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Rhenium and Technetium Tricarbonyl Complexes of N-Heterocyclic Carbene Ligands

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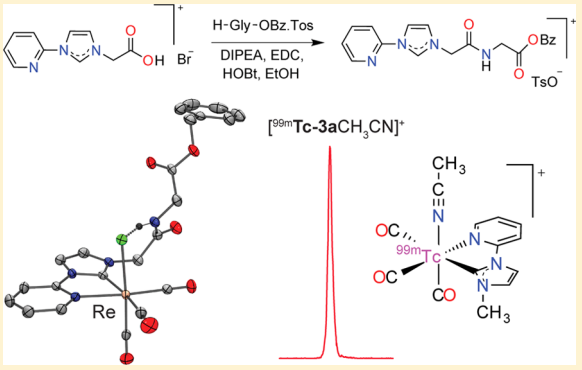
Supporting Information

ABSTRACT: A strategy for the conjugation of N-heterocyclic carbene (NHC) ligands to biomolecules via amide bond formation is described. Both 1-(2-pyridyl)imidazolium or 1-(2-pyridyl)-benzimidazolium salts functionalized with a pendant carboxylic acid group were prepared and coupled to glycine benzyl ester using 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide. A series of 10 rhenium(I) tricarbonyl complexes of the form $[ReX(CO)_3(\hat{C}N)]$ ($\hat{C}N$ is a bidentate NHC ligand, and X is a monodentate anionic ligand: Cl^-, RCO_2^-) were synthesized via a Ag_2O transmetalation protocol from the Re(I) precursor compound $Re(CO)_5Cl$. The synthesized azolium salts and Re(I) complexes were characterized by elemental analysis and by ^1H and ^{13}C NMR spectroscopy, and the molecular structures for one imidazolium salt and seven Re(I) complexes were determined by single-crystal X-ray diffraction. ^1H NMR and mass spectrometry studies for an acetonitrile-d_3 solution of [ReCl(CO)$_3$(1-(2-pyridyl)-3-methylimidazolylidene)] show that the monodentate chloride ligand is labile and exchanges with this solvent yielding a cationic acetonitrile adduct. For the first time the labeling of an NHC ligand with technetium-99m is reported. Rapid Tc-99m labeling was achieved by heating the imidazolium salt 1-(2-pyridyl)-3-methylimidazolium iodide and Ag_2O in methanol, followed by the addition of *fac*-$[^{99m}Tc(OH_2)_3(CO)_3]^+$. To confirm the structure of the ^{99m}Tc-labeled complex, the equivalent ^{99}Tc complex was prepared, and mass spectrometric studies showed that the formed Tc complexes are of the form $[^{99m/99}Tc(CH_3CN)(CO)_3$(1-(2-pyridyl)-3-methylimidazolylidene)$]^+$ with an acetonitrile molecule coordinated to the metal center.



INTRODUCTION

Radiopharmaceutical imaging agents are routinely used for the rapid and noninvasive assessment of organ function and disease diagnosis. Much work in the development of contemporary diagnostic imaging agents has focused on radiolabeled biomolecules, which localize at a disease site (e.g., cancer) through interactions with specific cell receptors.[1,2] Numerous radioisotopes are used in diagnostic imaging, and among these, the metastable isotope of technetium, ^{99m}Tc, is of great importance due to its optimal nuclear properties, which include intermediate half-life ($t_{1/2}$ = 6.02 h), almost pure γ emission (E_γ = 140 keV), low cost, and convenient availability from a ^{99}Mo/^{99m}Tc generator.[3,4] ^{99m}Technetium-based diagnostic imaging agents are used for imaging a variety of organ conditions and disease states; examples include: ^{99m}Tc-HMPAO (Ceretec) for cerebral blood flow imaging, ^{99m}Tc-MAG$_3$ (TechneScan) for the assessment of renal function, and the organometallic myocardial perfusion imaging agent, ^{99m}Tc-Sestamibi (Cardiolite).[1]

N-heterocyclic carbenes (NHCs) are of considerable importance in contemporary organometallic chemistry.[5] This popularity results from the framework flexibility displayed by NHC ligands and the outstanding activity of NHC-metal complexes in homogeneous catalytic applications.[6−10] Complexes of NHCs often display high stability, which can be attributed to the strong σ-donating properties of NHCs and the robust metal-carbene bond.[10,11] Despite the attractive features of NHC-based ligand systems, little attention has been devoted to the potential medicinal and bioanalytical applications of these molecules and their metal complexes. Although NHC complexes of metals including Ag,[12,13] Au,[14,15] Pd,[16] and Pt[17] have been evaluated as antitumor agents, there have been very few reports into the potential radiopharmaceutical applications of NHCs. Youngs and co-workers have extensively investigated the antimicrobial properties of Ag(I)-NHC complexes[18,19] and have reported the potential application of using preformed Ag(I)-NHC complexes for the delivery of NHC ligands in radiopharmaceutical synthesis.[20,21] Abram and co-workers reported the first example of a ^{99}Tc-NHC complex **1** (Figure 1)[22] and have subsequently described the synthesis of a number of ^{99}Tc-NHC and Re-NHC complexes.[23−25] This group has also described the synthesis of Re(V)-NHC complexes via a transmetalation reaction from Ag(I)-NHCs.[26] Recently, a series

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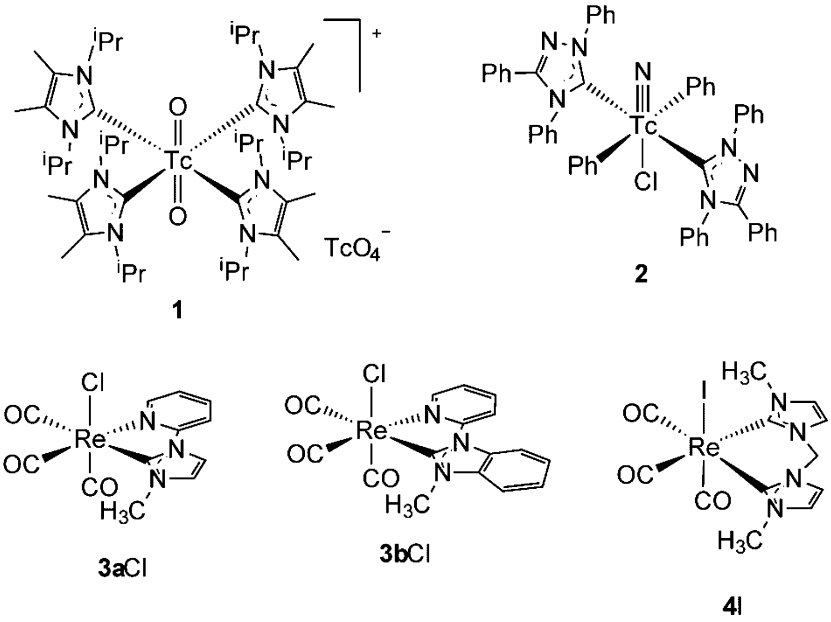
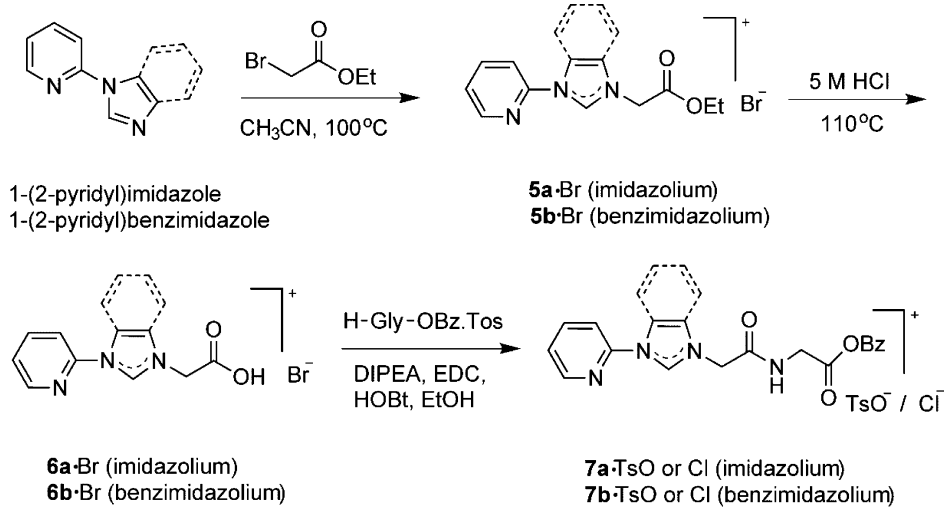


Figure 1. Structures of Tc and Re complexes of N-heterocyclic carbene ligands.

Scheme 1. Synthesis of Ester and Carboxylic-Functionalized Azolium Salts and Glycine Benzyl Ester-Coupled Products



of water stable ^{99}Tc(V)-NHC complexes of the nitridotechnetium core (e.g., **2**, Figure 1)[27] and the dioxotechnetium core[28] were described.

N-heterocyclic carbene complexes of the tricarbonyl core for both Re(I) and Tc(I) are the focus of the research reported in this paper. Although there have been no reports of $Tc(CO)_3$ complexes of NHC ligands, a number of *fac*-$Re(CO)_3$–NHC complexes have been previously described. A series of tricarbonyl chloride complexes of pyridyl-substituted imidazolylidene- and benzimidazolylidene-based NHC ligands have been prepared, for example, **3a**Cl and **3b**Cl (Figure 1) and their luminescent properties evaluated.[29−31] Bidentate NHC ligands have also been utilized, and in an early study by Hermann and co-workers, the *bis*(NHC)Re(I) complex **4l** (Figure 1) was prepared from the precursor Re(I) complex $[N(CH_3)_4]$-$[Re_2(CO)_6(\mu\text{-}OCH_3)_3]$.[32] Subsequently these researchers have synthesized related compounds with monodentate[33] and a range of bidentate *bis*-NHC ligands.[34−36]

Bifunctional chelating agents (BFC) provide functionality for both metal ion coordination and biomolecule conjugation, and given the large number of metallic radionuclides available for both imaging and therapeutic applications, there is an associated need for new BFCs.[2] Various strategies have been reported for the bioconjugation of NHC-based ligands and their metal complexes. One approach involves the combination of a biologically active ligand with an NHC–metal complex. For example, a series of Au(I)-NHC–tetraacetylthioglucose analogues of Auranofin have been described.[37] A number of groups have reported methods for the conjugation of NHC ligands to peptides for metals including Ru,[38] Au(I),[39,40] and Rh.[41] Using a 'click' chemistry approach a Pt(II)-NHC–estrogen bioconjugate was recently described.[42]

We are interested in the development of luminescent[43,44] and radiolabeled[45,46] coordination compounds for biological imaging and sensor applications. Here we report a strategy for the conjugation of biologically active molecules to carboxylic acid functionalized 1-(2-pyridyl)azolium salt, NHC ligand precur-

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sors, using the peptide coupling reagent 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide (EDC). Using these functionalized ligands and their precursors, a family of $Re(CO)_3$–NHC complexes was synthesized using a Ag_2O transmetalation protocol, and for the first time, an NHC ligand has been radiolabeled with the $^{99m}Tc(CO)_3$ core. By preparing the analogous Tc-99 compound, the structure of the ^{99m}Tc complex was confirmed to be an acetonitrile adduct.

