Inorg. Chem. **2006**, *45*, 902–909

Oxorhenium(V) and Oxotechnetium(V) [NN][S]$_3$ Complexes of 2-Phenylbenzothiazole Derivatives

Stamatia Tzanopoulou,[†] Ioannis C. Pirmettis,[‡] Georgios Patsis,[§] Catherine Raptopoulou,[||] Aris Terzis,[||] Minas Papadopoulos,[‡] and Maria Pelecanou*[,†]

Institutes of Biology, Radioisotopes-Radiodiagnostic Products, and Materials Science, National Centre for Scientific Research "Demokritos", 15310 Athens, Greece, and Biomedica Life Sciences S.A., Athens, Greece

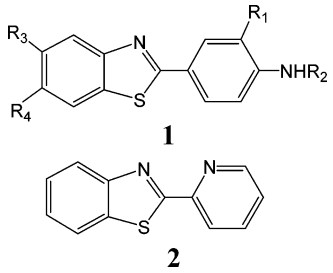
Received September 9, 2005

The reaction of 2-(2′-pyridyl)benzothiazole, [NN], with the $ReO(V)^{3+}$ and $TcO(V)^{3+}$ cores in the presence of thiophenols, [S] (RC_6H_4SH, R = H, 4-CH_3, 4-OCH_3), as coligands led to the isolation of hexacoordinated complexes of the MO[NN][S]$_3$ type (M = Re, Tc). In all cases, two geometric *mer* isomers were formed, as evidenced by NMR spectroscopy and confirmed by X-ray crystallography. In both isomers, the coordination geometry about the metal ion is a distorted octahedral defined by the two nitrogen atoms of the bidentate ligand, the three sulfur atoms of the monodentate thiols, and the oxygen atom of the oxo group. The apical positions of the octahedron are occupied by the oxygen of the oxo group and, in one of the isomers, the nitrogen of the pyridyl moiety of 2-(2′-pyridyl)-benzothiazole, while, in the second isomer, the imine nitrogen of 2-(2′-pyridyl)benzothiazole. The complexes are stable, neutral, and lipophilic. Complete ^{1}H and ^{13}C NMR assignments are reported for all complexes. The synthetic reaction was also successfully transferred at the technetium-99m tracer level by ligand exchange reaction using ^{99m}Tc–glucoheptonate as precursor in the presence of 2-(2′-pyridyl)benzothiazole and 4-$CH_3C_6H_4SH$. The structure of the technetium-99m complex was established by high-performance liquid chromatographic comparison with the analogous oxotechnetium and oxorhenium complexes. The 2-(2′-pyridyl)benzothiazole ligand serves as a preliminary model for 2-(4-aminophenyl)benzothiazole, which possesses interesting properties for the development of technetium and rhenium radiopharmaceuticals for tumor imaging and/or radiotherapy as well as in vivo diagnosis of Alzheimer's disease.

Introduction

In the past decade the structurally simple and easily accessible class of 2-(4-aminophenyl)benzothiazoles was shown to possess remarkable properties of potential pharmaceutical applications.[1] The original unsubstituted member of this series, 2-(4-aminophenyl)benzothiazole, **1** (Chart 1, $R_1 = R_2 = R_3 = R_4 = H$), exhibits potent and selective activity against certain breast carcinoma cell lines in vitro (MCF-7, MDA 468, $IC_{50} < 1$ nM).[2] Introduction of a methyl or halogen substituent into the 3-position of the 4-aminophenyl group (**1**, R_1 = Me, Cl, Br, I, $R_2 = R_3 = R_4 = H$) was shown to enhance potency and extended the spectrum of

Chart 1



1

2

* To whom correspondence should be addressed. E-mail: pelmar@bio.demokritos.gr. Phone: +30210 6503555. Fax: +30210 6511767.
[†] Institute of Biology, National Centre for Scientific Research "Demokritos".
[‡] Institute of Radioisotopes-Radiodiagnostic Products, National Centre for Scientific Research "Demokritos".
[§] Biomedica Life Sciences S.A.
[||] Institute of Materials Science, National Centre for Scientific Research "Demokritos".

(1) Bradshaw, T. D.; Stevens, M. F. G.; Westwell, A. D. *Curr. Med. Chem.* **2001**, *8*, 203−210.
(2) Shi, D.-F.; Bradshaw, T. D.; Wrigley, S.; McCall, C. J.; Lelieveld, P.; Fichtner, I.; Stevens, M. F. G. *J. Med. Chem.* **1996**, *39*, 3375−3384.

10.1021/ic051538e CCC: $33.50
Published on Web 12/17/2005

action to certain colon, lung, melanoma, renal, and ovarian cell lines.[3] Subsequent circumvention of deactivating metabolic steps led to the identification of the most potent derivative, 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole (**1**, $R_1 = Me$, $R_2 = H$, $R_3 = F$, $R_4 = H$),[4] the lysylamide derivative of which is currently the focus of pharmaceutical and preclinical development.[5]

Furthermore, 2-(4-aminophenyl)benzothiazole derivatives have demonstrated promising qualities as imaging probes of brain amyloid plaques in Alzheimer's disease, since they bind to amyloid with high affinity and cross the blood−brain barrier well.[6−11] A successful positron emission tomography (PET) imaging study in Alzheimer's disease patients with the ^{11}C-labeled 2-(4-methylaminophenyl)-6-hydroxybenzothiazole (**1**, $R_1 = H$, $R_2 = CH_3$, $R_3 = H$, $R_4 = OH$) indicates that this benzothiazole tracer can provide quantitative information on amyloid deposits in living subjects.[12]

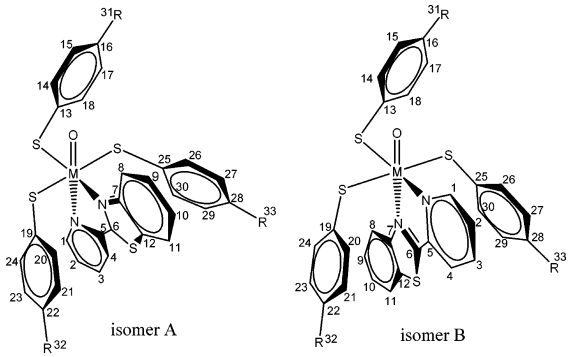
The interesting properties of 2-(4-aminophenyl)benzothiazoles render this chemical class an important candidate for the development of technetium (Tc) and rhenium (Re) radiopharmaceuticals for tumor imaging and/or radiotherapy, as well as in vivo diagnosis of Alzheimer's disease. Technetium-99m, the metastable isotope of Tc, continues to be the most commonly used radionuclide in diagnostic nuclear medicine for single photon emmission computed tomography (SPECT) imaging due to its favorable physical properties ($t_{1/2} = 6$ h, $E_\gamma = 140$ keV) and availability.[13] On the other hand, rhenium, the periodic group VIIA congener of Tc, has two radionuclides ^{186}Re ($t_{1/2} = 3.8$ d, $E_{max} = 1.07$ MeV) and ^{188}Re ($t_{1/2} = 0.7$ d, $E_{max} = 2.12$ MeV) suitable for radiotherapeutic applications due to their favorable β-emitting properties.[14] The occurrence of technetium and rhenium in the same periodic group in combination with the "lanthanide contraction", which causes the two elements to have almost identical radii, ensures that these metals generally produce analogous complexes, with similar physical and biodistribution properties.[15]

