

Research Article

Green Synthesis, Characterization and Biological Evaluation of Divalent Transition Metal Complexes of Substituted Aminopyrimidine Novel Schiff Base Ligand

Dhondiram Tukaram Sakhare* 

UG., PG. & Research Centre, Department of Chemistry, Shivaji, Art's, Comm. & Science College Kannad. Dist. Chhatrapati Sambhajanagar, India

Abstract

The aminopyrimidines so obtained were converted into Schiff bases by treating with different substituted aldehydes, The study of novel heterocyclic Schiff base ligands 3-{[(4,6-dihydroxy pyrimidin-2-yl)Imino]methyl}Naphthalen-2-ol or 2-(((2-hydroxynaphthalen-1-yl)methylene)amino)pyrimidine-4,6-diol derived from 2-amino-4, 6-dihydroxypyrimidine and 2-hydroxy-1-naphthaldehyde (L) were synthesized. These ligands have been used in the synthesis of Cr(II) complexes. The ligand coordinates to the metal ions in the ratio 2L: 1M, through the azomethine N and naphthol O atoms, resulting in N_2O_2 chromophores around the central metal atom. The structures of synthesized compounds were confirmed by physical parameters and spectral studies. The synthesized compounds were characterized using FT-IR, 1H -NMR, UV-Vis techniques for the ligands, Thin layer chromatography (TLC) for all reactions, and molar conductivity and magnetic susceptibility measurements for the corresponding reactions. The general formula of the complexes is $[Cr(L)_2(H_2O)_2]$. The complexes are paramagnetic in nature. Molar conductivity measurements showed that all complexes in (DMSO) are non electrolytes. Octahedral geometry of all complexes. The ligands are bidentate (L) due to the phenolic (OH) nitrogen and the azomethine nitrogen. The ligands and their complexes were examined for antifungal and antibacterial activity against *Aspergillus niger*, *Penicillium chrysogenum*, *Fusarium moneriforme*, and *Aspergillus flavus*, as well as *Escherichia coli*, *Salmonella typhi*, *Staphylococcus aureus*, and *Bacillus subtilis*. The results showed that the complexes have excellent antifungal and antibacterial effects.

Keywords

Schiff Base, 2-Hydroxy-1-Naphthaldehyde, 2-Amino-4,6-Dihydroxypyrimidine, Antibacterial Activity

1. Introduction

In recent years, the Schiff foundation has attracted much attention due to its various activities and enterprises. [1] They are 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) at certain temperature and pH conditions [2]. They were first created by Hugo

Schiff in 1864 and named after him [3]. They consist of imine units ($HC = N-$) with the general formula $RN = CR'R''$ (azomethyl base group), where R, R' and R'' are differently substituted alkyl, aryl, heteroaryl base or cycloalkyl groups, etc. These chemicals are usually called arylenes, imines or methamines. Schiff bases play an important role in many areas of chemistry

*Corresponding author: sakharedhondiram@yahoo.com (Dhondiram Tukaram Sakhare)

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(bioinorganic, biomedicine, supramolecular, catalysis and information, etc.) and can be combined with working groups by selecting appropriate products of amines and aldehydes or ketones. [4-7] Various applications of Schiff bases include corrosion inhibitors, catalyst supports, heat-resistant materials, metal coordination ligands, biological or pharmacological systems. Biologically active Schiff bases have antibacterial, antifungal, antibacterial and free radical scavenging properties, in addition to working as enzyme intermediates or inhibitors. The wide spectrum of biological activity of these compounds is due to their specificity because the azomethine group has a pair of electrons in the sp^2 hybridized orbital of the nitrogen atom. In addition, the electrophilic carbon and nucleophilic nitrogen of the imine bond ($-C=N-$) form compounds that bind well to various nucleophiles and electrophiles, thereby inhibiting bacteria, enzymes, or DNA replication. [8, 9] In general, they have the characteristics of simple technology, strong versatility, and wide range of applications. Therefore, the synthesis of Schiff base compounds, especially heterocyclic compounds, has attracted much attention from chemists in recent years. Heterocyclic compounds are important for the synthesis of Schiff bases due to their many uses in biology, chemistry (inorganic, analytical products and organic chemical intermediates), agricultural chemistry and plant protection. [10-13] It is seen that many physical, chemical and various reactions of heterocyclic compounds prove that heterocyclic compounds are an important part of heterocyclic chemistry. Similarly, heterocyclic Schiff bases have attracted attention due to their many applications. Pyrimidine is an organic heterocyclic compound having a 6-membered unsaturated ring having two nitrogen atoms at positions 1 and 3. It is one of the many synthetic substrates used in chemical synthesis. [14-17] Schiff bases derived from pyrimidines are pharmacologically useful as analgesics, antiepileptic drugs, antibiotics, antihypertensive drugs, minoxidil drugs, antimycobacterial drugs, cancer drugs and antimalarials, and potent phosphodiesterase inhibitors. [18-20] Therefore, researchers want to design and produce pyrimidine-derived Schiff bases using suitable methods of aldehydes or ketones. Molecular docking technology is widely used in modern drug discovery to understand drug-receptor interactions. This method is widely used to predict the binding and orientation of small drugs to their target proteins. [21] Binding can occur in many different ways called binding types. [22] The two main goals of this research are structural design and accurate prediction of drug molecules. [23] Bioinformatics and computational biology tools are used in computer-aided drug design and virtual analysis of large data sets of natural products, simplifying the traditional drug development process. [24, 25]

