



Synthesis, Structure Delineation and Antibacterial Activity Study of Metal (II) Complexes of Schiff Base Derived from Kanamycin and Methyl Ester of Amoxicillin

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Authors' contributions

This work was carried out in collaboration between both authors. Author NKC designed the study, managed the analyses, wrote the protocol and first draft of the manuscript. Author PM performed molecular modeling of the study and furnished the final draft of the manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

A novel Schiff base ligand was synthesized from Kanamycin and methyl ester of Amoxicillin in stoichiometric ratio. Three metal chlorides viz. $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ and ZnCl_2 were used for the synthesis of respective metal complexes from synthesized novel ligand. The proposed structure of the complexes have been established by various microanalytical and spectral techniques like elemental analysis, TG/DTA studies, conductivity measurement, IR, ^1H NMR, Electronic and mass spectrometry. Various shifting in the band positions in IR spectra of the complexes suggested coordination of metal ions through azomethine N and O-atoms of the novel ligand. Spectral studies concluded pentadentate nature of ligand. The correct stereochemistry of the complexes was optimized by MM2 calculations programmed in CsChem3D Ultra-11 software. The crystal

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structures of the complexes have been determined by X-ray powder diffraction techniques. The particle size calculation by Scherrer's formula suggested nanocrystalline nature of the complexes. The Coats-Redfern equation was used to calculate the thermal decomposition kinetic parameters of the metal complexes. Non-spontaneous decomposition of the complexes has been suggested by positive ΔG and negative ΔS values. The pharmacological potentiality of the Schiff base ligand and its metal complexes were assayed in vitro by Kirby Bauer paper disc diffusion method against four bacterial pathogens viz. *S. aureus*, *E. coli*, *B. subtilis* and *K. pneumoniae*. The results of these studies revealed moderate to better antibacterial potency of the complexed Schiff base against uncomplexed.

Keywords: Kanamycin; β -Lactam; antibacterial study; XRPD; Schiff base; MM2.

1. INTRODUCTION

Aminoglycosides and β -lactam antibiotics are considered the new compounds for the formation of Schiff base which is the condensation product of active carbonyl group and amine. Azomethine linkage (-CH=N-) along with many potential donor atoms in it provides uniqueness in coordination chemistry. Moreover, the multifunctional applications of transition metal complexes of Schiff base viz. antibacterial, [1,2] antitumor, [3-5] antifungal, [6,7] catalytic [8-10] & luminescence [11-13] properties etc. have spurred the interest of coordination chemists to develop new type of compounds with superior biological functions and drew the researcher's intelligence in the field of chemical and medical sciences. Recently, Schiff bases have considered as a privileged ligand, as most of the bio-molecules in the living system are structurally similar to this class of compound, so more attentions have to be paid in its structural design and synthesis [14]. The abundance of potential anchoring sites in this ligand, due to presence of various donor atoms viz. N, O and S etc., make easy in the coordination process with metal ions of various types at different oxidation states, which form stable chelate complexes [15]. π -electrons sharing in conjugation with metal ions in the ring of metal complexes authenticate stability of the complexes [16,17].

Kanamycin, in complex form has three component units: Kanamycin A [major component], B and C. The disulphate of Kanamycin A, at its low concentration is a broad spectrum antibiotic, very actively used to treat the infections caused by many gram-positive bacteria. In unmodified form, Kanamycin has shown severe toxic effects like nephrotoxicity and ototoxicity which results in kidney failure and

irreversible loss of hearing respectively [18,19]. The four amine groups in Kanamycin A, in combination with seven hydroxyl groups serve it as a better substrate to obtain semi synthetic and improved antibiotics. Amine groups in sugar rings of Kanamycin A, not only provide anchoring sites for the metal ions but also serve as the reactive site for the formation of Schiff base by the condensation with active carbonyl groups. Besides four amine groups of Kanamycin, amine-1 is best-fit search for ligand formation that has been supported by energy optimization calculation through MM2 software and minimum steric structural effect. Amoxicillin is a class of β -lactam antibiotic, widely used in clinical therapy for the treatment of severe infections caused by various gram-negative bacteria. The bio-functional activity of amoxicillin is related to lactam ring that inhibits bacterial growth by proteolysis mechanism. Many of this class of drugs are under bacterial resistance because of anti-chemical transformation by forming β -lactamase enzyme, which are responsible for failures of antimicrobial therapy by hydrolyzing β -lactam ring [20]. Several research papers revealed that classic drugs used to treat bacterial pathogens have become outdated.

So, in order to address their therapeutic failures and serious limitations, their structural design in derived form has considered as a topic of research [21]. In the present investigation, we report here the synthesis, spectral characterizations coordination behavior and antibacterial activity of M(II) complexes of novel Schiff base ligand derived from Kanamycin and esterifies Amoxicillin, in order to study their combined antibacterial activities against different species of bacteria. The chemical structures of these antibiotics are given in the Figs. 1 and 2:

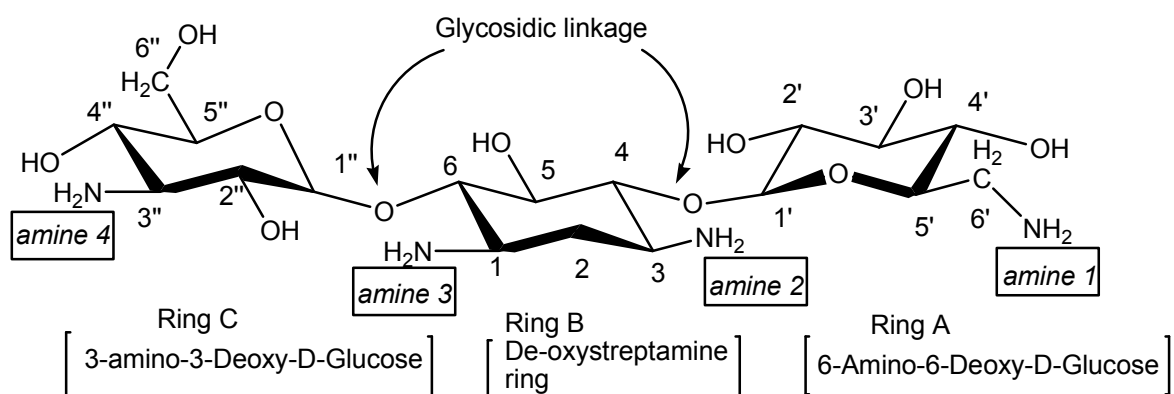


Fig. 1. Molecular structure of Kanamycin A [KA]

