Research Article

Metal Complexes of a Novel Schiff Base Based on Penicillin: Characterization, Molecular Modeling, and Antibacterial Activity Study

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A novel Schiff base ligand of type HL was prepared by the condensation of amoxicillin trihydrate and nicotinaldehyde. The metal complexes of Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+} were characterized and investigated by physical and spectral techniques, namely, elemental analysis, melting point, conductivity, $^1H$ NMR, IR, UV-Vis spectra, ESR, SEM, and mass spectrometry measurements. They were further analyzed by thermal technique (TGA/DTA) to gain better insight about the thermal stability and kinetic properties of the complexes. Thermal data revealed high thermal stability and nonspontaneous nature of the decomposition steps. The Coats-Redfern method was applied to extract thermodynamic parameters to explain the kinetic behavior. The molar conductance values were relatively low, showing their nonelectrolytic nature. The powder XRD pattern revealed amorphous nature except copper complex (1c) that crystallized in the triclinic crystal system. The EPR study strongly recommends the tetrahedral geometry of 1c. The structure optimization by MM force field calculation through ArgusLab 4.0.1 software program supports the concerned geometry of the complexes. The in vitro antibacterial activity of all the compounds, at their two different concentrations, was screened against four bacterial pathogens, namely, *E. coli*, *P. vulgaris*, *K. pneumoniae*, and *S. aureus*, and showed better activity compared to parent drug and control drug.

1. Introduction

Schiff bases containing penicillin and heterocyclic structural units with N, N donor atoms are considered the most prominent research area in the field of coordination chemistry [1–3]. The various donor atoms in them offer special ability for binding metals. The incorporated metals in the lattice of donor atoms of Schiff base change the physiological, morphological, and pharmacological activities of the compounds. The penicillin based Schiff base is of promising research interest owing to the widespread antibacterial resistance of the medical science. Moreover, the revival of research is essential to generate new Schiff base metal complexes with a diverse range of applications. Schiff base complexes have been used as drugs and have valuable antibacterial [4, 5], antifungal [6–8], antiviral [9, 10], anti-inflammatory [11], and antitumor activities [12]. Besides these, they also bear strong catalytic activity in various chemical reactions in chemistry [13] and surfactant activities [14] and as memory storage devices in electronics [15–17]. One of the compounds used to prepare ligand is amoxicillin, a $\beta$-lactam antibiotic. It is a broad spectrum, semisynthetic penicillin type antibiotic that has potent bactericidal activity against many gram positive and gram negative bacterial pathogens [18]. It takes action against bacteria by preventing them from forming the cell wall and stopping them from growing. In medical science, it has important application for the treatment of bronchitis, ear infection, pneumonia, throat infections, tonsillitis, typhoid, and urinary tract infections. In combination with other antibiotics, it bears potential applications for the successful treatment of many pathogenic infections. However, synthetic modification in amoxicillin by coordination with metal ions of various types has been found to bear enhanced credibility, as documented in several research papers. Cisplatin is the
first metal based drug that emerged in the 20th century and enlightened the world as a promising anticancer drug [19]. Since then several research findings culminated the ideas of inclusion of metals in medicine. Many biological molecules containing pyridine moiety as a part of their structural unit bear enzymatic functions as well as the compounds of diverse biological interest. The pyridine derivatives are reported to have herbicidal, fungicidal, and insecticidal activities and also constitute the major core part of biological enzymes, important vitamins, and toxic alkaloids. Its wide applications in agroindustry and as pharmaceutical ingredients in drug discovery are the key points for this research investigation. Nicotinaldehyde (also called pyridine-3-carboxaldehyde) is a class of heterocyclic compound that has pyridine ring and an aldehyde group at meta-position [20]. Among the other pyridine aldehydes, nicotinaldehyde is suitably preferred for the prevention and treatment of Acne vulgaris, a kind of skin disease [21].

In the present paper, we have focused on the synthesis of novel Schiff base ligand, by the condensation of amoxicillin trihydrate and nicotinaldehyde and its four metal complexes with cobalt(II), nickel(II), copper(II), and zinc(II) salts (Scheme 1). The coordination behavior of the ligand towards transition metal ions was fully investigated by various spectral and thermal techniques. The geometry of the complexes was confirmed by energy optimization through MM2 calculation supported in ChemOffice and ArgusLab software program.

In continuation of our antibiotic research, we have also evaluated the antibacterial efficacy of ligand and its metal complexes against S. aureus, E. coli, K. pneumoniae, and P. vulgaris bacteria.

2. Experimental Section

2.1. Materials. All the chemicals and solvents used were of analytical reagent grade. The title compounds amoxicillin trihydrate and nicotinaldehyde in extra pure form were procured from Duchefa Biochemie, Netherlands, and Spectrochem, Mumbai, India, and used without further purification. Distilled methanol (Qualigen) was used as solvent for the synthesis. The metal salts (Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+} chlorides) (Merck) were used for the synthesis of metal complexes.

