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14. ABSTRACT The project investigated the development of ligand linked Flutamide analogs for complexing a M(CO) ₃ (Re,99mTc) organometallic species to target prostate cancer for imaging and therapy. The project has been successful in developing new synthetic strategies for this application. A general method was developed for preparing a universal flutamide analog that can be applied to number of ligands to yield a flutamide targeted species capable of delivery of M(CO) ₃ to the cancer cell. The chemical stability (heat, pH) was investigated and the application of this general coupling methodology was applied to several tridentate ligands(i.e., cysteine, histidine). The resulting flutamide linked ligand system were complexed with the M(CO) ₃ to yield the desired metal complex. The 99mTc complexes were prepared in excellent yields(>95%) at (10 ⁻⁴ ,10 ⁻⁵ M) ligand concentration at biologically relevant pH and compared to the corresponding rhenium analogs through radioHPLC techniques.					
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Introduction

The focus of the research as highlighted in the proposal is the development of new diagnostic agents for identifying and probing prostate cancer. Flutamide, a non steroidal antagonist of the androgen receptor, is a current medical treatment of prostate cancer.¹ The proposed work involves the synthesis of novel modified flutamide derivatives that incorporates radionuclides (^{99m}Tc , ^{188}Re) into the framework of the system as unique organometallic species, $\text{M}(\text{CO})_3^+$. These radionuclides have an important contribution to the molecule by providing a mechanism to directly image and therapeutically treat prostate cancer at the primary and potentially secondary sites. The potential outcome of this work would be the development of radioactive incorporated flutamide compounds that can be used to actively monitor existing treatment protocols and to provide an enhanced therapeutic value in conjunction with associated emissions. The compounds may also have potential use in evaluating hormone refractory syndrome as cancer cells become drug resistant or mutations occur.

Body

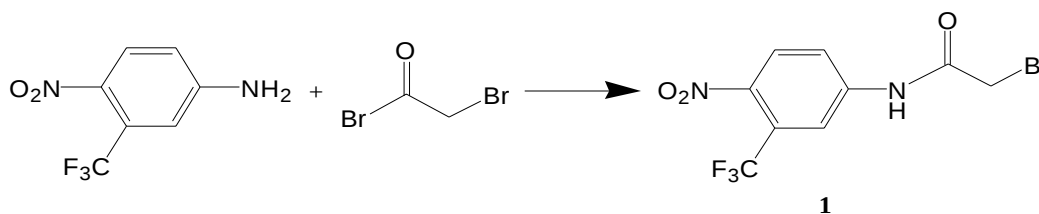
The proposed scope of work for year two has been generally achieved. The objectives listed in the scope of work initiate the synthesis of flutamide modified compounds and the preliminary characterization of complex experimentation with Re and Tc-99m as listed in the year two objectives illustrate in bold below.

Year Two Objectives

- **Continued synthesis and characterization of flutamide linked chelate**

Initial work in year one focused on the development of a generic flutamide species that had the potential to serve as a general alkylation species for a number of ligands. The proposed species is formed by the reaction of 3-trifluoromethyl-4-nitro aniline with bromo acetyl bromide to yield an amide linkage between the aryl amine and the acetyl bromide to yield 2-Bromo-N-(4-nitro-3-trifluoromethyl-phenyl)-acetamide (**1**). The laboratory progress has succeeded in the development of a synthetic pathway for the formation of a general multi-functional precursor of flutamide to link with ligands. (Figure 1) Although the synthesis was originally considered to be straightforward, product decomposition and relative low synthetic yields initially hindered results. We have since optimized the production and the purification of the compound to average yields of >85%. We have also expanded the synthetic methodology established with **1** to incorporate a longer spacer group between the flutamide binding end and the chelating ligand. An (CH₂)₅ analog to **1** was prepared in good yields 40-50%. A (CH₂)₃ analog was attempted according to the established procedure, however, no product was identified in the reaction mixture, which suggested decomposition products.

Figure 1. Synthesis of the generic linkable Flutamide derivative, 2-Bromo-N-(4-nitro-3-trifluoromethyl-phenyl)-acetamide (**1**)



In year one, we were also able to prepare a cysteine linked flutamide analog, however, the histidine analog remained a synthetic challenge. Additional deprotection methods of the hisflute compound (Figure 2) were attempted with no product isolated. In an alternative approach, the histidine flute analog was successfully prepared by utilizing the rhenium analog

and treating with 10 equivalents of peroxide at pH=3 (Figure 3). The compound was isolated by prep HPLC in reasonable yields and fully characterized.