In fact, in the case of tumor treatment, analogous complexes of technetium and rhenium are considered as "matched pairs" for diagnosis and therapy, since an existing ^{99m}Tc radiopharmaceutical which accumulates in cancerous tissue can be used as a model for the development of a $^{186/188}$Re analogue aiming at targeted radiotherapy. Under the supposition that the $^{186/188}$Re analogue will exhibit a similar to ^{99m}Tc biodistribution pattern, it is anticipated that a therapeutically significant radiation dose will be delivered to the tumor site without adversely affecting normal tissue.[16−23] Technetium and rhenium complexes of 2-(4-aminophenyl)-benzothiazole derivatives aiming at diagnosis and therapy of tumors sensitive to this chemical class have not been presented so far.

In addition, labeling of a 2-(4-aminopheny)lbenzothiazole derivative with technetium-99m may provide a radiodiagnostic agent that combines affinity for amyloid plaques with the excellent imaging properties of technetium. To our knowledge, all 2-(4-aminophenyl)benzothiazole derivatives presented as potential imaging agents for amyloid plaques are labeled with cyclotron-produced isotopes.[6−12] Alternative labeling with technetium may provide an efficient imaging agent for SPECT which is of lower cost and wider availability. Previous attempts toward the development of technetium-99m imaging agents for targeting the amyloid plaques in the brain of Alzheimer's patients include the ^{99m}Tc-labeled derivatives of the azo dyes chrysamine G and Congo red[24−26] and derivatives of biphenyls.[27] The azo dye ^{99m}Tc complexes are large, charged molecules and unlikely to penetrate the blood−brain barrier; however, the neutral and lipophilic ^{99m}Tc-labeled biphenyls provided encouraging evidence that the development of a ^{99m}Tc-labeled agent for imaging of the plaques may be feasible.

(3) Bradshaw, T. D.; Wrigley, S.; Shi, D.-F.; Schultz, R. J.; Paull, K. D.; Stevens, M. F. G. *Brit. J. Cancer* **1998**, *77*, 745−752.
(4) Hutchinson, I.; Chua, M.-S.; Browne, H. L.; Trapani, V.; Bradshaw, T. D.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **2001**, *44*, 1446−1455.
(5) Bradshaw, T. D.; Westwell, A. D. *Curr. Med. Chem.* **2004**, *11*, 1009−1021.
(6) Klunk, W. E.; Wang, Y.; Huang, G.-f.; Debnath, M. L.; Holt, D. P.; Mathis, C. A. *Life Sci.* **2001**, *69*, 1471−1484.
(7) Mathis, C. A.; Bacskai, B. J.; Kajdasz, S. T.; McLellan, M. E.; Frosch, M. P.; Hyman, B. T.; Holt, D. P.; Wang, Y.; Huang, G.-F.; Debnath, M. L.; Klunk, W. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 295−298.
(8) Zhuang, Z.-P.; Kung, M.-P.; Hou, C.; Skovronsky, D.; Gur, T. L.; Plössl, K.; Trojanowski, J. Q.; Lee, V. M.-Y.; Kung, H. F. *J. Med. Chem.* **2001**, *44*, 1905−1914.
(9) Kung, M.-P.; Hou, C.; Zhuang, Z.-P.; Zhang, B.; Skovronsky, D.; Trojanowski, J. Q.; M.-Y. Lee, V.; Kung, H. F. *Brain Res.* **2002**, *956*, 202−210.
(10) Wang, Y. M.; Klunk, W. E.; Debnath, M. L.; Huang, G.-f.; Holt, D. P.; Shao, L.; Mathis, C. A. *J. Mol. Neurosci.* **2004**, *24*, 55−62.
(11) Mathis, C. A.; Holt, D. P.; Wang, Y.; Huang, G.-F.; Debnath, M. L.; Klunk, W. E. *J. Nucl. Med.* **2002**, *43*, 166P.
(12) Klunk, W. E.; Engler, H.; Nordberg, A.; Wang, Y.; Blomqvist, G.; Holt, D. P.; Bergström, M.; Savitcheva, I.; Huang, G.-f.; Estrada S.; Ausén, B.; Debnath, M. L.; Barletta, J.; Price, J. C.; Sandell, J.; Lopresti, B. J.; Wall, A.; Koivisto, P.; Antoni, G.; Mathis, C. A.; Langström, B. *Ann. Neurol.* **2004**, *55*, 306−319.
(13) (a) Steigman, J.; Eckelman, W. C. *The Chemistry of Technetium in Medicine*; National Academy Press: Washington, DC, 1992. (b) Bandoli, G.; Dolmella, A.; Porchia, M.; Refosco, F.; Tisato, F. *Coord. Chem. Rev.* **2001**, *214*, 43−90.
(14) Hashimoto, K.; Yoshihara, K.*Topics in Current Chemistry*; Springer-Verlag: Berlin, Heidelberg, Germany, 1996; Vol. 176, p 275.
(15) (a) Deutsch, E.; Libson, K.; Vanderheyden, J.-L.; Ketring, A. R.; Maxon, H. R. *Nucl. Med. Biol.* **1986**, *13*, 465−477. (b) Dilworth, J.; Parrot, S. *Chem. Soc. Rev.* **1998**, *27*, 43−55.
(16) Schubiger, P. A.; Alberto, R.; Smith, A. *Bioconjugate Chem.* **1996**, *7*, 165−179.
(17) (a) Zamora, P. O.; Gulhke, S.; Bender, H.; Diekmann, D.; Rhodes, B. A.; Biersack, H. J.; Knapp, F. F., Jr. *Int. J. Cancer* **1996**, *65*, 214−220. (b) Zamora, P. O.; Marek, M. J.; Knapp, F. F., Jr. *Appl. Radiat. Isot.* **1997**, *48*, 305−309.
(18) Safavy, A.; Khazaeli, M. B.; Qin, H.; Buchsbaum, D. J. *Cancer* **1997**, *80*, 2354−9.
(19) Volkert, W. A.; Hoffman, T. J. *Chem. Rev.* **1999**, *99*, 2269−2292.
(20) Heeg, M. J.; Jurisson, S. S. *Acc. Chem. Res.* **1999**, *32*, 1053−1060.
(21) Gali, H.; Hoffman, T. J.; Sieckman, G. L.; Owen, N. K.; Katti, K. V.; Volkert, W. A. *Bioconjugate Chem.* **2001**, *12*, 354−363.
(22) Heppeler, A.; Froidevaux, S.; Eberle, A. N.; Maecke, H. R. *Curr. Med. Chem.* **2000**, *7*, 971−994.
(23) (a) Miao Y.; Owen, N. K.; Fisher, D. R.; Hoffman, T. J.; Quinn, T. P. *J. Nucl. Med.* **2005**, *46*, 121−129. (b) Miao, Y.; Owen, N. K.; Whitener, D.; Gallazzi, F.; Hoffman, T. J.; Quinn, T. P. *Int. J. Cancer* **2002**, *101*, 480−487.
(24) Han, H.; Cho, C.-G.; Lansbury, P. T., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 4506−4507.
(25) Zhen, W.; Han, H.; Anguiano, M.; Lemere, C. A.; Cho, C. G.; Lansbury, P. T., Jr. *J. Med. Chem.* **1999**, *42*, 2805−2815.
(26) Dezutter, N. A.; Dom, R. J.; de Groot, T. J.; Bormans, G. M.; Verbruggen, A. M. *Eur. J. Nucl. Med.* **1999**, *26*, 1392−1399.
(27) Zhuang, Z.-P.; Kung, M.-P.; Hou, C.; Plössl, K.; Kung, H. F. *Nucl. Med. Biol.* **2005**, *32*, 171−184.