2.2. Physical Measurements. Elemental microanalysis of the compounds was performed on EURO VECTOR EA 3000 micro analyzer. Melting points of the ligand and its complexes were recorded on an OMEGA melting point apparatus. The pH measurement was done on the Elico-16 pH meter. The infrared (FTIR) spectra of the prepared ligand and metal complexes were recorded on Perkin-Elmer Spectrum version 10.03.06 FT-IR spectrometer that was run as KBr discs in the range 4000–400 cm^{-1}. The ^1H NMR spectra were recorded on Bruker Avance III, 400 MHz spectrometer, using
DMSO-d$_6$ as solvent. The electronic absorption spectra of the complexes were recorded on single beam microprocessor Labtronics UV-Vis spectrophotometer (LT-290 model) in the range 200–1000 nm in DMSO solvent. EPR-JEOL spectra of the complexes were recorded on JES-FA200 ESR spectrometer with X-band at room temperature. ESI-MS spectra were recorded in positive mode on Agilent Q-TOF mass spectrometer equipped with an electron spray ionization source in the mass range of 20 to 1100. X-ray powder diffraction determinations were accomplished using Bruker AXS D8 Advance X-ray diffractometer with monochromatized Cu-Kα line at wavelength 1.5406 Å as the radiation source and the measurements were taken over the range of 2θ (10 to 70°).

The thermal events of the compounds (TGA/DTA) were recorded on a Perkin-Elmer thermal analyzer with a linear heating rate of 20°C min$^{-1}$ in the range of 40–730°C. The surface morphology of the synthesized ligand and metal complexes was analyzed by scanning electron microscopy technique. JEOl JSM-6390 LV scanning electron microscope was used for this investigation.

2.3. Synthesis of Ligand (HL). Amoxicillin trihydrate (2.097 g, 5 mmol) in distilled methanol (30 ml) was stirred under hot conditions for 3 hs. Solubility in methanol was marked at the temperature elevation state. Its pH was adjusted to neutral by adding 0.1N NaOH solution. Nicotinaldehyde (0.5378 g, 5 mmol) was added slowly to the well stirred amoxicillin trihydrate solution and refluxed under stirring condition. Then after the mixture solution was refluxed for 1 h over water bath which resulted in green colored complex, yield (65%). M. pt. 260°C. Anal. C$_{44}$H$_{22}$N$_2$O$_9$S$_2$ (969.18): Calcd. C 54.45, H 4.36, S 6.61; Found C 54.52, H 4.49, S 6.73. IR (KBr pellet, selected bands): $\nu$$_{max}$ = 3379 (b, O-H str.), 1634 (s, C=O), 964 (s, N=N) nm. ESI-MS, positive: $m/z$ = 964.18 [M + H]$^+$.

Conductivity: $\Lambda_m$ = 19.9 μS/cm.

2.4. Synthesis of Metal Complexes

2.4.1. Ni(II) Complex (1b). The nickel complex (1b) was prepared according to the procedure adopted for the preparation of 1a. A solution of NiCl$_2$·6H$_2$O (0.1188 g, 0.5 mmol) in 5 ml methanol was used for this purpose. The mixed solution of ligand (HL) and Ni$^{2+}$ salt was refluxed for 1 and 1/2 h over water bath which resulted in green colored complex, yield (62%). M. pt. 270°C. Anal. C$_{58}$H$_{22}$N$_2$O$_9$S$_2$ (964.18): Calcd. C 52.74, H 4.63, N 11.28, S 6.44; Found C 52.74, H 4.63, N 11.28, S 6.44. IR (KBr pellet, selected bands): $\nu$$_{max}$ = 3417 (b, O-H str.), 1633 (s, C=O), 1510, 1443 (s, COOH), 606 ($\rho_\omega$, H$_2$O), 526 (Co-O). UV/Vis: $\lambda$$_{max}$ = 263, 346–371, 457–488, 549 nm. ESI-MS, positive: $m/z$ = 1001.2 [M + H]$^+$. Conductivity: $\Lambda_m$ = 21.8 μS/cm.

2.4.2. Cu(II) Complex (1c). The copper complex (1c) was also prepared according to the procedure adopted for the preparation of 1a and 1b. A solution of CuCl$_2$·2H$_2$O (0.085 g, 0.5 mmol) in 5 ml methanol was used for this purpose. The mixed solution of ligand (HL) and Cu$^{2+}$ salt was refluxed for 1 and 1/2 h over water bath which resulted in green colored complex, yield (65%). M. pt. 260°C. Anal. C$_{44}$H$_{22}$N$_2$O$_9$S$_2$ (969.18): Calcd. C 54.45, H 4.36, N 11.57, O 16.49, S 6.64; Found C 54.41, H 4.39, N 11.55, O 16.55, S 6.67. IR (KBr pellet, selected bands): $\nu$$_{max}$ = 3379 (b, O-H str.), 1636 (s, C-N), 1512, 1436 (s, COOH), 686 ($\rho_\omega$, H$_2$O), 444 (Ni-N). UV/Vis: $\lambda$$_{max}$ = 227, 259, 337, 448, 447 nm. ESI-MS, positive: $m/z$ = 969 [M + H]$^+$.

Conductivity: $\Lambda_m$ = 35.2 μS/cm.

