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Rhenium and Technetium Complexes with Pentadentate Thiocarbamoylbenzamidines: Steps toward Bioconjugation

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Supporting Information

ABSTRACT: Thiocarbamoylbenzimidoyl chlorides, PhC-(Cl)=N-(C=S)-NR¹R², react with 2-(iminodiacetic acid)benzylamine under formation of the potentially pentadentate ligands H₃L (R¹, R² = Et) and H₃L-COOEt (R¹ = Me, R² = C₆H₄-4-COOEt) in high yields. Hydrolysis of H₃L-COOEt in NaOH/MeOH gives quantitatively another benzamidine ligand H₃L-COOH. The novel ligands readily react with (NBu₄)-[MOCl₄] (M = Re, Tc) under formation of stable complexes with the general composition [MO(L)], in which they are triply deprotonated and fully occupy the remaining five coordination positions of the {MO}³⁺ cores. In a "proof-ofprinciple" reaction for possible bioconjugations, the complex [ReO(L-COOH)] has been labeled with triglycine ethyl ester in high yields.

INTRODUCTION

Technetium and rhenium are important in the field of nuclear medicine due to the availability of radioisotopes suitable for diagnostic radiopharmaceuticals (^{99m}Tc: γ -emitter, $E\gamma = 140$ keV, $t_{1/2} = 6.0$ h),^{1,2} or potential therapeutic agents for various forms of cancer or arthritis (¹⁸⁶Re and ¹⁸⁸Re: both β^- -emitters with $t_{1/2}$ of 89.3 and 17.0 h, respectively).³ Thus, thermodynamically stable and/or kinetically inert technetium and rhenium complexes, which do not undergo easy ligand exchange reactions in the plasma, are of constant interest for the development of new radiopharmaceuticals.⁴ In this scene, pentadentate ligand systems would be perfectly suitable for the complexation of the common $\{Re^VO\}^{3+}$ and $\{Tc^VO\}^{3+}$ cores, which can easily be obtained by the reduction of $[MO_4]^-$ ions available from the commercial generator systems. Surprisingly, only a few examples of oxidotechnetium(V) or -rhenium(V) complexes with pentadentate ligands are hitherto structurally well characterized.⁵⁻⁹ This may be understood by the facts that the syntheses of pentadentate ligands are frequently timeconsuming procedures and the targeted oxido cores request systems with preferably oxygen donors for coordination in trans position of the normally *trans*-labilizing O^{2-} ligands.

Recently, we have reported a series of multidentate benzamidine ligands, which are formed in relatively simple reactions between benzimidoyl chlorides and functionalized primary amines.^{10,11} Thus, the synthesis of pentadentate systems via reactions of benzimidoyl chlorides and potentially tetradentate ligands having a terminal primary amine group could be a very facile approach. Additionally, our interests in this type of ligand are due to the flexibility of modifications in



their periphery.^{12,13} This fact may play a role when the obtained technetium and rhenium complexes shall be used as chelating sites in conjugates with biologically targeting molecules, which rapidly and efficiently transport the radionuclides to the biological target.

In the present work, we describe the syntheses of novel pentadentate dialkylamino(thiocarbonyl)benzamidine ligands (Chart 1) and some of their rhenium and technetium complexes. The modification of the ligand sphere with an additional carboxylic group and the examination of a coupling reaction of the rhenium complex using triglycine ethyl ester are also demonstrated.

Chart 1. Ligands Used in This Work



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EXPERIMENTAL SECTION

Materials. All chemicals used in this study were reagent grade and used without further purification. Solvents were dried and used freshly distilled unless otherwise stated. $(NBu_4)[ReOCl_4]$ and $(NBu_4)-[TcOCl_4]$ were prepared by standard procedures.^{14,15} The synthesis of the *N*,*N*-[(diethylamino)(thiocarbonyl)]benzimidoyl chloride was performed by the standard procedure of Beyer et al.¹⁶ *N*-(*tert*-Butoxycarbonyl)-2-aminobenzylamine (1) was synthesized following the literature procedure,¹⁷ except that the purification was carried out by recrystallization from CH_2Cl_2/n -hexane.

Radiation Precautions. ⁵⁹Tc is a weak β^{-} -emitter. All manipulations with this isotope were performed in a laboratory approved for the handling of radioactive materials. Normal glassware provides adequate protection against the low-energy beta emission of the technetium compounds. Secondary X-rays (bremsstrahlung) play an important role only when larger amounts of ⁹⁹Tc are used.

Physical Measurements. Infrared spectra were measured as KBr pellets on a Shimadzu FTIR spectrometer between 400 and 4000 cm⁻¹. NMR spectra were taken with JEOL 400 MHz and Bruker 500 MHz multinuclear spectrometers. ESI mass spectra were measured with Agilent 6210 ESI-TOF (Agilent Technology) and LTQ Orbitrap XL (Thermo Scientific) mass spectrometers. All MS results are given in the form: m/z, assignment. Elemental analyses of carbon, hydrogen, nitrogen, and sulfur were determined using a Heraeus vario EL elemental analyzer. The ⁹⁹Tc values were determined by standard liquid scintillation counting.

Syntheses of the Ligands. *N*-(*tert-Butoxycarbonyl*)-2-(*amino-diacetic acid diethyl ester*)benzylamine (2). *N*-(*tert*-Butoxycarbonyl)-2-aminobenzylamine (1) (8.891 g, 40 mmol), ethyl bromoacetate (13.8 mL, 125 mmol), *i*-Pr₂EtN (27.8 mL, 160 mmol), and finely powdered KI (1 g) in toluene (150 mL) were heated under reflux for 48 h. After being cooled to room temperature, water (50 mL) was added. The two layers were separated. The aqueous phase was extracted with toluene (50 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residual was heated at ca. 80 °C under a pressure of 20 mmHg for 4 h to remove the remaining ethyl bromoacetate. The obtained yellow oil, which contained mainly the diester 2 and traces of ethyl bromoacetate, was used in the next step without further purification. Yield is about 95% (14.989 g).

Anal. Calcd for $C_{20}H_{30}N_2O_6$: C, 60.9; H, 7.7; N, 7.1. Found: C, 61.5; H, 7.7; N, 7.0. ¹H NMR (400 MHz, CDCl₃, ppm): 1.13 (t, *J* = 7.1 Hz, 6H, OCH₂<u>CH₃</u>), 1.36 (s, 9H, CH₃), 3.90 (s, 4H, NCH₂CO), 4.05 (q, *J* = 7.1 Hz, 4H, O<u>CH₂CH₃</u>), 4.31 (d, *J* = 5.9 Hz, 2H, <u>CH₂NH</u>) 6.12 (s, br, 1H, NHCO), 7.01 (t, *J* = 7.5 Hz, 1H, C₆H₄), 7.14 (t, *J* = 7.7 Hz, 1H, C₆H₄), 7.22 (d, *J* = 7.7 Hz, 1H, C₆H₄), 7.25 (d, *J* = 8.0 Hz, 1H, C₆H₄).

N-(*tert-Butoxycarbonyl*)-2-(*aminodiacetic acid*)*benzylamine* (3). Compound 2 (7.889 g, 20 mmol) and NaOH (2.400 g, 60 mmol) in 50 mL of MeOH were stirred at room temperature for 24 h, and then the reaction mixture was evaporated to dryness in vacuum. The remaining solid was dissolved in 50 mL of cold brine solution, and cold HCl (6 M) was slowly added. The temperature was kept at 5–10 °C during this procedure until a pH of 6 was obtained. The product was extracted with THF (3 × 30 mL). The combined organic phases were dried over MgSO₄, filtered, and evaporated in vacuo to dryness. The obtained residue was recrystallized from CHCl₃ to give the pure product as a colorless solid. Yield 70% (4.737 g).

Anal. Calcd for $C_{16}H_{22}N_2O_6$: C, 56.8; H, 6.5; N, 8.3. Found: C, 56.2; H, 6.5; N, 8.1. IR (KBr, cm⁻¹): 3394 (s), 3124 (br, s), 1755 (vs), 1705 (vs), 1662 (vs), 1523 (s), 1488 (m), 1454 (m), 1392 (m), 1369 (m), 1303 (m), 1253 (s), 1212 (s), 1184 (s), 1049 (m), 972 (m), 856 (m), 779 (m), 682 (m), 590 (m). ¹H NMR (400 MHz, CDCl₃, ppm): 0.900 (s, 9H, CH₃), 3.41 (s, 4H, NCH₂CO), 3.80 (s, 2H, <u>CH₂NH</u>), 6.20 (s, br, 1H, NHCO), 6.52 (t, *J* = 7.4 Hz, 1H, C_6H_4), 6.66 (t, *J* = 7.6 Hz, 1H, C_6H_4), 6.73 (d, *J* = 7.6 Hz, 1H, C_6H_4), 6.80 (d, *J* = 7.9 Hz, 1H, C_6H_4). ¹³C NMR (400 MHz, CDCl₃, ppm): 28.76 (C(<u>CH₃)₃</u>), 40.45 (N<u>CH₂Ph</u>), 55.01 (N<u>CH₂CO), 78.19 (<u>C</u>(CH₃)₃), 123.32 (C_{aryl}), 124.32 (C_{aryl}), 127.55 (C_{aryl}), 128.43 (C_{aryl}), 135.25 (C_{aryl}),</u>

148.73 (C_{aryl}–N), 156.41 (<u>C</u>ONH), 172.65 (NCH₂<u>C</u>O). ESI⁺ MS (m/z): 339.0, 50%, [M + H]⁺; 361.1, 70%, [M + Na]⁺; 377.1, 20%, [M + K]⁺. ESI⁻ MS (m/z): 337.3, 100%, [M – H]⁻.

2-(Aminodiacetic acid)benzylammonium Bis-trifluoroacetate Salt (4). Compound 3 (4.737 g) and CF_3COOH (15 mL) were stirred in dry CH_2Cl_2 (15 mL) at room temperature for 2 h. The organic solvents were removed under vacuum to give quantitatively compound 4 as a colorless powder.

