Synthesis, Characterization, Electrochemical Studies, and In Vitro Antibacterial Activity of Novel Thiosemicarbazone and Its Cu(II), Ni(II), and Co(II) Complexes

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Metal complexes were prepared by the reaction of thiosemicarbazone with CuCl₂, NiCl₂, CoCl₂, Cu(OAc)₂, Ni(OAc)₂, and Co(OAc)₂. The thiosemicarbazone coordinates to metal through the thionic sulfur and the azomethine nitrogen. The thiosemicarbzone was obtained by the thiosemicarbazide with 3-acetyl-2,5-dimethylthiophene. The identities of these compounds were elucidated by IR, 1H, 13C-NMR, and GC-MS spectroscopic methods and elemental analyses. The antibacterial activity of these compounds was first tested in vitro by the disc diffusion assay against two Gram-positive and two Gram-negative bacteria, and then the minimum inhibitory concentration (MIC) was determined by using chloramphenicol as reference drug. The results showed that compound 1.1 is better inhibitor of both types of tested bacteria as compared to chloramphenicol.

1. Introduction

Most of the tropical and subtropical regions of the world are suffering from parasitic diseases. The intestinal causative agent of amoebiasis is protozoan parasite Entamoeba histolytica, which is affecting millions of people throughout the world. Millions of people die every year because of these diseases [1]. Major side effects such as neurological complications and the possible selection of a resistant E. histolytica strain have been reported by using metronidazole [2]. Therefore, it has become a topic of interest for the researchers to find some new amoebicidal drug and the treatment of infectious diseases still remains an important and challenging problem. Numerous compounds have been synthesized to treat such infectious diseases, but their medical use has been limited by their relatively high toxicity, bacterial resistance, and pharmacokinetic deficiencies. It is found that transition metals and their complexes have varying utility and interesting chemistry. Metal complexes with suitable ligands are said to be chemically more significant and specific than the metal ions [3]. Preparation of transition metal complexes with thiosemicarbazone ligands has been paid considerable attention due to the pharmacological properties of both ligands and complexes [4, 5]. Thiosemicarbazone derivatives form an important class of organic compounds due to their structural chemistry and biological activities, such as antibacterial, antivirus activities. Heterocyclic sulfur and oxygen containing thiosemicarbazones have been the subjects of extensive investigation because of their use for the biological applications [6, 7]. Thiosemicarbazones have received great interest because of their bonding modes, biological implications, structural diversity, and ion-sensing ability [8]. The biological application and properties of metal complexes differ from those of either ligands or the metal ions, and increased and/or decreased biological activities of transition metal complexes like Cu(II) are reported in the literature [9–11]. Thiosemicarbazone compounds are also applicable in fields of inorganic chemistry. They are used as a chelating ligand for the formation of metal complexes because of variety of flexible donor sets of sulfur and nitrogen.
Cu(II), Ni(II), and Co(II) metal complexes of thiosemicarbazone dramatically increase the biological activities such as antibacterial, antifungal, anti-HIV, and anti-inflammatory [12]. Thiosemicarbazones and their metal complexes are also applicable in the field of material sciences such as nonlinear optical (NLO) [13], electrochemical sensing [14], and Langmuir film [15]. Various thiosemicarbazone derivatives and their metal complexes are notable for their second harmonic generation (SHG) [16]. People are working from last many years on the synthesis and characterization of transition metal complexes with thiosemicarbazones [17–20], but very little work has been done so far on Cu(II), Ni(II), and Co(II) complexes with substituted thiosemicarbazone ligands. Metal thiosemicarbazone complexes are promising as new class of experimental anticancer chemotherapeutic agents which shows evidence of inhibitory behavior against cancer [21]. These are also a useful model for bioinorganic processes [22, 23]. Due to wide range of application of the thiosemicarbazones and their metal complexes, we have synthesized, characterized, and studied the antibacterial activity of thiosemicarbazone and its Cu(II), Ni(II), and Co(II) metal complexes.

2. Experimental

2.1. General. All melting points were measured with a capillary apparatus and were uncorrected. All the compounds were routinely checked by IR, 1H NMR, mass spectrometry, and elemental analysis. IR spectra were recorded in KBr discs on a Perkin-Elmer model 1620 FTIR spectrometer. 1H NMR spectra were recorded at ambient temperature using a Bruker spectrometer DPX-600 MHz spectrometer in CDCl3 and DMSO-d6. The following abbreviations were used to indicate the peak multiplicity as s: singlet, d: doublet, t: triplet, and m: multiplet. FAB mass spectra were recorded on a JEOL SX102 mass spectrometer using argon/xenon (6kV, 10mB). The reactions were monitored by precoated aluminum silica gel 60F254 thin layer plates procured from Merck (Germany).