2.4.3. Zn(II) Complex (1d). The zinc complex (1d) was prepared according to the above procedure and by using Zn$^{2+}$ salt (0.07 g, 0.5 mmol). The mixed solution was refluxed for 2h over water bath which resulted in light yellow colored complex, yield (57%). M. pt. 250°C. Anal. C$_{49}$H$_{22}$N$_2$O$_9$S$_2$Zn (970.18): Calcd. C 54.35, H 4.35, N 11.52, O 16.45, S 6.60; Found C 54.41, H 4.34, N 11.57, O 16.49, S 6.57. IR (KBr pellet, selected bands): $\nu$$_{max}$ = 3340 (b, O-H str.), 1629 (s, C-N), 1512, 1437 (s, COOH), 657 ($\rho_\omega$, H$_2$O), 415 (Zn-N). $^1$H NMR (400 MHz, [D$_8$] DMSO): $\delta$ = 10.123 (s, 1 H, COOH), 9.425 (b, 1H, Ar-OH). UV/Vis: $\lambda$$_{max}$ = 700, 925, 935, 944 (C-H methyl) ppm. UV/Vis: $\lambda$$_{max}$ = 263, 346 nm. ESI-MS, positive: $m/z$ = 970 [M + H]$^+$.

Conductivity: $\Lambda_m$ = 5.6 μS/cm.

2.5. Antibacterial Susceptibility Test. The antimicrobial potency of the synthesized compounds was done by assaying antibacterial activity study. The experimental portion of the study was accomplished in the laboratory of the Department of Microbiology at Mahendra Morang Adarsh Multiple Campus, Biratnagar. The compounds (HL and 1a–1d) were tested in vitro by standard Kirby-Bauer paper disk diffusion method against some gram positive and gram negative human pathogenic bacteria [12, 22, 23]. The recommended NCCLS guideline was followed for the study [24]. Well sterilized filter paper discs of 5 mm size (Whatman-model)
were used as antibiotic assay discs for testing of compounds. The discs were loaded with test compounds at two different concentrations (100 and 50 mcg/ml in DMSO) under UV laminar flow to reduce bacterial contamination [25]. The loaded discs were dried in the laminar flow chamber by blowing hot air through hair dryer. Sterilized nutrient agar media were carefully poured in the Petri plate and kept in rest for few hours in the sterilized zone for solidification. Fresh bacterial culture, revived before injection, was swabbed on the media and the loaded discs were stuck over it. One disc soaked with DMSO was used as the solvent control and amikacin (30 mcg/disc) was used as positive control.

Fresh bacterial culture, revived before injection, was swabbed in electron density and force constant of the metal with the metal centers. The formation of cobalt complex (1a) was confirmed by ESI-MS peak at $m/z = 1002$, attributable to $[M + H]^+$. The well resolved IR band at 3417 cm$^{-1}$, for complex (1a), corresponds to the $ν$(O-H) stretching vibration (Figure 1) [29]. The evidence of bonding in 1a is also shown by the observation of new bands in the lower frequency regions at 425 and 526 cm$^{-1}$ characteristic to $ν$(Co-O) and $ν$(Co-O) stretching vibrations that are not observed in the IR spectrum of ligand. The less intense IR band at 606 cm$^{-1}$ is assignable to bending vibration of two lattice water molecules of the outer sphere region. The observed molecular mass of nickel complex (1b) was evidenced by ESI mass spectrum peak value at $m/z = 964$, assignable to molecular ion peak. The formation of this complex was verified by FTIR spectroscopy, where specific bands are observed at 1625 cm$^{-1}$ $ν$(CH=N), 3337 cm$^{-1}$ $ν$(O-H), 429 cm$^{-1}$ $ν$(Ni-N), and 687 cm$^{-1}$ for outer sphere lattice water molecules. The formation of the complex 1c is further evidenced by the ESI-MS peak at $m/z = 970$, attributed to $[M + H]^+$. The positive ion ESI mass spectrum showed peaks at $m/z = 971$ for zinc complex (1d), attributed to $[M + H]^+$. Its formation was strongly evidenced by FTIR and $^1$H NMR spectral data. The strong azomethine band at 1629 cm$^{-1}$ $ν$(CH=N) for this complex has shifted by 11 cm$^{-1}$ towards a lower wave number relative to that of the free ligand, indicating metal coordination with azomethine nitrogen. The metal nitrogen coordination is further evidenced by a sharp peak at 415 cm$^{-1}$ in the FTIR spectrum of 1d. The $^1$H NMR spectrum is also consistent with the suggested structure. The downfield shift of $^1$H NMR signal for azomethine proton from $δ$ 9.094 ppm for ligand to $δ$ 9.295 ppm for zinc complex (1d) also supports coordination of the azomethine nitrogen to the zinc(II) ion. Two doublets observed at $δ$ 6.718–7.625 for HL and 6.72–7.66 ppm for zinc complex 1d are attributed to aromatic ring protons. The methyl protons of amoxicillin moiety in both HL and 1d appear as a singlet peak in the region of $δ$ 1.118–1.562 ppm. Amide NH proton for HL executes signal at 8.241–8.271 ppm, which is absent in the spectrum of 1d, and this confirms the coordination of amide N-atom with metal center via deprotonation [30]. In the spectrum of HL, the signal due to carboxylic proton appears at $δ$ 10.122 ppm, which is still present in the $^1$H NMR spectrum of zinc complex (1d).

3. Results and Discussion

3.1. Physical Characterization. The physical properties and the microanalytical data of the ligand (HL) and metal complexes (1a–1d) are summarized in the experimental section. The analytical results show (1:2) metal ligand ratio, that is, $ML_2$ type. The color change from ligand to metal complexes is in support of metal ligand interaction which is further reinforced by conductivity and pH change. The ligand (HL) was soluble in methanol. The complexes were soluble in DMSO and DMF. The nickel complex (1b) was found to be hygroscopic.

