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Synthesis, Characterization and Veterinary Therapeutic Potential of Copper(II) Complexes of Bioactive Heterocyclic Ligands

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Abstract
Copper plays a crucial role in animal physiology due to its redox activity and involvement in enzymatic defense mechanisms. In this study, novel Copper(II) complexes of heterocyclic ligands were synthesized and evaluated for their antimicrobial and antioxidant potential relevant to veterinary applications. The complexes were characterized by UV–Visible, FTIR, ESR, PXRD, TGA-DTA, and elemental analysis. Spectral data suggested octahedral geometry around Cu(II) ions. The synthesized complexes demonstrated enhanced antibacterial and antifungal activity compared to free ligands against common veterinary pathogens, including *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans*. The Cu(II) complexes exhibited superior free radical scavenging ability due to redox cycling between Cu(II)/Cu(I). These findings highlight the potential application of copper complexes as alternative therapeutic agents in livestock disease management.

Keywords: Copper complexes, Veterinary antimicrobial agents, Heterocyclic ligands, Antioxidant activity, Livestock pathogens

Introduction

Infectious diseases continue to represent a major challenge in veterinary medicine, causing substantial economic losses in livestock production and compromising animal welfare worldwide. Conditions such as mastitis, enteric infections, respiratory diseases, and dermatological disorders are frequently associated with bacterial and fungal pathogens that have increasingly developed resistance to conventional antibiotics. The rapid emergence of antimicrobial resistance (AMR) has been identified as a critical global health threat affecting both human and animal populations (World Health Organization, 2020; O'Neill, 2016). In veterinary practice, the extensive prophylactic and therapeutic use of antibiotics in food-producing animals has accelerated resistance development, thereby necessitating alternative therapeutic strategies with novel mechanisms of action and reduced resistance potential.

Transition metal complexes have emerged as promising candidates in the search for alternative antimicrobial agents. Among them, copper-based compounds are of particular importance due to copper's essential biological role in animals. Copper functions as a vital cofactor in numerous metalloenzymes, including superoxide dismutase, cytochrome c oxidase, ceruloplasmin, and lysyl oxidase, which are involved in oxidative stress regulation, cellular respiration, connective tissue formation, and immune defense (Gaetke & Chow, 2003; Tapiero et al., 2003). Unlike traditional organic antibiotics that often act on a single molecular target, copper complexes exert antimicrobial effects through multiple pathways, including disruption of cell membranes, protein oxidation, nucleic acid interaction, and generation of reactive oxygen species (ROS). This multifaceted mode of action reduces the likelihood of rapid resistance development (Lemire et al., 2013; Djoko et al., 2015).

Among nitrogen-containing chelating ligands, 1,10-phenanthroline and its derivatives have attracted considerable attention due to their strong bidentate coordination ability and intrinsic biological activity. The rigid planar aromatic structure of 1,10-phenanthroline enables efficient chelation with Cu(II) ions through two nitrogen donor atoms, forming highly stable complexes. Furthermore, the extended π-conjugated system facilitates intercalation into microbial DNA, thereby enhancing antimicrobial and cytotoxic activity (Sigman et al., 1993; Kellett et al., 2019). Chelation with copper increases the lipophilicity of the ligand, improving membrane permeability and intracellular accumulation, as explained by Tweedy's chelation theory (Tweedy, 1964). This increased lipophilicity enhances biological efficacy compared to the free ligand.

Copper(II)–1,10-phenanthroline complexes are also known for their redox properties. The Cu(II)/Cu(I) redox couple enables catalytic generation of hydroxyl radicals via Fenton-like reactions in the presence of biological reductants. These ROS induce oxidative damage to bacterial DNA, proteins, and lipid membranes, leading to microbial cell death (Halliwell & Gutteridge, 2015). Importantly, coordination with phenanthroline derivatives modulates copper's redox potential, allowing controlled reactivity and potentially reducing nonspecific toxicity in animal systems. Structural modifications of the phenanthroline ring through electron-donating or electron-withdrawing substituents can further influence complex stability, redox behavior, and biological performance, enabling optimization through structure–activity relationship approaches.

