

Spectroscopic studies and biological evaluation of some transition metal complexes of Schiff-base ligands derived from pyridine-2-carbaldehyd

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ABSTRACT

Two Schiff bases, 1-(2-pyridine-carboxylidene)thiosemicarbazide (L_1) and 2-pyridincarboxyl-idene, 2-(pyridine-carboxylidene)-4-aminophenol (L_2), have been used to prepare metal complexes of Ni(II), Co(II) Cu(II), Cd(II), Ag and Zn(II) in an alcoholic medium. All compounds except copper and zinc complexes were non-electrolytes in dimethyl sulfoxide solvent (DMSO). The chemical structures of the Schiff base ligands and their metal complexes were confirmed by elemental analysis, molar conductance studies and spectroscopic methods like IR, UV-Vis, ^1H NMR. On the basis of elemental and spectral studies, six coordinated geometry was assigned for most of these complexes. In the light of these results, it is suggested that L_1 acts as tridentate and L_2 as bidentate ligand. Coordinating atoms in both ligands are nitrogens of azomethine and pyridine moieties. The third coordination site in L_1 is sulfur atom of thion group which provides resonance structure for prepared complexes. The free Schiff bases (L_2 and L_1) and metal complexes were also tested for their antibacterial activity (*Escherichia coli*, *Staphylococcus aureus*) to assess their inhibiting potential. The anti-bacterial activities with MIC values of compounds were evaluated.

Keywords: Schiff bases, 4-Aminophenol, Pyridine-2-carbaldehyd, Anti-bacterial.

1. INTRODUCTION

Coordination compounds exhibit different characteristic properties which depend on the nature of the metal ion to which they are bound (the type of ligand etc.). Nitrogen-containing ligands such as Schiff bases and their metal complexes played an important role in the development of coordination chemistry resulting in an enormous number of publications, ranging from pure synthetic work to physicochemical [1] and biochemically relevant studies of metal complexes [2-6]. Coordination chemistry of mixed hard-soft NS donor ligands is a field of current interest. Thiosemicarbazone ligands that are most widely studied are sulfur and nitrogen consisting ligands derived from the combination of a thiosemicarbazide and an aldehyde or ketone [7]. Interest in these ligands has been driven, in part, by potentially beneficial biological activity of ligands and their metal complexes, including, antifungal, antimicrobial, anticancer, fungicide, bactericide, enzyme inhibition, anti-inflammatory and antiviral activities [8-13]. The biological activities of these compounds showed a high dependence on their chelating properties or their substituents [14-16]. Minor modifications in

the structure of thiosemicarbazones can lead to widely different biological activities. Thiosemicarbazone ligands have good complexing ability, and their activity increases upon complexation with transition metal ions [15]. Thiosemicarbazones have variable bonding modes, ability to form stable chelates with metal ions, and structural diversity [17]. The toxicological importance of the $-\text{NH}-\text{C}=\text{S}$ moiety has been well established in antifungal, antibacterial agents and pesticide activities [18]. The sulfur, oxygen and nitrogen may be involved in coordination providing a useful model for bioinorganic processes [19]. It has been suggested that the azomethine linkage in Schiff bases is responsible for the biological activities such as antitumor, antibacterial, antifungal, and herbicidal activities [20]. Nickel(II) complexes have found several potential applications in medicine, and very recently they have been screened for inhibition of cancer cell proliferation [21-22].

