Bangladesh Pharmaceutical Journal ***28****(1): 11-19, 2025 (January)*

Characterization and Antimicrobial Studies of Cobalt(II) Complexes with Some Antibacterial Agents

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(Received: June 12, 2024; Accepted: October 10, 2024; Published (web): October 20, 2024)

Abstract

Metal complexes of antibiotics have shown promising antimicrobial activities against some resistant strain of bacteria by inhibiting the growth or killing the microorganisms. This phenomenon has lot of impact when the pathogenic microorganisms develop continuous resistance to the available antibiotics via various cellular defense mechanisms. Therefore, the search for alternative drug-molecules is of prime importance to combat antimicrobial resistance microorganisms. Antibiotic complexes with metal ions have attracted the attention of scientists looking for new drugs and to increase the activity of currently available antibiotics. The bioactivity of antibiotics can be improved by coordination of metal ions. To do so, cobalt(II) complexes of different antibiotics have been prepared from reaction of cobalt(II) nitrate with the antibiotics viz. amoxicillin, cefpodoxime proxetil (CFP), gatifloxacin, metronidazole, sulfamethoxazole, ketoconazole and levofloxacin. The synthesized compounds were characterized by TLC, solubility testing, melting point determination, UV-spectrophotometry and FTIR analysis. The compounds were screened for antibacterial activity against *Bacillus cereus, Pseudomonas aeruginosa, Salmonella typhi, Staphylococcus aureus, Escherichia coli* and *Salmonella abony*, and it was found that the synthesized complexes exhibited potent antibacterial activity.

Key words: Cobalt complex, amoxicillin, cefpodoxime, gatifloxacin, metronidazole, sulfamethoxazole, ketoconazole, levofloxacin.

Introduction

The fusion of cutting-edge medications and advanced technology stands as a remarkable boon and unlocking diverse dimensions in the realm of infectious disease treatment. A pivotal triumph within this landscape is the revelation of antimicrobial drugs, an extraordinary blessing for human well-being. These groundbreaking discoveries and innovations not only alleviate suffering but also herald a new era of health and vitality, exemplifying the powerful synergy between modern science and our pursuit of a healthier, thriving world (Mayegowda *et al*., 2022). Antimicrobials encompass therapeutic agents employed to prevent or treat infections, comprising antiseptics, antibiotics, antivirals, antifungals, and antiparasitics. Disinfectants, on the other hand, are antimicrobial substances utilized on inanimate surfaces. These agents have the ability to eliminate or hinder the growth of microorganisms by targeting essential processes in cellular metabolism. This may involve disrupting the synthesis of biological macromolecules, influencing the activity of cellular enzymes, or impacting cellular structures like the cell wall and membranes (DiMartino, 2022; Romani *et al*., 2022; Hood and Khan, 2020).

The recognition of the pivotal role of metal ions in biological systems has been long-standing. Metals exhibit distinctive features such as redox activity, coordination site availability, and reactivity with organic groups. Elevated concentrations of metal ions are linked to various pathological effects, including the development of cancer. Consequently, the field of medicinal chemistry finds coordination metal

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DOI: https://doi.org/10.3329/bpj.v28i1.79435

complexes as drug candidates highly compelling and intriguing, given their unique attributes (Lippard and Berg, 1994; Penland *et al*., 1957; Aktar *et al*., 2020; Aktar *et al*., 2021; Aktar *et al*., 2022; Dey *et al*., 2021a; Dey *et al*., 2021b). Metal ions play crucial roles in both catalytic and structural aspects of biological systems. Approximately one-third of the proteins encoded by the human genome incorporate a metal ion as a cofactor, highlighting their significance in various biological processes. For instance, iron (Fe) serves as a pivotal ion within blood proteins (e.g. hemoglobin) involved in respiration and electron transport, underscoring its essential role in these physiological pathways (Hsia, 1998).