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In veterinary medicine, copper supplementation has long been used to improve growth performance and immune response in livestock. However, inorganic copper salts often exhibit limited bioavailability and may contribute to environmental accumulation. Structurally defined copper–phenanthroline complexes offer improved stability, enhanced bioavailability, and targeted antimicrobial action. Recent investigations have demonstrated significant activity of copper–phenanthroline derivatives against veterinary pathogens such as *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*, organisms commonly implicated in mastitis, wound infections, and systemic diseases in animals (Kellett et al., 2019; Frei et al., 2020). Additionally, their antioxidant properties may mitigate oxidative stress associated with inflammatory conditions in livestock.

Despite these promising attributes, comprehensive studies focusing on substituted 1,10-phenanthroline copper complexes with specific relevance to veterinary pathogens remain limited. Therefore, the present study aims to synthesize and characterize Copper(II) complexes containing substituted 1,10-phenanthroline derivatives and to evaluate their antimicrobial and antioxidant potential for veterinary therapeutic applications. This work contributes to the development of metal-based alternatives to conventional antibiotics for sustainable and effective livestock disease management.

2. Experimental: Materials and Methods

All reagents and solvents were of analytical grade and used without further purification. Copper(II) chloride dihydrate ($CuCl_2 \cdot 2H_2O$) and 1,10-phenanthroline monohydrate were purchased from Sigma-Aldrich. Substituted 1,10-phenanthroline derivatives were synthesized according to modified literature procedures involving electrophilic substitution or condensation reactions depending on the substituent pattern (Kellett et al., 2019). Solvents such as ethanol, methanol, dimethyl sulfoxide (DMSO), and acetonitrile were purified and dried using standard methods prior to use.

2.1 Synthesis of Copper(II) Complexes

Copper(II) complexes were synthesized via a conventional reflux method. An ethanolic solution (25 mL) containing the substituted 1,10-phenanthroline ligand (2 mmol) was prepared and stirred magnetically at room temperature. To this solution, an ethanolic solution (20 mL) of $CuCl_2 \cdot 2H_2O$ (1 mmol) was added dropwise under continuous stirring. The reaction mixture was refluxed at 70–80°C for 3–4 h. The color of the solution gradually changed to deep green/blue, indicating complex formation. The mixture was allowed to cool to room temperature and left undisturbed for slow evaporation. The resulting precipitate was filtered, washed with cold ethanol and diethyl ether to remove unreacted ligand, and dried under vacuum over anhydrous calcium chloride. The complexes were obtained in good yield (65–80%) and were stable under ambient conditions. The formation of Cu(II)–phenanthroline complexes was characterized using analytical and spectroscopic techniques.

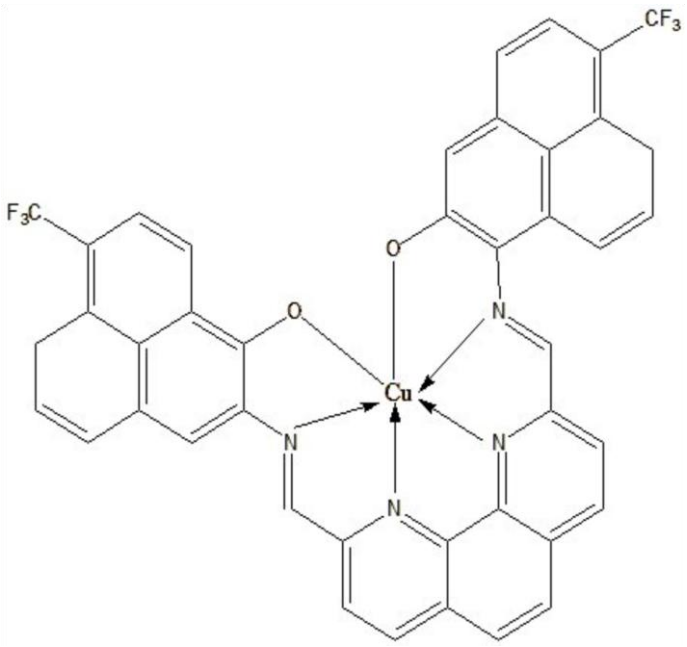

Figure 1. Structure of Copper complex

2.2 Physicochemical Characterization

Elemental analyses (C, H, N) were performed using a CHN analyzer to confirm stoichiometry. Molar conductance measurements were carried out in DMSO (10^{-3} M) at room temperature using a digital conductivity meter to determine the electrolytic nature of the complexes (Geary, 1971). Magnetic susceptibility measurements were recorded at room

temperature using a Gouy balance, and magnetic moment values were calculated to confirm the paramagnetic nature of Cu(II) complexes.

