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

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Abstract:

The novel Schiff base ligand (E)-2-(((2-hydroxynaphthalen-1-yl)methylene)amino)-6-methylpyrimidin-4-ol has been attained through the condensation of 2-amino-4-hydroxy-6-methylpyrimidine and 2-hydroxy-1-naphthaldehyde. Metal complexes of the Schiff base were formed by the interaction of the Schiff base and metal nitrate in an ethanol solution. The complexes were isolated, cleaned, and dried. The Schiff base appears pale yellow, whereas the Cu(II) and Ni(II) complexes exhibit a light yellow color. The synthesized compounds have been characterized by FT-IR, ^{1}H-NMR, and UV-Vis techniques for the ligands, while FT-IR, UV-Vis, along with all reactions monitored by TLC, molar conductivity, and magnetic susceptibility measurements were employed for the corresponding complexes. The complexes are paramagnetic. The results from the molar conductivity measurements indicated that all complexes are non-electrolytes in (DMSO). An octahedral geometry is anticipated for all the complexes. The ligands are bidentate (L) through phenolic (OH) and azomethine nitrogen. The ligand and its complexes were evaluated for their antifungal and antibacterial efficacy against *Aspergillus niger, Penicillium chrysogenum, Fusarium moniliforme, Aspergillus flavus, Escherichia coli, Salmonella typhi, Staphylococcus aureus,* and *B. subtilis*. The results demonstrated that the complexes exhibited significant 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 garnered significant interest in recent years owing to their extensive array of biological activities and industrial applications” [1]. They are the condensation products of aldehydes (CHO) or ketones (CO) and primary imines (NH_2) in the presence of organic solvents such as methanol, ethanol, or tetrahydrofuran (THF) under specific temperature and pH conditions [2]. “They were initially synthesized in 1864 by Hugo Schiff and named in his honor” [3]. “These compounds feature an imine unit (HC=N-) represented by the general formula RN = CR`R"(azomethine group), where R, R`, and R" denote various substituted alkyl, aryl, heteroaryl, or cycloalkyl groups” [4]. “These substances are commonly referred to as anylenes, imines, or azomethines. Schiff bases hold significance in multiple areas of chemistry (bioinorganic, biomedical, supramolecular, catalysis, and materials, etc. and can be produced by choosing suitable derivatives of amines and aldehydes or ketones with the desired functional groups” [5]. “The broad range of uses for Schiff bases encompasses corrosion inhibitors, catalyst supports, thermostable materials, ligands for metal coordination, and biological or pharmacological systems” [6]. “Biologically active Schiff bases display antibacterial, anticancer, antifungal, and radical scavenging activities in addition to serving as enzyme intermediates or inhibitors” [7]. The broad spectrum of biological efficacy of these compounds is attributable to their distinctive characteristics, as the azomethine group possesses a lone pair of electrons in the sp^2 hybrid orbital of the nitrogen atom. Furthermore, the electrophilic carbon and nucleophilic nitrogen of the imine bond (-C=N-) yield compounds that effectively engage with various nucleophiles and electrophiles, thereby impeding target diseases, enzymes, or DNA replication [8,9]. “Overall, they are defined by straightforward synthesis methodologies, versatility, and extensive applications. Consequently, the creation of Schiff base compounds, particularly heterocyclic compounds, has attracted considerable attention from chemical researchers in recent times. Heterocyclic compounds are essential for the synthesis of Schiff bases due to their wide-reaching applications in biology, chemistry (inorganic, analytical products, and intermediates in organic reactions), agricultural chemistry, and crop protection” [10-13]. Thus, the multitude of physicochemical characteristics and assorted reactions of heterocyclic compounds affirm their significance in heterocyclic chemistry. Likewise, heterocyclic Schiff bases have piqued substantial interest because of their multifaceted applications. Pyrimidines, which are organic heterocyclic compounds, consist of a six-membered unsaturated ring structure containing two nitrogen atoms at positions 1 and 3, making them among the most versatile synthetic substrates for pharmaceutical synthesis [14].

