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Novel Gold(I)− and Gold(III)−N-Heterocyclic Carbene Complexes: Synthesis and Evaluation of Their Anticancer Properties

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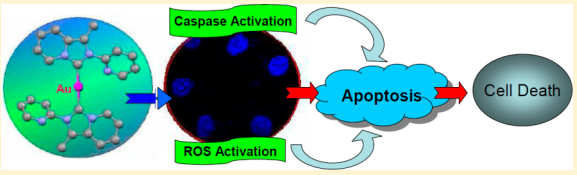
Supporting Information

ABSTRACT: A novel Au(III)−N-heterocyclic carbene organometallic complex supported by two N-heterocyclic carbene (NHC) ligands was synthesized from $Au(SMe_2)Cl$ and 1-methyl-2-pyridin-2-yl-2*H*-imidazo[1,5-*a*]pyridin-4-ylium hexafluorophosphate via a Ag intermediate. X-ray crystallography revealed the first example of a square planar geometry adopted by a Au(III) species stabilized by two NHCs and two chloride ligands. The aforementioned Au(I)− and Au(III)−NHC complexes were found to be more potent than cisplatin against the HCT 116, HepG2, A549, and MCF7 cell lines.



Organogold chemistry is finding increasing utility in a range of catalytic and biomedical applications.[1] Many of the complexes used in these applications contain gold ions in either the +1 or +3 oxidation state and are stabilized with phosphine-based or N-heterocyclic carbene (NHC)-based ligands.[1a−c] The Au complexes supported by NHCs, in particular, have been widely studied for their abilities to facilitate C−C, C−O, and C−N bond-forming reactions[2] as well as for their potential to function as anticancer, antiarthritis, and antibacterial agents.[3] While the majority of literature reports describing the chemistry of Au−NHC complexes involve gold ions in the +1 oxidation state, recent attention has been directed toward Au(III)−NHC complexes.[4] Such complexes are generally synthesized via treatment of the corresponding Au(I) complex with Cl_2, Br_2, or I_2.[4b,c] For comparison, more direct syntheses that utilize a Au(III) precursor (e.g., $KAuCl_4$) typically require specially designed NHC ligands,[5] although we recently circumvented this limitation by developing a disproportionation scheme that obviates the need for Cl_2 or Br_2.[4d,e]

Recent biomedical studies involving various Cu(I)−, Ag(I)−, Au(I)−, Pd(II)−, and Pt(II)−NHC complexes revealed their potential for use as anticancer agents.[3,4,6] Many of these studies were prompted by the discovery of the antitumor properties of cisplatin,[7] $PtCl_2(NH_3)_2$, by Rosenberg in 1963, which established the field of metallo-organic therapeutics. As a result of some of cisplatin's setbacks, including resistance and other side effects,[8] promising new strategies for overcoming these obstacles have been explored, many of which use other transition metal complexes.[9]

Although the use of gold salts in medicinal chemistry has been known for centuries, recent studies have capitalized on their strong antiproliferative[3,4,6,9] and bacteriostatic properties, particularly for the treatment of tuberculosis.[9a] Unfortunately, the *in vitro* biochemistry of gold remains largely unknown, mainly because of the paucity of adequate models and an inadequate understanding of its mechanism of reactivity.[3,4b,6] As such, the synthesis and study of Au−NHC complexes in therapeutic applications are warranted. Herein, we present the synthesis, characterization, and anticancer properties of Au(I) and Au(III) complexes supported by a novel NHC.