In this research study, Schiff base ligands derived from 2-amino-4,6-dihydroxypyrimidine and 2-hydroxy-1-naphthaldehyde (L) (Figure 5) and transition metals were synthesized. Furthermore, the structures of the prepared ligands were verified using FT-IR, 1H -NMR and UV-Vis techniques, and the prepared complexes were characterized using FT-IR, UV-Vis, molar conductivity and magnetic susceptibility measurements.

2. Experimental Section

2.1. Materials

Chemicals and reagents used in this study: 2-Hydroxy-1-naphthaldehyde, 2-amino-4,6-dihydroxypyrimidine, $Cr(NO_3)_3 \cdot 9H_2O$ were purchased from Sigma-Aldrich Chemical Company.

2.2. Instrumentation

The IR spectra were recorded on a FTIR (ATR)-BRUKER-TENSOR37 spectrometer using KBr pellets in the range of $4000-400\text{ cm}^{-1}$. 1H NMR (modified mercury 300 MHz) spectra of the ligands were measured in DMSO using TMS as internal standard. X-RD was recorded on a BRUKER D8 Advance. TGA-DTA was recorded on a Shimadzu. Carbon, hydrogen and nitrogen contents were measured on a SHIMADZU Elemental model Vario spectrometer. The molar conductivity of the complexes was measured with an Elico CM 180 conductivity meter using 10^{-4} M solutions in DMSO. Magnetic susceptibility measurements of metal chelates were performed on a Guoy balance at room temperature using $Hg[Co(SCN)_4]$ as a calibration agent.

2.3. Procedures

2.3.1. Synthesis of Schiff Base Ligand (L)

The ligand was prepared by modifying the method described [26]. The Schiff base ligand was prepared by refluxing a mixture of 0.01 mol (1.2015 g) 2-hydroxy-1-naphthaldehyde and 0.01 mol (1.2710 g) 2-amino-4,6-dihydroxypyrimidine in 50 ml of synthetic ultra-dry ethanol for about 4 hours. The Schiff base thus formed was cooled to room temperature, collected by filtration, then recrystallized in ethanol and dried under vacuum over anhydrous calcium chloride (yield: 79%).

2.3.2. Synthesis of Metal Complexes $[M(L)_2]$

The two moles of ligand and one mole of metal nitrate (25 ml) were introduced into a heated ethanol solution (25 ml) while maintaining continuous stirring. The pH of the reaction mixture was adjusted to a range of 7-8 by incorporating a 10% ammonia solution, followed by refluxing for approximately 3 hours. The resulting precipitated metallic complex was filtered while still hot, subsequently washed with hot ethanol, and dried over calcium chloride within a vacuum desiccator. (Yield: 89%) [27]

3. Results and Discussion

The some physical properties of Schiff base ligands and their metal complexes are shown in (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.°C	Colour	Molar Conduc. Mho. $\text{cm}^2\text{mol}^{-1}$
L		281	221	Yellow	---
Cr-L		618	>300	Dark Brown	10.25

Table 2. Elemental Analysis of Cr(II) Complex.

