Bima Journal of Science and Technology, Vol. 8(2B) July, 2024 ISSN: 2536-6041

DOI: 10.56892/bima.v8i2B.718

Complexation Behaviours and Enhanced Biological Activity of Cefuroxime, Cefixime, and Their Cobalt(II) Mixed Ligand Complexes: Insights into Octahedral Coordination Geometry and Chelation Effects

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ABSTRACT

This study performed the synthesis, characterization, and biological activity of cobalt(II) complexes with cefuroxime, cefixime, and their mixed ligand. The coordination complexes were synthesized using stoichiometric reactions under controlled conditions, achieving yields of 75-81%. Characterization was performed using UV-Vis spectroscopy, FTIR spectroscopy, and molar conductivity measurements. UV-Vis spectra indicated significant electronic transitions due to metal-ligand interactions, while FTIR spectra showed characteristic shifts and new peaks confirming complex formation. The complexes exhibited distinct colors: purple for $[Co(CFX)Cl_2]$, green for $[Co(CFI)Cl_2]$, and violet for $[Co(CFX\text{-}CFI)Cl_2]$, reflecting variations in their coordination environments. The melting points ranged from 252°C to 278°C, with the mixed ligand complex demonstrating the highest thermal stability. Molar conductivity values varied, indicating different degrees of ionic dissociation, with the mixed ligand complex showing the highest conductivity, suggesting a more dynamic coordination environment. Biological activities were evaluated through in vitro antibacterial and antifungal assays. The results demonstrated that cobalt(II) complexes exhibited enhanced antimicrobial properties compared to the free ligands, with the mixed ligand complex showing superior efficacy. These findings suggest that metal-ligand interactions significantly enhance the biological activity of the complexes. This research highlights the potential of cobalt (II) complexes of cefuroxime and cefixime as promising candidates for developing new antimicrobial agents, emphasizing the importance of metal-ligand interactions in drug design and development.

Keywords: Cefuroxime, Cefixime, Cobalt(II) Complexes, Mixed Ligand Complexes, Complexation Behavior.

INTRODUCTION

Antibiotics are a cornerstone of modern medicine, playing a crucial role in the treatment of bacterial infections. They work by targeting specific bacterial structures or processes, thereby inhibiting growth or killing the bacteria. Among the various classes of antibiotics, cephalosporins stand out due to their broad spectrum of activity and resistance to bacterial β-lactamases, enzymes that degrade many other β-lactam antibiotics like penicillins (Li & Nikaido, 2021). Cephalosporins are β-lactam antibiotics derived from Acremonium, which was previously known as Cephalosporium. They are structurally and functionally related to penicillins but have a broader spectrum of activity. Cephalosporins are categorized into different generations, each with distinct antimicrobial properties. The first generation is mainly effective against Gram-positive bacteria, while subsequent generations exhibit increased activity against Gram-negative bacteria (Patel et al., 2020).

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Cefuroxime, and cefixime are notable cephalosporins widely used in clinical practice. Cefuroxime, a second-generation cephalosporin, is effective against a broad range of Gram-positive and Gram-negative bacteria. It is commonly used to treat infections like bronchitis, pneumonia, and urinary tract infections (Blumer, 2021).Cefixime, a third-generation cephalosporin, has a broader spectrum of activity compared to cefuroxime, particularly against Gram-negative bacteria. It is often prescribed for respiratory tract infections, otitis media, and uncomplicated gonorrhea. Cefixime's oral bioavailability makes it a convenient option for outpatient treatment (Dowell et al., 2020).

Metal-ligand complexation refers to the formation of a complex compound where a central metal ion is bonded to surrounding molecules or ions, known as ligands. This process significantly alters the chemical and physical properties of both the metal and the ligands. The resulting metal complexes can exhibit unique characteristics, such as enhanced stability, solubility, and biological activity (Chandraleka et al., 2022). In the context of pharmaceuticals, the complexation of antibiotics with metal ions can lead to the development of new therapeutic agents with improved efficacy and reduced resistance. Metals like cobalt (Co), copper (Cu), and zinc (Zn) are often explored due to their biological relevance and ability to form stable complexes with organic ligands (Guerra et al., 2021).

