Homodimeric and Heterodimeric Bis(amino thiol) Oxometal Complexes with Rhenium(V) and Technetium(V). Control of Heterodimeric Complex Formation and an Approach to Metal Complexes that Mimic Steroid Hormones

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We have investigated the possibility of preparing complexes of rhenium and technetium whose shape resembles that of ligands for steroid receptors. The general structure of N_2S_2 complexes of oxorhenium(V) and oxotechnetium(V) is such that they could replace the BC ring system of steroid, thereby generating a metal complex system with considerable size and shape similarity to a steroid. Such a metal-integrated steroid-shaped complex can be constructed as a heterodimer of two different amino thiols; complexes of rhenium and technetium with such heterodimeric bis-bidentate structure have not been systematically studied. In this investigation, we have shown that complexes of this nature form readily when appropriate metal precursors are combined with a mixture of amino thiols. In the systems we have studied, heterodimeric complex formation is preferred over homodimeric complex formation, and in one system where we were able to obtain an X-ray crystal structure, this oxorhenium heterodimer had the desired trans geometry. These rhenium and technetium-99m complexes are reasonably stable toward ligand exchange; they can be readily purified by chromatography under appropriate conditions, and the one technetium-99m complex studied in vivo shows some persistence in blood and gives good initial uptake in several tissues. The convenient and selective formation of such bis-bidentate heterodimeric complexes suggests that the development of metal-integrated complexes that resemble ligands for receptors may be possible.

Introduction

Diagnostic imaging agents based on technetium-99m have the advantage of radionuclide availability through the molybdenum-99/technetium-99m generator system,[1] and as a result, almost all routine in vivo radioimaging is based on technetium-99m. The radionuclide rhenium-188, of interest because of its potential therapeutic activity, is also available through the tungsten-188/rhenium-188 generator.[2] A major class of technetium and rhenium complexes involves a chelate molecule that uses four heteroatoms (most often two nitrogen and two sulfur atoms; N_2S_2 system) as donors to an oxometal(V) core.[3] A considerable variety of such complexes has been prepared, evaluated, modified, and optimized in the attempt to achieve appropriate chemical stability, biochemical properties, and in vivo distribution behavior for specific imaging purposes.[4] While highly selective localization has been achieved in some cases, the biochemical or physiological mechanisms responsible for the in vivo distribution of these complexes have generally involved aspects of the overall physicochemical properties of these molecules—their size, charge, or polarity—rather than their shape. The type of detailed complementarity of shape and functionality that characterizes the interaction of a ligand with a receptor, for example, has not yet been addressed in a major way in the design and development of these metal complexes.

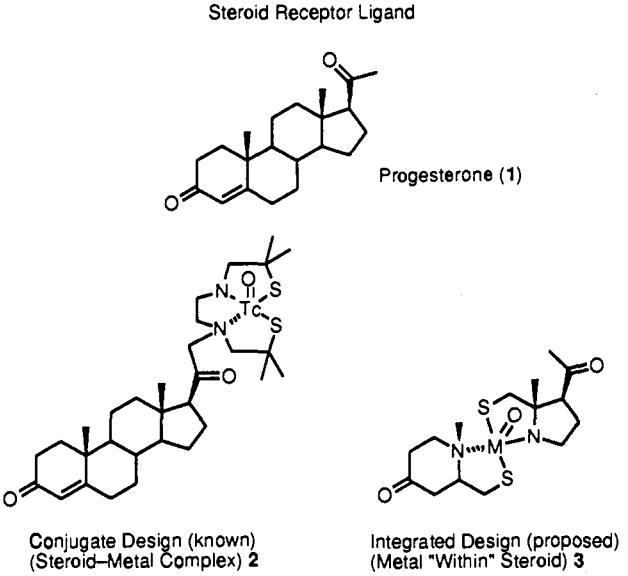

Figure 1. Two different approaches of metal complexes mimicking hormones.

One can imagine two approaches to the development of technetium or rhenium metal complexes as ligands for receptors (Figure 1). The first, the "conjugate" approach, involves the attachment of a stable metal complex to the ligand for a receptor, such as a steroid, in a way that does not perturb receptor binding. In this case, the bulky metal chelate system, whose size and mass may equal or even exceed that of the receptor ligand itself, can be a major impediment to receptor binding and in vivo distribution. In all but a few cases where the conjugate approach has been tried, it has not been successful.[5,6] The alternate approach is to try to design a metal complex whose overall structure mimics that of the receptor ligand. Here, the

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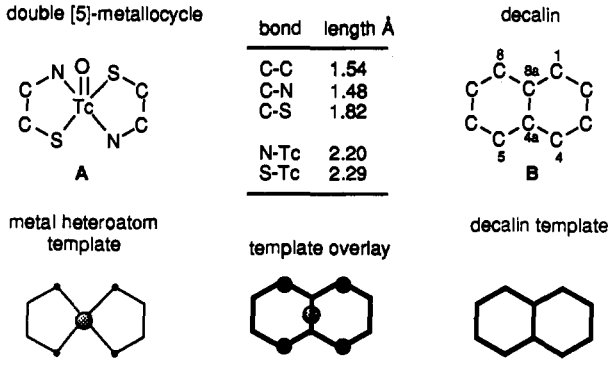


Figure 2. Definition of metal heteroatom and decalin templates.

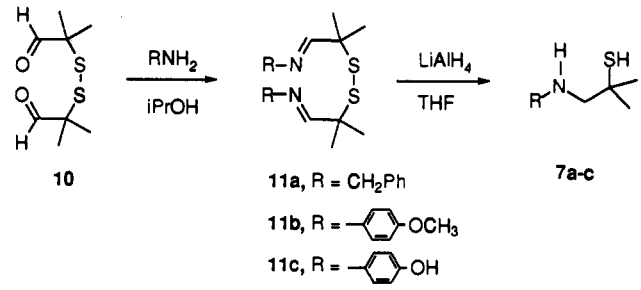
character of the metal-containing complex and the steric and functional contour of the ligand are "integrated".

As part of a program to develop metal complexes of technetium and rhenium that may behave as ligands for steroid receptors, we have begun an investigation of heterodimeric amino thiol complexes that mimic certain steroidal and nonsteroidal ligands for the estrogen receptor.[7] In this report, we describe the preparation of a number of homo- and heterodimeric oxometal complexes of amino thiols and rhenium(V). The preparation of these complexes, particularly the heterodimeric ones, raises interesting issues of competitive complexation kinetics of different amino thiols. The structures of these complexes are characterized, and their in vivo stability are investigated.

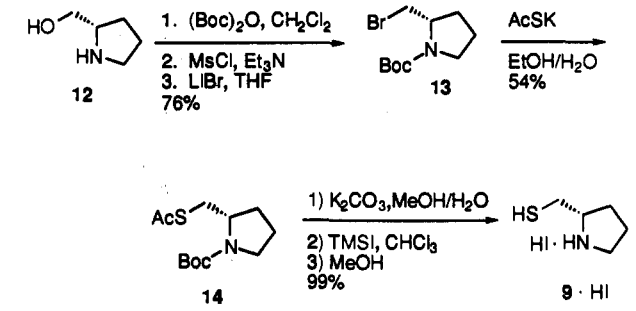
Results and Discussion

Metal Complex Systems Investigated and Their Relationship to Steroidal and Nonsteroidal Ligands for the Estrogen Receptor. While structural comparisons between the technetium complex and the receptor ligands can be made in detail using computer graphics methods, the simple analysis given in Figure 2 suffices to outline the fundamentals of our approach. A key feature of oxotechnetium(V) amino thiol complexes is the double five-membered metallocycle **A** shown in Figure 2. Because the lengths of the metal–heteroatom bonds are ca. 2.1–2.4 Å, 40% greater than those of the carbon-heteroatom bonds (ca. 1.5 Å), this metallocycle is nearly congruent with the fused, double six-membered ring system (decalin, **B**) of first-row elements. The metallocycle can be represented as a template (the heteroatoms are dark circles and the metal is a larger, shaded circle), and the overlay of this template with the decalin template shows how the metal atom is placed at the middle of the 4a,8a bond of the decalin system. With this simple molecular tool in hand, one can envision novel bis-bidentate complexes (Figure 3): simply identify in a steroid such as estradiol (**4**) the internal decalin system comprising the B and C rings and then make the overlay with the metal heteroatom template **5**. As in the basic template overlay (Figure 2), the metal atom in these

Scheme 1



Scheme 2



complexes occupies a position at the middle of a bond, between carbons 8 and 9 in the steroid; from this overlay, one can conceive of the steroid-mimic integrated metal complex **6**.

