

Syntheses, Characterizations, and a Preliminary Comparative Cytotoxicity Study of Gold(I) and Gold(III) Complexes Bearing Benzimidazole- and Pyrazole-Derived N-Heterocyclic Carbenes

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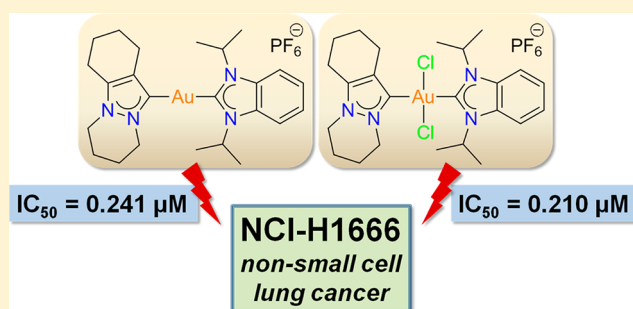
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Supporting Information

ABSTRACT: A series of Au(I) and Au(III) mono-, homobis-, and heterobis(carbene) complexes, [AuCl(FPyr)] (2), [Au(ⁱPr₂-bimy)₂]PF₆ (3), [Au(FPyr)₂]PF₆ (4), [Au(FPyr)(ⁱPr₂-bimy)]PF₆ (5), [AuCl₃(ⁱPr₂-bimy)] (6), [AuCl₃(FPyr)] (7), [AuCl₂(ⁱPr₂-bimy)₂]PF₆ (8), [AuCl₂(FPyr)₂]PF₆ (9), and [AuCl₂(FPyr)(ⁱPr₂-bimy)]PF₆ (10), bearing the benzimidazole-derived ⁱPr₂-bimy (1,3-diisopropylbenzimidazolin-2-ylidene) and/or the pyrazole-derived FPyr (1,2,3,4,6,7,8,9-octahydropyridazino[1,2-*a*]indazolin-11-ylidene) N-heterocyclic carbene (NHC) ligands have been synthesized. Complexes 2–10 have been fully characterized using multinuclei NMR spectroscopy, ESI mass spectrometry, and elemental analysis.

X-ray diffraction analyses have been performed on 2, 3, 5, 6, and 8. Together with the previously reported [AuCl(ⁱPr₂-bimy)] (1), the cytotoxic activities of all 10 complexes have been studied *in vitro* with the NCI-H1666 non-small cell lung cancer cell line. The cationic bis(carbene) complexes 3–5 and 8–10 show better cytotoxicity in comparison to cisplatin. In particular, the heterobis(carbene) complexes 5 and 10 have superior activity, with IC₅₀ values of around 0.2 μM.



INTRODUCTION

Platinum-based complexes such as cisplatin, carboplatin, and oxaliplatin have long proven to be robust, versatile, and effective drugs for chemotherapy. However, the various side effects of the drugs, as well as the development of resistance against these drugs, have triggered new research interest directed at finding alternatives.^{1,2} Apart from considering other platinum-based complexes,¹ researchers have also begun to look at other metals whose compounds may have equal, if not better, anticancer activities.² Among such metals, gold features quite prominently, with its anticancer properties having been investigated extensively over the last several years.^{3,4} Much of this interest stems from the finding that auranofin, an antirheumatic agent, and several other Au(I) complexes show considerable antiproliferative activity.^{2–5} It has also been shown that their cytotoxic mechanism of action is distinctively different from that of platinum complexes, with the former targeting the mitochondrial membrane and/or inhibiting thioredoxin reductase, ultimately leading to mitochondria-induced apoptosis.^{3–6} Pt drugs, on the other hand, are well-known to target specific sequences on DNA, causing apoptosis.¹

Furthermore, it has been reported that a pertinent consideration for mitochondrial membrane permeability is a balance between the hydrophilic and lipophilic properties of gold complexes.^{4,6} It therefore comes as no surprise that there is growing interest in introducing N-heterocyclic carbenes

(NHCs) in such complexes,⁷ given that NHC precursors can easily be electronically and sterically tuned by varying the N-substituents,⁸ thus allowing for synthetic control of the hydro- and lipophilicity of their complexes.

To date, a wide range of Au(I) NHC complexes that display noteworthy anticancer activity have been developed. However, most of these works have focused primarily on imidazolin-2-ylidenes,^{4,6a–g,7,9} while very few examples with benzimidazolin-2-ylidenes have been reported.^{6h,10} To the best of our knowledge, nonclassical NHCs have not yet been employed for such purposes. Furthermore, most studies have been primarily concerned with the cytotoxicity of Au(I) mono- and homobis(carbene) complexes, whereas Au(I) heterobis(carbene) complexes have not been widely explored. Au(III) NHC complexes have also been left out of many studies. As our contribution to this bio-organometallic area, we herein report on the syntheses, characterization, and preliminary comparative cytotoxicities of a series of Au(I) and Au(III) mono-, homobis-, and heterobis(carbene) complexes bearing a classical benzimidazole-derived NHC ligand and/or a nonclassical pyrazole-derived NHC ligand.

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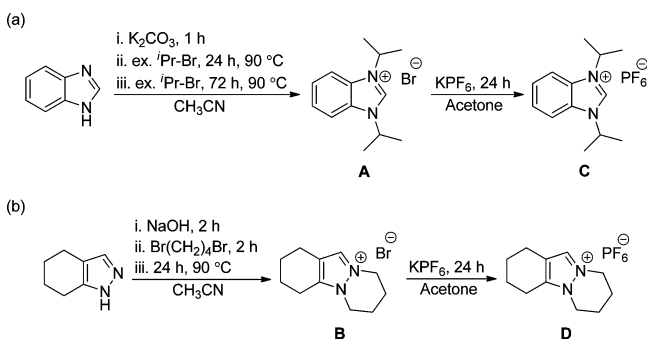
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RESULTS AND DISCUSSION

Syntheses of the Ligand Precursors. We have previously reported the synthesis of the ligand precursor for the benzimidazole-derived $^i\text{Pr}_2$ -bimy ligand (1,3-diisopropylbenzimidazolin-2-ylidene), $^i\text{Pr}_2$ -bimy-HBr (**A**),¹¹ which was converted to its hexafluorophosphate analogue $^i\text{Pr}_2$ -bimy-HPF₆ (**C**) via a salt metathesis reaction with KPF₆ (Scheme 1a). The

Scheme 1. Syntheses of the (a) $^i\text{Pr}_2$ -bimy and (b) FPyr Ligand Precursors A–D



ligand precursor for the new pyrazole-derived FPyr ligand (1,2,3,4,6,7,8,9-octahydropyridazino[1,2-*a*]indazolin-11-ylidene), FPyr-HBr (**B**), was synthesized straightforwardly from 4,5,6,7-tetrahydro-1H-indazole (Scheme 1b), in a manner similar to the synthesis of a previously reported indazolium salt.¹² Following N-deprotonation of the starting material, two stepwise nucleophilic substitution reactions occur with 1,4-dibromobutane, resulting in the cyclized product, which was obtained as an off-white powder in a reasonable yield of 67%. Salt **B** is slightly hygroscopic and readily dissolves in water and other polar organic solvents such as acetone, acetonitrile, CH₂Cl₂, and chloroform. It is insoluble in less polar organic solvents such as ethyl acetate, diethyl ether, and hexane. Similar to the formation of **C**, the hexafluorophosphate analogue of salt **B**, FPyr-HPF₆ (**D**), was also generated (Scheme 1b).