Figure 2. Synthetic route for Histidine linked flutamide derivatives

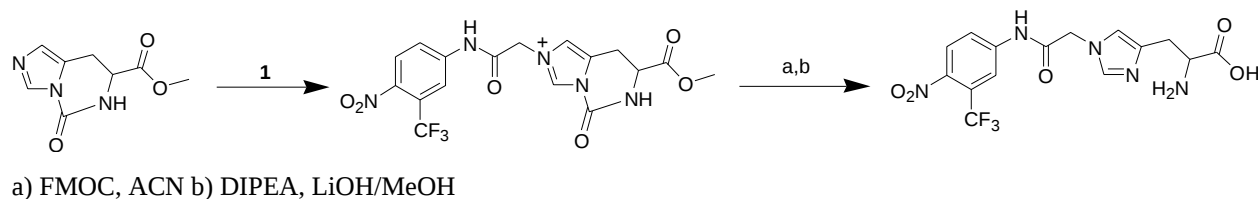
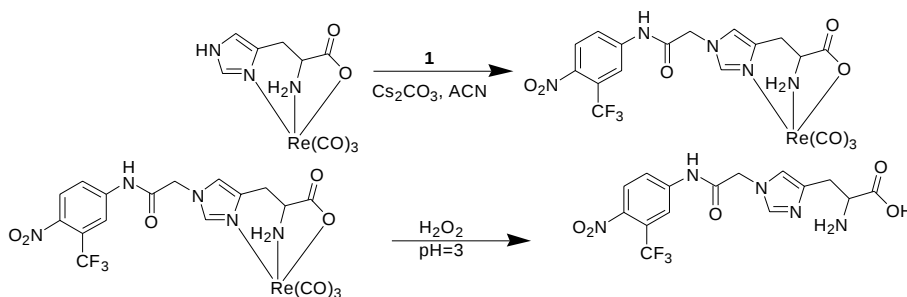


Figure 3. The synthesis of $\text{Re}(\text{CO})_3\text{HisFlute}$ with compound **1** and the demetalization with H_2O_2 to yield the free ligand HisFlute



Additional analogs of flutamide linked ligands were prepared. The first ligand utilized iminodiacetic acid (IDA) as a tridentate metal chelator a known ligand for complexing $\text{Re}/\text{Tc}(\text{CO})_3$. The Flute is covalently linked through the central nitrogen by alkylation the *tert*-butyl ester IDA with **1** to yield a protected IDA flute ligand (Figure 4). The *tert*-butyl ester groups deprotected under acidic conditions to yield the free ligand purified by prep HPLC. The $(\text{CH}_2)_5$ analog of **1** was reacted with IDA to yield the flute linked complex. Another flute analog involved the preparation of imidazole flute (Figure 5). The synthesis involved the alkylation of imidazole with **1**. The product was obtained in high yield. The aromatic nitrogen in imidazole is a strong donor towards $\text{Re}/\text{Tc}(\text{CO})_3$.