The validity of this simple template-replacement approach for the design of technetium complexes that mimic the structure of steroids can be appreciated by two more quantitative representations, the stereoview of a computer graphics overlay of the metal complex **6** and the steroid **4** and a comparison of the space-filling structures (Figure 4). Both the geometry (cf. overlays) and the bulk and shape (space filling) of the receptor ligands are mimicked remarkably well by the metal complexes; the only significant deviation in shape is due to the metal oxo group, but since this bond is relatively short (1.7 Å), the deviation in shape is not too large.

Synthesis of the Amino Thiol Ligands. We have synthesized a variety of bis-bidentate ligands (Figure 5) in order to prepare new complexes of oxorhenium as models for hormone mimics such as **4**, and we have studied their structure and stability. The synthesis of the amino thiol ligands is shown in Schemes 1 and 2. Amino thiols **7a–c** were prepared by procedures similar to those of D'Amico and Corbin.[8] The treatment of diimines **11a–c** with lithium aluminum hydride affords amino thiol **7a–c** in 64%, 60% and 13% (unoptimized) yield, respectively, from aldehyde **10**. The disulfide bond is not cleaved when diimine **11a** was treated with sodium borohydride in EtOH, but both imines were reduced, giving the diamine disulfide.

Scheme 2 illustrates the synthetic route utilized in the preparation of the amino thiol (*S*)-2-(mercaptomethyl)-

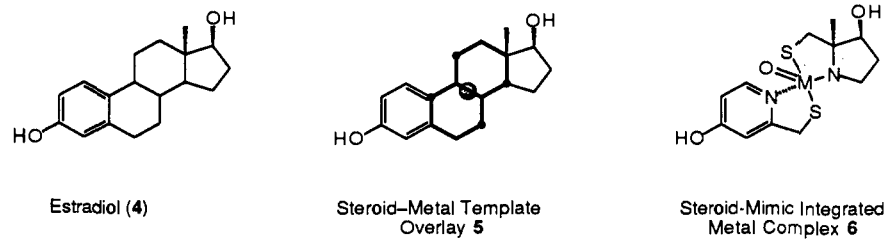


Figure 3. Conceptive of steroid-mimic integrated metal complexes.

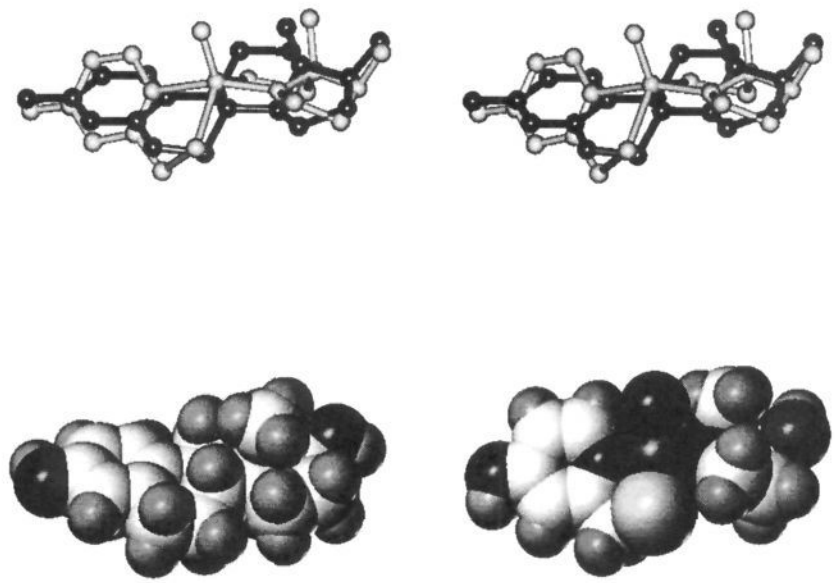


Figure 4. (Upper panel) Computer-generated stereoview of estradiol **4** (black) and a bis-bidentate oxotechnetium(V) $(NS)_2$ complex, **6** (gray) that mimics estradiol. (Lower panel) Space-filling model representations of estradiol **4** (left) and complex **6** (right) showing the volume similarity of the two molecules.

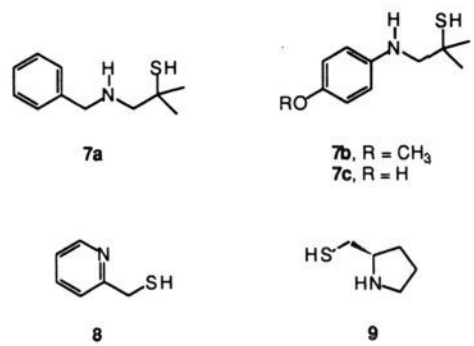


Figure 5. Bidentate ligands.

pyrrolidine hydroiodide (**9**·HI), which mimics a steroid D ring. *N*-(*tert*-Butyloxy)carbonyl (Boc) protection of pyrrolidinemethanol **12** and bromination via the methanesulfonate provided (bromomethyl)pyrrolidine **13** in high yield. Conversion of this bromide to the thioacetate was achieved by reaction with the potassium salt of thiolacetic acid in EtOH. Base hydrolysis of the acetate and removal of the Boc group with trimethylsilyl iodide (TMSI) afforded (*S*)-2-(mercaptomethyl)pyrrolidine (**9**) as the hydroiodide salt. We were unable to obtain compound **9** by treatment of **14** with trifluoroacetic acid, the reagent typically used for Boc deprotection.

Synthesis of the Metal Complex Systems. In contrast to most complexes labeled with technetium-99m which are tetradentate, a bis-bidentate complex such as **4** has two separate bidentate amino thiol components. In order to mimic natural compounds such as hormones, complexes with bis-bidentate ligands may be more useful than tetradentate ligands, as they can be more readily "fine tuned" in structural design.[7] Key issues in the preparation of such bidentate complexes are (1) Can a stable complex be formed from two bis-bidentate ligands? (2) Can a mixed or heterocomplex be formed in preference to a homocomplex? and (3) Will the complex adopt a geometry with the matched heteroatoms in a trans configuration (vs cis)?

We have prepared a number of new complexes of oxotechnetium and oxorhenium from a variety of bis-

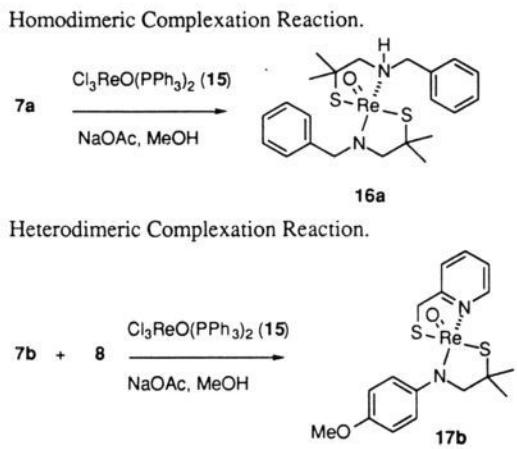


Figure 6. Typical homodimeric and heterodimeric complexation reactions.

bidentate ligands in Figure 5. Some of these complexes have been prepared as model compounds in order to solve the above three questions. Figure 6 shows typical homodimeric and heterodimeric complexation reactions, and Table 1 presents a summary of the complexation reactions. A substitution reaction of oxotrichlorobis(triphenylphosphine)rhenium(V) (**15**) in the presence of 2 equiv of one kind of NS ligand provided homodimeric bis-bidentate oxorhenium complexes **16a–c** in essentially quantitative yield. Reactions were usually done with 200 μmol of the oxorhenium species **15** and 400 μmol of the NS ligands **7a–c** by warming in MeOH in the presence of NaOAc as a weak base. Complexes **16a,b** were sufficiently nonpolar that they precipitated when the reaction mixture was cooled to room temperature. The crude products, collected by filtration in greater than theoretical yield, showed clean proton NMR signals. The results of microanalysis of these unpurified materials showed them to be about 90–99% pure; they contained an inorganic impurity, presumed to be Re_2O_7. Further purification was effected by flash chromatography or recrystallization. The proton NMR of complex **16a** showed only one component, while those of **16b,c** showed a minor amount of a second component;

Table 1. Homo- and Heterodimeric Complexation Reactions

entry	ligand	mmol	ligand	mmol	complex	yield (%)
1	**7a**	0.40			**16a**	90–99[a]
2	**7b**	0.40			**16b**	90–99[a]
3	**7c**	0.40			**16c**	90–99[a]
4	**7b**	0.20	**8**	0.20	**17b**	95–99[a]
5	**7c**	0.20	**8**	0.20	**17c**	95–99[a]
6	**9**	0.20	**8**	0.20	**18**	63

[a] Yields were essentially quantitative. Isolation yields were varied by isolation methods and their stabilities.

these are assumed to be the trans and cis isomers, present in the ratio are 85:15 for **16a** and 77:23 for **16c**, respectively.

