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NOVEL N-HETEROCYCLIC CARBENE SILVER(I) AND GOLD(I) COMPLEXES: SYNTHESIS, STRUCTURAL CHARACTERIZATION, ANTIMICROBIAL STUDIES

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Abstract:

In this study, new synthesized bis-benzimidazolium salt that are connected with a 1,2,3-triazol moiety. The proligand of the bis-benzimidazolium-1,2,3-triazole salt as N-heterocyclic carbene (NHC) precursors have been prepared by reacting the initially synthesized 1-octyl-1H-benzimidazole with propargyl bromide in 1:1 molar ratio to produce benzimidazolium salt (2). On the other hand, barbital azide reacted with prepared benzimidazolium salt (2) to obtained proligand bis-benzimidazolium-1,2,3-triazole salt (3). The Au(I) and Ag(I) complexes [M2(nNHC-NHC)2]PF6. FTIR and NMR spectroscopy were used to confirm all of the produced ligands and their complexes. Au(I) and Ag(I) complexes and the generated bis-benzimidazolium salt were tested for their biological activity against a few microbial strains. The substances that were examined demonstrated good activity.

Keywords: N-Heterocyclic Carbenes, Benzimidazolium salts, Ag(I)-NHC, Au (II)-NHC, 1,2,3-Triazole, N-Heterocyclic–Ag(I) Complexes, Biological Activity.

Introduction

For many years, organometallic chemistry has placed a great emphasis on N-heterocyclic carbenes (NHCs) and their transition metal complexes. Strong metal–carbon bonds seen in NHC metal complexes have traditionally been used as effective catalysts in a variety of reactions. The NHC-Ag(I) complex is one of the most significant of these complexes. One of the most popular techniques is to employ these complexes as carbene transfer reactive to create transition metal complexes. [1-5] NHCs have notable chemical features, including high binding ability and facile modification of electronic and steric properties. [1-3] One well-known class

of ligands that can process complexes with numerous main metal groups, including transition metals and rare earth metals, are *N*-heterocyclic carbene derivatives (NHCs) [6,7]. Furthermore, the simple grafting of substituents on the NHC enables the inclusion of chiral groups as well as the adjustment of their physical characteristics, including steric hindrance and solubility. The carbene–metal bond is typically strong and shows good stability in a variety of settings after coordination with transition metals [8,9]. This has enabled significant applications in several fields of catalysis. [10-13] and clinical chemistry, including antimalarial, anticancer, and antioxidant [14-17]. Strong binding ability and ease of modifying electronic and steric properties are two of NHCs' most notable chemical characteristics. Furthermore, the simple grafting of substituents on the NHC enables the inclusion of chiral groups as well as the adjustment of their physical characteristics, including steric hindrance and solubility. The carbene–metal bond is typically strong and shows excellent stability in a variety of settings following coordination with transition metals.[18] Another significant field where NHC–silver compounds have shown exceptional effectiveness is antimicrobial research. [19, 20]. Chemical and biological activity of organic complexes is not limited to the metal or organic ligand; it can also be fine-tuned by tiny changes in the complexes' electronic and steric properties, as well as by varying the metal's oxidation state. These characteristics offer a flexible drug design platform that is now being used in a number of fields. Silver compounds have long been recognized for their intriguing biological characteristics, including strong antibacterial capabilities. [21-24]. Additionally, prior to the development of antibiotics in the early 20th century, they were widely used treatments for colds and gonorrhea, as well as treating rheumatism and tetanus in the 19th century. [25]. Silver compounds are also utilized to treat nicotine addiction, epilepsy, and mental disease [26,27]. Additionally, silver compounds have come back into favor as a treatment for infections that occur in burns, open wounds, and chronic ulcers. [28-31] Bis-imidazolium salts were made in this study and complexed with certain metals, Ag(I) and Au(I), to ascertain their possible antimicrobial qualities. Mosquitoes are an annoyance and health risk due to their tendency for biting and their capacity to spread diseases. Additionally, Several spectroscopic techniques such as Fourier transform infrared spectroscopy (FTIR), 1H, 13C, and nuclear magnetic resonance (NMR) were used to characterize and accurately determine the chemical structures of all the prepared salts and complexes.