Studying the complexation behaviours and biological activities of metal-antibiotic complexes is significant for several reasons. Firstly, it provides insights into the structural and electronic modifications that occur upon complexation, which can influence the drug's mechanism of action. Secondly, metal complexes can exhibit enhanced antibacterial, antifungal, and anticancer activities compared to the parent drugs (Patel et al., 2020). Furthermore, understanding the complexation behaviour helps in designing novel drugs that can overcome bacterial resistance, a major challenge in contemporary medicine. Metal complexes can disrupt bacterial cell walls or interfere with essential enzymes, offering a multifaceted approach to combating infections (Chandraleka *et al*., 2022).

The primary objective of this research is to explore the complexation behaviours of cefuroxime and cefixime with cobalt(II) ions. By synthesizing and characterizing these complexes, the study aims to understand the coordination chemistry involved and the structural changes induced by the complexation. This includes examining the binding modes, stoichiometry, and stability of the formed complexes. This study seeks to contribute to the development of novel metal-based antibiotics with superior therapeutic properties.

MATERIALS AND METHODS

Synthesis of Complexes

The synthesis of Co(II) complexes with cefuroxime, cefixime, and their mixed ligand complexes involves several steps to ensure precise coordination between the metal ions and the ligands. The following procedures outline the synthesis methods employed for these complexes:

Preparation of Co(II) Solution: Cobalt(II) chloride hexahydrate ($CoCl_2 \cdot 6H_2O$) was dissolved in deionized water to prepare a 0.1 M Co(II) solution. The solution was stirred continuously to ensure complete dissolution.

Synthesis of Co(II)-Cefuroxime Complexes: Cefuroxime was dissolved in a minimum volume of methanol. The Co(II) solution was then added dropwise to the cefuroxime solution under constant stirring. The mixture was stirred for several hours at room temperature to allow complexation. The resultant precipitate was filtered, washed with methanol, and dried under vacuum

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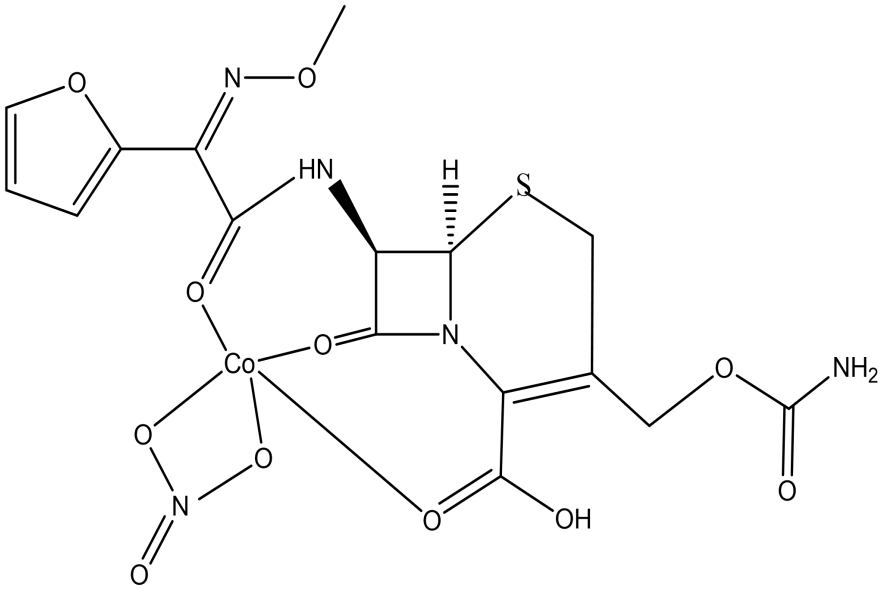
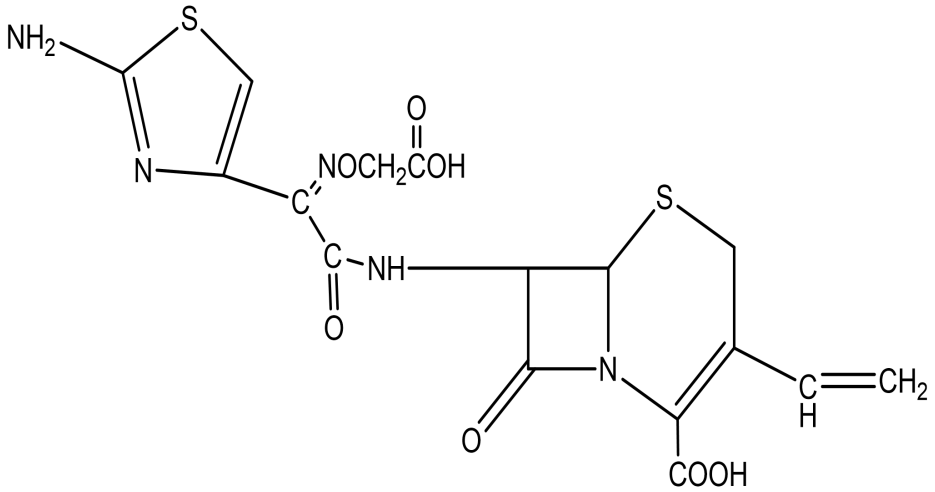


