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Synthesis, Studies and Antibacterial Activities Novel Symmetrically Benzimidazolium Salts and their Silver (I)-*N*-Heterocyclic Carbene Complexes

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Abstract: This study describes the synthesis and characterization of some new benzimidazolium salts, which are symmetrically substituted with (L1-L5) and their silver(I)-NHC complexes (C1-C5). The ligands were synthesized via alkylation reactions and then complexed with Ag_2 O, forming dinuclear Ag(I)-NHC complexes. Their structures were confirmed by FT-IR and NMR spectroscopy, showing the formation of carbene-Ag bonds by change in C-N stretching frequencies from 1247-1235 cm^{-1} to 1345-1338 cm^{-1} and the carbene carbon signal moving to a higher field (~144 ppm to ~184 ppm). The complexes were tested for their antibacterial activity against Staphylococcus aureus (Gram-positive) and Escherichia coli (Gram-negative). They exhibited moderate inhibition zones of 3.9-6.6 mm, less potent than ciprofloxacin. The results further indicate that a synergetic interaction between the silver(I) center and the NHC ligands is responsible for the antimicrobial activity. Hence, these complexes may be good candidates to combat antibiotic resistance. Additional optimization of activity and toxicity tests would give more insight into their therapeutic applicability.

Keywords: Silver complexes**,** Ligand**,** *N*-heterocyclic carbine**,** Antibacterial activity**,** Benzimidazole

Introduction

One of the primary challenges in the field of medicinal chemistry is the design and development of novel molecules that are effective against multiple biological pathways. Diseases, especially complex ones such as cancer, neurodegenerative disorders, and infectious diseases, often involve multiple molecular targets and signaling mechanisms. Therefore, targeting just one specific protein or pathway may not be sufficient for achieving a significant therapeutic effect. To address this, researchers aim to develop compounds that can interact with more than one biological target, a strategy known as multi-target drug design or polypharmacology. This approach has gained considerable attention because it can potentially lead to better clinical outcomes, reduced drug resistance, and fewer side effects compared to traditional single-target drugs [1]. However, designing multi-target compounds presents significant scientific and technical challenges. It requires a deep understanding of the molecular mechanisms of disease, as well as precise knowledge of how different targets interact with one another. Additionally, the molecule must maintain a favorable pharmacokinetic and safety profile while exerting activity on multiple pathways, which adds complexity to the drug development process. Advances in computational methods such as molecular docking, structure-based drug design, and in silico screening have played a crucial role in addressing these challenges. These tools allow researchers to predict how a molecule will bind to various targets, helping to optimize its design before synthesis and testing [1]. The increasing resistance of bacteria and fungi to the available antimicrobial agents is currently considered one of the most critical threats to global health in the 21st century. Organisms infecting humans become resistant due to repeated and improper applications of suitable chemicals, making the infections quite serious and lifetaking for the patients. Therefore, new innovative strategies are being approached by research to develop more efficient antimicrobial therapies [2]. Among these, silver-based compounds have proved striking activity against bacteria with comparative less toxicity to human being in the last decade. While much of the organometallic drug research was centered on platinum and gold complexes, good prophylactic value is shown by silver salts [3,4]. In the 1960s, Moyer first brought to light the antimicrobial properties of silver, specifically with silver nitrate in burn treatment, from where it was revealed that silver compounds could kill bacteria at very low concentrations [5].

