



## Synthesis, Characterization and antibacterial Activity of Copper(II) Mixed Ligand Complexes with Salen Type Ligands and Dithiocarbamates

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### ABSTRACT

Mixed ligand complexes of Cu(II) with salen type ligands, namely *N, N'*-bis(salicylidene)-1,2-ethylenediamine (*salen*) and *N, N'*-bis(salicylidene)-1,2-phenylenediamine (*salophen*) as primary ligands and pyrrolidine dithiocarbamate (*pdtc*) as a secondary ligand were prepared. The structural characterization of the synthesized complexes was carried out via analytical as well as various spectral studies. The obtained results reinforce that stoichiometry of the mononuclear mixed ligand complexes can be represented as  $NH_4[Cu(II)\text{-Schiff base}(L)\text{-}pdtc(B)]$  and both *H2L* and (*B*) ligands can act as tetra and bidentates respectively. Additionally, both the schiff bases and the secondary *pdtc* ligands bind with copper(II) ion to build a stable six, five, six and four membered chelate rings with an octahedral geometry. The mass spectral data confirms the monomeric structure of the metal complexes while the study of the conductivity measurement indicated the 1:1 electrolyte nature of the complexes. The free Salen type ligands and their mixed copper(II) complexes have been tested for their antibacterial activity by using disc diffusion method and the results discussed.

**Keywords:** Salen, Mixed Copper(II) complexes, Dithiocarbamate Ligand, Spectrophotometry, Antibacterial.

### INTRODUCTION

A considerable attention has been given on Salen-type ligands owing to their simple synthesis, structural versatility, and wide range of applications in many fields including catalysis [1], luminescence [2], magnetism [3] and material science [4]. Salen Schiff base ligands and their metal complexes have been reported to show a variety of biological actions by influence of the azomethine linkage, which is responsible for various antibacterial, antifungal, herbicidal, and in the study of the interaction with DNA [5-8]. Salen schiff base ligands derived from diamines and 2-hydroxybenzaldehyde typically lose two protons and function as quadridentate chelates with O, N, N, O atoms. This provides sufficient coordination sphere, in accordance with the length of carbon-chain linkage that allow metal ions to find an easy approach to bind to the N2O2 ligand. Generally, these N2O2 tetradentate donors coordinate to d-block transition metals to afford stable mononuclear complexes [9]. In addition, there are a number of reports on homometallic as well as heterometallic di- and trinuclear complexes with d-block metals consisting of two salen molecules [10-12]. In these complexes,  $\mu_2$ -phenoxo bridging plays an important role in assembling metal ions and the two salen ligands [13].

Dithiocarbamate ligands have received great consideration, their small bite-angle and the soft nature of the dithiocarbamate moiety makes them capable of stabilizing wide range of metal ions in different oxidation states [14]. Dithiocarbamate ligands are mono anionic chelating ligands and can bind to metal ions in various coordination modes with the monodentate and anisobidentate modes. Dithiocarbamates complexes have been reported to gain wide applications in medicine, agriculture, industry, in analytical and organic chemistry [15-17].

The coordination chemistry of copper has attracted increasing interest among the transition metal complexes, because copper is biocompatible and exhibits many significant roles in biological systems [18]. Copper complexes of salen schiff base ligands have engrossed considerable interest because of their variable bonding properties, structural diversity, and pharmacological properties [19-21]. Several copper Salen complexes and their mixed complexes with anionic co-ligands have been synthesized and their structural diversity was investigated [22, 23]. Biswas and Ghosh have synthesized trinuclear copper(II) salen complexes and have found that the shape of the trinuclear species may vary from linear to triangular depending upon coordination mode of the anionic coligand, coordination ability of the solvent molecules and the nature of the central metal ion [24]. Also, Dong et. al. have reported two novel Cu(II) complexes with Salen type ligands possessing different structural features and investigated the different performance of the ligand [25]. Recently, Asatkar and coworkers synthesized mononuclear cuprous complexes with Salen ligands that have strong binding affinity towards ct-DNA [26].

Taking into consideration the above facts, mixed Cu(II) complexes of Schiff base (derived from condensation of ethylenediamine or o-phenylenediamine with salicylaldehyde) and dithiocarbamate were synthesized. The synthesized compounds were characterized using various spectral techniques and evaluated for their microbial studies against *Staphylococcus aureus*, *Streptococcus*, *Klebsiella pneumonia*, *Pseudomonas*

and *Escherichia coli*.