Anal. Calcd for $C_{15}H_{16}F_6N_2O_8$: C, 38.6; H, 3.5; N, 6.0. Found: C, 38.2; H, 3.4; N, 6.1. IR (KBr, cm⁻¹): 3144 (br, s), 1782 (vs), 1720 (vs), 1608 (s), 1492 (m), 1458 (m), 1404 (w), 1250 (s), 1218 (s), 1196 (s), 1168 (s), 1068 (w), 968 (w), 786 (w), 721 (w), 698 (w), 605 (w). ¹H NMR (400 MHz, DMSO- d_{69} ppm): 3.92 (s, 4H, NCH₂CO), 4.10 (d, J = 5.1 Hz, 2H, CH₂NH), 7.16 (t, J = 7.3 Hz, 1H, C₆H₄), 7.35 (m, 2H, C₆H₄), 7.44 (d, 1H, 7.4 Hz, C₆H₄), 8.27 (s, br, 4H, OH). ¹³C NMR (400 MHz, CDCl₃, ppm): 41.13 (NCH₂Ph), 55.12 (NCH₂CO), 116.39 (q, $J_{CF} = 290.0$ Hz, CF₃), 124.11 (C_{aryl}), 124.59 (C_{aryl}), 130.11 (C_{aryl}), 130.42 (C_{aryl}), 131.53 (C_{aryl}), 149.48 (C_{aryl}-N), 159.00 (q, $J_{CF} = 35.0$ Hz, CF₃CO), 173.27 (NCH₂CO). ESI⁺ MS (m/z): 239.1, 100%, [M + H]⁺; 261.0, 10%, [M + Na]⁺.

4-(*N-Methylamino*)benzoic Acid Ethylester (5). Compound 5 was prepared by the method of Kadin.¹⁸ A solution of ethyl 4aminobenzoate (16.52 g), succinimide (11.90 g), and 9.1 mL of 37% aqueous formaldehyde in 100 mL of ethanol was heated on reflux for 3 h. After cooling to room temperature, the formed colorless precipitate of ethyl 4-(aminomethylsuccinimide)benzoate was collected by suction filtration. It was dissolved in 50 mL of DMSO, and NaBH₄ (3.33 g) was added in small portions over a period of 15 min. After being heated to 80 °C for 15 min, the reaction mixture was poured into cold water. The resulting mixture was extracted three times with ether. The combined ether extracts were dried, and the solvent was removed in vacuum. The remaining solid was recrystallized from $CH_2Cl_2/MeOH$, which gave colorless crystals of 5. Yield: 62.0% (11.10 g).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.3; N, 7.8. Found: C, 67.2; H, 7.2; N, 7.8. IR (KBr, cm⁻¹): 3385 (s), 2975 (w), 2935 (w), 2900 (w), 1685 (s), 1605 (vs), 1535 (s), 1475 (m), 1370 (m), 1310 (w), 1275 (s), 1175 (s), 1105 (m), 770 (m). ¹H NMR (400 MHz, CDCl₃, ppm): 1.29 (t, *J* = 7.2 Hz, 3H, CH₂CH₃), 2.82 (s, 3H, NCH₃), 4.12 (s, 1H, NH), 4.24 (q, *J* = 7.2 Hz, 2H, <u>CH₂CH₃</u>), 6.48 (d, *J* = 6.8 Hz, 2H, Ph), 7.82 (d, *J* = 6.8 Hz, 2H, Ph).

N-(4-Ethoxycarbonylphenyl)-N-(methyl)-N'-benzoylthiourea (6). The synthesis of 6 was performed by the standard procedure using 5 as starting material.¹⁹ Benzoyl chloride (7.00 g, 50 mmol) in 5 mL of dry acetone was added dropwise to a solution of NH₄SCN (3.80 g, 50 mmol) in 10 mL of dry acetone. After the addition was completed, the mixture was kept at 40 °C for 1 h and the formed precipitate of NH₄Cl was filtered off. Compound 5 (8.96 g, 50 mmol) in 5 mL of dry acetone was slowly added to the resulting yellow solution, which then was stirred at room temperature for 3 h. After the volume of the solvent was reduced to about 10 mL, the mixture was kept at 0 °C and the formed precipitate was filtered off, washed with cold MeOH and diethyl ether, and dried in vacuum. Yield: 73.0% (12.50 g).

Anal. Calcd for $C_{18}H_{18}N_2O_3S$: C, 63.1; H, 5.3; N, 8.2; S, 9.4. Found: C, 62.9; H, 5.1; N, 8.3; S, 9.3. IR (KBr, cm⁻¹): 3225 (m), 3190 (w), 3060 (w), 2985 (w), 2940 (w), 2905 (w), 1710 (s), 1690 (s), 1605 (m), 1510 (s), 1450 (w), 1430 (m), 1365 (s), 1315 (m), 1275 (vs), 1180 (m), 1110 (s), 720 (s). ¹H NMR (400 MHz, CDCl₃, ppm): 1.34 (t, *J* = 7.1 Hz, 3H, CH₂CH₃), 3.77 (s, 3H, NCH₃), 4.31 (q, *J* = 7.1 Hz, 2H, <u>CH₂CH₃)</u>, 7.38 (d, 4H, Ph), 7.50 (t, *J* = 7.3 Hz, 1H, Ph), 7.57 (d, *J* = 7.4 Hz, 2H, Ph), 8.01 (d, *J* = 8.7 Hz, 2H, Ph), 8.36 (s, 1H, NH). ¹³C NMR (400 MHz, CDCl₃, ppm): 14.42 (OCH₂CH₃), 43.37 (NCH₃), 61.38 (O<u>C</u>H₂CH₃), 124.54 (C_{aryl}), 128.23 (C_{aryl}), 128.79 (<u>C_{aryl}</u>), 129.52 (C_{aryl}), 129.63 (C_{aryl}), 132.28 (C_{aryl}), 136.17 (C_{aryl}), 140.64 (<u>C_{aryl}</u>-N), 165.73 (COO), 168.51 (C=O), 175.26 (C=S). ESI⁺ MS (*m*/*z*): 343.1, 100%, [M + H]⁺; 365.2, 40%, [M + Na]⁺.

Bis-[N-(4-ethoxycarbonylphenyl)-N-methyl-N'-benzoylthioureato]nickel(II) (7). The synthesis of 7 from 6 was adopted from the general procedure.¹⁶ Compound 6 (10.27 g, 30

mmol) was dissolved in boiling EtOH (50 mL) and slowly added to a hot solution of Ni(CH₃COO)₂·4H₂O (3.72 g, 15 mmol) in 30 mL of MeOH, which resulted in the precipitation of a red-brown solid of 7. The reaction mixture was refluxed for additional 30 min and then cooled to room temperature. Compound 7 was collected by suction filtration and dried in vacuo. Yield: 93.0% (10.32 g).

Anal. Calcd for $C_{36}H_{34}N_4NiO_6S_2$: C, 58.3; H, 4.6; N, 7.6; S, 8.7. Found: C, 58.3; H, 4.8; N, 7.3; S, 8.5. IR (KBr, cm⁻¹): 3065 (w), 2975 (w), 2925 (w), 2855 (w), 1720 (s), 1605 (w), 1525 (s), 1420 (s), 1375 (s), 1285 (s), 1110 (m), 1020 (m), 910 (m), 710 (m), 705 (m). ¹H NMR (400 MHz, CDCl₃, ppm): 1.41 (t, *J* = 7.0 Hz, 6H, CH₂<u>CH₃</u>), 3.60 (s, 6H, NCH₃), 4.40 (q, *J* = 7.0 Hz, 4H, <u>CH₂CH₃</u>), 7.3–8.1 (m, 18H, Ph). ¹³C NMR (400 MHz, CDCl₃, ppm): 14.40 (OCH₂<u>CH₃</u>), 41.94 (NCH₃), 61.23 (O<u>C</u>H₂CH₃), 124.55 (C_{aryl}), 127.11 (C_{aryl}), 128.02 (C_{aryl}), 129.38 (C_{aryl}), 130.68 (C_{aryl}), 131.93 (C_{aryl}), 136.02 (C_{aryl}), 149.44 (C_{aryl}–N), 165.72 (COO), 165.93 (C=O), 175.44 (C=S). ESI⁺ MS (*m*/*z*): 741.0, 50%, [M + H]⁺; 762.9, 10%, [M + Na]⁺.

N-(4-Ethoxycarbonylphenyl)-*N*-methyl-*N'*-benzimidoyl Chloride (8). The synthesis of 8 was adopted from the general procedure.¹⁶ A solution of SOCl₂ (1.60 mL, 22.0 mmol) in 20 mL of dry CH_2Cl_2 was added dropwise into a stirred solution of compound 7 (8.16 g, 11.0 mmol). The reaction mixture was stirred at room temperature for an additional 2 h and then heated on reflux for 30 min. The formed precipitate of NiCl₂ was filtered off, and the filtrate was evaporated under reduced pressure. Compound 8 was obtained as yellow, microcrystalline solid. Yield: 65.0% (5.16 g).

Anal. Calcd for $C_{18}H_{17}CIN_2O_2S$: C, 59.9; H, 4.8; N, 7.8; S, 8.9. Found: C, 59.9; H, 4.8; N, 7.8; S, 8.9. IR (KBr, cm⁻¹): 3055 (w), 2981 (w), 2935 (w), 2900 (w), 1716 (s), 1639 (s), 1600 (m), 1505 (m), 1454 (m), 1365 (s), 1273 (s), 1164 (s), 1103 (s), 1014 (m), 910 (m), 775 (m), 690 (m). ¹H NMR (400 MHz, CDCl₃, ppm): 1.36 (t, *J* = 7.1 Hz, 3H, CH₂CH₃), 3.80 (s, 3H, NCH₃), 4.33 (q, *J* = 7.1 Hz, 2H, CH₂CH₃), 7.34 (d, *J* = 8.2 Hz, 4H, Ph), 7.45 (t, *J* = 7.3 Hz, 1H, Ph), 7.74 (d, *J* = 7.8 Hz, 2H, Ph), 8.01 (d, *J* = 8.3 Hz, 2H, Ph). ¹³C NMR (400 MHz, CDCl₃, ppm): 14.27 (OCH₂CH₃), 43.38 (NCH₃), 61.36 (OCH₂CH₃), 125.25 (C_{aryl}), 128.48 (C_{aryl}), 129.12 (C_{aryl}), 130.10 (C_{aryl}), 130.79 (C_{aryl}), 132.92 (C_{aryl}), 133.62 (C_{aryl}), 144.39 (C_{aryl}-N), 147.68 (C-Cl), 165.49 (COO), 188.06 (C=S). ESI⁺ MS (*m*/z): 361.0, 70%, [M + H]⁺.

