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Silver–*N*-Heterocyclic Carbene Complexes: Synthesis, Characterization, and Antimicrobial Properties

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Six new silver complexes containing symmetrical *N*-heterocyclic carbene (NHC) ligands were synthesized by the reaction of azolium salts with Ag_2O in CH_2Cl_2. These complexes were tested against Gram-negative bacterial strains (*Escherichia coli* and *Pseudomonas aeruginosa*), Gram-positive bacterial strains (*Enterococcus faecalis* and *Staphylococcus aureus*), and fungal strains (*Candida albicans* and *Candida tropicalis*), and all tested complexes showed good activity against the different microorganisms.

Keywords: *N*-Heterocyclic carbene; Azolium salts; Silver–*N*-heterocyclic carbene complexes; Antimicrobial activity.

INTRODUCTION

N-Heterocyclic carbenes (NHCs) are neutral two-electron donors and are known to be strong Lewis bases and excellent nucleophiles that bind metals better than phosphines.[1,2] NHCs have been widely studied for their intriguing structural properties. These properties make these ligands desirable for a range of catalytic applications. NHCs have been employed widely as very important ligands in many applications.[3–8] Transition-metal complexes of NHCs, which serve as catalysts for a variety of useful synthetic reactions in organometallic chemistry and homogeneous catalysis, have attracted much attention in recent years.[9–17]

Over the last few years, transition-metal complexes of NHCs have gained real practical importance as antimitochondrial, antimicrobial, and anticancer agents for medicinal applications.[18–26] Silver–NHC complexes are the most studied metal–NHC complexes because of their easy preparation. Although many silver–NHC complexes have been reported, their catalytic properties have rarely been investigated. Therefore, silver–NHC complexes have been used as bioactive compounds in bioorganometallic applications.[27–30]

Most of the biomedical studies on silver–NHC complexes have been conducted with regard to their antimicrobial properties.[31–36] Although the cytotoxic effects of silver compounds against bacteria have long been established, the mechanisms of action are not completely understood. Sporadic studies of the cell toxicity mechanisms of silver compounds suggest that silver ions kill organisms through a variety of ways.[37–44] In this area, many articles have been recently published on the synthesis and applications of silver–NHC complexes. Recently we reported the bioorganometallic studies by silver and gold complexes of imidazolin-2-ylidene and benzimidazol-2-ylidene ligands for antimicrobial applications.[45–49]

Here we describe the synthesis, characterization, and antimicrobial applications of the new silver complexes containing symmetrical NHC ligands (**3a**,**b** and **4a–d**). The structures of all silver–NHC complexes were characterized by elemental analysis as well as by ^{1}H-NMR, ^{13}C-NMR, and IR spectroscopic techniques. The antimicrobial activities of these complexes were tested against Gram-negative bacteria, Gram-positive bacteria, and fungi. We show that these new silver–NHC complexes are efficient antimicrobial agents against different microorganism.

