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Pd(II) and trinuclear Ag(I) *bis*-*N*-heterocyclic carbene complexes: Synthesis, structural and in vitro anticancer activity

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ABSTRACT

The synthesis and characterization of two Ag(I)- *N*-heterocyclic carbene complexes 3 and 4 of imidazole-based NHC proligands 1 and 2, respectively, are described. The findings revealed that the choice of the counter ions is crucial, which can lead to different supramolecular architectures. Complex 3 is a trinuclear, whereas its analogue complex 4 is mononuclear. Despite being structurally different entities, these complexes form *cis*-palladium-NHC complex 5 by trans-metallation method, which is a *cis*-platinum analogue. All the reported compounds 1-5 were tested for their anticancer activities, where compounds 2 and 3 found more potent than the rest.

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1. Introduction

The use of *N*-heterocyclic carbene (NHC) as a ligand for the synthesis of *bis*-carbene-transition metal complexes has received much current interest. Especially, the carbene chemistry of late transition metal complexes gained much recent attention due to their versatile structural motifs. Among them, NHC-silver complexes act as highly efficient candidates for the numerous biological applications [1,2]. Alternatively, the palladium complexes bearing NHC ligand system are also favorable and can serve as promising candidates in both biological and catalytic applications [3-6]. Aforementioned metal-carbene complexes are an interesting class of anticancer agents with properties similar to platinum-based metallo-therapeutics. However, despite their potential applications as anticancer agents, only a limited number of palladium-NHC complexes were reported for anticancer activity. Silver-NHC complexes have almost the same mode of action against the cancer cells, which involves the slow release of silver(I) ions at the infected site to interrupt their function. Therefore, it must be noted that release of silver(I) ions at the required site is depending on the carbene-silver bond strength, which can prevent or allow the quick release silver(I) ions to enter into the cell membranes [7,8].

Several silver-carbene complexes of polydentate NHC ligands have been reported for various applications. Some of these complexes have shown fascinating coordination chemistry due to the presence of additional coordinating sites and interesting intra and intermolecular silver-silver interactions [1,2]. These interactions in the polynuclear silver complexes of non-functionalized NHCs, however, are still more interesting as they do not possess additional donor sites. Since these complexes still contain a free halide ion for silver coordination, it can be anticipated that new polynuclear silver complexes connected by halide units to form a feasible supramolecular architecture.

Due to structural and thermodynamic correlations between palladium and platinum-NHC complexes, some of palladium-NHC complexes are reported for the anticancer applications against different human cancer cell lines [9]. Conversely, the mode of action of palladium-based carbene complexes towards cancer cells is presumed to be same as platinum-derived complexes employed for cancer treatment, targeting DNA in the infected cell. Like platinum ions, palladium ions can also able to interact with DNA, showing distinctive binding modes that affect cell replication including apoptosis [10].

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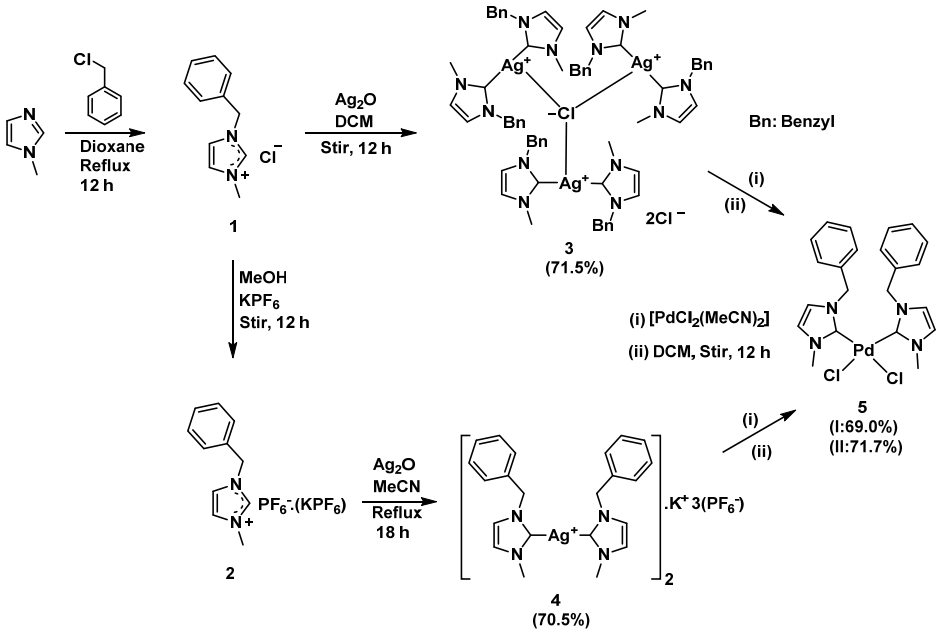


