

Synthesis, Characterization And Biological Activity of New Pyrimidine Schiff Base And Its Cu(II), Ni(II) Complexes

Abstract:

The novel Schiff base ligand (E)-2-(((2-hydroxynaphthalen-1-yl)methylene)amino)-6-methylpyrimidin-4-ol has been synthesized by the condensation of 2-amino-4-hydroxy-6-methylpyrimidine & 2-hydroxy-1-naphthaldehyde. Metal complexes of the Schiff base were prepared by the reaction of the Schiff base and Iron nitrate in ethanol solution. The complexes isolated, washed and dried. The Schiff base is pale yellow, while Cu(II) and Ni(II) complexes are light yellow. The synthesized compounds have been characterized by FT-IR, ¹H-NMR and UV-Vis techniques for the ligands and FT-IR, UV-Vis, all reactions monitored by TLC, molar conductivity and magnetic susceptibility measurements for the corresponding complexes. The complex is paramagnetic. The results of the molar conductivity measurements indicated that all complexes are non-electrolytes in (DMSO). An octahedral geometry for all the complexes. The ligands are bidentate, (L) through phenolic (OH) and azomethine nitrogen. The ligand and its complexes were screened for their antifungal and antibacterial activity against *Aspergillus niger*, *Penicillium chrysogenum*, *Fusarium moniliforme*, *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 and 2-amino-4-hydroxy-6-methylpyrimidine, Biological Activity.

Introduction:

Schiff bases have attracted much attention in recent years due to their wide range of biological activities and industrial applications. [1] They are the condensation products of aldehydes (CHO) or ketones (CO) and primary imines (NH₂) in the presence of organic solvents such as methanol, ethanol, or tetrahydrofuran (THF) at specific temperature and pH conditions [2]. They were first synthesized in 1864 by Hugo Schiff and named after him [3]. They contain an imine unit (HC=N-) of the general formula RN = CR'R'' (azomethine group), where R, R', and R'' are different substituted alkyl, aryl, heteroaryl, or cycloalkyl groups, etc. [4]. These compounds are commonly known as anylenes, imines, or azomethines. Schiff bases are important in various fields of chemistry (bioinorganic, biomedical, supramolecular, catalysis and materials, etc.) and can be synthesized by selecting appropriate derivatives of amines and aldehydes or ketones with the required functional groups.[8-10] The wide range of applications of Schiff bases includes corrosion inhibitors, catalyst supports, thermostable materials, ligands for metal coordination, and biological or pharmacological systems.[5] Biologically active Schiff bases exhibit antibacterial, anticancer, antifungal, and radical scavenging properties in addition to functioning as enzyme intermediates or inhibitors.[6] The wide spectrum of biological activity of these compounds is due to their unique role, since the azomethine group has a lone

pair of electrons in the sp^2 hybrid orbital of the nitrogen atom. Moreover, the electrophilic carbon and nucleophilic nitrogen of the imine bond ($-C=N-$) produce compounds that bind well with various nucleophiles and electrophiles, thereby inhibiting target diseases, enzymes, or DNA replication. [7-9] Overall, they are characterized by simple synthesis techniques, versatility, and wide range of applications. Therefore, the synthesis of Schiff base compounds, especially heterocyclic compounds, has attracted much attention from chemical researchers in recent years. Heterocyclic compounds are important for the synthesis of Schiff bases because of their wide range of applications in biology, chemistry (inorganic, analytical products, and intermediates in organic reactions), agricultural chemistry, and crop protection. [10-13] Thus, the numerous physicochemical properties and various reactions of heterocyclic compounds prove that heterocyclic compounds are an important part of heterocyclic chemistry. Similarly, heterocyclic Schiff bases have attracted great attention due to their versatile applications. Pyrimidines, organic heterocyclic compounds, consist of a six-membered unsaturated ring structure with two nitrogen atoms at positions 1 and 3 and are one of the most versatile synthetic substrates for pharmaceutical synthesis. [14].

