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ENHANCED ANTIMICROBIAL ACTIVITY OF METAL-LIGAND COMPLEXES OF AMPICILLIN: SYNTHESIS, CHARACTERIZATION, AND EVALUATION AGAINST FUNGAL AND BACTERIAL PATHOGENS

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ABSTRACT

This study explores the synthesis, characterization, and antimicrobial evaluation of metal complexes of ampicillin. The complexes were synthesized and characterized using various analytical techniques, including UV-Vis spectroscopy, FTIR spectroscopy, and physical analysis. The solubility of the complexes was assessed in different solvents, providing insights into their physicochemical properties. Antimicrobial evaluation against both fungal and bacterial strains revealed that the metal complexes exhibited enhanced antimicrobial activity compared to free ampicillin. The results demonstrate the potential of metal complexation as a strategy to enhance the efficacy of antibiotics against microbial pathogens. Further research is warranted to elucidate the mechanisms underlying the enhanced antimicrobial activity of the metal complexes and to explore their potential applications in medicine and biotechnology.

Keywords: Synthesis, Metal Complexes, Nickel, Manganese, Ampicillin, Antimicrobial Resistance.

I. INTRODUCTION

Antimicrobial resistance (AMR) poses a significant global health threat, leading to increased morbidity, mortality, and healthcare costs (Ventola, 2012; World Health Organization (WHO), 2020). As conventional antibiotics become less effective against resistant pathogens, there is a growing need for alternative antimicrobial strategies. Metal complexes of antibiotics have emerged as promising candidates due to their unique chemical properties and potential to overcome resistance mechanisms.

Antibiotic resistance has become a pressing global health concern, necessitating the exploration of alternative strategies to combat microbial infections. Metal complexes of antibiotics have emerged as promising candidates with enhanced antimicrobial properties. In particular, the combination of antibiotics with metal ions offers opportunities to overcome resistance mechanisms and broaden the spectrum of activity. Recent studies have demonstrated the potential of metal complexes in enhancing the efficacy of antibiotics against both fungal and bacterial pathogens (Gholivand et al., 2015; Shaterian et al., 2016).

Ampicillin, a broad-spectrum β-lactam antibiotic, is commonly used to treat bacterial infections. However, its efficacy is increasingly compromised by the emergence of resistant strains (Shaterian et al., 2016). Metal complexation of ampicillin offers a strategy to enhance its antimicrobial activity and expand its spectrum of action (Palčić et al., 2012).

Recent studies have demonstrated the effectiveness of metal complexes of antibiotics against resistant microbial strains. For example, Palčić et al. (2012) synthesized and evaluated metal complexes of ampicillin, reporting enhanced antimicrobial activity compared to free ampicillin. Similarly, Chohan (2007) investigated metal complexes of various antibiotics and observed potent antimicrobial effects against multidrug-resistant bacteria.

In this study, we aim to synthesize, characterize, and evaluate the antimicrobial activity of metal complexes of ampicillin against both fungal and bacterial pathogens. We hypothesize that metal complexation will enhance the antimicrobial efficacy of ampicillin, offering a promising approach to combatting AMR. The complexes will

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be characterized using various analytical techniques, including UV-Vis spectroscopy, FTIR spectroscopy, and physical analysis. The solubility of the complexes in different solvents will also be assessed to provide insights into their physicochemical properties.

By elucidating the antimicrobial properties of the synthesized metal complexes, this study seeks to contribute to the development of novel antimicrobial agents with improved efficacy and therapeutic potential. Understanding the structure-activity relationships of metal complexes of antibiotics is crucial for advancing their application in combating microbial infections and addressing the global challenge of antibiotic resistance.

II. MATERIALS AND METHODS

Synthesis of Metal Complexes

Ampicillin was used as the ligand for the synthesis of metal complexes. Metal salts such as nickel chloride ($NiCl_2$) and manganese chloride ($MnCl_2$) were employed as metal precursors. The metal complexes were synthesized by reacting the appropriate metal salt with ampicillin in a suitable solvent under controlled conditions. The reaction progress was monitored using standard analytical techniques.

Characterization Techniques

The UV-Vis spectra of the synthesized complexes were recorded using a UV-Vis spectrophotometer to investigate their electronic transitions and identify any shifts or changes compared to free ampicillin. Fourier-transform infrared spectra of the complexes were obtained to analyze their molecular vibrations and identify characteristic functional groups present in the complexes. The physical properties of the complexes, such as color, melting point, and percentage yield, were determined to assess their purity and stability. The solubility of the metal complexes was evaluated in various solvents, including methanol, ethanol, dimethyl sulfoxide (DMSO), toluene, and dimethylformamide (DMF). The solubility behavior of the complexes in different solvents was recorded as soluble (SS) or not soluble (NS).

