

**SYNTHESIS, SPECTRAL CHARACTERISATION AND ANTIMICROBIAL ACTIVITIES OF Cu (II), Co (II), Cr (III), COMPLEXES DERIVED FROM 4-AMINOANTIPYRINE AND DIHYDROPYRIMIDINONE OF BENZALDEHYDE****D.MOHANAMBAL AND S. ARULANTONY\****P.G and Research Department, Presidency, Chennai-600 005***ABSTRACT**

A new series of transition metal complexes Cr (III), Co (II), and Cu (II) were synthesized from the Schiff base ligand derived from 4-aminoantipyrine and Ethyl 4- methyl -oxo-6-phenylhexahydro pyrimidine-5-carboxylate. The structural features were derived and confirmed by elemental analysis, melting point, molar conductance, Mass, Uv-Vis, FTIR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, and ESR spectroscopy. The data supported that the complexes have the composition of ML<sub>2</sub> type. The Uv-Vis, magnetic susceptibility and ESR spectral data of the complexes suggest that, the square-planar geometry around the central metal ion coordination through the ring carbonyl oxygen and nitrogen atom of the azomethine -C=N group. The antimicrobial screening tests were recorded by the disc diffusion method, proving more activity complexes as compared to free ligand.

**KEYWORDS:** Transition Metal Complex, 4-aminoantipyrine, Antimicrobial, DHPMs, Schiff base,**S. ARULANTONY***P.G and Research Department, Presidency, Chennai-600 005*

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## INTRODUCTION

The Schiff bases containing O N donor atoms act as superior chelating agents for the transition and non transition metal ions and showed remarkable biological activities<sup>1, 2</sup>. Coordination of these compounds with metal ions, such as Copper, Cobalt often enhances their activities<sup>3</sup>. Many metal complexes have been identified as the powerful antimicrobial activities in day-to-day use in medicinal field<sup>4</sup>. Thus inorganic elements play crucial role in biological and biomedical processes. Many drugs possess modified toxicological and pharmacological properties in the form of metal complexes<sup>5</sup>. The incorporation of metals in the form of complexes is showing some degree of antibacterial<sup>6</sup>, antifungal<sup>7</sup>, antitumour<sup>8</sup>, and anti-inflammatory activity<sup>9, 10</sup>. Schiff base complexes derived from heterocyclic compounds have increased interest in the field of bioinorganic chemistry. The coordinating property of 4-aminoantipyrine ligand has been modified to give a flexible ligand system, formed by condensation with variety reagents like aldehydes, ketones and carbazides<sup>11, 12</sup>. Meanwhile Dihydropyrimidinone heterocyclic (DHPMs) and their derivatives have attracted considerable interest because of their pharmaceutical and therapeutic properties. The simple and direct method for the synthesis of Dihydropyrimidinone was first reported by Biginelli, involving a one-pot condensation of an aldehyde,  $\beta$ -ketoester and urea under strongly acidic conditions<sup>13, 14</sup>. The literature survey reveals that, more attention has been given to Schiff's base derived from 4-aminoantipyrine with several aldehydes. But less work has been reported on the condensation process in 4-aminoantipyrine with Ethyl 4-methyl-2-oxo-6-phenyl hexa hydroypyrimidine-5-carboxylate. Hence, the synthesis, characterization and antimicrobial studies of transition metal complexes containing a novel bidentate Schiff base derived from Ethyl 4-methyl-2-oxo-6-phenylhexahydropyrimidine-5-carboxylate (DHPMs) and 4-aminoantipyrine. The structural elucidation of the complexes has been evaluated using elemental analysis, melting

point, molar conductance and further confirmed by Mass, Uv-Vis, FTIR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, and ESR spectroscopic studies.

