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SYNTHESIS, CHARACTERIZATION, THERMAL AND ANTIBACTERIAL ACTIVITY OF COPPER (II) COMPLEXES DERIVED FROM 4-ACYL PYRAZOLONE

SOMAIYA CP*, PADHIYAR SM, NATHAVANI JG, BAVISKAR GU, GOHIL RS AND PATEL MC

Department of Chemical Science, Parul Institute of Applied Sciences, Parul University, Vadodara, Gujarat (India)

***Corresponding Author: Dr. Chintan P. Somaiya: E Mail: chintan.somaiya23775@paruluniversity.ac.in**

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ABSTRACT

The research work investigates the synthesis, spectroscopic characterization, thermal analysis, and *in vitro* antibacterial activity of Cu(II) transition metal complexes. The metal complexes were synthesized by reacting the respective 4-acyl pyrazolone based ligands. Synthesized ligands were characterized by 1H NMR, Mass, IR, and elemental analysis, while their respective complexes were characterized by IR and elemental analysis. Moreover, thermal studies like TGA, DTG and DSC were also carried. The results confirmed that synthesized Cu(II) metal complexes have promising antibacterial activity against Gram-positive (*Bacillus megaterium*) and Gram-negative (*E.coli*) microorganisms, which makes them potential candidates for the development of new antibacterial agents.

Keywords: Cu(II) complexes, Schiff base, Acyl Pyrazolone, Thermal studies and antibacterial activity

INTRODUCTION

In the field of biology, metal ions are indispensable for their roles as both therapeutic agents and diagnostic tools. Transition metals, which encompass elements like copper, iron, nickel, and manganese, Cobalt among others, play important roles in a wide array of biological processes. These include electron transfer, catalysis, as well as

serving as integral components of enzyme and protein active sites. Recent advancements in inorganic chemistry have significantly improved our ability to harness metal complexes, enhancing their effectiveness as medicinal agents **[1, 2]**.

Inorganic compounds have played a significant role in advancing and enriching the field of medical science, which, in turn, has greatly impacted human health **[3]**. Copper(II) complexes, in particular, have garnered substantial attention due to their remarkable biological and catalytic capabilities. Notably, copper(II), Nickel(II) and other transition complexes have demonstrated a higher degree of effectiveness as anti-inflammatory, anti-bacterial, anti-fungal and anticancer agents compared to their constituent ligands in their uncomplexed form **[4, 5]**. When it comes to applications in biology and pharmacology, metal complexes featuring specific bioactive ligands can often exhibit enhanced efficiency when compared to the same ligands in their free, unbound state **[6]**.

Pyrazoles, a class of five-membered heterocycles, play a significant role in organic compound synthesis. They belong to the well-studied azole family of chemical compounds and have diverse applications across various industries, including technology, healthcare, and agriculture. The pyrazole nucleus, with its versatile structural arrangements, enables the development of a wide range of compounds, including antibacterial, antifungal, anticancer, antidepressant, anti-inflammatory, anti-tuberculosis, antioxidant, and antiviral drugs. Additionally, pyrazoles are employed as protein glycation inhibitors **[7]**, highlighting their importance in modern pharmaceutical and chemical research.

Pyrazolone-based metal complexes offer several advantages, including stability, straightforward synthesis, ease of modification, and good bioactivity. These attributes have garnered significant attention within the scientific community **[8]**. Schiff bases, on the other hand, have been a focus of extensive research due to their selectivity, versatile synthesis methods, and diverse biological applications. Many pharmaceuticals and bioactive natural alkaloids incorporate pyrazolone scaffolds **[9, 10]**, further highlighting the importance of these compounds in medicinal and scientific endeavours.

Copper(II) complexes, characterized by the presence of copper ions in the +2 oxidation state, represent a fascinating and versatile class of coordination compounds that have garnered significant attention in the field of inorganic chemistry. The unique electronic configuration of copper(II) ions, coupled with their ability to adopt diverse coordination geometries, imparts distinct and often dynamic properties to these complexes. These compounds play significant role in various biological, catalytic, and material

science applications, contributing to the understanding of fundamental chemical principles and showcasing the intricate interplay between ligands and metal centres. The rich coordination chemistry of Cu(II) complexes, their redox activity, and their potential for catalysis underscore their importance in the exploration of innovative technologies and the development of new materials with tailored properties. This introduction aims to provide a glimpse into the intriguing world of copper(II) complexes, offering a foundation for further exploration into their synthesis, structure, and multifaceted applications **[11-14]**.