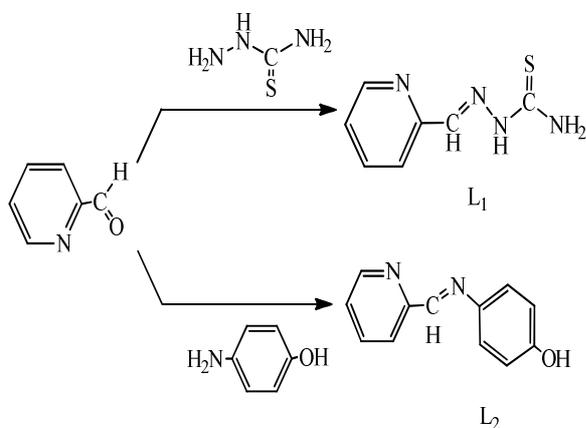
2. EXPERIMENTAL

All the chemicals used in the synthesis were of reagent grade and used without further purification. ^1H -NMR spectra were recorded on Bruker advance II 400 NMR Spectrometer,

infrared spectra (400–4000 cm^{-1}) were recorded on KBr pellets on a PerkinElmer Spectrum 65 spectrometer. The metal contents measured by absorption spectra were recorded by applying Analyst 300, Perkin Elmer Co. USA spectrophotometer. Elemental analyses were carried out on a CHNS analyzer, CHNS-932, Leco, USA elemental analyzer. Melting points were determined on an Electro Thermal IA900 apparatus. The molar conductance was obtained on a DDS-11 conductimeter. The electronic spectra were performed by UV-Vis methods with a PG Instruments T70 spectrophotometer. 1-(pyridine-2-ylmethylene) thiosemicarbazide (L_1) has been prepared based on the published procedure [23].

2.1. Preparation of 2-pyridincarboxylidene,4-aminophenol (L_2)

In a round bottom flask (1.091 g) 10 mmol of 4-aminophenol was dissolved in 25 ml of ethanol and (0.951 ml) 10 mmol pyridin-2-carbaldehyd in 25ml of ethanol was added and mixed well. Then 2-3 drops of glacial acetic acid as catalyst was added to the mixture and refluxed for 2 hours at 60°C. Then the reaction mixture was concentrated to 10ml and was cooled to 0°C. The solid was filtered off and recrystallized from ethanol and dried at room temperature (Yield: 86%)(Scheme 1).



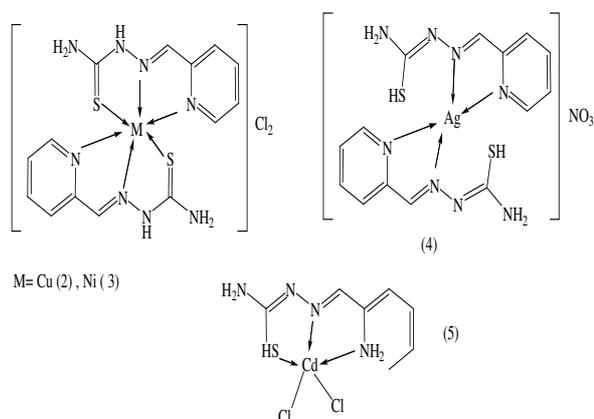
Scheme - 1: Reaction scheme for synthesis of Schiff bases.

2.2. Preparation of Schiff base metal (II) complexes

The metal complexes of L_1 and L_2 with Co(II), Ni(II), Zn(II), Cd(II), Cu(II) and Ag salts (chloride and acetate) have been synthesized in an analogous procedure, and a typical procedure for synthesis is given below for each case:

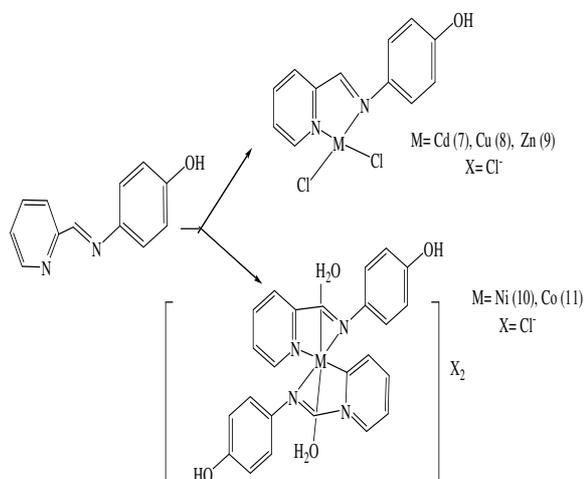
An alcoholic solution (45 ml) of Schiff base L_1 (2 mmol) was mixed with alcoholic solution (5 ml) of 1 mmol of $\text{MCl}_2 \cdot x\text{H}_2\text{O}$ and refluxed for 2 hours. Then, 2 mmol of sodium acetate was added to the reaction mixture and was refluxed for 3 hours. The progress of reaction