Scheme 1

However, *trans*-palladium-NHC complexes found more effective than their *cis*-counterparts, whose mode of action cannot be explained on the basis of platinum complexes. Recently, we have reported that silver and palladium-NHC complexes can serve as excellent antibacterial and anticancer agents against *E. coli* and *S. aureus* strains and human colorectal cancer (HCT 116) cell line, respectively [11,12]. Herein, we report the synthesis, molecular structures and anticancer efficiencies of both silver and palladium-NHC complexes. Furthermore, two of the reported complexes have been characterized by single crystal X-ray diffraction technique.

2. Experimental

2.1. Materials and instrumentation

All chemicals and solvents were obtained from commercial sources and all reagents and solvents were of analytical grade and used without further purifications. NHC precursors **1** and **2**, and silver complex **4** were reported in our previous reports [13,14]. NMR spectra were recorded using Bruker 400 MHz Ultrashield TM and Bruker Avance 300 MHz spectrometers at ambient temperature. The ^{1}H and ^{13}CNMR peaks were labeled as singlet (s), doublet (d), triplet (t), and multiplet (m). Chemical shifts were referenced with respect to solvent signals. Elemental analysis was carried out on a Perkin-Elmer Series II, 2400 microanalyzer. The X-ray diffraction data were collected using a Bruker SMART APEX2 CCD area-detector diffractometer. The above-mentioned instruments are available at the School of Chemical Sciences and the School of Physics, Universiti Sains Malaysia (USM).

2.2. Synthesis of Ag(I) and Pd(II)-NHC complexes

2.2.1. Synthesis of complex 3

Ag_2O (0.4 g, 1.7 mmol) was added to a solution of compound **1** (0.5 g, 2.4 mmol) in 30 mL of dichloromethane. The reaction mixture was stirred for 12 h in a round bottom flask in dark to exclude light. Colorless solution with a black suspension was obtained, which was filtered through a pad of celite. The solvent was removed under reduced pressure to afford a grey precipitate, which was recrystallized several times using dichloromethane to produce light-grey solid **3** (Scheme 1) **9**. Yield: 71.5%. M.p.: 142-143 °C. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.77 (s, 18H, N-CH_3), 5.31 (s, 12H, benzylic CH_2), 7.29-7.35 (m, 30H, 10 × Ar-*H*), 7.45 (d, 6H, *J* = 5.2 Hz, imidazolium *H*5′) and 7.53 (d, 6H, *J* = 5.2 Hz imidazolium *H*4′). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 39.0 (N-CH_3), 54.9 (benzylic CH_2) 123.0, 124.2 (imidazolium *C*5′ and *C*4′), 128.5, 128.8, 129.6, 138.2 (4 × Ar-*C*H) and 179.9 (*C*2'-Ag).

2.2.2. Synthesis of complex 4

To a stirred solution of compound **2** (0.5 g, 1.57 mmol) in acetonitrile (40 mL), Ag_2O (0.37 g, 1.6 mmol) was added. The mixture was refluxed at 70 °C for 18 h in dark to exclude the light. Resultant solution was passed through a bed of celite to remove unreacted Ag_2O and the solvent was evaporated under reduced pressure. So obtained white residue of complex **4** was washed with diethyl ether (2 × 3 mL) to afford an off-white powder (Scheme 1). Yield: 70.3%. M.p.: 148-149 °C. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.76 (s, 6H, 2 × CH_3), 5.31 (s, 4H, 2 × benzylic CH_2), 7.26-7.33 (m, 10H, 10 × Ar-*H*), 7.44 (d, 2H, *J* = 5.8 Hz, 2 × imidazolium *H*5′), 7.54 (d, 2H, *J* = 5.8 Hz, 2 × imidazolium *H*4′). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 39.0 (*C*H$_3$), 54.8 (benzylic *C*H$_2$) 123.2, 124.1 (imidazolium *C*5′ & *C*4′), 128.4 (2 × Ar-*C*H), 128.9 (4 × Ar-*C*H), 129.6 (4 × Ar-*C*H), 138.2 (2 × Ar-*C*H) and 180.6 (*C*2′-Ag).

