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Mixed Amodiaquine-Acetylsalicylic Acid Metal Complexes: Characterization and Antimicrobial Potentials

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ABSTRACT

Series of new mixed Amodiaquine and Acetylsalicylic acid ligand donors with some transition metals in the mole ratio 1:1:1, lead to the formation of compound type: [M(AMQ)(ASA)], where M = Co(II), Ni(II), Zn(II), and Cu(II) ions. The complexes were characterized to understand the nature of the metal bonding to the free ligands. The geometry of the synthesized complexes was proposed based on their properties and spectroscopic techniques: melting point, ultraviolet-visible, infrared, molar conductance, elemental analysis and atomic absorption spectroscopic. The compounds were found to be in a tetrahedral environment for zinc complex, and copper in square planar geometry. Based on the molar conductivities, it was observed that the as-synthesized compounds were non-electrolytic in nature. The as-synthesized complexes were screened against some isolated organisms: *B. Subtilis, K. Pneumonia, E. coli, P. aeruginosa*, and *S. aureus*. It was observed that the complexes exhibited better activities than the free ligands. [Zn(AMQ)(ASA)] complex possessed the highest zone of inhibition (49 mm) at 40 µl/ml against *E. coli* strains.

Keywords: Amodiaquine; Physicochemical; Acetylsalicylic acid; Metal complexes; Antibacterial

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1. Introduction

The chemistry of the ligands has received great attention due to their use as a potential organic chromophore for numerous numbers of transition metals [1]. A spread of resistant parasites to different types of drug is on the increase in tropical regions [2]. Increase in the effectiveness of some chelating agent is due to their ability to coordinate to the central metal ions, thus enhancing research on possible alternatives for some of the parent drugs or agents [3]. A combination of drugs for resistance has been suggested by the WHO, advocating that combination therapy should be used instead of a single drug where multi-drug resistance to the organism is a challenge [4]. More efforts have been contributed in the combination of inflammatory drugs for effectiveness to fight against the disease [5].

The introduction of fluorine in complexes helps to prolong the effect on the area of biological activity and the properties of the aromatic compound [6]. In developing new drugs against these resistant parasites, studies have shown that the use of transition metal complexes had received great attention a few years back [7-9]. Since the discovery of the anti-inflammatory drugs, the need for the drug has been developed exponentially as a result of a broad range of use of these drugs. It has been observed that the presence of carbonyl in Acetylsalicylic acid plays an important role in biological activities. Synthesis of some new metal complexes has been momentously acknowledged in the coordination chemistry field [10]. Derivatives of these coordination compounds act as potential oral drugs to cure the diseases [11]. Some metal complexes have revealed widespread pharmacological potential such as antituberculosis, antibacterial, and anticancer effects [8, 12-13].

Applications of complexes have great interest among chemist researchers. Some of them are thermally stable, flexible, and found to be useful as clinical diagnostic and chemotherapeutic agents. Synthesis and development of inorganic complexes based on coordinate bond and non-covalent forces have helped toward growing the area of chemotherapeutic agent research [14]. The introduction of a central metal ion into the biological system could be for therapeutic or diagnostic use. The effectiveness of the therapeutic and diagnostic agents have been known to increase upon coordination to a metal [4, 8]. The importance of metal drug complexes is gaining ground in the design of drugs on coordination with a central metal ion. This has helped to synthesize a variety of complexes with a wide ranging spectrum of biological and pharmacological potential [8, 15]. Owing to the past studies on metal-based therapeutic mediators' preparations and characterizations [8, 12, 15], we present the synthesis, characterization and antibacterial activity of mixed Amodiaquine-Acetylsalicylic metal complexes.

2. Materials and Methods

2.1 Materials

All chemicals and substances used for the synthesis of the complexes in this research work were of analytical grade purity. The UV spectra of the the free ligands and the complexes were recorded using spectrophotometer Aquamate V 4.60 at the University of Ilorin. The FT-IR spectra were recorded on the KBr pellet. The molar conductance in DMSO was also recorded on HANNA conductivity meter at a cell constant of 1.24. The ligands and their complex melting point analysis were performed on the Gallenkamp melting point. The elemental analysis (CHN) was reported at Medac Ltd, Brunel Science center, Egham, United Kingdom (Control Equipment CE 440 Analyzer) from Exeter Analytical. Atomic absorption spectroscopy was carried out on Alpha 4 atomic absorption spectrometer at the Obafemi Awolowo University, Ile-Ife, Nigeria.