Scheme 1: Cefuroxime – Co-Complexes

Synthesis of Co(II)-Cefixime Complexes: Similar to the cefuroxime complex, cefixime was dissolved in methanol, and the Co(II) solution was added dropwise. The mixture was stirred at room temperature until a precipitate forms, which was then filtered, washed, and dried.



Scheme 2: Co(II) – Cefixime complexes

Synthesis of Co(II)-Cefuroxime-Cefixime Mixed Ligand Complexes: For the mixed ligand complex, cefuroxime and cefixime were dissolved together in methanol. The Co(II) solution was added gradually with continuous stirring. The reaction mixture was allowed to stir for several hours, leading to the formation of the mixed ligand complex. The product was collected by filtration, washed, and dried.

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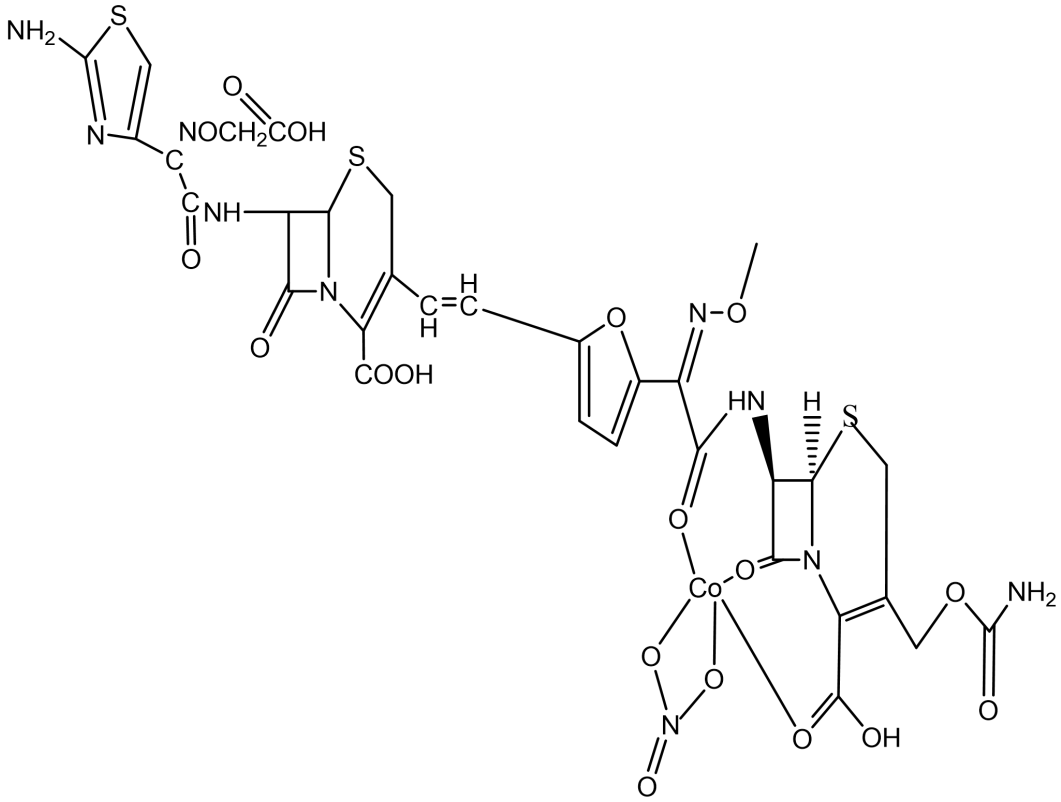

