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Pyridine−*tert*-Nitrogen−Phenol Ligands: N,N,O-Type Tripodal Chelates for the $[M(CO)_3]^+$ Core (M = Re, Tc)

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The design rationale, synthesis, and preliminary radiolabeling evaluation of new N,N,O-type pyridyl−*tert*-nitrogen−phenol ligands for the $[M(CO)_3]^+$ core, where M = ^{99m}Tc or Re, are described. The capability of the ligands to bind this technetium core is initially demonstrated by using the cold surrogate $[Re(CO)_3]^+$. NMR studies of the relevant rhenium tricarbonyl complexes indicate the formation of either a monomeric or a possible dimeric complex with each phenolic O atom bridging between two metal centers. Labeling with $[^{99m}Tc(CO)_3]^+$ provided further insight into the differences in complex formation on the dilute, no carrier added, level compared to the macroscopic scale at which the Re^{I} counterparts were made. These new tridentate, monoanionic ligands are competent chelates in binding the $[^{99m}Tc(CO)_3]^+$ core because radiolabeling yields ranged from 85 to 99% and the resulting complexes were stable to cysteine and histidine challenges for as long as 24 h.

Introduction

Interest in radiopharmaceuticals incorporating ^{99m}Tc and $^{186/188}$Re has gained significant momentum in recent years. The commonality and ideal properties of these group VII metals have made them valuable tools for diagnosis and therapy.[1] The ease of generation, isolation, and supply of ^{99m}Tc partnered with its ideal nuclear properties ($t_{1/2}$ = 6.01 h; γ = 140.5 keV) have led to its tremendous importance in single-photon emission-computed tomography; well over 85% of all diagnostic nuclear medicine scans use ^{99m}Tc in some chemical form.[2] On the other hand, rhenium (^{186}Re, $t_{1/2}$ = 3.68 days, β = 1.07 MeV, γ = 137 keV; ^{188}Re, $t_{1/2}$ = 16.98 h, β = 2.12 MeV, γ = 155 keV) has particle-emitting radioisotopes, providing a potentially useful tool for applications in therapeutic nuclear medicine.[3] Unlike ^{123}I or ^{18}F, which can be directly substituted for atoms such as hydrogen in a biomolecule, technetium and rhenium are transition metals that require chelation and "masking" as part of their incorporation.[4–10] The shared bulk properties (e.g., reactivity, affinity and preference for donor atoms) of these group VII metals make the development of ligands that could be used to provide an agent for both diagnosis (Tc) and therapy (Re) for a given condition a feasible and worthwhile goal.

The recent advances leading to the development of the aqua complex *fac*-$[^{99m}Tc(H_2O)_3(CO)_3]^+$ have stirred a plethora

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(1) Dilworth, J. R.; Parrott, S. J. *Chem. Soc. Rev.* **1998**, *27*, 43–55.
(2) Jurisson, S. S.; Lydon, J. D. *Chem. Rev.* **1999**, *99*, 2205–2218.
(3) Volkert, W. A.; Hoffman, T. J. *Chem. Rev.* **1999**, *99*, 2269–2292.
(4) Yang, D. J.; Kim, C. G.; Schechter, N. R.; Azhdarinia, A.; Yu, D. F.; Oh, C. S.; Bryant, J. L.; Won, J. J.; Kim, E. E.; Podoloff, D. A. *Radiology* **2003**, *226*, 465–473.
(5) Rollo, F. D.; Bryant, J.; Yang, D. J.; Bai, C.; Kim, E. E.; Yu, D. F.; Ye, J.; Da Silva, A. J.; Durbin, M. K.; Garrard, J.; Shao, L. 51st Society for Nuclear Medicine Annual Meeting. *Journal of Nuclear Medicine*; Society of Nuclear Medicine: Reston, VA, 2004; Vol. *45*, p 336p (No. 1062).
(6) Schraml, F. V.; Beason-Held, L. L.; Fletcher, D. W.; Brown, B. P. *J. Cereb. Blood Flow Metab.* **2006**, *26*, 321–329.
(7) Banerjee, S. R.; Maresca, K. P.; Francesconi, L.; Valliant, J.; Babich, J. W.; Zubieta, J. *Nucl. Med. Biol.* **2005**, *32*, 1–20.
(8) Jaouen, G.; Top, S.; Vessieres, A.; Alberto, R. *J. Organomet. Chem.* **2000**, 23–36.
(9) Schibli, R.; Schubiger, P. A. *Eur. J. Nucl. Med.* **2002**, *29*, 1529–1542.
(10) Liu, S. *Chem. Soc. Rev.* **2004**, *33*, 445–461.
(11) Stichelberger, A.; Waibel, R.; Dumas, C.; Schubiger, P. A.; Schibli, R. *Nucl. Med. Biol.* **2003**, *30*, 465–470.
(12) Ferreira, C. L.; Bayly, S. R.; Green, D. E.; Storr, T.; Barta, C. A.; Steele, J.; Adam, M. J.; Orvig, C. *Bioconjugate Chem.* **2006**, *17*, 1321–1329.
(13) James, S.; Maresca, K. P.; Babich, J. W.; Valliant, J. F.; Doering, L.; Zubieta, J. *Bioconjugate Chem.* **2006**, *17*, 590–596.

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of research utilizing this core for imaging.[11–30] It is easily prepared from a kit (Isolink, Mallinckrodt Inc.) under aqueous conditions using a boranocarbonate anion as the reducing agent and an in situ CO source.[31,32] The three labile water molecules are easily exchanged for suitable chelates in a *fac* arrangement. Examples of bioconjugates ranging from derivatized amino acids,[14] carbohydrates,[27] peptides,[11,28,33] nucleosides,[21] and others[18,25,34,35] have been investigated to fine-tune the targeting, improve the biodistribution properties, and increase the clearance from blood pools and organs of the resulting radiotracers.

Technetium-based radiotracers can be classified as technetium-essential and technetium-tagged.[7] Technetium-essential are tracers wherein the metal plays a predefined role in the fate of the biomolecule, e.g., the Tc^{I} core in the hexakis(methoxyisobutylisonitrile) complexes of $[Tc(CNR)_6]^+$.[36] This monocationic complex has a lipophilic

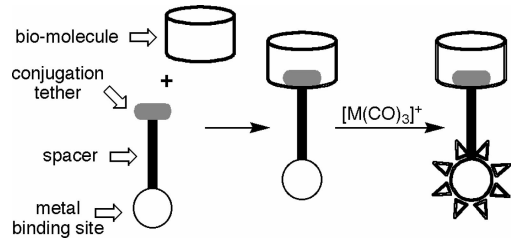


Figure 1. Bioconjugate radiotracer construction.

outer coordination sphere that enables it to penetrate the heart muscle and be retained. Without the technetium binding these six ligands together, the complex would not exist, let alone exhibit its characteristic biodistribution. Technetium-tagged tracers, on the other hand, incorporate a biomolecule that displays a particular affinity for a biological target in the absence of technetium or rhenium. Most of the tracers designed for the $[^{99m}Tc(H_2O)_3(CO)_3]^+$ core utilize this latter concept.

Designs of technetium-tagged tracers, though seemingly elaborate, have similar core constructions (Figure 1). These constructions are composed of a biomolecule, a spacer, and a chelator. A judicious choice of the metal binding pocket is vital to ensure that the complex remains intact in vivo.[37] For example, bidentate ligands for the tricarbonyl core have shown only moderate stability due to ligand exchange and, consequently, exhibit poor clearance in vivo, likely due to the binding of the unsaturated metal center to plasma protein.[12,19,22] Tridentate (neutral, monoprotic, and diprotic) ligands producing more strongly bound (respectively monocationic, neutral, and monoanionic) complexes have fared much better.[11,16,19,23,24,26,28,38–41]

Several functionalities with differing donor atoms have been incorporated into tridentate ligands for the $[^{99m}Tc(H_2O)_3(CO)_3]^+$ core.[11,15–17,19–21,23,28,30,31,39–48] The list includes nitrogen donors such as alkyl and aromatic amines (pyridine, imidazole, and pyrazole), phosphorus donors such as phosphines, sulfur donors such as thiols, thioethers, thiophenes, dithiocarboxylates, and thiones, and oxygen donors such as alcohols and carboxylates. It has been suggested, however, that the ideal donor set should contain an aromatic amine in combination

