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*Research Article*

# Synthesis, Characterization and Antimicrobial Activities of New Mixed Ligand Complexes of Copper(II) with 1,10-Phenanthroline and Thymine

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**Abstract** A novel mixed ligand complexes having the formulae $[Cu(L_1)_2(H_2O)_2]Cl_2$ and $[Cu(L_1)_2L_2H_2O]Cl$ ($L_1$ = 1,10-phenanthroline, $L_2$ = thymine) have been prepared and characterized by various physicochemical studies such as elemental analysis, molar conductance in nonaqueous solvent, infrared and electronic spectra. Both the ligands as well as the metal complexes were used further to investigate the biological activities (antibacterial) against *Staphylococcus aureus* (SA) (ATCC 25923), *Streptococcus pneumonia* (SP) (clinical isolate), methicillin-resistant *Staphylococcus aureus* (MRSA) (clinical isolate), *Klebsiella pneumoniae* (KP) (clinical isolate), *Escherichia coli* (EC) (clinical isolate), and *Shigella boydii* (SBD) (ATCC 12022). On comparing the biological activities, the complexes showed enhanced antimicrobial activity compared to the free metal salt with thymine being lower than that of 1,10-phenanthroline.

**Keywords** Cu(II) complexes; 1,10-phenanthroline; thymine; antimicrobial activity; physicochemical studies

## 1. Introduction

The therapeutic and diagnostic properties of transition metal complexes have attracted considerable attention leading to their application in many areas of modern medicine [1]. Many coordination compounds of transition metal ions are feasible for nucleolytic cleavage. In this regard, mixed ligand metal complexes are found to be particularly useful because of their potential binding ability to DNA [2]. Studies on the incorporation of good intercalators such as 1,10-phenanthroline and 2,2′-bipyridine found high affinity between DNA base pairs and their planar structure through stacking interaction. A significant advantage in the use of these metallo-intercalators for such studies is that both the ligands and the metal ion can be varied in an easily controlled manner to facilitate individual applications [3]. In some cases, the metal complexes have higher activity than that of the free ligands. This is probably due to the larger lipophilic nature of the complexes. Such an increased activity of the metal chelate can be explained on the basis of overtones concept and chelation theory [1].

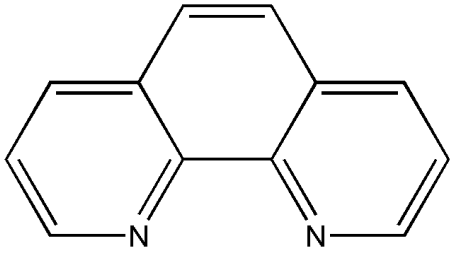



**Figure 1:** The chemical structure of 1,10-phenanthroline.

Metal mixed-ligand complexes were found to be particularly useful because of their potential to bind DNA via multitude of interactions and to cleave the duplex by virtue of their intrinsic chemical, electrochemical, and photochemical reactivity [2,3]

1,10-Phenanthroline (Figure 1) represents one of the most frequently used chelate ligands in inorganic chemistry. It forms strong complexes with most metal ions. When coordinated with copper, it possesses nuclease activity that has been used to study DNA-protein interactions [4]. Moreover, considerable attention has been focused on the use of 1,10-phenanthroline complexes as intercalating agents of DNA and as artificial nucleases [3]. Most 1,10-phenanthroline metal complexes bind with DNA either through noncovalent interaction within base pairs or within major and minor grooves. The charge transfer band from metal to ligand of some complexes as found in experimental studies is an important characteristic of ligand intercalation. Such noncovalent interactions also partly contribute to the stabilization of metal complexes within DNA [1,2].

