Synthesis of a Tetradentate Oxorhenium(V) Complex Mimic of a Steroidal Estrogen

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We are developing oxometal(V) complexes as high affinity ligands for the estrogen receptor. When labeled with technetium-99m, these complexes might be used as imaging agents for estrogen receptor-positive breast tumors. We describe the synthesis of a tetradentate oxorhenium(V) amino amido thioether thiol (AATT) complex in which the metal complex replaces the CD ring portion of estradiol. This complex is a close steric congener of the steroid and has a similar molecular volume. It was synthesized from norphenylephrine via an efficient Pictet−Spengler cyclization to give a tetrahydroisoquinoline that was then readily elaborated into the tetradentate chelate system. Treatment with an oxorhenium(V) salt led to the formation of the desired complex as a mixture of two diastereomers in modest yield. The relative stereochemistry of these isomers was easily assigned from their NMR spectra. On the basis of their octanol−water partition coefficients, these complexes are considerably more hydrophilic than is estradiol, and their binding affinity for the estrogen receptor is low. The AATT unit in these complexes represents a new chelation system for the oxometal(V) complexes of group 7 transition metals, and compared to other closely related bis-bidentate and other tetradentate systems we have studied, these complexes are quite stable. Nevertheless, the low binding affinity of these complexes for the estrogen receptor emphasizes the fact that metal complexes must most likely have an electronic complementarity with good receptor ligands, as well as a size and shape complementarity, in order for them to exhibit high affinity receptor binding.

Introduction

Technetium-99m is a radionuclide which has played a central role in diagnostic medical imaging for several years. Because ^{99m}Tc may be conveniently produced from the decay of ^{99}Mo ($t_{1/2}$ 67 h) using commercially available generator systems, it is more widely available for use in imaging with ^{99m}Tc by single-photon emission computed tomography (SPECT) than are many other nuclides used in imaging by positron emission tomography (PET). Combined with other favorable characteristics (γ decay, 140 keV) and a convenient half-life (6 h), which allows for complex synthesis and prolonged imaging, ^{99m}Tc has emerged as a preeminent radionuclide, and it is used in over 80% of all routine diagnostic nuclear medicine procedures.[1]

Recently, technetium-labeled receptor-specific small molecule radiopharmaceuticals have been the subject of a flurry of research.[2−12] Agents with specific binding to the dopamine transporter,[3,4] the serotonin receptor,[5] and the GP IIb/IIIa receptor[6−8] have set standards for the successful development of other receptor-binding radiopharmaceuticals. In our work toward estrogen receptor-specific radiopharmaceuticals for imaging breast cancer, we have also synthesized various metal-labeled compunds for diagnostic purposes.[9−13] Both technetium-99m and, in preliminary studies, its nonradioactive congener rhenium, have been used in these studies.

Being a metal, however, technetium is not readily incorporated in a covalent manner into an organic ligand. There are two possible designs by which technetium may be associated with a steroidal framework, such as progesterone (Figure 1). The conjugate (or pendent) approach, such as **1**, attaches a metal chelate at a site on the receptor ligand which is tolerant to bulky substituents, and the integrated approach (e.g., **2**) replaces part of the receptor ligand with a metal chelate system, while ideally maintaining a size and binding affinity similar to that of the original molecule.

A conjugate approach has been evaluated for the progesterone receptor in a series of rhenium and technetium complexes.[9,10] While the best complexes, in fact, exhibited a binding affinity for progesterone receptor three times that of progesterone itself, their biodistribution showed unacceptably high nonspecific binding, and only low uptake in the principal target tissue (uterus).[10,11] This was attributed to the high mass and large size of the complexes, which may have led to problems in traversing the cell membrane barrier.[2]

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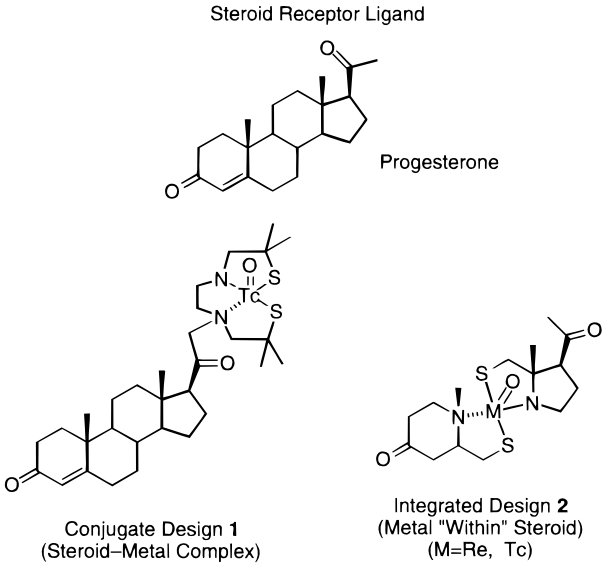

Figure 1. Conjugated and integrated technetium(V) complexes based on progesterone.

An integrated approach toward a mimic of 5α-dihydrotestosterone (DHT) was also developed to image the androgen receptor. After promising initial studies on bis-bidentate rhenium(V) complexes, which showed some compounds to be stable *in vivo*,[14,15] a bis-bidentate complex that was an accurate steric mimic of DHT was synthesized. However, it proved insufficiently stable in vivo for further development.[12] As a result, other, more stable, coordination schemes were evaluated for use in technetium radiopharmaceuticals for steroid receptors.[16] We hereby report the results on our work toward estrogen receptor-specific agents with the synthesis of a novel tetradentate oxorhenium(V) complex based on estradiol. In the process, we have established the stability of a new coordination scheme for oxorhenium(V) systems, the NNSS amine amide thioether thiol (AATT) chelation sphere.

Results and Discussion

Design Considerations. We have previously described work whereby the B and C rings of the potent estrogen estradiol (**3**) were replaced with a tetradentate oxometal(V)−heteroatom core (Figure 2).[16] Though the synthesized complex **4** appeared to be a good structural mimic of estradiol, it was surprisingly unstable to aqueous conditions. This was presumed to be a consequence of the poor donor ability of the aromatic thioether linkage.

