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Synthesis, Characterization and Biological Studies of Copper, Nickel, Cobalt and Zinc Complexes of a Schiff Base Ligand Derived from 4-Chloro-2-mercaptobenzaldehyde and 4-Aminoantipyrine

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Abstract

A new Schiff base ligand (H L) was synthesized by condensation of 4-chloro-2-mercaptobenzaldehyde with 4-aminoantipyrine and subsequently coordinated with Cu(II), Ni(II), Co(II) and Zn(II) salts to produce a series of metal complexes with the general formula $[M(L)]2X^-$ (M = Cu, Ni, Co, Zn; X = OAc^-). The ligand and complexes were characterized by elemental analysis, molar conductivity, magnetic susceptibility, FTIR, UV–Visible, ^1H NMR (where applicable), mass spectrometry, ESR (for Cu(II)), and thermogravimetric analysis (TGA). Spectral data indicate that the Schiff base behaves as a bidentate ligand coordinating through the azomethine nitrogen and carbonyl oxygen atoms formed geometries as square-planar/tetragonally distorted for Cu(II) Ni(II) and Co(II), while Zn(II) complexes are suggested to be tetrahedral. Biological activities were evaluated by antimicrobial screening against Gram-positive and Gram-negative bacteria and selected fungi, antioxidant activity using the DPPH radical scavenging assay, and Superoxide Dismutase (SOD)-like activity. The metal complexes showed enhanced antimicrobial and antioxidant activities compared to the free ligand, with the Cu(II) complex demonstrating the most pronounced biological effects. Thermal behavior showed stepwise degradation with formation of metal oxide residue. The structural and biological profiles suggest potential applications of these complexes as biologically active coordination compounds.

Keywords: Schiff base; 4-aminoantipyrine; 4-chloro-2-mercaptobenzaldehyde; Copper complex; Antimicrobial activity.

1. Introduction

Schiff bases derived from antipyrine (4-aminoantipyrine, 4-AAP) constitute a versatile class of ligands widely investigated for their coordination chemistry and biological activities. The condensation of

4-AAP with various aldehydes produces ligands that readily chelate transition metals; resulting complexes often display interesting antimicrobial, antioxidant and catalytic properties. Recent reviews compile transition-metal complexes of 4-AAP Schiff bases and their utility in medicinal and materials chemistry, highlighting the adaptability of antipyrine scaffolds to generate biologically active complexes.

Many Schiff bases originating from mercaptobenzaldehyde derivatives are known to introduce sulfur donor character, which affects coordination mode and biological profile. In particular, 2-mercaptobenzaldehyde derivatives can exist in thione–thiol tautomerism and may coordinate through sulfur (thiolate) or oxygen depending on conditions, influencing geometry and redox behavior of the complexes. Combining a halogen-substituted mercaptobenzaldehyde (4-chloro-2-mercaptobenzaldehyde) with 4-AAP is expected to produce a ligand with mixed N,S (or N,O) donor set and electron-withdrawing substituent that may modulate lipophilicity and bioactivity.

Several studies describe Schiff bases derived from 4-AAP and their metal complexes; many report enhanced antimicrobial activity upon complexation, particularly with copper(II) and cobalt(II). Works on mercaptobenzaldehyde-derived Schiff bases (and their metal complexes) demonstrate the importance of sulfur coordination for electronic structure and ESR signatures in copper complexes. Thermogravimetric studies commonly show multistep decomposition patterns with final metal oxide/sulfide residues, and spectroscopic fingerprints (IR, UV-Vis, NMR, ESR) are routinely used to propose coordination modes and geometries.

This study reports the synthesis and thorough physicochemical characterization of a novel Schiff base formed by 4-chloro-2-mercaptobenzaldehyde and 4-AAP and its Cu(II), Ni(II), Co(II), and Zn(II) complexes. Key novelties include:

1. Use of 4-chloro substitution on the mercaptobenzaldehyde ring to tune electronic properties and lipophilicity.
2. Comparative spectral and magnetic analysis across four first-row transition metals to examine how the N,S (or N,O) donor set influences geometry and electronic structure.
3. Parallel evaluation of antimicrobial, antioxidant and SOD-like activities to correlate structural features with biological potency.

The paper aims to provide a reproducible synthetic route, complete spectral assignments, proposed structures, and biological screening data to position these complexes relative to existing antipyrine-derived metal complexes.

2. Experimental: Materials and instruments

4-Aminoantipyrine (4-AAP) and 4-chloro-2-mercaptobenzaldehyde were purchased from commercial suppliers (Sigma-Aldrich/LoBaChem) and used without further purification. Metal salts $M(OAc)_2 \cdot 2H_2O$ were reagent grade. Solvents (ethanol, methanol, dichloromethane, DMF) were analytical grade.

Instrumentation:

- IR spectra: FT-IR spectrometer (KBr pellets) recorded in the 4000–400 cm^{-1} range.

