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ARTICLE

Synthesis and Cytotoxic Characteristics Displayed by a Series of Ag(I)-, Au(I)- and Au(III)-Complexes Supported by a Common N-Heterocyclic Carbene

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The synthesis, structures and anticancer of studies of a series of precious metal complexes supported by pyridyl[1,2-a]{2-acetylylphenylimidazol}-3-ylidene (**1**) have been highlighted. The Ag(I) (**2**), Au(I) (**3**) and Au(III) (**4**) complexes were prepared using standard methods and characterized by a range of techniques, including NMR spectroscopy, X-ray crystallography and elemental analyses. The *in vitro* cytotoxicity activities displayed by **2** - **4** were explored against human colon adenocarcinoma (HCT116), lung cancer (A549) and breast cancer (MCF7) cell lines. A series of assays revealed that all of the complexes exhibited significant growth inhibition in the aforementioned cell lines. Inspection of the data collected revealed that the Au(I) and Ag(I) complexes were more potent than their Au(III) congener, a trend that was found to be consistent with molecular docking studies considering BCL-2 protein for model studies, as BCL-2 is a founding member of BCL family, that regulate the cell death through apoptosis.

Introduction

The *N*-heterocyclic carbenes (NHCs) have emerged as an important class of ancillary ligands for a broad range of transition metals.[1] When compared to their phosphine analogues, metal complexes supported by NHCs often exhibit increased stabilities toward elevated temperatures, oxygen, and water, which frequently facilitates practicality.[2] Silver(I) complexes bearing NHCs, in particular, have attracted significant attention for their chemical,[3] structural[4] and photophysical properties.[5] More recently, the biological applications [6] displayed by Ag(I) and Au(I)-NHC complexes have steadily gained interest for their potential as new classes of metal-based drugs,[7] especially for the treatment of cancer and drug-resistant pathogens.[8,9] Although several reviews describe the utilities of Ag(I)-NHC complexes against various cancer lines, analogous Au(I) complexes may hold greater potential.[10] Gold has a long history of use as a medicine in ancient China and numerous gold-based drugs are being investigated for their activities against various ailments (e.g., auranofin as an anti-rheumatic agent), including cancer.[11] Unfortunately, many of these complexes are readily metabolized *in vivo* by thiols,[12] which significantly reduces their activities. To overcome this limitation, gold-complexes bearing stabilizing NHCs have been explored as alternatives, often with good results.[13] For example, Panda and Ghosh reported[14] that Au(I)-NHC complex, [1-benzyl-3-tbutylimidazole-2-ylidene]AuCl, exhibited excellent efficiency against the proliferation of HeLa cells (1.7% proliferation at $[Au]_0$ = 10 μM). Ott and co-workers discovered [15] that Au(I)-NHC-based thiotetrazolates are effective thioredoxin reductase inhibitors and antiproliferative agents against breast and colon carcinoma cells. Likewise, Berners-Price and Filipovska described [16] a new approach to based antitumor agents, where selective mitochondria targeting and thioredoxin by Picquet and Casini as anticancer agents against human ovarian A2780 and human lung cancer A549 cell lines with good anti-proliferative results.[17] We have also reported[18] a series of annelated Au(I)-NHC complexes that exhibited excellent anticancer properties against a panel of lung, breast, colon cancer cell lines.

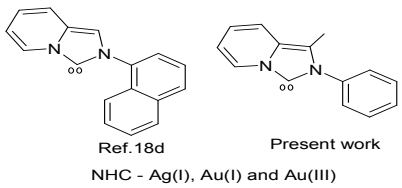
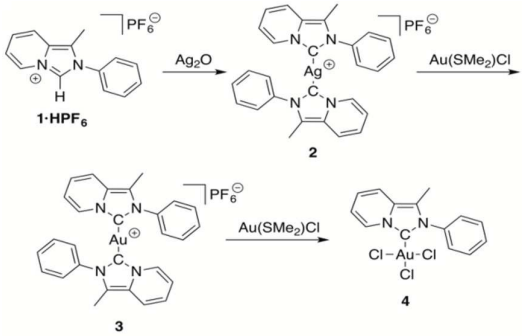


Chart 1. Naphthyl and phenyl wingtip NHC



Scheme 1. Synthesis of Ag(I)-, Au(I)- and Au(III)-NHC complexes.

[a] *Address here.*
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† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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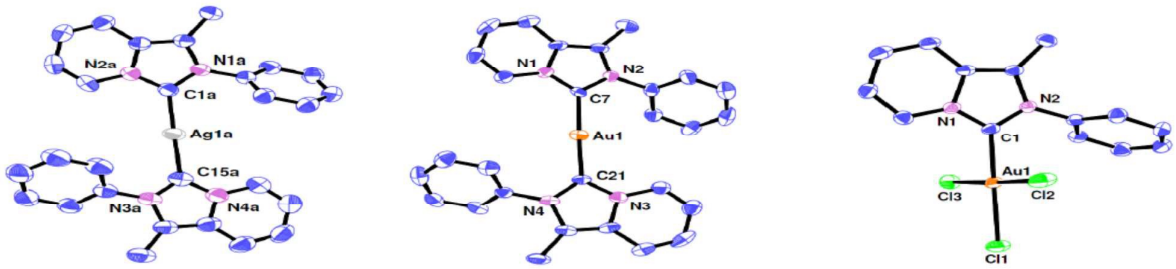

Figure 1. ORTEP views of the solid-state structures of **2** with the atoms shown at 50% probability (upper left), **3** with the atoms shown at 50% probability (upper middle), and **4** with the atoms shown at 40% probability (upper right). The H atoms and the PF_6 counteranions were removed for clarity.

