Tridentate Ligands Containing the SNS Donor Atom Set as a Novel Backbone for the Development of Technetium Brain-Imaging Agents

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Received April 25, 1994®

In developing ^{99m}Tc complexes as potential brain-imaging agents, we investigated the coordination chemistry of ligands containing sulfur and nitrogen donor atoms with the general formula R-$CH_2CH_2N(CH_2CH_2SH)_2$ (R = C_2H_5S, $(C_2H_5)_2N$). These ligands act as tridentate SNS chelates to the TcO^{3+} core, leaving open one coordination site cis to the oxo group. In reactions with the highly reactive $[^{99}TcOCl_4]^-$ precursor, this vacancy was occupied by a chlorine atom. When the ligands reacted in the presence of 4-methoxythiophenol, using ^{99}Tc(V)-gluconate as precursor, the vacancy was filled with 4-methoxythiophenol, which acted as coligand. Thus neutral mixed ligand complexes of the general formula [TcO($(SCH_2CH_2)_2NCH_2CH_2R$)X], where X = Cl or 4-methoxythiophenol, were synthesized. The complexes were characterized by UV–vis, IR, ^{1}H NMR, crystallographic, and elemental analyses. The crystal structures of **3a** (R = C_2H_5S, X = Cl) and **4b** (R = $(C_2H_5)_2N$, X = 4-methoxythiophenol) demonstrated that the coordination geometry is trigonal bipyramidal with the N1 and Cl or S3 occupying the apical positions and the basal plane defined by the S1 and S2 of the tridentate ligand and the oxo group. The complexes **4a**(^{99m}Tc) (R = C_2H_5S, X = 4-methoxythiophenol) and **4b**(^{99m}Tc) were prepared using ^{99m}Tc-glucoheptonate as precursor and were purified by HPLC. Biodistribution in mice showed high initial brain uptake (3.68% and 3.56% dose/organ for **4a**(^{99m}Tc) and **4b**(^{99m}Tc), respectively). Complex **4b**(^{99m}Tc) displayed significantly higher brain/blood values and prolonged retention in brain as well. The results suggest that structural modifications based on configurations **4a**,**b** may provide novel ^{99m}Tc brain-imaging agents with improved biological characteristics.

Introduction

Brain perfusion imaging with single-photon emission computerized tomography (SPECT) requires suitable radiotracers that display high initial uptake and sufficient retention in the brain. Several derivatives such as selenium-75-labeled amines[1] or iodinated amphetamine analogs[2,3] have been proposed in the past as possible brain radiotracers. However, due to certain drawbacks, these compounds have never gained worldwide application.

Thus, considerable work was focused on the development of neutral, lipid soluble ^{99m}Tc complexes, capable of penetrating the blood brain barrier (BBB). Until now, two ligand systems have been proposed as suitable backbones for the development of potential technetium-99m brain-imaging agents: (a) the propylenediamine dioxime (PnAO), N_4O_2 backbone and (b) the diaminedithiol (DADT), N_2S_2 ligand system. Both backbones can form neutral lipophilic complexes, containing the TcO^{3+} core, which are characterized, in most cases, by high initial brain uptake.

Extensive work performed on a series of ^{99m}Tc-labeled PnAO derivatives[4] generated ^{99m}Tc-HMPAO,[5,6] which has found routine application in brain scintigraphy as a commercial kit. Trapping in the brain is believed to be due to the formation of a less lipophilic complex in brain cells.[7] Apart from the wide clinical application of ^{99m}Tc-HMPAO, its in vitro instability is considered a disadvantage for the routine assessment of brain perfusion.[8]

The choice of the tetradentate N_2S_2 backbone for the development of neutral Tc(V) complexes generated a series of DADT derivatives[9] labeled with technetium-99m. The TcO^{3+} core coordinates with N and S donor atoms of the DADT backbone to form a complex with three 5-membered rings, which is very stable in vitro and easily crosses the BBB. Brain uptake and/or retention can be influenced by modification of the ligand structure, e.g., by introducing amine side chains in the DADT moiety. However, the formation of isomers, in relation to the central TcO^{3+} core,[10] is considered the major disadvantage of ^{99m}Tc-DADT complexes.

A recently developed DADT derivative, ^{99m}Tc-ethyl cysteinate dimer[11] (^{99m}Tc-ECD), overcame the problem of isomer formation and presented excellent uptake and retention characteristics for SPECT imaging of the brain. The prolonged retention of ^{99m}Tc-ECD is based on a specific enzymatic process occurring in the brain of primates.

In our search for new backbones as chelators of pentavalent technetium, we investigated, at carrier level, the formation of complexes with tertiary aminodithiol ligands of the general type R-$CH_2CH_2N(CH_2CH_2SH)_2$, where R = C_2H_5S or $(C_2H_5)_2N$. These derivatives can function as tetradentate tripodal chelates and have been reported to form octahedral complexes with the *cis*-MoO_2^{2+} core.[12,13] However our study demonstrated that they act as tridentates toward the TcO^{3+} core, leaving open one cis site to the oxo group in the coordination

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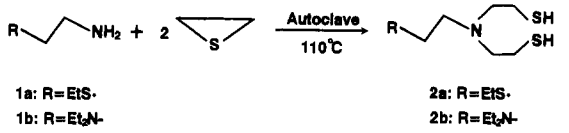
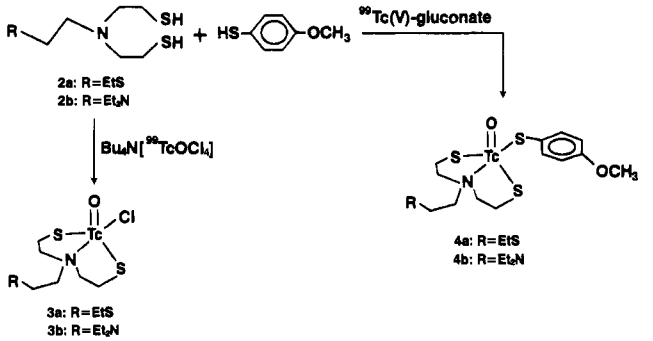
® Abstract published in *Advance ACS Abstracts*, August 15, 1994.

0022-2623/94/1837-3212$04.50/0

Scheme 1



Scheme 2



sphere of the metal. Thus, neutral mixed ligand Tc(V) complexes can be formed by occupation of the open site by a monodentate coligand. In the present study, the biodistribution of mixed ligand complexes, prepared at technetium tracer level (^{99m}Tc) from the tridentate SNS ligands 4-methoxythiophenol and ^{99m}Tc-glucoheptonate, was also investigated. The results are discussed in terms of brain uptake and retention.

Results and Discussion

Chemistry. The ligands *N,N*-bis(2-mercaptoethyl)-2-(ethylthio)ethylamine (**2a**) and *N,N*-bis(2-mercaptoethyl)-*N',N'*-diethylethylenediamine (**2b**) were synthesized[12] by reacting 2-(ethylthio)ethylamine or *N,N*-diethylethylenediamine with ethylene sulfide in an autoclave, at 110 °C (Scheme 1). After the reaction was completed, the compounds were purified by high-vacuum distillation.

Further on, the coordination of compounds **2a,b** with oxotechnetium(V) has been investigated. The ligands leave upon tridentate coordination to the TcO^{3+} core, opening one coordination site cis to the oxo group. Thus, a monodentate ligand was investigated in order to assess binding to the vacant coordination site. As a first step, the labile precursor tetrachlorooxotechnetate was used to study the coordination chemistry of **2a,b**. In a second step, the coordination was studied with the less reactive oxotechnetium precursor $^{99}Tc(V)$-gluconate in the presence of 4-methoxythiophenol as coligand.