The synthesis of the requisite NHC precursor 1-methyl-2-pyridin-2-yl-2*H*-imidazo[1,5-*a*]pyridin-4-ylium hexafluorophosphate (**1**) was accomplished using a previously reported procedure.[10] The transfer of imidazolium-derived NHC-based ligands to group d^{10} metal complexes is often achieved via a Ag(I) carbene transfer method;[11] indeed, as summarized in Scheme 1, Au(I)−NHC complex **2** was obtained via a similar approach. The disappearance of the C2-H signal from the ^1H nuclear magnetic resonance (NMR) spectrum recorded at 10.32 ppm and the shift of the ^{13}CNMR signal of C2 from 136.6 to 172.4 ppm indicated that **2** was successfully formed.[4]

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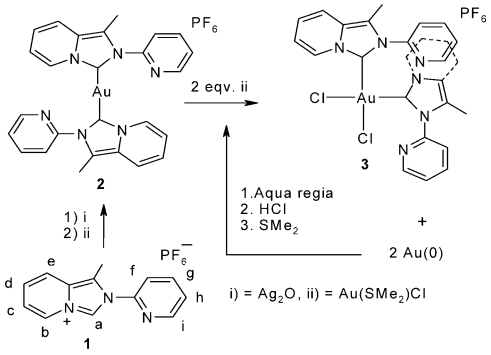
Scheme 1. Synthesis of Au(I)− and Au(III)−NHC Complexes



With Au(I)−NHC complex **2** in hand, gold(III)complex **3** was synthesized by treating the former with $Au(SMe_2)Cl$. Stirring a clear colorless acetonitrile solution of gold(I)−NHC complex **2** and $Au(SMe_2)Cl$ at room temperature for 6 h resulted in a change in the color to yellow, which was accompanied by the formation of a precipitant. After separation and purification, the desired Au(III)−NHC complex **3** was obtained as a yellow solid in 33% yield. Notably, this synthetic process capitalizes on a disproportionation reaction, wherein the Au(I) supported by the NHCs underwent oxidation and was accompanied by reduction of the $Au(SMe_2)Cl$ to Au(0), which was subsequently isolated and reused.[4d,e] Regardless, the ^{1}H NMR spectrum recorded for complex **3** was found to be similar to the spectrum recorded for complex **2**. In particular, the resonance assigned to the NCN group in the ^{13}C NMR spectrum of **2** was found to be shifted downfield by 22.9 ppm (173.38 ppm) compared to the signal for the same carbon in **1** (150.47 ppm). For comparison, the carbene nucleus was recorded at 159.55 ppm in **3**, because of an increase in the Lewis acidity of the gold center.[4a] All of the new complexes were also characterized by mass spectrometry to confirm that their solution structures were similar to those observed in the solid state. In the case of **2**, a signal was recorded at m/z 615.3 and assigned to the binuclear species $[Au(\mathbf{1}\text{-}H)_2]^+$; likewise, a signal was observed at m/z 406.3 and assigned to $[Au(\mathbf{1}\text{-}H)]^+$ (Figure S1 of the Supporting Information). Mass analysis of **3** afforded a signal at m/z 847.2, which was assigned to $\{[Au(\mathbf{1}\text{-}H)_2Cl_2](PF_6)\text{-}(H_2O)\}\text{-}2H]$ followed by signals at m/z 615.3 and 486.3 that were assigned to $[Au(\mathbf{1}\text{-}H)_2]^+$ and $[Au(\mathbf{1}\text{-}H)]^+$, respectively (Figure S2 of the Supporting Information). The largest m/z signal observed for **3** stems from the removal of hydrogen via a water contaminant, a result that was supported by elemental analysis and X-ray crystallography.

To gain additional insight into the coordination chemistry and the structural parameters of complexes **2** and **3**, single crystals were grown by slow evaporation of concentrated acetonitrile solutions of the respective complexes into Et_2O and characterized by X-ray diffraction analysis. The molecular structure of **2** is depicted in Figure 1. Typical Au−$C_{carbene}$ bond lengths of 2.008(5) Å [Au(1)−C(7)] and 2.018(5) Å [Au(1)−C(14)] were measured and determined to be shorter than the sum of the van der Waals length (Au−C = 2.108 Å) but consistent with other monocarbene and biscarbene systems.[3f,6c] The Au(1)−C(7) separation is slightly longer than the Au−$C_{carbene}$ separation [1.988(3) Å] recently reported by Tacke[3f] for the anticancer potent Au(I)−NHC complex. The $C_{carbene}$−Au(1)−$C_{carbene}$ bond angle [C(1)−Au(1)−C(14) = 176.7(2)°]

