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Silver(I)-*N*-heterocyclic carbene complexes of nitrile-functionalized imidazol-2-ylidene ligands as anticancer agents

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ABSTRACT

Reactions of symmetrically and non-symmetrically substituted nitrile-functionalized imidazolium salts (**1**–**3**) with silver(I) oxide in methanol at room temperature afforded complexes (**4**–**6**) of the type [NHC-Ag-NHC]PF_6, (NHC: imidazol-2-ylidene). All reported compounds have been characterized by spectral (^{1}H, ^{13}C NMR and FTIR) and elemental analysis. The structure of bis-imidazolium salt **3** and silver complex **4** was unambiguously elucidated by the single-crystal X-ray diffraction method. The effect of substitutions on the anticancer activity of compounds **1–6** has been investigated by *in vitro* cytotoxicity studies against human colorectal (HCT 116) cancer cell line, using the MTT assay method. All three silver complexes (**4**–**6**) displayed promising anticancer activity with IC_{50} values of 6.0 ± 0.2, 14.0 ± 0.6 and 4.0 ± 0.2 μM, while imidazolium salts, **1**–**3**, showed least (>200 μM) to moderate (20.3 ± 0.2 and 95.0 ± 2 μM) anticancer potential, respectively. Bis-imidazolium salt **3** and binuclear complex **6** displayed good activity against human breast (MCF-7) cancer line with IC_{50} values of 82.4 ± 2.5 and 0.9 ± 0.4 μM, respectively.

N-heterocyclic carbenes (NHCs) are formally derived from azolium salts such as 1,3-disubstituted imidazolium salts by deprotonating the C2 proton by a strong base. The interest in this area has increased impressively in the last decade due to the potential applicability of NHC–metal complexes in a large quantity of fields [1]. The study of the specific properties of NHC–metal complexes continues to spring many interesting facts ranging from catalysis to medicinal chemistry. Variety of silver(I)–NHC complexes can be composed by both, functionalized and/or non-functionalized NHCs [2], adopting standard synthetic pathways suggested by Lin and Wang [3] to afford a plethora of structural motifs highly dependent on reaction conditions, nature of metal centre and solvent choice. The most widespread line in progressive expansion in this particular field is the family of N-functionalized NHC–metal complexes that contain imidazole core [4]. The electronic tunability of N-functionalized NHCs and variety of established reactivity make their carbene complexes a promising choice in the expansion of targeted synthesis of anticancer agents.

Despite their extensive potential as anticancer agents, the supramolecular chemistry and structural diversity in N-functionalized NHC–metal complexes are of continuous interest. Traditionally, the N-functionalized complexes involved in both catalysis and pharmacology possess amides, amines and/or N-heterocyclic systems attached at the N-terminals of an azole-based NHC ligand [5]. However, other types of N-functionalized ligands such as nitrile-functionalized NHCs have demonstrated a great utility to afford structurally divergent motifs. Especially, the silver(I) complexes derived from the nitrile-functionalized NHCs have established an excessive utility as anticancer agents, for instance, 1-methyl-3-(4-nitrilebenzyl)-benzimidazol-2-ylidenesilver acetate displayed promising anticancer potential against the human renal cancer cell line, but, failed to show tumor growth inhibition *in vivo* in a xenograft model [6]. Recently, we have reported [7] that rare structural motifs can result from nitrile-functionalized NHC precursors, even from apparently simple and commonly used experimental methods. One early surprising outcome was the formation of a binuclear silver–NHC complex formed by the coordination of a carbene carbon and a nitrile nitrogen atoms to the silver(I) centre in an almost linear coordination geometry. By analogy, we intend to take benefit of the nitrile-functionality either in the coordination or in the formation of supramolecular architectures. Recently, we have reviewed the biological applications of silver(I)–NHC complexes bearing different NHCs and found that these are important synthons in anticancer research [8]. The present nitrile-functionalized imidazolium salts are specifically designed to link one or two metal centres. Imidazolium salt **2** is a symmetric version of unsymmetric salt **1**, while salt **3** is its dimeric entity. In the present communication, three different nitrile-functionalized silver(I)–NHC complexes have been prepared, methodically characterized and studied for their potential as anticancer agents against HCT 116 and MCF-7 cancer cell lines.

