thiol coligands.[62]

The DuPont group (Edwards) has demonstrated the utility and advantages of a ternary ligand system consisting of tricine, the water-soluble phosphine TPPTS (trisodium triphenylphosphine-3,3′,3″-trisulfonate), and the HYNIC conjugate in a study targeting a platelet receptor associated with thrombosis.[65] Results were compared with their previous agents which used a $TcO(N_2S_2)$ chelation motif with the peptide appended to the central ethylene backbone, and the ternary HYNIC system was shown to offer pharmacokinetic advantages.[66] This system is an improvement on earlier binary ligand systems (e.g., one HYNIC and two tricines) which, although they successfully imaged arterial and venous thrombi, suffered from instability and/or multiple isomers. The ternary HYNIC system yields complexes of the form ^{99m}Tc(tricine)(HYNIC−peptide)(L), where L is an ancillary ligand (e.g., TPPTS).[66]

The Edwards group later expanded this same principle to develop a similar ternary ligand combination by substitution of an imine-N-containing heterocycle (e.g., pyridine and imidazole derivatives) for the triarylphosphine ligand.[67] All of the compounds utilize the HYNIC bioconjugate bound in either a mono- or bidentate fashion, a tricine (tri- or tetradentate), and a selected imine-N-containing heterocycle. Through mixed-ligand experiments, they determined that these ternary ligand complexes could be formed in one-pot reactions (i.e., $^{99m}TcO_4^-$, HYNIC−peptide, tricine, L, and $SnCl_2$) and contained only one HYNIC conjugate of the form ^{99m}Tc(HYNIC)(L)(tricine), where L is the N-heterocycle. Surprisingly, the one-step three-ligand reaction resulted in only two detectable diastereomers. One of the stated advantages of this ternary ligand system is the ability to tailor the lipophilicity by the choice of coligands. These compounds exhibited good in vitro stability.

Recently, Davison et al.[62] continued their basic study of organo hydrazino complexation with the direct reduction of $^{99}TcO_4^-$ and ReO_4^- with hydrazino ligands (2-hydrazinopyridine and 2-hydrazinoimidazoline), resulting in analogous stable complexes with one monodentate hydrazine and a second hydrazine acting as a bidentate ligand through hydrazine and heterocyclic nitrogens. The remaining three octahedral coordination sites are occupied by chlorides. Reaction of this trichlorobis(HYNIC)technetium complex with pyridinethiol and pyrimidinethiol yielded compounds of the type [Tc(η^1-SRN)(η^2-SRN)(η^1-NNR)(η^2-HNNR)] which were structurally characterized.[62] These complexes contain both monodentate and bidentate hydrazines and iminethiols coordinated to the technetium(V) center. A study of ^{99m}Tc HYNIC adducts with pyridinethiol and pyrimidinethiol coligands was also undertaken. The thiols were reacted with ^{99m}Tc(mannitol)(HYNIC−peptide), and the products were analyzed by HPLC. The identity of the ^{99m}Tc complex remains uncertain regarding the nature of the HYNIC coordination mode and the number and coordination modes of the iminethiol coligand.

B. $N_xS_{(4-x)}$ Chelates

There are three basic classes of $N_xS_{(4-x)}$ chelates that will be discussed: general $N_xS_{(4-x)}$ tetradentate chelates, peptide-based analogues of MAG_3, and the 3 + 1 class of tridentate and monodentate thiol-containing ligands. The unifying feature in these ligand systems is that all contain thiol groups for coordination to the technetium and all are used to form Tc(V) mono-oxo complexes.

1. General $N_xS_{(4-x)}$ Ligands

Interest has continued in the general class of N_2S_2 bisaminoethanethiol (BAT) ligands, although recent additions have yielded diamino−thioether−thiol and (amino/amido)−thioether−dithiol ligand systems for technetium and rhenium. In one study, the ^{99}Tc and Re complexes of a series of new S_3N chelates of the general form shown as **1** in Figure 9a were evaluated.[68] Example **2** (Figure 9b) is the prototype bifunctional chelator of this series. Although conventional Re(V)oxo complexes were obtained which were stable, the Tc chemistry was not analogous but appeared to yield Tc(IV) species. It was hypothesized that this difference was due to the more oxidizing TcO^{3+} core which is reduced by the thiol-rich ligand. These Tc complexes were not fully characterized due to slow decomposition.