Figure 4. The synthesis and deprotection of Iminodiacetic acid (IDA) flute

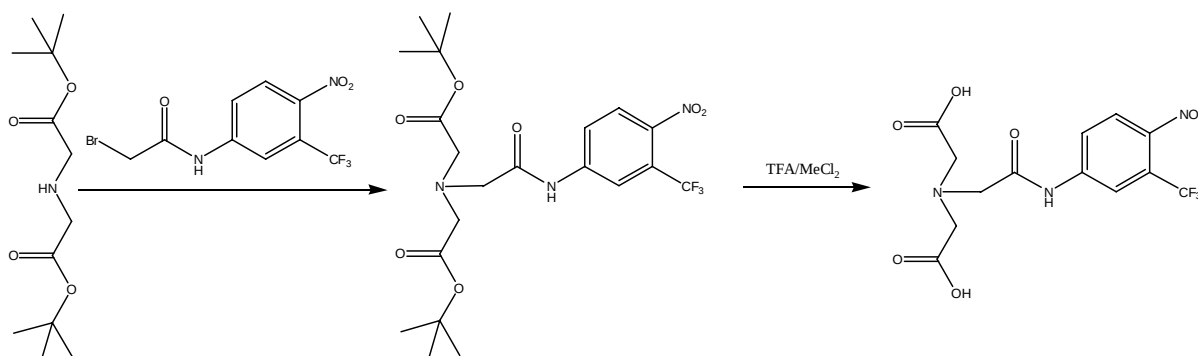
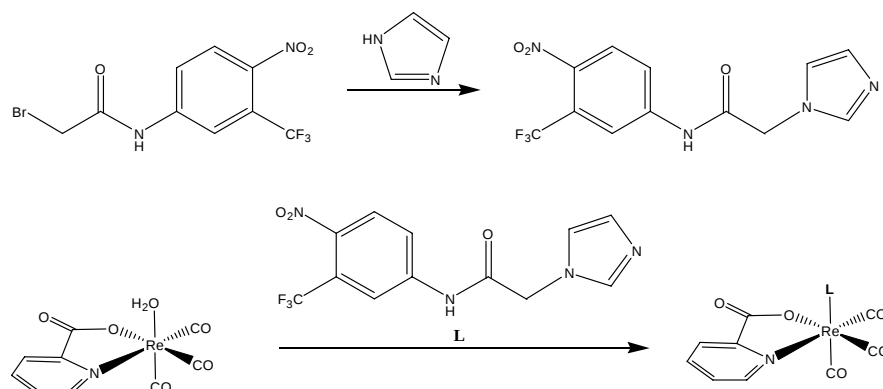


Figure 5. The synthesis of Imidazoleflute and the formation of the 2+1 complex of $\text{Re}(\text{CO})_3(\text{Pic})$ ImidazoleFlute



- **Continue complexing new ligands with metals (Re) and radiometals (Tc-99m)**

In year two, we have continued to prepare and to characterize complexes formed by reacting $[\text{NET}_4]_2[\text{fac-ReBr}_3(\text{CO})_3]$ with the corresponding ligand. We have also found a $[\text{fac-Re}(\text{OH}_2)_3(\text{CO})_3]$ Triflate species to have improved reactivity with the ligands and aqueous solubility. We have optimized the preparation and thoroughly characterized the ReHisflute and ReCysflute analogs. We are currently trying to obtain an X-ray structure of the complexes that would be useful for modeling the complex interacting with the androgen receptor. We have a partially solved structure of the ReHisflute, however, the solvent molecules are disordered are limiting the overall data. The ReCysflute compound appears to be more complex yielding coordination isomers of the prochiral thio ether. Low temperature NMR experiments are being conducted to characterize the complex. The prepared imidazole flute was reacted with $\text{Re}(\text{OH}_2)(\text{Picolinate})(\text{CO})_3$ to yield a 2 +1 complex (Figure 6). The complex was prepared and purified in reasonable yields 40 %. Complexation and identification with the IDA analogs are currently under investigation to optimize complex formation.

We have continued to Tc-99m label flutamide linked chelates and compare to the rhenium analogs. Although, we reported labeling at pH 7.4 and 95 °C with Cysflute. These conditions may not be suitable for all ligand systems. As in the synthetic developments, the sensitivity of the amide bond to basic pH and high temperatures can potential limit the effectiveness of the complex. The Hisflute was reacted with $\text{Tc}(\text{CO})_3^+$ at several different temperatures at pH 7.4. The yields of the $\text{Tc}(\text{CO})_3\text{Hisflute}$ at 95 °C were minimal and a major peak was determined to be the amide cleaved $\text{Tc}(\text{CO})_3\text{His}^{\text{N-CH}_2\text{OCO}^-}$ species. To avoid the cleavage products, the pH of the solution was adjusted to 5.2 prior to labeling. At this pH, the complex $\text{Tc}(\text{CO})_3\text{Hisflute}$ could be identified on HPLC when compared to the rhenium analog. Even at pH 5.2, a small percent of cleavage product could be seen at 95 °C. However, after

carefully examining the product formation vs. temperature, we found at 65 °C the product is prepared in quantitative yield at 10^{-5} M. The $\text{Tc}(\text{CO})_3\text{Hisflute}$ complex solutions were adjusted to biological pH (7.4) after complexation and the stability of the complex were measure for 24 hours. At room temperature, the $\text{Tc}(\text{CO})_3\text{Hisflute}$ remains stable and no cleavage products were observed in the radioHPLC. In light of this new information, we are reexamining the cystflute experiments to insure that cleavage products are not seen as in the case with hisflute.

