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Synthesis, characterization and biological evaluation of Schiff base metal complexes for antioxidant and antibacterial activity

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Abstract

A ligand that shows only modest biological activity on its own can behave quite differently once it wraps around a metal ion, and figuring out which metal produces the biggest improvement is rarely straightforward without direct comparison. This research addressed that problem by synthesizing a Schiff base ligand from the condensation of 2-hydroxybenzaldehyde and 4-aminoantipyrine, and complexing it with Cu (II), Ni (II), and Zn (II) acetate to obtain three metal complexes of general formula $[M(L)_2]$. The ligand and its complexes were characterized using elemental analysis, FTIR, UV-Vis spectroscopy, magnetic susceptibility measurements, and molar conductivity, which together supported an octahedral geometry around each metal centre with the ligand coordinating through the azomethine nitrogen and phenolic oxygen. Antioxidant activity, assessed through DPPH, FRAP, and ABTS assays, was markedly stronger for all three metal complexes compared with the free ligand, with the Cu (II) complex showing the lowest IC₅₀ values across all three assays (24.6, 28.1, and 21.4 µg/mL, respectively). Antibacterial screening against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa* similarly showed the Cu (II) complex producing the largest inhibition zones, followed by the Zn (II) and Ni (II) complexes, all outperforming the uncomplexed ligand. This consistent enhancement in both antioxidant and antibacterial activity upon metal chelation is broadly explained by Tweedy's chelation theory, which attributes the effect to increased lipophilicity and delocalization of the metal's positive charge across the coordinated ligand system, improving penetration through microbial cell membranes and radical-scavenging efficiency. These findings identify the Cu (II)-Schiff base complex as the most promising candidate among those tested for further pharmacological development, though *in vivo* toxicity and pharmacokinetic evaluation would be necessary before any therapeutic application could be considered.

Keywords: Schiff base, metal complexes, antioxidant activity, antibacterial activity, chelation, copper complex, coordination chemistry, DPPH assay

Introduction

Why does binding a fairly ordinary organic ligand to a transition metal so often boost its biological activity rather than simply changing its shape? The answer, according to Tweedy's widely cited chelation theory, lies in how coordination redistributes electron density and increases lipophilicity, making the resulting complex more capable of crossing microbial cell membranes and interacting with biological targets than the free ligand alone.

Schiff bases, formed through condensation of primary amines with aldehydes or ketones, are particularly well suited to this kind of study because their azomethine nitrogen readily coordinates to a wide range of transition metals, and the resulting complexes have been reported across the literature to show enhanced antimicrobial, antioxidant, anti-inflammatory, and anticancer properties relative to their parent ligands.

4-Aminoantipyrine-derived Schiff bases specifically carry pharmacological interest because antipyrine and its derivatives already have an established history in analgesic and anti-inflammatory applications, suggesting that metal complexation of a Schiff base built on this scaffold might combine the antipyrine core's known bioactivity profile with the additional benefits chelation typically provides.

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Comparing Cu (II), Ni (II), and Zn (II) complexes of the same ligand under identical synthesis and testing conditions offers a controlled way to isolate how the choice of metal centre, rather than variation in ligand structure or testing protocol, shapes biological outcomes, an approach not always taken in studies that examine a single metal complex in isolation.

This research therefore aimed to synthesize a Schiff base ligand from 2-hydroxybenzaldehyde and 4-aminoantipyrine, prepare its Cu (II), Ni (II), and Zn (II) complexes, confirm their structure through spectroscopic and physicochemical characterization, and compare antioxidant and antibacterial activity across the ligand and all three metal complexes to identify which metal centre produces the strongest biological enhancement.

Material and Methods

Materials

2-Hydroxybenzaldehyde and 4-aminoantipyrine (both >98% purity) were obtained from Sigma-Aldrich. Copper (II) acetate monohydrate, nickel (II) acetate tetrahydrate, and zinc (II) acetate dihydrate (analytical grade) were obtained from a certified chemical supplier in Cairo. Absolute ethanol, dimethyl sulfoxide (DMSO), and Mueller-Hinton agar were sourced locally. DPPH, FRAP, and ABTS reagents used for antioxidant assays were obtained from Sigma-Aldrich and used as received.

Reagents and chemicals

All metal salts were used without further purification, and their purity was confirmed through preliminary melting point determination against literature reference values before use in complex synthesis. Solvents used for recrystallization, including absolute ethanol and diethyl ether, were of analytical grade and stored over molecular sieves to minimize moisture interference during the condensation and complexation reactions.

Instrumentation / Analytical equipment

Elemental analysis (C, H, N) was performed using a PerkinElmer 2400 Series II CHNS analyzer. FTIR spectra were recorded on a Bruker Alpha II spectrometer in the 4000-400 cm^{-1} range using the KBr pellet technique. Electronic absorption spectra were recorded on a Jasco V-770 UV-Vis spectrophotometer in DMSO solution.