RESULTS AND DISCUSSION

Synthesis. The carboxylic acid-functionalized azolium salts **6a**·Br and **6b**·Br (Scheme 1) were prepared to allow for bioconjugate formation with amine-bearing biomolecules using the standard peptide coupling reagent EDC. As shown in Scheme 1, initially the ethyl ester-functionalized 1-(2-pyridyl)-azolium salts **5a**·Br and **5b**·Br were prepared by the alkylation of either 1-(2-pyridyl)imidazole or 1-(2-pyridyl)benzimidazole with ethyl 2-bromoacetate (1:1 ratio) in acetonitrile. Ester hydrolysis was carried out by heating either **5a**·Br or **5b**·Br in 5 M HCl for 2 h, yielding the carboxylic acid-functionalized azolium salts (**6a**·Br and **6b**·Br, Scheme 1). To evaluate the suitability of these compounds for EDC coupling to biologically relevant molecules, compounds **6a**·Br and **6b**·Br were coupled to glycine benzyl ester (H-Gly-OBzl.TsO) using EDC in combination with hydroxybenzotriazole (HOBt). Because of the positive charge associated with the azolium salts, it was necessary to use a polar reaction solvent (ethanol) for the conjugation reactions to achieve suitable solubility. Initial reactions produced the glycine-coupled azolium salts **7a**·TsO and **7b**·TsO with the tosylate anion. Because of difficulties encountered in the Re(I) complex synthesis when these azolium salts were used it was necessary to convert the anion associated with **7a** and **7b** to chloride via anion exchange. In all cases the synthesized azolium salts (**5**·Br–**7**·TsO/Cl) gave relatively simple ^{1}H NMR spectra, with a characteristic downfield signal for the strongly deshielded azolium NC*H*N (pro-carbenic) proton, which resonate within the range of 10.04–11.69 ppm for these molecules. The formation of the glycine-coupled products were accompanied by the appearance of a broad triplet signal (9.77 and 10.02 ppm for **7a**·Cl and **7b**·Cl, respectively) corresponding to the amide N–H protons for these compounds.

A series of rhenium(I) tricarbonyl complexes of the form $[ReCl(CO)_3(\hat{C}N)]$, where $\hat{C}N$ is a bidentate NHC ligand derived from the azoles **5a**·Br, **5b**·Br, **7a**·Cl, and **7b**·Cl, were prepared (Figure 2). In the cases of **6a**·Br and **6b**·Br, dinuclear Re(I) complexes were formed with the carboxylate groups of each NHC ligand bridging between the Re(I) centers. All prepared Re(I) complexes were synthesized using a standard Ag(I) transmetalation protocol, where the chosen 1-(2-pyridyl)azolium salt was treated with Ag_2O in dichloromethane, followed by addition of the precursor Re(I) compound $Re(CO)_5Cl$. The previously reported Re(I) tricarbonyl chloride complexes **3a**Cl and **3b**Cl[29] were prepared and, in the case of **3a**Cl, crystallographically characterized (see Structural Studies section). For **3a**Cl the Re(I) center adopts an octahedral coordination geometry, with three facially arrayed carbonyl ligands, the chelating bidentate NHC–pyridyl unit, and a monodentate chloride ligand (Figure 1). Similarly, the structurally analogous Re(I) complexes **8a**Cl and **8b**Cl were obtained from the ester-functionalized azolium salts (**5a**·Br and **5b**·Br) (Figure 2).

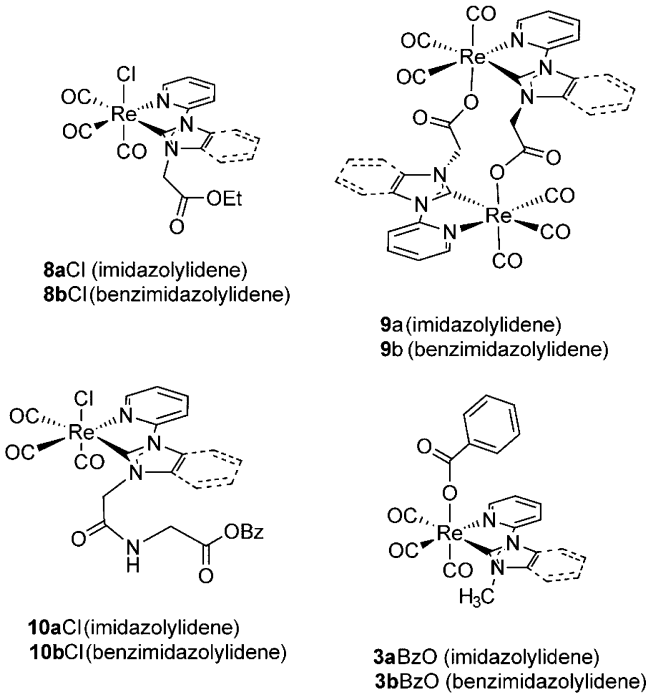

Figure 2. Structures of the Synthesized Re(I) Complexes.

The direct bioconjugation of Re/Tc-NHC complexes is of interest for potential diagnostic imaging applications, and as such efforts were made to prepare Re(I) complexes with a free carboxylic acid functional group from the azolium salts **6a**·Br or **6b**·Br. However, rather than the expected mononuclear Re(I) complexes, dinuclear complexes were obtained (**9a** and **9b**, Figure 2). For these compounds the monodentate chloride ligand had been displaced by a bridging carboxylate group from the second Re complex in the dinuclear pair. The glycine-coupled azolium salts (**7a**·Cl and **7b**·Cl), where the carboxylic acid was group protected as a benzyl ester, gave the expected mononuclear Re(I) complexes **10a**Cl and **10b**Cl, respectively. If the glycine-coupled azolium salts (**7a**·TsO and **7b**·TsO, tosylate anion) were used in the Re(I) synthetic reactions, a mixture of two complexes that differed in the nature of the anionic monodentate ligand (either Cl^- or TsO^-) were formed. Despite repeated attempts, this mixture could not be separated; however, crystals of **10b**TsO with the tosylate group coordinated to the Re(I) center were grown from this mixture, and the X-ray crystal structure was obtained (see Structural Studies section). This interesting capacity for these Re(I) complexes to bind hard oxygen donor ligands (RCO_2^- and RSO_3^-) has been observed previously for complexes of the $Re(I)(CO)_3$ core[47] and can be rationalized by considering the π-acidic (π-electron withdrawing) properties of the three carbonyl ligands, increasing the propensity of the Re(I) center to bind hard donor ligands. To further probe the capacity of these complexes to bind carboxylate donors and the influence of this donor on spectroscopic properties, the chloride ligands of **3a**Cl and **3b**Cl were substituted for a benzoate ligand by treatment with silver benzoate, yielding **3a**BzO and **3b**BzO (Figure 2).

The predicted number of signals were obtained in the ^{1}H and ^{13}C spectra for the synthesized $[ReX(CO)_3(\hat{C}N)]$ complexes. As expected, upon coordination of the NHC group, the signal for the azolium salt, pro-carbenic proton was absent from the

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Table 1. Selected Bond Distances (Å) from the X-ray Structures of the Re(I) Complexes 3aCl, 3aBzO, 3bBzO, 8aCl, 9b, 10aCl, and 10bTsO

	3aCl	3aBzO	3bBzO	8aCl	9b	10aCl	10bTsO
Re1−C1	1.922(8)	1.915(4)	1.924(9)	1.910(3)	1.905(8)	1.910(3)	1.917(3)
Re1−C2	1.965(9)	1.933(4)	1.956(11)	1.962(3)	1.957(7)	1.958(3)	1.979(3)
Re1−C3	1.919(10)	1.904(4)	1.900(10)	1.925(3)	1.898(9)	1.897(3)	1.906(3)
Re1−C9	2.151(8)	2.120(4)	2.150(9)	2.121(2)	2.126(4)	2.126(3)	2.118(3)
Re1−N1	2.197(6)	2.179(3)	2.178(7)	2.212(2)	2.183(3)	2.193(2)	2.194(3)
Re1−Cl1	2.501(2)			2.5167(9)		2.5115(8)	
Re1−O9							2.187(2)
Re1−O4		2.137(2)	2.152(6)		2.122(7)		

^{1}H NMR spectra, and a characteristic downfield chemical shift was observed for the carbenic carbon atom, occurring at 168.0, 153.0, 170.0, 167.7, 169.0, 168.7, 153.4, and 153.5 ppm for the complexes **8a**Cl, **8b**Cl, **9a**, **9b**, **10a**Cl, **10b**Cl, **3a**BzO, and **3b**BzO, respectively. The asymmetry of the ĈN ligand and the trans disposition of the axial CO and monodentate anionic ligand (Cl^- and RCO_2^-) give rise to chirality and two enantiomeric forms of each complex. The chirality at the metal center has a marked influence on the ^{1}H NMR spectra of these compounds. For example, compound **8a**Cl (functionalized with an ethyl ester group) shows a doublet signal for each of the methylene group protons adjacent to the imidazolylidene unit (NCH_2). Because of their proximity to the chiral metal center, the methylene group protons are diastereotopic and inequivalent.

Structural Studies. Crystallographic data for the imidazolium salt **5a**·Br and the Re(I) complexes **3a**Cl, **3a**BzO, **3b**BzO, **8a**Cl, **9b**, **10a**Cl, and **10b**TsO are given in Table S1 (Supporting Information), and selected bond distances are collated in Table 1. The structure of the imidazolium salt **5a**·Br is shown in Figure S1 (Supporting Information). A short C6−H···Br1 distance of 2.5582(4) Å, indicative of a hydrogen bond, is found between the pro-carbenic proton and the bromide counterion. In all cases, the Re(I) metal centers display slightly distorted octahedral coordination geometries, with three facially arrayed carbonyl ligands, the chelating bidentate NHC−pyridine unit and an anionic, monodentate donor group (Cl^-, RCO_2^-, and RSO_3^-). Compounds **3a**Cl, **8a**Cl, and **10a**Cl (Figure 3), which incorporate an imidazolylidene-based NHC unit and a monodentate chloride ligand, crystallized in the centrosymmetric space group $P2_1/c$. The bond distances for these compounds (Table 1) are similar to those reported for a related series of imidazolylidene-containing complexes.[29,31] A marked increase is evident for the Re−CO bond distances trans to the NHC unit (Re1−C2) compared to those trans to the pyridyl group (Re1−C1). The strong trans influence exerted by NHCs is well-known and has been described previously for related complexes.[43,44] For compound **10a**Cl (Figure 3c), the benzyl ester-protected glycine molecular fragment is displaced above the plane defined by the imidazolylidene-pyridine unit toward the chloride ligand. A hydrogen-bonding interaction is evident between the N−H group of the amide linkage and the coordinated chloride anion, with the N4−Cl1 distance being 3.279 08(9) Å.

The dinuclear complex **9b** (Figure 4a) crystallized in the centrosymmetric space group C_2/c, and the asymmetric unit contains one-half of the dinuclear complex and an acetonitrile molecule of crystallization. Extensive positional disorder was evident, and as a result, the metal−ligand bond lengths were not determined to a degree of accuracy to allow for a thorough

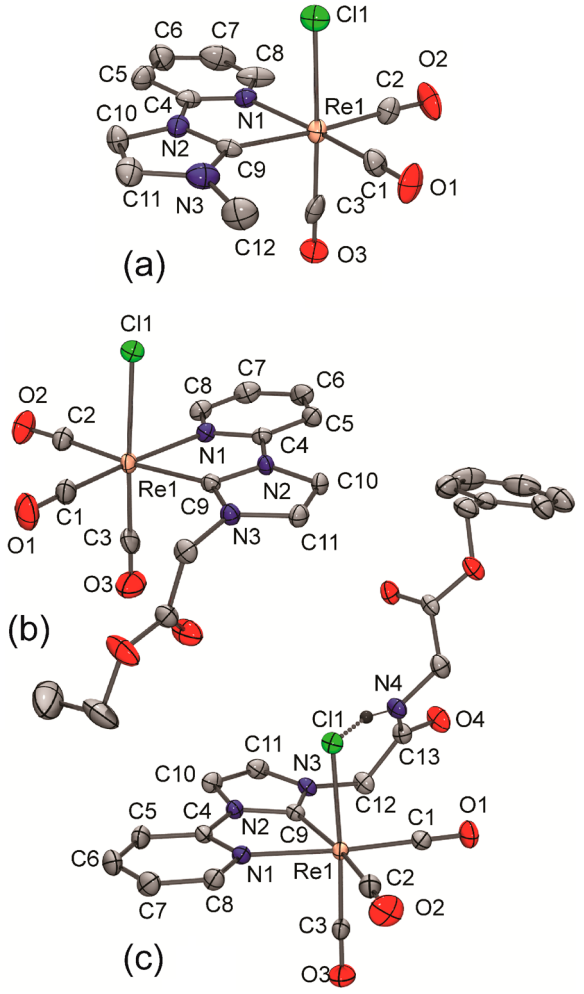

Figure 3. ORTEP[48] structures of (a) **3a**Cl, (b) **8a**Cl, and (c) **10a**Cl (a cocrystallized dichloromethane molecule omitted for clarity). Thermal ellipsoids are shown at 50% probability.

analysis of the metrical parameters. The complex is dinuclear due to a bridging interaction between the acetate functional groups on each of the benzimidazolylidene units. Crystals of **10b**TsO (Figure 4b) were obtained from a sample of **10b**, where either Cl^- and TsO^- was bound to the Re(I) center (see Synthetic Studies Section). The tosylate group is coordinated to the Re(I) center via a sulfonate oxygen atom, with a π-stacking interaction apparent between the toluene ring and the benzimidazolylidene molecular fragment, with a plane-to-plane distance of ∼3.5 Å.