(14) James, S.; Maresca, K. P.; Allis, D. G.; Valliant, J. F.; Eckelman, W.; Babich, J. W.; Zubieta, J. *Bioconjugate Chem.* **2006**, *17*, 579–589.
(15) Allali, M.; Cousinié, S.; Gressier, M.; Tessier, C.; Beauchamp, A. L.; Coulais, Y.; Dartiguenave, M.; Benoist, E. *Inorg. Chim. Acta* **2006**, *359*, 2128–2134.
(16) Rattat, D.; Eraets, K.; Cleynhens, B.; Knight, H.; Fonge, H.; Verbruggen, A. *Tetrahedron Lett.* **2004**, *45*, 2531–2534.
(17) Storr, T.; Sugai, Y.; Barta, C. A.; Mikata, Y.; Adam, M. J.; Yano, S.; Orvig, C. *Inorg. Chem.* **2005**, *44*, 2698–2705.
(18) Alberto, R.; Schibli, R.; Schubiger, A. P.; Abram, U.; Pietzsch, H. J.; Johannsen, B. *J. Am. Chem. Soc.* **1999**, *121*, 6076–6077.
(19) Schibli, R.; La Bella, R.; Alberto, R.; Garcia-Garayoa, E.; Ortner, K.; Abram, U.; Schubiger, P. A. *Bioconjugate Chem.* **2000**, *11*, 345–351.
(20) La Bella, R.; Garcia-Garayoa, E.; Bahler, M.; Blauenstein, P.; Schibli, R.; Conrath, P.; Tourwe, D.; Schubiger, P. A. *Bioconjugate Chem.* **2002**, *13*, 599–604.
(21) Schibli, R.; Netter, M.; Scapozza, L.; Birringer, M.; Schelling, P.; Dumas, C.; Schoch, J.; Schubiger, P. A. *J. Organomet. Chem.* **2003**, *668*, 67–74.
(22) Bayly, S. R.; Fisher, C. L.; Storr, T.; Adam, M. J.; Orvig, C. *Bioconjugate Chem.* **2004**, *15*, 923–926.
(23) Liu, G.; Dou, S.; He, J.; Vanderheyden, J.-L.; Rusckowski, M.; Hnatowich, D. J. *Bioconjugate Chem.* **2004**, *15*, 1441–1446.
(24) Stephenson, K. A.; Banerjee, S. R.; Besanger, T.; Sogbein, O. O.; Levadala, M. K.; McFarlane, N.; Lemon, J. A.; Boreham, D. R.; Maresca, K. P.; Brennan, J. D.; Babich, J. W.; Zubieta, J.; Valliant, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 8598–8599.
(25) van Staveren, D. R.; Waibel, R.; Mundwiler, S.; August Schubiger, P.; Alberto, R. *J. Organomet. Chem.* **2004**, *689*, 4803–4810.
(26) van Staveren, D. R.; Mundwiler, S.; Hoffmanns, U.; Pak, J. K.; Spingler, B.; Metzler-Nolte, N.; Alberto, R. *Org. Biomol. Chem.* **2004**, *2*, 2593–2603.
(27) Schibli, R.; Dumas, C.; Petrig, J.; Spadola, L.; Scapozza, L.; Garcia-Garayoa, E.; Schubiger, P. A. *Bioconjugate Chem.* **2005**, *16*, 105–112.
(28) Alves, S.; Paulo, A.; Correia, J. D. G.; Gano, L.; Smith, C. J.; Hoffman, T. J.; Santos, I. *Bioconjugate Chem.* **2005**, *16*, 438–449.
(29) Banerjee, S. R.; Schaffer, P.; Babich, J. W.; Valliant, J. F.; Zubieta, J. *Dalton Trans.* **2005**, 3886–3897.
(30) van Staveren, D. R.; Benny, P. D.; Waibel, R.; Kurz, P.; Pak, J.-K.; Alberto, R. *Helv. Chim. Acta* **2005**, *88*, 447–460.
(31) Alberto, R.; Schibli, R.; Egli, A.; Schubiger, A. P.; Abram, U.; Kaden, T. A. *J. Am. Chem. Soc.* **1998**, *120*, 7987–7988.
(32) Satpati, D.; Mallia, M.; Kothari, K.; Pillai, M. R. A. *J. Label. Compd. Radiopharm.* **2004**, *47*, 657–668.
(33) Harris, T. D.; Kalogeropoulos, S.; Nguyen, T.; Dwyer, G.; Edwards, D. S.; Liu, S.; Bartis, J.; Ellars, C.; Onthank, D.; Yalamanchili, P.; Heminway, S.; Robinson, S.; Lazewatsky, J.; Barrett, J. *Bioconjugate Chem.* **2006**, *17*, 1294–1313.
(34) Müller, C.; Schubiger, P. A.; Schibli, R. *Bioconjugate Chem.* **2006**, *17*, 797–806.
(35) Yigit, U. S.; Lambrecht, F. Y.; Ünak, P.; Biber, F. Z.; Medine, E. I.; Çetinkaya, B. *Chem. Pharm. Bull.* **2006**, *54*, 1–3.
(36) Prats, E.; Aisa, F.; Abós, M. D.; Villavieja, L.; García-López, F.; Asenjo, M. J.; Razola, P.; Banzo, J. *J. Nucl. Med.* **1999**, *40*, 296–301.
(37) Alberto, R.; Pak, J. K.; van Staveren, D. R.; Mundwiler, S.; Benny, P. *Biopolymers* **2004**, *76*, 324–333.
(38) Petrig, J.; Schibli, R.; Dumas, C.; Alberto, R.; Schubiger, P. A. *Chem.—Eur. J.* **2001**, *7*, 1868–1873.
(39) Vitor, R. F.; Alves, S.; Correia, J. D. G.; Paulo, A.; Santos, I. *J. Organomet. Chem.* **2004**, *689*, 4764–4774.
(40) Storr, T.; Fisher, C. L.; Mikata, Y.; Yano, S.; Adam, M. J.; Orvig, C. *Dalton Trans.* **2005**, 654–655.
(41) Lazarova, N.; Babich, J.; Valliant, J.; Schaffer, P.; James, S.; Zubieta, J. *Inorg. Chem.* **2005**, *44*, 6763–6770.
(42) Banerjee, S. R.; Levadala, M. K.; Lazarova, N.; Wei, L. H.; Valliant, J. F.; Stephenson, K. A.; Babich, J. W.; Maresca, K. P.; Zubieta, J. *Inorg. Chem.* **2002**, *41*, 6417–6425.
(43) Banerjee, S. R.; Babich, J. W.; Zubieta, J. *Inorg. Chem. Commun.* **2004**, *7*, 481–484.
(44) Palma, E.; Correia, J. D. G.; Domingos, A.; Santos, I.; Alberto, R.; Spies, H. *J. Organomet. Chem.* **2004**, *689*, 4811–4819.
(45) Levadala, M. K.; Banerjee, S. R.; Maresca, K. P.; Babich, J. W.; Zubieta, J. *Synthesis* **2004**, 1759–1766.
(46) Karagiorgou, O.; Patsis, G.; Pelecanou, M.; Raptopoulou, C. P.; Terzis, A.; Siatra-Papastaikoudi, T.; Alberto, R.; Pirmettis, I.; Papadopoulos, M. *Inorg. Chem.* **2005**, *44*, 4118–4120.
(47) Mundwiler, S.; Waibel, R.; Spingler, B.; Kunze, S.; Alberto, R. *Nucl. Med. Biol.* **2005**, *32*, 473–484.

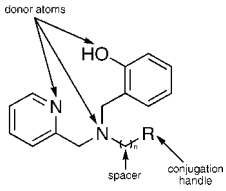


Figure 2. Tridentate monoprotic ligands.

with other donors such as a tertiary amine and a monoprotic ligand such as a carboxylic acid.[19] This will enable the formation of a neutral complex with $[^{99m}Tc(CO)_3]^+$. It is surprising, then, that a phenol-type ($pK_a = \sim 9.95$) ligand, which can deprotonate upon coordination to a metal, combined with a tertiary amine and an aromatic amine, has, to our knowledge, not been studied extensively with this core, with the only report coming from our laboratory and involving a bidentate analogue.[22] Reports on the utilization of phenols to bind rhenium have been limited to its incorporation into bidentate ligands: 2-(1-methyl-*H*-benzoimidazol-2-yl)phenol, 2-benzothiazol-2-ylphenol, and 2-benzoxazol-2-ylphenol, and the N_2O_2 and N_2O tripodal coordination of Re^V.[49–51] In this regard, we have investigated the potential of phenol-based donors for the $[M(CO)_3]^+$ core. The versatility of our approach complements the excellent work of Schibli and co-workers on tailor-made bifunctional chelating agents.[11] Our approach to tridentate chelation is to combine pyridine and tertiary nitrogen atoms with a phenol as donors (Figure 2). As for future construction of bioconjugates, the synthesis lends itself to conjugation by providing an easily manipulated functional group such as a primary amine, cyano, or terminal alkene (R groups in Figure 2). The initial evaluation of these promising chelates and their complexes are presented.

Experimental Section

Instruments and Materials. All solvents and reagents were used as received. $Re(CO)_5Br$ is commercially available (Strem). $[Re(H_2O)_3(CO)_3]Br$,[52] *tert*-butyl (2-aminoethyl)carbamate (**2a**),[53] *tert*-butyl (3-aminopropyl)carbamate (**2b**),[54] and 2-[(pyridin-2-ylmethylamino)methyl]phenol (**7**)[55] were prepared as previously described.