Compound	% Found (Calculated)			
	C	H	N	M
L	51.54 (53.21)	3.57 (3.85)	16.64 (16.89)	----
Cr-L	44.43 (44.35)	3.37 (3.29)	14.17 (14.15)	9.90 (9.88)

3.1. ^1H -NMR Spectra of Ligand

The ^1H NMR spectrum of the loose ligand at room temperature suggests the subsequent signals: 5.08 δ (s, 2H, phenolic (OH) hydrogen of the pyrimidine ring), 6.68 δ (s, 1H, hydrogen connected to the pyrimidine ring), 7.95 δ (s, 1H, hydrogen connected to the azomethine carbon), 7.68-7.29 δ (D, 4H, Aromatic Ha, Hb, protons of the phenyl ring).

3.2. IR Spectra

The infrared spectrum of the unbound ligand depicted in Figures 1 and 2 reveals distinctive peaks at 3430, 1654, 1486, 1209, and 1038 cm^{-1} that relate to the stretching vibrations νOH (intramolecular hydrogen bond), $\nu\text{C}=\text{N}$ (azomethine), $\nu\text{C}=\text{C}$ (aromatic), $\nu\text{C}-\text{N}$ (arylazomethine), and $\nu\text{C}-\text{O}$ (enol) [24]. The lack of faint broad peaks in the 3200-3400 cm^{-1} region in the spectra of the metal complexes signifies the removal of the proton from the intermolecular hydrogen bond OH group during the complex formation, leading to the subsequent bonding of the phenolic oxygen to the metal ion. This

hypothesis is further corroborated by the downward shift of $\nu\text{C}-\text{O}$ (phenol) [28] when compared to the unbound ligand. Following complexation, the $\nu\text{C}=\text{N}$ [29] band experiences a shift to a lower wavenumber compared to the unbound ligand, suggesting that the nitrogen within the azomethine group is coordinated to the metal ion. Additionally, the $\nu\text{C}-\text{N}$ band also shifts to a lower wavenumber relative to the unbound ligand. The IR spectra of the metal chelates exhibit new bands within the ranges of 500-600 cm^{-1} and 400-500 cm^{-1} , which can be attributed to $\nu\text{M}-\text{O}$ and $\text{M}-\text{N}$ vibrations, respectively [30]. The IR spectrum of Ni(II) demonstrates strong bands within the 3060-3600 cm^{-1} range, indicating the presence of coordinated water within these metal complexes. The confirmation of coordinated water is further supported by the emergence of non-ligand bands in the 830-840 cm^{-1} region, corresponding to the rocking mode of water. The existence of coordinated water is also validated by the TG/DTA analysis of these complexes. Thus, it is concluded that the coordination transpires through the phenolic oxygen and azomethine nitrogen of the ligand molecules, as illustrated in Table 3 below.

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

Bond vibrational modes	O-H Free Stretching()	C = N Azomethine Stretching()	C = C Aromatic ring stretching()	C -- N Aryl azomethine stretch ()	C -- O Enolic stretching ()	M--O	M--N
L	3430	1654	1486	1209	1038	--	--
Cr-L	3625.55	1633.23	1351.21	1290.22	1130.31	561.30	451.23