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RESULTS AND DISCUSSION

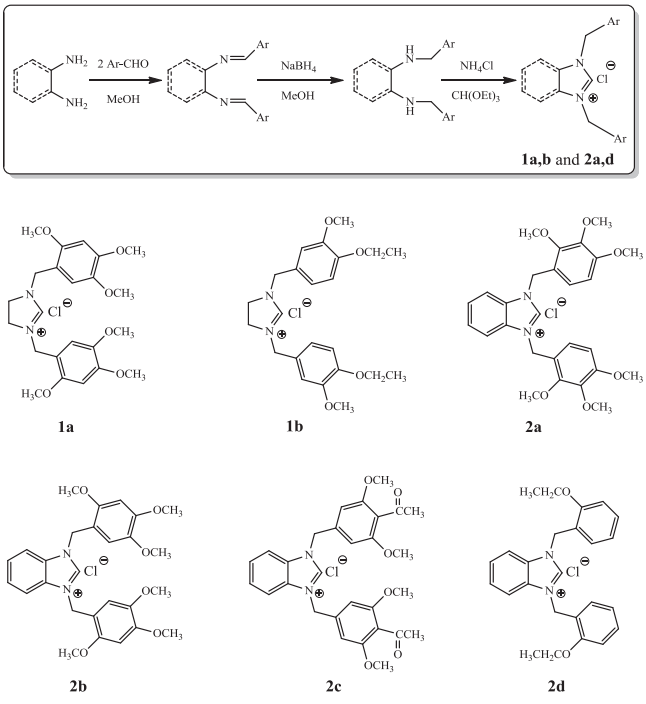
Synthesis of the azolium salts

The synthesized symmetrical NHC salts (**1a**,**b** and **2a–d**) in this study have already been reported in the literature.[50,51] These salts were prepared according to the general reaction pathway shown in Scheme 1. The azolium salts were air- and moisture-stable both in the solid state and in solution. The structures of the salts were determined by their characteristic spectroscopic data and elemental analyses. The results are consistent with those in the literature.[50,51]

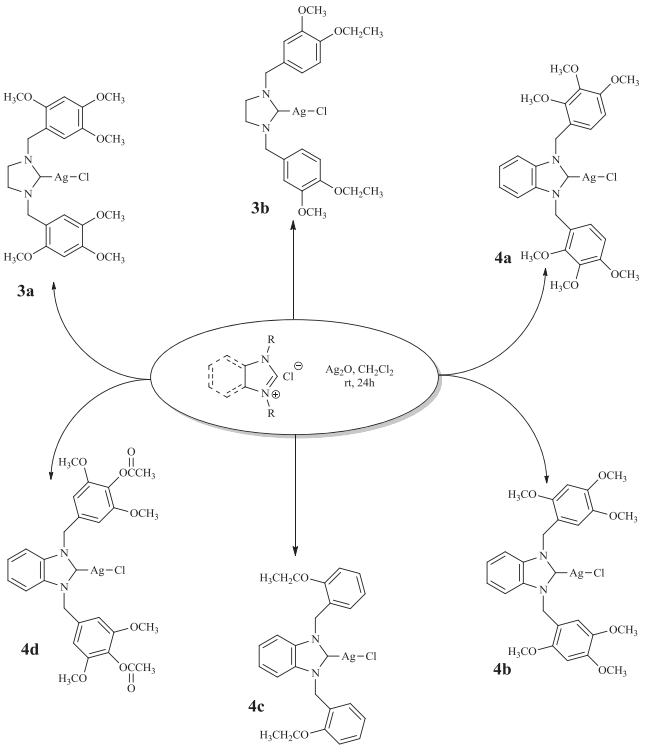
Synthesis of the silver–NHC complexes

Silver–NHC complexes are readily prepared from azolium salts and Ag_2O, Ag_2CO_3, or Ag(OAc) and contain relatively strong silver–carbon bonds. In this study, silver–NHC complexes (**3a**,**b** and **4a–d**) were prepared by treating the azolium salts with Ag_2O in dry CH_2Cl_2 at room temperature for 24 h (Scheme 2). All the silver–NHC complexes are air-stable. They are soluble in organic solvents such as acetone, dichloromethane, chloroform, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), ethanol, and acetonitrile.

The structures of the silver–NHCs were determined by their characteristic spectroscopic data and elemental analyses. The characteristic peak of the Ag–carbene resonance for the compound **4b** displays a singlet at 178.6 ppm in the ^{13}C-NMR spectra. In the **4a**, **4c**, and **4d** complexes, the resonances for Ag–carbene were not observed, which has also been mentioned in the literature and given as a reason for the fluxional behavior of the NHC complexes.[52–54] Silver–NHC complexes exhibit a characteristic $\nu_{(CN)}$ band at 1440, 1417, 1466, 1451, 1448, and 1463 cm^{-1}, respectively, for **3a**,**b** and **4a–d**.



Scheme 1. Synthesis of imidazolidinium (**1a**,**b**) and benzimidazolium (**2a–d**) salts.



Scheme 2. Synthesis of imidazolidin-2-ylidene (**3a**,**b**) and benzimidazol-2-ylidene (**4a–d**) silver–NHC complexes.

Antimicrobial applications of the silver–NHC complexes

Silver–NHC complexes were initially tested against bacterial strains with ampicillin and ciprofloxacin as standard drugs. The minimum inhibitory concentrations (MICs) of the silver–NHC complexes against bacterial strains are summarized in Table 1. When tested against bacteria at concentrations of 200–50 μg/mL, the silver–NHC complexes showed antibacterial activity. It was found that all complexes showed high levels of activity against Gram-negative and Gram-positive bacteria. Complex **4c** was found to be effective at inhibiting the growth of all bacterial strains, with MIC values between

Table 1. MIC values of compounds (**3a,b** and **4a–d**) used against bacterial strains in antimicrobial test.