Various first-row transition metals, such as iron, copper, zinc, manganese and cobalt, play crucial roles as essential elements for human well-being. Essential elements are defined by their necessity for life, and the absence of these elements can lead to death or severe malfunction in organisms. It is noteworthy that beyond mammals, the biosphere encompasses diverse organisms, and for many of them, additional metal ions are indispensable for their growth and development. It's crucial to highlight that an element's essentiality can differ based on whether the focus is on humans or other organisms (Van Cleave and Crans, 2019).

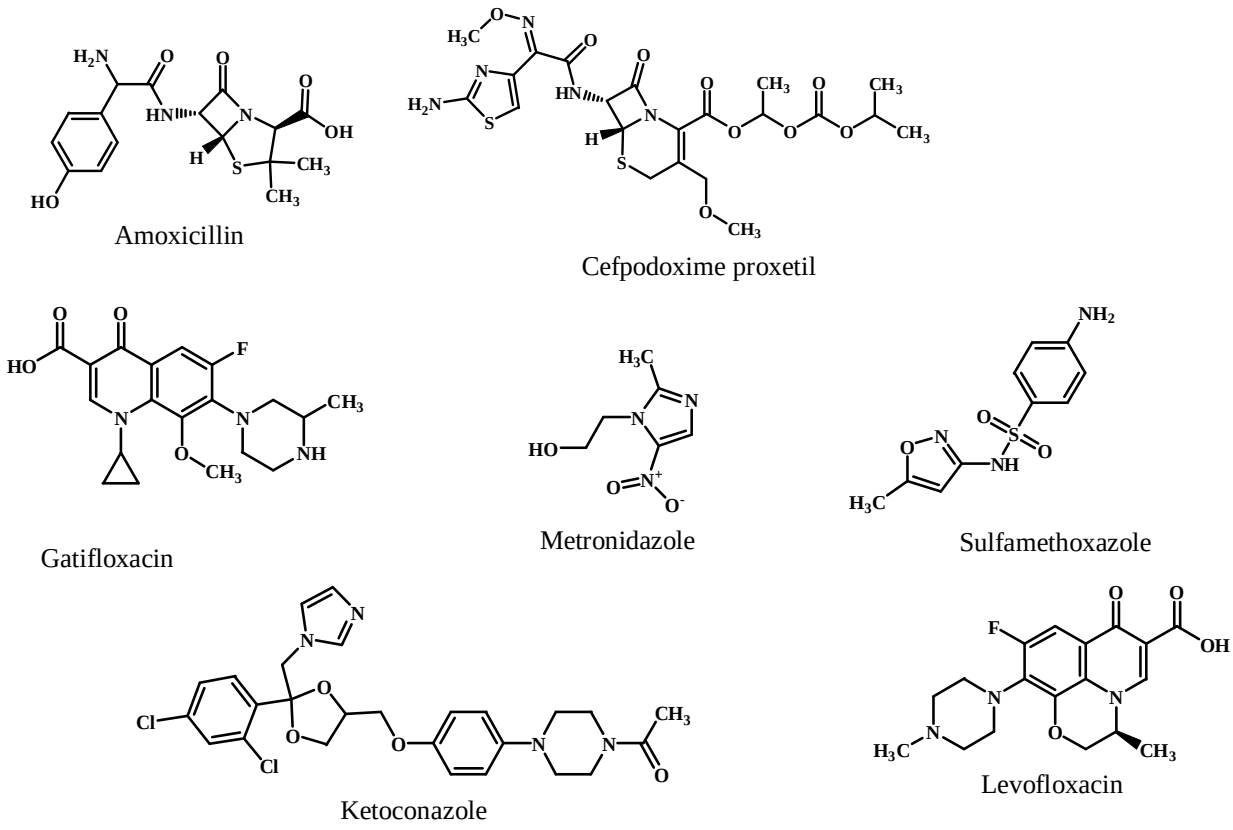

Figure 1. Structures of the selected antibiotics for complex formation.