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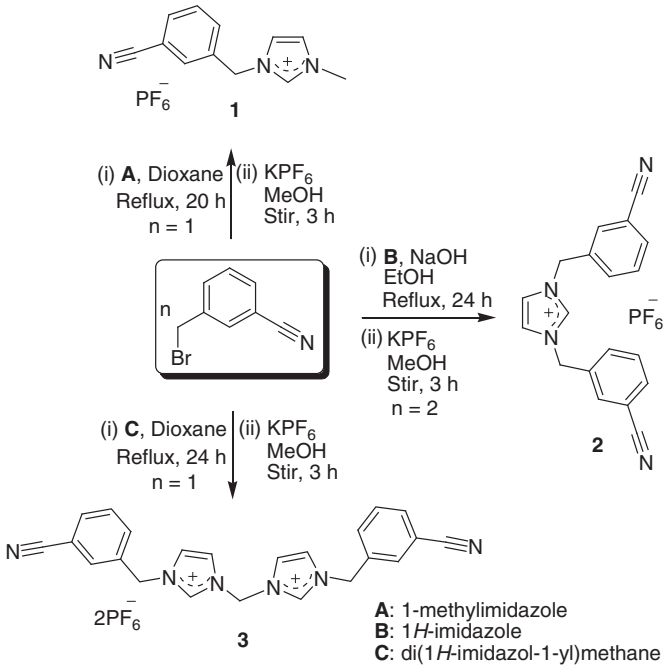
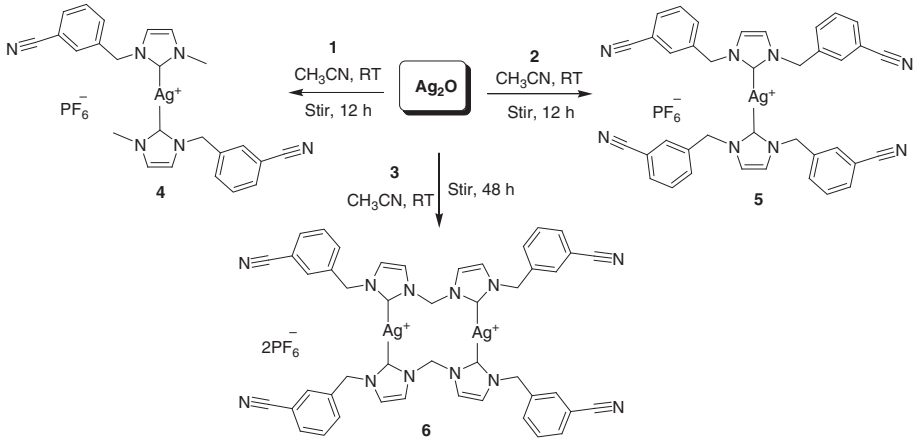


Scheme 1. Synthesis of nitrile-functionalized mono- and bis-imidazolium salts.