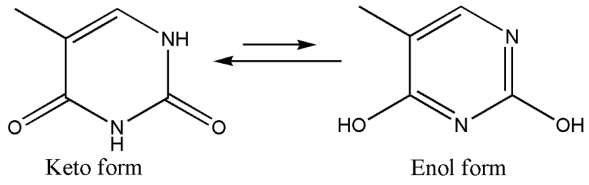



**Figure 2:** Tautomeric forms of thymine.

In most cases, thymine (Figure 2) acts as a bidentate ligand with Cu(II) complexes. Coordination occurs through the ring nitrogen and carbonyl oxygen atoms. At alkaline pH, the hydrogen N(1) for thymine is removed [5]. Thymine exists in two tautomeric forms: the keto form and the enol form, where the keto form is strongly favored in equilibrium which is important in coordination [6]. In view of the above-mentioned coordination possibilities and physiological activities, it is worthwhile to synthesize the complexes derived from 1,10-phenanthroline and thymine. 1,10-phenanthroline, thymine, and the copper(II) complexes show antimicrobial activity in bacterial strains like *Staphylococcus aureus* (SA) (ATCC 25923), *Streptococcus pneumonia* (SP) (clinical isolate), methicillin-resistant *Staphylococcus aureus* (MRSA) (clinical isolate), *Klebsiella pneumoniae* (KP) (clinical isolate), *Escherichia coli* (EC) (clinical isolate), and *Shigella boydii* (SBD) (ATCC 12022) with varying intensity [3].

## 2. Experimental

### 2.1. Materials and reagents

The metal salt $CuCl_2 \cdot 2\,H_2O$ (Analar BDH) and the ligands 1,10-phenanthroline and thymine are purchased from Sigma Aldrich and used as such. All the solvents used are of reagent grade quality.

### 2.2. Synthesis of complexes

#### *2.2.1. Preparation of complex 1*

To a solution of $CuCl_2 \cdot 2\,H_2O$ (0.1490 g, 1 mmol) in 20 mL of methanol using 100 mL round bottom flask being stirred magnetically in an ice bath, solution of 1,10-phenanthroline (0.2434 g, 2 mmol) in 30 mL of methanol was added drop wise to the bulk salt solution from a 50 mL burette very slowly in 9 h, till a greenish blue homogeneous solution was obtained. The solvent was removed using rotary evaporator and a greenish blue powder was collected then washed three times with diethyl ether. It was dried in an oven and put in desiccators until use; yield: 0.26 (84%).

#### *2.2.2. Preparation of complex 2*

To a solution of 1 (0.25 g, 1 mmol) in 40 mL distilled water in a 100 mL round bottom flask being stirred magnetically in water bath at room temperature, solution of thymine (0.07 g, 1 mmol) that was treated with NaOH (0.07 g, 1 mmol) in 15 mL of water was added drop wise very slowly from a 50 mL burette within 3 h. A deep blue homogeneous solution was obtained. The sodium chloride formed as a byproduct was removed by adding dichloromethane in which the complex is soluble while sodium chloride is insoluble. The complex prefers dichloromethane rather than water. Since water and dichloromethane are immiscible, they were separated by using a separating funnel. The solvent dichloromethane was removed using a rotary evaporator. Deep blue powder was collected and was washed with diethyl ether three times. It was dried in an oven and kept in a desiccator until use; yield: 0.28 g (75%).

### 2.3. Antimicrobial activity study

The test was done using the diffusion agar technique. Agar wells were prepared by using a sterilized cork borer with 6 mm diameter, 4 mm deep and 2.5 cm apart to minimize overlapping of zones. The ligands, metal salt, complexes, controls (methanol and water), and reference drugs (ciprofloxacin and chloramphenicol) were tested for their antibacterial activities against six pathogenic bacteria: SA (ATCC 25923), SP (clinical isolate), MRSA (clinical isolate), KP (clinical isolate), EC (clinical isolate), and SBD (ATCC 12022). A 0.1 mL of the bacterial suspensions were inoculated onto surface of Muller-Hinton agar plate and streaked (swabbed) by sterile cotton swab over the entire sterile agar surface. A 50 $\mu$L volume of aqueous solutions of test compounds (5 mg sample potency) was poured into sterile petri dishes agar holes. The dishes were incubated at 37 °C for 48 h where clear inhibition zones (IZs) were detected around each hole. Antibacterial activities were calculated as a mean of three replicates.