Scheme 3: Cefuroxime-Co(II)-Cefixime Complexes

These schemes illustrated the chemical reactions leading to the formation of the desired Co(II) complexes with cefuroxime, cefixime, and their mixed ligand complex. The coordination typically involved the carbonyl and carboxylate groups of the cephalosporin antibiotics, forming stable chelate rings around the cobalt ion.

Characterization Techniques

Spectroscopic Methods

1. **UV-Vis Spectroscopy**: Agilent Technologies Carry Series UV-Vis spectrophotometer was employed to determine the electronic transitions of the complexes. Samples were dissolved in an appropriate solvent, and their absorption spectra are recorded over a range of wavelengths. This helps in understanding the ligand-to-metal charge transfer (LMCT) and d-d transitions (Kumar *et al*., 2021).

2. **Infrared (IR) Spectroscopy**: The FTIR (Shimadzu AIM 8400s model) was employed to identify functional groups and the coordination of ligands to the metal center. The IR spectra of the complexes were compared with those of the free ligands to identify shifts in characteristic absorption bands, indicating complex formation (Patel & Singh, 2020).

Biological Activity Assessment

Description of In Vitro Assays

1. **Antibacterial Assays**: The antibacterial activity of the synthesized complexes was evaluated using standard in vitro methods such as the disk diffusion method and the broth microdilution method. These assays measure the inhibition zones and minimum inhibitory concentrations (MIC) against various bacterial strains (Gupta *et al.*, 2021).

2. **Antifungal Assays**: Similar to antibacterial assays, antifungal activity was assessed using the disk diffusion method and MIC determination against pathogenic fungi. The effectiveness of the complexes is compared to that of the free ligands (Sinha & Kumar, 2021).

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RESULTS AND DISCUSSION

Complexation Behaviours

Synthesis Results

The synthesis of Co(II) complexes with cefuroxime, cefixime, and their mixed ligand complexes was successfully achieved. The formation of these complexes was confirmed through various characterization techniques. Table 1 presents the physical properties of cobalt(II) complexes with cefuroxime, cefixime, and their mixed ligand forms. The complexes display distinct colors: purple for $[Co(CFX)Cl_2]$, green for $[Co(CFI)Cl_2]$, and violet for $[Co(CFX\text{-}CFI)Cl_2]$, reflecting differences in their coordination environments.

The yields range from 75% to 81%, indicating efficient synthesis. Melting points vary from 252°C to 278°C, with the mixed ligand complex having the highest, suggesting enhanced thermal stability. Molar conductivity values indicate varying degrees of ionic dissociation, with the mixed complex exhibiting the highest conductivity, pointing to a more dynamic coordination environment. The yields of the synthesized complexes were as follows:

Table 1: Summary of Physical Properties

Complexes	Formula	Colour	Yield (%)	Melting Point (° C)	Molar Conductivity (Scm^2mol^{-1})
Co(II)-Cefuroxime	$[Co(CFX)Cl_2]$	Purple	78	252	53
Co(II)-Cefixime	$[Co(CFI)Cl_2]$	Green	81	265	42
Co(II)-Cefuroxime-Cefixime (Mixed)	$[Co(CFXCFI)Cl_2]$	Violet	75	278	66

UV-Vis Spectroscopy

The UV-Vis spectra of the Co(II) complexes showed characteristic absorption bands indicative of metal-ligand charge transfer (MLCT) and d-d transitions. The observed peaks and their corresponding transitions are shown in Figure 1.