In recent years, N-heterocyclic carbenes have come to substantial visibility as a multipurpose group of compounds playing numerous biological roles such as antimicrobial, anticancer, and anti-inflammatory activities once coordinated with metals [6,7]. Silver(I)-complexed NHCs especially present augmented stability and adjustable characteristics which make them favorable for possible medical uses [8]. Normally, a ligand does not have any biological activity, however, the presence of NHC ligands with a metal center leads to excellent biological activity due to the reason that the metal center disrupts the bacterial cell membrane while the organic framework enhances solubility and target specificity [9]. Benzimidazole derivatives are preferred as precursors for NHC ligands due to their structural rigidity which helps in forming stable metal complexes [10]. Recent studies show high antibacterial activity of symmetrically substituted benzimidazolium salts and their silver(I) complexes against both the mentioned strains [11]. But the mode of action is not reported. However, the nature of the structural modifications, for example, the alkyl chain length and antibacterial activity is ill-defined. The metal complexes of N-Heterocyclic Carbenes (NHCs) have since gained repute due to remarkable biological activities [8–10] with potential applications in the biomedical field as antitumor [12], antioxidant [13], anti-inflammatory [14], anticancer [15], anti-HIV [16], antimicrobial [17,18], antiproliferative [19], and antiseptic agents [20]. Ideally, silver-based drugs are to be very effective in their bioavailability as much as in the sustained and controlled release over time [21]. Bio-organometallic chemistry of silver is a research topic of long-standing tradition [22], with the last few years having brought a strong upsurge of interest in silver(I) complexes presenting with N-heterocyclic carbene (NHC) ligands of both imidazole and N-benzimidazole frameworks [23]. These Ag(I)-NHC complexes have a good potential application as drugs and at the same time are good carbene transfer agents [24,25]. So this paper will show the synthesis of new benzimidazolium salt derivatives with alkyl-substituted nitrogen atoms along with stable silver-NHC chelates. The compounds were characterized structurally by spectroscopic methods including NMR and FT-IR, and their anticancer activity was also studied.

Experimental

All reagents and solvents used were of analytical grade and procured commercially from Fluka and Sigma-Aldrich. The infrared spectra of the produced compounds were recorded using Bruker Alpha FTIR spectrometer at the College of Science, University of Kufa. The NMR spectra were taken on a Bruker instrument operating at 300 MHz for 1H NMR and 75 MHz for 13C NMR at Shahid Beheshti University, Iran. The solvent used for recording NMR spectra and internal standard for TMS were the same for all samples. The synthesis of the ligands and their silver complexes was confirmed using an electrothermal melting point apparatus.

Synthesis of benzimidazolium salts

In a round bottom flask, (0.002 mol) of *N*-alkylated were prepared in previous study [26] was placed, and 30.0 mL of organic solvent 1,4-dioxane was added. It was dissolved all reactants after a half-hour of heating and continual stirring. Then, with steady stirring, 0.01 mol of 1,4-bis(chloromethyl)benzene was added carefully, dropwise to the solution. At 90°C, the reaction mixture was refluxed for 24 hours. The flask was then withdrawn, 15 mL of organic solvent n-hexane was added to the mixture solution, and the flask was gently shaken. After allowing the combination to sit for one hour, the result was filtered. The end product was washed twice with n-hexane and dried in the oven.

Ligand (L1): It was obtained as off-white powder crystalline powder; with a melting point of 144–146 °C, yield 77%. Its structural identity was established by complete spectroscopic analysis, Confirming its structure by spectroscopic characterization: FT-IR (cm^{-1}); 3074 (C-H aromatic) 2957 and 2865 (C-H aliphatic), indicative of aromatic and aliphatic C-H stretches, 1247 (C-N) confirms the presence of the benzimidazole C-N linkage; 1H NMR (δ, ppm): 8.92 (s, 1H, NCHN) singlet, acidic proton benzimidazolium core, 7.51–7.18 (m, 12H, Ar-H) multiplet, aromatic protons, 4.82 (s, 4H, N-CH2benzyl) singlet, benzylic methylene protons, 4.28 (t, J = 7.1 Hz, 4H, N-CH2) triplet, N-alkyl chain methylene protons adjacent to nitrogen, 1.88–1.79 (m, 4H, N-CH2-CH2) multiplet, methylene protons in the alkyl chain, 1.28–1.21 (m, 28H, 14×CH2) long aliphatic chain methylene protons, 0.85 (t, J = 6.5 Hz, 3H, -CH3) terminal methyl triplet; 13C NMR(δ, ppm): 146.95 (NCHN) carbene carbon signal, 143.95–110.24 (Ar-C) aromatic carbons, 55.72 (N-CH2-benzyl) benzylic methylene carbon, 47.71 (N-CH2 methylene carbon adjacent to nitrogen, 31.75–22.61 (aliphatic CH2 groups) long alkyl chain carbons, 14.07 (CH3) terminal methyl carbon.