2.2 Synthesis of the complexes

The procedure previously reported [12, 16] was adopted with slight modifications. Solution of Amodiaquine (0.178 g, 0.001 mol) in ethanol and solution of Acetylsalicylic acid dissolved in ethanol were mixed with 0.001 mol of (0.064 g, 0.059 g, 0.059 g and 0.065 g) of Co(II), Ni(II), Zn(II), and Cu(II), respectively, separately in distilled water (10 ml). The mixed solution was refluxed for 5 h with continuous stirring. Afterwards, it was left to stand and cooled to room temperature. The precipitate formed was filtered and washed with ethanol to eliminate any impurity and other starting materials that might be present. It was allowed to dry over silica gel in a desiccator for further analysis.

2.3 Antimicrobial assay

The antimicrobial assay of the ligands and the synthesized complexes were screened against the designated organisms: *K. Pneumonia, B. Subtilis, E. coli, P. aeruginosa, S. aureus*, and *S. faecalis* using agar diffusion as reported by Hoda et al. [17]. The ligands and their complexes were made ready by mixing each of the compounds (20 mg) in 1 mL of dimethyl sulfoxide. The solvent was used as a negative control. Amodiaquine and Acetylsalicylic acid were used as the ligands. The bacterial were cultured and used to lawn a Hinton agar plate with the use of sterile swab. About 6 mm diameter of the paper disc was impregnated each with a constant amount of 100 µg/mL of each compound. The prepared agar plates were then incubated at 37 °C for 24 h. The antimicrobial potentials of each of the complexes were then assessed by assessing the zone of inhibition diameter. The activities of the as-synthesized complexes were compared with the free ligands [17]. The solvent used as control showed no zone of inhibitions.

3. Results and Discussion

3.1 Physico-chemical properties of the ligands and complexes

The physicochemical properties of the free ligands and the corresponding metal complexes are presented in Table 1. The melting point of the ligands and the complexes showed the purity of the compounds and indicated the stability of the complexes [18]. Based on the elemental analysis data, the purity and chemical structure of the complexes as presented. It showed that there is a good agreement of the proposed structure with the theoretical values in percentages [4, 19]. Fig. 1 shows the suggested arrangements for the complexes.

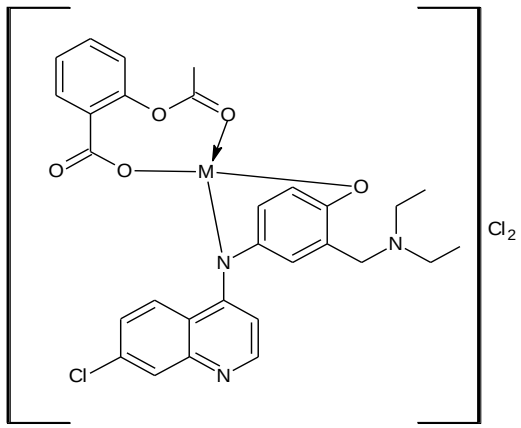
The attained complexes are powders with distinctive colour, stable in air, not soluble in common solvents, and even water but dissolve easily in polar solvents DMF and DMSO. The values for the magnetic moment of the complexes reveal that they are in the range of octahedral geometry except for Zn(II) and CuII) complexes which are in the tetrahedral and square-planar environment, respectively [12, 19]. The molar conductivity of all the metal (II) complexes was in the range of 5.46 – 7.03 $\Omega^{-1}cm^2/mol$ at room temperature. Hence, they exhibited a non-electrolytic character [12, 20].