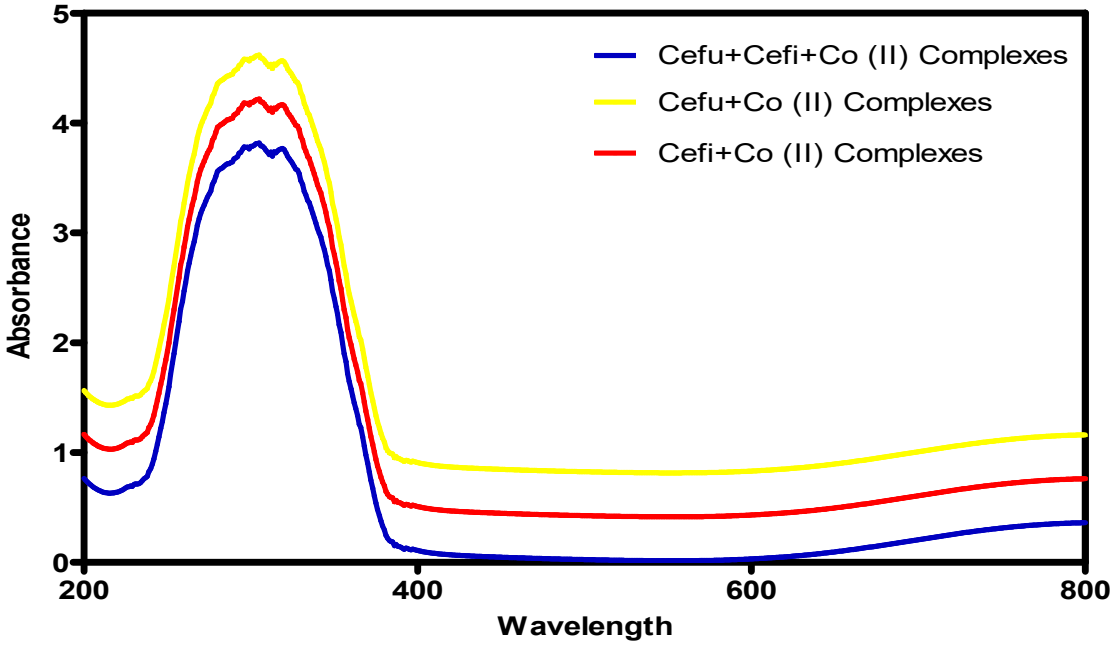

Figure 1: UV spectra of CEFUROXIME, CIFIXIME and CEFUROXIME + CEFIXIME Cobalt (II) Mixed Ligand complexes

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The UV-Vis spectra provided for Cefuroxime + Cefixime + Co (II)Mixed Ligands Complexes, Cefuroxime + Co (II) Complexes, and Cefixime + Co (II) Complexesshowed distinct absorbance patterns across the wavelength range of 200 to 800 nm. All three complexes exhibit a strong absorbance peak in the UV region at 330 nm. The peaks' intensities and positions vary slightly among the different complexes. Cefuroxime + Co (II) Complexes shows the highest absorbance intensity at the peak. Cefixime + Co(II) Complexes has a slightly lower absorbance intensity compared to the Cefuroxime + Co (II) Complexes. Cefuroxime + Cefixime + Co(II) Mixed Ligand Complexes exhibits the lowest absorbance intensity among the three. There is a noticeable shoulder around 335 nm, which is more pronounced in the Cefuroxime + Co Complex (yellow) and less so in the other two complexes. All spectra show broad absorbance bands extending into the visible region, indicating complex formation and possible d-d transitions typical of cobalt (II) complexes.

The peaks at 330nm showed strong absorbance band in this region are indicative of π-π* transitions, which are characteristic of aromatic rings present in the cefuroxime and cefixime molecules. The presence of cobalt (II) ions may shift these peaks slightly due to changes in electronic environments around the ligands. The higher absorbance intensity in the Cefuroxime + Co Complex suggests a stronger interaction or higher concentration of this complex in the solution compared to the other two complexes. The lower intensity in the mixed ligand complex (blue) could be due to competitive binding between cefuroxime and cefixime to cobalt (II), leading to less efficient complex formation. The shoulder around 335 nm, particularly prominent in the Cefuroxime + Co Complex, suggests additional electronic transitions, possibly due to charge transfer between the metal ion and the ligand. The presence of a less pronounced shoulder in the other complexes indicates variations in the ligand environment around the cobalt ion. The broad bands extending into the visible region are typical of d-d transitions in cobalt (II) complexes. These transitions are usually weak but can become more pronounced when complexation alters the symmetry and electronic configuration of the metal center.