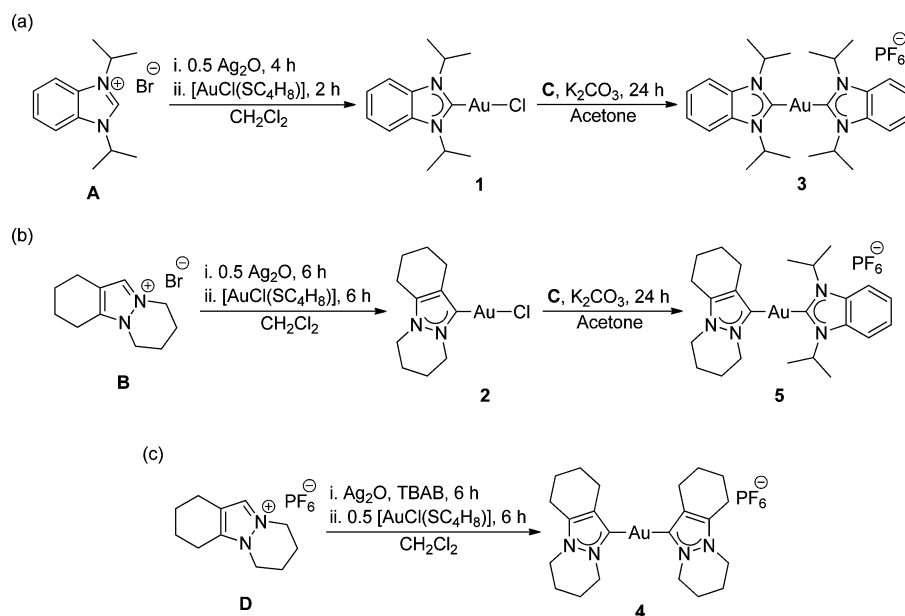
The formation of salt **B** was confirmed by its ¹H NMR spectrum, where a characteristic downfield signal is observed as a singlet at 8.29 ppm, corresponding to the acidic NCH proton. Two triplets observed at 4.56 and 4.32 ppm for the two sets of NCH₂ protons also support the successful reaction. ESI (MS) corroborates the NMR spectroscopic evidence, with a base peak noted at *m/z* 177 for the [M – Br]⁺ fragment.

Syntheses of Au(I) Complexes. The synthesis of the chlorido-monocarbene Au(I) complex [AuCl($^i\text{Pr}_2$ -bimy)] (**1**) was previously reported.¹³ In a similar manner, [AuCl(FPyr)] (**2**) was synthesized using the silver-carbene transfer method developed by Lin and co-workers.¹⁴ Salt **B** was reacted with Ag₂O in CH₂Cl₂, following which the reaction mixture was filtered directly into a solution of [AuCl(SC₄H₈)] in CH₂Cl₂ (Scheme 2b). The immediate precipitation of AgBr indicated the successful transfer of the NHC ligand from the Ag(I) NHC intermediate to the gold metal center. Complex **2** was obtained as a white powder in a very good yield of 84% and is soluble in most polar organic solvents such as DMSO, acetone, acetonitrile, CH₂Cl₂, and chloroform.

The homobis(carbene) complex [Au($^i\text{Pr}_2$ -bimy)₂]PF₆ (**3**) was synthesized by treating complex **1** with K₂CO₃ and 1 equiv of salt **C** (Scheme 2a) in analogy to its previously reported tetrafluoroborate analogue.¹³ The desired complex **3** was obtained in a very good yield of 84% and is soluble in common polar organic solvents. The bis(carbene) complex [Au(FPyr)₂]PF₆ (**4**), on the other hand, could not be prepared in a similar manner from **2**, given the lower acidity of pyrazolium salts, which renders K₂CO₃ too weak a base for the purpose of NCH deprotonation.¹² It was thus prepared by direct silver-carbene transfer involving the reaction of salt **D** with Ag₂O in the presence of NBu₄Br (TBAB) and subsequent transmetalation to [AuCl(SC₄H₈)] (Scheme 2c).¹² Complex **4**, obtained in a fair yield of 62%, is soluble in most polar organic solvents.

The ability to deprotonate salt **C** with the use of K₂CO₃ in a straightforward manner also gives access to the heterobis(carbene) Au(I) complex [Au(FPyr)($^i\text{Pr}_2$ -bimy)]PF₆ (**5**), where complex **2** serves as the precursor (Scheme 2b).

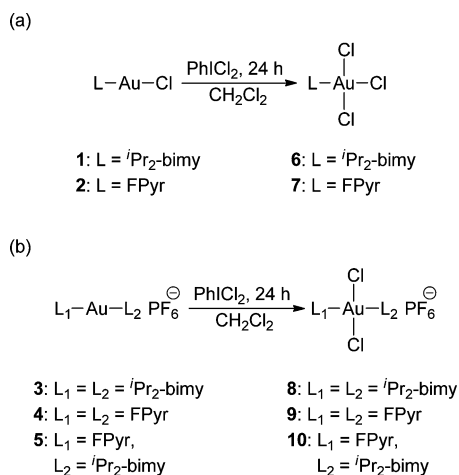
Scheme 2. Syntheses of Au(I) Monocarbene, Bis(carbene) and Hetero-Bis(carbene) Complexes 1–5



Complex **5**, obtained in a yield of 79%, is soluble in polar organic solvents such as DMSO, CH₂Cl₂, and chloroform but insoluble in less polar solvents such as ethyl acetate and diethyl ether.

Syntheses of Au(III) Complexes. Following the successful syntheses of mono-, homobis-, and heterobis(carbene) Au(I) complexes, we sought to synthesize their Au(III) derivatives via oxidative addition reactions (Scheme 3).

Scheme 3. Syntheses of Au(III) Complexes 6–10 via Oxidative Addition Reactions



Complexes **1–5** were treated with PhICl₂, which is a useful and far less toxic source of Cl₂,¹⁵ affording Au(III) complexes **6–10** in excellent yields ranging from 90 to 99%. While most of the Au(III) derivatives showed solubility similar to that of their Au(I) precursors, complexes **8** and **9** were an exception, being only slightly soluble in chloroform. Furthermore, unlike the white or off-white Au(I) complexes, the Au(III) species were pale to bright yellow.