EXPERIMENTAL

MATERIALS AND METHODS

The compounds l-phenyl-3-methyl-5-pyrazolone, 4-sulphonamide phenyl hydrazine and $CuCl_2{\cdot}6H_2O$ were purchased from TCI (Japan). Acylchlorides were purchased from spectrochem, Mumbai (India).

Step-1: Synthesis of 4-acyl pyrazolone

In the synthesis of 4-acyl pyrazolone, a two-necked round-bottom flask is charged with 0.01 mol of 1-Phenyl 3-methyl 5-pyrazolone, followed by stirring for approximately 30 minutes. Subsequent addition of 20 ml of 1,4-Dioxane ensures complete dissolution of the pyrazolone derivative within the flask. The resulting mixture is then dissolved at room temperature by stirring with a magnetic stirrer. To this solution, 0.02 mol of calcium hydroxide powder is added, and 0.02 mol acylating agent is gradually introduced using an additional funnel over 15 minutes, noting the change in thickness indicative of complex formation, resulting in a dark brown solution. The mixture is refluxed for four to five hours at a temperature range of 90 to 110 degrees Celsius. Pour the reaction mixture into crushed ice and 2M HCl with constant stirring. After a brief period, the resulting solution is filtered to obtain the desired product.

Step-2: Synthesis of 4-acyl pyrazolone based ligands (L1-L6)

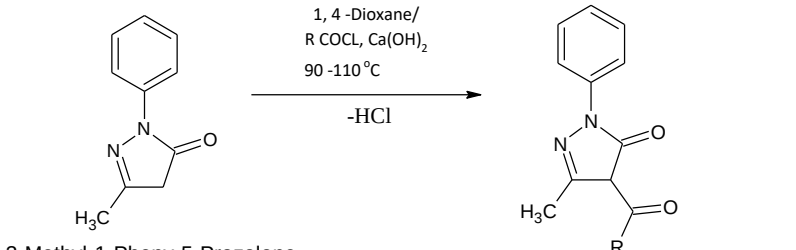
4-acyl Pyrazolone and 4-Sulphonamide based ligands were synthesized using established methods **[15]**. In this experimental procedure, a solution comprising 0.01 mol of 4-acyl pyrazolone in 30 ml of methanol was combined with a solution containing (0.01 mol) of 4-sulphonamide phenyl hydrazine in 20 ml of methanol. Little amount of acetic acid was added as a catalyst. The resulting mixture was refluxed for a duration of 4 hours and subsequently allowed to cool. During this process, a yellow precipitate was formed and subsequently isolated through vacuum filtration.

Step-3: Synthesis of 4-acyl pyrazolone based Cu(II) complexes

In the synthesis of complexes, a 10 ml methanolic solution containing 0.1 mol of ligands (L1-L2) was carefully introduced into a round-bottom flask (RBF). Over a span of

15 minutes, 0.1 mol of a methanolic solution of $CuCl_2 \cdot 6H_2O$ was added dropwise to this solution. To maintain the pH of the solution, an aqueous solution of NaOH was judiciously incorporated. The resulting mixture underwent reflux for 4-5 hours at a temperature range of 60-70°C. Throughout the reaction, a distinctive colored precipitate emerged. Post-reaction, the precipitate was carefully dried, filtered, and stored in a desiccator over $CaCl_2$.