FTIR spectra were recorded in the range 4000–400 cm^{-1} using KBr pellet technique. Coordination of the ligand to the Cu(II) center was confirmed by the shift of the azomethine (C=N) stretching frequency and the appearance of new bands in the 500–450 cm^{-1} region attributable to Cu–N vibrations (Nakamoto, 2009). UV–Visible spectra were recorded in DMSO within 200–900 nm using a double-beam spectrophotometer. The d–d transition bands observed in the visible region were used to assign geometry around the Cu(II) ion. ESR spectra were recorded at room temperature, and g-values ($g\parallel$ and $g\perp$) were calculated to confirm axial symmetry and distorted octahedral geometry (Hathaway, 1987).

Thermogravimetric analysis (TGA) was performed under nitrogen atmosphere from room temperature to 800°C at a heating rate of 10°C/min to evaluate thermal stability and decomposition pattern. The final residue was compared with calculated values for CuO formation.

2.3 Determination of DNA Binding Ability (Optional Biological Mechanism Study)

The DNA binding ability of selected copper complexes was evaluated using UV–Visible absorption titration with calf thymus DNA in Tris-HCl buffer (pH 7.2). Incremental addition of DNA to a fixed concentration of complex resulted in hypochromism and bathochromic shifts, indicating intercalative binding mode (Wolfe et al., 1987). Binding constants (Kb) were calculated using the Benesi–Hildebrand equation.

2.4 In Vitro Antimicrobial Assay

The antimicrobial activity of the synthesized complexes was evaluated using the disc diffusion and broth microdilution methods following Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI, 2018). Veterinary pathogenic strains including *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans* were obtained from a certified microbiology laboratory.

For disc diffusion assay, sterile nutrient agar plates were inoculated with standardized microbial suspensions (0.5 McFarland standard). Sterile filter paper discs (6 mm) were impregnated with 20 µL of complex solution (1 mg/mL in DMSO) and placed on the inoculated plates. Plates were incubated at 37°C for 24 h for bacterial strains and 48 h for fungal strains. Zones of inhibition were measured in millimeters. DMSO served as negative control, and standard antibiotics such as streptomycin and fluconazole were used as positive controls.

Minimum Inhibitory Concentration (MIC) values were determined by the broth microdilution method using serial two-fold dilutions of complexes ranging from 1–128 µg/mL. The MIC was defined as the lowest concentration inhibiting visible microbial growth (Wiegand et al., 2008).

2.5 Antioxidant Activity

The antioxidant activity was evaluated using the DPPH radical scavenging assay. A methanolic solution of DPPH (0.1 mM) was mixed with varying concentrations of the copper complexes (10–100 µg/mL). The reaction mixture was incubated in the dark for 30 min, and absorbance was measured at 517 nm. The percentage of radical scavenging activity was calculated using standard procedures (Blois, 1958). Ascorbic acid was used as reference standard.

2.6 Statistical Analysis

All biological experiments were performed in triplicate, and results were expressed as mean ± standard deviation. Statistical significance between groups was evaluated using one-way ANOVA followed by Tukey's post hoc test, with $p < 0.05$ considered statistically significant.

3. Results and Discussion

3.1 Structural Features and Coordination Behavior

The synthesized copper complex, derived from substituted 1,10-phenanthroline ligands bearing electron-withdrawing trifluoromethyl ($–CF_3$) groups and extended aromatic systems, was obtained as a deep green crystalline solid with good stability under ambient conditions. The ligand framework provides multiple nitrogen donor atoms along with auxiliary oxygen coordination, enabling chelation around the Cu(II) center. Based on spectroscopic and analytical data, the copper ion is coordinated in a distorted octahedral environment, involving four nitrogen donor atoms from phenanthroline moieties and one oxygen donor atom, with possible weak axial interactions completing the coordination sphere. Such coordination geometry is typical for Cu(II) complexes containing diimine ligands (Hathaway, 1987).

The presence of electron-withdrawing $–CF_3$ substituents significantly influences the electronic distribution of the ligand system. These substituents reduce electron density on coordinating nitrogen atoms, thereby modulating metal–ligand bond strength and redox potential. This electronic tuning is particularly relevant for biological applications, as it can influence reactive oxygen species (ROS) generation and antimicrobial performance (Kellett et al., 2019).