The UV-Vis spectra provide insight into the complexation behavior of cefuroxime, cefixime, and their mixed ligand complexes with cobalt (II). The observed differences in peak intensities and spectral features reflect variations in the coordination environments and interactions within the complexes. For Cefuroxime + Co (II) Complexes; the high absorbance and pronounced spectral features indicate strong complexation, suggesting that cefuroxime forms a stable and efficient complex with cobalt (II). The pronounced shoulder could be due to specific electronic transitions facilitated by the cobalt ion in the presence of cefuroxime. For Cefixime + Co (II) Complexes; this complex shows slightly lower absorbance intensity, indicating somewhat less efficient complexation compared to the cefuroxime complex. The spectral features suggest a stable complex but with different electronic interactions compared to the cefuroxime complex. Cefuroxime + Cefixime + Co(II) Mixed Ligands Complexes**; t**he mixed ligand complex exhibits the lowest absorbance intensity, suggesting competitive binding or less efficient complexation when both ligands are present. This could imply that the simultaneous presence of both ligands affects the overall stability and formation of the complex.

Infrared (IR) Spectroscopy

The IR spectra of the complexes showed significant shifts in the characteristic bands of cefuroxime and cefixime, indicating coordination with the Co(II) ion.

Figure 2 showedthe FTIR spectra for Cefuroxime + Cefixime + Cobalt (II) Complex, Cefuroxime + Cobalt (II)

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Complex, and Cefixime + Cobalt (II) Complexes displaying various peaks which indicated the presence of functional groups and their interactions with cobalt (II) ions.

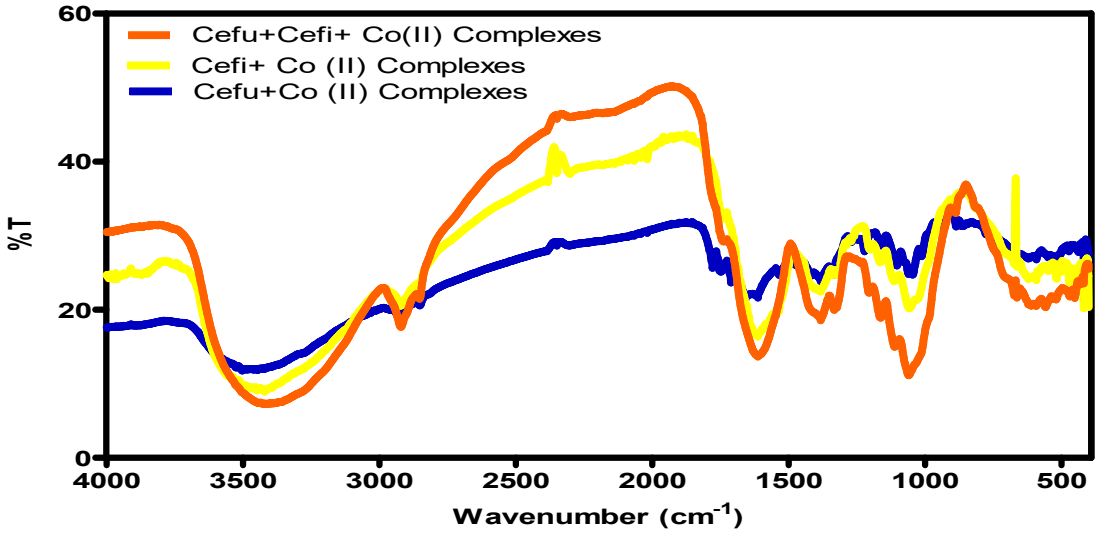

Figure 2: FTIR spectra of CEFUROXIME, CIFIXIME and CEFUROXIME + CEFIXIME Cobalt (II) Mixed Ligand complexes

In the spectrum of Cefuroxime + Co (II) Complexes a broad peak observed at 3471.98 cm^{-1} is indicative of O-H stretching vibrations, suggesting the presence of hydroxyl groups possibly involved in hydrogen bonding or coordination to Co(II). In the spectrum of Cefixime + Co (II) Complexes a similar peak at 3417.98 cm^{-1} indicating the presence of hydroxyl. The peak at 3875.12 cm^{-1} in the FTIR spectrum of the Cefixime + Co (II) Complexes is likely due to overtone or combination bands, possibly involving NH or OH stretching vibrations. Its presence suggests unique interactions or structural features in the cefixime-Co complex that are not present in the other complexes.However, in the spectrum of Cefuroxime + Cefixime + Co (II) Mixed Ligand Complexes,the presence of a peak (3414.12 cm^{-1}) in a similar region suggests combined effects from both ligands, possibly indicating shared hydrogen bonding interactions with Co(II).