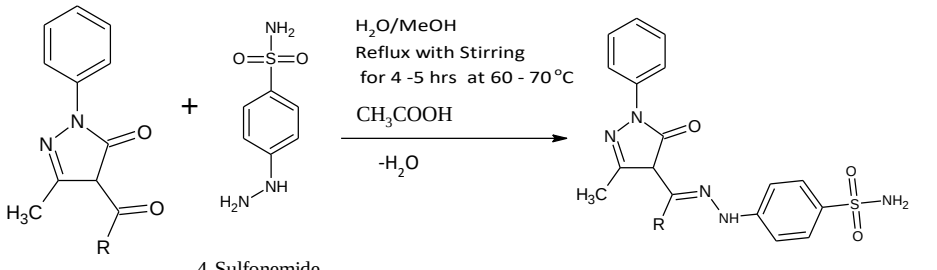
Step-1



3-Methyl-1-Pheny-5-Prazolone

4-Acyl-3-Mehyl-1-Phenyl-5-Pyrazolone

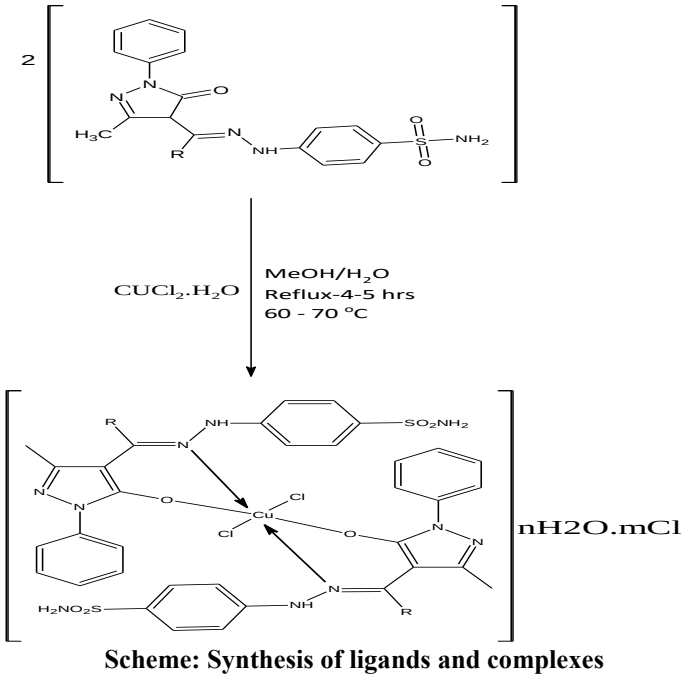
Step-2



4-Sulfonemide Phenylhydrazine

4-Acyl-3-Methyl-1-Phenyl-5-Pyrazolone
4-Sulfonemide Phenylhydrazine

Step-3



Scheme: Synthesis of ligands and complexes

Sr.No.	Ligand	R
1	L1	$-C_4H_3O$
2	L2	$-C_2H_5$
3	L3	$-CH_3$
4	L4	$-C_3H_7$
5	L5	$-C_6H_5NO_2$
6	L6	$-C_6H_5$

NMR data & spectra of ligand

1H NMR data of ligand for L1-L6:

L1: 1H NMR (400 MHz, DMSO-d6): δ (ppm)=1.88 (3H, s, -CH3); 7.01 -8.65 (Ar-H); L2: 1H NMR (400 MHz, DMSO-d6): δ (ppm)=3.0 (3H, s, -CH3); 1.79-1.88 (2H, q, -CH2), 2.79-2.86 2H, m, -CH2);0.97-1.60(3H, t, -CH3);6.89-7.99 (Ar-H); L3: 1H NMR (400 MHz, DMSO-d6): δ (ppm)=2.08 (3H, s, -CH3); 1.34-1.40 (3H, t, -CH3);2.66- 2.68(2H, q, -CH2) 6.98-7.99 (Ar-H); L4: 1H NMR (400 MHz, DMSO-d6): δ (ppm)=2.06 (3H, s, -CH3); 2.67-2.69 (3H, s, -CH3); 6.98-7.56 (Ar-H); L5: 1H NMR (400 MHz, DMSO-d6): δ (ppm)= 2.12 (3H, s, -CH3); 7.56-8.99 (Ar-H); L6: 1H NMR (400 MHz, DMSO-d6): δ (ppm)= 1.98 (3H, s, -CH3); 6.87-7.98(Ar-H).