We hypothesized that Au(III)-NHC complexes,[19,20] which are relatively less explored than their Au(I)-NHC analogues, may hold potential for use in biomedical applications.[21] We reasoned that the relatively high electrophilicities of the former may facilitate their biological properties. Herein we describe the synthesis and characterization of a series of Ag(I), Au(I), and Au(III)-NHC complexes that are supported by a common NHC ligand, and explore their utilities against various cancer lines.

Results and Discussion

Using a previously reported procedure,[22] the imidazolium salt 1-methyl-2-(phenyl)imidazo[1,5-a]pyridine-2-iumhexaflurophosphate (**1**.HPF_6) was synthesized through a formylative cyclization of the corresponding Schiff base followed by ion metathesis with KPF_6 in aqueous media. As shown in Scheme 1, the Ag(I)- and Au(I)-complexes supported by **1** were prepared using standard[3] trans-metallation methodology: treating **1**.HPF_6 with Ag_2O afforded Ag complex **2** and ultimately its gold derivative (**3**). Although most Au(III)-NHC complexes are synthesized by treating the corresponding Au(I)-NHC complex with chlorine or bromine, we utilized our relatively benign disproportionation process[23] to prepare gold(III) complex **4**. Complexes **2**, **3** and **4** were characterized using ^1H and ^{13}C NMR spectroscopy as well as elemental analyses; the results obtained were consistent with the proposed formulations. For example, the ^1H NMR spectrum recorded for the Ag(I) complex **2** confirmed that the imidazolium NC*H*N signal associated with **1**.HPF_6 (δ 9.97 ppm in DMSO-d_6) had disappeared and that the salient aryl proton signal α to the N-atom shifted downfield (from 8.65 ppm to 8.85 ppm). The ^{13}C NMR spectrum recorded for **2** revealed a signal expected for a carbenic nucleus at 162.72 ppm. Similar ^1H and ^{13}C NMR data were collected for **3**, although the respective signals were relatively downfield shift (i.e., 8.83 ppm and 163.62 ppm, respectively). The carbene nucleus in **4** was observed to resonate at 158.32 ppm, which is upfield from that recorded for **3** and in accord with other reports.[19b,d]

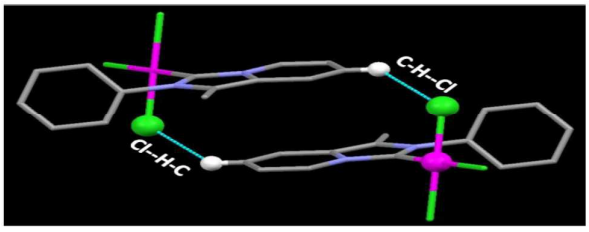

Figure 2. Packing view of **4**, showing dimmer nature through C--H--Cl interactions.

Crystals suitable for X-ray diffraction were independently grown by slowly diffusing diethyl ether into acetonitrile saturated with **2**, **3**, or **4** ORTEP drawings of the corresponding structures are shown in Figure 1, selected bond parameters are listed in Table 1 and key crystallographic parameters are summarized in Table 2. The symmetry of the lattices of **2** was found to be monoclinic and fit to the *P2₁/n* (Z = 8) space group. Two independent Ag complexes are contained in the crystallographic asymmetric unit with essentially identical metric parameters. The C–Ag(I)–C bond angle in the d^{10} complex was measured to be nearly linear (175.1(2)°), and the Ag(I)–C bond lengths (2.064(4)-2.086(4) Å) are comparable with the sum of the individual covalent radii of the silver (1.46 Å) and carbon (0.76 Å) and in accord with analogous values reported in the literature.[18b] Similarly, two Au complexes of the isomorphous crystal **3** are contained in the crystallographic asymmetric unit and fit to the same *P2₁/n* (Z = 8) space group. The Au(I)–Au(I) distance was measured to be approximately 3.54 Å, which is consistent with an 'aurophilic interaction' yet shorter than the analogous 1-methyl-3-picolyl-2-imidazoline-gold(I)tetrafluoroborate complex reported in the literature.[24] The Au(I)-C bond distances in the linear d^{10} complex (C-Au(I)-C, 175.7(4)°) were measured (2.008(5)-2.023(5) Å) to be comparable with known Au(I)-NHC complexes[18c] and also comparable with sum of the covalent radii of the gold (1.37 Å) and carbon (0.76 Å). Au-$C_{carbene}$ separation shorter than Ag-$C_{carbene}$ because of shorter covalent radii of Au. The Au(III) center in complex **4**, which crystallized in the *C2/c* space group, was occupied by three chlorides plus one $C_{carbene}$ ligand and adopted a pseudo square planar geometry in agreement with the d^8 configuration of the metal.

Table 1. Selected bond lengths (Å) and angles (°).