2.2.3. Synthesis of complexes 5

To a stirred solution of compound **3** or **4** (0.05 mmol) in 15 mL of dichloromethane, [$PdCl_2(CH_3CN)_2$] (27 mg, 0.102 mmol) was added and was stirred overnight. A yellow solution with black precipitate was obtained, which was filtered off through a bed of celite to give a clear yellow solution. This filtrate was concentrated to 3 mL under vacuum, and then petroleum ether 20 mL was added. The resulted precipitate was isolated by decantation and washed with petroleum ether (2 × 5 mL) to give a pale-yellow solid which was recrystallized

using dichloromethane several times (Scheme 1). Yield = 69.0% from compound **3** and 71.7% from compound **4**. M.p.: 189-190 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.06 (s, 3H, N-C*H*$_3$), 4.21 (s, 3H, N-C*H*$_3$), 5.65 (s, 2H, benzylic C*H*$_2$), 5.84 (s, 2H, benzylic C*H*$_2$), 6.68 (s, br, 2H, imidazolium *H*5′ and *H*4′), 6.81 (d, 2H, *J* = 8.0 Hz, imidazolium *H*5′ and *H*4′), 7.28 (t, 2H, *J* = 7.5 Hz, Ar*H*), 7.40 (t, 4H, *J* = 7.2 Hz, 2 × Ar*H*), 7.56 (d, 4H, *J* = 7.2, 2 × Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 38.3 (*C*H$_3$), 54.6 (benzylic *C*H$_2$) 120.9, 122.8 (imidazolium *C*5′ and *C*4′), 128.5 (2 × Ar-*C*H), 129.1 (4 × Ar-*C*H) 129.6 (4 × Ar-*C*H), 136.8 (2 × Ar-*C*H) and 170.1 (*C*2′-Pd). Anal. cald. for $C_{22}H_{24}Cl_2N_4Pd$: C, 50.6; H, 4.6; N, 10.7. Found: C, 51.2; H, 4.3; N, 10.5%.

2.3. Anticancer activity

2.3.1. Cell culture

Initially, HCT 116 cells were allowed to grow under optimal incubator conditions. Cells that reached a confluence of 70-80% were chosen for cell plating purposes. The old medium was carefully aspirated out of the plate. Next, cells were washed twice using sterile phosphate buffered saline (PBS) with a pH of 7.4. The PBS was completely discarded after washing, and then trypsin was added and distributed evenly onto the cell surfaces. The cells were incubated at 37 °C in 5% CO_2 for 1 min. Then, the flasks containing the cells were gently tapped to aid cell segregation and then observed under an inverted microscope (if cell segregation was not sufficient, the cells were incubated for another minute). Trypsin activity was inhibited by adding 5 mL of fresh complete media of 10% fetal bovine serum (FBS). The cells were counted, diluted to obtain a final concentration of 2.5 × 10^5 cells/mL, and inoculated into wells (100 mL cells per well). Finally, the plates containing the cells were incubated at 37 °C with an internal atmosphere of 5% CO_2.

2.3.2. MTT assay

The cancer cells (100 mL cells per well, 1.5 × 10^5 cells/mL) were inoculated in wells of a microtiter plate, which was incubated in a CO_2 incubator overnight to facilitate cell attachment. A total of 100 mL of test complexes were added into each well containing the cells. The test complexes were diluted with media into the desired concentrations from the stock. The plates were incubated at 37 °C with an internal atmosphere of 5% CO_2 for 72 h. A 20 mL MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] reagent was added into each well, which was incubated again for 4 h. Next, 50 mL MTT lysis solution (DMSO) was added into the wells. The plates were further incubated for 5 min in a CO_2 incubator. Finally, the plates were read at 570 and 620 nm wavelengths using a standard ELISA microplate reader (Ascent Multiskan). Data were recorded and analyzed for the assessment of the effects of the test complexes on cell viability and growth inhibition. The percentage of growth inhibition was calculated from the optical density (OD), which was obtained from the MTT assay. 5-FU was used as the standard reference drug. The formula used for the calculation of growth inhibition was carried out using the following equation.