Chart 2



3 M = Re, R = H
4 M = Re, R = CH_3
5 M = Re, R = OCH_3
6 M = ^{99}Tc, R = CH_3
7 M = ^{99m}Tc, R = CH_3

As a first step in the investigation of the possible modes of complexation of the phenylbenzothiazole derivatives with Tc and Re, we report herein the reaction of the 2-(2′-pyridyl)-benzothiazole, **2** (Chart 1), with the oxotechnetium and oxorhenium cores and thiophenols as coligands. In **2**, the active 2-(4-aminopheny)lbenzothiazole structure is modified by the incorporation of a second heterocyclic nitrogen on the phenyl moiety to make the molecule capable of directly binding to the oxometal cores. Similar modifications have been applied before in the case of the amyloid binding fibril binding molecules without affecting the affinity of the modified molecules for amyloid fibrils.[28] The synthesis and characterization of the complexes were initially carried out with stable rhenium (a mixture of ^{185}Re and ^{187}Re isotopes) that does not require any special handling and, subsequently, with the pseudostable technetium-99 isotope, before being transferred at the γ-radioactive technetium-99m level. In all cases, two types of isomeric complexes A and B shown in Chart 2 were produced: **3**−**5** with the $ReO(V)^{3+}$ core and thiophenol, 4-methylthiophenol, and 4-methoxythiophenol as coligands, respectively, and **6** with the $^{99}TcO(V)^{3+}$ core and 4-methylthiophenol as coligand.

Experimental Section

Safety Note. Technetium-99 is a weak β-emitter (292 keV) with a half-life of 2.12×10^5 years. All manipulations of solutions and solids containing this radioisotope were carried out in a dedicated laboratory approved for the handling of low-energy particle-emitting radioisotopes and supervised by radiation safety authorities. Technetium-99m is a γ-emitter (140 keV) with a half-life of 6 h. Handling of solutions containing this radionuclide always proceeded behind lead shielding and following routine safety protocols to prevent contamination.

Materials and Methods. Standard literature procedures were used to obtain the precursors $ReOCl_3(PPh_3)_2$[29] and ^{99}Tc−gluconate.[30] Reagents and solvents used were purchased from Aldrich Chemical Co. or Fluka Chemical Co. and were used without further purification. ^{99}Tc was purchased as ammonium pertechnetate, $[NH_4][^{99}TcO_4]$, from the Oak Ridge National Laboratory. The impure black solid was purified prior to its use by treatment overnight with hydrogen peroxide and ammonium hydroxide in methanol. Evaporation of the solvent afforded ammonium pertechnetate as a white powder. $Na^{99m}TcO_4$ was obtained in physiological saline as commercial ^{99}Mo/^{99m}Tc generator eluate (Mallinckrodt Medical BV). All laboratory chemicals were reagent grade. IR spectra were recorded as KBr pellets in the range 4000−500 cm^{-1} on a Perkin-Elmer 1600 FT-IR spectrophotometer. NMR spectra were acquired at room temperature in $CDCl_3$ on a 500 MHz Bruker DRX-Avance spectrometer, using two-dimensional ^{1}H−^{1}H (COSY, NOESY) and ^{1}H−^{13}C (HSQC, HMBC) correlation techniques. TMS was used as the internal reference. High-performance liquid chromatography (HPLC) was conducted on a Waters 600 Millennium chromatography system coupled to both a Waters 991 photodiode array detector (UV trace for ^{99}Tc, Re, and ligands) and a GABI γ detector from Raytest (γ trace for ^{99m}Tc). Separations were achieved on a Techsil C18RP (10 μm, 250 mm × 4 mm) column eluted with a binary gradient system at a 1.0 mL/min flow rate. Mobile phase A consisted of MeOH with 0.1% TFA, while mobile phase B was H_2O with 0.1% TFA. The elution profile was isocratic with 50% A from 0 to 1 min followed by a linear gradient to 90% A from 1 to 12 min and ending with isocratic elution of 90% A from 13 to 25 min. Prior to each injection, the column was reequilibrated by applying the initial conditions for 10 min. Solvents used in chromatographic analysis were HPLC grade. Elemental analyses were performed on a Perkin-Elmer 2400/II automated analyzer.

NMR data for **3**−**6** are reported in the NMR and Supporting Information sections.

Synthesis. 2-(2′-Pyridyl)benzothiazole (2). Synthesis of the bidentate ligand 2-(2′-pyridyl)benzothiazole was achieved by oxidative condensation of equimolar quantities of 2-aminothiophenol and 2-pyridinaldehyde in DMSO.[2] To a solution of 2-aminothiophenol (3.75 g, 30 mmol) in DMSO (15 mL) was added a solution of 2-pyridinaldehyde (3 g, 30 mmol) in DMSO (15 mL). After being heated at 170 °C and stirred for 40 min, the reaction mixture was allowed to cool and diluted with water. The solid formed was collected by filtration and recrystallized from ethyl acetate to afford pale yellow crystals. Mp: 136 °C (lit.[31] mp: 135−136 °C). Yield: 50%.