In work targeted at ^{99m}Tc (and ^{186}Re) bifunctional chelation, an efficient synthesis was reported for some new N_2S_2 pseudopeptide-derived ligands containing N-terminal bioactive appendages with known seratonin receptor affinity.[69] This chelate system (Figure 9c) contains a diamide−thioether−thiol coordinating moiety, rather than the more usual (diamino/diamido)dithiol ligand system. The same N_2S_2 coordination motif conjugated through the terminal amide nitrogen to an active ester (tetrafluorophenyl ester) coupling group was reacted with Re(V) to give two different complexes depending on the Re starting material used.[70] Reaction of this ligand with $(Bu_4N)[ReOCl_4]$ yielded the classical [ReO(SSNN)] complex, while reaction with [ReO(glucoheptonate)$_2$−] resulted in $[ReO(L)_2]$ with each N_2S_2 ligand bound in a bidentate mode through the thioether and thiolate sulfur atoms.[70]

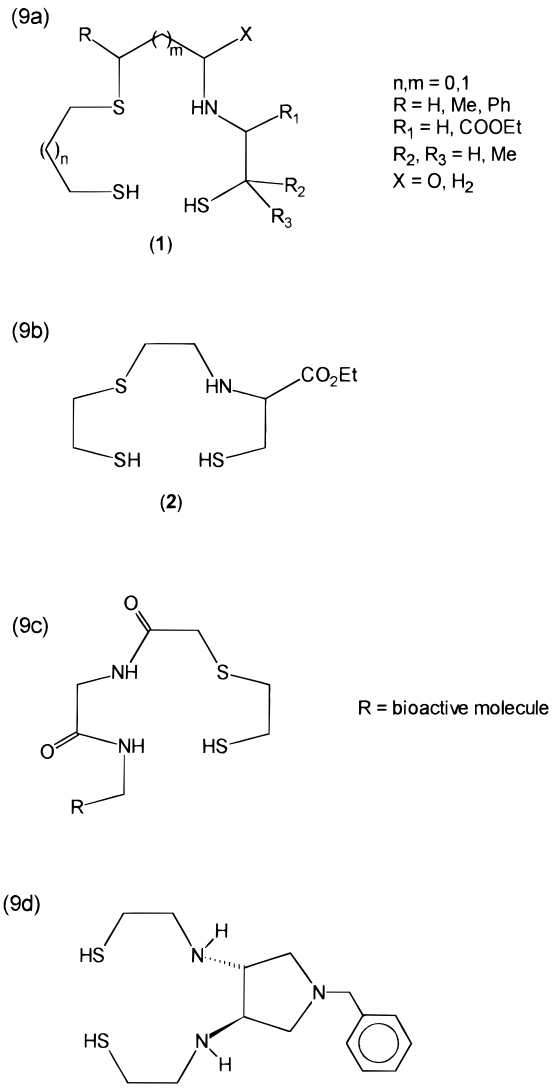


Figure 9. NS-containing bifunctional chelates: (a) general class of NS_3 ligands, (b) prototypic NS_3 ligand, (c) diamide−thioether−thiol ligand, (d) *trans*-P−BAT.

One problem which has hindered many of these systems has been the formation of multiple isomers differing in their pharmacokinetic properties. For example mono-*N*-alkylated N_2S_2 bisaminoethanethiol (BAT) tetradentate ligand commonly used as a scaffold for bifunctional chelation results in syn and anti isomers plus their enantiomers upon complexation. In recent work, a variation on this backbone was developed that can reduce the isomer problem. Complexation of *trans*-*N*-benzyl-3,4-di-(*N*-2-mercaptoethyl)amino pyrrolidine (*trans*-P−BAT, Figure 9d) by a $^{99m}Tc^{(V)}O$ core was shown to result in a single isomer. Comparison to the analogous meso ligand which yielded syn and anti isomers showed substantial differences in lipophilicity and biodistribution.[71]

2. Peptide-Based Ligands

Expanding on the well-known tetradentate amine/amide thiol Tc(V) oxo complexes as carriers of bioactive molecules, the Mallinckrodt group prepared a series of novel diamide thiolate ^{99m}Tc and ^{188}Re complexes which contain pyridyl, morpholino, and imidazolyl groups at the fourth coordination site of the basal plane.[72] A pyridyl example of this class of molecules is shown in Figure 10a. On the basis of their high stability and favorable pharmacokinetic properties, the imidazole complexes were judged to be the most promising for future study as potential bifunctional chelating agents.