While several homodimeric bis-bidentate complexes of oxorhenium(V) and oxotechnetium(V) have been reported in the literature,[9] a simple heterodimeric complex that is nearly symmetrical has been reported.[10] We have prepared heterodimeric complexes with two different ligands—the amino thiols **7b,c** or (*S*)-2-(mercaptomethyl)pyrrolidine (**9**) and 2-(mercaptomethyl)pyridine (**8**). When 1 equiv of ligands **7b** and **8** was used (Table 1, entry 4), the heterodimeric complex **17b** was formed in a very selective, quantitative manner, such that the homodimeric complex **16b** could not be detected. We have previously reported the selective formation of the heterodimeric oxorhenium-(V) complex **17b** under various conditions, and we showed by X-ray crystallographic analysis that complex **17b** has the trans configuration. These results provide answers to all three of the above questions: (1) *A stable complex can be formed from two bis-bidentate ligands.* (2) *A mixed or heterocomplex can be formed in preference to a homocomplex.* (3) *Such a complex prefers to adopt a geometry with the matched heteroatoms in the trans configuration.*

Structural Characterization of Metal Complex Systems. An X-ray structure of the heterodimeric complex **17b** was reported previously.[7] In addition, we have synthesized another metal complex heterodimer, (*S*)-[2-(mercaptomethyl)pyridinato][2-(mercaptomethyl)pyrrolidinato]oxorhenium(V) (**18**), from ligand **8** and (*S*)-2-(mercaptomethyl)pyrrolidine hydroiodide (**9**·HI). Because ligand **9** was prepared as the hydroiodide salt, 1 equiv of Et_3N was added as an acid scavenger. Complex **18** is formed in 63% yield in the presence of Et_3N and in 41% yield without any base. All 15 hydrogen and 11 carbon atoms of complex **18** were resolved by HETCOR and COSY NMR experiments (Figure 7). The ^1H NMR spectrum of **18** shows four CH peaks from the pyridine unit and 11 aliphatic CH peaks. The two protons of the methylene group next to pyridine (C6) appear as a pair of doublets at δ 4.12 and 5.03 with a geminal coupling of J = 18.9 Hz. The two protons of the methylene group next to the pyrrolidine ring (C11) show both geminal coupling and vicinal coupling with H7 and appear at δ 2.62 (t, J = 10.9 Hz) and 3.46 (dd, J = 11.0, 5.8 Hz). An examination of a molecular model of complex **18** shows that protons H11β and H7 are arranged in a gauche conformation, whereas protons H11α and H7 are arranged in nearly an anti conformation. Thus, the triplet peak at δ 2.62 (having the larger vicinal coupling of 10.9 Hz) is assigned to H11α, while the doublet of doublet at δ 3.46 (with the smaller 5.8-Hz vicinal coupling) is assigned to H11β. The three protons next to the nitrogen in the pyrrolidine ring (H7 and H10α,β) resonate between δ 4.18 and 4.76. From the HETCOR spectrum, the peak at δ 67.0 is coupled with two multiplet peaks at δ 4.23–4.35 and 4.65–4.76; thus,

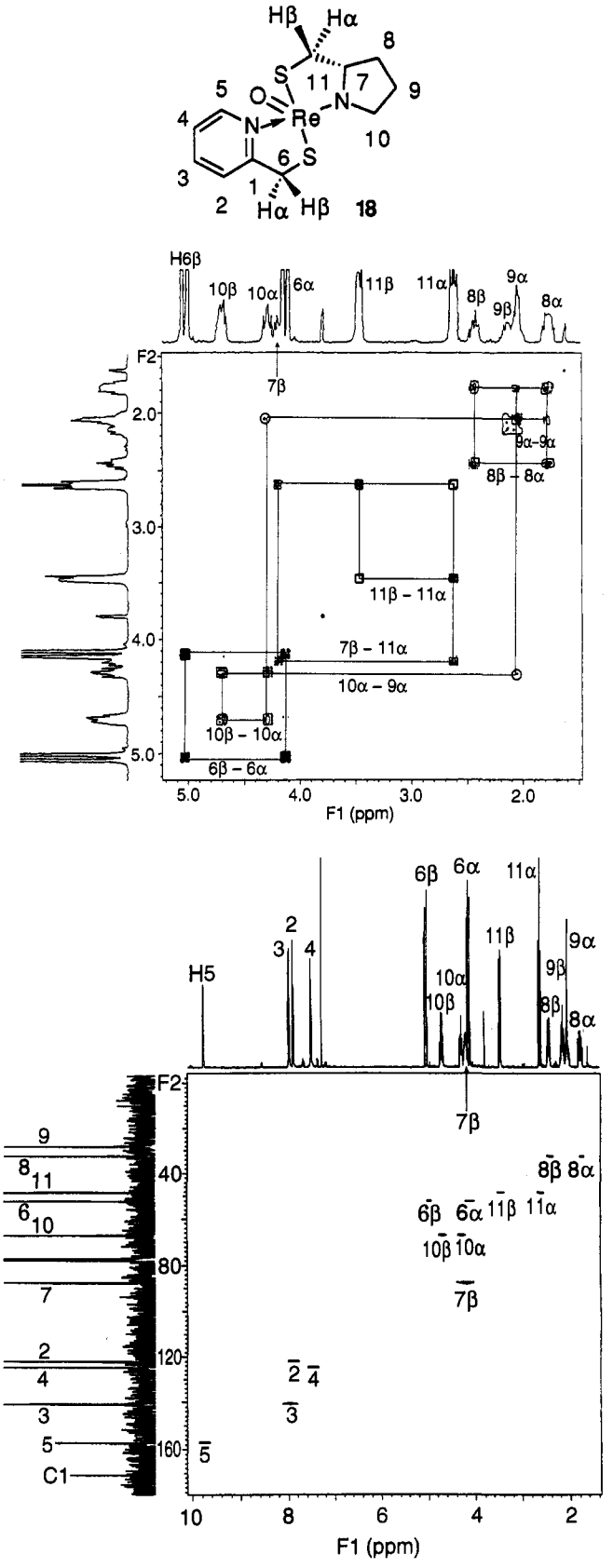


Figure 7. COSY and HETCOR spectra of complex **18**.

these are assigned as C10 and H10α,β. The geminal coupling of H10α,β can be shown in the COSY spectrum. The peak at δ 87.4 in the HETCOR spectrum is coupled with only one proton at δ 4.18–4.23; those are assigned as C7 and H7. In a similar manner, the remaining four protons in the pyrrolidine ring (H8α,β and H9α,β), resonating at δ 1.71–2.48, were assigned to their respective

Table 2. Biodistribution of Heterodimeric Bis-Bidentate [^{99m}Tc]**17b** as Percent Injected Dose/g of Tissue in Sprague–Dawley Rats (70 g, n = 5) following Intervenous Injection