Nitrile-functionalized imidazolium salts, **1**–**3**, are accessible in two steps starting from N-alkyl/aryl imidazole as shown in Scheme 1. Treatment of 1-methylimidazole with 3-bromomethylbenzonitrile in dioxane at refluxing conditions, followed by the salt metathesis with potassium hexafluorophosphate yields the imidazolium salt **1** in quantitative yield. Symmetrically substituted imidazolium salt **2** and the corresponding silver(I)–NHC complex **5** were synthesized according to the reported procedure [9] via the reaction of 1*H*-imidazole with 3-bromomethylbenzonitrile in ethanol at basic conditions and metallation with silver(I) oxide, respectively. Finally, bidentate NHC proligand **3** was prepared via the reaction of 3-bromomethylbenzonitrile with di(1*H*-imidazol-1-yl)methane in dioxane at refluxing conditions, followed by the salt metathesis with potassium hexafluorophosphate. NHC transition metal complexes are often prepared via reaction of an (benz)imidazolium salt with a basic metal source such as Ag_2O or $Pd(OAc)_2$ to afford the desired complex. Thus, the imidazolium salts **1**–**3** were treated with Ag_2O in acetonitrile at room temperature for 12–48 h under exclusion of light. The target mono- or binuclear silver(I)–NHC complexes **4**–**6** can then be isolated in good yield by solvent removal under reduced pressure. The reactions involved in the preparation of mono- and binuclear silver(I)–NHC complexes **4**–**6** are shown in Scheme 2. Both, imidazolium salts and corresponding silver complexes are non-hygroscopic in nature and readily soluble in common organic solvents such as methanol, ethanol, acetonitrile, DMF and DMSO. Elemental analysis data along with spectroscopic data is in well agreement with the proposed structure of the compounds, which is further complemented by means of the data obtained by single crystal X-ray diffraction.

The ^{1}H NMR spectra of the imidazolium salts show a distinguished singlet in the range 9.15–9.51 ppm, corresponding to the imidazolium C2 proton, and a couple of doublet resonances at around 7.9 ppm for backbone C4 and C5 protons [10]. In the silver complex spectra, the peak corresponding to the C2 proton of the salt is completely disappeared, indicating its deprotonation and coordination of the C2 carbon to the metal centre [11]. However, resonances for methyl and benzylic protons were observed at around 3.85 and 5.50 ppm, respectively, in all spectra. Further, the coordination of C2 carbon to the metal centre is confirmed by the ^{13}C NMR spectral technique. The silver(I) bound carbene carbon is identified in the ^{13}C NMR spectra of the complexes at the typically high-frequency shift at around 180 ppm, indicating the successful formation of the desired complexes [12]. In the case of complex **6**, the most downfield resonance for the carbene carbon nuclei appeared as two doublets centred at 180.1 ppm due to the presence of ^{13}C–^{107}Ag and ^{13}C–^{109}Ag couplings with the average coupling constant of 190.6 Hz [13]. In addition to this, there is a negligible difference in the peak position and integration of the resonances for the rest of the carbon nuclei compared with ^{13}C NMR spectra of the corresponding salts. Interestingly, the ^{1}H NMR spectrum of complex **6** also shows two separate broad resonances at 5.30 and 6.46 ppm, ascribed to the central methylene spacer. This might be due to the endo and exo arrangement of the two protons orienting towards and away from the metallacycle, respectively [14]. Also, it is speculated that endo protons that are orienting toward the metallacycle show interaction with the metal centres.

Conventional FTIR spectroscopy was effectively used to understand the possibility of nitrile nitrogen involvement in the coordination with the metal centre. In the spectra of the imidazolium salts, a sharp band with medium intensity was observed at around 2230 cm^{-1}, corresponding to the stretching vibrational modes of nitrile functionality. Interestingly, in the complex spectra this band was not affected, attributing to the non-involvement of the nitrile nitrogen in the coordination [15]. This is further confirmed by single crystal X-ray analysis. On the other hand, imidazole ring vibrations shifted to a lesser energy region in the complexes, indicating the successful formation of silver(I)–NHC complexes. C–H vibrations of imidazole ring and benzyl frameworks were observed at around 2860 and 2940 cm^{-1} in all the compounds.



Scheme 2. Synthesis of nitrile-functionalized mono- and binuclear silver–NHC complexes.

