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PAPER

Enhanced cytotoxicity of silver complexes bearing bidentate N-heterocyclic carbene ligands

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A diverse library of cationic silver complexes bearing bis(N-heterocyclic carbene) ligands have been prepared which exhibit cytotoxicity comparable to cisplatin against the adenocarcinomas MCF7 and DLD1. Bidentate ligands show enhanced cytotoxicity over monodentate and macrocyclic ligands.

Introduction

Over the past two decades metal complexes of N-heterocyclic carbenes (NHCs) have become extremely important in catalytic processes such as cross-coupling, metathesis, C–H bond activation and polymerisation.[1–4] To a much lesser extent they have been investigated in biomedical applications, showing promise as antimicrobial (silver–NHCs) and as antitumour agents.[5–7] The antimicrobial properties of silver are well established and have resulted in silver being incorporated into several materials such as wound dressings, creams, deodorants and even clothing.[8–10] The toxicity of silver is thought to be relatively low which has enabled its wide use. Silver–NHC complexes are emerging as new and improved antimicrobial agents to overcome problems associated with conventional silver antibiotics such as fast loss of activity and resistance.[5,11–13] It has been suggested that the increased stability of silver NHCs results in a slower release of silver, rendering the compounds active over a longer period of time.

Studies have been carried out which indicate that metal–NHC complexes may also be useful in cancer chemotherapy. Specifically, NHC complexes of palladium, copper, gold and silver have been reported which exhibit cytotoxicity against various cancer cell lines.[6,12,14–16] Most of the cytotoxic silver NHCs reported are neutral complexes, bearing a monodentate NHC donor and an acetate ligand (Fig. 1A).[16–21] Youngs *et al.* have reported cationic monodentate NHC complexes that are effective against the H460 lung cancer cell line, though cytotoxicity was not superior to cisplatin (Fig. 1B).[22] Herein, we report the preparation of a range of chelating and macrocyclic bis-imidazolium precursors and their coordination to form cationic silver bis(NHC) complexes (Fig. 3). The cytotoxicity of the complexes was evaluated against the cancer cell lines MCF7 (breast) and DLD1 (colon) to assess the effect of bidentate ligands on activity. The nitrogen substituents (R), position of the carbene moiety (*meta* or *para*) and the counterion (X) were varied to gain structure–activity relationships. In addition, a monodentate derivative was prepared and tested to compare the activity of multidentate ligands compared to their monodentate counterparts. Testing of simple silver salts (AgBr, $AgBF_4$), and imidazolium salt precursors in the absence of silver, suggests that both the silver and the ligand moieties are essential for their activity.

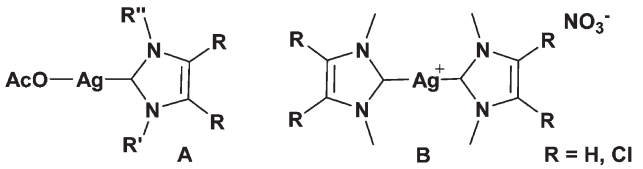

Fig. 1 Neutral (A) and cationic (B) cytotoxic silver NHCs.

Results and discussion

Imidazolium salts **1–4** were prepared through reaction of an N-substituted imidazole with a bromomethylated core (Scheme 1).[23,24] Reactions were generally performed in dichloromethane, with the bromide salts precipitating within 1 hour. Counterion exchange was performed using NH_4BF_4 in methanol. A characteristic shift of the C2 proton from ~7.5 to ~9 ppm in the ^{1}H NMR spectra of the resulting white solids show the desired products to have formed.