	2 min	15 min	30 min	60 min	120 min
blood	0.681 ± 0.097	0.316 ± 0.030	0.213 ± 0.035	0.202 ± 0.022	0.192 ± 0.002
lung	4.236 ± 2.527	0.830 ± 0.149	0.434 ± 0.052	0.344 ± 0.063	0.224 ± 0.030
liver	4.121 ± 0.607	3.690 ± 0.521	2.987 ± 0.793	3.309 ± 0.433	2.892 ± 0.317
kidney	3.117 ± 0.512	1.291 ± 0.184	1.075 ± 0.220	1.281 ± 0.088	1.779 ± 0.215
muscle	0.364 ± 0.102	0.379 ± 0.079	0.255 ± 0.030	0.167 ± 0.036	0.107 ± 0.042
fat	0.241 ± 0.149	0.511 ± 0.198	0.297 ± 0.135	1.071 ± 0.370	1.128 ± 0.210
heart	3.285 ± 0.823	0.721 ± 0.071	0.386 ± 0.071	0.305 ± 0.017	0.151 ± 0.013
rest of brain	1.346 ± 0.189	0.630 ± 0.061	0.283 ± 0.055	0.185 ± 0.019	0.128 ± 0.009

^{13}C NMR signals. The configurational assignments (α vs β) of the four remaining sets of methylene protons are assisted by the large magnetic anisotropy of the metal oxide bond,[11] which effects a strong deshielding of protons that are on the same face of the complex as the oxygen (syn to the oxygen). Thus, in each case, the downfield signal is assigned to the β disposed proton (syn). On the basis of analogy with complex **17b**, we presume that complex 18 has the trans geometry, although this is not evident from the NMR data. We are endeavoring to obtain an X-ray structure of complex 18.

Stability and Preferential Heterodimers Complex Formation. It has been reported that bis-bidentate oxorhenium(V) complexes may be subject to ligand exchange,[12] but we could not find a clear evidence of ligand exchange in the literature. We could have encountered ligand exchange during HPLC analysis of the complexes **16a–c**, but these complexes were quite well behaved on HPLC under a variety of polarity and eluting solvent systems.

We have obtained evidence that the preferential stability of the heterodimeric complex **17b** vs the homodimeric complex **16b** is at least in part thermodynamic through the following ligand-exchange experiments that we have performed. (1) When a solution of homodimeric complex **16b** (0.01 M in MeOH/$CHCl_3$ 1:1) is heated at 75 °C for 1 h in the presence of 1 or 4 equiv of ligand 8, the final ratio of hetero- to homodimeric complexes **17b**:**16b** is 65:35 or 86:14, respectively. Thus, even when the ratio of amino thiol components **7b** and 8 is 2:1 (as in the first case where 1 equiv of **16b** (which contains 2 equiv of **7b**) is warmed with only 1 equiv of 8), a predominance of the heterocomplex **17b** is produced at equilibrium. (2) When a solution of homodimeric complex **16b** (0.01 M in MeOH/$CHCl_3$ 1:1) is heated at 75 °C for 1 h in the presence of 1 equiv of ligand 8 with 10 equiv of NaOAc, the final ratio of hetero- to homodimeric complexes **17b**:**16b** is 17:83. It is not clear by what means the excess of NaOAc reduces the rate or extent of ligand exchange.

Estrogen-Receptor-Binding Affinity. Compounds **16c** and **17c** have a phenol group which is essential for estrogen receptor binding, even though their structures are quite different to estradiol. As we expected, the receptor-binding affinity of compounds **16c** and **17c** was quite low, being 0.007% and 0.014%, respectively (estradiol, 100%).

Radiochemical Synthesis with ^{99m}Technetium. The ^{99m}Tc complexes **16a** and **17b** could be readily formed at the tracer level in good yields (ca. 40–50% isolated by HPLC, decay uncorrected) and with high radiochemical purity. Representative reactions are shown in Figure 8. The heterodimeric complex **17b** is still formed with great selectivity, even at the tracer level. Even with a 1:1 ratio of amino thiols **7b** and 8, the heterodimeric [^{99m}Tc]**17b**

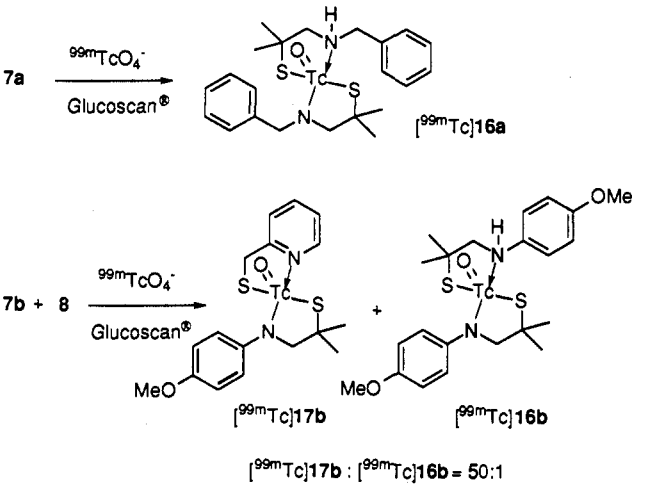


Figure 8. Typical homodimeric and heterodimeric complexation reactions with ^{99m}Tc labels.

and homodimeric [^{99m}Tc]**16b** complexes formed at a ratio of 50:1. These complexes can be readily purified by HPLC on cyanopropyl-capped silica gel (Figure 9). Ligand exchange occurs to a much lesser degree on reversed-phase than normal phase HPLC. When complexes [^{99m}Tc]**16a–c** and [^{99m}Tc]**17b–c** are monitored by TLC (silica gel or basic alumina plate), it is essential to develop the plate immediately after sample application in order to prevent decomposition by ligand exchange.

In Vivo Stability of ^{99m}Tc-Labeled Complexes 16a and 17b. In order to test the stability of the ^{99m}Tc-labeled complexes in vivo, the labeled compounds were dissolved in 20% EtOH/saline solution or 100% EtOH. The heterodimeric complex [^{99m}Tc]**17b** was very stable in 100% EtOH and in 20% EtOH/saline after 2 h. By contrast, most of the homodimeric complex [^{99m}Tc]**16a** underwent decomposition in 20% EtOH/saline within 2 min, while it was stable in 100% EtOH.

Since compound [^{99m}Tc]**17b** was stable in 20% EtOH/saline, it was injected into Sprague–Dawley rats, and the stability in rat plasma was measured over time. TLC analysis of the rat plasma indicated that by 2-h postinjection, 20% of [^{99m}Tc]**17b** remained intact in the blood (Figure 10). This in vivo stability is comparable to those we observed for ^{18}F-labeled steroids.[13]

Biodistribution of ^{99m}Tc-Labeled 17b in Sprague–Dawley Rats. The tissue distribution of the heterodimeric complex [^{99m}Tc]**17b** was studied in immature Sprague–Dawley rats. The results, expressed as percent injected dose/g (%ID/g), are summarized in Table 2. Of particular interest is the high initial uptake in both the heart and the brain. The %ID/organ for heart and brain 2 min after administration were 2.13 ± 0.44 and 2.13 ± 0.13, respectively. The brain uptake is approximately 2 times that observed for the highest uptake of a series of