The analytical thin-layer chromatography (TLC) plates were aluminum-backed ultrapure silica gel 60, 250 μm; the glass-backed preparative TLC, 1000 μm, and the flash column silica gel (standard grade, 60 Å, 32–63 mm) used were provided by Silicycle. ^{1}H and ^{13}C NMR, ^{13}C NMR APT, 2D ^{1}H−^{1}H COSY, and ^{1}H−^{13}C HMQC spectra were recorded on Bruker AV300, AV400, or DRX400 instruments; the NMR spectra are expressed on the δ scale and were referenced to residual solvent peaks or internal tetramethylsilane. IR spectra were recorded on a Nicolet 4700 FT-IR (Fourier transform infrared) spectrophotometer in transmission mode as KBr disks between 400 and 4000 cm^{-1} at a resolution of ±4 cm^{-1}. Melting points were measured using a Mel-Temp apparatus by Laboratory Devices, Cambridge, MA, and were uncorrected. Electrospray ionization mass spectrometry (ESI-MS) spectra were recorded on a Micromass LCT instrument at the Department of Chemistry, University of British Columbia. High-resolution mass spectra (Micromass LCT TOFMS) and elemental analysis (Carlo Erba analytical instrument) were provided by the Analytical Services Facility, Department of Chemistry, University of British Columbia. High-performance liquid chromatography (HPLC) analysis of cold compounds was done on a Phenomenex Synergi 4 μm Hydro-RP 80A column (250 × 4.6 mm) in a Waters WE 600 HPLC system equipped with a 2478 dual-wavelength absorbance UV detector run using the *Empower* software package. HPLC analyses of radiolabeled complexes were performed on a Knauer Wellchrom K-1001 HPLC equipped with a K-2501 absorption detector and a Capintec radiometric well counter. A Phenomenex Hydro-Synergi 4 μm C18 RP analytical column with dimensions of 250 × 4.6 mm was used. The purity of the novel compounds was assessed by elemental analysis. Their identities were confirmed by ^{1}H and ^{13}C NMR spectroscopy (^{1}H and ^{13}C NMR spectra of all final ligands and complexes are shown in the Supporting Information).

***tert*-Butyl [2-[(Pyridin-2-ylmethyl)amino]ethyl]carbamate (3a).** To a solution of **2a** (2.08 g, 12.96 mmol) in $ClCH_2CH_2Cl$ (100 mL) was added 2-pyridinecarboxaldehyde (1.24 mL, 12.98 mmol). The resulting solution was stirred at ambient temperature for 1 h followed by the addition of $NaBH(OAc)_3$ (5.50 g, 26 mmol). The mixture was further stirred at ambient temperature for 16 h and subsequently quenched with saturated Na_2CO_3 (50 mL). The resulting mixture was partitioned and the aqueous layer extracted with CH_2Cl_2 (2 × 75 mL). The organic layers were combined, washed with brine (75 mL), and dried over $MgSO_4$. Filtration of the drying agent was followed by rotary evaporation of the filtrate to yield crude **3a**. Column chromatography (silica−CH_2Cl_2/5% MeOH to CH_2Cl_2/10% MeOH) was used to isolate and purify **3a** as an oil (1.14 g, 35% yield): $R_f = 0.28$ (silica−CH_2Cl_2/10% MeOH). ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 8.50 (d, $J = 4.0$ Hz, 1H), 7.53 (t, $J = 7.6$ Hz, 1H), 7.42 (d, $J = 8.0$ Hz, 1H), 7.25 (d, $J = 6.6$ Hz, 1H), 6.79 (br t, $J = 5.2$ Hz, 1H), 3.84 (s, 2H), 3.06 (q, $J = 6.0$ Hz, 2H), 2.61 (t, $J = 6.4$ Hz, 2H) 1.37 (s, 9H). ^{13}C NMR (DMSO-d_6, 100 MHz, D1 = 1.5 s, δ): 159.3, 155.6, 148.7, 136.5, 122.0, 121.9, 77.6, 53.8, 48.3, 39.6, 28.2. IR (NaCl, cm^{-1}): 3319 (br), 2976 (br), 1722 (s), 1143 (m) 870 (m), 761 (m). MS (ES$^+$, 100% CH_3CN, 30 V): *m*/*z* 252 (MH^+). HR-MS (ES$^+$ of MH^+). Calcd for $C_{13}H_{22}N_3O_2$: *m*/*z* 252.1712. Found: *m*/*z* 252.1702.

***tert*-Butyl [3-[(Pyridin-2-ylmethyl)amino]propyl]carbamate (3b). 3b** was prepared from **2b** and 2-pyridinecarboxaldehyde as an oil in 47% yield as described for **3a**: $R_f = 0.24$ (silica−CH_2Cl_2/10% MeOH). ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 8.47 (d, $J = 4.0$ Hz, 1H), 7.73 (t, $J = 7.6$ Hz, 1H), 7.41 (d, $J = 7.8$ Hz, 1H), 7.22 (d, $J = 6.2$ Hz, 1H), 6.79 (br t, $J = 4.7$ Hz, 1H), 3.75 (s, 2H), 2.96 (q, $J = 6.1$ Hz, 2H), 2.51–2.32 (m, 2H), 1.53 (m, 2H), 1.36 (s, 9H). ^{13}C NMR (DMSO-d_6, 100 MHz, D1 = 1.5 s, δ): 160.5, 156.0, 149.1, 136.8, 122.3, 122.1, 77.7, 54.8, 46.7, 38.5, 30.1, 28.7. IR (NaCl, cm^{-1}): 3335 (br), 3005 (br), 2975 (br), 2931 (br), 1713 (s), 1592 (m), 1531 (m), 1365 (m), 1275 (m), 1252 (m), 1169 (m), 759

(48) Wei, L.; Babich, J.; Zubieta, J. *Inorg. Chim. Acta* **2005**, *358*, 3691–3700.
(49) Czerwieniec, R.; Kapturkiewicz, A.; Anulewicz-Ostrowska, R.; Nowacki, J. *J. Chem. Soc., Dalton Trans.* **2002**, 3434–3441.
(50) Abrahams, A.; Cowley, A. R.; Gerber, T. I. A.; Imrie, C.; Mayer, P. *J. Coord. Chem.* **2003**, *56*, 1299–1306.
(51) Mondal, A.; Sarkar, S.; Chopra, D.; Guru Row, T. N.; Rajak, K. K. *Dalton Trans.* **2004**, 3244–3250.
(52) Lazarova, N.; James, S.; Babich, J.; Zubieta, J. *Inorg. Chem. Commun.* **2004**, *7*, 1023–1026.
(53) Eisenfuhr, A.; Arora, P. S.; Sengle, G.; Takaoka, L. R.; Nowick, J. S.; Famulok, M. *Bioorg. Med. Chem.* **2003**, *11*, 235–249.
(54) Montero, A.; Goya, P.; Jagerovic, N.; Callado, L. F.; Meana, J. J.; Giron, R.; Goicoechea, C.; Martin, M. I. *Bioorg. Med. Chem.* **2002**, *10*, 1009–1018.
(55) Johansson, A.; Abrahamsson, M.; Magnuson, A.; Huang, P.; Martensson, J.; Styring, S.; Hammarstrom, L.; Sun, L. C.; Akermark, B. *Inorg. Chem.* **2003**, *42*, 7502–7511.

(m). MS (ES^+, 100% CH_3CN, 30 V): *m/z* 266 (MH^+). HR-MS (ES^+ of MH^+). Calcd for $C_{14}H_{24}N_3O_2$: *m/z* 266.1869. Found: *m/z* 266.1872.

