

Synthesis, Characterization And Biological Evaluation for Some Divalent Metal Complexes with New Pyrimidine Schiff Base Ligand

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Abstract:

The new Heterocyclic schiff base Cu(II) complexes. The Schiff base ligand derived from 2-hydroxy-1-naphthaldehyde & 2,6-diamino-4-chloropyrimidine to form schiff base (L) was synthesized and characterized by IR and electronic spectroscopies, melting points, percentage metal analysis, conductance and magnetic susceptibility measurements. The IR spectra indicated that the Schiff base (L) coordinated to the metal ions using N donor atom of imine and O donor atom of the naphthalenol moieties. The percentage metal analysis, room temperature magnetic moment and electronic spectroscopy showed that the complexes assumed an octahedral geometry. The molar conductance measurements in DMSO confirmed the non-ionic nature of the complexes. The *in-vitro* antibacterial & antifungal acclivity indicated that the Schiff base and their heteroleptic metal complexes exhibited very good antifungal and antibacterial activity against *Aspergillus niger*, *Penicillium chrysogenum*, *Fusarium moneliforme* and *Aspergillus flavus* and *Escherichia coli*, *Salmonella typhi*, *Staphylococcus aureus*, *B. subtilis*. The result indicated that the complexes exhibited good antifungal and antibacterial activities.

Keywords: Heterocyclic Schiff bases, 2-hydroxy-1-naphthaldehyde & 2,6-diamino-4-chloropyrimidine, Biological Activity.

1. Introduction:

An excellent type of ligand and a common source of ligands in coordination chemistry are compounds known as Schiff bases that contain a (-C=N-) azomethine group. In organic synthesis, the creation of a carbon-nitrogen double bond (-C=N-) is important. This is achieved by the reactivity of carbonyl compounds with amines in acidic media, leading to the formation of Schiff bases (imines). In the past decade, much research has been done on Schiff bases and their biologically active complexes. These imines can react with metal ions to form a variety of coordination metal complexes, which are used in many industries [1]. They possess essential biological properties such as anticancer [2], antitumor [3], anti-inflammatory [4], insecticidal [5], antibacterial [6], tuberculostatic [7], antimicrobial [8], spasmolytic [9], antioxidant [10] and anthelmintic [11] activities. Schiff bases are also used as flexible components in nucleophilic addition and cycloaddition processes with organometallic reagents [12]. The ligands with many donor atoms attached to the rings have recently attracted significant scientific attention. This is mainly due to their unique ability to bind and transport metal ions, allowing the synthesis and analysis of their mixed-valent forms. These ligands also serve as valuable models for metalloproteins.

Moreover, their applications span across various scientific disciplines and have attracted great interest in both basic and applied sciences, especially in the field of coordination chemistry. To pursue these research interests, three Schiff base ligands (SBLs) were synthesized and characterized by condensation reactions. These ligands exhibit increased biological activity when complexed with transition metals, highlighting their potential in medicinal chemistry. Furthermore, the presence of both the metal and the ligand in the complex reduces host cytotoxicity, further improving the suitability of the ligand for biomedical applications [13].

Pyrimidines are widely distributed in nature as components of many other natural and synthetic compounds, including nucleic acids (cytosine, thymine, uracil) and drugs, and over time have become known as powerful pharmacophores [14]. On the other hand, pyrimidine-Schiff bases belong to the class of compounds with imine or azomethine functional groups and were first described in 1864 [15]. They still attract the interest of scientists due to their wide range of pharmacological activities, including antibacterial [16], anticancer [17], anti-inflammatory [18] or analgesic [19] properties, among others. In general, imines are formed by the condensation of primary amines with carbonyl compounds, followed by the elimination of water. Numerous synthetic methods have been described. The most common methods are the removal of water [20], the addition of catalytic amounts of acids [21], the use of Lewis acids as catalysts [22], and irradiation techniques [23]. The synthesis of Schiff bases containing the pyrimidine backbone has also been investigated. Pyrimidines are widespread in nature as components of many other natural and synthetic compounds, including nucleic acids, thymine, and drugs [24], and over time, pyrimidines have become known as powerful pharmacophores. In the most common cases, they are the amino acids. The groups attached to the pyrimidine ring are used to react with aldehydes to form imine groups in reaction with aldehyde [25].