Electrochemical properties of the synthesised metal complexes were examined with CH Instruments, USA (Model 110A-Electrochemical analyzer, Version 4.01), in CHCl3 in the presence of tetrabutylammonium hexafluorophosphate (0.10 mol L−1) as supporting electrolyte. All CV measurements were recorded at room temperature with a conventional three-electrode configuration consisting of a platinum wire working electrode, a platinum counter electrode, and an SCE (saturated calomel electrode) reference electrode under argon. Electrochemical band gaps were calculated from onset potentials of the anodic and cathodic waves. In order to improve the sensitivity and resolution of the voltammetric peaks and to provide a reproducible active surface, the glassy carbon electrode was polished to a mirror finish with 0.3-micron alumina on a smooth polishing cloth and then rinsed with methanol and double distilled water prior to each electrochemical measurement. All the metal complex solutions investigated by electrochemical techniques were purged for 10 min with water-saturated nitrogen.

2.2. Synthesis of Thiosemicarbazone: A General Method. Thiosemicarbazone was synthesized (Scheme 1) by refluxing the solution of thiosemicarbazide (0.03 mol) in methanol and the alcoholic solution of 3-acetyl-2,5-dimethylpyrrole (0.03 mol) at 60°C for 5 h with continuous stirring. After cooling the compounds were filtered and recrystallized from methanol [24, 25].

(2E)-2-[1-(2,5-Dimethylthiophen-3-yl)ethyldenedihydrazone-carbothio-amide (I). Yield: 88%; m.p. 158°C; Anal. Calc. for C18H26N6S2Cl2: C, 47.55; H, 5.76; N, 18.48, S, 28.21. Found: C, 47.48; H, 5.74; N, 18.42; S, 28.15. IR (KBr discs) $\nu_{\text{max}}$ cm$^{-1}$: 3400 (N–H), 3286 (N–H), 2910 (C–H), 1612 (C–C), 1585 (C–N), 1144 (C–N), 945 (C=S); $^{1}$H NMR (DMSO-d6) δH: 10.85 (s, 2H, NH2), 8.92 (s, 1H, –NH), 6.74 (s, 1H, C aromatic), 3.25 (s, 3H, –CH3), 3.20 (s, 3H, –CH3), 2.16 (s, 3H, –CH3). $^{13}$C NMR (DMSO-d6) (δ): 173.23 (C=S), 148.50 (C=N), 22.11, 15.92 (CH3), 15.90 (CH3), 15.12 (CH3). Mass spectra (M$^+$) at m/z: 228 (60).

2.3. Preparation of Cu(II) Complex. A solution of cupric chloride/copper acetate (2 mmol) dissolved in minimum quantity of methanol was added with stirring to the hot solution of ligand (4 mmol) in methanol (20 mL) and the reaction mixture was heated under reflux for 3 h. On keeping the solution to ambient temperature for overnight, the solid formed was separated by filtration, washed with hot water, followed by small quantity of methanol, and dried. Recrystallization was carried out from methanol [26–29].

C18H26N6S2CuCl2 (1.1) Yield: 78%; m.p. 182.4°C; Anal. Calc. for C18H26N6S2CuCl2: C, 42.06; H, 5.06; N, 16.35; Found: C, 41.8; H, 4.96; N, 16.31; IR (KBr discs) $\nu_{\text{max}}$ cm$^{-1}$: 3423 (N–H), 3220 (N–H), 2953 (C–H), 1577 (C=N), 1199 (C–N), 1075 (N–N), 925 (C=S), 435 (Cu–N), 322 (Cu–S); $^{1}$H NMR (DMSO-d6) δH: 10.82 (s, 2H, NH2), 8.62 (s, 1H, –NH), 6.81 (s, 1H, CH aromatic), 2.59 (s, 3H, –CH3), 2.48 (s, 3H, –CH3), 2.38 (s, 3H, –CH3). Mass spectra (M$^+$) at m/z: 515 (55).