As a result, we applied an alternate design strategy to devise the target compound **5** from estradiol. A tetradentate metal−chelate system replaced the C and D rings of the steroid, with the metal being positioned between C-13 and C-14 of estradiol. In this design, the axial methyl and 17β-hydroxyl groups are replaced by parts of the tetradentate chelation moiety. This approach places the metal−heteroatom core near one end of the steroid, where it is closer to one of the polar functional groups (the 17β-hydroxyl), rather than near the center

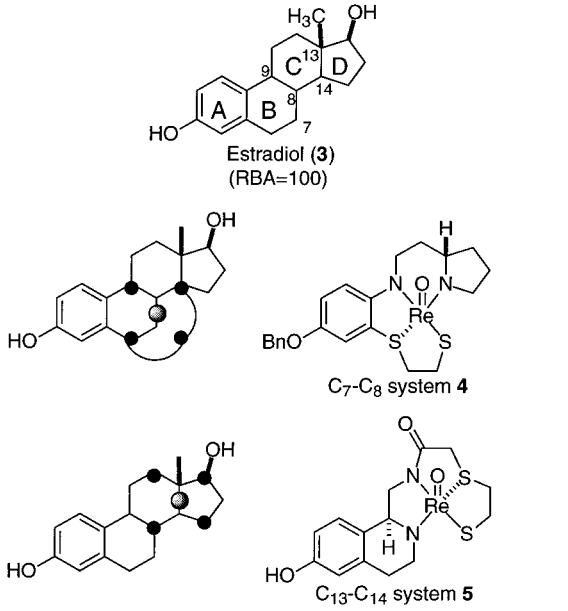

Figure 2. Design of an integrated tetradentate oxometal complex from an estradiol template.

of the nonpolar hydrocarbon core (B and C rings) of a steroid, as has been done previously (cf. Figure 1, complex **2**).[12]

Computer modeling supports the validity of this replacement on a steric basis (Figure 3). Sybyl v.6.1 calculations with an empirical Tc force field[17] revealed that complex **5** occupied slightly more volume than estradiol, mainly with the carbonyl function in the 12β-direction and with extra bulk beyond carbons 15 and 16. Molecular volume calculations indicate that the proposed mimic **5** is only 5% larger than estradiol (281 Å^3 for **5** vs 267 Å^3 for **3**). This increased size is not of great concern since the receptor is known to accommodate molecules, such as hexestrol and benzestrol, which are larger than estradiol.

The steric agreement with the A and B (and part of the C) rings is excellent. Although in this design the polar metal oxo group in **5** is closer to the 17β-hydroxyl group than it was with the previously prepared complexes, it is still disposed closer to C-15 than to C-17. In this regard, it is reassuring that a number of steroidal and nonsteroidal estrogens with polar functions in this same region are still high-affinity ligands for the estrogen receptor (Figure 4). These include the D-ring hydroxyl-substituted steroids estriol (**6**)[18,19] and estetrol (**7**)[18,20−23] and 15-oxaestradiol (**8**),[24,25] as well as ketone **9**[26] and ester **10**[27] analogs of the nonsteroidal estrogen hexestrol. It seemed likely that at least one of these analogs would

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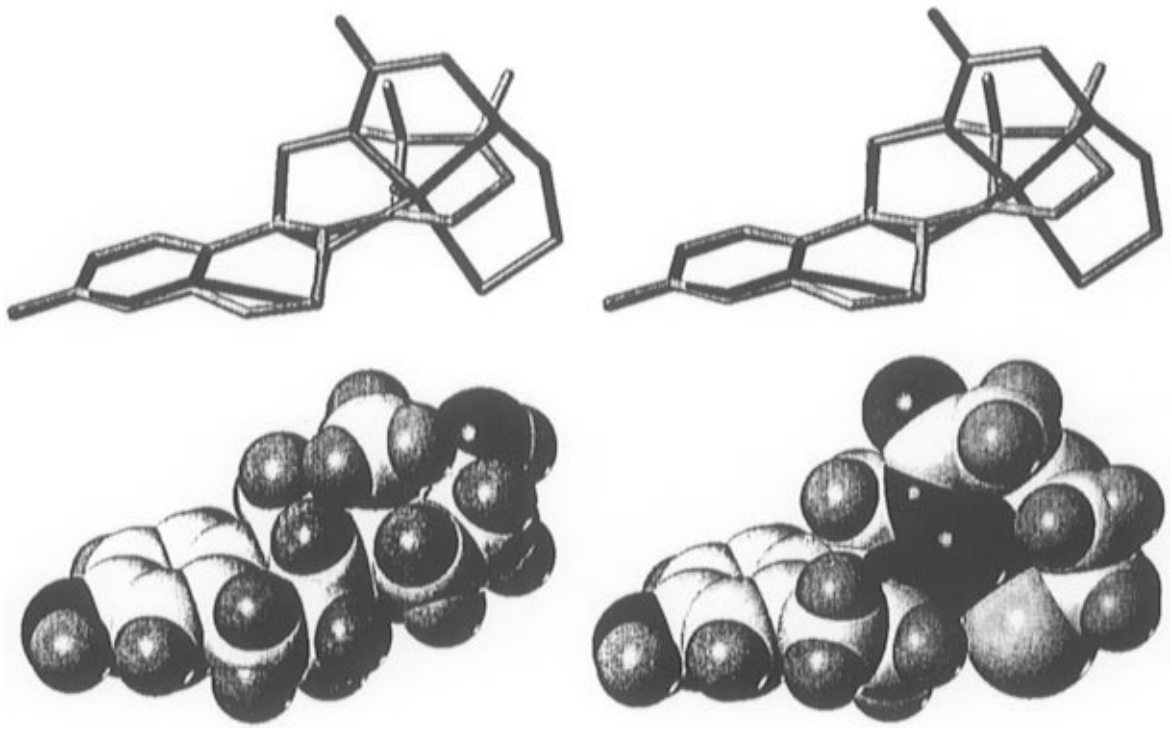

Figure 3. Top: crossed stereo overlay views of estradiol (**3**) (light shading) and proposed mimic **5** (dark shading). Bottom: space filling models of **3** (left) and **5** (right).

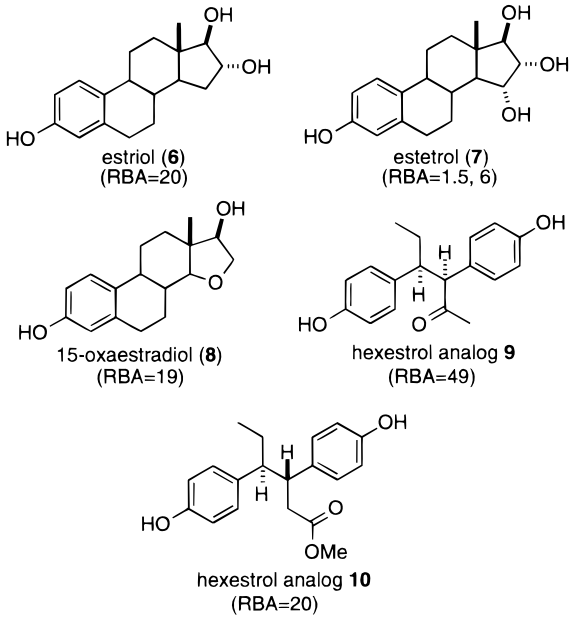

Figure 4. Potent steroidal and nonsteroidal estrogens, placing polar functionality in the same region of space as the metal oxo bond in compound **5**. RBA is relative binding affinity (where the RBA of estradiol is 100), determined by a radiometric competitive binding assay. (For details, see text.)

be placing a polar hydroxyl, ether, or carbonyl function in the same region of the estrogen receptor into which the metal oxo function of **5** would be presented.