The 2+1 approach was also explored with the imidazole flute. Picolinic acid (bidentate) and Imidazoleflute (monodentate) ligands were reacted with the $\text{Tc}(\text{CO})_3$ core. At pH =7.4, the formation of the $\text{Tc}(\text{Imidazoleflute})(\text{Picolinate})(\text{CO})_3$ was not observed. Adjusting the pH to 5.3 and changing the concentration ratios did positively indicate that the complex could be formed in good yields, however, optimization of the system is in progress to reach labeling yield for biological applications.

- **Examine other modes of linking radiometals to target materials**

We have successfully developed a system to allow an *in situ* ligand formed complex. The method involves the preparation of a two step process that uses the reactivity of the metal center to form a tridentate ligand from two bidentate ligands. The foundational study proves the capabilities of the process. The work also indicates the reactivity of the metal center upon complexation and the introduction of additional ligands. A copy of the submitted paper is in the appendices. We are currently working on developing a flutamide linked analog that utilizes this approach.

- **Develop and conduct preliminary binding experiments on prostate cells**

We have been working on developing assays to for testing the radioactive compounds. The assays will test the viability of the compounds for androgen expressing and non-expressing prostate cancer cells. We have been granted the proper administrative approval to conduct experiments. The approval for transportation of radioactive materials to and from the preparation/ counting rooms to the cell laboratory (separate buildings) required additional protocols and handling methods. Although we do not have any reportable data at this time, we do have all of the necessary documentation and protocols to begin experimentation of the radioactive species with cell lines.

- **Prepare and optimize radioactive Re-186/188 analogs of successful Tc-99m compounds**

We obtained the necessary experimental protocols to produce Re-186/188 analogs and have production methods developed for the WSU reactor. However, due to the complexity of the synthesis and the interpretation of the data Re-186/188 vs. Tc-99m, it was thought more to be prudent to examine the Tc analogs prior to conducting the Re analogs.

Key Research Accomplishments

- *Expanded of basis chemistry of the synthetic flutamide derivatives to incorporate spacer groups between the chelate and flutamide
- *Preparation of several new ligand Flute coupled complexes
- *Developed a new labeling strategy for in situ ligand formation
- *Prepared a 2+1 flutamide Re/Tc complex
- *Development of an excellent radiochemical labeling system (>95%) of HisFlute achieved with $^{99m}\text{Tc}(\text{CO})_3$ pH= 5.2 that maintains the stability of the amide bond in flutamide.

Reportable Outcomes

Presentations

- 1) Benny, P DOD Prostate Cancer Meeting 9/2007 Atlanta, GA

Manuscripts

- 1) Metal Assisted *In situ* Formation of a Tridentate Acac Ligand for Complexation of *fac*- $\text{Re}(\text{OH}_2)_3(\text{CO})_3^+$ for Radiopharmaceutical Applications. Paul D. Benny^{†*}, Glenn A. Fugate[†], Adam Barden[†], Jennifer E. Morley[†], Elsa Silva-Lopez[†], and Brendan Twamley
Submitted to Inorganic Chemistry 9/28/2007

Conclusions

The results presented here illustrate potential viability of the compounds for prostate cancer. The second years research has established several important milestones to measure the success of the project. Several key synthetic hurdles were overcome to demonstrate the chemistry of derivitization of flutamide analogs as a real possibility. Several new synthetic strategies were developed for the project. A general method for preparing a tridentate complex from two bidentate ligands using the reactivity of the metal center. Preparation of flutamide linked histidine analogs using rhenium analog and acidic deprotection method yielded the desired product. In the past year, a number stability of issues were investigated and it was found that the proposed compounds are stable in biological pH and the radiochemical/ metal complexes can be formed in good yields by varying the temperature and pH. The combination of temperature and base has a dramatic impact on the stability of the compounds. The development of radiochemical labeling methods that gave the desired compound in high yield (>95%) in a biologically friendly media was critical to the potential application in cells and humans. We were able to adjust the pH to optimize labeling while reducing cleavage products. This insures the products have potential application for the next stage of research investigating the cellular interaction of the compounds with the androgen receptors. A solid foundation understanding of the chemistry of the compounds is imperative to demonstrate the effectiveness of the compounds vs the decomposition. Application to cancer cells that may require structural adjustments, which we have already been developing, and refining the targeting methodology to improve target specificity towards prostate cancer cells. The development of the synthetic pathways developed during the first year can be utilized and adjusted to facilitate the synthesis of additional compounds for imaging and treating prostate cancer.