NMR Spectroscopic Analysis of Complexes. All 10 complexes have been fully characterized by multinuclei NMR spectroscopy. The ¹H NMR spectra of the complexes show the expected ligand signals with no significant findings that require additional discussion. Their ¹³C NMR spectra are more conclusive, and Table 1 gives the chemical shifts for the carbene carbon atoms in complexes **1–10**.

Table 1. Chemical Shifts (ppm) of the Carbene Carbon Atoms in Complexes 1–10^a

complex	FPyr	ⁱ Pr ₂ -bimy
1		175.8 ¹³
2	167.8	
3		187.5
4	184.6	
5	179.6	192.5
6		150.8
7	134.9	
8		159.2
9	155.4	
10	151.2	168.5

^a¹³C NMR spectra of **1–6** and **10** were measured in CDCl₃, while those of **7–9** were measured in DMSO-*d*₆.¹⁶

A 2D-HMBC NMR spectroscopic analysis of heterobis(carbene) complex **5** was conducted in order to correctly assign the two downfield signals at 192.5 and 179.6 ppm to the ⁱPr₂-bimy and the FPyr ligands, respectively (see the Supporting Information). The relative positions of the two signals were then applied in assigning the similarly observed downfield signals in the ¹³C NMR spectrum of complex **10**.

On comparison of the chlorido-monocarbene complexes **1** and **2** with the bis(carbene) complexes **3–5**, it is noted that the C_{carbene} resonances in the latter are much more downfield as compared to those in the former. This can be explained by the presence of a second strongly σ-donating NHC ligand, which lowers the overall Lewis acidity of the metal center, resulting in the observed downfield shift.^{12,13,17} In contrast, an increase in the Lewis acidity due to oxidation from Au(I) to Au(III) causes an upfield shift of the C_{carbene} signals, as is observed in the cases of **6–10** in comparison to their respective Au(I) precursors.^{12,13} This upfield shift is therefore a good indication of the successful oxidative addition reaction.

It is also worth mentioning that the ¹³C NMR signal due to the isopropyl methine carbon of the ⁱPr₂-bimy ligand in complex **10** could not be resolved, despite a high sample concentration and extended acquisition time. In order to probe this unexpected observation, a 2D-HMQC NMR spectroscopic analysis was conducted, which suggested a direct connectivity between the isopropyl methine proton, resonating at 5.34 ppm in the ¹H NMR spectrum, and the carbon atom in question, which should have a ¹³C NMR signal at ~55 ppm (Figure 1).

The apparent signal suppression could be due to the unhindered rotation of the ⁱPr₂-bimy ligand about the Au–C bond at ambient temperature, which results in the equivalence of the isopropyl methine carbon atoms on the ¹³C NMR time scale, causing signal coalescence. This premise was confirmed by a variable-temperature (VT) ¹³C NMR spectroscopic analysis of **10** (Figure 2). At 263 K, two distinct resonances at 55.9 and 54.8 ppm were noted, corresponding to the two inequivalent methine carbon atoms of the isopropyl groups, as a result of thermally arrested rotation of the ⁱPr₂-bimy ligand about the Au–C bond. At temperatures lower than 243 K, signal suppression is once again observed, possibly due to poor solubility of the complex at such low temperatures. On the other hand, no significant changes were observed in the ¹H NMR spectra across the various temperatures (see the Supporting Information). It is also noteworthy that such a phenomenon was not observed in its Au(I) precursor complex **5**. This suggests that the increased steric crowding in complex **10**, due to the square-planar geometry about the metal center, affects the rotation of the two NHC ligands about their respective Au–C bonds.

X-ray Diffraction Analyses of Complexes. Single crystals of complexes **2**, **3**, **5**, **6**, and **8** were subjected to X-ray diffraction analysis (Figure 3).

The Au–C_{carbene} bond lengths in all five complexes are well within the range reported for other similar complexes.^{12,13,18} Complexes **2**, **3**, and **5** adopt an essentially linear geometry about the Au(I) metal center with slight deviations. It is interesting that the two NHC ligands of **3** lie on separate planes with a dihedral angle of ~62°, which is unlike its tetrafluoroborate analogue, where the two NHC ligands are essentially coplanar.¹³ The Au(III) complexes **6** and **8** adopt a square-planar geometry about the metal center. It is noted that in **6** the two chlorido ligands *cis* to the NHC ligand point toward the carbene carbon, with a Cl1–Au1–Cl1A bond angle

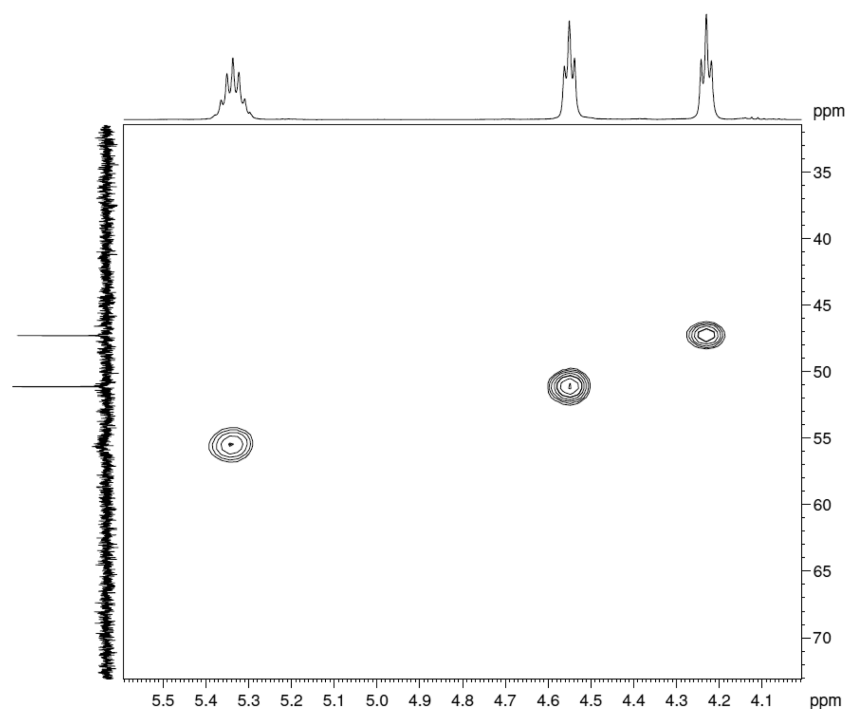


Figure 1. Section of the 2D-HMQC NMR spectrum of **10** in CDCl_3 .

