REVIEW ARTICLE

Synthesis, Characterization and Antibacterial Activity of Some Transition Metal Complexes Derived from the Ligand N-Benzylimidazole Against Methicillin-Resistantt *Staphylococcus Aureus* (Mrsa)

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ABSTRACT

Metal complexes of the ligand N-benzylimidazole (BnIm) and their *in vitro* antibacterial study are reported. The complexes of Co(II), Ni(II), Cu(II), Zn(II), and Ag(I) were synthesized by the reaction of the ligand with appropriate metal salt in 1:4 metal to ligand mole ratio. All the synthesized ligand and their complexes were characterized by physicochemical and spectroscopic techniques. Further, the compounds were screened for their antibacterial activity against a multi-resistance strain of *Staphylococcus aureus* (MRSA) using ciprofloxacin as a standard antibiotic. In general, all the tested compounds showed antibacterial activities at minimum inhibition concentration (MIC) level.

Keywords: Antibacterial, Imidazole; Metal complexes, Methicillin-resistantt *Staphylococcus aureus* (MRSA), MIC value.

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INTRODUCTION

Staphylococcus aureus is one of the most significant opportunistic bacteria and the principal nosocomial pathogen around the world. It can become a Methicillin-resistant *S. aureus* by the acquisition of the mecA gene, which encodes the penicillin-binding protein (PBP2a). PBP2a has little affinity for all β-lactam agents; hence there are restricted therapy choices for infections caused by MRSA strains.[1,2]

Community-associated *S. aureus* (CA-MRSA) strains, which began outside hospitals, are likewise prevalent in some areas, some have moved into hospitals and have converted to be progressively resistant to drugs other than beta-lactam agents. Currently available antibacterials became less effective against infectious diseases, particularly with MRSA strains. Therefore, numerous scientists have focused on synthetic products, probiotic products, and plant extracts as a wellspring of new bioactive molecules. So it has sparked keen attention in developing modern potent drugs with low toxicity (improved therapeutic index) and elevated bioavailability.[3,4]

So, searching for different types of antibiotics with different features and modes of action has become an urgent necessity. The heterocyclic compounds are of great interest in pharmaceutical chemistry and attracted the attention of many researchers because of their special characteristics. Among these compounds, imidazole is an aromatic organic compound with the formula $C_3H_4N_2$. It is the parent compound for imidazoles that are a class of heterocycles with similar ring structure but varying substituents.

Imidazole analog systems are present in different important natural products, such as purine, histamine, histidine, and etc. (Chart 1).

Imidazole derivatives took a very important place in the field of medicinal chemistry because of their high therapeutic properties and have been used as a building block to synthesize a large number of novel chemotherapeutic agents as well.[5] Based on the literature, imidazole derivatives showed different pharmacological activities such as; antibacterial, antifungal,

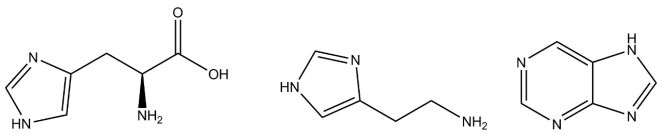

Chart 1: Some of the natural product contains imidazole analog system.

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antitumor, anticancer, anti-inflammatory, analgesic activity and etc.[6-10]

Both imidazoles and benzimidazoles act as good ligands to transition metal ions,[11] and they exhibit different coordination modes (Chart 2) with a variety of applications, particularly the catalytical and biological ones.[12-18]

Herein, we present the synthesis and the *in vitro* antibacterial studies of Co(II), Ni(II), Cu(II), Zn(II), and Ag(I) complexes derived from the ligand *N*-benzylimidazole (BnIm). The antibacterial activities of the ligand and its prepared complexes were determined against a multi-resistance strain of *Staphylococcus aureus* using ciprofloxacin as a standard antibiotic.

EXPERIMENTAL

Reagents and Instruments

The chemicals and solvents used in the present work were obtained from commercial sources and were in good purity and used without further purifications. Infrared spectra were recorded on KBr disks in the range 4000-400 cm^{-1} using a SHIMADZU spectrometer. CHN analysis was carried using Euro EA elemental analyzer CHNS, EA3000 analyzer. The abovementioned techniques are available in Al-Mustansiriyah University, the department of chemistry- College of Science, Iraq. Uv-vis spectra were recorded using Sp-3000 nano optima spectrophotometer in the range 200-800 nm, which is available in Wasit University, the department of chemistry, college of science, Iraq. 1H and 13C NMR spectra were recorded using Bruker UltraShield TM 500MHz spectrometer in d_6-DMSO at ambient temperature with TMS as an internal reference.