$$\% \text{ Growth inhibition} = \{OD_{(control)}\text{-}OD_{(survived)}/OD_{(control)}\} \times 100 \quad (1)$$

3. Results and discussion

3.1. Synthesis and characterization

In analogy to the potent anticancer activity of *cis*-platin and its analogues, *cis*-palladium-NHC complexes having varied ancillary ligands were targeted. The synthetic route for the preparation of NHC precursors and their silver and palladium complexes is outlined in Scheme 1. Synthesis, structural and detailed spectral and analytical characterizations of compound **3**, **4** and **5** are presented in the present work along with biological activates of compound **1**-**5**. Compound **1** was easily generated by treatment of 1-methylimidazole with benzyl chloride in dioxane at refluxing temperature for 12 h. This compound was converted into its hexafluorophosphate counterpart **2** following standard procedures for the salt metathesis reactions [15]. To better understand the effect of counter ions on the structure of silver complexes and their reactivity in the formation of corresponding palladium complexes, therefore, compound **1** and **2** were treated with half an equivalent of Ag_2O to get corresponding silver complexes **3** and **4**, respectively, in good yields. Further, both the silver complexes (**3** and **4**) were stirred with one equivalent of $[PdCl_2(MeCN)_2]$ for 12 h in DCM to yield *cis*-palladium-NHC complex **5** via the technique of trans-metallation. From both reactions, *cis*-palladium complex **5** was isolated as a pale yellow solid in appreciable yields.

Both, NHC proligands and their carbene complexes were fully characterized by ^{1}H and ^{13}C NMR and elemental analysis. The ^{1}H and ^{13}C NMR spectra of compound **1** and **2** showed the diagnostic C2' proton/carbon resonances at downfield regions δ 8.58, 9.2 and 133.9 and 137.5 ppm, respectively, indicating the formation of desired salts. The most significant resonance spectroscopic feature of carbene complexes **3**-**5** is the absence of C2' proton resonance in their ^{1}H NMR spectra and the presence of a distinguished singlet at δ 179.9, 180.6 and 170.1 ppm corresponding to the carbenic carbon nuclei in their ^{13}C NMR spectra. These observations are well within the range reported for the similar silver and palladium-NHC complexes [16,17]. Interestingly, a mixture of two palladium complexes was observed with similar proton NMR resonance patterns in the spectrum of complex **5**. These two conformers of complex **5** are indicative of the presence of high degree of flexibility of the NHC ligand system. This observation has been noted previously for numerous palladium-NHC complexes having analogues ligand architectures and is assigned to the existence of isomeric complexes in solution [18]. Therefore, it can be concluded that the carbene ligand in complex **5** is non-equivalent, which is due to the bulkier hindrance around the Pd-C bond arising from the phenyl substitution.

3.2. Crystallographic determination

Single crystal X-ray diffraction studies of carbene complexes confirmed the above structural assignments. Crystals of these complexes suitable for X-ray diffraction studies were grown at low temperature by slow evaporation for compound **3** in DCM, and slow evaporation of compound **5** in dichloromethane:diethyl ether (3:1, *v*:*v*). The crystallographic data and selected bond lengths and angles of complexes are presented in Table 1-4. Silver complex **3** is crystallized in trigonal space group R-3c, as an unsymmetrical trinuclear compound having a triply bridged chloride anion bonded to the three silver centers. A perspective view of the complex is shown in Figure 1. This is a rare example of a trinuclear cationic silver carbene complex having triply bridged chloride.

The bond angles between the silver centers through bridging chloride anion and the bond distances of silver centers with bridged chloride anion are 120 ° and 2.9956(1) Å, respectively, and are almost identical to each other. The bond distance between triply bridged chloride and the three silver centers is much longer than those of the non-bridged and doubly bridged Ag-Cl bonds, indicating the presence of a weak bonding. These bond distances and angles are well in the range compared to a similar trinuclear silver complex having triply bridged iodide anion [19]. In each silver complex unit, the metal center is coordinated by two carbene carbon atoms of the two NHC ligands in highly distorted linear geometry [C(1)-Ag(1)-C(1a) = 167.06 (7) °] with the bond distances of Ag(1)-C(1) and Ag(1)-C(1a) are 2.1046(13) Å.

