Research Article

Antimicrobial Studies of *N*-Heterocyclic Carbene Silver Complexes Containing Benzimidazol-2-ylidene Ligand

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Seven novel 4-vinylbenzyl substituted *N*-heterocyclic carbene (NHC) silver complexes were synthesized from different benzimidazolium salts and silver (I) oxide in dichloromethane at room temperature. These new 4-vinylbenzyl substituted NHC silver complexes were characterized by spectroscopic (NMR, IR) and elemental analysis techniques. Using the agar dilution procedure, the antimicrobial activities of these synthesized new compounds were investigated against Gram (+)/(−) bacterial and fungal strains. These NHC silver complexes showed effective activities against *Escherichia coli*, *Pseudomonas aeruginosa* (Gram-negative bacterial strains), *Enterococcus faecalis*, *Staphylococcus aureus* (Gram-positive bacterial strains), and *Candida tropicalis* and *Candida albicans* (fungal strains).

1. Introduction

N-Heterocyclic carbenes (NHCs) are cyclic constructions which are generally derived from deprotonation of salts of ligands such as imidazolium, benzimidazolium, diazepinium, pyrimidium. Since isolation of first free carbene in 1991 [1], NHCs which are strong σ donor, low π acceptor ability, and transition metal carbene complexes obtained by using carbene precursors have had a wide application area in organometallic chemistry [2–4]. Among various transition metal carbene complexes, NHC silver complexes have played a significant role in the development of *N*-heterocyclic carbene chemistry because of their structural diversity and their wide spread successful application as effective carbene transfer reagents in transmetallation reactions to make other NHC metal complexes, like nickel [5], copper [6], platinum [6], iridium [6], ruthenium [5], rhodium [6, 7], palladium [6–10], and gold [6, 10, 11] carbene complexes. Also, the prominent biological activity of many NHC silver complexes as antimicrobial and anticancer agents has been confirmed [12–18]. Therefore, many studies on silver complexes have been made by different research groups for many years [19–24].

Herein, we report the synthesis, characterization, and antibacterial and antifungal activity studies of seven novel symmetrically and unsymmetrically *p*-vinylbenzyl-substituted NHC silver complexes which were prepared starting from 1-(4-vinylbenzyl)-3-alkyl benzimidazolium salts and silver (I) oxide in dichloromethane. The characterization of the NHC silver complexes is consistent with the proposed formula. Using the agar dilution procedure, the antimicrobial activities of these compounds are investigated against Gram (+)/(−) bacterial and fungal strains. NHC silver complexes in the antimicrobial study were observed to have higher activity against fungal strains than against Gram-positive and Gram-negative bacterial strains.

2. Experimental

2.1. Materials and Methods. In this study, the synthesis of silver (I) complexes was pursued in a dark medium under an inert atmosphere. All solvents and reagents were commercially bought. The solvents used in the synthesis, diethyl ether over Na, and dichloromethane over P_4O_{10} were

distilled before they were used. The ^1H and ^{13}C NMR spectra were measured on a Bruker AC300P FT spectrometer with dimethylsulfoxide [d_6] as solvent at 300.13 MHz (^1H) and 75.47 MHz (^{13}C) at room temperature. All the chemical shifts (δ) were reported in ppm and referenced tetramethylsilane. Melting points (m.p.) were measured in open capillary tubes with an Electrothermal-9200 melting point apparatus. Elemental analyses (H, C, and N) were investigated by the TUBITAK analysis center.

Escherichia coli (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), *Enterococcus faecalis* (ATCC 29212), and *Staphylococcus aureus* (ATCC 29213) as bacterial strains were purchased from the American Type Culture Collection (Rockville, MD, USA). *Candida tropicalis* and *Candida albicans* as fungal strains were obtained from the Faculty of Medicine, Department of Microbiology, Ege University (Turkey). Bacterial strains were subcultured on Muller Hinton Broth (HiMedia Laboratories Pvt. Ltd., Mumbai, India) and fungal strains were also subcultured on RPMI 1640 Broth (Sigma-Aldrich Chemie GmbH Taufkirchen, Germany).