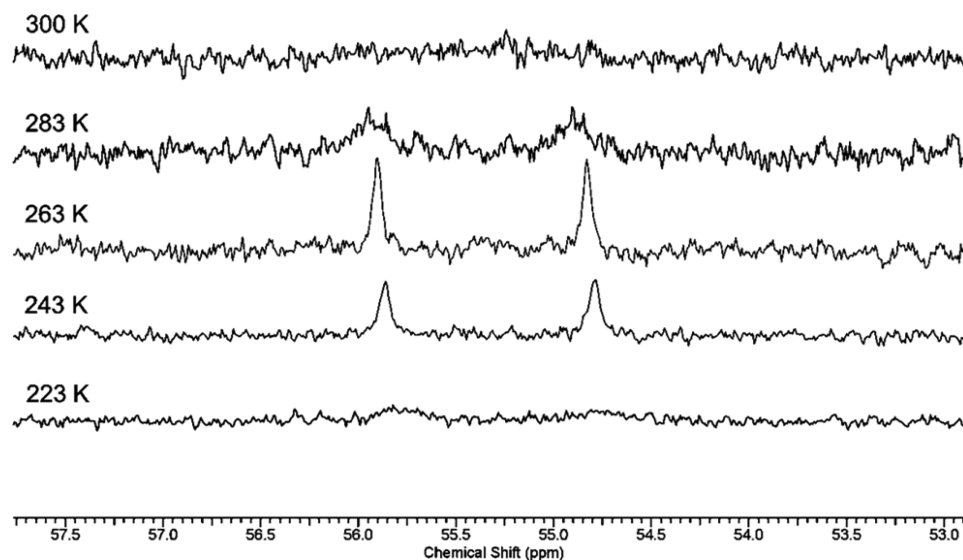


Figure 2. Section of the variable-temperature (VT) ^{13}C NMR spectrum of **10** in CDCl_3 .

of $175.19(7)^\circ$. This possibly indicates interactions between the lone pairs of electrons on the chlorido ligands and the formally empty p-orbital of the carbene carbon atom, as has been observed in other NHC complexes.^{11,12,19} The $\text{C1}\cdots\text{Cl1}$ and $\text{C1}\cdots\text{Cl1A}$ interatomic distance of 2.970 \AA is also well within the sum of the van der Waals radii for carbon and chlorine ($\sim 3.45 \text{ \AA}$), thus supporting this premise. As for complex **8**, it should be mentioned that the chlorido ligands were disordered over two positions with a 50:50 occupancy ratio. Furthermore, unlike the case for **3**, the two NHC ligands in **8** are close to coplanarity, with a small dihedral angle of $\sim 17^\circ$.

Cytotoxicity Studies. The cytotoxic activities of complexes **1–10** were investigated through a cell proliferation assay conducted on the NCI-H1666 non-small cell lung cancer cell line (see the Supporting Information). Figure 4 presents the

compiled dose–response curves, while the IC_{50} values of all 10 complexes are shown in Table 2. Although the cytotoxicity of cisplatin on this cell line has been reported,²⁰ we have determined its IC_{50} value again under the same experimental conditions for a more valid comparison.

The neutral monocarbene complexes **1**, **2**, **6**, and **7** were found to be less toxic than cisplatin and in general displayed 1–2 orders of magnitude lower activity as compared to the cationic homo- and heterobis(carbene) complexes **3–5** and **8–10**. This finding agrees with what has been previously referred to as delocalized lipophilic cations (DLCs), which have the ability to readily pass through the lipid membrane of mitochondria and accumulate within the mitochondria as result of the large mitochondrial membrane potential, eventually leading to mitochondria-induced apoptosis.^{4,6d–f,7a}

