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Synthesis, Physicochemical, and Antimicrobial Activity of Copper and Zinc Complexes with N, O - Bidentate Schiff Base

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ABSTRACT

This paper is intended to prepare new antimicrobial complexes with proven efficiency. The Schiff base, through the condensation process of salicylaldehyde and *p*-toludine, and its Cu and Zn complexes were successfully synthesized. The Schiff base and its complexes were characterized using molar conductivity, Ultraviolet-visible (UV-Vis), atomic absorption spectroscopy (AAS), and Fourier transform infrared (FTIR) techniques. Accordingly, these characterizations not only confirmed that the synthesized Schiff base acted as N,O bidentate ligand (through azomethine nitrogen and phenoxide oxygen) and chelated with Cu(II) and Zn(II) in the metal-to-ligand ratio of 1:2 but also revealed the characteristic electronic-transition of $\pi\rightarrow\pi^*/n\rightarrow\pi^*$ of the ligand, and ligand-metal charge transfer and d-d of the metal complexes. Moreover, both Cu and Zn complexes recorded weak molar conductance of 54.12 and 51.41 S cm^2 mol^{-1}, respectively. Further, their antibacterial activities were evaluated by disc diffusion assay against *Staphylococcus aureus* (gram-positive), *Escherichia coli* (gram-negative), and *Bacillus cereus* (gram-negative) bacteria. For all microbial, the metal complexes recorded higher activities than the parent ligand; such increased activity of the complexes may be due to the chelation of the metal ion in the complexes, which enhances the lipophylic character favoring its permeation through the lipid layer of the cell membrane. Such metal complexes can therefore be explored in the future as an option for decreasing the pathogenic potential of infecting bacteria.

Keywords: Metal complex, Schiff base, Condensation reaction, Antimicrobial activity, Salicylaldehyde.

1. INTRODUCTION

Organometallic-composites, organic and inorganic hybrid systems, represent a class of advanced materials with novel properties for a wide range of applications- biomedicine, food, cosmetics, agriculture, paints, catalysis, and textiles (Emam, 2019; Nazirkar et al., 2019; Saranya et al., 2020; Sathiyavimal et al., 2018; Vasantharaj et al., 2019). Such materials encompassed transition metals and macro-organic molecules; notably, Schiff bases have been well-known counterparts. Schiff bases, imine compounds with azomethine (C=N) functional group, are typically formed by the condensation of a primary amine and an aldehyde or a ketone; the resultant compound has a

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general formula of $R_1R_2C=NR_3$, where R_1 is an aryl group, R_2 is a hydrogen atom, and R_3 is either an alkyl or aryl group (Abdulkarem et al., 2017; Hossain et al., 2018; Rehman et al., 2019). Despite their synthetic problem, a wide variety of ligands that vary in denticity, flexibility, nature of donor atoms, and electronic properties can be tuned. Particularly, chelating ligands containing N, S, and O donor atoms are regarded as privileged ligands due to their ability to form stable complexes with a wide range of transition metals (Cipurković et al., 2021; Fasina et al., 2012; Frei 2020; Mehmet Tuèmer et al., 1999; Saranya et al., 2020; Zhao et al., 2015). Notably, Schiff bases and their complexes are reported to possess a broad range of important biological activity like antimicrobial, antibacterial, antifungal, anticancer, anti-flammatory agents, anti-HIV, antimalarial, antiproliferative, antipyretic properties, anti-depressant and diuretic activities (Lakshmanan et al., 2018; Revathi and Thambidurai, 2017; Shiekh et al., 2013). For instance, a series of 1-(5-substituted-2-oxoindolin-3-ylidene)-4-(substituted-pyridin-2-yl) thiosemicarbazide derivatives were screened and evaluated for *in-vitro* antibacterial and antifungal activity against *B. subtilis, S. aureus, E. coli, P. aeruginosa, C. albicans,* and *A. niger*; they were exhibited a moderate to antibacterial/fungal activities (Arulmurugan et al., 2010). Similarly, it is revealed that the Me_2dibenzo[b,l]dipyridyl[g,q][1,5,11,15]-tetraaza-6,10,16,20-tetraoxocycloeicosane macro-cyclic complexes of Mn(II) and Co(II) have demonstrated antibacterial activities against *E. coli, P. aeruginosa, B. cereus, S. aureus,* and *antifungal against C. albicans* (Kumar et al., 2015).