Synthesis of the ligand N-benzylimidazole (BnIm)

In 150 ml round bottom flask containing 25 ml of DMSO, 3 g of imidazole and 1.8 g of sodium hydroxide is added. The mixture was heated using an oil bath at ≈ 80 °C for 2 hours with constant stirring. Then it was slowly cooled down to about 50 °C, followed by the addition of 7.6 g of benzyl bromide. The reaction was maintained at the same conditions for 1-hour, then the mixture was poured in a 400 ml beaker immersed in ice-bath and containing 200 mL of distilled water. The resulted beige precipitate was left standing for 30 min, then collected by filtration, washed with plenty of cold distilled water, and left to dry at room temperature. The yield was 5.8 g (84%). Anal. Cal. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71 %. Found: C, 75.78, H, 6.44, N, 17.64 %. FT-IR: *v* (C=N): 1510 cm^{1-}. ^{1}H NMR (500 MHz, DMSO): δ 5.21 (2H, s, benzylic CH_2), 7.24-7.34 (5H, m, 5 × Ar-H), 7.02 (1H, t, imidazole H5′), 7.39 (1H, t, imidazole H4′) and 8.12 (1H, s, imidazole H2′); ^{13}C{1H} NMR (125 MHz, DMSO): δ 49.1 (benzylic CH2) 120.2, 126.6 (imidazole C5′ & C4′), 127.0 (2 × Ar-CH), 127.03 (Ar-CH), 127.8 (2 × Ar-CH), 136.3 (Ar-C) and 138.0 (imidazole C2′).

Synthesis of the Complexes

To a solution of N-benzylimidazole (0.4 g, 2.5 mmol) dissolved in 10 ml of ethanol, 0.625 mmol of the appropriate salt (except $AgNO_3$) dissolved in 10 mL of ethanol, was added dropwise. The mixture was heated with constant stirring for 1 h at 60-70 ^{0}C. The resulted precipitates were filtered off and washed with fresh ethanol (2 × 5mL) and distilled water.

Synthesis of dichlorotetrakis (N-benzylimidazole)cobalt(II). Monohydrate

The complex was synthesized in the same method described above by the reaction of the ligand with $CoCl_2$. The reaction produced the complex as a deep blue precipitate (0.47 g, 55%). Anal. Cal for $C_{40}H_{40}N_8Cl_2Co$ (H_2O): C, 61.54; H, 5.42; N, 14.35; found C, 61.58; H, 5.53; N, 14.28. IR: *v* (C = N): 1477 cm^{-1}.

Synthesis of dichlorotetrakis(N-benzylimidazole)nickel(II). Dihydrate

The complex was synthesized by the reaction of the ligand with $NiCl_2.6H_2O$. The reaction produced the complex as blue solution which was left standing for 3 days to give a light-blue crystals (0.8 g, 74%). Anal. Cal for $C_{40}H_{40}N_8Cl_2Ni.(2H_2O)$: C, 60.17; H, 5.55; N, 14.03; found C, 60.08; H, 5.62; N, 13.85. IR: *v* (C=N): 1468 cm^{-1}.

Synthesis of dichlorotetrakis(N-benzylimidazole)cooper(II)

The complex was synthesized by the reaction of the ligand with $CuCl_2$. The reaction produced the complex as an azure precipitate (0.58 g, 62%). Anal. Cal for $C_{40}H_{40}N_8Cl_2Cu$: C, 62.62; H, 5.26; N, 14.60; found C, 62.08; H, 5.13; N, 14.27. IR: *v* (C=N): 1474 cm^{-1}.