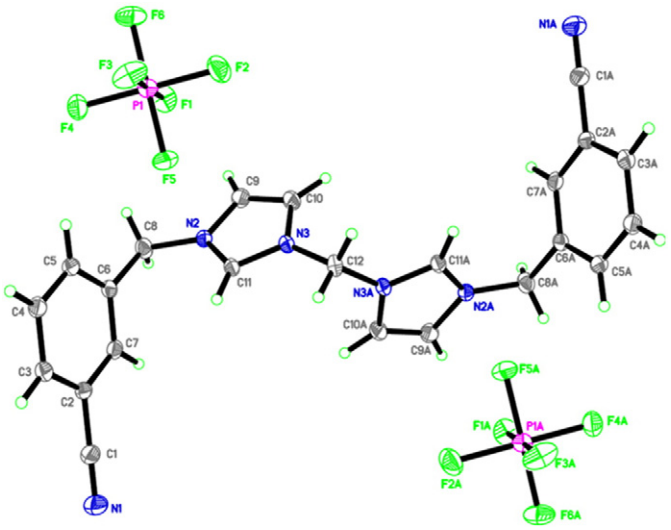


Fig. 1. Molecular structure of bis-imidazolium hexaflurophosphate salt **3**. Selected bond distances (Å): C1 – N1: 1.1522(13), C1 – C2: 1.4414(12), C8 – N2: 1.4831(11), N2 – C11: 1.3254(11), C11 – N3: 1.3406(10) and N3 – C12: 1.4567(11). Selected bond angles (°): N1 – C1 – C2: 179.77(13), C6 – C8 – N2: 111.28(7), N2 – C11 – N3: 108.22(7) and N3 – C12 – N3A: 109.08(11).

The structure of bidentate NHC proligand **3** and silver(I)–NHC complex **4** has been unambiguously determined by single-crystal X-ray diffraction studies. The crystal structure of salt **1** has been reported in our earlier article [16]. Single crystals of **3** and **4** suitable for X-ray crystallographic studies were grown by slow evaporation of salt solution in acetonitrile and slow diffusion of diethyl ether into the complex solution in methanol, respectively at room temperature. Pertinent bond parameters of the NHC proligand **3** and silver(I)–NHC complex **4** are presented along with the captions of their molecular structures,

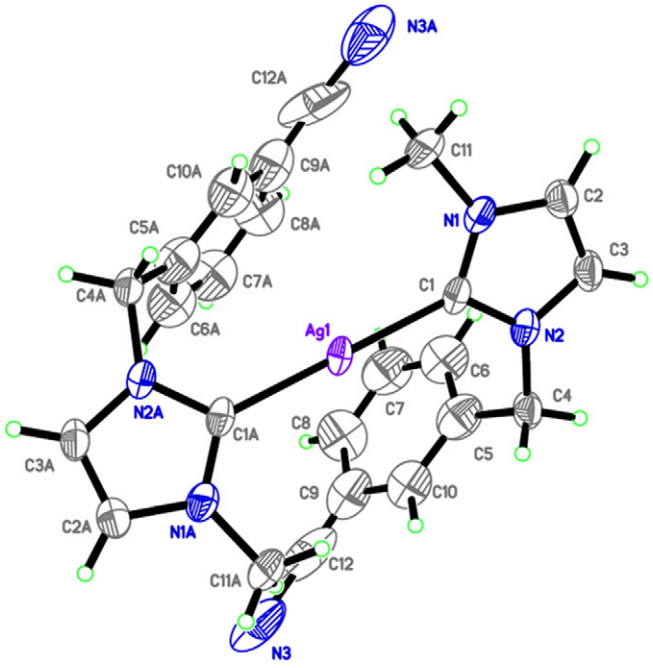


Fig. 2. Molecular structure of silver–NHC complex **4**. Hexafluorophosphate anion has been omitted for clarity. Selected bond distances (Å): Ag1 – C1: 2.090(8), C1 – N1: 1.347(11), C1 – N2: 1.363(9), N1 – C11: 1.450(11), N2 – C4: 1.459(10) and C12 – N3: 1.46(2). Selected bond angles (°): C1 – Ag1 – C1A: 179.7(4), N1 – C1 – N2: 103.6(7), C1 – N1 – C11: 124.8(7), C1 – N2 – C4: 123.5(7) and C9 – C12 – N3: 173.9(18).