Ligand (L2): It was obtained as pale yellow crystalline powder; mp 185–187 °C; yield 72%;. Its structural identity was established by complete spectroscopic analysis: FT-IR Analysis (cm^{-1}), 3077 (C-H Aromatic C-H), 2982 & 2866 (C-H A),1258 (C-N) benzimidazole C-N; confirm heterocyclic core: 1H NMR (δ, ppm): 8.91 (s, 1H, NCHN), 7.58–7.19 (m, 12H, Ar-H),4.82 (s, 4H, N-CH2-benzyl), 4.31 (t, J = 7.1 Hz, 4H, N-CH2), 1.89–1.78 (m, 4H, N-CH2-CH2), 1.28–1.20 (m, 32H, 16×CH2), 0.89 (t, J = 6.5 Hz, 3H, CH3); 13C NMR (δ, ppm): 146.62 (NCHN),143.24–111.55 (Ar-C),55.81 (N-CH2-benzyl),48.17 (N-CH2),31.87–22.63 (aliphatic CH2 groups),14.11 (CH3).

Ligand (L3): It was obtained as off-white crystal powder; with a melting point of 192-194 °C, yield 66%. Its structural identity was established by complete spectroscopic analysis, Confirming its structure by spectroscopic characterization: FT-IR (cm^{-1}): νmax (cm-1) at 3054 (C-H aromatic), 2941 (C-H aliphatic), 2875 (C-H aliphatic), 1239 (C-N in benzimidazole); ^{1}H NMR (δ, ppm): 8.94 (s, 1H, N-CHN benzimidazolium), 7.60-7.20 (m, 12H, aromatics), 4.82 (s, 4H, benzylic CH_2), 4.28 (t, J = 7.1 Hz, 4H, N-CH_2 adj. to N), 1.86-1.76 (m, 4H, N-CH_2 -CH_2), 1.31-1.21 (m, 36H, —$(CH_2)_{18}$), 0.89 (t, J = 6.5 Hz, 3H, —CH_3), ^{13}C NMR (δ, ppm): 146.57 (N-CHN), 143.72-112.58 (aromatics), 56.12 (benzylic CH_2), 48.54 (N-CH_2), 31.92-22.57 (aliphatic, incl 12—CH_2), 14.12 (—CH_3)

Ligand (L4): It was obtained as a white crystalline powder; with a melting point of 158-160°C, yield 70%. Its structural identity was established by complete spectroscopic analysis, Confirming its structure by spectroscopic characterization: FT-IR (cm^{-1}): 3071 (C-H aromatic), 2952 (C-H aliphatic), 2857 (C-H aliphatic), 1235 (C-N benzimidazole); ^{1}H NMR (δ, ppm): 8.92 (s, 1H, NCHN), 7.25-7.6 (m, 8H, aromatic), 4.82 (s, 4H, benzylic CH_2), 4.3 (t, J = 7.1 Hz, 4H, N-CH_2), 1.74-1.86 (m, 8H, N-CH_2 -CH_2), 1.22-1.31 (m, 40H, 20×CH_2), 0.85 (t, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR (δ, ppm): 146.78 (carbene NCHN), 112.04-143.88 (aromatic), 55.52 (benzylic CH_2), 48.15 (N-CH_2), 22.52-31.94 [14(14×CH_2)], 14.14 (CH_3).