## MATERIALS AND METHODS

All the chemicals and solvents were procured from Sigma-Aldrich. The synthetic steps were monitored by TLC performed on silica gel plates (Merck). Melting points were measured in open capillary tubes. The elemental analysis of the complexes was carried out by Perkin Elmer 2400. Molar conductance measurements were carried out with  $10^{-3}$  mol/L solutions of the complexes in DMSO at room temperature using ELICO-CM180. Magnetic susceptibility was recorded at room temperature using Lake Shore Model 7410 VSM using standard Ni as calibrate. The IR spectra were recorded JASCO FT/IR-4100 spectrometer in  $4000-400\text{ cm}^{-1}$  using KBr pellets. The electronic spectra were reordered by JASCO UV Vis Model V-650. NMR spectra were recorded in  $\text{CDCl}_3$  using Bruker 300MHz spectrometer. The ESI mass spectra of the ligand and its complexes were recorded using Mass QTOF micromass spectrometer using nitrogen atmosphere ( $\text{CE-}8\text{e}^- \text{V}$ ,  $\text{CV -}278\text{e}^- \text{V}$ ). The ESR was recorded using JEOL instrument at 300K. The measurement was done in the X band on micro crystalline powder at room temperature using DPPH as standard. The antimicrobial activity was determined by disc diffusion method. Stock solutions were prepared by dissolving the compounds in DMSO and serial dilutions of the compounds in sterile distilled water to determine the minimum inhibition concentration (MIC).

### **Synthesis of Ethyl 4-methyl-2-oxo-6-phenylhexahydropyrimidine-5-carboxylate (DHPMs)**

The Ethyl 4-methyl-2-oxo-6-phenyl hexa hydroypyrimidine-5-carboxylate has been synthesized according to the reported procedure<sup>15, 16</sup>. The product (yield 72%, literature yield 78.5%)<sup>17</sup> was obtained as a white solid, typical mp  $198^\circ\text{C}$  (lit. mp 200 to

202°C)<sup>18</sup>. The spectral data matched with reported data<sup>19</sup>.

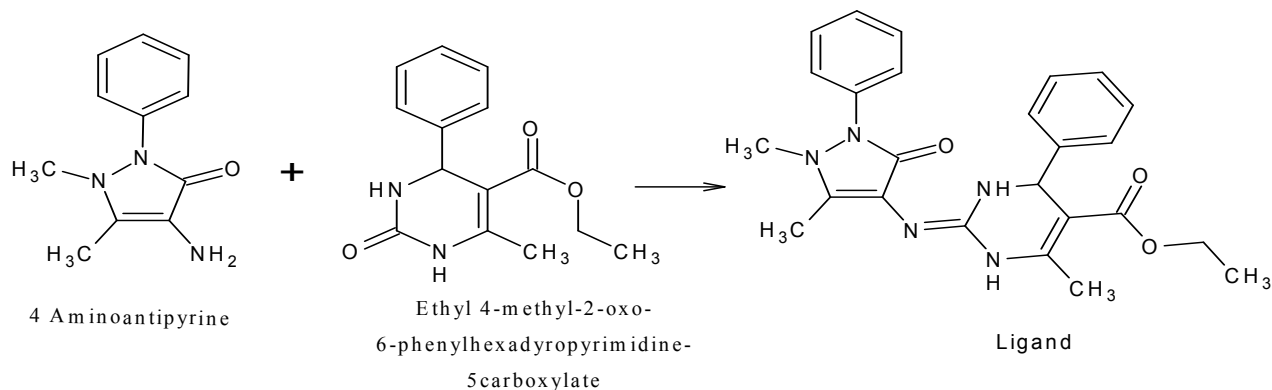
### Preparation of Schiff base

An ethanolic solution of 4-aminoantipyrene (2.03 g, 0.01mol, 20 ml) was added to the ethanolic solution of Ethyl 4-methyl-2-oxo-6-phenylhexahydropyrimidine-5-carboxylate (2.6 g, 0.01 mol, 20 ml) with constant stirring at 60°C for 4 hours. After cooling the solution, the precipitate was separated, filtered, recrystallized with ethanol, and dried over anhydrous calcium chloride under vacuum. The general structures of ligands obtained from

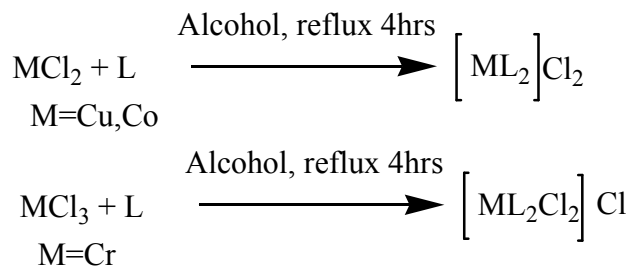
chemical analysis and spectral methods, are given in Scheme (1).

### Synthesis of complexes

A solution of metal (II) chloride in ethanol (0.01mol) and hot ethanolic solution of Schiff base (L) (0.02 mol) were mixed together and refluxed for 4 hrs at 50°C (scheme 2). On cooling, the colored solid metal complexes were precipitated and then washed with ethanol followed by diethyl ether and dried. Recrystallization from hot aqueous ethanol (1:2) gives the TLC-pure product.