Exchange reaction of compounds **2a,b** with the tetrabutylammonium tetrachlorooxotechnetate ($[Bu_4N][^{99}TcOCl_4]$) precursor in alcohol resulted in the formation of the pentacoordinated complexes **3a,b** (Scheme 2). In this case, the three chlorine atoms of $[TcOCl_4]^-$ were replaced by the SNS set of the ligands, while the fourth chlorine remained in the coordination sphere of the TcO^{3+} core. However, the yield of the reaction was relatively low (15%). Isolated crystals were subjected to FT-IR, ^1H NMR in solution, and elemental analysis. The IR spectra showed intense single bands for Tc=O stretch at 945 cm^{-1} for **3a** and at 936 cm^{-1} for **3b**. The band in the region 2650–2480 cm^{-1} confirmed the formation of an amine salt for **3b**. The results were found consistent with elemental analyses and ^1H NMR chemical shifts.[14] Crystals of **3a** were obtained from a $EtOH/MeOH/CH_2Cl_2$ solution cooled at 4 °C. The

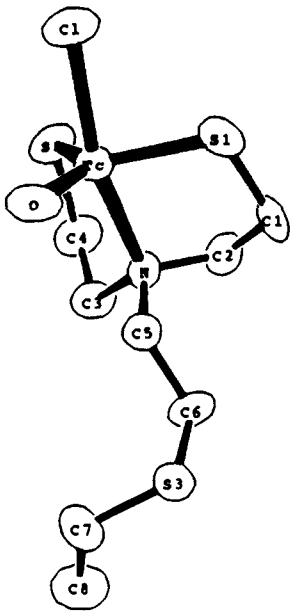


Figure 1. ORTEP diagram of **3a** with thermal ellipsoid at 50% probability.

crystallographic data demonstrated that the coordination geometry of complex **3a** is trigonal bipyramidal (Figure 1). Both sulfur atoms undergo ionization during complexation so that the complex is neutral. The technetium lies 0.053 Å above the basal plane of the trigonal bipyramid formed by the S1 and S2 atoms and the oxo group, with the N and Cl atoms occupying the two apical positions where the C1—Tc—N angle is 160.5°. The metal–oxygen bond distance, **1**.674 Å, is within the range of several well-characterized monooxo complexes of technetium.[15] The metal–sulfur bond distances, 2.261 and 2.249 Å, are shorter than those found in a series of analogous complexes. The Tc—N bond length, 2.171 Å, is longer than the average Tc—N bond length (2.02 Å) reported for a number of Tc—N bonds. The Tc—Cl bond distance was found to be 2.374 Å, which is longer than the Tc—Cl bond in $[TcOCl_4]^-$ (2.31 Å) but within the range of Tc—Cl bond lengths in a variety of complexes.[15] Complexes **3a,b** prepared at tracer-added level (^{99}Tc + ^{99m}Tc) were tested in animals in order to investigate their biodistribution. However no specific accumulation in any organ was obtained, and thus they were not further evaluated.[16]

Mixed complexes **4a,b** were prepared by reacting ligands **2a** or **2b** with oxotechnetium(V) in the presence of 4-methoxythiophenol in a tridentate:monodentate ligand ratio of 1:1.2 (Scheme 2). Attempts to synthesize these complexes using $[Bu_4N][^{99}TcOCl_4]$ as the precursor failed and did not result in the expected monomeric products. The reaction yielded a black powder, suggesting that the formation of the desired quadridentate chelates did not occur due to competitive reactions, when the starting material was the highly reactive halide complex. IR spectra of the isolated solids demonstrated the absence of the $Tc{=}O^{3+}$ core. Formation of complexes **4a,b** was finally achieved (yield 50%) by replacing $[Bu_4N][^{99}TcOCl_4]$ with the less reactive $^{99}Tc(V)$-gluconate precursor. This complex can be easily prepared by reduction of pertechnetate with stannous chloride in aqueous sodium gluconate solution. Thus, a mixture of ligand **2a** or **2b** and 4-methoxythiophenol in acetone was added to the aqueous Tc(V)-gluconate

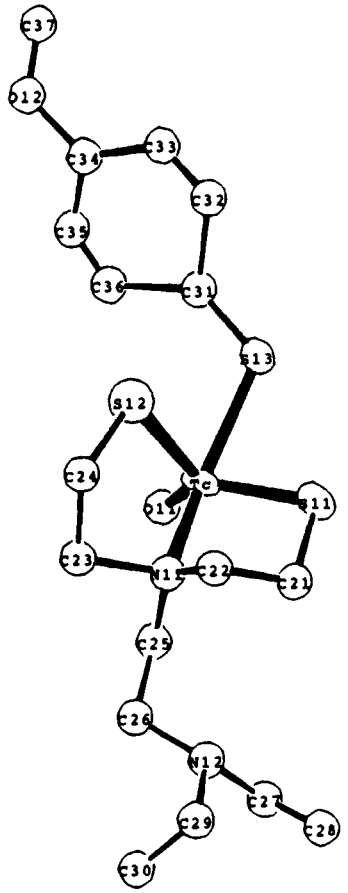


Figure 2. ORTEP drawing of **4b** showing the atom numbering.

solution. Acetone was removed from the reaction mixture, and the complex was extracted with dichloromethane. The organic solvent was reduced in volume, and pentane was added to give crystals of the desired products. A distinct $Tc{=}O^{3+}$ absorption peak at 920 cm^{-1} for **4a** and at 921 cm^{-1} for **4b** was observed in the FT-IR spectra. The UV–vis spectra exhibited strong absorption bands at 273 (ϵ 20 590) and 526 nm (ϵ 4520) for **4a** and at 276 (ϵ 17 860) and 522 nm (ϵ 6770) for **4b**. Complexes **4a,b** also showed correct elemental analyses, while ^1H NMR spectra confirmed the analytical data.[14]

The X-ray crystallographic data for **4b** gave the structure shown in Figure 2. Only one of the two independent molecules in the asymmetric unit is shown. The crystal was of poor quality and very small. The only reason the collection of data and the determination of the structure were continued was to determine the coordination sphere of the metal. Over half of the data collected was considered unobserved ($I < 3\sigma(I)$). As expected, all sulfur atoms underwent ionization during complexation. This pattern of ionization led to the formation of a neutral complex. The coordination geometry of the neutral complex **4b** is trigonal bipyramidal. The basal plane of the bipyramid is defined by the S1, S2, and O1 atoms, and the two apical positions are occupied by the S3 of the coligand and the N1 of the tridentate ligand.