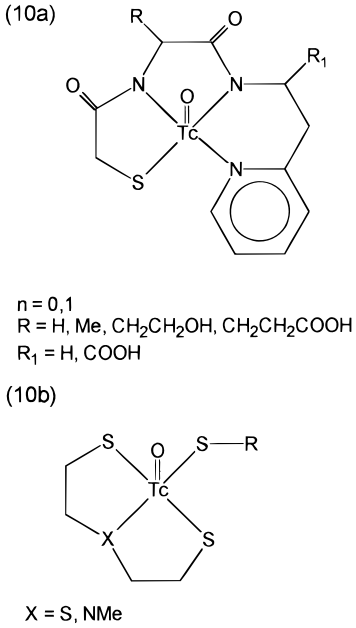


Figure 10. (a) Diamide−thiol−nitrogen heterocycle ligands. (b) TcO-3 + 1 complexes.

The DuPont group reported a study in which they compared the labeling efficiencies of a variety of tetradentate N_2S_2 and N_3S amino and/or amido thiolates for ^{99m}Tc using ^{99m}Tc−glucoheptonate competition experiments.[73] They determined that the amine functionality enhanced the kinetics of labeling relative to the amides. They also evaluated radiolabeling a HYNIC surrogate with ^{99m}Tc using glucoheptonate as a coligand and found that its kinetics of formation were comparable to the best of the amide/amine thiol ligands.[73]

Four tripeptide variations on *N*-hydroxysuccinimide (NHS) modified MAG_3 have been synthesized and evaluated in a simple scheme as bifunctional chelation agents for ^{99m}Tc.[74] Each of the bifunctional chelates prepared were conjugated to biocytin, a primary amine, complexed with ^{99m}Tc, and evaluated for in vitro stability. The authors suggest that their methodology might be used to screen a large library of bifunctional chelating agents for the desired properties as a chelate for ^{99m}Tc.

3. 3 + 1 Ligand System for Tc

A series of TcO(3 + 1) complexes of the type TcO(SXS + RS), where X = S or NCH_3 has been prepared as a potential chelate system for conjugation with receptor binding molecules in which the monodentate thiolate bears the receptor avid moiety.[75] These complexes are of the form shown in Figure 10b. Problems were found with the stability of the complexes in vitro and in vivo (rats) in whole blood due to metabolism and replacement of the RS^- group through transchelation by glutathione.[76] However, this effect was found to be dependent on small

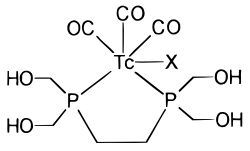
structural variations, especially in the SXS tridentate ligand, with X = NCH_3 complexes significantly more stable than X = S complexes. Stability in human whole blood (in vitro) was found to be substantially better than in the original rat model. Various other examples of the 3 + 1 system developed originally by Johannsen and co-workers have been cited above in the previous sections on receptor specific molecules and illustrated in Figures 2d−g, 3b, 5c, 8d, and 8e.[15,18,19,26,34,60]

B. $Tc(CO)_3^+$-Containing Chelates

Almost all ^{99m}Tc radiopharmaceuticals are based on Tc(V)oxo or octahedral Tc(III) cores. Organometallic low-oxidation state ^{99m}Tc agents are less common, partly because of the difficulty of controlling the reduction of the Tc(VII) starting material to the reduced Tc(I) oxidation state. The most notable example is the hexakis(isonitrile) complex $[^{99m}Tc(MIBI)_6]^+$, ^{99m}Tc−sestamibi, used as a myocardial perfusion agent. The Tc(I) oxidation state is particularly advantageous because of the kinetic inertness inherent in its low-spin d^6 configuration.