## EXPERIMENTAL SECTION

## Materials and Instruments

Ethylenediamine, o-phenylenediamine, salicylaldehyde and ammonium pyrrolidine dithiocarbamate were commercial products (from Alfa and Merck) and were used without further purification. Solvents were of reagent grade and were purified by the usual methods. Copper(II) acetate monohydrate was procured from Scharlau Chemie and used as received. The ligands N, N'-bis(salicylidene)ethylenediamine (H2L1) and N, N'-bis(salicylidene)-o-phenylenediamine (H2L2) were prepared according to the published procedure [27] and their purities were checked by spectroscopic data.

Elemental analysis was carried out with a Perkin Elmer model 2400 equipment. Conductivity measurements of 10<sup>-3</sup> M solutions in DMSO at room temperature were carried on a Jenway 470 conductivity meter. Infrared spectra were recorded on a PerkinElmer FT-IR Spectrometer (Frontier)-USA. Magnetic susceptibilities at room-temperature were done by using Sherwood Scientific magnetic balance, Cambridge science, England Model no.MKI, Serial no. MSBI/230/95/680. The UV-Vis spectra were recorded in DMSO solution on Agilent Technologies Cary 60 UV-Vis spectrophotometer in 200-800 nm range. The FAB mass spectra were recorded using a Micromass Autospec spectrometer.

Synthesis of the Complexes, NH<sub>4</sub>[CuL<sub>n</sub>(pdtc)], n=1,2 (Complexes 1 and 2)

Cu(CH<sub>3</sub>COO)<sub>2</sub>·H<sub>2</sub>O (1mmol, 0.2g) solution in methanol (20 mL) was added to a solution of ammonium pyrrolidine dithiocarbamate (1mmol, 1.64g) in methanol (10 mL). The resulting mixture was refluxed for 1h. The corresponding Schiff base H2L1 (1 mmol, 0.268 g) or H2L2 (1 mmol, 0.316g) in 20 mL methanol was then added in the reaction mixture and refluxed for 4 h. The precipitates obtained were filtered, washed successively with water and ethanol and then dried in air.

## Antibacterial Study

The ligands H2L1, H2L2 and their complexes were tested against the bacterial species *Staphylococcus aureus*, *Streptococcus*, *Klebsiella pneumonia*, *Pseudomonas* and *Escherichia coli* using the standardized Agar-Well diffusion method [28]. The antibiotic Ciprofloxacin was used as the standard reference. The antibacterial activities were done in DMSO solvent. The solutions of ligands and the two complexes 1 and 2 were added to the agar plates. Incubation of the plates was done at 37°C for 24 hours. Zones of inhibition were recorded in millimeters and the experiment was repeated three times.

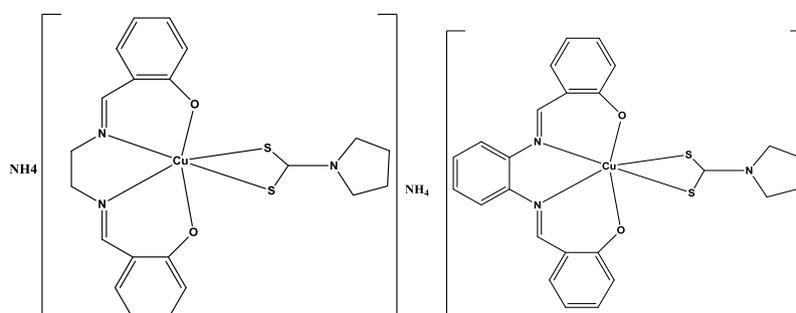
## Statistical Analysis

Experiments were performed in triplicate and the values obtained are presented as the mean ± standard error. The data were statistically performed by SPSS statistical software version 21 (SPSS Inc. Chicago IL, USA).