***tert*-Butyl [2-[(2-Hydroxybenzyl)(pyridin-2-ylmethyl)amino] ethyl]carbamate (4a).** To **3a** (0.70 g, 2.79 mmol), dissolved in $ClCH_2CH_2Cl$ (40 mL), was added salicylaldehyde (0.32 mL, 3 mmol). After stirring at ambient temperature for 0.5 h, $NaBH(OAc)_3$ (1.18 g, 4.72 mmol) was then added. The resulting mixture was further stirred at ambient temperature overnight and quenched with saturated Na_2CO_3 (30 mL). The mixture was then partitioned and the aqueous layer further extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extract was washed with brine (20 mL) and dried with $MgSO_4$. After filtration of the drying agent, the filtrate was taken to dryness by rotary evaporation to yield crude **4a**. Column chromatography (silica−CH_2Cl_2/5% MeOH) was used to isolate and purify **4a** as an oil (0.79 g, 80% yield). R_f = 0.21 (silica−CH_2Cl_2/5% MeOH). ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 10.19 (br s, 1H), 8.51 (d, J = 4.8 Hz, 1H), 7.77 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 7.28 (t, J = 6.8 Hz, 1H), 7.16 (d, J = 7.2 Hz, 1H), 7.08 (t, J = 8.4, 1H), 6.78–6.72 (m, 3H), 3.84 (s, 2H), 3.79 (s, 2H), 3.08 (dd, J = 6.4 Hz, 2H), 2.52 (t, J = 6.8 Hz, 2H), 1.35 (s, 9H). ^{13}C NMR (DMSO-d_6, 100 MHz, D1 = 1.5 s, δ): 158.3, 156.6, 155.5, 148.7, 136.7, 129.6, 128.1, 123.5, 123.0, 122.3, 118.7, 115.4, 77.5, 58.7, 54.5, 52.8, 37.5, 28.2. IR (NaCl, cm^{-1}): 3350 (br), 2976 (br), 1714 (s), 1592 (m), 1519 (m), 1504 (m), 1366 (m), 1252 (m), 1150 (m), 1037 (m), 965 (m), 870 (m), 757 (s). MS (ES^+, 100% CH_3CN, 30 V): *m/z* 358 (MH^+). HR-MS (ES^+ of MH^+). Calcd for $C_{20}H_{28}N_3O_3$: *m/z* 358.2131. Found: *m/z* 358.2117.

***tert*-Butyl 3-[(2-Hydroxybenzyl)(pyridin-2-ylmethyl)amino] propyl carbamate (4b). 4b** was prepared as an oil in 72% yield from **3b** and salicylaldehyde as described for **4a**. Column chromatography (silica−CH_2Cl_2/10% CH_3CN to CH_2Cl_2/20% CH_3CN); R_f = 0.23 (silica−CH_2Cl_2/10% CH_3CN). ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 10.40 (br s, 1H), 8.52 (d, J = 4.0 Hz, 1H), 7.78 (t, J = 7.8 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.29 (m, 1H), 7.13 (d, J = 7.2 Hz, 1H), 7.08 (t, J = 8.0 Hz, 1H), 6.75–6.67 (m, 3H), 3.74 (s, 2H), 3.64 (s, 2H), 2.85 (q, J = 6.4 Hz, 2H), 2.44 (t, J = 7.6 Hz, 2H), 1.61 (p, J = 7.2 Hz, 2H), 1.33 (s, 9H). ^{13}C NMR (DMSO-d_6, 100 MHz, D1 = 1.5 s, δ): 158.2, 156.7, 155.4, 148.8, 136.8, 129.4, 128.1, 123.4, 123.0, 122.3, 118.6, 115.4, 77.3, 58.5, 54.8, 50.6, 38.1, 28.2, 26.4. IR (NaCl, cm^{-1}): 3347 (br), 2974 (br), 2930 (br), 1710 (s), 1589 (m), 1513 (m), 1489 (m), 1365 (m), 1251 (s), 1168 (s), 756 (s). MS (ES^+, 100% CH_3CN, 30 V): *m/z* 372(MH^+). HR-MS (ES^+ of MH^+). Calcd for $C_{21}H_{30}N_3O_3$: *m/z* 372.2287. Found: *m/z* 372.2284.

2-{[(2-Aminoethyl)(pyridin-2-ylmethyl)amino]methyl}phenol (5a). To **4a** (0.67 g, 1.87 mmol) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (TFA; 5 mL). After stirring at ambient temperature overnight, the solution was evaporated to dryness and the oily residue was retaken up in saturated $NaHCO_3$ (∼30 mL) until the pH was basic to litmus. The aqueous phase was then extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extract was washed with brine (15 mL), dried over $MgSO_4$, and filtered. The resulting filtrate was taken to dryness by rotary evaporation to yield crude **5a**. Column chromatography (silica−CH_2Cl_2/5% MeOH, CH_2Cl_2/10% MeOH, to CH_2Cl_2/20% MeOH) was used to isolate and purify **5a** as a white solid (0.17 g, 35% yield): R_f = 0.64 (silica−CH_2Cl_2/20% MeOH). Mp: 118–120 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 8.53 (d, J = 4.4 Hz, 1H), 8.24 (br, 2H), 7.78 (t, J = 7.6 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.30 (t, J = 6.4 Hz, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.75 (t, J = 7.2 Hz, 1H), 3.79 (s, 2H), 3.68 (s, 2H), 2.95 (t, J = 6.8 Hz, 2H), 2.72 (t, J = 6.8 Hz, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz, D1 = 1.5 s, δ): 158.4, 156.1, 148.7, 136.8, 130.4, 128.2, 123.5, 123.0, 122.3, 118.8, 115.4, 58.2, 52.9, 50.4, 36.6. IR (KBr, cm^{-1}): 3439 (br), 3059 (br), 2941 (br), 2883 (br), 2832 (br), 1691 (s), 1601 (s), 1458 (s), 1438 (m), 1272 (s), 1198 (s), 1169 (s), 1131(s), 831 (m), 796 (m), 767 (s), 721 (m). MS (ES^+, 100% MeOH, 30 V): *m/z* 258 (MH^+). HR-MS (ES^+ of MH^+). Calcd for $C_{15}H_{20}N_3O$: *m/z* 258.1606. Found: *m/z* 258.1609.

2-{[(3-Aminopropyl)(pyridin-2-ylmethyl)amino]methyl}phenol (5b). 5b was prepared in 92% yield (0.18 g) from **4b** and TFA as a white solid (0.27 g, 0.71 mmol) as described for **5a**. Column chromatography (silica−CH_2Cl_2/10% MeOH); R_f = 0.18 (silica−CH_2Cl_2/10% MeOH). Mp: 96–99 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 8.93 (br, 2H), 8.53 (d, J = 4.4 Hz, 1H), 7.80 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 6.4 Hz, 1H), 7.16 (d, J = 6.6 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 6.79–6.73 (m, 2H), 3.76 (s, 2H), 3.63 (s, 2H), 2.73 (t, J = 7.2 Hz, 2H), 2.53 (t, J = 6.8 Hz, 2H), 1.78 (p, J = 7.2 Hz, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz, D1 = 1.5 s, δ): 158.2, 156.4, 148.8, 137.0, 130.0, 128.3, 123.5, 123.1, 122.4, 118.7, 115.5, 58.3, 53.8, 50.6, 37.9, 24.1. IR (KBr, cm^{-1}): 3443 (br), 3057 (br), 2930 (br), 2826 (br), 1685 (s), 1671 (s), 1602 (s), 1463 (m), 1199 (s), 1175 (s), 1128 (s), 769 (s), 721 (m). MS (ES^+, 100% MeOH, 30 V): *m/z* 272 (MH^+). HR-MS (ES^+ of MH^+). Calcd for $C_{16}H_{22}N_3O$: *m/z* 272.1763. Found: *m/z* 272.1761.

2-{[Allyl(pyridin-2-ylmethyl)amino]methyl}phenol (8). 2-{[(Pyridin-2-ylmethyl)amino]methyl}phenol (**7**; 0.70 g, 3.27 mmol) was dissolved in CH_3CN (10 mL); Na_2CO_3 (2.77 g, 26.14 mmol) and allyl bromide (0.58 mL, 6.74 mmol) were added, and the mixture was stirred at ambient temperature under N_2 for 24 h. The solid was filtered from the reaction mixture and the filtrate reduced to dryness by rotary evaporation. Column chromatography (silica−CH_2Cl_2/1% MeOH) was used to isolate and purify **8** (0.62 g, 75% yield) as an oil: R_f = 0.20 (silica−CH_2Cl_2/1% MeOH). ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 10.36 (br s, 1H), 8.53 (d, J = 5.2 Hz, 1H), 7.79 (t, J = 7.6 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.29 (t, J = 6.6 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 6.76–6.73 (m, 2H), 5.94–5.84 (m, 1H), 5.23–5.16 (m, 2H), 3.76 (s, 2H), 3.65 (s, 2H), 3.09 (d, J = 6.4 Hz, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz, D1 = 1.0 s, δ): 158.2, 156.8, 148.8, 136.8, 134.4, 129.5, 128.2, 123.2, 122.9, 122.3, 118.7, 118.4, 115.5, 58.2, 55.4, 54.1. IR (NaCl, cm^{-1}): 3073 (br), 1643 (m), 1615 (s), 1589 (s), 1571 (s), 1488 (s), 1435 (m), 1245 (m), 1036 (m), 997 (m), 980 (m), 927 (m), 756 (m). MS (ES^+, 100% MeOH, 30 V): *m/z* 255 (MH^+). HR-MS (ES^+ of MH^+). Calcd for $C_{16}H_{18}N_2O$: *m/z* 255.1497. Found: *m/z* 255.1499.