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Appendices

List of Personnel supported by this funding

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Position

Professor, director of research
Post Doc (8/1/07-current)
Undergraduate researcher (06/1/06-current)
Graduate Student (6/1/2006-current)

Metal Assisted *In situ* Formation of a Tridentate Acac Ligand for Complexation of $fac\text{-Re}(\text{OH}_2)_3(\text{CO})_3^+$ for Radiopharmaceutical Applications.

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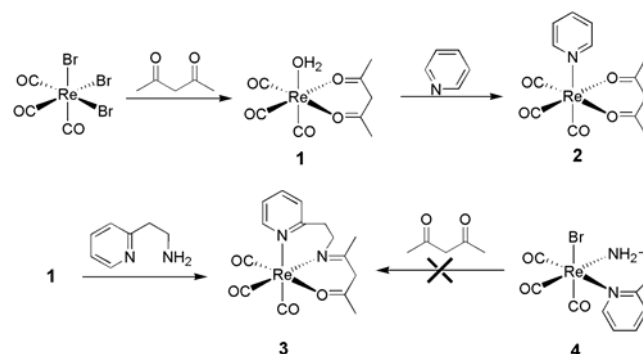
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ABSTRACT. Reaction of $[\text{NEt}_4]_2[\text{ReBr}_3(\text{CO})_3]$ with 2,4 pentadione (acac) yields a complex of the type $fac\text{-Re}(\text{acac})(\text{OH}_2)(\text{CO})_3$ (**1**) under aqueous conditions. **1** was further reacted with a monodentate ligand (pyridine) to yield a $fac\text{-Re}(\text{acac})(\text{Pyridine})(\text{CO})_3$ complex (**2**). Complex **1** was found to react with primary amines to generate a Schiff Base (imine) in aqueous solutions. Utilizing a mixed nitrogen donor bidentate ligand, 2-(2-aminoethyl)pyridine, that has different coordination affinities for the $fac\text{-Re}(\text{acac})(\text{OH}_2)(\text{CO})_3$, a unique tridentate ligand was formed *in situ* utilizing a metal assisted Schiff Base formation to yield a complex $fac\text{-Re}(\text{CO})_3[3[(2\text{-phenylethyl})\text{imino}]-2\text{-pentanone}]$ (**3**). Tridentate ligand formation was found to occur only with the Re coordinated acac ligand. Reactions of acac with $fac\text{-Re}(\text{CO})_3\text{Br}(2\text{-(2-aminoethyl)pyridine})$ (**4**) or a mixture of $[\text{NEt}_4]_2[\text{ReBr}_3(\text{CO})_3]$, acac, and 2-(2-aminoethyl)pyridine did not yield the formation of complex **3** in water.

Technetium-99m ($t_{1/2}=6.02$ hr $\gamma=140$ KeV) is the radionuclide of choice in hospitals comprising 90% of all nuclear medicine imaging scans.¹ Development of organometallic technetium complexes, such as $(fac\text{-}^{99m}\text{Tc}(\text{CO})_3(\text{OH}_2)_3)^+$, has provided new avenues of complex formation for diagnostic imaging.^{2,3} Current labeling strategies include incubation of monodentate, bidentate, tridentate, or a combination (2+1) ligand systems with the $fac\text{-}^{99m}\text{Tc}(\text{CO})_3(\text{OH}_2)_3^+$ moiety.^{4,5} Some of the best ligand systems (histidine, cysteine, 2,3-diamino propanoic acid) forms tridentate complexes at > 90% at 10^{-6} M.⁶⁻⁹ However, complex formation below 10^{-6} M appears limited by the thermodynamics of ligand substitution of the Tc(I) center.¹⁰

Interest in developing new modes of complex formation has led us to investigate 2,4 pentadione or acetylacetone

(acac) as a potential ligand system. Acac is a well established bidentate ligand that coordinates a number of transition metals. Acac can also be synthetically modified to incorporate a linked biotargeting moiety at carbon C1, and/or C3. The Schiff base or imine versions of acac are prepared by reacting a primary amine with the ligand in organic solvents. The stability of the Schiff base ligand in water may be limited by the hydrolytic nature of the imine bond. The mixed donor (O, N) acac derived Schiff base ligand provides an excellent ligand for rhenium with improved stability over the acac ligand alone.^{11,12}



Scheme 1. Synthetic route for preparation of acac rhenium complexes and subsequent reactions with mono and bidentate ligands to yield “2+1” and *in situ* formed tridentate complexes.