## RESULTS AND DISCUSSION

The reaction of the free Salen ligands H2L1 and H2L2 with Cu(OAc)<sub>2</sub>·H<sub>2</sub>O and ammonium pyrrolidinedithiocarbamate in 1:1:1 molar ratio afforded the mononuclear mixed copper(II) complexes, (1 and 2), (Scheme 1). The physical properties and analytical data of the prepared complexes are summarized in Table 1. The complexes are stable to air and moisture and soluble in DMF, DMSO and insoluble in acetone, chloroform, and ether. The molar conductance measured at 25°C (10<sup>-3</sup> M) in a DMSO solution suggests that the complexes are 1:1 electrolyte in nature [29] and thus may be formulated as NH<sub>4</sub>[CuL(pdtc)]. The results of the elemental analysis of the mixed ligand complexes are in good agreement with those required by the proposed formula. At room temperature, the magnetic moment of complexes NH<sub>4</sub>[CuL1(pdtc)] and NH<sub>4</sub>[CuL2(pdtc)] are 2.04 and 2.00 B.M, respectively corresponding to one unpaired electron which indicates an octahedral geometry [30].

Scheme 1: The proposed structure of complexes 1 (left) and 2 (right)



**Table 1:** Physical and Analytical Data of Cu(II) mixed complexes

| Compound formula                              | Melting point (°C) | Color      | Yield (%) | Elemental analysis (%) found (calc.) |            |              |             |
|---|--------------------|------------|-----------|--------------------------------------|------------|--------------|-------------|
|   |                    |            |           | C                                    | H          | N            | $\Lambda_M$ |
| NH <sub>4</sub> [CuL <sup>1</sup> (pdtc)] (1) | 276                | Brown      | 73        | 50.94(50.21)                         | 5.50(5.30) | 11.32(11.66) | 58          |
| NH <sub>4</sub> [CuL <sup>2</sup> (pdtc)] (2) | 275                | Dark brown | 66        | 55.28(55.26)                         | 5.01(4.97) | 10.31(10.38) | 62          |

### Infrared Spectra

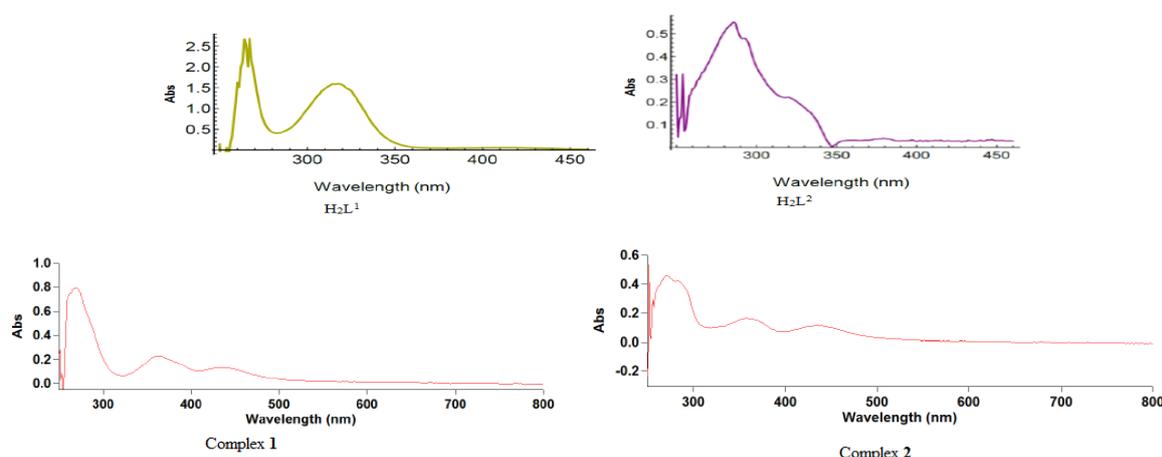
The assignments of the more significant IR absorption bands of the free ligands and their mixed ligand complexes are shown in Table 2. The IR spectra of complexes 1 and 2 were analyzed in comparison with that of their free schiff base ligands H<sub>2</sub>L<sup>1</sup> and H<sub>2</sub>L<sup>2</sup>. The strong sharp absorption band around 1629 and 1614 cm<sup>-1</sup> in the spectra of the free ligands H<sub>2</sub>L<sup>1</sup> and H<sub>2</sub>L<sup>2</sup> can be assigned to the C=N stretching, but in the complexes these bands are shifted to higher frequencies to 1647 and 1648 cm<sup>-1</sup>, respectively, which can be attributed to the coordination of the azomethine nitrogen to the metal center [31]. A strong band at about 1281 cm<sup>-1</sup> in the free schiff base ligands, has no corresponding band in the copper complexes 1 and 2 and is assigned to the hydrogen-bonded in-plane bending vibration. The IR spectra of these ligands also showed a broad band of weak intensity in the region 2900-2700 cm<sup>-1</sup> which proves the presence of intramolecular hydrogen-bonded [32]. The absence of O-H stretching and  $\delta$ (O-H) vibrations in the spectra of the complexes indicated deprotonation of the -OH group. However, coordination of the phenolic oxygen to copper(II) ion is confirmed by the shift of the strong band at about 1149 cm<sup>-1</sup> in the free ligands, which is attributed to C-O stretching vibrations, to higher frequency at ca. 1163 cm<sup>-1</sup> in complexes 1 and 2 [33]. Furthermore, the IR spectra of the mixed ligand complexes 1 and 2 showed new band at (1444 complex 1, 1459 complex 2), which is attributed to the  $\nu$ C-N vibration of the N-CSS- moiety in the secondary ligand, pyrrolidine dithiocarbamate. This band was intermediate between the values expected for a single bond  $\nu$ C-N (1350-1250cm<sup>-1</sup>) and double bond  $\nu$ C=N (1680-1640 cm<sup>-1</sup>) indicating partial double bond character in the C—N bond [34]. The bands observed at 1053 and 1097 cm<sup>-1</sup> in complexes 1 and 2, respectively were assigned to  $\nu$ C-S mode and a single absorption band in this region suggests a bidentate behavior of pyrrolidine dithiocarbamate in these complexes [35].