	2	3	4
M–C (Å)	2.064(4) - 2.086(4)	2.012(8) - 2.055(10)	1.997(5)
N–C (Å)	1.350(5) - 1.373(5)	1.340(12) - 1.370(12)	1.341(7) - 1.342(8)
C–M–C (°)	175.1(2)	175.7(4)	179.2(1)
N–C–N (°)	102.9(3)- 104.1(3)	102.8(7) - 104.9(8)	106.3(4)
Au–Cl (Å)	n/a	n/a	2.264(2) - 2.309(1)

The Au(III)-$C_{carbene}$ bond length was determined to be slightly shorter (1.997(5) Å) than the Au(I)-$C_{carbene}$ bond distances measured in the solid-state structure of **3**, although consistent with other reported Au(III)-complexes supported by annelated NHCs reported.[18,19,23] Ionic radii of Au(III) is 0.82 Å, where as in case of Au(I) it is 1.51 Å, so Au(III)-NHC is shorter than Au(I)-NHC. The solid-state structure of the complex also featured several C—H-F and anion--π interactions (not shown). Dimmer nature of **4** through C-H--Cl interactions are shown in Figure 2. The anticancer properties of complexes **2**, **3**, and **4**

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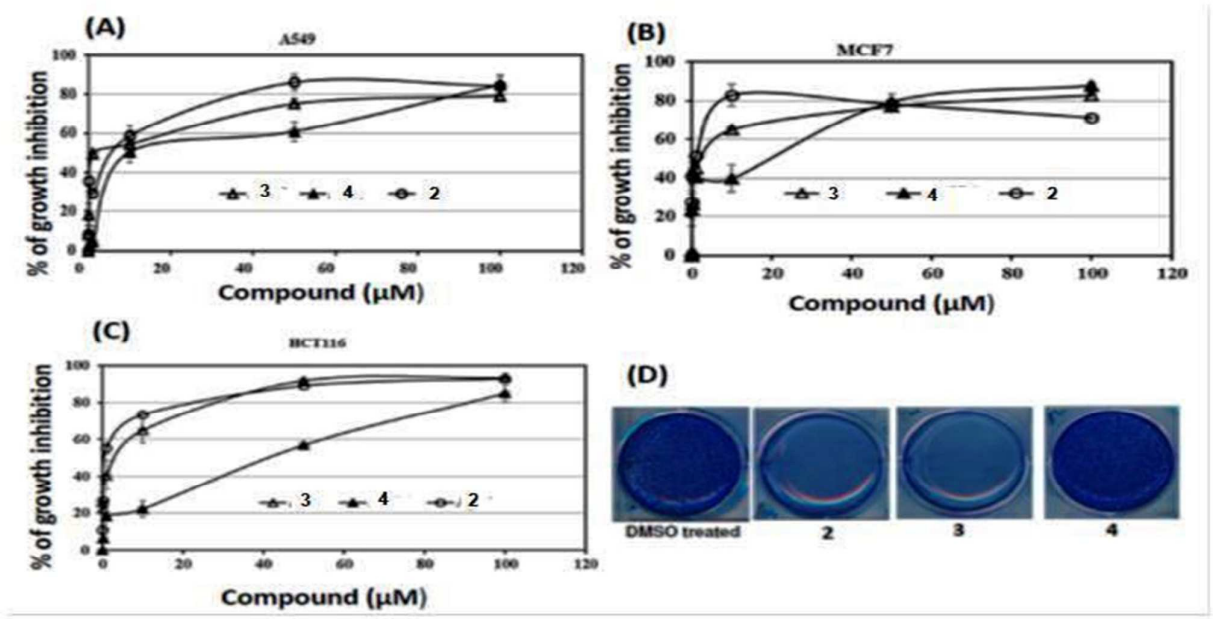

Figure 3. Proliferation of (A) A549, (B) MCF7 and (C) HCT116 cells versus the concentration of various complexes (indicated). (D) The MCF7 cells (4×10^4) were seeded in each well, treated with 1 μM of DMSO or a complex (indicated) for 3 d, and then allowed to grow for another 5 d before being stained

were independently tested against the breast cancer cell line MCF7, the colon cancer cell line HCT116 and the lung cancer cell line A549 using standard 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays. As summarized in Figure 3 and Table 3, the complexes significantly suppressed the growth of the aforementioned cancer cell lines.

Inspection of the data revealed that the Au(I)-NHC complex **3** is more effective at inhibiting the growth of each cancer cell line than its Au(III) congener (**4**), a trend consistent with reports detailing the growth inhibitory effects of other gold-NHC complexes against panels of cancer cell lines.[18] The relatively lower activity displayed by the gold(III)-NHC complex may be attributed to the reduction of gold (III) → gold (I) upon interaction with intracellular thiols.[12,13] For comparison, the Ag(I) complex is also effectively inhibited the growth of all of the cancer cell lines; the highest activity was observed against the A549 line (IC_{50} = 2 ± 0.71). Further analysis of the MTT data revealed that the Au(I) complex exhibited a more potent effect on HCT116 and MCF7 cells than the Ag(I) complex, which may reflect cell specificity or selectivity due to, in part, their lipophilicities.[7] All the cases complex 2,3 and 4 are more potent than reference standard drug cisplatin (Table 3). Gautier previously reported that the activities displayed by various Ag-NHC complexes depend upon the substituents appended to the constituent imidazole rings as well as the degree of saturation.[7] Likewise, Berners-Price and Filipovska demonstrated that Au(I)-NHC complexes are potent inducers of mitochondrial membrane permeabilization, but less so than auranofin.[16] Raubenheimer summarized[25] the cytotoxicity properties of a lipophilic, bis-ferrocenylated NHC-gold(I) complex toward HeLa and CoLo 320 cell lines.[18d]

Table 2. Crystal data and refinement parameters for complexes **2 – 4**.