Interest in developing acac based ligand systems for potential radiopharmaceutical applications, we utilized rhenium complexes as surrogates to help elucidate the chemistry and structural information that would be found with radioactive ^{99m}Tc and $^{186/188}\text{Re}$. The rhenium complexes reported within were prepared in water to simulate reaction conditions that would be found in preparing the corresponding radioactive complexes. The rhenium acac complex can be formed by heating $[\text{NEt}_4]_2[\text{ReBr}_3(\text{CO})_3]$ with acac at 70 °C for two hours in 10.0 mL water to yield $fac\text{-Re}(\text{acac})(\text{OH}_2)(\text{CO})_3$, (**1**) (Scheme 1). The product, **1**, remains quite soluble in water, but can be isolated as colorless solid in high yield

through concentrating and cooling the solution in the refrigerator ($\sim 2^\circ\text{C}$) overnight. HPLC studies of the solution and the isolated solid revealed a single peak of complex **1** at 20.6 min verified by NMR (Figure 1).

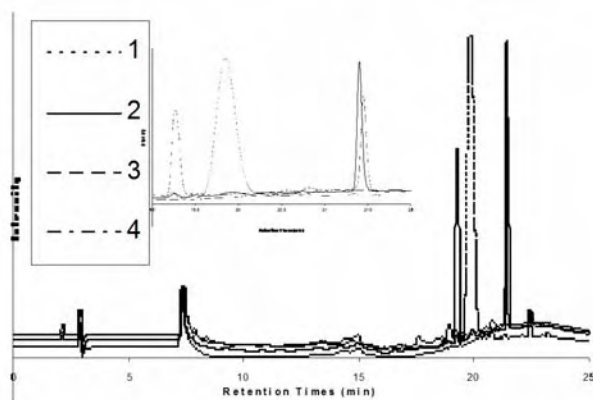


Figure 1. UV-HPLC trace at 220 nm of **1**, **2**, **3**, and **4**

Complex **1** is a versatile reagent as it can be isolated as a solid or utilized directly from the reaction mixture. The addition of a monodentate ligand would generate a “2+1” style of complex. Reacting **1** with pyridine at 70°C overnight, the complex *fac*-Re(acac)(CO)₃py (**2**) can be prepared in high yield. **2** is the only product observed from the solution. Even in the presence of excess pyridine, displacement of the acac ligand was not observed. The formation of **2** can be observed by the appearance of a new peak at 22.3 min in the HPLC (Figure 1). The X-ray structure of **2** was obtained by diffusion of pentane into a dichloromethane solution of **2** (Figure 2).¹³ The octahedral complex has comparable Re-CO bonds (1.89–1.92 Å) with an asymmetric axis elongated along the Re pyr (Re1-N1 2.20 Å) and acac axis (Re-O1 or Re-O2 2.12 Å).

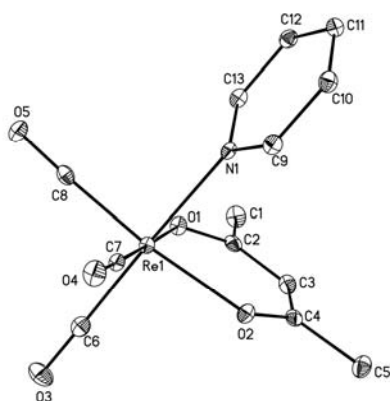
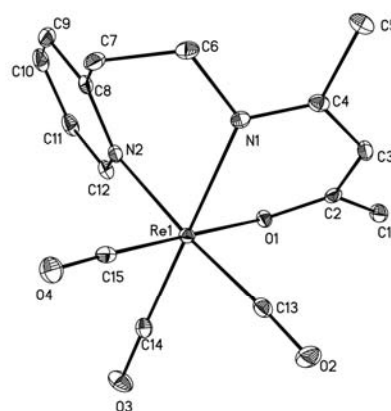