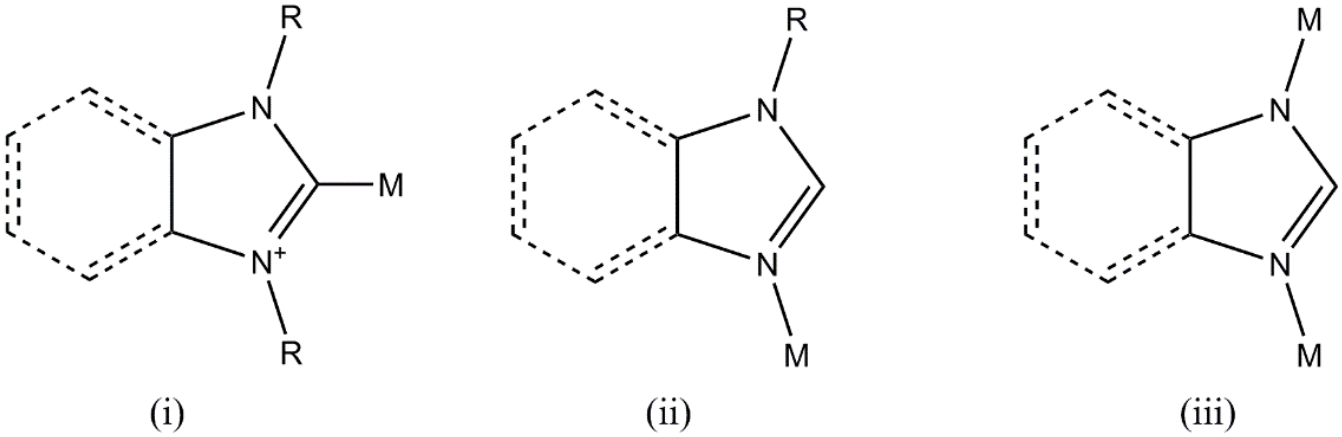


Chart 2: Coordination modes in benz(imi)dazoles.

Synthesis of dichlorotetrakis(N-benzylimidazole)zinc(II)

The complex was synthesized by the reaction of the ligand with $ZnCl_2$. The reaction produced the complex as a white precipitate (1.07 g, 85%). Anal. Cal for $C_{40}H_{40}N_8Cl_2Zn$: C, 62.47; H, 5.24; N, 14.57; found C, 62.23; H, 5.41; N, 14.39. IR: *v* (C=N): 1482 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 5.29 (s, 2H, bezylic CH_2), 7.04 (t, 1H, imidazole H5′), 7.30-7.38 (5H, m, 5 × Ar-H), 7.42 (t, 1H, imidazole H4′), 8.20 (1H, s, imidazole H2′). $^{13}C\{1H\}$ NMR (125 MHz, DMSO): δ 50.15 (benzylic CH2) 120.84, 127.01 (imidazole C5′ & C4′), 127.79 (2 × Ar-CH), 128.08 (Ar-CH), 128.79 (2×Ar-CH), 136.70 (Ar-C) and 138.13 (imidazole C2′).

Synthesis of bis(N-benzylimidazole)silver(I) nitrate

The complex was synthesized by the reaction of the ligand (2.5 mmol) and AgNO3 (1.25 mmol). The reaction produced the complex as a light grey precipitate (1.15 g, 86%). Anal. Cal for $C_{20}H_{20}N_5O_3Ag$: C, 49.40; H, 4.15; N, 14.40; found C, 49.67; H, 4.34; N, 14.56. IR: *v* (C=N): 1488 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz): δ 5.30 (s, 2H, bezylic CH_2), 7.12 (t, 1H, imidazole H5′), 7.29-7.39 (5H, m, 5 × Ar-H), 7.46 (t, 1H, imidazole H4′), 8.16 (1H, s, imidazole H2′). $^{13}C\{1H\}$ NMR (125 MHz, DMSO): δ 50.15 (benzylic CH_2) 120.54, 129.29 (imidazole C5′ & C4′), 127.70 (2 × Ar-CH), 128.07 (Ar-CH), 128.79 (2 × Ar-CH), 136.70 (Ar-C) and 139.3 (imidazole C2′).

Antibacterial Activity

Source of the pathogenic isolates

The pathogenic isolates used in the present study were obtained from the Dr.Zainab Nashaat Al-Saadi and were kept on nutrient agar slants (Oxoid, UK). These isolates were identified using VITEK system Healthcare, biomerieux. The characterization of isolates as MRSA was conducted in previous studies.[1,2]