2. Experimental Part

All solvents used in the preparation of all compounds as well as the chemical raw materials used in the preparation were provided from commercial sources and international chemical processing companies such as Fluka and Merck. The infrared spectra of all prepared compounds were recorded using an infrared spectrometer FTIR (FTIR-8400s, Shimadzu). On the other hand, the nuclear magnetic resonance (NMR) spectra of the prepared compounds and complexes were recorded using a Bruker 400 MHz spectrometer at room temperature.

2.1. Synthesis of 1-octyl-1*H*-benzimidazole (1) [32]

To a solution of benzimidazole (14.7 mmol,1.00 g) in (20 mL) DMSO, KOH (29.4 mmol, 1.65 g) was added. The reaction mixture was continue stirred at room temperature for 30 minutes which then the bromooctane (14.7 mmol, 2.83 g) was added slowly drop by drop. Then, after complete bromooctane addition the solution was stirred until the reaction was complete and then the reaction mixture poured into (250 mL) of water and separated with chloroform (3x30 mL). The residue was got after the solvent was evaporated. The sold powder was recrystallized with acetonitrile. Yield: (83%). Chemical formula: $C_{15}H_{22}N_2$, ^{1}H NMR δ, ppm: 9.84 (1H, NCHN, s), 7.54-7.24 (4H, Ar-H, m), 4.29 (2H, -CH_2-N, t, *J* = 7.1 Hz), 1.84-1.93 (2H, -CH_2-, m), 1.22-1.33(10H, -CH_2-, m), 0.88 (3H, -CH_3, t, *J* = 7.1Hz), ^{13}C NMR δ, ppm: 143.27 (NCHN) ,141.45, 134.68,123.67, 122.24, 119.53, 109.97 (6C of benzimidazole ring), 45.57 (CH2-N), 31.80, 29.28, 28.89, 28.78, 26.24, 22.66 (6(-CH_2-), 14.04 (CH3), FTIR: in cm^{-1}, 1238 (C-N), 1591 (C=N), 2865(C-H_{aliph}), 2974 (C-H_{aliph}).

2.2. Synthesis of benzimidazolium salt (2)[32]

1-Octyl-1H-benzimidazole (5.5 mmol) was reacted with propargyl bromide (2 mL) in acetonitrile (35 mL) under reflux for 24 hours. The resulting viscous solution was then separated and repeatedly washed with diethyl ether and 1,4-dioxane. The obtained compound was directly subjected to a metathesis reaction with KPF_6 (5.5 mmol) in a mixture of methanol (25 mL) and water (25 mL) at room temperature, yielding its hexafluorophosphate anion counterpart. The end product washed (3x8 mL) with distilled water to remove residual of KPF_6. The sold powder was recrystallized with acetonitrile. Yield: (77%). Chemical formula : [$C_{18}H_{27}N_2^+$] PF_6^-, ^{1}H NMR δ, ppm: 9.91 (1H, NCHN, s),7.51-7.22 (4H, Ar-H, m), 4.25 (2H, propagyl-CH_2,s), 3.71 (2H, -CH_2-N, t, *J*=7.0 Hz), 2.52 (1H, -C≡CH,s), 1.89-1.95 (2H, -CH_2-, m), 1.21-1.31 (10H, -CH_2-, m), 0.87 (3H, -CH_3, t, *J*=7.0Hz), ^{13}CNMR δ, ppm: 144.07 (NCHN), 140.60, 133.06, 127.84, 126.79, 122.01, 111.73(6C of benzimidazole ring), 73.71(-C≡CH), 68.17(≡CH), 47.18(CH2-N), 40.25(acetylene-CH_2-N), 31.78, 29.33, 28.35, 26.80, 26.62, 22.70 (6(-CH_2-),14.04(CH3), FTIR: in cm^{-1}, 1232 (C-N), 1585(C=N), 2128(-C≡C-),2884 (C-Haliph), 2965 (C-Haliph), 3274 (C-H-acetylene).