	MIC (μg/mL)			
	Gram-negative bacteria		Gram-positive bacteria	
Silver–NHC complex	*E. coli*	*P. aeruginosa*	*S. aureus*	*E. faecalis*
3a	200	200	200	200
3b	100	100	100	100
4a	100	100	100	100
4b	100	100	100	100
4c	100	100	50	50
4d	100	100	100	100
Ampicillin	3.12	–	3.12	1.56
Ciprofloxacin	1.56	3.12	0.39	0.78

50 and 100 μg/mL. These complexes were particularly effective against Gram-positive bacterial strains.

The silver–NHC complexes (**3a**,**b** and **4a–d**) were evaluated for their antifungal activity against *Candida albicans* and *Candida tropicalis* using fluconazole as the standard drug. The MICs of silver–NHC complexes against fungal strains are summarized in Table 2.

The tested silver–NHC complexes showed antifungal activity with a range of MICs between 12.5 and 100 μg/mL. The complexes **3b**, **4a**, and **4d** showed similar activities against both fungi, but the compound **4c** displayed high activity with an MIC of 12.5 μg/mL. These results show that silver–NHC complexes containing benzimidazol-2-ylidene (**4a–d**) are more efficient than those with imidazolidin-2-ylidene (**3a**,**b**).

EXPERIMENTAL

Materials and methods

All reactions were carried out under argon using standard Schlenk line techniques. The chemicals and solvents were purchased from Sigma-Aldrich Co. (Poole, Dorset, UK). Elemental analyses were performed at the İnönü University Scientific and Technological Research Center (İBTAM). Melting points were measured in open capillary tubes with an Electrothermal-9200 melting point apparatus. IR spectra were recorded as KBr pellets in the range 400–4000 cm^{-1} on an ATI Unicam 1000 spectrometer. ^{1}H-NMR and ^{13}C NMR spectra were recorded using a Varian As 300 Merkur spectrometer operating at 300 MHz (^{1}H-NMR) and at 75 MHz (^{13}C-NMR) in $CDCl_3$. The NMR studies were carried out in high-quality 5 mm NMR tubes. Chemical shifts (δ) are reported in ppm relative to $CDCl_3$. Coupling constants (*J*-values) are given in hertz. ^{1}H-NMR spectra are referenced to residual protiated solvents (δ = 7.26 ppm for $CDCl_3$), and ^{13}C chemical shifts are reported relative to deuterated solvents (δ = 77.16 ppm for $CDCl_3$).

Table 2. MIC values of compounds (**3a**,**b** and **4a–d**) used against fungal strains in antimicrobial test.

	MIC (μg/mL)	
Silver–NHC complex	*C. albicans*	*C. tropicalis*
3a	100	100
3b	50	50
4a	50	50
4b	100	100
4c	25	12.5
4d	50	50
Fluconazole	3.12	3.12

The MIC for each compound was investigated against standard bacterial strains: *Staphylococcus aureus* (ATCC 29213), *Enterococcus faecalis* (ATCC 29212), *Escherichia coli* (ATCC 25922), and *Pseudomonas aeruginosa* (ATCC 27853). These were obtained from American Type Culture Collection (Rockville, MD, USA). The fungal strains *C. albicans* (ATCC 10231) and *C. tropicalis* (ATCC 13803) were obtained from the Department of Microbiology, Faculty of Medicine, Ege University (Turkey). Bacterial strains were subcultured in Muller–Hinton broth (HiMedia Laboratories Pvt. Ltd, Mumbai, India) and fungal strains in RPMI 1640 broth (Sigma-Aldrich Chemie GmbH, Taufkirchen, Germany).