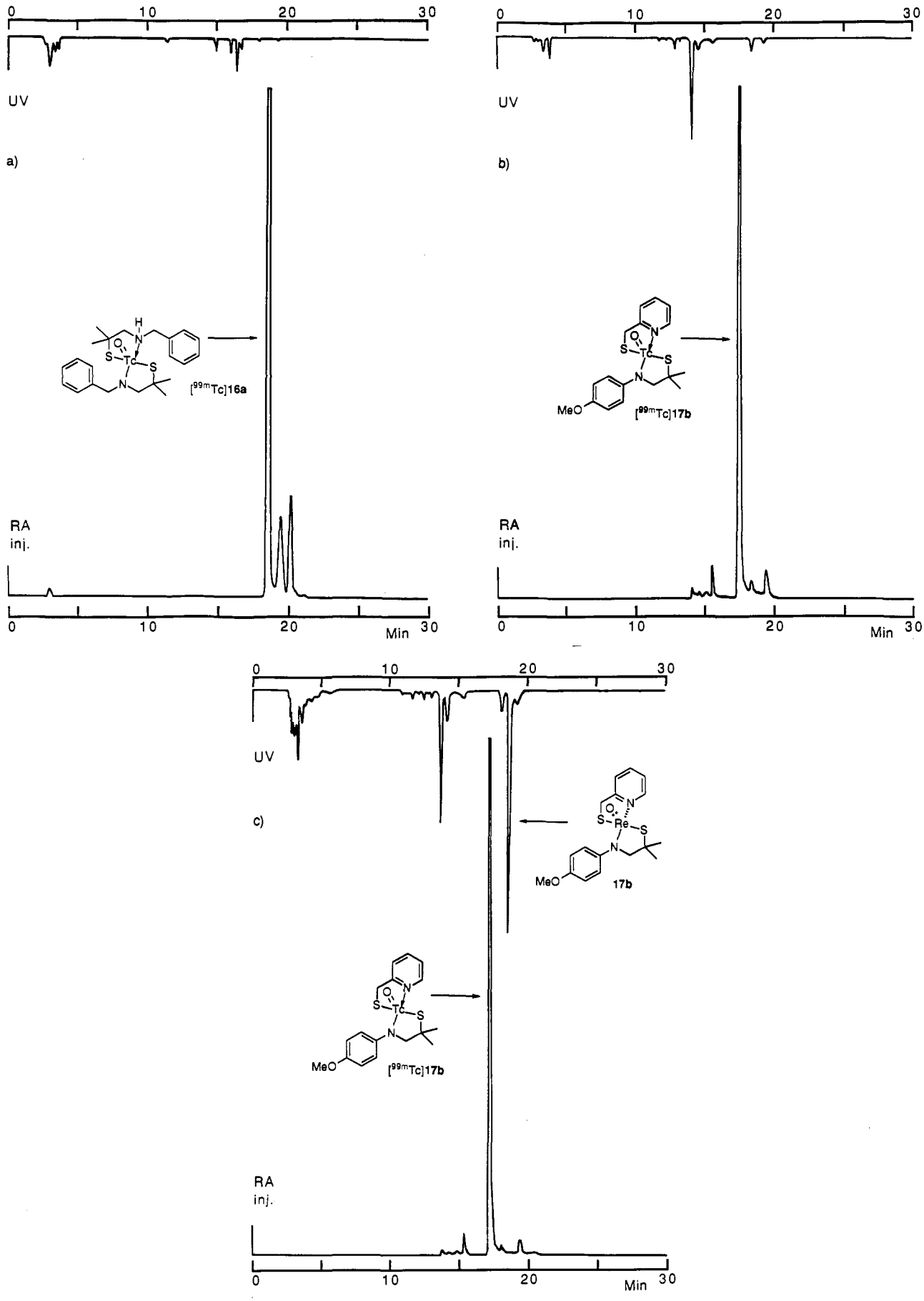


Figure 9. HPLC traces of [^{99m}Tc]**16a** and [^{99m}Tc]**17b** complexes on cyanopropyl silica gel column. HPLC conditions are given in the Experimental Section (UV detector, 254 nm, intensity 0.05 aufs; radioactive detector (RA) sensitivity 1×10^5). (a) [^{99m}Tc]**16a**, 72 μCi injected in 500 μL hexane. (b) [^{99m}Tc]**17b**, 70 μCi injected in 100 μL of hexane. (c) [^{99m}Tc]**17b**, 72 μCi injected in 500 μL of hexane with rhenium complex **17b**.

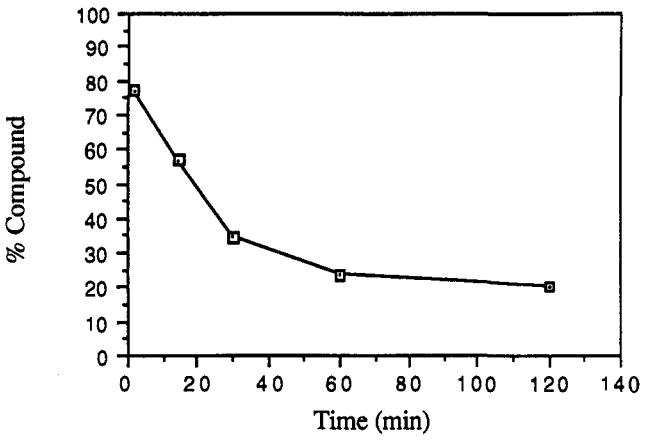


Figure 10. Percent of heterodimeric [^{99m}Tc]**17b** remaining unmetabolized in vivo in blood.

eight PnAO homologues.[14] The heart uptake is less than that observed for the better myocardial imaging agents.

Conclusion

In this investigation, we have demonstrated that it is possible to prepare heterodimeric bis-bidentate amino thiol complexes of oxorhenium(V) and oxotechnetium-99m(V). The formation of these complexes is rapid and efficient, and at least in the systems we have studied so far, there appears to be a strong thermodynamic preference for the formation of the heterodimeric complex vs the homodimeric one. Where we have been able to determine stereochemistry definitively, these dimeric complexes have a trans geometry. The complexes have reasonable stability toward ligand exchange, and one complex shows some persistence in vivo. These results suggest that it should be possible to design metal complexes of rhenium and technetium-labeled complexes that will bind to receptors.

Experimental Section

General. Solvents and reagents were purchased from the following commercial sources: Aldrich, Mallinckrodt, Sigma, Fisher, Baker, Eastman, or Alfa. Ethanolic solution of pyridine-2-methanethiol (10%) was purchased from Penta Manufacturing Company (Fairfield, NJ). Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl immediately prior to use. Other solvents were used as received, unless otherwise noted. Glucoscan kits (^{99m}Tc-glucoheptonate kits) were purchased from E. I. DuPont de Nemours Co., N. Billerica, MA.

Analytical thin-layer chromatography (TLC) was performed with Merck silica gel F-254 glass-backed plates. Visualization was achieved by phosphomolybdic acid (PMA), $KMnO_4$, or anisaldehyde spray reagents, iodine, or UV illumination. Flash chromatography was performed according to Still[15] using Woelm silica gel (0.040–0.063 mm) or basic alumina. High-performance liquid chromatography (HPLC) was performed isocratically on a Spectra-Physics Model 8700 or a Varian 5060 liquid chromatograph with an analytical 5-mm SiO_2 cyanopropyl column (4.6 mm × 30 cm, Supelco LC-CN) or a preparative SiO_2 cyanopropyl column (10 mm × 50 cm, Phenomenex IB-SIL). The UV absorbance of the eluent was monitored at 254 or 410 nm. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a General Electric QE-300 (300 MHz) spectrometer and are reported in parts per million downfield from internal tetramethylsilane. COSY and HETCOR spectra were obtained on a Varion Unity (400 MHz) spectrometer. Mass spectra were obtained on Finnigan MAT CH5 and MAT 731 spectrometers for low- and high-resolution spectra, respectively. Both low- and high-resolution fast atom bombardment (FAB) mass spectra were obtained on a VG instrument (ZAB HF). Elemental analyses were performed by the Microanalytical Service, School of Chemical Sciences, University of Illinois.

1-(Benzylamino)-2-methylpropane-2-thiol (7a). This material was prepared according to a literature procedure[8] from benzylamine (1.07 g, 10.0 mmol) and α,α'-dithiodiisobutyraldehyde (**10**, 1.03 g, 5.0 mmol). Purification by Kugelrohr distillation provided a colorless oil, **7a** (1.25 g, 64% from benzylamine): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 6, $2CH_3$), 1.80 (b s, 2, NH + SH), 2.61 (s, 2, CH_2), 3.87 (s, 2, CH_2), 7.30–7.40 (m, 5, Ph); MS (EI, 10 eV) 195 (M^+, 3), 162 (2), 120 (100), 106 (3), 91 (31). Anal. ($C_{11}H_{17}NS$) C, H, N.

1-[(4-Methoxyphenyl)amino]-2-methylpropane-2-thiol (7b). This material was prepared according to a literature procedure[8] from *p*-methoxyaniline (1.23 g, 10.0 mmol) and α,α'-dithiodiisobutyraldehyde (**10**, 1.03 g, 5.0 mmol). Purification by Kugelrohr distillation provided a colorless oil, **7b** (1.27 g, 60% from *p*-methoxyaniline): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 6, $2CH_3$), 1.80 (b s, 1, NH or SH), 3.10 (s, 2, CH_2), 3.75 (s, 3, OCH_3), 3.82 (b s, 1, NH or SH), 6.64 (dd, 2, J = 6.8, 2.1 Hz, aromatic H), 6.78 (dd, 2, J = 6.8, 2.1 Hz, aromatic H); MS (EI, 70 eV) 211 (M^+, 10), 178 (3), 136 (100), 123 (6), 108 (12). Anal. ($C_{11}H_{17}NOS$) C, H, N, S.