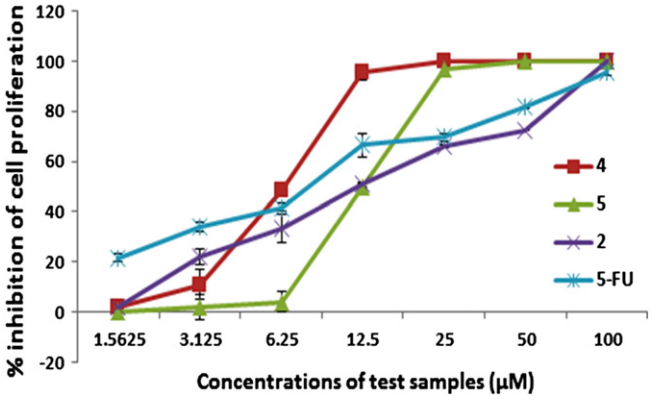


Fig. 3. MTT assay results of imidazolium salt **2** and silver–NHC complexes (**4** and **5**) versus HCT 116 cell lines.

respectively. The asymmetric unit of compounds **3** and **4** contains one half of a molecule of imidazolium salt **3** with one hexafluorophosphate anion and one half of a molecule of complex cation with one half of a molecule of hexafluorophosphate anion, respectively. Both, imidazolium salt **3** and silver complex **4**, crystallize in the monoclinic space group C2/c. Molecular structures of compound **3** and **4** along with the pertinent bond angles and bond distances are shown in Figs. 1 and 2, respectively.

Salt **3** is a well ordered bis-imidazolium salt having two hexafluorophosphate counter ions. The molecule possesses a zig-zag structure having each imidazole ring and the attached benzonitrile planes are perpendicular to each other. The internal bond angles at N2 – C11 – N3 (and N2A – C11A – N3A) and nitrile module N1 – C1 – C2 (and N1A – C1A – C2A) are 108.22(7) and 179.77(13)°, respectively

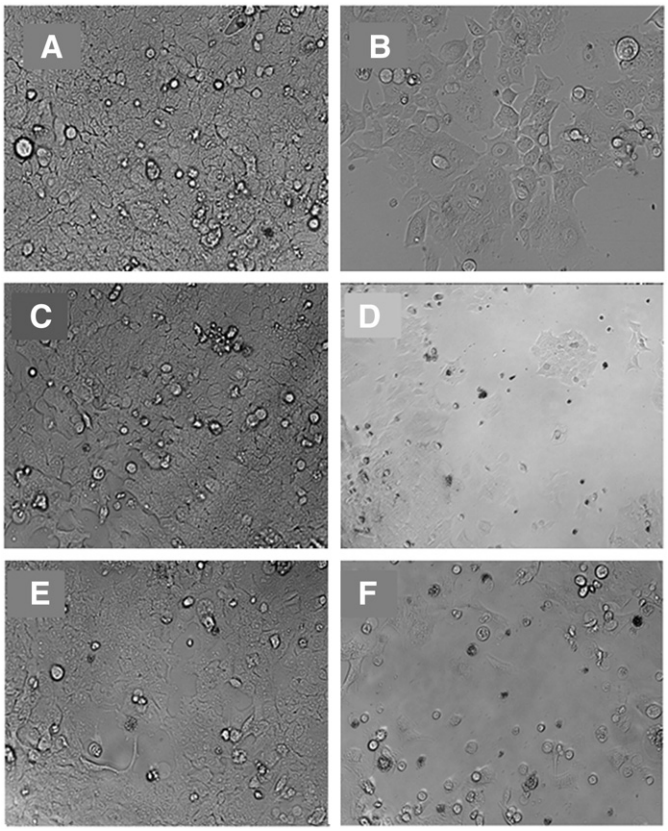


Fig. 4. Images of the control HCT116 cells (A), cells treated with the standard 5-fluorouracil (B) and cells treated with imidazolium salts **1** (C) and **2** (D) and silver–NHC complexes **4** (E) and **5** (F).