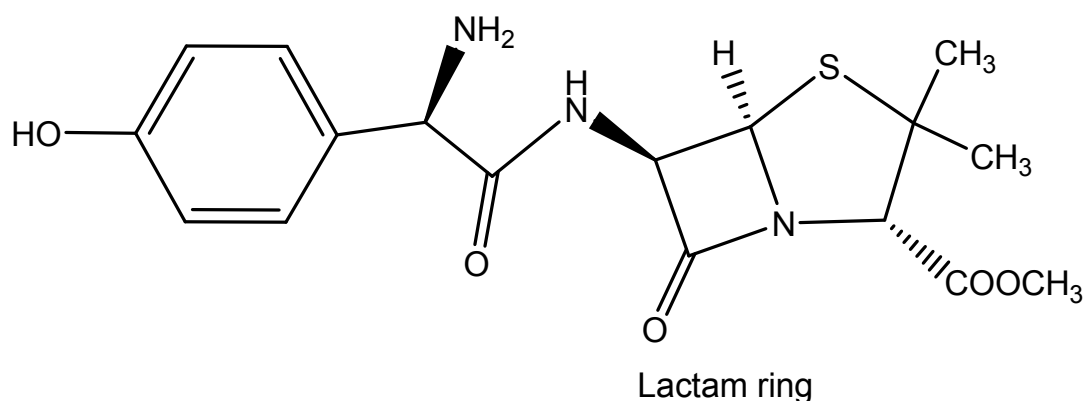


Fig. 2. Molecular structure of methyl ester of amoxicillin [MEA]

2. EXPERIMENTAL DETAILS

2.1 Materials

The necessary chemicals and solvents used in the experiment were of analytical reagent grade and were purchased from local dealers of BDH, Merk & Sigma Aldrich (USA). Methanol was redistilled by standard techniques before use. The base chemicals used for the synthesis of Schiff base viz. Kanamycin sulphate and Amoxicillin trihydrate in extra pure form were procured from Alfa-Aesar. Chloride salts of Cobalt, Copper and Zinc viz. $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ and ZnCl_2 were used as supplied for the synthesis of metal complexes of novel ligand. Distilled methanol mixed with double distilled water had been used as solvent for the synthesis.

2.2 Physical Measurements

The elemental microanalysis (C, H and N) of the complexes were carried out on Elementar vario EL III (Germany) model Analyzer. Double check

method was done to get the accuracy of the data. Characteristic shifts in IR band positions had been analyzed by intimate observations of infrared spectra of ligand and metal complexes that were run as KBr discs in the range $4000-400 \text{ cm}^{-1}$ on a Shimadzu Infrared Spectrophotometer. ^1H NMR spectra were recorded in DMSO- d_6 solvent on a Bruker advance 400 MHz instrument using TMS as internal reference. Mass spectra were carried out TOF-MS on water KC-455 model in DMSO. The electronic spectra that reveal d-d & n- π transitions of ligand and its complexes were recorded in Perkin-Elmer spectrophotometer using DMSO as the solvent and internal reference chemical. The TG and DTA studies were recorded on Shimadzu TGA-50H thermal analyser scanning at a heating rate of $10^\circ\text{C min}^{-1}$. The XRD powder pattern was recorded on a vertical type Philips PW 1130/00 x-ray diffractometer, operated at 40kV and 50 Ma generator using the monochromitised Cu K α line at wavelength 1.54056 Å as the radiation source and measurements were taken over the range of $2\theta = 10 - 80^\circ$. Crystallographic data were analyzed by CRYSFIRE and CHECKCELL

software programme. The molecular structure of the complexes was optimized by CsChem 3D Ultra-11 programme.

2.3 Synthesis of Methyl Ester of Amoxicillin (MEA)

The compound MEA was prepared by mixing amoxicillin trihydrate (4 mmol, 1.678 gm) in 30 ml distilled methanol. The reaction mixture was then refluxed at 25°C for 4 hrs at pH 4.5 in the presence of little amount of conc. H₂SO₄. The volume reduction of clear solution resulted colorless crystalline solid. It was purified by re-crystallization process and dried under vacuum over anhydrous CaCl₂.

2.4 Synthesis of Novel Schiff Base Ligand [H₂L]

To 4 mmol (2.33 g) of Kanamycin sulphate in 30 ml warm and homogenously stirred aqueous methanol (1:1), was added a well stirred and hot solution of 4 mmol (1.5 gm) methyl ester of Amoxicillin (MEA) dissolved in 30 ml distilled methanol, as reported in the previous literatures [22]. The pH 7 of the solution was adjusted by adding few drops of NaOH solution. The mixture was stirred under heat on magnetic stirrer and was refluxed for 15 hrs at 35°C. The light yellow solid was obtained by reducing its volume by placing over the hot plate. It was further re-crystallized and dried under vacuum over anhydrous CaCl₂. Yield 70% and m. p. 180°C.

2.5 Synthesis of Metal Complexes of Schiff Base [ML]

To the hot and magnetically stirred 50 ml (1:1) aqueous methanolic solution of novel Schiff base ligand (2 mmol, 1.662 gm), was added 5 ml (2 mmol) methanolic solution of metal chloride salts. The mixture was then stirred and refluxed alternately at 45°C for another 15 hrs. On cooling, the precipitates of metal complexes of different color were obtained, filtered and washed with methanol. The complexes were purified by re-crystallization from DMSO/H₂O mixture. Yield 55-65%, m. p. > 275°C. The synthesis of the ligand and its metal complexes is given in Scheme 1.