They are considered the basic building blocks of nucleic acids in the form of nitrogenous bases (cytosine, thymine, and uracil) and are used as precursors in the synthesis of biologically active molecules. [15] Schiff bases derived from pyrimidines act pharmacologically as analgesics, antiepileptics, antivirals, antihypertensives, minoxidil, antimycobacterial, cancer and malarial drugs, and as effective phosphodiesterase inhibitors. [16-18] Therefore, researchers are interested in the development and synthesis of pyrimidine-derived Schiff bases using condensation methods with appropriate aldehydes or ketones. The technique of molecular docking is widely used in modern drug discovery to understand drug-receptor interactions. This method is widely used to predict the binding affinity and orientation of small drug molecules to their target sites in proteins. [19] Binding can occur in several possible conformations, called binding modes. [20] The two main goals of this research are accurate structural modeling and accurate prediction of drug molecule activity. [21] Bioinformatics and computational biology tools have been used for computer-aided drug design and virtual screening of large databases of natural compounds, which have accelerated the process of traditional drug design. [22]

A literature survey indicates that no work has been done on Schiff base transition metal complexes derived from 2-hydroxy-1-naphthaldehyde and 2-amino-4-hydroxy-6-methylpyrimidine. In this communication, we report the synthesis of a bidentate Schiff base formed by condensation of 2-hydroxy-1-naphthaldehyde and 2-amino-4-hydroxy-6-methylpyrimidine (Figure 3). Solid complexes of these ligands with Cu(II) and Ni(II) were prepared and characterized using various physicochemical methods.

Materials And Methods

Reagents and solvents

2-amino-4-hydroxy-6-methylpyrimidine (Aldrich sigma), 2-hydroxy-1-naphthaldehyde, metal nitrate of AR grade was used for synthesis of ligand and metal complex.

Synthesis of ligand

The ligand was prepared by a modification of the reported methods [23-25]. The Schiff base ligand has been synthesized by refluxing a mixture of 0.01 mol (1.2015g)

of 2-hydroxy-1-naphthaldehyde and 0.01 mol (1.2710 g) of 2-amino-4-hydroxy-6-methylpyrimidine 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:78%).

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: 70%)

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 CDCl_3 using TMS as internal standard. X-RD were recorded on BRUKER D8 Advance. TGA- DTA were recorded on Shimadzu. The carbon, hydrogen and nitrogen contents were determined on Elementar model vario EL-III. The UV-visible spectra of the complexes were recorded on model Jasco V-530 UV-Vis 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.

Results And Discussion

Schiff bases of 2-amino-4-hydroxy-6-methylpyrimidine and its complexes have a variety of applications including biological, clinical and analytical. The coordinating possibility of 2-amino-4-hydroxy-6-methylpyrimidine has been improved by condensing with a variety of carbonyl compounds. An attempt has been made to synthesize Schiff bases from 2-amino-4-hydroxy-6-methylpyrimidine with 2-hydroxy-1-naphthaldehyde. Physical characteristics, micro analytical, 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 M= Cu(II) and Ni(II)]. The magnetic susceptibilities of Cu(II) and Ni(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 TGA-DTA analysis. The metal chelate solutions in DMSO show low conductance and supports their non-electrolyte nature.(Table 1)

$^1\text{H-NMR}$ spectra of ligand

The $^1\text{H-NMR}$. Spectra of free ligand at room temperature show the following signals. 2.35 δ (s, 3H, Methyl hydrogen bonded to pyrimidine ring), 2.35 δ (s, 3H, Methyl hydrogen bonded to phenyl ring), 5.47 δ (s, 1H, Phenolic (OH) hydrogen of pyrimidine ring), 6.77 δ (s, 1H, Hydrogen bonded to pyrimidine ring), 7.84 δ (s, 1H, hydrogen bonded to azomethine carbon), 7.2-7.42 δ (D,4H, Aromatic Ha, Hb, protons of phenyl ring).

IR Spectra

The IR spectra of the complexes are compared with that of the ligand to determine the changes that might have taken place during the complexation. The bands at 3363, 1678, 1516, 1309, and 1186 cm^{-1} assignable to ν OH (intramolecular hydrogen bonded), ν C=C (aromatic), ν C=N (azomethine), ν C-N (aryl azomethine) and ν C-O (phenolic) stretching modes respectively [26-28]. 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 intramolecular 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 Cu (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 TGA/DTA analysis of these complexes. Hence it is concluded that the coordination takes place via phenolic oxygen and azomethine nitrogen of ligand molecule.