3.2. Spectral Characterization. The formation of HL was confirmed by ESI mass spectrometry, which showed peaks at $m/z = 455$, attributable to $[M + H]^+$. The FTIR spectrum is also in line with the proposed structure of HL, with characteristic stretching vibrations at 1640 cm$^{-1}$ assignable to azomethine group [27]. A broadband with absorption maximum of 3303 cm$^{-1}$ is possibly due to collapse of N-H and O-H stretching peaks. Other significant strong bands at 1510 and 1433 cm$^{-1}$ for HL are attributed to $ν$(C=O) asymmetric and symmetric stretch. The $^1$H NMR spectrum of HL executes a sharp singlet at 9.09 ppm corresponding to azomethine proton. On complexation, $ν$(C=N) stretching band for HL has shifted to lower absorption frequency of 1633 cm$^{-1}$ (1a), 1625 cm$^{-1}$ (1b), 1636 cm$^{-1}$ (1c), and 1629 cm$^{-1}$ (1d), indicating the coordination of azomethine nitrogen atom to the metal ion [28]. This lower frequency shift of azomethine group in the complexes is due to the decrease in electron density and force constant of the metal with the azomethine nitrogen lone pair. In all the complexes, FTIR absorption bands corresponding to $ν$(O-H) execute in the range 3337–3417 cm$^{-1}$ relative to 3303 cm$^{-1}$ for HL. The complexes exhibit $ν$(COOH) stretching vibrations at the equivalent positions of the ligand, suggesting their noncoordination.

3.3. Electronic Absorption Spectra and Magnetic Moment Measurement. The electronic absorption spectrum of ligand (HL) displays high energy bands in the ultraviolet region at 206 and 262 nm, corresponds to $π → π^*$ transitions of the aromatic and pyridinium ring, and, at 356 nm, corresponds to $n → π^*$ intraligand charge transfer band with the involvement of C=N group [31]. However, the additional bands in the higher wavelength region are observed in the complexes.
which signify metal ligand coordination. The cobalt complex (1a) exhibits two distinct bands in high wavelength region of the spectrum at 457–488 nm and 549 nm. The former band is assignable to $^{4}T_{1g}(F) \rightarrow ^{4}T_{1g}(P)$ and latter band indicates $^{4}T_{1g} \rightarrow ^{4}A_{2g}$ transition, confirming its octahedral geometry [32]. The magnetic moment value (4.75 BM) further supports this geometry. The high energy bands for this complex are observed at 263 and 346–371 nm, assignable to $\pi \rightarrow \pi^{*}$ and $n \rightarrow \pi^{*}$ LMCT transitions, respectively. The electronic absorption spectrum of nickel complex (1b) displays d-d transition band at 346 nm assignable to $^{1}A_{1g} \rightarrow ^{1}B_{1g}$ transition along with the bands in the low wavelength region at 261 and 346 nm [33, 34]. The diamagnetic nature of this complex is suggestive of the complete distortion of octahedral geometry and confirms its square planar geometry. The magnetic moment value (1.82 BM) and electronic absorption spectrum of paramagnetic copper complex (1c) exhibit absorption band in the high wavelength region at 485 nm, attributed to $^{2}T_{2g} \rightarrow ^{2}E_{g}$ transition which is suggestive of tetrahedral geometry [35]. Other high energy bands for this complex are observed at 227 and 259 nm for $\pi \rightarrow \pi^{*}$ transition and 337 and 344 nm for $n \rightarrow \pi^{*}$ LMCT transition. The zinc complex (1d) displays an absorption band at 346 nm assignable to the LMCT transition, compatible with tetrahedral geometry, and this is further supported by its diamagnetic nature and absence of d-d band, due to its complete d$^{10}$ electronic configuration.

3.4. TGA/DTA Studies. The TGA/DTA curves for the complexes were carried out within the temperature range from room temperature to 700°C with the linear heating rate of 20°C/min in the nitrogen atmosphere. Correlation of the thermal events at elevated temperatures with kinetic parameters provides useful physicochemical information of the compounds. Thermo gravimetric analysis is one such important instrumental technique to observe thermal changes with respect to increase in temperatures [36]. The computed thermal decomposition data in Table 1 are in good agreement with the suggested microanalytical data. The following findings have been achieved in our research analysis.

The thermogram of cobalt complex (1a) (Figure 2) exhibited four decomposition steps in the temperature range of 50–380°C. The first decomposition step in the temperature range of 50–110°C with % mass loss of 4.826% (0.226 mg) is assignable to the loss of two lattice water molecules from the outer sphere [37, 38]. The second and third decomposition steps with % mass loss of 25.923% (0.829 mg) and 33.837% (0.729 mg) in the temperature range of 241–273°C and 279–300°C have considered the loss of organic ligand moiety. The last decomposition step with % mass loss of 52.247% (0.306 mg) represents a complete loss of ligand from the complex in the temperature range of 338–380°C, leaving cobalt oxide as stable residue. The nickel complex (1b) exhibited thermal decomposition in two distinct steps. The first step with % mass loss of 5.6% (0.153 mg) is assignable to the loss of outer sphere lattice water molecules in the temperature range of 44–113°C. The exothermic peak with 30.86% (0.484 mg) mass loss in the temperature range of 232–403°C is attributed to loss of ligand moiety. The thermograms of other two complexes 1c and 1d are complement to the analyzed data of 1a and 1b. The first step decomposition in 1c and 1d occurred in the temperature range around 45–107°C with $T_{\text{DTG}}$ 76.79 and 75.46°C and this again suggests the loss of two lattice water molecules. The final thermal decomposition step in all the metal complexes is noticed above 400°C, which is indicated by the formation of the horizontal TG curve. This step interprets the formation of stable metal oxide residue.