3-[(2-Hydroxybenzyl)(pyridin-2-ylmethyl)amino]propanenitrile (9). 7 (1.02 g, 4.78 mmol) was dissolved in CH_3CN (25 mL). 1,4-Diazabicyclo[2.2.2]octane (DABCO; 0.54 g, 4.80 mmol) and 3-bromopropionitrile (0.40 mL, 4.80 mmol) were added, and the mixture was stirred under reflux for 5 days. The solution was taken to dryness by rotary evaporation. Column chromatography (silica−EtOAc) was used to isolate and purify **9** as an oil (0.63 g, 49% yield): R_f = 0.67 (silica−EtOAc). ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 9.84 (s, 1H), 8.52 (d, J = 4.4 Hz, 1H), 7.80 (t, J = 7.6 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.30–7.25 (m, 2H), 7.09 (t, J = 7.6 Hz, 1H), 6.79–6.75 (m, 2H), 3.81 (s, 2H), 3.67 (s, 2H), 2.74 (s, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz, D1 = 2.0 s, δ): 158.3, 156.2, 148.7, 136.8, 130.0, 128.2, 123.4, 122.8, 122.3, 119.8, 118.8, 115.4, 58.2, 52.4, 48.3, 14.9. IR (NaCl, cm^{-1}): 3072 (br), 2845 (br), 2721 (br), 2247 (s), 1615 (s), 1593 (s), 1573 (s), 1494 (m), 1240 (m), 1150 (m), 1124 (m), 1095 (m), 1038 (s), 1006 (s), 980 (s), 751

(m). MS (ES^+, 100% MeOH, 30V): *m/z* 290 (MNa^+). HR-MS (ES^+ of MNa^+). Calcd for $C_{16}H_{17}N_3ONa$: *m/z* 290.1269. Found: *m/z* 290.1268.

General Procedure for the Synthesis of $LRe(CO)_3$ Complexes. Method A. Equivalent amounts of ligand and $[Re(H_2O)_3(CO)_3]Br$ in MeOH were stirred under reflux conditions for 24 h. The solvent was then removed by rotary evaporation, and the pure complex was isolated by either column chromatography or preparative TLC.

Method B. To 1 mmol of ligand in ethanol was added 3 equiv of NaOEt, and the reaction mixture was stirred at ambient temperature for 0.5 h. An equimolar amount of $[Re(H_2O)_3(CO)_3]Br$ was then added and stirred under reflux conditions for 24 h. Rotary evaporation of the solvent afforded the crude complex, which was purified by preparative TLC or column chromatography.

Synthesis of 5a-Re(CO)$_3$. The reaction was performed in 3 mL of MeOH, and the product was isolated as a white solid (0.064 g, 80% yield) by method A, column chromatography (silica−CH_2Cl_2/10% MeOH), or after reaction in 1.5 mL of EtOH (0.024 g, 59% yield) by method B, preparative TLC (silica−CH_2Cl_2/10% MeOH). $R_f = 0.72$ (silica−CH_2Cl_2/20% MeOH). Mp: 227–231 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 8.74 (d, $J = 5.2$ Hz, 1H), 8.09 (t, $J = 7.6$ Hz, 1H), 7.68 (d, $J = 7.6$ Hz, 1H), 7.58–7.53 (m, 2H), 7.30 (t, $J = 7.8$ Hz, 1H), 6.98 (d, $J = 8.0$ Hz, 1H), 6.92 (t, $J = 7.2$ Hz, 1H), 5.67–5.64 (m, 1H), 4.92 (d, $J = 16$ Hz, 1H), 4.73 (d, $J = 13.6$ Hz, 1H), 4.58 (d, $J = 13.6$ Hz, 1H), 4.56 (m, 1H), 4.41 (d, $J = 16.4$ Hz, 1H), 3.13–3.09 (m, 1H), 2.92–2.90 (m, 1H), 2.46–2.45 (m, 1H), 2.25–2.20 (m, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz, D1 = 2 s, δ): 196.9, 196.1, 195.2, 160.9, 156.8, 153.5, 140.8, 134.2, 131.2, 126.0, 123.7, 119.7, 118.7, 116.1, 65.8, 62.3, 57.4, 43.9. IR (KBr, cm^{-1}): 3448 (br, w), 3187 (br, w), 3103 (br, w), 2026 (s), 1910 (s), 1608 (m), 1457 (m), 762 (m). MS (ES^+, 100% MeOH, 30 V): *m/z* 526 ($M - {}^{185}ReH^+$), 528 ($M - {}^{187}ReH^+$). HR-MS (ES^+ of $M - {}^{187}ReH^+$). Calcd for $C_{18}H_{19}N_3O_4{}^{187}Re$: *m/z* 528.0933. Found: *m/z* 528.0934.

Synthesis of 5b-Re(CO)$_3$. Following a reaction in 3 mL of MeOH, the product was isolated as a white solid (0.072 g, 72% yield) by method A, column chromatography (silica−CH_2Cl_2/10% MeOH). $R_f = 0.48$ (silica−CH_2Cl_2/20% MeOH). Mp: 217–220 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 8.68 (d, $J = 4.8$ Hz, 1H), 7.94 (br t, J =6.8 Hz, 1H), 7.84 (br s, 2H, exchanges with D_2O), 7.48 (br d, $J = 4.0$ Hz, 1H), 7.41 (br t, $J = 5.6$ Hz, 1H), 6.93 (d, $J = 7.2$ Hz, 1H), 6.88 (t, $J = 7.2$ Hz, 1H), 6.33–6.30 (m, 2H), 4.60 (d, $J = 15.6$ Hz, 1H), 4.48 (d, $J = 15.6$ Hz, 1H), 3.65 (br d, $J = 12$ Hz, 1H), 3.58 (br t, $J = 11.6$ Hz, 1H), 3.38 (q, $J = 6.8$ Hz, 2H), 2.93 (m, 2H), 2.28 (m, 1H), 2.07 (m, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz, D1 = 20 s, LB = 5 Hz, δ): 198.7, 197.1, 196.2, 166.4, 160.4, 151.9, 140.0, 130.3, 130.2, 125.3, 124.2, 123.3, 118.5, 115.2, 64.7, 61.5, 56.4, 36.9, 22.2. IR (KBr, cm^{-1}): 3448 (br, w), 2948 (br, w), 2014 (s), 1890 (s), 1482 (m), 1264 (m), 771 (m). MS (ES^+, 100% CH_3CN, 30V): *m/z* 540 ($M - {}^{185}ReH^+$), 542 ($M - {}^{187}ReH^+$). HR-MS (ES^+ of $M - {}^{185}ReH^+$). Calcd for $C_{19}H_{21}N_3O_4{}^{185}Re$: *m/z* 540.1062. Found: *m/z* 540.1057.

Synthesis of 7-Re(CO)$_3$. After reaction in 1 mL of EtOH, the product was isolated as a white solid (0.033 g, 72% yield) by method B, column chromatography (silica−CH_2Cl_2/5% MeOH). $R_f = 0.48$ (silica−CH_2Cl_2/10% MeOH). Mp: 217–220 °C. ^{1}H NMR (MeOH-d_4, 400 MHz, 25 °C, δ): 8.63 (d, $J = 5.3$ Hz, 1H), 7.60 (td, $J = 7.8$ and 1.5 Hz, 1H), 7.15 (t, $J = 6.6$ Hz, 1H), 7.07 (d, $J = 7.8$ Hz, 1H), 7.00 (bs, 1H), 6.82 (dd, $J = 7.4$ and 1.4 Hz, 1H), 6.75 (td, $J = 7.8$ and 1.6 Hz, 1H), 6.34 (td, $J = 7.3$ and 0.92 Hz, 1H), 6.20 (d, $J = 8.0$ Hz, 1H), 4.35 (m, 2H), 4.03 (dd, $J = 11.9$ and 2.0 Hz, 1H), 3.73 (dd, $J = 11.9$ and 3.6 Hz, 1H). ^{13}C NMR (MeOH-d_4, 100.63 MHz, 25 °C, δ): 199.2, 198.9, 197.0, 163.4, 162.5, 153.1, 140.3, 131.4, 131.0, 125.4, 124.9, 122.6, 120.7, 117.6, 60.4, 54.5. IR (KBr, cm^{-1}): 3398 (br, w), 2023 (s), 1909 (s), 1887 (s), 1610 (w), 1458 (m), 759 (m), 647 (w), 630 (w), 530 (w). LR-MS (AP^+): *m/z* 483 ($M^{185}ReH^+$, 50%), 485 ($M^{187}ReH^+$, 100%). HR-MS (ES^+ of MH^+). Calcd for $C_{16}H_{14}N_2O_4{}^{187}Re$ *m/z* 485.0511. Found: *m/z* 485.0509. Anal. Calcd for $C_{16}H_{15}N_2O_5Re$ (**7**-$Re(CO)_3$·H_2O): C, 38.32; H, 3.01; N, 5.59. Found: C, 37.87; H, 2.85; N, 5.61.