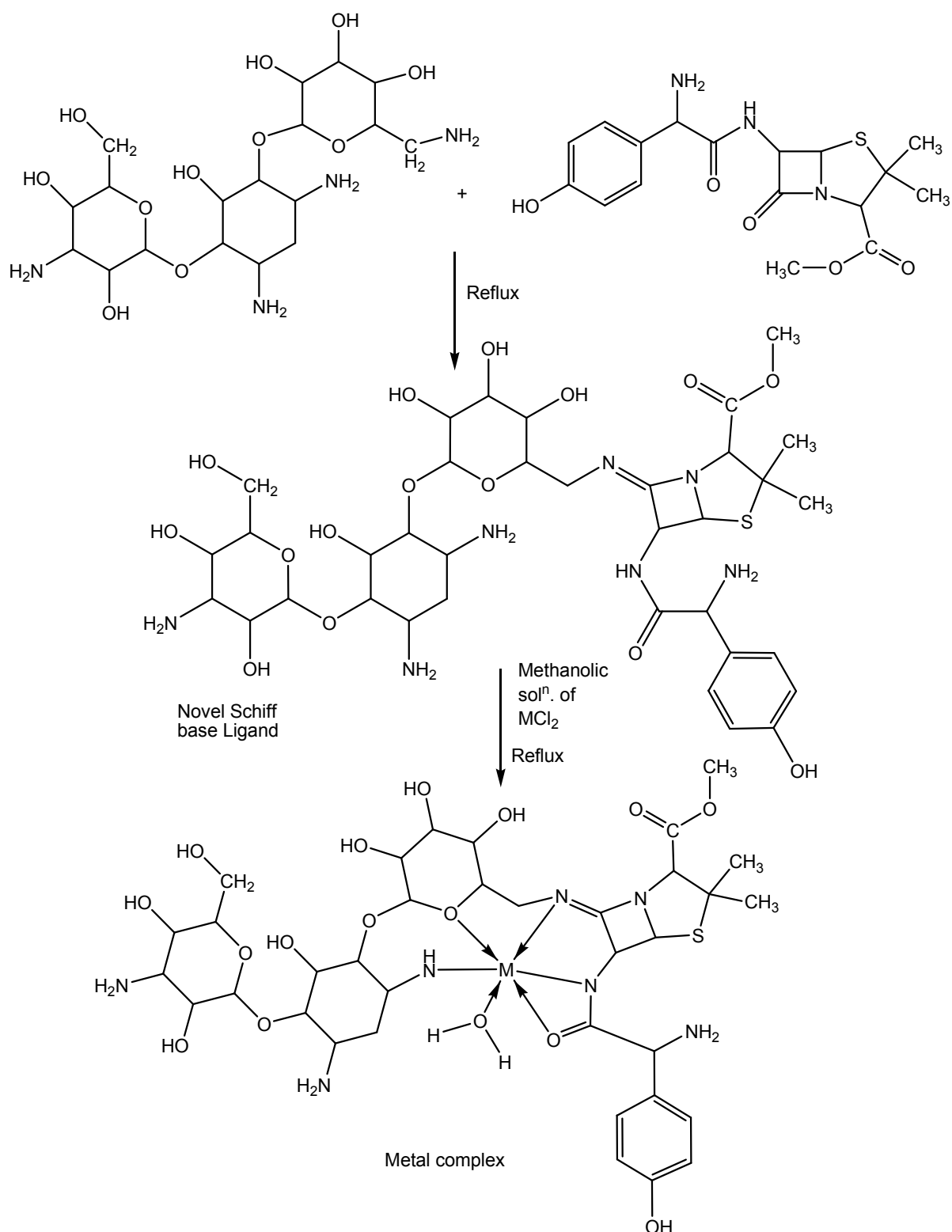
2.6 Antibacterial Study

In vitro antibacterial potency of newly synthesized novel Schiff base and metal

complexes were assayed by Kirby Bauer paper disc diffusion method, [23,24] using Mueller-Hinton's nutrient agar media. The pH was maintained at 7.4 for better bacterial growth. Several well isolated colonies of the fresh cultures of standard bacteria viz. *E. coli*, *B. subtilis*, *S. aureus* and *Klebsiella pneumoniae* were collected from microbiology laboratory of Suraksha Prashuti Hospital, Biratnagar, Nepal and inoculated in 5 ml of tryptone soya broth. The broth was incubated for 5 hrs at 37°C until there was visible growth shown by opaqueness. The broth was spread over nutrient agar media, prepared as usual in Petri plates using stick swab and the well sterilized Paper discs of 6 mm diameter (Whatman no. 1) impregnated with test compounds at the concentration of 10 µg/µl in DMSO were stuck on the previously seeded bacterial culture [25,26]. Gentamicin 30 µg per disc of 6 mm size (HIMEDIA co.) was used as standard (+ve control). DMSO, which exhibited no antimicrobial activity against the test bacterial pathogens, was used as negative control. Afterwards, the Petri plates were incubated at 37°C and the diameter of zone of inhibition around each disc was measured by using antibiogram zone measuring scale after 48 hrs of incubation.

3. RESULTS AND DISCUSSION

Presence of -COOH group in amoxicillin might interfere in Schiff base formation that can interact with amine group of Kanamycin, so this reaction of amide formation was inhibited by the formation of MEA. Esterifies amoxicillin now safely interact with amine group of Kanamycin. The ligand was soluble in hot methanol and polar solvents like DMSO and DMF. The melting points of ligand (180°C) and metal complexes (> 275°C) suggest that the complexes are much more stable than the ligand and all of them are air and moisture stable. Different coloured metal complexes were obtained by synthetic routes proposed in Scheme-1. IR spectral measurements are completely in consistent with the proposed formulation of the ligand and complexes. The metals are bound to the ligand through the azomethine nitrogen, N-atom of amine-1 and cyclic O-atom of Kanamycin moiety and amide N and O-atoms of Amoxicillin moiety, as evidenced by negative shift in band positions of such groups due to sharing of electrons towards the metal centers. IR spectral data are presented in the Table 2.



Scheme 1. Proposed route for the synthesis of Schiff base ligand & metal complex

One H_2O molecule coordinated with metal center in the inner sphere of the crystal system satisfies the proposed crystal structure of the complexes.

XRD measurements revealed the crystalline nature of complexes with particle size in nanometer range, so called nano-structured

molecules. Thermograms of colored complexes revealed complete decomposition above 600°C. Higher dehydration temperature of the complexes suggested that the water molecule is coordinated to the metal ion, which is also supported by broad IR absorption band above 3100 cm⁻¹. Molar conductance values of the soluble complexes in DMSO (1 x 10⁻³ M) at room temperature vary from 5.1 to 20.1 Ω⁻¹ cm² mol⁻¹ revealing non-electrolytic nature of the complexes.

3.1 Elemental Analysis

The data for the elemental analysis and other physical measurements of the Schiff base and its metal complexes are computed in the Table 1 and showed 1:1 ratio of the type ML.H₂O. The results are in good agreement with the proposed formulation of the ligand C₃₅H₅₅N₇O₁₅S and revealed general formula C₃₅H₅₃N₇O₁₅SM.H₂O (where M = Co, Cu & Zn), for the complexes.

3.2 Infrared Spectra

The IR spectra of the Schiff base and its metal complexes as presented in the Table 2 suggest that, the ligand binds to metal centre through five anchoring sites, behaving as a pentadentate ligand that use N atom of azomethine and amide group and also O-atom of amide carbonyl group and ring O-atom. The ligand behaves as a dinegative ion that coordinates to metal centre by forming covalent bond using deprotonation of amine-2 and C-NH of lactam ring. The lactam ν(C=O) band appears at 1774 cm⁻¹ in the spectrum of MEA. The IR spectrum of ligand shows no band due to lactam ν(C=O) vibrational mode coming from MEA. The real coordination mode of the ligand towards metal ion has been deduced by IR spectral comparison of the free ligand and coordinated ligand [27]. The

significant differences in the absorption frequencies were observed in the region between 1775-1200 cm⁻¹ and at lower frequencies below 600 cm⁻¹. Some characteristic and recognizable spectral changes have been noticed in the IR spectra of metal complexes compared to free ligand that provide additional support of the bonding mode. The absence of lactam ν(C=O) band in Schiff base ligand and appearance of new band at 1644 cm⁻¹ has been attributed to ν(C=N) of Schiff base ligand. The IR spectra of metal complexes display absorption bands in the range of 1635-1641 cm⁻¹ range which can be assigned to (C=N) stretching frequencies of coordinated ligand. In fact, in all the complexes, the absorption band for ν(C=N) were shifted to lower wave numbers, indicating their participation in the coordination with metal ions. The IR absorption band at 1675 cm⁻¹, due to amide carbonyl group in Schiff base ligand has undergone negative shift at 1660-1668 cm⁻¹ in metal complexes. This confirmed the participation of amide (C=O) group for ligation with metal ions. The C-N stretch band for amide and amine groups at 1442 cm⁻¹ in IR spectra of Schiff base ligand have gone to negative shift in IR band positions in the range of 1424-1435 cm⁻¹ in metal complexes and these suggest the participation of such groups in coordination process.