A search of literature reveals that no work has been done on the transition metal complexes of the Schiff bases derived from 2,6-diamino-4-chloropyrimidine and 2-hydroxy-1-naphthaldehyde. In this communication we report the synthesis of bidentate Schiff bases formed by the condensation of 2,6-diamino-4-chloropyrimidine and 2-hydroxy-1-naphthaldehyde (Fig.5). The solid complexes of Cu (II) with these ligands have been prepared and characterized by different physico-chemical methods.

2. Materials And Methods:

2.1 Reagents and Solvents :

2,6-diamino-4-chloropyrimidine (Aldrich sigma) and 2-hydroxy-1-naphthaldehyde (AR grade) were used for synthesis of ligand. AR grade metal nitrate were used for the complex preparation.

2.2 Synthesis of Ligand:

The ligand was prepared by a modification of the reported methods [26]. The Schiff base ligand has been synthesized by refluxing a mixture of 0.01 mol (1.4057 g) of, 2-hydroxy-1-naphthaldehyde and 0.01 mol (1.2710 g) of 2,6-diamino-4-chloropyrimidine in 50 ml super dry ethanol refluxed for about 4h. Schiff base thus formed was cooled to room temperature and collected by filtration, followed by recrystallization in ethanol and dried in vacuo over anhydrous calcium chloride (Yield:70%).

2.3 Synthesis of Metal Complexes:

To a hot ethanol solution (25ml) of the ligand (2 mol) and (25ml) of metal Nitrate (1mol) was added with constant stirring. The pH of reaction mixture was adjusted to 7-8 by adding 10% alcoholic ammonia solution and refluxed for about 3 h. The

precipitated solid metal complex was filtered off in hot condition and washed with hot ethanol and dried over calcium chloride in vacuum desiccators. (Yield: 60%) [27]

2.4 Physical Measurement:

IR spectra were recorded on FTIR (ATR)-BRUKER-TENSOR37 spectrometer using KBr pellets in the range of 4000-400 cm^{-1} . $^1\text{H-NMR}$ (Varian mercury 300MHZ) spectra of ligand were measured in DMSO using TMS as internal standard. X-RD was recorded on BRUKER D8 Advance. TGA- DTA was recorded on Shimadzu. The carbon, hydrogen and nitrogen contents were determined on Elemental model vario EL-III. The UV-visible spectra of the complexes were recorded on model UV-1800, SHIMADZU spectrometer. Molar conductance of complexes was measured on Elico CM 180 conductivity meter using 10^{-4} M solution in DMSO. Magnetic susceptibility measurements of the metal chelates were done on a Guoy balance at room temperature using $\text{Hg}[\text{Co}(\text{SCN})_4]$ as a calibrant.

3. Results And Discussion:

Schiff bases of 2,6-diamino-4-chloropyrimidine and its complexes have a variety of applications including biological, clinical and analytical. The coordinating possibility of 2,6-diamino-4-chloropyrimidine has been improved by condensing with a variety of carbonyl compounds. An attempt has been made to synthesize Schiff bases from 2,6-diamino-4-chloropyrimidine with 2-hydroxy-1-naphthaldehyde. Physical characteristics, microanalytical, and molar conductance data of ligand and metal complexes are given in (Table 1 and 2) The analytical data of complexes reveals 2:1 molar ratio (ligand: metal) and corresponds well with the general formula $[\text{ML}(\text{H}_2\text{O})_2]$ (where $\text{M} = \text{Cu}(\text{II})$). The magnetic susceptibilities of $\text{Cu}(\text{II})$ complexes at room temperature are consistent with high spin octahedral structure with two water molecules coordinated to metal ion. The presence of two coordinated water molecules was confirmed by TG-DTA analysis. The metal chelate solutions in DMSO show low conductance and supports their non-electrolyte nature (Table 1)

Table 1: Physical properties of Schiff base ligands (L_1) and their metal complexes.