2.3. Syntheses of bis-1,2,3-triazolebenzimidazolium salt (3) [33,34]

Benzimidazolium salt **(2)** (3.4 mmol), sodium-L-ascorbate (1.18 mmol), and coppersulfate pentahydrate (1.16 mmol) was dissolved in DMF (35 mL) and stirred for 35 minutes. 1,3-bis(Azidoeylmethyl)barbital [35] (1.7 mmol) were then added, and the mixture was stirring at 25 °C for 72 h. Afterward, the solvent was evaporated under vacuum; the residue was dissolved in (50 mL) of DCM and washed(3×50 mL) with water. The organic solvent was dried over anhydrous Na_2SO_4, and the organic solvent was then removed. Yield: (77%). Chemical formula: [$C_{45}H_{66}N_{12}^+$]$2PF_6^{-2}$, ^{1}H NMR δ, ppm: 9.95 (1H, NCHN, s), 7.87(2H, triazole H,s),7.47-7.20 (4H, Ar-H, m), 4.94 (4H, triazole ring-CH_2,s), 4.51 (2H, -CH_2-N, t, *J*=7.0 Hz), 1.84–1.95 (2H, -CH_2-, m), 1.24–1.35 (12H, -CH_2-, m), 1.98 (4H, -CH_2-, of ethyl group in

barbital, q, *J*=9.14 Hz), (0.94 (6H, -CH_3 of methyl in barbital, t, *J*=7.0Hz), 0.82 (3H, -CH_3 of alkyl tail, t, *J*=7.0Hz),^{13}CNMR δ, ppm:173.28 (carbon of carbonyl group in position 2 in pyrimidine ring), 168.57 (carbon of carbonyl group in position 4 and 6 in pyrimidine ring), 141.9 (NCHN), 140.54, 133.47, 127.28, 126.17, 122.14, 113.71(6C of benzimidazole ring), 124.21 (triazole-C4), 122.74 (triazole-C5),59.87(c5 of pyrimidine ring) 54.25(-CH2-triazole ring), 49.14(-CH_2-N), 31.07, 29.74, 27.24, 26.27, 24.60, 21.89 (6(-CH_2-)37.14(-CH2- of ethyl group in barbital), 15.87(CH3 of barbital), (14.04(CH3 of methyl in alkyl chain), FTIR: in cm^{-1}, 1241 (C-N), 1598 (C =N), 2874(C-Haliph), 2968 (C-Haliph), 3074(C-H triazole).

2.4. Synthesis of the Silver(I) Complex (4) [32,36]

The proligand (3) (0.13 mmol) and Ag_2O (0.87 mmol) was dissolved in (25 mL) of CH_3CN, and the reaction mixture was continued stirring for 48 h at 85 °C. Afterward, it was isolated by filtration on Celite, and the organic solvent was evaporated under vacuum. Yield: (85%). ($[Ag_2L_2PF_6]^+$) ,^{1}H NMR δ, ppm: 7.86 (4H, triazole H,s), 4.92 (4H, triazole ring-CH_2,s), 4.51 (8H, -CH_2-N, t, *J*=7.0 Hz), 1.87–1.94 (8H, -CH_2-, m), 1.22–1.37(40H, -CH_2-, m), 1.97 (4H, -CH_2, ethyl in pyrimidine ring, q),0.89(6H, -CH_3, methyl in pyrimidine ring, t, *J*=7.2Hz), 0.81 (12H, -CH_3, methyl in terminal of alkyl chain, t, *J*=7.0Hz), ^{13}C NMR δ, ppm: 183.78 (C-Ag nNHC),174.85 (carbon of carbonyl group in position 2 in pyrimidine ring), 169.47 (carbon of carbonyl group in position 4 and 6 in pyrimidine ring), 141.14, 132.17, 129.18, 127.28, 124.74, 115.49 (6C of benzimidazole ring), 122.17(triazole-C4), 120.18 (triazole-C5), 56.87 (C5 of pyrimidine ring), 49.74(-CH_2-N-triazole ring), 46.87(-CH_2-N-alkyl chain), 32.01, 29.97, 28.11, 27.07, 25.71, 22.92 (6(-CH_2-), 38.24(-CH_2- of ethyl group in barbital), 14.98(-CH_3, of barbital), 13.19(-CH_3, of methyl in alkyl chain), FTIR: in cm^{-1}, 1251 (C-N), 1584(C =N), 2857(C-Haliph), 2984 (C-Haliph), 3083(C-H triazole).

