

**SYNTHESIS, CHARACTERIZATION, ESR STUDIES, ANTIMICROBIAL AND
ANTHELMINTIC ACTIVITY OF COPPER COMPLEXES WITH 5, 5-
DIMETHYLCYCLOHEXANE 1, 3-DIONE DERIVATIVES****Kavita S. Mundhe***

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Kavita S. MundheAnantrao Thopte College,
Bhor. Dist. Pune,
Maharashtra, India.**ABSTRACT**

Many Schiff bases are medicinally important hence used to design medicinal compounds. Chelation with metal may increase the biological activity of the Schiff bases. Transition metal complexes of O-donor ligands possess antibacterial, antifungal and anti-inflammatory activity. Transition metal complexes of N-donor ligands (Schiff bases) showed anti-Candida activities. Copper complexes are important due to the variety in their coordination chemistry, technical applications, catalysis, spectroscopic properties, anion selectivity, and their biological significance. Taking into consideration the important applications of these compounds the study of dimedone derivatives and their copper complexes have been carried out. The copper complexes of 5, 5-dimethyl-3-(phenylimino) cyclohexanone (L₁), 5, 5 -dimethyl-3-(o-phenylimino) cyclohexanone (L₂), 5,5-dimethyl-3-(m-phenylimino) cyclohexanone (L₃), 5,5-dimethyl-3-(p-phenylimino) cyclohexanone (L₄) have been synthesized. The synthesized complexes are characterized by using magnetic measurements, thermogravimetric analysis and spectral techniques. These metal complexes have been evaluated for their antimicrobial and anthelmintic activity. It is observed that the Schiff bases coordinated to metal ions through amine nitrogen and oxygen of carbonyl group. The anti microbial study shows that the metal complexes show better activity against bacterial strain *Staphylococcus aureus* in comparison to the ligands. The copper complex shows significant anthelmintic activity.

KEYWORDS: Dimedone derivatives, Copper Complexes, Spectral and Bioactivity study.**INTRODUCTION**

Metal ions play an important role in the structural organization of biochemical molecules and the functional processes.^[1] The interaction of metal ions with organic molecules results in modifying properties. It is noted that one third of all enzymes have a metal ion as an essential component.^[2] Many critical life processes require metal ions including dioxygen transport, respiration, nerve impulse transmission, muscle contraction etc. Some complexes are used as diagnostic probes or drugs.^[3] A large number of metal complexes are biologically important. Change in the metal or substituent on the porphyrin ring results in change in the activity of complexes. Biological activity of the ligands can be enhanced or controlled by coordination to metals; hence many times metal complexes show better activity than the free ligands.^[4] β -diketones and its metal complexes have been used in different areas because of their structural features, chemical functionalities and electroluminescence properties.^[5] The metal ion itself might be the toxic agent. An excess of toxic metal ion in the living system can be removed using a chelating agent. D-Penicillamine is known to be a good chelating

agent for the emission of copper ions in patients with Wilson's disease, and hence finds use in controlling this disease, indicating chelating agents are important in medicine.^[6-10] The metal complexes of biologically important ligands such as benzimidazoles, Schiff bases derived from amino acids, thiosemicarbazones etc, play a significant role in determining the function of a number of biologically important metal complexes.^[11-12] Transition metal complexes with Schiff bases have played important role in the development of coordination chemistry. Many studies have been carried out on transition metal complexes of Schiff bases containing nitrogen and oxygen donors.^[13] This may be attributed to their stability, substrate chirality, and ability to coordinate to different metals and stabilize them in various oxidation states. They also have applications in many fields such as catalysis and biological activity.^[14-18] Copper complexes are important due to their variety in coordination chemistry, technical application, catalysis, spectroscopic properties, anion selectivity, and their biological significance^[19-20]

MATERIALS AND METHODS

The ligands (L_1 to L_4) have been prepared by reported literature method.^[21] The Synthesis characterization and bioactivity study of ligands have been reported.^[22] The Cu (II) complexes of Ligands ($L_1 = C_{14}H_{17}NO$), ($L_2 = C_{15}H_{19}NO$), ($L_3 = C_{15}H_{19}NO$) and ($L_4 = C_{15}H_{19}NO$) are prepared by the reaction of $CuCl_2 \cdot 2H_2O$ (0.4mmol, 100 mg) in methanol (1:1) with ligands L_1 , L_2 , L_3 , & L_4 (0.4 mmol, 100-108mg) under reflux. After refluxing for 5hrs color change from yellow to brown was observed. A solid is separated by concentration, washed with hexane, diethyl ether and dried in vacuum and recrystallized using ethanol.