In both cases, compounds **3a**BzO and **3b**BzO crystallized in the monoclinic space group $P2_1/n$, and the structures of these

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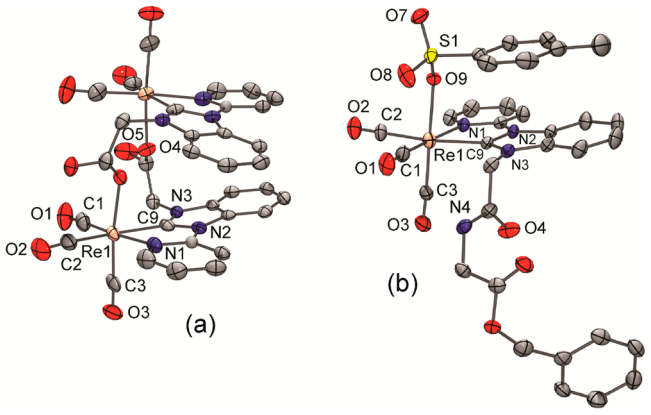

Figure 4. ORTEP[48] structures of (a) **9b** (cocrystallized acetonitrile molecule omitted for clarity) and (b) **10b**TsO (cocrystallized dichloromethane molecule omitted for clarity). Thermal ellipsoids are shown at 50% probability.

molecules are shown in Figure 5. As expected, the anionic chloride ligand of the precursor compounds (**3a**Cl and **3b**Cl)

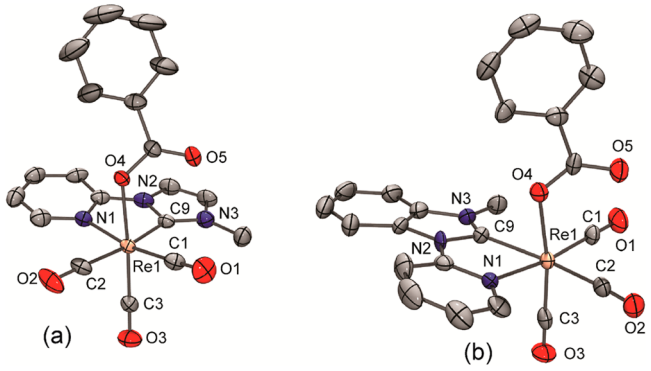

Figure 5. ORTEP[48] structures of (a) **3a**BzO and (b) **3b**BzO. Thermal ellipsoids are shown at 50% probability.

was replaced by a benzoate ligand, which is bound to the Re(I) center by one of the carboxylate oxygen atoms (O4). The Re(I)−O4 bond lengths are 2.137(2) Å and 2.152(6) Å, respectively, for **3a**BzO and **3b**BzO, and this is comparable to the Re(I)−O4 bond length observed for the dinuclear compound **9b** (2.122(7) Å).

Absorption and Emission Spectroscopic Studies for 3aBzO and 3bBzO. Compounds **3a**BzO and **3b**BzO were prepared from **3a**Cl and **3b**Cl, respectively, to allow the influence of the carboxylate donor group on spectroscopic properties to be evaluated. The UV−visible absorption profiles for **3a**Cl, **3b**Cl, **3a**BzO, and **3b**BzO recorded from chloroform solutions are shown in Figure S2 (Supporting Information). In the cases of the imidazolylidene-based complexes **3a**Cl and **3a**BzO, a strong absorption band is observed at ∼276 nm (intraligand $\pi-\pi^*$ transition),[29] with a weaker low-energy band centered at 258 nm (metal-to-ligand charge transfer (MLCT) transition),[29] while for the benzimidazolylidene-based complexes **3b**Cl, and **3b**BzO, the $\pi-\pi^*$ transition is red-shifted to ∼285 nm, and the MLCT transition is slightly red-shifted to 261 nm. All complexes were luminescent from aerated chloroform solutions, and the emission spectra are shown in Figure 6. Similar spectra were obtained for **3a**Cl (λ_{em} = 505 nm) and **3b**Cl (λ_{em} = 501 nm), with the emissions for the

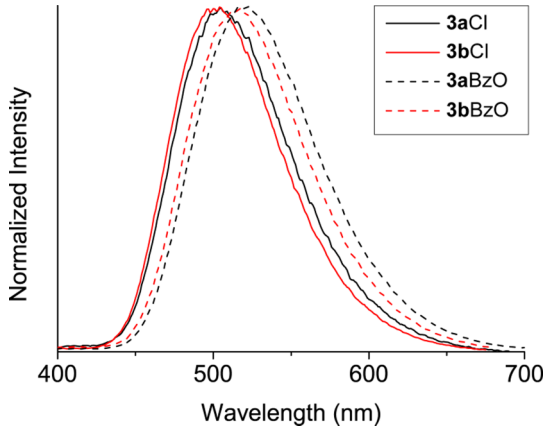

Figure 6. Photoluminescence spectra for chloroform solutions of the Re(I) complexes: **3a**Cl (black line), **3b**Cl (red line), **3a**BzO (black dashed line), and **3b**BzO (red dashed line) (λ_{ex} = 350 nm).

benzoate complexes **3a**BzO (λ_{em} = 519 nm) and **3b**BzO (λ_{em} = 515 nm) being slightly red-shifted by 14 nm in both cases relative to the parent complexes. The excited states for **3a**Cl and **3b**Cl and similar complexes have been previously assigned to a triplet metal-to-ligand (^{3}MLCT) excited state.[29,31] It is apparent from the absorption and emission studies that introduction of the benzoate ligand, in the place of chloride, induces only minor changes in the spectral properties. This is consistent with previous studies of diimine complexes, which suggest that the carboxylate group can impede connection between the R-group and the metal in R−CO_2−Re$(CO)_3$ systems.[49]

Chloride Ligand Exchange. Upon dissolution of the [Re$Cl(CO)_3$(ĈN)] complexes (**3a**Cl, **3b**Cl, **8a**Cl, **8b**Cl, **10a**Cl, and **10b**Cl) in the coordinating solvent, acetonitrile, a slow ligand-exchange reaction takes place, where the anionic chloride ligand is replaced by a molecule of acetonitrile, yielding a cationic complex. The changes observed in the aromatic region of the ^{1}H NMR spectrum for a solution of **3a**Cl in CD_3CN are shown in Figure 7. During the exchange reaction, a new set of signals for the NHC−pyridine unit associated with the complex with CD_3CN coordinated become evident at ∼2.2 h, and over the course of the reaction this becomes the dominant species in solution. The positive ion mass spectrum collected after the last ^{1}H NMR spectrum was recorded (Figure S3, Supporting Information) shows a main peak consistent with the expected cationic molecule [**3a**CD_3CN]$^+$ where a molecule of CD_3CN is coordinated to the metal center.

Kinetic analysis of the ^{1}H NMR data was performed by fitting speciation plots (Figures S4 and S5, Supporting Information) to the pseudo-first-order (CD_3CN in large excess) kinetic model depicted in eq 1. Using a single concentration, estimated forward and reverse rate constants were k_f = 0.097 M^{-1} h^{-1} and k_r = 0.018 M^{-1} h^{-1}, respectively.

$$\mathbf{3a}\mathrm{Cl} + \mathrm{CD_3CN} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} [\mathbf{3a}\mathrm{CD_3CN}]^+ + \mathrm{Cl}^- \ (\mathrm{CD_3CN\ in\ large\ excess}) \quad (1)$$

Exchange of an anionic halide ligand (Cl^- or Br^-) for acetonitrile has been noted previously for acetonitrile solutions of a closely related series of complexes, and these studies suggest that dissociation of the halide ligand may be photochemical in origin.[30,31] In contrast, the present study was conducted strictly in the absence of light, indicating a

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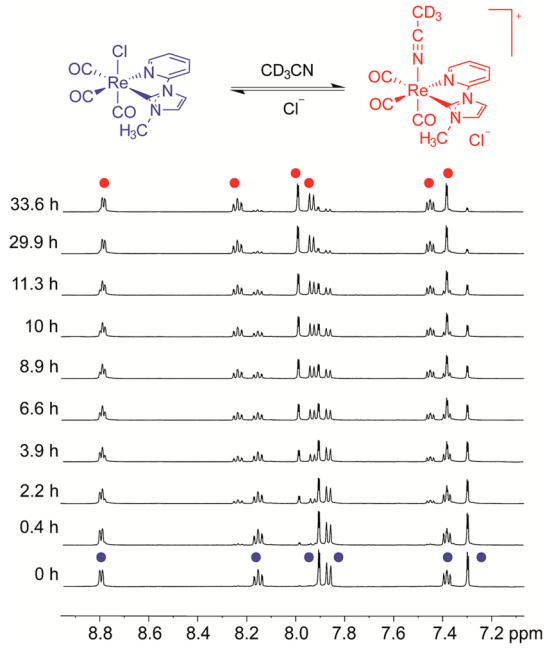

Figure 7. ^{1}H NMR spectra recorded for a solution of **3a**Cl in CD_3CN recorded over a period of 33.6 h at 25.0 ± 0.1 °C showing the exchange of the chloride ligand for a molecule of CD_3CN.

thermal rather than photochemical process. Additionally, for *bis*(NHC)Re(I) complexes, where the anion is noncoordinating, for example, PF_6^-, a series of cationic acetonitrile complexes was isolated and characterized.[36]

$^{99/99m}$Tc Labeling Studies. Because of the relative ease with which $[ReX(CO)_3(\hat{C}N)]$ complexes of 1-(2-pyridyl)-azolylidene NHC ligands could be synthesized using the Ag_2O transmetalation protocol, we became interested in the use of this approach to allow the preparation of the analogous $[^{99m}TcX(CO)_3(\hat{C}N)]$ complexes. The imidazolium salt, NHC proligand, 1-(2-pyridyl)-3-methylimidazolium iodide was radiolabeled with ^{99m}Tc by heating a methanol solution of the proligand and Ag_2O at 80 °C for 10 min followed by the addition of an aqueous solution of *fac*-$[^{99m}Tc(OH_2)_3(CO)_3]^+$ (prepared using a commercial Isolink labeling kit from $^{99m}TcO_4^-$). The radio-high-performance liquid chromatography (HPLC) chromatogram (mobile phase: acetonitrile and water) obtained for the ^{99m}Tc-labeled complex formed under these reaction conditions shows a single radioactive peak, which eluted at 12.94 min (Figure 8a, red trace). The radiochemical yield of the synthesized ^{99m}Tc-**3a** complex was determined giving a decay-corrected value of 78.9%. Initially, in an effort to characterize the ^{99m}Tc-**3a** labeled species the HPLC chromatogram for a freshly prepared acetonitrile solution of the analogous complex **3a**Cl was recorded (Figure 8b, black trace), with the complex eluting at 13.95 min. It was apparent that, although the retention times were similar, the HPLC chromatogram for ^{99m}Tc-**3a** did not match that of **3a**Cl. However, after incubation of the solution of **3a**Cl in acetonitrile at room temperature (RT) for 12 h (allowing for the exchange of the chloride ligand for a molecule of acetonitrile) the HPLC chromatogram for the aged solution (Figure 8c, blue trace) exhibits a peak (elution time = 12.78 min) associated with the cationic complexes $[\mathbf{3a}CH_3CN]^+$, which matches that of the ^{99m}Tc labeled species ^{99m}Tc-**3a**.