Antibacterial assay

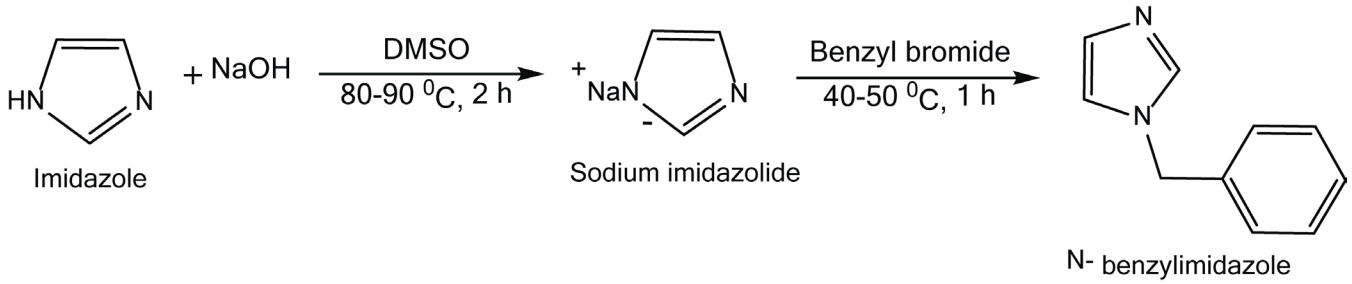
The antibacterial effectiveness of synthesized compounds was tested against a multi-resistance strain of *Staphylococcus aureus*. The antibacterial activity was estimated in terms of MICs using agar dilution method according to the CLSI guidelines.[19] All the tested compounds were dissolved in dimethylsulfoxide (DMSO), which later was used as a negative control with concentrations ranging from 25 to 325 µg/mL. Trade antibiotics ciprofloxacin in the same range of concentrations was used as a positive control. The MRSA stock cultures were maintained on nutrient agar plates. A loopful of Staphylococcal cells from the nutrient agar plates was inoculated into 10 mL nutrient broth and then adjusted to a 0.5 McFarland standard (approximately 1.5×10^8 CFU/ml). The compounds were diluted with fresh media to give final serial dilution from 25 to 325 µg/ml. Fifty µL of standardized 18 h incubated MRSA culture was introduced into petri dishes with media followed by the addition of various concentrations of the compounds studied. The MIC was listed as the lowest concentration that inhibits the growth of the MRSA strains. MIC's values are given in µg/mL, and all assays were carried out in triplicate.

RESULTS AND DISCUSSION

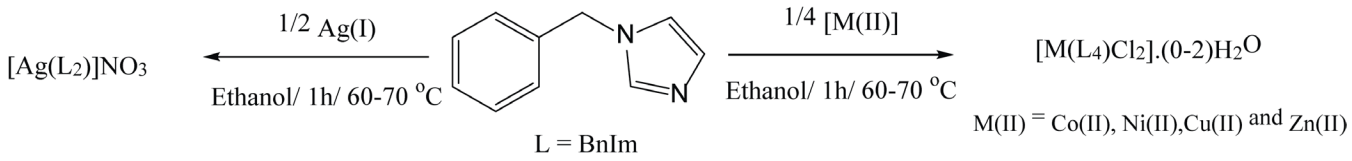
Synthesis and Characterization

In the present work, the ligand N-benzylimidazole was prepared according to our previous work.[20,21] The reaction of equimolar of imidazole with NaOH in hot DMSO produced sodium imidazolide, then after cooling the mixture to 40 °C, 1 equivalent of benzyl bromide was added (Scheme 1). The mixture was stirred at the same condition for 2 hours, then poured in icy water to give the product as a beige precipitate which was filtered of and washed with cold distilled water and left to dry at ambient temperature. The metal complexes were prepared by the reaction of the ethanolic solution of the ligand with the appropriate metal salts in a 1:4 mole ratio for Co(II), Ni(II), Cu(II) and Zn(II) and 1:2 mole ratio for Ag(I). The reaction mixture was heated for 1 hours between 60–70°C to afford the complexes as solid products (Scheme 2).

The FT-IR spectrum of the free ligand showed the common bands for other substituted azole derivatives.[20] A band appeared at 3000-3100 cm^{-1} is assigned to the stretching of



Scheme 1: Synthesis of the ligand N-benzylimidazole (BnIm)



Scheme 2: Synthesis of the complexes

Table 1: Antibacterial activity (μg/mL) of the tested compounds against MRSA

Concentrations (μg/mL) Complexes	*25*	*50*	*75*	*100*	*125*	*150*	*175*	*200*	*225*	*250*	*275*	*300*	*325*
Ligand	+	MIC	-	-	-	-	-	-	-	-	-	-	-
Co(II) complex	+	+	+	+	+	+	+	+	MIC	-	-	-	-
Ni(II) complex	+	+	+	+	+	+	+	+	+	+	+	+	+
Cu(II) complex	+	+	+	+	+	+	MIC	-	-	-	-	-	-
Zn(II) complex	+	+	+	+	+	+	MIC	-	-	-	-	-	-
Ag(I) complex	+	MIC	-	-	-	-	-	-	-	-	-	-	-
Ciprofloxacin*	+	+	+	+	+	+	+	MIC	-	-	-	-	-
Control**	+	+	+	+	+	+	+	+	+	+	+	+	+

- = No growth, + = growth

* Ciprofloxacin is used as a positive control for the experiment.