$ReO[C_{12}H_8N_2S][C_6H_5S]_3$ (3). The precursor $ReOCl_3(PPh_3)_2$ (166 mg, 0.2 mmol) was added to a solution of CH_3COONa (21 mg, 0.26 mmol) in MeOH (12−15 mL). To this suspension were added **2** (43 mg, 0.2 mmol) and thiophenol (60 mg, 0.6 mmol) under stirring. The mixture was refluxed until the yellow-green suspension turned to dark brown solution, about 1 h. After being cooled to room temperature, the reaction mixture was diluted with CH_2Cl_2 and then washed with water. The organic layer was separated from the mixture and dried over $MgSO_4$. The volume of the solution was reduced to 10 mL, and then, 3−5 mL of MeOH was added. Slow evaporation of the solvents at room temperature afforded brown crystals. Crystals suitable for X-ray crystallography were obtained by recrystallization from CH_2Cl_2/MeOH. Yield: 50%. HPLC retention time: 16.75 min. FT-IR (KBr, cm^{-1}): 951 (Re═O). Anal. Calcd for $C_{30}H_{23}N_2OReS_4$: C, 48.22; H, 2.97; N, 3.40; S, 17.51. Found: C, 48.56; H, 3.12; N, 3.78; S, 17.29.

$ReO[C_{12}H_8N_2S][4\text{-}CH_3C_6H_4S]_3$ (4). Complex **4** was synthesized by following the same procedure as that described for **3** and

(28) Ashburn, T. T.; Han, H.; McGuiness, B. F.; Lansbury, P. T., Jr. *Chem. Biol.* **1996**, *3*, 351−358.
(29) Chatt, J.; Rowe G. A. *J. Chem. Soc.* **1962**, 4019−4033.
(30) Johannsen, B.; Spies, H. In *Chemistry and Radiopharmacology of Technetium Complexes*; Akademie der Wissd. DDR: Dresden, East Germany, 1981.
(31) Deligeorgiev, T. G. *Dyes Pigm.* **1990**, *12*, 243−248.

replacing 4-thiophenol with 4-methylthiophenol (69 mg, 0.6 mmol). Recrystallization from CH_2Cl_2/MeOH afforded complex **4** as dark brown crystals. Yield: 56%. HPLC retention time: 17.46 min. FT-IR (KBr, cm^{-1}): 943.2 (Re═O). Anal. Calcd for $C_{33}H_{29}N_2ORES_4$: C, 50.09; H, 3.62; N, 3.33; S, 16.11. Found: C, 50.55; H, 3.73; N, 3.57; S, 16.36.

ReO[C$_{12}$H$_8$N$_2$S][4-CH$_3$OC$_6$H$_4$S]$_3$ (5). Complex **5** was synthesized by following the same procedure as that described for **3** and replacing thiophenol with 4-methoxylthiophenol (84 mg, 0.6 mmol). Crystals of **5** suitable for X-ray crystallography were obtained by recrystallization from CH_2Cl_2/MeOH. Yield: 52%. HPLC retention time: 16.74 min. FT-IR (KBr, cm^{-1}): 944 (Re═O). Anal. Calcd for $C_{33}H_{29}N_2O_4ReS_4$: C, 47.51; H, 3.62; N, 3.11; S, 15.80. Found: C, 47.64; H, 3.51; N, 3.37; S, 15.41.

^{99}TcO[C$_{12}$H$_8$N$_2$S][4-CH$_3$C$_6$H$_4$S]$_3$ (6). Tin(II) chloride (45 mg, 0.24 mmol) dissolved in HCl (1 M, 0.1 mL) was added dropwise to an aqueous solution (4 mL) of [NH$_4$][^{99}TcO$_4$] (36 mg, 0.2 mmol) containing ^{99m}TcO$_4^-$ (0.1 mL, 0.5 mCi) and sodium gluconate (200 mg). The reaction mixture was stirred for 20 min, and subsequently the pH was adjusted to 7.5 with NaOH (1 M). To the resulting solution of the $^{99/99m}$Tc−gluconate precursor were added the bidentate ligand **2** (0.2 mmol, 43 mg) and 4-methylthiophenol (0.6 mmol, 69 mg) dissolved in 1 mL of CH_2Cl_2 each. The solution was stirred for 4 h and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and filtered, and the solvent was evaporated to dryness. The residue was washed with ether. Further purification of the residue was achieved by silica gel column chromatography, using ether as eluent solvent, to give pure product as dark brown solid. Structural characterization was carried out after ^{99m}Tc decay. Yield: 40%. HPLC retention time: 17.22 min. FT-IR (KBr, cm^{-1}): 918 (^{99}Tc═O).

^{99m}TcO[C$_{12}$H$_8$N$_2$S][4-CH$_3$C$_6$H$_4$S]$_3$ (7). A vial containing a lyophilized mixture of 50 mg of sodium glucoheptonate (Gluco/Demoscan manufactured by NCSR "Demokritos") and 0.2 mg of tin(II) chloride ($SnCl_2$) was reconstituted with 3−5 mL of pertechnetate (Na$^+$^{99m}TcO$_4^-$) (10−50 mCi). The mixture was left to react at room temperature for 30 min to afford the ^{99m}Tc(V)−glucoheptonate precursor complex. A 1 mL volume of the solution was added to a centrifuge tube containing equimolar quantities of the bidentate ligand **2** (0.02 mmol, 4.2 mg) and 4-methylthiophenol (0.02 mmol, 2.5 mg) dissolved in 0.6 mL of $CHCl_3$. The mixture was agitated in a vortex mixer and left to react at room temperature for 15 min. The complex was extracted with $CHCl_3$ (3 × 1.5 mL), and the extracts were combined, dried over $MgSO_4$, and filtered. About 50% of the activity was recovered in the organic layer. The characterization of the ^{99m}Tc complex **7** was confirmed by chromatographic correlation (HPLC) with the analogous ^{99}Tc and Re complexes. HPLC retention time: 17.40 min.