Meanwhile, antimicrobial resistance is alarmingly becoming a global concern with rapid increment in multidrug-resistant microbial. With the help of specific drug treatment, most diseases are cured; however, these days, some pathogens are uncured since they developed resistance to the specific treatment. For instance, *Staphylococcus aureus*, and *Enterococcus* became resistant to methicillin, and vancomycin antibiotic drugs, respectively (Rafique et al., 2010; Siddappa et al., 2014; Srivastava et al., 2010; Zhang and Lippard, 2003). Furthermore, this drug-resistance microbial class comprises *Enterococcus faecalis, M. tuberculosis, Escherichia coli, Shigella flexeneri, Pseudomonas aeruginosa, Salmonella typhi,* and *Bacillus subtilis*. Even some fungal pathogens showed resistance features against *Candida albicans, Aspergillus flavus, Fusarium solani,* and *Candida glaberata* drugs (Saha et al., 2009). Consequently, there is an urgency to develop new and more effective drugs with low toxicity; otherwise, they will emerge

as one of the most dangerous threats to the successful treatment of microbial/insecticidal diseases and human well-being.

The aim of this paper, therefore, was to prepare new antimicrobial complexes with proven efficiency- including synthesizing and characterizing Cu(II) and Zn(II) metal complexes of Schiff base derived from the condensation of salicylaldehyde with *p*-toludine. Furthermore, investigating their antimicrobial activities against *Staphylococcus aureus*, *Escherichia coli*, and *Bacillus cereus* by using the disc diffusion method was the other motive.

2. EXPERIMENTAL DESIGN

2.1. Chemicals

Important chemicals such as *p*-toludine (95%, Sigma Aldrich, USA), salicylildehyde (95%, Sigma Aldrich, USA), $ZnCl_2.6H_2O$ (98%, Sigma Aldrich, USA), $CuCl_2.2H_2O$ (98%, Sigma Aldrich, USA), KOH (Fluka, Switzerland), ethanol (Nice, India), ether (Finkem, India), acetone (Loba, India), HCl (Fluka, Switzerland), H_2SO_4 (Fluka, Switzerland) and Dimethylsulphoxide (DMSO, Finkem, India) were purchased; all the chemicals were analytical grade and used without further purification. Similarly, Nutrient agar medium, Mueller-Hinton agar medium, inoculating wire loop, sterilized 6 mm paper discs, antibiotic zone scale, and ampicillin were deployed. The microorganisms for checking the antimicrobial activities were *Staphylococcus aureus* (gram-positive), *Escherichia coli*, and *Bacillus cereus* (gram-negative), which were verified and donated from the microbiology division of Mekelle University.

2.2. Physical Measurements

Melting points of the ligands and their metal complexes were determined by an open capillary method using electro-thermal melting point apparatus. Similarly, their conductance measurements were carried out using an Elico conductivity bridge and dip-type conductivity cell. Notably, their elemental analyses and FTIR spectra were recorded with an Elemental Vario EL III model and a Perkin Elmer Spectrum BX FT-IR spectrophotometer (USA) as KBr pellets in the range of 4,000-400 cm^{-1}, respectively. The electronic transition of the ligand and metal complexes were studied using a Spectronic Genesys 2PC UV-Vis spectrophotometer (USA) in the range of 200-750nm.

2.3. Syntheses Methods

2.3.1. Syntheses of Schiff base

The Schiff base was synthesized by a modified procedure (Khaled et al., 2013); specifically, 10 mmol of salicylaldehyde and 0.5 mol of ethanol were put in a 250-mL round bottom flask while stirring for 5 min in a hot water bath. To this mixture, 10 mmol of *p*-toludine was added and stirred for 10 min. Then, it was transferred to a reflux setup and refluxed in a hot water bath (80-90 ^{o}C) for 4 h after adding 0.5 mmol of conc. HCl. Subsequently, the product was filtered and washed with cold ethanol, acetone, and ether. Finally, it was recrystallized from ethanol.