## 3. Results and discussion

### 3.1. Synthesis and characterization studies

The formation of the complexes can be represented by the following equations and Scheme 1:

$$CuCl_2 \cdot 2\,H_2O + 2\,L_1 \longrightarrow Cu(L_1)_2(H_2O)_2Cl_2, \quad (1)$$

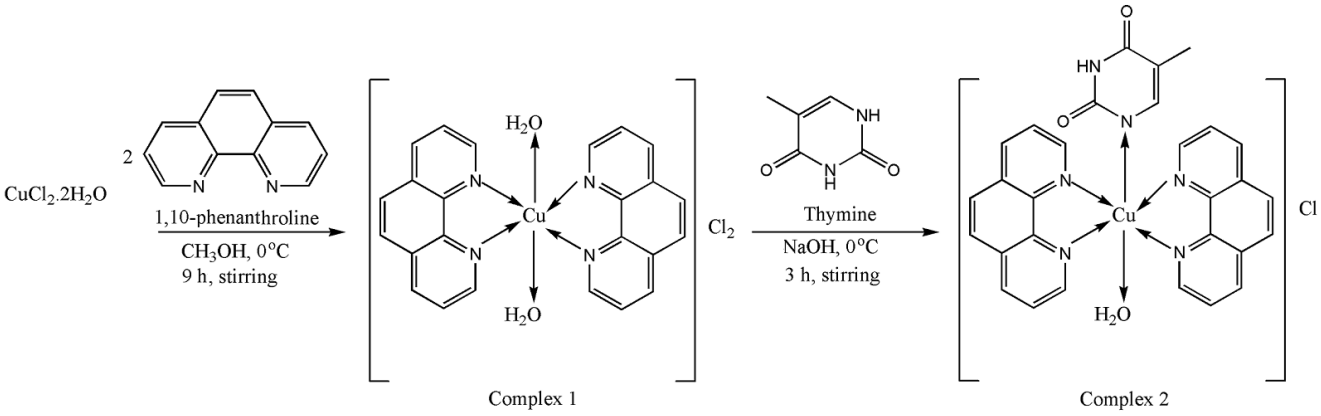
$$Cu(L_1)_2(H_2O)_2Cl_2 + L_2 \longrightarrow Cu(L_1)_2L_2H_2OCl_2, \quad (2)$$

where $L_1$ = 1,10-phenanthroline and $L_2$ = thymine.

Complex 1 is a greenish, nonhygroscopic solid. It is soluble in water and acetonitrile but insoluble in acetone and methanol; whereas complex 2 is a deep blue nonhygroscopic solid that is soluble in water, dichloromethane, and acetonitrile but insoluble in acetone and methanol.

The analytical data (Table 1) show that complexes 1 and 2 can be represented by the formulae $Cu(L_1)_2(H_2O)_2Cl_2$ and $Cu(L_1)_2L_2H_2OCl$, respectively (where $L_1$ = 1,10-phenanthroline and $L_2$ = thymine).

The molar conductance of the complexes ($10^{-3}$ M solutions) in acetonitrile (Table 1) falls in the range expected




**Scheme 1:** Schematic representation for the formation of complexes 1 and 2.

**Table 1:** Analytical and conductance data of the Cu(II) complexes of 1 and 2.

| Compound | Color | MW | Experimental (theoretical) (%) | | | | | MP (°C) | Molar conductance in acetonitrile* |
|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | Cu | Cl | | |
| 1,10-phenanthroline ($L_1$) | White | 180.00 | 79.92 (80.00) | 4.42 (4.44) | 15.54 (15.56) | — | — | 97 | — |
| Thymine ($L_2$) | White | 126.00 | 46.44 (47.62) | 4.75 (4.68) | 22.20 (22.22) | — | — | 317 | — |
| $[Cu(L_1)_2(H_2O)_2]Cl_2$ | Greenish blue | 530.50 | 54.27 (54.29) | 5.56 (3.77) | 10.16 (10.56) | 10.51 (11.97) | 13.24 (13.38) | 327 | 250.13 |
| $[Cu(L_1)_2L_2H_2O]Cl$ | Deep blue | 603.00 | 57.69 (57.71) | 10.80 (3.81) | 9.27 (13.93) | 10.72 (10.53) | 5.83 (5.89) | 235 | 140.08 |

*$ohm^{-1}cm^2mole^{-1}$.