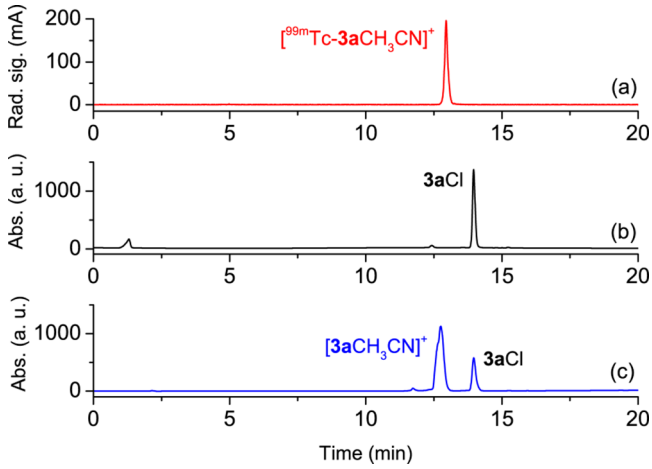

Figure 8. HPLC chromatograms obtained for: (a) ^{99m}Tc-**3a** (radioactivity) (b) a freshly prepared acetonitrile solution of (**3a**Cl) (absorbance at 254 nm) and (c) a solution of **3a**Cl in acetonitrile which has been incubated at RT for 12 h (allowing for the formation of $[\mathbf{3a}CH_3CN]^+$) (absorbance at 254 nm).

The HPLC experiments involving the Re(I) complex **3a**Cl and $[\mathbf{3a}CH_3CN]^+$ suggested that the ^{99m}Tc-labeled complex was also an acetonitrile adduct, that is, $[^{99m}$Tc-**3a**$CH_3CN]^+$. To confirm the identity of the ^{99m}Tc complex, the equivalent ^{99}Tc complex was prepared from $Na^{99}TcO_4$. As our radiochemistry laboratory is only licensed to handle very low quantities of ^{99}Tc ($t_{1/2}$ = 2.1 × 10^5 years), a large-scale synthesis of the desired ^{99}Tc-**3a** complex was not possible. As such, *fac*-$[^{99}Tc(OH_2)_3(CO)_3]^+$ was prepared by adding an aqueous solution of $Na^{99}TcO_4$ (1 mg/mL, 1 mL) to a Isolink labeling kit, and this was used to prepare ^{99}Tc-**3a** in a similar manner to ^{99m}Tc-**3a** (Experimental Section). In addition to the experiments where samples of ^{99m}Tc-**3a** and ^{99}Tc-**3a** were prepared separately, mixed samples of ^{99m}Tc-**3a** and ^{99}Tc-**3a** were prepared from mixtures of *fac*-$[^{99m}Tc(OH_2)_3(CO)_3]^+$ and *fac*-$[^{99}Tc(OH_2)_3(CO)_3]^+$ (Experimental Section). The radioactivity (^{99m}Tc-**3a**) and absorbance (254 nm) (^{99}Tc-**3a**) HPLC chromatograms obtained from samples of the Tc-labeled complexes prepared in separate reactions are shown in Figure S6 (Supporting Information). The radioactivity (^{99m}Tc-**3a**, blue) and a portion (10−16 min) of the absorbance (254 nm) (^{99}Tc-**3a**, red) HPLC chromatograms obtained for the Tc-labeled complexes prepared in the same synthetic reaction are shown in Figure 9 (full chromatograms in Figure S7, Supporting Information). A peak corresponding to the ^{99}Tc-**3a** complex (retention time 12.83 min), was detected under these conditions (Figure 9). The $^{99/99m}$Tc-**3a** complexes (eluting at 12.5−13.5 min) were collected, and the solution was subjected to electrospray ionization-mass spectroscopy (ESI-MS) analysis; the main (base) peak observed in the mass spectrum (Figure 9 inset, full spectrum Figure S8, Supporting Information) corresponds to the cationic acetonitrile complex $[^{99}$Tc-**3a**$CH_3CN]^+$, confirming the structure of the ^{99m}Tc-labeled complex as $[^{99m}$Tc-**3a**$CH_3CN]^+$. ESI-MS analysis of the same peak collected from the individual ^{99}Tc-labeling experiment produced the same base peak corresponding to the $[^{99}$Tc-**3a**$CH_3CN]^+$, confirming that this complex is generated from the *fac*-$[^{99}Tc(OH_2)_3(CO)_3]^+$ precursor. Very similar results were obtained when a mixture of *fac*-$[^{99m}Tc(OH_2)_3(CO)_3]^+$ and *fac*-$[^{99}Tc(OH_2)_3(CO)_3]^+$ (prepared from a mixture of $^{99m}TcO_4^-$ and $Na^{99}TcO_4$ in the same Isolink labeling kit) was

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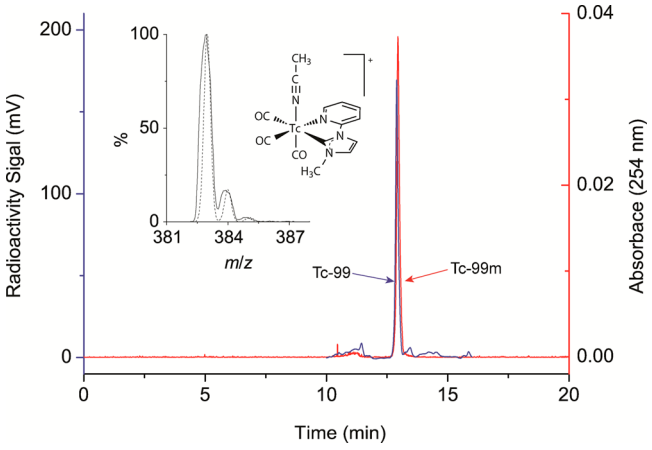

Figure 9. Superimposed radioactivity (red) and absorbance (254 nm, blue) HPLC chromatograms obtained for a mixture of $[^{99m}$Tc-**3a**$CH_3CN]^+$ and $[^{99}$Tc-**3a**$CH_3CN]^+$ prepared in the same reaction. The radioactive peak corresponding to ^{99m}Tc-**3a** (12.94 min) and the absorbance peak corresponding to ^{99}Tc-**3a** (12.83 min) are coincident (allowing for the arrangement of the radioactivity and UV-detection systems). (inset) The peak eluting at 12.83 min was collected and subjected to mass spectral analysis; experimental (solid) and theoretical (dotted) mass spectrum for $[^{99}$Tc-**3a**$CH_3CN]^+$.

used to prepare the $^{99/99m}$Tc-**3a** complexes (Supporting Information, Figure S9). These results shows that the $^{99/99m}$Tc complexes were analogous in structure to the Re(I) complex $[$**3a**$CH_3CN]^+$ formed in acetonitrile solutions upon exchange of the chloride ligand for CH_3CN (see Chloride Ligand Exchange section). The formation of this compound can be readily rationalized, as acetonitrile was used in combination with water as the mobile phase for the HPLC studies. Although the structures of the $^{99/99m}$Tc-**3a** complexes formed in the reaction (prior to injection onto the HPLC system and formation of the $[^{99/99m}$Tc-**3a**$CH_3CN]^+$ cationic complex) were not identified, it is likely that the sixth coordination site was occupied by a water molecule, that is, $[^{99/99m}$Tc-**3a**$H_2O]^+$ retained from the *fac*-$[^{99/99m}$Tc$(OH_2)_3(CO)_3]^+$ precursor.

CONCLUSION

A novel strategy for coupling carboxylic acid-functionalized azolium salt, NHC ligand precursors, to amine-bearing biomolecules using the common peptide coupling reagent EDC has been developed. The carboxylic acid-functionalized azolium salts were prepared by alkylation of either 1-(2-pyridyl)imidazole or 1-(2-pyridyl)benzimidazole with 2-bromoethyl acetate followed by ester hydrolysis under acidic conditions. As a proof-of-concept these molecules were coupled to benzyl ester-protected glycine via amide bond formation. This work provides a new approach to those strategies previously described for coupling azolium salts and NHC metal complexes to biomolecules[38−41] and is significant in the context of developing targeted radiopharmaceuticals based on NHC ligands.

Using the prepared azolium salts, a family of Re(I) complexes of the form $[ReX(CO)_3(C^{\wedge}N)]$ (where $C^{\wedge}N$ is a pyridyl−NHC ligand, and X is an anionic ligand: Cl^- or $R-CO_2^-$) were prepared. These complexes were synthesized in a relatively straightforward manner via a Ag(I) transmetalation protocol utilizing Ag_2O. A striking feature of the chemistry displayed by these systems was the relatively labile nature of the monodentate anionic X ligand. In the cases of complexes **3a**Cl, **3b**Cl, **8a**Cl, and **8b**Cl, the chloride ligand, originating from the $Re(CO)_5Cl$ precursor, was retained regardless of the anion associated with the azolium salt (e.g., Br^- or I^-). However, in the case of the carboxylic acid-functionalized azolium salts (**6a**·Br and **6b**·Br), dinculear Re(I) complexes were obtained where the chloride ligand had been displaced by a bridging interaction between the carboxylate functional groups on each of the azolylidene units. Additionally, when the azolium salts (**7a**·TsO and **7b**·TsO) were used in the Re(I) complex syntheses, an intractable mixture of complexes were obtained where X was either chloride or tosylate. ^{1}H NMR studies for **3a**Cl show that the chloride ligand is labile in acetonitrile solution and a that slow ligand exchange reaction takes place, where the chloride group was exchanged for an acetonitrile molecule yielding a cationic complex.

For the first time, an NHC ligand (1-(2-pyridyl)-3-methylimidazolylidene) has been labeled with the important medical radioisotope ^{99m}Tc. The ^{99m}Tc-NHC labeling was achieved using a Ag(I) transmetalation synthetic reaction by treating the imidazolium salt with Ag_2O followed by the addition of the synthetically versatile precursor compound $[^{99m}Tc(H_2O)_3(CO)_3]^+$ first reported by Alberto and co-workers,[50,51] which was conveniently prepared using the commercially available Isolink labeling kit. To confirm the structure of the radiolabeled complex, HPLC experiments were conducted, initially using the Re(I) complex **3a**Cl. This study showed that the ^{99m}Tc-**3a** complex had the same retention time as the acetonitrile adduct $[$**3a**$CH_3CN]^+$, suggesting that the formed ^{99m}Tc-**3a** complex was also an acetonitrile complex. To confirm this finding the equivalent ^{99}Tc-labeled complex ^{99}Tc-**3a** was prepared, and HPLC in combination with ESI-mass spectrometry confirmed that the identified complex was the acetonitrile adduct $[^{99/99m}$Tc-**3a**$CH_3CN]^+$. These studies show that NHC ligands can indeed be labeled with ^{99m}Tc in a time frame suitable for radiopharmaceutical development. It is clear, however, that the bidentate NHC ligand systems described here will be unsuitable for radiopharmaceutical development due to the labile nature of the additional monodentate ligand (e.g., Cl^- for Re and CH_3CN for Tc). It has been well-documented that monodentate and bidentate chelators often form ^{99m}Tc-tricarbonyl complexes with low solution stability resulting in high protein binding in the blood.[52]

EXPERIMENTAL SECTION

General Procedures. All reagents were purchased from Sigma-Aldrich or Alfa Aesar, were of analytical grade or higher, and were used without further purification unless otherwise stated. All manipulations were performed under nitrogen unless otherwise stated. 1-(2-Pyridyl)imidazole, 1-(2-pyridyl)benzimidazole,[53] and H-Gly-OBzl.TsO[54] were prepared according to literature methods. NMR spectra were recorded on either a Bruker Avance ARX-300 (300.14 MHz for ^{1}H, 75.48 MHz for ^{13}C), a Bruker Avance ARX-400 (400.13 MHz for ^{1}H, 100.61 MHz for ^{13}C), or a Bruker Avance ARX-500 (500.13 MHz for ^{1}H, 125.77 MHz for ^{13}C) spectrometer and were internally referenced to solvent resonances. Mass spectra were obtained using a Bruker Esquire6000 mass spectrometer fitted with an Agilent electrospray ion (ESI) source. UV−visible spectra were recorded using an Agilent Technologies Cary 300 UV−visible spectrophotometer using quartz cuvettes (1 cm). Fluorescence spectra were recorded on a Varian Cary Eclipse spectrofluorimeter (5 nm band-pass, 1 nm data interval, PMT voltage: 600 V) using quartz cuvettes (1 cm). Microanalyses were performed by the Microanalytical Laboratory

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at the ANU Research School of Chemistry, Canberra, Australia. All compounds were prepared in air unless otherwise specified.