### Scheme 1 Synthesis of Schiff Base Ligand



Scheme-2

### Antimicrobial activity

The *in vitro* antibacterial (*E.coli*, *Staphylococcus aureus*, *Bacillus spp.*, *Salmonella spp.*) the *in vitro* antifungal (*Candida*, *Aspergillus niger*,) studies were carried out using test organisms and are maintained on Mueller Hinton Agar solid media (MHA) and Sabouraud's dextrose (SDA) media.<sup>20-22</sup>

### Assay of Antimicrobial Activity

Agar diffusion assay was carried out to evaluate the antimicrobial activity of some synthesized compounds. The plates were incubated at 37°C for 24 h, during which activity was evidenced by the presence of a zone of inhibition surrounding the well and antibacterial and antifungal activity was expressed as the mean diameter of inhibition zones (mm) produced by the synthesized compounds when

compared to controls. The minimum inhibitory concentration (MIC) value was recorded as the lowest concentration of drug in the medium that showed no microbial growth by visual observation.

## RESULTS AND DISCUSSION

The analytical data of the ligand and the complexes together with some physical properties are summarized in Table 1. All metal complexes are characteristically colored, stable in air. These are insoluble in water and soluble in organic solvents such as DMF, DMSO. The

molar conductance data of the complexes shows that the complexes are 1:2 non electrolytes in DMSO<sup>23</sup>.

### IR spectra

The FTIR data of Schiff base ligand and their complexes are given in Tables 2 (Fig 1). There are some distinguished bands observed in the spectra of the complexes while compared to free ligand, which is helpful in detection of donation sites. Generally, the IR spectra of the free ligand showed a broad band around 3425 cm<sup>-1</sup> which could be attributed to N-H stretching vibration of benzimidazole moiety.

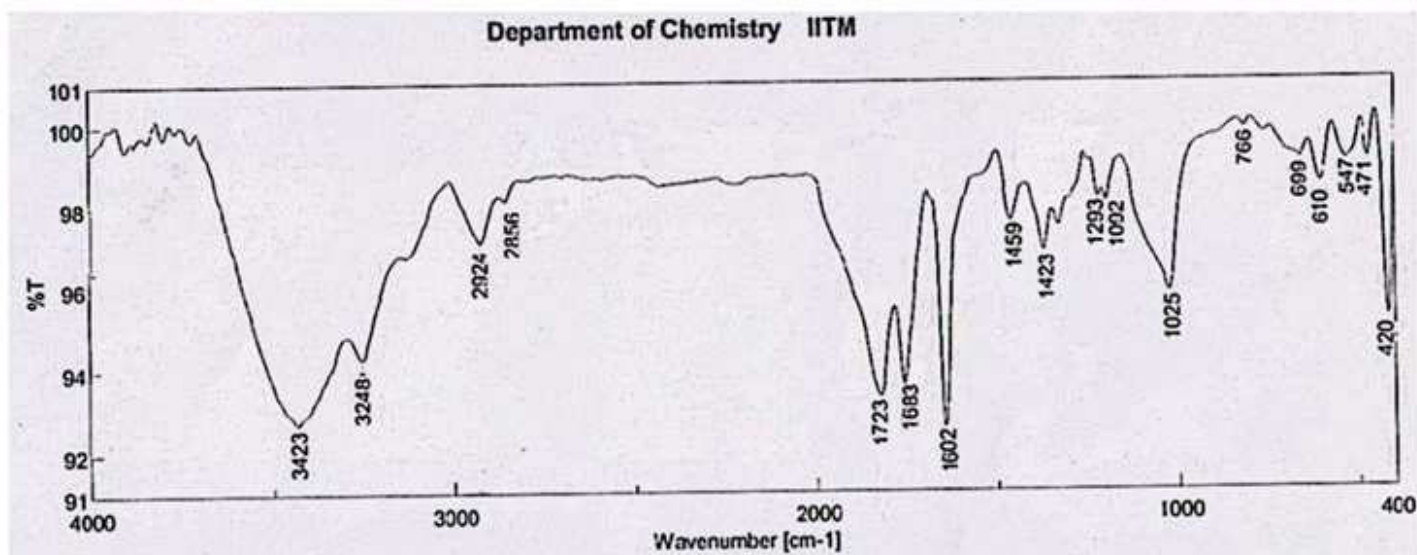
**Table 1**  
**Analytical data and Physical properties of the ligand and its complexes**