was monitored by TLC. The solid was then filtered off and recrystallized from ethanol and dried under reduced pressure for 9 h, to isolate a greenish solid (Yield: 68-87%) (Scheme 2).



Scheme - 2: Reaction scheme for synthesis of L_1 complexes.

An alcoholic solution (60 ml) of Schiff base L_2 (2 mmol) was added to an alcoholic solution (5 ml) of 1 mmol of $\text{MCl}_2 \cdot x\text{H}_2\text{O}$. The mixture was refluxed for 5 hours at 60°C. The progress of reaction was monitored by TLC. The solid was then filtered off and recrystallized from ethanol and dried under reduced pressure for 9 h (Yield: 58-88%)(Scheme 3).



Scheme - 3: Reaction scheme for synthesis of L_2 complexes.

2.3. Antibacterial screening

Antibacterial activity of the ligands and their complexes were tested against gram-positive *Staphylococcus aureus* and gram-negative *Escherichia coli* bacteria using dilution susceptibility testing methods to determine the minimal concentration of antimicrobial to inhibit or kill the microorganism. This can be achieved by dilution of antimicrobial in either agar or broth media. Antimicrobials are tested in \log_2 serial dilutions (two fold). Testing samples and control samples were prepared in DMSO. Because very

faint turbidity may be given by the inoculum itself, the inoculated tube kept in the refrigerator overnight may be used as the standard for the determination of complete inhibition. Standard strain of known MIC value run with the test is used as the control to check the reagents and conditions.

The synthesized ligands and complexes (2, 4, 8, 16, 32 mg) were dissolved in test solution (DMSO, 150 μ l) and 850 μ l of Mueller-Hinton agar was added followed by 1000 μ l McFarland standard. The blank sample was prepared with the same procedure without complex or ligands. All samples were incubated for 48 h. MIC is expressed as the lowest dilution, which inhibited growth judged by lack of turbidity in the tube. Because colored media may not provide the proper contrast with McFarland equivalence standards, a 20 ml of the prepared samples were grown by grass cultivated method in a plate prepared by nutrient agar [24].

3. RESULTS AND DISCUSSION

The complexes were synthesized by reacting ligands with metal ions in 2:1 or 1:1 (L:M) molar ratio in ethanolic medium. Thiosemicarbazone was expected to behave as a tridentate with one sulphur and two nitrogen as donor atoms or coordination sites. Besides azomethine and pyridine coordination sites in both ligands, L₁ has a third coordination sulfur atom for formation of six coordinate metal complex. The present thiosemicarbazone ligands exist as both the thione and thiol form since it has NHC=S thioamide and N=CSH thiol groups; although, in many instances, equilibrium mixture of both forms have

been observed in thiosemicarbazones. Both ligands with copper, cobalt, nickel and silver form ionic 6 coordinate compounds by reacting in 1:2 ratios of M:L but with cadmium form a 4 or 5 nonionic coordinate compound by reaction with 1:1 ratio of M:L (Scheme 2-3). The analytical data and spectral analyses agree well with the proposed composition of formed complexes. All the complexes have shown good solubility in all the common organic solvents but were found insoluble in ether, water, acetone, and benzene.