1-[(4-Hydroxyphenyl)amino]-2-methylpropane-2-thiol (7c). This material was prepared according to a literature procedure[8] from *p*-aminophenol (1.09 g, 10.0 mmol) and α,α'-dithiodiisobutyraldehyde (**10**, 1.03 g, 5.0 mmol). Purification by flash column chromatography and recrystallization provided a white solid, **7c** (250 mg, 13% from *p*-aminophenol): mp 97–97.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (b s, 1, NH or SH), 3.10 (s, 2, CH_2), 4.20–4.50 (b s, 2, 1 of NH or SH + OH), 6.62 (d, 2, J = 8.8 Hz, aromatic H), 6.71 (d, 2, J = 8.8 Hz, aromatic H); MS (EI, 70 eV) 197 (M^+, 8), 164 (4), 122 (100), 108 (5), 94 (6). Anal. ($C_{10}H_{15}NOS$) C, H, N, S.

(*S*)-2-(Hydroxymethyl)-1-[(*tert*-butyloxy)carbonyl]pyrrolidine. (*S*)-2-pyrrolidinemethanol (**12**, 2.0 g, 20.0 mmol) was dissolved in 10 mL of CH_2Cl_2. Di-*tert*-butyl dicarbonate (4.37 g, 20.0 mmol) in 10 mL of CH_2Cl_2 was added dropwise. After being stirred for 30 min, the reaction mixture was passed through a short silica gel column (10 cm), and the silica gel column was washed with EtOAc (300 mL). Removal of solvent in vacuo and bulb-to-bulb distillation (140 °C at 0.5 mmHg) gave 4.00 g (99%) of colorless liquid of N-protected alcohol: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9, $3CH_3$), 1.47–1.60 (m, 1), 1.70–1.90 (m, 2), 1.95–2.05 (m, 1), 3.25–3.35 (m, 1), 3.40–3.50 (m, 1), 3.55–3.65 (m, 2), 3.85–4.02 (m, 1), 4.70–4.75 (b s, 1, OH); MS (EI, 10 eV) 210 (M^+, 3), 170 (50), 128 (9), 114 (100), 70 (86), 57 (40). Anal. ($C_{10}H_{19}NO_3$) C, H, N.

(*S*)-2-(Bromomethyl)-1-[(*tert*-butyloxy)carbonyl]pyrrolidine (13). (*S*)-2-(Hydroxymethyl)-1-[(*tert*-butyloxy)carbonyl]-pyrrolidine (4.00 g, 19.9 mmol) and Et_3N (4.25 g, 42.0 mmol) were dissolved in 20 mL of CH_2Cl_2 and cooled to 0 °C. Methanesulfonyl chloride in 10 mL of CH_2Cl_2 was added slowly. The resulting mixture was stirred for 30 min at 0 °C, and the mixture was extracted with H_2O/CH_2Cl_2. The organic layer was washed with water and dried (Na_2SO_4). After evaporation of the solvent, the residue (pale yellow syrup, considered as mesylate) was dissolved in dried THF (30 mL) and lithium bromide (4.00 g, 46.0 mmol) was added. The reaction mixture was refluxed for 20 h. After evaporation of THF, the residue was extracted with H_2O/CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (10% EtOAc/hexane) to give 4.00 g (15.2 mmol, 76%) of (bromomethyl)pyrrolidine **13** as a colorless oil. An analytical sample was prepared by bulb-to-bulb distillation (110 °C at 0.5 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9, $C(CH_3)_3$), 1.75–2.10 (m, 4), 3.23–3.50 (m, 3), 3.61 (b dd, 1, J = 27.7, 9.1 Hz), 3.93–4.11 (m, 1); MS (EI, 10 eV) 265 (M^+, 3), 263 (M^+, 3), 210 (8), 192 (6), 190 (6), 170 (57), 128 (8), 114 (86), 70 (100), 57 (88). Anal. ($C_{10}H_{18}BrNO_2$) C, H, N, Br.

(*S*)-2-[(Acetylthio)methyl]-1-[(*tert*-butyloxy)carbonyl]-pyrrolidine (14). Thiolacetic acid (760 mg, 10.0 mmol) was dissolved in 5 mL of absolute EtOH. Aqueous KOH (560 mg, 10.0 mmol) in a minimum amount of water was added to make the solution neutral. (Bromomethyl)pyrrolidine **13** (2.64 g, 10.0 mmol) was added dropwise, and the solution was stirred for 30 min at room temperature. The reaction was refluxed for 4 h.

The solution was concentrated under reduced pressure, and the residue was extracted with EtOAc/H_2O. The organic layer was washed with a saturated $NaHCO_3$ solution and dried (Na_2SO_4). Removal of solvent and column chromatography (10–20% EtOAc/hexane) provided thioacetate **14** (1.41 g, 54%) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9, $3CH_3$), 1.65–2.02 (m, 4), 2.34 (s, 3, CH_3), 2.85–3.50 (m, 4), 3.80–4.02 (m, 1); MS (EI, 70 eV) 259 (M^+, 3), 183 (3), 170 (15), 144 (17), 114 (59), 70 (100), 57 (89). Anal. ($C_{12}H_{21}NO_3S$) C, H, N, S.

(*S*)-2-(Mercaptomethyl)pyrrolidine Hydroiodide (9·HI). Thioacetate 14 (1.29 g, 4.99 mmol) was dissolved in methanol (20 mL) and water (10 mL). To this solution was added potassium carbonate (1.38 g, 9.98 mmol). The reaction mixture was stirred for 15 min at room temperature. MeOH was removed under reduced pressure, and the residue was extracted with CH_2Cl_2/H_2O. The organic layer was dried (Na_2SO_4), and the solvent was removed, providing crude (*S*)-2-(mercaptomethyl)-1-[(*tert*-butyloxy)carbonyl]pyrrolidine (1.08 g, quantitative yield). This crude product was dissolved in $CHCl_3$ (50 mL). To this solution was added trimethylsilyl iodide (1.62 g, 8.08 mmol). The reaction mixture turned to a red solution immediately, to a yellow solution after 5 min, and to a faint yellow solution after 10 min. MeOH (15 mL) was added, and the mixture was stirred overnight. The solvent was removed under reduced pressure and under high vacuum, providing a yellow syrup **9**·HI (1.30 g, 99%, slowly turned to a solid in a freezer). This crude product was used in a metal complexation reaction without further purification: ^1H NMR (300 MHz, D_2O) δ 1.79–1.86 (m, 1, CH in pyrrolidine), 2.07–2.15 (m, 2, 2CH in pyrrolidine), 2.29–2.35 (m, 1, CH in pyrrolidine), 2.97 (dd, 1, J = 14.7, 9.6 Hz, SCH_2), 3.23 (dd, 1, J = 14.7, 4.6 Hz, SCH2), 3.34–3.41 (m, 2, 2NCH), 4.03–4.80 (m, 1, NCH); MS (EI, 70 eV, off scale) 254 (I_2^+, 12), 127 (I^+, 16), 117 (M^+, 3), 70 (100).

General Procedure. Homodimeric ReO-Insertion Reaction. Exemplified by ReO insertion into **15** to form **16a–c**, the following method is completely general and was used to form all the homodimeric Re chelates.