Synthesis of 8-Re(CO)$_3$. Following a reaction in 2 mL of MeOH, the product was isolated by preparative TLC (silica−CH_2Cl_2/5% MeOH) as a white solid (0.10 g, 88% yield) by method A or after reaction in 1 mL of EtOH by method B (0.054 g, 80% yield). $R_f =$ 0.68 (silica−CH_2Cl_2/5% MeOH). Mp: 170–174 °C. ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 8.68 (d, $J = 4.4$ Hz, 1H), 7.92 (br t, 1H), 7.47–7.41 (br m, 2H), 6.88 (d, $J = 6$ Hz, 2H), 6.41–6.28 (m, 3H), 5.60–5.56 (m, 2H), 4.57 (d, $J = 15.6$ Hz, 1H), 4.48 (d, $J =$ 15.6 Hz, 1H), 4.03 (br m, 1H), 3.95 (br m, 1H), 3.65 (br m, 1H), 3.30 (br m, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz, D1 = 10 s, lb = 5 δ): 198.8, 197.2, 196.2, 166.0, 160.2, 151.7, 139.7, 130.8, 130.0, 129.9, 125.0, 124.1, 123.0, 118.3, 114.6, 66.0, 64.8, 57.5. IR (KBr, cm^{-1}): 3430 (br, vw), 3191 (br, vw), 2015 (s), 1870 (s), 1596 (m), 1478 (s), 1458 (m), 1448 (m), 1271 (m), 768 (m). MS (ES^+, 100% MeOH, 30V): *m/z* 1069 ($M_2 - {}^{185}Re^{187}ReNa^+$), 1071 ($M_2 - {}^{187}Re^{187}ReNa^+$). MS ($ES^+$, 100% MeOH, 45 V): *m/z* 545 ($M - {}^{185}ReNa^+$), 547 ($M - {}^{187}ReNa^+$). HR-MS (ES^+ of $M - {}^{187}ReH^+$). Calcd for $C_{19}H_{18}N_2O_4{}^{187}Re$: *m/z* 525.0824. Found: *m/z* 525.0826. HR-MS (ES^+ of $M_2 - {}^{185}Re^{187}ReNa^+$). Calcd for $C_{38}H_{34}N_4O_8{}^{187}ReNa$: *m/z* 1069.1362. Found: *m/z* 1069.1361. Anal. Calcd for $C_{19}H_{17}N_2O_4Re$: C, 43.59; H, 3.27; N, 5.35. Found: C, 43.19; H, 3.65; N, 5.26.

Synthesis of 9-Re(CO)$_3$. 9-Re(CO)$_3$ was prepared as described in method A above, using 2 mL of MeOH. Isolation and purification was done by column chromatography (silica−CH_2Cl_2/5% MeOH to CH_2Cl_2/10% MeOH), affording **9-Re(CO)$_3$** as a white solid (0.133 g, 70% yield): $R_f = 0.26$ (silica−CH_2Cl_2/10% MeOH). Mp: 185–187 °C. ^{1}H NMR (DMSO-d_6, 300 MHz, δ): 10.3 (br, 1H), 9.17 (s, 1H), 8.91 (d, $J = 5.3$ Hz, 1H), 8.12 (t, $J = 7.8$ Hz, 1H), 7.77 (d, $J = 7.8$ Hz), 7.64 (t, $J = 6.5$ Hz, 1H), 7.48 (d, $J = 7.4$ Hz, 1H), 7.32 (t, $J = 7.6$ Hz, 1H), 7.01 (d, $J = 8.1$ Hz, 1H), 6.92 (t, J = 7.4 Hz, 1H), 4.87 (d, $J = 14.4$ Hz, 2H), 4.63 (d, $J = 14.0$ Hz, 1H), 3.81 (s, 3H), 3.02 (m, 1H), 2.88 (m, 1H), 2.30 (d, $J = 17.3$ Hz, 1H), 2.11 (t, $J = 16.4$ Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz, D1 = 2 s, δ): 197.0, 195.4, 193.9, 175.8, 160.3, 157.6, 153.3, 141.0, 134.7, 131.4, 126.3, 124.7, 119.6, 118.2, 116.5, 66.7, 61.5, 56.4, 50.6, 31.3. IR (KBr, cm^{-1}): 3439 (br, w), 3100 (br, w), 2027 (s), 1905 (s), 1642 (s), 1608 (m), 1457 (m), 1408 (m), 1229 (m), 763 (m). MS (ES^+, 100% MeOH, 30 V): *m/z* 568 ($M - {}^{185}ReH^+$), 570 ($M - {}^{187}ReH^+$). HR-MS (ES^+ of $M - {}^{187}ReH^+$). Calcd for $C_{20}H_{21}N_3O_5{}^{187}Re$: *m/z* 570.1039. Found: *m/z* 570.1038. Anal. Calcd for $C_{20}H_{21}BrN_3O_5Re$ (**9-Re(CO)$_3$·HBr**): C, 36.98; H, 3.26; N, 6.47. Found: C, 37.11; H, 3.50; N, 6.35.

Solid-State Structure Determination for 5a-Re(CO)$_3$Br. Colorless needle crystals of **5a-Re(CO)$_3$Br** were obtained via slow vapor diffusion of diethyl ether into a concentrated methanol solution of the Re compound. The sample was mounted on a glass fiber and cooled to 173 K. Data sets were collected on a Rigaku/ADSC CCD area detector with graphite-monchromated Mo Kα radiation ($\lambda = 0.710\,73$ Å). Data were collected and integrated using the Bruker *SAINT*[56] software package and corrected for Lorentz and polarization effects as well as for absorption (*SADABS*).[57] The

(56) *SAINT*; Bruker AXS Inc.: Madison, WI, 1999.
(57) *SADABS*; Bruker AXS Inc.: Madison, WI, 1999.

structure was solved by direct methods (*SIR92*).[58] Non-hydrogen atoms were refined anisotropically, while hydrogen atoms were added but not refined. Final refinement was completed using *SHELXL-97*.[59]

General Procedure for Radiolabeling with $[^{99m}Tc(H_2O)_3(CO)_3]^+$. The organometallic precursor $[^{99m}Tc(H_2O)_3(CO)_3]^+$ was prepared from a saline solution of $Na[^{99m}TcO_4]$ (1 mL, 100 MBq) using an Isolink kit generously provided by Mallinckrodt Inc. A 1 mL solution of $Na[^{99m}TcO_4]$ was added to an Isolink kit, and the vial was heated to reflux for 20 min. Upon cooling, ~0.12 mL of a 1 M HCl solution was added to adjust the pH to 9–10. To a 0.50 mL solution of compound **5**, **7**, **8**, or **9** ($\sim 10^{-3}$ M) in EtOH was added 3 equiv of NaOEt (~0.15 mL, $\sim 10^{-2}$ M in EtOH) followed by 0.10 mL of $[^{99m}Tc(H_2O)_3(CO)_3]^+$. The resulting solution was heated to 80 °C for 0.5 h and cooled to ambient temperature prior to HPLC analysis.

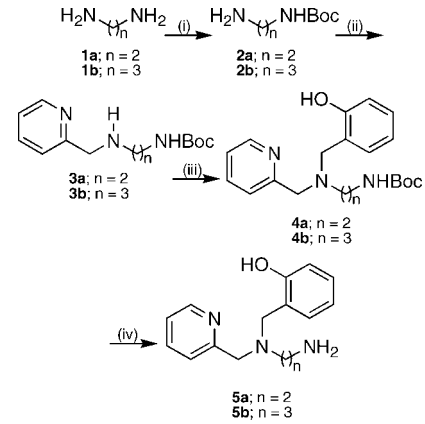
Cysteine and Histidine Challenge Experiments. To either cysteine or histidine in phosphate-buffered saline at pH 7.4 (1 mM, 0.9 mL) was added a solution of the ^{99m}Tc complex (0.1 mL, to make the final ligand concentration $\sim 10^{-5}$ M, with final activity of ~1.8 MBq/sample, ~1.8 MBq/mL). The samples were incubated at 37 °C, and aliquots were removed at 0.5, 4, and 24 h for HPLC analysis.

Results and Discussion

$[^{99m}Tc(CO)_3]^+$ complexes formed with tridentate ligands have been reported to have a higher stability and better in vivo clearance than their bidentate counterparts.[16,37] This has been our motivation for developing chemistry that facilitates the synthesis of libraries of well-behaved tridentate ligands for the tricarbonyltechnetium core. Consideration has also been given to a pendant tether that can easily be functionalized and conjugated to a biomolecule. Schibli and coworkers have shown that glycine and 1,5-diaminopentane can be utilized for this purpose.[11] While carboxylic acids, imidazoles, pyridines, tertiary amines, and various combinations have all been investigated exhaustively and are good donor sets for the $[M(CO)_3]^+$ core, little is known about the potential of phenols for chelation of technetium or rhenium.