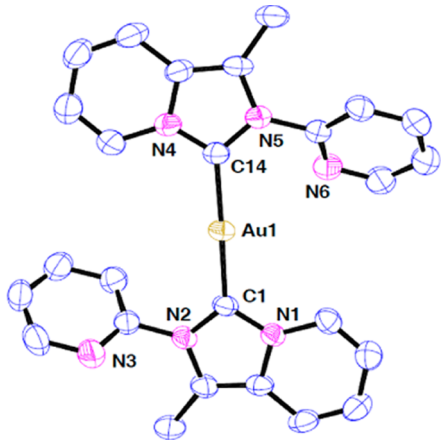


Figure 1. ORTEP view of **2** (30% probability). The PF_6 counteranion and the H atoms have been omitted for the sake of clarity. Key bond lengths (angstroms) and angles (degrees): Au(1)−C(1) = 2.008(5), Au(1)−C(14) = 2.018(5), N(1)−C(1) = 1.373(8), N(2)−C(1) = 1.359(7), C(14)−N(4) = 1.354(7), C(14)−N(5) = 1.351(7), C(1)−Au(1)−C(14) = 176.7(2), N(1)−C(1)−N(2) = 104.1(5), and N(4)−C(14)−C(5) = 103.5(5). Note that two asymmetric units were present.

indicated that the structure was nearly linear. Moreover, bond distances consistent with aurophilic interactions were measured [Au(1)−Au(2) = 3.3794(3) Å] and supported by a weak luminescence observed at 410 nm. In the square planar Au(III) complex (**3**), the Au(III)−$C_{carbene}$ lengths, Au(1)−C(1) and Au(1)−C(14), were measured to be 1.996(6) and 2.014(5) Å, respectively, and comparable to similar distances observed in Au(I)−NHC complex **2**. For complex **3**, the $C_{carbene}$−Au(III) distances were in accord with known NHC−gold(III) chloride complexes.[4] The Cl−Au distances of 2.2984(16)−2.3150(16) Å were shorter than reported values for known NHC−$AuCl_3$ complexes.[4d,e] It is important to note that the NHCs described herein can stabilize both Au(I) and Au(III) centers; in general, linear biscarbene Au(I)−NHC complexes release one ligand when they are oxidized to Au(III),[4d,e] but in **3**, both ligands remain intact after the oxidation of the precursor **2** (Figure 2).

In addition to the characterization of the aforementioned complexes **2** and **3**, their cytotoxicities were tested against known human cancer cell lines, including HCT 116, HepG2, A549, and MCF7, and compared to that displayed by cisplatin,[4b] Close inspection of the results (Table 1 and Figure S3 of the Supporting Information) revealed that **2** was more potent than **3** and that both complexes were more efficient than cisplatin. Complex **2** is more potent toward MCF7 cancer cells than Au(I)−NHC complexes recently reported by Tacke.[3f] The lower potency of **3** in comparison to that of **2** may due to the reduction of Au(III) complexes via cellular compounds containing thiols.[9b] However, the ligand showed negligible cytotoxicity toward the cancer cells (Table S1 of the Supporting Information), and the complexes themselves showed negligible cytotoxicity toward human peripheral blood mononuclear cells (PBMCs) (Table S2 of the Supporting Information).