Thermogravimetric analysis

The dynamic TGA with the percentage mass loss at different steps have been recorded. The simultaneous TGA/DTA analysis of Cu (II) was studied from ambient temperature to 1000 $^{\circ}\text{C}$ in nitrogen atmosphere using $\alpha\text{-Al}_2\text{O}_3$ as reference. An analysis of the thermogram of the complexes indicated that Cu (II) complexes ligand L (Figure 1) show two step decomposition. The first weight loss 5.61%, in between temp. 50-195 $^{\circ}\text{C}$ could be correlated with the loss of two molecules of lattice water (calcd 6.50 %). The anhydrous compound does not remain stable at higher temperature, it undergoes rapid decomposition in the range 195-570 $^{\circ}\text{C}$, with 79.45 % mass loss corresponds to decomposition of the complex (calcd. 79.14 %) in second step. The decomposition is completed leading to the formation of stable residue of metal oxide CuO obs. 11.23 % (calcd. 14.35 %). Kinetic and thermodynamic viz the energy of activation (E_a), frequency factor (Z), entropy change ($-\Delta S$) and free energy change (ΔG) for the non-isothermal decomposition of complexes have been determined by employing Horowitz-Metzger method [32] values are given in Table 3. 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 [33].

Magnetic measurements and electronic absorption spectra

The electronic spectral studies of metal complexes of Cu (II) with Schiff bases were carried out in DMSO solution. The absorption spectrum of the Cu(II) complex shows bands at 13812 cm^{-1} and 30030 cm^{-1} are assigned to $^2\text{B}_{1g} \rightarrow ^2\text{A}_{1g}$ and charge transfer

respectively in an octahedral field [34]. The Cu (II) complexes were diamagnetic in nature.

Molar Conductivity Measurements

The metal (II) complexes were dissolved in DMSO and the molar conductivity of 10^{-4}M of their solution at room temperature was measured. The lower conductance values of the complexes support their non-electrolytic nature of the compounds.

Table1. Physical characterization, analytical and molar conductance data of compounds

Compound Molecular formula	Mol.Wt.	M.P. Decomp temp. °C	Colour	μ_{eff}	Molar Conduc. Mho $\text{Cm}^2\text{mol}^{-1}$
L	279.29	207	Yellow	--	----
Cu- L	658.13	>300	Dark Gray	1.93	11.10
Ni- L	653.59	>300	Dark Green	1.89	12.04

Table 2. Elemental Analysis of Cu(II) and Ni(II) Complex:-

Compound	Found (Calculated)			
	C	H	N	M
L	69.71 (68.71)	4.77 (4.77)	15.49 (15.49)	--
Cu-L	61.99 (61.97)	3.95 (3.93)	13.62 (13.53)	10.46 (10.43)
Ni-L	62.99 (61.97)	4.15 (4.13)	14.22 (14.20)	9.86 (9.73)

Powder x-ray diffraction

The x-ray diffractogram of Cu (II) complexes of L_8 was scanned in the range $20\text{--}80^\circ$ at wavelength $1.543 \text{ \AA}$ (Figure 2). The diffractogram and associated data depict the 2θ value for each peak, relative intensity and inter-planar spacing (d-values). The diffractogram of Cu(II) complex of L had fifteen reflections with maxima at $2\theta = 12.89^\circ$ corresponding to d value $6.86 \text{ \AA}$. The x-ray diffraction pattern of these complexes with respect to major peaks of relative intensity greater than 10% has been indexed by using computer programmed [35] The above indexing method also yields Miller indices (hkl), unit cell parameters and unit cell volume. The unit cell of Cu(II) complex of L yielded values of lattice constants, $a = 9.76 \text{ \AA}$, $b = 10.24 \text{ \AA}$, $c = 27.24 \text{ \AA}$ and unit cell volume $V = 2722.43096 \text{ \AA}^3$. In concurrence with these cell parameters, the condition such as $a = b = c$ and $\alpha = \beta = \gamma = 90^\circ$ required for sample to be Monoclinic were tested and found to be satisfactory. Hence it can be concluded that Cu(II) complex has Orthorhombic crystal system. Hence it can be concluded Cu (II) complex of L_8 has monoclinic crystal system. The experimental density values of the complexes were determined by using specific gravity method [31] and found to be 0.8968 gcm^{-3} for Cu (II) complexes respectively. By using experimental density values, molecular weight of complexes, Avogadro's number and volume of the unit cell were calculated. Number of molecules per unit cell were calculated by using equation $\rho = nM/NV$ and was found Cu (II) complexes respectively. With these values, theoretical density were computed and found to be 0.8858 gcm^{-3} for respective complexes. Comparison of experimental and theoretical density shows good agreement within the limits of experimental error [33].