Following literature procedures, *N*-Boc-protected diaminoethane **2a**[53] and diaminopropane **2b**[54] were synthesized (Scheme 1). Reductive amination of each with 2-pyridinecarboxaldehyde in the presence of $NaBH(OAc)_3$ afforded secondary amines **3a** and **3b**, respectively. Further reductive amination of **3a** and **3b** with salicylaldehyde furnished the desired products **4a** and **4b**, respectively. Subsequent deprotection of the *N*-Boc-protected amine with TFA afforded compounds **5a** and **5b**. The derivatives have the expected spectroscopic properties, confirming their assigned structure. These compounds are of significant interest for the potential of using these binding motifs and spacer groups coupled to biomolecules. The building block approach to making tridentate ligands lends itself to easy manipulation of the binding motif donor sets as well as to changing the length of the methylene spacers between the pendant amino functionality and the binding motif (e.g., instead of starting with 1,2-diaminoethane, 1,10-diaminodecane can be used).

Scheme 1[a]



[a] Reaction conditions: (i) 0.1 equiv of Boc_2O, $CHCl_3$, 24 h, 25 °C;[53,54] (ii) 1.01 equiv of 2-pyridinecarboxaldehyde, 2 equiv of $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, 24 h, 25 °C; (iii) 1.01 equiv of salicylaldehyde, 2 equiv of $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, 24 h, 25 °C; (iv) TFA, CH_2Cl_2, 24 h, 25 °C.

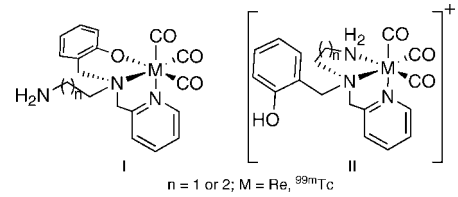
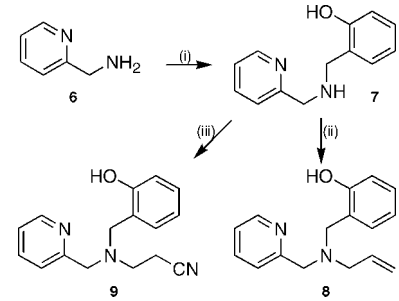


Figure 3. Possible complexes of **5a** and **5b**.

Scheme 2[a]



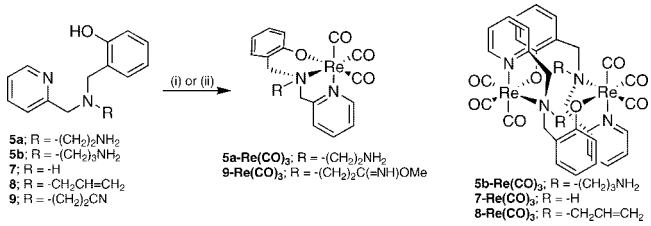
[a] Reaction conditions: (i) 1 equiv of salicylaldehyde, $NaBH_4$, MeOH, 25 °C;[55] (ii) 1.03 equiv of allyl bromide, 8 equiv of Na_2CO_3 CH_3CN, N_2, 25 °C, 24 h; (iii) 1 equiv of bromopropionitrile, DABCO, CH_3CN, Δ, 5 days.

The pendant primary amines in **5a** and **5b**, vital to our studies for their role in linker formation, are a concern because technetium and rhenium, being second- and third-row transition metals, are "softer" metals and may prefer binding to the amino nitrogen rather than to the phenolic oxygen, and indeed this seems to be the case (vide infra). This will lead to a cationic complex **II** instead of the desired neutral complex **I** (Figure 3).

To evaluate this possibility, we have prepared a compound that does not contain a pendant arm [**7-Re(CO)$_3$**] and compounds whose pendant arms are incapable of binding the metals of interest (**8-Re(CO)$_3$** and **9-Re(CO)$_3$**; Scheme 2). In addition, these compounds carry functional groups that can quickly be converted (e.g., from cyano or alkene to

(58) Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115–119.
(59) *SHELXL*; Bruker AXS Inc.: Madison, WI, 1997.

Scheme 3[a]



[a] Reaction conditions: (i) $[Re(H_2O)_3(CO)_3]Br$, MeOH, Δ, 1 day; (ii) $[Re(H_2O)_3(CO)_3]Br$, 3 equiv of NaOEt, EtOH, Δ, 4 h.

amine, amide, carboxylic acid, or aldehyde)[60] to groups easily incorporated into biomolecules. The reaction of 2-picolylamine and salicylaldehyde via a literature procedure yielded known compound **7**.[55] Subsequent alkylation of **7** with allyl bromide or 3-bromopropionitrile afforded **8** and **9**, respectively. All products possess the expected spectroscopic properties. Compounds **7**−**9** are expected to bind the $[Re(CO)_3]^+$ core solely through the desired N,N,O-donor sets provided by the pyridyl nitrogen, tertiary nitrogen, and phenol moiety. We envisioned that these molecules would provide a standard to which we would be able to compare spectroscopic data among derivatives of **5** and their corresponding rhenium complexes.

The reaction of **5a**, **5b**, and **7**−**9** with $[Re(H_2O)_3(CO)_3]Br$ in refluxing MeOH (see method A in the Experimental Section) yielded the expected neutral complexes (Scheme 3). Qualitative evaluation by TLC indicated the relative nonpolarity of these complexes compared to their ligands because R_f values of 0.72 (silica−CH_2Cl_2/20% MeOH), 0.48 (silica−CH_2Cl_2/20% MeOH), 0.48 (silica−CH_2Cl_2/10% MeOH), 0.68 (silica−CH_2Cl_2/5% MeOH), 0.26 (silica−CH_2Cl_2/10% MeOH), respectively, were observed. ESI-MS of the complexes confirmed the presence of 1:1 metal-to-ligand complexes. As an example, values of *m*/*z* 526 (**5a**-^{185}**Re(CO)$_3$H**$^+$), 528 (**5a**-^{187}**Re(CO)$_3$H**$^+$), 540 (**5b**-^{185}**Re(CO)$_3$H**$^+$), and 542 (**5b**-^{187}**Re(CO)$_3$H**$^+$) in the expected isotopic ratios were observed. Comparing the IR spectra of the ligands to their respective complexes showed the disappearance of the broad phenol−OH stretch at ∼3000 cm^{-1} upon metal complexation. Additionally, carbonyl peaks for **5a-Re(CO)$_3$** (2026 and 1910 cm^{-1}), **5b-Re(CO)$_3$** (2014 and 1890 cm^{-1}), **7-Re(CO)$_3$** (2023 and 1909 cm^{-1}), **8-Re(CO)$_3$** (2015 and 1870 cm^{-1}), and **9-Re(CO)$_3$** (2027 and 1905 cm^{-1}) are significantly higher than the rhenium precursor carbonyl stretches at 2000 and 1868 cm^{-1}. Taken altogether, the IR results point to the coordination of the $[Re(CO)_3]^+$ core in the desired *N,N,O-fac*-$[Re(CO)_3]$ fashion.

Shifts in ^{1}H NMR resonances unambiguously confirm the formation of these complexes. For example, the methylene groups of free ligands appeared as two single peaks at 3.79 and 3.68 ppm for **5a** and 3.76 and 3.64 ppm for **5b** (see the Supporting Information). These singlets, upon coordination, split into two sets of doublets at 4.92 ppm (16.O Hz), 4.41 ppm (16.4 Hz) and 4.73 ppm (13.6 Hz), 4.58 ppm (13.6 Hz) for **5a-Re(CO)$_3$** and 4.60 ppm (15.6 Hz), 4.48 (15.6 Hz) and 3.65 ppm (12.0 Hz), 3.58 (11.6 Hz) for **5b-Re(CO)$_3$**, forming an AB spin system pattern. This feature is in accordance with other similar tridentate chelates wherein the metal is bound to a tertiary nitrogen, a pyridyl nitrogen, and a carboxylic acid.[11] The pyridine and phenol aromatic hydrogens also shifted upon coordination. These shifts are, to some extent, similar but are not congruent. Observations are as follows: (i) pyridyl hydrogens have shifted downfield for all complexes; (ii) phenolic hydrogens have shifted upfield for **5b-Re(CO)$_3$**, **7-Re(CO)$_3$**, and **8-Re(CO)$_3$** and downfield for **5a-Re(CO)$_3$** and **9-Re(CO)$_3$**. Initially, we attributed this observation to the primary amine in some of the ligands binding to Re^+ to form a cationic complex with an N,N,N-binding sphere, but as pointed out earlier, these complexes are relatively nonpolar, thus eliminating this possibility. On the other hand, in work reported by Li and co-workers,[61,62] Ru^{2+} (isoelectronic with Re^+)-bipy complexes titrated with phenol resulted in an upfield ^{1}H NMR shift of the corresponding phenolic hydrogens. This observation was attributed to the resulting π stacking between the phenol and the electron-deficient bipy ligands in the complex. The observed upfield proton shift of **5b-Re(CO)$_3$**, **7-Re(CO)$_3$**, and **8-Re(CO)$_3$** phenolic hydrogens is consistent with the observations for this Ru^{2+}-bipy counterpart. We propose that the coordinated electron-deficient pyridine ring is stabilized by a π-stacking interaction from an intermolecular phenolic ring. This π-stacking arrangement is not sterically possible in a monomeric complex and so may be the driving force for the formation of the less polar dimeric complexes (Scheme 3). Further, ESI-MS of **8-Re(CO)$_3$** in MeOH showed solely a dimer mass ion (no monomer) at low ionization cone voltage (15 V); this was gradually converted to the expected monomer upon a systematic increase of the cone voltage. The reaction conditions for complex formation were also altered to ascertain the influence of predeprotonation of the phenol before the addition of $[Re(H_2O)_3(CO)_3]Br$ (see the Experimental Section, complex synthesis, method B). Sodium ethoxide was added to an ethanolic solution of **5a** and **8** before the addition of the rhenium precursor, and the complexes formed showed spectroscopic properties identical with those prepared using method A. During the preparation of **9-Re(CO)$_3$**, the cyano group reacted with methanol (used as the solvent) to form methyl imidate. ^{1}H NMR spectroscopy validated the methoxy group of the imidate. In DMSO-d_6, it appeared as a singlet at 3.81 ppm that integrates to 3 ppm as opposed to residual MeOH, which has a resonance at around 3.10 ppm. ESI-MS and elemental analysis also support the formation of the imidate.