X-ray Crystallography. Single crystals of the imidazolium salt **5a**·Br were grown by slow evaporation of a dichloromethane solution of this compound. Single crystals of the Re(I) complexes **3a**Cl, **3a**BzO, **3b**BzO, **8a**Cl, **10a**Cl, and **10b**TsO were grown by the diffusion of vapors between a solution of the title compound in dichloromethane and ether and **9b** by slow evaporation of an acetonitrile solution of this compound. Crystallographic data for all structures determined are given in Table S1 (Supporting Information). For all samples, crystals were removed from the crystallization vial and immediately coated with Paratone oil on a glass slide. A suitable crystal was mounted in Paratone oil on a glass fiber and cooled rapidly to 173 K in a stream of cold N_2 using an Oxford low-temperature device. Diffraction data were measured using an Oxford Gemini diffractometer mounted with Mo Kα λ = 0.710 73 Å and Cu Kα λ = 1.541 84 Å. Data were reduced and corrected for absorption using the CrysAlis Pro program.[55] The SHELXL2013−2[56] program was used to solve the structures with direct methods, with refinement by the full-matrix least-squares refinement techniques on F^2. The non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed geometrically and refined using the riding model. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. All calculations were carried out using the program Olex^2.[57] Images were generated by using ORTEP-3.[48] Further XRD details are provided in the Supporting Information.

Radiochemistry. All radiochemistry reactions involving ^{99}Tc or ^{99m}Tc were carried out in suitably lead-shielded fume hoods. Radioactivity measurements were performed on a CAPINTEC CRC-15R Dose Calibrator with calibration factor set to #080. Purification of the $^{99/99m}$Tc-**3a** radiocomplex was performed on a Waters Empower^2 controlled HPLC with a Waters 600E pump, a Rheodyne manual injection port, Waters 2998 Photodiode Array, and Carroll & Ramsay Associates 105S γ-detector with a sodium iodide crystal. A Waters Atlantis T3 analytical C18 column 5 μm 4.6 × 150 mm was used with a flow rate of 1 mL/min. Gradient elution was carried out as follows: mobile phase = (A) 0.1% trifluoroacetic acid (TFA) in H_2O and (B) 0.1% TFA in acetonitrile; 0−15 min, 90% A, 10% B to 10% A 90% B; 15−17 min 10% A 90% B, 17−17.5 min,10% A, 90%B to 90% A, 10%B, with at least 5 min prior to the next injection. The injection volume was 50 μL.

The radiochemical yield for ^{99m}Tc-**3a** was determined using the same HPLC system and solvent conditions as those described above, except a Waters Atlantis T3 prep C18 10 × 250 mm, 5 μm column was used with a flow rate of 3.5 mL/min. The peak corresponding to the ^{99m}Tc-**3a** radiocomplex eluted at 13.18 min.

***$^{99/99m}$*Tc3a Radiolabeling.** Samples of *fac*-[^{99m}Tc$(OH_2)_3(CO)_3]^+$ and *fac*-[^{99}Tc$(OH_2)_3(CO)_3]^+$ were synthesized separately, and a mixture of *fac*-[^{99m}Tc$(OH_2)_3(CO)_3]^+$ and *fac*-[^{99}Tc$(OH_2)_3(CO)_3]^+$ was prepared in a combined reaction using the commercially available Isolink labeling kit (kindly supplied by Covidien).

***fac*-[^{99m}Tc$(OH_2)_3(CO)_3]^+$.** A ^{99} Mo/^{99m}Tc generator (GENTECH, ANSTO Radiopharmaceuticals) was eluted with 4 mL of 0.9% saline (total activity = 3.30 GBq), and 1 mL of this eluent (825 MBq) was added to an Isolink labeling kit; this solution was heated at 100 °C for 1 h.

***fac*-[^{99}Tc$(OH_2)_3(CO)_3]^+$.** One milliliter of a solution of $Na^{99}TcO_4$ (1 mg/mL in 0.9% saline) was added to an Isolink labeling kit, and this solution was heated at 100 °C for 1 h.

***fac*-[$^{99m/99}$Tc$(OH_2)_3(CO)_3]^+$ and *fac*-[^{99}Tc$(OH_2)_3(CO)_3]^+$ (Combined Synthesis).** A ^{99} Mo/^{99m}Tc generator (GENTECH, ANSTO Radiopharmaceuticals) was eluted with 10 mL of 0.9% saline (total activity = 4.26 GBq), and 0.5 mL of this eluent (210 MBq) was combined with 0.5 mL of a solution of $Na^{99}TcO_4$ (1 mg/mL in 0.9% saline). The total reaction mixture (1 mL) was then added to an Isolink labeling kit, and this solution was heated at 100 °C for 1 h.

***^{99m}*Tc-3a.** A 1 mL microcentrifuge tube containing 1-(2-pyridyl)-3-methylimidazolium iodide (200 μg), Ag_2O (1 mg), and methanol (300 μL) was heated at 80 °C for 10 min. To this mixture *fac*-[^{99m}Tc$(OH_2)_3(CO)_3]^+$ (2 μL) was then added, and heating was continued for a further 15 min.

***^{99}*Tc-3a.** A 1 mL microcentrifuge tube containing 1-(2-pyridyl)-3-methylimidazolium iodide (200 μg), Ag_2O (1 mg), and methanol (200 μL) was heated at 80 °C for 10 min. To this mixture *fac*-[^{99}Tc$(OH_2)_3(CO)_3]^+$ (20 μL) was then added, and heating was continued for a further 15 min. At the conclusion of the reaction the resultant ^{99}Tc-**3a** reaction mixture was filtered through a 0.2 μm filter prior to injection into the HPLC system.

***$^{99/99m}$*Tc3a.** A 1 mL microcentrifuge tube containing 1-(2-pyridyl)-3-methylimidazolium iodide (300 μg), Ag_2O (1 mg), and methanol (450 μL) was heated at 80 °C for 10 min. To this mixture was added *fac*-[^{99m}Tc$(OH_2)_3(CO)_3]^+$ (2 μL) and *fac*-[^{99}Tc$(OH_2)_3(CO)_3]^+$ (20 μL) (prepared separately), and heating was continued for a further 15 min.

***$^{99/99m}$*Tc3a.** A 1 mL microcentrifuge tube containing 1-(2-pyridyl)-3-methylimidazolium iodide (300 μg), Ag_2O (1 mg), and methanol (450 μL) was heated at 80 °C for 10 min. To this mixture was added a mixture of *fac*-[^{99m}Tc$(OH_2)_3(CO)_3]^+$ and *fac*-[^{99}Tc$(OH_2)_3(CO)_3]^+$ (20 μL) (prepared simultaneously in a combined reaction from a mixture of $^{99m}TcO_4^-$ and $Na^{99}TcO_4$), and heating was continued for a further 15 min. The retention times for ^{99m}Tc**3a** and ^{99}Tc**3a** (12.06 and 12.33 min respectively) prepared under these conditions are slightly different than those obtained in the above experiments due to a different arrangement for the HPLC radioactivity and UV detection systems.

***^{99m}*Tc-3a** *for Radiochemical Yield Measurement.* A 1 mL microcentrifuge tube containing 1-(2-pyridyl)-3-methylimidazolium iodide (200 μg), Ag_2O (1 mg), and methanol (300 μL) was heated at 80 °C for 10 min. To this mixture *fac*-[^{99m}Tc$(OH_2)_3(CO)_3]^+$ (1.5 μL, 5.89 MBq) was added, and heating was continued for a further 15 min. After cooling, H_2O (250 μL) was added, and the entire contents were filtered through a 0.45 μm filter and injected into the HPLC system (actual injection 4.79 MBq). The radioactive peak corresponding to ^{99m}Tc-**3a** (eluting at 13.18 min) was collected, and the activity was measured (3.68 MBq) giving a decay-corrected radiochemical yield of 78.9%.

Synthesis. ***5a*·Br.** A solution of 1-(2-pyridyl)imidazole (0.50 g, 3.44 mmol) and ethyl 2-bromoacetate (0.58 g, 3.44 mmol) in acetonitrile (30 mL) was heated at 110 °C for 24 h. After cooling to RT a colorless solid precipitated, which was collected and washed with ether (Yield: 0.83 g, 77%). ^{1}H NMR (deuterated dimethyl sulfoxide (DMSO-d_6)): δ (ppm) 10.10 (s, 1H, H_{imi}(NC*H*N)), 8.65 (d, 1H, $^3J_{HH}$ = 4.80 Hz, H_{py}), 8.58 (dd, 1H, $^3J_{HH}$ = 1.95 Hz, $^4J_{HH}$ = 2.10 Hz, H_{imi}), 8.22 (dd, 1H, $^3J_{HH}$ = 7.80 Hz, $^3J_{HH}$ = 8.10 Hz, H_{py}), 8.05 (d, 1H, $^3J_{HH}$ = 8.10 Hz, H_{py}), 8.02 (dd, 1H, $^3J_{HH}$ = 1.95 Hz, $^4J_{HH}$ = 2.10 Hz, H_{imi}), 7.66 (dd, 1H, $^3J_{HH}$ = 4.80 Hz, $^3J_{HH}$ = 7.80 Hz, H_{py}), 5.36 (s, 2H, NCH_2C), 4.24 (q, 2H, $^3J_{HH}$ = 7.20 Hz, OCH_2C), 1.25 (t, 3H, $^3J_{HH}$ = 7.20 Hz, CH_3). ^{13}C NMR (DMSO-d_6): δ (ppm) 166.5 C_q, 149.4 C_{py}, 146.2 C_q, 140.8 C_{py}, 136.2 C_{imi}(NCHN), 125.5 C_{py}, 125.1 C_{imi}, 119.1 C_{imi}, 114.4 C_{py}, 62.1 OCH_2, 50.1 NCH_2, 14.0 CH_3. Anal. Calcd for $C_{12}H_{14}BrN_3O_2$: C, 44.23; H, 2.85; N, 7.93%. Found: C, 46.16; H, 4.53; N, 13.47%.

***5b*·Br.** This compound was prepared as described for **5a**·Br from 1-(2-pyridyl)benzimidazole (0.50 g, 2.56 mmol) and ethyl 2-bromoacetate (0.43 g, 2.56 mmol). (Yield: 0.81 g, 87%). ^{1}H NMR (DMSO-d_6): δ (ppm) 10.69 (s, 1H, $H_{benzimi}$(NC*H*N)), 8.78 (d, 1H, $^3J_{HH}$ = 3.90 Hz, H_{py}), 8.46−8.43 (m, 1H, $H_{benzimi}$), 8.30 (dd, 1H, $^3J_{HH}$ = 8.10 Hz, $^3J_{HH}$ = 7.80 Hz, H_{py}), 8.21−8.18 (m, 1H, $H_{benzimi}$), 8.11 (d, 1H, $^3J_{HH}$ = 8.10 Hz, H_{py}), 7.97−7.72 (m, 1H, H_{py} and 2H, $H_{benzimi}$), 5.78 (s, 2H, NCH_2C), 4.25 (q, 2H, $^3J_{HH}$ = 6.90 Hz, OCH_2C), 1.28−1.23 (t, 3H, $^3J_{HH}$ = 6.90 Hz, CH_3). ^{13}C NMR (DMSO-d_6): δ (ppm) 166.2 C_q, 149.6 C_{py}, 146.9 C_q, 143.3 $C_{benzimi}$(NCHN), 140.7 C_{py}, 131.9 C_q, 129.0 C_q, 127.8 $C_{benzimi}$, 127.5 $C_{benzimi}$, 125.4 C_{py}, 117.2 C_{py}, 115.7 $C_{benzimi}$, 114.4 $C_{benzimi}$, 62.3 OCH_2, 48.1 NCH_2C, 14.0 CH_3. Anal. Calcd for $C_{16}H_{16}BrN_3O_2.0.5H_2O$: C, 51.77; H, 4.62; N, 11.32%. Found: C, 51.84; H, 4.55; N, 11.39%.