Cancer cell death is often achieved through apoptosis.[12] The induction of apoptosis by **2** on HCT 116 cells was probed by examining the different characteristic cellular changes in apoptosis. Microscopic studies were used to distinguish between control and treated cells undergoing apoptosis. In particular, HCT 116 cells became rounded after treatment with **2** (at the IC_{50} concentration) for 24 h. Moreover, upon being

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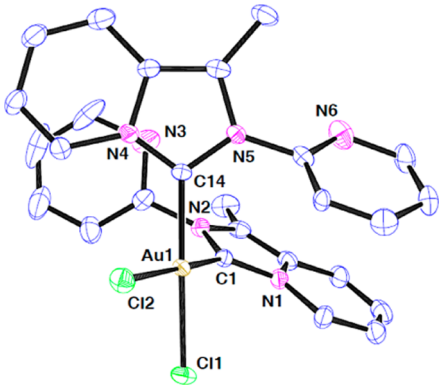

Figure 2. ORTEP view of **3** (30% probability). The H, PF_6, and H_2O species have been omitted for the sake of clarity. Pertinent bond lengths (angstroms) and angles (degrees): Au(1)−C(1) = 1.996(6), Au(1)−C(14) = 2.014(5), Au(1)−Cl(1) = 2.2984(16), Au(1)−Cl(2) = 2.3150(16), N(1)−C(1) = 1.360(7), N(2)−C(1) = 1.363(8), C(14)−N(4) = 1.338(7), C(14)−N(5) = 1.347(7), N(1)−C(1)−N(2) = 105.3(5), N(4)−C(14)−C(5) = 106.2(4), C(1)−Au(1)−C(14) = 89.9(2), C(1)−Au(1)−Cl(1) = 88.08(17), C(14)−Au(1)−Cl(1) = 177.89(15), C(1)−Au(1)−Cl(2) = 177.91(17), C(14)−Au(1)−Cl(2) = 90.22(16), and Cl(1)−Au(1)−Cl(2) = 91.86(7).

Table 1. Summary of Measured IC_{50} Values (micromolar)[a]

complex	A549	HCT 116	HepG2	MCF7
2	5.2 ± 1.5	3.6 ± 4.1	3.7 ± 2.3	4.7 ± 0.8
3	5.2 ± 3.0	5.9 ± 3.6	5.1 ± 3.8	6.2 ± 1.4
cisplatin	8.1 ± 3.2	8.8 ± 2.8	8.9 ± 1.3	9.4 ± 1.0

[a]Legend: A549, human non-small lung carcinoma; HCT 116, human colorectal carcinoma; HepG2, human hepatocellular carcinoma; MCF-7, human breast adenocarcinoma. Cells were treated with different concentrations of cisplatin or complexes **2** and **3** ranging from 0 to 10 μM for 24 h. The IC_{50} values were calculated from an MTT assay. Values are means ± the standard deviation and represent one of three representative experiments.

stained with the nuclear staining dye 4,6-diamidino-2-phenylindole (DAPI), the cells showed bright, fragmented nuclei under the fluorescence microscope (Figure 3). Both of the aforementioned results are typical hallmarks of apoptosis.[12] Another important feature of apoptosis is the externalization of

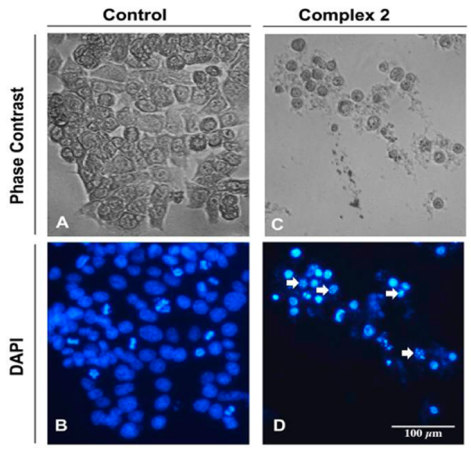

Figure 3. Fluorescent micrographs of the HCT 116 cells following treatment with **2** (at the IC_{50} concentration) for 24 h and subsequent staining with DAPI. The arrows denote DNA fragmentation.

phosphatidylserine from the inner cellular membranes to the outer membranes, which can bind with the protein annexin V. Using a fluorescein isothiocyanate (FITC)-labeled annexin V, exposure of phosphatidylserine to the outer membranes of cells during apoptosis was measured by fluorescence-activated cell sorting analysis.[13] Upon treatment with complex **2** (IC_{50} concentration), the HCT 116 cells showed a 55.55% apoptotic cell population compared to a 0.97% cell population in the control after 24 h (Figure 4). Collectively, these findings