The metal-ligand binding was further substantiated by the appearance of a new absorption band in the region of 420-435 cm⁻¹ and a medium intensity band in the region of 500-530 cm⁻¹ assignable for ν_{M-N} and ν_{M-O} stretching vibrations, which were absent in free ligand [28]. These overall data suggest that there is coordination of Schiff base ligand with metal ions through azomethine-N, amide-N, amine-2 N of Kanamycin moiety, heterocyclic-O and amide-O of the ligand.

Table 1. Elemental analysis and physical properties measurement data

Ligand/ complexes	M. F.	Mol. Wt.	Colour	Yield (%)	Calculated (found) (%)					
					C	H	N	O	S	M
H ₂ L	C ₃₅ H ₅₅ N ₇ O ₁₅ S	845.92	Light yellow	71	49.72 (49.12)	6.48 (6.38)	11.64 (11.75)	28.40 (28.9)	3.75 (3.91)	-
Co-L	C ₃₅ H ₅₅ CoN ₇ O ₁₆ S	920.85	Purple	65	45.70 (44.99)	6.10 (6.20)	10.62 (10.78)	27.85 (27.89)	3.53 (3.55)	6.40 (6.51)
Cu-L	C ₃₅ H ₅₅ CuN ₇ O ₁₆ S	925.46	Light blue	68	45.38 (45.48)	5.89 (5.92)	10.64 (10.66)	27.71 (27.75)	3.45 (3.48)	6.89 (6.92)
Zn-L	C ₃₅ H ₅₅ N ₇ O ₁₆ SZn	927.30	Yellow	56	45.39 (45.35)	5.95 (5.88)	10.52 (10.75)	27.55 (27.68)	3.51 (3.48)	7.15 (7.21)

Table 2. Main vibrational IR band positions (cm⁻¹) of ligand and metal complexes

Ligand/ complexes	v(OH, NH)	v(C=N) azomethines	v(C=O) amide	v(C-N) amide/amine	v(M-N)	v(M-O)
H ₂ L	3442	1644 (s)	1675	1442	-	-
Co-L	3419 (br)	1641 (s)	1668	1434	429 (m)	502(m)
Cu-L	3425(br)	1637 (s)	1660	1428	425 (m)	528 (m)
Zn-L	3432(br)	1635 (s)	1663	1424	433 (m)	520(m)

3.3 ¹H NMR Spectra

¹H NMR spectral comparison of novel Schiff base ligand and its metal complexes was made to confirm the binding nature of ligand with metal ions viz. Co(II), Cu(II) and Zn(II). The integral intensities of each signal in the ¹H NMR spectra of ligand and metal ion complexes are found to agree with the number of different types of protons present. In the ¹H NMR spectrum of Schiff base ligand, single peak attributed to CH₃, COOCH₃ and Ar-OH groups appeared at 1.79, 3.65 and 12.5 ppm respectively. These peaks were still present in the metal complexes, indicating no participation of these groups in coordination process. Multiple peaks in the range of 6.6-7.8 ppm due to Ar-H were also present. Doublet peaks at 4.75 and 5.45 ppm correspond to N-CH and N=C-CH protons on the β-lactam ring and at 9.05 ppm due to NH proton lying between amide carbonyl and β-lactam ring were observed. Disappearance of NH proton peak (9.05 ppm) in the metal complexes is the indication of deprotonation which involve in coordination process. Side chain methylene proton of kanamycin moiety linked to azomethine nitrogen showed doublet peak at 2.09 ppm. No appreciable shift in ¹H NMR peak positions have shown in the spectra of metal complexes that were due to kanamycin moiety except decrease in intensity of NH₂ peak. Ring protons of kanamycin showed resonance as triplet at 3.5-3.8 ppm. The intense single peak at 3.2 and 4.07 ppm may be attributed to NH₂ and OH protons of Kanamycin. The decrease in peak intensity of NH₂ protons in metal complexes is also an indicative of its participation in coordination. The ¹H NMR spectrum of Zn-complex is shown in the Fig. 3.

3.4 Mass Spectra

The mass spectra of ligand and its metal complexes were recorded and are used to compare their stoichiometric compositions. The mass spectrum of Schiff base ligand shows a molecular ion peak at m/z 845. The molecular ion

(MH)⁺ peaks for metal complexes appear at m/z 921, 925 & 927 for Co, Cu and Zn complexes respectively and confirmed the stoichiometry of metal chelates as ML.H₂O type. It was in good agreement with the microanalytical data.

3.5 Electronic Spectra, Magnetic Moment and Molar Conductivity

The electronic transition spectrum of free ligand showing absorption band higher than 430 nm have shifted to lower frequencies (bathochromic shift) due to coordination of the ligand with metal centers. The entire complexes showed electronic absorption band in the visible region of spectrum which may be attributed to charge transfer band. The electronic spectrum of Cu-complex showed absorption band at 660 nm which may be assigned to ²A_{1g}^(F) → ²B_{1g}^(P) transition and corresponds to square planar geometry of the complex. The magnetic moment value 1.81 BM of the complex further supports the observed geometry. The electronic transition at 235 nm may be due to π-π* transition and three closely spaced bands at 325, 322 and 350 nm may be due to n-π* transition [29,30]. The d-d transition band displayed at 670 nm is in good agreement with the square planar geometry of the Cu-complex. The electronic absorption spectrum of Co(II) complex display d-d transition band at 615 nm which corresponds to ⁴T_{1g} → ⁴T_{1g}^(P) transition and revealed octahedral geometry of the complex. The observed magnetic moment value of 3.12 BM further supports octahedral geometry. The electronic spectrum of Zn(II) complex exhibited a sharp band of high intensity at 365 nm, which has been due to ligand metal charge transfer and assigned tetrahedral environment around Zn(II) ion. With a view to study the electrolytic nature of the metal complexes, their molar conductivities were recorded in DMF at 10⁻³ M. The molar conductivity (Λ_M) values of the complexes are in the range of 5.1 - 20.1 Ω⁻¹ mol⁻¹ cm², which indicate their non-electrolytic nature. This further generates the idea of lack of any counter ions in the proposed structure of the mononucleate metal complexes.