 $H_{3}L$. N-[(Diethylamino)(thiocarbonyl)]benzimidoyl chloride (686 mg, 2.7 mmol), compound 4 (1.409 g, 2.5 mmol), and NEt₃ (2.02 g, 20 mmol) were stirred in 20 mL of dry EtOH for 6 h at room temperature and then at 40 °C for 1 h. The organic solvent was evaporated under reduced pressure to dryness. The residue was dissolved in 20 mL of THF, and brine solution (20 mL) was added. The organic layer was separated, dried over MgSO₄, filtered, and the solvent was removed in vacuo. The residue was washed with diethyl ether and dried in vacuum to give H₃L as a colorless solid. Yield: 65% (742 mg).

Anal. Calcd for C23H28N4O4S: C, 60.5; H, 6.2; N, 12.3; S, 7.0. Found: C, 60.3; H, 6.3; N, 12.2; S, 7.2. IR (KBr, cm⁻¹): 3250 (br, s), 1720 (br, s), 1631 (br, s), 1573 (s), 1539 (s), 1489 (m), 1454 (s), 1423 (s), 1311 (m), 1257 (s), 1199 (s), 1138 (s), 1076 (m), 968 (w), 883 (w), 779 (m), 698 (m). ¹H NMR (400 MHz, DMSO-*d*₆, ppm): 1.07 (t, J = 7.0 Hz, 3H, CH₃), 1.13 (t, J = 7.0 Hz, 3H, CH₃), 3.52 (q, J = 7.0 Hz, 2H, N<u>CH₂CH₃</u>), 3.78 (q, J = 7.0 Hz, 2H, N<u>CH₂CH₃</u>), 3.99 (s, 4H, NCH₂CO), 4.64 (d, J = 5.2 Hz, 2H, <u>CH₂NH</u>), 7.12 (t, J = 7.3 Hz, 1H, C_6H_4), 7.25 (t, J = 7.2 Hz, 1H, C_6H_4), 7.30 (d, J = 8.0 Hz, 1H, C_6H_4), 7.36 (d, J = 7.6 Hz, 1H, C_6H_4), 7.47 (m, 5H, Ph), 8.35 (s, br, 1H, NHCO), 12.76 (s, br, 1H, COOH). ¹³C NMR (400 MHz, DMSO-*d*₆, ppm): 12.34, 13.45 (CH₂<u>C</u>H₃), 46.42, 46.98 (N<u>C</u>H₂CH₃), 56.56 (N<u>C</u>H₂), 67.51 (N<u>C</u>H₂CO), 118.21 (C_{aryl}), 125.23 (C_{aryl}), 127.48 (C_{aryl}), 127.90 (C_{aryl}), 128.87 (C_{aryl}), 129.55 (C_{aryl}), 130.04 (C_{aryl}) , 132.68 (C_{aryl}) , 135.34 (C_{aryl}) , 149.54 $(C_{aryl}-N)$, 166.24 (C=N), 172.50 (COO), 180.18 (C=S). ESI⁺ MS (m/z): 457.1, 100%, [M + H]⁺; 479.2, 60%, $[M + Na]^+$. ESI⁻ MS (*m*/*z*): 455.1, 100%, [M -Н]-.

 H_3L –COOEt. The synthesis of H_3L –COOEt was adopted from the procedure described for H_3L except that the benzimidoyl chloride **8** was used.

Anal. Calcd for C29H30N4O6S: C, 61.9; H, 5.4; N, 10.0; S, 5.7. Found: C, 61.6; H, 5.2; N, 9.8; S, 5.8. IR (KBr, cm⁻¹): 3348 (br, s), 1712 (br, s), 1605 (s), 1542 (s), 1493 (m), 1446 (s), 1276 (s), 1202 (s), 1138 (s), 1099 (s), 1018 (m), 972 (w), 775 (m). ¹H NMR (400 MHz, DMSO- d_{61} ppm): 1.40 (t, J = 7.1 Hz, 3H, CH₂CH₃), 3.56 (s, 3H, NCH₃), 3.83 (s, 4H, NCH₂CO), 4.37 (q, J = 7.1 Hz, 2H, <u>CH</u>₂CH₃), 4.49 (s, 2H, PhC<u>H</u>₂NH), 6.86 (t, br, 1H, Ph), 6.93 (d, br, 1H, Ph), 7.14 (t, br, 1H, Ph), 7.19 (d, br, 1H, Ph), 7.47 (m, 7H, Ph), 7.91 (d, J = 8.6 Hz, 2H, Ph), 8.67 (s, br, 1H, NH) 12.13 (s, br, 2H, COOH). ¹³C NMR (400 MHz, DMSO-*d*₆, ppm): 14.34 (OCH₂<u>C</u>H₃), 42.89 (NCH₃), 61.15 (OCH₂CH₃), 59.20 (NCH₂Ph), 66.54 (N-<u>CH</u>₂CO), 120.01 (C_{aryl}), 124.43 (C_{aryl}), 125.51 (C_{aryl}), 126.70 (C_{aryl}), 128,99 (C_{aryl}), 129.12 (C_{aryl}), 130.68 (C_{aryl}), 130.97 (C_{aryl}), 131.03 (Carvl), 131.48 (Carvl), 133.20 (Carvl), 135.76 (Carvl), 148.57 (Carvl-N), 152.95 (C_{aryl}-N), 165.30 (Ph<u>C</u>OO), 166.93 (C=N), 172.62(COO), 180.77 (C=S). ESI⁺ MS (m/z): 563.2, 100%, [M + H]⁺; 585.2, 60%, $[M + Na]^+$; 601.1, 20%, $[M + K]^+$. ESI⁻ MS (m/z): 561.2, 100%, [M– H]-.

 H_3L –COOH. H_3L –COOEt (562 mg, 1 mmol) was added to a solution of NaOH (400 mg, 10 mmol) in MeOH (5 mL). The reaction mixture was stirred at room temperature for 12 h, and then the solvent was removed under vacuum. The resulting residue was dissolved in brine solution (5 mL). After being neutralized with 10 mmol of HCl, the mixture was extracted with THF (2 × 5 mL). The organic phases were collected, dried over MgSO₄, and the solvent was removed under vacuum to give compound H_3L –COOH as a slightly yellow powder. Yield: 80% (427 mg).

Anal. Calcd for $C_{27}H_{26}N_4O_6S$: C, 60.7; H, 4.9; N, 10.5; S, 6.0. Found: C, 60.4; H, 4.8; N, 10.3; S, 6.1. IR (KBr, cm⁻¹): 3368 (br, s), 1717 (s), 1605 (s), 1562 (s), 1423 (s), 1492 (m), 1423 (m), 1381 (m), 1272 (s), 1176 (s), 775 (m), 698 (m). ¹H NMR (400 MHz, DMSO- d_6 , ppm): 3.58 (s, 3H, NCH₃), 3.98 (s, 4H, NCH₂CO), 4.55 (s, 2H, PhC<u>H</u>₂NH), 6.87 (t, br, 1H, Ph), 6.96 (d, br, 1H, Ph), 7.21 (t, br, 1H, Ph), 7.29 (d, br, 1H, Ph), 7.40 (m, 7H, Ph), 7.94 (d, *J* = 8.2 Hz, 2H, Ph), 8.70 (s, br, 1H, NH), 12.74 (s, 3H, COOH). ¹³C NMR (400 MHz, DMSO- d_6 , ppm): 43.70 (NCH₃), 56.37 (N<u>C</u>H₂Ph), 66.03 (N–<u>C</u>H₂CO), 119.90 (C_{aryl}), 125.01 (C_{aryl}), 125.95 (C_{aryl}), 126.66 (C_{aryl}), 127.05 (C_{aryl}), 128.31 (C_{aryl}), 128.84 (C_{aryl}), 129.60 (C_{aryl}), 130.56 (C_{aryl}), 131.39 (C_{aryl}), 132.31 (C_{aryl}), 134.76 (C_{aryl}), 146.01 (C_{aryl}–N), 149.32 (C_{aryl}–N), 166.03 (Ph<u>C</u>OO), 168.12 (C=N), 173.13 (COO), 180.21 (C=S). ESI⁺ MS (m/z): 535.2, 40%, [M + H]⁺; 557.2, 100%, [M + Na]⁺; 573.1, 80%, [M + K]⁺. ESI⁻ MS (m/z): 533.2, 100%, [M – H]⁻.

Syntheses of the Complexes. [ReO(L)] (9). H₃L (46 mg, 0.1 mmol) and Et₃N (50 μ L) were added to a stirred solution of (NBu₄)[ReOCl₄] (58 mg, 0.1 mmol) in 5 mL of MeOH. The reaction mixture was heated under reflux for 30 min. After being cooled to room temperature, the formed purple solid of 9 was filtered off, washed with cold MeOH, and dried under vacuum. Yield: 67% (44 mg).

Compound 9 can also be synthesized from other precursors such as $[Re^VNCl_2(PPh_3)_2], \ [Re^V(NPh)Cl_3(PPh_3)_2], \ or \ [Re^{III}Cl_3(MeCN)-(PPh_3)_2] by heating them with H_3L in the presence of a base (Et_3N), water, and air.$

Anal. Calcd for $C_{23}H_{25}N_4O_5ReS$: C, 42.1; H, 3.8; N, 8.5; S, 4.9. Found: C, 42.0; H, 3.6; N, 8.3; S, 4.7. IR (KBr, cm⁻¹): 3055 (w), 2963 (m), 2926 (m), 1720 (vs), 1666 (vs), 1512 (s), 1442 (m), 1404 (m), 1350 (m), 1311 (m), 1041 (w), 964 (m), 941 (m), 910 (m), 771 (m), 702 (m). ¹H NMR (400 MHz, CDCl₃, ppm): 1.30 (t, *J* = 7.2 Hz, 3H, CH₃), 1.33 (t, *J* = 7.1 Hz, 3H, CH₃), 3.77 (m, 1H, N<u>CH₂CH₃</u>), 3.84 (m, 1H, N<u>CH₂CH₃</u>), 3.89 (s, 2H, Ph<u>CH₂N</u>), 4.03 (m, 1H, N<u>CH₂CH₃</u>), 4.09 (m, 1H, N<u>CH₂CH₃</u>), 4.53 (d, *J* = 15.5 Hz, 1H, NCH₂CO), 4.83 (d, *J* = 14.0 Hz, 1H, NCH₂CO), 5.06 (d, *J* = 13.8 Hz, 1H, NCH₂CO), 5.68 (d, *J* = 15.6 Hz, 1H, NCH₂CO), 7.00 (d, *J* = 7.6 Hz, 1H, C₆H₄), 7.22 (t, *J* = 7.5 Hz, 2H, Ph). ¹H NMR (400 MHz, DMSO-*d*₆, ppm): 1.26 (t, *J* = 7.2 Hz, 3H, CH₃), 1.29 (t, *J* = 7.2 Hz)