2.5. Synthesis of the Au(I) Complex (5) [37]

The proligand (3) (0.13 mmol) and Ag_2O (0.87 mmol) was dissolved in(15 mL) of CH_3CN, and the reaction mixture was continued stirring for 48 h at 85 °C. Afterward, it was isolated by filtration on Celite, and (0.088 mmol) of a solution of $AuCl(SMe_2)$ that dissolved in (10 mL) of acetonitrile was added. The reaction mixture was continued stirring at room temperature for 3 h and then isolated by filtration on Celite; then, the organic solvent was evaporated under vacuum. Recrystallization by Et_2O/CH_3CN, ($[Au_2L_2PF_6]^+$),^{1}H NMR δ, ppm: 7.84 (4H, triazole H,s), 4.88 (8H, -CH_2- triazole ring, s), 4.50 (8H, -CH_2-N, t, *J*=7.0 Hz), 1.85–1.91 (8H, -CH_2-, m), 1.26–1.32(56H, -CH_2-, m), 1.99 (4H, -CH_2, ethyl in pyrimidine ring, q),0.91(6H, -CH_3, methyl in pyrimidine ring, t, *J*=7.2Hz), 0.80 (12H, -CH_3, methyl in terminal of alkyl chain, t, *J*=7.0Hz),^{13}C NMR δ, ppm: 179.58(C-Au-NHC), 174.52 (carbon of carbonyl group in position 2 in pyrimidine ring), 169.45 (carbon of carbonyl group in position 4 and 6 in pyrimidine ring), 140.24, 134.32, 129.74, 129.54, 125.24, 118.28 (6C of benzimidazole ring), 122124.5(triazole-C4), 122.9 (triazole-C5), 57.47 (C5 of pyrimidine ring), 48.47(-CH_2-N-triazole ring), 45.97(-CH_2-N-alkyl chain), 33.14, 30.17, 29.24, 28.24, 26.47, 22.27 (6(-CH_2-), 39.12(-CH_2- of ethyl

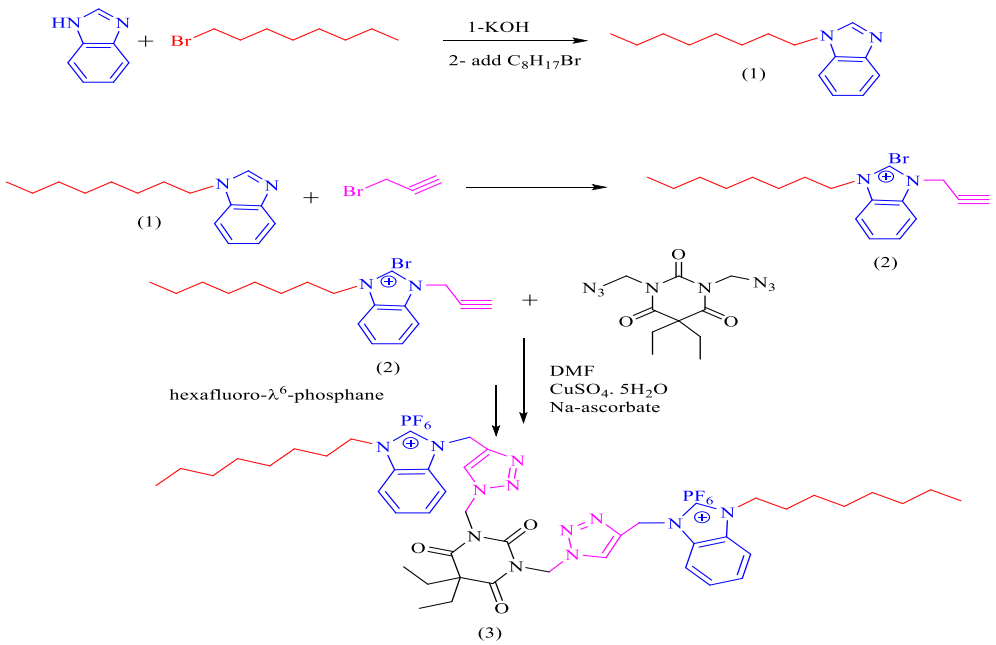
group in barbital), 14.09(-CH_3, of barbital), 12.87(-CH_3, of methyl in alkyl chain), FTIR: in cm^{-1}, 1227 (C-N), 1581(C =N), 2875(C-Haliph), 2984 (C-Haliph), 3095(C-H triazole).