***6a*·Br.** A solution of **5a**·Br (0.60 g, 1.92 mmol) in 5 M HCl (15 mL) was heated at 110 °C for 2 h. After cooling to RT the solvent was removed under reduced pressure, and the crude product was recrystallized by slowly adding acetone to a solution of the crude

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product in hot methanol, yielding a colorless crystalline powder (Yield: 0.51 g, 93%). ^{1}H NMR (DMSO-d_6): δ (ppm) 10.04 (s, 1H, H_{imi}(NC*H*N)), 8.63 (d, 1H, $^3J_{HH}$ = 4.80 Hz, H_{py}), 8.52 (dd, 1H, $^3J_{HH}$ = 1.95 Hz, $^4J_{HH}$ = 2.10 Hz, H_{imi}), 8.19 (dd, 1H, $^3J_{HH}$ = 7.80 Hz, $^3J_{HH}$ = 8.10 Hz, H_{py}), 8.02 (d, 1H, $^3J_{HH}$ = 8.10 Hz, H_{py}), 7.97 (dd, 1H, $^3J_{HH}$ = 1.95 Hz, $^4J_{HH}$ = 2.10 Hz, H_{imi}), 7.63 (dd, 1H, $^3J_{HH}$ = 4.80 Hz, $^3J_{HH}$ = 7.80 Hz, H_{py}), 5.20 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6): δ (ppm) 167.7 C_q, 149.3 C_{py}, 146.2 C_q, 140.7 C_{py}, 136.0 C_{imi}(NCHN), 125.4 C_{py}, 125.0 C_{imi}, 118.9 C_{imi}, 114.3 C_{imi}, 105.9 C_{py}, 50.3 CH_2. Anal. Calcd for $C_{10}H_{10}BrN_3O_2.0.5(CH_3)_2CO$: C, 44.11; H, 4.18; N, 13.42%. Found: C, 43.91; H, 4.04; N, 15.28%. The reported elemental analysis results are provided to illustrate the best values obtained to date. Copies of the NMR spectra (^{1}H and ^{13}C) are provided in the Supporting Information (Figure S10) as additional evidence of purity.

***6b*·*Br*.** This compound was prepared as described for **6a**·Br from **5b**·Br (0.50 g, 1.38 mmol) (Yield: 0.40 g, 87%). ^{1}H NMR (DMSO-d_6): δ (ppm) 10.50 (s, 1H, $H_{benzimi}$(NC*H*N)), 8.79 (d, 1H, $^3J_{HH}$ = 3.30 Hz, H_{py}), 8.45−8.42 (m, 1H, $H_{benzimi}$), 8.29 (dd, 1H, $^3J_{HH}$ = 7.95 Hz, $^3J_{HH}$ = 8.10 Hz, H_{py}), 8.19−8.16 (m, 1H, $H_{benzimi}$), 8.06 (d, 1H, $^3J_{HH}$ = 8.10 Hz, H_{py}), 7.8−7.72 (m, 1H, H_{py} and 2H, $H_{benzimi}$), 5.59 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6): δ (ppm) 167.5 C_q, 149.7 C_{py}, 147.0 C_q, 143.4 $C_{benzimi}$(NCHN), 140.8 C_{py}, 132.0 C_q, 129.2 C_q, 127.9 $C_{benzimi}$, 127.5 $C_{benzimi}$, 125.5 C_{py}, 117.3 C_{py}, 115.7 $C_{benzimi}$, 114.4 $C_{benzimi}$, 48.1 CH_2. Anal. Calcd for $C_{14}H_{12}BrN_3O_2.0.5CH_3OH$: C, 49.73; H, 4.03; N, 12.00%. Found: C, 49.84; H, 4.31; N, 12.16%.

***7a*·*TsO*.** A mixture of H-Gly-OBzl.TsO (0.25 g, 0.74 mmol) and *N*,*N*-diisopropylethylamine (DIPEA) (0.10 g, 0.74 mmol) in ethanol was stirred for 35 min, followed by the addition of **6a**·Br (0.21 g, 0.74 mmol), DIPEA (0.10 g, 0.74 mmol) and hydroxybenzotriazole (HOBt) (0.02 g, 0.15 mmol). The mixture was cooled to 10 °C in an ice water bath, and EDC (0.21 g, 1.11 mmol) was added,; stirring was continued for 48 h. After purification on silica, with dichloromethane (95%) and methanol (5%) as the eluent, the product was obtained as a white crystalline solid. (Yield: 0.15 g, 39%). ^{1}H NMR (DMSO-d_6): δ (ppm) 10.05 (s, 1H, H_{imi}(NCHN)), 8.96 (t, 1H, $^3J_{HH}$ = 5.70 Hz, N*H*), 8.65 (d, 1H, $^3J_{HH}$ = 4.80 Hz, H_{py}), 8.52 (dd, 1H, $^3J_{HH}$ = 1.95 Hz, $^4J_{HH}$ = 2.10 Hz, H_{imi}), 8.21 (dd, 1H, $^3J_{HH}$ = 6.90 Hz, $^3J_{HH}$ = 8.40 Hz, H_{py}), 8.02 (d, 1H, $^3J_{HH}$ = 8.40 Hz, H_{py}), 7.94 (dd, 1H, $^3J_{HH}$ = 1.95 Hz, $^4J_{HH}$ = 2.10 Hz, H_{imi}), 7.65 (dd, 1H, $^3J_{HH}$ = 6.90 Hz, $^3J_{HH}$ = 4.80 Hz, H_{py}), 7.46 (d, 2H, $^3J_{HH}$ = 7.80 Hz, H_{Ar-SO3}), 7.37−7.31 (m, 5H, H_{Ar}), 7.09 (d, 2H, $^3J_{HH}$ = 7.80 Hz, H_{Ar-SO3}), 5.18 (s, 2H, OCH_2), 5.14 (s, 2H, imi−CH_2), 4.04 (d, 2H, $^3J_{HH}$ = 5.70 Hz, NCH_2), 2.27 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ (ppm) 169.3 C_q, 165.3 C_q, 149.4 C_{py}, 146.3 C_q, 145.9 C_q, 140.7 C_{py}, 137.5 C_q, 136.2 C_{imi}(NCHN), 135.8 C_q, 128.5 C_{Ar-SO3}, 128.2 C_{Ar}, 128.0 C_{Ar}, 125.5 C_{Ar-SO3}, 125.4 C_{py}, 125.2 C_{imi}, 118.8 C_{imi}, 114.3 C_{py}, 66.1 O-CH_2, 51.0 imi-CH_2, 41.0 NCH_2, 20.8 CH_3. Anal. Calcd for $C_{26}H_{26}N_4O_6S.H_2O$: C, 57.77; H, 5.22; N, 10.36%. Found: C, 57.94; H, 5.16; N, 10.31%.

***7a*·*Cl*.** To a stirred solution of **7a**·OTs (0.1 g, 0.19 mmol) in methanol (5%) and water (95%) (5 mL) was added to a solution of KPF_6 (0.04 g, 0.22 mmol) in water (5 mL). After 10 min a residue oil was separated, which was isolated by centrifugation and resuspended in tetrahydrofuran (THF) (5 mL), followed by the addition of a solution of Bu_4NCl (0.06 g, 0.22 mmol) in THF (5 mL). The mixture was stirred for 15 min, and the crude product separated as a colorless oil, which was isolated by centrifugation. The oil was redissolved in dichloromethane, and ether was added until the product separated as a white hygroscopic crystalline solid. (Yield: 0.07 g, 94%). ^{1}H NMR ($CDCl_3$): δ (ppm) 11.25 (s, 1H, H_{imi}(NC*H*N)), 9.77 (t, 1H, $^3J_{HH}$ = 5.40 Hz, N*H*), 8.54 (d, 1H, $^3J_{HH}$ = 4.80 Hz, H_{py}), 8.12 (dd, 1H, $^3J_{HH}$ = 1.60 Hz, $^4J_{HH}$ = 1.60 Hz, H_{imi}), 8.05 (d, 1H, $^3J_{HH}$ = 8.40 Hz, H_{py}), 7.99 (dd, 1H, $^3J_{HH}$ = 7.40, $^3J_{HH}$ = 8.40 Hz, H_{py}), 7.62 (dd, 1H, $^3J_{HH}$ = 1.60 Hz, $^4J_{HH}$ = 1.60 Hz, H_{imi}), 7.46 (dd, 1H, $^3J_{HH}$ = 7.40 Hz, $^3J_{HH}$ = 4.80 Hz, H_{py}), 7.32−7.26 (m, 5H, H_{Ar}), 5.50 (s, 2H, imi−CH_2), 5.07 (s, 2H, OCH_2), 4.06 (d, 2H, $^3J_{HH}$ = 5.40 Hz, NHCH_2). ^{13}C NMR ($CDCl_3$): δ (ppm) 169.2 C_q, 165.3 C_q, 149.6 C_{py}, 146.2 C_q, 140.7 C_{py}, 136.4 C_q, 135.5 C_{imi}(NCHN), 128.8 C_{Ar}, 128.6 C_{Ar}, 128.5 C_{Ar}, 125.5 C_{py}, 123.9 C_{imi}, 118.5 C_{imi}, 114.6 C_{py}, 67.3 OCH_2, 52.6 imi-CH_2, 41.7 NHCH_2. ESI-MS: m/z = 351.2 $[C_{19}H_{19}N_4O_3]^+$. This compound was very hygroscopic, and accurate elemental analysis results could not be obtained; ^{1}H and ^{13}C NMR spectra are provided in the Supporting Information (Figure S11) as additional evidence of purity.

***7b*·*TsO*.** This compound was prepared as described for **7a**·TsO from **6b**·Br (0.23 g, 0.69 mmol). The product was obtained as a colorless oil. (Yield: 0.18 g, 47%). ^{1}H NMR ($CDCl_3$): δ (ppm) 10.77 (s, 1H, $H_{benzimi}$(NC*H*N)), 9.33 (t, 1H, $^3J_{HH}$ = 5.70 Hz, N*H*), 8.61 (d, 1H, $^3J_{HH}$ = 4.80 Hz, H_{py}), 8.52−8.49 (m, 1H, $H_{benzimi}$), 8.16 (d, 1H, $^3J_{HH}$ = 8.10 Hz, $H_{benzimi}$), 7.96−7.91(m, 1H, H_{py} and 1H, $H_{benzimi}$), 7.72 (d, 2H, $^3J_{HH}$ = 8.10 Hz, 2H_{Ar-SO3}), 7.59−7.54 (m, 1H, H_{py} and 1H, $H_{benzimi}$), 7.43 (dd, 1H, $^3J_{HH}$ = 4.80 Hz, $^3J_{HH}$ = 7.35 Hz, H_{py}), 7.23 (s, 5H, H_{Ar}), 7.03 (d, 2H, $^3J_{HH}$ = 8.10 Hz, 2H_{Ar-SO3}), 5.85 (s, 2H, benzimi−CH_2), 4.98 (s, 2H, CH_2-Ar), 3.98 (d, 2H, $^3J_{HH}$ = 5.70 Hz, NCH_2), 2.25 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ (ppm) 168.7 C_q, 164.8 C_q, 148.5 C_{py}, 147.6 C_q, 142.3 C_q,141.9 $C_{benzimi}$(NCHN), 140.0 $C_{benzimi}$, 139.3 C_q, 134.9 C_q, 132.0 C_q, 129.4 C_q, 128.3 C_{Ar-SO3}, 128.1 C_{Ar}, 127.8 C_{Ar}, 127.7 C_{Ar}, 127.4 C_{py} and $C_{benzimi}$, 125.5 C_{Ar-SO3}, 124.2 C_{py}, 116.4 $C_{benzimi}$, 113.8 C_{py}, 66.4 CH_2−Ar, 49.4 benzimi-CH_2, 41.1 NCH_2, 20.8 CH_3. Anal. Calcd for $C_{30}H_{28}N_4O_6S.H_2O$: C, 61.00; H, 5.12; N, 9.49%. Found: C, 60.86; H, 5.39; N, 9.18%.