3.2 Infrared spectra of the free ligands and complexes

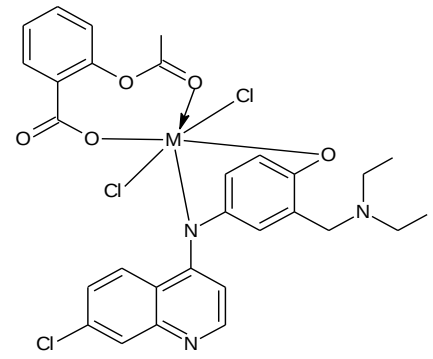
The FT-IR spectra of the free ligands and their complexes indicate the absorption band (Fig. 2) of the functional group present in the compounds as presented in Table 2. Infrared spectra of the free ligands showed bands around 3534 cm^{-1} and 3552 cm^{-1} for Amodiaquine and Acetylsalicylic acid, respectively, which are attributable to hydroxyl group ν(O–H) present [19, 21]. These bands were absent in the complexes' spectra; which is a suggestion of the deprotonation and participation of the hydroxyl cluster of the free ligands in the

bond created with the metal ions [19]. Based on the results obtained, it was observed that the bands around 3422 – 3518 cm^{-1} in the as-synthesized complexes as compared to the free ligands, shifted to lower wavenumbers which is an indication of the existence of water fragments as a result of lattice water. In the Amodiaquine molecule, the v(N–H) band appeared around 3308 cm^{-1}; this band shifted to higher frequency within 3315 – 3395 cm^{-1} in complex spectra, which indicates the contribution of the v(N–H) group of the Amodiaquine ligand in bond formation. The observed strong band around 1711 cm^{-1} in the free Acetylsalicylic acid ligand spectrum is a type of the carbonyl v(C=O) vibrations.

Upon complex materialization, there was a shift to higher frequency from 1728 cm^{-1} to 1751 cm^{-1} by this vibration, designating the attachment of unsaturated oxygen of the carbonyl group of Acetylsalicylic acid to the metal (II) ions [22]. This modification can be elucidated further by the electrons' contribution from oxygen to the metal ions unfilled d-orbitals [12]. As a result, new bands between 568 and 625 cm^{-1} ascribed to v(M–O) and bands within 501 – 534 cm^{-1} allocated to v(M–N) were detected. The bands observed within the range of 424 – 468 cm^{-1} are owing to M–Cl vibration supporting the presence of chlorine in the complex coordination spheres [19, 23]. The shift observed in the absorption band of the as-synthesized compounds when likened to that of the free ligands denotes the differences in the vibrational nature of the ligands upon coordination to the transition metal ions.



M = Cu(II) and Zn(II)



M = Co(II) and Ni(II)

Fig. 1. Proposed structure of the complexes.

3.3 Ultraviolet–visible spectra of the free ligands and complexes

The Ultraviolet-visible spectra of the free ligands and complexes are presented in Table 3. The absorption bands of Amodiaquine at 242 nm and 292 nm remain attributed to aromatic $\pi \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ respectively, and the band around 316 nm could be attributable to $n \rightarrow \pi^*$. The Acetylsalicylic acid ligand exhibited absorption bands at 223 nm and 266 nm, which are characteristics of intraligand $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ respectively. Upon complex materialization, $n \rightarrow \pi^*$ transition of the free ligands undergoes a bathochromic shift to a lengthier wavelength; an indication of the free ligand coordination to metal (II) ions [19]. The Cu(II) complex spectrum showed two absorption bands at 361 nm and 387 nm that are accredited to $^2B_{1g} \rightarrow {}^2E_{1g}$ and $^2B_{1g} \rightarrow$

$^2A_{1g}$ transitions, respectively. This complex is found to be in a square-planar environment [19, 24].

The Co(II) complex spectrum exhibited three bands which are attributed to $^4T_{1g} \rightarrow {}^4T_{1g}(P)$, $^4T_{1g} \rightarrow {}^4A_{2g}(F)$, and $^4T_{1g} \rightarrow {}^4T_{2g}(P)$ transitions, suggesting an octahedral geometry [19]. The spectrum of the nickel complex shows three absorption bands around 357 nm, 384 nm and 445 nm which are assigned to $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$, $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$, and $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$ respectively, which is characteristic of an octahedral geometry [12]. Zn(II) complex has bands around 341 nm and 359 nm that are allocated to a charge transfer transition L → M (LMCT) and found to be in tetrahedral geometry [12].