Cobalt, a precious constituent of the Earth's crust, holds a vital role for mammals, particularly in the indispensable form of cobalamin, also known as vitamin B_{12}. In human diets, cobalt intake fluctuates between 5 and 50 μg/day, predominantly in its inorganic state, with vitamin B_{12} constituting only a fraction of this essential element (Lison, 2007). Cobalt, with its two predominant valence states of

cobaltous(II) and cobaltic(III), finds its prime application in the chemical industry, with cobaltous being the prevalent choice. Occurring naturally in arsenides, oxides, and sulfides, cobalt serves as a cornerstone in the production of cobalt superalloys, primarily in its metallic form (Barceloux and Barceloux, 1999).

Complexes of cobalt with the selected antibiotics (Figure 1) viz. amoxicillin, cefpodoxime, gatifloxacin, metronidazole, sulfamethoxazole, ketoconazole and levofloxacin were synthesized and characterized through solubility testing, melting point determination, UV-spectroscopy, and FTIR analysis. The synthesized cobalt complexes were then subjected to *in vitro* assessment for antibacterial and antifungal activities against a panel of multidrug-resistant pathogens including *Bacillus cereus, Pseudomonas aeruginosa, Salmonella typhi, Staphylococcus aureus, Escherichia coli* and *Salmonella abony*.

Materials and Methods

Chemicals and reagents: Antibiotics i.e. amoxicillin (99.11%), cefpodoxime proxetil (CFP) (99.05%), gatifloxacin (99.61%), metronidazole (98.22%), sulfamethoxazole (99.40%), ketoconazole (99.28%), and levofloxacin (99.72%) were collected from Eskayef Pharmaceuticals Ltd., Dhaka, Bangladesh. Cobalt nitrate, methanol and DMSO were purchased from Merck, Germany. The chemicals used in this experiment were of analytical grade, and double-distilled water was used to prepare the analytical solutions. Silica gel coated thin layer chromatographic (TLC) plate from Merck, Germany was used for purification and analytical studies.

Instrumentation: FT-IR spectra were recorded with the IRTracer-100 type FTIR-8400S spectrometer (Shimadzu, Japan), which shows stable dynamic alignment mechanism and a high S/N ratio of 60,000:1 for highly sensitive and accurate measurements. UV analyses were carried out by using UV-Spectrophotometer (Model: UV 1800, Shimadzu, Japan). Melting points were determined with BUCHI melting point B-545 apparatus.

Drug-metal interaction: Cobalt antibiotic-complexes were prepared by mixing cobalt nitrate and antibiotics at a molar ratio of cobalt: drug (1:1) in aqueous methanol (Shalash and Abu Ali, 2017). 91.47 mg cobalt nitrate was used to prepare 500 mL of 1 mMol solution in methanol and 1 mMol 25 mL of antibiotic solution was prepared by using 9.135 mg, 10.69 mg, 9.38 mg, 4.28 mg, 6.332 mg 13.28 mg 7.258 mg and 9.034 mg of amoxicillin, cefpodoxime, gatifloxacin, metronidazole, sulfamethoxazole, ketoconazole, trimethoprim, and levofloxacin, respectively. Then 25 ml of cobalt solution was mixed with 25 mL of drug solution. All the prepared solutions were filtered using 0.45 µm filter. The mixtures were then heated at 70-75 °C for 6.30 hour in a water bath with occasional stirring. The mixtures were kept in an oven for overnight for drying. Solvent was removed by using rotavapor under reduced pressure. Then it was dried in oven at 40 ^{0}C and stored in desiccator at room temperature. The metal complexes were found to be air and moisture stable at room temperature.

Characterization: Cobalt-antibiotic complexes were characterized by melting point study, thin-layer chromatography (TLC) and FT-IR spectrophotometry. For FT-IR study, potassium bromide and metal-antibiotic complex (1:1 ratio, w/w) was used to prepare the KBr disc. Samples were mixed with KBr in a mortar and then pressed for 2-3 minutes to form a semitransparent pellet which lets light be transmitted to the detector. The disc was then placed directly into the path of the infrared beam for each measurement.