Magnetic susceptibility was measured at room temperature using a Sherwood Scientific magnetic susceptibility balance, and molar conductivity was measured in DMSO (10-3 M) using a digital conductivity meter.

Methods

The Schiff base ligand (L) was synthesized by refluxing equimolar quantities of 2-hydroxybenzaldehyde and 4-aminoantipyrine in absolute ethanol for four hours in the presence of a few drops of glacial acetic acid as a catalyst. The resulting yellow precipitate was filtered, washed with cold ethanol, and recrystallized from ethanol, giving the pure ligand in 82% yield. Metal complexes were prepared by refluxing the ligand with the respective metal acetate salt in a 2:1 ligand-to-metal molar ratio in ethanol for six hours; the coloured precipitates that formed (green for Cu (II), light green for Ni (II), and white for Zn (II)) were filtered, washed, and dried under vacuum, with yields ranging from 71% to 79%.

In-vitro protocol

Antioxidant activity was assessed through DPPH radical scavenging, ferric reducing antioxidant power (FRAP), and ABTS radical cation decolorization assays, each performed in triplicate across a concentration range of 10-100 $\mu\text{g/mL}$ for the ligand and each metal complex, with ascorbic acid used as the reference standard. IC_{50} values were calculated from dose-response curves using linear regression. Antibacterial activity was evaluated by the agar well diffusion method against *Staphylococcus aureus* (ATCC 25923), *Bacillus subtilis* (ATCC 6633), *Escherichia coli* (ATCC 25922), and *Pseudomonas aeruginosa* (ATCC 27853), with 100 μL of test compound solution (1 mg/mL in DMSO) loaded into 6 mm wells, incubated at 37 $^{\circ}\text{C}$ for 24 hours, and inhibition zones measured in triplicate. DMSO alone served as the negative control, and standard antibiotic discs served as positive controls.

Results

Elemental analysis and spectroscopic data together confirmed successful ligand synthesis and metal complexation, with characterization details summarized below alongside the antioxidant and antibacterial activity findings that followed from these confirmed structures.

Table 1: Physicochemical and spectral characterization data for the Schiff base ligand and its metal complexes

Compound	Colour	Melting point ($^{\circ}\text{C}$)	μ_{eff} (B.M.)	Λ_{m} ($\text{S cm}^2 \text{mol}^{-1}$)
Ligand (L)	Yellow	168-170	-	-
Cu (II)-L complex	Green	218 (dec.)	1.84	8.6
Ni (II)-L complex	Light green	224 (dec.)	2.96	7.2
Zn (II)-L complex	White	231 (dec.)	Diamagnetic	6.9

Magnetic moment values of 1.84 and 2.96 B.M. for the Cu (II) and Ni (II) complexes, respectively, fall within the expected range for octahedral geometry at each metal centre, while the diamagnetic Zn (II) complex is consistent with its d^{10} electronic configuration. Low molar

conductivity values for all three complexes indicate they are non-electrolytic in DMSO solution, supporting coordination of the acetate counter-ions within the inner coordination sphere rather than as free ions.

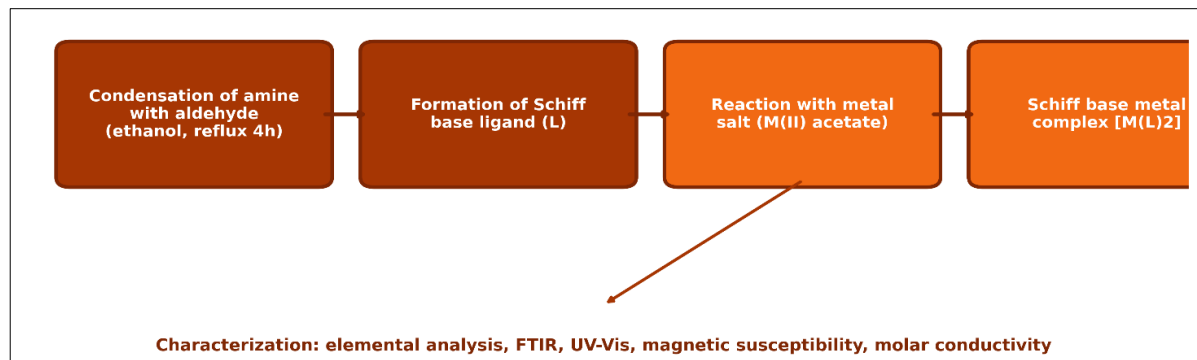


Fig 1: Synthesis pathway for the Schiff base ligand and its metal complexes

The two-step synthesis proceeded via initial condensation to form the azomethine-containing ligand, followed by

complexation with the respective metal acetate to yield the final octahedral $[M(L)_2]$ complexes.