Antimicrobial Evaluation

The antifungal activity of the metal complexes was assessed against fungal strains including Rhizoctonia solani, Ceratoistis paradoxa, Cercospora capsici, and Trichoalerma rubrium. The inhibition zone diameter was measured using the agar well diffusion method. The antibacterial activity of the complexes was evaluated against bacterial strains such as Xanthomones spp, Escherichia coli, Klebsiella spp, Streptomyces sulphale, Streptomyces aureus, and Bacillus cereus. The inhibition zone diameter was determined using the agar disc diffusion method. Ampicillin and appropriate positive controls were included in the antimicrobial assays to validate the experimental results and ensure the accuracy of the measurements.

Statistical Analysis

The antimicrobial data were subjected to statistical analysis, and the mean values of inhibition zone diameters were calculated. Statistical significance was determined using appropriate tests such as ANOVA, followed by post-hoc analysis.

By employing these materials and methods, comprehensive insights into the synthesis, characterization, and antimicrobial evaluation of metal complexes of ampicillin were obtained, providing valuable information for understanding their potential as antimicrobial agents.

III. RESULTS

Table 1: Results of physical analysis of the metal complexes

COMPOUNDS	COLOUR	%YIELD	MELTING POINT	%METALS
[Ni(amp)]1:1	White	38.75	180-181	3.40
[Ni(amp)]1 :2	White	44.55	191-197	1.87
[Mn(amp)] 1:1	Pale pink	41.76	187-189	3.17
[Mn(amp)] 1:2	Pale pink	52.10	192-195	1.52

The physical analysis results provided in the Table 1 offer valuable insights into the synthesized metal complexes of ampicillin and lay the groundwork for further discussion on their properties and potential applications, particularly in antimicrobial research. The color of a complex can provide initial information about its structure and coordination environment. In this case, both nickel and manganese complexes appear

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white or pale pink, suggesting similar coordination geometries or ligand environments for both metals when bound to ampicillin. The percentage yield indicates the efficiency of the synthesis process. Higher yields generally indicate better efficiency and reproducibility. Comparing the yields of different complexes can help assess the effectiveness of the synthesis method and identify any factors that may influence yield, such as reaction conditions or stoichiometry. The melting point range provides information about the thermal stability and purity of the complexes. A narrow melting point range suggests high purity and uniformity of the product, while a broader range may indicate impurities or variations in composition. In this case, the melting point ranges for the complexes fall within relatively narrow ranges, indicating good purity and thermal stability. The percentage of metals in each complex indicates the stoichiometry of the metal-ligand complexation. It appears that both nickel and manganese complexes are synthesized in 1:1 and 1:2 metal-to-ligand ratios. This information is crucial for understanding the coordination chemistry of the complexes and elucidating their structural features.

Table 2: Results of Solubility test results

COMPOUND	METHANOL	ETHANOL	DMSO	TOLUENE	DMF
[Ni(amp)]1:1	SS	SS	NS	NS	NS
[Ni(amp)]1 :2	SS	SS	NS	NS	NS
[Mn(amp)] 1:1	SS	SS	NS	NS	NS
[Mn(amp)] 1:2	SS	SS	NS	NS	NS

NS: not soluble; SS: soluble

The solubility test results provided in Table 2 offer crucial insights into the solubility characteristics of the synthesized metal complexes of ampicillin in different solvents. The complexes are soluble in both methanol and ethanol (denoted as SS), indicating good solubility in polar protic solvents. This solubility behavior aligns with the polar nature of ampicillin and its metal complexes. Polar solvents like methanol and ethanol can effectively solvate the ionic and polar components of the complexes, facilitating their dissolution. The complexes are not soluble (denoted as NS) in dimethyl sulfoxide (DMSO), toluene, and dimethylformamide (DMF). These solvents vary in polarity and hydrogen bonding capability. DMSO is a highly polar aprotic solvent, while toluene is nonpolar. DMF lies in between, being polar aprotic. The lack of solubility in these solvents suggests that the complexes may have limited interaction with nonpolar or less polar solvents.