We have previously reported the coordination of bis(imidazolium) hexafluorophosphate and tetrafluoroborate salts to silver using the common Ag_2O route.[24,25] Basic silver oxide reacts with an imidazolium salt causing *in situ* deprotonation of the C2 proton and coordination to silver, with concomitant silver salt formation. The reaction conditions are dependent upon the ligand used and the counterion, with the tetrafluoroborate salts formed in dimethylsulphoxide at 80 °C. As the C2 proton of the imidazolium bromide salts is more acidic, reactions to coordinate the carbene ligand to silver can be performed at room temperature. Initial reactions were conducted in anhydrous methanol with the use of molecular sieves to remove the water formed during the reaction. It was found that the resulting complexes were air sensitive, with solids becoming oily and depositing a

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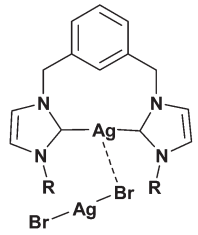


Fig. 2 Metal halide bridge formation.

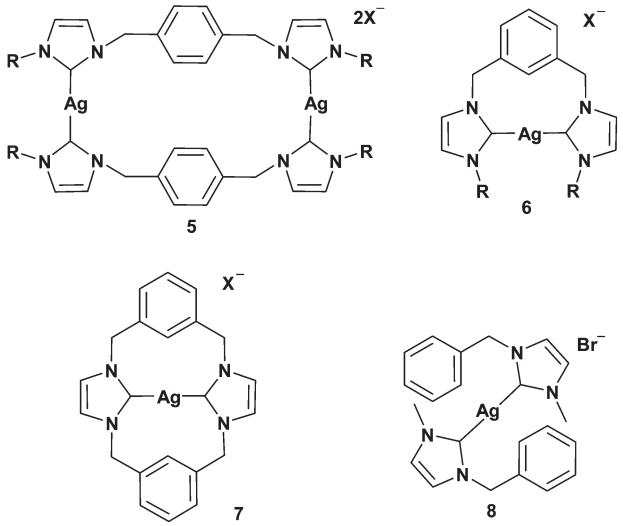
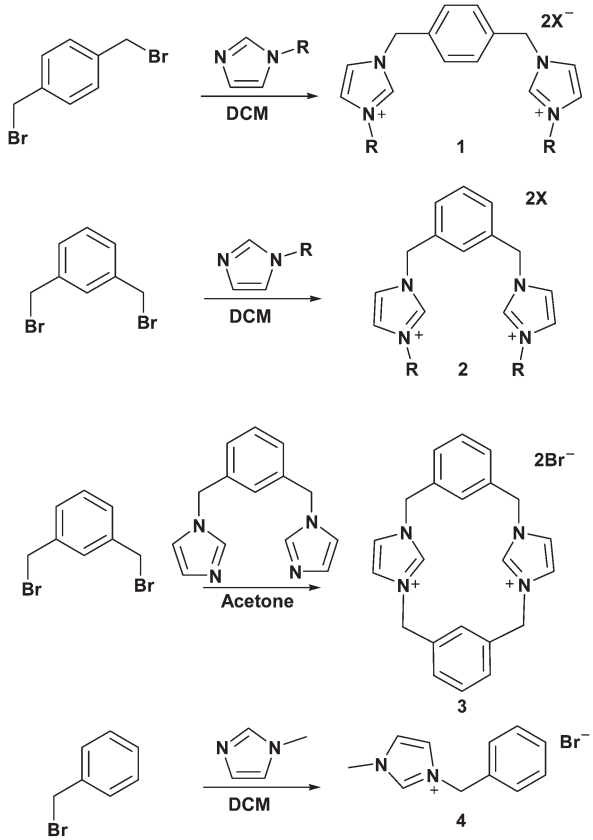


Fig. 3 Silver bis(NHCs) **5–8**. a: R = Me, X = Br; b: R = ^{n}Pr, X = Br; c: R = ^{t}Bu, X = Br; d: R = Me, X = BF_4.