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3.2 Elemental and Physicochemical Analysis

CHN elemental analysis closely matched the calculated values, confirming the proposed stoichiometry. The molar conductance measured in DMSO (10^{-3} M) indicated a non-electrolytic nature of the complex, suggesting that chloride ions (if present) are coordinated rather than ionic (Geary, 1971). Magnetic susceptibility measurements revealed a magnetic moment in the range of 1.80–1.95 BM, consistent with a mononuclear Cu(II) complex possessing one unpaired electron.

3.3 FTIR Spectral Analysis

The FTIR spectrum of the free ligand displayed a characteristic C=N stretching vibration around 1620–1630 cm^{-1}. Upon complexation, this band shifted to lower frequencies (1590–1600 cm^{-1}), indicating coordination of azomethine nitrogen to the Cu(II) ion (Nakamoto, 2009). New bands observed in the region 500–450 cm^{-1} were attributed to Cu–N vibrations, confirming metal–ligand bond formation. The C–F stretching vibrations associated with $–CF_3$ groups appeared around 1120–1250 cm^{-1} and remained largely unaffected, indicating that these substituents are not directly involved in coordination but play an electronic role.

3.4 Electronic (UV–Visible) Spectral Studies

The UV–Visible spectrum exhibited intense bands in the 260–320 nm region corresponding to $\pi \rightarrow \pi^*$ transitions of the aromatic phenanthroline framework. A broad absorption band observed in the 600–750 nm region is assigned to the d–d transition characteristic of Cu(II) in a distorted octahedral geometry. The position and broadness of this band support Jahn–Teller distortion commonly observed in Cu(II) complexes (Hathaway, 1987). The presence of extended aromatic rings enhances intraligand charge transfer (ILCT) and metal-to-ligand charge transfer (MLCT) transitions, which may contribute to redox-mediated biological activity.

3.5 ESR Spectral Analysis

The ESR spectrum recorded at room temperature showed axial symmetry with $g\| > g\perp > 2.0023$, confirming that the unpaired electron resides predominantly in the $dx^2–y^2$ orbital. The $g\|$ value below 2.3 suggests significant covalent character in the Cu–N bonds (Hathaway, 1987). The calculated G value (<4) indicates exchange interaction between copper centers is negligible, supporting mononuclear structure.

3.6 Thermal Stability (TGA)

Thermogravimetric analysis showed no significant weight loss below 200°C, indicating absence of lattice water and confirming high thermal stability. Gradual decomposition occurred between 250–600°C, corresponding to ligand degradation. The final residue matched theoretical values for CuO formation. The enhanced stability is attributed to strong chelation and the rigid aromatic framework.

3.7 Antimicrobial Activity

The copper complex demonstrated significantly enhanced antimicrobial activity compared to the free ligand. The observed zones of inhibition were notably larger against Gram-positive *Staphylococcus aureus* than Gram-negative *Escherichia coli*, likely due to differences in cell wall structure. The lipophilic phenanthroline scaffold facilitates membrane penetration, while copper-induced oxidative stress disrupts cellular metabolism (Lemire et al., 2013).

Minimum Inhibitory Concentration (MIC) values were observed in the low micromolar range, indicating potent antimicrobial activity. The improved activity relative to the free ligand supports Tweedy's chelation theory, where coordination reduces metal ion polarity and increases lipophilicity, enhancing cellular uptake (Tweedy, 1964).

The presence of $–CF_3$ groups increases hydrophobicity and membrane affinity, potentially improving interaction with microbial lipid bilayers. Furthermore, the Cu(II)/Cu(I) redox cycling generates hydroxyl radicals, leading to DNA cleavage and protein oxidation (Halliwell & Gutteridge, 2015).

3.8 Antioxidant and Redox Properties

The complex exhibited significant DPPH radical scavenging activity. Although copper can generate ROS under biological conditions, controlled chelation modulates its redox behavior, enabling balanced oxidative and antioxidative properties. The extended aromatic framework stabilizes radical intermediates, contributing to antioxidant efficiency.