Antimicrobial activity (in-vitro): The synthesized imine complexes of copper (II) were screened in vitro for their antibacterial activity against bacterial strains, *Escherichia coli* (ATCC No. 11246), *Salmonella abony* (ATCC No. 23564), *Pseudomonas aeruginosa* (ATCC No. 27853), and *Staphylococcus aureus* (ATCC No. 6538P) and also tested for Antifungal activity against yeast strains as, *Saccharomyces cerevisiae* (ATCC No. 9763), *Aspergillus niger* (ATCC No. 16404). The well diffusion method was used. Test samples of each complex (20 mg) were dissolved in ethyl alcohol (1 ml). Sterile 8.00 mm diameter well was impregnated with 40 μ L of test solutions and performed under sterile conditions. Streptomycin (10 μ g/disc) and fluconazole discs (50 μ g/disc) were used as positive controls.

Anthelmintic activity (in -vitro): The in- vitro anthelmintic study were carried out as per the standard method with some minor changes and modifications. The Indian Earthworm was selected because of its resemblance in anatomy and physiology with the intestinal round parasite of human being. The concentration of copper (II) complexes (5, & 10, mg / ml) in normal saline solution were tested, which involved determination of time of paralysis and death of the worms. Albendazol was used as a standard (5&10mg / ml) and normal saline served as control. Three groups of four earthworms were released into 10 ml of normal saline. Observations were made for the time taken for the paralysis and death of individual worms. Time for paralysis was noted when no movement is observed. Death is concluded when the worms lost their movement followed by fading of their body colour.

RESULTS AND DISCUSSION

All the copper complexes are dark brown, nonhygroscopic, insoluble in water but are soluble in acetone, methanol, DMF & DMSO, and decompose at higher temperature. Solutions of all the complexes in DMF are nonconducting indicating their nonelectrolytic nature. The physicochemical parameters of these complexes are given in Table 1. The important IR stretching frequencies for the ligand and complexes are shown Table 2. Thermal analyses (TGA) of the Copper complexes have been given in Table 3. The electronic absorption spectra (ESR) of ligands and their complexes

have been recorded over the range 200 – 800 nm in DMF and their λ max values are summarized in Table 4.

Reaction of L_1 with $CuCl_2 \cdot 2H_2O$ in methanol yielded a brown coloured complex (3a) decomposing at 175 $^{\circ}C$. The mass spectrum (Figure 1) of the copper (II) complex (3a) shows the molecular ion peak [$M - 1$] at $m/z = 390$. Subsequent peaks at 351, 317 and 284 can be assigned to the fragments obtained due to loss of water molecules, chloride ions and the ligand. The base peak is observed at 216, suggests an empirical formula $MLCl_2 \cdot 2H_2O$ for the complex. The elemental analysis is in agreement with the suggested formula.

The infra red spectrum (Figure 2) shows a band of medium intensity at 3449 cm^{-1} assignable to $\nu -OH$ stretching of co-ordinated water molecules. The strong band observed due to $\nu -NH$ stretching at 3237 cm^{-1} in the ligand shows a shift to 3261 cm^{-1} in the complex which indicates the binding of $-NH$ group to the metal. The observed shift to higher frequency in the complex rather than the expected lowering of $-NH$ stretching frequency could be due to intermolecular hydrogen bonding in the ligand prior to binding. The strong band in the ligand observed at 1640 cm^{-1} due to $\nu C=O$ is lowered to 1600 cm^{-1} indicating the co-ordination of carbonyl oxygen. Bands observed at 499, 476 and 378 cm^{-1} are assigned to $\nu(M-O)$, $\nu(M-N)$ and $\nu(M-Cl)$ which indicate coordination of ligand and chloride ion to metal.

The electronic spectrum of complex displays one broad band at 17574 cm^{-1} which can be assigned to $2E_g \rightarrow 2T_{2g}$ transition, suggesting an octahedral geometry^[23] around the copper ion. No peak was observed for the ligand in this region. The magnetic moment (μ_{eff}) of complex 3a was found to be 1.87 BM corresponding to one unpaired electron and is in agreement with the proposed octahedral structure and monomeric nature of the complex.