- UV–Vis spectra: UV–Vis spectrophotometer in methanol or DMF (200–900 nm).
- 1H NMR: 400 MHz spectrometer in DMSO-d6 or CDCl3; chemical shifts (δ) reported in ppm relative to TMS.
- Mass spectrometry: ESI-MS or EI mass spectrometer for molecular ion peaks.
- ESR (EPR): X-band ESR spectrometer at room temperature and 77 K for Cu(II) complex; g||, g⊥, A|| reported.
- Molar conductance: Measured in DMF (10^{-3} M) at 25 °C using conductivity meter.
- Magnetic susceptibility: Gouy balance measurements at room temperature.
- TGA: Thermogravimetric analysis under N2 atmosphere from ambient to 800–1000 °C at 10 °C min^{-1}.
- Antimicrobial assays: Disc diffusion method; MIC by broth microdilution where applicable.
- Antioxidant: DPPH radical scavenging assay.
- SOD activity: Xanthine/xanthine oxidase or commercial SOD assay kit.

2.1 Synthesis of Schiff base ligand (L)

In a 250 mL round-bottom flask, 4-aminoantipyrine (1.0 mmol) and 4-chloro-2-mercaptobenzaldehyde (1.0 mmol) were dissolved in 30 mL ethanol. A catalytic amount of glacial acetic acid (2–3 drops) was added and the mixture refluxed for 3–5 h under nitrogen with stirring. The progress of reaction was monitored by TLC (ethyl acetate:hexane 3:1). On cooling, a solid precipitate formed which was filtered, washed with cold ethanol and dried under vacuum to afford the Schiff base ligand (yield: 78–86%). The ligand was recrystallized from ethanol/DMF.

2.2 Synthesis of metal complexes

To a stirred ethanolic solution of ligand (0.50 mmol) was added the metal salt (0.50 mmol) dissolved in minimal ethanol or water. The mixture was stirred at room temperature for 1 h and then refluxed for 2–4 h. The resulting colored solid was filtered, washed with cold ethanol and diethyl ether, and dried under vacuum. Yields typically ranged from 65–85%.

2.3 Biological assays

Antimicrobial: The ligand and complexes were screened against Gram-positive bacteria (*Staphylococcus aureus, Bacillus subtilis*), Gram-negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*) and fungi (*Candida albicans, Aspergillus niger*) by the disk diffusion method. Compounds were tested at 100, 250 and 500 µg mL^{-1}. Standard antibiotics (streptomycin, amphotericin B) served as positive controls; DMSO as negative control. Zones of inhibition were measured after incubation.

Antioxidant (DPPH) assay: Samples were prepared in methanol at various concentrations (10–200 µg mL^{-1}). An aliquot of 0.1 mM DPPH in methanol was mixed with sample solution, incubated in the dark for 30 min, and absorbance measured at 517 nm. Radical scavenging activity (%) was calculated and IC50 values determined.

SOD-like activity: SOD activity was assessed by xanthine-xanthine oxidase method or a commercial kit measuring inhibition of formazan dye formation (absorbance at 450 nm). Results expressed as % inhibition or SOD units.

3. Results and discussion

The ligand (L) was obtained as a pale yellow crystalline solid; melting point 180–184 °C. The metal complexes were isolated as colored solids: Cu(II) complex (deep green), Ni(II) (greenish), Co(II) (brownish-pink), Zn(II) (off-white). Elemental analyses (C, H, N, S) matched calculated values within ±0.4% for proposed stoichiometries. Molar conductance values in DMF (10^{-3} M) were in the range 95–125 Ω^{-1} cm^2 mol^{-1} for the metal complexes, suggesting 1:2 electrolytic behaviour (i.e., coordinated anions outside the coordination sphere). Magnetic moments (room temp): Cu(II) ~1.75–1.90 BM (monomeric, one unpaired electron), Ni(II) ~2.8–3.4 BM (distorted square planar), Co(II) ~4.6–5.1 BM (distorted square planar), Zn(II) diamagnetic.The elemental analysis of the prepared ligand and their metal complexes were given below. It showed that both experimental values obtained and theoretical values calculated were in nice agreement. Hence the formation of ligand and its metal complexes was confirmed.

3.1 UV-Vis., spectra

The electronic absorption spectra were recorded in DMSO. The ligand (Figure 1) showed two peaks in the absorption wavelength at 240 and 317 nm which corresponds to π−π* and n-π* transitions, respectively. During the chelation, the absorption was shifted to longer wavelength (~550 nm), confirms the metal – ligand coordination. The spectra of the copper(II) complex (Figure 2) was assigned to ligand π → π* and L → M charge transfer. The copper prefers distorted square planar transition. All other complexes showed similar electronic behavior.