2.3.2. Syntheses of Metal Complexes

The Cu(II) and Zn(II) complexes were prepared via a modified procedure (Aiyelabola et al., 2012; Khaled et al., 2013); typically, 2 mmol of the as-prepared Schiff base and 0.5 mol of ethanol were put in the bottom flask while stirring in hot water-bath for 5 min. To this mixture, 1 mmol of $ZnCl_2.6H_2O$ was added and stirred for 20 min. Next, the as-obtained mixture was refluxed in a water bath (80-90 °C) for 5 h with stirring after adding 0.4 mmol NaOH solution step-wise. Then, the Zn complex was filtered and washed thoroughly with water, ethanol, ether, and acetone. Finally, it was dried in a desiccator. The same procedure was followed for preparing the Cu complex except for replacing $ZnCl_2.6H_2O$ with $CuCl_2.2H_2O$.

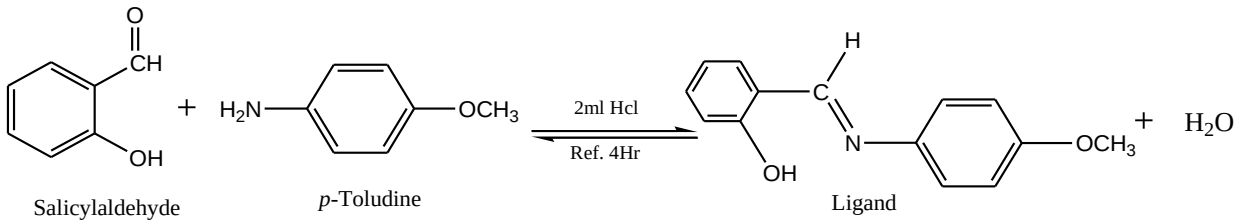
2.4. Evaluation of Antimicrobial Activity

Nutrient broth (peptone, 10; Yeast extract, 5; NaCl, 10 in (g/L)) was used for culturing of *Staphylococcus aureus*, *Escherichia coli*, and *Bacillus cereus;* 10% DMSO solution was used as a solvent. The media and glassware were autoclaved for 15 min at 121°C under 15 psi pressure. After cooling, a loop of each bacteria strain was inoculated in 50 mL autoclaved media and incubated at 37 °C for 24 h. Then, 100 µL of the culture was uniformly plated on Petri plates using a sterile rod. A sterilized circular paper disk (of 6 mm diameter) was placed in the center of Petri plates in contact with the culture, and Schiff base and complexes were pipetted onto it (Khaled et al., 2013; Shiekh et al., 2013). The concentration of Schiff base and the complexes were varied at 500 µg/mL, 800 µg/mL, and 1 mg/mL. ampicillin was used as a standard drug. After 24 h of incubation at 37 °C, all plates were examined for possible inhibition zone in millimeters (mm).

3. RESULTS AND DISCUSSION

3.1. The Physical and Chemical Properties

The Schiff base, the ligand, was prepared through a condensation reaction of the carbonyl group of the salicylaldehyde and the $–NH_2$ group of the toludine (Scheme 1) with a 47% yield. Since the reaction is slow and reversible, in favor of the forward reaction, HCl was added as a catalyst. While the complexes of Cu(II) and Zn(II) were prepared using metal-to-ligand in a 1:2 mole ratio; the pH of the reaction was adjusted by adding aqueous NaOH. The presence of the base, NaOH, enhances the nucleophilicity of the ligand and affords uni-negative chelation with metal ions (Khaled et al., 2013), which boosts % yield of Cu and Zn complexes with 60% and 67% yield, respectively (Table 1). Form the series of solubility tests, it was found that the ligand is readily soluble in benzene; sparingly soluble in methanol, ethanol, and acetonitrile; but partially soluble in chloroform and petroleum ether.