Antibacterial study: The antibacterial study of the complexes was investigated against *B. cereus, Ps. aeruginosa, S. typhi, S. aureus, E. coli* and *S. abony* using disc diffusion method (Anjum *et al*., 2016; Anjum *et al*., 2021; Bauer *et al*., 1966) and incubated at 37 ^{o}C for 24 hours. After incubation period, the diameter of the zone formed around the paper disc were measured and expressed in mm (Inouye *et al*., 2001).

Results and Discussion

Cobalt-antibiotic complexes were characterized by melting point study, TLC and FT-IR spectrophotometry. Physical characteristics of cobalt salt and antibiotics, % yield and melting point (MP) of cobalt(II)-antibiotic complexes are shown in Tables 1 and 2.

From tables 1 and 2, it is obvious that the melting points (MP) were found to be different for the cobalt(II)-antibiotics complexes indicated the formation of new complex molecules.

TLC is an important method for qualitative as well as quantitative analysis of drugs. TLC analysis of the ligands and complexes were carried out over precoated silica gel plate using methanol-DCM (7:3) and the R_f values of the complexes were found to be different from the corresponding ligand (Table 3). Single spots of the complexes on TLC plate (Figure 2) as well as the different R_f values (Table 3) indicated the formation of the complexes.

Characterization of the complexes by FT-IR: The FT-IR spectra of different antibiotics and their cobalt(II) complexes were recorded in the region between 4000 and 400 cm^{-1}. These spectra were compared with the spectra of the noncomplexed

Table 1. Physical characteristics of cobalt salt and antibiotics.

Sample	MW	Appearance/color	Solubility	MP (^oC)
Cobalt nitrate hexahydrate	291.03	Red crystalline (hexahydrate)	Water and alcohol	55
Amoxicillin	419.4	Nearly white, crystalline powder/ powder	Water	288
Cefpodoxime *proxetil*	427.45	White powder	Water	148
Gatifloxacin	375.4	White to pale yellow in color	DMSO and dimethyl formamide (DMF)	126-128
Metronidazole	171.15	White to pale yellow crystalline powder.	Water (1.0), ethanol (0.5), ether (<0.05) and chloroform (<0.05).	159 to 163
Sulphamethoxazole	253.28	White to off-white crystalline powder	Low soluble in water, in ethanol is approximately 0.25 mg/mL and approximately 50 mg/ml in DMSO and DMF.	169
Ketoconazole	531.4	White to slightly beige, odorless powder	Very low solubility (17 µg/mL) in water, freely soluble in dichloromethane; soluble in methanol; sparingly soluble in ethanol (~750 g/l) TS	148-152
Levofloxacin	361.4	Light yellowish white to yellow-white crystal or crystalline powder	In glacial acetic acid, chloroform; sparingly soluble in water	213-218

Table 2. Percent yield and melting point (MP) of cobalt(II)-antibiotics complexes.

Name of complex	Color	% Yield	MP (^oC)
Co(II)-amoxycillin	Yellowish grey	80	156.3
Co(II)-cefpodoxime	Deep ash	75	255.5
Co(II)-gatifloxacin	White	81	401.6
Co(II)-metronidazole	Reddish	80	*
Co(II)-sulfamethoxazole	Reddish	76	*
Co(II)-ketoconazole	Pink	85	*
Co(II)-levofloxacin	Purple	82	*