Table 1. Crystal data and structure refinement details for complexes **3** and **5**.

Compound	**3**	**5**
Formula	$C_{22}H_{24}AgN_4Cl$	$C_{44}H_{48}Cl_4N_8Pd_2(CH_2Cl_2)$
Formula weight	487.77	1128.43
Crystal System	trigonal	monoclinic
space group	R-3c (No.167)	P21/c (No. 14)
a (Å)	12.8985(3)	15.3386(14)
b (Å)	12.8985(3)	9.6356(8)
c (Å)	68.2152(16)	34.681(3)
α (°)	90°	90°
β (°)	90°	90.256(2)°
γ (°)	120°	90°
V (Å^3)	9828.6(4)	5125.7(8)
Z	18	4
D(calc) g/cm^{-3}	1.483	1.462
F(000)	4464	2280
Crystal Size (mm)	0.23 × 0.25 × 0.33	0.06 × 0.25 × 0.51
Temperature (K)	293	293
Θmin, max (°)	1.8, 34.4°	1.8, 32.1
Total data	93204	117035
Unique Data	4615	17720
R_{int}	0.033	0.059
R_1	0.0279	0.0733
wR_2	0.0749	0.2907
S	1.05	1.09

Table 2. Selected bond lengths (Å) and angles (°) for complex **3**.

Bond lengths (Å)			
Ag1-C1	2.1046(13)	N2-C1	1.3497(17)
Ag1-C1a	2.1047(13)	N2-C11	1.457(2)
N1-C1	1.3480(17)	N1-C4	1.501(9)
Bond angles (°)			
C1-Ag1-C1a	167.04(7)	N1-C1-N2	103.88(11)
N1-C4-C5	106.4(9)	N2-C1-Ag1	128.52(10)

Table 3. Selected bond lengths (Å) and angles (°) for compound **5A**.

Bond lengths (Å)			
Pd1-Cl1	2.3573(12)	Pd1-Cl2	2.3883(16)
Pd1-C8	1.992(5)	Pd1-C19	1.999(4)
Bond angles (°)			
Cl1-Pd1-Cl2	91.76 (5)	C8-Pd1-C19	92.68(19)
Cl2-Pd1-C19	88.30(15)	Cl1-Pd1-C8	87.27(12)
Cl2-Pd1-C8	178.87(12)	Cl1-Pd1-C19	179.23(15)

Table 4. Selected bond lengths (Å) and angles (°) for compound **5B**.

Bond lengths (Å)			
Pd1-Cl1	2.3562(14)	Pd1-Cl2	2.3839(19)
Pd1-C8	2.005(6)	Pd1-C19	1.992(5)
Bond angles (°)			
Cl1-Pd1-Cl2	92.92(6)	C8-Pd1-C19	90.7(2)
Cl2-Pd1-C19	178.83(15)	Cl1-Pd1-C8	177.5(2)
Cl2-Pd1-C8	89.2(2)	Cl1-Pd1-C19	87.23(13)

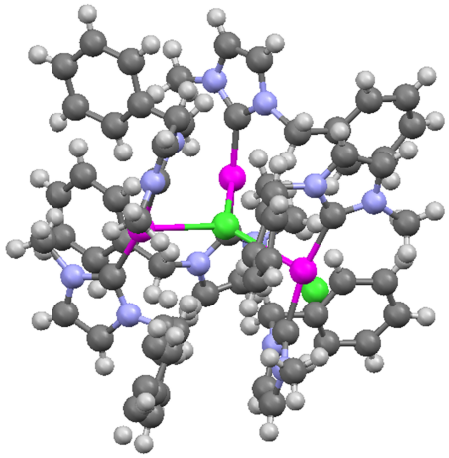


Figure 1. Solid-state structure of trinuclear silver-NHC complex **3** with displacement ellipsoids drawn at 50% probability. Hydrogen atoms and independent chloride ions have been omitted for clarity.