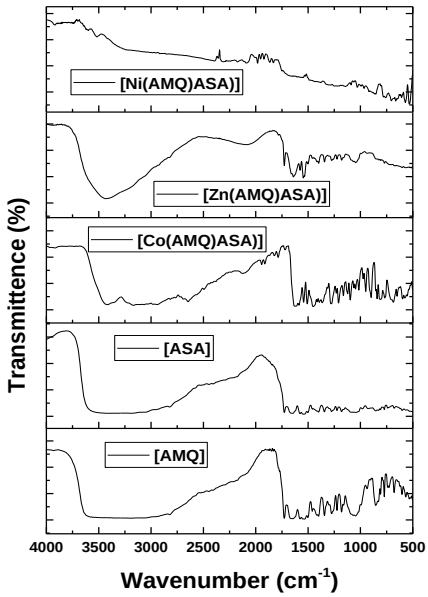


Fig. 2. FT-IR spectra of the ligands and metal complexes.

3.4 Antibacterial activity of the free ligands and its complexes

Methods reported by Batool et al. [16] and Hoda et al. [17] were adopted for this study. The synthesized complexes and their free ligands were screened to evaluate the antimicrobial activity against some bacterial strains: *K. Pneumonia*, *S. aureus*, *B. Subtilis*, *P. aeruginosa*, *E. coli*, and *S. faecalis* using the disc diffusion technique for MIC and MBC as presented in Tables 4 and 5. The data obtained for the as-synthesized complexes were likened with the zone of inhibition of the free parent ligands in Figs. 3 and 4. It was observed that the complexes showed higher activities than the free ligands concerning the studied organisms. Zn(II) complex exhibited the highest clear zone of inhibitions when compared to the other complexes.

However, the antimicrobial screening revealed that there was a decreased zone of inhibition for the ligands. These activities were enhanced through bond creations between the free ligands and metal (II) ions as compared with the free ligands against the selected organisms [9, 24]. The compounds exhibited activities at both concentrations against the *E. coli* strain in the order: [Zn(AMQ)(ASA)] > [Cu(AMQ)(ASA)] > [Co(AMQ)(ASA)] > [Ni(AMQ)(ASA)] > Amodiaquine [AMQ] > Acetylsalicylic acid [ASA]. After screening using the disc diffusion method, all the complexes were evaluated by MIC and MBC determinations. In Minimum Inhibitory Concentration, the Zn(II) complex exhibits the highest zone of inhibition (49 mm) at 40 µg/g against *E. coli* (Figures 3 and 4). Cu(II) and Co(II) possess the same zone of inhibition (25 mm) at 40 µg/g against *S. faecalis*.

In Minimum Bacteria Concentration, Ni(II) followed by Co(II) showed the highest zone of inhibition (49 mm) at 40 µg/g against *S. aureus*. Some factors responsible for the increased antibacterial activity of the metals could be conductivity, solubility, and bond length between the metal ion and ligand [25]. Other observed increased activity of the metal complexes as compared to the free ligands can be elucidated on the foundation of Overtone's cell permeability insight and Tweedy's chelation model. Chelation increases the delocalization of π-electrons over the whole

chelate sphere and improves the infiltration of the compounds into lipid membranes, while Overtone's theory of the cell penetrability describes the process in which the soluble lipid materials are allowed to pass through cell lipid membrane as a significant feature of antimicrobial activity [12-17, 19].

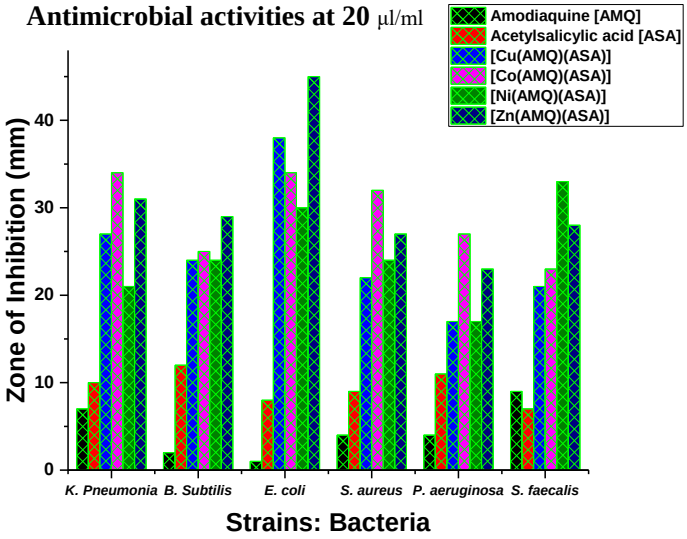


Fig. 3. Antimicrobial potentials of the ligands and complexes at 20µl/ml.