***7b*·*Cl*.** To a stirred solution of **7b**·TsO (0.10 g, 0.17 mmol) in methanol (5%) and water (95%) (5 mL) was added to a solution of KPF_6 (0.04 g, 0.22 mmol) in water (5 mL). After 10 min, a residue oil was separated, which was isolated by centrifugation and resuspended in THF (5 mL), followed by the addition of a solution of Bu_4NCl (0.06 g, 0.22 mmol) in THF (5 mL). Addition of ether (2 mL) into the solution afforded the product as white hygroscopic needles. (Yield: 0.06 g, 80%). ^{1}H NMR ($CDCl_3$): δ (ppm) 11.69 (s, 1H, $H_{benzimi}$(NC*H*N)), 10.02 (t, 1H, $^3J_{HH}$ = 6.0 Hz, N*H*), 8.68 (d, 1H, $^3J_{HH}$ = 5.0 Hz, H_{py}), 8.58−8.56 (m, 1H, $H_{benzimi}$), 8.22 (d, 1H, $^3J_{HH}$ = 7.5 Hz, H_{py}), 8.07 (dd, 1H, $^3J_{HH}$ = 7.50 Hz, $^3J_{HH}$ = 6.25 Hz, H_{py}), 8.03−8.01 (m, 1H, $H_{benzimi}$), 7.67−7.66 (m, 2H, $H_{benzimi}$) 7.51 (dd, 1H, $^3J_{HH}$ = 6.25 Hz, $^3J_{HH}$ = 5.0 Hz, H_{py}), 7.26−7.21 (m, 5H, H_{Ar}), 5.81 (s, 2H, benzimi−CH_2), 5.00 (s, 2H, OCH_2), 4.06 (d, 2H, $^3J_{HH}$ = 6.0 Hz, NHCH_2). ^{13}C NMR ($CDCl_3$): δ (ppm) 169.1 C_q, 165.0 C_q, 149.5 C_{py}, 148.2 C_q, 142.2 C_q, 140.7 $C_{benzimi}$(NCHN), 135.5 C_{py}, 132.5 C_q, 130.0 C_q, 128.7 C_{Ar}, 128.5 C_{Ar}, 128.4 $C_{benzimi}$, 128.3 C_{Ar}, 128.2 $C_{benzimi}$, 125.1 C_{py}, 117.1 $C_{benzimi}$, 116.9 $C_{benzimi}$, 114.4 $C_{benzimi}$, 67.1 OCH_2, 50.5 benziimi-CH_2, 41.6 NHCH_2. ESI-MS: m/z = 401.2 $[C_{23}H_{21}N_4O_3]^+$. This compound was very hygroscopic, and accurate elemental analysis results could not be obtained; ^{1}H and ^{13}C NMR spectra are provided in the Supporting Information (Figure S12) as additional evidence of purity.

***3a*Cl.** A mixture of $Re(CO)_5Cl$ (0.05 g, 0.14 mmol), 1-(2-pyridyl)-3-methylimidazolium iodide (0.04 g, 0.14 mmol), and Ag_2O (0.06 g, 0.28 mmol) in dichloromethane (30 mL) was heated at 70 °C for 24 h. The mixture was filtered through Celite. The filtrate was concentrated on the rotary evaporator, and a small amount of ether was added, resulting in a bright yellow precipitate, which was collected and recrystallized by the addition of ether into a solution of the crude product in dichloromethane. The product was obtained as a crystalline yellow solid (Yield: 0.05 g, 77%). ^{1}H NMR (DMSO-d_6): δ (ppm) 8.82 (d, 1H, $^3J_{HH}$ = 6.00 Hz, H_{py}), 8.42 (d, 1H, $^3J_{HH}$ = 2.10 Hz, H_{imi}), 8.34−8.22 (m, 2H, 2H_{py}), 7.66 (d, 1H, $^3J_{HH}$ = 2.10 Hz, H_{imi}), 7.49 (dd, 1H, $^3J_{HH}$ = 6.00 Hz, $^3J_{HH}$ = 6.60 Hz, H_{py}), 3.92 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ (ppm) 153.2 C_{py}, 152.7 NCN, 142.3 C_{py}, 125.0 C_{imi}, 124.0 C_{py}, 117.3 C_{imi}, 112.8 C_{py}, 38.5 CH_3. Anal. Calcd for $C_{12}H_{12}ClN_3O_3Re$: C, 30.80; H, 2.59; N, 8.98%. Found: C, 31.03; H, 2.69; N, 9.05%.

***3b*Cl.** This compound was prepared as described for **3a**Cl from 1-(2-pyridyl)-3-methylbenzimidazolium iodide (0.05 g, 0.16 mmol). (Yield: 0.05 g, 61%). ^{1}H NMR (DMSO-d_6): δ (ppm) 8.95 (d, 1H, $^3J_{HH}$ = 5.10 Hz, H_{py}), 8.62 (d, 1H, $^3J_{HH}$ = 8.10 Hz, H_{py}), 8.47−8.44 (m, 1H, $H_{benzimi}$), 8.35 (dd, 1H, $^3J_{HH}$ = 7.80 Hz, $^3J_{HH}$ = 8.10 Hz, H_{py}), 7.93−7.91 (m, 1H, $H_{benzimi}$), 7.61−7.55 (m, 1H, H_{py} and 2H, $H_{benzimi}$), 4.19 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ (ppm) 201.5 C_q, 198.7 C_q, 197.8 C_q, 188.7 C_q, 153.9 C_{py}, 153.2 NCN, 142.5 C_{py}, 135.3 C_q, 130.3 C_q, 125.4 2$C_{benzimi}$, 123.7 C_{py}, 113.9 C_{py}, 113.1 $C_{benzimi}$, 112.7

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$C_{benzimi}$, 35.9 CH_3. Anal. Calcd for $C_{16}H_{14}ClN_3O_3Re$: C, 37.10; H, 2.72; N, 8.11%. Found: C 37.27; H 2.65; N 8.19%.

***3a**BzO*. A mixture of **3a**Cl (0.02 g, 0.043 mmol) and silver benzoate (10 mg, 0.043 mmol) in dichloromethane (30 mL) was refluxed for 24 h. The resultant mixture was filtered through Celite, and the solution was concentrated on the rotary evaporator. The addition of ether resulted in a bright yellow precipitate, which was collected and recrystallized by the addition of ether into a solution of the crude product in dichloromethane. The product was obtained as a crystalline yellow solid. (Yield: 0.02 g, 85%). ^{1}H NMR (DMSO-d_6): δ (ppm) 8.92 (d, 1H, $^3J_{HH}$ = 6.50 Hz, H_{py}), 8.38 (d, 1H, $^3J_{HH}$ = 2.00 Hz, H_{imi}), 8.32 (dd, 1H, $^3J_{HH}$ = 7.00 Hz, $^3J_{HH}$ = 8.00 Hz, H_{py}), 8.22 (d, 1H, $^3J_{HH}$ = 8.00 Hz, H_{py}), 7.65 (d, 1H, $^3J_{HH}$ = 2.00 Hz, H_{imi}), 7.52 (dd, 1H, $^3J_{HH}$ = 6.50 Hz, $^3J_{HH}$ = 7.00 Hz, H_{py}), 7.35 (d, 2H, $^3J_{HH}$ = 8.00 Hz, $2H_{Ar}$), 7.25 (dd, 1H, $^3J_{HH}$ = 7.75 Hz, $^3J_{HH}$ = 8.00 Hz, H_{Ar}), 7.15 (dd, 2H, $^3J_{HH}$ = 7.75 Hz, $^3J_{HH}$ = 8.00 Hz, $2H_{Ar}$), 4.01 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ (ppm) 191.8 C_q, 154.0 C_{py}, 153.4 NCN, 143.0 C_{py}, 135.9 C_q, 130.4 C_{Ar}, 129.1 $2C_{Ar}$, 128.0 $2C_{Ar}$, 125.4 C_{imi}, 124.4 C_{py}, 117.6 C_{imi}, 112.9 C_{py}, 38.9 CH_3. Anal. Calcd for $C_{19}H_{14}N_3O_5Re$: C, 41.45; H, 2.56; N, 7.63%. Found: C, 41.66; H, 2.81; N, 7.40%.

***3b**BzO*. This compound was prepared as described for **3a**BzO from **3b**Cl (0.02 g, 0.038 mmol) and silver benzoate (9 mg, 0.038 mmol). A yellow solid was obtained. (Yield: 0.018 g, 81%). ^{1}H NMR (DMSO-d_6): δ (ppm) 9.04 (d, 1H, $^3J_{HH}$ = 5.70 Hz, H_{py}), 8.61 (d, 1H, $^3J_{HH}$ = 8.40 Hz, H_{py}), 8.44–8.33 (m, 1H, H_{py} and 1H, $H_{benzimi}$), 7.95–7.92 (m, 1H, $H_{benzimi}$), 7.63–7.55 (m, 1H, H_{py} and 2H, $H_{benzimi}$), 7.35–7.32 (d, 2H, $^3J_{HH}$ = 7.20 Hz, H_{Ar}), 7.25 (dd, 1H, $^3J_{HH}$ = 7.20 Hz, $^3J_{HH}$ = 7.20 Hz, H_{Ar}), 7.11 (dd, 2H, $^3J_{HH}$ = 7.20 Hz, $^3J_{HH}$ = 7.20 Hz, H_{Ar}), 4.28 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ (ppm) 206.5 C_q, 202.1 C_q, 199.0 C_q, 169.8 C_q, 154.2 C_{py}, 153.5 NCN, 142.9 C_{py}, 135.4 C_q, 135.3 C_q, 130.3 C_q, 130.1 C_{Ar}, 128.7 $2C_{Ar}$, 127.5 $2C_{Ar}$, 125.4 $C_{benzimi}$, 125.3 C_{py}, 123.7 $C_{benzimi}$, 113.7 C_{py}, 113.1 $C_{benzimi}$, 112.8 $C_{benzimi}$, 36.0 CH_3. Anal. Calcd for $C_{23}H_{16}N_3O_5Re.H_2O$: C, 44.66; H, 2.93; N, 6.79%. Found: C, 44.83; H, 3.01; N, 6.81%.

***8a**Cl*. This compound was prepared as described for **3a**Cl from $Re(CO)_5Cl$ (0.10 g, 0.28 mmol), ligand **5a**·Br (0.09 g, 0.28 mmol), and Ag_2O (0.13 mg, 0.56 mmol) in dichloromethane (50 mL). (Yield: 0.08 g, 54%). ^{1}H NMR ($CDCl_3$): δ (ppm) 8.86 (d, 1H, $^3J_{HH}$ = 4.80 Hz, H_{py}), 8.00 (dd, 1H, $^3J_{HH}$ = 7.80 Hz, $^3J_{HH}$ = 8.40 Hz, H_{py}), 7.63 (d, 1H, $^3J_{HH}$ =1.80 Hz, H_{imi}), 7.61 (d, 1H, $^3J_{HH}$ = 8.40 Hz, H_{py}) 7.31 (dd, 1H, $^3J_{HH}$ = 5.30 Hz, $^3J_{HH}$ = 7.80 Hz, H_{py}), 7.12 (d, 1H, $^3J_{HH}$ = 1.80 Hz, H_{imi}), 5.19 (d, 1H, $^2J_{HH}$ = 17.70 Hz, NCH_2), 4.87 (d, 1H, $^2J_{HH}$ = 17.70 Hz, NCH_2), 4.35–4.28 (m, 2H, OCH_2), 1.32 (t, 3H, $^3J_{HH}$ = 7.20 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ (ppm) 230.4 C_q, 218.7 C_q, 197.4 C_q, 188.1 C_q, 168.0 NCN, 153.8 C_{py}, 141.3 C_{py}, 123.6 C_{imi}, 123.7 C_{py}, 116.4 C_{imi}, 112.0 C_{py}, 63.0 OCH_2, 53.0 NCH_2, 14.2 CH_3. Anal. Calcd for $C_{15}H_{16}ClN_3O_5Re$: C, 33.37; H, 2.99; N, 7.78%. Found: C, 33.65; H, 2.83; N, 7.93%.