formula $C_{23}H_{25}N_4O_5ReS$ $C_{23}H_{32}N_4O_5STc$ $C_{3025}H_{32}N_4O_{825}ReS$ MW655.73567.53801.86crystal systemmonoclinicmonoclinictriclinic $a/Å$ 32.448(3)32.213(2)9.949(1) $b/Å$ 7.160(1)7.187(1)10.980(1) $c/Å$ 20.521(2)20.453(2)16.796(2) a/deg 9090100.54(1) β/deg 100.69(1)100.29(1)92.32(1) γ/deg 9090113.36(1) $V/Å^3$ 4684.8(9)4659.2(8)1643.0(3)space group $C2/c$ $C2/c$ $P\overline{1}$ crystal size0.5 × 0.2 × 0.040.2 × 0.15 × 0.030.1 × 0.067 × 0.05Z882 D_{calc}/g cm ⁻³ 1.8591.6181.621 μ/mm^{-1} 5.3200.7513.816no. of reflns14.46220.47917.975no. of indep, R_{int} 6207, 0.10026270, 0.11198768, 0.1067no. of parameters326326380R1/wR20.0477/0.07760.0505/0.11090.0668/0.1695GOF0.8720.9071.068GDF0.0477/0.07760.0507.0.1090.0668/0.1695GOF0.8720.9071.068GDF0.0477/0.07760.0505/0.11090.0668/0.1695		[ReO(L)] (9)	[TcO(L)] (10)	[ReO(L-COOEt)]·1.25 MeOH (11)
MW655.73567.53801.86crystal systemmonoclinicmonoclinictriclinic $a/Å$ 32.448(3)32.213(2)9.949(1) $b/Å$ 7.160(1)7.187(1)10.980(1) $c/Å$ 20.521(2)20.453(2)16.796(2) a/deg 9090100.54(1) a/deg 9090100.54(1) $b/Ågeg$ 100.69(1)100.29(1)92.32(1) r/deg 9090113.36(1) $V/Å^3$ 4684.8(9)4659.2(8)1643.0(3)space groupC2/cC2/c $P\overline{1}$ crystal size0.5 × 0.2 × 0.040.2 × 0.15 × 0.030.1 × 0.067 × 0.05Z882 $D_{calc}/g cm^{-3}$ 1.8591.6181.621 μ/mm^{-1} 5.3200.7513.816no. of reflns14.46220.47917.975no. of indep, R_{int} 6207, 0.10026270, 0.11198768, 0.1067no. of parameters326326380R1/wR20.477/0.07760.9071.068GOF0.8720.9071.068GDFCCDC 1058104CCDC 1058105CCDC 1058106	formula	$C_{23}H_{25}N_4O_5ReS$	$C_{23}H_{25}N_4O_5STc$	$C_{30.25}H_{32}N_4O_{8.25}ReS$
crystal systemmonoclinicmonoclinictriclinic $a/Å$ 32.448(3)32.213(2)9.949(1) $b/Å$ 7.160(1)7.187(1)10.980(1) $c/Å$ 20.521(2)20.453(2)16.796(2) a/deg 9090100.54(1) β/deg 100.69(1)100.29(1)92.32(1) γ/deg 9090113.36(1) $V/Å^3$ 4684.8(9)4659.2(8)1643.0(3)space groupC2/cC2/c $\overline{P1}$ crystal size0.5 × 0.2 × 0.040.2 × 0.15 × 0.030.1 × 0.067 × 0.05Z882 $D_{calc}/g cm^{-3}$ 1.8591.6181.621 μ/mm^{-1} 5.3200.7513.816no. of reflns1.4 46220.47917.975no. of indep, R_{int} 6207, 0.10026270, 0.11198768, 0.1067no. of parameters326326380R1/wR20.0477/0.07760.055/0.1090.0668/0.1695GOF0.8720.9071.068CSDCCDC 1058104CCDC 1058105CCDC 1058105	MW	655.73	567.53	801.86
$a/Å$ $32.448(3)$ $32.213(2)$ $9.949(1)$ $b/Å$ $7.160(1)$ $7.187(1)$ $10.980(1)$ $c/Å$ $20.521(2)$ $20.453(2)$ $16.796(2)$ α/\deg 90 90 $100.54(1)$ β/\deg $100.69(1)$ $100.29(1)$ $92.32(1)$ γ/\deg 90 90 $113.36(1)$ γ/\deg 90 90 $113.36(1)$ γ/\deg 90 90 $113.36(1)$ $\gamma/Ås^3$ $4684.8(9)$ $4659.2(8)$ $1643.0(3)$ space group $C2/c$ $C2/c$ $P\overline{1}$ crystal size $0.5 \times 0.2 \times 0.04$ $0.2 \times 0.15 \times 0.03$ $0.1 \times 0.067 \times 0.05$ Z 8 8 2 $D_{calc}/g cm^{-3}$ 1.859 1.618 1.621 μ/mm^{-1} 5.320 0.751 3.816 no. of reflns 14.462 20.479 17.975 no. of indep, R_{tat} $6207, 0.1002$ $6270, 0.1119$ $8768, 0.1067$ no. of parameters 326 326 380 R1/wR2 $0.0477/0.0776$ $0.0505/0.1109$ $0.0668/0.1695$ GOF 0.872 0.907 1.068	crystal system	monoclinic	monoclinic	triclinic
$b/Å$ 7.160(1)7.187(1)10.980(1) $c/Å$ 20.521(2)20.453(2)16.796(2) α/\deg 9090100.54(1) β/\deg 100.69(1)100.29(1)92.32(1) γ/\deg 9090113.36(1) γ/deg 9090113.36(1) $V/Å^3$ 4684.8(9)4659.2(8)1643.0(3)space group $C2/c$ $C2/c$ $P\overline{1}$ crystal size0.5 × 0.2 × 0.040.2 × 0.15 × 0.030.1 × 0.067 × 0.05 Z 882 $D_{calc}/g cm^{-3}$ 1.8591.6181.621 μ/mm^{-1} 5.3200.7513.816no. of reflns14.46220.47917.975no. of indep, R_{int} 6207, 0.10026270, 0.11198768, 0.1067no. of parameters326326326380R1/wR20.0477/0.07760.0505/0.11090.0668/0.1695GOF0.8720.9071.058106	a/Å	32.448(3)	32.213(2)	9.949(1)
$c/Å$ 20.521(2)20.453(2)16.796(2) α/\deg 9090100.54(1) β/\deg 100.69(1)100.29(1)92.32(1) γ/\deg 9090113.36(1) γ/deg 9090133.36(1) $V/Å^3$ 4684.8(9)4659.2(8)1643.0(3)space group $C2/c$ $C2/c$ $P\overline{1}$ crystal size0.5 × 0.2 × 0.040.2 × 0.15 × 0.030.1 × 0.067 × 0.05Z882 $D_{calc}/g cm^{-3}$ 1.8591.6181.621 μ/mm^{-1} 5.3200.7513.816no. of reflns14.46220.47917.975no. of indep, R_{int} 6207, 0.10026270, 0.11198768, 0.1067no. of parameters326326380R1/wR20.0477/0.07760.0505/0.11090.0668/0.1695GOF0.8720.9071.068	b/Å	7.160(1)	7.187(1)	10.980(1)
α/\deg 9090100.54(1) β/\deg 100.69(1)100.29(1)92.32(1) γ/\deg 9090113.36(1) γ/deg 9090113.36(1) $V/Å^3$ 4684.8(9)4659.2(8)1643.0(3)space group $C2/c$ $C2/c$ $P\overline{1}$ crystal size0.5 × 0.2 × 0.040.2 × 0.15 × 0.030.1 × 0.067 × 0.05 Z 882 D_{calc}/g cm ⁻³ 1.8591.6181.621 μ/mm^{-1} 5.3200.7513.816no. of reflns14.46220.47917.975no. of indep, R_{int} 6207, 0.10026270, 0.11198768, 0.1067no. of parameters326326380R1/wR20.0477/0.07760.0505/0.11090.0668/0.1695GOF0.8720.9071.068	c/Å	20.521(2)	20.453(2)	16.796(2)
β/deg100.69(1)100.29(1)92.32(1)γ/deg9090113.36(1)V/ų4684.8(9)4659.2(8)1643.0(3)space group $C2/c$ $C2/c$ $P\overline{1}$ crystal size0.5 × 0.2 × 0.040.2 × 0.15 × 0.030.1 × 0.067 × 0.05Z882 $D_{calc}/g cm^{-3}$ 1.8591.6181.621µ/mm^{-1}5.3200.7513.816no. of reflns14 46220 47917 975no. of indep, R_{int} 6207, 0.10026270, 0.11198768, 0.1067no. of parameters326326326380R1/wR20.0477/0.07760.0505/0.11090.0668/0.1695GOF0.8720.9071.068	α/\deg	90	90	100.54(1)
γ/\deg 9090113.36(1) $V/Å^3$ 4684.8(9)4659.2(8)1643.0(3)space group $C2/c$ $C2/c$ $P\overline{1}$ crystal size $0.5 \times 0.2 \times 0.04$ $0.2 \times 0.15 \times 0.03$ $0.1 \times 0.067 \times 0.05$ Z 882 $D_{calc}/g cm^{-3}$ 1.8591.6181.621 μ/mm^{-1} 5.3200.7513.816no. of reflns14.46220.47917.975no. of indep, R_{int} 6207, 0.10026270, 0.11198768, 0.1067no. of parameters326326380R1/wR20.0477/0.07760.0505/0.11090.0668/0.1695GOF0.8720.9071.068	β/\deg	100.69(1)	100.29(1)	92.32(1)
$V/Å^3$ 4684.8(9)4659.2(8)1643.0(3)space group $C2/c$ $C2/c$ $P\overline{1}$ crystal size $0.5 \times 0.2 \times 0.04$ $0.2 \times 0.15 \times 0.03$ $0.1 \times 0.067 \times 0.05$ Z 8 8 2 $D_{calc}/g cm^{-3}$ 1.859 1.618 1.621 μ/mm^{-1} 5.320 0.751 3.816 no. of reflns 14.462 20.479 17.975 no. of indep, R_{int} $6207, 0.1002$ $6270, 0.1119$ $8768, 0.1067$ no. of parameters 326 326 380 R1/wR2 $0.0477/0.0776$ $0.0505/0.1109$ $0.0668/0.1695$ GOF 0.872 0.907 1.068	γ/deg	90	90	113.36(1)
space group $C2/c$ $C2/c$ $P\overline{1}$ crystal size $0.5 \times 0.2 \times 0.04$ $0.2 \times 0.15 \times 0.03$ $0.1 \times 0.067 \times 0.05$ Z882 $D_{calc}/g \ cm^{-3}$ 1.859 1.618 1.621 μ/mm^{-1} 5.320 0.751 3.816 no. of reflns 14.462 20.479 17.975 no. of indep, R_{int} $6207, 0.1002$ $6270, 0.1119$ $8768, 0.1067$ no. of parameters 326 326 380 R1/wR2 $0.0477/0.0776$ $0.0505/0.1109$ $0.0668/0.1695$ GOF 0.872 0.907 1.068	$V/Å^3$	4684.8(9)	4659.2(8)	1643.0(3)
crystal size $0.5 \times 0.2 \times 0.04$ $0.2 \times 0.15 \times 0.03$ $0.1 \times 0.067 \times 0.05$ Z882 $D_{calc}/g \text{ cm}^{-3}$ 1.8591.6181.621 μ/mm^{-1} 5.3200.7513.816no. of reflns14.46220.47917.975no. of indep, R_{int} 6207, 0.10026270, 0.11198768, 0.1067no. of parameters326326380R1/wR20.0477/0.07760.0505/0.11090.0668/0.1695GOF0.8720.9071.068CSDCCDC 1058104CCDC 1058105CCDC 1058106	space group	C2/c	C2/c	$P\overline{1}$
Z882 $D_{calc}/g cm^{-3}$ 1.8591.6181.621 μ/mm^{-1} 5.3200.7513.816no. of reflns14 46220 47917 975no. of indep, R_{int} 6207, 0.10026270, 0.11198768, 0.1067no. of parameters326326380R1/wR20.0477/0.07760.0505/0.11090.0668/0.1695GOF0.8720.9071.068CSDCCDC 1058104CCDC 1058105CCDC 1058106	crystal size	$0.5 \times 0.2 \times 0.04$	$0.2 \times 0.15 \times 0.03$	$0.1 \times 0.067 \times 0.05$
$ \begin{array}{cccc} D_{\rm calc}/{\rm g}~{\rm cm}^{-3} & 1.859 & 1.618 & 1.621 \\ \mu/{\rm mm}^{-1} & 5.320 & 0.751 & 3.816 \\ {\rm no.~of~reflns} & 14.462 & 20.479 & 17.975 \\ {\rm no.~of~indep,~R_{\rm int}} & 6207, 0.1002 & 6270, 0.1119 & 8768, 0.1067 \\ {\rm no.~of~parameters} & 326 & 326 & 380 \\ {\rm R1/wR2} & 0.0477/0.0776 & 0.0505/0.1109 & 0.0668/0.1695 \\ {\rm GOF} & 0.872 & 0.907 & 1.068 \\ {\rm CSD} & {\rm CCDC}~1058104 & {\rm CCDC}~1058105 & {\rm CCDC}~1058106 \\ \end{array} $	Z	8	8	2
μ/mm ⁻¹ 5.320 0.751 3.816 no. of reflns 14 462 20 479 17 975 no. of indep, R _{int} 6207, 0.1002 6270, 0.1119 8768, 0.1067 no. of parameters 326 326 380 R1/wR2 0.0477/0.0776 0.0505/0.1109 0.0668/0.1695 GOF 0.872 0.907 1.068	$D_{\rm calc}/{ m g}~{ m cm}^{-3}$	1.859	1.618	1.621
no. of reflns 14 462 20 479 17 975 no. of indep, R _{int} 6207, 0.1002 6270, 0.1119 8768, 0.1067 no. of parameters 326 326 380 R1/wR2 0.0477/0.0776 0.0505/0.1109 0.0668/0.1695 GOF 0.872 0.907 1.068	μ/mm^{-1}	5.320	0.751	3.816
no. of indep, R _{int} 6207, 0.1002 6270, 0.1119 8768, 0.1067 no. of parameters 326 326 380 R1/wR2 0.0477/0.0776 0.0505/0.1109 0.0668/0.1695 GOF 0.872 0.907 1.068 CSD CCDC 1058104 CCDC 1058105 CCDC 1058106	no. of reflns	14 462	20 479	17 975
no. of parameters 326 326 380 R1/wR2 0.0477/0.0776 0.0505/0.1109 0.0668/0.1695 GOF 0.872 0.907 1.068 CSD CCDC 1058104 CCDC 1058105 CCDC 1058106	no. of indep, R _{int}	6207, 0.1002	6270, 0.1119	8768, 0.1067
R1/wR2 0.0477/0.0776 0.0505/0.1109 0.0668/0.1695 GOF 0.872 0.907 1.068 CSD CCDC 1058104 CCDC 1058105 CCDC 1058106	no. of parameters	326	326	380
GOF 0.872 0.907 1.068 CSD CCDC 1058104 CCDC 1058105 CCDC 1058106	R1/wR2	0.0477/0.0776	0.0505/0.1109	0.0668/0.1695
CSD CCDC 1058104 CCDC 1058105 CCDC 1058106	GOF	0.872	0.907	1.068
	CSD	CCDC 1058104	CCDC 1058105	CCDC 1058106