The thermogram (Figure 3) of complex 3a over temperature range $35^{\circ}C$ to $800^{\circ}C$ shows weight loss in the three steps. The loss of 8.6% (cal. 9.35%) from 100 to $180^{\circ}C$ indicates the loss of co-ordinated water molecules which is in accordance with literature reports.^[24] A further loss of 17.63% (18.44%) up to $252^{\circ}C$ indicates loss of chloride ions, while a loss of 56.9 % (cal.55.84%) between $287- 594^{\circ}C$ corresponds to the loss of ($C_{14}H_{17}NO$). The observed mass of the residue is in agreement with the calculated mass (cal.20.52%).

Ligands L_2 , L_3 and L_4 on reaction with $CuCl_2 \cdot 2H_2O$ yielded compounds whose mass spectra and elemental analysis differed from the copper complex of L_1 . The mass spectrum of complex 5a shows molecular ion peak at 628.6, while 7a and 9a exhibit peaks at 652 due to association of molecular ion with Na^+ . This suggests an empirical formula $M(L)_2Cl_2 \cdot 2H_2O$ which also complies with their elemental analysis. The mass spectra of the

complexes also display peaks due to different daughter ions formed by the loss of water molecules, chloride ions and the ligand moiety, leaving behind a residue, the weight of which corresponds to the expected weight of the metal oxide.

IR spectra of complexes 5a, 7a and 9a exhibit broad bands between 3550 and 3400 cm^{-1} , due to ν (-OH) indicating presence of water molecules in these complexes. The bands observed at 3190, 3211 and 3244 cm^{-1} assignable to ν (-NH) of free ligands, L_2 , L_3 and L_4 respectively appear as slightly broad bands at 3223, 3257 and 3259 cm^{-1} in the respective copper complexes. The shift in ν (-NH) suggests coordination of the ligands through nitrogen. The shift towards higher frequency may be attributed to break down of hydrogen bonding in the ligand during complexation. It should be noted that the ligand L_2 exhibits intermolecular hydrogen bonding which is unambiguously established by its X-ray studies.^[22] The strong bands due to ν -C=O observed at 1640, 1680 and 1660 cm^{-1} in the IR spectra of L_2 , L_3 and L_4 show shifts to lower frequency and appear at 1618, 1600 and 1640 cm^{-1} in the respective complexes, implying participation of the carbonyl group in bonding. The bands observed between 500 to 590 cm^{-1} are assignable to ν (M-O). The bands between 440 to 490 cm^{-1} and 350 to 370 cm^{-1} can be assigned to ν (M-N) and ν (M-Cl) respectively. Complex 5a, 7a and 9a display one absorption band in their electronic spectra in the range 18010-18552, cm^{-1} which can be assigned to $2E_g \rightarrow 2T_{2g}$ transition in the copper complexes.

Magnetic moments of these complexes are found to be 1.85, 1.65 and 2.07 respectively, corresponding to single unpaired electron in the individual complexes. The electronic spectral data and magnetic moments confirm the octahedral geometry of the complexes. On the basis of above data the proposed structures have been represented in Figure 1a.

Thermo gram of complex 5a shows a two step decomposition pattern. The first stage is seen between RT to 260 $^{\circ}\text{C}$. The second stage is observed in the temperature range 275 to 640 $^{\circ}\text{C}$. The first step between RT to 260 $^{\circ}\text{C}$ seems to be consistent with the evolution of two molecules of lattice water and chloride ions (found 15.78%, cal. 17.00%). The next step corresponds to a weight loss of 71.88% suggesting the loss of the organic ligand. The daughter ion peaks observed in the mass spectra of the complexes substantiate this finding.

Thermal studies of copper complex 7a indicate that the complex decomposes in two steps. In the first stage weight loss of 15.77% (cal. 17.00%) in the temperature range RT – 217 $^{\circ}\text{C}$ corresponds to lattice water molecules and chloride ions. The second stage observed in the range 290 – 616 $^{\circ}\text{C}$ shows further loss in weight 71.48 % (cal. 72.92%) corresponds to the loss of two ligands leaving behind the residue of copper oxide.

The thermo gram of complex 9a consists of two steps (I) RT – 148 $^{\circ}\text{C}$ and (II) 240 - 648 $^{\circ}\text{C}$. The weight loss 15.95 % (cal. 17.00%) in the first step indicates the presence of two lattice water molecules and chloride ions. The further loss in weight in second step 72.59 % (cal. 72.92%) corresponds the loss of two ligands leaving behind the residue of copper oxide.