Figure 2. Molecular structure of **2** (thermal displacement 30%). Hydrogen atoms omitted for clarity. Bond distances (Å) Re1-O1 2.1189(19), Re1-O2 2.1226(19), Re1-C6 1.926(3), Re1-C7 1.896(3), Re1-C8 1.903(3), Re1-N1 2.209(2) Bond Angles ($^\circ$) O1-Re-O2 85.07(8), O1-Re-C6 95.29(10), O1-Re-C7 177.72(10), O1-Re-C8 92.76(10), O2-Re-N1 82.67(8), O2-Re-C6 95.62(11), O2-Re-C7 94.55(10), O2-Re-C8 174.08(10), N1-Re-C6 177.88(10), N1-Re-C7 94.39(10), N1-Re-C8 91.62(11)

The acac ligands show a minimally constrained bite angle (O1-Re-O2 85.07 $^\circ$). The pyridine N1 is equidistant to the O1/O2 of the acac ligand (O-Re-N1 82.67–83.3 $^\circ$).

Although the “2+1” complex **2** is coordinatively saturated, stability towards substitution of the ligands may limit the effectiveness of the complex. The formation of a similar tridentate ligand would have increased stability towards substitution. The “2+1” complex of **2** can be transformed by an *in situ* reaction into a tridentate complex utilizing the reactivity of acac in **1** to form an imine with a primary amine. An analogous rhenium pyridine aldehyde complex was previously demonstrated to form a bidentate imine complex system with a primary amine, however, the bidentate complex had limited stability toward ligand substitution.^{14,15}

Re(CO)₃[(2-phenylethyl)imino]-2-pentanone] (**3**) was prepared in a two step process; the formation of acac complex **1** followed by the addition of second bidentate ligand (Scheme 1). Complex **3** was formed either stepwise or as a single pot reaction. The formation of the imine bond in **3** was observed by addition of 2-(2-aminoethyl)pyridine to an aqueous solution of complex **1** followed by heating at 70°C . The product precipitated as a colorless solid upon cooling to room temperature. The reaction progress was monitored by HPLC, where the disappearance of **1** and the appearance of **3** at 21.4 min were observed (Figure 1). Crystals of **3** were



obtained by slow evaporation of a methanol/water solution at room temperature (Figure 3).

Figure 3. Molecular structure of **3** (30% thermal displacement). Hydrogen atoms omitted for clarity. Bond distances (Å) Re1-O1 2.1336(18), Re1-N1 2.166(2), Re1-N2 2.197(2) Re1-C13 1.925(3), Re1-C14 1.933(3), Re1-C15 1.901(3), Bond Angles ($^\circ$) O1-Re-N1 82.24(8), O1-Re-C13 93.27(10), O1-Re-C14 92.46(9), O1-Re-C15 178.39(9), N1-Re-N2 80.36(8), N1-Re-C13 96.05(10), N1-Re-C14 173.77(9), N1-Re-C15 99.16(10), N2-Re1-C13 175.54(10), N2-Re1-C14 149.85(10), N2-Re1-C15 95.76(10)

The solid state structures of the “2+1” complex **2** and the tridentate complex **3** have many structural similarities in bond distances (i.e., Re-pyridine, ~ 2.2 Å, Re-O1, 2.13 Å, Re-CO, ~ 1.9 Å) and angles (O1-Re-N1, 82.24(8) $^\circ$ in **3** has a similar bite angle to the acac ligand in **2**). However, the methylene carbons (C6, C7) have larger than typical bond angles (113–115 $^\circ$). C3 of the acac ligand in **3** is also positioned slightly out of plane due the steric restraints of

the linked pyridine and the imine bond of the tridentate system in **3** compared to **2**.

The Schiff base formation of the tridentate complex utilizes distinct differences in coordination strength of the bidentate ligand 2-(2-aminoethyl)pyridine, containing a primary amine and an aromatic amine. It is proposed that the pyridine ligand first coordinates to the rhenium center replacing the labile aquo ligand, as opposed to the amine. The uncoordinated amine donor is available for nucleophilic attack at the C2 of the coordinated acac ligand. The coordinated oxygen from the acac ligand is converted to water during the Schiff base condensation and probably remains coordinated for a brief moment prior to displacement by the more favorable imine donor from the tridentate ligand. Reactivity of the amine donor with the acac ligand is believed to depend on the effective chelate ring size and steric constraints of the number of methylene carbons between the pyridine and the amine.