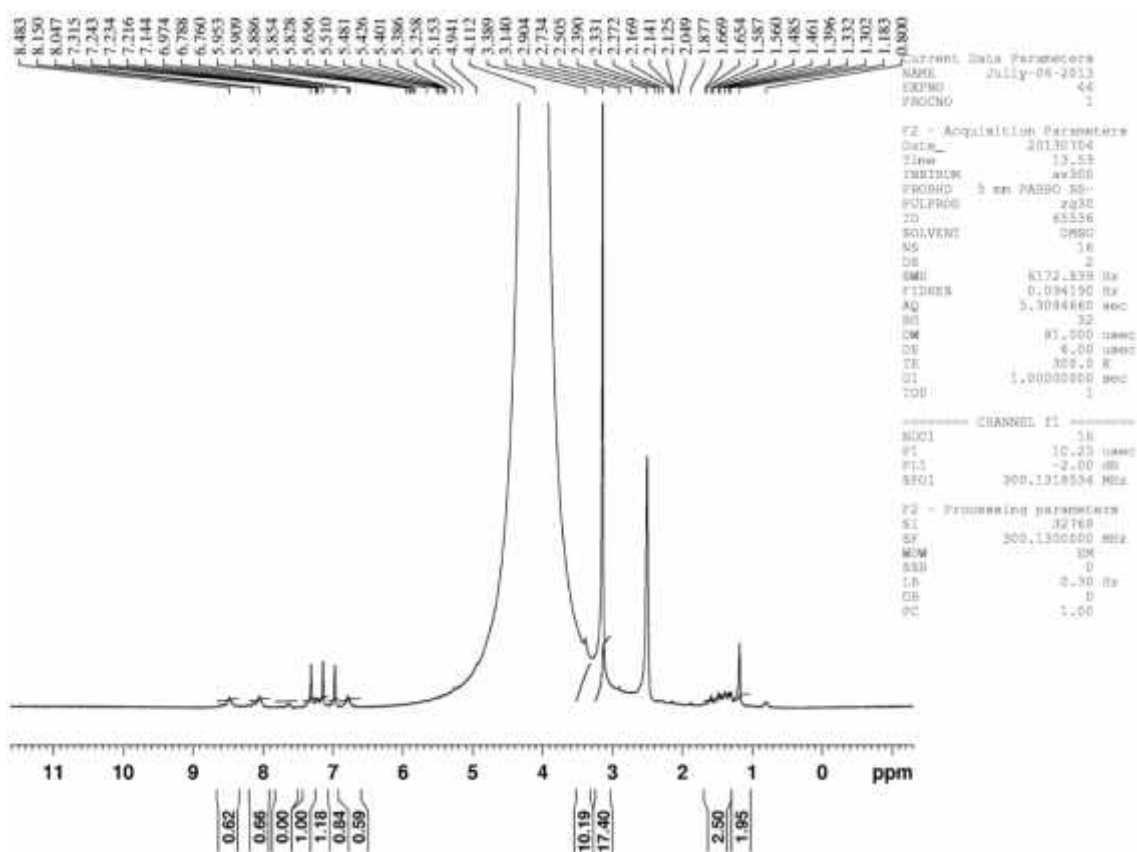


Fig. 3. ^1H NMR spectra of Zn-complex

3.6 X-ray Powder Diffraction Study

So far, single crystal growth of the complexes had been unsuccessful, X-ray powder diffraction technique was carried to get useful crystal information data to deduce accurate cell parameters, crystal system and the cell volume [31]. Powder diffraction patterns of ligand and the metal complexes were recorded over the $2\theta = 10^\circ$ - 80° range and crystallographic data are listed in the Table 3. The indexing procedures were performed using Crysfire program package software. The diffraction pattern revealed well defined crystalline peaks indicating crystalline nature of the complexes and the data confirmed the triclinic crystal systems for ligand, Co and Cu complexes. Zn complex exhibited orthorhombic crystal system. The average particle size of the crystalline metal complexes was calculated using Scherrer's formula ($d_{\text{XRD}} = 0.9\lambda / \beta \cos\theta$) by measuring the full width at half maximum of the XRD peaks [32-34]. The average particle size in the range of 45-66 nm suggests nanocrystalline nature of the compounds.

3.7 Thermal Analysis

Thermal stability of the complexes was extensively studied by TG/DTA analytical techniques with a heating rate of 10°C / minute and their decomposition profiles were noticed at different stages of temperature ranges, resulting various thermally stable products, as explained according to the Scheme 2.

TG/DTA profile of the complexes revealed change in curve area corresponding to their decomposition at various temperature ranges. Nearly 2% weight loss due to coordinated water molecule in all the complexes occurred in the temperature range of 120 - 135°C . Thermogram of Co-complex showed that nearly 50% of the total mass of complex reduced at 150 - 170°C , followed by considerable decomposition above 550°C that corresponds to the decomposition of ligand moiety leaving Co_2O_3 as stable end residue. Similarly, thermogram of Cu and Zn-complexes showed 50% weight loss in between 350 - 375°C and final decomposition above 450 - 600°C resulting into final pyrolysis product i.e. stable metal oxide (CuO and ZnO) residue [35,36].

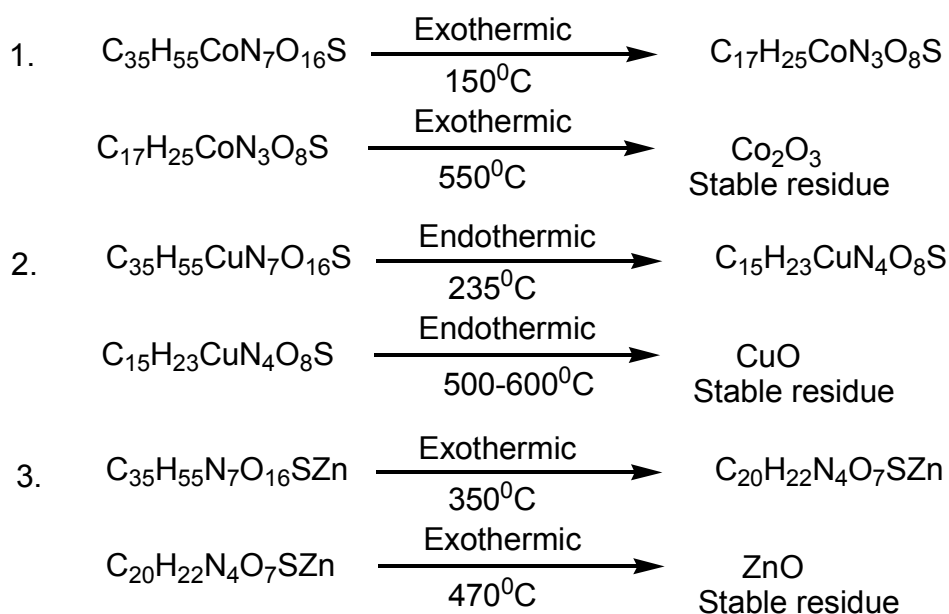
Above this temperature, horizontal curve showed no further loss in weight. This inferred metal oxide as the final residue. The calculated metal content in the oxide residue was compared with that obtained from analytical determinations. Hence these decomposition patterns were in good agreement with suggested formulae of the complexes.