Ligand (L5): It was obtained as a white solid; with a melting point of 192-194°C, yield 69%. Its structural identity was established by complete spectroscopic analysis, Confirming its structure by spectroscopic characterization: FT-IR (cm^{-1}): 3084 (C-H arom), 2941 (C-H ali), 2832 (C-H ali), 1235 (C-N); ^1H NMR(δ, ppm): 8.93 (s, 1H, NCHN), 7.61-7.25 (m, 8H, arom), 4.82 (s, 4H, benzylic CH_2), 4.32 (t, J = 7.1 Hz, 4H, N-CH_2), 1.89-1.75 (m, 8H, N-CH_2 -CH_2), 1.30-1.21 (m, 44H, 22×CH_2), 0.83 (t, J = 6.5 Hz, 3H, terminal CH_3); ^{13}C NMR (δ, ppm): 146.07 (NCHN), 143.98-113.25 (arom), 55.87 (benzylic CH_2), 48.15 (N-CH_2), 32.28-22.17 (alkyl chain, incl 16×CH_2), 14.11 (terminal CH_3).

Syntheses of Silver(I)−*N*HC Complexes

The dinuclear Ag(I)-NHC compounds (c1-c5) were made by dissolving (0.006 mol) of disubstituted benzimidazolium bromide (L1-L5) in 1,4-dioxane and performing an in-situ deprotonation process (25 mL). Then, with continual stirring, (2.0 equiv.) of Ag_2O was added to the mixture, completely covering the flask. The reaction mixture was stirred for 48 hours, at room temperature. To eliminate unreacted Ag_2O, the flask was removed and the solution was filtered via a layer of celite in the dark place. The solvent was then removed under reduced pressure, and the resultant powder product [26].

Complex (C1): The white powder of the target compound was obtained, with a percentage yield of 61%, and it melted within a range of 174–176 °C , which signified its purity. It was fully characterized by complete spectral analysis. Results of the FT-IR analysis are as follows (cm^{-1}): 3086 C-H stretching (aromatic), 2958, 2874 C-H stretching (aliphatic), 1345 C-N stretching; ^1H NMR (δ, ppm) 7.51–7.25 (m, 8H, Ar-H), 4.88 (s, 4H, N-CH_2 -benzyl protons) 4.35 (t, J 7.1 Hz, 4H, N-CH_2) 1.89–1.78 (m, 4H, N-CH_2 -CH_2), 1.27–1.20 (m, 28H, 14 × CH_2 aliphatic) 0.88 (t, J 6.5 Hz, 3H, Terminal CH_3); ^{13}C NMR (δ, ppm) 184.75 (C-Ag), 142.38–112.71 (Ar-C), 58.17 (N-CH_2 -benzyl), 49.85 (N-CH_2), 31.87–22.48 (Aliphatic CH_2), 14.11 (Terminal CH_3).

Complex (C2): The off-white powder of the target compound was obtained, with a percentage yield of 65%, and it melted within a range of 184-186 °C, which signified its purity. It was fully characterized by complete spectral analysis. Results of the FT-IR analysis are as follows (cm^{-1}): 3092C-H stretching (aromatic), 2971, 2855C-H stretching (aliphatic), 1351C-N stretching; ^1H NMR (δ, ppm): 7.55-7.22 (m, 8H) aromatic protons, 4.89 (s, 4H) benzylic N-CH_2 protons, 4.37 (t, J = 7.1 Hz, 4H) N-CH_2 protons, 1.89-1.77 (m, 4H) N-CH_2 -CH_2 protons, 1.32-1.25 (m, 32H) 16 aliphatic CH_2 protons, 0.88 (t, J = 6.5 Hz, 3H) terminal CH_3 protons; ^{13}C NMR (δ, ppm): 184.24 (Ag-C), 143.57-113.38 aromatic carbons, 58.65 benzylic N-CH_2 , 49.78 N-CH_2 , 31.57-22.08 aliphatic CH_2 (10 distinct environments), 14.08 terminal CH_3 .