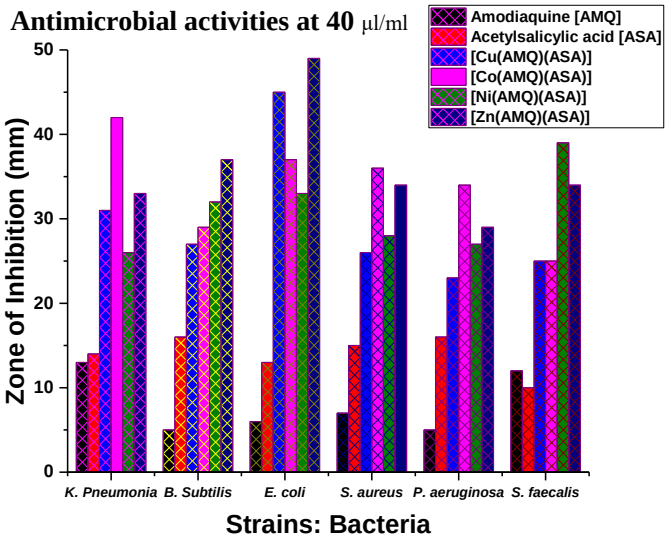


Fig. 4. Antimicrobial potentials of the ligands and complexes at 40 µl/ml.

Table 1. Physico-chemical properties of the free ligands and the as-synthesized complexes.

Ligands/ Complexes	**Yield (%)**	**Melting Point (°C)**	**Colour**	**Conductivity** $\Omega^{-1}cm^2/mol$	**μeff (B.M)**	**Elemental % Found (Calcd.)**			
						C	**H**	**N**	**M**
Amodiaquine [AMQ]		170-172	Yellow	-	-	-	-	-	-
Acetylsalicylic acid [ASA]		133-135	White	-	-	-	-	-	-
$[Cu(AMQ)(ASA)]Cl_2$	78	234-236	Green	6.85	1.75	51.45 (51.98)	4.32 (4.48)	6.37 (6.27)	9.53 (9.41)
$[Co(AMQ)(ASA)Cl_2]$	65	212-214	Pink	7.03	4.20	52.05 (52.30)	4.27 (4.51)	6.86 (6.31)	8.73 (8.86)
$[Ni(AMQ)(ASA)Cl_2]$	46	195-197	Blue	6.71	3.10	52.11 (52.32)	4.28 (4.51)	6.17 (6.31)	8.51 (8.82)
$[Zn(AMQ)(ASA)]Cl_2$	56	203-205	Brown	5.46	Diamagnetic	51.00 (51.79)	4.39 (4.47)	6.12 (6.25)	9.64 (9.73)

Table 2. FT-IR spectra of the free ligands and the as-synthesized complexes.

Ligands/ Complexes	**υ(O-H)**	**υ(N-H)**	**υ(CH_2/CH_3)**	**υ(C=O)**	**υ(C-N)**	**υ(C-O)**	**υ(M-O)**	**υ(M-N)**	**υ(M-Cl)**
Amodiaquine [AMQ]	3534	3308	3010, 2998	-	1649	1274, 1048	-	-	-
Acetylsalicylic acid [ASA]	3552	-	3176, 3044	1711	-	1272, 1044	-	-	-
$[Cu(AMQ)(ASA)]C_{l2}$	3422	3394	3124, 2980	1734	1639	1256, 1032	625	501	468
$[Co(AMQ)(ASA)Cl_2]$	3426	3386	3174, 3012	1744	1620	1290, 1098	598	502	424
$[Ni(AMQ)(ASA)Cl_2]$	3518	3318	3074, 2986	1751	1604	1280, 1030	570	534	444
$[Zn(AMQ)(ASA)]Cl_2$	3450	3361	3076, 2982	1728	1640	1258, 1026	568	508	454

Table 3. UV spectra of the free ligands and the as-synthesized complexes.