X-ray Crystallography. Crystals of **3A** and **5B** suitable for X-ray analysis were mounted in air on a Crystal Logic dual goniometer diffractometer using graphite-monochromated Mo Kα radiation. Unit cell dimensions were determined by using the angular settings of 25 automatically centered reflections in the range $11 < 2\theta < 23°$, and they appear in Table 3. Intensity data were recorded using a $\theta-2\theta$ scan. Three standard reflections monitored every 97 reflections showed less than 3% variation and no decay. Lorentz, polarization, and φ-scan absorption corrections were applied using Crystal Logic software. The structures were solved by direct methods using SHELXS-86[32] and refined by full-matrix least-squares techniques on F^2 using SHELXL-97.[33] Further crystallographic details for **3A**: $2\theta_{max} = 50°$; scan speed 3°/min; scan range 2.3 + $\alpha_1\alpha_2$ separation; reflections collected/unique/used 5261/5094 (R_{int} = 0.0157)/5094; 429 parameters refined; $[\Delta\rho]_{max}/[\Delta\rho]_{min}$ = 0.801/−0.848 e/Å^3; $[\Delta/\sigma]_{max}$ = 0.006; R1/wR2 (for all data) = 0.0444/0.1015. All hydrogen atoms were located by difference maps and were refined isotropically (except those on C4 and C28, which were introduced at calculated positions as riding on bonded atom), and all non-H atoms were refined anisotropically. Further crystallographic details for **5B**: $2\theta_{max} = 47°$; scan speed 1.5°/min; scan range 2.2 + $\alpha_1\alpha_2$ separation; reflections collected/unique/used 4896/4770 (R_{int} = 0.0266)/4770; 498 parameters refined; $[\Delta\rho]_{max}/[\Delta\rho]_{min}$ = 0.885/−1.165 e/Å^3; $[\Delta/\sigma]_{max}$ = 0.017; R1/wR2 (for all data) = 0.0660/0.1121. All hydrogen atoms were located by difference maps and were refined isotropically (except those on C29 and C33, which were introduced at calculated positions as riding on bonded atom), and all non-H atoms were refined anisotropically.

Results and Discussion

Synthesis of Complexes 3−6. The oxorhenium ReO[NN][S]$_3$ complexes **3**−**5** were prepared by ligand exchange reactions using $ReOCl_3(PPh_3)_2$ as precursor. The complexes were isolated as dark brown crystals by slow evaporation from CH_2Cl_2/methanol and were fully characterized by elemental analysis and IR and NMR spectroscopies. In each case, the NMR spectra of the isolated product indicated the presence of two complexes of similar structure, in agreement with formation of the two possible *mer* diastereoisomers (Chart 2, isomers A and B) that differ in the positioning of the 2-(2′-pyridyl)benzothiazole moiety relative to the oxygen of the oxorhenium core. Formation of similar isomers has not been reported in the literature. Attempts to separate the two isomers chromatographically under a variety of conditions were not successful. These complexes give only one peak in the HPLC chromatograms; their presence, however, was evident in the NMR spectra and was subsequently confirmed by the X-ray crystallographic analysis. Formation of *mer*-MO[NN][S]$_3$ (M = Tc, Re) complexes has been also reported from the simultaneous action of the NN ligand 2,2′-bipyridine and an aromatic thiol on the ^{99}Tc−gluconate and $ReOCl_3(PPh_3)_2$ precursors.[34] Furthermore, in the absence of thiol coligands, hexacoordinated *mer*-ReO[NN][Cl]$_3$ complexes have been obtained by the action of 2,2′-bipyridine,[35,36] 2,2′-biimidazole,[36] **2**,[37] and diazabutadienes[38] on the $ReOCl_3(OPPh_3)(SMe_2)$, $ReOCl_3(OPPh_3)_2$, and $ReOCl_3(AsPh_3)_2$ precursors, and in all cases, a single species was isolated.

(32) Sheldrick, G. M. *SHELXS-86, Structure Solving Program*; University of Göttingen: Göttingen, Germany, 1986.

(33) Sheldrick, G. M. *SHELXL-97, Program of Crystal Structure Refinement*; University of Göttingen: Göttingen, Germany, 1997.

(34) Papachristou, M.; Pirmettis, I. C.; Tsoukalas, Ch.; Papagiannopoulou, D.; Raptopoulou, C.; Terzis, A.; Stassinopoulou, C. I.; Chiotellis, E.; Pelecanou, M.; Papadopoulos, M. *Inorg. Chem.* **2003**, *42*, 5778−5784.

(35) Bryan, J. C.; Stenkamp, R. E.; Tulip, T. H.; Mayer, J. M. *Inorg. Chem.* **1987**, *26*, 2283−2288.

(36) Fortin, S.; Beauchamp, A. L. *Inorg. Chem.* **2000**, *39*, 4886−4893.

(37) Gangopadhyay, J.; Sengupta, S.; Bhattacharyya, S.; Chakraborty, I.; Chakravorty, A. *Inorg. Chem.* **2002**, *41*, 2616−2622.

(38) Das, S.; Chakraborty, I.; Chakravorty, A. *Inorg. Chem.* **2003**, *42*, 6545−6555.

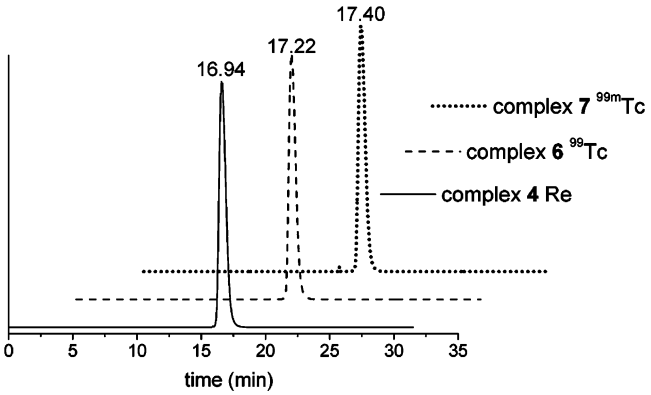


Figure 1. Schematic representation of comparative reverse-phase HPLC chromatograms of complexes **4** and **6** (photometric detection) and **7** (radiometric detection).

The Re═O stretch of both isomers of **3**−**5** occurs at 950, 951, and 945 cm^{-1}, respectively, well within the range of oxorhenium complexes with aminothiolate ligands.[34,39]

The oxotechnetium $TcO[NN][S]_3$ analogue **6**, having 4-methylthiophenol as coligand, was prepared using ^{99}Tc−gluconate as precursor. Its Tc═O stretch occurs at 918 cm^{-1}, and the approximately 30 cm^{-1} difference from the oxorhenium complex **4** is a typical one between analogous oxotechnetium and oxorhenium complexes.[34,39]

The complexes are soluble in $CHCl_3$ and CH_2Cl_2, less soluble in MeOH and EtOH, and insoluble in ether. They are stable in the solid state and in organic solutions for a period of several months as shown by HPLC and NMR. Their stability is not affected by the presence of moisture or air.

Synthesis of ^{99m}Tc Complex 7. The complex was prepared at the tracer level by ligand exchange reactions using ^{99m}Tc-(V)−glucoheptonate as precursor complex and was extracted with CH_2Cl_2 from the reaction mixture. HPLC analysis of this extract showed one major radioactive peak with retention time similar to that of the analogous oxotechnetium-99 (**6**) and oxorhenium (**4**) complexes. This fact indicates that complex **7** prepared at the tracer level has the same chemical structure as complexes **4** and **6** prepared at the macroscopic level. Schematic representation of comparative reverse-phase HPLC chromatograms of complexes **4**, **6**, and **7** is given in Figure 1. The radioactivity recovery of the HPLC column after the injection of complex **7** was monitored and found to be quantitative.