Kinetic Parameters. The thermal dehydration and decomposition of the complexes were studied by using an integral method applying a very popular Coats-Redfern method [39, 40]. The thermodynamic activation parameters of decomposition processes are essential to describe the thermal stability.
and free energy of activation (ΔG) versus 1/𝑇 in all the complexes. These parameters are evaluated graphically as well as the nature and rates of thermal decomposition of the complexes. These parameters are evaluated graphically by plotting of data based on Coats-Redfern relation in the following form:

\[\ln \left\{ \frac{-\ln (1-\alpha)}{T^2} \right\} = \ln \left[ \frac{AR}{\beta E^*} \right] - \frac{E^*}{RT}, \tag{1}\]

where α represents the decomposition fraction at temperature T K and β denotes linear heating rate (dT/dt). E* and A denote the activation energy and Arrhenius preexponential factor, respectively. R represents gas constant. Molding the equation for the straight line (𝑦 = 𝑚𝑥 + 𝑐), a linear plot of left side versus 1/T of Coats-Redfern equation gives a straight line, whose slope E*/R furnishes activation energy parameter and the preexponential factor (A) can be determined from the intercept. The other thermodynamic parameters such as entropy of activation (ΔS*), enthalpy of activation (ΔH*), and free energy of activation (ΔG*) have been calculated by using the following relation:

\[ΔS^* = R \ln \left( \frac{Ah}{k_B T} \right) \tag{2}\]

\[ΔH^* = E^* - RT \]

\[ΔG^* = ΔH^* - TΔS^* .\]

The computed data of thermodynamic activation parameters of various decomposition steps of the metal complexes are listed in Table 2. In the present work, the plot of left hand side of Coats-Redfern equation versus 1000/T in all the decomposition steps of all complexes shows a best fit for first-order reaction kinetics [41]. The high and increasing values of activation energy in the subsequent steps of all the complexes reflect high thermal stability, which may be due to covalent bond character. The entropy of activation value of first decomposition step in all the complexes is negative, which indicates nonspontaneous dehydration reaction process. Most of this value of other steps is positive and infers the dissociation character of decomposition [42]. This also attributes more ordered activated state than the reactants. The positive ΔG* values of all the complexes justify the nonspontaneous nature of decomposition steps. The enthalpy of activation values (ΔH*) in most of the decomposition steps is positive which reveals endothermic processes. However, this nature also depends upon the value of other thermodynamic activation parameters. The computed data of correlation coefficient (r) obtained from the graphical plot reflect a good fit of the data with linear function [43, 44].

### Table I: Thermal decomposition data of metal complexes.

| Comp. | Step | ΔH%, found | T_i | T_f | T_{D_{TG}} | Mass loss | T_{a_k} | Peak |
|-------|------|------------|-----|-----|------------|-----------|--------|------|
| 1a    | 1    | 4.826      | 50  | 110.2 | 80.85      | -0.226    | 103.68 | Endo |
|       | 2    | 25.923     | 241.63 | 276.73 | 268.38     | -0.829   | —      | —    |
|       | 3    | 33.837     | 279  | 300  | 284.05     | -0.729   | —      | —    |
|       | 4    | 52.247     | 338  | 380  | 357.21     | -0.306   | 334.9  | Endo |
| 1b    | 1    | 5.601      | 44  | 113  | 85.91      | -0.153   | 105.33 | Endo |
|       | 2    | 30.861     | 232  | 403  | 278.16     | -0.484   | 382.91 | Endo |
| 1c    | 1    | 2.699      | 49  | 105  | 76.79      | -0.100   | 111.23 | Endo |
|       | 2    | 8.814      | 148  | 163  | 159.86     | -0.395   | —      | —    |
|       | 3    | 21.635     | 187  | 246  | 237.13     | -0.310   | —      | —    |
|       | 4    | 42.395     | 293  | 390  | 326.01     | -0.244   | 385.92 | Exo  |
| 1d    | 1    | 3.047      | 46  | 107  | 75.46      | -0.121   | 115.75 | Endo |
|       | 2    | 18.233     | 230  | 287  | 260.99     | -0.491   | 339.24 | Endo |
|       | 3    | 36.441     | 310  | 410  | 330.41     | -0.238   | 365.88 | Exo  |