*above 450 ^oC

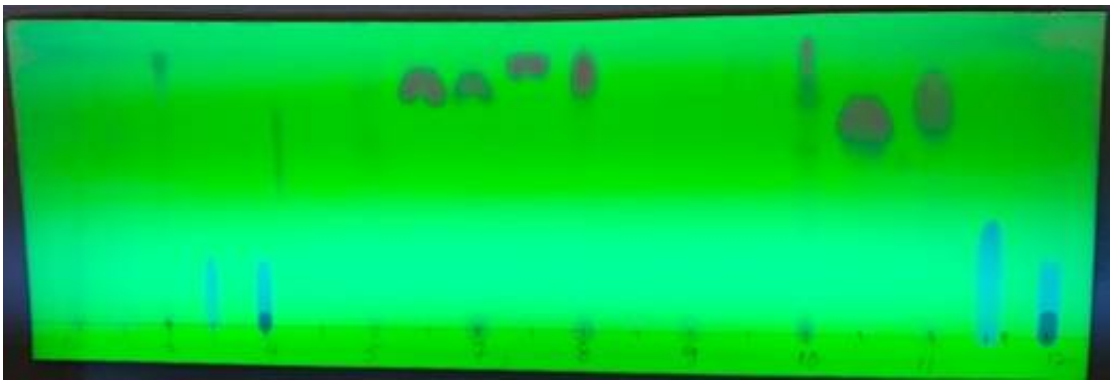

Figure 2. TLC spots of cobalt(II)-antibiotics complexes.

Table 3. R_f values of cobalt(II)-antibiotics complexes in methanol-DCM (7:3).

Complexes	R_f Value
Co(II)-amoxycillin	0.98
Co(II)-cefpodoxime	0.60
Co(II)-gatifloxacin	0.28
Co(II)-metronidazole	0.88
Co(II)-sulfamethoxazole	0.78
Co(II)-ketoconazole	0.25
Co(II)-levofloxacin	0.20

(parent) drugs. The results of the FT-IR measurements of antibiotics as well as metal complexes have been shown in Figure 3. The summarized assignments of the main bands (those affected by coordination) were identified and described as follows:

a) Co(II)-amoxicillin complex displayed strong stretching peaks at 3423.65, 3774.69, 2926.01, 1643.35, 1354.03, 1165, 837.11,759.95, 567.07 cm^{-1} whereas the pure amoxicillin displayed peaks at 3780.48, 3658.96, 1784.51, 1583.56, 1479.40, 1384.89, 1319.31, 1251.80, 839.03 cm^{-1} which indicated the formation of Co(II)-amoxicillin complex (Figure 3A).

b) The complex of Co(II) and cefpodoxime revealed strong and broad peaks at 3398.57 cm-1 and 1384.89 cm^{-1} and other peaks at 3776.62, 1761.0, 1625.99, 1049.28, 825.53, 596.00 cm^{-1} which were different from peaks of the pure cefpodoxime proxetil obtained at 3948.29, 3784.34, 3657.04, 2958.81, 2819.93, 2372.44, 2318.44, 1768.72, 1271.09 and 1074.35 cm^{-1}). These indicated the formation of Co(II)-cefpodoxime complex (Figure 3B).

c) Pure gatifloxacin exhibited FT-IR peaks at 3782.41, 3655.11, 3431.36, 2374.37, 1732.08, 1627.92, 1446.61, 1323.17, 1278.81 cm^{-1} which were shifted in the spectrum of the Co(II)-gatifloxacin complex and showed strong characteristic bands at 3772.76, 3417.86 2926.01, 2850.79, 1618.28, 1460.11, 1371.39, 1058.92 cm^{-1}. This also indicated the formation of Co(II)-gatifloxacin complex (Figure 3C).

d) The mixture of Co(II) and metronidazole displayed strong bands at 3402.43 and 1384.89 cm^{-1} and other peaks at 2933.73, 2858.51, 2490.10, 2293.36, 1554.63, 1481.33 cm^{-1}. On the other hand the pure metronidazole revealed peaks at 32.21.12 (strong stretching), 3097.68, 2946.16, 2845, 2738.92, 2650.19, 2520.96, 2366.66, 2139.06, 1479.40 cm^{-1}. The different peaks of the mixture from that of the parent drug also concluded the production of a new complex molecule (Figure 3D).

e) The mixture of Co(II) and sulphamethoxazole displayed absorptions at 3329.14, 2360.87, 2337.72, 1660.71, 1614.42, 1560.41 and 1381.03 $cm^{-1.}$ On the contrary, pure sulfamethoxazole gave peaks at 3325.28, 3163.26, 2924.09,