“They are regarded as the fundamental components of nucleic acids in the form of nitrogenous bases (cytosine, thymine, and uracil) and serve as precursors in the fabrication of biologically active compounds” [15]. Schiff bases originating from pyrimidines exhibit pharmacological properties as analgesics, antiepileptics, antivirals, antihypertensives, minoxidil, antimycobacterial agents, cancer and antimalarial drugs, as well as effective phosphodiesterase inhibitors [16-18]. “Consequently, scholars are focused on the advancement and synthesis of pyrimidine-derived Schiff bases employing condensation techniques with suitable aldehydes or ketones. The approach of molecular docking is extensively utilized in contemporary drug discovery to comprehend drug-receptor interactions” [19]. This methodology is frequently applied to forecast the binding affinity and orientation of small drug molecules to their target sites in proteins. “Binding may take place in various conceivable conformations, referred to as binding modes” [20]. The two primary objectives of this investigation are precise structural modeling and accurate prediction of drug molecule efficacy [21]. “Bioinformatics and computational biology instruments have been utilized for computer-assisted drug design and virtual screening of extensive databases of natural substances, enhancing the speed of traditional drug design processes” [22]. A review of the literature reveals that no studies have been conducted on Schiff base transition metal complexes derived from 2-hydroxy-1-naphthaldehyde and 2-amino-4-hydroxy-6-methylpyrimidine. In this report, we present the synthesis of a bidentate Schiff base resulting from the condensation of 2-hydroxy-1-naphthaldehyde and 2-amino-4-hydroxy-6-methylpyrimidine. Solid complexes of these ligands with Cu(II) and Ni(II) were synthesized and characterized using various physicochemical techniques.

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 synthesized through a modification of previously described methodologies [23-25]. The Schiff base ligand was produced by refluxing a combination of 0. 01 mol (1. 2015 g) of 2-hydroxy-1-naphthaldehyde and 0. 01 mol (1. 2710 g) of 2-amino-4-hydroxy-6-methylpyrimidine in 50 ml of super dry ethanol for approximately 4 hours. The resulting Schiff base was allowed to cool to ambient temperature and subsequently collected via filtration, followed by recrystallization in ethanol and drying in vacuo over anhydrous calcium chloride (Yield: 78%).

Synthesis of Metal Complexes

To a heated ethanol solution (25 ml) containing the ligand (2 mol) and (25 ml) of metal nitrate (1 mol), constant stirring was applied. The pH of the reaction mixture was adjusted to 7-8 by the addition of a 10% alcoholic ammonia solution and refluxed for around 3 hours. The precipitated solid metal complex was filtered out while hot and washed with hot ethanol, then dried over calcium chloride in vacuum desiccators (Yield: 70%).

Physical Measurement

Infrared spectra were recorded using an FTIR (ATR)-BRUKER-TENSOR37 spectrometer with KBr pellets over the range of 4000-400 cm^{-1}. ^1H NMR spectra of the ligand were acquired on a Varian Mercury 300 MHz spectrometer in CDCl3, utilizing TMS as the internal standard. X-ray diffraction (XRD) data were obtained using a BRUKER D8 Advance. Thermogravimetric analysis (TGA) and differential thermal analysis (DTA) were conducted on a Shimadzu instrument. The content of carbon, hydrogen, and nitrogen was analyzed using an Elementar model Vario EL-III. UV-visible spectra of the complexes were recorded with a Jasco V-530 UV-Vis spectrometer. Molar conductance of the complexes was measured on an Elico CM 180 conductivity meter utilizing a 10^{-4} M solution in DMSO. Magnetic susceptibility measurements of the metal chelates were performed on a Gouy balance at room temperature, using $Hg[Co(SCN)_4]$ as a calibrant.

Results and Discussion

Schiff bases derived from 2-amino-4-hydroxy-6-methylpyrimidine and their complexes possess a broad range of applications in biological, clinical, and analytical fields. The coordination capability of 2-amino-4-hydroxy-6-methylpyrimidine has been enhanced through condensation with various carbonyl compounds. An endeavor was made to synthesize Schiff bases from 2-amino-4-hydroxy-6-methylpyrimidine and 2-hydroxy-1-naphthaldehyde. Physical properties, microanalytical data, and molar conductance measurements of the ligand and metal complexes are presented in (Tables 1 and 2). The analytical data of the complexes reveal a 2:1 molar ratio (ligand: metal), consistent with the general formula $[ML(H_2O)_2]$ (where M = Cu(II) and Ni(II)). The magnetic susceptibilities of Cu(II) and Ni(II) complexes at room temperature align with a high-spin octahedral structure featuring two water molecules coordinated to the metal ion. The presence of these two coordinated water molecules was confirmed through TGA-DTA analysis. The metal chelate solutions in DMSO exhibited low conductance, reinforcing their characterization as non-electrolytes (Table 1).