Compound Molecular formula	Mol.Wt.	M.P. Decomp temp. $^{\circ}\text{C}$	Colour	Molar Conduc. Mho. $\text{Cm}^2\text{mol}^{-1}$
L_1	280	98	Yellow	---
Cu-L_1	621	>300	Dark Yellow	20.21

Table: 2. Elemental Analysis of $\text{Cu}(\text{II})$ Complex

Compound	% Found (Calculated)			
	C	H	N	M
L_1	51.52 (53.11)	3.58 (3.75)	16.54 (16.79)	----

Cu-L1	44.42	3.38	14.16	9.90
	(44.35)	(3.29)	(14.15)	(9.88)

3.1 ¹H-NMR Spectra of Ligand:

The ¹H-NMR. Spectra of free ligand at room temperature show the following signals. 5.9 δ (s, 2H, Phenolic (OH) hydrogen of pyrimidine ring), 6.66 δ(s, 1H, Hydrogen bonded to pyrimidine ring), 7.94 δ (s, 1H, hydrogen bonded to azomethine carbon), 7.69-7.28 δ (D,4H, Aromatic Ha, Hb, protons of phenyl ring).

3.2 IR Spectra:

The IR spectrum in Fig.1 & 2 of free ligands shows characteristic bands at 3325, 1738, 1487,1207 and 1089 cm⁻¹ assignable to νOH (intramolecular hydrogen bonded), ν C=N (azomethine), ν C=C(aromatic), ν C-N (aryl azomethine) and ν C-O (Enolic) stretching modes respectively [28] The absence of a weak broad band in the 3200-3400 cm⁻¹ region, in the spectra of the metal complexes suggests deprotonation of the intermolecular hydrogen bonded OH group on complexation and subsequent coordination of phenolic oxygen to the metal ion. This is further supported by downward shift in ν C-O (phenolic) [29] with respect to free ligand. On complexation, the ν (C=N) [30] band is shifted to lower wave number with respect to free ligand, denoting that the nitrogen of azomethine group is coordinated to the metal ion. The ν C-N band is shifted to lower wave number with respect to free ligand, The IR spectra of metal chelates showed new bands in between the 500-600 and 400-500 cm⁻¹ regions which can be assigned to ν M-O and M-N [31] vibrations respectively The IR spectra of Co(II) show a strong band in the 3050-3600 cm⁻¹ region, suggesting the presence of coordinated water in these metal complexes. The presence of coordinated water is further confirmed by the appearance of non-ligand band in 830-840 cm⁻¹ region, assignable to the rocking mode of water. The presence of coordinated water is also established and supported by TG/DTA analysis of these complexes. Hence it is concluded that the coordination takes place via phenolic oxygen and azomethine nitrogen of ligand molecule in below Table 3.

Table: 3 Salient features of IR spectral data of ligands & Metal complex

Bond vibrational modes	O-H Free Stretching(ν)	C = N Azomethine Stretching(ν)	C = C Aromatic ring stretching(ν)	C -- N Aryl azomethine stretching (ν)	C -- O Enolic stretching (ν)	M-- O	M-- N
L	3322	1637	1485	1206	1088	--	--
Cu-L	1625.55	1433.23	1351.21	1190.22	1210.31	501.30	451.23