It is important to mention here that in both compounds, **3a** and **4b**, the carbon (C5/C25) atom of the side chain bonded to the N1 atom of the tridentate ligand is in cis configuration with respect to the oxo group. In a series of analogous complexes synthesized in our laboratory and characterized by X-ray structure analysis, it was noted that the cis configuration is a common feature of all complexes having trigonal bipyramidal geometry around technetium.[17]

The preparation of mixed ligand complexes **4a,b** at tracer level was accomlished by using ^{99m}Tc-glucoheptonate as the precursor (see the Experimental Section). The labeling yield for both compounds was over 80%, calculated by organic solvent extraction of the aqueous reaction mixture. The radiochemical purity of the extracts was checked by HPLC. A major peak at 7.2 min was monitored for **4a**(^{99m}Tc) in the radiochromatogram (C-18 Bondapack, MeOH:H_2O, 70:30, 1.5 mL/min), while the major peak for **4b**(^{99m}Tc) was detected at 6.0 min (μ-Porasil, CH_2Cl_2: MeOH, 85:15, 1 mL/min). The radioactivity of the peak in each case was more than 95% of the radiochromatogram. When ^{99m}Tc and ^{99}Tc complexes were coinjected, both radioactivity (for tracer) and UV–vis (for carrier) detectors exhibited identical chromatographic profiles, demonstrating that the same chemical structure was formed under both chelating conditions. **4b**(^{99m}Tc) was slightly less lipophilic than **4a**(^{99m}Tc) (log P = 2.63 vs 3.02 at pH 7.4), probably due to the presence of the amine residue in the molecule. Complexes prepared at carrier and tracer levels were found to be stable at room temperature for a prolonged period of time (monitored by HPLC).

Biology. Biodistribution studies were carried out in Swiss albino mice and Wistar rats. In Table 1, the distribution data of complexes **4a**(^{99m}Tc) and **4b**(^{99m}Tc) in mice, at 1–60 min pi, are presented. In mice, both complexes demonstrated a rather fast blood clearance, since approximately only 5% of the injected dose was measured in blood samples 1.0 min pi. Complexes also presented a high initial brain uptake of 3.68% and 3.56%, respectively (dose/organ, 1.0 min pi). However, complex **4b**(^{99m}Tc) demonstrated higher brain values at 5–60 min pi as compared to **4a**(^{99m}Tc). The brain/blood (Br/Bl) ratios of the two complexes displayed significant differences. Complex **4a**(^{99m}Tc) showed poor retention in the brain. Thus, the high Br/B1 values observed at 5 and 10 min pi (4.53 and 4.25, respectively) were significantly decreased at the late time intervals (0.60 Br/Bl 60 min pi). In contrast, the high Br/Bl ratio of 4.71 observed for **4b**(^{99m}Tc) at 10 min pi remained practically unchanged over the entire observation period. Brain uptake and retention characteristics of **4a**(^{99m}Tc) and **4b**(^{99m}Tc) in mice are well defined in Figure 3. Complex **4b**(^{99m}Tc) displayed significantly higher Br/Bl values and prolonged retention in the mouse brain. Both complexes showed considerable accumulation in the liver and gastrointestinal tract of mice. Lung uptake was higher for complex **4b**(^{99m}Tc), 27.19% of the injected dose 1.0 min pi, clearing from the lungs in time (1.79%, 60 min pi). Stomach values were within acceptable levels, indicating no decomposition of the complex in vivo. Data in mice for **4b**(^{99m}Tc) were confirmed by distribution studies in rats, at 5–60 min pi (Table 2). Blood clearance and brain washout rates in rats (Figure 4) were found comparable to those obtained in mice (Figure 3).

Conclusions

Mixed neutral oxotechnetium(V) complexes of tridentate ligands containing monodentate thiols as coligands have been previously described[18] as an approach to

Table 1. Biodistribution of **4a**(^{99m}Tc) and **4b**(^{99m}Tc) in Mice

organ	% dose/organ				
	1 min	5 min	10 min	30 min	60 min
			4a(^{99m}Tc)		
blood	5.77 ± 0.79	1.66 ± 0.27	1.24 ± 0.22	0.80 ± 0.06	0.79 ± 0.08
liver	3.58 ± 0.36	16.97 ± 1.64	24.79 ± 2.41	24.36 ± 2.54	18.03 ± 2.90
heart	4.02 ± 0.61	0.59 ± 0.12	0.31 ± 0.04	0.11 ± 0.01	0.05 ± 0.00
kidney	2.30 ± 0.46	2.45 ± 0.30	1.76 ± 0.12	1.04 ± 0.20	0.54 ± 0.16
stomach	0.35 ± 0.14	0.73 ± 0.24	1.02 ± 0.73	0.37 ± 0.06	1.10 ± 0.76
intestine	4.14 ± 0.90	9.31 ± 0.85	15.44 ± 3.57	43.12 ± 3.60	44.30 ± 5.88
spleen	0.06 ± 0.02	0.21 ± 0.04	0.16 ± 0.04	0.06 ± 0.00	0.03 ± 0.01
muscle	34.39 ± 4.86	25.57 ± 5.62	20.29 ± 2.99	10.41 ± 3.59	5.27 ± 3.64
lungs	5.25 ± 0.80	1.52 ± 0.26	1.05 ± 0.12	0.52 ± 0.10	0.26 ± 0.03
brain	3.68 ± 0.20	2.43 ± 0.49	1.57 ± 0.35	0.39 ± 0.11	0.15 ± 0.04
urine	–	–	0.27 ± 0.01	0.77 ± 0.33	1.79 ± 0.50
Br/Bl[a]	2.07	4.53	4.25	1.68	0.60
			4b(^{99m}Tc)		
blood	5.24 ± 0.36	2.02 ± 0.24	1.53 ± 0.20	1.29 ± 0.16	1.21 ± 0.13
liver	1.96 ± 0.39	10.73 ± 1.85	14.14 ± 0.84	25.58 ± 2.87	35.12 ± 1.56
heart	3.60 ± 0.27	0.74 ± 0.05	0.46 ± 0.07	0.19 ± 0.01	0.12 ± 0.01
kidney	1.70 ± 0.26	3.14 ± 0.25	3.18 ± 0.01	2.19 ± 0.16	1.59 ± 0.26
stomach	0.15 ± 0.06	0.96 ± 0.14	1.20 ± 0.23	1.24 ± 0.31	2.34 ± 0.74
intestine	2.61 ± 0.94	8.31 ± 0.55	9.61 ± 0.72	18.99 ± 0.96	33.70 ± 0.80
spleen	0.03 ± 0.01	0.28 ± 0.03	0.36 ± 0.05	0.38 ± 0.01	0.21 ± 0.02
muscle	17.26 ± 4.53	24.17 ± 4.40	16.49 ± 2.13	8.18 ± 0.29	6.86 ± 0.52
lungs	27.19 ± 1.84	15.37 ± 1.63	9.78 ± 1.33	3.09 ± 0.36	1.79 ± 0.14
brain	3.56 ± 0.17	3.01 ± 0.06	2.47 ± 0.27	1.71 ± 0.09	1.54 ± 0.11
urine	–	–	1.10 ± 0.08	5.06 ± 0.70	6.87 ± 1.37
Br/Bl[a]	2.49	4.42	4.71	4.16	4.23

[a] Brain/blood: % dose/g ratio.