NMR Studies. ^{1}H and ^{13}C NMR chemical shifts for ligand **2** and complexes **4** and **6**, having the 4-methylthiophenol as coligand, are given in Tables 1 and 2. Atom numbering is shown in Chart 2.

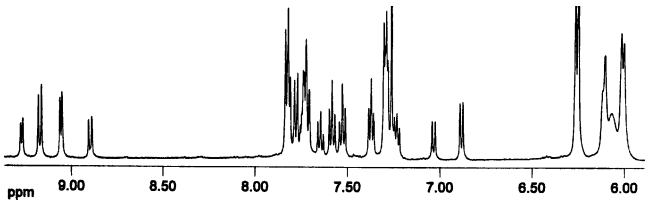


Figure 2. ^{1}H NMR spectrum (aromatic region, range 9.36−5.90 ppm) of complex **4** in $CDCl_3$ at 25 °C.

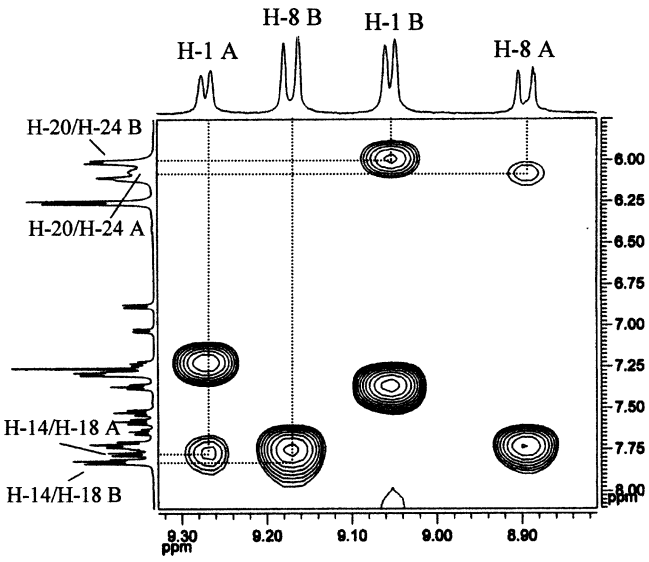


Figure 3. Phase-sensitive NOESY spectrum (aromatic region) (range: f_2 9.33−8.81 ppm; f_1 8.09−5.75 ppm) of complex **4** showing the characteristic nOe correlation peaks that allowed the distinction of isomers **A** and **B**.

In the ^{1}H NMR spectrum of ligand **2** all aromatic protons appear as distinct resonances in the region of 8.7−7.4 ppm, as previously reported.[37]

In the ^{1}H spectra of complexes **3**−**6**, the presence of two products of similar structure, each carrying three aromatic thiols and one 2-(2′-pyridyl)benzothiazole moiety, is evident (Figure 2) suggesting the formation of isomeric hexacoordinated $ReO[NN][S]_3$ complexes. In each of the products, two of the aromatic thiols appear together as broad peaks at the relatively upfield chemical shifts of 6.0−6.2 ppm, while the third aromatic thiol appears at the expected chemical shift of 7.3−7.8 ppm. This observation suggests the existence of a plane of symmetry in the molecule that will render the two thiophenol rings equivalent and is in agreement with the meridional (*mer*) configuration of a hexacoordinated, octahedral complex. In this configuration, the three identical ligands coordinate in a plane that includes rhenium and a plane of symmetry is generated in the complex (incorporating the Re═O core, the planar 2-(2′-pyridyl)benzothiazole structure and the central thiophenol) that may render the two side thiophenols magnetically equivalent (Chart 2). The *mer* arrangement can also account for the upfield shift of the two side thiophenols in the spectrum due to the paramagnetic effect exerted by the planar 2-(2′-pyridyl)benzothiazole ring. The alternative facial (*fac*) arrangement, where the three thiophenols coordinate on one face of the octahedron in a plane that does not include the metal core, would generate three magnetically nonequivalent thiophenols, a fact that is not observed.

(39) (a) Papadopoulos, M. S.; Pelecanou, M.; Pirmettis, I. C.; Spyriounis, D. M.; Raptopoulou, C. P.; Terzis, A.; Stassinopoulou, C. I.; Chiotellis, E. *Inorg. Chem.* **1996**, *35*, 4478−4483. (b) Papadopoulos, M. S.; Pirmettis, I. C.; Pelecanou, M.; Raptopoulou, C. P.; Terzis, A.; Stassinopoulou, C. I.; Chiotellis, E. *Inorg. Chem.* **1996**, *35*, 7377−7383. (c) Bouziotis, P.; Pirmettis, I.; Pelecanou, M.; Raptopoulou, C. P.; Terzis, A.; Papadopoulos, M.; Chiotellis, E. *Chem.—Eur. J.* **2001**, *7*, 3671. (d) Chryssou, K.; Pelecanou, M.; Pirmettis, I. C.; Papadopoulos, M. S.; Raptopoulou, C. Terzis, A.; Chiotellis, E.; Stassinopoulou, C. I. *Inorg. Chem.* **2002**, *41*, 4653−4663.

Table 1. ^{1}H NMR Chemical Shifts (ppm) for Ligand **2** and Complexes **4** and **6** in $CDCl_3$ at 25 °C

atom(s)	**2**	**4A**	**4B**	**6A**	**6B**
H-1	8.70	9.27	9.06	9.00	9.13
H-2	7.39	7.23	7.37	7.25	7.41
H-3	7.86	7.72	7.53	7.67	7.68
H-4	8.39	7.03	6.88	7.04	6.86
H-8	8.11	8.89	9.17	8.91	8.98
H-9	7.51	7.73	7.72	7.74	7.68
H-10	7.43	7.64	7.58	7.62	7.57
H-11	7.97	7.74	7.82	7.75	7.76
H-14/H-18		7.78	7.83	7.77	7.82
H-15/H-17		7.28	7.30	7.26	7.28
H-20/H-24 and H-26/H-30		6.07	6.02	6.15	6.07
H-21/H-23 and H-27/H-29		6.12	6.27	6.10	6.24
H-31		2.43	2.43	2.41	2.40
H-32 and H-33		2.02	2.06	1.98	2.06