Proposed mimic **5** contains the novel coordination scheme of an NNSS or amine amide thioether thiol (AATT) system (Figure 5). In typical, stable oxorhenium(V) and oxotechnetium(V) complexes, there are often two nitrogen and two sulfur donor atoms; however, most known complexes involve a diamine dithiol (DADT) or similar coordination motif. Though thioether donors are

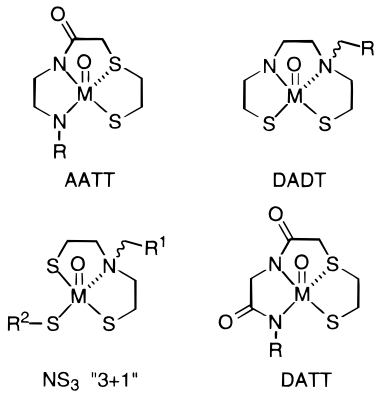

Figure 5. Amine amide thioether thiol (AATT) and other coordination motifs for oxometal(V) systems.

found in stable oxorhenium(V) systems,[28] they have not been extensively investigated. However, there have been some studies of the diamide thioether thiol (DATT) motif,[29,30] which has shown interesting properties, such as low binding to blood plasma protein.[30] DATT and the related AATT system may be simpler to work with than other motifs such as the DADT or the amino dithiol monothiol "3 + 1" system, because the former two lack a stereogenic center in the chelation sphere. By contrast, DADT-like systems contain a quaternary nitrogen donor and may require diastereomer separation for proper

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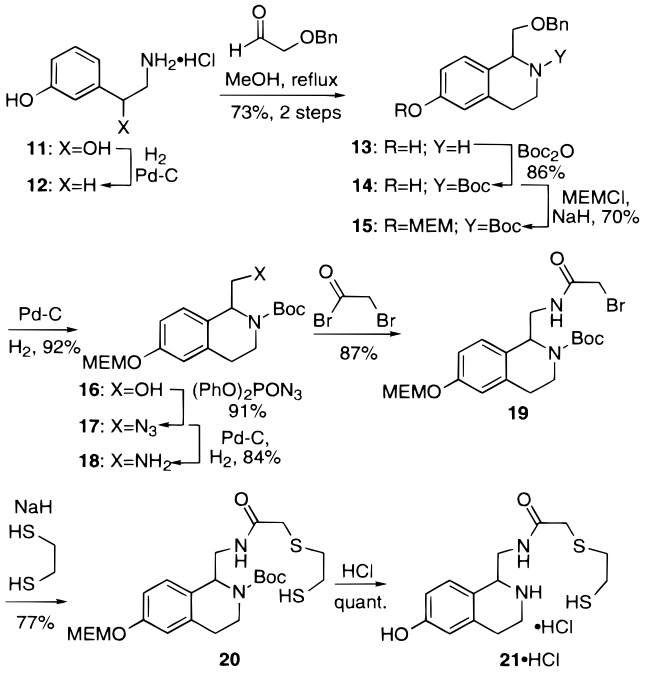
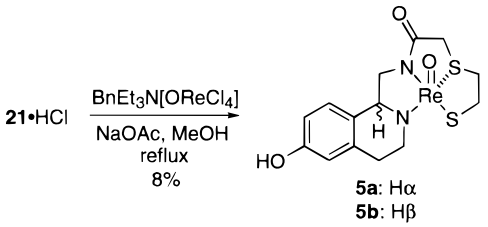
Scheme 1



chemical and biological characterization. To our knowledge, the AATT system which we have proposed has not been utilized previously in oxorhenium(V) or oxotechnetium(V) complexes.

Synthesis. The sequence used to synthesize the requisite tetradentate ligand is illustrated in Scheme 1. From 3-hydroxyphenethylamine hydrochloride (**12**·HCl), which can be readily obtained by hydrogenolysis of norphenylephrine (**11**),[31] Pictet−Spengler cyclization[32,33] with (benzyloxy)acetaldehyde[34,35] afforded the tetrahydroisoquinoline **13**. Sequential protection of the amino and phenolic substituents as the *tert*-butyloxycarbonyl (Boc) and the 2-methoxyethoxymethyl (MEM) ether derivatives, respectively, followed by hydrogenolysis of the benzyl protecting group, provided the differentially protected tetrahydroisoquinoline alcohol **16** in good yield. In our hands, the most efficient method for conversion of the alcohol function to a primary amine was achieved via the azide **17**, which was formed in excellent yield using diphenylphosphoryl azide in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) as in situ protecting agents for the carbamate carbonyl.[36] Due to the steric hindrance of the adjacent Boc-protected amine, activation of the alcohol with methanesulfonyl chloride followed by treatment with sodium azide in DMF or DMSO resulted in formation of a large amount of the cyclic carbamate. Hydrogenation of the azide then gave amine **18**. Treatment of the free primary amine with bromoacetyl bromide provided the amido bromide **19**, which underwent reaction with an excess of 1,2-ethanethiol to give the protected form of the tetradentate ligand **20**. Simultaneous deprotection of the secondary amine and phenolic moieties using anhydrous HCl allowed for the isolation of the hydrochloride salt of the desired tetradentate ligand **21**.

Scheme 2



Coordination of oxorhenium(V) from a $BnEt_3N[OReCl_4]$ precursor by the free chelate **21** under mildly basic conditions,[12,15] followed by standard workup, allowed for isolation of the desired metal complexes as the two diastereomers **5a** and **5b** in modest yield (Scheme 2). ^1H and $^1H-^1H$ COSY NMR spectroscopy provided partial assignment of resonances. The diagnostic resonance which allowed for identification of diastereomer stereochemistry was that of the lone methine proton. As the unique methine in key intermediates **13**−**21**, it could be readily assigned, appearing in the range of δ 4.5−5.2 ppm as either a triplet or doublet of doublets. With this information and the NMR data from **5a** and **5b**, the methine signals of each diastereomer could also be assigned, at δ 4.71 for **5a** and δ 5.56 for **5b**. Due to the large magnetic anisotropy of the O═Re bond, one would expect the *syn* isomer (with the methine hydrogen and the metal oxygen on the the same (top or β) face) to exhibit a methine proton resonance much farther downfield than that of the corresponding *anti* methine proton. This behavior has been noted numerous times in both oxorhenium(V)[12,37,38] and oxotechnetium(V)[39,40] complexes. As a result, compound **5a** was assigned as the *anti* and **5b** as the *syn* diastereomer.