Table: 3 The kinetic and thermodynamic parameters for decomposition of metal complexes

Complex	Step	Decomp . Temp. ($^{\circ}\text{C}$)	n	Ea (kJmole $^{-1}$)	Z (S $^{-1}$)	ΔS (JK $^{-1}$ mole $^{-1}$)	ΔG (kJmole $^{-1}$)	Correl - ation coefficient
Cu-L	I	150	0.1	3.77	4.77×10^4	-177.78	12.81	0.994
	II	490	0.8	12.26	1.48×10^4	-172.88	28.12	0.987

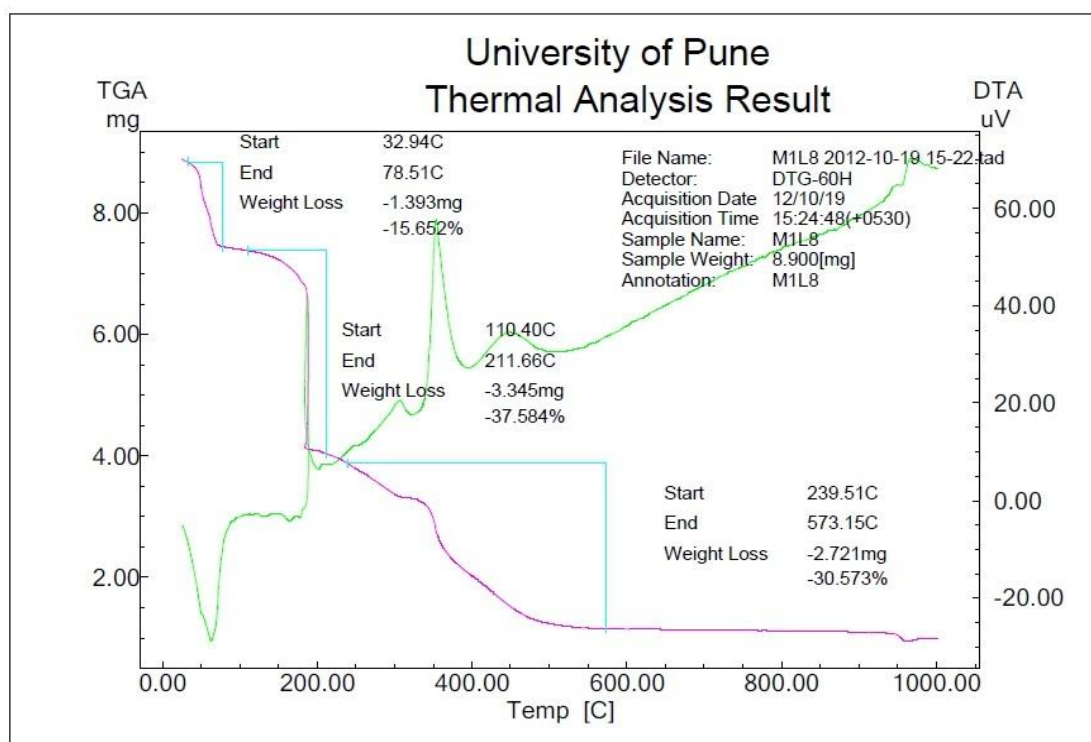


Fig. 1 TGA-DTA Curve of Cu(II) Complex of Ligand L

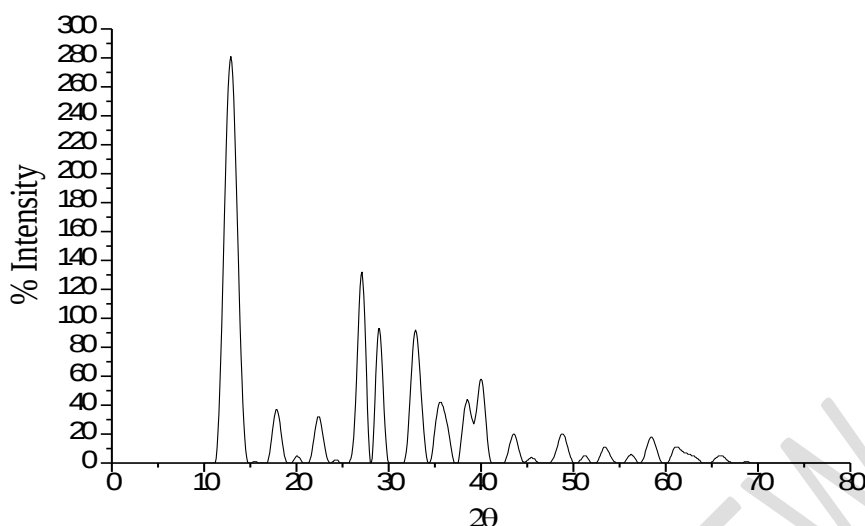


Fig.2 X-ray Diffractogram of Cu (II) complex of L

Antibacterial 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*, *S. Aurious* And *Bacillus subtilis* by paper disc plate method [36-39] The compounds were tested at the concentrations 1% and 2% in DMSO and compared with known antibiotics viz *Griseofulvin* and *Penicilin*. (Table 4 and 5)., it is found 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 [40]

Table 4 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%
L	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