**Table 2:** IR Spectral assignments for the Schiff base ligands and their mixed Cu(II) complexes

| Compound                                     | Schiff base |             | Dithiocarbamate |             |
|--|-------------|-------------|-----------------|-------------|
|  | $\nu$ (C=N) | $\nu$ (C-O) | $\nu$ (C=N)     | $\nu$ (C-S) |
| H <sub>2</sub> L <sup>1</sup>                | 1629        | 1149        | -               | -           |
| H <sub>2</sub> L <sup>2</sup>                | 1614        | 1148        | -               | -           |
| NH <sub>4</sub> [CuL <sup>1</sup> (pdtc)](1) | 1647        | 1164        | 1444            | 1053        |
| NH <sub>4</sub> [CuL <sup>2</sup> (pdtc)](2) | 1648        | 1163        | 1459            | 1097        |

### Electronic Spectra

The electronic spectra of the schiff base ligands and the two mixed ligand complexes in DMSO were recorded in the range of 200-800 nm at room temperature and are shown in Figure 1. The electronic spectra of free Schiff base ligands H<sub>2</sub>L<sup>1</sup> and H<sub>2</sub>L<sup>2</sup> showed mainly two bands, a maximum absorption at about ~270 nm were attributed to  $\pi - \pi^*$  transitions of  $\pi$  electrons within the structure and a broad band at about ~318 nm is attributed to a n-  $\pi^*$  transition associated with the azomethine chromospheres. The spectra of the mixed complexes generally show the characteristic bands of the free ligands with some changes both in frequencies ( $\lambda_{max}$ ) and intensity together with appearances of new bands at longer wavelengths. Upon the coordination, the  $\pi - \pi^*$  and n-  $\pi^*$  transitions observed in the spectra of the two ligands were shifted to longer wavelength values (red shift) along with lower intensities which confirm the coordination of the schiff base with copper ion. Meanwhile, a new moderately intense absorption peak is observed at 435 nm in complexes 1 and 2 which may be attributed to MLCT most probably, from Cu(II) d orbitals to d orbitals in sulfur atom of pyrrolidine dithiocarbamate [36]. The broad band observed in the spectra of complexes 1 and 2 at 696 nm and 515nm, respectively are assigned as crystal field (d-d) transitions.