3H, CH₃), 4.00 (m, 4H, N<u>CH₂</u>CH₃), 4.10 (d, J = 18.3 Hz, 1H, Ph<u>CH₂</u>N), 4.40 (d, J = 18.2 Hz, 1H, Ph<u>CH₂</u>N), 4.78 (d, J = 15.2 Hz, 1H, NCH₂CO), 4.82 (d, J = 14.1 Hz, 1H, NCH₂CO), 5.37 (d, J = 14.5 Hz, 1H, NCH₂CO), 5.63 (d, J = 15.6 Hz, 1H, NCH₂CO), 7.13 (d, J = 7.6 Hz, 1H, C₆H₄), 7.29 (t, J = 7.4 Hz, 1H, C₆H₄), 7.43 (m, 2H, C₆H₄), 7.57 (m, 3H, Ph), 7.67 (d, J = 8.0 Hz, 2H, Ph). ¹³C NMR (400 MHz, DMSO-d₆, ppm): 13.01, 13.23 (NCH₂CH₃), 46.75, 47.13 (N<u>C</u>H₂CH₃), 64.03 (N<u>C</u>H₂Ph), 65.37, 66.71 (N<u>C</u>H₂CO), 119.38 (C_{aryl}), 127.84 (C_{aryl}), 128.57 (C_{aryl}), 128.78 (C_{aryl}), 129.56 (C_{aryl}), 130.83 (C_{aryl}), 131.54 (C_{aryl}), 132.67 (C_{aryl}), 137.02 (C_{aryl}), 153.81 (C_{aryl}-N), 170.44 (C=N), 173.34 (COORe), 173.67 (COORe), 183.61 (C=S). ESI⁺ MS (m/z): 657.2, 100%, [M + H]⁺.

[TcO(L]] (10). The technetium complex 10 was prepared from (NBu₄)[TcOCl₄] by the procedure described above as for its rhenium analogue 9. Compound 10 was isolated as a green solid. Yield: 75% (43 mg).

Anal. Calcd for $C_{23}H_{25}N_4O_5TcS$: Tc, 17.4. Found: Tc, 17.5. IR (KBr, cm⁻¹): 3066 (w), 2954 (w), 2923 (w), 1701 (vs), 1654 (vs), 1500 (s), 1442 (m), 1407 (m), 1350 (m), 1311 (s), 1288 (m), 1045 (w), 944 (m), 910 (m), 771 (m). ¹H NMR (400 MHz, DMSO- d_6 , ppm): 1.29 (m, 6H, CH₃), 3.79 (m, 2H, N<u>CH₂CH₃</u>), 3.84 (s, 2H, Ph<u>CH₂N</u>), 3.93 (m, 2H, N<u>CH₂CH₃</u>), 4.43 (d, J = 15.3 Hz, 1H, NCH₂CO), 4.79 (d, J = 14.1 Hz, 1H, NCH₂CO), 5.01 (d, J = 14.1 Hz, 1H, NCH₂CO), 7.04 (d, J = 7.5 Hz, 1H, C₆H₄), 7.23 (t, J = 7.6 Hz, 1H, C₆H₄), 7.45 (m, 7H, Ph).

[*ReO*(*L*–*COOEt*)] (11). H₃L–COOEt (56 mg, 0.1 mmol) and Et₃N (50 μ L) were added to a stirred solution of (NBu₄)[ReOCl₄] (58 mg, 0.1 mmol) in 5 mL of MeOH. The reaction mixture was heated under reflux for 30 min. After being cooled to room temperature, the formed purple solid of 11 was filtered off, washed with cold MeOH, and dried under vacuum. Yield: 63% (48 mg).

Anal. Calcd for $C_{29}H_{27}N_4O_7ReS$: C, 45.7; H, 3.6; N, 7.4; S, 4.21. Found: C, 45.6; H, 3.6; N, 7.2; S, 4.1. IR (KBr, cm⁻¹): 2985 (w), 2931 (w), 2851 (w), 1717 (vs), 1527 (s), 1496 (m), 1388 (m), 1280 (s), 1226 (w), 1114 (w), 1096 (m), 1018 (w), 988 (w), 936 (w), 910 (m), 779 (m), 706 (w). ¹H NMR (400 MHz, DMSO- d_6 , ppm): 1.33 (t, J = 6.9 Hz, 3H, OCH₂CH₃), 3.85 (s, 3H, NCH₃), 4.14 (d, J = 18.1 Hz, 1H, PhCH₂N), 4.34 (q, J = 6.9 Hz, 2H, OCH₂CH₃), 4.44 (d, J = 18.0 Hz, 1H, PhCH₂N), 4.78 (d, J = 15.5 Hz, 1H, NCH₂CO), 4.90 (d, J = 15.5 Hz, 1H, NCH₂CO), 5.69 (d, J = 16.1 Hz, 1H, NCH₂CO), 7.20 (s, br, 1H, Ph), 7.28 (t, J = 7.4 Hz, 1H, Ph), 7.4–7.6 (m, 9H, Ph), 8.11 (d, J = 7.9 Hz, 2H, Ph). ¹³C NMR (400 MHz, DMSO- $d_{6^{\circ}}$ ppm): 14.64 (OCH₂<u>C</u>H₃), 43.04 (NCH₃), 61.59 (O<u>C</u>H₂CH₃), 64.21 (N<u>C</u>H₂Ph), 65.61 (N–<u>C</u>H₂CO), 67.00 (N–<u>C</u>H₂CO), 119.91 (C_{aryl}), 128.08 (C_{aryl}), 128.34 (C_{aryl}), 129.30 (C_{aryl}), 129,59 (C_{aryl}), 130.23 (C_{aryl}), 131.07 (C_{aryl}), 131.10 (C_{aryl}), 131.73 (C_{aryl}), 131.82 (C_{aryl}), 133.30 (C_{aryl}), 136.93-(C_{aryl}), 147.88 (C_{aryl}-N), 154.33 (C_{aryl}-N), 165.38 (Ph<u>C</u>OO), 171.35 (C=N), 173.90 (COORe), 174.74 (COORe), 184.08 (C=S). ESI⁺ MS (m/z): 763.1, 100%, [M + H]⁺; 784.9, 10%, [M + Na]⁺.