Cu- L	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
Ni- L	-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 5 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	14mm	18mm	16mm	18mm	20mm	25mm	19mm	22mm
Cu- L	11mm	16mm	15mm	16mm	14mm	22mm	15mm	18mm
Ni- L	14mm	16mm	15mm	19mm	18mm	22mm	14mm	18mm
DMSO	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
Penicillin	14mm	14mm	17mm	17mm	30mm	30mm	19mm	19mm

Ligand & Metal: - ve - No Antibacterial Activity
Zone of inhibition - --mm

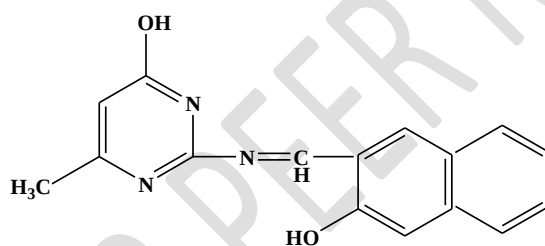


Figure 3. Structure of ligand

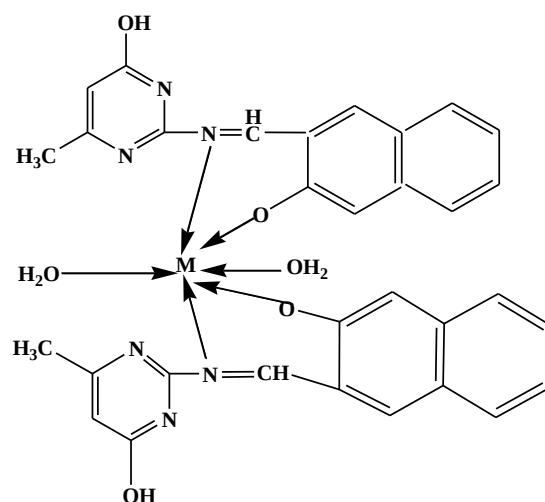


Figure 4. The proposed Structure of the complexes

When M= Cu (II) and Ni(II).

Conclusion

In the light of above discussion we have proposed octahedral geometry for Cu (II) and Ni(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.4. 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 orthorhombic crystal system for Cu (II) and Ni(II) complexes.

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