Scheme 1. Formation of new Schiff base

However, the Cu and Zn complexes are readily soluble in DMSO and DMF; hardly soluble in ethanol, methanol, or chloroform; and insoluble in benzene. Meanwhile, both the ligand and its Cu/Zn complexes decomposed above 280 and 350 ℃, respectively (Table 1) without showing melting point, which was similarly reported elsewhere (Ahamad et al., 2012). Chemically, the ligand and its complexes are stable in the atmosphere, revealing they are non-hygroscopic. However, the former is found sensitive to water; it hydrolyses to respective parent compounds. On the other hand, the ligand shows only a single spot on the TLC test, which indicates it is pure. Contrarily, since the complexes are insoluble in most common solvents, they had not been tested. Meanwhile, using Volhard's test, the chloride test for Cu(II) and Zn(II) complexes was found negative, indicating there is no chlorine ion either in the inner or outer sphere of the complexes (Rama and Selvameena, 2014).

Table 1. Physical properties of the Schiff base and its metal complexes.

Molecular Formula	***Molecular Weight (g/mol)***	***Physical Appearance***	***Color***	***Decompose (ºC)***	***Yield (%)***	***Average Inhibition Zone (mm)***
$L(C_{14}H_{13}O_2N)$	227.26	Fine powder	greenish-yellow	> 280 °C	47	2.56
$CuL_2(H_2O)_4$ ($[Cu(C_{14}H_{12}O_2N)_2(H_2O)_2].2H_2O$)	588.12	Fine powder	dark brown	> 350 °C	60	7.91
$ZnL_2(H_2O)_2$ ($[Zn(C_{14}H_{12}O_2N)_2(H_2O)_2]$)	553.93	Fine powder	White	> 350 °C	67	7.49

Molar conductance was determined from conductivity measurement of the complexes in DMSO at 24 °C using the relation $\Lambda_m = 10^3$ L/C, where Λ_m is the molar conductance of the complexes, L is the specific conductance, and C is the molar concentration of the metal complex solutions (Mohamed et al., 2014). Accordingly, the molar conductances of the Cu and Zn complexes were found to be 54.12 and 51.41 S cm^2 mol^{-1}, respectively, indicating their non-electrolyte nature (Mahal et al., 2015). Moreover, rendering to the elemental analysis, it is noted that the experimental Cu metal percentage is 9.47% which is close to the calculated value of 10.81% for the formula $CuL_2(H_2O)_2.2H_2O$. Similarly, the recorded experimental Zn metal percentage of 10.96 % is close to the calculated value of 11.80% for the formula $ZnL_2(H_2O)_2$. Thus, the metal-to-ligand ratio is found to be 1:2 which is the same as the mole ratio used for the complex synthesis.

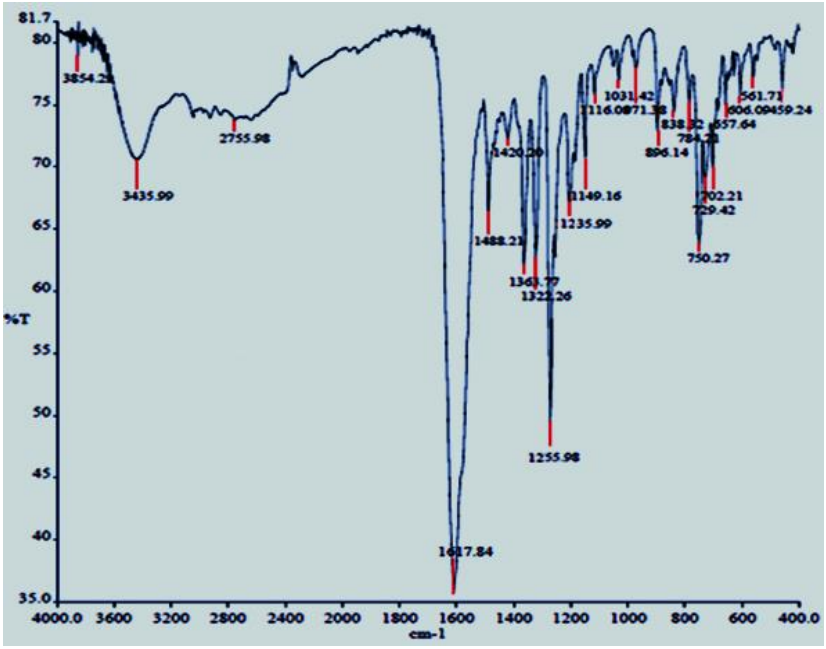


Figure 1. FTIR spectrum of the ligand.