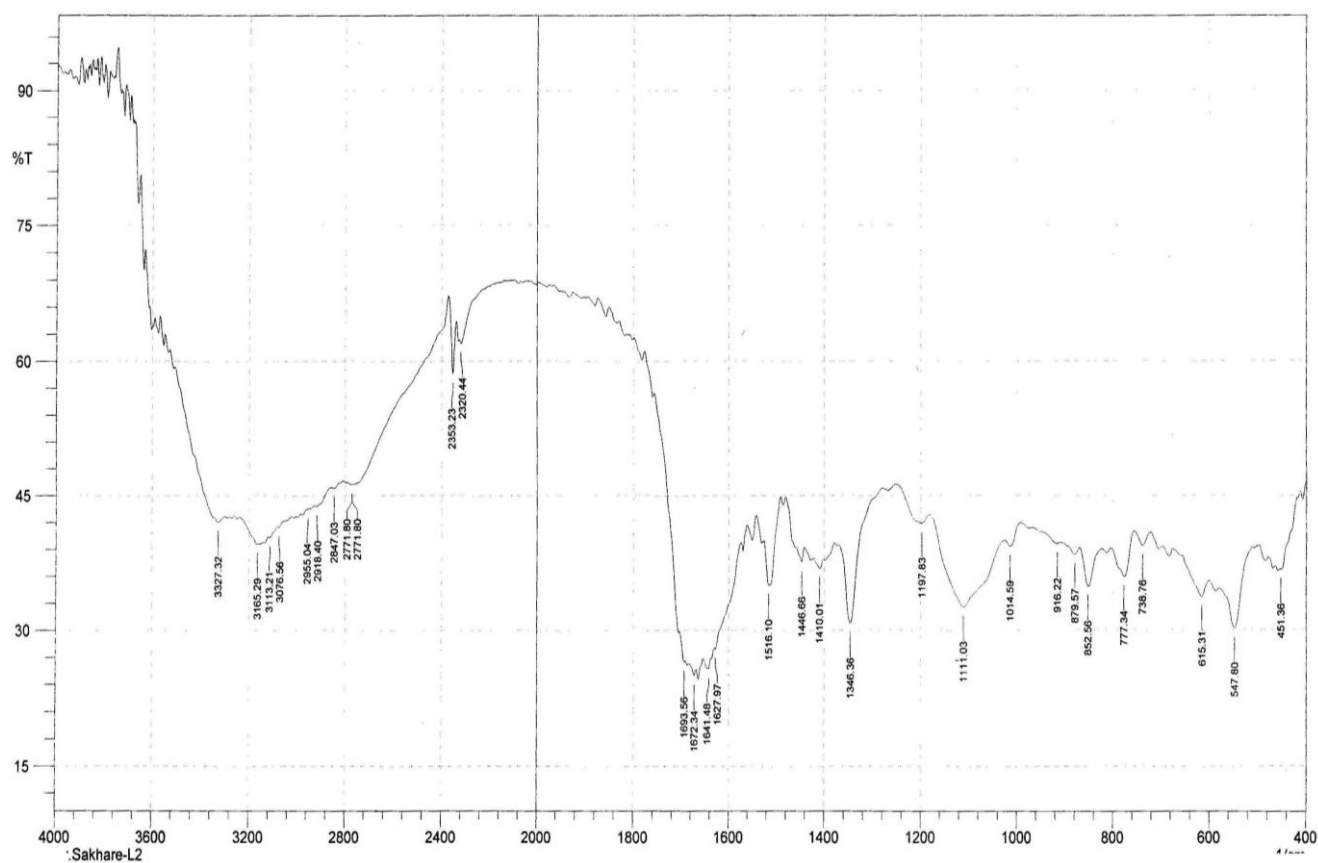


Figure 1. Infrared Spectra of Ligand L.