3. Antimicrobial Activity assay of the benzimidazolium salt, silver(I) and Gold(I) Complexes [38,39]

Ligand (**3**) and complexes (**4** and **5**) were screened for antibacterial activity against positive and negative bacteria in Muller Hinton agar by measuring the inhibition zone in. As an antibacterial and an antifungal reference agent, ciprofloxacin and fluconazole were used, respectively. Then, four holes were made in the solidified medium. (0.5 mL) of prepared compounds ((100 µg/ µL and 200 µg/ µL) of the compound dissolved in 1 ml of DMSO solvent) were packed with these gaps. These plates were incubated at 37 ^{0}C and the zone inhibition was assessed after 24 hours.

4. Results and Discussion

Numerous cytotoxic metals, including copper, nickel, palladium, platinum, silver, gold, and ruthenium, are strongly bound by N-heterocyclic carbenes (NHCs). Nearly all transition metals and the complexes examined for catalytic and biological uses have been bound to NHCs. Given the lengthy history of using silver in antimicrobial medications to treat various infectious diseases, both silver and gold have been of interest in medical study. The first compound N-alkylation (1) was performed using KOH as a base for the elimination of acidic protons from imidazole (N-H) in DMSO as a solvent and the corresponding bromooctane. All of the generated asymmetrically substituted *N,N*-disubstitutedimidazolium bromide salts were obtained in solid form in good yield.. depicted in Scheme 1.



Scheme 1: Syntheses of bis-1,2,3-triazolebenzimidazolium salt

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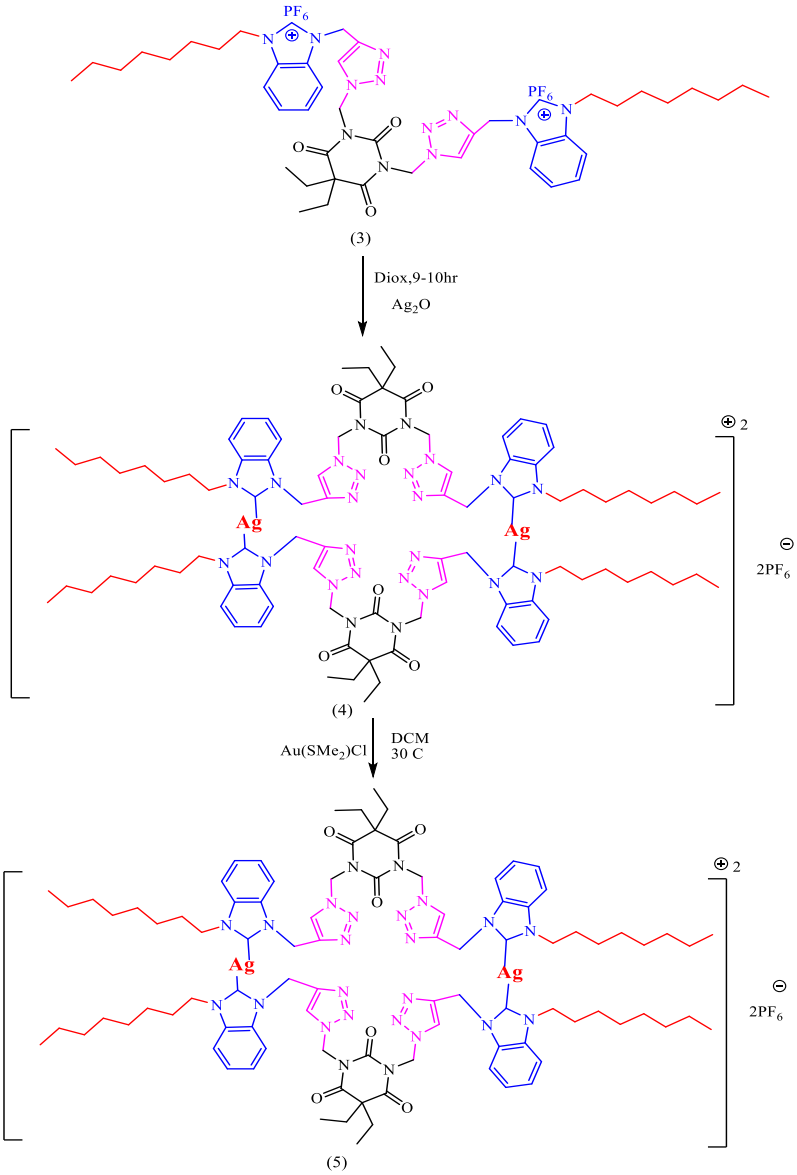
The in-situ method using Ag_2O [32] for the synthesis of carbene ligand and its complexation with silver(I). After two days of stirring the reaction solution comprising N,N-disubstitute dimidazolium bromide salt in CH3CN with Ag2O (2:1), the Ag(I) complex was purified by filtration through celite to remove any unreacted Ag2O and insoluble AgBr. A metathesis reaction was used to transform the generated NHC-Ag(I) complex in bromide derivative to hexafluorophosphate derivative. The compound of N,N-disubstitutedimidazole-2-ylidene silver(I) hexafluorophosphate were synthesized with good yield in powder form. The compound is insoluble in diethyl ether, petroleum ether, and methanol, but readily soluble in DMSO and acetonitrile. The Au(I) complex synthesis was prepared by adding AuCl(SMe2) to the solution of bis-NHC-Ag(I) complexes in acetonitrile, and then the reaction mixture was left stirring at room temperature for 3 hours. Scheme 2.