3.2.Infrared Spectra

FTIR is a powerful technique for determining the functional groups of the targeted molecule. The FTIR spectrum of the ligand displays the characteristic vibration frequencies (Fig 1) and reveals that the targeted Schiff base has been synthesized. The broad band centered at 3435 cm^{-1} is inferred to be phenolic O-H with its intra/intermolecular hydrogen bonding around 3600 cm^{-1} (Ali et al., 2018; Cao et al., 2019). The strong sharp band located at 1617 cm^{-1} is attributed to the C=N stretching of the azomethine group; along with the absence of carbonyl bond (C=O) and amine (N–H), vibrations around 1744 and 1587 cm^{-1}, respectively, it strongly confirms that the condensation reaction took place, leading to the formation of azomethine group (Azamia et al., 2017; Jia et al., 2021; Revathi and Thambidurai, 2017).

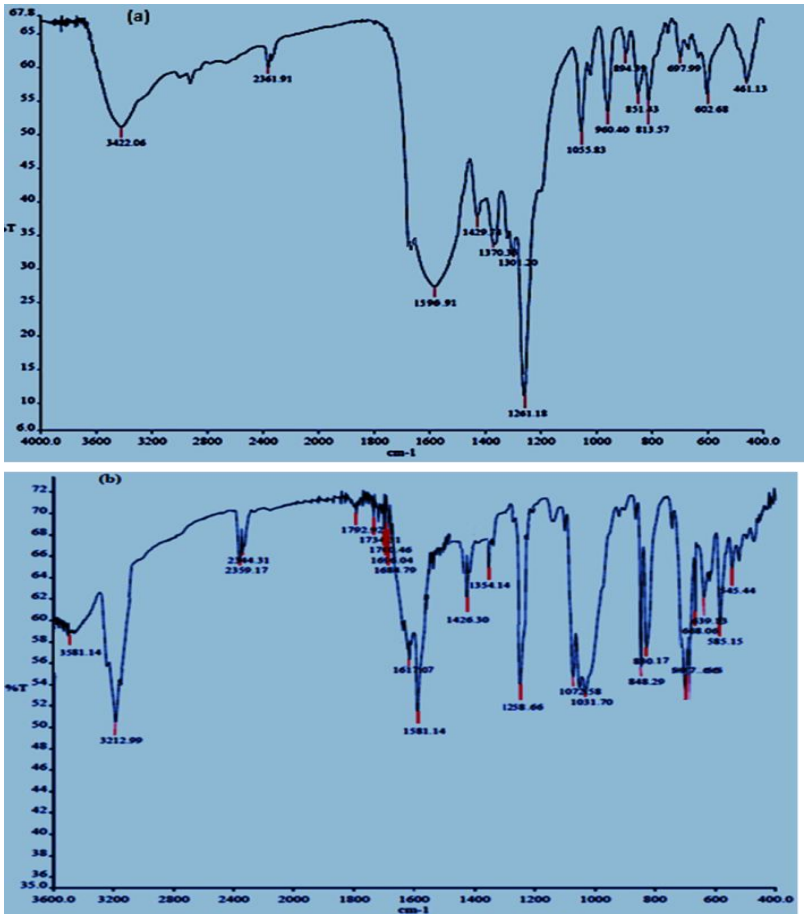


Figure 2. FTIR spectra of Cu (a) and Zn complex (b).

Whereas, the C=C stretching of the aromatic ring is observed at 1488 cm^{-1}. Notably, the N-O stretching, around 1449 cm^{-1}, is not reordered, indicating no oxidized nitrogen groups

(Azamia et al., 2017). The other strong band at 1255 cm^{-1} could be assigned to C-O stretching of the phenolic/methoxy group while the bands at 1149, 750, and 729 cm^{-1} correspond to the bending frequencies of O-H phenolic, C-H of the methoxy, and aromatic ring of the ligand, respectively (Foorginezhad and Zerafat, 2018; Zhou et al., 2020). Meanwhile, comparing the spectrum of the ligand with its Cu(II) and Zn(II) complexes, a significant shift of characteristics bands can be observed that reveals the complexation has occurred (Fig 2).