**Table 2:** Characteristic IR absorption ($cm^{-1}$) of ligands $L_1$ and $L_2$ and complexes 1 and 2.

| Compound | $\nu$ (OH) | $\nu$ (C=N) | $\nu$ (C−N) | $\nu$ (C=O) | $\nu$ (C=C) | $\nu$ (N−H) |
|---|---|---|---|---|---|---|
| 1,10-phenanthroline ($L_1$) | — | 1,418 | — | — | 1,585, 1,506 | — |
| Thymine ($L_2$) | — | — | 1,493 | 1,743 | 1,674 | 3,194 |
| $[Cu(L_1)_2(H_2O)_2]Cl_2$ | 3,444 | 1,595 | — | — | 1,602 | — |
| $[Cu(L_1)_2L_2H_2O]Cl$ | 3,507 | 1,516 | 1,587 | 1,732 | 1,619 | Merged with OH |

for 1:2 for complex 1 and 1:1 for complex 2 [7]. Thus the complexes should be formulated as $[Cu(L_1)_2(H_2O)_2]Cl_2$ and $[Cu(L_1)_2L_2H_2O]Cl$.

### *3.1.1. Infrared spectra*

The important infrared (IR) spectral band of the ligands and the corresponding complexes is given in Table 2.

The broad absorption peaks of 3,444 $cm^{-1}$ and 3,507 $cm^{-1}$ in complexes 1 and 2 are indicative of coordination of water molecules to the central metal ion. The C=N stretching vibration of $L_1$ at 1,418 $cm^{-1}$ is shifted to 1,595 $cm^{-1}$ and 1,516 $cm^{-1}$, respectively in complexes 1 and 2 indicating the coordination of C=N group [8]. In addition to this, the peak corresponding to 1,493 $cm^{-1}$ (C−N) in $L_2$ is shifted to 1,587 $cm^{-1}$ in complex 2 proving the coordination of thymine moiety to the central metal ion in the deprotonated mode [9]. The $\nu$ (C=O) at 1,743 $cm^{-1}$ in $L_2$ is almost unaltered and appeared around 1,732 $cm^{-1}$ in complex 2, indicating noncoordination of (C=O) of $L_2$.

### *3.1.2. Electronic spectra*

The electronic spectra of the ligands and the corresponding complexes 1 and 2 with tentative assignments are presented in Table 3.

The spectrum of the ligands shows two band maxima at 33,895 $cm^{-1}$ and 35,087 $cm^{-1}$ corresponding to $\pi$–$\pi^*$ transition occurring in $L_1$ and $L_2$, respectively. In complexes 1 and 2, both these bands are found as blue shifted and appeared at 34,246 $cm^{-1}$ and 34,246 $cm^{-1}$, respectively. In complex 1, the band at 16,025 $cm^{-1}$ corresponding to $^2B_{1g} \rightarrow {}^2A_{1g}$ and the band at 15,625 $cm^{-1}$ is in accordance with $^2B_{1g} \rightarrow {}^2B_{2g}$ indicating an octahedral coordination around the central metal ion [8,9]. In complex 2, the d−d transition occurring at 15,060 $cm^{-1}$ and 15,037 $cm^{-1}$ is in

**Table 3:** Electronic spectral data (in Nujol) of ligands $L_1$ and $L_2$ and complexes 1 and 2.

| Compound | $\nu$ ($cm^{-1}$) | Tentative assignments |
|---|---|---|
| 1,10-phenanthroline ($L_1$) | 33,898 | $\pi$–$\pi^*$ |
| Thymine ($L_2$) | 35,087 | $\pi$–$\pi^*$ |
| $[Cu(L_1)_2(H_2O)_2]Cl_2$ | 34,246 | $\pi$–$\pi^*$ |
| | 16,025 | $^2B_{1g} \rightarrow {}^2A_{1g}$ |
| | 15,625 | $^2B_{1g} \rightarrow {}^2B_{2g}$ |
| $[Cu(L_1)_2L_2H_2O]Cl$ | 34,246 | $\pi$–$\pi^*$ |
| | 15,060 | $^2B_{1g} \rightarrow {}^2A_{1g}$ |
| | 15,037 | $^2B_{1g} \rightarrow {}^2B_{2g}$ |

accordance with $^2B_{1g} \rightarrow {}^2A_{1g}$ and $^2B_{1g} \rightarrow {}^2B_{2g}$ confirming the octahedral coordination around copper(II) [10]. Based on the above results, structures as shown in Figure 3 can be assigned to the complexes.