**Figure 1:** Electronic spectra of Schiff base ligands and their mixed copper complexes

## Mass Spectra

The mass spectra of the synthesized complexes were carried out to determine and confirm the molecular weights. The observed mass spectra of the complex  $\text{NH}_4[\text{CuL}_2(\text{pdtc})]$  ( $\text{CuC}_{25}\text{H}_{26}\text{N}_4\text{O}_2\text{S}_2$ ) is 542 equal to its molecular mass. This mass spectrum (Figure 2) observation confirms and supports the proposed structure for this complex. The possible pathway for the fragmentation of Cu(II) complex is shown in Scheme 2. The molecular ion peak may lose the ammonium ion to give a peak at  $m/z=522$ , assigned to the complex ion  $[\text{CuL}_2(\text{pdtc})]^+$ . The complex ion is fragmented by loss of  $[\text{C}_4\text{H}_3\text{O}]$  to give the peak at  $m/z=461$ . The last peak is further fragmented to give peaks at  $m/z$  420, 316 and 210 due to a loss of  $\text{C}_3\text{H}_6$ ,  $\text{C}_6\text{H}_6\text{N}_2$  and  $\text{C}_7\text{H}_7\text{O}$  moieties, respectively while the peak at  $m/z$  182 was probably due to the loss of  $\text{C}_2\text{H}_4 \cdot 2$ .

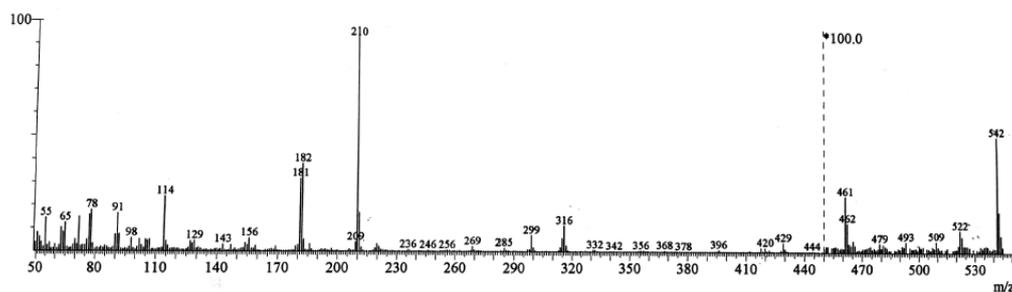
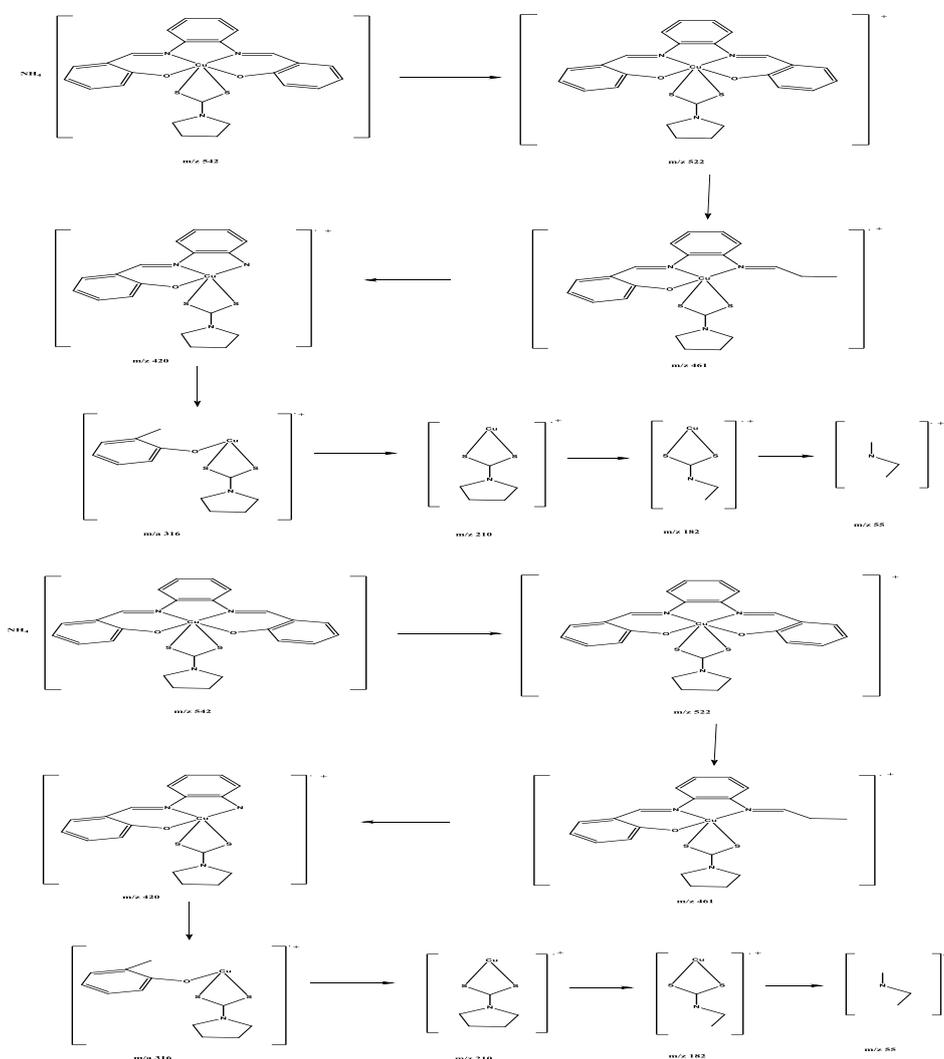