Scheme 2: Synthesis of the Ag(I), Au(I) complexes

4.1. FT-IR analysis

The FT-IR data of the synthesized ligand carbene and their complexes of Ag(I), Au(I) was recorded by utilizing the KBr disk method. 1-octyl-1*H*-imidazole (1), has alkyl chain substituent that appear in the functional group region the absorptions of the (-C-H) aliphatic stretching at 2800–2990 cm^{-1}. In benzimidazole ring the stretching vibrations of (C═N) appear among 1600 and 1550 cm^{-1} while the stretching vibrations of (C-N) give a band in the region 1150–1250 cm^{-1}.[32] On the other hand, new band appear at 3265 cm^{-1} and 2128 cm^{-1} due to acetylene moiety in compound (2). Also, the bands of acetylene was disappearance when reacted 1,3-bis(Azidoeylmethyl)barbital [35] with 1-octyl-1*H*-benzimidazole (1) to form 1,2,3-triazole derivative (3). The stretching vibrations in the region 3100–3050 cm^{-1} due to stretching vibrations of the (-C-H) aromatic in 1,2,3-triazole ring. No indication of the (C-Ag) and (C-Au) bands in FT-IR spectrum whose stretching vibrations appear less than 400 cm^{-1}, indicating that all NHC-Ag(I) and NHC-Au(I) complexes have the similar absorption bands as the *N*,*N*-disubstituted benzimidazolium bromide salts.

4.2. NMR analysis

^{1}HNMR spectra of all the imidazolium bromide salts and complexes were recorded in DMSO-*d6*. In the spectrum of the salt, the resonances of protons in octyl chain with their predicted multiplicity are obviously observed. The methyl protons give a triplet about 0.79-0.9 ppm in the most up field region, while the methylene(-CH_2-) protons show a number of multiplets signal at 1-2 ppm. A simple triplet is observed in the deshelled area about 4.5 ppm that can be due to the most deshelled methylene(-CH_2-) protons attached with benzimidazolium ring (N-CH_2-). In the most deshelled area, the most distinctive resonance about 9.95 ppm in proligand(3), as a singlet signal, is due to the benzimidazolium ring's most deshelled (NCHN)acidic proton. Whereas, new signal at 2.53 ppm due to acetylic proton in compound (2). Singlet-signal of aromatic 1,2,3-triazole ring proton resonances are observed in the 7.87, 7.86 and 7.84 ppm in ligand (3) and complexes (4,5) respectively. The salt undergoes the elimination of the acidic proton upon reaction with Ag_2O, producing of carbene that coordinates with Ag(I) and Au (I). Subsequently, the most important shift in the ^{1}HNMR spectra on the conversion of the ligand to Ag(I) and Au(I) complexes is the absence of the resonance about 9.95 ppm, indicating the production of carbine complexes. [32,36] The most characteristic resonance appearing about 141-144 ppm is due to the C2 carbon (NCHN) which, according to the literature, is the most deshelled carbon in the ^{13}CNMR. [32,36] When Ag(I) and Au(I) are deprotonated and coordinated with carbene ligand. Aromatic carbon resonances in the 1,2,3-triazole ring are between 121 and 125 ppm, while methyl(-CH_3) and methylene(-CH_2-) protons have resonances in the 12-50 ppm region.