2792.93, 2586.54, 1653, 1562.34, 1506.41 cm^{-1}. This shifting of the peaks of pure sulfamethoxazole also indicated the formation of Co(II)-sulphamethoxazole complex (Figure 3E).

f) The mixture of Co(II) and ketoconazole showed strong and broad peaks at 3404.36, 1382.96 cm^{-1} and at 1635, 1111, 831.32, 650.01, 470.63 cm^{-1}. Besides, the pure ketoconazole exhibited peaks at 3176.76, 2899.01, 1398.39, 1186.22, 711.73 cm^{-1} wavelengths which indicated the formation of Co(II)- ketoconazole complex (Figure 3F).

g) Finally, the pure levofloxacin showed peaks at 3784.34, 3427.51, 3269.34, 2981.95, 2806.43, 1890.24, 1720.50 and 1446.61 cm^{-1} in its FT-IR spectrum whereas Co(II)-levofloxacin complex displayed peaks at 3765.05, 3697.54, 3431.36, 2926.01, 2858.51, 2754.35, 1624.06, and 1354.03 cm^{-1}. Hence, the formation of Co(II)-levofloxacin complex (Figure 3G) was confirmed.

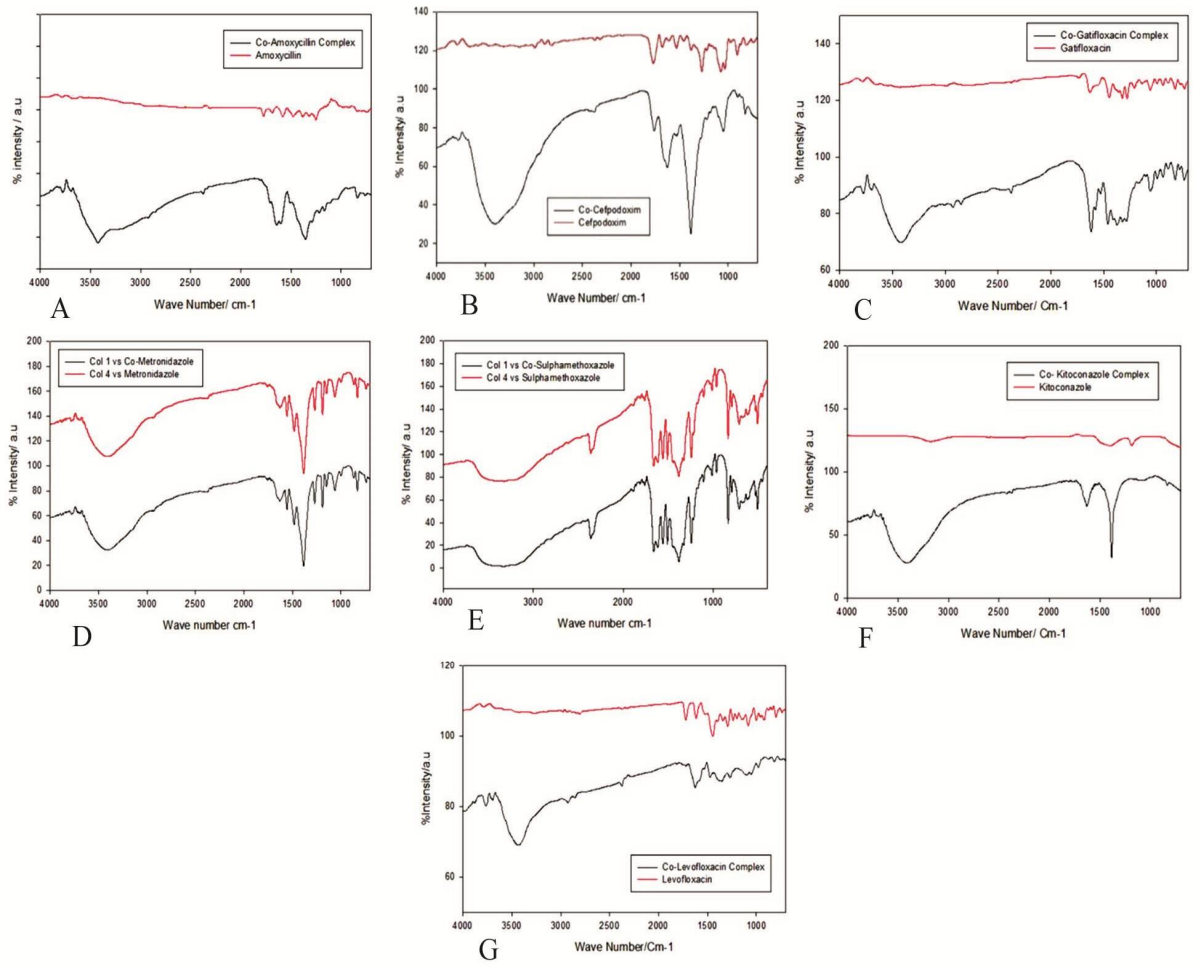

Figure 3. FT-IR spectra of amoxicillin and Co(II)-amoxicillin complex (A), cepfodoxim and Co(II)-cepfodoxim complex (B), gatifloxacin and Co(II)-gatifloxacin complex (C), metronidazole and Co(II)-metronidazole complex (D), sulphamethoxazole and Co(II)-sulphamethoxazole (E), ketoconazole and Co(II)-ketoconazole complex (F), levofloxacin and Co(II)-levofloxacin complex (G).

Table 4. Antibacterial activity of some standard drugs and cobalt-drug complexes.

Test sample (50 µg/disc)	Zone of inhibition (mm)					