Table 2. ^{13}C NMR Chemical Shifts (ppm) for Ligand **2** and Complexes **4** and **6** in $CDCl_3$ at 25 °**C**

atom(s)	**2**	**4A**	**4B**	**6A**	**6B**
C-1	149.6	150.8	147.5	150.8	147.2
C-2	125.3	125.8	123.9	124.8	124.3
C-3	137.1	137.2	138.3	137.0	138.0
C-4	120.8	122.8	122.2	122.9	122.9
C-5	151.4	144.6	147.3	144.3	147.0
C-6	169.3	161.2	159.0	161.2	158.4
C-7	154.2	146.8	147.3	147.0	147.0
C-8	126.6	123.3	125.0	123.5	124.8
C-9	126.3	128.4	128.4	128.0	127.8
C-10	125.7	128.0	128.2	127.6	127.8
C-11	122.0	121.6	121.8	121.6	121.4
C-12	136.1	132.9	131.4	133.4	131.6
C-13		144.7	144.4	141.4	141.4
C-14/C-18		134.0	133.6	133.8	133.6
C-15/C-17		128.8	128.8	128.7	130.6
C-16		136.1	136.1	136.5	136.5
C-19 and C-25		141.5	141.5	139.5	139.5
C-20/C-24 and C-26/C-30		133.1	133.3	133.6	134.1
C-21/C-23 and C-27/C-29		128.0	128.0	127.4	127.4
C-22 and C-28		134.9	134.9	135.2	135.7
C-31		21.1	21.1	21.0	21.0
C-32 and C-33		20.8	20.8	21.1	20.9

Table 3. Summary of Crystal, Intensity Collection, and Refinement Data for Complexes **3A** and **5B**

param	**3A**	**5B**
empirical formula	$C_{30}H_{23}N_2OReS_4$	$C_{33}H_{29}N_2O_4ReS_4$
fw	741.94	832.02
temp (K)	298	298
wavelength (λ, Å)	Mo Kα (0.710 730)	Mo Kα (0.710 730)
space group	$P2_1/c$	$I4_1/a$
a (Å)	15.588(6)	38.48(2)
b (Å)	9.973(4)	38.48(2)
c (Å)	19.202(7)	8.837(4)
β (deg)	104.27(1)	
V (Å^3)	2893(2)	13082(9)
Z	4	16
D_{calcd}/D_{measd} (Mg m^{-3})	1.703/1.69	1.690/1.67
abs coeff μ (mm^{-1})	4.516	4.011
F(000)	1456	6592
goodness-of-fit on F^2	1.113	1.093
R indices	R1 = 0.0393[a]	R1 = 0.0410[b]
	wR2 = 0.0982[a]	wR2 = 0.0937[b]

[a] For 4580 reflections with $I > 2\sigma(I)$. [b] For 4770 reflections with $I > 2\sigma(I)$.

Under this assumption, the two isomers observed in the NMR spectra would result from the different arrangement of the nonsymmetrical 2-(2′-pyridyl)benzothiazole moiety relative to the oxorhenium core generating the two possible *mer* isomers shown in Chart 2. Formation of the two isomers was confirmed by X-ray crystallographic analysis that showed in two separate crystalline samples (complexes **3A** and **5B**) the existence of the two *mer* isomeric arrangements.

In all complexes **3**−**6** the relative ratio of isomer **A**:isomer **B** was shown by integration of the NMR spectra to be approximately 1:2. Differentiation of the chemical shifts belonging to one isomer from those of the other was based on the NOESY spectra. Specifically, examination of the three-dimensional model of the complexes shows that the middle thiophenol ring, which is chemically shift differentiated from the shielded side ones, can only interact with proton H-1 in the case of the isomer **A** and with proton H-8 in the case of isomer **B**. Figure 3 shows part of the NOESY spectrum of complex **4** in which the peaks between the middle thiophenols and the protons H-1 and H-8 are marked. In the same spectrum of Figure 3, nOe correlation peaks between the side thiophenols and protons of the 2-(2′-pyridyl)benzothiazole moiety further confirm the assignment: in isomer **A** the side phenols have correlations with the H-8 proton, while in isomer **B** the side thiophenols correlate with the H-1 proton.

Comparison of the chemical shifts of the 2-(2′-pyridyl)-benzothiazole moiety in the complexes **3**−**6** to those of the free ligand **2** reveals the pronounced shielding of H-4 (approximately 1.5 ppm) and of C-5, C-6, and C-7 (7−8

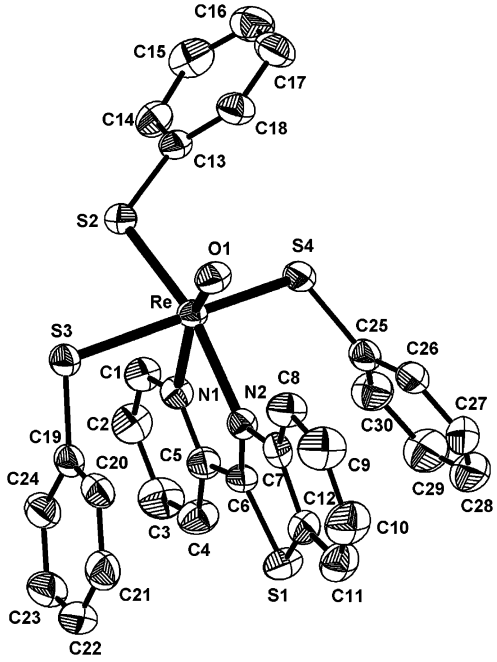


Figure 4. Molecular structure of complex **3A** with the atomic labeling. (Thermal ellipsoids are shown with 40% probability.)

ppm) upon complexation. Smaller upfield or downfield shifts are noted for the rest of protons and carbons of the 2-(2′-pyridyl)benzothiazole moiety.

Comparison of the chemical shifts of the two isomers of complexes **3**−**6** shows that chemical shifts are not appreciably affected by the specific placement of the 2-(2′-pyridyl)benzothiazole moiety with respect to the oxometal core; the chemical shift differences recorded between the isomers **A** and **B** (Tables 1 and 2 and Supporting Information) range between ±0.01−0.20 ppm for the protons and ±0.2−3.6 ppm for the carbons. These chemical shift differences are adequate to allow for the distinction of the two isomers **A** and **B** but not sufficient for any further conclusions to be reached on the existence of shielding and deshielding zones in this type of complex.