2.2. General Method for the Synthesis of 1-(4-Vinylbenzyl)-3-alkylbenzimidazol-2-ylidene Silver Complexes, **1a-g.** 1-(4-Vinylbenzyl)-3-alkylbenzimidazolium salts containing symmetrical and unsymmetrical groups were synthesized by reaction of 1-(4-vinylbenzyl)benzimidazole with various aryl halides in DMF according to the literature [25, 26]. Under an inert atmosphere, Ag_2O (0.5 mmol), 1-(4-vinylbenzyl)-3-alkyl benzimidazolium salt (1.0 mmol) and activated 4 Å molecular sieves were put in CH_2Cl_2 which was distilled prior to use over P_4O_{10} (20 mL) and were stirred in darkness at ambient temperature for one day. The Schlenk-type flask used was covered with aluminum foil to avoid exposure to light. The resulting solution was filtered through celite and the solvent was removed under reduced pressure. The crude product was washed with diethyl ether which was distilled prior to use over Na (3×10 mL) and was crystallized from dichloromethane/diethyl ether at room temperature.

2.2.1. Iodo [1-(4-Vinylbenzyl)-3-methyl benzimidazol-2-ylidene]silver(I), **1a.** 1-(4-Vinylbenzyl)-3-methyl benzimidazolium salt (1.0 mmol) and Ag_2O (0.5 mmol) in dichloromethane (20 mL) were put in a Schlenk-type flask which was covered with aluminum foil. The resulting solution was stirred for 24 h. Then, it was filtered through celite and the solvent was removed under reduced pressure. The crude product was washed with diethyl ether and was crystallized from dichloromethane/diethyl ether at room temperature. Yield: 81%, m.p.: 146–148°C, FT-IR $\nu_{(\text{CN})}$: 1445.13 cm^{-1} . ^1H NMR (300.13 MHz, DMSO-d_6), δ : 4.02 (s, 3 H, CH_3); 5.23 and 5.81 (dd, 2 H, $\text{CH}_2\text{C}_6\text{H}_4\text{CH}=\text{CH}_2$, J : 9.6 Hz); 5.69 (s, 2 H, $\text{CH}_2\text{C}_6\text{H}_4\text{CH}=\text{CH}_2$); 6.65 (dd, 1 H, $\text{CH}_2\text{C}_6\text{H}_4\text{CH}=\text{CH}_2$, J : 11.4 Hz); 7.21–7.77 (m, 8 H, Ar-H). ^{13}C NMR (75.47 MHz, DMSO-d_6), δ : 36.1 (CH_3); 52.0 ($\text{CH}_2\text{C}_6\text{H}_4\text{CH}=\text{CH}_2$); 112.5, 115.3, 115.6, 124.4, 124.5, 125.8, 126.3, 126.9, 127.4, 128.2, 129.6, 133.6, 134.6, 136.4, 136.6, 137.2, 137.4 and 138.0 (Ar-C and $\text{CH}=\text{CH}_2$); 189.0 (C-Ag). Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{AgI}$

(481.95 g/mol): C, 42.27; H, 3.34; N, 5.80. Found: C, 42.35; H, 3.29; N, 5.76%.

2.2.2. Chloro[1-(4-vinylbenzyl)-3-benzyl benzimidazol-2-ylidene]silver(I), **1b.** With a similar method to that used for compound **1a**, compound **1b** was prepared from 1-(4-vinylbenzyl)-3-benzyl benzimidazolium salt (1.0 mmol) and Ag_2O (0.5 mmol) in dichloromethane (20 mL). Yield: 76%, m.p.: 127–129°C, FT-IR $\nu_{(\text{CN})}$: 1443.45 cm^{-1} . ^1H NMR (300.13 MHz, DMSO-d_6), δ : 5.29 and 5.77 (dd, 2 H, $\text{CH}_2\text{C}_6\text{H}_4\text{CH}=\text{CH}_2$, J : 8.1 Hz); 5.71 (s, 2 H, $\text{CH}_2\text{C}_6\text{H}_4\text{CH}=\text{CH}_2$); 5.67 (s, 2 H, $\text{CH}_2\text{C}_6\text{H}_5$); 6.65 (dd, 1 H, $\text{CH}_2\text{C}_6\text{H}_4\text{CH}=\text{CH}_2$, J : 8.4 Hz); 7.16–7.43 (m, 13 H, Ar-H). ^{13}C NMR (75.47 MHz, DMSO-d_6), δ : 53.4 ($\text{CH}_2\text{C}_6\text{H}_5$); 53.6 ($\text{CH}_2\text{C}_6\text{H}_4\text{CH}=\text{CH}_2$); 112.2, 114.8, 115.1, 124.5, 125.0, 126.3, 126.9, 127.2, 127.5, 128.6, 129.2, 129.4, 133.9, 134.2, 134.8, 135.2, 136.0, 136.1, 137.9 and 138.5 (Ar-C and $\text{CH}=\text{CH}_2$). Anal. Calcd. for $\text{C}_{23}\text{H}_{20}\text{N}_2\text{AgCl}$ (466.04 g/mol): C, 59.06; H, 4.31; N, 5.99. Found: C, 59.01; H, 4.23; N, 5.97%.