General procedure for the preparation of azolium salts

Treatment of the diamine (ethylenediamine or 1,2-phenylenediamine) (10.0 mmol) with aromatic aldehyde

(20.0 mmol) in methanol (25 mL) at r.t. led to the formation of the corresponding diimines. The diimine was collected as a white solid. Next, it was filtered through a filter paper and recrystallized from an alcohol/ether mixture (1:2 ratio). The diimine (10.0 mmol) was subsequently reduced by $NaBH_4$ (30.0 mmol) in methanol (30 mL). The solution was then treated with 1 N HCl solution, and the organic phase was extracted with CH_2Cl_2 (3 × 30 mL). After drying over $MgSO_4$ and evaporation, the diamine was isolated as a solid and then treated in a large excess of triethylorthoformate (50 mL) in the presence of NH_4Cl (10.0 mmol) at 110°C in a distillation apparatus until the removal of ethanol ceased. Upon cooling to r.t., a colorless solid precipitated, which was collected by filtration and dried under vacuum. The crude product was recrystallized from absolute ethanol to give colorless needles, and the solid was washed with diethyl ether (2 × 10 mL) and dried under vacuum.

These known compounds were synthesized and characterized by ^{1}H-NMR, ^{13}C-NMR, IR, and elemental analyses. The results of the analyses were consistent with those in the literature.[50,51]

General procedure for the preparation of the silver–NHC complexes

Silver–NHC complexes (**3a**,**b** and **4a–d**) were prepared by the treatment of the benzimidazolium or imidazolidinium salts (1.0 mmol) with Ag_2O (0.5 mmol) and activated 4 Å molecular sieves in dry CH_2Cl_2 (20 mL) at r.t. for 24 h. The reaction mixture was filtered through celite, and the solvent was removed under reduced pressure. The crude product was recrystallized from dichloromethane/diethylether (1:2 ratio).

1,3-Bis(2,4,5-trimethoxybenzyl)imidazolidin-2-ylidene silver(I) chloride (3a): Yield: 0.49 g, 82%, mp: 141–142°C, IR (cm^{-1}) $\nu_{(CN)}$: 1440. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.49 (t, J = 5.8 Hz, 4H, NCH_2CH_2N); 3.84, 3.85 and 3.89 (s, 18H, $NCH_2C_6H_2((OCH_3)_3)$-2,4,5); 4.62 (s, 4H, NCH_2-$C_6H_2((OCH_3)_3)$-2,4,5); 6.52 and 6.83 (s, 4H, $NCH_2C_6H_2$-$((OCH_3)_3)$-2,4,5). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 56.2, 56.5, and 57.0 ($NCH_2C_6H_2((OCH_3)_3)$-2,4,5); 49.6 (N$CH_2C_6H_2$-$((OCH_3)_3)$-2,4,5); 48.7 (NCH_2CH_2N); 143.0, 143.4, 148.7, 150.0, 152.2, 152.3 ($NCH_2C_6H_2((OCH_3)_3)$-2,4,5). Ag–$C_{carbene}$: not observed. Anal. Calcd. for $C_{23}H_{30}O_6N_2AgCl$ (%): C, 48.14; H, 5.27; N, 4.88. Found: C, 48.16; H, 5.29; N, 4.90.

1,3-Bis(4-ethoxy-3-methoxybenzyl)imidazolidin-2-yli- denesilver(I) chloride (3b): Yield: 0.55 g, 88%, mp: 140–141°C, IR (cm^{-1}) $\nu_{(CN)}$: 1417. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.89 (s, 6H, $NCH_2C_6H_3((OCH_3)_3$-3-(OCH_2CH_3)-4); 4.07 (q, J = 5.0 Hz, 4H, $NCH_2C_6H_3((OCH_3)_3$-3-(OCH_2CH_3)-4); 1.47 (t, 6H, J = 5.1 Hz, $NCH_2C_6H_3((OCH_3)_3$-3-(OCH_2CH_3)-4); 4.65 (s, 4H, $NCH_2C_6H_3((OCH_3)_3$-3-(OCH_2CH_3)-4); 3.49 (t, J = 5.8 Hz, 4H, NCH_2CH_2N). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 64.4 ($NCH_2C_6H_3((OCH_3)_3$-3-(OCH_2CH_3)-4); 56.2 ($NCH_2C_6H_3((OCH_3)_3$-3-(OCH_2CH_3)-4); 14.8 ($NCH_2C_6H_3$-$((OCH_3)_3$-3-(OCH_2CH_3)-4); 55.3 ($NCH_2C_6H_3((OCH_3)_3$-3-(OCH_2CH_3)-4); 48.4 (NCH_2CH_2N); 111.4, 112.7, 120.5, 127.3, 148.5, 149.5 ($NCH_2C_6H_3((OCH_3)_3$-3-(OCH_2CH_3)-4). Ag–$C_{carbene}$: not observed. Anal. Calcd. for $C_{23}H_{30}O_4N_2AgCl$ (%): C, 50.99; H, 5.58; N, 5.17. Found: C, 50.96; H, 5.55; N, 5.19.