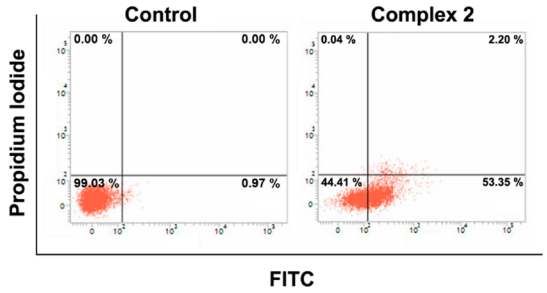

Figure 4. Flow cytometric analysis of the induction of apoptosis in HCT 116 cells upon treatment with **2** (IC_{50} concentration) for 24 h.

suggested to us that **2** induced the death of HCT 116 cells because of apoptosis in a manner similar to previous reports involving Au(I)−NHC complexes on other cancer cell lines[4b] as well as a Ag(I)−NHC complex.[14] However, to the best of our knowledge, this is the first example of apoptotic induction in HCT 116 cells using a Au(I)−NHC complex.

Au(I)−NHC complexes have been reported to generate reactive oxygen species (ROS), which may be due to the inhibition of the thioredoxin reductase (TrxR), which is a key enzyme in a cell's antioxidant defense system, and loss of membrane potential ($\Delta\Psi$m) following treatment of cancer cells.[15,16] Treatment of HCT 116 cells with complex **2** (at the IC_{50} concentration) for 24 h led to the generation of ROS with a FITC mean at 198 and 448, indicating a shift in the generation of ROS from the control to complex **2** (IC_{50} concentration) as determined by the H2DCFDA assay (Figure 5 A). Treatment of HCT 116 cells with complex **2** (IC_{50} concentration) for 24 h led to the loss of the mitochondrial

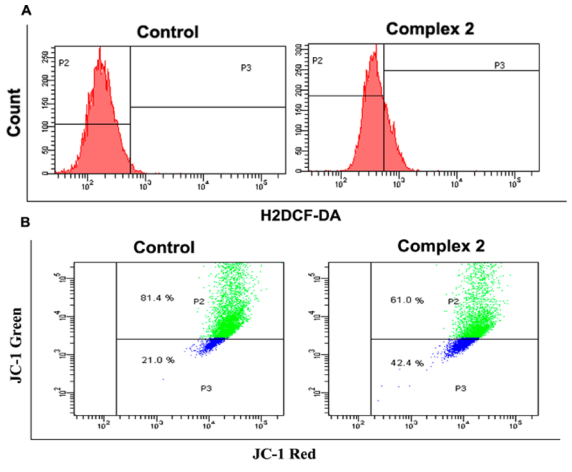

Figure 5. (A) Flow cytometric analysis of reactive oxygen species generation in cells following treatment with complex **2** (IC_{50} concentration) after 24 h. (B) Flow cytometry analysis of the loss of $\Delta\Psi$m in the presence of complex **2** (IC_{50} concentration) after 24 h.

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membrane potential ($\Delta\Psi$m), with 21.0 and 42.4% of the cells showing loss of $\Delta\Psi$m following treatment with complex **2** (IC_{50} concentration) as compared to the control cells after 24 h as determined by the JC-1 assay (Figure 5B). Collectively, these data indicate that **2** can mediate apoptosis in HCT 116 cells by the generation of ROS and loss of $\Delta\Psi$m.

Apoptosis of cancer cells following treatment with Au(I)−NHC complexes was further explored by monitoring the expression of caspase 9 and caspase 3 to determine if a mitochondrial death pathway was involved.[17] Treatment of HCT 116 cells with complex **2** (at the IC_{50} concentration) for 24 h led to an increase in the caspase 9 (initiation phase) and caspase 3 (execution phase) activities. As such, it appears that complex **2**-mediated cell death proceeds via a mitochondrial death pathway (Figure 6).