3.8 Thermal Decomposition Kinetics

Thermal decomposition profiles obtained by thermo gravimetric (TG) and differential thermo gravimetric (DTA) analysis were used to calculate thermodynamic and kinetic parameters for the non-isothermal decomposition of the complexes such as order of reaction (n),

Table 3. Crystal lattice parameters for Ligand and metal complexes

Compounds	H ₂ L	Co-L	Cu-L	Zn-L
Formula	C ₃₄ H ₅₅ N ₇ O ₁₅ S	C ₃₄ H ₅₅ CoN ₇ O ₁₆ S	C ₃₄ H ₅₅ CuN ₇ O ₁₆ S	C ₃₄ H ₅₅ N ₇ O ₁₆ SZn
FW	845.92	920.85	925.46	927.30
Temp (K)	298 K	298 K	298 K	298 K
Wavelength	1.54056	1.54056	1.54056	1.54056
Crystal System	Triclinic	Triclinic	Triclinic	Orthorhombic
Space group	P1	P1	P1	Pmmm
Unit cell dimensions				
a(Å)	7.3029	5.7771	3.6035	23.2423
b(Å)	6.9291	11.4059	10.4736	9.6121
c(Å)	10.6422	19.394	23.4791	8.0821
α°	70.4605	77.569	46.473	90.00
β°	123.7612	101.502	69.481	90.00
γ°	120.2416	51.169	61.6011	90.00
Volume (Å ³)	385.66	832.62	564.84	1805.6
θ range (°)	10- 80	10- 80	10- 80	10- 80
Limiting indices	-4 ≤ h ≤ 3	-2 ≤ h ≤ 0	-1 ≤ h ≤ 0	0 ≤ h ≤ 2
	-4 ≤ k ≤ 3	-3 ≤ k ≤ 0	-3 ≤ k ≤ 4	0 ≤ k ≤ 1
	0 ≤ l ≤ 7	0 ≤ l ≤ 8	0 ≤ l ≤ 11	0 ≤ l ≤ 3
Particle size(nm)	47.35	51.23	58.29	65.45
Density	1.32	1.45	1.23	1.35
Z	1	1	1	2



Scheme 2. Thermal decomposition of the complexes with respect to temperature

enthalpy change of activation (ΔH^\ddagger), activation energy (E^\ddagger), entropy change of activation (ΔS^\ddagger) and Gibb's free energy change of activation (ΔG^\ddagger) [37]. By the analysis of the non-isothermal TG, using the integral method of Coats-Redfern relation, kinetic parameters of decomposition were calculated [38].

$$\ln \left[-\frac{\ln(1-\alpha)}{T^2} \right] = \ln \left[\frac{AR}{\phi E^\ddagger} \right] - \frac{E^\ddagger}{RT}$$

Where α is the mass loss up to the temperature T , R is the gas constant, E^\ddagger is the activation energy in J mole^{-1} and ϕ is the linear heating rate. A straight line plot of left hand side of the equation against $1000/T$ gave a slope from which E^\ddagger was calculated while its intercept value corresponds to frequency factor (A). The entropy of activation ΔS^\ddagger in $\text{J K}^{-1} \text{mol}^{-1}$, enthalpy change (ΔH^\ddagger) and Gibb's free energy change (ΔG^\ddagger) [39] were calculated by using the equations:

$$\begin{aligned} S^\ddagger &= R \ln \left[\frac{Ah}{k_B T} \right] \\ H^\ddagger &= E^\ddagger - RT \\ G^\ddagger &= H^\ddagger - T S^\ddagger \end{aligned}$$

Where, k_B is the Boltzmann constant, h the plank's constant and T is the DTG peak temperature. The Coats-Redfern linearization plots, confirmed the first order kinetics for the decomposition process. The calculated values of thermodynamic activation parameters for the decomposition steps of the metal complexes are reported in Table 4. The high value of activation energy of the complexes revealed their high thermal stability. The positive sign of ΔG^\ddagger and negative sign of ΔS^\ddagger suggested that the thermal decomposition steps are non-spontaneous process. Further negative entropies of activation of complexes indicated that the studied complexes are in more ordered state and the decomposition reactions proceed with a much slower rate than the normal. Among metal complexes, activation energy increases as Zn-complex < Co-complex < Cu-complex. Thus, thermal stability of metal complexes follows the order Co-complex > Zn-complex > Cu-complex.

3.9 Coordination Sites

The novel Schiff base ligand obtained from Kanamycin and amoxicillin has many potential donor atoms at various positions which can bind to metal center forming multinucleate chelate. In the present investigation, spectral studies

revealed penta-dentate nature of ligand, encapsulating metal through azomethine nitrogen (C=N), carbonyl oxygen of amide group, cyclic oxygen of ring A, nitrogen of amine 2 of kanamycin moiety and nitrogen of CH-N of lactam ring. Besides these, there is coordination with one water molecules and form octahedral geometry of Co-complex and square planar geometry of Cu-complex.

3.10 Antibacterial Activity

The novel Schiff base ligand and its metal complexes were screened in vitro against four bacterial pathogens viz, *E. coli*, *B. subtilis*, *S. aureus* and *K. pneumoniae* to assess their antibacterial potency. The results are quite promising. The prescription of the antimicrobial results showed graphically (Fig. 4) reveals that they exhibited moderate to better antibacterial activity [40,41]. Further, metal complexes were found to have higher biological activity than the parent Schiff base. Such increased activity of metal complexes may be considered due to insertion of metal ions in chelation process with Schiff base that cause to increase lipophilic nature of these complexes due to delocalization of π -electrons over the whole chelate ring. This increased lipophilicity enhances the penetration of complexes into the lipid membranes and blocks the metal binding sites in enzymes of microorganisms [42]. These complexes also disturb the respiration process of the cell by deactivating enzymes responsible for this and thus block the synthesis of proteins, which restricts further growth of the organism. The potential activity of the complexes against bacterial pathogens may be related to cell wall structure of the bacteria which possibly occurs due to inhibition of synthesis step of peptidoglycan layer of bacterial cell wall. The data revealed that the activity of the ligand enhanced on complexation comparable to the standard used. Overall comparison of observed data gave information that metal complexes are more active than free ligand against all bacteria. Specifically, Zn-complex showed better antibacterial potency against *S. aureus* bacteria.

4. MOLECULAR MODELLING

3D molecular modeling of the proposed structure of the metal complexes were studied by CsChem 3D Ultra program package and optimized structures revealed octahedral geometry for Co, square planar geometry for Cu and tetrahedral geometry for Zn-complexes [43]. This

investigated geometry of the complexes is also supported by several spectral techniques. The correct stereochemistry was assured through, manipulation and modification of the molecular coordinates to obtain reasonable and low energy molecular geometries. Energy minimization was repeated several times to find the minimum [44,45]. The energy minimization values for the metal complexes suggested their maximum

stability. The change in bond length values of metal-nitrogen and metal-oxygen in the complexes compared with ligand further suggested their coordination. The details of the bond lengths and bond angles as per 3D structure of the metal complexes optimized by MM2 calculations are given in the Table 5 and the optimized structures of the metal complexes are shown in the Figs. 5-7.