1,3-Bis(2,3,4-trimethoxybenzyl)benzimidazol-2-ylide-nesilver(I) chloride (4a): Yield: 0.53 g, 88%, mp: 232–233°C, IR (cm^{-1}) $\nu_{(CN)}$: 1466. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.84, 3.86 and 3.87 (s, 18H, $NCH_2C_6H_2((OCH_3)_3)$-2,3,4); 5.54 (s, 4H, $NCH_2C_6H_2((OCH_3)_3)$-2,3,4); 6.60–6.62 and 6.92–6.94 (d, 4H, J = 8.7 Hz, $NCH_2C_6H_2((OCH_3)_3)$-2,3,4); 7.28–7.55 (m, 4H, NC_6H_4N). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 56.0, 60.8 and 61.8 ($NCH_2C_6H_2((OCH_3)_3)$-2,3,4); 48.3 ($NCH_2C_6H_2((OCH_3)_3)$-2,3,4); 107.4, 112.1, 120.6, 123.7, 124.1, 133.9, 142.1, 151.2, 154.3 ($NCH_2C_6H_2((OCH_3)_3)$-2,3,4) and (NC_6H_4N). Ag–$C_{carbene}$: not observed. Anal. Calcd. for $C_{27}H_{30}O_6N_2AgCl$ (%): C, 52.15; H, 4.86; N, 4.50. Found: C, 52.17; H, 4.89; N, 4.53.

1,3-Bis(2,4,5-trimethoxybenzyl)benzimidazol-2-ylide-nesilver(I) chloride (4b): Yield: 0.49 g, 81%, mp: 155–156°C, IR (cm^{-1}) $\nu_{(CN)}$: 1451. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.86, 3.87, and 3.88 (s, 18H, $NCH_2C_6H_2((OCH_3)_3)$-2,4,5); 5.55 (s, 4H, $NCH_2C_6H_2((OCH_3)_3)$-2,4,5); 6.52 (s, 4H, $NCH_2C_6H_2((OCH_3)_3)$-2,4,5); 7.28–7.57 (m, 4H, NC_6H_4N). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 56.1, 56.2, and 56.8 ($NCH_2C_6H_2((OCH_3)_3)$-2,4,5); 47.8 ($NCH_2C_6H_2((OCH_3)_3)$-2,4,5); 97.2, 112.1, 113.6, 114.7, 123.7, 134.0, 143.2, 150.1, 151.5 ($NCH_2C_6H_2((OCH_3)_3)$-2,4,5) and (NC_6H_4N); Ag–$C_{carbene}$: 178.6. Anal. Calcd. for $C_{27}H_{30}O_6N_2$-AgCl (%): C, 52.15; H, 4.86; N, 4.50. Found: C, 52.20; H, 4.90; N, 4.55.

1,3-Bis(2-ethoxybenzyl)benzimidazol-2-ylidene silver(I) chloride (4c): Yield: 0.58 g, 92%, mp: 216–217°C, IR (cm^{-1}) $\nu_{(CN)}$: 1448. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.44 (t, 6H, J = 6.9 Hz, $NCH_2C_6H_4((OCH_2CH_3)$-2); 4.12 (q, 4H, J = 6.6 Hz, $NCH_2C_6H_4((OCH_2CH_3)$-2); 5.65 (s, 4H, $NCH_2C_6H_4$-((OCH$_2$CH$_3$)-2); 7.26–7.43 (m, 12H, NC_6H_4N and $NCH_2C_6H_4((OCH_2CH_3)$-2). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 15.0 ($NCH_2C_6H_4$-((OCH$_2$CH$_3$)-2); 63.7 ($NCH_2C_6H_4((OCH_2CH_3)$-2); 49.6 ($NCH_2C_6H_4((OCH_2$ CH$_3$)-2); 111.4, 112.2, 120.6, 123.2, 123.9, 128.5, 129.7, 134.0, 156.2 (NC_6H_4N and $NCH_2C_6H_4((OCH_2CH_3)$-2); Ag–$C_{carbene}$: not observed. Anal. Calcd. for $C_{25}H_{26}O_2N_2$-AgCl (%): C, 56.67; H, 4.95; N, 5.29. Found: C, 56.70; H, 4.93; N, 4.31.