3.1. IR spectra of Complexes

In the absence of a powerful technique such as X-ray crystallography, IR spectra have proven to be the most suitable technique to give enough information to elucidate the mode of bonding of the ligands to the metal ions. In order to study the binding mode of the Schiff base to the metal ion in complexes, the IR spectra of the free ligands were compared with the spectra of corresponding complexes. The important absorption frequencies of ligands and all metal complexes and their assignments are given in table 2.

A number of bands in the range 1640-1400 cm^{-1} in the spectra of both ligands and complexes are ascribed to Py ring vibrations, as well as to the $\nu(\text{C}=\text{N})$ and $\sigma(\text{NH}_2)$ of the chain. Strong bands are observed at 1609 and 1623 cm^{-1} in the infrared spectra of the free Schiff bases L₁ and L₂ respectively which are characteristic of the azomethine group. In the spectra of all new complexes, this band is shifted to the 1590-1580 cm^{-1} region indicating the coordination of the Schiff bases through nitrogen atom of the azomethine group (table 2) [1].

Table - 1: Physical characterization and analytical data of the prepared Schiff bases and metal complexes (1-11)

Compound	Color	m.p. (°C)	C% Found (Calcd.)	H% Found (Calcd.)	N% Found (Calcd.)	S% Found (Calcd.)	M% Found (Calcd.)	λ_m ($\Omega^{-1}\text{cm}^2\text{mol}^{-1}$)
(C ₇ H ₈ N ₄ S) (1)	pale yellow		46.09(46.65)	4.65(4.47)	31.28(31.09)	17.18(17.79)		---
C ₁₄ Cl ₂ CuH ₁₆ N ₈ S ₂ (2)	dark green	219	33.66(33.98)	3.26(3.26)	22.64(22.64)	11.59(12.96)	13.67(12.84)	43
C ₁₄ Cl ₂ H ₂₀ N ₈ NiO ₂ S ₂ (3)	light brown	277	31.60(31.96)	3.50(3.83)	21.10(21.30)	12.20(12.19)	10.420(11.16)	48
AgC ₁₄ H ₂₀ N ₉ O ₅ S ₂ (4)	pale yellow	210	29.43(29.69)	3.49(3.56)	22.13(22.26)	11.18(11.32)	19.58(19.05)	46
C ₇ CdCl ₂ H ₁₂ N ₄ O ₂ S (5)	yellow	266	20.73(21.04)	2.48(3.03)	13.78(14.02)	8.004(8.02)	27.91(28.13)	25
L ₂ (C ₁₂ H ₁₀ N ₂ O) (6)	yellow-green	193	72.22(72.71)	5.05(5.08)	14.22(14.13)	----	----	----
C ₁₂ CdCl ₂ H ₁₄ N ₂ O ₃ (7)	yellow	324	34.30(34.52)	3.34(3.38)	6.79(6.71)	----	27.91(26.92)	24
C ₁₂ Cl ₂ CuH ₁₀ N ₂ O (8)	dark Brown	240	42.37(43.32)	3.97(3.03)	8.18(8.42)	----	18.99(19.10)	22
C ₁₂ Cl ₂ H ₁₀ N ₂ O ₃ Zn (9)	yellow	377	42.97(43.09)	2.93(3.01)	8.18(8.37)	----	19.2(19.55)	27
C ₂₄ Cl ₂ H ₂₈ N ₄ NiO ₆ (10)	light brown	248	48.33(48.20)	3.98(4.72)	9.45(9.37)	----	9.66(9.81)	55
C ₂₄ Cl ₂ CoH ₂₄ N ₄ O ₄ (11)	orange	178	51.32(51.26)	4.21(4.30)	9.56(9.96)	----	9.96(10.48)	52

Coordination of imine nitrogen is also consistent with the presence of a band at 500–657 cm^{-1} , assignable to $\nu(\text{M-N})$. Another band at 616 and 626 cm^{-1} in the free ligands is due to $\nu(\text{C=N})$ bond of the Py moiety and is also shifted toward higher frequency. This indicates that the nitrogen atom of the pyridine group is also involved in complex formation.