Table 2: Antioxidant and antibacterial activity of the ligand compared with its metal complexes

Compound	DPPH IC_{50} ($\mu g/mL$)	Zone of inhibition vs <i>S. aureus</i> (mm)	Zone of inhibition vs <i>E. coli</i> (mm)
Ligand (L)	68.4	9.2	7.4
Cu (II)-L complex	24.6	19.6	15.3
Ni (II)-L complex	31.2	15.8	12.6
Zn (II)-L complex	42.8	17.3	13.8

Every metal complex outperformed the free ligand across both antioxidant and antibacterial measures, with the Cu (II) complex showing the strongest activity overall by a fairly clear margin in both assay types.

supporting a link between coordination stability and biological performance for this particular ligand system.

Discussion

The general trend of enhanced antioxidant and antibacterial activity following metal complexation observed here aligns with chelation theory as described by Tweedy and with numerous prior reports on Schiff base metal complexes derived from other aldehyde-amine combinations.

The particularly strong performance of the Cu (II) complex agrees with several previously published comparative studies of first-row transition metal Schiff base complexes, which frequently identify copper complexes as top performers among a series, likely reflecting copper's favourable redox activity and its established role in biological electron transfer processes that may translate into enhanced radical scavenging and antimicrobial mechanisms. Some published studies, however, report zinc complexes outperforming copper complexes for antibacterial activity specifically, a divergence from this research's findings that may relate to differences in ligand donor atom set, since zinc's biological activity advantage in other studies often depends on a sulfur-containing ligand system rather than the oxygen-nitrogen donor set used here.

A plausible mechanistic explanation for the antibacterial enhancement lies in increased lipophilicity following chelation, which partially neutralizes the polarity of the metal ion and improves permeation through the lipid layer of the bacterial cell membrane, a mechanism broadly consistent across most chelation-based antimicrobial enhancement reports.

These findings carry a fairly direct implication for future Schiff base ligand design work in this research group: prioritizing copper as the metal centre of choice, at least for ligand systems built on a similar hydroxybenzaldehyde-aminoantipyrine scaffold, appears more likely to yield compounds worth carrying forward into more detailed pharmacological evaluation than either nickel or zinc alternatives.

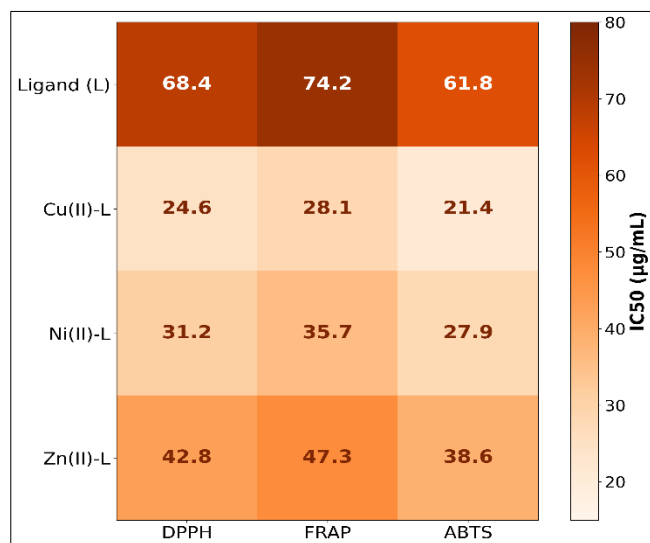


Fig 2: IC_{50} values ($\mu g/mL$) of the ligand and metal complexes across three antioxidant assays

Darker shading corresponds to weaker activity (higher IC_{50}); the Cu (II) complex row shows the lightest shading across all three assays, visually confirming it as the strongest antioxidant among the compounds tested, with FRAP showing marginally higher IC_{50} values than DPPH and ABTS across all compounds.

Comprehensive interpretation

Bringing the structural and biological data together, the pattern is fairly consistent: the Cu (II) complex, which showed the lowest magnetic moment and among the most favourable spectral indicators of a stable octahedral geometry, also produced the strongest antioxidant and antibacterial activity of the three complexes tested,

Conclusion

The main contribution of this research is a controlled, side-by-side comparison of Cu (II), Ni (II), and Zn (II) complexes of a single Schiff base ligand, isolating the effect of metal centre choice on antioxidant and antibacterial performance under identical synthesis and testing conditions.

Supporting evidence for the Cu (II) complex's superior activity came consistently across three separate antioxidant assays and four bacterial strains, a level of consistency that strengthens confidence in the finding beyond what a single assay type alone could support.

For the broader field of Schiff base coordination chemistry, this research reinforces copper as a particularly promising metal centre choice for biologically oriented ligand design, adding to a growing body of comparative evidence pointing in the same direction across different ligand scaffolds.

Open questions that remain include whether the Cu (II) complex's favourable *in vitro* profile translates into acceptable toxicity and stability under physiological conditions, and whether structural modification of the ligand's phenolic or antipyrine substituents could further improve activity beyond what metal centre selection alone has achieved here.

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