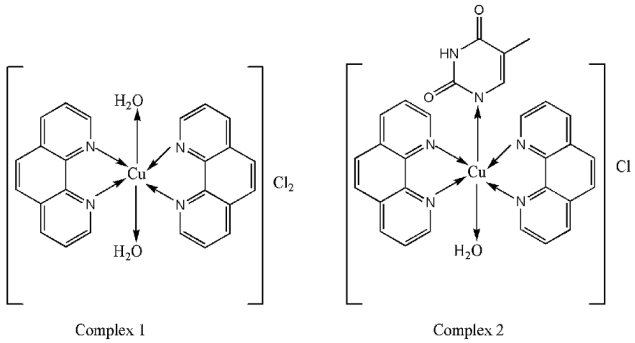



**Figure 3:** Tentative structure of complexes 1 and 2.

### 3.2. Antimicrobial activity study

When compared with the commercially available antibiotics ciprofloxacin and chloramphenicol, the newly synthesized Cu(II) complexes showed appreciable antibacterial activities (Figure 4). The ligand thymine and solvents (water and methanol) exhibited no activity (NA) against all bacterial species while the standard antibiotics ciprofloxacin and chloramphenicol exhibited high activities with IZs ranging from $21.3 \pm 0.31$ mm to $28.3 \pm 0.32$ mm and $26.3 \pm 0.24$ mm to $32.3 \pm 0.23$ mm, respectively. The free ligand 1,10-phenanthroline exhibited the greatest antimicrobial activities with IZs ranging from $31.3 \pm 0.24$ mm to $41.7 \pm 0.34$ mm (Table 4) for all the six organisms due to its flat geometry and extended conjugation which enable it to intercalate with base pairs of DNA of microbes [7,8]. However, after coordination its geometry becomes planar and extended conjugation relatively minimized as a result of possible $\pi$-electron donation for the central metal ion that reduced its activity. On the other hand, the metal salt showed a relatively lower effect on the tested bacteria IZs [9,10] ranging from $11.8 \pm 0.28$ mm to $28.4 \pm 0.33$ mm.

The newly prepared complexes 1 and 2 showed lower antibacterial activities than the free ligand 1,10-phenanthroline and greater antibacterial activities than the free metal ion which in fact is in agreement with the literature [11] ranging from $22.7 \pm 0.16$ mm to $30.0 \pm 0.20$ mm and $27.3 \pm 0.23$ mm to $35 \pm 0.36$ mm, respectively, and the minimum inhibitory concentration (MIC) determined for all bacterial pathogens was 600 $\mu$g/mL. This can be attributed to the planarity and extended conjugation of the coordinated 1,10-phenanthroline aromatic rings [10] which slice the purine and pyrimidine bases of DNA, allowing for the coordinated rigid ligand thymine to make a hydrogen bond via its nitrogen and oxygen atoms with the corresponding nucleobases adenine. Accordingly, these Cu(II) complexes

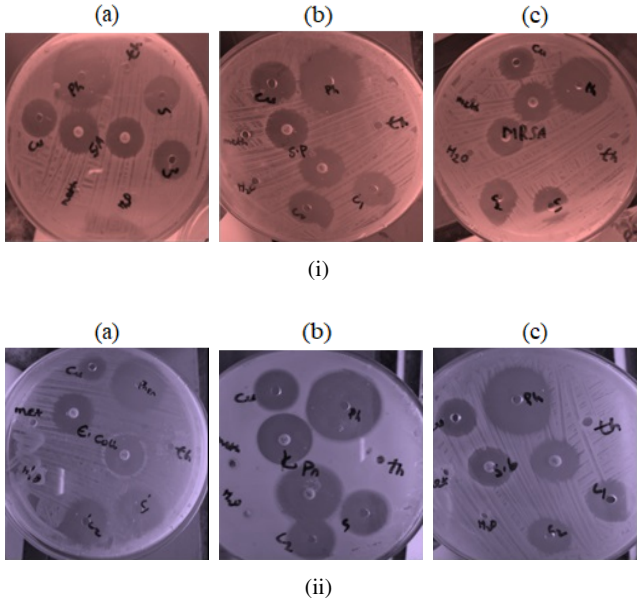



**Figure 4:** Comparative IZs of $L_1$ and $L_2$, complexes 1 and 2, $CuCl_2 \cdot 6\,H_2O$ and commercial antibiotics; (i) (a)–(c) gram positive bacteria SA (ATCC 25923), SP (clinical isolate), MRSA (clinical isolate), KP (clinical isolate), EC (clinical isolate), and SBD (ATCC 12022).

delay cell-cycle progression and increase cell death [8,9] on the tested microbes.