Scheme 1 Preparation of ligand precursors **1–4**. a: R = Me, X = Br; b: R = ^{n}Pr, X = Br; c: R = ^{t}Bu, X = Br; d: R = Me, X = BF_4.

dark brown solid. Elemental analyses confirmed that the complexes contained large excesses of silver bromide, which is potentially incorporated into the structures through metal halide bridge systems (Fig. 2). When a solvent mixture of dichloromethane–methanol (7 : 1) was used for the reaction, the resulting isolated solids were significantly more stable to air and found not to contain excess silver bromide. Presumably the less polar solvent causes the precipitation of silver bromide, hence the salt does not become incorporated into the structure. The resonance in the ^{1}H NMR spectra attributable to the C2 proton disappears upon deprotonation and resulting carbene formation, and a shift at approximately 180 ppm in the ^{13}C NMR spectra shows the C2 carbon coordinating to silver.

Reaction of imidazolium bromide salts **2** and **3** with silver oxide to prepare neutral silver–NHC complexes, in which each silver centre coordinates one NHC and one bromide atom, has previously been reported.[23,26] High resolution mass spectrometry and elemental analytical data following our reaction conditions are consistent with the formation of the cationic bis(NHC) complexes depicted in Fig. 3.† Each silver coordinates to two NHC centres with a non-coordinating bromide atom. Using the *meta*-substituted ligands **2** and **3**, it is possible for either a pincer (**6** and **7**) or polymeric complex to occur, whereas the *para*-substituted ligand is more likely to bridge two separate silver centres (**5**). Literature precedence suggests that complexes **6** and **7** are likely to form dinuclear or polynuclear complexes, with the NHC moieties of each ligand twisting away from each other and coordinating to different silver centres.[23,26,27] NMR data of complex **7** also shows the diastereotopic nature of the methylene protons.

The *in vitro* cytotoxicity of silver bis(NHC) complexes **5–8** was determined using MTT-based assays involving a 6 day drug-exposure period.[28] Compounds were tested for their activity against the human breast adenocarcinoma MCF7 and the colon adenocarcinoma DLD1. In addition to chelating and macrocyclic silver bis(NHCs) (**5–7**), the complex bearing the monodentate ligand (**8**), imidazolium salts **1a** and **2a**, AgBr and $AgBF_4$ were also tested. The results are summarized in Table 1, Fig. 4 and Fig. 5 and are compared to cisplatin.

The monodentate complex **8** against MCF7 (IC_{50} = 17.8 ± 3.8 μM) is clearly less effective than complexes bearing bidentate ligands (IC_{50} range including error = 1.5 to 9.7 μM). This may be explained by the bidentate nature of the ligands rendering the complexes more stable. In a similar manner to antimicrobial silver NHCs, it is possible that increased stability results in a slower release of silver so higher activity. The macrocyclic effect generally leads to even higher complex stability relative to the chelating effect. The macrocyclic complex **7**, however, is less cytotoxic than some of the chelating complexes (IC_{50} = 13.1 ± 4.8 μM). It is possible that a complex can become too stable and doesn't release sufficient silver, hence becomes less efficient over the drug-exposure period.

Against MCF7, the bidentate complexes **5–6** show similar IC_{50} values to each other suggesting that the N-substituent of the ligand and the position of the NHC (*meta* or *para*) does not have any considerable effect on cytotoxicity against this cell line.

Table 1 Response of MCF7 and DLD1 cell lines to cisplatin, silver salts, imidazolium salts and silver complexes. Values presented are IC_{50} (μM) ± SD for three independent experiments

Compound	MCF7	DLD1
Cisplatin	1.3 ± 0.7	2.4 ± 1.0
AgBr	>100	>100
$AgBF_4$	>100	>100
1a	>100	>100
2a	>100	>100
5a	6.3 ± 2.2	4.1 ± 0.6
5b	5.6 ± 4.1	5.4 ± 0.4
5c	4.3 ± 0.3	7.9 ± 0.9
5d	3.5 ± 0.1	4.6 ± 0.3
6a	7.9 ± 0.8	2.3 ± 1.3
6c	4.2 ± 0.5	1.1 ± 0.2
7	13.1 ± 4.8	—
8	17.8 ± 3.8	—