3.5. XRPD Study. Single crystal growth of the synthesized compounds was unsuccessful, so their crystallinity was established by X-ray powder diffraction study. The ligand (HL) and complexes (1a, 1b, and 1d) were found amorphous. The crystal structure of copper complex (1c) was worked out by its well resolved crystalline peaks (Figure 3), which crystallized in a triclinic crystal system with P1 space group. The diffractogram of this complex registered 22 reflection peaks in the range of (θ) 0 to 50° with maxima at 15.974° with corresponding d spacing value of 5.58 Ǻ. The cell dimensions a (6.228 Ǻ), b (109390 ˚A), c (20.3388 ˚A), α (63.1585°), β (113.5723°), and γ (64.269°) are in good agreement with the refined triclinic crystal system. The unit cell volume of this compound was calculated to be 747.4131 ˚A³ with FOM 31. The details of crystallographic data are summarized in Table 3. The particle size was calculated from Scherer's formula α = 0.91/β cosθ, where λ is the wavelength, β is the full-width half maximum of the characteristic peak, and θ is the
Table 2: Kinetic and thermodynamic parameters of metal complexes.

| Comp. Step | Step | $r$  | $A$ (s$^{-1}$) | $T_{\text{max}}$ (K) | $E^*$ (kJ/mol) | $\Delta S^*$ (J/K·mol) | $\Delta H^*$ (kJ/mol) | $\Delta G^*$ (kJ/mol) |
|------------|------|------|---------------|-----------------------|----------------|----------------------|----------------------|----------------------|
| 1a         | 1    | $-0.98495$ | $5.62 \times 10^6$ | 353.85 | 58.36 | $-117.92$ | 55.4719 | 97.19789 |
|            | 2    | $-0.99209$ | $5.06 \times 10^{19}$ | 541.38 | 229.22 | 126.559 | 224.718 | 156.202 |
|            | 3    | $-0.99052$ | $1.19 \times 10^{36}$ | 557.05 | 403.95 | 18.3647 | 399.319 | 389.089 |
|            | 4    | $-0.99343$ | $1.14 \times 10^{22}$ | 630.21 | 288.1474 | 170.339 | 282.907 | 175.525 |
| 1b         | 1    | $-0.99453$ | $7.054 \times 10^6$ | 358.91 | 59.62 | $-40.236$ | 56.634 | 71.075 |
|            | 2    | $-0.9887$ | $1.35 \times 10^{15}$ | 551.16 | 160.7139 | 35.4267 | 160.288 | 140.762 |
| 1c         | 1    | $-0.99401$ | $4.064 \times 10^7$ | 349.79 | 63.4725 | $-110.3698$ | 60.564 | 64.191 |
|            | 2    | $-0.99698$ | $10.06 \times 10^{51}$ | 510.13 | 129.453 | $-24.716$ | 125.2115 | 137.819 |
|            | 3    | $-0.99643$ | $5.98 \times 10^{11}$ | 599.01 | 93.1345 | $-140.1638$ | 92.6438 | 176.603 |
|            | 4    | $-0.99604$ | $6.55 \times 10^5$ | 603.41 | 96.5845 | $-103.320$ | 91.567 | 153.911 |

3.6. EPR Analysis. The solid state X-band EPR spectrum of the copper complex (1c) was recorded at room temperature under the frequency 9447.606 MHz with no marker lines used and center line at 316.213 mT. The standard lines that are used in EPR model are of Mn, which has been omitted in the graph. The EPR spectrum of complex provides useful information about the metal ion environment within the complex. The highly symmetrical EPR spectrum of copper complex (1c) (Figure 4) delivered a single isotropic signal with $g_\parallel$ value of 2.18 and $g_\perp$ value of 2.08 [47]. The absence of poorly resolved hyperfine signal may be attributed to the considerable exchange coupling interaction of the Cu$^{+2}$ ions in the complex. The order of splitting factors $g_\parallel > g_\perp > 2.0023$ clearly indicates the localized unpaired electron in the d orbital of Cu$^{+2}$ ion and is characteristic of axial symmetry [6, 48]. The calculated $g_{av}$ value is 2.11 whose deviation from the free electron (2.003) is due to covalent character of the metal ligand bond. This fact is further supported by $g_\parallel$ value less than 2.3. The value of exchange coupling interaction parameter "G" = 2.25 is less than 4 and suggests considerable exchange interaction in the complex [49]. All these parameters are in support of tetrahedral geometry of copper complex (1c).

3.7. SEM Analysis. The metal coordination to ligand significantly changes the surface morphology of the complexes and this was investigated by SEM analysis. The SEM micrograph of ligand (HL) and metal complexes are shown in Figure 5 and the differences are seen in surface morphology of the metal complexes due to changes in the metal ions. The SEM micrograph of ligand demonstrates nonuniform platelet-like structure with variable lateral dimensions [50]. Moreover,
Table 3: X-ray powder diffraction data of copper complex (1c).