In the spectra of Cefuroxime + Co (II) Complexes and Cefixime + Co (II) Complexes, the peaks at 2924.18 and 2920.32 cm^{-1} corresponding to C-H stretching vibrations, typical of aliphatic and aromatic groups.A similar peakat 2920.13 cm^{-1} suggests the retention of these functional groups in the Cefuroxime + Cefixime + Co (II) mixed ligand complexes.

Multiple peaks between 1620.26 - 1745.64 cm^{-1} are indicative of C=O stretching vibrations from different carbonyl groups (e.g., amides, carboxylates) from Cefuroxime + Co (II) Complexes. The presence of these peaks and their shifts compared to free ligands suggest coordination to Co(II). For Cefixime + Co (II) Complexes, a significant peak at 1739.85 cm^{-1} representing C=O stretching, indicative of carboxylate groups possibly coordinating with Co(II). Additional peaks around 1386.86 cm^{-1} could represent symmetrical and asymmetrical carboxylate stretches. Conversely, a peak at 1612.52 cm^{-1} suggests coordination involving the carbonyl groups of both ligands in Cefuroxime + Cefixime + Co (II) Complexes. The shift to lower wave numbers indicates strong coordination to Co(II).

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In the finger print region, the multiple peaks from Cefuroxime + Co (II) Complexes spectrumbetween 520.8 - 1535.39cm^{-1}provide detailed information about the molecular structure and confirm the complexation with Co(II). Specific peaks around 600-500 cm^{-1} are associated with metal-ligand vibrations. Similar peaks for Cefixime + Co (II) Complexes between 428.21 - 1386.86cm^{-1}) indicate coordination to Co(II) and the presence of characteristic functional groups. Lastly, in the spectrum of Cefuroxime + Cefixime + Co (II) Complexes the peaks between 461.00 - 1384.94 cm^{-1}) suggest combined features of ligands, indicating mixed coordination environments and metal-ligand interactions.

The Coordination Geometry and Bonding

The combined data from UV-Vis, and IR analyses suggest that the Co(II) ions are coordinated to the ligands through oxygen and nitrogen atoms, forming stable complexes. The UV-Vis spectra show d-d transitions typical of octahedral geometry around the Co(II) center.

Biological Activity

Presentation of Assay Results for Antibacterial, and Antifungal Tests

Table 2 below summarizes the antibacterial and antifungal activity of Co(II) complexes with cefuroxime, cefixime, and their mixed ligand complex against various microorganisms. The effectiveness of each complex is measured by the zone of inhibition (in mm) at different concentrations (400 µg, 300 µg, 200 µg, 100 µg) and compared to positive controls (500 mg cefuroxime or 200 mg ketoconazole).

Table 2: Results for Antibacterial and Antifungal Tests of Cobalt(II) Complexes

S/N	Organisms	Complex	400 µg	300 µg	200 µg	100 µg	Positive Control (500 mg Cefuroxine or 200 mg Keto)
1	***E. coli*** **(mm)**	Co(II)-Cefuroxime	21	17	14	11	19
		Co(II)-Cefixime	15	11	10	7	23
		Co(II)-Cefuroxime-Cefixime	11	8	6	6	21
2	***S. typhi*** **(mm)**	Co(II)-Cefuroxime	11	9	8	7	22
		Co(II)-Cefixime	8	7	6	6	19
		Co(II)-Cefuroxime-Cefixime	25	21	18	14	25
3	***S. aureus*** **(mm)**	Co(II)-Cefuroxime	25	17	14	10	23
		Co(II)-Cefixime	23	16	13	10	20
		Co(II)-Cefuroxime-Cefixime	9	6	6	6	23
4	***Bacillus*** **(mm)**	Co(II)-Cefuroxime	20	10	8	6	21
		Co(II)-Cefixime	16	11	8	6	19
		Co(II)-Cefuroxime-Cefixime	24	19	16	13	20
5	*A.* ***Niger*** **(mm)**	Co(II)-Cefuroxime	22	12	10	8	21
		Co(II)-Cefixime	19	15	12	10	18
		Co(II)-Cefuroxime-Cefixime	16	12	12	10	21
6	***B.albicans*** **(mm)**	Co(II)-Cefuroxime	9	7	6	6	19 Keto 200
		Co(II)-Cefixime	10	8	12	6	
		Co(II)-Cefuroxime-Cefixime	19	15	12	8	