Compound	Molecular weight	Color	% yield	m.p (°C)	Found (Calc). (%)				Molar conductance Ohm <sup>-1</sup> cm <sup>2</sup> mol <sup>-1</sup> x 10 <sup>-3</sup>
					C	H	N	M	
L C <sub>25</sub> H <sub>27</sub> N <sub>5</sub> O <sub>3</sub>	445	Yellow	62.9	233	66.89 (67.40)	6.08 (6.11)	15.89 (15.72)	-	-
[CuL <sub>2</sub> ]Cl <sub>2</sub> [Cu(C <sub>25</sub> H <sub>27</sub> N <sub>5</sub> O <sub>3</sub> ) <sub>2</sub> ]Cl <sub>2</sub>	1025	Deep Brown	55.4	265	58.33 (58.56)	5.02 (5.31)	13.98 (13.66)	5.97 (6.20)	2.4
[CoL <sub>2</sub> ]Cl <sub>2</sub> [Co(C <sub>25</sub> H <sub>27</sub> N <sub>5</sub> O <sub>3</sub> ) <sub>2</sub> ]Cl <sub>2</sub>	1020	Brown	64.3	260	58.66 (58.83)	5.48 (5.33)	13.87 (13.72)	5.07 (5.77)	2.4
[CrL <sub>2</sub> Cl <sub>2</sub> ]Cl [Cr(C <sub>25</sub> H <sub>27</sub> N <sub>5</sub> O <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> ]Cl	1049	Green	54.22	247	57.33 (57.23)	5.22 (5.19)	13.38 (13.35)	4.89 (4.95)	1.6

The position of this band remained at nearly the same frequency in the spectra of the metal complexes suggesting the absence of the N-H group coordination<sup>24</sup>. The stretching frequency of carbonyl group of ligand  $\nu(\text{C}=\text{O})$  at 1702 cm<sup>-1</sup> is shifted to lower frequency range 1683-1672 cm<sup>-1</sup> in complexes. Similarly the frequency corresponding to  $\nu(\text{C}=\text{N})$  at 1647 cm<sup>-1</sup> shifted range 1602-1591 cm<sup>-1</sup> in complexes. The shifting in wave number and their intensities of referenced bands led to predict the chelation behavior, i.e., co-ordination occur through ring carbonyl oxygen atom and nitrogen atom of azomethine group. The spectra of metal complexes also shows additional bands in 317 cm<sup>-1</sup> and 610-617 cm<sup>-1</sup>, 546-563 cm<sup>-1</sup> which are probably due to the formation of  $\nu(\text{M}-\text{Cl})$ ,  $\nu(\text{M}-\text{O})$ ,  $\nu(\text{M}-\text{N})$  bond respectively<sup>25-26</sup>.

**Table 2**  
**FTIR spectral data of ligand and complexes (in  $\text{cm}^{-1}$ )**

Compound	$\nu_{\text{C=O}}$	$\nu_{\text{C=N}}$	$\nu_{\text{M-O}}$	$\nu_{\text{M-N}}$	$\nu_{\text{M-Cl}}$
L	1702	1647	-	-	-
$[\text{CuL}_2]\text{Cl}_2$	1677	1594	614	557	-
$[\text{CoL}_2]\text{Cl}_2$	1683	1602	610	546	-
$[\text{CrL}_2\text{Cl}_2]\text{Cl}$	1672	1591	612	563	317