The uncomplexed thiosemicarbazones show the thioamide band, which possesses considerable contribution from $\nu(\text{CS})$, in the 880 cm^{-1} range. This band shifts 60 to 90 cm^{-1} to lower energy when coordination occurs with deprotonation at N and formation of a single C-S bond [26]. The shift is 5 to 25 cm^{-1} to lower frequencies when the thiosemicarbazones coordinate the metal in the neutral form [26]. Nevertheless, the $\nu(\text{SH})$ band (at 2500 cm^{-1}) is missing from the spectra of the L_1 , copper and nickel complex, so that it can be concluded that the thio/keto form is predominant in these structures. Conversely, for cadmium and silver complex the $\nu(\text{SH})$ band appears at 1660 and 1669 cm^{-1} and a new $\nu(\text{N=C})$ band at 1639 and 1620 cm^{-1}

¹ is often resolved due to formation of thiol form [27]. The FT-IR spectra data of ligand and all the complexes are shown in table 2.

3.2. Electronic spectra

The electronic spectra of L_1 and L_2 show three bands at 236–360 nm related to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ of aromatic ring and azomethine group respectively. As usual, absorption bands observed in the 400–766 nm range most likely arise from a d-d transition of metal centers of these complexes. The Ni(II) complex (5, 10) show two bands at 404, 595 and 475, 765 nm related to ${}^3A_{2g} \rightarrow {}^3T_{1g(p)}(u_2)$ and ${}^3A_{2g} \rightarrow {}^3T_{1g(F)}(u_3)$, Co(II) complex (8) two absorptions at 672 and 596 nm related to ${}^4T_{1g(F)} \rightarrow {}^4A_{2g(F)}(u_2)$ and ${}^4T_{1g(F)} \rightarrow {}^4T_{2g(F)}(u_3)$ transitions and Cu(II) complex (2) shows one band in 616 nm due to ${}^2E_{2g} \rightarrow {}^2T_{2g}$ transitions in the octahedral environment. For Cu(II) complex (9) a band at 689 nm related to ${}^2T_2 \rightarrow {}^2E_2$ transition in tetrahedral or square planar geometry is observed [28–29]. The ν_1 could not be observed due to the limited range of the instrument. The electronic spectra data of the compounds prepared are reported in table 2.

Table - 2: FT-IR data of the prepared Schiff bases and metal complexes (1-11)

Compound	UV/Vis $\lambda_{\text{max}}(\epsilon)$, nm($\text{M}^{-1}\text{cm}^{-1}$)	IR(cm^{-1})					
		$\nu(\text{S-H})$	$\nu(\text{C=N})$	$\nu(\text{C=S})$	$\nu(\text{O-H})$	$\nu(\text{M-N})$	$\nu(\text{Py-N})$
L_1 (1)	236(758), 268(483), 325(264)	---	1610	880,	---	---	616
$[\text{Cu}(\text{L}_1)_2]\text{Cl}_2$ (2)	324 (7410), 409 (4271), 616 (2842)	---	1606, 1583	873	---	565	624
$[\text{Ni}(\text{L}_1)_2(\text{H}_2\text{O})_2]\text{Cl}_2$ (3)	219 (7510), 300 (5942), 360 (3725), 404 (1642), 595 (1071)	---	1603, 1548	875	---	515	624
$[\text{Ag}(\text{L}_1)_2 \cdot 2\text{H}_2\text{O}]\text{NO}_3$ (4)	220 (5673), 266 (4282), 325 (3425)	2660	1639, 1555	819	---	516	632
$[\text{Cd}(\text{L}_1)(\text{H}_2\text{O})_2]\text{Cl}_2$ (5)	263 (5410), 320 (3261), 322 (3123), 378(3045)	2669	1620, 1584	790	---	511	655
(6)	237 (6423), 286 (3721), 348 (2912), 360 (1412)	---	1623, 1506	---	3425	---	626
$[\text{Cd}(\text{L}_2)(\text{H}_2\text{O})_2]\text{Cl}_2$ (7)	250 (5632), 286 (3455), 361 (2892)	---	1595, 1508	---	3369	511	640
$[\text{Cu}(\text{L}_2)\text{Cl}_2]$ (8)	246 (7632), 370 (4632), 382 (3124), 689 (1052)	---	1592, 1508	---	3300	521	643
$[\text{Zn}(\text{L}_2)\text{Cl}_2]$ (9)	237 (6542), 286 (4325), 362 (2347)	---	1598, 1508	---	3361	513	652
$[\text{Ni}(\text{L}_2)_2(\text{H}_2\text{O})_4]\text{Cl}_2$ (10)	222 (7432), 249 (5628), 358 (3902), 365 (3881), 475 (1824), 765 (1024)	---	1589, 1506	---	3412	503	626
$[\text{Co}(\text{L}_2)_2(\text{H}_2\text{O}_2)]\text{Cl}_2$ (11)	249 (7563), 356 (4657), 364 (3175), 596 (1357), 672 (1186)	---	1589, 1507	---	3421	500	657