Figure 2: The mass spectrum of  $\text{NH}_4[\text{CuL}_2(\text{pdte})]$  (2)



Scheme 2: Pathway for the fragmentation of Cu(II) complex

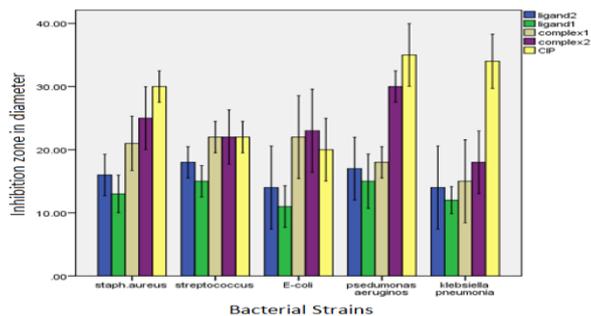
## Antibacterial Activity

The *in vitro* antibacterial activity of the Salen type Schiff base ligands and their mixed Cu(II) complexes have been carried out against five bacterial strains, *Staphylococcus aureus* and *Streptococcus* as gram-positive bacteria and *Klebsiella pneumoniae*, *Pseudomonas* and *Escherichia coli* as gram-negative bacteria using classical agar diffusion method in dimethylsulphoxide. The results of antibacterial activities of the two ligands and their complexes are given in Table 3 and shown in Figure 3. All the measurements were repeated thrice and the average inhibition data has been represented in Figure 4. The results showed that the copper(II) complexes are more active than their Schiff base ligand. The