Complex (C3): The white to yellow crystalline powder of the target compound was obtained, with a percentage yield of 68%, and it melted within a range of 181-183°C, which signified its purity. It was fully characterized by complete spectral analysis. Results of the FT-IR analysis are as follows (cm^{-1}): 3085 (ν C-H, aromatic), 2992, 2875 (ν C-H, aliphatic), 1350 (ν C-N) FT-IR; ^{1}H NMR (400 MHz, δ ppm): 7.55-7.20 (m, 12H, Ar-H), 4.89 (s, 4H, N-CH_2 -benzyl), 4.38 (t, J = 7.1 Hz, 4H, N-CH_2), 1.89-1.79 (m, 4H, N-CH_2 -CH_2), 1.31-1.24 (m, 36H, 18×CH_2), 0.86 (t, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, δ ppm): 184.87 (C-Ag) and 143.74-113.08 (Ar-C), 58.32 (N-CH_2 -benzyl), 49.87 (N-CH_2), 31.98-22.08 (12×CH_2), 14.07 (CH_3).

Complex (C4): The off- yellow crystalline powder of the target compound was obtained, with a percentage yield of 70%, and it melted within a range of 190-192°C, which signified its purity. It was fully characterized by complete spectral analysis Results of the FT-IR analysis are as follows (cm^{-1}): 3080 (ν C-H, aromatic), 2974, 2858 (ν C-H, aliphatic), 1339 (ν C-N); ^{1}H NMR (δ, ppm): 7.60-7.25 (m, 12H), 4.87 (s, 4H), 4.39 (t, J = 7.1 Hz, 4H), 1.86-1.76 (m, 4H), 1.31-1.24 (m, 40H), 0.87 (t, J = 6.5 Hz, 3H); ^{13}C NMR (δ, ppm): 184.87 (C-Ag), 144.04-113.38 (aromatic carbons), 58.74 (benzylic N-CH_2), 49.28 (N-CH_2), 31.91-22.68 (14 aliphatic CH_2), 14.10 (CH_3).

Complex (C5): The off- yellow crystalline powder of the target compound was obtained, with a percentage yield of 64%, and it melted within a range of 149-151°C, which signified its purity. It was fully characterized by complete spectral analysis Results of the FT-IR analysis are as follows (cm^{-1}): 3058 ν C-H, aromatic), 2947, 2839 (ν C-H, aliphatic), 1338 (ν C-N); ^{1}H NMR (δ, ppm): 7.51–7.20 (m, 12H, Ar-H), 4.87 (s, 4H, N-CH2-benzyl), 4.38 (t, J = 7.1 Hz, 4H, N-CH2), 1.88–1.78 (m, 4H, N-CH2-CH2), 1.33–1.24 (m, 44H, 22×CH2), 0.86 (t, J = 6.5 Hz, 6H, CH3); ^{13}C NMR (δ, ppm): 184.76 (C-Ag), 143.85, 136.27, 133.61, 129.74, 124.18, 122.58, 121.07, 114.24 (Ar-C), 58.92 (N-CH-benzyl), 49.68 (N-CH2), 32.09, 31.91, 29.82, 29.71, 29.54, 29.20, 29.03, 28.78, 28.25, 27.75, 27.38, 26.21, 25.94, 25.38, 23.47, 22.05 (16×CH2), 14.13 (CH3).

Antibacterial activity

The agar well diffusion method was used to study the antibacterial activities of the synthesized compounds against Escherichia coli and Staphylococcus aureus. Fresh bacterial cultures were grown in nutrient broth. These were then standardized to a 0.5 McFarland turbidity. The bacterial suspension was inoculated on Mueller-Hinton agar plates, and depressions approximately 6 mm in diameter were made on the agar. After that, the test compounds were added into these wells. They were solutions in DMSO, and the final volume applied from all of them was the same. The plates were then further incubated at 37°C for 24 hours. After incubation, the diameters of the clear zones around and adjacent to the wells were measured. DMSO served as one negative and a standard antibiotic served as the positive control in the assays.