	B. cereus	*Ps. aeruginosa*	*S. typhi*	*S. aureus*	*E. coli*	*S. abony*
Amoxicillin (Standard)	45±0.58	46±1.15	44±1.15	0	43±0.58	42±1.15
Cefpodoxime proxetil (Standard)	45.67±0.67	44.67±0.58	47±0.58	0	43.67±0.58	36±0.58
Levofloxacin (Standard)	48.67±1.20	46.67±0.88	51.67±0.88	0	45.67±1.20	49±1.15
Co(II)-amoxicillin	0	0	0	0	0	47.33±0.88
Co(II)-cepfodoxim	34.67±0.88	35±0.58	15.67±0.67	34.33±1.20	11±0.58	0
Co(II)-gatifloxacin	32.33±0.67	37.33±0.88	50±0.58	15±1.15	18±1.73	23±0.58
Co(II)-metronidazole	26.67±0.88	15±1.15	15±0.58	12.33±0.88	0	44±1.15
Co(II)-sulphamethoxazole	20.33±0.88	15.33±0.67	26.67±0.88	11.33±0.88	20±0.58	24.33±0.67
Co(II)-ketoconazole			28.33±0.88	12±1.15	38±0.58	15.67±0.88
Co(II)-levofloxacine	40±1.15	47.33±0.88	44±1	15±0.58	47±0.58	14±0.588

Values are presented as the Mean ± SEM (n=3).

Cobalt(II) complex with amoxicillin showed significant activity against *S. abony* and it was found to be inactive against *B. cereus*, *Ps. aeruginosa*, *S. typhi*, *S. aureus* and *E. coli*. Other complexes were showed moderate to significant activity against all the strains tested (Table 4). Among them Co(II)-gatifloxacin and Co(II)-metronidazole demonstrated maximum antibacterial activity against *S. typhi* and *S. abony*. It was noted that in most cases the complexes showed higher activity than the parent drugs with few exceptions like Co(II)-metronidazole against *Ps. aeruginosa* and Co(II)-sulphamethoxazole, Co(II)-ketoconazole, Co(II)-levofloxacin against *S. aureus*.