1,3-Bis(4-acetoxy-3,5-dimethoxybenzyl)benzimidazol-2-ylidenesilver(I) chloride (4d): Yield: 0.48 g, 81%, mp: 172–173°C, IR (cm^{-1}) $\nu_{(CN)}$: 1463. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 6H, $NCH_2C_6H_2((OCO$ $CH_3)$-4-$(OCH_3)_2$-3,5); 3.76 (s, 12H, $NCH_2C_6H_2((OC$ $OCH_3)$-4-$(OCH_3)_2$-3,5); 5.56 (s, 4H, $NCH_2C_6H_2((OCO$ $CH_3)$-4-$(OCH_3)_2$-3,5); 6.64 (s, 4H, $NCH_2C_6H_2((OCO$ $CH_3)$-4-$(OCH_3)_2$-3,5); 7.28–7.49 (m, 4H, NC_6H_4N). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 20.5 ($NCH_2C_6H_2((OCO$ $CH_3)$-4-$(OCH_3)_2$-3,5); 56.4 ($NCH_2C_6H_2$-((OCOCH$_3$)-4-$(OCH_3)_2$-3,5); 53.6 ($NCH_2C_6H_2((OCOCH_3)$-4-$(OCH_3)_2$-3,5); 168.6 ($NCH_2C_6H_2((OCOCH_3)$-4-$(OCH_3)_2$-3,5); 104.3, 112.0, 124.5, 128.7, 133.5, 133.9, 152.6 (NCH_2 $C_6H_2((OCOCH_3)$-4-$(OCH_3)_2$-3,5) and (NC_6H_4N). Ag–$C_{carbene}$: not observed. Anal. Calcd. for $C_{29}H_{30}O_8N_2$-AgCl (%): C, 51.38; H, 4.46; N, 4.13. Found: C, 51.41; H, 4.49; N, 4.16.

Antimicrobial activities of the silver–NHC complexes

The antimicrobial activities of the silver–NHC complexes were determined using the agar dilution procedure recommended by the Clinical and Laboratory Standards Institute.[55,56] The MICs for each compound were investigated, and the antimicrobial activity of silver–NHC complexes was tested against the standard bacterial strains *S. aureus* (ATCC 29213), *E. faecalis* ATCC (29212), *E. coli* (ATCC 25922), and *P. aeruginosa* (ATCC 27853) and the fungal strains *C. albicans* (ATCC 10231) and *C. tropicalis* (ATCC 13803). Bacterial strains were subcultured in Mueller–Hinton broth (HiMedia Laboratories Pvt. Ltd., Mumbai, India), and the fungal strains were also cultured in RPMI 1640 broth (Sigma-Aldrich Chemie GmbH, Taufkirchen, Germany). Their turbidities matched that of a McFarland no. 0.5 turbidity standard.[57] The stock solutions of all compounds were prepared in DMSO. All dilutions were done with distilled water. The concentrations of the tested compounds were 800, 400, 200, 100, 50, 25, and 12.5 μg/mL. Ampicillin and ciprofloxacin were used as standard antimicrobial drugs, while fluconazole was used as a standard antifungal drug, with known MIC values. A loopful (0.01 mL) of the standardized inoculum of the bacteria and yeasts (10^6 CFU/mL) was spread over the surfaces of agar plates. All inoculated plates were incubated at 35°C, and the results were evaluated after 16–20 h of incubation for bacteria and 48 h for yeasts. The lowest concentrations of the compounds that prevented visible growth were taken as the MICs.

CONCLUSIONS

A series of new silver complexes containing symmetrical NHC ligands were synthesized and characterized by spectroscopic and analytical techniques. Antimicrobial activities of these new silver complexes were reported. The silver–NHC complex **4c** showed better antimicrobial activity against the bacteria and fungi than other complexes, even at the much lower concentrations. The obtained results are helpful for the synthesis of silver–NHC complexes possessing high antimicrobial activity.

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Supporting information

^{1}H-NMR and ^{13}C-NMR of silver–NHC complexes.

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