^{1}H-NMR spectra of ligand

The ^{1}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 infrared spectra of the complexes are contrasted with that of the ligand to ascertain the alterations that may have occurred during the complexation process. The bands at 3363, 1678, 1516, 1309, and 1186 cm^{-1} attributed to OH (intramolecular hydrogen bonded), C=C (aromatic), C=N (azomethine), C-N (aryl azomethine), and

C-O (phenolic) stretching modes, respectively. The absence of a faint broad band in the 3200-3400 cm^{-1} range in the spectra of the metal complexes indicates the deprotonation of the intramolecular hydrogen-bonded OH group upon complexation and the subsequent coordination of phenolic oxygen to the metal ion. This observation is corroborated by a downward shift in υ C-O (phenolic) with respect to the free ligand. Upon complexation, the (C=N) band is shifted to a lower wavenumber relative to the free ligand, signifying that the nitrogen of the azomethine group is coordinated to the metal ion. The C-N band also shifts to a lower wavenumber when compared to the free ligand. The IR spectra of the metal chelates displayed new bands in the 500-600 and 400-500 cm^{-1} regions, which can be ascribed to M-O and M-N vibrations, respectively. “The infrared spectra of Cu (II) exhibit a prominent band in the 3050-3600 cm^{-1} range, indicating the presence of coordinated water in these metal complexes. The existence of coordinated water is further validated by the appearance of a non-ligand band in the 830-840 cm^{-1} range, attributable to the rocking mode of water. The presence of coordinated water is additionally established and supported by TGA/DTA analysis of these complexes. Therefore, it is deduced that the coordination occurs via phenolic oxygen and azomethine nitrogen of the ligand molecule” [32].

Thermogravimetric analysis

“The dynamic TGA along with the percentage mass reduction at various stages has been documented. The concurrent TGA/DTA evaluation of Cu (II) was examined from room temperature to 1000 °C in a nitrogen environment utilizing α-Al2O3 as reference. An examination of the thermogram of the complexes suggested that Cu (II) complex with ligand L (Figure 1) exhibits a two-step decomposition. The initial mass reduction of 5. 61% observed between 50-195 °C can be associated with the loss of two lattice water molecules (calculated 6. 50%). The anhydrous compound fails to maintain stability at elevated temperatures, undergoing rapid decomposition within the range of 195-570 °C, with a 79. 45% mass loss corresponding to the decomposition of the complex (calculated 79. 14%) during the second stage. The decomposition concludes with the formation of a stable residue of metal oxide CuO observed at 11. 23% (calculated 14. 35%). Kinetic and thermodynamic parameters such as the activation energy (Ea), frequency factor (Z), entropy change (-S), and free energy change (G) for the non-isothermal decomposition of the complexes have been determined using the Horowitz-Metzger method” [32]. “the results are presented in Table 3. The calculated values of the activation energy for the complexes are comparatively low, indicating the autocatalytic effect of the metal ion on the thermal decomposition of the complex. The negative value of the activation entropy suggests that the activated complexes were more organized than when the reaction occurred slowly. This more ordered characteristic may be attributed to the polarization of bonds in the activated state, potentially arising from charge transfer transitions” [33].

Magnetic measurements and electronic absorption spectra

The electronic spectral investigations of metal complexes of Cu (II) with Schiff bases were conducted in DMSO solution. The absorption spectrum of the Cu (II) complex exhibits bands at 13812 cm^{-1} and 30030 cm^{-1}, which are attributed to $^2B_{1g} \rightarrow {}^2A_{1g}$ and charge transfer, respectively, within an octahedral field [34]. The Cu (II) complexes displayed diamagnetic characteristics.

Molar Conductivity Measurements

The metal (II) complexes were solubilized in DMSO, and the molar conductivity of their 10^{-4} M solution at ambient temperature was assessed. The reduced conductance values of the complexes corroborate their non-electrolytic characteristic.