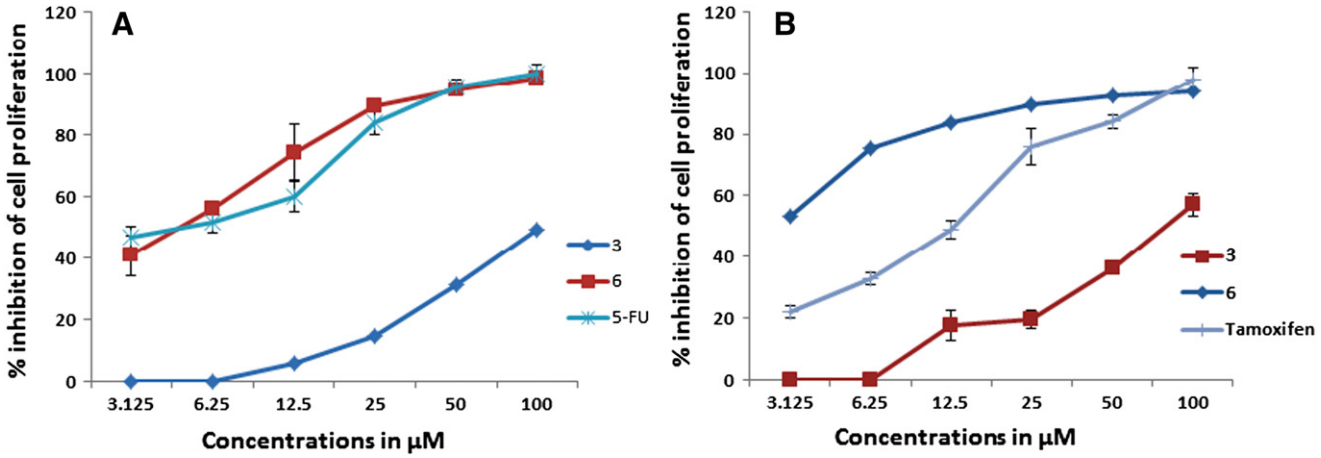


Fig. 5. MTT assay results of imidazolium salt **3** and silver–NHC complex **6** versus HCT 116 (a) and MCF-7 cell lines (b).

which are in agreement with the previous reports [17]. In addition, a weak π–π stacking interactions are observed between the two benzonitrile rings of two adjacent molecules with the interaction distances in the range 3.845–3.862 Å. Note that nitrile-functionality is pointing away from the carbene carbon moiety, and is apart by 3.819(3) Å with the neighboring nitrile module of adjacent molecule. This separation is short enough to accommodate another metal centre in between two terminal nitriles of adjacent molecules. Thus, the possibility of polymeric silver complex formation is overlooked. Finally, in the crystal packing, C – H—F (2.538(6) Å) and C – H—N (2.561(2) Å) hydrogen bonding interactions were observed. These hydrogen bonding interactions along with the aforementioned stacking interactions formed the 3-dimensional architecture.

The silver(I) of complex **4** is in a dicoordinate environment, which is best described as almost linear coordination geometry, with the carbene carbon atoms of two NHC ligands. The C1 – Ag – C1A coordination angle of 179.7(4)° is in well agreement with those of the other similar silver(I)–NHC complexes reported by us [18] as well as many others [19]. Both the nitrile entities are however, pointing away from the metal centre, showing their non-involvement in the coordination. The bond distances of C1 – Ag (2.090(8) Å) and C1A – Ag (2.090(8) Å) and internal bond angles at carbene carbon centre N1 – C1 – N2 (103.6(7)°) and N1A – C1A – N2A (103.6(7)°) are well within the range for a linear silver(I)–NHC complex. The planes of imidazole and benzonitrile rings are almost perpendicular to each other with the dihedral angle of 108.7(7)°. Both the benzonitrile substitutions are located on one side of the imidazole planes with *anti-* arrangement of the NHC ligands around the metal centre. Interestingly, weak π–π stacking interactions of 3.569(6) Å are observed between the imidazole rings parallel to the *bc* plane. In the extended structure, complex cations are connected with hexafluorophosphate anions *via* intra and intermolecular hydrogen bonds of C – H—F (2.629(2) Å) and C – H—N (2.474(7) Å), leading to the 3-dimensional arrangement.