Alberto and co-workers have, over the last 5 years, substantially developed the basic chemistry of six-coordinate Tc(I) and Re(I) tricarbonyl complexes containing the *fac*-$M(CO)_3$ moiety. Syntheses of the important intermediates $[MX_3(CO)_3]^{2-}$, where X = Cl^- and Br^-, and $[M(OH_2)_3(CO)_3]^+$ were refined so they could be conveniently reached in a facile manner from the permetalate salts in 1 atm of CO. These were then used as synthons for the efficient production of a variety of complexes involving substitution of the halo or aquo ligands while maintaining the *fac*-$M(CO)_3$ core.[77−81] Recently, the same group reported a facile route to the ^{99m}Tc and ^{188}Re aquo complexes, $[M(OH_2)_3(CO)_3]^+$, in high yield from MO_4^-, $NaBH_4$, and 1 atm CO in aqueous saline, opening the avenue to a variety of potential ^{99m}Tc radiopharmaceuticals which will be kinetically inert because of the low-spin d^6 Tc(I) center.[82] Subsequently, they attached a bifunctional chelating ligand on a dithioether to yield the complex $[^{99m}TcCl(CO)_3(RSCH_2CH_2SCH_3)]$, where R is an estradiol analogue for targeting the estrogen receptor (Figure 5d).[36] This $[MCl(CO)_3$(dithioether)] motif was pioneered in earlier ^{99}Tc and Re work by Alberto.[77,80] The bidentate thioether and chloride ligands make the resultant molecule neutral in charge. Very recently, a diphosphine complex of the form $[^{99m}TcX(CO)_3(R_2PCH_2CH_2PR_2)]$, where R = CH_2-OH and X = Cl^- or H_2O (Figure 11), has been prepared and characterized.[83] These complexes showed good in vitro stability and were efficiently cleared from the blood pool through the urinary and hepatobiliary pathways. These properties hold promise for bifunctional chelation using appropriately modified phosphines as the coligand for these tricarbonyltechnetium(I) complexes.

(11)



X = Cl or H_2O

Figure 11. $TcX(CO)_3$(1,2-bis(hydroxymethyl)phosphinoethane).

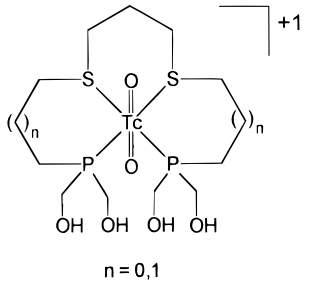
Closely related to the *fac*-$M(CO)_3$ subgroup discussed above is the $CpTc(CO)_3$ class of molecules. $CpTc(CO)_3$ is a kinetically stable, lipophilic core on which biomolecules can be appended through modification of the Cp ring. In 1992, the first synthesis was reported for $RCp^{99m}Tc(CO)_3$, where R = acid, ester, amide, or ketone, by reduction of $^{99m}TcO_4^-$ in the presence of derivatized ferrocene and $Mn(CO)_5Br$.[84] Unfortunately, contamination with Mn byproducts voided practical application of this clever scheme. Using the model Re system, Katzenellenbogen improved on this "double ligand transfer" reaction by modifying the reduction and carbonylation reagents.[85] Later this was successfully extended to the analogous ^{99}Tc system, and model peptide conjugates (with BSA and octreotide) were prepared to test the practicality of the system for bifunctional chelation.[86] Most recently, this protocol has been applied to prepare $Cp^{99m}Tc(CO)_3$−octreotide conjugate in five steps with 8% radiochemical yield. Although the yield was not practical for a ^{99m}Tc radiopharmaceutical, the complex showed receptor-mediated uptake (pancreas and adrenals) which was blocked in the presence of excess octreotide.[86]