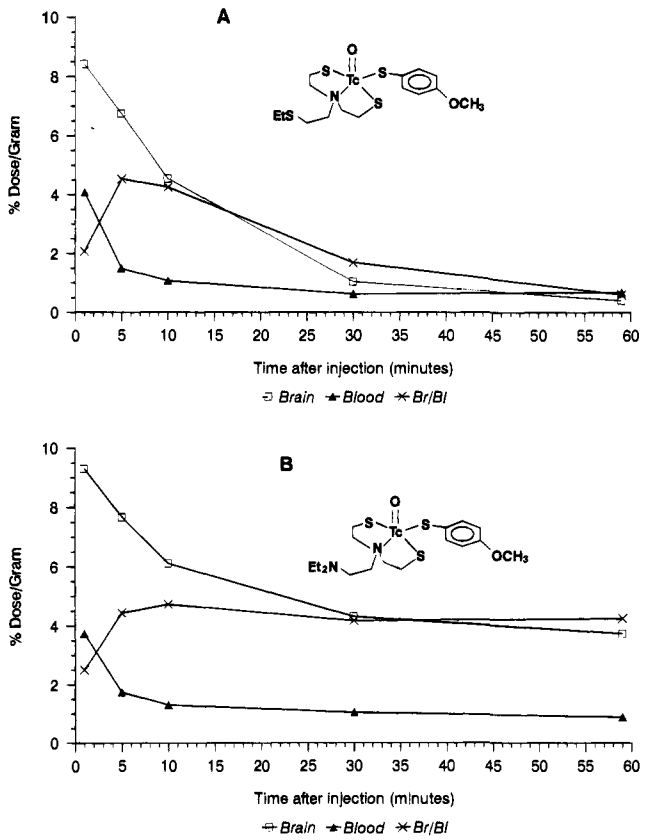


Figure 3. Brain and blood clearance curves and brain to blood ratio of **4a**(^{99m}Tc) (A) and **4b**(^{99m}Tc) (B) showing the significant retention of **4b**(^{99m}Tc) within the mouse brain.

design complexes capable of penetrating the BBB. In this case, tridentate SSS, SOS, ligand, or ONS and ONO Schiff bases were reacted with the TcO^{3+} core in the presence of monodentate thiol R-SH. However animal studies[19] demonstrated negligible uptake of the complexes by brain tissue.

Table 2. Biodistribution of **4b**(^{99m}Tc) in Rats

organ	% dose/organ			
	5 min	10 min	30 min	60 min
		4b(^{99m}(Tc)		
blood	18.89 ± 1.87	17.72 ± 2.26	7.47 ± 0.87	4.80 ± 0.96
liver	19.32 ± 4.64	24.09 ± 2.49	29.63 ± 4.63	35.74 ± 6.02
heart	0.64 ± 0.08	0.51 ± 0.09	0.17 ± 0.03	0.15 ± 0.02
kidney	3.22 ± 0.86	4.26 ± 0.57	6.33 ± 1.09	8.73 ± 0.56
stomach	2.18 ± 1.09	2.37 ± 0.78	2.19 ± 0.70	2.05 ± 0.56
s intes	5.96 ± 1.92	6.34 ± 1.08	7.55 ± 1.79	8.15 ± 3.20
l intes	2.64 ± 0.88	2.70 ± 0.55	1.27 ± 0.15	1.05 ± 0.60
spleen	0.58 ± 0.16	0.77 ± 0.17	0.30 ± 0.06	0.46 ± 0.14
muscle	28.64 ± 4.08	27.89 ± 5.45	16.52 ± 1.89	10.60 ± 3.11
lungs	9.38 ± 1.46	7.78 ± 1.52	2.08 ± 0.03	1.14 ± 0.28
brain	1.45 ± 0.15	1.16 ± 0.13	0.53 ± 0.05	0.46 ± 0.08
Br/Bl[a]	0.4	0.4	0.5	0.6

[a] Brain/blood: % dose/g ratio.

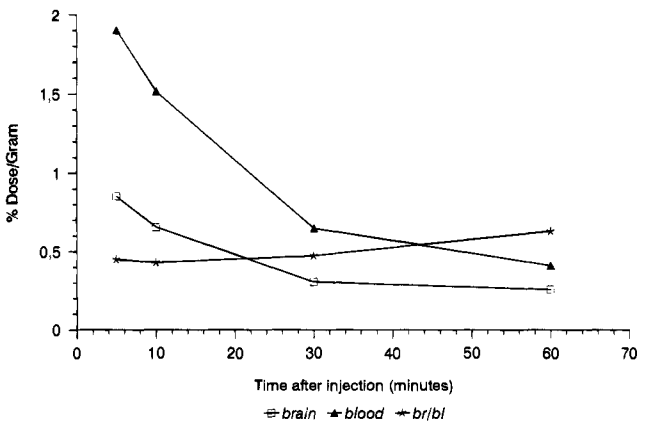


Figure 4. Brain and blood clearance curves and brain to blood ratio of **4b**(^{99m}Tc) in rats.

In the present study, novel complexes of oxotechnetium(V) were developed on the basis of the mixed ligand approach. Tertiary aminodithiol ligands containing the SNS donor set were chosen for coordination studies with the TcO^{3+} core. Although they could function as tetra-

dentate tripodals, these ligands acted as tridentates and wrapped around the metal core, leaving open one coordination site cis to the oxo group. The chemical studies demonstrated that this coordination site could be occupied by a monodentate thiol. Thus, neutral mixed ligand complexes were isolated in high yield using *p*-methoxythiophenol as coligand. The mixed ligand complexes **4a,b** (Scheme 2) were also formed in a reproducible way at technetium tracer level (^{99m}Tc). Corroboration of the structure was achieved by comparing the high-performance liquid chromatographic profiles of the technetium-99/technetium-99m complexes. Biodistribution of **4a**(^{99m}Tc) and **4b**(^{99m}Tc) in mice demonstrated high initial brain uptake. Complex **4a**(^{99m}Tc) did not display prolonged brain retention, as compared to **4b**(^{99m}Tc). The latter demonstrated significant retention in brain tissue, displaying high Br/Bl ratios in mice, 5–60 min pi. However, the **4b**(^{99m}Tc) retention mechanism is yet unknown and has to be investigated. Our findings so far suggest that these tridentate SNS ligands, outlined in Scheme 1, form a challenging backbone for further development of ^{99m}Tc brain agents based on mixed ligand strategy. Structure–activity relationship studies by modifying R functionalities of the tridentate SNS and/or the monodentate ligand are in progress.

Experimental Section

Ligands **2a,b** were synthesized, via the reaction presented in Scheme 1, by methods previously described.[12] Commercially available 4-methoxythiophenol was purified by distillation. [Bu_4N][^{99}$TcOCl_4$] and ^{99}Tc(V)-gluconate complexes were synthesized by literature methods.[20,21] Technetium complexes **3a,b** were synthesized by reacting the ligands **2a,b** with [Bu_4N][^{99}$TcOCl_4$] in organic solvent (Scheme 2, **3a,b**). Mixed ligand complexes of compounds **2a,b** with 4-methoxythiophenol as coligand were synthesized by ligand exchange reaction using ^{99}Tc(V)-gluconate (Scheme 2, **4a,b**). Preparation, at tracer level, of **4a,b** was accomplished by reacting **2a** or **2b** and the coligand with ^{99m}Tc(V)-glucoheptonate (prepared from a commercial kit). Complexes, prepared at carrier level, were characterized by IR, UV–vis, and ^{1}H NMR spectra, as well as by elemental analysis. IR spectra were obtained from KBr pellets on a Perkin-Elmer 1600 FT-IR spectrophotometer. UV–vis spectra were obtained in methanol or dichloromethane on a Beckman DU-65 spectrophotometer. The ^{1}H NMR spectra were obtained on a Bruker FT-NMR/250AF spectrometer. Details of the NMR chemical shift assignments are given in ref 14. High-performance liquid chromatography (HPLC) analyses of technetium mixed ligand complexes, prepared at carrier as well as at tracer level, were performed on a LDC Milton Roy chromatography gradient system, equipped with a UV–vis detector [LDC Milton Roy, MP 3000] and a Beckman 171 detector for γ or low β detection. The radioactivity of the biological samples, as well as of the solutions used to determine partition coefficients, was counted in a well-type γ-counter [NaI(Tl)] crystal Canberra Packard Auto-Gamma 5000 series instrument.