The band centered at 3422 and 3113 cm^{-1} can be assigned to the O-H stretching of the coordinated water in Cu(II) and Zn(II) complexes, of $CuL_2(H_2O)_2.2H_2O$ and $ZnL_2(H_2O)_2$ formula; and its coordinated water molecule exhibits rocking, twisting and waging modes in the lower frequency region ranging from 1000-700 cm^{-1} (Mohamed et al., 2014). Like the ligand, the bands in the range of 2950-2360 cm^{-1} can be assigned to the C-H stretching of aromatic/methoxy groups of the complexes (Chauhan et al., 2019). The characteristic stretching band of the C=N group in the free ligand, which was 1617 cm^{-1}, is shifted to a lower frequency to 1590 and 1581 cm^{-1} in the Cu(II) and Zn(II) complexes, respectively (Mahal et al., 2015). Consequently, this negative shift in frequency of the C=N band of the free ligand deduces the involvement of the nitrogen atom of the azomethine group in complexation (Cipurković et al., 2021; Mahal et al., 2015; Rama and Selvameena, 2014). Not only this, the positive shift of C-O stretching to 1261 in Cu(II) and 1258 cm^{-1} in Zn(II) indicates the deprotonation of the phenolic group, which was 1149 cm^{-1} in the ligand. Subsequently, this happened when the oxygen atom of the phenoxide is attached to metal in the complex (Akila et al., 2012; Nazirkar et al., 2019). Furthermore, another fingerprint of the metal complex has been disclosed in the less than 1000 cm^{-1} vibration frequency; the bands at 698 and 602 cm^{-1} in Cu(II), and 668 and 585 cm^{-1} in Zn(II) can be assigned for M–O, and M–N stretching, respectively (Cipurković et al., 2021; El-Yazeed and Ahmed, 2019; Ghobashy, 2017; Mahal et al., 2015). Therefore, the FTIR analysis confirms that the ligand behaves as an N,O-bidentate in both complexes, coordinating via the nitrogen of the azomethine and oxygen of the phenoxide. The main characteristics of stretching bands for the Schiff base and complexes of Cu and Zn are summarized in table 2.

Table 2. FTIR spectral data of the ligand and its Cu and Zn complexes.

Samples	$\upsilon_{C=N}$ ***(cm^{-1})***	υ_{O-H} ***(cm^{-1})***	υ_{C-O} ***(cm^{-1})***	υ_{C-H} ***(cm^{-1})***	υ_{M-N} ***(cm^{-1})***	υ_{M-O} ***(cm^{-1})***
Ligand	1617	3550-2950	1255	3050	-	-

Cu-L_2 complex	1590	3530-2900	1261	2950	602	698
Zn-L_2 complex	1581	3400-2900	1258	2359	585	668

3.3.UV-Vis Spectra of the Ligand and Metal Complexes

UV-Vis technique determines how the electron transition between the ligand moieties and the metal ion is. The UV-Vis spectra of the ligand and complexes are presented (Fig 3). According to, the ligand displays high-intensity bands at 28,248 cm^{-1} (354 nm) with a shoulder absorption of 27,472 (364 nm) which is fairly assigned to a combination of $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transition characteristic of the azomethine chromophore, respectively. This once again confirms the successful preparation of the ligand with the C=N functional group.