ESR Study

In order to get a better insight to the structure of the metal complex and information about the location of unpaired electron in the copper complexes, X – band ESR spectra of copper complex 3a, 5a, 7a and 9a, have been recorded in DMSO at room temperature (300 K) and are shown in Figure 4-7. The calculated ESR parameters are summarized in Table 5. ESR spectra of metal complexes give an insight to the stereochemistry and environment around central metal atom. The 'g' values help in determining the ground state of the metal. The 'g' values of the transition metal complexes determine structure of the complex. The ESR spectra of these complexes display signals with two g values, g^{\parallel} and g^{\perp} , indicating a slightly distorted geometry at the copper centre. In a perfectly cubic environment 'g' is isotropic. Compression or elongation results in non isotropic g values. When $g^{\parallel} > g^{\perp} > 2$, the unpaired electron is predicted to be in the $dx^2 - y^2$ orbital. The complex 3a, 5a, 7a and 9a exhibit g^{\parallel} values of 2.09, 2.23, 2.20 & 2.19 and g^{\perp} values 2.0070, 2.0109, 2.0100 & 2.0131 respectively. The observed g values reveal that, $g^{\parallel} > g^{\perp} > 2$ indicating unpaired electron lies in the $dx^2 - y^2$ orbital in all the complexes and there is a contribution of covalence in the metal - ligand bond. The higher g^{\parallel} values indicate a slight distortion from regular octahedral geometry. The broadening of g^{\perp} could be due to spin lattice relaxation that results from the interaction of paramagnetic ion with the thermal vibrations of the lattice.

The spin orbit coupling constant, λ values for these complexes have been calculated using the relations, $g_{av} = 1/3 [g^{\parallel} + g^{\perp}]$ and $g_{av} = 2 (1 - 2\lambda / 10 Dq)$ which are found to be -166, -392, -351 & -350 cm^{-1} for 3a, 5a, 7a and 9a respectively, which are less than that for free Cu (II) ion (-832 cm^{-1}). These values support the covalent character of metal ligand bond in the complexes. The covalency parameter, α can be calculated using the equation, $\alpha = - (A_{\parallel} / 0.036) + (g^{\parallel} - 2.0023) + 3/7 (g^{\perp} - 2.0023) + 0.04$.

Value of $\alpha = 0.5$, indicates complete covalent bonding while the value of $\alpha = 1.0$ suggests complete ionic bonding. The observed values of α (0.116, 0.6, 0.4212 & 0.2884) for the copper complexes are less than unity indicating that the complexes have covalent character. 'G' value which is a measure of exchange interaction between Cu^{2+} centers in a complex is calculated using the equation, $G = g^{\parallel} - 2.0023 / g^{\perp} - 2.0023$. The observed G values of 18.46, 26.12, 25.52 & 17.88 for complex 3a, 5a, 7a and 9a are greater than 4, indicates

negligible exchange interactions between copper in the complexes.

It can be concluded that the geometry of the copper complexes is tetragonally elongated. g_{\parallel} and g_{\perp} peaks are separated but no super hyperfine splitting has been identified on these peaks. From the above data proposed structures for copper complexes are shown in Figure 1a.

Antimicrobial activity

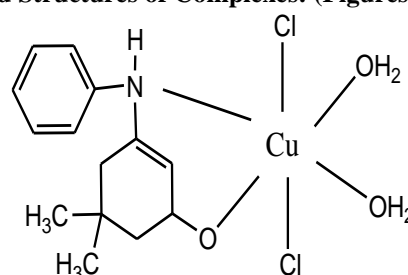
The antibacterial activity for copper complexes (Table 6) shows clear zone around the well indicates the inhibitory activity of the compound on the organism. The results clearly indicate that all complexes are active against *S. aureus* while they are inactive against other strains. A considerable zone of inhibition is shown by all complexes where as the ligands do not exhibit any inhibition in the growth of *S. aureus*.^[22] This could be due chelation of the ligands with the metals. In chelates the positive charge of the metal is partially shared with the donor atoms present in the ligand and there may be delocalization of the π electron cloud over the entire chelate ring resulting in inhibition in the growth of the organism. Of all the studied complexes copper complex (5a) in which the ligand has a -CH₃ group ortho to the imine group shows maximum inhibition while complex (9a) with the CH₃ group at the para position is least active. This shows the effect of substituent position on the biological activity. Complex (3a) which has an unsubstituted ligand also shows better activity than 7a and 9a.