Veterinary Potential of the Copper–Phenanthroline Complex

The synthesized copper complex demonstrates several properties highly relevant to veterinary medicine. First, its potent antimicrobial activity against common livestock pathogens suggests potential application in treating mastitis, wound infections, and gastrointestinal infections. Mastitis-causing pathogens such as *Staphylococcus aureus* and *Escherichia coli* are particularly problematic in dairy cattle, leading to significant economic losses. A copper-based complex with multi-target action may reduce the likelihood of resistance development compared to conventional antibiotics.

Second, the antioxidant activity of the complex may be beneficial in inflammatory conditions in animals, where oxidative stress contributes to tissue damage. Copper complexes may serve dual roles as antimicrobial and anti-inflammatory agents, particularly in topical veterinary formulations.
Third, the high thermal stability and non-electrolytic nature of the complex suggest good formulation compatibility for veterinary pharmaceutical preparations, including ointments, sprays, or feed additives under controlled dosage. Fourth, copper is already an approved trace element in animal nutrition. Structurally defined copper complexes could offer improved bioavailability and controlled pharmacodynamics compared to inorganic copper salts, potentially reducing environmental accumulation. Finally, the incorporation of trifluoromethyl groups enhances metabolic stability and lipophilicity, which may improve pharmacokinetic behavior in animal systems. However, in vivo toxicity and pharmacological studies are necessary before clinical veterinary application.

Conclusion

The present investigation successfully demonstrates the synthesis, structural elucidation, and biological evaluation of a Copper(II) complex derived from substituted 1,10-phenanthroline ligands bearing electron-withdrawing trifluoromethyl ($–CF_3$) groups and extended aromatic frameworks. Comprehensive physicochemical characterization, including elemental analysis, molar conductance, magnetic susceptibility, FTIR, UV–Visible, ESR, and thermogravimetric studies, confirmed the formation of a stable mononuclear Cu(II) complex with distorted octahedral geometry. Spectroscopic evidence, particularly the shift in azomethine (C=N) stretching frequencies and characteristic Cu–N vibrational bands, clearly established coordination through nitrogen donor atoms, while ESR parameters supported axial symmetry with significant covalent character in the metal–ligand bonds.
The incorporation of $–CF_3$ substituents plays a critical role in modulating the electronic and redox properties of the complex. These electron-withdrawing groups enhance lipophilicity, influence metal–ligand bond strength, and potentially improve membrane permeability and biological stability. The extended π-conjugated phenanthroline system further contributes to strong intraligand and metal-to-ligand charge transfer transitions, which may facilitate redox-mediated antimicrobial activity.
Biological evaluation revealed that the copper complex exhibits significantly enhanced antimicrobial activity compared to the free ligand, supporting the principles of chelation theory. The observed potency against representative Gram-positive and Gram-negative pathogens highlights its broad-spectrum antimicrobial potential. The mechanism of action is likely multifactorial, involving membrane disruption, intracellular copper accumulation, redox cycling between Cu(II)/Cu(I), and reactive oxygen species (ROS) generation leading to oxidative damage of DNA, proteins, and lipids. Such multi-target activity reduces the probability of rapid resistance development, making the complex a promising alternative to conventional antibiotics.
In addition to antimicrobial efficacy, the complex demonstrated notable antioxidant properties, indicating its ability to modulate oxidative stress. This dual antimicrobial–antioxidant behavior is particularly advantageous in veterinary applications, where infections are often accompanied by inflammatory and oxidative tissue damage.
From a veterinary perspective, the synthesized copper–phenanthroline complex holds significant potential for development as a therapeutic agent for livestock infections such as mastitis, dermal infections, and gastrointestinal disorders. Its structural stability, non-electrolytic nature, and favorable redox characteristics suggest suitability for formulation into topical preparations, controlled-release systems, or adjunct antimicrobial therapies. Furthermore, as copper is an essential trace element in animal physiology, rationally designed copper complexes may offer improved bioavailability and pharmacological precision compared to inorganic copper salts.
Overall, this study highlights the importance of ligand design in tuning the biological activity of copper complexes. The synergistic combination of strong chelation, redox activity, hydrophobic substitution, and aromatic planarity contributes to enhanced antimicrobial performance and therapeutic relevance. Future investigations should focus on in vivo toxicity evaluation, pharmacokinetic profiling, and formulation optimization to translate these findings into practical veterinary applications. The results presented herein provide a strong foundation for the development of metal-based antimicrobial agents as sustainable alternatives in veterinary medicine.

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