Since metal-based pharmaceuticals of groups 10 and 11 play a substantial role as therapeutic medicine for the treatment of cancer, the development of novel related entities remains an interesting and extensively studied area of research in medicinal chemistry [20]. Displaying structural features very similar to that of trademarked methylcaffeine derived silver-based NHC complex Silvamist® and also exhibiting considerable antimicrobial and cytotoxicity [21], the reported silver(I)–NHC complexes naturally qualify for screening against human derived cancer cell lines. In light of our recent information on the promising anticancer potentials of silver(I)–NHC complexes against HCT 116 and MCF-7 cancer cell lines, the reported imidazolium salts and corresponding silver complexes have been studied for their anticancer abilities using MTT assay [22,23]. The surviving cells were determined by measuring their ability to reduce the yellow dye 3-(4,5-dimethyl-2-thiozolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) to a purple formazan product. Though the unsymmetrically substituted salt **1** exhibited least activity (IC_{50} value of >200 μM) towards HCT 116 cells, its symmetric version, salt **2**, displayed moderate activity with the IC_{50} value of 20.3 ± 0.2 μM. However, treatment of salt **1** with HCT 116 cells showed an insignificant inhibitory effect on proliferation as the growth and morphology of the cells were unaltered with respect to that of the negative control. In the case of salt **2**, the viability of the HCT 116 cells was severely affected, showing a moderate anti-proliferative effect. The silver(I) complexes **4** and **5** exhibited significant anticancer potential against HCT 116 cells with the IC_{50} values of 6.0 ± 0.2 and 14.0 ± 0.6 μM, respectively. Specifically, complex **4** displayed a strong anti-proliferative activity in culture, which is nearly equal to the potential of the standard used (5-fluorouracil IC_{50} = 5.2 ± 1.0 μM). The treatment of complex **4** reduced the doubling time of HCT 116 cells drastically so that the population of cells decreased significantly when compared to the negative control. While the photomicrograph of the cells treated with complex **5** illustrated a significant anti-proliferative effect of the complex. The cells showed marked signs of cytotoxicity caused by affecting the cellular morphology and viability. MTT assay results imidazolium salts and corresponding silver complexes are shown in Fig. 3. Images of control HCT 116 cells and the cells treated with the test compounds are shown in Fig. 4.

Quite significantly, the binuclear silver(I)–NHC complexes exhibit remarkable anti-cancer properties due to the fact that, these complexes are more stable than their mononuclear counterparts and the existence of possible cooperative effects between metal centres [7,8,22,23].

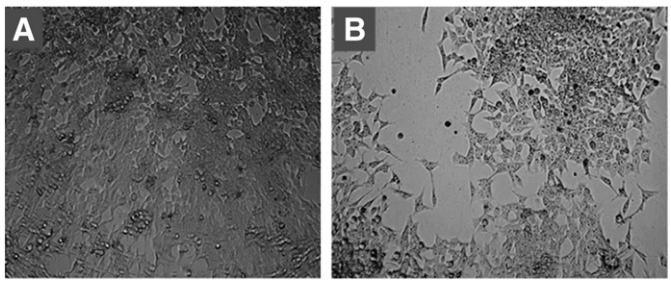


Fig. 6. Images of the HCT 116 cells treated with the imidazolium salt **3** (A) and silver–NHC complex **6** (B).