As expected, all complexes formed showed three carbonyl carbon signals between 194 and 199 ppm in the ^{13}C APT spectrum (see the Supporting Information). Indications of the desired N,N,O coordination were deduced from the shifts (between 1 and 7 ppm) of the pyridyl, methylene, and

(60) Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*; Wiley-VCH: New York, 1999.

(61) Li, C.; Sun, H.; Hoffman, M. Z. *J. Photochem. Photobiol., A* **1997**, *108*, 129–133.

(62) Li, C.; Hoffman, M. Z.; Pizzocaro, C.; Maihot, G.; Bolte, M. *Inorg. Chem.* **1998**, *37*, 3078–3082.

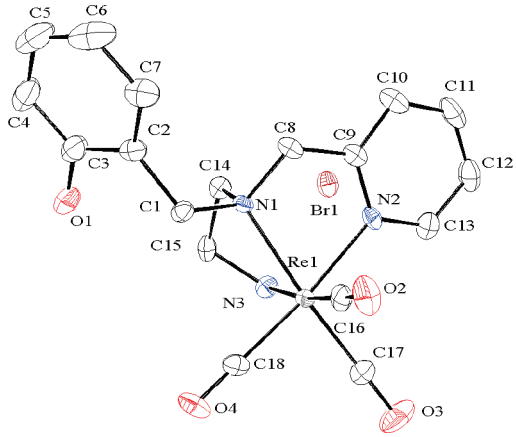


Figure 4. ORTEP view of **5a-Re(CO)$_3$Br**.

Table 1. Selected Bond Lengths (Å) and Angles (deg) in **5a-Re(CO)$_3$Br**

Re1–N1	2.238(5)	N1–Re1–N2	75.11(2)
Re1–N2	2.168(5)	N1–Re1–N3	78.61(2)
Re1–N3	2.193(5)	N2–Re1–N3	85.9(2)
Re1–C16	1.916(7)	N1–Re1–C16	95.2(2)
Re1–C17	1.906(7)	N1–Re1–C17	172.1(3)
Re1–C18	1.930(7)	N1–Re1–C18	98.8(2)
		C16–Re1–C17	89.8(3)
		C16–Re1–C18	90.4(3)
		C17–Re1–C18	87.3(3)

phenolic carbons of the complexes compared to the unbound compounds. The slow spin–lattice relaxation time (T1) of some carbons of **5b-Re(CO)$_3$**, **7-Re(CO)$_3$**, and **8-Re(CO)$_3$** obviated a direct measurement of their ^{13}C NMR signals. Relaxation times are the direct result of the capability of a molecule to transfer its energy to its surroundings.[63] They do so via interaction of their magnetic vectors with the fluctuating local fields of sufficient strength and a fluctuation frequency on the order of the Larmor frequency of the nuclear spin type. The inability of these complexes to efficiently transfer their energy can be interpreted as slow molecular motion that affects the dipole–dipole relaxation mechanism, further verifying the dimeric nature of these compounds in solution.

Slow vapor diffusion of diethyl ether into a methanolic solution of **5a-Re(CO)$_3$Br** gave colorless needle crystals suitable for X-ray diffraction. The resulting structure is depicted in Figure 4, with selected bond lengths and angles in Table 1. These properties are comparable to those seen in similar tridentate chelates binding with a slightly distorted octahedral coordination sphere to a *fac*-Re(CO)$_3^+$ core.[17] The Re1−C$_{carbonyl}$ bond lengths of 1.91–1.93 Å are exactly as expected for such a compound. The Re1−N bond lengths range from 2.17 to 2.24 Å. The Re1–N2 bond is the shortest of the three because N2 is an sp^2-hybridized nitrogen as opposed to N1 and N3, which are sp^3-hybridized. The difference in bond lengths between Re1−N1 (2.24 Å) and Re1−N3 (2.19 Å) can be explained by the different steric demands of the two nitrogens; N3 is a primary amine while N1 is a tertiary amine bridging the two five-membered chelate rings. The most notable bond angles are those that define the N-coordination sphere. N1−Re1−N2 and N1−Re1−N3 are 75.1 and 78.6°, respectively, showing a significant deviation from octahedral geometry, as imposed by the formation of the two five-membered chelate rings.

It is interesting to note that, in the crystal structure shown here, the rhenium has a binding sphere different from that seen in solution; N,N,N compared to N,N,O. In the solid state, the rhenium tricarbonyl core is bound by three nitrogen atoms: a pyridyl nitrogen, a tertiary amine, and a primary amine. Rigorous NMR analysis shows that in solution the primary amine is pendant and the phenolate oxygen is bound to the rhenium. While the N_3 binding sphere is not the coordination mode of preference in this study, it is interesting to observe and does inform donor preferences in the absence of the primary amine functionalization. The ultimate fate of this ligand is to be conjugated to a biomolecule via the primary amine that is coordinating to the rhenium in the solid state. When the primary amine of **5a** is further elaborated, for instance with glucose, we predict that the resulting system will have the expected N,N,O coordination, as noted in solution. Pertinent studies are in progress.

Radiolabeling of the ligands with ^{99m}Tc was simple, fast, and high-yielding. The radiochemical yields were 85%, 99%, 99%, 99%, and 92% for **5a-^{99m}Tc(CO)$_3$**, **5b-^{99m}Tc(CO)$_3$**, **7-^{99m}Tc(CO)$_3$**, **8-^{99m}Tc(CO)$_3$**, and **9-^{99m}Tc(CO)$_3$** respectively. HPLC traces of the cold rhenium complexes and the radiolabeled technetium complexes are shown in the Supporting Information. When the stability of the radiolabeled compounds was assessed, the ^{99m}Tc complexes were challenged with an excess of the potentially metal binding amino acids (cysteine and histidine), which are ubiquitous in vivo. All complexes were stable out to 24 h, with no appreciable degradation species. This suggests the potential utility of these complexes for radiopharmaceutical application because of their robustness to these challenge experiments.

Conclusions

In conclusion, pyridyl−*tert*-nitrogen−phenol donors with differing pendant arms were prepared and fully characterized. While compounds **5a** and **9** form monomeric complexes with the [Re(CO)$_3$]$^+$ core, **5b**, **7**, and **8** form two metal-center dimeric complexes. These dimers, naturally, were not observed at the more dilute tracer level and so are irrelevant in the ultimate imaging applications of these molecules. The radiolabeled complexes formed with [^{99m}Tc(CO)$_3$]$^+$ using these types of donors are stable even in the presence of a large excess of competitive chelators, suggesting their possible utility for radiopharmaceutical applications via conjugation of these binding motifs to biomolecules.

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(63) Breitmaier, E.; Spohn, K.-H.; Berger, S. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 144–159.

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Supporting Information Available: ^{1}H and ^{13}C NMR traces of compounds **3a**, **3b**, **4a**, **4b**, **5a**, **5b**, **7**−**9**, **5a-[Re(CO)$_3$]**, **5b-[Re(CO)$_3$]**, **7-[Re(CO)$_3$]**, **8-[Re(CO)$_3$]**, **9-[Re(CO)$_3$]**, UV and radiation HPLC traces of **5a-M(CO)$_3$**, **5b-M(CO)$_3$**, **7-M(CO)$_3$**, **8-M(CO)$_3$**, and **9-M(CO)$_3$**, where M = Re and ^{99m}Tc, and selected crystallographic data for **5a-Re(CO)$_3$Br**. This material is available free of charge via the Internet at http://pubs.acs.org.

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