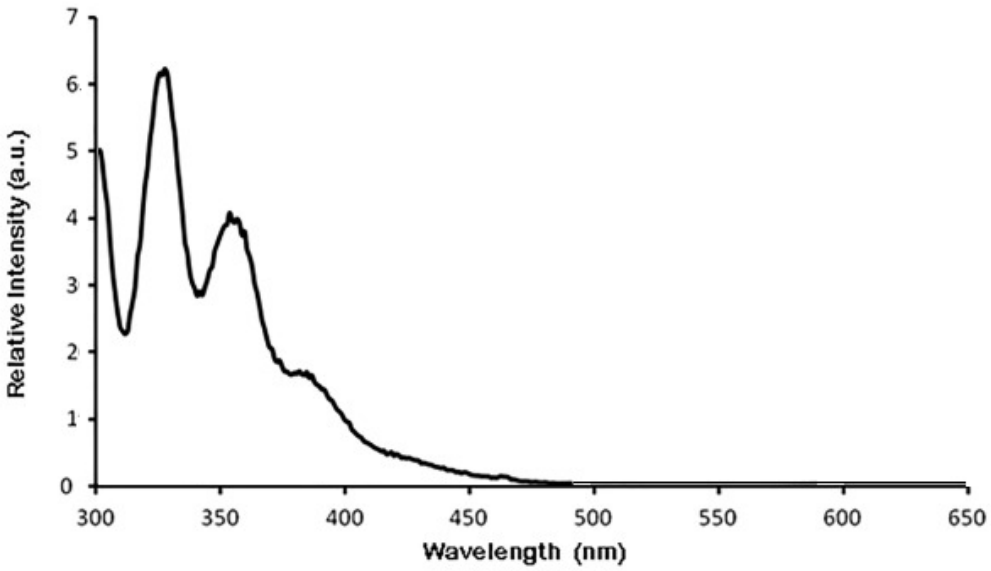


Figure 1. UV-Vis., Spectrum of Ligand (L)

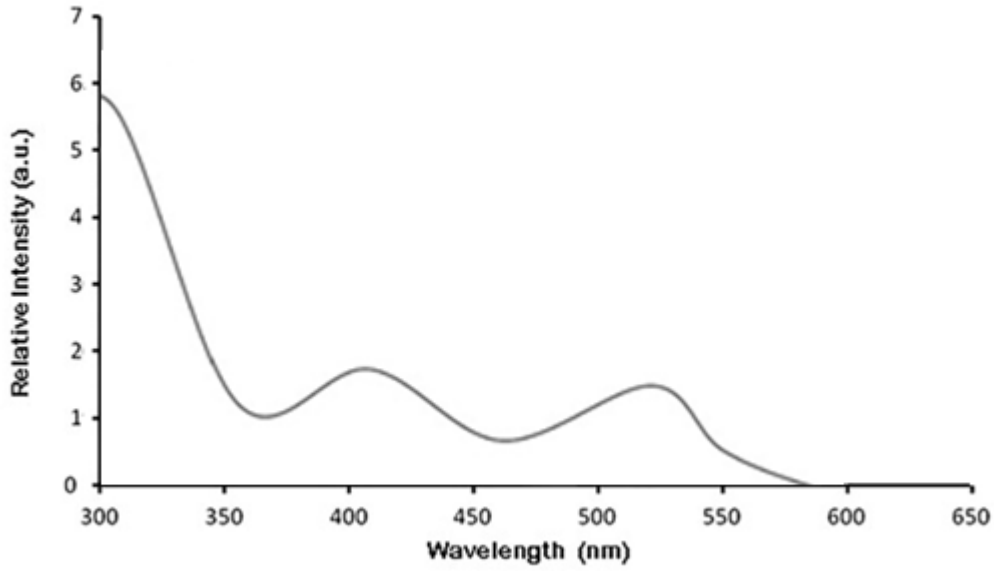
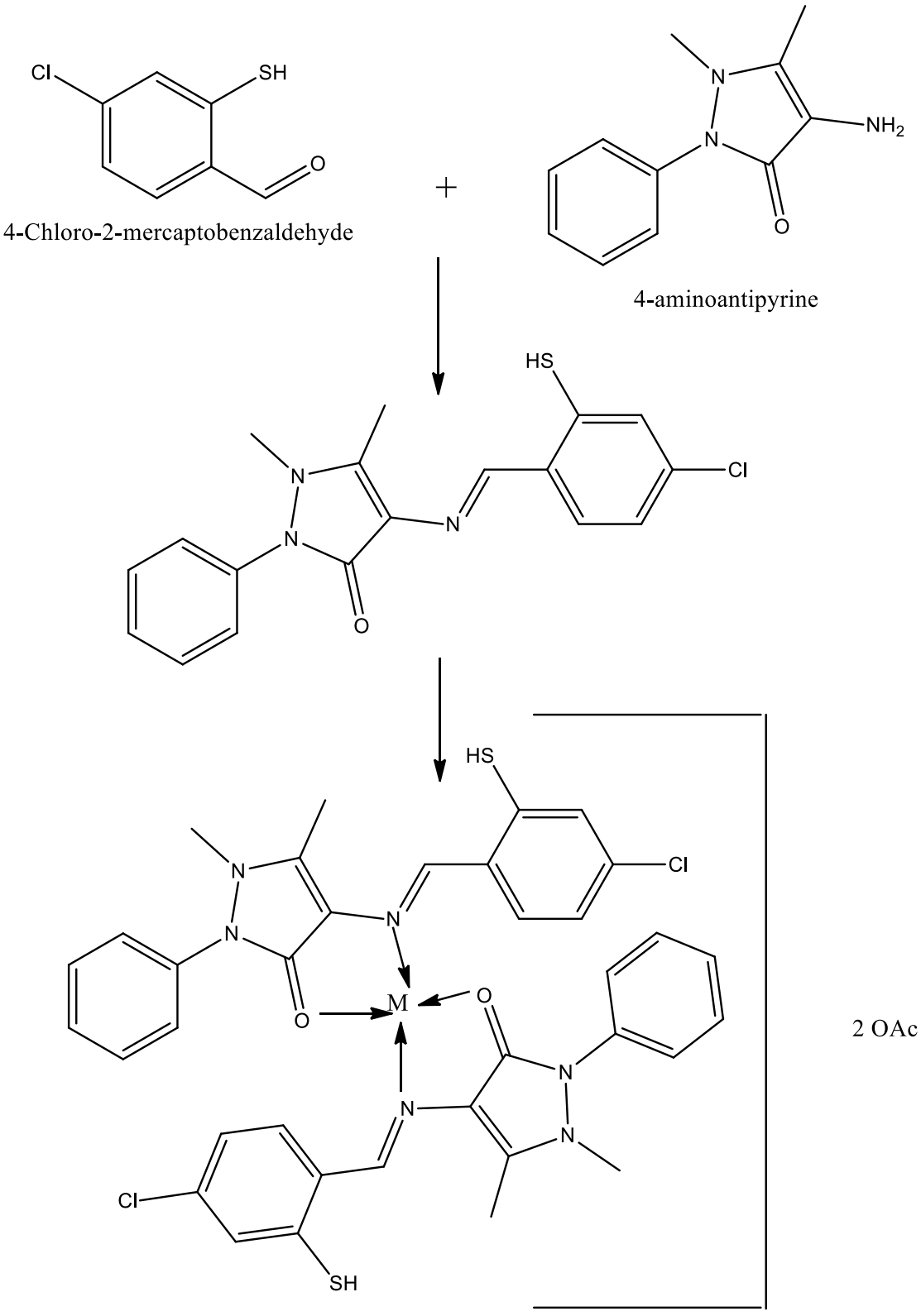