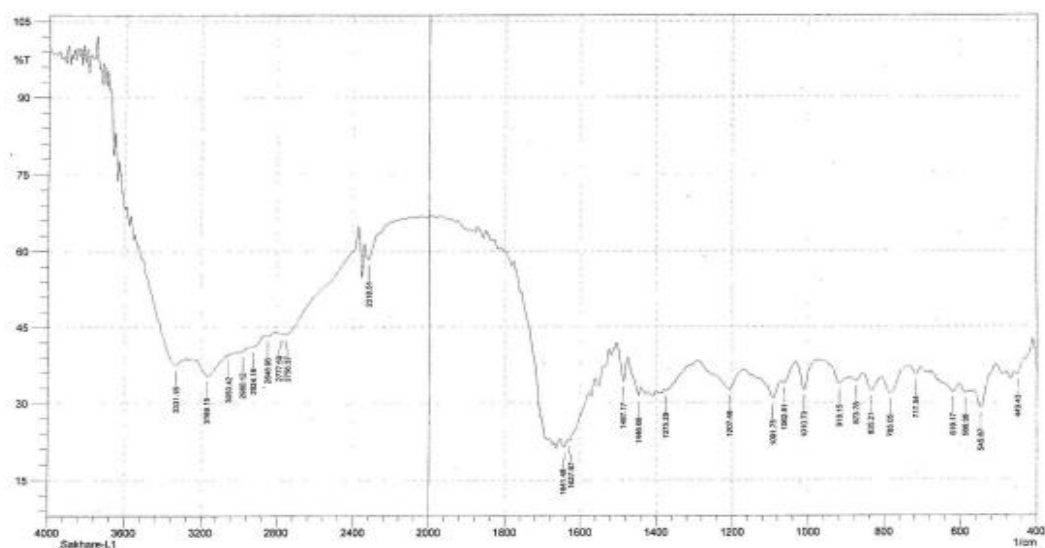


Fig. 1 Infrared Spectra of Ligand L₁

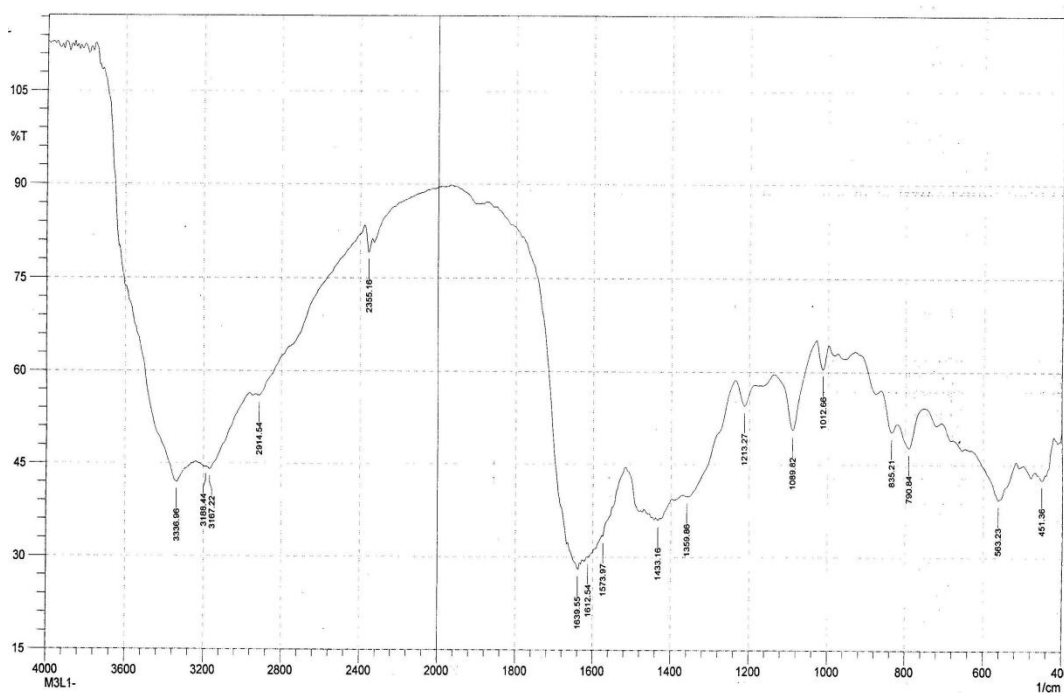


Fig. 2 Infrared Spectra of Cu(II) Complex of Ligand L₁

3.3 Molar Conductance Measurements:

The conductivity measurements of the complexes were recorded for (10^{-3} M), the solution of the samples was in (DMSO) at room temperature. The molar conductance values of the complexes showed in (Table 4). We concluded from the results that the Cu(II) complexes of the ligand (L_1) have a molar conductivity values in the range ($10.5 - 72.4 \Omega^{-1} \text{ mol}^{-1} \text{ cm}^2$). Which indicates that complexes are non-ionic therefore, they are considered as non-electrolytes [32].