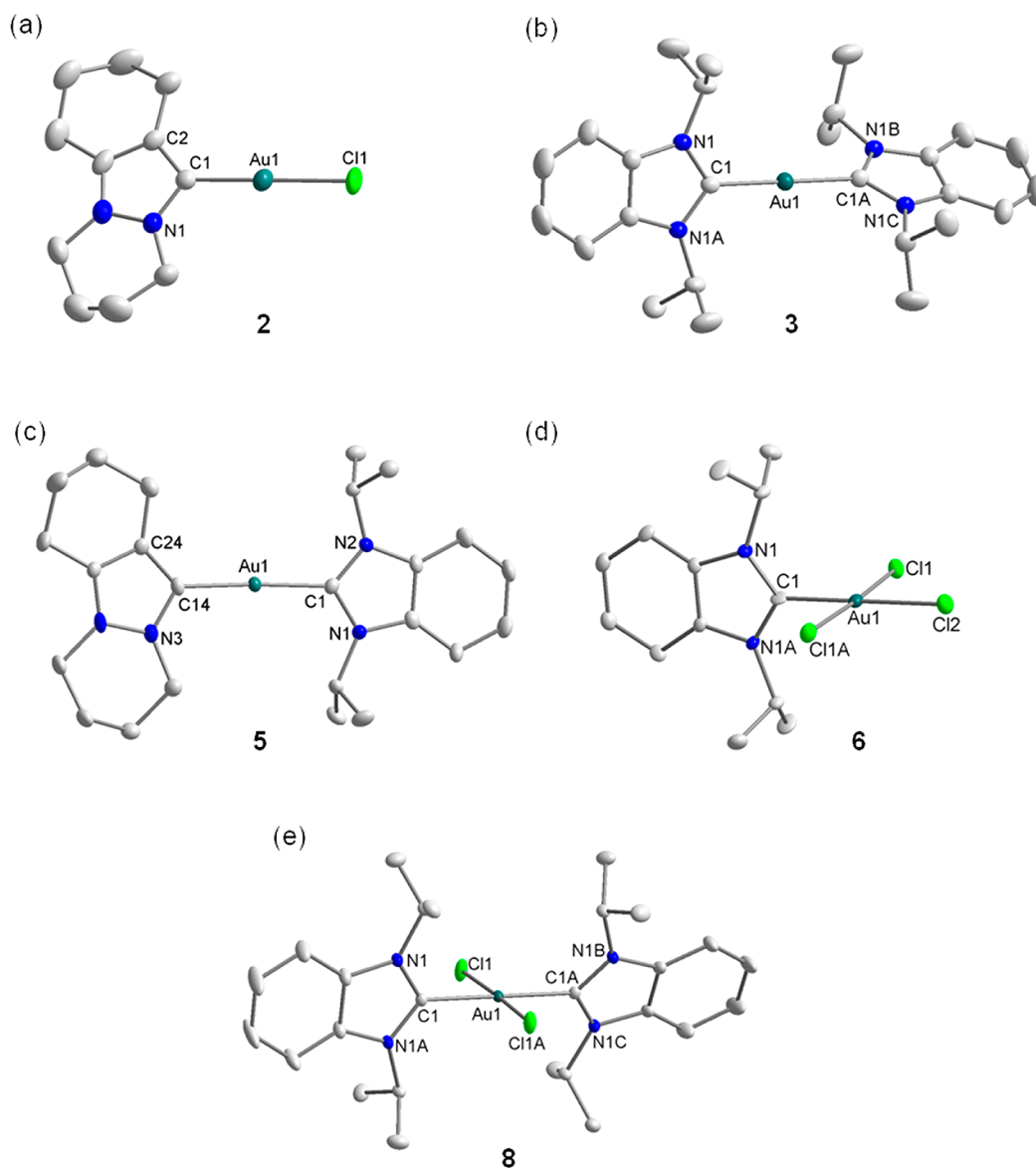


Figure 3. Molecular structures of **2**, **3**, **5**, **6**, and **8** showing 50% probability ellipsoids. Hydrogen atoms and PF_6^- anions (if any) have been omitted for clarity. Selected bond lengths (\AA) and bond angles (deg) are as follows. (a) **2**: Au1–C1 = 1.980(7), Au1–Cl1 = 2.3248(18); C1–Au1–Cl1 = 178.6(2). (b) **3**: Au1–C1 = 2.016(6), Au1–C1A = 2.016(6); C1–Au1–C1A = 180.000(2). (c) **5**: Au1–C1 = 2.024(5), Au1–C14 = 2.026(5); C1–Au1–C14 = 177.2(2). (d) **6**: Au1–C1 = 1.989(7), Au1–Cl1 = 2.2914(13), Au1–Cl1A = 2.2914(13), Au1–Cl2 = 2.3155(17); C1–Au1–Cl2 = 180.000(12), Cl1–Au1–Cl1A = 175.19(7). (e) **8**: Au1–C1 = 2.048(3), Au1–C1A = 2.048(3), Au1–Cl1 = 2.2812(10), Au1–Cl1A = 2.2812(10); C1–Au1–C1A = 180.000(1), Cl1–Au1–Cl1A = 176.65(4).

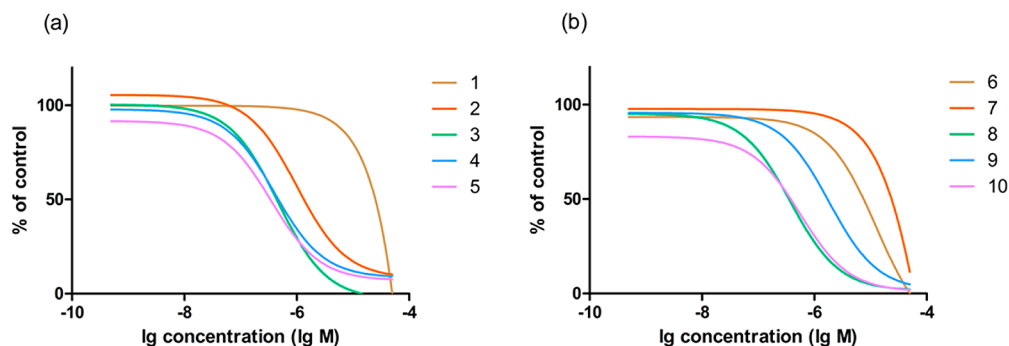


Figure 4. Best-fit dose–response curves for (a) Au(I) complexes **1–5** and (b) Au(III) complexes **6–10**.

The neutral monocarbene complexes, while having a certain degree of lipophilic properties, lack an overall cationic

character, which seems necessary for targeting mitochondria. It is interesting to note the lack of significant differences in the

Table 2. Cytotoxicity in the NCI-H1666 Cell Line Expressed as IC₅₀ Values (μM)^a

compound	IC ₅₀ (μM)
1	>10
2	8.97 ± 0.87
3	0.284 ± 0.11
4	2.35 ± 0.07
5	0.241 ± 0.01
6	>10
7	>10
8	0.536 ± 0.19
9	1.46 ± 0.09
10	0.210 ± 0.04
cisplatin	2.51 ± 0.11

^aIC₅₀ values were determined from best-fit curves on the basis of three independent experiments.

relative performance of cationic Au(I) and Au(III) bis(carbene) complexes, which could be due to the redox activities that occur in the cellular environment, favoring one oxidation state over the other.²¹

Among the homobis(carbene) complexes of the same gold oxidation state, those bearing ⁱPr₂-bimy ligands (**3** and **8**) are noted to be more active than those bearing two FPyr ligands (**4** and **9**). This seems to indicate some form of ligand detachment process in the mechanism of action of such cationic complexes. The vacant coordination site that ensues as a result of ligand detachment could be used for binding with donor atoms on target proteins, such as the selenol groups in thioredoxin reductase that is found in both cytoplasm and mitochondria, the inhibition of which has been shown to lead to apoptosis of cancer cells.^{4a,c,e,6d,f-h,7a,b,9c,d,10} The FPyr ligand is a better σ-donor and is expected to be more strongly bound to the gold center as compared to the ⁱPr₂-bimy ligand. Thus, the former is far less labile as compared to the latter, and any biological activation of the complexes via ligand detachment is more likely for complexes bearing the ⁱPr₂-bimy ligand. Extrapolating this proposition to the heterobis(carbene) complexes **5** and **10**, the presence of the FPyr ligand could potentially have a significant *trans* effect on the ⁱPr₂-bimy ligand, thus stabilizing it further than in complexes **3** and **8**. While this would account for the superior performance of the heterobis(carbene) complexes in comparison to the homobis(carbene) complexes, further studies into this proposed activation step of the complexes would be necessary to better appreciate the significance of the relative activities of the compounds.

CONCLUSION

We have reported the syntheses and characterization of a series of Au(I) and Au(III) NHC complexes bearing the benzimidazole-derived ⁱPr₂-bimy ligand and/or the pyrazole-derived FPyr ligand. Similar to the synthesis of the previously reported [AuCl(ⁱPr₂-bimy)] (**1**), the formation of the chlorido-monocarbene Au(I) complex [AuCl(FPyr)] (**2**) was achieved via the silver-carbene transfer method. The homobis(carbene) complexes [Au(ⁱPr₂-bimy)₂]PF₆ (**3**) and [Au(FPyr)₂]PF₆ (**4**) were synthesized via reaction with ⁱPr₂-bimy-HPF₆ in the presence of a base and using the silver-transfer method, respectively. **2** was also reacted with ⁱPr₂-bimy-HPF₆ in the presence of a base for the synthesis of the heterobis(carbene) complex [Au(FPyr)(ⁱPr₂-bimy)]PF₆ (**5**). Oxidative addition reactions of **1–5** with PhICl₂ yielded the trichlorido-

monocarbene Au(III) complexes [AuCl₃(ⁱPr₂-bimy)] (**6**) and [AuCl₃(FPyr)] (**7**), as well as the dichlorido-homobis(carbene) Au(III) complexes [AuCl₂(ⁱPr₂-bimy)₂]PF₆ (**8**) and [AuCl₂(FPyr)₂]PF₆ (**9**) and the heterobis(carbene) complex [AuCl₂(FPyr)(ⁱPr₂-bimy)]PF₆ (**10**). The cytotoxic activities of all 10 complexes were studied with the NCI-H1666 non-small cell lung cancer cell line. The cationic bis(carbene) complexes showed better activities in comparison to cisplatin, with the heterobis(carbene) complexes **5** and **10** presenting superior cytotoxicity. We endeavor to continue the investigation of these complexes by examining their selectivity and mechanism of action *in vitro*. We also look forward to studying other similar complexes designed on the basis of our findings here, as well as extending the cytotoxicity studies to other cell lines in the future.