In addition to the NNSS system of complex **5a**, we also worked toward a *trans*-NSNS diamine thioether thiol oxorhenium(V) system (**22**) (Figure 6). A *trans*-NSNS system such as **22** has not been reported in the literature thus far. Based on the concept of trans influence,[41] one would expect that the coordination complex arrangement in **22**, with two strongly donating, trans-disposed ligands, would be less stable than complexes such as **5a**, in which the strongly donating amide and amine donors are cis, or **23**, where the deprotonated amine donor is balanced with a trans weakly donating dative amine. Complex **22** proved difficult to form under the coordination conditions used to synthesize **5a** and, as predicted, exhibited a low stability, undergoing a moderate degree of decomposition when subjected to silica chromatography. As a result, complex **22** was not investigated further.

Lipophilicity and Binding Affinity. The lipophilicity of each of the diastereomers was assessed by

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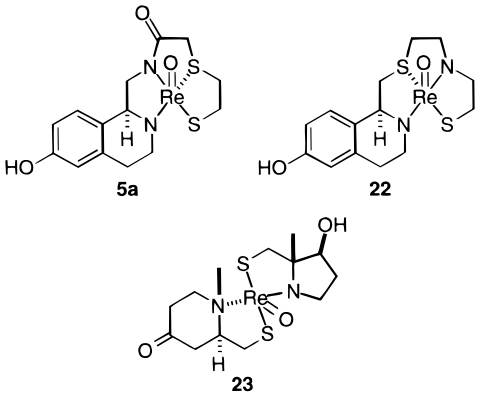
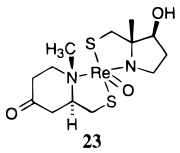


Figure 6. AATT complex **5a**, *trans*-NSNS complex **22**, and dihydrotestosterone bis-bidentate mimic **23**.

Table 1. Octanol−Water Partition Coefficents (log $P_{o/w}$) and Relative Binding Affinities (RBA) of Oxorhenium(V) Complexes for the Estrogen Receptor (ER) and the Androgen Receptor (AR)

compound	log $P_{o/w}$[a]	RBA (receptor)[b]
estradiol (**3**)	3.53	100 (ER)
5a	2.62	0.003 (ER)
5b	2.69	0.007 (ER)
estriol (**6**)[18]	2.54	20 (ER)
 **23**	1.47	<0.02 (AR)
DHT[18]	3.90	61(AR)

[a] log $P_{o/w}$ values were determined by reversed phase HPLC according to the method of Minick.[42] [b] RBA (relative binding affinity) values were determined in a radiometric competitive binding assay according to previously described methods (see Experimental Section). For binding to the estrogen receptor (ER), immature female lamb uterine cytosol was used as a source of receptor and [^{3}H]estradiol was the tracer (K_d = 0.2 nM). For binding to the androgen receptor (AR), mature castrated rat male ventral prostate cytosol was used as a source of receptor and [^{3}H]methyltrienolone (R1881) was used as the tracer (K_d = 0.3 nM). Typical coefficients of variation in these determinations are 0.3.

determination of their octanol−water partition coefficients (log $P_{o/w}$) by an HPLC method (Table 1).[42] While the lipophilicity of our tetradentate complex with the metal centered at the C and D rings (**5a** and **5b**) was much higher than that demonstrated by the bis-bidentate mimic of dihydrotestosterone **23**,[12] both complexes **5a** and **5b** were still about ten times less lipophilic than estradiol.[18]

Relative binding affinities (RBA) of the complexes toward the estrogen receptor (ER) were also measured relative to estradiol, using a competitive radiometric assay. Both diastereomers **5a** and **5b** exhibited low μM affinity for ER. The values were similar to those observed with weak synthetic estrogens, such as *tert*-octylphenol[43] and bis-phenol A.[44] The affinity of such compounds may be attributed to the presence of the phenolic functions found in the isomers of **5**; however, the replacement of the C and D rings with the rhenium chelate clearly reduced binding affinity a great deal. The low lipophilicity of the tetradentate rhenium complexes may have also contributed to the low observed RBA values.

Structure−Affinity Relationships. It is instructive to consider which factors are most likely to contribute to the low binding affinity of the complexes **5a** and **5b** for the estrogen receptor. The molecular volume of these complexes and their shape are similar to that of estradiol and related high-affinity ligands (cf. Figure 3). Their lipophilicity, while lower than that of estradiol, is not very different from that observed for other good estrogens such as compounds **6** and **9** (cf. Figure 4).

A large dipole moment is expected for the metal oxo bond in these oxorhenium(V) complexes **5**. By modeling the dipole moments of complexes **5a** and **5b** and those associated with the other estrogens we have considered in the design of this molecule (Sybyl v.6.1a), we found that the magnitude of the dipoles in **5a** and **5b** were large, but still comparable to other polar estrogens, such as estetrol (**7**)[20−23] and 11β-(chloromethyl)estradiol,[45] which are much higher affinity ligands than **5a** or **5b**. Estradiol itself has a measured dipole moment of 2.3 D;[46] the more polar estrogens, such as **7**, as well as the complexes **5a** and **5b**, have dipole moments in the 3.5−4 D range. In all cases, the dipole moment is directed essentially parallel with the C_9-C_{11} bond, tilted to a small degree in the β direction. Replacement of the amido carbonyl in complexes **5** with a methylene substituent greatly alters the direction and reduces the magnitude of the dipole, such that the resultant oxorhenium(V) species has a dipole moment of about the same magnitude, but opposite the direction, as estradiol. This suggests that much of the polarity in **5a** and **5b** is a result of only the amide carbonyl that places a polar function in a 12β-like position. So, despite the reasonable size, shape, and overall polarity match of these complexes with respect to other high-affinity receptor ligands, the match of their electronic distribution may be much less satisfactory and thus more poorly tolerated by the estrogen receptor. In addition, the complexes lack certain functionality found in high-affinity estrogens, such as the D-ring hydroxyl group. This may contribute further to their low binding affinity. These factors will be considered in refining the design of these and related complexes.