The arrangement of NHC ligands of the complex **3** in a typical asymmetric fashion is likely caused by the repulsive steric interaction between the benzyl substitutions. In one of the complex units of trinuclear silver compound **3**, both the benzyl modules are disordered over two sets with negligible bond angles and bond distances as shown in Figure 2. In all three complex units both the imidazole rings are not being coplanar showing a dihedral angle of 50.31(11) °. The internal bond angle at the carbene carbon center (N1-C1-N2) of complex system is 103.88(11) °, which is well short of N-C-N bond angles mentioned for the free NHCs. In the extended crystal structure, the trinuclear complex units are connected via CH---Cl (independent chloride ions) hydrogen bonds (2.878-2.879 Å) forming three-dimensional networks.

The structure of the *cis*-palladium complex **5** is solved in the monoclinic space group P21/c, having occupied two *cis*-complex and two dichloromethane molecules in an asymmetric unit. Interestingly, two crystallographically different variants of *cis*-palladium complex **5** were found in the crystal structure. Perspective views of the two variants, A and B, of complex **5** are shown in Figure 3.

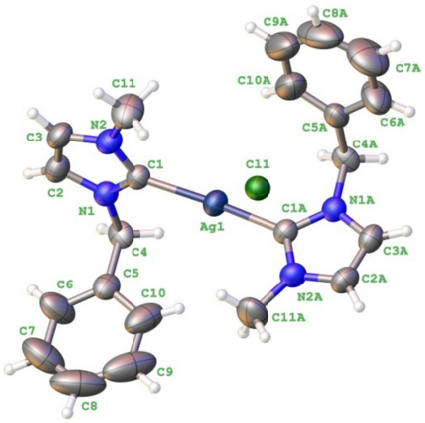
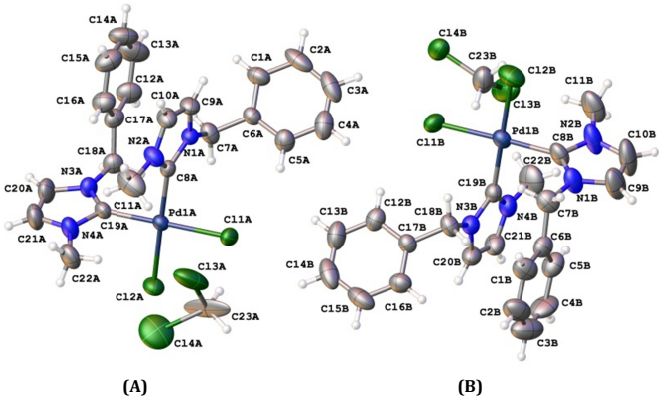


Figure 2. Solid-state structure of one of the units of trinuclear silver-NHC complex **3** with displacement ellipsoids drawn at 50% probability.



(A) **(B)**

Figure 3. Solid-state structure of the components **A** and **B** of the *cis*-palladium-NHC complex **5** with displacement ellipsoids drawn at 50% probability.

Bond distances and angles of these structurally independent species differ to a small extent; whereas their chemical composition remains same. As depicted in these figures, the structure determination reveals complex **5** to be a *cis*-palladium complex having *syn* arrangement of the NHC ligands around the metal in solid state [20]. The palladium center in complex **5** is coordinated by two NHC ligands and two chloride moieties in a slightly distorted square planar coordination geometry. The Pd-C8 and The Pd-C19 bonds [1.992(5) and 1.999(4) Å] are much shorter than that of their trans Pd-Cl2 and Pd-Cl1 bonds [2.3883(16) and 2.3573(12) Å], indicating the stronger *cis*-influence of the coordinating species. Each imidazole ring is coordinated to palladium center which is almost perpendicular to its *cis*-imidazole ring parallel to *ab* and *bc* planes with a dihedral angle of 79.3(5) °. In the extended structure, complex units are connected by PdCl···HCH (3.708 Å), PdCl···$HCHCl_2$ (3.408 Å), $ClCH_2Cl···H_{imi}$ (3.326 Å) and $ClCH_2Cl···H_2CCl_2$ (2.859 Å) hydrogen bonds to form a three-dimensional network.

3.3. Antibacterial and anticancer results

Prompted by the successful formation of imidazolium salts and their carbene complexes, we were interested in determining the anticancer potentials of *cis*-platin analogue *cis*-palladium complex **5**, its precursor silver complexes and NHC proligands. The distinct compounds tested for aforementioned biological studies differ mainly in counter ions and chemical environment of the metal center(s).