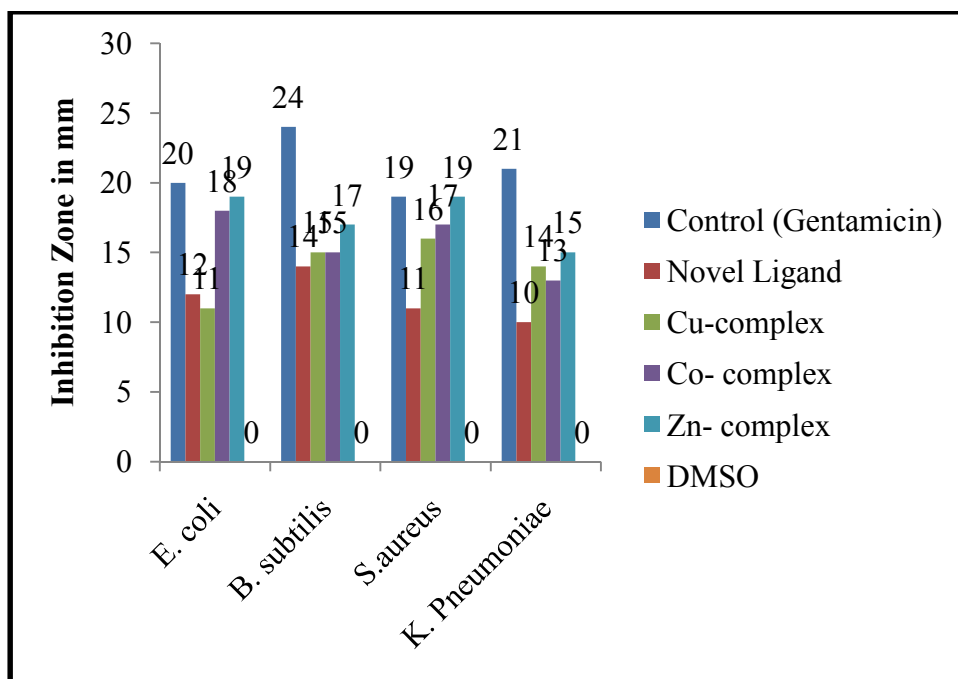


Fig. 4. Antibacterial sensitivity bar graph for synthesized compounds

Concentration of test compounds: 10 µg/µl, Concentration of control drug: 30 µg/disc, 0 = No sensitivity