	Complex **2**	Complex **3**	Complex **4**
Empirical formula	$C_{28}H_{24}AgN_4, PF_6$	$C_{28}H_{24}AuN_4PF_6$	$C_{14}H_{12}AuCl_3N_2$
Formula weight	669.35	758.45	511.57
Temperature (K)	295	150	295
Wavelength (Mo-Kα) (Å)	0.71073	0.71073	0.71073
Symmetry	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/n$	$C2/c$
a (Å)	14.5412(2)	14.5519(15)	16.1038(4)
b (Å)	24.2255(3)	24.245(3)	12.5836(3)
c (Å)	15.7374(2)	15.6387(16)	15.5456(4)
α = γ (º)	90	90	90
β (º)	97.5947(6)	97.2860(10)	94.8190(9)
Volume	5495.2(1)	5472.9(10)	3139.1(1)
Z	8	8	8
Cald. density (Mg/m^3)	1.618	1.841	2.165
μ (Mo-Kα) mm^{-1}	0.858	5.501	9.863
θ range (◦)	1.64 - 27.50	1.56 - 25.00	3.25 - 30.00
No. of reflns collected	44680	39089	25039
No. of ind. reflns	12565	9644	4560
R_{int}	0.0455	0.0581	0.0830
Obs. reflns [I>2σ(I)]	9256	6683	3906
Goodness-of-fit (F^2)	1.032	1.056	1.079
Final R indices [I>2σ(I)]	R1 = 0.0514 wR2 = 0.1458	Wr1 = 0.1527	R1 = 0.0423 wR2 = 0.1014
R indices (all data)	R1 = 0.0742, wR2 = 0.1645	R1 = 0.0842, wR2 = 0.1714	R1 = 0.0517, wR2 = 0.1055

Present compounds are much more potent than the naphthyl-annelated Ag(I), Au(I) and Au(III)-NHC complexes reported by our group,[18d] probably due to comparatively smaller lyophobic phenyl wingtip in comparison to naphthyl group. The long-term growth suppression effects of the

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aforementioned complexes were assessed using colony formation assays. The results obtained were consistent with the MTT data and revealed that the Au(I) and Ag(I) complexes significantly inhibited colony formation whereas the Au(III) complex had a minimal effect.[25]

Table 3. Inhibitory concentrations displayed by complexes **2**, **3** and **4** (μM).

Cell Line	**2**	**3**	**4**	**cisplatin**
A549	2 ± 0.71	5.75 ± 1.09	10 ± 3.17	20±1.00
HCT116	2.7 ± 0.81	0.82 ± 0.17	21.25 ± 1.37	33.3±0.57
MCF7	1.18 ± 0.25	0.8 ± 0.28	25.51 ± 1.61	7.5±0.66

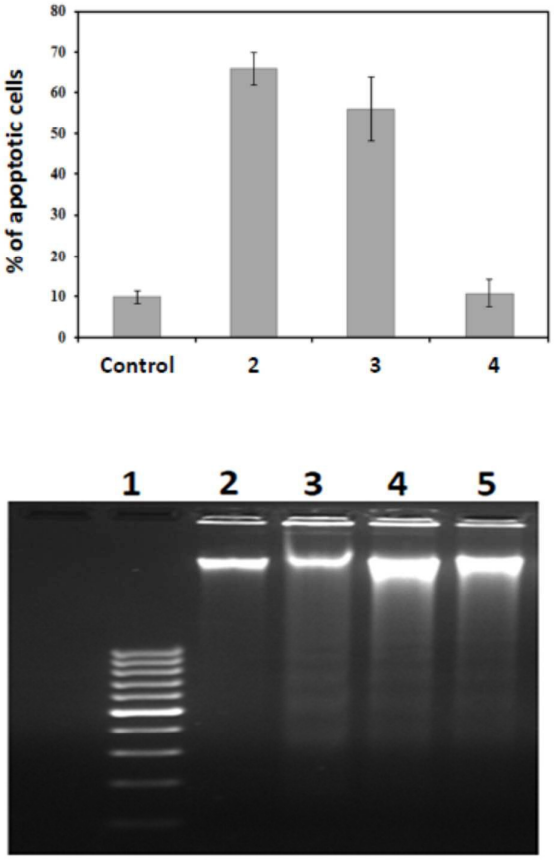

Figure 4. (Above) Effects of various complexes (indicated; 1 μM) on the apoptosis of MCF7 cells. (bellow) Effects of complexes on DNA fragmentation of MCF7 cells. (Lane 1: 1 Kb DNA ladder; lane 2: control; lane 3: complex **3**; lane 4: complex **2**; lane 5: complex **4**.

Next, we examined whether the aforementioned complexes induce apoptosis using fluorescence-activated cell sorting (FACS).[26] Breast cancer cell line MCF7 cells were independently treated with 1 μM of **2**, **3**, or **4** for 48 h, and then stained with propidium iodide. As summarized in Figure 4, the Au(I) and Ag(I) complexes were each found to significantly increase the sub-G1 population of the MCF7 cells, consistent with apoptosis induction.[27] Results indicative of DNA fragmentation were also observed. Since previous reports have noted that the extracellular signal–regulated kinases (ERK) can be promoted through intrinsic or extrinsic apoptotic pathways by inducing the release of mitochondrial cytochrome c, we probed for elevated ERK levels. As shown in Figure 5, immunoblotting data revealed the presence of significant quantities of phosphorylated ERK after treatment with either **2** or **3**. Collectively, these results suggested to us that the Au(I) and Ag(I) complexes exhibit anticancer activity inhibit cell growth through the induction of apoptosis.