Preparation of Technetium Complexes at Carrier Level. Chloro[*N,N*-bis(2-mercaptoethyl)-2-(ethylthio)-ethylamine]oxotechnetium(V) (3a). Tetrabutylammonium tetrachlorooxotechnetate (100 mg, 0.2 mmol) was dissolved in 15 mL of absolute ethanol purged for 15 min with dry argon. A solution of 45 mg (0.2 mmol) of *N,N*-bis(2-mercaptoethyl)-2-(ethylthio)ethylamine (**2a**) in 1.5 mL of dichloromethane was added, dropwise, to the [$TcOCl_4$]$^-$ solution, under magnetic stirring. During addition, a red brown precipitate was formed. The reaction mixture was then heated gently for 1–2 min; the red brown precipitate turned to a deep brown, which was filtered and washed with hot, absolute ethanol. The filtrate was then cooled at 4 °C overnight, giving dark red crystals of the desired product **3a**, yield 9 mg (12%). IR (KBr): 943 (Tc=O), 431 cm^{-1} (Tc–N). UV–vis (dichloromethane): 287 (ϵ 17 070), 417 (ϵ 3220), 472 (ϵ 1180). ^{1}H NMR ($CDCl_3$): δ 1.31 (t, 3H, J = 7.4 Hz, SCH_2CH_3*), 2.62 (q, 2H, J = 7.4 Hz, SCH_2*CH_3), 2.95 (m, 2H, EtSCH_2*CH_2N), 3.87 (m, 2H, EtSCH_2-CH_2*N), 3.29, 3.65 (m, 4H, SCH_2CH_2*N), 3.10, 3.69 (m, 4H, SCH_2*CH_2N). Anal. ($C_8H_{17}NS_3OTcCl$) C, H, N. Red crystals suitable for X-ray crystallographic analysis were obtained by recrystallization from EtOH/MeOH/CH_2Cl_2 (4:2:1) at 4 °C for several days.

Chloro[*N,N*-bis(2-mercaptoethyl)-*N',N'*-diethylethylenediamine]oxotechnetium(V), Hydrochloride (3b). Compound **3b** was prepared using a procedure similar to that described for compound **3a** to yield 15% of orange crystals. IR (HCl salt, KBr): 2650–2480 (N^+–H hydrochloric salt), 936 (Tc=O), 433 cm^{-1} (Tc–N). UV–vis (methanol): 278 (ϵ 20 880), 421 (ϵ 4580), 475 sh (ϵ 2590). ^{1}H NMR (CD_3CN): δ 1.38 (t, 6H, NCH_2CH_3*), 3.18 (q, 4H, NCH_2*CH_3), 3.50 (m, 2H, Et_2-NCH_2*CH_2N), 4.23 (m, 2H, $Et_2NCH_2CH_2$*N), 3.11, 3.33, 3.73, 3.87 (m, 8H, SCH_2CH_2N). Anal. ($C_{10}H_{23}N_2S_2OTcCl_2$) C, H, N, S.

[4-(Methoxythio)phenolato][*N,N*-bis(2-mercaptoethyl)-2-(ethylthio)ethylamine]oxotechnetium(V) (4a). ^{99}Tc(V)-gluconate was prepared as previously described[21] by the addition of 45 mg of stannous chloride in 0.1 N HCl to a solution of 200 mg of sodium gluconate and 36.2 mg (0.2 mmol) of $NH_4^{99}TcO_4$ in 4 mL of water containing 0.1 mL of ^{99m}TcO_4^- (0.5 mCi). After dilution of Tc(V)-gluconate with 2 mL of acetone, a solution of *N,N*-bis(2-mercaptoethyl)-2-(ethylthio)-ethylamine (45 mg, 0.2 mmol) and 28 mg (0.226 mmol) of 4-methoxythiophenol in 2 mL of acetone was added, dropwise, under magnetic stirring. The solution, which became purple, was stirred for 30 min, and a deep brown oily layer was separated from the reaction mixture. The acetone was carefully removed by rotary evaporation, and the mixture was extracted three times with 20 mL of dichloromethane. The organic extracts were dried over $MgSO_4$, and the volume was reduced to 10 mL by rotary evaporation at room temperature. The solution, after addition of a small volume of pentane, was left at 4 °C for 3 days to give crystals of a dark red color, 48 mg, yield 50%. IR (KBr): 920 (Tc=O), 1240, 1025 (C–O–C), 831 (C–H aromatic), 428 cm^{-1} (C–N). UV–vis (dichloromethane): 273 (ϵ 20 590), 357 (ϵ 3700), 526 (ϵ 4520), 636 sh (ϵ 970). ^{1}H NMR ($CDCl_3$): δ 1.31 (t, 3H, J = 7.4 Hz, SCH_2CH_3*), 2.64 (q, 2H, J = 7.4 Hz, SCH_2*CH_3), 2.98 (m, 2H, Et-SCH_2*CH_2N), 4.09 (m, 2H, EtSCH_2CH_2*N), 2.72, 3.49 (m, 4H, SCH_2CH_2*N), 2.99, 3.57 (m, 4H, SCH_2*CH_2N), 3.84 (s, 3H, OCH_3), 7.56 (m, 2H, aromatic 2, 6), 6.92 (m, 2H, aromatic 3, 5). Anal. ($C_{15}H_{24}NS_4O_2Tc$) C, H, N.

[4-(Methoxythio)phenolato][*N,N*-bis(2-mercaptoethyl)-*N',N'*-diethylethylenediamine]oxotechnetium(V) (4b). Compound **4b** was prepared by a procedure similar to that described for compound **4a**. Dark red crystals, 40 mg (50% yield), were isolated. IR (KBr): 921 (Tc=O), 1241, 1032 (C–O–C), 827 (C–H aromatic), 423 cm^{-1} (Tc–N). UV–vis (dichloromethane): 276 (ϵ 17 860), 358 (ϵ 5710), 522 (ϵ 6770), 627 sh (ϵ 1360). ^{1}H NMR ($CDCl_3$): δ 1.07 (t, 6H, J = 7.1 Hz, NCH_2CH_3*), 2.60 (q, 4H, J = 7.1 Hz, NCH_2*CH_3), 2.90 (t, 2H, J = 6.5 Hz, Et_2NCH_2*CH_2N), 4.05 (t, 2H, J = 6.5 Hz, Et_2NCH_2-CH_2*N), 2.81, 3.61 (m, 4H, SCH_2CH_2*N), 2.96, 3.59 (m, 4H, SCH_2*CH_2N), 3.84 (s, 3H, OCH_3), 7.56 (m, 2H, aromatic 2, 6), 6.91 (m, 2H, aromatic 3, 5). Anal. ($C_{17}H_{29}N_2S_3O_2Tc$) C, H, N, S. Crystals for X-ray crystallographic analysis were prepared from a MeOH/CH_2Cl_2/H_2O solution.

Labeling with Technetium-99m. A vial containing a lyophilized mixture of 200 mg of sodium glucoheptonate and 0.2 mg of $SnCl_2$ (TES-7 manufactured by NCSR "Demokritos") was reconstituted with 10 mL of water, and then 1.0 mL of this solution was mixed with 0.5–1.0 mL of pertechnetate (5–10 mCi). The resulting ^{99m}Tc(V)-glucoheptonate complex was added to a centrifuge tube containing equimolar quantities of the tridentate ligands (0.02 mmol of **2a** or **2b**) and 4-methoxythiophenol (0.02 mmol). The mixture was agitated in a vortex mixer and left to react at room temperature for 10 min. The aqueous phase was extracted with three successive 1.5 mL portions of CH_2Cl_2, and the combined organic extracts were

dried over $MgSO_4$ and filtered. More than 80% of the activity was recovered by the organic layer.