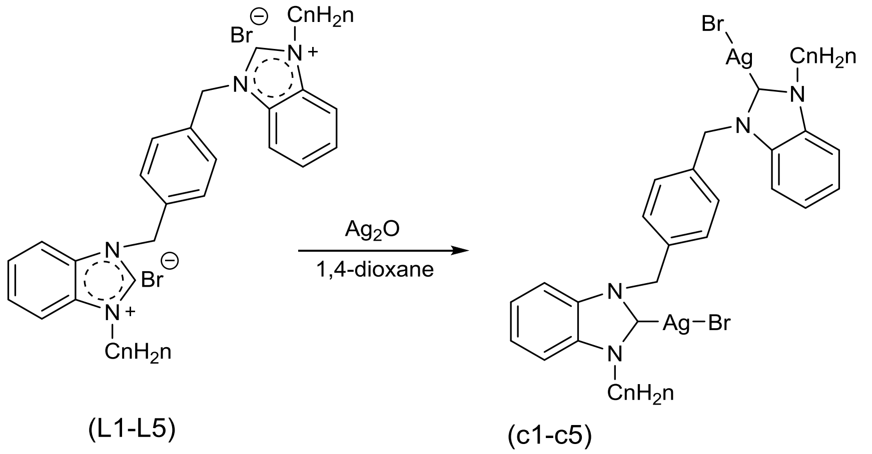
Minimum inhibitory Concentrations (MIC)

A described literature, measured zone inhibition [29]. An amount of the final products first was diluted with dimethyl sulfoxide (DMSO) solvent. It made different dilution levels in the ranges of 50–0.1 L. 100 liters of each dilution of the samples placed in the well dishes, setting in three replications. The wells filled with the samples for the targets already prepared. Then other wells filled with 50 L of Mueller Hinton broth solution. A 3.7 g resazurin tablet added to 40 ml distilled water to prepare the resazurin solution. The sample placed in the same well with a 10 L solution of resazurin indicator mixture. Then add 10 L more of bacterial suspension to the same wells. Pour 30 L of Mueller Hinton solution into each well of the plate. Finally, we sealed each plate with a tight cling film cover, to avoid drying out the wee beasties. Each plate has two control sets: positive drug (ciprofloxacin) and negative control. We divide each prepared sample into three parts, and incubate them for one whole day at 37°C.

Result and Discussion

Synthesis of Benzimidazolium derivatives and Ag(I)-NHC Complexes

Synthesis of benzimidazolium salts (L1-L5) comprised a two-step reaction: benzimidazole was made to react with alkyl bromide in the presence of potassium hydroxide [30–32]. This was followed by the synthesis of binuclear silver(I)-N-heterocyclic carbene (Ag(I)-NHC) complexes (c1-c5) through the in-situ deprotonation of the respective benzimidazolium salts by using Ag_2 O in 1,4-dioxane under dark conditions to avoid photodegradation [33,34]. The complexes were obtained as white powders in yields that ranged from 61% to 70%, and their structures were confirmed using many spectroscopy methods such as FT-IR, and NMR.



Where n=10,12,14,16,18

Scheme 1: Synthesis of Ag-NHC complexes

Spectroscopic Characterization

FT-IR Analysis: The stretching vibrations of C-H (aliphatic and aromatic) and the C-N groups were observed from the spectra of the ligands (L1-L5) at ν 3074–2857 and 1247–1235 cm−1, respectively. These values changed upon complexation with Ag(I) to be observed at 1345–1338 cm−1 in the corresponding stretches of C-N for complexes (c1-c5). Disappearance of the peak due to the acidic protons attached to nitrogen in the complexes gives additional proof for successful carbene formation.

NMR Spectroscopy: Singlet observed in the 1H NMR spectra of the ligands for the acidic proton (NCHN) at a chemical shift of ~8.9 ppm was found to disappear upon complexation due to silver coordination. The 13C NMR spectra showed the signal of carbene carbon to be shifted to a considerable downfield from ~144 ppm in the ligands to ~184 ppm in the complexes, supporting the formation of Ag(I)-carbene bonds.

Antibacterial Activity

Check the Ag(I)-NHC complexes (c1-c5) against their activities on the bacteria of both strains; one being Staphylococcus aureus, which is gram-positive, and the other Escherichia coli, a gram-negative species. This was done with the pour plate technique and MIC assays.