3.4 Magnetic Susceptibility:

The values of effective magnetic moment of metal complexes were summarized in (Table 1), which were measured at room temperature. The complexes $[\text{Cu}(L_1)]$ have

(μ_{eff}) in the range (2.81-2.97 B.M) this value is within the range of octahedral geometry [33].

3.5 Thermogravimetric Analysis:

Thermal decomposition studies of complex have been carried out as to corroborate the information obtained from the IR spectral studies to know the presence of water molecule in these complexes as well as to know their decomposition pattern. The simultaneous TGA/DTA analysis of Cu(II) was studied from ambient temperature to 1000^oC in nitrogen atmosphere using α -Al₂O₃ as reference. An analysis of the thermogram of the complexes indicated that Co(II) complexes Fig. 3 shows two step decomposition. The first weight loss 6.66 0%, in between temp. 55-230^oC could be correlated with the loss of two coordinated water (calculated 6.01 %). The anhydrous compound does not remain stable at higher temperature; it undergoes rapid decomposition in the range 230-650^oC with 79.72 % mass loss corresponds to decomposition of the complex (calcd. 80.70%) in second step.

The decomposition is completed leading to the formation of stable residue of metal oxide CuO obs. 13.12 % (calcd. 13.28 %). The kinetic and thermodynamic viz the energy of activation (Ea), frequency factor (Z), entropy change (- Δ S) and free energy change (Δ G) for the non-isothermal decomposition of complexes have been determined by employing Horowitz-Metzger method [34] values are given in Table 4. The Calculated values of the given activation energy of the complexes are relatively low, indicating the autocatalysis effect of metal ion on the thermal decomposition of the complex. The negative value of activation entropy indicates that the activated complexes were more ordered than the reaction was slow. The more ordered nature may be due to the polarization of bonds in the activated state, which might occur through charge transfer transitions [35].

Table 4

The kinetic and thermodynamic parameters for decomposition of metal complexes

Complex	Step	Decomp. Temp. (°C)	n	Ea (kJmole⁻¹)	Z (S⁻¹)	ΔS (JK⁻¹mole⁻¹)	ΔG (kJmole⁻¹)	Correlation coefficient
Cu-L ₁	I	430	0.9	10.41	1.26 × 10 ⁴	-173.56	25.08	0.969