The solubility characteristics observed here have implications for the potential applications of the complexes. Solubility in polar protic solvents like methanol and ethanol may be advantageous for applications where these solvents are used as reaction media or solvents for biological assays. On the other hand, the limited solubility in nonpolar or less polar solvents may restrict certain applications where solvents like DMSO or toluene are preferred. The solubility behavior observed in this study aligns with previous reports on the solubility of metal complexes of ampicillin and related compounds. For example, studies on metal complexes of other β-lactam antibiotics have shown similar solubility characteristics, with better solubility observed in polar protic solvents compared to nonpolar solvents (Palčić et al., 2012; Isab et al., 2017). These findings support the reliability and consistency of the solubility data obtained in this study.

Table 3: Prominent region of Uv-visible and FTIR spectra

Complexes	Uv-Vis(nm)	VN-H	VC=O	VC=N	COO^-	OH^-	M-N	M-O
Ampicillin	325, 229	3027	1309	1507	1707	-	-	-
Ni(Amp)	755, 725	3194	-	1684	1774	3486	542	443
$Ni(Amp)_2$	740, 680	3194	1499	1687	-	3486	588	440
Mn(Amp)	732, 644	3205	1496	1688	1590	3404	575	430
$Mn(Amp)_2$	760, 680	3209	1499	1663	1609	3407	573	432

Table 3 presents the prominent regions of UV-visible and FTIR spectra for the synthesized complexes of ampicillin with nickel (Ni) and manganese (Mn). UV-Vis spectroscopy provides information about the electronic

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transitions occurring within a molecule or complex. The wavelengths (in nm) listed in the table correspond to absorption peaks observed in the UV-Vis spectra of the complexes.

The absorption peaks in the UV-Vis spectra of the complexes are likely attributed to electronic transitions involving metal-ligand interactions. The observed peaks can vary depending on the nature of the metal center and the coordination environment around the metal ion. The shifts in absorption peaks compared to the free ampicillin molecule may indicate changes in the ligand environment upon complexation with the metal ions. These shifts can provide insights into the coordination geometry and bonding mode of the metal complexes.

Fourier-transform infrared (FTIR) spectroscopy is used to study molecular vibrations, including stretching and bending vibrations of functional groups within a molecule. The table lists various vibrational modes observed in the FTIR spectra of the complexes, including vibrations associated with functional groups such as VN-H (stretching vibration of primary amine), VC=O (stretching vibration of carbonyl group), VC=N (stretching vibration of imine), COO- (stretching vibration of carboxylate), and OH- (stretching vibration of hydroxyl). Changes in the frequencies or intensities of these vibrational modes compared to the free ampicillin molecule can indicate modifications in the chemical environment of the functional groups upon complexation. These changes are indicative of metal-ligand interactions and can provide insights into the coordination mode and bonding nature of the complexes.

The spectral features observed in the UV-Vis and FTIR spectra of the complexes are consistent with those reported in the literature for metal complexes of β-lactam antibiotics, including ampicillin (Aravindakshan and Mohanan, 2008; Muthu and Natarajan, 2010). The shifts in absorption peaks and changes in vibrational frequencies reflect the coordination of the metal ions with the functional groups of ampicillin, such as nitrogen and oxygen donors from the amine, carbonyl, and carboxylate groups.

Table 4: Antifungal activities in %

COMPLEXES	R.S	C.P	C.C	T.R
Ni(Amp)	68.50	69.40	69.80	67.50
$Ni(Amp)_2$	66.00	70.40	70.10	68.00
Mn(Amp)	61.50	66.00	67.40	59.70
$Mn(Amp)_2$	55.00	68.40	68.00	60.00
Ampicillin	10	18	21	19
Control	80.50	80.65	78.42	78.65

R.S = Rhizoctonia solani; C.P = Ceratoistis paradoxa; C.C = Cercospora capsici; T.R = Trichoalerma rubrium

Table 4 presents the antifungal activities (in percentages) of the synthesized metal complexes of ampicillin, along with ampicillin itself and a control, against four different fungal strains: Rhizoctonia solani (R.S), Ceratoistis paradoxa (C.P), Cercospora capsici (C.C), and Trichoalerma rubrium (T.R).

The antifungal activities of the metal complexes and ampicillin are compared against each fungal strain, providing insight into their effectiveness as antifungal agents. Table 4 shows that the metal complexes generally exhibit higher antifungal activities compared to free ampicillin against all tested fungal strains. This suggests that metal complexation enhances the antifungal properties of ampicillin. Metal complexation of antibiotics has been reported to improve their antimicrobial properties, including antifungal activity. Metal complexes can exhibit enhanced stability, altered mode of action, and increased bioavailability compared to the parent antibiotic (Palčić et al., 2012; Chohan, 2007).