Analysis of **4a**(^{99m}Tc) (50 μL, 50–100 μCi) performed by reversed phase HPLC (C-18 Bondapack column, methanol: water, 70:30, 1.5 mL/min) showed a major radioactive peak (>95%) with a retention time of 7.2 min. Compound **4b**(^{99m}Tc) was analyzed by normal phase HPLC (μ-Porasil column, dichloromethane:methanol, 85:15, 1 mL/min). In this case, the main radioactive peak (>95%) was detected at 6.0 min. Identity of **4a**(^{99m}Tc) and **4b**(^{99m}Tc) was confirmed by coinjection with authentic samples (^{99}Tc) of **4a,b**, respectively.

Crystal Data. $C_8H_{17}NOS_3ClTc$ (**3a**): red, orthorhombic, $P2_1nb$ (No. 33), a = 7.9049(7) Å, b = 9.0904(8) Å, c = 19.262(2) Å, V = 1384.16 Å^3, Z = 4, fw = 372.88, D_c = 1.789 g/mL, μ = 6.80 cm^{-1}. $C_{17}H_{29}N_2O_2S_3Tc$ (**4b**): dark red, monoclinic, $P2_1/n$ (No. 14) (systematic absences, $0k0$, k = odd; $h0l$; $h + l$ = odd), a = 11.8318(9) Å, b = 10.4952(8) Å, c = 33.800(2) Å, β = 94.483(3)°, V = 4184.3(3) Å^3, Z = 8, fw = 487.63, D_c = 1.548 g/mL, μ(Mo) = 3.50 cm^{-1}. Unit cell dimensions were determined and refined by using the angular settings of 25 automatically centered reflections in the range $11 \leq 2\theta \leq 24$.

Data Collection and Treatment. Diffraction measurements were made on a $P2_1$ Nicolet diffractometer upgraded by Crystal Logic using Zr-filtered Mo radiation (σ = 0.71073 Å) with a $\theta - 2\theta$ scan to $2\theta_{max} = 54°$ with scan speed 4.5°/min and scan range $2.6 + \alpha_1\alpha_2$ separation for **3a** and a $2\theta_{max} = 46°$ with scan speed 1.5°/min and scan range $2.2 + \alpha_1\alpha_2$ separation for **4b**. Three standard reflections monitored every 97 reflections showed less than 3% variation and no decay. Lorentz, polarization, and ψ-scan absorption corrections were applied using Crystal Logic software. For **3a**, symmetry equivalent data were averaged with R = 0.0264 to give 2870 independent reflections from a total 4981 collected reflections and for **4b**, R = 0.056, 5318 unique reflections, 6325 collected reflections.

Solution and Refinement. The structures were solved by direct methods using SHELXS-86.[22] The structure of **3a** was refined by full-matrix least-squares with SHELX76[22] using only 2436 reflections with $F > 5\sigma(F_o)$ and refining 146 parameters. All hydrogen atoms were introduced in calculated positions as riding on bonded atoms. All non-hydrogen atoms were refined anisotropically. The final values for R, R_w, and GOF are 0.0480, 0.0732, and 1.86 and for all data 0.0604, 0.0798, and 2.01, respectively. $(\Delta\rho)_{max}$ = 3.380, $(\Delta\rho)_{min}$ = −1.148 e/Å^3 (in the vinicity of the heavy metal), and $(\Delta/\sigma)_{max}$ = 0.031. The structure with all coordinates inverted was refined to R = 0.0489, R_w = 0.0745, and GOF = 1.89.

As we mentioned above, the crystallographic data for **4b** was of poor quality (over 50% of the data unobserved), and refinement was continued only for the purposes of establishing the connectivity of the molecule (Figure 2). Final R = 0.1746 (3690 reflections, $F > 4\sigma(F)$).

Animal Distribution Studies. Complexes **4a,b**, prepared at tracer level (^{99m}Tc), were studied in mice and rats. Five groups of male Swiss albino mice (at least five animals/group) were injected, in the vein tail, with HPLC-purified and 50% methanol-reconstituted **4a**(^{99m}Tc) and **4b**(^{99m}Tc) (0.1 mL, 2–3 μCi). The animals were sacrificed by cardiectomy under slight ether anesthesia at a predesigned time interval (1–60 min pi). Samples of blood and muscle were collected, while the other organs of interest were removed intact and weighed. Their radioactivity was measured in a γ-counter. A standard of 1% of the injected dose was used and the percent dose/organ and the percent dose/g were calculated. For blood and muscle, the calculation was based upon the measured activity, the sample weight, and the body composition data (considered as 7% and 43% of the body weight, respectively). The brain/blood ratio was calculated from the corresponding percent dose/g values. In rat experiments, the animals were dosed with 0.1 mL of 3–6 μCi through the femoral vein under ether anesthesia. Biodistribution was performed 5–60 min pi.

Determination of Partition Coefficients. The partition coefficients were determined by mixing the HPLC-purified ^{99m}Tc complexes (100 μL) with an equal volume of 1-octanol and phosphate buffer (0.125 M, pH 7.4) in a centrifuge tube. The mixture was vortexed at room temperature for 3 min and finally centrifuged at 5000 rpm for 5 min. Three weighted samples from the octanol and aqueous layers were then counted in a γ-counter. Partition coefficients were calculated as the mean value of each cpm/g of octanol layer divided by that of buffer. Samples from the octanol layer were subsequently repartitioned with new buffer until constant values were obtained. This was usually achieved in three runs. The final partition coefficient values were expressed as log P.

Acknowledgment. C.P.R. is grateful to John Boutari and Son Co. for financial support.

Supplementary Material Available: Tables of fractional atomic coordinates, anisotropic positional thermal parameters, and bond distances and angles for **3a** (3 pages); tables of observed and calculated structure factors (12 pages). Ordering information is given on any current masthead page.

References

(1) (a) Kung, H. F.; Blau, M. Synthesis of selenium-75 labeled tertiary diamines: New brain imaging agents. *J. Nucl. Med.* **1980**, *23*, 1127–1130. (b) Kung, H. F.; Blau, M. Regional intracellular pH shift: A proposed new mechanism for radiopharmaceuticals uptake in brain or other tissues. *J. Nucl. Med.* **1980**, *21*, 147–152.

(2) (a) Tramposch, K. M.; Kung, H. F.; Blau, M. Radioiodine labeled N,N,N,N′-trimethyl-N′-(2-hydroxyl-3-alkyl-5-iodobenzyl)-1,3-propanediamines for brain perfusion imaging. *J. Nucl. Med.* **1983**, *26*, 121–125. (b) Kung, H. F.; Tramposch, K. M.; Blau, M. A new brain perfusion imaging agent: [I-131]HIPDM: N,N,N′-trimethyl-N′-[2-hydroxyl-3-methyl-5-benzyl]-1,3-propanediamine. *J. Nucl. Med.* **1983**, *24*, 66–72.