EXPERIMENTAL SECTION

General Considerations. Unless otherwise noted, all operations were performed without taking precautions to exclude air and moisture, and all solvents and chemicals were used as received. ¹H, ¹³C, ¹⁹F, and ³¹P NMR spectra were recorded on a Bruker ACF 300 spectrometer or a Bruker AMX 500 spectrometer. 2D-HMBC and HMQC NMR spectra were recorded on a Bruker DRX 500 spectrometer. The chemical shifts (δ) were internally referenced to the residual solvent signals relative to tetramethylsilane (¹H and ¹³C) or externally to CF₃CO₂H (¹⁹F) and 85% H₃PO₄ (³¹P). ESI mass spectra were measured using a Finnigan LCQ spectrometer. Elemental analyses were performed on an Elementar Vario Micro Cube elemental analyzer at the Department of Chemistry, National University of Singapore. Salt **A**,¹¹ PhICl₂,²² and complex **1**¹³ were synthesized as previously reported. Salts **C** and **D** were synthesized from **A** and **B**, respectively, by anion exchange with excess KPF₆ in acetone, on stirring for 24 h at ambient temperature. [AuCl(SC₄H₈)] was synthesized as a combination of two independent literature procedures, where HAuCl₄ was first synthesized²³ and subsequently reduced to the desired [AuCl(SC₄H₈)] complex.²⁴

FPyr-HBr (B). NaOH (77 mg, 1.93 mmol) was added to a solution of 4,5,6,7-tetrahydro-1*H*-indazole (138 mg, 1.13 mmol) in acetonitrile (20 mL), and the resulting mixture was stirred for 2 h at ambient temperature. 1,4-Dibromobutane (240 μL, 2.01 mmol) was then added, and the resulting mixture was stirred for a further 2 h at ambient temperature. Subsequently, the reaction mixture was heated to reflux at 90 °C for 24 h. The solvent of the reaction mixture was removed under vacuum, and the residue was suspended in CH₂Cl₂ (25 mL) and filtered. The solvent of the filtrate was removed under vacuum, and the residue was washed with ethyl acetate (3 × 15 mL) and dried under vacuum. The product was obtained as a slightly hygroscopic off-white powder (194 mg, 0.75 mmol, 67%). ¹H NMR (500 MHz, CDCl₃): δ 8.29 (s, 1 H, NCH), 4.56 (t, 2 H, ³J(H,H) = 6.30 Hz, NCH₂), 4.32 (t, 2 H, ³J(H,H) = 5.70 Hz, NCH₂), 2.68 (t, 2 H, ³J(H,H) = 6.30 Hz, CH₂), 2.44 (t, 2 H, ³J(H,H) = 6.30 Hz, CH₂), 2.18 (m, 2 H, CH₂), 2.11 (m, 2 H, CH₂), 1.78 (m, 2 H, CH₂), 1.66 (m, 2 H, CH₂). ¹³C{¹H} NMR (125.8 MHz, CDCl₃): δ 146.7 (s, NCH), 134.5 (s, NCCH₂), 118.7 (s, NCHC), 49.9, 47.1 (s, NCH₂), 22.1, 21.5, 21.3, 20.2, 20.1, 20.0 (s, CH₂). Anal. Calcd for C₁₁H₁₇N₂Br: C, 51.37; H, 6.66; N, 10.89. Found: C, 51.60; H, 6.39; N, 10.76. ESI (MS): *m/z* 177 [M - Br]⁺.

[AuCl(FPyr)] (2). Ag₂O (16 mg, 0.07 mmol) was added to a solution of **B** (29 mg, 0.11 mmol) in CH₂Cl₂ (15 mL), and the resulting mixture was stirred for 6 h at ambient temperature, shielded from light. The reaction mixture was then filtered through Celite into a solution of [AuCl(SC₄H₈)] (37 mg, 0.12 mmol) in CH₂Cl₂ (10 mL), and the resulting mixture was stirred for 6 h at ambient temperature. The reaction mixture was then filtered through Celite, and the solvent of the filtrate was removed under vacuum. The residue was subsequently washed with diethyl ether (3 × 15 mL) and dried under vacuum, affording the product as a white powder (38 mg, 0.09 mmol, 84%). ¹H NMR (500 MHz, CDCl₃): δ 4.36 (t, 2 H, ³J(H,H) =

6.00 Hz, NCH₂), 3.99 (t, 2 H, ³J(H,H) = 5.45 Hz, NCH₂), 2.54 (t, 2 H, ³J(H,H) = 6.00 Hz, CH₂), 2.49 (t, 2 H, ³J(H,H) = 6.00 Hz, CH₂), 2.13 (m, 4 H, CH₂), 1.84 (m, 2 H, CH₂), 1.72 (m, 2 H, CH₂). ¹³C{¹H} NMR (125.8 MHz, CDCl₃): δ 167.8 (s, C_{carbene}), 144.4 (s, NCCH₂), 126.1 (s, NC_{carbene}CCH₂), 51.7, 46.4 (s, NCH₂), 23.3, 23.1, 22.7, 22.1, 21.50, 21.48 (s, CH₂). Anal. Calcd for C₁₁H₁₆N₂AuCl: C, 32.33; H, 3.95; N, 6.85. Found: C, 32.24; H, 3.96; N, 6.46. ESI (MS): *m/z* 549 [M - Cl + FPyr]⁺.

[Au(Pr₂-bimy)₂]PF₆ (3). A mixture of **1** (92 mg, 0.21 mmol) and salt **C** (74 mg, 0.21 mmol) were dissolved in acetone (30 mL). K₂CO₃ (50 mg, 0.36 mmol) was added to the solution, and the resulting mixture was stirred for 24 h at ambient temperature. Subsequently, the solvent of the reaction mixture was removed under vacuum. The resulting residue was dissolved (partially) in CH₂Cl₂ and filtered over Celite. The solvent of the filtrate was removed under vacuum, and the resulting residue was washed with ethyl acetate (3 × 20 mL) and dried under vacuum, affording the product as a white powder (133 mg, 0.18 mmol, 84%). ¹H NMR (500 MHz, CDCl₃): δ 7.73 (dd, 2 H, Ar H), 7.45 (dd, 2 H, Ar-H), 5.38 (m, 2 H, ³J(H,H) = 6.95 Hz, NCH), 1.85 (d, 12 H, ³J(H,H) = 6.95 Hz, CH₃). ¹³C{¹H} NMR (125.8 MHz, CDCl₃): δ 187.5 (s, C_{carbene}), 133.3, 125.4, 113.8 (s, Ar C), 54.4 (s, NCH), 23.1 (s, CH₃). ³¹P{¹H} NMR (202.4 MHz, CDCl₃): δ -143.7 (m, PF₆). ¹⁹F{¹H} NMR (282.4 MHz, CDCl₃): δ 0.78 (d, PF₆). Anal. Calcd for C₂₆H₃₆N₄AuPF₆: C, 41.83; H, 4.86; N, 7.51. Found: C, 41.58; H, 4.78; N, 7.45. ESI (MS): *m/z* 601 [M - PF₆]⁺.