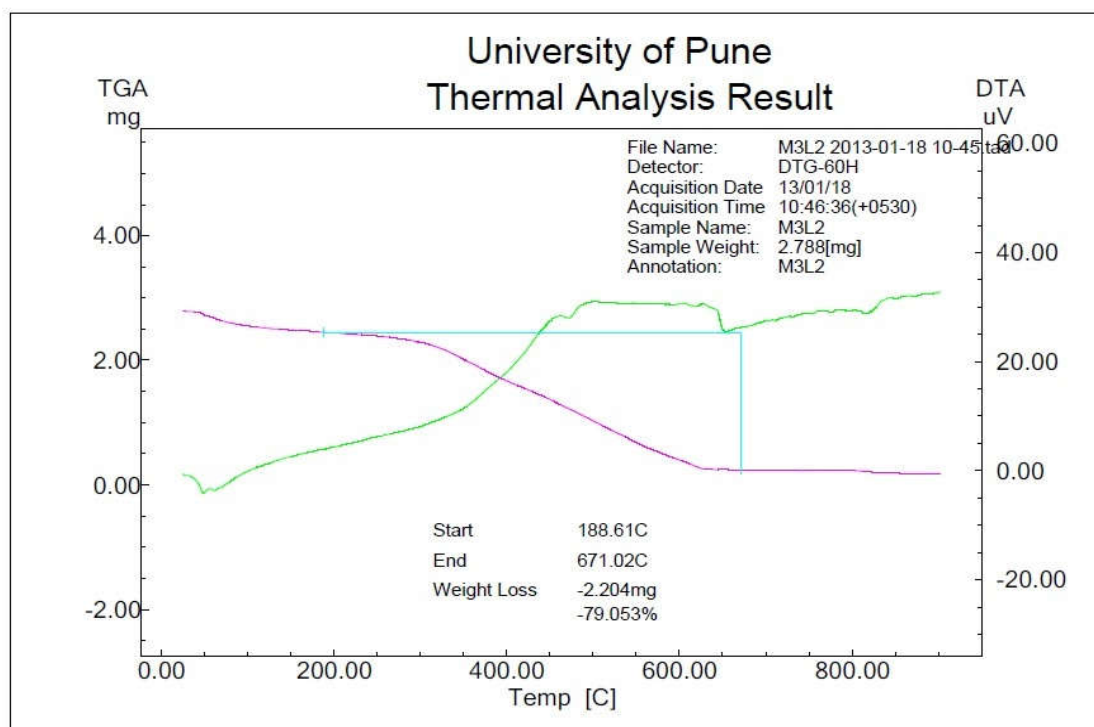


Fig. 3 TGA-DTA Curve of Cu(II) Complex of Ligand L₁

3.6 Electronic Spectra:

The electronic spectra of Schiff base ligand (L₁) show absorption bands at (42553cm⁻¹ and 27027cm⁻¹) which are attributed to ($\pi \rightarrow \pi^*$) and ($n \rightarrow \pi^*$) transitions respectively, the complex of Cu(II) shows band at (42553cm⁻¹) which due to ($\pi \rightarrow \pi^*$) transition, the band at (23255cm⁻¹) is due to charge transfer (C.T), the band at (14814cm⁻¹) is due to the transition $^3A_{2g} \rightarrow ^3T_{2g}$ the complexes are octahedral geometry [36].

3.7 X – Ray Diffraction Studies of Metal Complexes:

The Cu(II) complexes of ligand L₁ was selected for X-ray powder diffraction studies (Fig.4). X-ray powder data of all the main peaks have been indexed independently by trial and error method. The unit cell data crystal lattice parameters and the data obtained after indexing the powder data is presented in Table 4

The Cu(II) complex of ligand L₁ showed fourteen reflections with maxima at $2\theta = 9.77^\circ$ corresponding to d value 4.54Å. The unit cell values of lattice constants are $a = 6.8760 \text{ \AA}$, $b = 9.2456 \text{ \AA}$, $c = 24.234 \text{ \AA}$, $\alpha = \beta = 90^\circ$ $\gamma = 120^\circ$ and unit cell volume $V = 1334.21763 (\text{ \AA})^3$. The Co(II) complex of ligand L₅ showed nine reflections with maxima at $2\theta = 6.49^\circ$ corresponding to d value 6.80Å. The unit cell values of lattice constants are $a = 8.765 \text{ \AA}$, $b = 11.234 \text{ \AA}$, $c = 15.345 \text{ \AA}$, $\alpha = \beta = 90^\circ$ $\gamma = 120^\circ$ and unit cell volume $V = 1308.53064 (\text{ \AA})^3$

Table: 5 Indexed X-ray Diffraction Data of Cu(II) Complex of Ligand L₁

Peak No.	2 θ (observed)	2 θ (calculated)	d (observed)	d (calculate d)	Miller indices of Planes			Relative intensities (%)
					h	k	l	
1	6.65786	6.63628	6.64495	6.66544	-1	0	1	100.00