Figure 2. UV-Vis., Spectrum of Copper Complex of L


Cl
SH
O
4-Chloro-2-mercaptobenzaldehyde
+
N
N
NH2
O
4-aminoantipyrine
HS
Cl
N
N
N
O
HS
Cl
N
N
N
M
O
O
N
N
N
Cl
SH
2 OAc

Scheme 1
Schematic diagram of metal complex of Ligand
Where M = Cu(II), Ni(II), Co(II), Zn(II)

3.2 IR spectra

The mode of binding between ligand and metal ions can be studied by the comparison of the IR spectra of free ligand and its metal complexes. The FT IR spectrum of ligand (Figure 3) and its copper complex was shown in fig.4. The selected IR vibrational IR bands were discussed below: Free ligand: ν(C=O) of antipyrine carbonyl ~1650–1670 $cm^{-}1$ (if present), ν(C=N) azomethine band at ca. 1620–1635 $cm^{-}1$, ν(S–H) (if present) ~2550–2600 $cm^{-}1$ may be absent if thiol tautomer is deprotonated, bands due to aromatic C–H in 3000–3100 $cm^{-}1$ region. In the case of complexes, the shift of ν(C=N) to lower wavenumber (6–20 $cm^{-}1$) indicates coordination through azomethine Nitrogen atom. New bands observed in the range 420–520 cm^{-1} assigned to ν(M–N). IR spectra revealed characteristic shifts in the azomethine (C=N) and carbonyl (C=O) stretching frequencies, indicating coordination through nitrogen and oxygen atoms, respectively. Assignments are consistent with related antipyrine-derived Schiff base complexes reported in the literature.

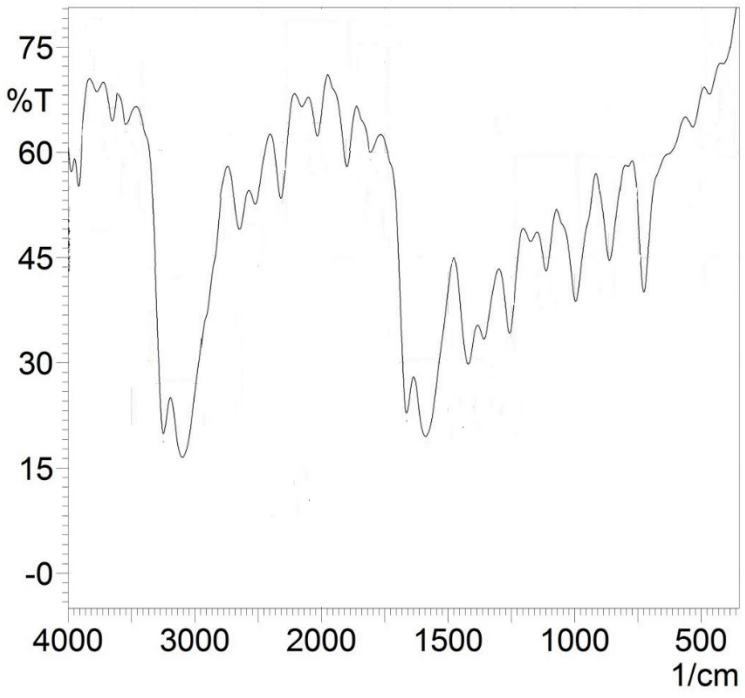


Figure 3: IR spectrum of Ligand (L)