Conclusions

The synthesis of an integrated tetradentate rhenium(V) complex based on the replacement of the C and D rings of estradiol with a novel amine amide thioether thiol (AATT) coordination system has been achieved. Formation of the tetrahydroisoquinoline core by Pictet−Spengler cyclization and heteroatom manipulation allowed for facile generation of these compounds. The tetradentate complexes **5** were more stable than the bis-bidentate rhenium(V) mimic of dihydrotestosterone **23** (Figure 6) and exhibited a higher lipophilicity; however, they demonstrated only weak binding to the estrogen receptor and are therefore not suitable to further development.

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Based on the findings of this study, we are continuing to refine our design of rhenium and ultimately technetium-labeled metal complexes as high-affinity ligands for the estrogen receptor.

Experimental Section

Molecular Modeling. Molecular modeling calculations were performed on a Silicon Graphics Indigo Elan computer. Compound **5a** was built using the SYBYL Molecular Modeling Package (Version 6.1a, Tripos Associates, St. Louis, MO) with empirically derived parameters for technetium.[17] The compound was energy minimized to a gradient of <0.05 kcal/mol Å with the Tripos force field. Dipole calculations were performed after the energy of each molecule was calculated using the Gasteiger−Marzilli method, assuming zero overall charge. Molecular volume calculations were performed in Macromodel v.5.5[47] after translating the Sybyl generated molecules into a data file readable by the Macromodel program.

General. All reagents and solvents were obtained from Aldrich, Eastman, Fisher, or Mallinckrodt and were used as received unless otherwise indicated. All reactions were performed under a nitrogen atmosphere. (Benzyloxy)acetaldehyde was prepared by literature procedures.[34] Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl immediately prior to use. Methylene chloride (CH_2Cl_2) was distilled from calcium hydride prior to use in reactions. Triethylamine was dried by distillation from calcium hydride and stored over KOH. Dimethylformamide (DMF) was distilled from and stored over 4 Å molecular sieves. Hexanes were distilled from calcium sulfate (Drierite) before use in flash chromatography.

Reaction progress was monitored with analytical thin-layer chromatography (TLC) on 0.25 mm Merck F-254 silica gel glass plates. Visualization was achieved using $KMnO_4$ or ninhydrin spray reagents, or UV illumination. Flash chromatography was performed according to the method of Still[48] with Woelm silica gel (0.040−0.063 mm) packing. Melting points are uncorrected.

^1H and ^{13}C NMR 1D and 2D spectra were obtained at 400 or 500 MHz and are reported in parts per million (ppm) downfield from internal tetramethylsilane or from resonances resulting from incomplete deuteration of the NMR solvent (δ scale). Coupling constants (J) and $\Delta\nu$ are reported in Hertz and ppm, respectively. The last number in the parentheses that follows each peak is the number of protons represented in that peak. Microanalyses were performed by the Microanalytical Service at the University of Illinois at Urbana−Champaign.

Synthesis of Tetradentate Ligand. 1-(Benzyloxymethyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (13). 3-Hydroxyphenethylamine hydrochloride (**12**·HCl) (3.72 g, 21 mmol), which was synthesized from norphenylephrine hydrochloride (**11**·HCl) according to literature procedures,[32] was dissolved in MeOH (30 mL), and to it was added (benzyloxy)-acetaldehyde (3.53 g, 1.1 equiv) with stirring at rt. This mixture was then heated to reflux for 18 h to near dryness. Further concentration and flash chromatography of the brown residue yielded a brown foam as product (4.2 g, 73% from norphenylephrine). A sample of this residue was subjected to successive trituration from $MeOH/CH_2Cl_2$ to give a light gray powder. Recrystallization attempts from various solvent systems were unsuccessful: ^1H NMR (DMSO-d_6, 400 MHz) δ 2.92 (ABX$_2$, J_{AB} = 17.5, $\Delta\nu$ = 0.089, J_{AX} = J_{BX} = 5.9, 2), 3.27 (ABX$_2$, J_{AB} = 12.6, $\Delta\nu$ = 0.17, J_{AX} = 6.1, J_{BX} = 5.5, 2), 3.88 (ABX, J_{AB} = 10.7, $\Delta\nu$ = 0.14, J_{AX} = 3.7, J_{BX} = 8.2, 2), 4.55 (t, J = 3.9, 1), 4.58 (AB q, J_{AB} = 12.0, $\Delta\nu$ = 0.053, 2), 6.61 (d, J = 2.2, 1), 6.67 (dd, J = 8.4, 2.3, 1), 7.07 (d, J = 8.5, 1), 7.26−7.32 (m, 1), 7.32−7.40 (m, 4), 9.56 (b s, 1), 9.65 (b s, 1); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 25.1, 38.7, 53.3, 70.0, 72.4, 114.2, 114.9, 119.6, 127.4, 127.6, 127.7, 128.2, 133.9, 137.7, 156.8; MS (CI, CH_4) m/z 270 (M + H^+, 100), 268 (21), 162 (27), 148 (79), 91 (22), 79 (45); HRMS calcd for $C_{17}H_{20}NO_2^+$ 270.1494, found 270.1492.

1-(Benzyloxymethyl)-2-(*tert*-butoxycarbonyl)-6-((2-methoxyethoxy)methoxy)-1,2,3,4-tetrahydroisoquinoline (15). To a suspension of compound **13** (4.2 g, 15.6 mmol) in CH_2Cl_2 (200 mL) were added triethylamine (2.2 mL, 16 mmol) and di-*tert*-butyl dicarbonate (3.46 g, 15.9 mmol) in portions at rt with vigorous stirring. After 45 min, TLC (R_f 0.31 in 5% $MeOH/CH_2Cl_2$) indicated complete conversion of starting material to a less polar spot. The mixture was then concentrated, and flash chromatography (0−5% $MeOH/CH_2Cl_2$) afforded a light yellow foam as product **14** (4.95 g, 86%).