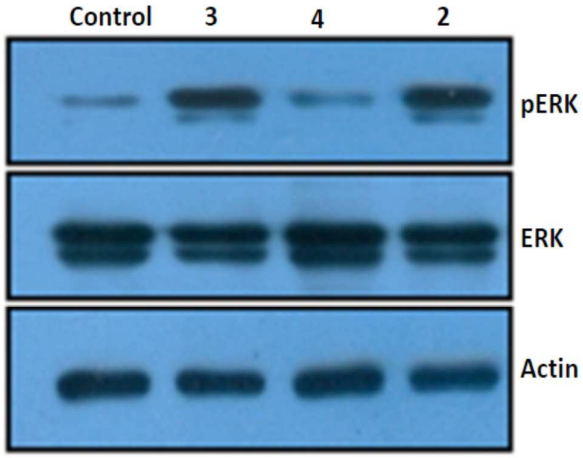

Figure 5. Expression of stress response protein p-ERK after treatment of MCF7 cells with complexes **2**, **3** or **4** (indicated; 1 μM) for 48 h; β-actin was used as a loading control.

Molecular docking studies were performed to better understand how **2**, **3** and **4** could interact at the molecular level with CLL/lymphoma 2 (BCL-2) cells as well as with human topoisomerase I (Topol I) coupled with a DNA strand. We consider BCL-2 protein for model studies, because BCL-2 is a founding member of BCL family, (regulator proteins) that regulate the cell death (apoptosis). As in present case cancer cells death happen through Au(I) and Ag(I)-NHC induced apoptosis, so this docking studies will help to understand the action of mechanism. The data obtained from molecular docking consistent with the *in vitro* activities described above (Table 3), the host: guest complexes involving **3** exhibited the relatively highest affinities when compared those of **2** or **4** (Table 4), which may reflect the accuracy of the computational simulations.

Table 4. Calculated binding constants (kcal.mol^{-1}) for the molecular complexes formed between the ligands **2**, **3** or **4** and the receptors Bcl-2 or Topoisomerase I (indicated).

Complex	BCL-2	Topoisomerase I
Ag(I)-NHC **2**	-8.2	-9.2
Au(I)-NHC **3**	-8.4	-9.4
Au(III)-NHC **4**	-6.4	-7.1

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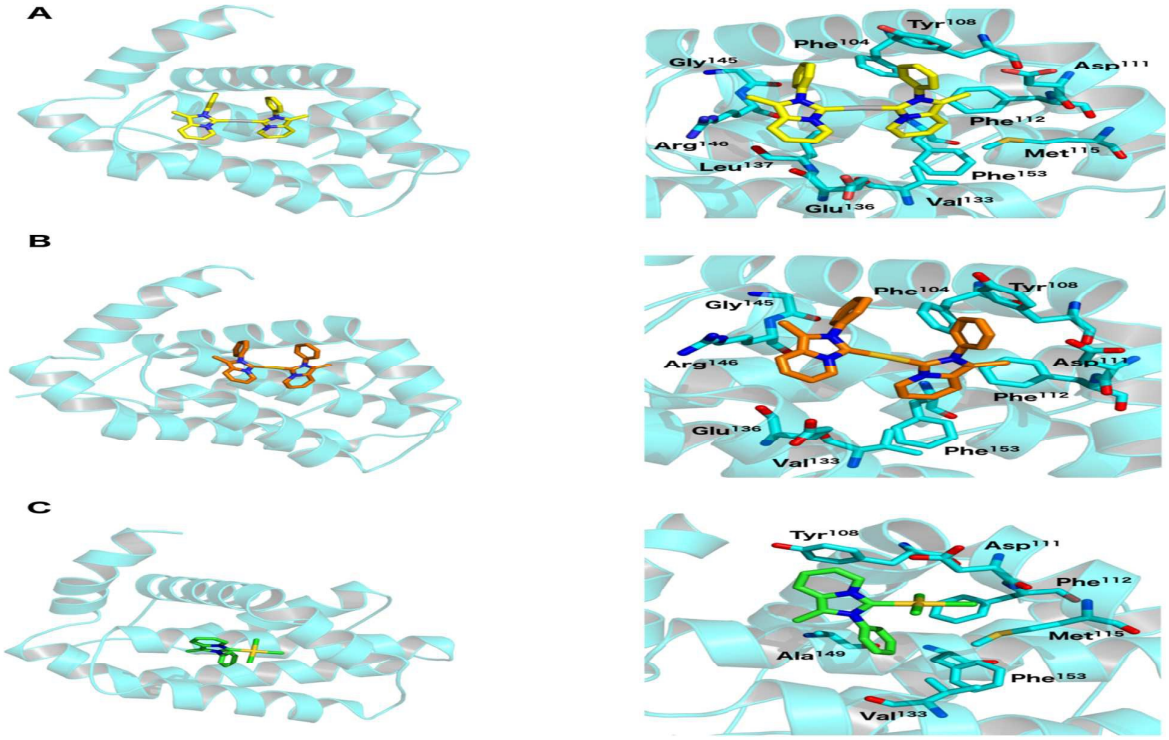

Figure 6. Molecular complexes of (A) Ag(I)-NHC, (B) Au(I)-NHC or (C) Au(III)-NHC docked with BCL-2. The predicted amino acid residues involved in the stabilization of each complex are highlighted.