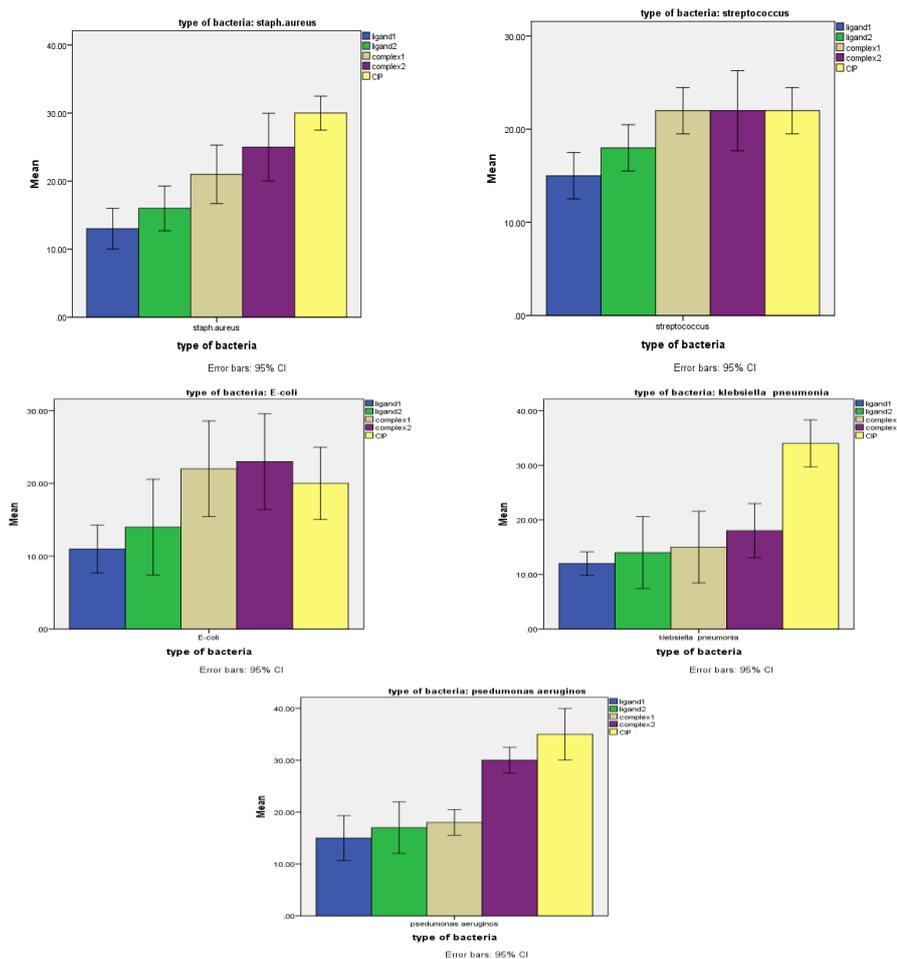
increase in the activity of the copper complexes could be due to the greater lipophilic nature of metal complexes [37]. However, the mixed copper complex  $\text{NH}_4[\text{CuL}^1(\text{pdtc})]$  (1) showed moderate activity against all bacterial strains while the complex  $\text{NH}_4[\text{CuL}^2(\text{pdtc})]$  (2) was found to be more active against the gram negative bacteria *Pseudomonas aeruginosa* with an inhibition zone diameter of 30mm.

**Table 3:** Antibacterial activity of Salen ligands and their Cu(II) mixed complexes

| Compound                                     | Bacterial Zone of Inhibition (mm) |                      |                |                               |                             |
|--|-----------------------------------|----------------------|----------------|-------------------------------|-----------------------------|
|  | <i>Staph. aureus</i>              | <i>Streptococcus</i> | <i>E. coli</i> | <i>Pseudomonas aeruginosa</i> | <i>Klebsiella pneumonia</i> |
| $\text{H}_2\text{L}^1$                       | 13 ± 0.69                         | 15 ± 0.57            | 11 ± 0.76      | 15 ± 1.00                     | 12 ± 0.50                   |
| $\text{H}_2\text{L}^2$                       | 16 ± 0.76                         | 18 ± 0.57            | 14 ± 1.52      | 17 ± 1.15                     | 14 ± 1.52                   |
| $\text{NH}_4[\text{CuL}^1(\text{pdtc})]$ (1) | 21 ± 1.00                         | 22 ± 0.57            | 22 ± 1.52      | 18 ± 0.57                     | 15 ± 1.52                   |
| $\text{NH}_4[\text{CuL}^2(\text{pdtc})]$ (2) | 25 ± 1.15                         | 22 ± 1.00            | 23 ± 1.52      | 30 ± 0.57                     | 18 ± 1.15                   |
| Ciprofloxacin (control)                      | 30 ± 0.57                         | 22 ± 0.57            | 20 ± 1.15      | 35 ± 1.15                     | 34 ± 1.00                   |



**Figure 3:** Biological evaluation diagram of Schiff base ligands and their complexes against some kind of bacteria.



**Figure 4:** Comparison of antibacterial activities of  $\text{H}_2\text{L}^1$ ,  $\text{H}_2\text{L}^2$ , complex 1 and complex 2. Data are means of three replicates along with standard error bars

**CONCLUSION**

Two new mixed copper(II) complexes of Salen type ligands and dithiocarbamate were synthesized and characterized. The Salen coordinates to the Cu(II) ion as dibasic tetradentate ONNO chelating ligand whereas the dithiocarbamate bounded to Cu(II) ion as uninegative anisobidentate ligand. From the analytical and spectral data, it was observed that the prepared copper(II) chelates adopted an octahedral geometry. The antibacterial study shows that the mixed copper(II) complexes exhibit good antibacterial property than that of free Salen ligands.

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