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

Compound Molecular formula	**Mol.Wt.**	**M.P. Decomp temp. ^{0}C**	**Colour**	**$\mu_{eff.}$**	**Molar Conduc. Mho Cm^2mol^{-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 L8 was analyzed in the interval of 20-80° at a wavelength of 1.543 Å (Figure 2). The diffractogram and its corresponding data illustrate the 2θ value for each peak, relative intensity, and inter-planar spacing (d-values). The diffractogram of the Cu(II) complex of L exhibited fifteen reflections with maxima at $2\theta = 12.89°$, corresponding to a d value of 6. 86 Å. The x-ray diffraction pattern of these complexes concerning significant peaks with relative intensity exceeding 10% has been indexed using a computer program" [35]. "This indexing procedure also provides Miller indices (hkl), unit cell parameters, and unit cell volume. The unit cell of the Cu(II) complex of L yielded lattice constants of a = 9. 76 Å, b = 10. 24 Å, c = 27. 24 Å, and a unit cell volume V = 2722. 43096 Å³. In conjunction with these cell parameters, the conditions such as $a = b = c$ and $\alpha = \beta = \gamma = 90°$, necessary for the sample to be Monoclinic, were evaluated and found to be satisfactory. Therefore, it can be concluded that the Cu(II) complex has an Orthorhombic crystal system. Thus, it can be affirmed that the Cu(II) complex of L8 possesses a Monoclinic crystal system. The experimental density values of the complexes were ascertained using the specific gravity method" [31] and were determined to be 0. 8968 gcm^{-3} for the Cu(II) complexes. "Utilizing the experimental density values, molecular weight of the complexes, Avogadro's number, and volume of the unit cell were calculated. The number of molecules per unit cell was assessed using the equation $\rho = nM/NV$ and was found for the Cu(II) complexes respectively. With these figures, theoretical density was computed and found to be 0. 8858 gcm^{-3} for the respective complexes. The comparison of experimental and theoretical density indicates good concordance within the confines of experimental error" [33].

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

Complex	**Step**	**Decomp. Temp.** (^{0}C)	**n**	**Ea** (kJmole^{-1})	**Z** (S^{-1})	**ΔS** (JK^{-1}mole^{-1})	**ΔG** (kJmole^{-1})	**Correl - ation coeffici- ent**
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