Anthelmintic activity

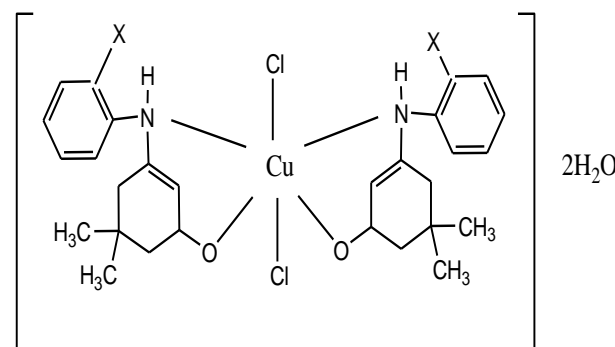
The synthesized complexes are evaluated for anthelmintic activity against Earthworm, *Eicinia foetida*. The complexes are screened for activity by time taken for complete paralysis and death of worms. The reference drug Albendazole required 60 min to paralyze the worms and death occurred after 85 min. All the complexes exhibit significant activity which is independent of the dose. The result (table 7) indicates, although the paralysis time for all the complexes is much more than the standard, the death time after paralysis is comparable to Albendazole or in some complexes even

less than the standard. One can cautiously conclude that the paralysis caused by most of the complexes is more severe leading to death. The least time is due to complex 9a at 10 mg/ml dose which is even less than the standard at the same dose. In case of copper complexes a significant variation in the anthelmintic activity can be seen in compound 9a and the others. All the copper complexes shows better anthelmintic activity than their respective ligands showing effect of chelation on the interference of these compounds in metabolic process and neuromuscular physiology of the parasites. Further study needs to be carried out in order to investigate the effect of possible groups that are responsible for anthelmintic activity and their mechanism of action.

Proposed Structures of Complexes: (Figures 1a)



Complex: 3a



Complex: 5a, x = o-CH₃,
7a, x = m-CH₃,
9a, x = p-CH₃

Spectral data for Copper complexes.

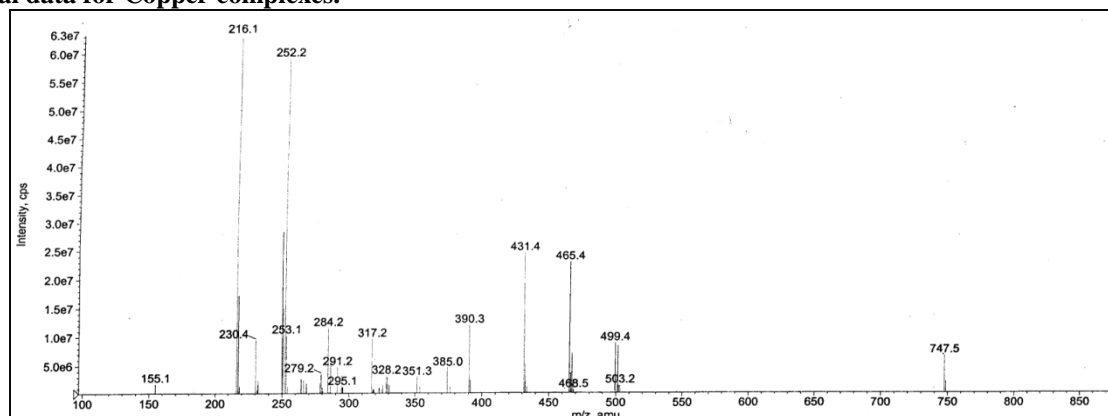


Figure 1: Mass spectrum (3a).