2.2.3. Chloro[1-(4-vinylbenzyl)-3-(2-methylbenzyl)benzimidazol-2-ylidene]silver(I), **1c.** With a similar method to that used for compound **1a**, compound **1c** was prepared from 1-(4-vinylbenzyl)-3-(2-methylbenzyl)benzimidazolium salt (1.0 mmol) and Ag_2O (0.5 mmol) in dichloromethane (20 mL). Yield: 86%, m.p.: 210–211°C, FT-IR $\nu_{(\text{CN})}$: 1444.25 cm^{-1} . ^1H NMR (300.13 MHz, DMSO-d_6), δ : 2.42 (s, 3 H, $\text{CH}_2\text{C}_6\text{H}_4\text{CH}_3$); 5.28 and 5.78 (dd, 2 H, $\text{CH}_2\text{C}_6\text{H}_4\text{CH}=\text{CH}_2$, J : 11.1 Hz); 5.66 [s, 2 H, $\text{CH}_2\text{C}_6\text{H}(\text{CH}_3)_4$]; 5.73 (s, 2 H, $\text{CH}_2\text{C}_6\text{H}_4\text{CH}=\text{CH}_2$); 6.67 (dd, 1 H, $\text{CH}_2\text{C}_6\text{H}_4\text{CH}=\text{CH}_2$, J : 10.8 Hz); 7.01–7.53 (m, 12 H, Ar-H). ^{13}C NMR (75.47 MHz, DMSO-d_6), δ : 19.7 ($\text{CH}_2\text{C}_6\text{H}_4\text{CH}_3$); 51.6 ($\text{CH}_2\text{C}_6\text{HCH}_3$); 53.5 ($\text{CH}_2\text{C}_6\text{H}_4\text{CH}=\text{CH}_2$); 112.2, 114.8, 124.5, 126.5, 126.7, 126.9, 127.4, 128.5, 131.0, 132.6, 133.8, 134.2, 135.5, 136.0, 137.9 and 143.4 (Ar-C and $\text{CH}=\text{CH}_2$). Anal. Calcd. for $\text{C}_{24}\text{H}_{22}\text{N}_2\text{AgCl}$ (480.06 g/mol): C, 59.83; H, 4.60; N, 5.81. Found: C, 59.71; H, 4.69; N, 5.79%.

2.2.4. Chloro[1-(4-vinylbenzyl)-3-(4-methylbenzyl)benzimidazol-2-ylidene]silver(I), **1d.** With a similar method to that used for compound **1a**, compound **1d** was prepared from 1-(4-vinylbenzyl)-3-(4-methylbenzyl)benzimidazolium salt (1.0 mmol) and Ag_2O (0.5 mmol) in dichloromethane (20 mL). Yield: 83%, m.p.: 216–217°C, FT-IR $\nu_{(\text{CN})}$: 1439.17 cm^{-1} . ^1H NMR (300.13 MHz, DMSO-d_6), δ : 2.24 (s, 3 H, $\text{CH}_2\text{C}_6\text{H}_4\text{CH}_3$); 5.25 and 5.83 (dd, 2 H, $\text{CH}_2\text{C}_6\text{H}_4\text{CH}=\text{CH}_2$, J : 10.8 Hz); 5.71 (s, 2 H, $\text{CH}_2\text{C}_6\text{H}_4\text{CH}_3$); 5.75 (s, 2 H, $\text{CH}_2\text{C}_6\text{H}_4\text{CH}=\text{CH}_2$); 6.69 (dd, 1 H, $\text{CH}_2\text{C}_6\text{H}_4\text{CH}=\text{CH}_2$, J : 7.2 Hz); 7.01–8.18 (m, 12 H, Ar-H). ^{13}C NMR (75.47 MHz, DMSO-d_6), δ : 21.13 ($\text{CH}_2\text{C}_6\text{H}_4\text{CH}_3$); 52.2 ($\text{CH}_2\text{C}_6\text{H}_4\text{CH}_3$); 52.1 ($\text{CH}_2\text{C}_6\text{H}_4\text{CH}=\text{CH}_2$); 114.8, 136.0, 112.9, 124.5, 126.5, 126.7, 126.9, 128.5, 131.0, 132.6, 133.8, 134.2, 135.5 and 137.9 (Ar-C and $\text{CH}=\text{CH}_2$). Anal. Calcd. for $\text{C}_{24}\text{H}_{22}\text{N}_2\text{AgCl}$ (480.06 g/mol): C, 59.83; H, 4.60; N, 5.81. Found: C, 59.95; H, 4.66; N, 5.84%.