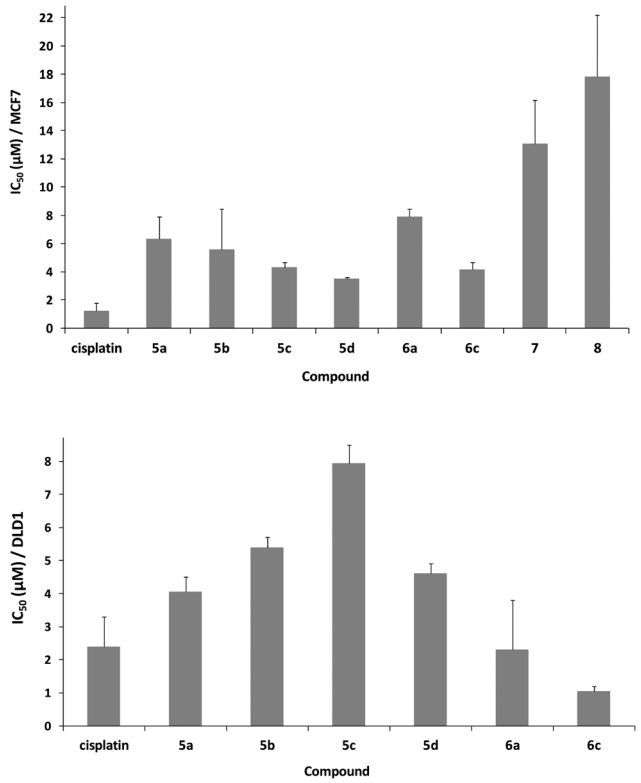


Fig. 4 Response of MCF7 (top) and DLD1 (bottom) cell lines to cisplatin and silver complexes. Values presented are IC_{50} (μM) ± SD for three independent experiments.

Against DLD1, however, it appears that the *meta*-chelating NHC complexes (**6**) have enhanced cytotoxicity over the *para*-complexes (**5**), with **6c** in particular showing cytotoxicity values superior to cisplatin (IC_{50} = 1.1 ± 0.2 μM for *meta*-**6c** *vs.* IC_{50} = 7.9 ± 0.9 μM for *para*-**5c** and 2.4 ± 1.0 μM for cisplatin). This may again be due to complex stability, as the *meta* ligands are able to chelate a silver centre whereas the *para* ligands are unable to achieve the bite angle to do this. The N-^{t}Bu substituent of **6c** will also provide steric stability.

There is a hint of selectivity of **6a** and **6c** towards DLD1, providing the possibility of targeting (Fig. 5). These complexes

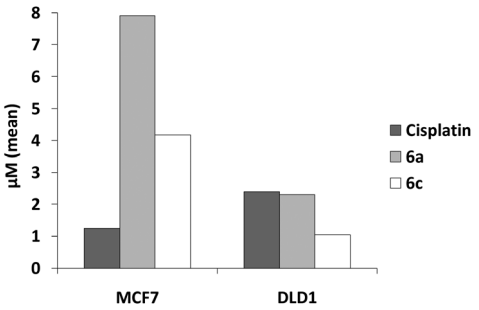


Fig. 5 Response of MCF7 and DLD1 to cisplatin and meta-substituted silver complexes **6a** and **6c**. Values presented are IC_{50} (μM).

exhibit IC_{50} values against DLD1 in the same range as cisplatin, whereas against MCF7 there is above a 4-fold increase in IC_{50} values compared to cisplatin. Surprisingly the counterion (Br^- or BF_4^-) does not appear to have an effect on cytotoxicity values. The counterion is expected to affect complex solubility and possible transmembrane diffusion, though this is likely to be very subtle and the fact that all the complexes are cationic gives them similar properties. AgBr, $AgPF_6$ and imidazolium salts **1a** and **2a** exhibit IC_{50} values above 100 μM, which was the highest concentration tested for these compounds, hence the synergistic effect of both the silver centre and the NHC ligand clearly has a role in the cytotoxicity of silver NHCs.