The Boc-protected tetrahydroisoquinoline **14** (4.95 g, 13.4 mmol) was dissolved in THF (60 mL) and cooled to 0 °C. Sodium hydride (60% suspension in mineral oil, 700 mg, 1.3 equiv) was then added in portions to this solution. The resulting suspension was allowed to stir at 0 °C for 30 min until hydrogen evolution ceased. (2-Methoxyethoxy)methyl chloride (MEM chloride) (2.6 mL, 1.6 equiv) was added at 0 °C, and then this solution was allowed to warm to rt after 30 min. After 2 h, reaction was quenched with MeOH and the mixture concentrated. Flash chromatography (R_f 0.33 in 20−30% EtOAc/hexanes) provided the fully protected tetrahydroisoquinoline **15** as a colorless oil (4.29 g, 70%): ^1H NMR (DMSO-d_6, 400 MHz, 100 °C) mixture of two rotamers: major δ 1.42 (s, 9), 2.70−2.82 (m, 2), 3.25 (s, 3), 3.25−3.35 (m, 2), 3.48 (t, J = 5.0, 2), 3.67 (ABX, J_{AX} = 6.6, J_{BX} = 5.0, J_{AB} = 10.4, $\Delta\nu$ = 0.059, 2), 3.73 (t, J = 5.1, 2), 4.50 (AB, J_{AB} = 12.4, $\Delta\nu$ = 0.061, 2), 5.15 (t, J = 5.9, 1), 5.20 (s, 2), 6.81 (d, J = 2.5, 1), 6.84 (dd, J = 8.4, 2.7, 1), 7.16 (d, J = 8.5, 1), 7.24−7.34 (m, 5); minor δ 1.41 (s, 9), 2.65−2.72 (m, 2), 2.99−3.06 (m, 2), 3.25 (s, 3), 3.48 (t, J = 5.0, 2), 3.64 (ABX, J_{AX} = 6.6, J_{BX} = 5.0, J_{AB} = 10.2, $\Delta\nu$ = 0.065, 2), 3.73 (t, J = 5.1, 2), 4.49 (AB, J_{AB} = 12.2, $\Delta\nu$ = 0.060, 2), 5.10 (t, J = 5.9, 1), 5.20 (s, 2), 6.55 (d, J = 2.4, 1), 6.60 (dd, J = 8.4, 2.4, 1), 7.02 (d, J = 8.3, 1), 7.24−7.34 (m, 5); MS (CI, CH_4) m/z 458 (M + H^+, 8), 402 (11), 386 (10), 359 (29), 358 (100), 336 (34), 282 (31), 280 (39), 270 (42), 236 (18), 192 (15), 148 (10), 91 (18), 89 (18); HRMS calcd for $C_{26}H_{36}NO_6^+$ 458.2543, found 458.2533. Anal. Calcd for $C_{26}H_{35}NO_6$: C, 68.25; H, 7.71; N, 3.06. Found: C, 68.29; H, 7.97; N, 2.86.

1-(Hydroxymethyl)-2-(*tert*-butoxycarbonyl)-6-((2-methoxyethoxy)methoxy)-1,2,3,4-tetrahydroisoquinoline (16). The fully protected tetrahydroisoquinoline **15** (512 mg, 1.1 mmol) was dissolved in ethanol (10 mL), and 10% palladium on carbon (258 mg) was added. This was placed under a H_2 atmosphere for 5 h with stirring, after which TLC indicated complete conversion. The palladium was removed by filtration through Celite, and the filtrate was concentrated. Flash chromatography (40−50% EtOAc/hexanes) gave a colorless oil, which could be triturated from Et_2O/CH_2Cl_2 to give the title compound as a white solid (377 mg, 92%): R_f 0.29 (40% EtOAc/hexanes); mp 52.5−53 °C; ^1H NMR (DMSO-d_6, 400 MHz, 100 °C) δ 1.44 (s, 9), 2.73 (t, J = 6.0, 1), 3.25 (s, 3), 3.33 (dt, J = 13.2, 6.8, 1), 3.49 (t, J = 4.9, 2), 3.6158 (AB q, J_{AB} = 11.0, $\Delta\nu$ = 0.021, 2), 3.6160 (AB q, J_{AB} = 10.7, $\Delta\nu$ = 0.059, 2), 3.73 (t, J = 4.9, 2), 3.86 (dt, J = 12.9, 5.2, 1), 4.92 (t, J = 5.9, 1), 5.19 (s, 2), 6.79 (d, J = 2.4, 1), 6.83 (dd, J = 8.3, 2.4, 1), 7.14 (d, J = 8.3, 1); MS (CI, CH_4) m/z 368 (M + H^+, 2), 336 (18), 312 (20), 296 (15), 280 (34), 268 (100), 250 (18), 236 (28), 192 (56), 89 (81); HRMS calcd for $C_{19}H_{30}NO_6^+$ 368.2073, found 368.2074. Anal. Calcd for $C_{19}H_{29}NO_6$: C, 62.11; H, 7.95; N, 3.81. Found: C, 62.31; H, 8.03; N, 3.64.

1-(Azidomethyl)-2-(*tert*-butoxycarbonyl)-6-((2-methoxyethoxy)methoxy)-1,2,3,4-tetrahydroisoquinoline (17). Triphenylphosphine (1.43 g, 5.45 mmol) was dissolved in THF (30 mL) and then cooled to 0 °C. Diethyl azodicarboxylate (DEAD) (0.86 mL, 5.44 mmol) was then added by syringe at 0 °C. After the solution was stirred for 15 min, the alcohol **16** (1.07 g, 2.91 mmol) in THF (5 mL) was slowly added to the light orange solution, followed immediately by diphenyl phosphorylazide (1.17 mL, 5.43 mmol). The reaction mixture was

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allowed to warm to rt and stir for 12 h. Concentration and flash chromatography (20−30% EtOAc/hexanes) yielded a colorless oil as product (1.04 g, 91%): R_f 0.69 (50% EtOAc/hexanes); IR ($CDCl_3$, cm^{-1}) 2103 (N═N═N), 1682 (C═O); ^1H NMR (DMSO-d_6, 400 MHz, 100 °C) δ 1.43 (s, 9), 2.68−2.83 (m, 2), 3.25 (s, 3), 3.26−3.36 (m, 1), 3.55 (ABX, J_{AB} = 12.7, $\Delta\nu$ = 0.092, J_{AX} = 7.8, J_{BX} = 4.9, 2), 3.6045 (AB q, J_{AB} = 5.4, $\Delta\nu$ = 0.23, 2), 3.6050 (AB q, J_{AB} = 4.5, $\Delta\nu$ = 0.25, 2), 3.90 (dt, J = 13.2, 4.9, 1), 5.16 (dd, J = 7.6, 5.1, 1), 5.20 (s, 2), 6.83 (d, J = 2.4, 1), 6.86 (dd, J = 8.3, 2.4, 1), 7.20 (d, J = 8.3, 1); MS (CI, CH_4) m/z 393 (M + H^+, 5), 337 (22), 336 (37), 294 (24), 293 (95), 291 (18), 281 (20), 280 (100), 250 (30), 236 (38), 218 (13), 217 (40), 192 (45), 148 (49); HRMS calcd for $C_{19}H_{28}N_4O_5^+$ 393.2138, found 393.2132.