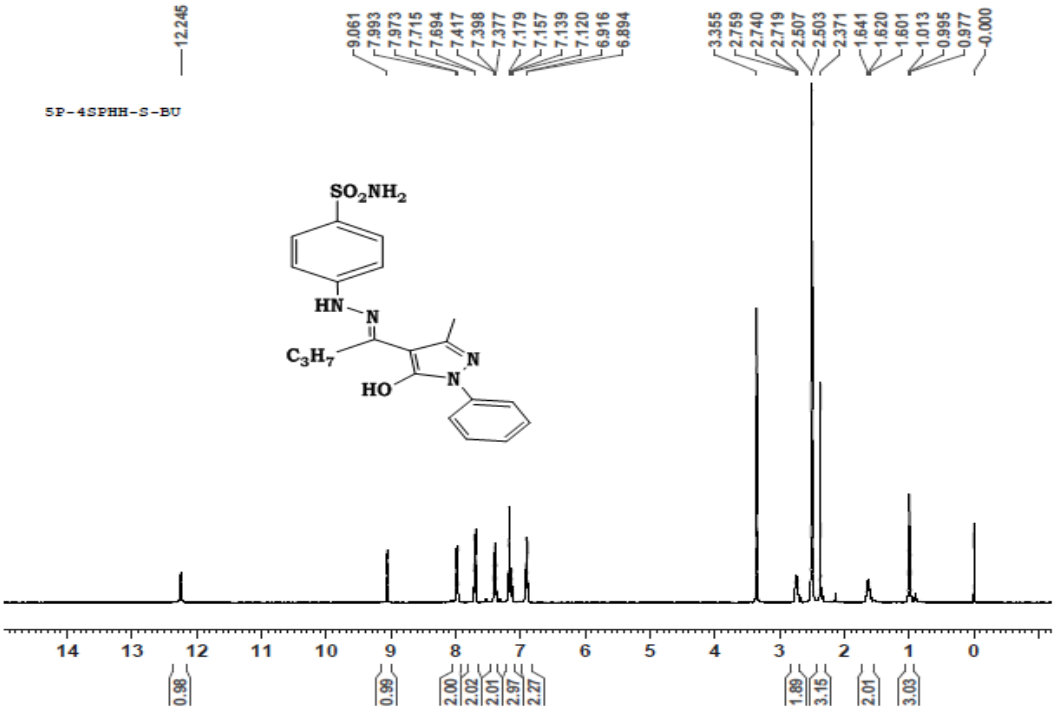
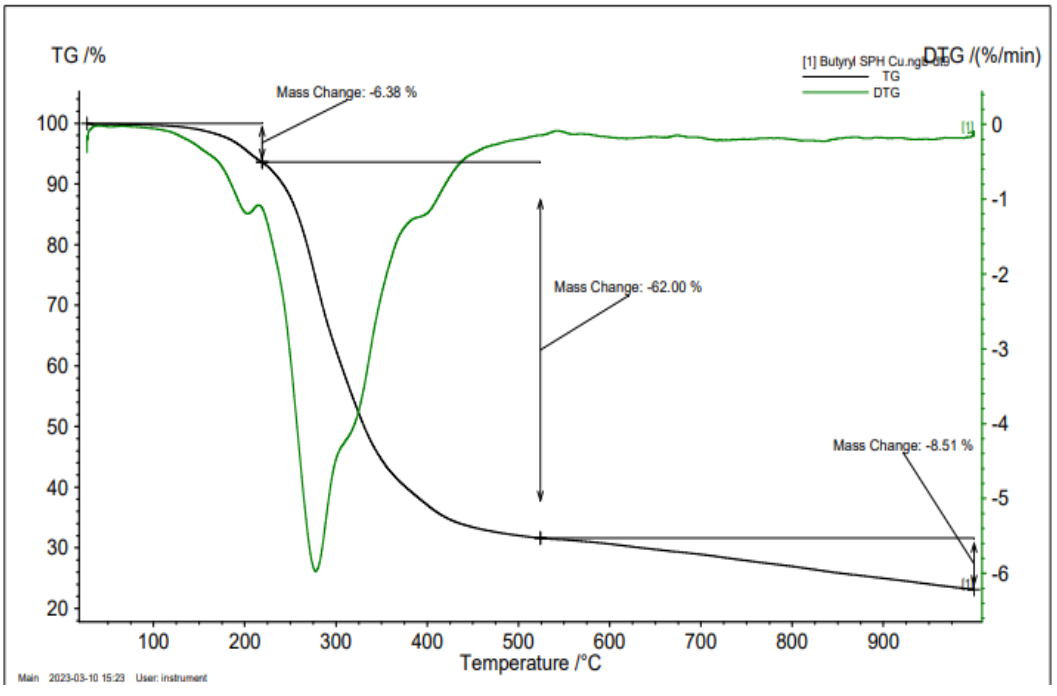