The newly synthesized copper(II) complexes minimized the over antimicrobial activity (toxicity) of the free ligand 1,10-phenanthroline after coordinated with the Lewis acid ($Cu^{2+}$ ion) as a result of Lewis basicity due to the coordination. However, the activity of thymine has increased as a result of access of hydrogen bonding due to its rigidity following its coordination with the metal in the complex. Complex 2 has higher antibacterial activity than the precursor complex 1 on all bacterial species due to the presence of coordinated thymine in complex 2 (Tables 5 and 6).

The MIC assay of complex 2 against the six bacterial pathogens is shown in Table 7.

**Table 4:** Comparative antibacterial activities of $L_1$ and $L_2$ synthesized complexes 1 and 2, ligands, metal salt, and commercially available antibiotics.

| Bacteria | Antibacterial activity (IZ diameter in mm) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| SA | $13.12 \pm 0.3$ | $35.3 \pm 0.32$ | NA | $25 \pm 0.23$ | $35.0 \pm 0.4$ | NA | NA | $24.0 \pm 0.32$ | $27.3 \pm 0.21$ |
| SP | $17.9 \pm 0.36$ | $38.0 \pm 0.20$ | NA | $24.7 \pm 0.3$ | $34.0 \pm 0.2$ | NA | NA | $24.0 \pm 0.21$ | $26.7 \pm 0.35$ |
| MRSA | $17.8 \pm 0.35$ | $36.7 \pm 0.13$ | NA | $27.7 \pm 0.2$ | $31.3 \pm 0.2$ | NA | NA | $23.3 \pm 0.22$ | $26.3 \pm 0.24$ |
| EC | $11.8 \pm 0.28$ | $31.3 \pm 0.24$ | NA | $22.7 \pm 0.2$ | $28.8 \pm 0.3$ | NA | NA | $21.3 \pm 0.31$ | $28.7 \pm 0.26$ |
| KP | $28.4 \pm 0.33$ | $41.7 \pm 0.3$ | NA | $24.7 \pm 0.4$ | $40.0 \pm 0.2$ | NA | NA | $28.3 \pm 0.32$ | $32.3 \pm 0.23$ |
| SB | $22.56 \pm 0.2$ | $41.7 \pm 0.3$ | NA | $30.0 \pm 0.2$ | $27.3 \pm 0.3$ | NA | NA | $25.0 \pm 0.41$ | $27.3 \pm 0.21$ |

Note: Relative standard deviation of all data is less than 5% (acceptable). 1 = $CuCl_2 \cdot 2H_2O$, 2 = 1,10-phenanthroline, 3 = thymine, 4 = $[Cu(phen)_2(H_2O)_2]Cl_2$, 5 = $[Cu(Phen)_2(thy)(H_2O)]Cl$, 6 = water, 7 = methanol, 8 = reference antibiotic (ciprofloxacin), 9 = reference antibiotic (chloramphenicol), and NA = no activity.

**Table 5:** Comparative activity index of complexes 1 and 2 with reference drug ciprofloxacin.

| Complex | Name of bacterial pathogens | | | | | | Activity |
|---|---|---|---|---|---|---|---|
| | SA | SP | MRSA | EC | KP | SB | |
| $[Cu(L_1)_2(H_2O)_2]Cl_2$ | 1.50 | 1.40 | 1.30 | 1.3 | 1.2 | 1.2 | Greater than ciprofloxacin in all species |
| $[Cu(L_1)_2L_2H_2O]Cl$ | 1.04 | 1.01 | 1.18 | 1.06 | 0.87 | 1.09 | Greater than ciprofloxacin except in KP |