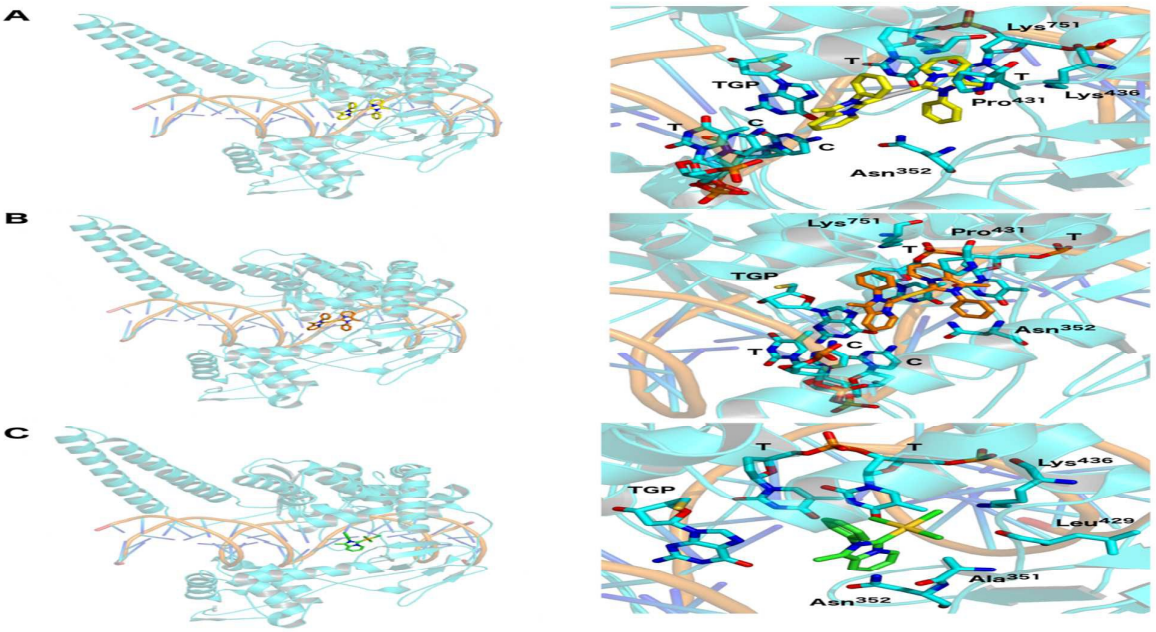

Figure 7. Molecular complexes of (A) Ag(I)-NHC, (B) Au(I)-NHC or (C) Au(III)-NHC docked with Topoisomerase-I in contact with DNA. The amino acid residues and the nitrogenous bases involved in the stabilization of each complex are highlighted. Legend: C: cytosine; T: thymine; TGP: 5'-thio-2'-deoxy-guanosine phosphonic acid.

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Additional efforts were directed toward predicting all possible interactions between **2**, **3**, or **4** and BCL-2, Topoisomerase I or a DNA strand. When compared to analogous complexes formed by **2** or **4**, higher numbers of hydrophobic interactions and shorter hydrogen bonds were observed in complexes that contained **3**. BCL-2 is a family of key regulators of the apoptotic process and is responsible for the evasion of cancerous cells to apoptosis. As such, BCL-2 protein family members have been targeted for the development of new anti-cancer agents. As summarized in Figure 6, we predicted that **2**, **3** or **4** should localize in the BCL-2 hydrophobic binding pocket, as has been described for other BLC-2 inhibitors, including navitoclax,[27] venetoclax,[28] 2-indole-acylsulfonamide,[29] various phenylacylsulfonamides,[30] and acyl-sulfonamide-based ligands[31], among others. Apart from these crystallographic studies, others have shown through molecular docking simulations that a gold complex exhibited a high affinity toward BCL-2 with binding constants similar to those reported for the acyl-sulfonamide-based ligands.[32] Residues similar to our predictions were reported as being responsible for the stabilization of the gold complex, leading to BCL-2 inhibition followed by cell apoptosis.

The enhanced abilities of cancerous cells to proliferate underscores the importance of enzymes involved in nuclear processes, including replication, recombination and transcription.[33] As such, novel anti-cancer drugs have also targeted human topoisomerases-I. We also found that **2**, **3** or **4** bind to the major groove of a DNA strand in a topoisomerase/DNA complex with different binding affinities (see Table 4), which may interrupt the ability of the enzyme to hydrolyze the DNA phosphodiester bonds. Similar results have been described for other anti-cancer compounds, including the camptothecins,[34] the indolocarbazoles,[35] and the indenoisoquinolines.[36] It has also been reported [37] that cyclometallated gold(III) complexes supported by NHCs could inhibit topoisomerase I. Similar to our results (see Figure 7), amino acids such as Lys, Asn and Asp were predicted to be the main residues interacting with the added complexed metallo-drug, although different coordinating geometries may be operative.[37] Collectively, the computational and experimental results indicate that complexes **2**, **3** and **4** initiate apoptotic cascades in cancerous cells through the inhibition of BCL-2 and the topoisomerases I.

Conclusion

The synthesis of a series of Ag(I), Au(I) and Au(III)-complexes supported by pyridyl[1,2-a]{2-acetylylphenylimidazol}-3-ylidene were reported. The complexes were characterized using a range of techniques, including NMR spectroscopy, elemental analyses, and X-ray diffraction analyses. Their cytotoxic characteristics against breast cancer, colon cancer and lung cancer cell lines were also explored. The gold (I) complex **3** was found to exhibit higher cytotoxicities than its analogous silver (I) (**2**) and gold(III) (**4**) analogues. Through a series of assays and molecular docking studies, the Au(I) and Ag(I) complexes were found to suppress the growth of the aforementioned cancer cell lines through the induction of apoptosis. We expect that these results will help guidance the development of pharmaceutical agents that based on gold to effect anticancer and other important biological functions.

Conflicts of interest

There are no conflicts of interest to state.

Experimental Section

General Procedures

Unless otherwise stated, all reagents were purchased from Sigma-Aldrich, and used without further purification. The complex $Au(SMe_2)Cl$ was prepared as reported in the literature.[38] Unless noted otherwise, all experiments were performed under ambient atmosphere. All solvents were distilled over appropriate drying agents and purged with nitrogen prior to use. NMR spectra were measured on a Bruker 300 MHz and 100.5 MHz spectrometers at 25 °C against tetramethylsilane as an internal standard. Electronic spectra were recorded on Shimadzu UV-1601 spectrometer.