Bis[*N*-benzyl-*N*-(2-mercapto-2-methylpropyl)aminato]oxorhenium(V) (16a). A sample vial (5 mL) was charged with oxotrichlorobis(triphenylphosphine)rhenium(V) (**15**, 166.6 mg, 0.20 mmol) and 2.0 mL of 1 N methanolic NaOAc (2.0 mmol). Amino thiol (0.40 mmol) was added to this solution. The reaction mixture was heated at 75 °C for 20 min and then allowed to cool to room temperature. The purple solid that formed was collected by filtration and washed with cold methanol, yielding **16a** (110 mg, 95%) as a purple solid. The proton NMR of this solid showed only signals for complex **16a**, but microanalysis showed the presence of ca. 10% of other inorganic material (presumed to be Re_2O_7). Additional product **16a** (5 mg, 4%) was also obtained by flash chromatography (basic alumina, 20% EtOAc/hexane) of the filtrate. An analytical sample was prepared by recrystallization in methanol, providing a purple solid, **16a**: mp 199–200 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 3, CH_3), 1.30 (s, 3, CH_3), 1.70 (s, 3, CH_3), 1.72 (s, 3, CH_3), 2.98 (t, 1, J = 12.0 Hz, CH_2), 3.32 (dd, 1, J = 11.1, 3.1 Hz, CH_2), 3.69 (d, 1, J = 11.4 Hz, CH_2), 3.75 (b s, 1, NH), 3.84 (d, 1, J = 11.4 Hz, CH_2), 4.29 (dd, 1, J = 14.1, 11.0 Hz, CH_2), 5.37 (d, 1, J = 14.8 Hz, CH_2), 5.35–5.42 (m, 1, CH_2), 5.76 (d, 1, J = 14.4 Hz, CH_2), 7.20–7.49 (m, 10, aromatic CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.4 (CH_3), 29.3 (CH_3), 29.5 (CH_3), 30.0 (CH_3), 56.0 (C), 63.4 (C), 64.2 (CH_2), 70.2 (CH_2), 78.5 (CH_2), 86.9 (CH_2), 126.5 (CH), 128.2 (2CH), 128.5 (2CH), 128.8 (CH), 129.0 (2CH), 129.4 (2CH), 137.1 (C), 142.1 (C); MS (CI, methane) 594 (0.3), 593 (2), 592 (7), 591 (17), 590 (M^+, 63), 589 (10), 588 (M^+, 36), 499 (16), 497 (8), 262 (41), 183 (30), 91 (100); UV and vis λ_{max} (CH_2Cl_2) 380, 326, 276, 234 nm. Anal. ($C_{22}H_{31}N_2ORe S_2$) C, H, N, Re, S.

Bis[*N*-(2-mercapto-2-methylpropyl)-*N*-(4-methoxyphenyl)aminato]oxorhenium(V) (16b). When the reaction mixture was cooled to room temperature, the purple solid formed. Collection by filtration and washing with cold methanol yielded **16b** (130 mg, 105%, same as **16a**—contains inorganic impurity) as a green solid: mp 195–197 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 3, CH_3), 1.50 (s, 3, CH_3), 1.70 (s, 3, CH_3), 1.71 (s, 3, CH_3), 3.55–3.80 (m, 2, CH_2NH), with 1 drop of D_2O, these multiplet peaks turned to two doublets at 3.58 (d, 1, J = 11.2 Hz, CH_2ND), 3.70 (d, 1, J = 11.2 Hz, CH_2ND), 3.828 (s, 3, OCH_3), 3.833 (s, 3, OCH_3), 4.06 (d, 1, J = 11.9 Hz, CH_2N), 4.41 (d, 1, J = 11.9 Hz, CH_2N), 4.90 (b d, 1, J = 12.0 Hz, NH), 6.88 (d, 2, J = 8.8 Hz, 2CH in Ph), 6.95 (d, 2, J = 8.9 Hz, 2CH in Ph), 7.11 (d, 2, J = 8.8 Hz, 2CH in Ph), 7.41 (d, 2, J = 8.9 Hz, 2CH in Ph), other isomer with 1 drop of D_2O at 2.63 (d, 1, J = 10.6 Hz, CH_2ND), 3.18 (d, 1, J = 10.6 Hz, CH_2ND), 4.08 (d, 1, J = 11.8 Hz, CH_2N), 4.49 (d, 1, J = 11.8 Hz, CH_2N), 4.90 (b d, 1, J = 12.0 Hz, NH); MS (EI, 70 eV) 622 (M^+, 15), 620 (M^+, 12), 411 (3), 409 (1), 389 (2), 387 (2), 178 (100), 162 (11), 136 (26), 122 (41); UV and vis λ_{max} (CH_2Cl_2) 416, 308, 236 nm. HREI calcd for $C_{22}H_{31}N_2O_3ReS_2$, 622.1331; found 622.1334.

Bis[*N*-(2-mercapto-2-methylpropyl)-*N*-(4-hydroxyphenyl)aminato]oxorhenium(V) (16c). The desired product was soluble in methanol and did not precipitate at the end of the reaction. Column chromatography (basic alumina, 60% EtOAc/hexane) provided a green solid, **16c** (110 mg, 93%): ^1H NMR (300 MHz, acetone-d_6) δ 1.21 (s, 3, CH_3), 1.49 (s, 3, CH_3), 1.58 (s, 3, CH_3), 1.81 (s, 3, CH_3), 3.62–3.75 (m, 2, CH_2NH), 3.85 (d, 1, J = 11.6 Hz, CH_2N), 4.33 (d, 1, J = 11.6 Hz, CH_2N), 6.74 (d, 2, J = 8.7 Hz, 2CH in Ph), 6.85 (d, 2, J = 8.8 Hz, 2CH in Ph), 6.95 (d, 2, J = 8.7 Hz, 2CH in Ph), 7.50 (d, 2, J = 8.8 Hz, 2CH in Ph); MS (EI, 70 eV, off scale) 594 (M^+, 9), 592 (M^+, 7), 164 (100), 120 (100); UV and vis λ_{max} (CH_2Cl_2) 414, 310, 232 nm.

General Procedure. Heterodimeric ReO-Insertion Reaction. The general procedure for heterodimeric complexation is the same as for the homodimeric ReO-insertion reaction, with the exception that two different amino thiol ligands are added instead of one.

[*N*-(2-Mercapto-2-methylpropyl)-*N*-(4-methoxyphenyl)aminato][2-(mercaptomethyl)pyridinato]oxorhenium(V) (17b). A sample vial (5 mL) was charged with oxotrichlorobis(triphenylphosphine)rhenium(V) (**15**, 166.6 mg, 0.20 mmol) and 2.0 mL of 1 N methanolic NaOAc (2.0 mmol). To this solution were added amino thiol **7b** (42.2 mg, 0.20 mmol) and **8** (25.0 mg, 0.20 mmol). The reaction mixture was heated at 75 °C for 20 min and then allowed to cool to room temperature. The brownish purple solid that formed was collected by filtration and washed with cold methanol, yielding **17b** (108 mg, 98%) as a brownish purple solid. Additional product **17b** (2 mg, 2%) was also obtained by flash chromatography (basic alumina, 40% EtOAc/hexane) of the filtrate: mp 191–192 °C; ^1H NMR (300 MHz, acetone-d_6) δ 1.64 (s, 3, CH_3), 1.66 (s, 3, CH_3), 3.79 (s, 3, OCH_3), 3.95 (d, 1, J = 19.4 Hz, NCH_2), 4.20 (d, 1, J = 11.9 Hz, SCH_2), 4.48 (d, 1, J = 11.9 Hz, SCH_2), 5.05 (d, 1, J = 19.4 Hz, NCH_2), 6.87 (d, 2, J = 8.9 Hz, 2CH in Ph), 7.15 (d, 2, J = 8.9 Hz, 2CH in Ph), 7.72 (t, 1, J = 6.4 Hz, C5-H in py), 8.11 (d, 1, J = 7.7 Hz, C4-H in py), 8.20 (td, 1, J = 7.7, 1.3 Hz, C3-H in py), 9.65 (d, 1, J = 5.6 Hz, C6-H in py); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.6 (CH_3), 28.9 (CH_3), 51.1 (SCH_2), 55.3 (OCH_3), 58.0 ($C(CH_3)_2$), 86.5 (NCH_2), 112.8 (2CH in Ph), 121.9 (C3 in py), 124.2 (C5 in py), 125.8 (2CH in Ph), 140.3 (C4 in py), 155.4 (C in Ph), 156.8 (C6 in py), 159.8 (C in Ph), 171.8 (C6 in py); MS (EI, 70 eV, off scale) 536 (M^+, 9), 534 (M^+, 5), 401 (5), 343 (8), 341 (5), 294 (86), 277 (94), 262 (100), 183 (100), 108 (100); UV and vis λ_{max} (CH_2Cl_2) 424, 308, 232 nm. HREI calcd for $C_{17}H_{21}N_2O_2ReS_2$, 536.0592; found, 536.0602.