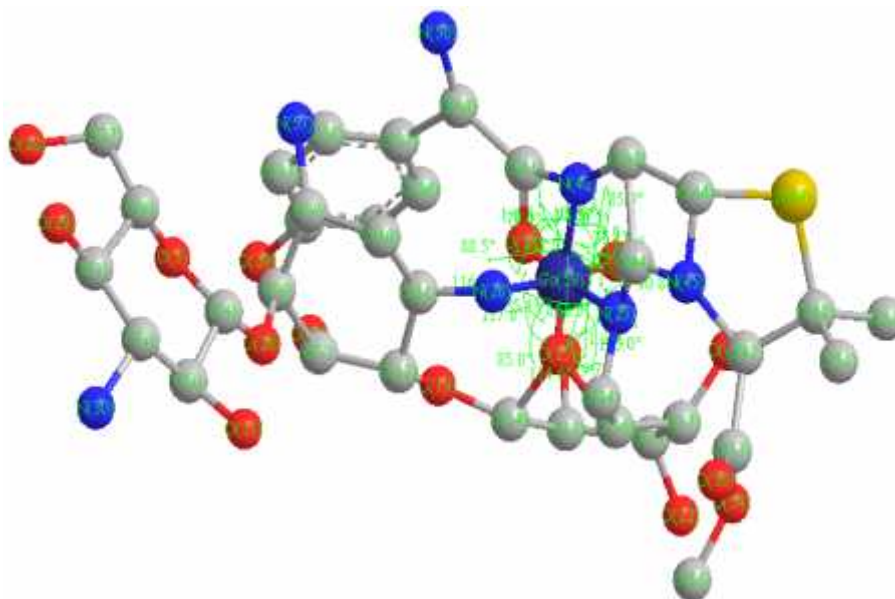


Fig. 5. Optimized structure of cobalt complex

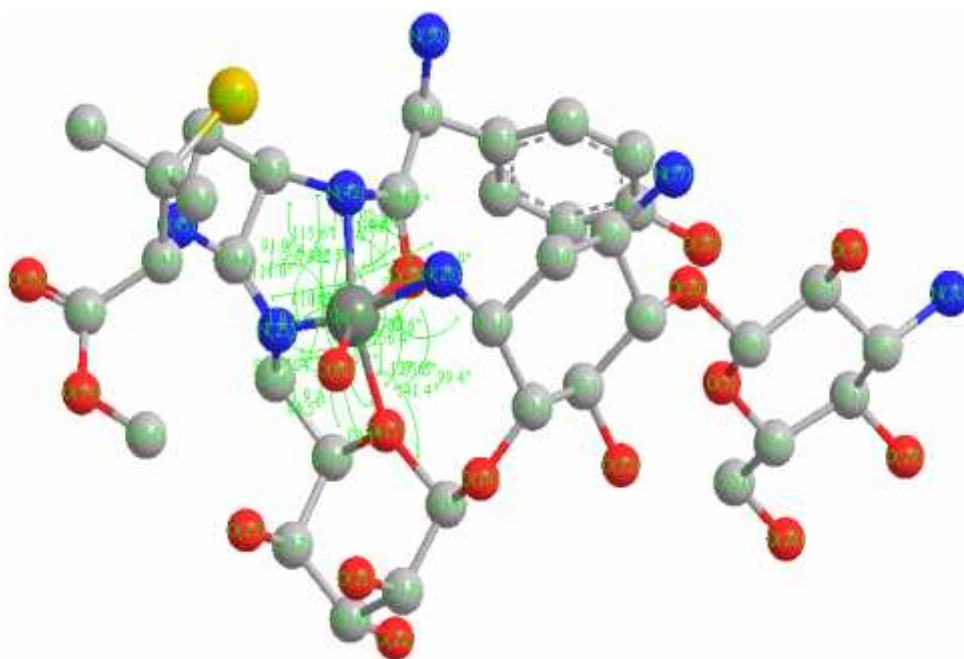


Fig. 6. Optimized structure of copper complex

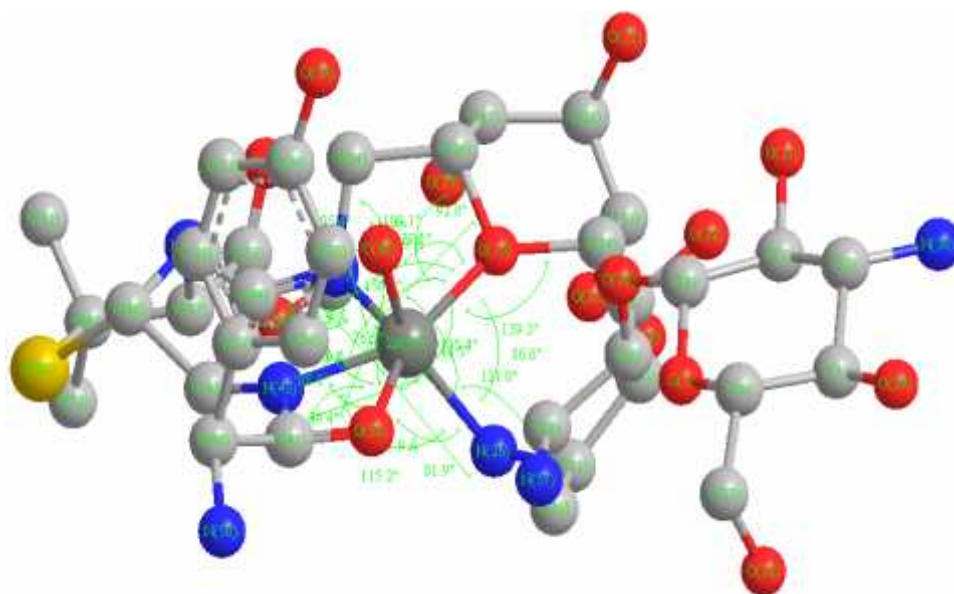


Fig. 7. Optimized structure of zinc complex

Table 4. Thermodynamic activation parameters of the metal complexes

Complex	Order/n	Steps	E*/ kJmol ⁻¹	A/sec ⁻¹	ΔS*/J K ⁻¹ mol ⁻¹	ΔH*/ J mol ⁻¹	ΔG*/ kJ mol ⁻¹	k×10 ⁴ s ⁻¹	Thermal effect
Co-L	1	I	57.68	1.35×10 ⁵	-147.68	114.76	45.157	13.19	Exo.
		II	67.81	1.31 ×10 ⁵	-147.89	78.42	45.186	13.16	Exo.
Cu-L	1	I	65.32	4.32×10 ⁵	-143.95	125.76	89.806	42.65	Endo.
		II	75.45	6.45 × 10 ⁵	-140.61	85.36	87.689	63.56	Exo.
Zn-L	1	I	45.32	5.27 ×10 ⁵	-141.60	120.76	81.207	52.2	Exo.
		II	57.23	4.32 ×10 ⁴	-143.25	65.32	82.151	42.68	Endo.

Table 5. Bond length and bond angle results of metal complexes

Co-L		Cu-L		Zn-L	
Bond lengths		Bond lengths		Bond lengths	
O(58)-Co(59)	1.059	N(25)-Cu(59)	1.369	N(25)-Zn(59)	1.938
O(60)-Co(59)	1.215	O(60)-Cu(59)	1.858	O(60)-Zn(59)	1.926
O(15)-Co(59)	1.197	Cu(59)-O(58)	1.834	Zn(59)-O(58)	1.911
N(25)-Co(59)	1.854	O(15)-Cu(59)	1.866	O(15)-Zn(59)	1.941
N(26)-Co(59)	1.860	N(26)-Cu(59)	1.860	N(26)-Zn(59)	1.930
N(42)-Co(59)	1.824	N(42)-Cu(59)	1.879	N(42)-Zn(59)	1.951
Bond angles		Bond angles		Bond angles	
O(58)-Co(59)-O(60)	98.308	N(25)-Cu(59)-O(60)	91.570	N(25)-Zn(59)-O(60)	95.362
O(58)-Co(59)-O(15)	117.640	N(25)-Cu(59)-O(58)	109.978	N(25)-Zn(59)-O(58)	131.455
O(58)-Co(59)-N(25)	157.046	N(25)-Cu(59)-O(15)	94.527	N(25)-Zn(59)-O(15)	78.095
O(58)-Co(59)-N(26)	88.509	N(25)-Cu(59)-N(26)	164.131	N(25)-Zn(59)-N(26)	127.588
O(58)-Co(59)-N(42)	84.499	N(25)-Cu(59)-N(42)	91.908	N(25)-Zn(59)-N(42)	72.477
O(60)-Co(59)-O(15)	105.039	O(60)-Cu(59)-O(58)	156.406	O(60)-Zn(59)-O(58)	76.493
O(60)-Co(59)-N(25)	90.790	O(60)-Cu(59)-O(15)	83.091	O(60)-Zn(59)-O(15)	91.984
O(60)-Co(59)-N(26)	163.160	O(60)-Cu(59)-N(26)	82.572	O(60)-Zn(59)-N(26)	135.402
O(60)-Co(59)-N(42)	85.927	O(60)-Cu(59)-N(42)	128.450	O(60)-Zn(59)-N(42)	86.165
O(15)-Co(59)-N(25)	79.650	O(58)-Cu(59)-O(15)	85.650	O(58)-Zn(59)-O(15)	148.519
O(15)-Co(59)-N(26)	85.026	O(58)-Cu(59)-N(26)	78.885	O(58)-Zn(59)-N(26)	81.859
O(15)-Co(59)-N(42)	152.633	O(58)-Cu(59)-N(42)	62.399	O(58)-Zn(59)-N(42)	59.392
N(25)-Co(59)-N(26)	77.576	O(15)-Cu(59)-N(26)	99.361	O(15)-Zn(59)-N(26)	86.610
N(25)-Co(59)-N(42)	75.129	O(15)-Cu(59)-N(42)	147.628	O(15)-Zn(59)-N(42)	150.187
N(26)-Co(59)-N(42)	79.386	N(26)-Cu(59)-N(42)	80.454	N(26)-Zn(59)-N(42)	115.163
Co(59)-O(58)-C(41)	108.810	Cu(59)-O(58)-C(41)	107.965	Zn(59)-O(58)-C(41)	108.006
Co(59)-N(42)-C(43)	135.675	Cu(59)-N(42)-C(43)	110.956	Zn(59)-N(26)-C(11)	120.989
Co(59)-N(42)-C(41)	70.740	Cu(59)-N(42)-C(41)	96.622	Zn(59)-N(25)-C(44)	119.075
Co(59)-N(26)-C(11)	116.164	Cu(59)-N(26)-C(11)	127.557	Zn(59)-N(25)-C(24)	109.051
Co(59)-N(25)-C(44)	120.265	Cu(59)-N(25)-C(44)	115.600	Zn(59)-O(15)-C(16)	112.492
Co(59)-N(25)-C(24)	114.600	Cu(59)-N(25)-C(24)	109.417	Zn(59)-O(15)-C(14)	139.324
Co(59)-O(15)-C(16)	126.875	Cu(59)-O(15)-C(16)	104.264		
Co(59)-O(15)-C(14)	135.084	Cu(59)-O(15)-C(14)	141.376		

5. CONCLUSION

In the present study, we have successfully synthesized referenced metal(II)-complexes of novel Schiff base ligand from Kanamycin and methyl ester of Amoxicillin. Instrumental protocols like spectral, thermal and other analytical data measurements revealed the real correlation with the proposed and suggested structure. The investigated Schiff base ligand act as neutral pentadentate ligand. The electronic transition band observed at lower wavenumbers in metal complexes may be ascribed to d-d electronic transition within the metal ions which were absent in the spectrum of free ligand. Molar conductivity measurement recommended nonelectrolytic nature of the complexes. Further molecular modeling and electronic spectral data measurement strongly recommend square planar geometry for Cu-complex, octahedral geometry for Co-complex and tetrahedral geometry for Zn-complex. Negative entropy values obtained by thermal decomposition calculation by using

Coats-Redfern equation indicated slow pyrolytic decomposition of metal complexes. Two antibiotics in conjugation with metals lead to better antibiotic activities. The antibacterial screening of the synthesized ligand and its metal complexes against various pathogenic bacteria suggested remarkable antibacterial activities. Comparable antibacterial sensitivity test of the ligand and metal complexes showed that they bear strong activity against *S. aureus*.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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