2	13.78489	13.80857	3.23302	3.22735	-2	3	1	5.72
3	15.48359	15.48257	2.88561	2.88561	0	2	3	6.18
4	18.66505	18.64768	2.40705	2.40908	1	3	1	2.22
5	21.30374	21.33357	2.12031	2.11739	-4	4	1	4.07
6	22.75576	22.74044	1.99153	1.99272	-2	2	5	1.79
7	24.06751	24.05905	1.88893	1.88948	-5	2	0	2.70
8	28.54683	28.56116	1.61197	1.61118	-3	2	6	2.60
9	29.49267	29.50032	1.5647	1.56429	-2	6	3	5.57
10	31.01021	30.99851	1.49522	1.49568	0	6	1	3.53
11	32.08422	32.07778	1.45025	1.45047	5	1	2	3.08
12	32.88802	32.89497	1.41864	1.41834	4	1	5	2.78
13	34.50318	34.49533	1.3599	1.36014	-2	7	3	4.04
14	37.49484	37.49073	1.26553	1.26562	-3	5	7	3.50
15	38.64195	38.64348	1.23359	1.23352	-2	8	2	2.88
16	39.44056	39.43407	1.21257	1.21271	-6	3	6	2.43

Unit cell data and crystal lattice parameter

$$a \text{ (Å)} = 9.564$$

$$b \text{ (Å)} = 10.456$$

$$c \text{ (Å)} = 11.234$$

$$\alpha = 90.00$$

$$\beta = 90.00$$

$$\gamma = 120.00$$

$$\text{Porosity} = 1.06\%$$

$$\text{Volume(V)} = 972.90452 \text{ (Å)}^3$$

$$\text{Density(obs.)} = 1.0412 \text{ gcm}^{-3}$$

$$\text{Density(cal.)} = 1.0302 \text{ gcm}^{-3}$$

$$Z = 1$$

Crystal system = Monoclinic

$$\text{Standard deviation (\%)} = 0.049$$

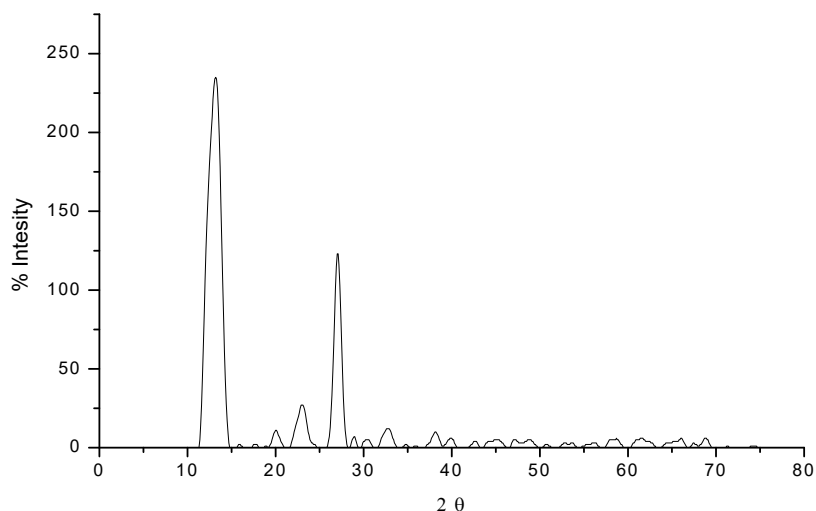


Fig. 4 X-ray Diffractogram of Cu (II) complex of L₁

4. Biological Activity :

4.1 Antibacterial Activity & Antifungal Activity:

Antifungal activity and Antibacterial activity of ligand and metal complexes were tested in vitro against fungal such as *Aspergillus niger*, *Penicillium chrysogenum*, *Fusarium moneliforme*, *Aspergillus flavus* and bacteria such as *E. Coli*, *B. Subtilis*, *Staphylococcus aureus* and *Bacillus subtilis* by paper disc plate method [37] The compounds were tested at the concentrations 1% and 2% in DMSO and compared with known antibiotics viz *Griseofulvin* and *Penicillin*. (Table 5 and 6). From Table 6 and 7, it is clear that the inhibition by metal chelates is higher than that of a ligand and results are in good agreement with previous findings with respect to comparative activity of free ligand and its complexes [38] Such enhanced activity of metal chelates is due to the increased lipophilic nature of the metal ions in complexes. The increase in activity with concentration is due to the effect of metal ions on the normal cell process. The action of compounds may involve the formation of hydrogen bond with the active centre of cell constituents, resulting in interference with the normal cell process.