Zone of Inhibition: The complexes showed moderate activity with a zone of inhibition in the range of 5.1-6.7 mm against S. aureus and 3.9-5.5 mm against E. coli compared to that of ciprofloxacin (10.2 mm; 10.7 mm). Results of the trend in activity show that the silver core is responsible for retarding the growth of the bacteria, though it is less potent than the standard drug.

MIC Values: The MIC assays proved dose-dependent, with the lowest concentration inhibiting visible bacterial growth being varied from one complex to the other. From the results obtained it can be inferred that Ag(I)-NHC complexes do indeed possess notable antibacterial potential, very likely due to the synergistic effect between the silver ion and the NHC ligand. Figure 1

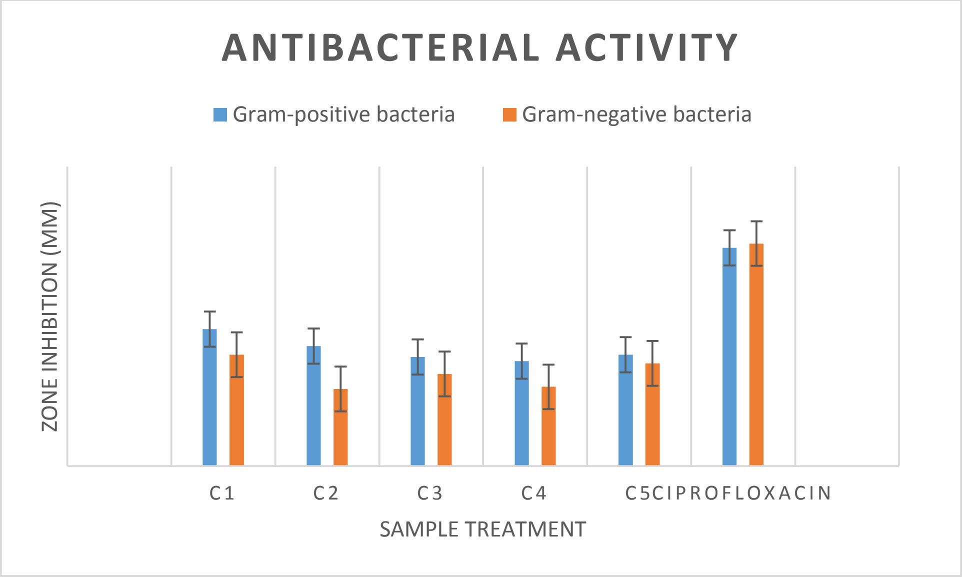


Figure 1: Antibacterial activity of synthesized complexes (c1-c5) at a concentration

Conclusion

This study reports the successful synthesis and characterization of a new series of dinuclear benzimidazolium salts (L1−L5) and their corresponding silver(I)-N-heterocyclic carbene (Ag(I)-NHC) complexes (C1−C5). Characterization of the ligands and complexes was achieved by spectroscopic evidence (FT-IR, ^{1}H NMR, and ^{13}C NMR) which showed in part: FT-IR: Shift in C-N stretching frequencies from 1247−1235 cm^{-1} (ligands) to 1345−1338 cm^{-1} (complexes) and disappearance of acidic proton peaks. NMR: Carbene carbon signal shows a very high field shift (~144 ppm for ligands and ~184 ppm for complexes) and the NCHN proton singlet disappears upon complexation, confirming binding between the carbene and Ag(I). These NHC complexes also showed moderate antibacterial activities against Staphylococcus aureus and Escherichia coli with zones of inhibition between 3.9 and 6.6 mm, less potent than ciprofloxacin (10.2−10.7 mm). The observed activity is proposed to be due to a synergistic effect between the silver(I) center and the NHC ligands which act by disrupting the growth of the bacteria. The results obtained indicate that Ag(I)-NHC complexes may be used as antimicrobial agents, especially in the view of the increasing antibiotic resistance that is observed. More work is deserved to perform structural changes aimed at increasing the activity and to study toxicities to make applications for therapy.

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