| Peak number | 2θ  | θ   | Sinθ | Sin²θ | h² + k² + l² | hkl | d   | FWHM % int. | a in nm |
|-------------|-----|-----|------|-------|--------------|-----|-----|-------------|--------|
| 1           | 7.2685 | 3.63425 | 0.06338 | 0.004017 | 1 | 0 0 1 | 12.16238 | 0.2244 | 16.00 | 61.22 |
| 2           | 13.7483 | 6.87415 | 0.11968 | 0.014323 | 1 | 0 1 0 | 6.44119 | 0.6731 | 21.90 | 20.37 |
| 3           | 15.9738 | 7.9869 | 0.13894 | 0.019304 | 2 | 1 1 0 | 5.54843 | 0.0935 | 100.00 | 146.64 |
| 4           | 16.3780 | 8.189 | 0.14243 | 0.020286 | 1 | 0 1 0 | 5.41242 | 0.1496 | 42.23 | 91.65 |
| 5           | 17.7380 | 8.87415 | 0.15968 | 0.024323 | 1 | 0 1 0 | 5.21487 | 0.2244 | 6.47 | 61.102 |
| 6           | 23.9666 | 11.7983 | 0.20446 | 0.031803 | 2 | 1 1 0 | 3.77046 | 0.1870 | 28.72 | 73.323 |
| 7           | 26.0686 | 13.0343 | 0.22553 | 0.038863 | 6 | 1 1 0 | 3.41826 | 0.1309 | 44.73 | 104.747 |
| 8           | 27.7288 | 13.8644 | 0.23962 | 0.043817 | 1 | 1 0 0 | 3.21726 | 0.1496 | 38.35 | 91.654 |
| 9           | 32.3941 | 16.1970 | 0.27894 | 0.067807 | 20 | 2 0 −4 | 2.76379 | 0.1122 | 70.54 | 122.205 |
| 10          | 33.2184 | 16.6092 | 0.28584 | 0.068174 | 40 | 2 0 −6 | 2.69707 | 0.2057 | 91.73 | 66.657 |
| 11          | 35.6718 | 17.8339 | 0.30629 | 0.079813 | 2 | 1 −1 0 | 2.51700 | 0.2244 | 8.91 | 61.103 |
| 12          | 37.2666 | 18.6333 | 0.31951 | 0.082086 | 20 | 2 0 −4 | 2.41287 | 0.3739 | 7.05 | 36.671 |
| 13          | 40.3520 | 20.1775 | 0.34490 | 0.11895 | 80 | 0 4 8 | 2.23521 | 0.2617 | 23.89 | 52.394 |
| 14          | 43.0415 | 21.5207 | 0.36683 | 0.13845 | 9 | 1 −2 −2 | 2.1057 | 0.4487 | 11.08 | 30.5585 |
| 15          | 44.3550 | 22.1775 | 0.37774 | 0.14248 | 30 | 2 5 1 | 2.04234 | 0.2244 | 11.90 | 61.103 |
| 16          | 45.3976 | 22.6988 | 0.38588 | 0.14890 | 69 | 2 1 −8 | 1.99783 | 0.2244 | 15.90 | 61.103 |
| 17          | 47.7559 | 23.8779 | 0.40478 | 0.16384 | 25 | 3 4 0 | 1.90454 | 0.1870 | 16.97 | 73.324 |
| 18          | 48.6714 | 24.3357 | 0.41211 | 0.16983 | 58 | 3 0 −7 | 1.87083 | 0.2991 | 5.79 | 45.843 |
| 19          | 49.3094 | 24.6547 | 0.41714 | 0.174 | 18 | 3 3 0 | 1.84658 | 0.2736 | 7.79 | 50.116 |

Average particle size 69.3474

inhomogeneous matrix with broken ice-like structure has been observed in the SEM micrograph of nickel complex (1b). The SEM micrograph of copper complex (1c) displays agglomerated morphology with small sized grains scattered in homogenous matrix and gives the appearance of coral-like structure. In the SEM micrograph of zinc complex (1d), small sized particles crumbled together to give rock-like structure with somewhat cotton-like appearance.

3.8. Molecular Modeling. The computational study of the compounds furnishes a clear idea about the three-dimensional arrangement of different atoms in the molecules. The energy optimization of the ligand (HL) and metal complexes (1a–1d) was done by Universal Force Field (UFF) technique with minimum RMS gradient 0.100, supported in ArgusLab 4.0.1 version software [51, 52]. The details of the bonding and energy parameters optimized by molecular modeling calculations of the metal complexes are depicted in Table 4. For ligand, single point energy calculation with Hamiltonian AM1 revealed final SCF energy and heat of formation, −132288.8349 and 45.0637 kcal/mol, respectively [53]. After the geometry optimization by molecular mechanics (UFF) technique, the final geometrical energy of HL has been reported to 139.2725 kcal/mol. On ESP mapped electron density surface of HL (Figure 6), red color indicates the highest electron density region which is around O-atom. The second highest electron density region is around an azomethine N-atom which is shown by mixed green and yellow colors. This is the region for stability of coordinated metal ions and supports its linkage with azomethine N-atom. It seems clear that the coordination with O-atoms is restricted due to greater electronic repulsion and field obstruction. In the nickel complex (1b), the high electron density (Figure 7) around the coordinated azomethine N-atom, indicated by red color, is in favor of its proposed geometry. Similar study and computational data of the complexes (1a to 1d) are in good support of their proposed structures.