**Figure 1**  
**IR Spectrum of  $[\text{Co}(\text{L}_2)]\text{Cl}_2$**

### **$^1\text{H}$ NMR and $^{13}\text{C}$ -NMR Studies**

The  $^1\text{H}$  NMR and  $^{13}\text{C}$ -NMR spectra of the Ligand (L) in  $\text{CDCl}_3$  solution shows the following signals (Fig 3). The  $^1\text{H}$  NMR spectra shows a multiplet at  $\delta$  6.10 to 7.52ppm (m,10H,Ar) are due to phenyl group,  $-\text{N}-\text{CH}_3$  at  $\delta$  2.3ppm (s,3H),  $=\text{C}-\text{CH}_3$  at  $\delta$  1.72ppm (s,6H,2  $=\text{C}-\text{CH}_3$ ),  $\text{CH}_3-\text{CH}_2$  at  $\delta$  1.137 - 1.17ppm (t,3H), CH at  $\delta$  5.386-5.497ppm (d,1H,CH)  $\text{CH}_3-\text{CH}_2$  at  $\delta$  4.05 - 4.07ppm (q,2H), NH at  $\delta$  8.31ppm (s,br,1H). The  $^{13}\text{C}$ NMR spectrum of Ligand shows the following signals: 165.64 (C-11,C-17), 153.36(C-10), 146.32(C-9,C-16), 143.730(C-3), 133.013(C-18), 128.82(C-22, C-20), 128.709(C-19,C-23), 127.944(C-1,C-5), 127.57(C-2,C-4), 126.604(C-6), 119.760(C-21), 109.766(C-15), 101.35(C-8), 60.24(C-12), 55.741(C-7), 35.09(C-24), 18.64(C-14,C-25), 14.135(C-13)<sup>27-29</sup>.

### **Electronic absorption spectra and Magnetic moment Studies**

The Electronic Spectra of Ligand and its complexes were recorded in ethanol in the range 800-200nm. The absorption regions, assignments and the geometry of the complexes are given in Table-3 and fig 2&3. In the electronic spectrum of the ligand there are two absorption bands assigned to  $n-\pi^*$  and  $\pi-\pi^*$  transitions. These transitions are also found

in the spectra of the complexes, but they are shifted towards longer wavelength from ligand to complex, indicating coordination of ligand to metals through the azomethine moiety. The magnetic moment of Cu (II) complex is 1.78 B.M.<sup>30</sup>. The electronic spectrum showed at 524nm is assigned to  $^2\text{B}_{1g} \rightarrow ^2\text{A}_{1g}$  transition. These values suggested a square planar geometry<sup>31</sup>. As no bands are observed above 1000 nm; the complex might have a square

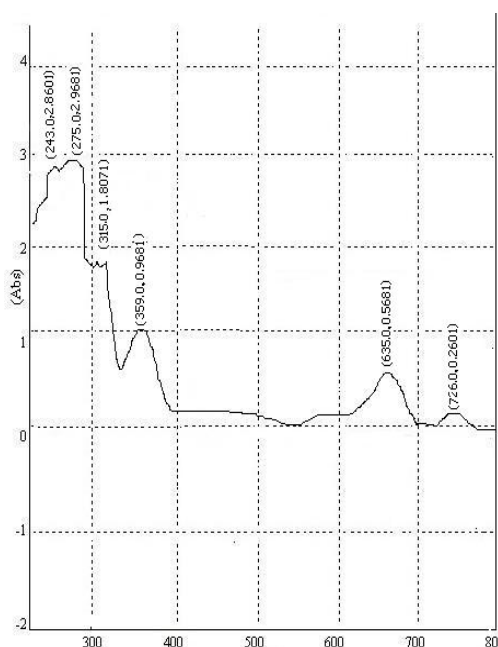
planar or close to square planar structure<sup>32</sup>. In the Co (II) complex the band at 612 nm and 426nm are attributed to d-d electronic transition type  ${}^2A_{1g} \rightarrow {}^2B_{1g}$ ,  ${}^2A_{1g} \rightarrow {}^2E_g$ , suggesting square planar about Co ions<sup>33</sup>. The magnetic moment value (2.10 B.M)<sup>34,35</sup> also supported the square planar structure and shown in Figure (4). The electronic spectra of the Cr (III) complex show

absorption three bands at 726nm, 659nm and 359nm which may be assigned to  ${}^4A_{2g} \rightarrow {}^4T_{2g}$  (F),  ${}^4A_{2g} \rightarrow {}^4T_{1g}$  (F) and  ${}^4A_{2g} \rightarrow {}^4T_{1g}$  (P) spin allowed d-d transition, respectively, suggesting an octahedral geometry<sup>36</sup>. The observed magnetic moment 3.87 BM<sup>37</sup> is in agreement with this structure (Figure-5)