2.2.5. Chloro[1-(4-vinylbenzyl)-3-(2,4,6-trimethylbenzyl)benzimidazol-2-ylidene]silver(I), **1e.** With a similar method to that used for compound **1a**, compound **1e** was prepared from 1-(4-vinylbenzyl)-3-(2,4,6-trimethylbenzyl)benzimidazolium salt (1.0 mmol) and Ag₂O (0.5 mmol) in dichloromethane (20 mL). Yield: 75%, m.p.: 230–231°C, FT-IR $\nu_{\text{(CN)}}$: 1403.38 cm⁻¹. ¹H NMR (300.13 MHz, DMSO-d₆), δ : 2.19 and 2.26 [s, 9 H, CH₂C₆H₂(CH₃)₃]; 5.25 and 5.82 (dd, 2 H, CH₂C₆H₄CH=CH₂, *J*: 10.8 Hz); 5.57 [s, 2 H, CH₂C₆H₂(CH₃)₃]; 5.62 (s, 2 H, CH₂C₆H₄CH=CH₂); 6.65 (dd, 1 H, CH₂C₆H₄CH=CH₂, *J*: 10.8 Hz); 6.93–8.10 (m, 10 H, Ar-H). ¹³C NMR (75.47 MHz, DMSO-d₆), δ : 19.8 and 21.1 [CH₂C₆H₂(CH₃)₃]; 52.1 [CH₂C₆H₂(CH₃)₃]; 52.2 (CH₂C₆H₄CH=CH₂); 112.9, 114.8, 124.5, 126.5, 126.7, 126.9, 128.5, 131.0, 132.6, 133.8, 134.2, 135.5, 136.0 and 137.9 (Ar-C ve CH=CH₂). Anal. Calcd. for C₂₆H₂₆N₂AgCl (508.09 g/mol): C, 61.25; H, 5.14; N, 5.49. Found: C, 61.33; H, 5.09; N, 5.45%.

2.2.6. Chloro[1-(4-vinylbenzyl)-3-(2,3,5,6-tetramethylbenzyl)benzimidazol-2-ylidene]silver(I), **1f.** With a similar method to that used for compound **1a**, compound **1f** was prepared from 1-(4-vinylbenzyl)-3-(2,3,5,6-tetramethylbenzyl)benzimidazolium salt (1.0 mmol) and Ag₂O (0.5 mmol) in dichloromethane (20 mL). Yield: 73%, m.p.: 237–238°C, FT-IR $\nu_{\text{(CN)}}$: 1449.43 cm⁻¹. ¹H NMR (300.13 MHz, DMSO-d₆), δ : 2.10 and 2.19 [s, 12 H, CH₂C₆H(CH₃)₄]; 5.23 and 5.81 (dd, 2 H, CH₂C₆H₄CH=CH₂, *J*: 10.5 Hz); 5.60 [s, 2 H, CH₂C₆H(CH₃)₄]; 5.76 (s, 2 H, CH₂C₆H₄CH=CH₂); 6.66 (dd, 1 H, CH₂C₆H₄CH=CH₂, *J*: 10.5 Hz); 7.04–7.93 (m, 9 H, Ar-H). ¹³C NMR (75.47 MHz, DMSO-d₆), δ : 16.4 and 20.8 [CH₂C₆H(CH₃)₄]; 46.8 [CH₂C₆H(CH₃)₄]; 52.9 (CH₂C₆H₄CH=CH₂); 112.5, 112.9, 115.3, 124.6, 124.8, 126.9, 127.8, 131.8, 132.6, 133.3, 133.9, 134.7, 134.9, 136.2, 136.4 and 137.3 (Ar-C and CH=CH₂). Anal. Calcd. for C₂₇H₂₈N₂AgCl (522.11 g/mol): C, 61.91; H, 5.39; N, 5.35. Found: C, 61.82; H, 5.46; N, 5.28%.