[Au(FPyr)₂]PF₆ (4). Salt **D** (35 mg, 0.11 mmol), tetrabutylammonium bromide (35 mg, 0.11 mmol), and Ag₂O (26 mg, 0.11 mmol) were stirred in CH₂Cl₂ (20 mL) for 6 h at ambient temperature, shielded from light. [AuCl(SC₄H₈)] (18 mg, 0.06 mmol) was then added to the reaction mixture, and stirring was continued for 6 h. The resulting mixture was filtered through Celite, and the solvent of the filtrate was removed under vacuum. The resulting residue was washed with ethyl acetate (3 × 5 mL) and dried under vacuum, affording the product as an off-white powder (24 mg, 0.03 mmol, 62%). ¹H NMR (500 MHz, CDCl₃): δ 4.39 (br t, 2 H, NCH₂), 4.01 (br t, 2 H, NCH₂), 2.57 (t, 4 H, ³J(H,H) = 5.65 Hz, CH₂), 2.14 (br t, 4 H, CH₂), 1.85 (br m, 2 H, CH₂), 1.75 (br m, 2 H, CH₂). ¹³C{¹H} NMR (125.8 MHz, CDCl₃): δ 184.6 (s, C_{carbene}), 144.2 (s, NCCH₂), 126.8 (s, NC_{carbene}C), 51.8, 46.6 (s, NCH₂), 23.4, 23.0, 22.7, 22.2, 21.4 (×2) (s, CH₂). ³¹P{¹H} NMR (202.4 MHz, CDCl₃): δ -143.9 (m, PF₆). ¹⁹F{¹H} NMR (282.4 MHz, CDCl₃): δ 2.57 (d, PF₆). Anal. Calcd for C₂₂H₃₂N₄AuPF₆: C, 38.05; H, 4.64; N, 8.07. Found: C, 38.39; H, 4.63; N, 7.92. ESI (MS): *m/z* 549 [M - PF₆]⁺.

[Au(FPyr)(Pr₂-bimy)]PF₆ (5). A mixture of **2** (32 mg, 0.08 mmol) and salt **C** (27 mg, 0.08 mmol) was dissolved in acetone (30 mL). K₂CO₃ (50 mg, 0.36 mmol) was added to the solution, and the resulting mixture was stirred for 24 h at ambient temperature. Subsequently, the solvent of the reaction mixture was removed under vacuum. The resulting residue was dissolved (partially) in CH₂Cl₂ and filtered. The solvent of the filtrate was removed under vacuum, and the resulting residue was washed with ethyl acetate (3 × 15 mL) and dried under vacuum, affording the product as a white powder (44 mg, 0.06 mmol, 79%). ¹H NMR (500 MHz, CDCl₃): δ 7.66 (dd, 2 H, Ar H), 7.41 (dd, 2 H, Ar H), 5.33 (m, 2 H, ³J(H,H) = 7.10 Hz, NCH), 4.44 (t, 2 H, ³J(H,H) = 5.15 Hz, NCH₂), 4.10 (t, 2 H, ³J(H,H) = 5.80 Hz, NCH₂), 2.62 (br m, 4 H, CH₂), 2.21 (br m, 4 H, CH₂), 1.88 (br m, 4 H, CH₂), 1.83 (d, 12 H, ³J(H,H) = 7.10 Hz, CH₃). ¹³C{¹H} NMR (125.8 MHz, CDCl₃): δ 192.5 (s, C_{carbene} (Pr₂-bimy)), 179.6 (s, C_{carbene} (FPyr)), 144.4 (s, NCCH₂), 133.4 (s, Ar C), 126.6 (s, NC_{carbene}CCH₂), 124.9 (s, Ar C), 113.4 (s, Ar-C), 53.9 (s, NCH), 51.9, 46.7 (s, NCH₂), 23.4 (s, CH₃), 23.2, 23.1, 22.6, 22.0, 21.3, 21.1 (s, CH₂). ³¹P{¹H} NMR (202.4 MHz, CDCl₃): δ -143.8 (m, PF₆). ¹⁹F{¹H} NMR (282.4 MHz, CDCl₃): δ 2.28 (d, PF₆). Anal. Calcd for C₂₄H₃₄N₄AuPF₆: C, 40.01; H, 4.76; N, 7.78. Found: C, 39.78; H, 4.82; N, 8.06. ESI (MS): *m/z* 575 [M - PF₆]⁺.

General Procedure for the Syntheses of Au(III) Complexes 6–10. The precursor Au(I) complex (1 equiv) and PhICl₂ (1.2 equiv) were dissolved in CH₂Cl₂ and stirred for 24 h at ambient temperature, shielded from light. The solvent of the reaction mixture was then

removed under vacuum, and the resulting residue was washed with hexane and diethyl ether several times and dried under vacuum.

[AuCl₃(Pr₂-bimy)] (6). Yellow powder, 99%. ¹H NMR (300 MHz, CDCl₃): δ 7.79 (dd, 2 H, Ar H), 7.48 (dd, 2 H, Ar H), 5.51 (m, 2 H, ³J(H,H) = 7.05 Hz, NCH), 1.81 (d, 12 H, ³J(H,H) = 7.05 Hz, CH₃). ¹³C{¹H} NMR (75.5 MHz, CDCl₃): δ 150.8 (s, C_{carbene}), 133.5, 125.8, 115.1 (s, Ar C), 56.2 (s, NCH), 21.6 (s, CH₃). Anal. Calcd for C₁₃H₁₈N₂AuCl₃: C, 30.88; H, 3.59; N, 5.54. Found: C, 30.54; H, 3.61; N, 5.68. ESI (MS): *m/z* 957 [2 M - 2Cl + OH]⁺.

[AuCl₃(FPyr)] (7). Pale yellow powder, 90%. ¹H NMR (500 MHz, DMSO-*d*₆): δ 4.42 (br t, 2 H, NCH₂), 4.28 (br t, 2 H, NCH₂), 2.67 (t, 2 H, ³J(H,H) = 5.65 Hz, CH₂), 2.54 (t, 2 H, ³J(H,H) = 6.30 Hz, CH₂), 2.07 (m, 4 H, CH₂), 1.79 (m, 2 H, CH₂), 1.72 (m, 2 H, CH₂). ¹³C{¹H} NMR (125.8 MHz, DMSO-*d*₆): δ 145.3 (s, NCCH₂), 134.9 (s, C_{carbene}), 119.6 (s, NC_{carbene}C), 50.0, 46.2 (s, NCH₂), 21.6, 20.9, 20.5, 20.1, 19.7, 19.1 (s, CH₂). Anal. Calcd for C₁₁H₁₆N₂AuCl₃: C, 27.55; H, 3.36; N, 5.84. Found: C, 27.67; H, 3.21; N, 5.72. ESI (MS): *m/z* 905 [2 M - 2Cl + OH]⁺.