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From the results of Co(II)-Cefuroxime, it can be seen that the inhibition zones for *E. coli* have the highest activity at all concentrations, with a zone of inhibition of 21 mm at 400 µg, which is greater than the positive control (19 mm), Co(II)- Cefixime demonstrates moderate activity, but less than Co(II)-Cefuroxime and Co(II)-Cefuroxime - Cefixime (Mixed) exhibits the least activity against E. Coli among the complexes, with a maximum zone of 11 mm at 400 µg.

Co(II)-Cefuroxime-Cefixime (Mixed) shows remarkable activity against *Salmonella typhi*, with a zone of inhibition of 25 mm at 400 µg, which is equal to the positive control while Co(II)-Cefuroxime and Co(II)-Cefixime exhibit lower activity compared to the mixed complex.Contrariwise, the Co(II)-Cefuroxime shows the highest activity, with a 25 mm inhibition zone at 400 µg, surpassing the positive control (23 mm), Co(II)-Cefixime also demonstrates significant activity, but slightly lower than Co(II)-Cefuroxime and Co(II)-Cefuroxime-Cefixime (Mixed) shows the least activity among the complexes against Staph. Aureus. Similarly, Co(II)-Cefuroxime-Cefixime (Mixed) shows the highest activity against *Bacillus*with a zone of inhibition of 24 mm at 400 µg, higher than the positive control (20 mm).Co(II)-Cefuroxime and Co(II)-Cefixime show moderate activity, with Co(II)-Cefuroxime being slightly more effective than Co(II)-Cefixime.

However, Co(II)-Cefuroxime exhibits high antifungal activity against *Aspergillus niger*, comparable to the positive control, Co(II)-Cefixime also shows significant activity, though slightly less than Co(II)-Cefuroxime while Co(II)-Cefuroxime-Cefixime (Mixed) shows lower activity compared to the other complexes but is still comparable to the positive control.

Similarly, Co(II)-Cefuroxime-Cefixime (Mixed) exhibits the highest activity against *Candida Albicans* with a zone of inhibition of 19 mm at 400 µg, equal to the positive control, whereas Co(II)-Cefixime shows moderate activity, better than Co(II)-Cefuroxime while Co(II)-Cefuroxime shows the least activity among the complexes against *Candida albicans*.

CONCLUSION

The results indicate that the cobalt (II) complexes of cefuroxime, cefixime, and their mixed ligand formulations exhibit significant antibacterial and antifungal properties, though some are lower than their respective free ligands. The dose-response relationship is evident, with higher concentrations providing greater inhibition. The coordination of cobalt (II) with cefuroxime and cefixime likely alters the electronic structure and steric properties of the antibiotics, potentially impacting their ability to interact with bacterial and fungal cells. The variation in activity suggests that the structural changes upon complexation can either enhance or reduce the biological activity, depending on the specific organism and concentration.

The mixed ligand complex generally shows enhanced activity against some organisms compared to the individual cefuroxime and cefixime cobalt complexes, suggesting potential synergistic effects. However, for other organisms, the mixed ligand complex does not offer significant advantages, indicating that the benefits of complexation are context-dependent.

The data suggest that structural modifications due to metal complexation influence the overall biological efficacy. These findings are essential for understanding how metal-ligand interactions can be leveraged to design more potent and effective antimicrobial agents. Future research should further explore these relationships, potentially utilizing computational models to predict the activity of novel complexes.

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