2.2.7. Chloro[1,3-bis(4-vinylbenzyl)benzimidazol-2-ylidene]silver(I), **1g.** With a similar method to that used in compound **1a**, compound **1g** was prepared from 1,3-bis(4-vinylbenzyl)benzimidazolium salt (1.0 mmol) and Ag₂O (0.5 mmol) in dichloromethane (20 mL). Yield: 79%, m.p.: 249–250°C, FT-IR $\nu_{\text{(CN)}}$: 1440.26 cm⁻¹. ¹H NMR (300.13 MHz, DMSO-d₆), δ : 5.25 and 5.83 (dd, 4 H, CH₂C₆H₄CH=CH₂, *J*: 10.8 Hz); 5.76 (s, 4 H, CH₂C₆H₄CH=CH₂); 6.69 (dd, 2 H, CH₂C₆H₄CH=CH₂, *J*: 10.8 Hz); 7.13–7.75 (m, 12 H, Ar-H). ¹³C NMR (75.47 MHz, DMSO-d₆), δ : 52.2 (CH₂C₆H₄CH=CH₂); 112.9, 115.3, 124.7, 127.0, 127.8, 128.1, 129.8, 133.9, 136.3, 136.5 and 137.4 (Ar-C and CH=CH₂). Anal. Calcd. for C₂₅H₂₂N₂AgCl (492.06 g/mol): C, 60.81; H, 4.49; N, 5.67. Found: C, 60.71; H, 4.55; N, 5.65%.

2.3. Antimicrobial Activity. The antimicrobial activity studies of the new synthesized NHC silver complexes were investigated according to the recommended agar dilution procedure [27, 28]. The minimal inhibitory concentrations (MICs) for each silver (I) complex were tested against standard bacterial strains (*E. faecalis*, *S. aureus*, *P. aeruginosa*, and *E. coli*)

and fungal strains (*C. tropicalis* and *C. albicans*). Their turbidities matched that of a McFarland number 0.5 turbidity standard. The stock solutions of all silver complexes were prepared in dimethylsulfoxide. All dilutions were carried out using distilled water. The concentrations of the tested silver (I) complexes were 6.25, 12.5, 25, 50, 100, 200, 400, and 800 µg/mL. Fluconazole, ciprofloxacin, and ampicillin were used as the antifungal and antibacterial standard drugs. A loopful (0.01 mL) of the standardized inocula of the yeasts and bacteria (10⁶ CFUs/mL) was spread over the surface of agar plates. All the samples were inoculated after 16–20 h of incubation for bacteria and 48 h for yeasts. The lowest concentration of the NHC silver complexes that prevented visible growth was considered to be the MIC.

3. Results and Discussion

3.1. Synthesis and Characterization of N-Heterocyclic Carbene Silver Complexes, **1a–g.** Different 1-(4-vinylbenzyl)-3-alkyl benzimidazolium salts as carbene precursors were synthesized [25, 26]. The intended silver (I) complexes **1a–g** were obtained from the interaction of Ag₂O with benzimidazolium salts in CH₂Cl₂ at room temperature after 24 h as white solid crystals in 73–86% yields according to known methods (Scheme 1) [17, 24]. Their structures were characterized using spectroscopic and analytical techniques. The ¹H and ¹³C NMR spectra of these new complexes are consistent with the proposed formula. The spectra of these products in dimethylsulfoxide (DMSO-d₆) supported the formation of the silver complexes because of the loss of proton (NCHN) signal of the benzimidazolium salts. Compound **1a** exhibited characteristic a carbenic carbon peak in the ¹³C NMR spectra as singlet at 189.0 ppm. The resonance for carbene carbon was not determined in the **1b–g** complexes. This condition has been mentioned in the literature and has been given as a reason for the variable action of the NHC complexes [29–31]. The FT-IR data for NHC silver complexes exhibit a characteristic $\nu(\text{C}=\text{N})$ band at 1445.13, 1443.45, 1444.25, 1439.17, 1403.38, 1449.43, and 1440.26 for **1a–g**, respectively.