General syntheses

1-Methyl-2-(pyridin-2-yl)imidazo[1,5-a]phenyl-2-iumhexaflurophosphate (1•HPF$_6$). Following previously reported procedures,[22] a mixture of 2-phenyl-*N*-(2-acetyplyridine)methylamine (2000 mg, 10.2 mmol), 2 drops of formic acid, 0.5 mL of triethylorthoformate, crushed 91% paraformaldehyde powder (306 mg, 10.2 mmol), and 20 mL of dioxane was stirred for 4 h at ambient temperature and then heated to reflux for 10 h. After cooling, 5 mL of 4 N HCl in diethyl ether was added slowly to the resulting slurry suspension which resulted in layering. The lower layer was a viscous, red-yellow liquid whereas the upper layer was a colorless liquid. After adding water (5 mL) to the mixture, the aqueous phase was separated and charged with saturated aqueous KPF_6. A white precipitate formed which was subsequently isolated by filtration, recrystallized from acetonitrile and diethyl ether, and then dried under reduced pressure. Yield: 71.2% (2520 mg, 7.12 mmol). ^{1}H NMR (DMSO-d_6, 25 °C, 300 MHz): δ 9.97 (s, 1H), 8.53 (d, *J* = 6.0 Hz, 1H), 8.05 (d, *J* = 6.0 Hz, 1H), 7.75 (d-t, 5H), 7.28 (m, 2H), 2.53 (s, 3H). ^{13}C NMR (CD_3CN, 100.5 MHz): 134.1**,** 131.4, 130.5, 126.9, 124.2, 123.8, 122.7, 118.7, 09.1. Anal. Calcd. for $C_{14}H_{13}N_2PF_6$: C, 47.46; H, 3.67; N, 7.91; Found: 47.41; H, 3.63; N, 7.87%.

Silver(I) complex 2. A mixture of **1•HPF$_6$** (250 mg, 0.71 mmol), silver oxide (85 mg, 0.37 mmol), dry acetonitrile (15 mL) was stirred at ambient temperature for 4 h and then filtered through a short column of Celite. The residual solvent was subsequently removed under reduced pressure and the resulting solid was recrystallized from acetonitrile and diethyl ether. Yield: 66.2% (314.3 mg, 0.47 mmol). ^{1}H NMR (DMSO-d_6, 300 Mz, 25 °C): δ 8.35 (d, *J* = 7.0 Hz, 1H), 7.72 (d, *J* = 7.2 Hz, 1H), 7.57 (d-t, 5H), 6.99 (t, *J* = 7.7 Hz, 1H), 6.83 (m, 1H), 2.35 (s, 3H, -CH_3). ^{13}C NMR (DMSO-d_6, 100.5 MHz, 25 °C): δ 162.7, 137.3, 135.1, 132.3, 127.0, 124.2, 123.9, 122.9, 118.7, 117.8, 9.2. Anal. Calcd. for $AgC_{28}H_{24}N_4PF_6$: C, 50.24; H, 3.59; N, 8.37; Found: 50.17; H, 3.54; N, 8.33%.

Gold(I) Complex 3. A mixture of **1•HPF$_6$** (250 mg, 0.71 mmol), silver oxide (85 mg, 0.37 mmol), dry acetonitrile (10 mL) was stirred at ambient temperature for 4 h and then filtered through a short column of Celite. Adding an solution of $Au(SMe_2)Cl$ (210 mg in 5 mL of acetonitrile) dropwise to resulting in the formation of a white precipitate, which was presumed to be AgCl, and removed by filtration. The residual solvent was subsequently removed under reduced pressure and the resulting solid was recrystallized from acetonitrile and diethyl ether. Yield: 60.6% (326 mg, 0.43 mmol). ^{1}H NMR (DMSO-d_6, 300 MHz, 25 °C): δ 8.31 (d, *J* = 7.0 Hz, 1H), 7.77 (d, *J* = 7.2 Hz), 7.60 (d-t, 5H), 7.03 (t, *J* = 7.7 Hz, 1H), 6.70 (m, 1H), 2.34 (s, 3H, -CH_3). ^{13}C NMR (DMSO-d_6, 100.5 MHz, 25 °C): δ 163.6, 137.5, 135.4, 132.4, 127.2, 124.3, 124.0, 123.0, 118.9, 117.9, 9.2. Anal. Calcd. for $AuC_{28}H_{24}N_4PF_6$: C, 44.33; H, 3.17; N, 7.39; Found: 44.25; H, 3.13; N, 7.34%.

Gold(III) Complex 4. After dissolving **3** (200 mg, 0.26 mmol) in acetonitrile (10 mL), $Au(SMe_2)Cl$ (230 mg, 0.78 mmol) was added and the

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resulting solution was stirred at ambient temperature. The color of the solution changed from colorless to light yellow over time. After 4 h, the residual solvent was removed under reduced pressure and the resulting yellow solid was recrystallized from acetonitrile and diethyl ether. Yield: 85% (113 mg, 0.22 mmol). ^{1}H NMR (DMSO-d_6, 300 MHz, 25 °C): δ 8.85 (d, J = 7.1 Hz, 1H), 7.92 (d, J = 7.2, 1H), 7.72 (d-t, 5H), 7.63 (t, J = 7.5 Hz, 1H), 7.15 (m, 1H), 2.33 (s, 3H, -CH_3). ^{13}C NMR (DMSO-d_6, 100.5 MHz, 25 °C): δ 158.3, 137.61, 135.5, 132.5, 127.3, 124.4, 124.1, 123.1, 119, 117.1, 9.2. Anal. Calcd. for $AuC_{14}H_{12}N_2Cl_3$: C, 32.84; H, 2.35; N, 5.47; Found: C, 32.79; H, 2.31; N, 5.42%.