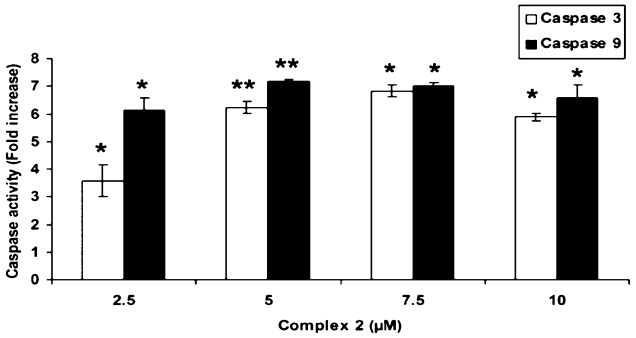

Figure 6. Increase in caspase 3 and caspase 9 activity following treatment of HCT 116 cells with complex **2** (0, 2.5, 5, 7.5, and 10 μM) for 24 h, as determined by a colorimetric caspase assay kit. Values are means ± the standard deviation and represent one of three representative experiments. *P < 0.05, and **P < 0.01.

In conclusion, the synthesis, characterization, and cytotoxicities of novel Au(I)− and Au(III)−NHC complexes are described. The Au(III)−NHC complex was synthesized directly from an appropriate Au(I) precursor by capitalizing on a disproportionation process. Gold(I) complex **2** was found to be more potent as an anticancer agent than **3** or cisplatin in four cell lines. Furthermore, treatment of HCT 116 cells with **2** at the IC_{50} concentration for 24 h yielded results that were hallmarks of apoptosis, including nuclear condensation, externalization of annexin V, production of ROS, and a loss of $\Delta\Psi$m. Finally, treatment of HCT 116 cells with complex **2** led to increased caspase 3 and caspase 9 activities, reflecting the fact that a pathway involving mitochondrial death is involved in the aforementioned processes.

EXPERIMENTAL SECTION

Synthesis of 2. The proligand **1** (250 mg, 0.70 mmol) and silver oxide (85 mg, 0.37 mmol) were added to dry acetonitrile (10 mL), and the mixture was stirred at room temperature for 4 h. The mixture was filtered through a plug of Celite to remove the unreacted Ag_2O. The filtrate was concentrated to dryness and the residue dried under reduced pressure. An acetonitrile solution of $Au(SMe_2)Cl$ (103 mg, 0.35 mmol) was added dropwise to the pre-prepared solution of the silver complex in acetonitrile (15 mL), and an immediate white precipitate was observed. The filtrate was evaporated to dryness and the solid dried over silica after removal of AgCl by filtration. The compound was recrystallized from a CH_3CN/Et_2O mixture to afford the desired complex in 70% yield (190 mg, 0.25 mmol): ^{1}H NMR (DMSO-d_6, 400 MHz, 25 °C) δ 8.65 (d, J = 6.0 Hz, 1H, H^a), 8.54 (d, J = 9.2 Hz, 1H, H^i), 8.04 (t, J = 10.0 Hz, 1H, H^i), 7.75 (m, 3H, H^i), 7.72 (m, 1H, H^c), 7.07 (t, J = 8.8 Hz, 1H, H^i), 6.95 (t, J = 8.7 Hz, 1H, H^i), 2.44 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 300 MHz, 25 °C) δ 173.38, 150.58, 150.02, 140.22, 127.76, 127.16, 126.14, 123.06, 122.54, 121.93, 118.68, 116.48, 9.74; MS (FAB+) m/z 615.3 ($M^+ - PF_6$); UV−vis (CH_3CN) λ_{max} [ε (×10^4 M^{-1} cm^{-1})] 230 (11.6), 244 (11.4), 345 br (2.1), 375 br (1.8) nm. Anal. Calcd for $Au_2C_{52}H_{44}N_{12}P_2F_{12}$: C, 41.05; H, 2.89; N, 11.05. Found: C, 40.84; H, 2.83; N, 10.87. Single-crystal data: $C_{52}H_{44}Au_2N_{12}P_2F_{12}$, M_r = 1520.86, monoclinic, space group $P2_1/n$, a = 14.18060(10) Å, b = 24.7767(2) Å, c = 15.1625(2) Å, β = 95.1790(5)°, U = 5305.57(9) Å^3, Z = 4, D_c = 1.904 g cm^{-3}, μ = 5.677 mm^{-1} (Mo Kα, λ = 0.71073 Å), T = 295 K, R [$I > 2\sigma(I)$] = 0.0462, R_w (F^2, all data) = 0.1220, and goodness of fit of 1.026 for 9294 observed data (12777 unique; R_{int} = 0.1308; 2θ < 56°) and 725 refined parameters. Denzo SMN, SHELXL-97, and SIR97 were used.[18]