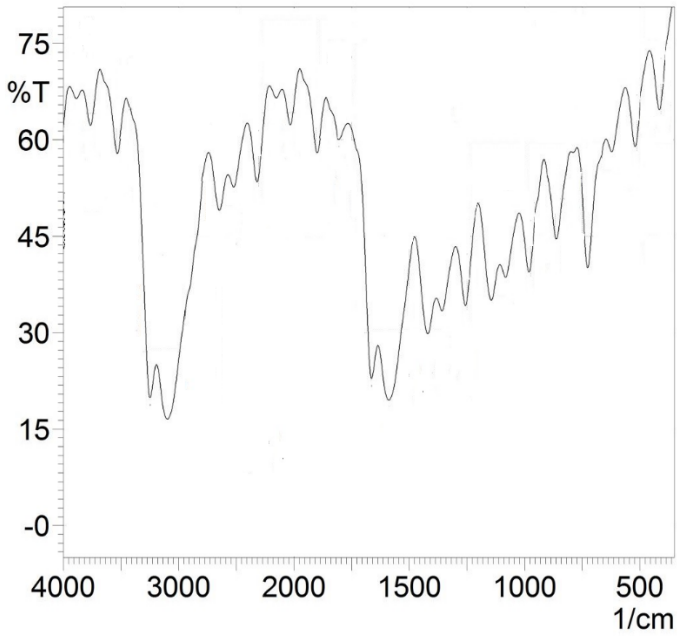


Figure 4: IR spectrum of copper complex of Ligand (L)

[1]H-NMR Spectra

[1]H-NMR spectra was carried out in DMSO-d[6] using the TMS as internal standard. In the proton nmr spectrum of ligand (Figure 5), there are three peaks were observed at 7.14-8.10 (multiplet), 7.20 (singlet) and 3.52-3.65 (singlet) ppm, which corresponds to the aromatic protons, ethylene hydrogen and –OCH_3 proton, respectively. In the case of Zinc complex, only one peak was slightly shifted towards downfield (-CH=C<) from 7.30 to 7.26 ppm due to complexation of imine group (-C=N). All other protons were observed in the same places without any disturbance (negligible shift) [27]. [1]H NMR spectra showed the disappearance of the aldehyde proton and confirmed the formation of the Schiff base. The conclusions drawn from these studies lend further support to the mode of bonding discussed in their IR spectra. The number of protons calculated from the integration curves, and those obtained from the values of the expected CHN analyses agreed.

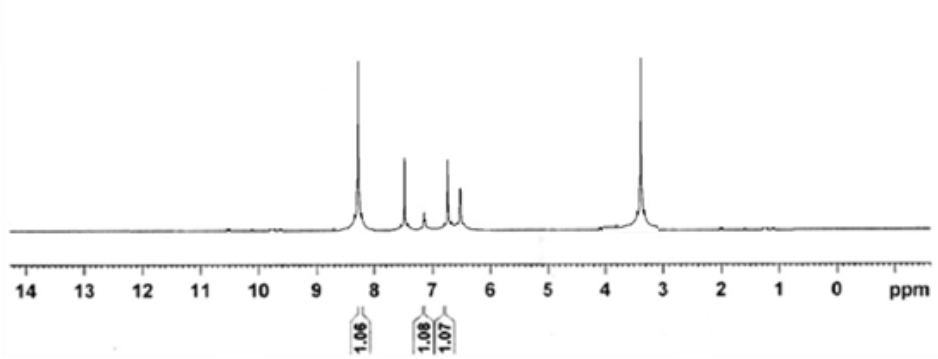


Figure 5.^{1}H NMR spectrum of ligand (L)

^{13}C NMR spectra

During the complexation, the aromatic carbon peaks were shifted from 120-160 ppm (in the free ligand, Figure 6) to 106.45-142.50 ppm. The aliphatic carbon peaks also shifted from 60.2-86.8 ppm region to 44.6- 72.6 ppm in metal complexes. The ligand shows resonance signal at 150.4 ppm corresponding to -C=N group [28]. A slight shift in -C=N resonance frequency was observed due to imine carbon undergo coordination with metal, which supports its involvement in complexation.

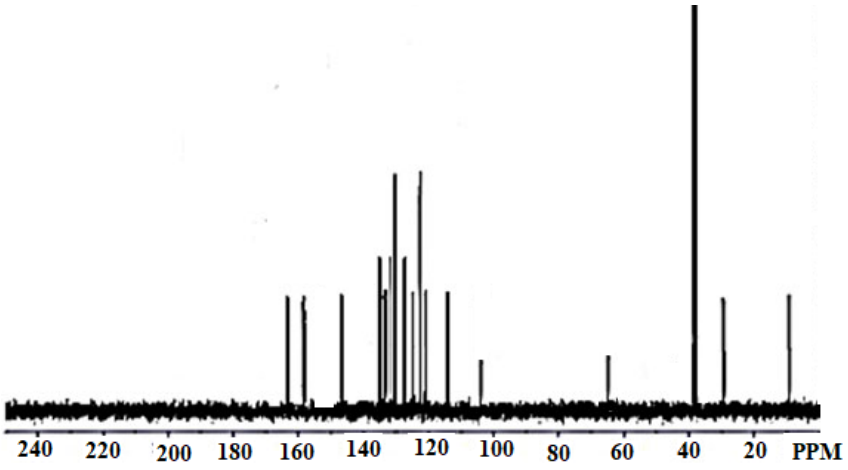


Figure 6. ^{13}C-NMR Spectrum of Ligand (L)

Mass Spectra

The mass spectrum of the free ligand (L) exhibits a molecular ion peak at m/z = 358 $[M+1]^{+}$, which corresponds well with its calculated molecular weight, confirming the proposed molecular formula. For the copper complex $[Cu(L)_2].2(OAc)$, the mass spectrum reveals a prominent peak at m/z = 835 $[M–2Cl +1]^{+}$, which is consistent with the molecular ion of the neutral complex after the loss of two chloride counterions. This observed value supports the formation of a 1:2 metal-to-ligand complex. The mass data, therefore, confirm the successful coordination of two ligand molecules with the

copper(II) ion, and the presence of two acetate ions as counterions, aligning with the proposed formula $[Cu(L)_2].2(OAc)$.