5. Antimicrobial Activity

N-Heterocyclic Carbene (NHC) complexes of silver(I) and gold(I) have gained significant attention due to their unique chemical properties and wide range of applications. Silver(I)-NHC Complexes: Exhibit strong antimicrobial, antifungal, and anticancer properties. Their ability to

disrupt bacterial cell membranes makes them potential alternatives to traditional antibiotics. Gold(I)-NHC Complexes: Show promising anticancer activity, particularly against drug-resistant cancer cells, by inhibiting enzymes like thioredoxin reductase and inducing apoptosis. Carbine ligand (3) and its complexes (4,5) were tested for antibacterial and antifungal properties. The antibacterial activity was assessed using two types of bacteria: Escherichia coli and Pseudomonas aeruginosa. However, two types of fungi were employed (Aspergillus Niger and Candia albicans). Fluconazole and ciprofloxacin are well-known antifungal and antibacterial medications. The final data of antibacterial activity are summarized. in Fig. 1.

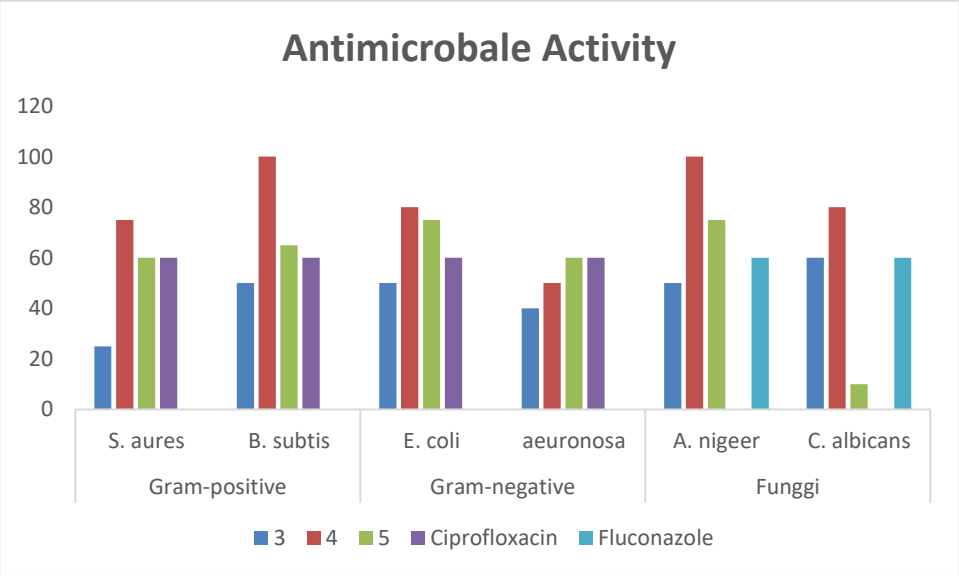


Fig. 1: (MIC, μg/mL) of the bis-1,2,3-triazolebenzimidazolium salt and Ag(I) and Au(I) complexes

The antibacterial and antifungal activity Ag(I) and Au(I) complexes showed high activity against used microorganism comparison control drugs.

6. Conclusions

Because of their low toxicity, the N-heterocyclic carbene-based silver complexes Ag(I) and Au(I) are now frequently employed as organometallic drug candidates in pharmaceutical and medical science studies. Interest in the synthesis and uses of Ag(I) and Au(I) complexes is growing quickly as a result of their success in biological applications. A novel class of bis-benzimidazolium salts and its bis-NHC-Ag(I) and bis-NHC-Au(I) complexes with wingtip mono N-alkyl groups and N-1,2,3-triazole were effectively synthesized and validated using spectroscopic data. The bis-1,2,3-triazolebenzimidazolium salt, as well as the Ag(I) and Au(I) complexes, demonstrated strong antimicrobial activity.

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