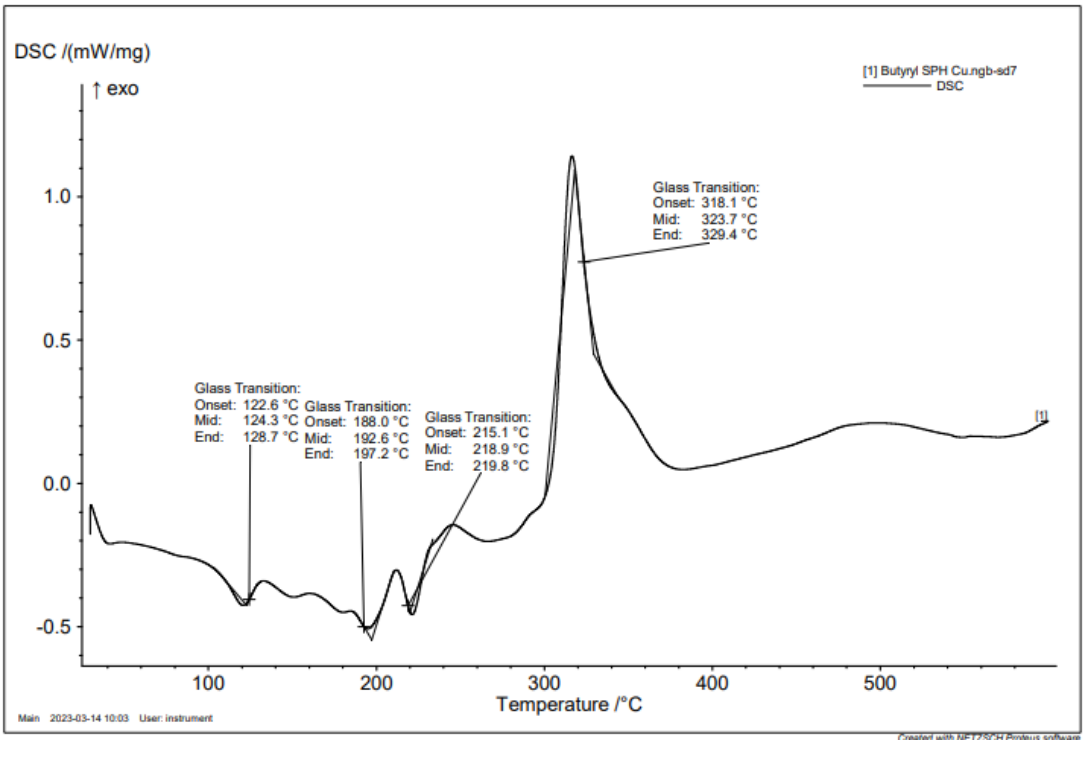
Figure 1: 1H NMR spectra of ligand

Table 1: FT-IR data of ligands And Metal Complexes (KBr, cm-1)						
Sr.No.	Ligand	v(O-H)	v(N-H)	v(C=O)	v(C=N)	v (M-O)
1	L1	3286	3198	1595	1506	-
2	L2	3348	3251	1600	1539	-
3	L3	3323	3285	1598	1534	-
4	L4	3358	3226	1618	1531	-
5	L5	3200	3076	1597	1558	-
6	L6	3242	3182	1595	1516	-
7	ML1	3235	2940	1588	1469	511
8	ML2	3346	2965	1580	1493	517
9	ML3	3242	2942	1579	1488	503
10	ML4	3352	2938	1582	1485	510
11	ML5	3157	2970	1569	1514	520
12	ML6	3180	2830	1562	1468	507

Thermal studies



Graph 1: TGA/DTG graph of complex ML1



Graph 2: DSC graph of complex ML1

Anti-bacterial Activity

Table 2: Action of ligands and their Cu metal complex against bacteria Zone of inhibition(mm)			
Sr. No.	Compound	Gram-Positive	Gram-Negative
		Bacillus Megaterium	*E. coli*
Ref. Drug	Penicillin	35	28
1	L1	21	13
2	L2	06	07
3	L3	17	10
4	L4	10	06
5	L5	15	20
6	L6	20	24
7	ML1	23	16
8	ML2	06	08
9	ML3	18	12
10	ML4	11	08
11	ML5	18	23
12	ML6	22	25

RESULTS AND DISCUSSION

1H NMR Study of ligands

The investigation into the tautomerism of pyrazolone has been a subject of extensive exploration through various studies. To explore this further, 1H NMR studies of Schiff base ligands were conducted in DMSO-d6 at room temperature. The experimental findings, detailed in the subsequent section, reveal distinctive features in the 1H NMR spectra of the ligands. Two sharp singlets, equivalent to one and two protons, were identified in the 12-13 δ ppm range, corresponding to the -OH group. Notably, this signal vanished upon performing a D2O exchange experiment. Aromatic protons were observed within the 6.8-9.0 δ ppm range, while singlets representing methyl groups in Schiff base ligands were detected in the 1.5 to 3.0 δ ppm range. Figure 1 illustrates the NMR spectrum of L1H. In certain instances, signals from –NH protons were observed to merge with aromatic protons, and these signals appeared closely spaced in the NMR spectrum. Consequently, assigning each signal to a specific aromatic or –NH proton became challenging. Based on the 1H NMR spectroscopic data, it is discerned that the Schiff base ligand predominantly exists in the Keto-Enol form in the solution state.