(3) (a) Winchell, H. S.; Baldwin, R. M.; Lin, T. H. Development of I-123 labeled amines for brain studies: Localization of I-123 iodophenylalkylamines in rat brain. *J. Nucl. Med.* **1980**, *21*, 940–947. (b) Winchell, H. S.; Horst, W. D.; Braun, L.; Oldendorf, W. H.; Hattner, R.; Parker, H. N-isopropyl-[^{123}I]-p-iodoamphetamine: Single-pass brain uptake and washout, binding to brain synaptosomes; and localization in dog and monkey brain. *J. Nucl. Med.* **1980**, *21*, 947–952. (c) Kuhl, D. E.; Barrio, J. R.; Huang, S. C.; Slin, C.; Ackermann, R. F.; Lear, J. L.; Wu, J. L.; Lin, T. H.; Phelps, M. E. Quantifying local cerebral blood flow by N′-isopropyl-p-[^{123}I]Iodoampetamine (IMP) tomography. *J. Nucl. Med.* **1982**, *23*, 196–203.

(4) (a) Cumming, S. A.; Nechvatal, G.; Canning, L. R.; Nowtnik, D. P.; Pickett, R. D.; Neirinckx, R. D.; Volkert, W. A.; Trounter, D. E.; Holmes, R. A. Development of technetium-99m regional celebral blood flow agents based upon the propylene amine oxime ligand (PnAO). *Eur. J. Nucl. Med.* **1985**, *11*, A107. (b) Nowotnik, D. P.; Canning, L. R.; Cumming, S. A.; Harrison, R. C.; Higley, B.; Nechvatal, G.; Pickett, R. D.; Piper, I. M.; Bayne, V. J.; Forster, A. M.; Weisner, P. S.; Neirinckx, R. D.; Volkert, W. A.; Trounter, D. E.; Holmes, R. A. Development of ^{99m}Tc-labelled radiopharmaceutical for SPECT imaging. *Nucl. Med. Commun.* **1985**, *6*, 499–506.

(5) (a) Neirinckx, R. D.; Canning, L. R.; Piper, I. M.; Nowotnik, D. P.; Pickett, R. D.; Holmes, R. A.; Volkert, W. A.; Forster, A. M.; Weisner, P. S.; Marriot, J. A.; Chaplin, S. B. Technetium-99m d,l,HMPAO: A new radiopharmaceutical for SPECT imaging of regional cerebral blood perfusion. *J. Nucl. Med.* **1987**, *28*, 191–202. (b) Podreka, I.; Suess, E.; Goldenberg, G.; Steiner, M.; Brucke, T.; Muller, Ch.; Lang, W.; Neirinckx, R. D.; Deecke, L. Initial experience with technetium-99m HMPAO brain SPECT. *J. Nucl. Med.* **1987**, *28*, 1657–1666. (c) Sharp, P. F.; Smith, F. W.; Gemmell, H. G.; Lyall, D.; Evans, N. T. S.; Gvozdanovic, D.; Davidson, J.; Tyrrell, D. A.; Pickett, R. D.; Neirinckx, R. D. Technetium-99m HMPAO stereoisomers as potential agents for imaging regional cerebral blood flow: Human volunteer studies. *J. Nucl. Med.* **1986**, *27*, 171–177. (d) Leonard, J. P.; Nowotnik, D. P.; Neirinckx, R. D. Tc-99m d,l-HMPAO: A new radiopharmaceutical for imaging regional brain perfusion using SPECT-A comparison with iodine-123 HIPDM. *J. Nucl. Med.* **1986**, *27*, 1819–1823.

(6) Jurisson, S.; Schlemper, E. O.; Trounter, D. E.; Canning, L. R.; Nowotnick, D. P.; Neirinckx, R. D. Synthesis and characterization and X-ray structural determinations of technetium(V)-oxo-tetradentate amine oxime complexes. *Inorg. Chem.* **1986**, *25*, 543–549.

(7) (a) Johannsen, B. Progress and problems in the chemistry of technetium-99m tracers. *Isotopenpraxis* **1987**, *24*, 449–454. (b) Ballinger, J. R.; Reid, R. H.; Gulenchyn, K. Y. Technetium-99m HMPAO stereoisomers: Differences in interaction with glutathione. *J. Nucl. Med.* **1988**, *29*, 1998–2000. (c) Neirinckx, R. D.; Burke, J. F.; Harrison, R. C.; Forster, A. M.; Adersen, A. R.; Lassen, N. A. The retention mechanism of technetium-99m-HM-PAO: Intracellular reaction with glutathione. *J. Cereb. Blood Flow Metab.* **1988**, *8*, S4.

(8) Hung, J. C.; Corlija, M.; Volkert, W. A.; Holmes, R. A. Kinetic analysis of technetium-99m d,l-HM-PAO decomposition in aqueous media. *J. Nucl. Med.* **1988**, *29*, 1568–1576.

(9) (a) Kung, H. F.; Molnar, M.; Billings, J.; Wicks, R.; Blau, M. Synthesis and biodistribution of neutral lipid soluble Tc-99m complexes that cross the blood brain barrier. *J. Nucl. Med.* **1984**, *25*, 326–332. (b) Lever, S. Z.; Burns, H. D.; Kervitsky, T. M.; Goldfarb, H. W.; Woo, D. V.; Wong, D. F.; Epps, L. A.; Kramer, A. V.; Wagner, H. N. Design preparation and biodistribution of a technetium-99m triaminedithiol complex to assess regional cerebral blood flow. *J. Nucl. Med.* **1985**, *28*, 1287–1294. (c) Epps, L.; Burns, H. D.; Lever, S. Z.; Goldfarb, H. W.; Wagner, H. N. Brain imaging agents: Synthesis and characterization of (N-piperidinyl hexamethyl diamino dithiolate)-oxo-technetium(V) complexes. Technetium aminothiolates as brain agents. *Appl. Radiat. Isot.* **1987**, 661–664. (d) Efange, S. M. N.; Kung, H. F.; Billings, J.; Guo, V. Z.; Blau, M. Technetium-99m bis(aminoethanethiol) (BAT) complexes with amine side chains-potential brain perfusion imaging agents for SPECT. *J. Nucl. Med.* **1987**, *28*, 1012–1019. (e) Efange, S. M. N.; Kung, H. F.; Billings, J. J.; Blau, M. The synthesis and biodistribution of ^{99m}Tc-labeled piperidinyl bis(aminoethanethiol) complexes: Potential brain perfusion imaging agents for single photon emission computed tomography. *J. Med. Chem.* **1988**, *31*, 1043–1047. (f) Chiotellis, E.; Varvarigou, A. D.; Maina, Th.; Stassinopoulou, C. I. Comparative evaluation of ^{99m}Tc-labeled aminothiols as possible brain perfusion imaging agents. *Nucl. Med. Biol.* **1988**, *15*, 215–233. (g) Scheffel, U.; Goldfarb, H. W.; Lever, S. Z.; Gungon, R. L.; Burns, D.; Wagner, H. N. Comparison of technetium-99m aminoalkyl diaminodithiol analogs as potential brain blood flow imaging agents. *J. Nucl. Med.* **1988**, *29*, 73–82. (k) Papadopoulos, M.; Stathaki, S.; Mastrostamatis, S.; Varvarigou, A.; Chiotellis, E. ^{99m}Tc-DADT complexes substituted with heterocycles amines: Effect of substitution on in vivo reactivity. *Nucl. Med. Biol.* **1993**, *20*, 105–115. (l) Kung, H. F. New Technetium 99m-labeled brain perfusion imaging agents. *Semin. Nucl. Med.* **1990**, *20*, 150–158. (m) Papadopoulos, M.; Chiotellis, E.; Varvarigou, A.; Mastrostamatis, S.; Cotsyfakis, C.; Vavouraki, H.; Stathaki, S. Correlation of lipophilicity to biodistribution of Tc-99m labeled aminothiols. *Nucl. Med. Biol.* **1993**, *20*, 101–104.