The *in vitro* anticancer activities of the carbene complexes **1**-**5** against HCT116 cell lines based on the MTT assay method using 5-fluorouracil (5-FU) as an internal standard reveal the potential of these complexes as anticancer agents. Among the tested compounds, silver complex **4** and palladium complex **5** revealed weak anticancer potential against HCT116 cell line with IC_{50} value of >200 μM. The cell growth did not affect much even after 72 h of incubation, whereas cellular morphology was changed to a lesser extent compared to that of untreated cells (Figure 4).

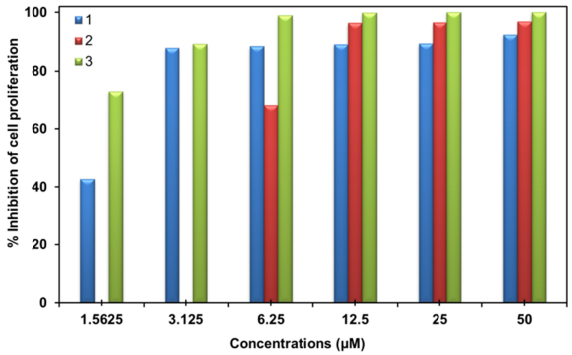


Figure 4. MTT assay results of imidazolium salts and their carbene complexes *vs.* the HCT 116 cell lines.

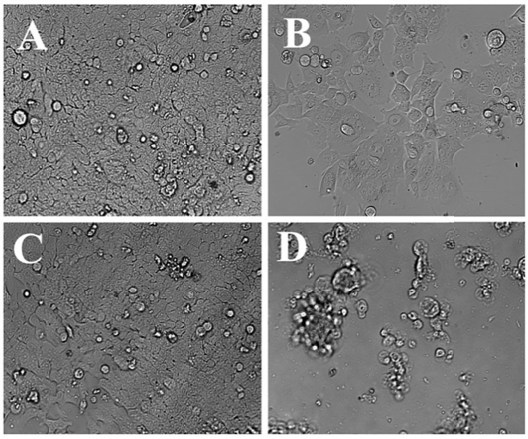


Figure 5. Images of the control HCT116 cells (A), cells treated with 5-FU (B) and compounds **1** (C) and **3** (D) after 72 h of incubation.

Surprisingly, compounds **1**, **2** and trinuclear silver complex **3** displayed potent anticancer potential with the IC_{50} values 8.32, 0.19 and 0.40 μM, respectively. Photomicrographs (Figure 5) of the cells treated with these compounds demonstrated the strong cytotoxic efficacies that can be compared with the standard reference 5-FU (IC_{50} = 5.2 μM). Similar antibacterial and anticancer potentials were observed for the analogues mono-NHC silver acetate complexes [21-23]. Cells treated with compounds **1**-**3** showed growth inhibition and morphology of the cells were completely changed with respect to that of the negative control. Especially, in the case of cells treated with complex **3**, except a few dead cells only debris can be seen in the photomicrograph.

4. Conclusions

Two Ag(I)-NHC complexes **3** and **4** were synthesized from imidazole-based NHC precursors **1** and **2**, respectively. Latter compounds differ in the counterion, which leads to the formation of different silver complexes. This finding shows that the choice of counterions is very crucial, which can lead to a range of structural architectures, including their nuclearity, arrangement of NHC ligands around the metal center, inter and intramolecular interactions and so on. Complex **3** is a trinuclear compound in which each of the metal centers is connected by a triply bridged chloride, whereas complex **4** is a mononuclear entity crystallized along with KPF_6 unit. Further, these structurally different NHC complexes were used to prepare palladium-NHC complexes, expecting two structurally different targets by transmetallation technique. However, both the complexes formed same *cis*-palladium-NHC complex **5**, which is characterized by X-ray diffraction method. Both, NHC precursors and carbene complexes **3**-**5**, were tested for anticancer potential, where both of the NHC precursors and complex **3** displayed higher anticancer potential against HCT116 cancer cell line.

Supplementary materials

Crystallographic data are available on request from Cambridge Crystallographic Data Centre on quoting the deposition numbers CCDC 866504 and 855688 for complexes **3** and **5**, respectively.

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