Conclusion

In conclusion, a series of monodentate, bidentate and macrocyclic cationic silver bis(NHC) complexes have been prepared. Their *in vitro* cytotoxicity has been assessed against the cancerous cell lines MCF7 and DLD1. We have found that the complexes display activity that is comparable to cisplatin, with those bearing chelating ligands showing superior cytotoxic values compared to their monodentate and macrocyclic counterparts. The stability of the complex appears to have a role, with the release rate of silver salt likely being the major factor in this. As these complexes have activities comparable to cisplatin and are likely to have a better toxicity profile, they may prove valuable. A major barrier to the continued development of these compounds is the lack of a defined mechanism of action or cancer specific target. The data in Fig. 5 indicate that compounds **6a** and **6c** are selectively exploiting some biological feature of DLD1 cells and further studies are required to decipher mechanisms of action. We are extending our studies to conduct a cell based screen designed to identify phenotypic and biochemical effects of silver–NHC complexes on cells.

Experimental

General considerations

All reagents were used as supplied or prepared as outlined without need for further purification. N-substituted imidazoles, imidazolium salts, and compound **5d** were prepared according to literature procedure.[23,24,29] Manipulations were performed using

standard Schlenk line and vacuum line techniques. N_2 was passed through a twin-column drying apparatus containing molecular sieves (4 Å) and potassium hydroxide. Solvents were passed over activated alumina to remove water, copper catalyst to remove oxygen and molecular sieves to remove any remaining water *via* the Dow–Grubbs solvent system. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX300 spectrometer (operating frequency 300.1 MHz for ^{1}H and 75.48 MHz for ^{13}C) or on a Bruker DRX500 spectrometer (operating frequency 500.13 MHz for ^{1}H and 125.80 MHz for ^{13}C). All spectra were recorded at 298 K in deuterated solvent. Chemical shift values are quoted in parts per million (ppm, δ) and coupling constants J are quoted in Hertz (Hz). Assignment of ^{1}H NMR spectra was aided by the use of 2D ^{1}H^{1}H COSY experiments and the assignment of ^{13}C{^{1}H} NMR spectra was aided by ^{13}C{^{1}H} dept 135 experiments. Microanalyses were performed by Mr Ian Blakeley in the University of Leeds, School of Chemistry. Mass spectra were collected by Ms Tanya Marinko-Covell either on a Bruker Daltonics (micro TOF) instrument operating in the electrospray mode or a GCT Premier (TOF) instrument operating in electron impact mode using methanol or acetonitrile as solvent.

Ag(NHC)Br (5a)

1a (522 mg, 1.24 mmol) was added to DCM (7 mL) giving a white suspension. To the suspension was added MeOH (1 mL) to give a clear solution to which was added Ag_2O (432 mg, 1.86 mmol) and 3 Å molecular sieves. The mixture was stirred for 18 hours in the dark to give a light brown precipitate (AgBr). This was filtered through Celite and the solvent removed from the filtrate *in vacuo* to give an off white solid. Yield: 443 mg (79%). ^{1}H NMR (d_4-MeOD, 500 MHz) δ: 7.32 (s, 8H, CH), 7.11 (s, 8H, ArH), 5.20 (s, 8H, CH_2), 3.91 (s, 12H, CH_3). ^{13}C NMR (d_4-MeOD, 75 MHz) δ: 182.9 (br d, C–Ag), 136.44 (CH), 128.51 (C), 122.96 (CH), 122.69 (CH), 54.28 (CH_2), 38.51 (CH_3). MS (ESI$^+$): m/z 374.1 [M − 2Br]$^{2+}$. Calcd for $C_{16}H_{18}N_4Ag$ [M − 2Br]$^{2+}$: 373.0582. Found: 373.0591. Anal. Calcd for $C_{32}H_{36}Ag_2Br_2N_8$: C, 42.32; H, 4.00; N, 12.34. Found: C, 43.05; H, 4.25; N, 11.90.†

Ag(NHC)Br (5b)