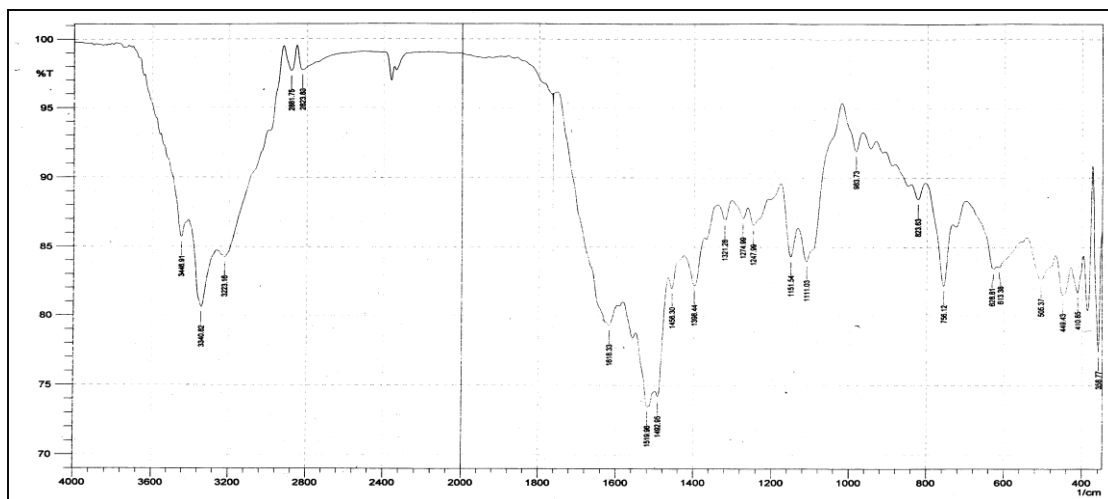


Figure 2: IR spectrum (3a).

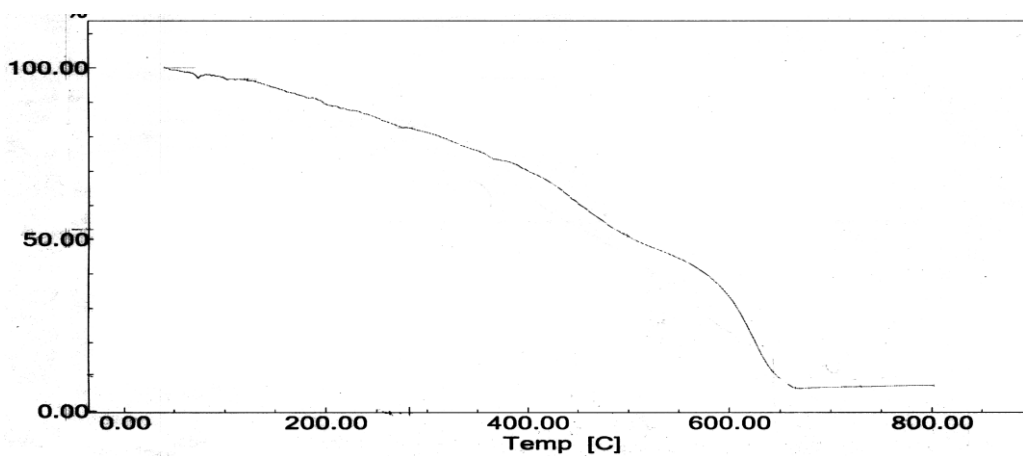


Figure 3: Thermogram (3a).

ESR of Copper complexes

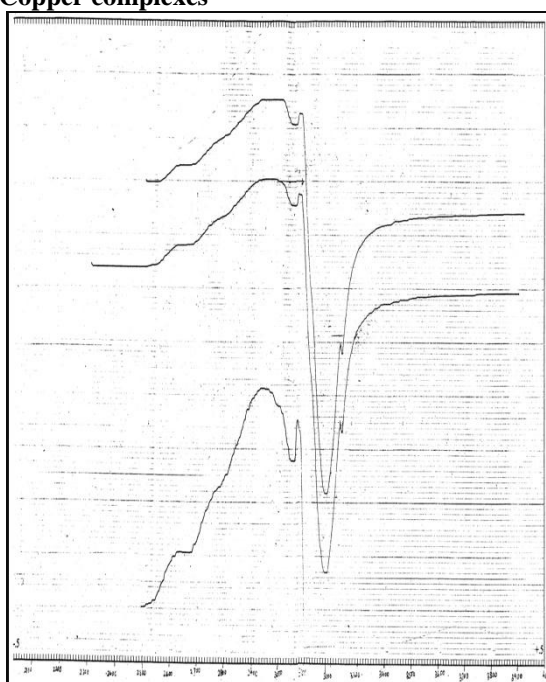


Figure 4: ESR spectrum (3a).