Ligands/ Complexes	Absorption bands (nm)	Electronic Configuration	Assignment	Geometry
Amodiaquine [AMQ]	242		$\pi \rightarrow \pi^*$	
	292	-	$\pi \rightarrow \pi^*$	-
	316		$n \rightarrow \pi^*$	
Acetylsalicylic acid [ASA]	223	-	$\pi \rightarrow \pi^*$	
	266		$n \rightarrow \pi^*$	-
$[Cu(AMQ)(ASA)]Cl_2$	361	d^9	$^2B_{1g} \rightarrow {}^2A_{1g}$	Square planar
	387		$^2B_{1g} \rightarrow {}^2E_{1g}$	
$[Co(AMQ)(ASA)Cl_2]$	341	d^7	$^4T_{1g} \rightarrow {}^4T_{1g}(P)$	Octahedral
	455		$^4T_{1g} \rightarrow {}^4A_{2g}(F)$	
	497		$^4T_{1g} \rightarrow {}^4T_{2g}(F)$	
$[Ni(AMQ)(ASA)Cl_2]$	357	d^8	$^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$	Octahedral
	384		$^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$	
	445		$^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$	
$[Zn(AMQ)(ASA)]Cl_2$	341	d^{10}	LMCT	Tetrahedral
	359			

Table 4. Minimum inhibition concentration of the free ligands and the as-synthesized complexes.

	Concentration (µg/g)											
	20	**40**	**20**	**40**	**20**	**40**	**20**	**40**	**20**	**40**	**20**	**40**
Ligand/ Complexes	***K. Pneumonia***		***B. Subtilis***		***E. coli***		***S. aureus***		***P. aeruginosa***		***S. faecalis***	
Amodiaquine [AMQ]	7	13	2	5	1	6	4	7	4	5	9	12
Acetylsalicylic acid [ASA]	10	14	12	16	8	13	9	15	11	16	7	10
[Cu(AMQ)(ASA)]	27	31	24	27	38	45	22	26	17	23	21	25
[Co(AMQ)(ASA)]	34	42	25	29	34	37	32	36	27	34	23	25
[Ni(AMQ)(ASA)]	21	26	24	32	30	33	24	28	17	27	33	39
[Zn(AMQ)(ASA)]	31	33	29	37	45	49	27	34	23	29	28	34

Table 5. Minimum bactericidal concentration of the free ligands and the as-synthesized complexes.

	Concentration (µg/g)											
	20	**40**	**20**	**40**	**20**	**40**	**20**	**40**	**20**	**40**	**20**	**40**
Ligand/ Complexes	***K. Pneumonia***		***B. Subtilis***		***E. coli***		***S. aureus***		***P. aeruginosa***		***S. faecalis***	
Amodiaquine [AMQ]	6	9	17	25	14	18	6	10	3	7	8	11
Acetylsalicylic acid [ASA]	3	8	1	3	6	7	16	18	11	15	14	20
[Cu(AMQ)(ASA)]	22	26	19	24	16	29	25	29	35	39	24	31
[Co(AMQ)(ASA)]	32	37	28	37	29	34	38	42	23	29	37	39
[Ni(AMQ)(ASA)]	24	31	27	39	25	36	36	44	20	26	31	35
[Zn(AMQ)(ASA)]	17	25	11	19	27	31	33	38	25	29	21	26

4. Conclusion

A new series of synthesized metal drug complexes were characterized by melting point, ultraviolet-visible, infrared, molar conductance, elemental analysis, and atomic absorption spectroscopic. The data observed support the proposed structure of the complexes. Conductivity capacities signpost that the as-synthesized complexes are non-electrolytes in solution. According to the spectra, Amodiaquine coordinated to the central metal ions via the oxygen of the hydroxyl group and nitrogen of the amine group, while Acetylsalicylic acid coordinated through the oxygen atom of the hydroxyl group and carboxyl group. The proposed structure for Ni(II) and Co(II) complexes were observed to be in an octahedral geometry, Cu(II) possessed a square-planar geometry, while Zn(II) complex exhibited a tetrahedral geometry. The antimicrobial potential of the free ligands and the as-synthesized complexes suggest that Zn(II) complex possesses better antibacterial activities than the other complexes and the free ligand against the investigated strains. Also, antimicrobial screening showed that the as-synthesized complexes exhibit better potency than their parent-free ligands.

Acknowledgments

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