C. Water-Soluble Phosphine Chelates

Phosphines have in the past proven useful for the chelation of ^{99m}Tc and form complexes which are stable in vivo. Two recent examples include the myocardial perfusion agents ^{99m}Tc−tetrofosmin (Myoview) and ^{99m}Tc−furifosmin (TechneScan Q12). The development of the various technetium complexes with diphosphines reported by Deutsch was the beginning of this rich chemistry.[87−93] Complexes of diphosphines were formed with technetium in oxidation states from +1 to +5, and the ^{99m}Tc(diphosphine)$_3^+$, $^{99m}TcX_2$(diphosphine)$_2^+$, and $^{99m}TcO_2$(diphosphine)$_2^+$ complexes were all evaluated for their potential utility as myocardial perfusion agents.[93,94] Deutsch was the first to recognize the utility of lipophilic ^{99m}Tc monocations as potential heart imaging agents, initially considered as K^+ mimics, even though none of the monocationic technetium complexes is taken up by the Na^+−K^+−ATPase pump.

However, most technetium phosphine complexes are based on monodentate and bidentate alkyl and aryl phosphines which are not suited to the development of bifunctional chelates (i.e., more than one biomolecule would be incorporated into the resultant complexes). Recently, some interesting chemistry has been developed based on complexation of novel water-soluble bis(hydroxymethyl)alkyl and -aryl phosphines.[94] Using this same functionality, Katti reported the synthesis of two novel ^{99m}Tc complexes of water-soluble S_2P_2 dithiabisphosphines (Figure 12a).[95] Advantages of this system include facile high-yield syntheses, good in vivo stability, and rapid clearance in animal models. Very recently, this motif has been applied to the development of a bifunctional chelating system by attachment of a tethered carboxylate to

(12a)



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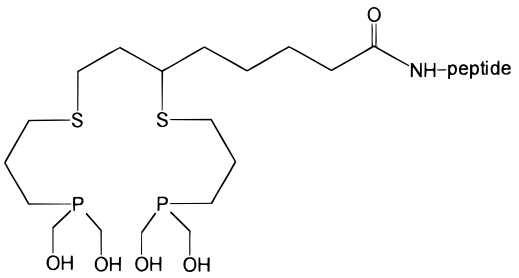

Figure 12. Water-soluble phosphine chelates. (a) General P_2S_2 tetradentate ligand. (b) Bifunctional P_2S_2 tetradentate ligand shown appended to a peptide.

the central S_2P_2 propylene backbone (Figure 12b).[96,97] This has been successfully conjugated to a bioactive peptide in high yield.[98]

D. Other Bifunctional Chelates

Phosphinimine complexes of Tc(VII) yield an interesting class of potential bifunctional chelates.[99,100] Phosphinimines, when reacted with TcO_4^-, first yield ion pairs of the type $[R_3P{=}NH_2^+][TcO_4^-]$ which can subsequently be dehydrated in an organic solvent to give the neutral complexes $[R_3P{=}N{-}TcO_3]$. This opens a route to Tc(VII) radiopharmaceuticals which can readily be prepared from pertechnetate and which do no require reduction of the Tc center. Appropriate derivatization of the phosphinimine would yield potential bifunctional chelates for ^{99m}Tc.

V. Conclusions

Small molecule technetium complexes continue to be an exciting area of active research. The search for the "ideal" bifunctional chelate for ^{99m}Tc radiopharmaceuticals will undoubtedly continue to progress and never be achieved. The greatest stride made in this area is the work by Alberto and co-workers[82] to translate the Tc(I) tricarbonyl chemistry to the tracer ^{99m}Tc level with a straightforward aqueous synthesis. This opens the door to kinetically inert, low-spin d^6 Tc(I) radiopharmaceuticals based on the *fac*-^{99m}Tc-$(CO)_3^+$ core. The charge of the resultant complex can be adjusted by the careful selection of coligands to yield anionic, neutral, or cationic species.

The greatest success in the small molecule receptor imaging area comes with the work reported on imaging the dopamine transporter by Kung[9−12] with [^{99m}Tc]TRODAT-1, Madras[13,14] with [^{99m}Tc]Technepine, and Alberto with [^{99m}Tc]TROTEC-1.[16] Normal human images with [^{99m}Tc]TRODAT-1 show the potential utility of this compound for clinical use. It will remain to be seen if the success of this compound will translate into a viable ^{99m}Tc-based receptor avid radiopharmaceutical.

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