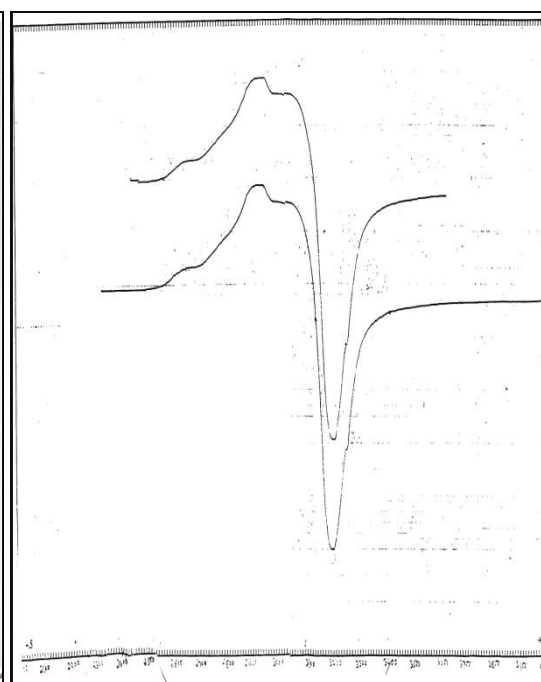


Figure 5: ESR spectrum (5a).

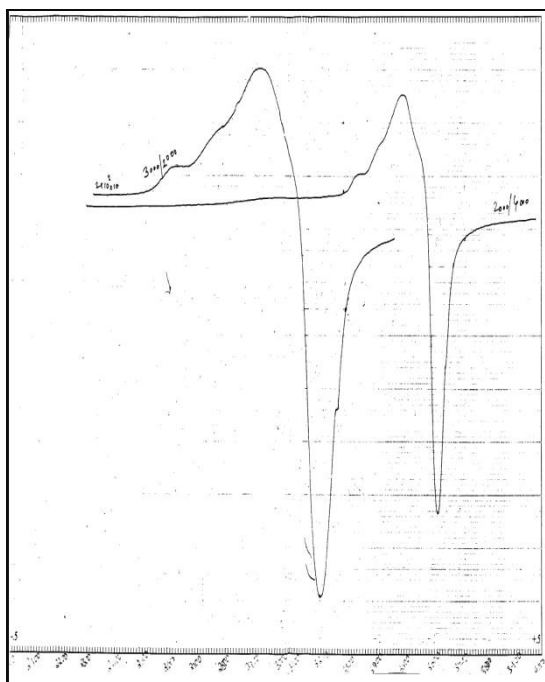


Figure 6: ESR spectrum (7a).

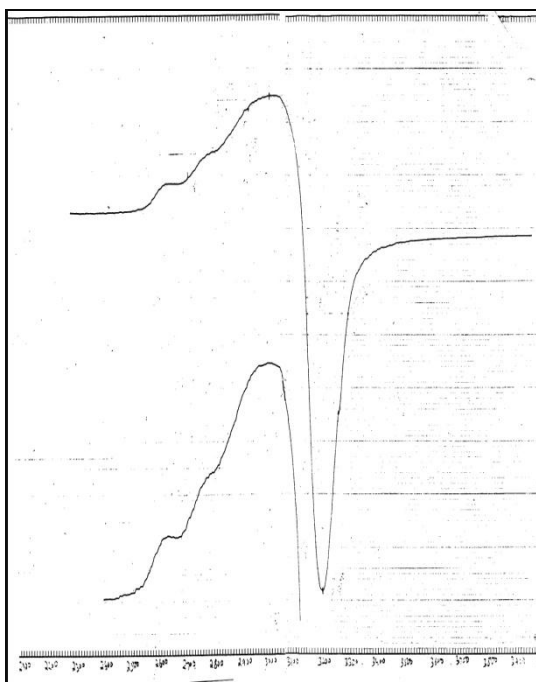


Figure 7: ESR spectrum (9a).

Table 1: Physicochemical data of Copper complexes.

Complex	Mol.Wt (g)	Colour	Observed (Cal.)		
			%C	%H	%N
Cu(L ₁).Cl ₂ .2H ₂ O	385	Brown	45.75 (43.63)	4.89 (5.45)	4.47 (3.63)
[Cu(L ₂) ₂ .Cl ₂] 2H ₂ O	628	Brown	54.09 (57.32)	5.70 (6.69)	4.91 (4.46)
[Cu(L ₃) ₂ .Cl ₂] 2H ₂ O	628	Brown	60.53 (57.32)	6.38 (6.69)	5.33 (4.46)
[Cu(L ₄) ₂ .Cl ₂] 2H ₂ O	628	Brown	60.25 (57.32)	6.30 (6.69)	5.009 (4.46)

Table 2: IR band assignments (cm⁻¹) for the ligand and its Copper complexes.