**Table -3**

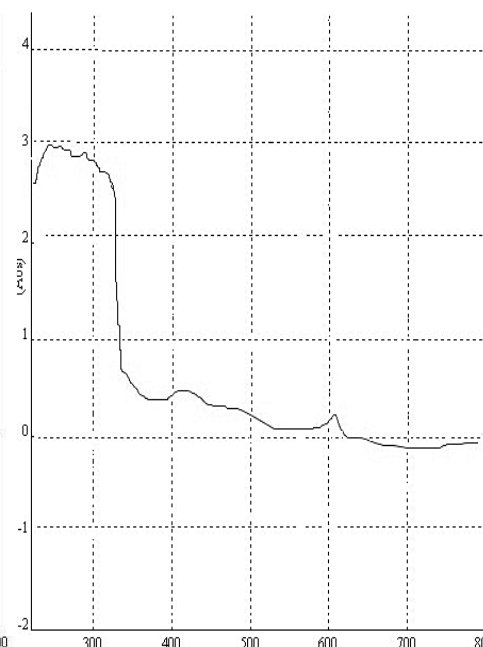
**Magnetic moment and Electronic spectral data of the Schiff bases and its Metal complexes**

Compound	Absorption Maxima (nm)	Band assignment	Magnetic moment B.M	Geometry
Ligand	242 301 284	$\pi-\pi^*$ $n-\pi^*$	-	-
[CuL <sub>2</sub> ]Cl <sub>2</sub>	320 524	INCT INCT ${}^2B_{1g} \rightarrow {}^2A_{1g}$	1.82	Square Planar
[CoL <sub>2</sub> ]Cl <sub>2</sub>	293 324 426 612	INCT INCT ${}^2A_{1g} \rightarrow {}^2E_g$ ${}^2A_{1g} \rightarrow {}^2B_{1g}$	2.10	Square Planar
[CrL <sub>2</sub> Cl <sub>2</sub> ]Cl	233 316 359 726 659	LMCT LMCT ${}^4A_{2g} \rightarrow {}^4T_{1g}$ (P) ${}^4A_{2g} \rightarrow {}^4T_{2g}$ (F), ${}^4A_{2g} \rightarrow {}^4T_{1g}$ (F)	3.87	Octahedral