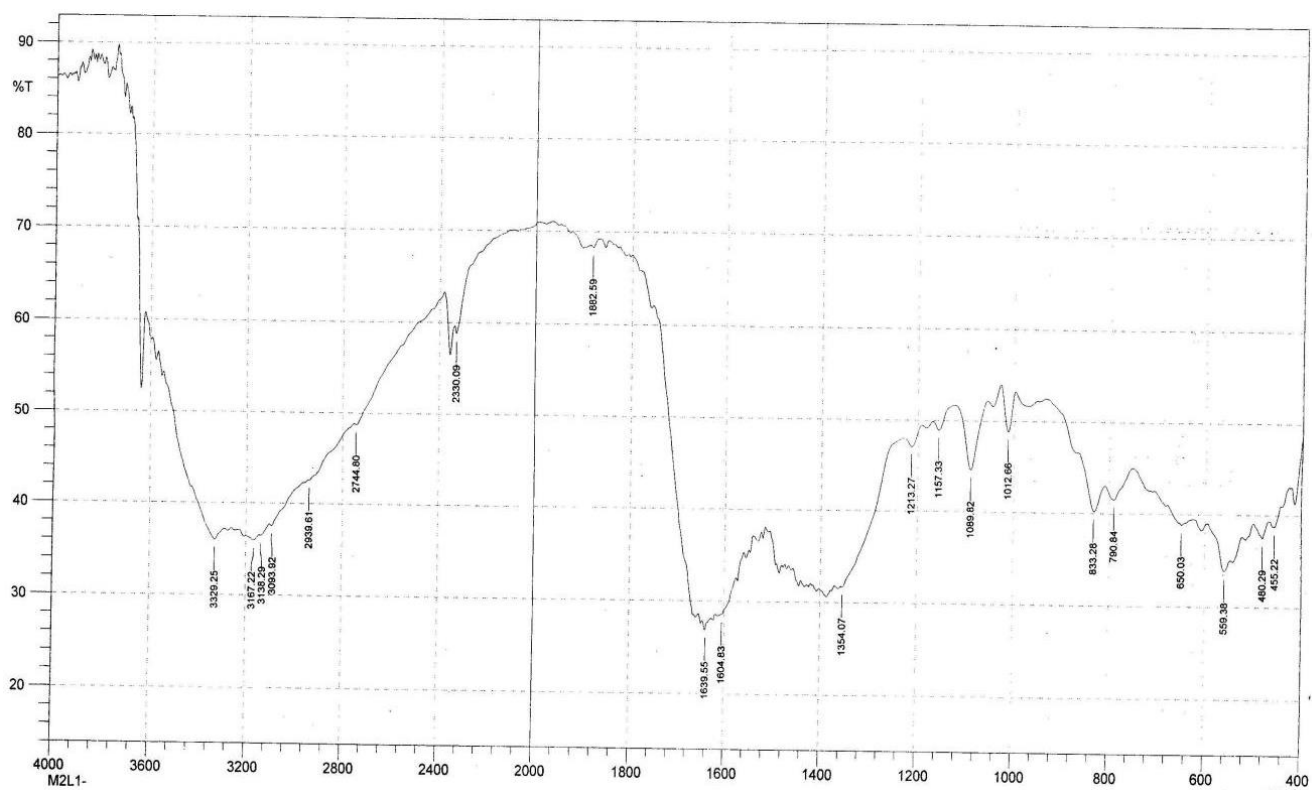


Figure 2. Infrared Spectra of Cr(II) Complex of Ligand L.

3.3. Molar Conductance Measurements

The conductivity assessments of the complexes were performed at a concentration of (10^{-3} M), with the sample solutions maintained at ambient temperature (DMSO). The values of molar conductivity for these complexes are presented in (Table 4). The findings indicate that the Cr(II) complexes of ligand (L) exhibit molar conductivity values ranging from (10.5 - $23.4 \Omega^{-1} \text{ mol}^{-1} \text{ cm}^2$). This infers that the complexes are non-ionic and can therefore be categorized as non-electrolytes [31].

3.4. Magnetic Susceptibility

The magnetic moment values of metal complexes are compiled in (Table 1). These values were determined at ambient temperature. The range of (μ_{eff}) for the complex [Cr(L)] spans from (2.71 to 3.87 B. M). This measurement falls within the typical range expected for octahedral geometry [32].

3.5. Thermogravimetric Analysis

The investigations into the thermal decomposition of the complexes were conducted to validate the insights gained from IR spectroscopy and to ascertain the existence of water molecules within these complexes and their decomposition behavior.

Simultaneous TGA/DTA analysis of Cr(II) was carried out from ambient temperature up to $10,000^\circ\text{C}$ in a nitrogen environment, utilizing $\alpha\text{-Al}_2\text{O}_3$ as a benchmark. The examination of the thermograms for the complexes indicated that the Cr(II) complex (Figure 3) undergoes a two-phase decomposition. The initial mass reduction observed between 55 and 2300°C is 6.68% , potentially linked to the loss of two specific amounts of water (estimated at 6.02%). The anhydrous substance proves to be unstable at elevated temperatures. Between 230 and 650°C , it decomposes swiftly, resulting in a mass loss of 79.73% , related to the second phase of the complex decomposition (estimated at 80.71%). The process concludes with the generation of a stable residue of CrO metal oxide (13.13% calculated; 13.29%). The kinetic and thermodynamic parameters, including activation energy (E_a), frequency factor (Z), entropy variation ($-\Delta S$), and free energy alteration (ΔG) of the non-isothermal breakdown of the h. h. complex, were ascertained using the Horowitz-Metzger method [33]. These values are presented in Table 3. The computed activation energies for the reported complexes are relatively low, suggesting an autocatalytic influence of metal ions on the thermal decomposition of the complexes. Negative activation entropy values indicate that the activated complexes exhibit a higher level of order and reduced reactivity. This increased order might result from bond polarization in the activated state, possibly occurring due to charge transfer transitions [34].