[TcO(L-COOEt)] (12). The technetium complex 12 was prepared from (NBu₄)[TcOCl₄] by the procedure described for its rhenium analogue 11. Compound 12 was isolated as a green solid. Yield: 67% (45 mg).

Anal. Calcd for $C_{29}H_{27}N_4O_7TcS$: Tc, 14.6. Found: Tc, 14.6. IR (KBr, cm⁻¹): 2977 (w), 1701 (vs), 1523 (vs), 1454 (m), 1388 (m), 1276 (s), 1218 (m), 1114 (m), 1018 (w), 956 (m), 910 (m), 779 (m), 705 (m). ¹H NMR (400 MHz, CDCl₃, ppm): 1.18 (s, 3H, OCH₂CH₃), 3.68 (d, J = 17.7 Hz, 1H, PhCH₂N), 3.96 (s, 3H, NCH₃), 4.36 (m, 3H, OCH₂CH₃ + PhCH₂N), 4.49 (d, J = 18.0 Hz, 1H, NCH₂CO), 4.74 (d, J = 15.4 Hz, 1H, NCH₂CO), 4.93 (d, J = 15.4 Hz, 1H, NCH₂CO), 7.1–7.4 (m, 11H, Ph), 8.08 (d, J = 7.6 Hz, 2H, Ph).

[ReO(L–COOH)] (13). H₃L–COOH (54 mg, 0.1 mmol) and Et₃N (50 μ L) were added to a stirred solution of (NBu₄)[ReOCl₄] (58 mg, 0.1 mmol) in 5 mL of MeOH. The reaction mixture was heated under reflux for 30 min. After standing at room temperature for 24 h, the formed purple solid was filtered off, washed with cold MeOH, and dried under vacuum. Yield: 52% (38 mg).

Anal. Calcd for $C_{27}H_{23}N_4O_7ReS$: C, 44.1; H, 3.4; N, 7.6; S, 4.4. Found: C, 44.2; H, 3.3; N, 7.5; S, 4.3. IR (KBr, cm⁻¹): 3166 (br, m), 1705 (vs), 1685 (vs), 1535 (s), 1496 (m), 1389 (m), 1354 (m), 1307 (m), 1230 (m), 1172 (w), 1118 (w), 1080 (w), 984 (m), 941 (w), 914 (m), 864 (m), 783 (m), 698 (m). ¹H NMR (400 MHz, DMSO- d_6 , ppm): 3.85 (s, 3H, NCH₃), 4.09 (d, J = 18.3 Hz, 1H, Ph<u>CH₂N</u>), 4.44 (d, J = 18.3 Hz, 1H, Ph<u>CH₂N</u>), 4.78 (d, J = 14.4 Hz, 1H, NCH₂CO), 4.89 (d, J = 15.6 Hz, 1H, NCH₂CO), 5.32 (d, J = 14.4 Hz, 1H, NCH₂CO), 5.69 (d, J = 15.6 Hz, 1H, NCH₂CO), 7.20(d, J = 7.6 Hz, 1H, Ph), 7.28 (t, J = 7.4 Hz, 1H, Ph), 7.4–7.6 (m, 9H, Ph), 8.09 (d, J = 8.4 Hz, 2H, Ph), 13.24 (s, 1H, COOH). ¹³C NMR (400 MHz, DMSO- d_6 , ppm): 42.57 (NCH₃), 63.71 (N<u>CH₂Ph</u>), 65.11 (N–<u>CH₂CO</u>), 66.49 (N–<u>CH₂CO</u>), 119.43 (C_{aryl}), 127.39 (C_{aryl}), 127.84 (C_{aryl}), 128.69 (C_{aryl}), 129.10 (C_{aryl}), 129.71 (C_{aryl}), 131.02 (C_{aryl}), 131.22 (C_{aryl}), 131.35 (C_{aryl}), 132.01 (C_{aryl}), 132.81 (C_{aryl}), 135.70 Scheme 1. Synthesis of the Potentially Pentadentate Ligand H₃L



 (C_{aryl}) , 144.06 $(C_{aryl}-N)$, 153.85 $(C_{aryl}-N)$, 166.44 $(Ph\underline{C}OO)$, 170.93 (C=N), 173.41 (COORe), 174.05 (COORe), 183.58 (C=S). ESI⁺ MS (m/z): 735.1, 100%, $[M + H]^+$; 757.2, 60%, $[M + Na]^+$. ESI⁻ MS (m/z): 733.1, 100%, $[M - H]^-$.

[*ReO*(*L*-*TriGlyCOOEt*)] (14). Compound 13 (37 mg, 0.05 mmol), *N*,*N'*-dicyclohexylcarbodiimide (14 mg, 0.07 mmol), and *N*-hydrobenzotriazole (9 mg, 0.07 mmol) were dissolved in 3 mL of dry DMF. The reaction mixture was stirred at room temperature for 30 min. Triglycine ethylester (17 mg, 0.07 mmol) then was added, and the mixture was stirred at room temperature for an additional 12 h. The solvent was removed under vacuum, and the residue was suspended in THF (5 mL). The insoluble urea was filtered off, and the filtrate was washed with 5 mL of brine solution. After the organic phase was dried over MgSO₄, the solvent was removed under vacuum. The residue was washed with cold MeOH and the red product was filtered off and dried under vacuum. Yield: 95% (45 mg).

Anal. Calcd for C35H36N7O10ReS: C, 45.1; H, 3.9; N, 10.5; S, 3.4. Found: C, 45.2; H, 3.8; N, 10.7; S, 3.4. IR (KBr, cm⁻¹): 3325 (m), 3062 (w), 2928 (m), 2850 (w), 1713 (vs), 1655 (vs), 1535 (s), 1497 (m), 1446 (w), 1384 (m), 1307 (m), 1219 (m), 1130 (w), 1084 (w), 980 (m), 941 (w), 910 (m), 864 (w), 787 (m), 605 (m). ¹H NMR (400 MHz, DMSO- d_6 , ppm): 1.17 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 3.75 (d, J = 5.9 Hz, 2H, NHCH₂CO), 3.85 (m, 5H, NCH₃ + $NHCH_2CO$), 3.93 (d, J = 5.7 Hz, 2H, $NHCH_2CO$), 4.07 (m, 3H, OC<u>H</u>₂CH₃ + NC<u>H</u>₂Ph), 4.43 (d, J = 18.4 Hz, 1H, N<u>CH</u>₂Ph), 4.79 (d, I = 14.5 Hz, 1H, NCH₂CO), 4.89 (d, J = 15.7 Hz, 1H, NCH₂CO), 5.30 (d, J = 14.5 Hz, 1H, NCH₂CO), 5.68 (d, J = 15.7 Hz, 1H, NCH₂CO), 7.20 (d, J = 7.4 Hz, 1H, Ph), 7.28 (t, J = 7.4 Hz, 1H, Ph), 7.4-7.6 (m, 9H, Ph), 8.03 (d, J = 8.4 Hz, 2H, Ph), 8.24 (t, br, 1H, NH), 8.29 (t, br, 1H, NH), 8.98 (t, br, 1H, NH). $^{13}\mathrm{C}$ NMR (400 MHz, DMSO-d₆, ppm): 14.07 (OCH₂CH₃), 40.64 (CONHCH₂), 41.76 (CONHCH2), 42.01 (CONHCH2), 42.98 (NCH3), 60.44 (O<u>C</u>H₂CH₃), 63.64 (N<u>C</u>H₂Ph), 65.23 (N-<u>C</u>H₂CO), 66.50 (N-<u>C</u>H₂CO), 120.03 (C_{aryl}), 126.36 (C_{aryl}), 127.35 (C_{aryl}), 128.67 (C_{aryl}), 129.01 (C_{aryl}), 129.27 (C_{aryl}), 131.10 (C_{aryl}), 131.56 (C_{aryl}), 131.99 (C_{arvl}), 132.32 (C_{arvl}), 132.93 (C_{arvl}), 136.42 (C_{arvl}), 143.55 (C_{arvl}-N), 152.87 (C_{arvl}-N), 167.44 (Ph<u>C</u>ONH), 168.03 (CH₂COOEt), 169.40 (CH₂<u>C</u>ONH), 169.69 (CH₂<u>C</u>ONH), 171.02 (C=N), 173.56 (COORe), 174.15 (COORe), 183.60 (C=S). ESI⁺ MS (m/z): 956.1718, 100%, [M + Na]⁺, 972.1576, 90%, [M + K]⁺.

X-ray Crystallography. The intensities for the X-ray determinations were collected on a STOE IPDS 2T instrument at 200 K with Mo K α radiation (λ = 0.71073 Å) using a graphite monochromator. Standard procedures were applied for data reduction and absorption correction. Structure solution and refinement were performed with SHELXS97 and SHELXL97.²⁰ Hydrogen atom positions were calculated for idealized positions and treated with the "riding model" option of SHELXL. More details on data collections and structure calculations are contained in Table 1. Disordered solvent methanol is contained in the lattice of 11. It has been modeled as three molecules with partial occupation. A similar situation has been found for the solid-state structure of the analogous technetium complex 12, which also crystallizes in the triclinic space group $P\overline{1}$ (a = 9.993(1), b = 11.505(2), c = 16.440(2) Å, $\alpha = 100.31(1)$, $\beta = 89.21(1)$, $\gamma =$ 118.66(1)°). Because the disorder in the latter structure could not be resolved with an appropriate model, the refinement resulted in

unsatisfactory R values. For this reason details of the crystallographic results obtained for **12** will not be discussed in this Article. The molecular structure of the complex, however, could be derived from the data set unambiguously and is in full agreement with the spectroscopic results.