3.9. Antibacterial Activity Study. The antibacterial efficacy of the ligand (HL) and metal complexes (1a–1d) was tested against S. aureus, E. coli, K. pneumoniae, and P. vulgaris bacteria. The antibacterial results are presented in the bar graph (Figure 8). Two different concentrations (100 and 50 mcg/ml) of the compounds have been selected for antibacterial assay. The results suggest enhanced antibacterial activity of the ligand (HL) and metal complexes (1a–1d). The compound (1c) showed little activity against all the bacterial pathogens, compared to ligand and other metal complexes. The ligand bears activity, even greater than parent drug amoxicillin and control drug amikacin at higher concentration. This higher activity of ligand is possibly due to interference in the normal cell process of organism caused by the formation...
of hydrogen bond through the azomethine group with the active center of cell constituents [54]. Further, the uncoordinated heteroatom of pyridine moiety also contributes to microbial growth inhibition. Moreover, the complexes deliver better antibacterial activity at their higher concentration. Precise observation reveals that the compounds are less active against S. aureus and more active against E. coli and P. vulgaris bacteria. This enhanced activity of the complexes may be attributed to chelation of Schiff base with metal ions that provide stability and more susceptibility against the bacterial pathogens [55, 56]. It has been suggested that the structural components possessing additional (C=N) bond with nitrogen and oxygen donor systems inhibit enzyme activity due to their deactivation by metal coordination. This permits their efficient permeation through the lipid layer of organisms and destroys their activity [6].
### Table 4: Selected bond lengths and bond angles of metal complexes.

| Complex | Atoms Bond length (Å) | Bond energy (Kcal/mol) | Atoms Bond angle | Bond angle energy | Final geom. energy |
|---------|-----------------------|------------------------|-----------------|------------------|-------------------|
| 1a      | N(3)-Co(34) 1.957     | 273.796                | N(3)-Co(34)-N(20) 90.00 | 300.46          | 349.2538 (Kcal/mol) (0.556 au) |
|         | N(20)-Co(34) 1.972   | 267.453                | N(3)-Co(34)-N(35) 90.00 | 304.025         |                   |
|         | Co(34)-N(35) 1.957   | 273.796                | N(3)-Co(34)-N(52) 90.00 | 300.46          |                   |
|         | Co(34)-N(52) 1.972   | 267.453                | N(3)-Co(34)-O(104) 90.00 | 273.401         |                   |
|         | Co(34)-O(104) 1.964  | 244.913                | N(35)-Co(34)-N(20) 90.00 | 300.46          |                   |
|         | Co(34)-O(113) 1.964  | 244.913                | N(35)-Co(34)-N(104) 90.00 | 273.401         |                   |
| 1b      | N(2)-Ni(33) 1.870    | 313.824                | N(2)-Ni(33)-N(19) 90.00 | 344.228         | 324.5763 (Kcal/mol) (0.517 au) |
|         | N(19)-Ni(33) 1.885   | 306.275                | N(2)-Ni(33)-N(34) 90.00 | 348.473         |                   |
|         | N(34)-Ni(33) 1.870   | 313.824                | N(2)-Ni(33)-N(51) 90.00 | 344.228         |                   |
|         | N(51)-Ni(33) 1.885   | 306.275                | N(34)-Ni(33)-N(19) 90.00 | 344.228         |                   |
|         | N(51)-Ni(33)-N(19) 90.00 | 340.090              | N(34)-Ni(33)-N(51) 90.00 | 344.228         |                   |
| 1c      | N(2)-Cu(33) 2.016    | 181.007                | N(2)-Cu(33)-N(19) 109.47 | 158.764         | 373.488 (Kcal/mol) (0.595 au) |
|         | N(19)-Cu(33) 2.031   | 176.938                | N(2)-Cu(33)-N(34) 109.47 | 160.587         |                   |
|         | N(34)-Cu(33) 2.016   | 181.007                | N(2)-Cu(33)-N(51) 109.47 | 158.764         |                   |
|         | N(51)-Cu(33) 2.031   | 176.938                | N(34)-Cu(33)-N(19) 109.47 | 158.764         |                   |
|         | N(51)-Cu(33)-N(19) 109.47 | 156.977              | N(34)-Cu(33)-N(51) 109.47 | 158.764         |                   |
| 1d      | N(2)-Zn(33) 1.888    | 164.142                | N(2)-Zn(33)-N(19) 109.47 | 193.167         | 352.3697 (Kcal/mol) (0.561 au) |
|         | N(19)-Zn(33) 1.903   | 160.260                | N(2)-Zn(33)-N(34) 109.47 | 195.503         |                   |
|         | N(34)-Zn(33) 1.888   | 164.142                | N(2)-Zn(33)-N(51) 109.47 | 193.167         |                   |
|         | N(51)-Zn(33) 1.903   | 160.260                | N(34)-Zn(33)-N(19) 109.47 | 193.167         |                   |
|         | N(51)-Zn(33)-N(19) 109.47 | 190.879              | N(34)-Zn(33)-N(51) 109.47 | 193.167         |                   |

### 4. Conclusion

The novel ligand (HL) and the metal complexes (1a–1d) were successfully synthesized. The ligand can complex the metal ion via N donor atoms. The electronic absorption spectral analysis in combination with ESR data revealed octahedral geometry for cobalt complex (1a), square planar geometry of nickel complex (1b), and tetrahedral geometry for both copper complex (1c) and zinc complex (1d). Several spectral data nicely support the above concerned geometry of the complexes. Furthermore, the metal complexes were screened in vitro for antibacterial assay. Based on the results of this study of synthesized compounds, it has been concluded that the ligand bears greater potency than amoxicillin and control drug amikacin. The complexes 1a, 1b, and 1d were even highly active against all the bacterial pathogens at their higher concentration; however the copper complex (1c) was less active than others. This greater activity might be due to azomethine linkage and heteroatoms present in these compounds.
Conflicts of Interest
The authors declare that they have no conflicts of interest.

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