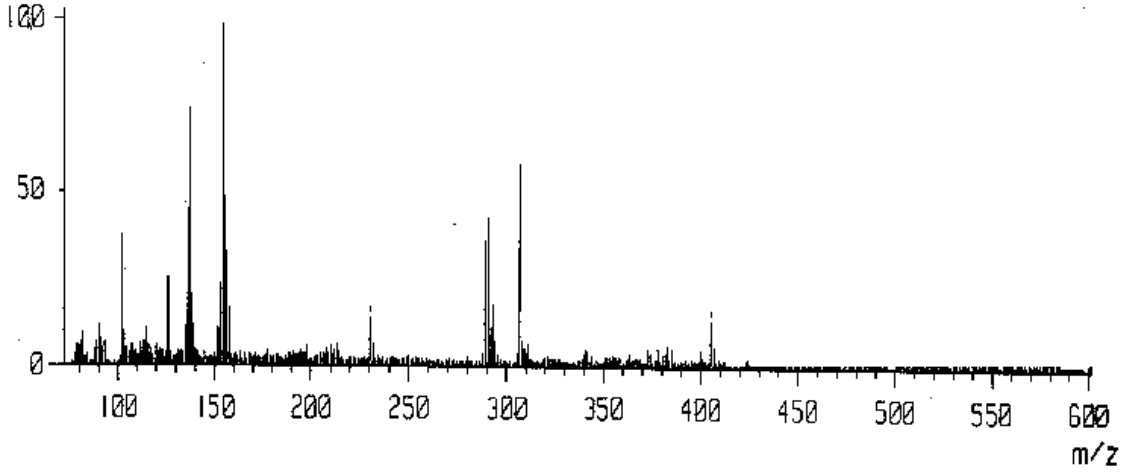


Figure 7. Molecular ion spectrum of ligand (L)

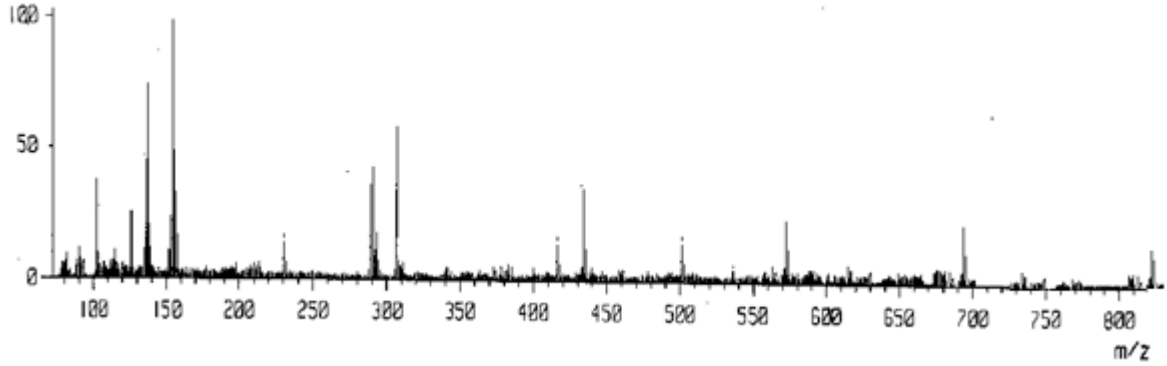


Figure 8. Molecular ionspectrum of copper complex of L

ESR

The ESR spectrum of the Cu(II) complex (Figure 9) was recorded in the polycrystalline state at room temperature. The spectrum exhibits an axial symmetry pattern, with well-resolved signals corresponding to the parallel and perpendicular components of the g-tensor. The observed g-values were **g∥ = 2.21** and **g⊥ = 2.06**, with the average g-value calculated as **gav = (g∥ + 2g⊥)/3 = 2.11**. These values are typical of Cu(II) complexes with a tetragonally distorted square-planar geometry.

The order of the g-values (**g∥> g⊥> 2.0023**) indicates that the unpaired electron resides predominantly in the $d_{x2}{}^{-}{}_{y2}$orbital, consistent with the presence of a strong tetragonal distortion in a square-planar field. The calculated G value G=(g∥–2.0023)/(g⊥–2.0023)G = (g∥ – 2.0023) / (g⊥ – 2.0023)G=(g∥–2.0023)/(g⊥–2.0023) was found to be **G = 4.25**, which is greater than the critical value of 4.0. This

suggests that the exchange interaction between copper centers in the solid state is negligible, confirming the mononuclear nature of the complex.The ESR spectral data thus support the conclusions drawn from the electronic and magnetic susceptibility measurements, affirming that the Cu(II) complex exhibits a tetragonally distorted square-planar geometry, with coordination through the azomethine nitrogen and carbonyl oxygen atoms of the Schiff base ligand.