[AuCl₂(Pr₂-bimy)₂]PF₆ (8). Pale yellow powder, 97%. ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.25 (dd, 2 H, Ar H), 7.60 (dd, 2 H, Ar H), 5.38 (m, 2 H, ³J(H,H) = 6.95 Hz, NCH), 1.85 (d, 12 H, ³J(H,H) = 6.95 Hz, CH₃). ¹³C{¹H} NMR (125.8 MHz, DMSO-*d*₆): δ 159.2 (s, C_{carbene}), 132.2, 125.6, 114.9 (s, Ar C), 55.0 (s, NCH), 20.7 (s, CH₃). ³¹P{¹H} NMR (202.4 MHz, DMSO-*d*₆): δ -143.0 (m, PF₆). ¹⁹F{¹H} NMR (282.4 MHz, DMSO-*d*₆): δ 5.80 (d, PF₆). Anal. Calcd for C₂₆H₃₆N₄AuCl₂PF₆: C, 38.20; H, 4.44; N, 6.85. Found: C, 38.64; H, 4.37; N, 6.76. Although these results lie outside the range viewed as establishing analytical purity, they are provided to illustrate the best values obtained to date. Multinuclei NMR spectra, which establish the absence of contaminants, are included in the Supporting Information. ESI (MS): *m/z* 671 [M - PF₆]⁺.

[AuCl₂(FPyr)₂]PF₆ (9). Yellow powder, 95%. ¹H NMR (500 MHz, DMSO-*d*₆): δ 4.45 (br t, 2 H, NCH₂), 4.23 (br t, 2 H, NCH₂), 2.67 (t, 2 H, ³J(H,H) = 5.05 Hz, CH₂), 2.62 (br t, 2 H, CH₂), 2.08 (br m, 4 H, CH₂), 1.80 (br m, 2 H, CH₂), 1.73 (br m, 2 H, CH₂). ¹³C{¹H} NMR (125.8 MHz, DMSO-*d*₆): δ 155.4 (s, C_{carbene}), 144.5 (s, NCCH₂), 121.1 (s, NC_{carbene}C), 49.7, 45.9 (s, NCH₂), 22.0, 21.2, 20.6, 20.2, 20.0, 19.4 (s, CH₂). ³¹P{¹H} NMR (202.4 MHz, DMSO-*d*₆): δ -143.0 (m, PF₆). ¹⁹F{¹H} NMR (282.4 MHz, DMSO-*d*₆): δ 5.80 (d, PF₆). Anal. Calcd for C₂₂H₃₂N₄AuCl₂PF₆: C, 34.52; H, 4.21; N, 7.32. Found: C, 34.26; H, 4.19; N, 7.13. ESI (MS): *m/z* 619 [M - PF₆]⁺.

[AuCl₂(FPyr)(Pr₂-bimy)]PF₆ (10). Pale yellow powder, 98%. ¹H NMR (500 MHz, CDCl₃): δ 7.77 (br m, 2 H, Ar H), 7.46 (dd, 2 H, Ar H), 5.34 (m, 2 H, ³J(H,H) = 6.95 Hz, NCH), 4.55 (t, 2 H, ³J(H,H) = 5.65 Hz, NCH₂), 4.23 (t, 2 H, ³J(H,H) = 6.30 Hz, NCH₂), 2.70 (m, 4 H, CH₂), 2.32 (br m, 2 H, CH₂), 2.24 (br m, 2 H, CH₂), 1.93 (br m, 4 H, CH₂), 1.87 (d, 12 H, ³J(H,H) = 6.95 Hz, CH₃). ¹³C{¹H} NMR (125.8 MHz, CDCl₃): δ 168.5 (s, C_{carbene} (Pr₂-bimy)), 151.2 (s, C_{carbene} (FPyr)), 146.0 (s, NCCH₂), 133.7 (s, Ar C), 125.6 (s, NC_{carbene}C), 122.8 (s, Ar C), 114.8 (s, Ar C), 51.4, 47.6 (s, NCH₂), 22.9, 22.21 (s, CH₂), 22.18 (s, CH₃), 21.8, 21.6, 21.5, 20.8 (s, CH₂). ³¹P{¹H} NMR (202.4 MHz, CDCl₃): δ -143.7 (m, PF₆). ¹⁹F{¹H} NMR (282.4 MHz, CDCl₃): δ 2.58 (d, PF₆). Anal. Calcd for C₂₄H₃₄N₄AuCl₂PF₆: C, 36.42; H, 4.33; N, 7.08. Found: C, 36.62; H, 4.32; N, 7.42. ESI (MS): *m/z* 645 [M - PF₆]⁺.

Cytotoxicity Studies. In vitro toxicities of **1–10** and cisplatin were determined by CellTiter 96 Aqueous Non-Radioactive Cell Proliferation Assay (MTS). NCI-H1666 cells were maintained in complete RPMI medium with 10% FBS and 1% PenStrep. Standard DMSO solutions of **1–10** and cisplatin were diluted with complete RPMI medium, with the final concentration of DMSO in each diluted solution being less than 0.5%. The cells were seeded in 96-well plates at a density of 2000 cells/well in 100 μL of complete RPMI medium without antibiotics and cultured overnight at 37 °C in a humidified atmosphere containing 5% CO₂. A 100 μL portion of media containing different concentrations of **1–10** and cisplatin was added in the wells to a final concentration from 0.0005 to 50 μM. Compound-free solvent controls were also included. After a 72 h incubation period, 20 μL of CellTiter 96 Aqueous One Reagent

containing the tetrazolium compound MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt) was added to each well. After incubation for about 3 h, the absorbance was measured at 490 nm using a Tecan Infinite M200 plate reader. Nonlinear regression analysis was performed using GraphPad Prism version 5.00 for Windows to calculate the IC_{50} value of each compound.

X-ray Diffraction Studies. X-ray data for **2**, **3**, **5**, **6**, and **8** were collected with a Bruker AXS SMART APEX diffractometer, using Mo $K\alpha$ radiation at 100(2) K (**3**, **5**, **6**, and **8**) or at 223(2) K (**2**) with the SMART suite of programs.²⁵ Data were processed and corrected for Lorentz and polarization effects with SAINT²⁶ and for absorption effects with SADABS.²⁷ Structural solution and refinement were carried out with the SHELXTL suite of programs.²⁸ The structures were solved by direct methods to locate the heavy atoms, followed by difference maps for the light, non-hydrogen atoms. All hydrogen atoms were placed in calculated positions. All non-hydrogen atoms were generally given anisotropic displacement parameters in the final model. A summary of the most important crystallographic data is provided in the Supporting Information.

■ ASSOCIATED CONTENT

● Supporting Information

2D-HMBC NMR spectrum of **5**, VT 1H NMR spectra of **10**, dose–response curves for **1**–**10** and cisplatin, multinuclei NMR spectra of **8**, a table of selected X-ray crystallographic data, and a single CIF file for complexes **2**, **3**, **5**, **6**, and **8** are available. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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