Remarkably, the cobalt complexes of the studied drugs exhibited significant antibacterial activity compared to the respected standard drugs (Saha *et al*., 2009). A recently reported cobalt complex features a mixed ligand arrangement, incorporating 1,10-phenanthroline (1,10-phen) and azide co-ligands. In these complexes, the equatorial and terminal azide ligands exhibit a non-linear coordination to the central cobalt ion. Two 1,10-phen ligands coordinate to the cobalt ion through four N-atoms, with two in the axial and two in the equatorial positions. The Co ion adopts a slightly distorted octahedral environment, involving four phenanthroline N-atoms and two nitrile N-atoms from the azides. The molecular structure is stabilized by weak C-H … O and C-H … N intermolecular interactions, along with face-to-face π–π stacking interactions between the aromatic rings of the 1,10-phen ligands. In preliminary antimicrobial screening, the complex was tested against four pathogenic bacteria and four fungi species (Gaëlle *et al*., 2016). Structural analysis demonstrates that the central cobalt ion adopts a distorted octahedral configuration, characterized by a CoN_4O_2 chromophore. Weak intermolecular hydrogen bonding and/or π-interactions facilitate the binding of molecular units within these complexes. Additionally, the antimicrobial efficacy of both the complexes and their constituent Schiff bases has been assessed against various bacteria and fungi (Ghosh *et al.*, 2018). Two cobalt imidazolate metal-organic frameworks were tested for their bactericidal properties against Gram-negative bacteria *Ps. putida* and *E. coli*. Even under challenging conditions, with bacteria in their exponential growth phase and in their respective culture media, these materials inhibited growth by over 50% at concentrations of 5-10 mg/l. The released metal maintained its antibacterial effectiveness for at least 3 months, demonstrating excellent durability. These cobalt-based materials can be easily prepared using inexpensive commercial ligands, suggesting a promising future for their application as affordable antimicrobial materials (Aguado *et al*., 2014). Cobalt

nanoparticles also showed activity against a number of bacterial strains (Ali *et al*., 2023).

It is also noted that the diverse properties of cobalt can be harnessed to create intriguing drug candidates. Reports indicate that cobalt complexes exert biological effects through various mechanisms, including the inhibition of proteins, modification of drug activity, and the activation of bioreductive processes (Heffern *et al.*, 2013). It has been reported that the presence of cobalt ions in vitamin B_{12} causes the activities of vitamins B_2 and P to be destroyed when given with vitamin B_{12} (Yarnykh *et al.*, 2020). No other incompatibilities have been reported. It is important to avoid taking cobalt-drug complexes alongside those vitamins that are prone to interaction. Recent studies indicated that the ongoing discussion implies that although the primary drug may develop resistance over time, certain complexes could emerge as promising candidates for new medications.

Conclusion

In this research endeavor, we embarked on a journey to unveil the intricate synthesis, meticulous characterization, and profound biological explorations of cobalt complexes with antimicrobial drugs. Synthesis of coordination/complex compounds consisting of Co(II) with some antibiotics such as amoxicillin, cefpodoxime, gatifloxacin, metronidazole, sulfamethoxazole, ketoconazole, trimethoprim and levofloxacin have been carried out. The characterization results provided an evidence of complexation involving the ligands through NH, COO and Cl groups. The *in vitro* antibacterial assays of the complexes demonstrated higher bactericidal efficacy than the parent molecules in most of the cases. This research represents a promising model for novel antibacterial therapeutic designs for future endeavors.

Acknowledgement

The authors would like to express their appreciation to the CARS (Centre for Advanced Research in Sciences) in University of Dhaka, Bangladesh and the Laboratory of Pharmaceutical Microbiology, International Islamic University Chittagong, Bangladesh for their support, resources and infrastructural facilities required to conduct this research.

Authors Contribution

MAS design, acquisition, analysis, interpretation of data and drafting of manuscript. MZS contributed to conception, design, and interpretation of data; revised the manuscript. MMM contributed to conception, supervised the work and revised the manuscript. MAR supervised the work, revised the manuscript and gave final approval.

Competing Interests: The authors declared no competing interests.

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