Synthesis of 3. Complex **2** (106 mg, 0.14 mmol) was dissolved in acetonitrile (10 mL) at room temperature. $Au(SMe_2)Cl$ (83 mg, 0.28 mmol) was then added to the solution, and the mixture was stirred for an additional 5−6 h. The color of the solution changed from colorless to yellow, which was accompanied by the formation of a precipitate. The precipitate, which was found to be metallic gold, was reused to synthesize $Au(SMe_2)Cl$. After filtration, the residual acetonitrile was evaporated under vacuum and at low temperature to yield a yellow powder. The yellow complex was recrystallized from acetonitrile and diethyl ether to give the desired compound in 33% yield (38 mg, 0.05 mmol): ^{1}H NMR (DMSO-d_6, 300 MHz, 25 °C) δ 8.48 (d, J = 6.4 Hz, 2H), 8.13 (d, J = 7.2 Hz, 2H), 7.84 (t, J = 12 Hz, 4H), 7.73 (d, J = 7.7 Hz, 2H), 7.26 (t, J = 9.2 Hz, 2H), 7.11 (m, 2H), 6.88 (d, J = 7.2 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (DMSO-d_6, 300 MHz, 25 °C) δ 159.7, 146.1, 141.3, 130.6, 126.0, 125.9, 125.73, 125.5, 125.0, 124.8, 119.4, 119.1, 118.8, 112.4, 110.4, 10.9; MS (FAB+) m/z 847.2; UV−vis (CH_2Cl_2) λ_{max} [ε (×10^4 M^{-1} cm^{-1})] 230 (12.1), 244 (11.8), 347 br (2.5), 425 br (2.1) nm. Anal. Calcd for $AuC_{26}H_{22}N_6P_2F_{12}Cl\cdot H_2O$: C, 36.75; H, 2.83; N, 9.89. Found: C, 36.58; H, 2.80; N, 9.87. Single-crystal data: $C_{26}H_{24}AuCl_2OF_6N_6P'$, M_r = 849.35, triclinic, space group $P\bar{1}$, a = 9.4952(12) Å, b = 10.7425(14) Å, c = 14.3591(19) Å, α = 85.821(3)°, β = 89.612(3)°, γ = 87.081(3)°, U = 1458.9(3) Å^3, Z = 2, D_c = 1.934 g cm^{-3}, μ = 5.352 mm^{-1} (Mo Kα, λ = 0.71073 Å), T = 293(2) K, R [$I > 2\sigma(I)$] = 0.0343, R_w (F^2, all data) = 0.0858, and goodness of fit of 1.051 for 4513 observed data (5115 unique; R_{int} = 0.0415; 2θ < 50°) and 381 refined parameters. Standard Bruker AXS control and integration software and SHELXTL were used.[18]

ASSOCIATED CONTENT

Supporting Information

Summary of biological studies, mass spectra, and crystallographic data for complexes **2** and **3** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

B.K.R. and A.N. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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