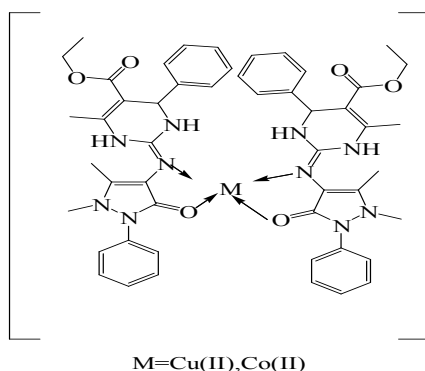
**Figure 2**

Electronic absorption spectra of Cr (III) complex

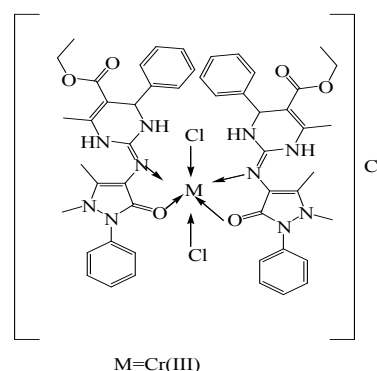


**Figure 3**

Electronic absorption spectra of Co (II) complex



**Figure 4**

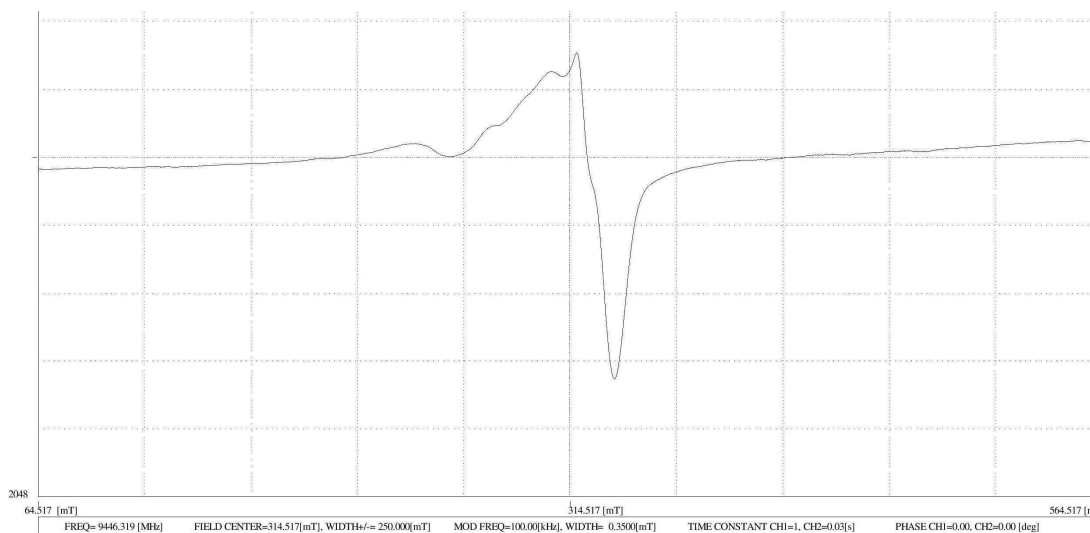


**Figure 5**

**ESR**

The ESR spectrum of copper complex is important in studying the metal ion environment. The spectra were recorded in DMSO (Fig 6). The copper complex exhibited the  $g_{\parallel}$  of 2.4,  $g_{\perp}$  value of 2.07 and  $g_{ave}$  value of 2.20. The parameter  $g_{ave}$  was obtained by equation  $[g_{ave}=1/3(g_{\parallel}+2g_{\perp})]$ . Neiman and Kivelson<sup>38</sup> have reported that  $g_{\parallel}$  is less than 2.3 for covalent character and greater than 2.3 for ionic character of the metal –ligand bond in complexes. The  $g_{\parallel}$  value for the present complex is slightly higher than 2.3 indicating the ionic character of the metal-ligand bond. The  $g$  tensor values of this Cu (II) complex can be used to derive the ground state environment. In

square-planar complexes, the unpaired electron lies in the  $d_{x^2-y^2}$  orbital giving  $g_{\parallel} > g_{\perp} > 2$  (ground state is  $^2B_{1g}$ ), while the unpaired electron lies in the  $d_z^2$  orbital giving  $g_{\perp} > g_{\parallel} > 2$ . From the observed values, it is clear that  $g_{\parallel} > g_{\perp} > 2$  suggesting that the complex is square-planar<sup>39-42</sup>. This is also supported by the magnetic moment of Cu (II) complex (1.82 B.M) which confirms the mononuclear nature of the complex. As evident from the value of the exchange interaction term  $G$ , estimated from the expression  $G= g_{\parallel}-2.0023/g_{\perp}-2.0023$ . The axial symmetry parameter ( $G$ ) value of the complex (greater than 4) suggested the exchange coupling interaction is negligible<sup>43</sup>.



**Figure 6**  
**ESR spectra of Cu (II) complexes**

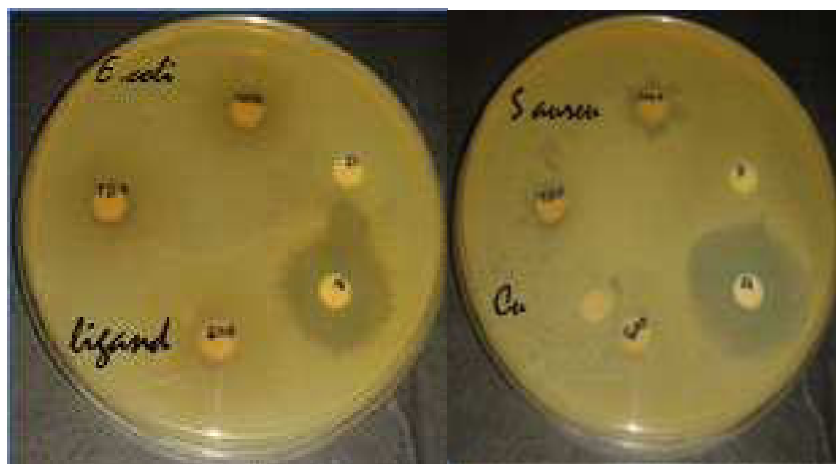
### Antimicrobial activities

The antimicrobial and antifungal activities of Ligand and the metal complexes were carried out by disc diffusion method<sup>44</sup> (Figures-7 & 8). The test solutions were prepared in DMSO and minimum inhibitory concentration values of the compounds have been summarized in Table-5 & 6. All of these tested compounds showed a remarkable biological activity against different types of Gram positive and Gram negative bacteria. It is found that metal complexes have higher anti-bacterial activity than the free ligand. The activity increases with increase of concentration of test solution containing metal complexes. Hence the complexation increases the antimicrobial activity<sup>45</sup>. Such increased activity of the metal complexes can be explained on the basis of Overtone's concept and the Tweedy chelation theory<sup>46,47</sup>. According to the Overtone's concept of cell permeability, the lipid membrane that surrounds the cell favours the passage of only lipid-soluble