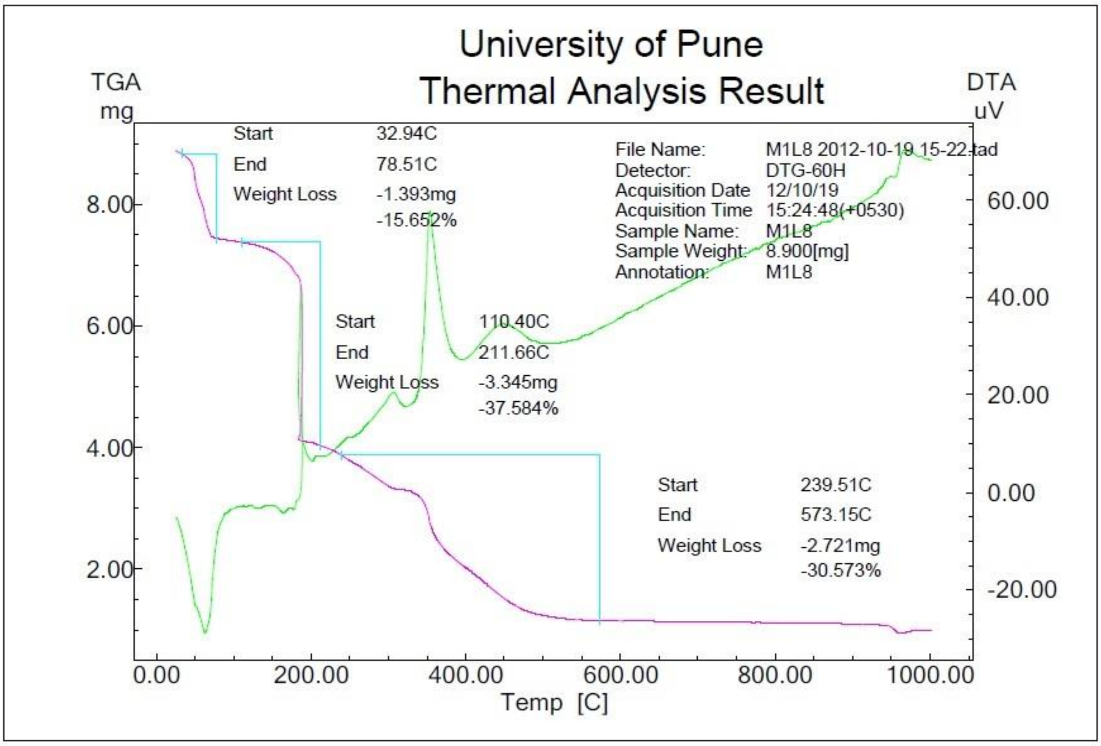

Fig. 1 TGA-DTA Curve of Cu(II) Complex of Ligand L

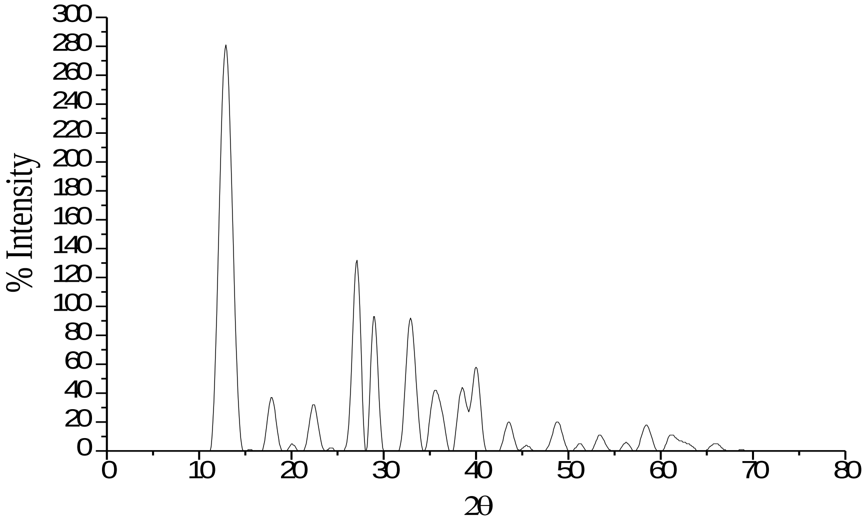

Fig.2 X-ray Diffractogram of Cu (II) complex of L

Antibacterial activity

“The antifungal and antibacterial efficacy of ligands and metal complexes was evaluated in vitro against fungi such as A*spergillus niger, Penicillium chrysogenum, Fusarium moneliforme, Aspergillus flavus,* and bacteria including *E. coli, B. subtilis, S. aureus, and Bacillus subtilis* utilizing the paper disc diffusion method” [36-39]. “The compounds were assessed at concentrations of 1% and 2% in DMSO and compared to established antibiotics such as Griseofulvin and Penicillin (Tables 4 and 5). It was observed that the inhibition caused by metal chelates exceeds that of the ligand, and the results are in substantial concordance with earlier studies regarding the comparative efficacy of the free ligand and its complexes” [40].

Table 4 Antifungal activity of ligands

Test Compound	**Antigungal growth**							
	Aspergillus niger		***Penicillium chrysogenum***		***Fusarium moneliforme***		***Aspergillus flavus***	
	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)**							
	E. Coli		***Salmonella typhi***		***Staphylococcu saureus***		***Bacillus subtlis***	
	1%	**2%**	**1%**	**2%**	**1%**	**2%**	**1%**	**2%**
L	14mm	18mm	15mm	19mm	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

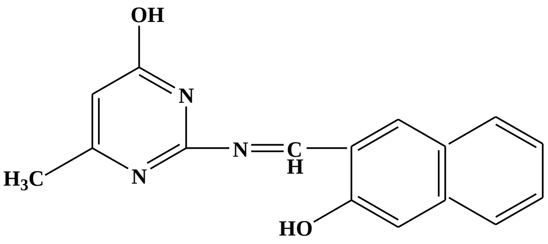

Figure 3. Structure of ligand

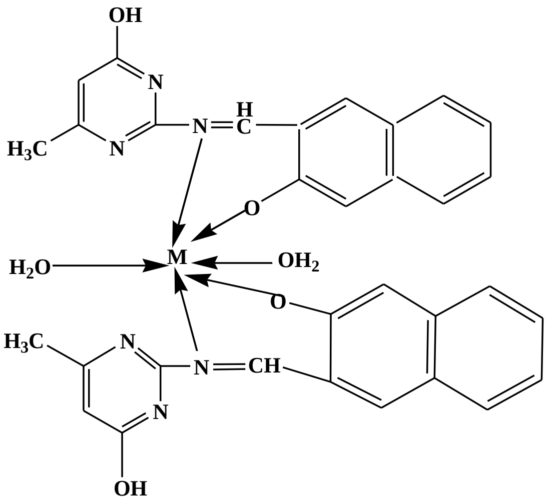

Figure 4. The proposed Structure of the complexes

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

Conclusion

In view of the aforementioned discussion, we have suggested octahedral geometry for Cu(II) and Ni(II) complexes. Based on the physicochemical and spectral data previously discussed, it can be inferred that the ligand exhibits dibasic behavior, not bidentate, coordinating through phenolic oxygen and imino nitrogen as depicted in Fig. 4. The complexes are biologically active and demonstrate improved antimicrobial activities in comparison to the free ligand. Thermal analysis indicates the thermal stability of the complexes. The X-ray analysis implies an orthorhombic crystal system for Cu(II) and Ni(II) complexes.

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Author Contributions:

D.T. Sakhare is the sole author. The author read and approved the final manuscript.

Conflicts of Interest:

The authors declare no conflicts of interest

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