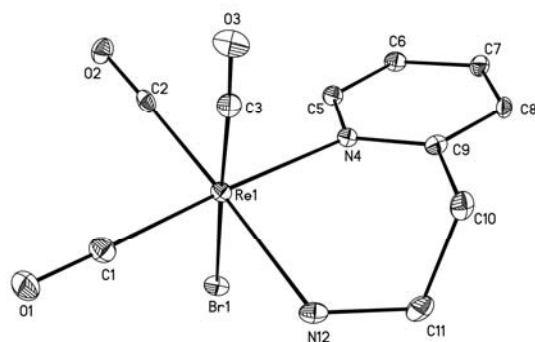


Figure 4. Molecular structure of **4** (thermal displacement 30%). Solvent molecule and hydrogen atoms omitted for clarity. Bond distances (Å) Re1-Br1 2.1189(19), Re1-O2 2.1226(19), Re1-C6 1.926(3), Re1-C7 1.896(3), Re1-C8 1.903(3), Re1-N1 2.209(2), Bond Angles (°) O1-Re-O2 85.07(8), O1-Re-C6 95.29(10), O1-Re-C7 177.72(10), O1-Re-C8 92.76(10), O2-Re-N1 82.67(8), O2-Re-C6 95.62(11), O2-Re-C7 94.55(10), O2-Re-C8 174.08(10)

Displacement of the acac ligand from complex **1** upon introduction of 2-(2-aminoethyl) pyridine was a primary concern. The potential byproduct of *fac*-Re(2-(2-aminoethyl)pyridine)Br(CO)₃ (**4**) was prepared by refluxing [NEt₄]₂[ReBr₃(CO)₃] with 2-(2-aminoethyl)pyridine in methanol (Scheme 1). HPLC of the reaction yielded a single peak at 20.0 min corresponding to **4**. The complex was characterized and utilized as a reference for HPLC comparison (Figure 1). Single crystals were obtained from methanol solution of **4** at 0 °C after several days (Figure 4). **4** was further evaluated to determine the dissociation/reactivity of the coordinated 2-(2-aminoethyl)pyridine by introducing excess acac ligand in water (Scheme 1). A second slightly more hydrophilic peak was observed in the HPLC over a prolonged period, which may be due to substitution of the coordinated Br in **4** with water. Regardless of the conditions, the formation of **3** was not observed via this pathway, suggesting the amine remains coordinated to the rhenium center without dissociation or displacement by acac to activate Schiff base formation. Although free ligand formation is possible, we examined the possibility that the ligand could be formed *in*

situ by the addition of acac and 2-[2-aminoethyl]pyridine in water followed by the addition of *fac*-[ReBr₃(CO)₃]²⁻. The mixture yielded **4** or the aquo coordinated complex as observed by HPLC and no formation of the tridentate ligand complex **3** was observed.

In conclusion, we have demonstrated that acetylacetone can be utilized as a bidentate ligand system in a “2+1” approach or utilizing coordination differences to generate a tridentate ligand system while coordinated to the rhenium metal center. This new methodology has the potential for linking to targeting molecules, such as small molecules, peptides, and antibodies, for generating *in situ* tridentate complexes for nuclear medicine applications.

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SUPPORTING INFORMATION AVAILABLE. Full syntheses, characterization of compounds, X-ray crystallographic bond angles and distances tables (PDF). X-ray structural information for **2**, **3**, and **4** (CIF). This information is available free of charge via the Internet at <http://pubs.acs.org>

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- 2**, monoclinic space group P2(1)/c with cell dimensions a = 14.9940(7) Å, b = 6.8687(3) Å, and c = 14.1746(6) Å and β = 104.698(1)° b V =
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- 3**, Monoclinic, C2/c (a = 16.929(2) Å, b = 11.5726(16) Å and c = 16.013(2) Å, β = 106.031(2)°)
- 4**, Monoclinic, C2/c (a = 25.129(4) Å, b = 9.2109(16) Å and c = 12.832(2) Å, β = 103.563(3)°)