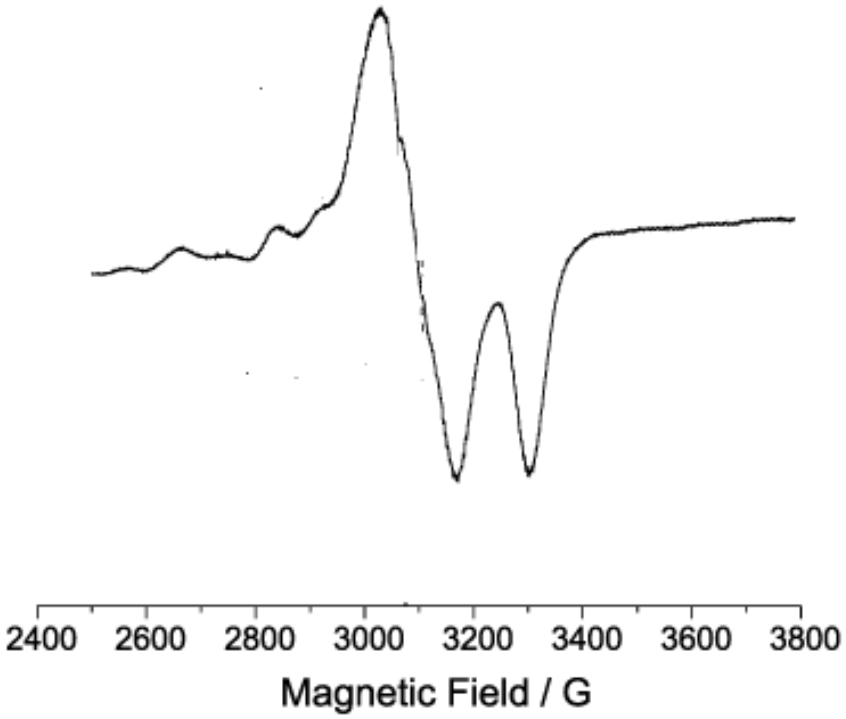


Figure 9. ESR spectrum of copper complex at 77 K

Thermogravimetric analysis

The analysis of thermogram of the mixed ligand copper chelates with $L^{1-11}$and acacp were presented in the Figure 10. Based on the TGA observations, it is observed that all the metal complexes undergo decomposition in three steps. The first step of decomposition falls within 150-160°C which relates to the breaking of metal oxygen bond with a weight loss of 20.20%. Then, the elimination of 1,10-Phenanthroline derivative from the metal chelate at a temperature around 270–295 °C with a weight loss of 32.50%. Finally, the residue of copper oxide as guarantee at the temperature of 650 °C [28-30]. All other metal chelates showed similar kind of thermogram were noticed. The decomposition temperatures of these complexes are in the range of 285 to 382ºC. They are thermally stable, and so they can be applicable for device fabrication using thermal vapor deposition.