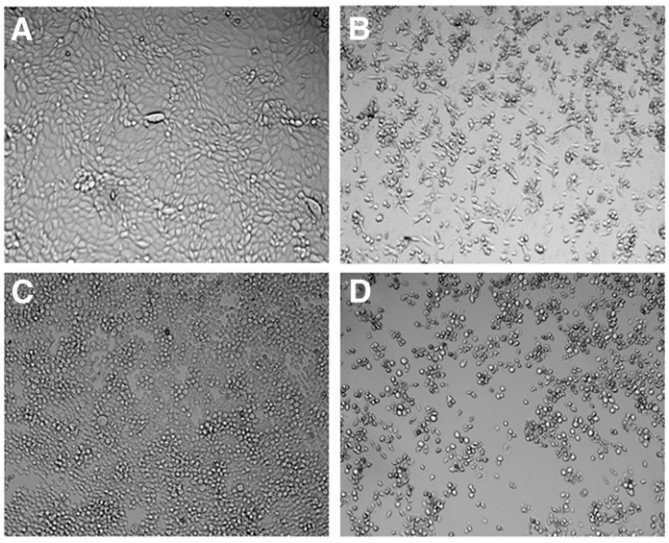


Fig. 7. Images of the control MCF-7 cells (A), cells treated with the standard drug tamoxifen (B), cells treated with imidazolium salt **3** (C) and silver–NHC complex **6** (D).

Therefore, the inhibition of cell proliferation using bis-imidazolium salt **3** and corresponding silver complex **6** was examined against two cancer cell lines, viz., HCT 116 and MCF-7. MTT assay results of compounds **3** and **6** against HCT 116 and MCF-7 are shown in Fig. 5. HCT 116 and MCF-7 cells treated with bis-imidazolium salt **3** showed moderate cytotoxic effects with the IC_{50} values of 95.0 ± 2 and 82.4 ± 2.5 μM, respectively by affecting the normal morphology of the cells. Binuclear complex **6** seems to be more stable compared with its mononuclear counterparts **4** and **5**, and is expected to be more active against both the cancer cell lines. This complex displayed 1.5–3.5 orders of magnitude higher activity against HCT cells as compared to the mononuclear counterparts with an IC_{50} value of 4.0 ± 0.2 μM. Cells treated with complex **6** showed a significant inhibitory effect on proliferation of cells, which can be compared with that of standard reference drug. Similarly, against MCF-7 cells, complex **6** displayed promising activity which is many fold higher than the corresponding bis-imidazolium salt with an IC_{50} value of 0.9 ± 0.4 μM that is nearly three-fold higher potential compared with the standard used (tamoxifen IC_{50} = 2.4 ± 0.5 μM). The MCF-7 cells displayed severe toxic signs as all the cells converted into round shaped morphology after losing the normal pseudopodial cellular projections. Figs. 6 and 7 depict the images of HCT 116 and MCF-7 cells treated with bis-imidazolium salt **3** and corresponding silver complex **6**, respectively.

In the context of the potential activity of reported silver complexes, it is worthy of note that the binuclear complex **6** displayed good activity compared with both the mononuclear counterparts, which could be assigned to the presence of two metal centres. Symmetrically substituted complex **5** however, showed 2-fold lesser activity than the non-symmetrically substituted complex **4**, which might be due to decreased lipophilic character as this is bearing symmetrically substituted NHCs. These observations are speculations and further studies are necessary to know the insights into the structure–activity relationships.

In conclusion, this study reported a series of imidazolium salts **1**–**3** and the corresponding silver(I)–NHC complexes **4**–**6**. All synthesized compounds were characterized by spectral and analytical techniques. Additionally, the molecular structure of bis-imidazolium salt **3** and silver complex **4** was unambiguously elucidated by the single crystal X-ray diffraction method. Along with hydrogen bonding interactions, a weak π–π stacking interactions were observed in both the cases that is leading to the formation of 3-dimensional architectures. Compounds **1**–**6** were tested for anti-cancer activity against HCT 116 cancer cell line. All the tested compounds displayed moderate to good anti-cancer property with the IC_{50} values in the range 6–20 μM, except imidazolium salt **1**. Further, bis-imidazolium salt **3** and corresponding silver complex **6** displayed promising anti-cancer potential against MCF-7 cancer cell line.

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Appendix A. Supplementary material

CCDC 985183 and 985184 contain the supplementary crystallographic data for the imidazolium salt **3** and the silver complex **4**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Experimental and characterization details of all new compounds, crystal data and packing diagrams of the imidazolium salt **3** and the silver complex **4** and effects of increasing amounts of imidazolium salts and silver–NHC complexes on the percentage inhibition of Q9 HCT 116/MCF-7 cell proliferation are also available as supplementary material. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.inoche.2014.03.016.

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