The observed increase in antifungal activity of the metal complexes compared to free ampicillin could be attributed to the chelation effect, which can enhance the interaction between the metal-complexed antibiotic and the fungal target. There is variation in antifungal activity among the different metal complexes. For example, $Ni(Amp)_2$ and Ni(Amp) show relatively higher activity against all tested fungal strains compared to Mn(Amp) and $Mn(Amp)_2$. This variation could be attributed to differences in the coordination chemistry, stability, and mode of action of the metal complexes.

Factors such as the nature of the metal ion, ligand environment, and coordination geometry can influence the biological activity of metal complexes (Vázquez-López et al., 2018; Kaushik and Kaushik, 2016). The observed

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enhancement of antifungal activity upon metal complexation of ampicillin is consistent with previous studies on metal complexes of other antibiotics, including β-lactams. Studies have shown that metal complexes of antibiotics can exhibit improved antimicrobial properties compared to the free antibiotics (Li et al., 2003; Demirbaş et al., 2019).

Table 5: Antibacterial activities in mm

COMPLEXES	1	2	3	4	5	6
Ni(Amp)	11.50	15.00	12.00	12.00	13.50	14.20
$Ni(Amp)_2$	13.00	17.00	13.50	19.00	18.00	19.50
Mn(Amp)	10.00	14.80	11.90	11.50	12.60	13.00
$Mn(Amp)_2$	12.50	16.00	13.00	17.50	17.80	18.50
Ampicillin	7.00	8.50	7.90	8.20	8.20	8.00
Control	28.65	30.62	38.50	38.86	28.80	27.47

Xanthomones spp; Escherichia coli; Klebsiella spp; Streptomycin sulphale; Streptomycin aureus; Bascillin cereus Table 5 presents the antibacterial activities (in mm) of the synthesized metal complexes of ampicillin, as well as ampicillin itself and a control, against six different bacterial strains. The antibacterial activities of the metal complexes and ampicillin are compared against each bacterial strain, providing insight into their effectiveness as antibacterial agents. The table shows that the metal complexes generally exhibit higher antibacterial activities compared to free ampicillin against all tested bacterial strains. This suggests that metal complexation enhances the antibacterial properties of ampicillin.

Metal complexation of antibiotics has been reported to improve their antibacterial properties, including enhanced potency and broader spectrum of activity. Metal complexes can interact with bacterial cells through multiple mechanisms, leading to increased efficacy (Palčić et al., 2012). The observed increase in antibacterial activity of the metal complexes compared to free ampicillin could be attributed to synergistic effects between the metal ions and the antibiotic, as well as alterations in the mode of action and uptake of the complexes by bacterial cells. There is variation in antibacterial activity among the different metal complexes and bacterial strains. For example, $Ni(Amp)_2$ and $Mn(Amp)_2$ show relatively higher activity against most tested bacterial strains compared to Ni(Amp) and Mn(Amp). This variation could be attributed to differences in the coordination chemistry, stability, and mode of action of the metal complexes, as well as variations in the susceptibility of different bacterial strains to the complexes (López et al., 2018).

The observed enhancement of antibacterial activity upon metal complexation of ampicillin is consistent with previous studies on metal complexes of other antibiotics. Studies have shown that metal complexes of antibiotics can exhibit improved antibacterial properties compared to the free antibiotics, with some complexes demonstrating potent activity against multidrug-resistant bacterial strains (Demirbaş et al., 2019).

IV. CONCLUSION

The synthesized metal complexes of ampicillin exhibit enhanced antimicrobial properties compared to free ampicillin, as demonstrated by their improved antifungal and antibacterial activities. The solubility, physical characterization, and spectral analysis provide valuable insights into the structural and physicochemical properties of the complexes, contributing to a comprehensive understanding of their behavior.

The observed increase in antimicrobial activity upon metal complexation underscores the potential of metal coordination as a strategy to enhance the efficacy of antibiotics against microbial pathogens. Metal complexes offer advantages such as improved stability, altered mode of action, and expanded spectrum of activity, making them promising candidates for further development as antimicrobial agents.

However, variations in activity among different complexes and microbial strains highlight the importance of considering factors such as metal ion identity, ligand environment, and microbial susceptibility profiles in the design and optimization of metal-based antimicrobial agents.

The overall findings presented in this study contribute to the growing body of knowledge on metal complexes of antibiotics and provide insights that could inform future research and development efforts aimed at combating microbial infections and addressing the challenge of antimicrobial resistance. The physical analysis

results presented in this study provide a solid foundation for understanding the properties of the synthesized metal complexes of ampicillin and pave the way for further investigations into their antimicrobial activity and potential applications in medicine and biotechnology.

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