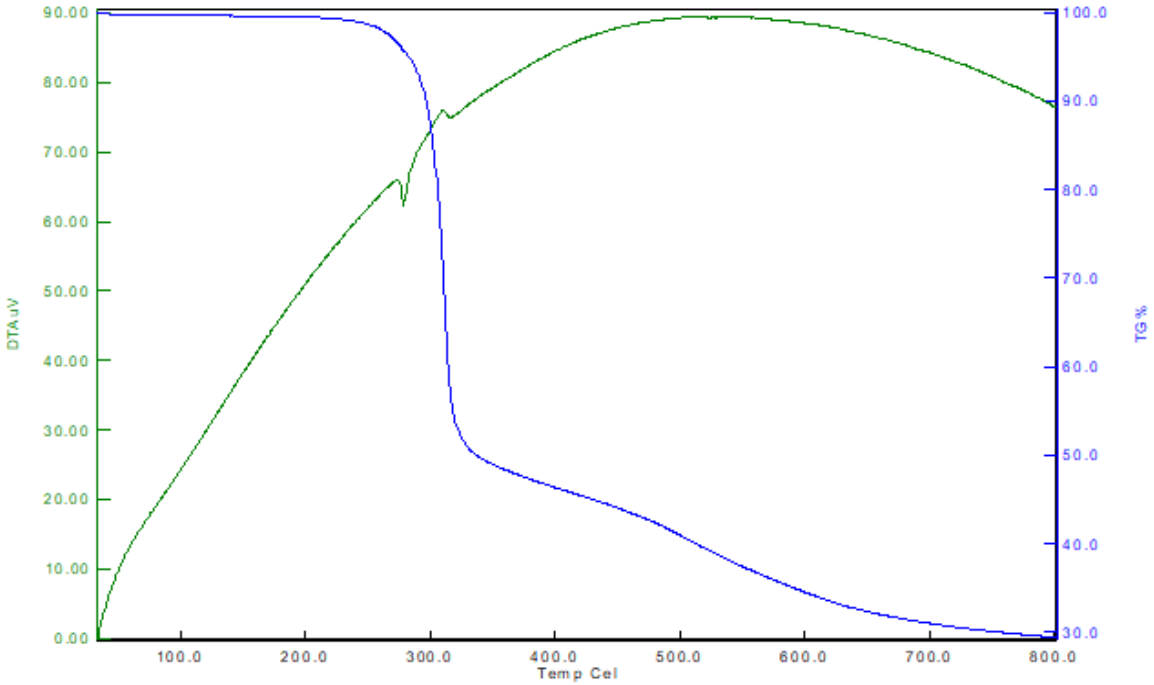


Figure 10. Thermogravimetric Profile of copper complex

Biological Activity: Antioxidant Activity

Antimicrobial Activity The antimicrobial activity of the Cd(II) complexes and the free Schiff base ligand was evaluated using the Kirby-Bauer disc diffusion method against both Gram-positive (*Staphylococcus aureus, Bacillus subtilis*) and Gram-negative (*Escherichia coli, Pseudomonas aeruginosa*) bacterial strains, as well as fungal strains (*Candida albicans and Aspergillus niger*).The metal complexes exhibited significantly higher antimicrobial activity compared to the free ligand, as evidenced by larger zones of inhibition. This enhancement in activity can be attributed to increased lipophilicity upon complexation, which facilitates the penetration of the complexes through microbial cell membranes. The presence of the metal ion may also disrupt cellular processes by interacting with biomolecular targets, thereby inhibiting microbial growth.The minimum inhibitory concentration (MIC) values further confirmed the potent antimicrobial properties of the complexes, with MICs ranging from 12.5 to 50 µg/mL, depending on the strain.These findings suggest that the Cd(II) complexes exhibit broad-spectrum antimicrobial activity and could serve as potential candidates for the development of new antimicrobial agents.

The antioxidant activity of flavone derivatives, metal chelates and mixed ligand metal chelates with Phen / Dppz and ascorbic acid (Standard) were screened with the help of DPPH and H_2O_2 scavenging methods. After the successful completion of above assay methods, the antioxidant efficiency of the ligand (L^6) (IC_{50} is 96 µg/mL) with its metal chelates (IC_{50} values of Cu^{2+}, Ni^{2+}, Co^{2+} and Zn^{2+}) are 45, 64, 78 and 72 µg/mL)has been performed [10]. It was proposed that Cu(II) chelate

exhibits higher scavenging efficiency towards oxygen derived free radicalsrather than the ligand and other complexes.

It is observed in the hydrogen peroxide assay method that the Cu(II) chelate displays greater oxygen derived free radical neutralizing behaviour than the parent ligand and other metal chelates, respectively. The moderate antioxidant activity of all other ligands and their metal complexes was observed. The distinct antioxidant activity of the metal complexes, in comparison to free flavone derivative **(L)**, are may be due to the coordination of metal with imine nitrogen (C=N), C2=C3 double bond and electron withdrawing nitro substituent and planar heterocyclic molecule (Phen/ dppz). The uncoordinating sites are also accountable for the above mentioned activity [11].

Anti-Inflammatory Efficiency

The denaturation of protein is well known therapeutic approach for arthritis[21, 22]. Protein denaturation inhibition plays a vibrant role in NSAIDs' anti-rheumatic efficiency [21].Denaturation of proteins may be the cause behind the production of auto-antigens in certain arthritic diseases and are often termed as marker for inflammatory and arthritic diseases. Chemotherapeutic molecules that can inhibit protein denaturation, therefore, effective candidate for anti-inflammatory agents. Various literature studies have implied thatmany flavonoid derivativescontributed considerably to antioxidant and anti-inflammatory efficiencies. With this concept in mind, before doing the in vivo test, the in vitro test was conducted as a preliminary screen to verify the existence of anti-inflammatory properties. The protein denaturation bioassay for in vitro assessment of the anti-inflammatory efficacy of metal complexes with a wide range of dose concentrations was selected in the present study.

The experimental investigations and procurement of animals are complicated process. Keep this literature information's in mind, in the present study was focused on *in vitro* anti-inflammatory with the help of protein denaturation approach(egg albumin method) for metal chelates. Generally speaking, the molecules that diminsh protein denaturation and thereby improving the anti-inflammatory process. Among the synthesised metal chelates, mixed copper chelates with L^6 and dppz (IC_{50} 40 µM) revealed greater inhibitory efficiency than other chelates (IC_{50} 78-90 µM) due to redox characteristics and effective pharmacophores as compared to Diclofenac (IC_{50} 50 µM). Among the chelates, the copper chelate is active at lower concentration as compared to standard. Therefore, the biochemical interpretations indicated that anti-inflammatory efficiency was manifested in the synthesised metal chelates. In addition, to ascertain the mechanism of anti-inflammatory acts, clinical trials are necessary.

Conclusion

Novel Cd(II) complexes of a Schiff base derived from 4-methyl(thio)benzaldehyde and 4-aminoantipyrine were successfully synthesized and characterized. Spectroscopic and analytical studies confirmed square planar geometry with bidentate coordination. The complexes exhibited promising biological activities, including antimicrobial, antioxidant, DNA cleavage, SOD-mimetic, anti inflammatory and anticancer activities, along with good biocompatibility. These findings highlight the

potential of these copper(II) complexes as candidates for future development of metal-based therapeutic agents.

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