IR Spectral Study of ligands and complexes

To elucidate the binding mode of Schiff bases (L1 to L6) with Cu(II) ions in complexes, a comparative analysis was conducted between the IR spectra of Schiff bases and their corresponding complexes. The Schiff base ligand in this study manifests a broad band cantered at 3199 to 3348 cm^{-1}, indicative of intramolecular H-bonding involving the 5-OH group. Additionally, the presence of a lone pair on the azomethine suggests the existence of the ligand in the enol form in the solid state. The Schiff base ligands (L1 to L6) exhibit a sharp and strong band at 1539 to 1595 cm^{-1}

corresponding to υ(C=N) of the acyclic azomethine group. The observed low-energy shift of this band in the complexes, suggests coordination of the azomethine nitrogen. Further analysis of the IR spectra of complexes reveals a significant negative shift of 15-20 cm^{-1} in the υ(C=O) absorption of the pyrazolone group, indicating a reduction in the stretching force constant of υ(C=O) due to coordination through the oxygen atom of the ligand. The provided table presents the detailed characterization of complexes, including their formula weight, color, yield percentage, and elemental analysis. Notably, the data affirm that Schiff bases function as dinegative bidentate ligands, forming conjugate chelate rings with the ligands existing in the complex in the enolic form. This comprehensive analysis provides valuable insights into the coordination behaviour of the studied Schiff base ligands with Cu(II) ions in complexes.

Thermal study

The TG/DTG curves for the thermal behaviour of the $[Cu(L1)Cl_2 \cdot 2H_2O]$ complex are presented in Graph 1. The decomposition of these complexes unfolds in three stages. In the initial stage (25 to 250°C), a single-step process of thermal dehydration and dehalogenation occurs, resulting in a mass loss of 6.38% (6.11%). This step involves the removal of two moles of crystalline H2O molecules and exhibits an associated endothermic effect at 124.3°C. The subsequent stage (251 to 550°C) signifies the decomposition of a portion of the L1 ligand, leading to a measured mass loss of 62.00% (62.41). The corresponding endothermic peak at 192.6°C, as indicated by the DSC curve, aligns with this decomposition stage. These findings contribute valuable insights into the thermal degradation behaviour of $[Cu(L_1)Cl_2 \cdot 2H_2O]$ complexes, providing a comprehensive understanding of the underlying processes.

Antibacterial Study

All the synthesized compounds were screened for their antibacterial study against some Gram-positive and Gram-negative bacterial strain and it is found that mostly complexes showed potent activity as compared to their respective ligands and this can be explained on the basis of Overtone concept and Chelation concepts.

CONCLUSION

In conclusion, the exploration of Cu(II) complexes as prospective antibacterial agents has yielded promising outcomes and valuable insights. The comprehensive analysis of the complexes thermal decomposition, conducted in multiple stages, provides crucial insights into their thermal behaviour, essential for potential applications. The identified endothermic peaks during decomposition stages align well with structural transformations, highlighting the stability and potential release of active species.

Moreover, the observed antibacterial effectiveness of the Cu(II) complexes underscores their potential as potent antimicrobial agents. The demonstrated inhibition of bacterial growth suggests that these complexes merit further exploration for therapeutic applications in combatting bacterial infections. The outcomes of this research contribute valuable information to the expanding knowledge on transition metal complexes and their potential utility in developing novel antibacterial agents.

While this study establishes a robust foundation for understanding the antibacterial properties of Cu(II) complexes, further research is imperative to delve into their mechanism of action, toxicity profiles, and practical applications in real-world medical settings. Overall, the findings presented here set the stage for future investigations into developing Cu(II) complexes as promising candidates for antibacterial interventions, with the potential to address the escalating challenges posed by antibiotic resistance.

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