Table 6. Antifungal activity of ligands

Test Compound	Antifungal Growth							
	<i>Aspergillus niger</i>		<i>Penicillium chrysogenum</i>		<i>Fusarium moneliforme</i>		<i>Aspergillus flavus</i>	
	1%	2%	1%	2%	1%	2%	1%	2%
L₁	-ve	-ve	RG	-ve	-ve	-ve	RG	-ve
Cu-L₁	-ve	-ve	-ve	-ve	-ve	-ve	-ve	+ve

+ve control	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve
-ve control (Griseofulvin)	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve

Ligand & Metal : +ve – Growth (Antifungal Activity absent)

-ve - Growth (Antifungal Activity present)

RG - Reduced Growth (More than 50% reduction in growth observed)

Table 7. Antibacterial activity of ligands and their metal complexes

Test Compound	Diameter of inhibition zone (mm)							
	<i>E. coli</i>		<i>Salmonella typhi</i>		<i>Staphylococcus aureus</i>		<i>Bacillus subtilis</i>	
	1%	2%	1%	2%	1%	2%	1%	2%
L	15mm	12mm	-ve	14mm	19mm	18mm	-ve	19mm
Cu-L	12mm	14mm	13mm	15mm	18mm	21mm	11mm	14mm
DMSO	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
Penicillin	14mm	14mm	18mm	18mm	31mm	31mm	19mm	19mm

Ligand & Metal: - ve - No Antibacterial Activity

Zone of inhibition - ---mm

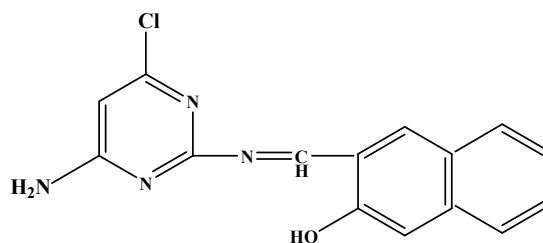


Fig. 5 Structure of Schiff Base Ligand L₁

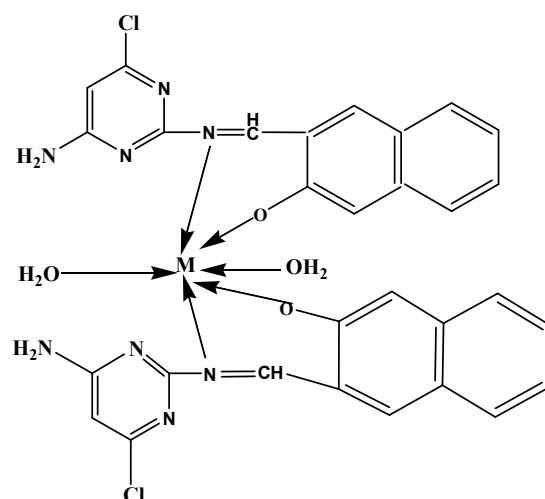


Fig. 6. The proposed Structure of the Metal complexes. [When M= Cu (II)]

5. Conclusion:

In the light of above discussion we have proposed octahedral geometry for Cu(II) complexes. On the basis of the physico-chemical and spectral data discussed above, one can assume that the ligand behave as dibasic, NO bidentate, coordinating via phenolic oxygen and imino nitrogen as illustrated in Fig.6. The complexes are biologically active and show enhanced antimicrobial activities compared to free ligand. Thermal study reveals thermal stability of complexes. The X-ray study suggests monoclinic crystal system for Cu(II) complexes.

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