[*N*-(2-Mercapto-2-methylpropyl)-*N*-(4-hydroxyphenyl)aminato][2-(mercaptomethyl)pyridinato]oxorhenium(V) (17c). Procedures are similar to those for **17b**. The desired product **17c** (100 mg, 96%) as a green solid was obtained by flash chromatography (basic alumina, 60% EtOAc/hexane): mp 215 °C dec; ^1H NMR (300 MHz, $CDCl_3$) δ 1.71 (s, 3, CH_3), 1.72 (s, 3, CH_3), 3.88 (d, 1, J = 19.1 Hz, NCH_2), 4.36 (d, 1, J = 12.0 Hz, SCH_2), 4.54 (d, 1, J = 12.0 Hz, SCH_2), 5.00 (d, 1, J = 19.1 Hz, NCH_2), 6.85 (d, 2, J = 8.9 Hz, 2CH in Ph), 7.18 (d, 2, J = 8.9 Hz, 2CH in Ph), 7.50 (t, 1, J = 6.4 Hz, C5-H in py), 7.82 (d, 1, J = 7.9 Hz, C4-H in py), 7.95 (t, 1, J = 7.5 Hz, C3-H in py), 9.76 (d, 1, J = 5.2 Hz, C6-H in py); UV and vis λ_{max} (CH_2Cl_2) 414, 310, 232 nm.

(*S*)-[2-(Mercaptomethyl)pyridinato][2-(mercaptomethyl)pyrrolidinato]oxorhenium(V) (18). A sample vial (5 mL) was charged with oxotrichlorobis(triphenylphosphine)rhenium(V) (**15**, 166.6 mg, 0.20 mmol) and 2.0 mL of 1 N methanolic NaOAc (2.0 mmol). To this solution were added amino thiol **9**·HI (49.0 mg, 0.20 mmol), **8** (25.0 mg, 0.20 mmol), and Et_3N (20.2 mg, 0.20 mmol). The reaction mixture was heated at 75 °C for 20 min and then allowed to cool to room temperature. Column chromatography (basic alumina, 40% EtOAc/hexane) provided

a dark orange solid, 18 (55 mg, 63%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71–1.84 (m, 1, C3-H in pyrrolidine), 2.00–2.11 (m, 1, C4 in pyrrolidine), 2.11–2.21 (m, 1, C4-H in pyrrolidine), 2.37–2.48 (m, 1, C3-H in pyrrolidine), 2.62 (t, 1, J = 10.9 Hz, SCH_2-pyrrolidine), 3.46 (dd, 1, J = 11.0, 5.8 Hz, SCH_2-pyrrolidine), 4.12 (d, 1, J = 18.9 Hz, SCH_2-pyridine), 4.18–4.23 (m, 1, C1-H in pyrrolidine), 4.23–4.35 (m, 1, C5-H in pyrrolidine), 4.65–4.76 (m, 1, C5-H in pyrrolidine), 5.03 (d, 1, J = 18.9 Hz, SCH_2-pyridine), 7.48 (t, 1, J = 6.4 Hz, C5-H in pyridine), 7.86 (d, 1, J = 7.8 Hz, C4-H in pyridine), 7.94 (t, 1, J = 7.7 Hz, C3-H in pyridine), 9.75 (d, 1, J = 5.5 Hz, C6-H in pyridine); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2 (C4 in pyrrolidine), 32.4 (C3 in pyrrolidine), 48.3 (SCH_2-pyrrolidine), 52.2 (SCH_2-pyridine), 67.0 (C5 in pyrrolidine), 87.4 (C2 in pyrrolidine), 122.0 (C3 in pyridine), 124.6 (C5 in pyridine), 140.7 (C4 in pyridine), 157.1 (C6 in pyridine), 170.6 (C2 in pyridine); MS (EI, 10 eV) 443 (17), 442 (M^+, 100), 441 (23), 440 (M^+, 94), 373 (93), 371 (34), 359 (14), 294 (12), 277 (97), 252 (12), 171 (12), 123 (12), 113 (11). HREI calcd for $C_{11}H_{15}N_2ORES_2$, 440.0156; found, 440.0155.

Estrogen-Receptor-Binding Affinity. These values were determined by a competitive radiometric binding assay, using rat uterine cytosol as a source of receptor, tritium-labeled estradiol as tracer, and dextran-coated charcoal adsorbent as free tracer, according to our previously published method.[18]

Typical ^{99m}Tc Labeling Procedure. Labeling was performed by adding 1–30 mCi of $Na^{99m}TcO_4$ in saline to a 500-μL aliquot of a prediluted (5 mL of H_2O) Glucoscan kit. The mixture was stirred at room temperature for 30 min. Ligand (homodimeric case; 20 μL of 0.01 mol/L ligand in MeOH) or mixed ligands (heterodimeric case; 20 μL of premixed ligands in 0.005 mol/L each ligand in MeOH) were added, and the reaction mixture was stirred at room temperature for 30 min. The reaction was extracted with 3 × 1 mL of CH_2Cl_2, and the organic layer was passed through a short disposable pipette column packed with Na_2SO_4 (4 cm) above basic alumina (1 cm). The typical radiochemical yield of the organic extract of most reactions was 60–70%. The collected organic layer was evaporated over a stream of nitrogen, redissolved in hexane, and purified by HPLC on a preparative cyanopropyl column, providing 70–75% collected yields (based on injected activity) of the desired Tc-99m labeled complexes at greater than 95% radiochemical purity.

HPLC Purification of ^{99m}Tc Complex. Fractions were collected manually in lead-shielded test tubes. The appropriate fractions were then combined, evaporated under a stream of nitrogen, and diluted to 20% EtOH/saline for biodistribution and biostability studies. HPLC conditions: solvent system A = 5% MeOH/CH_2Cl_2, solvent system B = hexane; for compound [^{99m}Tc]**16a**—0–3 min A = 0%, B = 100% (isocratic); 3–13 min, A = 0–5%, B = 100–95% (gradient); 13–30 min, A = 5%, B = 95% (isocratic); for compound [^{99m}Tc]**17b**—0–3 min, A = 0%, B = 100% (isocratic); 3–23 min, A = 0–20%, B = 100–80% (gradient); 23–30 min, A = 20%, B = 80% (isocratic).

Stability of ^{99m}Tc-Labeled 16a and 17b in Rats. The stability of ^{99m}Tc-labeled **17b** in vivo was determined in Sprague–Dawley rats. Two anesthetized rats were injected with 400 μCi of [^{99m}Tc]**17b**. The rats were allowed to recover, and at time points ranging from 2 min to 2 h, they were reanesthetized and 250 μL of blood was removed by direct cardiac puncture. Five hundred microliters of ethanol was added to the blood, and the mixture was homogenized in a Tekmar tissumizer. The homogenate was then centrifuged at 12 000 rpm for 5 min in a Sorvall RC2-B refrigerated centrifuge. The red-cell pellet was separated and counted, and the supernatant was analyzed by radio-TLC on a Bioscan System 200 imaging scanner for intact [^{99m}Tc]**17b** and metabolites. The percent of unmetabolized [^{99m}Tc]**17b** in the supernatant was calculated at each time point as previously described.[17]

Biodistribution of ^{99m}Tc Complex 17a. Female Sprague–Dawley rats (20-days old, 70 g) were injected (lateral tail vein), under methoxyfurane (2,2-dichloro-1,1-difluoroethyl methyl ether) anesthesia, with 20 μCi of [^{99m}Tc]**17a** in a 20% EtOH/saline solution. Five rats were injected for each time point. The animals were sacrificed by halothane inhalation at the times indicated, and samples of tissues and blood were removed, weighed, and counted in a Beckman Gamma 8000 automatic well-type γ counter.

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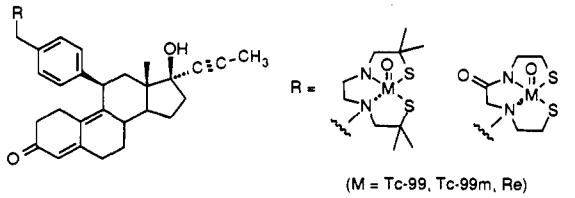
comparable or even greater than that of progesterone itself. Despite their high affinity for receptor, however, these compounds showed only modest target tissue selective uptake in vivo, possibly because of their large overall size.



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