X-ray Crystallography. The molecular structures of complex **3**, isomer **A** (**3A**), and complex **5**, isomer **B (5B)**, are given in Figures 4 and 5, respectively. Selected bond distances and angles are listed in Table 4. Complex **3A** crystallizes in the monoclinic space group $P2_1/c$, and complex **5B** crystallizes in the tetragonal space group $I4_1/a$ with one crystallographically independent molecule in the asymmetric unit. The coordination geometry about the metal ion in **3A** and **5B** is distorted octahedral defined by the two nitrogen atoms of the bidentate ligand, the three sulfur atoms of the monodentate thiols, and the doubly bonded oxygen atom. In complex **3A**, the apical positions of the octahedron are occupied by the pyridine nitrogen atom of the ligand and the doubly bonded oxo group, while in complex **5B** the imine nitrogen atom of the ligand is directed trans to the oxo group. Rhenium lies 0.41 and 0.31 Å above the equatorial plane in **3A** and **5B**, respectively. The Re═O bond axis is inclined at 83.4 and 83.1° in **3A** and **5B**, respectively, with respect to the equatorial plane which is almost perpendicular to the N−C−C−N chelating plane of the bidentate ligand (90.1 and 90.9° in **3A** and **5B**, respectively). In both complexes, the five-membered ring in the coordination sphere, defined by the N−C−C−N chelating atoms of the bidentate ligand and the metal ion, is planar and the N1−C5−C6−N2 dihedral angle is very small (2.9 and 3.6° in **3A** and **5B**, respectively). The angles around rhenium within the tetragonal plane of the octahedron range from 79.4(1) to 92.3(1)° (in **3A**) and from 80.3(1) to 96.7(2)° (in **5B**), whereas those involving the apical atoms range from 71.2(2) to 104.2(2)° (in **3A**) and from 70.7(2) to 104.0(3)° (in **5B**). As expected, the bite angle of the bidentate ligand (N1−M−N2) is the

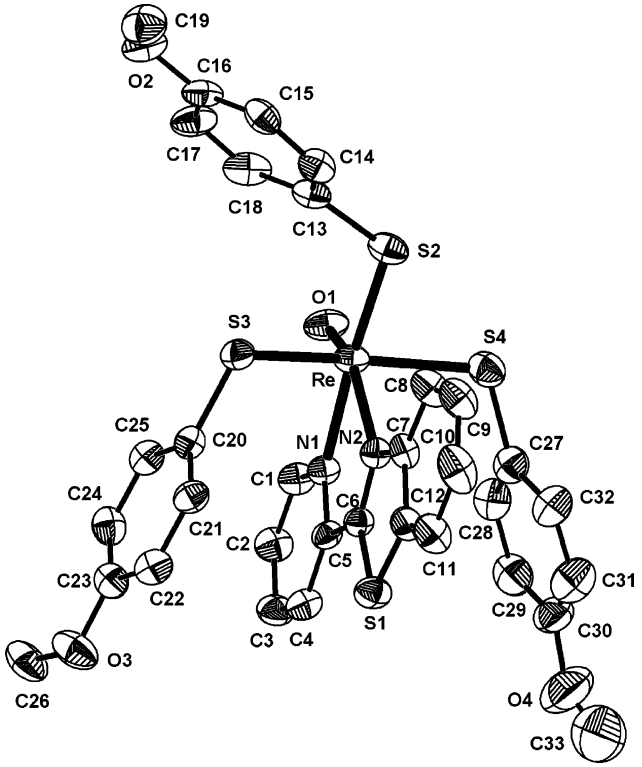


Figure 5. Molecular structure of **5B** with the atomic labeling. (Thermal ellipsoids are shown with 40% probability.)

Table 4. Selected Bond Distances (Å) and Angles (deg) for **3A** and **5B**

param	3A	5B
	Distances	
Re−O(1)	1.685(5)	1.681(6)
Re−N(1)	2.344(6)	2.203(7)
Re−N(2)	2.155(6)	2.288(6)
Re−S(2)	2.311(2)	2.312(2)
Re−S(3)	2.391(2)	2.367(3)
Re−S(4)	2.360(2)	2.377(3)
	Angles	
O(1)−Re−N(2)	94.1(2)	154.4(3)
O(1)−Re−S(2)	104.2(2)	101.7(2)
N(2)−Re−S(2)	160.9(2)	103.7(2)
O(1)−Re−N(1)	165.3(2)	83.8(3)
N(2)−Re−N(1)	71.2(2)	70.7(2)
S(2)−Re−N(1)	90.2(2)	174.1(2)
O(1)−Re−S(4)	102.8(2)	102.2(3)
N(2)−Re−S(4)	91.9(2)	79.6(2)
S(2)−Re−S(4)	89.3(1)	80.3(1)
N(1)−Re−S(4)	79.4(2)	96.7(2)
O(1)−Re−S(3)	100.1(2)	104.0(3)
N(2)−Re−S(3)	92.3(2)	79.9(2)
S(2)−Re−S(3)	79.4(1)	87.4(1)
N(1)−Re−S(3)	80.0(2)	93.3(2)
S(4)−Re−S(3)	156.4(1)	152.8(1)

smallest one in the coordination sphere. The Re═O and Re−S bond distances are in the ranges observed in oxorhenium complexes with amine and thiol ligands.[34,39] The M−N bond, trans to the doubly bonded oxygen, is slightly lengthened with respect to the second M−N bond distance, as expected.

In conclusion, [NN][S]$_3$ oxorhenium and oxotechnetium complexes of 2-(2′-pyridyl)benzothiazole and monodentate thiols were obtained in satisfactory yield and the reaction was successfully transferred at the technetium-99m tracer level showing that labeling of the 2-(2′-pyridyl)benzothiazole molecule with technetium and rhenium radioisotopes for radiopharmaceutical applications is feasible. The complexes are neutral and lipophilic, and as previously observed in similar hexacoordinated octahedral oxorhenium and oxotechnetium complexes with NN bidentate ligands, only the *mer* complexes were formed. The 2-(2′-pyridyl)benzothiazole ligand serves as a preliminary model for 2-(4-aminophenyl)-benzothiazole and its derivatives that display inhibitory activity against certain cancer types as well as affinity for the amyloid plaques of Alzheimer's disease. Therefore, the complexes synthesized may be considered as initial steps in the study of oxorhenium and oxotechnetium complexes of 2-(4-aminophenyl)benzothiazole derivatives with possible radiopharmaceutical applications in the diagnosis and therapy of specific tumors as well as in the diagnosis of Alzheimer's disease. The in vitro evaluation of the pharmacological properties of ligand **2** and complexes **3**−**6** is in progress by cell uptake experiments in cancer cell lines and by the determination of their affinity for amyloid plaques in Alzheimer's disease human brain sections. In addition, ligand **2** bearing an amine group at the same position as the original active analogue **1** has been prepared to evaluate the effects of the amine substituent on the synthetic procedure and the biological properties of the complexes.

Acknowledgment. M.P. and S.T. gratefully acknowledge the continuous and generous support of Professor David Mann, of the Greater Manchester Neurosciences Centre, University of Manchester, in setting up the Alzheimer's disease brain tissue experiments. M.P. gratefully acknowledges financial support by the National Bank of Greece.

Supporting Information Available: ^{1}H and ^{13}C NMR spectral data for both isomers of complexes **3** and **5** and crystallographic data in CIF format for the structures of complexes **3A** and **5B.** This material is available free of charge via the Internet at http://pubs.acs.org.

IC051538E