Crystal Structure Elucidation

Single crystals of **2**, **3** and **4** were independently grown by slowly diffusing diethyl ether into a saturated acetonitrile solution of the respective complex. The crystal data and details of the data collections are given in Table 1. X-ray data were collected on a CCD diffractometer (graphite monochromated Mo Ka radiation, k = 0.71073 A˚) by use of ω scans. The structures were solved by direct methods and refined on F^2 using all reflections with SHELX-97.[39] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms which were not bound to imidazolium-C2 atoms were placed in calculated positions and assigned to an isotropic displacement parameter of 0.08 Å. CCDC 1562513, 1562514, 1562515 contain the crystallographic data for **2, 3** and **4**, respectively, which can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Cell Cultures

The MCF7 cells were grown in DMEM media (Invitrogen); the A549 and HCT116 cells were grown in RPMI media (Invitrogen) supplemented with 10% fetal bovine serum (Gibco) penicillin and streptomycin (Invitrogen). Cells were grown at 37 °C in CO_2 incubator under humidified conditions.[40] All cells were periodically checked for mycoplasma contamination.

Cell Survival Assays

Standard 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays were independently performed to examine the effect of 2, 3, 4, and PDL1 on cell survival. Approximately five thousand cells (MCF7, A549 or HCT116) were seeded in each well of a 96-welled plate. After several h, the cells were treated with different concentrations of the aforementioned complexes (0.01 – 50 μM). After 48 h, 20 μL of the MTT reagent was added ($[MTT]_0$ = 5 mg/mL in 1X PBS) and the incubated for 4 h.[41] The media containing the MTT reagent was then replaced with 100 μL of MTT solvent (5 mM HCl and 0.1% Triton X-100 in isopropanol) and incubated for 10 min with gentle shaking at ambient temperature. The reduction of the MTT salt into its formazan derivative by the live cells was quantified at 575 nm using a Thermo Scientific Multiskan Go plate reader. An average of three experiments were plotted to calculate the IC_{50} of each compound. Growth of untreated cells was assumed to be 100%.

Colony Formation Assays

The MCF7, A549 or HCT116 cells (4×10^4) were independently seeded in six well plates and then treated with 1 μM of one of aforementioned complexes for 72 h. The media was then refreshed and cell growth was allowed to continue for an additional 5 days. Finally, the media was removed, colonies were stained with crystal violet and the difference in the number of colonies was quantified.[42]

Western Blotting Assays

Western blotting was used to compare the expression levels of ERK, p-ERK and other proteins. Briefly, cells were harvested, washed twice with 1X PBS, and then incubated with lysis buffer (50 mM Tris pH 7.4, 200 mM NaCl, 50 mM NaF, 1 mM Na_3VO_4, 0.5% Triton X-100 and protease inhibitor cocktail) for 20 min on ice. Lysed cell and protein concentrations were estimated using the Bradford method. After preparation in Laemmli buffers, proteins were resolved using SDS-PAGE, transferred to PVDF membranes and then subjected to immunoblot analyses.[43]

Fluorescence Activated Cell Sorting (FACS)

The MCF7 cells were either untreated or treated with 1 μM of one of the aforementioned complexes. After 48 h, the cells were collected, washed with ice cold PBS, fixed with 95% ethanol, subsequently washed again with ice cold PBS to remove the residual ethanol and finally stained with 50 μg/mL propidium iodide as well as 50 μg/mL RNAse in PBS. Data were acquired on BD FACS Calibur instrument and analyzed using Cell Quest Pro software.[44] All the experiments were performed in triplicate.

Molecular Docking Simulations

The crystal structures of the complexes (i.e., **2**, **3**, and **4**) were optimized using Avogadro v.1.2.0 [45] and the gold / silver atoms, which are not supported by AutoDock Tools 4,[46] were replaced by carbon atoms optimized on Maestro v.10.2.011 (Schrodinger). Grid boxes of $40 \times 40 \times 40$ and $25 \times 25 \times 25$ points with spacing of 1 Å were built using AutoDock Tools 4 for the ligand:receptor complexes involving BCL-2 (PDB code: 4lvt) [28] as well as Topoisomerase I (PDB code: 1t8i),[33] respectively. Fifty molecular docking simulations for each complex were performed using AutoDock Vina,[47] where all resulting complexes were ranked according to their affinity values in kcal/mol. The complexes exhibiting the highest affinities were selected, and their corresponding ligands were re-incorporated into Maestro v.10.2.011 and the minimized. The visualization and measurement of the molecular interactions were performed using PyMOL[48] with a maximum distance of 3.6 Å between the constituent atoms.

Supporting Information Available

Crystallographic data for the complexes **2**, **3** and **4** in CIF format are available free of charge via the Internet.

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Keywords: N-Heterocyclic Carbene • Gold(I)-NHC • Gold(III)-NHC • Molecular Docking • Cytotoxicity

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Synthesis and Cytotoxic Characteristics Displayed by a Series of Ag(I)-, Au(I)- and Au(III)-Complexes Supported by a Common N-Heterocyclic Carbene

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The design, synthesis and anticancer properties of a series of Ag(I), Au(I) and Au(III)-NHC complexes supported by pyridyl[1,2-a]{2-acetylylphenylimidazol}-3-ylidene are described.