1b (500 mg, 1.03 mmol) was added to DCM (7 mL) giving a white suspension. To the suspension was added MeOH (1 mL) to give a clear solution to which was added Ag_2O (359 mg, 1.55 mmol) and 3 Å molecular sieves. The mixture was stirred for 18 hours in the dark to give a light brown precipitate (AgBr). This was filtered through Celite and the solvent removed from the filtrate *in vacuo* to give an off white solid. Yield: 173 mg (33%). ^{1}H NMR (d_4-MeOD, 300 MHz) δ: 7.38 (d, ^3J = 1.7 Hz, 4H, CH), 7.34 (d, ^3J = 1.7 Hz, 4H, CH), 7.09 (s, 8H, ArH), 5.21 (s, 8H, CH_2), 4.18 (t, ^3J = 7.2 Hz, 8H, CH_2), 2.01–1.84 (m, 8H, CH_2), 0.95 (t, ^3J = 7.2 Hz, 12H, CH_3). ^{13}C NMR (d_4-MeOD, 75 MHz) δ: Ag–C not observed, 139.03 (CH), 129.29 (C), 123.82 (CH), 123.66 (CH), 55.80 (CH_2), 54.96 (CH_2), 26.49 (CH_2), 11.84 (CH_3). MS (ESI$^+$): m/z 430.1 [M − 2Br]$^{2+}$. HRMS (ESI$^+$): Calcd for $C_{20}H_{26}N_4Ag$ [M − 2Br]$^{2+}$: 429.1208. Found: 429.1204. Anal. Calcd for $C_{40}H_{52}Ag_2Br_2N_8$: C, 47.08; H, 5.14; N, 10.98. Found: C, 48.75; H, 5.70; N, 10.80.†

Ag(NHC)Br (5c)

1c (1 g, 1.95 mmol) was added to DCM (14 mL) giving a white suspension. To the suspension was added MeOH (2 mL) to give a clear solution to which was added Ag_2O (679 mg, 2.93 mmol) and 3 Å molecular sieves. The mixture was stirred for 18 hours in the dark to give a light brown precipitate (AgBr). This was filtered through Celite and the solvent removed from the filtrate *in vacuo* to give an off white solid. Yield: 550 mg (70%). ^{1}H NMR (d_4-MeOD, 500 MHz) δ: 7.56 (s, 4H, CH), 7.21 (s, 4H, CH), 6.97 (s, 8H, ArH), 5.26 (s, 8H, CH_2), 1.81 (s, 36H, CH_3). ^{13}C NMR (d_4-MeOD, 75 MHz) δ: Ag–C not observed, 138.59 (CH), 128.85 (C), 122.31 (CH), 121.98 (CH), 59.56 (C), 56.86 (CH_2), 32.63 (CH_3). MS (ESI$^+$): m/z 458.2 [M − 2Br]$^{2+}$. HRMS (ESI$^+$): Calcd for $C_{22}H_{30}N_4Ag$ [M − −2Br]$^{2+}$: 457.1521. Found: 457.1511. Anal. Calcd for $C_{44}H_{60}Ag_2Br_2N_8$: C, 49.09; H, 5.62; N, 10.41. Found: C, 50.20; H, 6.10; N, 10.25.†

Ag(NHC)Br (6a)

2a (1 g, 2.33 mmol) was added to DCM (14 mL) giving a white suspension. To the suspension was added MeOH (2 mL) to give a clear solution to which was added Ag_2O (812 mg, 3.50 mmol) and 3 Å molecular sieves. The mixture was stirred for 18 hours in the dark to give a light brown precipitate (AgBr). This was filtered through Celite and the solvent removed from the filtrate *in vacuo* to give an off white solid. Yield: 728 mg (69%). ^{1}H NMR (d_4-MeOD, 500 MHz) δ: 7.34 (br, 5H, CH & ArH), 7.16 (m, 3H, ArH), 5.19 (s, 4H, CH_2), 3.75 (s, 6H, CH_3). ^{13}C NMR (d_4-MeOD, 75 MHz) δ: 181.04 (br d, C–Ag), 139.59 (C), 131.30 (CH), 130.01 (CH), 128.86 (CH), 124.50 (CH), 124.07 (CH), 55.77 (CH_2), 39.40 (CH_3). MS (ESI$^+$): m/z 374.1 [M − Br]$^+$. HRMS (ESI$^+$): Calcd for $C_{16}H_{18}N_4Ag$ [M − Br]$^+$: 373.0582. Found: 373.0562. Anal. Calcd for $C_{16}H_{18}AgBrN_4$: C, 42.32; H, 4.00; N, 12.34. Found: C, 42.89; H, 4.19; N, 11.93.†