***8b**Cl*. This compound was prepared as described for **3a**Cl from $Re(CO)_5Cl$ (0.10 g, 0.28 mmol), ligand **5b**·Br (0.10 g, 0.28 mmol), and Ag_2O (0.13 g, 0.56 mmol). (Yield: 0.11 g, 68%). ^{1}H NMR (DMSO-d_6): δ (ppm) 8.96 (d, 1H, $^3J_{HH}$ = 5.70 Hz, H_{py}), 8.68 (d, 1H, $^3J_{HH}$ = 8.70 Hz, H_{py}), 8.52–8.49 (m, 1H, $H_{benzimi}$), 8.38 (dd, 1H, $^3J_{HH}$ = 8.25 Hz, $^3J_{HH}$ = 8.40 Hz, H_{py}), 8.02–8.00 (m, 1H, $H_{benzimi}$), 7.64–7.56 (m, 1H, H_{py} and 2H, $H_{benzimi}$), 5.77 (d, 1H, $^2J_{HH}$ = 17.40 Hz, N–CH_2), 5.36 (d, 1H, $^2J_{HH}$ = 17.40 Hz, N–CH_2), 4.26–4.18 (m, 2H, OCH_2), 1.22 (t, 3H, $^3J_{HH}$ = 7.50 Hz, CH_3). ^{13}C NMR (DMSO-d_6): δ (ppm) 197.9 C_q, 197.4 C_q, 187.8 C_q, 166.6 C_q, 153.9 C_{py}, 153.0 $C_{benzimi}$(NCN), 142.6 C_{py}, 135.0 C_q, 130.1 C_q, 125.6 $C_{benzimi}$, 125.4 $C_{benzimi}$, 123.9 C_{py}, 114.2 C_{py}, 113.2 $C_{benzimi}$, 112.7 $C_{benzimi}$, 61.6 OCH_2, 49.9 NCH_2, 13.9 CH_3. Anal. Calcd for $C_{19}H_{18}ClN_3O_5Re$: C, 38.68; H, 3.07; N, 7.12%. Found: C, 38.75; H, 2.97; N, 7.29%.

9a. This compound was prepared as described for **3a**Cl from $Re(CO)_5Cl$ (0.07 g, 0.19 mmol), **6a**·Br (0.05 g, 0.19 mmol), and Ag_2O (0.09 g, 0.38 mmol) in methanol (10%) and dichloromethane (90%) (30 mL). The resulting bright yellow precipitate was collected and recrystallized by the addition of ether into a solution of the crude product in methanol. (Yield: 0.10 g, 55%). ^{1}H NMR (DMSO-d_6): δ (ppm) 8.92 (d, 1H, $^3J_{HH}$ = 5.50 Hz, H_{py}), 8.41 (d, 1H, $^3J_{HH}$ = 2.00 Hz, H_{imi}), 8.29 (dd, 1H, $^3J_{HH}$ = 7.50 Hz, $^3J_{HH}$ = 80 Hz, H_{py}), 8.19 (d, 1H, $^3J_{HH}$ = 8.00 Hz, H_{py}), 7.54 (d, 1H, $^3J_{HH}$ = 2.00 Hz, H_{imi}), 7.47 (dd, 1H, $^3J_{HH}$ = 5.50 Hz, $^3J_{HH}$ = 7.50 Hz, H_{py}), 4.49 (d, 1H, $^2J_{HH}$ = 15.00 Hz, CH_2), 4.43 (d, 1H, $^2J_{HH}$ = 15.00 Hz, CH_2). ^{13}C NMR (DMSO-d_6): δ (ppm) 170.0 NCN, 154.3 C_{py}, 142.7 C_{py}, 138.8 C_q, 125.5 C_{imi}, 123.7 C_{py}, 117.2 C_{imi}, 112.6 C_{py}, 55.2 CH_2. ESI-MS: m/z = 966.9 $[C_{26}H_{19}N_6O_{10}Re_2Na]^+$, 982.9 $[C_{26}H_{19}N_6O_{10}Re_2K]^+$. Anal. Calcd for $C_{26}H_{19}N_6O_{10}Re_2.1.5H_2O$: C, 31.93; H, 2.58; N, 8.59%. Found: C, 31.70; H, 2.15; N, 8.57%.

9b. This compound was prepared as described for **9a** from $Re(CO)_5Cl$ (0.10 g, 0.28 mmol), **6b**·Br (0.08 g, 0.28 mmol), and Ag_2O (0.13 g, 0.56 mmol). (Yield: 0.13 g, 45%). ^{1}H NMR (DMSO-d_6): δ (ppm) 8.62 (d, 1H, $^3J_{HH}$ = 6.30 Hz, H_{py}), 8.04 (dd, 1H, $^3J_{HH}$ = 8.70 Hz, $^3J_{HH}$ = 8.70 Hz, H_{py}), 7.90 (d, 1H, $^3J_{HH}$ = 8.70 Hz, $H_{benzimi}$), 7.63 (d, 1H, $^3J_{HH}$ = 8.70 Hz, H_{py}), 7.45–7.34 (m, 1H, H_{py} and 1H, $H_{benzimi}$), 7.01 (d, 2H, $^3J_{HH}$ = 4.20 Hz, $H_{benzimi}$), 4.96 (d, 1H, $^2J_{HH}$ = 16.70 Hz, CH_2), 4.73 (d, 1H, $^2J_{HH}$ = 16.70 Hz, CH_2). ^{13}C NMR (DMSO-d_6): δ (ppm) 167.7 NCN, 153.0 C_{py}, 152.4 C_q, 143.1 C_q, 142.3 C_{py}, 134.7 C_q, 124.9 $C_{benzimi}$, 124.4 $C_{benzimi}$, 122.7 C_{py}, 113.0 C_{py}, 112.8 $C_{benzimi}$, 112.4 $C_{benzimi}$, 51.1 CH_2. ESI-MS: m/z = 1066.9 $[C_{34}H_{23}N_6O_{10}Re_2Na]^+$, 1082.9 $[C_{34}H_{23}N_6O_{10}Re_2K]^+$. Anal. Calcd for $C_{34}H_{23}N_6O_{10}Re_2.CH_3OH$: C, 38.81; H, 2.79; N, 7.76%. Found: C, 38.79; H, 2.93; N, 7.83%.

***10a**Cl*. This compound was prepared as described for **3a**Cl from $Re(CO)_5Cl$ (0.05 g, 0.14 mmol), **7a**·Cl (0.06 g, 0.14 mmol), and Ag_2O (0.06 g, 0.28 mmol). (Yield: 0.06 g, 66%). ^{1}H NMR ($CDCl_3$): δ (ppm) 8.89 (d, 1H, $^3J_{HH}$ = 5.80 Hz, H_{py}), 8.07 (dd, 1H, $^3J_{HH}$ = 7.14 Hz, $^3J_{HH}$ = 6.76 Hz, H_{py}), 7.59–7.57 (m, 2H, 1H, H_{imi} and 1H, H_{py}), 7.52 (t, 1H, $^3J_{HH}$ = 5.80 Hz, N*H*), 7.38–7.28 (m, 6H, 1H, H_{py}, and 5H, H_{Ar}), 7.15 (d, 1H, $^3J_{HH}$ = 1.80 Hz, H_{imi}), 5.24 (d, 1H, $^2J_{HH}$ = 16.16 Hz, imi–CH_2), 5.07 (s, 2H, OCH_2), 4.79 (d, 1H, $^2J_{HH}$ = 16.16 Hz, imi–CH_2), 4.25–3.92 (m, 2H, NCH_2). ^{13}C NMR ($CDCl_3$): δ (ppm) 216 C_q, 197 C_q, 195.2 C_q, 179.1 C_{py}, 169.0 NCN, 154.1 C_{py}, 145.9 C_q, 141.4 C_q, 129.8 C_{Ar}, 128.7 C_{Ar}, 128.5 C_{Ar}, 124.1 C_{imi}, and C_{py}, 116.0 C_q, 112.1 C_{py}, 109.1 C_{imi}, 67.2 OCH_2, 55.6 imi-CH_2, 41.7 NCH_2. Anal. Calcd for $C_{22}H_{18}ClN_4O_6Re$: C, 40.28; H, 2.77; N, 8.54%. Found: C, 40.18; H, 2.74; N, 8.45%.

***10b**Cl*. This compound was prepared as described for **3a**Cl from $Re(CO)_5Cl$ (0.09 g, 0.25 mmol), **7b**·Cl (0.11 g, 0.25 mmol), and Ag_2O (0.12 g, 0.50 mmol). (Yield: 0.12 g, 68%). ^{1}H NMR ($CDCl_3$): δ (ppm) 9.74 (d, 1H, $^3J_{HH}$ = 5.50 Hz, H_{py}), 8.15–8.14 (m, 2H, H_{py}), 7.92 (d, 1H, $^3J_{HH}$ = 7.50 Hz, $H_{benzimi}$), 7.66 (t, 1H, $^3J_{HH}$ = 5 Hz, N*H*), 7.63 (d, 1H, $^3J_{HH}$ = 7 Hz, $H_{benzimi}$), 7.51–7.48 (m, 2H, $H_{benzimi}$), 7.35 (dd, 1H, $^3J_{HH}$ = 9.50 Hz, $^3J_{HH}$ = 5.50 Hz, H_{py}), 7.28–7.21 (m, 5H, H_{Ar}), 5.73 (d, 1H, $^2J_{HH}$ = 16.5 Hz, benzimi–CH_2), 5.08 (d, 1H, $^2J_{HH}$ = 16.50 Hz, benzimi–CH_2), 5.01 (s, 2H, OCH_2), 4.14–3.81 (m, 2H, NCH_2). ^{13}C NMR ($CDCl_3$): δ (ppm) 205.0 C_q, 197.0 C_q, 196.9 C_q, 187.8 C_q, 168.7 NCN, 165.5 CONH, 154.4 C_{py}, 141.4 C_{py}, 135.6 C_q, 135.4 C_q, 131.3 C_q, 128.5 C_{Ar}, 128.4 C_{Ar}, 128.2 C_{Ar}, 126.4 $C_{benzimi}$, 126.2 $C_{benzimi}$, 123.4C_{py}, 113.4 C_{py}, 112.7 $C_{benzimi}$, 112.5 $C_{benzimi}$, 67.0 OCH_2, 53.5 benzimi-CH_2, 41.7 NCH_2. Anal. Calcd for $C_{26}H_{20}ClN_4O_6Re$: C, 44.23; H, 2.85; N, 7.93%. Found: C, 43.88; H, 2.74; N, 7.81%.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthetic details for the preparation of 1-(2-pyridyl)-3-methylimidazolium iodide and 1-(2-pyridyl)-3-methylbenzimidazolium iodide. Additional X-ray crystallographic details for the imidazolium salt **5a**·Br (and ORTEP structure) and the Re(I) complexes **3a**Cl, **3a**BzO, **3b**BzO, **8a**Cl, **9b**, and **10a**Cl and **10b**TsO. UV–vis spectra for **3a**, **3b**, **3a**BzO, and **3b**BzO and ESI-mass spectrum for **3a**CD_3CN. Additional details for the kinetic analysis of the reaction of **3a**Cl with CD_3CN and the $^{99/99m}$Tc labeling studies. ^{1}H and ^{13}C NMR spectra for **7a**·Cl and **7b**·Cl. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 997634–997640 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The

Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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Notes

The authors declare no competing financial interest.

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