materials, provided liposolubility is an important factor that controls antimicrobial activity. On chelation, the polarity of the metal ion will be reduced due to the overlapping of the ligand orbital and partial sharing of positive charge of the metal with donor groups<sup>48</sup>. Furthermore, it increases the delocalization of  $\pi$ -electrons over the whole chelate ring and enhances the lipophilicity of the complexes. This increased lipophilicity enhances the penetration of the complexes into lipid membranes and blocking of the metal binding sites in the enzymes of microorganisms. Investigation of antifungal activity of the ligand and its metal complexes revealed that, all the metal chelates are more fungi toxic than their parent ligand (Table 5). The antifungal activity of the ligand is found to enhance several times on being coordinated with metal ions. Antifungal activity of these complexes is found to be increased as the stability of the complex increased.

**Table 4**  
**Antibacterial Activity of Schiff Base and its Complexes**

Name of the bacterial strains	Diameter of Zone Inhibition (mm)												Solvent DMSO	Standard Drug
	Ligand			[CuL <sub>2</sub> ]Cl <sub>2</sub>			[CoL <sub>2</sub> ]Cl <sub>2</sub>			[CrL <sub>2</sub> ]Cl <sub>2</sub>				
	1000	750	500	1000	750	500	1000	750	500	1000	750	500		
<i>E. coli</i>	7	6	5	10	8	7	8	6	4	9	8	6	-	14
<i>Salmonella typhi</i>	3	3	3	12	10	6	8	7	7	8	7	6	-	14
<i>Bacillus subtilis</i>	7	5	4	8	8	6	6	5	5	6	6	6	-	9
<i>Staphylococcus aureus</i>	6	4	3	11	9	6	6	6	6	10	8	6	-	13

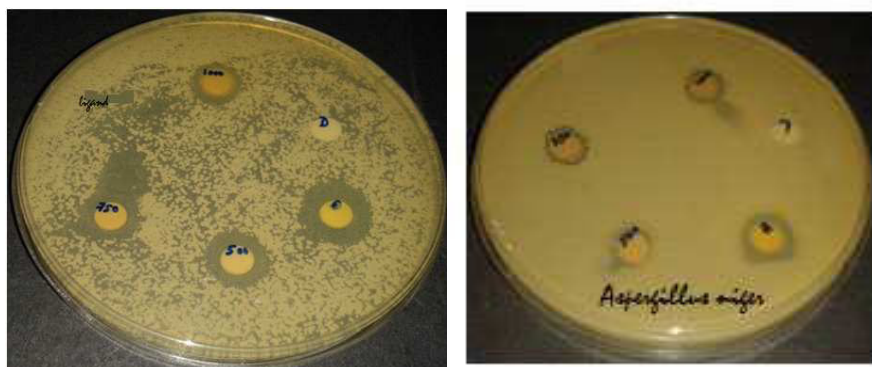


**Figure 7**  
**Antibacterial activity of Ligand and Cu (II) Complex**



**Table 5**  
**Antifungal Activity of Schiff Base and its Complexes**

Name of the fungal strains	Ligand			Diameter of Zone Inhibition (mm)									Solvent DMSO	Standard Drug
	1000	750	500	[CuL <sub>2</sub> ]Cl <sub>2</sub>			[CoL <sub>2</sub> ]Cl <sub>2</sub>			[CrL <sub>2</sub> ]Cl <sub>2</sub> Cl				
<i>Aspergillusniger</i>	5	-	-	7	6	5	5	5	4	5	5	5	-	7
<i>Candida</i>	7	-	-	8	7	7	5	5	5	5	5	4	-	10



**Figure 8**  
**Antifungal activity of Ligand and Cr (III) Complex**

## CONCLUSION

The synthesis of schiff base ligand derived from condensation of 4-aminoantipyrine with Dihydropyrimidinone and its metal (II) complexes has been described. The Schiff base behaves as a bidentate ligand and it coordinates through its azomethine nitrogen and the carbonyl group of the five member ring to the central metal atom. This is supported by infrared spectral data. The electronic spectral data observed Cu (II) Co (II) are square planar geometry has been assigned to the complexes except Cr (III) complex which has octahedral geometry. The complexes were formed in 1:2 (metal: ligand) ratio as confirmed by the microanalysis. The molar conductivity data of the complexes in DMSO indicated that they are non electrolytes. The biological activity of all the

complexes is higher than free Schiff base ligand indicating the metal chelation is significantly more effective than the antimicrobial behavior of the organic ligand.

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