Ag(NHC)Br (6c)

2c (1.2 g, 2.34 mmol) was added to DCM (14 mL) giving a white suspension. To the suspension was added MeOH (2 mL) to give a clear solution to which was added Ag_2O (814 mg, 3.51 mmol) and 3 Å molecular sieves. The mixture was stirred for 18 hours in the dark to give a light brown precipitate (AgBr). This was filtered through Celite and the solvent removed from the filtrate *in vacuo* to give an off white solid. Yield: 980 mg (78%). ^{1}H NMR (d_4-MeOD, 500 MHz) δ: 7.58 (s, 2H, CH), 7.29 (t, ^3J = 7.6 Hz, 1H, ArH), 7.22 (s, 2H, CH), 6.95 (d, ^3J = 7.6 Hz, 2H, ArH), 6.85 (s, 1H, ArH), 5.20 (s, 4H, CH_2), 1.80 (s, 18H, CH_3). ^{13}C NMR (d_4-MeOD, 75 MHz) δ: 180.34 (br d, C–Ag), 139.64 (C), 131.25 (CH), 127.86 (CH), 126.69 (CH), 122.54 (CH), 121.92 (CH), 59.57 (C), 56.93 (CH_2), 32.65 (CH_3). MS (ESI$^+$): m/z 458.2 [M − Br]$^+$. HRMS (ESI$^+$): Calcd for $C_{22}H_{30}N_4Ag$ [M − Br]$^+$: 457.1521. Found: 457.1514. Anal. Calcd for $C_{22}H_{30}AgBrN_4$: C, 49.09; H, 5.62; N, 10.41. Found: C, 50.60; H, 6.65; N, 10.10.†

Ag(NHC)Br (7)

3 (1.00 g, 2.00 mmol) was added to DCM (14 mL) giving a white suspension. To the suspension was added MeOH (2 mL) to give a clear solution to which was added Ag_2O (692 mg, 3.00 mmol) and 3 Å molecular sieves. The mixture was stirred for 24 hours in the dark to give a light brown precipitate (AgBr). The mixture was filtered through Celite and the solvent removed from the filtrate *in vacuo* to give a yellow oil. This was triturated with Et_2O to give a white solid. Yield: 712 mg (67%). ^{1}H NMR (d_4-MeOD, 500 MHz) δ: 7.14 (d, ^3J = 7.6 Hz, 4H, ArH), 7.09 (s, 2H, CH), 7.09 (s, 2H, CH), 7.06 (t, ^3J = 7.6 Hz, 2H, ArH), 7.06 (s, 2H, ArH), 5.18 (d, ^2J = 16.2 Hz, 4H, CH_2), 5.18 (d, ^2J = 16.2 Hz, 4H, CH_2). ^{13}C NMR (d_4-MeOD, 75 MHz) δ: 183.57 (dd, $^1J_{C\text{-}107\text{-}Ag}$ = 179 Hz, $^1J_{C\text{-}109\text{-}Ag}$ = 207 Hz), 139.48 (C), 130.66 (CH), 128.02 (CH), 124.57 (CH), 124.50 (CH), 122.80 (CH), 55.56 (CH_2). MS (ESI$^+$): *m/z* 448.1 [M − Br]$^+$. HRMS (ESI$^+$): Calcd for $C_{22}H_{20}N_4Ag$ [M − Br]$^+$: 447.0739. Found: 447.0714. Anal. Calcd for $C_{22}H_{20}AgBrN_4$: C, 50.03; H, 3.82; N, 10.61. Found: C, 50.65; H, 4.50; N, 9.95.†