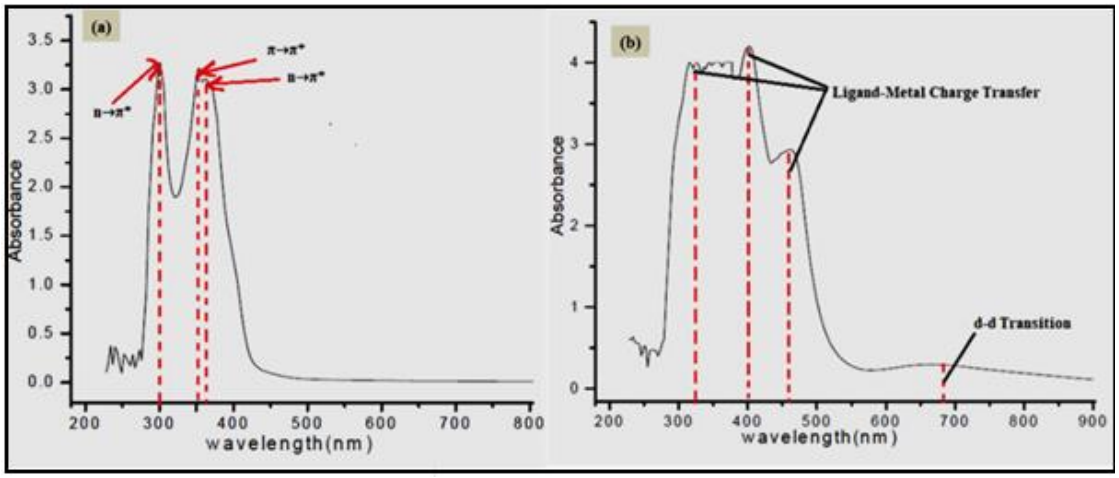


Figure 3. UV-Vis spectra of ligand (a) and Cu(II) complex (b).

Furthermore, the strong absorption at 33,333 cm^{-1} (300 nm) with weak multiple bands in the range of 42,553-36,231 cm^{-1} (235-276 nm) indicates $n \rightarrow \pi^*$ transitions of the substituted benzene moieties and the aromatic group, respectively (Mahal et al., 2015; Mohamed et al., 2014; Rama and Selvameena, 2014). Meanwhile, the electronic spectra of Cu(II) and Zn(II) complexes display important new prominent bands; for Cu(II) complex, high-intensity bands at 31,250 cm^{-1} (320 nm), and 24,875 cm^{-1} (402 nm) with a shoulder of 21,978 cm^{-1} (455 nm) are observed (Fig 3b), inferring the charge transfer between the phenolic and azomethine chromophores of the ligand with Cu metal, respectively. Compared with free ligands, this is because of a bathochromic shift in the absorption frequencies of phenolic and azomethine chromophores, as the result of their involvement in complexation (Amane et al., 2014; Mahal et al., 2015). This reconfirms the coordination through phenolic oxygen and azomethine nitrogen

with Cu(II). Similarly, for the Zn complex, the phenolic and azomethine bathochromic shift are spotted at 30,769 cm^{-1} (325 nm), and 24,096 cm^{-1} (415 nm). Furthermore, the broad band centered at 14492 cm^{-1}, (690 nm) for Cu(II) could be assigned to the combination of three possible transitions $^2B_1 \rightarrow {}^2A_1$, $^2B_1 \rightarrow {}^2B_2$, and $^2B_1 \rightarrow {}^2E$ which strongly suggests a distorted octahedral geometry around Cu(II) (Shiekh et al., 2013). Moreover, the Zn(II) complex shows no d-d band absorption, because of its electronic configuration, d^{10} (Amane et al., 2018; Mohamed et al., 2014).

3.4. Biological Activity

In assessing their potential antimicrobial agents, the antibacterial activity, *in-vitro*, of the ligand and its complexes at the concentration of 500 µg/mL, 800 µg/mL, and 1 mg/mL were tested against gram-positive *Staphylococcus aureus*, gram-negative *Escherichia coli*, and *Bacillus cereus* bacteria while comparing with ampicillin, a control antibacterial drug. The antimicrobial result is displayed in figure 4.