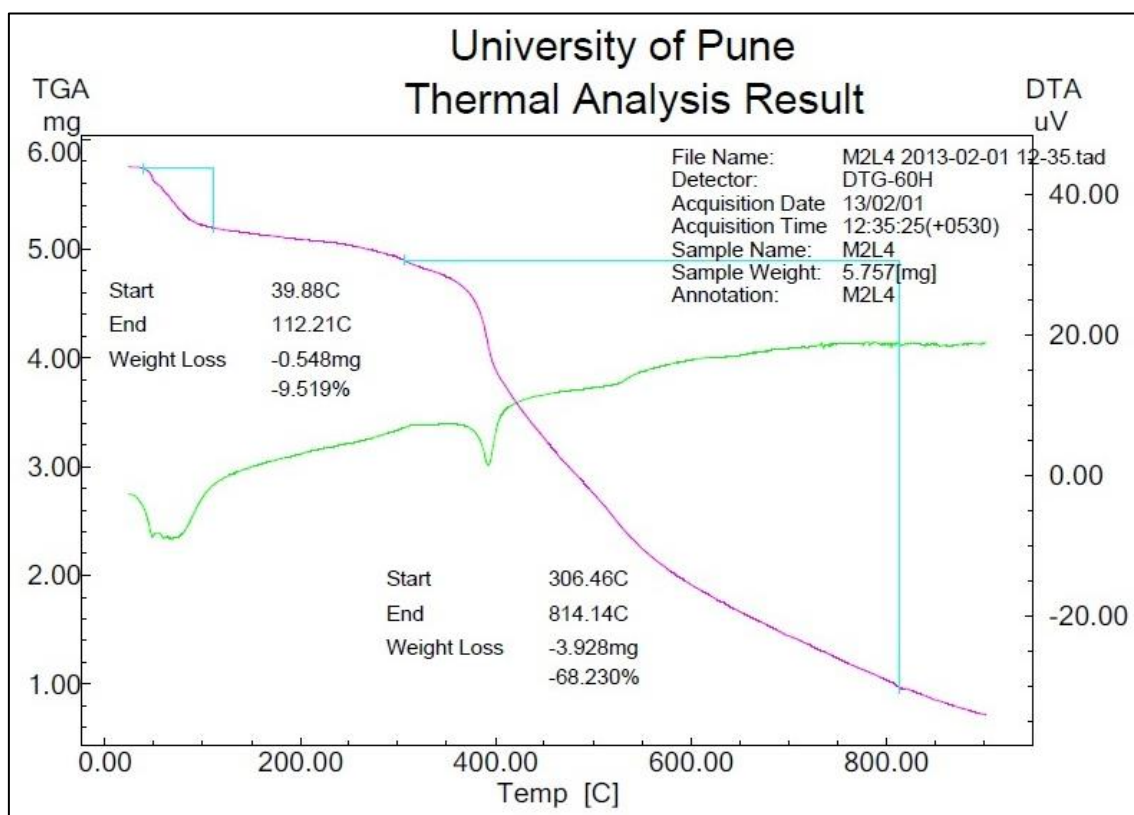


Figure 3. TGA-DTA Curve of Cr(II) Complex of Ligand L.

Table 4. The kinetic and thermodynamic parameters for decomposition of metal complexes.

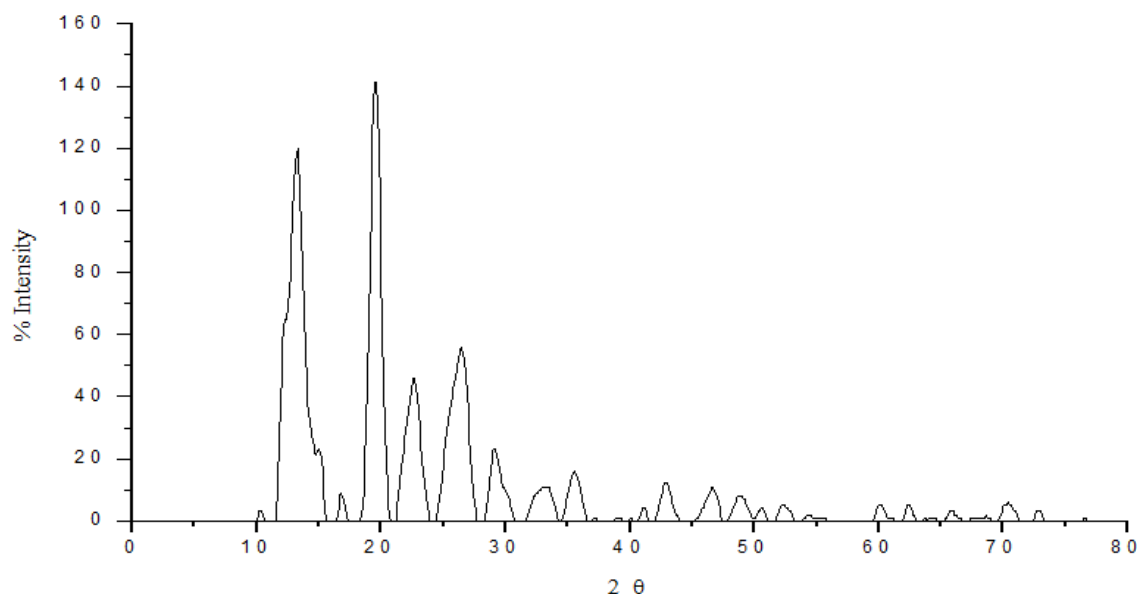
Complex	Step	Decomp. Temp. (°C)	n	E _a (kJmole ⁻¹)	Z (S ⁻¹)	ΔS (JK ⁻¹ mole ⁻¹)	ΔG (kJmole ⁻¹)	Correlation coefficient
Cr-L	I	432	0.9	11.13	1.27 × 10 ⁴	-173.57	26.09	0.970