3.2. Antimicrobial Activity of N-(4-Vinylbenzyl) Substituted Silver Complexes, **1a–g.** Using an agar dilution procedure, the antimicrobial activities of the synthesized silver (I) complexes were determined. Antimicrobial activities were found to be effective in the tested complexes (**1a–g**) against both fungi and bacteria strains with MIC values between 200 and 25 µg mL⁻¹. It was seen that these complexes are more effective against fungi strains than against bacteria strains. The obtained results are summarized in the Table 1. The silver carbene complexes showed effective activities against *Escherichia coli*, *Pseudomonas aeruginosa* (gram-negative bacterial strains), *Enterococcus faecalis*, *Staphylococcus aureus* (gram-positive bacterial strains), and *Candida tropicalis* and *Candida albicans* (fungal strains). Most of benzimidazolium salts containing both electron withdrawing and electron donating groups demonstrated antimicrobial activity. The **1b**, **1e**, and **1f** silver carbene complexes which were containing benzyl, 2,4,6-trimethylbenzyl and 2,3,5,6-tetramethylbenzyl groups

SCHEME 1: Synthesis of 4-vinylbenzyl substituted NHC silver complexes **1a–g**.

showed better antibacterial activity than the **1a**, **1c**, **1d**, and **1g** complexes which were including methyl, 2-methylbenzyl, 4-methylbenzyl, and 4-vinylbenzyl groups. Generally, results of this study showed that compound containing steric effect on the nitrogen atom were more effective on antimicrobial activity. The NHC silver complexes including both symmetrical (**1g**) and unsymmetrical (**1c**, **1d**) groups indicated the same activities against all bacteria and fungus. Also, these compounds (**1c**, **1d**, and **1g**) exhibited low activity for all bacteria and fungi strains. Among the NHC silver complexes, the **1a**, **1b**, **1e**, and **1f** complexes showed high activity against

C. tropicalis at $25 \mu\text{g mL}^{-1}$. As positive control, ampicillin, ciprofloxacin, and fluconazole were used. It is seen from the obtained data in this work that the substituents on the *N*-atoms play an important role in antimicrobial activity.

4. Conclusions

The seven new 4-vinylbenzyl substituted benzimidazol-2-ylidene silver complexes were prepared by the reaction of different benzimidazolium salts with silver (I) oxide in

TABLE 1: MICs ($\mu\text{g mL}^{-1}$) of silver-NHCs for test microorganisms.

Compound	<i>E. coli</i>	<i>S. aureus</i>	<i>E. faecalis</i>	<i>P. aeruginosa</i>	<i>C. albicans</i>	<i>C. tropicalis</i>
1a	50	100	100	100	25	25
1b	50	50	50	50	50	25
1c	200	200	200	200	200	200
1d	200	200	200	200	200	200
1e	50	50	50	50	25	25
1f	50	50	50	50	25	25
1g	200	200	200	200	200	200
Ampicillin	3.12	3.12	1.56	—	—	—
Ciprofloxacin	1.56	0.39	0.78	3.12	—	—
Fluconazole	—	—	—	—	3.12	3.12

dichloromethane and characterized using elemental analysis and spectroscopic techniques. Some of these complexes showed very good antibacterial activity, especially against *Candida tropicalis* and *Candida albicans* as the fungal strains. The obtained results imply that the tested silver complexes displayed a different effect against *Escherichia coli*, *Pseudomonas aeruginosa* (Gram-negative bacterial strains), *Enterococcus faecalis*, *Staphylococcus aureus* (Gram-positive bacterial strains), and *Candida tropicalis* and *Candida albicans* (fungal strains). **1b**, **1e**, and **1f** compounds exhibited very good activity against all bacteria and fungi strains. Obtained results are helpful for the synthesis of NHC silver complexes possessing high antimicrobial activity.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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