Table - 3: ${}^1\text{H-NMR}$ spectra (DMSO - d_6) of the compounds 1, 5, 11

Compound	O-H	NH_2	CH=N	Ar-H	Py
1	---	11.6, 7.35, 7.78	7.8	---	8.17, 8.27, 8.836, 8.54
3		9.7, 8.7, 8.1	8.6		7.9, 7.5, 7.3, 6.8
9	9.7	----	8.6	6.7, 7.2	7.6, 8, 8.8

3.3 ¹H NMR spectra

The ¹H NMR spectra of L₁ and [Ni(L₁)₂(H₂O)₂]Cl₂ (5) and [Zn(L₂)Cl₂] (11) complexes were recorded in DMSO-d₆ solvent. The signals due to NH(1H), NH₂ (1H) and NH₂(1H) protons of L₁ appear at δ(11.6, 7.35, 7.78) ppm and signals at δ(8.17, 8.27, 8.836, 8.54) ppm and at δ(7.8) ppm correspond to Py(4H) and CH=N proton respectively. The high δ values observed for N-H proton for N-N-S donor ligand were assumed to be due to intermolecular hydrogen bonding with DMSO solvent. The signals due to OH proton in Zn(II)complex (11) appears at δ 9.7 ppm, azomethine and pyridine proton signals are in the same region as Ni(II)complex (δ 8.6, 6.8-7.9)(Table 3) [30].

3.4. Antibacterial activity

The results of the antibacterial screening of the two Schiff bases and their complexes against gram-positive *Staphylococcus aureus* and gram-negative *Escherichia coli* bacteria are given in table 4-5. It is found that Schiff bases are less active, than corresponding metal ion complexes and the increased activity of the metal chelates can be explained on the basis of two factors [31]. On one hand an important factor that controls the antimicrobial activity is lipo solubility. According to Overtone's concept of cell permeability, the lipid membrane that surrounds the cell favors the passage of only lipid soluble materials. The polarity of the metal ion will be reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of positive charge of metal ion with donor groups upon chelation. In addition, lipophilicity of the complex increases by the delocalization of the π electrons over the whole chelate ring due to chelation. This