Additional information on the structure determinations has been deposited with the Cambridge Crystallographic Data Centre.

RESULTS AND DISCUSSION

The pentadentate benzamidine ligand H₃L can be obtained from 2-aminobenzyl amine in a multistep synthesis, which is shown in Scheme 1. The nonsymmetric diamine was chosen to allow a selective protection of one amine group and to functionalize the other one, which gives access to ligands with high denticity. Thus, in the first step, the aliphatic amine group of 2-aminobenzyl amine is selectively protected by the reaction with 1 equiv of di-tert.-butyl dicarbonate in dry CH₂Cl₂ to form o-NH₂C₆H₄CH₂NHBOC (1). The aromatic amine group then is converted to the iminodi(ethyl acetate) (2) by treatment with an excess amount of BrCH₂COOEt in the presence of a supporting base. The reaction between 1 and BrCH₂COOEt (with KI as catalyst) proceeds very slowly. Refluxing 1 with a large excess of BrCH₂COOEt (ca. 6 equiv) in MeCN and with solid K₂CO₃ used as a supporting base for 6 days resulted in a mixture of 2 (60%) and monosubstituted product (40%). However, with the use of toluene as solvent and a homogeneous supporting base such as *i*-Pr₂EtN instead of solid K_2CO_3 , the formation of 2 proceeds almost quantitatively with only 3 equiv of BrCH₂COOEt and a reflux period of 2 davs. Hydrolysis of the ester 2 with NaOH in MeOH at room temperature, followed by acidification with cold diluted HCl, gives the carboxylic acid 3. The aliphatic amine of 3 is then deprotected by CF₃COOH/CH₂Cl₂ (1:1), giving the tetradentate amine 4 as trifluoroacetate salt. Because of the poor solubility of 4 in acetone or THF, the synthesis of the pentadentate benzamidine H₃L from N₁N-diethylthiocarbonyl-N'-benzimidoyl chloride and 4 was carried out in dry EtOH. The ligand is obtained as a light yellow microcrystalline solid in high yields. No significant amount of side products by potential reactions of the benzimidoyl chloride and EtOH was detected.^{21,22}

The IR spectrum of $H_{3}L$ exhibits very strong broad bands in the region between 3500 and 2800 cm⁻¹, which are characteristic for the ν_{OH} stretches of free carboxylic groups. The absorption of the $\nu_{C=0}$ vibrations is very strong and broad and appears at 1720 cm⁻¹. It is partially overlapped with the strong absorption of the $\nu_{C=N}$ stretch at 1631 cm⁻¹. The ¹H NMR spectrum of $H_{3}L$ shows two well-separated signal sets of two ethyl groups due to the hindered rotation of the NEt₂ moiety around the C(S)–NEt₂ bond.^{10,11,23,24} While a singlet at 3.99 ppm is assigned to the methylene protons of <u>CH₂CO</u>, a

Scheme 2. Reactions of H₃L with (NBu₄)[MOCl₄]



Article



doublet at 4.64 with J = 5.2 Hz is typical for the methylene protons of <u>CH₂NH</u>. The chemical shifts of the aromatic protons belonging to the aminobenzylamine appear in the range from 6.8 to 7.3 ppm, which is at higher field as compared to those of the other phenyl group. Broad singlets at 8.35 and 12.76 ppm are assigned to the NH and COOH resonances, respectively.

The ligand H₃L reacts with the $(NBu_4)[MOCl_4]$ (M = Tc, Re) precursors in MeOH after addition of the supporting base Et₃N under formation of complexes of the composition [MO(L)] [M = Re (9), Tc (10)] (Scheme 2). While the rhenium complex is formed slowly and heating under reflux is required to complete the formation of the violet-purple powder, the technetium compound is readily precipitated from the reaction mixture at an ambient temperature as a green microcrystalline solid. Compounds 9 and 10 are stable as solids and in solution. Interestingly, compounds 9 and 10 are also obtained when H₃L is heated on reflux under aerobic conditions and without exclusion of water with other starting materials possessing different cores and contain the metal ions at different oxidation states such as [M^VNCl₂(PPh₃)₂], $[M^{V}(NPh)Cl_{3}(PPh_{3})_{2}]$, or $[M^{III}Cl_{3}(MeCN)(PPh_{3})_{2}]$ in almost quantitative yields. This strongly suggests that the formation of the oxidometal(V) complexes of H_3L is thermodynamically preferred and $\{MN\}^{2+}$, $\{MNPh\}^{3+}$, or $\{M\}^{3+}$ (M = Re, Tc) complexes are readily converted when oxidation/hydrolysis is possible.

In the IR spectra of complexes 9 and 10, no absorptions in the region above 3100 cm⁻¹, which correspond to $\nu_{\rm N-H}$ and $\nu_{\rm O-H}$ stretches in the free ligand, are observed. This is a strong hint for the triply deprotonated form of the ligand. While the $\nu_{\rm C=0}$ bands of two nonequivalent carboxylate groups in 9 appear at 1720 and 1666 cm⁻¹, the corresponding stretches in 10 reveal strong bands at 1701 and 1654 cm⁻¹. For both compounds, the formation of a benzamidinato chelate, which is normally accompanied by a large delocalization of π electrons, is indicated by a strong bathochromic shift of the $\nu_{C=N}$ to the 1500 cm⁻¹ region.^{10,11,24} The medium absorption bands at 964 and 944 cm^{-I} are assigned to the $\nu_{Re=O}$ and $\nu_{Tc=O}$ stretches, respectively.²⁵ The ¹H NMR spectra of 9 and 10 in $CDCl_3$ show no signals of O-H or N-H protons. The spectra reflect the rigid arrangement around the tertiary nitrogen atoms of the (CS)-NEt₂ moieties. This results in magnetic nonequivalence of its four methylene protons as is indicated by four separated signals with ABX₃ splitting patterns as previously mentioned.²⁶ The signals of the four methylene protons of NCH₂CO appear in two pairs of doublets at 4.53/5.68 ppm, 4.83/5.06 ppm for 9 and 4.79/5.01 ppm, 4.43/5.11 ppm for 10 with typical geminal spin coupling constants (I = 14.0-15.5 Hz). This observation indicates that the two carboxylates and the tertiary aromatic nitrogen atom coordinate to the metal centers under formation of two five-membered chelate rings. Two methylene protons in each ring are magnetically nonequivalent due to their different positions, up and down with respect to the ring plane. Because of the dissociation of the protons of the neighboring nitrogen atoms, the resonances of the methylene protons of the benzylamine groups are high-field shifted by about 0.8 ppm and appear as singlets at about 3.89 ppm (Figure 1a).



Figure 1. A part of the ¹H NMR spectrum of [ReO(L)] (a) in $CDCl_3$ and (b) in DMSO- d_6 .

Interestingly, in the ¹H NMR spectrum of **1** measured in DMSO- d_{60} this singlet is split into two doublets at 4.10 and 4.40 ppm with typical germinal coupling constants (J = 18.2 Hz) (Figure 1b). This can be explained by a restricted equilibrium between the chair and the boat conformations of the sixmembered chelate ring in DMSO.

Single-crystal X-ray diffraction studies on complexes 9 and 10 confirm the conclusions drawn from the spectroscopic studies. An ellipsoid representation of the molecular structure of 10 is depicted in Figure 2. The equivalent molecular structure of the rhenium complex 9 is virtually identical and, thus, not presented as an extra figure. However, selected bond lengths and angles of both compounds are compared in Table 2, where the atomic labeling scheme for compound 9 is adopted from that of the technetium complex shown in Figure 2. The metal atoms reveal a distorted octahedral coordination environment with a terminal oxido ligand. The remaining five coordination positions are occupied by the donor atoms of $\{L\}^{3-}$. One of the carboxylate oxygen atoms is expectedly in *trans* position to the



Figure 2. Molecular structure of [TcO(L)] (10). Hydrogen atoms were omitted for clarity.

oxido ligand. The distances from the metal atoms to the oxygen atoms *trans* to the oxido ligands are slightly shorter than the distances to the oxygen atoms in the equatorial coordination sphere. However, all of these distances fall into the range of rhenium–oxygen and technetium–oxygen single bonds found in some other carboxylato complexes.^{27,28} The M–N bonds to the tertiary nitrogen atoms N8 are longer by about 0.25 Å than the M–N5 bonds. Nevertheless, the M–N5 bond lengths are in the same range observed before for other technetium or rhenium thiocarbamoylbenzamidinato complexes.²⁹ The M–O10 bond lengths of 1.662(6) Å in 9 and 1.659(3) Å in 10 are unexceptional.

For the use of ligands of the type H_3L in bioconjugation, an additional anchor like a carboxylic or an amino group should be introduced to the periphery of the ligands. Generally, the ligand skeleton of H_3L can be modified in three different positions: (i) the phenyl group of the benzamidine, (ii) the aromatic ring of aminobenzylamine, or (iii) the thiourea $(CS)-NR^1R^2$ moiety. The latter is the most convenient one and shall be used as a demonstration for the ready variability of the novel ligand system.^{12,13} The desired pentadentate ligand H_3L –COOEt can be obtained by a multistep synthesis as is shown in Scheme 3. The syntheses of the benzoylthiourea 6 and its nickel complex 7, which contains an ester group, were carried out similar to the standard procedure,¹⁶ except using the secondary amine 5, which was prepared from 4-aminobenzoic ethyl ester. Because

of the poor solubility of the nickel complex 7 in CCl₄, dry CH_2Cl_2 was used as solvent for the synthesis of the corresponding benzimidoyl chloride **8**. The synthesis of H_3L -COOEt is similar to that of H_3L except using benzimidoyl chloride **8** instead of *N*,*N*-diethylthiocarbonyl-*N'*-benzimidoyl chloride. The reaction was also carried out in dry EtOH, and ligand H_3L -COOEt can be isolated in high yields.

The IR spectrum of H₃L-COOEt is characterized by a broad strong absorption ranging from 3450 to 2500 cm⁻¹, which is related to the carboxylic OH stretches. The $\nu_{C=0}$ stretches of protonated carboxylic acid groups appear as a broad strong band at 1712 cm⁻¹. Another strong absorption band at 1605 cm⁻¹ is assigned to the $\nu_{C=N}$ vibration, which is typical for benzamidine-type compounds. The ¹H NMR spectrum of H₃L-COOEt shows the expected signal pattern. A triplet at 1.40 ppm and a quartet at 4.37 ppm, respectively, belong to the resonances of the methyl and methylene protons of the ethyl ester. No hindered rotation effects, which are normally discussed for thiourea moieties, are observed for this compound. This is reflected by a sharp singlet at 3.56 ppm corresponding to the resonance of the N-CH₃ protons. The signals corresponding to the methylene groups of NCH₂CO and NCH₂Ph are found as singlets at 3.83 and 4.49 ppm, respectively. Two broad signals at 8.67 and 12.13 ppm can be assigned to the NH and COOH resonances.