(10) Kung, H. G.; Guo, Y. Z.; Yu, C. C.; Billings, J.; Subramanyam, V.; Calabrese, J. New brain perfusion imaging agents based on ^{99m}Tc-bis(aminoethanethiol) (BAT) complexes: Stereoisomers and biodistribution. *J. Med. Chem.* **1989**, *32*, 433–437.

(11) (a) Holman, B. L.; Hellman, R. S.; Goldsmith, S. J.; Mena, I. G.; Leveille, J.; Gherardi, P. G.; Moretti, J.-L.; Bischof-Delaloye, A.; Hill, T. C.; Rigo, P. M.; Van Heertum, R. L.; Ell, P. J.; Buell, U.; De Roo, M. C.; Morgan, R. A. Biodistribution, dosimetry, and clinical evaluation of technetium-99m ethyl cysteinate dimer in normal subjects and in patients with chronic cerebral infraction. *J. Nucl. Med.* **1989**, *30*, 1018–1024. (b) Walovitch, R. C.; Hill, T. C.; Garrity, S. T.; Cheesman, E. H.; Burgess, B. A.; O'Leary, D. H.; Watson, A. D.; Ganey, M. V.; Morgan, R. A.; Wiliams, S. J. Characterization of technetium-99m-L,L-ECD for brain perfusion imaging, Part 1: Pharmacology of technetium-99m ECD in nonhuman primates. *J. Nucl. Med.* **1989**, *30*, 1892–1901. (c) Leveille, J.; Demonceau, G.; De Roo, M.; Rigo, P.; Taillefer, R.; Morgan, R. A.; Kupranick, D.; Walovitch, R. C. Characterization of technetium-99m-L,L-ECD for brain perfusion imaging, Part 2: Biodistribution and brain imaging in humans. *J. Nucl. Med.* **1989**, *30*, 1902–1910. (d) Edwards, D. S.; Cheesman, E. H.; Watson, N. M.; Maheu, L. J.; Nguyen, S. A.; Dimitre, L.; Nason, T.; Watson, A. D.; Walovitch, R. Synthesis and characterization of technetium and rhenium complexes of N,N′-1,2-ethylenediyl-bis-L-cysteine. Neurolite and its metabolites. In *Technetium and Rhenium in Chemistry and Nuclear Medicine 3*; Nicolini, M., Bandoli, G., Mazzi, U., Eds.; Raven Press: New York, 1990; pp 433–444.

(12) Corbin, J. L.; Miller, K. F.; Pariyadath, N.; Wherland, S.; Bruce, L. A.; Stiefel, E. I. Preparation and properties of tripodal and linear tetradentate N,S-donor ligands and their complexes containing the MoO_2^{2+} core. *Inorg. Chim. Acta* **1984**, *90*, 41–51.

(13) Berg, M. J.; Hodgson, K. O.; Bruce, A. E.; Corbin, J. L.; Pariyadath, N.; Stiefel, E. I. The crystal and molecular structures of dioxo Mo(VI) complexes of tripodal tetradentate N,S-donor ligands. *Inorg. Chim. Acta* **1984**, *90*, 25–33.

(14) Stassinopoulou, C. I.; Pelecanou, M.; Mastrostamatis, S.; Chiotellis, E. ^{1}H and ^{13}C NMR structural studies in solution of oxotechnetium(V) complexes with N,N-bis(2-mercaptoethyl)-N′,N′-diethylethylenediamine and N,N-bis(2-mercaptoethyl)-2-ethylthioethylamine. *Magn. Reson. Chem.*, in press.

(15) (a) Davison, A.; Jones, A. G.; Orving, C.; Sohn, M. A new class of oxotechnetium(+5) chelate complexes containing a $TcON_2S_2$ core. *Inorg. Chem.* **1981**, *20*, 1629–1632. (b) Bandoli, G.; Mazzi, U.; Roncari, E.; Deutch, E. Crystal structures of technetium compounds. *Coord. Chem. Rev.* **1982**, *44*, 191–227. (c) Melnik, M.; Van Lier, J. E. Analyses of structural data of technetium compounds. *Coord. Chem. Rev.* **1987**, *77*, 275–324. (d) Rao, T. N.; Adhikesavalu, D.; Camerman, A.; Fritzberg, A. R. Technetium(V) and Rhenium(V) complexes of 2,3-bis(mercaptoacetamido) propanoate. Chelate ring stereochemistry and influence on chemical and biological properties. *J. Am. Chem. Soc.* **1990**, *112*, 5798–5804. (e) Ohmoro, Y.; Francesconi, L.; Kung, M.-P.; Kung, H. F. New conformationally restricted ^{99m}Tc N_2S_2 complexes as myocardial perfusion agents. *J. Med. Chem.* **1992**, *35*, 157–162. (f) Stassinopoulou, C. I.; Mastrostamatis, S.; Papadopoulos, M.; Vavouraki, H.; Terzis, A.; Hountas, A.; Chiotellis, E. Synthesis and structure of oxotechnetium(V) complexes of N,N′-ethylenebis(acetylacetonethioimine) and N,N′-ethylene-bis-(benzylacetone thioimine). *Inorg. Chim. Acta* **1991**, *189*, 219–224.

(16) Mastrostamatis, S.; Papadopoulos, M.; Chiotellis, E.; Hunt, F. C. Tripodal NS_3-donor ligands as new backbone for reduced technetium. *Eur. J. Nucl. Med.* **1990**, *16*, 109.

(17) Pirmettis, I. Unpublished data.

(18) (a) Pietzsch, H.-J.; Spies, H.; Hoffmann, S.; Stach, J. Lipophilic technetium complexes-V. Synthesis and characterization of (3-Thiapentane-1,5-dithiolato)(thiophenolato) oxotechnetium(V). *Inorg. Chem. Acta* **1989**, *161*, 15–16. (b) Pietzch, H.-J.; Spies, H.; Hoffmann, S.; Scheller, D. Lipophilic technetium complexes-VII. Neutral oxotechnetium(V) complexes of tridentates shiff-bases containing monothiols as co-ligands. *Appl. Radiat. Isot.* **1990**, *41*, 185–188.

(19) Spies, H.; Pietzch, H.-J.; Syhre, R.; Hoffmann, S. Lipophilic tecnetium complexes-VIII. Preparation and animal studies of oxotechnetium (V) complexes with tridentate/monodentate ligand coordination. *Isotopenpraxis* **1990**, *26*, 159–162.

(20) Davison, A.; Trop, H. S.; DePamphilis, B. V.; Jones, A. G. Tetrabutylammonium tetrachlorooxotechnetate(V). *Inorg. Synth.* **1982**, *21*, 160–162.

(21) Johannsen, B.; Spies, H. *Chemie und Radiopharmakologie von technetiumkomplexen*; Akademie der Wiss.d.DDR: Dresden, 1981.

(22) (a) Sheldrick, G. M. *SHELXS-86, Structure solving Program*; University of Gottingen: Germany, 1986. (b) Sheldrick, G. M. *SHELX76, Program for Crystal Structure Determination*; University of Gambridge: England, 1976. (c) Sheldrick, G. M. *SHELX93, Program for Crystal Structure Refinement*; University of Gottingen: Germany, 1993. (d) *International Tables for X-Ray Crystallography*; Kynoch: Birminghan, U.K., 1974; Vol. IV.