increased lipophilicity enhances the penetration of the complexes into lipid membrane and thus blocks the metal binding sites on enzymes of microorganisms (maybe by formation of a hydrogen bond through the azomethine group with the active center of cell constituents) [32-33]. On the other hand, metal complexes disturb the respiration process of the cell and thus block the synthesis of proteins, which restricts further growth of the organism. The variation in the activity of different complexes against different organisms depend either on the impermeability of the cells of the microbes or difference in ribosomes of microbial cells [34]. From the table 4 it is observed that the activity of L₂ is more than L₁ due to existence of extra aromatic ring which enhances the lipophilicity of this Schiff base and presence of hydroxyl group in L₂ which provide a good and nonhindered site for formation of hydrogen bonding with the active centers of cell constituents resulting in interferences with the normal cell process [35]. L₁ has no antibacterial activity against *E. coli* and *S. aureus* bacteria. Copper, cadmium and silver complexes of L₁ in all concentrations have 100% antibacterial affect against *E. coli* bacteria. Nickel complexes of L₁ (3) in 0.002 mg/ml 30-50%, in 0.004 mg/ml, 60-70% and in 0.008, 0.016 and 0.0032 mg/ml has 100% antibacterial activity against *E. coli* bacteria. Cadmium and copper complex of L₁ have 100% antibacterial affect against *S. aureus* bacteria in all concentrations, but silver complex has 30-50% antibacterial affect at 0.002 mg/ml and 100% antibacterial activity against *S. aureus* bacteria in all other concentrations. Nickel complex of L₁ has no antibacterial affect at 0.002 and 0.004 mg/ml, 30-50% at 0.008 mg/ml and 100% at 0.016 and 0.032 mg/ml against *S. aureus* bacteria (Table 4).

Table - 4: Antibacterial results of Schiff base L₁ and L₂ and their metal complexes *E. coli* and *S. aureus*

Compound	<i>E. coli</i> / <i>S. aureus</i>					MIC gr/ml	MBC gr/m
	0.002 mg/ml	0.004 mg/ml	0.008 mg/ml	0.016 mg/ml	0.032 mg/ml		
1	---	---	---	---	---	---	---
2	++++	++++	++++	++++	++++	++++	++++
3	++	---	+++	---	++	++++	++++
4	++++	++	++++	++++	++++	++++	++++
5	++++	++++	++++	++++	++++	++++	++++
6	++++	++++	++++	++++	++++	++++	++++
7	++++	++++	++++	++++	++++	++++	++++
8	++++	++++	++++	++++	++++	++++	++++
9	++++	++++	++++	++++	++++	++++	++++
10	++	++++	+++	++++	++++	++++	++++
11	+	---	+++	+++	++++	++++	++++

High active =+ +++(100%); good active = +++ (60-70%); Moderatively active (30-50%); Less active (10-20%), Inactive = ----

For antibacterial activity of L₂; cadmium, copper and zinc complexes have 100% antibacterial activity in all concentrations against both against *E. coli* and *S. aureus* bacteria. Cobalt complex has 10-20% at 0.002 mg/ml, 60-70% at 0.004 mg/ml and 100% at 0.008-0.0032 mg/ml antibacterial affect against *E. coli* bacteria. Cobalt complex has no antibacterial affect at 0.002 mg/ml, 60-70% at 0.004 mg/ml and 100% at 0.008-0.032 mg/ml shows antibacterial affect against *S. aureus* bacteria (Table 4).

4. CONCLUSION

The metal chelates of L₁ and L₂ have been structurally characterized. The metal ligand stoichiometry in these is 1:2 or 1:1 ratios, associated with water molecules in some cases. The complexes of the above ligands are electrolytes in DMSO except for compounds 5, 8 and 9 which form four coordinate compounds. Based on analytical, conductance and electronic spectral data, all these complexes are assigned to be in octahedral geometry. Biological studies reveal that complexes of L₁ show better activity compared to their respective ligand but in the case of L₂, ligand as well as its complexes is good antibacterial agent. These two ligands behave differently against *E. coli* and *S. aureus* bacteria which relate to the structure of these ligands, their complexes and the way they can interact with these bacteria or cells to prevent them from interact with each other which includes: impairing cell activity by deactivating cell proteins or cell wall permeability by the applied complexes, hydrogen bond formation between the azomethine of ligand or complex with cell which prevents from normal cell activity.

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