3.6. Electronic Spectra

The electronic absorption spectrum of the Schiff base ligand (L) reveals absorption peaks at (42560 cm⁻¹ and 27029 cm⁻¹) attributed to the transitions ($\pi \rightarrow \pi^*$) and ($n \rightarrow \pi^*$), correspondingly. The Cr(II) complex displays a peak at

(42558 cm⁻¹) arising from the transition ($\pi \rightarrow \pi^*$). Additionally, the peak at (23257 cm⁻¹) is linked to charge transfer (C. T), while the peak at (14819 cm⁻¹) corresponds to the transition $^3A_{2g} \rightarrow ^3T_{2g}$. This complex is characterized by an octahedral geometry [35].

3.7. X – Ray Diffraction Studies of Metal Complexes

**Figure 4.** X-ray Diffractogram of Cr (II) complex of L.

The Cr(II) coordination compound of ligand L was chosen for a powder X-ray diffraction analysis (Figure 4). The X-ray powder patterns of all principal peaks were indexed separately through a trial-and-error approach. The unit cell parameters, crystal lattice characteristics, and data retrieved post-indexing of the powder patterns are detailed in Table 4. The

Cr(II) coordination compound of ligand L1 exhibits 14 reflections with a peak at $2\theta = 9.77^\circ$, corresponding to a d spacing of 4.54 Å. The unit cell parameters consist of $a = 6.8760$ Å, $b = 9.2456$ Å, $c = 24.234$ Å, $\alpha = \beta = 90^\circ$, $\gamma = 120^\circ$, and the unit cell volume $V = 1334.21763$ (Å)³.

Table 4. Indexed X-ray Diffraction Data of Cr(II) Complex of Ligand L.

Peak No.	2θ (observed)	2θ (calculated)	d (observed)	d (calculated)	Miller indices of Planes			Relative intensities (%)
					h	k	l	
1	6.49527	6.49993	6.80483	6.80464	-1	0	1	100.00
2	11.91296	11.91217	3.73022	3.73185	-1	3	0	2.24

Peak No.	2 θ (observed)	2 θ (calculated)	d (observed)	d (calculated)	Miller indices of Planes			Relative intensities (%)
					h	k	l	
3	16.56698	16.57711	2.7008	2.69991	2	0	4	12.74
4	19.22149	19.22346	2.33924	2.33953	2	2	2	17.75
5	25.96779	25.97817	1.75893	1.75856	-3	5	5	5.76
6	29.5445	29.55077	1.56194	1.56186	4	1	4	8.57
7	31.37724	31.37821	1.47925	1.4794	-1	2	10	4.04
8	35.13069	35.12972	1.33847	1.33865	-6	1	1	2.51
9	36.34332	36.35103	1.29968	1.29958	-6	1	3	2.93

Unit cell data and crystal lattice parameter

a (Å) = 8.766 Volume(V) = 1308.53065 (Å)³

b (Å) = 11.235 Density(obs.) = 1.0789 gcm⁻³

c (Å) = 15.347 Density(cal.) = 1.0677 gcm⁻³

α = 90.00 Z = 3

β = 90.00 Crystal system = Monoclinic

γ = 120.00 Standard deviation (%) = 0.016 Porosity = 1.03%

as *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Bacillus subtilis*, utilizing paper discs and plates. Methods [36]. The substances were assessed at concentrations of 1% and 2% in DMSO and were compared to well-known antibiotics, specifically griseofulvin and penicillin (Tables 5 and 6). Tables 5 and 6 indicate that the inhibition caused by the metal chelates surpasses that of the ligands, which aligns well with earlier studies on the comparable effectiveness of the free ligands and their metal complexes [37, 38]. This enhancement in the efficacy of the metal chelates can be attributed to the heightened lipophilicity of the metal ions within the complexes. The increase in activity observed with higher concentrations is a result of the influence of the metal ions on standard cellular functions. The mechanism of action for these compounds may involve the establishment of hydrogen bonds with active sites on cellular structures, leading to a disruption in normal cellular functions.