Compound	ν -OH	ν -NH	ν -C=O	ν -M-O	ν -M-N	ν -M-Cl
L ₁	-	3237	1640			
3a	3449	3261	1600	499	476	378
L ₂	3354	3190	1640	-	-	-
5a	3440	3223	1618	505	449	358
L ₃	-	3211	1680	-	-	-
7a	3450	3257	1600	520	441	364
L ₄	-	3244	1660	-	-	-
9a	3530	3259	1649	592	489	370

Table 3: Thermal analysis (TGA) of the Copper complexes.

Complex	Species	Temp-range °C	TGA (% loss)	
			Observed	Calc.
[Cu (L ₁).Cl ₂ .2H ₂ O]	2H ₂ O	R.T. to 180	8.62	9.35
	2Cl	180 – 252	17.63	18.44
	C ₁₄ H ₁₇ NO	287 – 594	56.9	55.84
[Cu (L ₂) ₂ .Cl ₂]2H ₂ O	2H ₂ O & 2Cl	R.T. – 260	15.78	17.00
	2(C ₁₅ H ₁₉ NO)	275 – 640	71.88	72.92
[Cu (L ₃) ₂ .Cl ₂]2H ₂ O	2H ₂ O & 2Cl	R.T. – 217	15.77	17.00
	2(C ₁₅ H ₁₉ NO)	290 – 616	71.49	72.92
[Cu (L ₄) ₂ .Cl ₂]2H ₂ O	2H ₂ O & 2Cl	R.T. – 231	15.95	17.00
	2(C ₁₅ H ₁₉ NO)	240 – 648	72.59	72.92

Table 4: ESR data and magnetic moments of Copper complexes.

Complex	Transitions (cm ⁻¹)		μ_{eff}	Geometry
	ν_1	ν_2		
[Cu (C ₁₄ H ₁₇ NO)Cl ₂ .2H ₂ O]	17574	-	1.87	Octahedral
[Cu(C ₁₅ H ₁₉ NO) ₂ Cl ₂]2H ₂ O	19120	-	1.86	Octahedral
[Cu C ₁₅ H ₁₉ NO) ₂ Cl ₂]2H ₂ O	19493	-	1.65	Octahedral
[Cu C ₁₅ H ₁₉ NO) ₂ Cl ₂]2H ₂ O	19342	-	2.07	Octahedral

Table 5: ESR spectral data of Copper (II) complexes.

Compound	g_{\parallel}	g_{\perp}	$A_{\parallel} \times 10^{-4}$ cm ⁻¹	$A_{\perp} 10^{-4}$ cm ⁻¹	α^2	G	λ cm ⁻¹
3a	2.09	2.00	90	180	0.11	18.46	- 166
5a	2.23	2.01	230	230	0.60	26.12	- 392
7a	2.20	2.01	190	150	0.28	17.88	- 350
9a	2.19	2.01	240	150	0.42	25.51	-351

Table 6: Antimicrobial activities of copper (II) complexes.

Complex	Microorganism Zone of inhibition * (mm)					
	<i>Escherichia coli</i>	<i>Salmonella abony</i>	<i>P. aeruginosa</i>	<i>S. aureus</i>	<i>S. cerevisiae</i>	<i>A. niger</i>
3a	-	-	-	7	-	-
5a	-	-	-	13	-	-
7a	-	-	-	6	-	-
9a	-	-	-	5	-	-
Standard	20	29	25	25	-	-
Fluconazole					40	20

Table 7: Anthelmintic activity of copper (II) and cobalt (II) complexes.

Compound	Conc.(mg/ml)	<i>Eicinia foetida</i> (Earthworms)	
		Paralysis time (min)	Death time (min.)
3a	5	88	181
	10	80	181
5a	5	89	182
	10	89	182
7a	5	89	183
	10	89	183
9a	5	80	148
	10	60	128
Albendazole	05	45	120
	10	60	145

CONCLUSION

The present work describes the synthesis of copper (II) complexes of Schiff bases derived from condensation reaction of 3, 3 – dimethyl 1, 3 –cyclohexane dione with aniline and substituted anilines. The physicochemical analysis (magnetic measurements, TG & Spectral (UV – Vis, IR, ESR) of complexes suggests that the Schiff bases coordinate to metal ions through amine nitrogen and oxygen of carbonyl group. The presence of lattice and coordinated water in complexes was confirmed by IR and TG studies. The anti microbial study suggests that the metal complexes show better activity against bacterial strain *Staphylococcus aureus* in comparison to the ligands. The copper complexes show significant anthelmintic activity.

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