1-(Aminomethyl)-2-(*tert*-butoxycarbonyl)-6-((2-methoxyethoxy)methoxy)-1,2,3,4-tetrahydroisoquinoline (18). To a solution of azide **17** (1.01 g, 2.58 mmol) in ethanol (15 mL) was added 10% palladium on carbon (400 mg). The reaction mixture was then placed under a hydrogen atmosphere for 21 h. Palladium−carbon was then removed by filtering through Celite and rinsing with 10% MeOH/CH_2Cl_2. Concentration and flash chromatography (10% MeOH/CH_2Cl_2) gave the title compound as a somewhat air- and moisture-sensitive red oil (797 mg, 84%): R_f 0.018 (50% EtOAc/hexanes); IR ($CDCl_3$, cm^{-1}) 1682 (C═O); ^1H NMR (DMSO-d_6, 400 MHz, 100 °C) δ 1.44 (s, 9), 2.37 (b s, 2), 2.66−2.81 (m, 2), 3.25 (s, 3), 3.29 (tt, J = 8.4, 5.0, 1), 3.6065 (AB q, J_{AB} = 5.2, $\Delta\nu$ = 0.23, 2), 3.6070 (AB q, J_{AB} = 4.6, $\Delta\nu$ = 0.25, 2), 3.87 (dt, J = 13.2, 5.0, 1), 4.88 (t, J = 6.3, 1), 5.19 (s, 2), 6.80 (d, J = 2.0, 1), 6.84 (dd, J = 8.3, 2.4, 1), 7.14 (d, J = 8.3, 1); ^{13}C NMR (DMSO-d_6, 100 MHz, 100 °C) δ 27.7, 37.5, 46.3, 56.0, 57.46, 57.52, 66.9, 70.6, 78.4, 93.0, 113.9, 115.8, 127.6, 128.6, 135.4, 154.2, 155.2; MS (FAB) m/z 367 (M + H^+, 100), 336 (15), 311 (56), 280 (77), 267 (85), 250(24), 236 (26), 192 (16), 148 (22); HRMS calcd for $C_{19}H_{31}N_2O_5^+$ 367.2233, found 367.2233.

1-((Bromoacetamido)methyl)-2-(*tert*-butoxycarbonyl)-6-((2-methoxyethoxy)methoxy)-1,2,3,4-tetrahydroisoquinoline (19). Acylation of the amine was performed according to a literature method.[37] A solution of bromoacetyl bromide (24 μL, 0.275 mmol) in CH_2Cl_2 (1 mL) was cooled to −20 °C. A mixture of amine **18** (99 mg, 0.27 mmol) and triethylamine (40 μL, 0.287 mmol) was then added dropwise with stirring. The reaction mixture was allowed to warm to rt. After 10 min, the reaction mixture was concentrated, and flash chromatography (50−60% EtOAc/hexanes) gave a clear, colorless oil as product (114 mg, 87%): ^1H NMR (DMSO-d_6, 400 MHz, 100 °C) δ 1.43 (s, 9), 2.74 (dd, J = 9.8, 5.5, 2), 3.23−3.34 (m, 1), 3.25 (s, 3), 3.34−3.45 (m, 2), 3.49 (t, J = 5.0, 2), 3.73 (t, J = 5.0, 2), 3.83 (d, J = 2.0, 2), 3.84−3.94 (m, 1), 5.11 (dd, J = 8.2, 5.8, 1), 5.20 (s, 2), 6.81 (d, J = 2.4, 1), 6.85 (dd, J = 8.3, 2.4, 1), 7.11 (d, J = 8.3, 1), 7.99 (b s, 1); MS (FAB) m/z 489 (M + H^+, 15), 487 (M + H^+, 16), 390 (16), 389 (89), 388 (17), 387 (93), 336 (33), 309 (41), 281 (16), 280 (100), 236 (18), 192 (16), 155 (22), 119 (56); HRMS calcd for $C_{21}H_{32}N_2O_6{}^{81}Br^+$ 489.1423, found 489.1414. Anal. Calcd for $C_{21}H_{31}BrN_2O_5$: C, 53.51; H, 6.63; N, 5.94. Found: C, 53.79; H, 6.59; N, 6.15.

2-(*tert*-Butoxycarbonyl)-6-((2-methoxyethoxy)methoxy)-1-((((2-thioethyl)thio)acetamido)methyl)-1,2,3,4-tetrahydroisoquinoline (20). To a solution of 1,2-ethanedithiol (1.0 mL, 8.4 equiv) and bromide **19** (662 mg, 1 equiv, 1.36 mmol) in THF (30 mL), NaH (60% dispersion in mineral oil, 110 mg, 2 equiv) at 0 °C. After 45 min, the suspension was allowed to warm to rt and was stirred for an additional 1.5 h. The reaction mixture was subsequently quenched with MeOH and then concentrated. Flash chromatography (60% EtOAc/hexanes) gave a colorless oil as product (524 mg, 77%): R_f 0.52 (50% EtOAc/hexanes); ^1H NMR (DMSO-d_6, 400 MHz, 100 °C) δ 1.43 (s, 9), 2.29 (t, J = 7.7, 1), 2.66−2.80 (m, 5), 3.14 (d, J = 2.0, 2), 3.24−3.32 (m, 1), 3.25 (s, 3), 3.32−3.43 (m, 2), 3.49 (t, J = 4.9, 2), 3.73 (t, J = 4.8, 2), 5.09 (dd, J = 7.3, 5.6, 1), 5.20 (s, 2), 6.81 (d, J = 2.4, 1), 6.85 (dd, J = 8.5, 2.4, 1), 7.12 (d, J = 8.1, 1), 7.74 (b s, 1); MS (CI, CH_4) m/z 501 (M + H^+, 2), 429 (13), 403 (17), 402 (29), 401 (100), 369 (11), 341 (20), 309 (22), 280 (14), 61 (27); HRMS calcd for $C_{23}H_{37}N_2O_6S_2^+$ 501.2093, found 501.2084.