**Table 6:** Comparing activity index of complexes 1 and 2 with reference drug chloramphenicol.

| Compound | Name of bacterial pathogens | | | | | | Activity index of complexes |
|---|---|---|---|---|---|---|---|
| | SA | SP | MRSA | EC | KP | SB | |
| $[Cu(L_1)_2(H_2O)_2]Cl_2$ | 1.28 | 1.27 | 1.19 | 0.98 | 1.07 | 1.09 | Greater than chloramphenicol except in EC |
| $[Cu(L_1)_2L_2H_2O]Cl$ | 0.92 | 0.93 | 1.05 | 1.07 | 0.74 | 1.00 | Greater than chloramphenicol only in gram positive |

**Table 7:** MIC assay of complex 2 against bacterial pathogens.

| Name of bacterial pathogens | Observation of growth | | | | | | |
|---|---|---|---|---|---|---|---|
| | 100 $\mu$g/mL | 200 $\mu$g/mL | 300 $\mu$g/mL | 400 $\mu$g/mL | 600 $\mu$g/mL | 800 $\mu$g/mL | 1 mg/mL |
| SA | × | × | • | • | • | • | • |
| SP | × | × | × | × | • | • | • |
| MRSA | × | × | × | • | • | • | • |
| EC | × | • | • | • | • | • | • |
| KP | × | × | × | × | • | • | • |
| SB | × | × | × | • | • | • | • |

Note: × = bacteria growth; • = no bacteria growth.

The increase in the antibacterial activity of metal chelate may be due to the effect of the metal ion on the normal cell process. A possible mode of the activity increase may be considered in light of Tweedy's chelation theory. Chelation considerably reduces the polarity of the metal ion because of partial sharing of its positive charge with the donor groups and possible $\pi$-electron delocalization over the whole chelate ring [12]. Such chelation could enhance the lipophilic character of central metal atom, which subsequently favors its permeation through the lipid layers of cell membrane [13]. Furthermore, the mode of action of the compounds may involve formation of a hydrogen bond through the azomethine group with the active centers of cell constituents, resulting in interference with the normal cell processes. The variation in the effectiveness of the different compounds against different organisms depends either on the impermeability of the cells of the microbes or differences in ribosome of microbial cells [12].

### 3.3. Physical methods of analysis

All the complexes were analyzed for their metal and chloride contents by conventional methods [11]. The IR spectra of the ligands and the complexes were recorded using AVATAR 330 FT-IR, Nicolet Thermo-Spectrophotometer in the range of 4000–400 $cm^{-1}$. Electronic spectra of the ligands and the complexes in the solid state (using a paste with Nujol) were measured using Sanyo SP65 UV/VIS Spectrophotometer in the range of 200–800 nm regions. For the biological screening, commercially available antibacterial drugs ciprofloxacin and chloramphenicol were used as a reference.

Solvents (sterile distilled water and methanol) serving as controls were evaluated for their antibacterial activity and the result was compared with those of the free ligands, metal salt, and their metal complexes. The results of sensitivity of the tested bacterium towards the above compounds were judged by measuring the IZ growth diameter around the hole using a caliper.

## 4. Conclusions

New mixed ligand complexes of copper(II) containing 1,10-phenanthroline and thymine as ligands have been designed, synthesized, and characterized by elemental analysis, conductivity, IR, and electronic spectra measurements. Antimicrobial studies of the complexes against six bacteria pathogens showed that there is an increased activity of the metal ions upon coordination to these ligands. There is a decrease in the activities of 1,10-phenanthroline as well as an increase in the case of thymine upon coordination. Complex 1 exhibits lower activity than complex 2 and the higher antimicrobial activity of the later complex 2 is speculated to be due to coordination of the thyamino-ligand with the metal ion center, where it acquired a rigid arrangement that is conducive for hydrogen bonding with the DNA (nucleases) of the microbe. From the results obtained we concluded that the newly synthesized copper(II) complex could be used as good drug of choice to manage diseases caused by the investigated six bacterial pathogens after evaluating the in-vivo effect on experimental animals and clinical trials. Since the newly synthesized complexes are water soluble and nonpoisonous, they are environmentally friendly too.

**Conflict of interest** The authors declare that they have no conflict of interest.

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