** DMSO is used as a negative control for the experiment.

C-$H_{aromatic}$, while the bending of the same bond has appeared in the range 700-800 cm^{-1}. The stretching band of C-$H_{aliphatic}$ has appeared in the range 2850-2950 cm^{-1}. The most important band of ν(C=N) in imidazole has appeared at 1510 cm^{-1}.

In the complexes, most of the bands that appeared in the free ligand spectrum appeared in complexes spectra, but at different positions and in different intensities, particularly, the most significant band one ν(C=N) in imidazole, which was shifted down by 22-42 cm^{-1}. This shifting indicates to the coordination of the tertiary nitrogen in the ligand with the metal ion.[22,23] The ^{1}H NMR of the ligand N-benzylimidazole (BnIm), was recorded in the range δ 0-16 ppm using d_6-DMSO as a deuterated solvent. A singlet peak that appeared at δ 5.21 is belongs to the benzylic CH_2. Multiple bands that appeared in the range δ 7.24-7.34 belong to five protons of the mono-substituted benzene ring. Imidazole H5′ and H4' were appeared at δ 7.02 and δ 7.39, respectively. Last but not least, the signal of imidazole H2′ has appeared as a singlet at δ 8.12. In the ^{13}C NMR of the ligand, the benzylic C-H appeared at δ 49.1. Imidazole C5′ and C4′ appeared at δ 120.2 and δ 126.6, respectively. The signals that appeared at δ 127.0, 127.03, 127.8, and 136.3 belong to the carbons of the benzene ring. The carbon of imidazole C2' appeared at δ 138.0. In Zn(II) and Ag(I) complexes, the imidazole H2' proton is appeared at δ 8.20 and δ 8.16, respectively. At the same time, the imidazole C2' is appeared at δ 138.13 and δ 139.3, respectively. The observed shifting was reported as a significant signal for coordination with metal ions.[23,24] For other complexes and because of the paramagnetism, no NMR spectra have been recorded for them.

In the UV-vis spectra, the free ligand showed two bands in the range 285-350 nm. These bands are attributed to n→π* and π→ π* transitions in imidazole and benzene ring.[20,21] Significantly, the above-mentioned bands are shifted to higher wavelengths in the complexes, which is good evidence for complexation with metal ions. The charge transfer and d→d transitions bands appear in the range 410-560 nm.

Antibacterial activity

Since pathogenic microorganisms continuously developing the mechanisms of resistance to presently used anti-microbial agents, the discovery of novel and more potent bactericidal agents is the preferable way to overcome multiple bacterial resistance and develop influential new drugs. At the same time, many of azoles found to have different biological activities.[6-10] So, the present work is focusing on the synthesis and evaluation of the antibacterial activity of an imidazole derivative, N-benzylimidazole (BnIm) and some of its metal complexes. The antimicrobial activity of the synthesized compounds against MRSA strains was undertaken using the dilution agar technique. The antibacterial activity of the tested compounds is described as the minimum inhibitory concentration (MIC) method (Table 1). In general, all the tested compounds except Ni(II) complex showed good activity against the MRSA bacteria. In comparing with the positive control, Ciprofloxacin, the results showed that the ligand (BnIm) and it's Ag(I) complex exhibited the highest activity even more than the positive control, ciprofloxacin. Whilst, Ni(II) complex exhibited the lowest activity. Other complexes Zn (II), Cu(II), and Co (II) are exhibited moderate activity.

CONCLUSIONS

Some of the transitions metal complexes derived from the ligand n-benzylimidazole have been synthesized and characterized using different spectral techniques. The antibacterial activity of the ligand and its metal complexes were determined against a MRSA using Ciprofloxacin as a positive control.

Generally, all the tested compounds show antibacterial activity against the tested bacteria except Ni(II) complex.

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