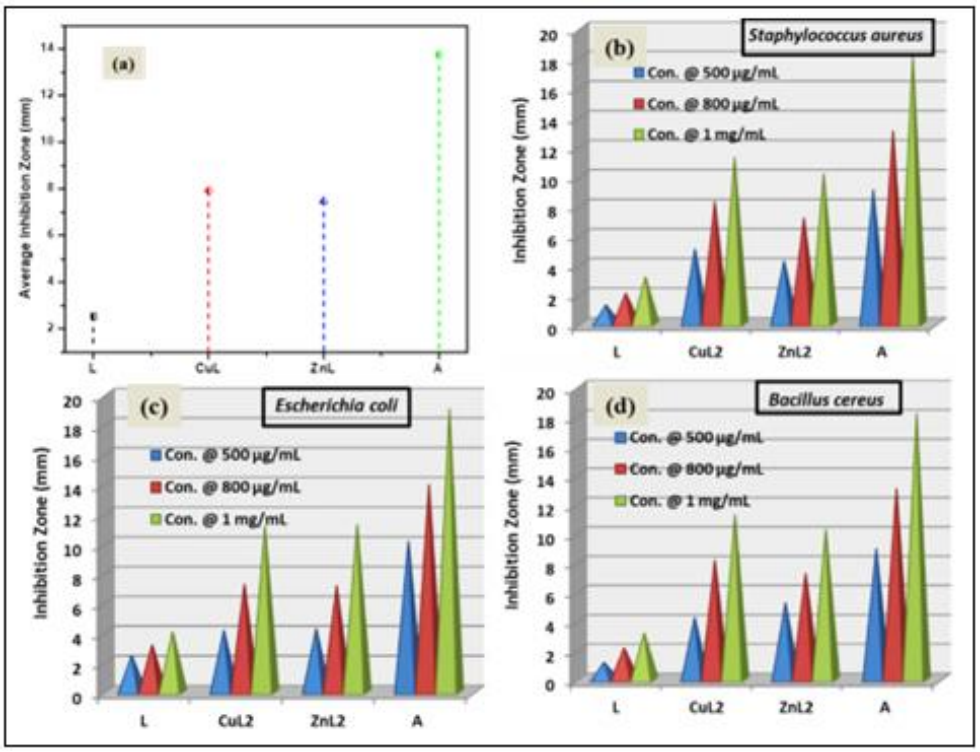


Figure 4. The average microbial activity of as-prepared Ligand (L), Cu complex (CuL_2), Zn complex (ZnL_2), and Ampicillin (A) against all bacteria (a), against *Staphylococcus aureus* (b), *Escherichia coli* (c), and *Bacillus cereus* (d) bacteria at the concentration range of 500 µg/mL (blue color), 800 µg/mL (red) and 1 mg/mL(green).

It can be seen that both Cu(II) and Zn(II) complexes demonstrate the higher biological activity with an average inhibition zone of 7.9 and 7.5 mm than the ligand (2.6 mm) against the three bacteria (Fig 4a). This could reveal that coordinating metals within the ligand enhance the biological activity of the ligand as reported and reviewed elsewhere too (Amane et al., 2014; Prakash and Adhikari, 2011; Tobriya, 2014). Such chelation enhances the lipophylic character favoring its permeation through the lipid membrane so which increases the activity of the metal complexes (Shiekh et al., 2013) The specific performance of as-prepared powders against each *Staphylococcus aureus*, *Escherichia coli*, and *Bacillus cereus* are displayed (Fig 4b-d); evidently, it does not only indicate the fair performance comparing with ampicillin but also increment of activity as the function of their concentration. Notably, all the samples record their highest performance at 1 mg/mL. The current observation may serve as a guide for studying the controlled release of these complexes which could be a promising future.

4. CONCLUSION

The Schiff base and its Cu(II), and Zn(II) complexes were successfully synthesized via condensation of salicylaldehyde and toluidine, and a common reflux method, respectively. The ligand acts as N, O-bidentate through the coordination of azomethine nitrogen and oxygen of the phenoxide. Further, their antibacterial activities were evaluated by disc diffusion assay against gram-positive *Staphylococcus aureus,* gram-negative *Escherichia coli*, and *Bacillus cereus* bacteria. Both Cu(II) and Zn(II) complexes displayed higher biological activity with an average inhibition zone of 7.9 and 7.5 mm than the ligand (2.6 mm) against the three bacteria; this performance is enhanced with the function of their concentration. In this regard, this study revealed that the metal complexes demonstrated higher activities than that of the parent ligand. Such increased activity of the metal complexes may be due to the chelation of the metal ion, which enhances the lipophylic character favoring its permeation through the lipid layer of the membrane. To the extent that our results are concerned, these metal complexes can therefore be explored in the future as an option for decreasing the pathogenic potential of infecting bacteria.

5. ACKNOWLEDGMENTS

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6. CONFLICT OF INTEREST

No conflict of interest.

7. REFERENCE

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