6-Hydroxy-1-((((2-thioethyl)thio)acetamido)methyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (21·HCl). The thiol **20** (524 mg, 1.05 mmol) was taken up in a minimal amount (0.5 mL) of THF at rt; then 4 N HCl in dioxane (10 mL) was introduced by syringe. After 15 min an off-white precipitate was deposited onto the sides of the reaction vessel. Concentration and repeated cycles of addition of dry Et_2O and evaporation to remove excess acid gave a white to off-white solid (365 mg, 100%) after concentration under vacuum. This was taken to the next step (metal complexation) without further purification. An analytical sample was purified by dissolution in 20% MeOH/CH_2Cl_2 and passage through a silica plug with elution with 20% MeOH/CH_2Cl_2. Collection of appropriate fractions allowed for the isolation of a colorless oil **16**: ^1H NMR (DMSO-d_6, 400 MHz, 100 °C) δ 2.76−3.00 (m, 5), 3.14−3.23 (m, 1), 3.20 (s, 2), 3.25 (s, 2), 3.37 (dt, J = 12.5, 6.3, 1), 3.54−3.68 (m, 2), 4.37 (dd, J = 7.6, 4.4, 1), 6.60 (d, J = 2.0, 1), 6.68 (dd, J = 8.4, 2.3, 1), 7.07 (d, J = 8.5, 1), 8.30 (s, 1), 9.20 (b s, 2); MS (CI, CH_4) m/z 313 (M + H^+, 0.5), 293 (10), 231 (21), 203 (100), 89 (12); HRMS calcd for $C_{14}H_{21}N_2O_2S_2^+$ 313.1045, found 313.1040.

Synthesis of Rhenium(V) Complexes. [6-Hydroxy-1-((((2-mercaptoethyl)thio)acetamido)methyl)-1,2,3,4-tetrahydroisoquinolinato-*S*,*N*,*N*′]oxorhenium(V) (5a and 5b). A sample of **21**·HCl (366 mg, 1.05 mmol) was dissolved in degassed MeOH (10 mL), and 1 N NaOAc in MeOH (10 mL) was added at rt. Benzyltriethylammonium tetrachlorooxorhenate(V)[49] (675 mg, 1.26 mmol) in degassed MeOH (30 mL) was added to this solution slowly with stirring at rt. The resulting red solution was then heated to reflux for 4 h. The reaction mixture was then cooled and concentrated, and the residue was taken up in CH_2Cl_2/H_2O. The layers were separated, and the aqueous layer was back-extracted with CH_2Cl_2. The organic extracts were combined, washed (saturated NaCl), dried ($MgSO_4$), and concentrated to leave a deep red residue. Flash chromatography (50% EtOAc/benzene) gave two closely eluting bands, one orange and one red, of which a small portion was separated for analytical characterization. Combined fractions of oxorhenium(V) products afforded 45 mg (8%) of a 1:1 diastereomeric mixture of **5a** and **5b**.

***anti* isomer (5a)**: ^1H NMR (acetone-d_6, 500 MHz) δ 1.92−2.02 (m, 1), 2.78 (td, J = 16.1, 2.6, 1), 2.85 (td, J = 13.8, 3.6, 1), 3.08 (ddd, J = 17.0, 11.1, 5.8, 1), 3.27 (t, J = 10.9, 1), 3.78 (d, J = 16.9, 1), 3.86 (ddd, J = 8.8, 3.6, 1.3, 1), 4.01 (dd, J = 13.5, 3.8, 1), 4.36 (td, J = 12.1, 3.8, 1), 4.66 (d, J = 16.9, 1), 4.71 (t, J = 8.7, 1), 4.87 (dd, J = 11.6, 7.1, 1), 4.94 (dd, J = 11.8, 5.3, 1), 6.62 (d, J = 2.1, 1), 6.68 (dd, J = 8.3, 2.6, 1), 7.04 (d, J = 8.3, 1), 8.13 (s, 1); MS (FAB) m/z 513 (M + H^+ for ^{187}Re, 8), 511 (M + H^+ for ^{185}Re, 8), 307 (47), 289 (32), 273 (21), 165 (18), 155 (65), 154 (100), 152 (36), 138 (78), 137 (90), 136 (97); HRMS calcd for $C_{14}H_{18}N_2O_2ReS_2^+$ 513.0317, found 513.0304.

***syn* isomer (5b)**: ^1H NMR (DMSO-d_6, 500 MHz) δ 1.94 (ddd, J = 14.6, 10.5, 4.5, 1), 2.63 (dt, J = 15.8, 2.7, 1), 2.75 (td, J = 13.7, 3.4, 1), 2.81 (ddd, J = 15.4, 11.9, 3.9, 1), 3.24−3.33 (m, 1), 3.66−3.70 (m, 1), 3.94 (d, J = 17.1, 1), 3.92−3.99 (m, 1), 4.01 (t, J = 11.2, 1), 4.44 (dd, J = 12.6, 7.2, 1), 4.66 (d, J = 17.1, 1), 4.83−4.89 (m, 1), 5.52 (t, J = 8.0, 1), 6.49 (d, J = 2.3, 1), 6.59 (dd, J = 8.3, 2.5, 1), 7.04 (d, J = 8.5, 1), 9.20 (s, 1); ^1H NMR (acetone-d_6, 500 MHz) δ 1.89−1.97 (m, 1), 2.01−2.08 (m, 1), 2.63−2.72 (m, 1), 2.77−2.90 (m, 1), 3.28 (dd, J = 12.2, 9.9, 1), 3.82 (d, J = 17.5, 1), 3.84 (ddd, J = 10.5, 3.7, 1.5, 1), 3.92−3.97 (m, 1), 3.97−4.03 (m, 1), 4.51 (dd, J = 12.6, 7.2, 1), 4.60 (d, J = 17.9, 1), 4.94 (ddd, J = 13.5, 4.6, 2.5, 1) , 5.56 (t, J = 8.3, 1), 6.60 (d, J = 2.5, 1), 6.70 (dd, J = 8.3, 2.6, 1), 7.08 (d, J = 8.5, 1), 8.14 (s, 1); MS (FAB) m/z 513 (M + H^+ for ^{187}Re, 7), 511 (M + H^+ for ^{185}Re, 7), 307 (41), 289 (25), 165 (13), 154 (100), 139 (30), 138 (63), 137 (86), 136 (95), 135 (15), 124 (19), 123 (15), 121 (17), 120 (26), 107 (55); HRMS calcd for $C_{14}H_{18}N_2O_2ReS_2^+$ 513.0317, found 513.0323.

Estrogen Receptor Binding Affinity. Receptor binding affinity (RBA) values were determined by a competitive

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radiometric binding assay, using lamb uterus cytosol as a source of receptor and tritium-labeled estradiol as tracer, according to a previously published method.[50]

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Supporting Information Available: ^{1}H NMR spectra of intermediates **13**, **15**, **17**−**21**, ^{13}C NMR spectra of **13** and **18**, and 1D ^{1}H and 2D ^{1}H−^{1}H COSY NMR spectra of complexes **5a** and **5b** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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