$Ag(NHC)_2AgBr_2$ (8)

4 (545 mg, 2.15 mmol) was dissolved in DCM (22 mL) and Ag_2O (249 mg, 1.08 mmol) was added. The mixture was stirred for 18 hours in the dark. The mixture was filtered through Celite and the solvent removed from the filtrate *in vacuo* to give an oil. This was triturated with Et_2O to give a white solid. Yield: 0.502 g (65%). ^{1}H NMR (d_6-DMSO, 300 MHz) δ: 7.54 (d, ^3J = 1.73 Hz, 2H, CH), 7.45 (d, ^3J = 1.73 Hz, 2H, CH), 7.38–7.27 (m, 10H, ArH), 5.31 (s, 4H, CH_2), 3.77 (s, 6H, CH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ: Ag–C not observed, 137.68 (C), 129.10 (CH), 128.32 (CH), 127.95 (CH), 123.61 (CH), 122.52 (CH), 54.35 (CH_2), 38.51 (CH_3). MS (ESI$^+$): *m/z* 452.1 [M − Br]$^+$. HRMS (ESI$^+$): Calcd for $C_{22}H_{24}N_4Ag$ [M − Br]$^+$: 451.1052. Found: 451.1045. Anal. Calcd for $C_{22}H_{24}AgBrN_4 \cdot AgBr$: C, 36.70; H, 3.36; N, 7.78. Found: C, 37.85; H, 3.45; N, 7.95.†

Cytotoxicity studies

In vitro cell tests were performed at the Institute of Cancer Therapeutics, Bradford, on the MCF7 (human adenocarcinoma of the breast) and DLD1 (human adenocarcinoma of the colon) cell lines. Cells were incubated in 96-well plates, at 2×10^3 cells per well in 200 μL of growth media (RPMI 1640 supplemented with 10% foetal calf serum, sodium pyruvate (1 mM) and L-glutamine (2 mM)). Cells were incubated for 24 hours at 37 °C in an atmosphere of 5% CO_2 prior to drug exposure. Silver compounds, imidazolium salts and cisplatin were dissolved in dimethylsulphoxide at a concentration of 25 mM and diluted with medium to obtain drug solutions ranging from 25 to 0.049 μM. The final dimethylsulphoxide concentration was 0.1% (v/v) which is non-toxic to cells. Drug solutions were applied to cells and incubated for 6 days at 37 °C in an atmosphere of 5% CO_2. The solutions were removed from the wells and fresh medium added to each well along with 20 μL MTT (5 mg mL^{-1}), and incubated for 4 hours at 37 °C in an atmosphere of 5% CO_2. The solutions were removed and 150 μL dimethylsulphoxide was added to each well to dissolve the purple formazan crystals. A plate reader was used to measure the absorbance at 540 nm. Lanes containing medium only, and cells in medium only (no drug), were used as blanks for the spectrophotometer and 100% cell survival respectively. Cell survival was determined as the absorbance of treated cells divided by the absorbance of controls and expressed as a percentage. The concentration required to kill 50% of cells (IC_{50}) was determined from plots of % survival against drug concentration. Each experiment was repeated 3 times and a mean value obtained. In the cases where an IC_{50} value was not obtained (AgBr, $AgBF_4$, **1a**, **2a**) experiments were repeated using a higher concentration of drug up to a maximum of 100 μM. Response of MCF7 and DLD1 cell lines to cisplatin, silver compounds and imidazolium salts are presented in the table below as IC_{50} (μM) ± SD for three independent experiments.

Notes and references

†Elemental analytical data gives carbon content slightly higher than expected for all the complexes. NMR spectroscopy and mass spectrometry data do not indicate impurities, and a higher than expected carbon value is clearly not a result of excess silver bromide The likely cause of this is therefore a small amount of halide exchange of bromide for chloride, with chloride ions being provided by dichloromethane during the reactions.

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