4. Biological Activity

4.1. Antibacterial Activity & Antifungal Activity

The antifungal and antibacterial properties of the ligands and their metal complexes were evaluated in vitro against fungi including *Aspergillus niger*, *Penicillium chrysogenum*, *Fusarium moneriforme*, *Aspergillus flavus*, and bacteria such

Table 5. Antifungal activity of ligands.

Test Compound	Antifungal Growth							
	<i>Aspergillus niger</i>		<i>Penicillium chrysogenum</i>		<i>Fusarium moneriforme</i>		<i>Aspergillus flavus</i>	
	1%	2%	1%	2%	1%	2%	1%	2%
L	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
Cr-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)

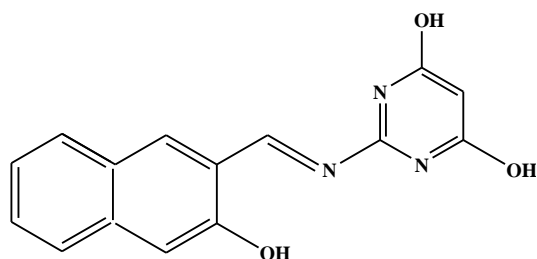
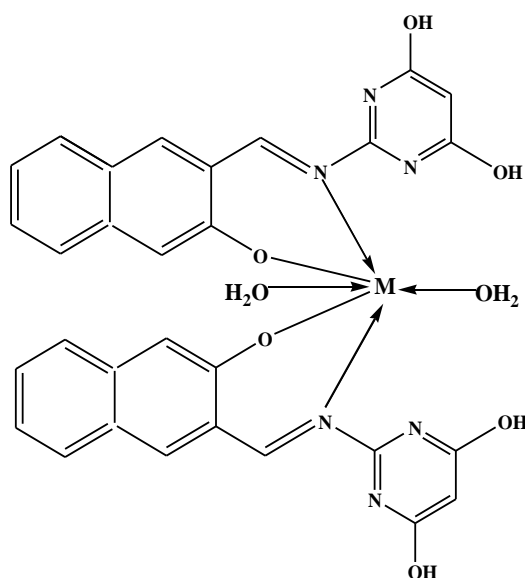
RG - Reduced Growth (More than 50% reduction in growth observed)

Table 6. 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	-ve	16mm	-ve	17mm	-ve	19mm	-ve	21mm
Cr-L	14mm	19mm	14mm	18mm	16mm	21mm	12mm	16mm
DMSO	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
Penicillin	14mm	18mm	18mm	18mm	31mm	31mm	19mm	21mm

Ligand & Metal: -ve - No Antibacterial Activity

Zone of inhibition - --mm

**Figure 5.** Structure of Ligand L.**Figure 6.** The proposed Structure of the Metal complexes. [When M= Cr (II)].

5. Conclusion

In light of the above discussion, we have proposed an oc-

tahedral geometry for the Cr(II) complex. Based on the physicochemical and spectral data discussed above, it can be inferred that the ligand behaves like a dibasic bidentate NO, coordinating through the phenolic oxygen and the imino nitrogen, as shown in (Figure 6). The complex is biologically active and exhibits enhanced antibacterial activity compared to the free ligand. Thermal studies indicate the thermal stability of the complex. X-ray studies suggest a monoclinic crystal system for the Cr(II) complex.

Abbreviations

IR	Infrared Spectra (IR)
FTIR	Fourier-Transform Infrared
TGA	Thermal Gravimetric Analysis
UV-Vis	Ultraviolet Visible Spectroscopy
XRD	X Ray Diffraction
¹ H-NMR	Hydrogen Nuclear Magnetic Resonance
TLC	Thin Layer Chromatography
STIC	Advanced Laboratory Instrumentation Centre
SAIF	Advanced Analytical Instrumentation Facility
CHN	Carbon, Hydrogen, Nitrogen
UG, PG	Under Graduate & Post Graduate Research
D. T.	Dhondiram Tukaram

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sessments.

Author Contributions

Dhondiram Tukaram 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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