 H_3L -COOEt readily reacts with (NBu₄)[MOCl₄] (M = Re, Tc) in refluxing MeOH with the addition of base under formation of a purple solid of the composition [ReO(L-COOEt)] (11) or the green technetium analogue [TcO(L-COOEt)] (12) (Scheme 4). Both compounds were isolated as pure crystalline solids in high yields.

The information, which can be derived from the IR spectra of **11** and **12**, is similar to that discussed for compounds **9** and **10**: coordinated carboxylato groups and the formation of the benzamidine chelate rings with delocalized π -electrons. Medium absorption bands at 988 and 956 cm⁻¹ are assigned to the $\nu_{Re=O}$ and $\nu_{Tc=O}$ vibrations.²⁵ Like the ¹H NMR spectrum of the uncoordinated ligand, those of **11** and **12** do not reveal a hindered rotation around the (CS--NMe(p-C₆H₄COOEt) bonds. This is indicated by only one set of well-resolved signals corresponding to protons of the NMe(p-C₆H₄COOEt) moiety. The absence of NH and COOH resonances suggests {L-COOEt}³⁻ being coordinated as a triply deprotonated ligand. The coordination of the ligand {L-COOEt}³⁻ in the expected fashion is also clearly confirmed by the appearance of six doublet signals with geminal coupling

	9	10		9	10
Bond Lengths					
M-O10	1.662(6)	1.659(3)	S1-C2	1.75(1)	1.746(5)
M-S1	2.290(2)	2.296(1)	C4-N5	1.35(1)	1.349(6)
M-N5	2.022(7)	2.000(4)	C62-O63	1.22(1)	1.222(6)
M–N8	2.253(6)	2.253(4)	C62-O64	1.309(9)	1.285(6)
M-064	2.078(6)	2.063(4)	C66–O67	1.20(1)	1.220(6)
M-068	2.030(7)	2.031(3)	C66–O68	1.31(1)	1.292(6)
Angles					
O10-M- S1	104.1(2)	104.5(1)	O10-M-O68	162.5(2)	162.4(1)
O10-M-N5	97.5(3)	97.0(1)	S1-M-N8	166.2(2)	165.5(1)
O10-M-N8	86.8(3)	87.2(1)	N5-M-O64	166.7(3)	167.8(1)
O10-M-O64	93.6(3)	93.7(1)	S1-M-N5	93.1(2)	92.8(1)

Table 2. Selected B	ond Lengths	(Å) and A	ngles (deg)	in [ReO	(L)] (9) and	[TcO(L)]	(10)
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Scheme 4. Reactions of H_3L -COOEt with $(NBu_4)[MOCl_4]$ (M = Re, Tc)



patterns belonging to the six methylene protons as previously discussed for complexes **9** and **10**.

Single crystals of 11 suitable for X-ray diffraction were obtained by slow diffusion of MeOH into solutions of the complex in DMSO. Figure 3 illustrates the molecular structure of 11. Selected bond lengths and angles are contained in Table 3. The structure of the analogous technetium complex is virtually the same. The metal atoms possess distorted octahedral environments; in each, one position is taken by a terminal oxido ligand and the five remaining positions are occupied by the donor atoms of $\{L-COOEt\}^{3-}$. The bond



Figure 3. Molecular structure of [ReO(L-COOEt)] (11). Hydrogen atoms were omitted for clarity.

Table 3. Selected Bond Lengths (Å) and Angles (deg) in [ReO(L-COOEt)] (11)

Re-010	1.651(8)	Re-064	2.059(6)
Re-S1	2.294(2)	Re-068	2.065(6)
Re-N5	2.047(7)	S1-C2	1.76(1)
Re-N8	2.219(7)	C4-N5	1.32(1)
O10-M-S1	105.0(3)	O10-M-O68	163.4(3)
O10-M-N5	96.9(3)	S1-M-N8	163.7(2)
O10-M-N8	87.8(3)	N5-M-O64	163.4(3)
O10-M-O64	98.3(3)	S1-M-N5	95.1(2)

lengths and angles in their molecular structures are very similar to those of 9 and 10 with minor differences in the substituted group of the thiourea moiety.

Hydrolysis of the ester $H_3L-COOEt$ in a MeOH solution of NaOH gave the salt Na₄L-COO, which was subsequently treated with the exact amount of aqueous HCl required to obtain the acidic form of the ligand, $H_3L-COOH$. The yield of the hydrolysis is almost quantitative, and no side-reactions were detected. The IR spectrum of $H_3L-COOH$ is similar to that discussed for $H_3L-COOEt$ except for a slight bathochromic shift of about 5 cm⁻¹ for the absorption band of the C==O vibrations. In the ¹H NMR spectrum of $H_3L-COOH$, the absence of resonances of the ethyl ester group is observed. The other signals appear in the same region as those in the spectrum of $H_3L-COOEt$.



Figure 4. ¹H NMR spectrum of (a) [ReO(L-COOEt)] (11) and (b) [ReO(L-COOH)] (13).

Scheme 5. Coupling Reaction of [ReO(L-COOH)] with Triglycine Ethyl Ester and Formation of 14



Like the H_3L -COOEt ligand, H_3L -COOH readily reacts with (NBu₄)[ReOCl₄] in MeOH after addition of Et₃N. This is indicated by an immediate change of the color of the reaction mixture from which a violet solid of the composition [ReO(L-COOH)] (13) was directly isolated. The amount of base, which is added, must not exceed 3 equiv of (NBu₄)[ReOCl₄], to minimize the formation of the anion [ReO(L-COO)]⁻, which is soluble in MeOH. Many attempts to obtain highquality single crystals of 13 for an X-ray structure study failed. However, the structure of 13, which is similar to that of 11, can readily be derived from the spectroscopic data.

A very broad band between $3450 \text{ and } 2500 \text{ cm}^{-1}$ remains in the IR spectrum of 13 and confirms the existence of the free carboxylic group of the thiourea site. The other structural features are similar to those of compound 11. The individual assignments of the bands are given in the Experimental Section. A part of the ¹H NMR spectra of 11 and 13 are compared in Figure 4. The ¹H NMR spectrum of 13 expectedly does not show any signals of ethyl ester protons, but reveals a broad signal at 13.24 ppm, which is typical for OH protons of carboxylic groups. The other resonances of 13 have almost the same chemical shifts as those in 11. This strongly confirms the analogous structures of the two compounds.

The additional carboxylic group in the periphery of ligand H₃L-COOH is intended to act as a linker to couple its rhenium or technetium complexes to bioactive compounds such as peptides. For this purpose, we can consider two alternative routes. In the first approach, the free ligand is coupled to a targeting compound before being treated with the (radioactive) metal ions. This approach follows the classical kitpreparation of 99mTc radiopharmaceuticals and will give "one kit-one target" solutions. In the second approach, a two-step solution, the radioactive chelate is prepared first as a "bioconjucation kit" and treated with the suitable biomolecule in a subsequent step. This, however, requires a chemically robust chelate and ideally the opportunity of an even rough separation of the preformed chelate from the bulk chelator to ensure an effective bioconjugation in the carrier-free tracer chemistry. On the other hand, such a "bioconjugation kit" would deliver a "one complex-many targets" solution on the basis of an optimized metal chelate.

The ligand system introduced in this Article is not particularly suitable for the first approach of bioconjugation, because the presence of three carboxylic groups in H_3L –COOH would require a complicated protection of those of the iminodiacetic acid site before conjugation to, for example, a peptide. For the second approach, however, the very stable

L



Figure 5. ¹H NMR spectrum of [ReO(L-TriGlyCOOEt)] (14).

metal chelate seems to be well suitable, because the iminodiacetic moiety is blocked by the formation of coordination bonds and the remaining carboxylic group of phenyl residue can selectively react with biomolecules. Thus, we undertook a "proof-of-principle" experiment. For this, a small peptide such as triglycine ethyl ester was used. The reaction of 13 and triglycine ethyl ester was done in dry DMF at room temperature with the addition of a slight excess of N,N'-dicyclohexylcarbodiimide (DCC) and N-hydroxybenzo-triazole (HOBT) to give the coupling product [ReO(L-TriGlyCOOEt)] (14) with yields of over 95% (Scheme 5).

Compound 14 is sparingly soluble in alcohol, CH_2Cl_2 , or $CHCl_3$, but soluble and stable in DMF or DMSO solutions. Good quality single crystals of 14 could not be obtained, but the structure of 14 is clearly elucidated by means of spectroscopic methods.

The IR spectrum of 14 exhibits a strong absorption at 3325 cm⁻¹ corresponding to the NH stretches of the triglycine residue. The spectral features belonging to the skeleton of the rhenium complex are identical to those in 13. The ¹H NMR spectrum of 14 (Figure 5) additionally confirms the presence of the triglycine ethyl ester by a triplet at 1.17 ppm and a quartet at 4.07 ppm belonging to ethyl ester protons, and three doublets at 3.75, 3.84, and 3.93 ppm and three triplets at 8.24, 8.29, and 8.99 ppm corresponding to the CH₂ and NH resonances, respectively. Moreover, the complex formation is clearly indicated by the presence of six doublets of the CH₂ protons of the chelate ring, which appear at 4.06 (overlapped with OCH₂ of the ethyl ester group), 4.43, 4.77, 4.89, 5.27, and 5.71 ppm with characteristic geminal coupling patterns. Additionally, the high-resolution mass spectrum of 14 shows only intense peaks at 956.1718 and 972.1576 corresponding to ions $[M + Na]^+$ (calcd 956.1699) and $[M + K]^+$ (calcd 972.1439).

CONCLUSIONS

The pentadentate H_3L is the first representative of a novel, versatile class of ligands, which are well-suited for the formation of stable complexes with rhenium(V) and technetium(V)

centers. The use of this new class of compounds in further experiments, particularly such as the synthesis of bioconjugates with ^{186,188}Re or ^{99m}Tc, is planned for the future in collaboration with partner researchers, because such studies are presently not possible in our laboratories.

ASSOCIATED CONTENT

Supporting Information

X-ray crystallographic data in CIF format. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.5b00769.

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Notes

The authors declare no competing financial interest.

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