C22H22N6S2O4Cu (I.2) Yield: 75%; m.p. 172°C; Anal. Calc. for C22H22N6S2O4Cu: C, 47.01, H, 5.69; N, 14.95. Found: C, 46.94; H, 5.62; N, 14.88. IR (KBr discs) $\nu_{\text{max}}$ cm$^{-1}$: 3418 (N–H), 3215 (N–H), 2922 (C–H), 1565 (C=N), 1195 (C–N), 1080 (N–N), 921 (C=S), 432 (Cu–N), 318 (Cu–S); $^{1}$H NMR (DMSO-d6) δH: 10.85 (s, 2H, NH2), 8.62 (s, 1H, –NH), 6.72 (s, 1H, CH aromatic), 2.65 (s, 3H, –CH3), 2.48 (s, 3H, –CH3), 2.38 (s, 3H, –CH3); $^{13}$C NMR (DMSO-d6) (δ): 175.52 (C=S), 151.36 (C=N), 18.26 (CH3), 16.03 (CH3), 15.04 (CH3). Mass spectra (M$^+$) at m/z: 563 (70).

2.4. Preparation of Ni(II) Complex. A solution of nickel chloride/nickel acetate (2 mmol) dissolved in minimum quantity of methanol was added with stirring to the hot solution of ligand (4 mmol) in methanol (20 mL) and the reaction mixture was heated under reflux for 3 h. On keeping the solution to ambient temperature for overnight, the solid formed was separated by filtration, washed with hot water, followed by
small quantity of methanol, and dried. Recrystallization was carried out from methanol.

\[ \text{C}_{18}\text{H}_{26}\text{N}_{6}\text{S}_{2}\text{NiCl}_{2} \] (1.3). Yield: 80%; m.p. 232°C; Anal. Calc. for \( (\text{C}_{9}\text{H}_{13}\text{N}_{3}\text{S})_{2}\text{NiCl}_{2} \): C, 41.64; H, 5.01; N, 16.19; S, Found: C, 41.58; H, 4.96; N, 16.15. IR (KBr discs) \( \nu_{\text{max}} \) cm\(^{-1} \): 3412 (N–H\(_2\)), 3284 (N–H), 2975 (C–H), 1575 (C=N), 1162 (C–N), 1099 (N–N), 922 (C=S), 432 (Cu–S); \(^1\text{H NMR} \) (DMSO-d\(_6\)) \( \delta \): 10.80 (s, 2H, N–H\(_2\)), 8.47 (s, 1H, –NH), 6.45 (s, 1H, C\textsubscript{aromatic}), 2.64 (s, 3H, –CH\(_3\)), 2.51 (s, 3H, –CH\(_3\)), 2.41 (s, 3H, –CH\(_3\)) \(^{13}\text{C NMR} \) (DMSO-d\(_6\)) (δ): 194.00 (C=S), 146.80 (C=N), 15.90 (CH\(_3\)), 15.82 (CH\(_3\)), 15.05 (CH\(_3\)). Mass spectra (M\(^{+}\)) at \( m/z \): 521 (62).

\[ \text{C}_{22}\text{H}_{32}\text{N}_{6}\text{S}_{2}\text{O}_{4}\text{Ni} \] (1.4). Yield: 65%; m.p. 242°C; Anal. Calc. for \( \text{C}_{22}\text{H}_{32}\text{N}_{6}\text{S}_{2}\text{O}_{4}\text{Cu} \): C, 46.58; H, 5.60; N, 14.82; Found: C,
2.5. Preparation of Co(II) Complex. A solution of cobalt chloride/cobalt acetate (2 mmol) in the presence of thiosemicarbazone (4 mmol) in methanol (20 mL) was added with stirring to the hot solution of thiosemicarbazone at 40 °C. The reaction mixture was heated under reflux for 3 h. On keeping the solution to ambient temperature for overnight, the solid formed was separated by filtration, washed with hot water, followed by small quantity of methanol, and dried. Recrystallization was carried out from methanol.

C₁₈H₂₆N₆S₄CoCl₂ (1.5). Yield: 85%; m.p. 248 °C; Anal. Calc. for C₁₈H₂₆N₆S₄CoCl₂: C, 41.62; H, 5.01; N, 16.18. Found: C, 41.58; H, 4.96; N, 16.14. IR (KBr discs) ðmax cm⁻¹: 3435 (N−H), 3235 (N−H), 2927 (C−H), 1566 (C=N), 1143 (C−N), 1088 (N−N), 923 (C=S), 435 (Cu−N), 326 (Cu−S); ¹H NMR (DMSO-d₆) δH: 10.85 (s, 2H, −N−H), 8.59 (s, 1H, −NH), 6.42 (s, 1H, CH aromatic), 2.63 (s, 3H, −CH₃), 2.52 (s, 3H, −CH₃), 2.43 (s, 3H, −CH₃); ¹³C NMR (DMSO-d₆) (δ): 188.50 (C=S), 145.57 (C=N), 15.85 (CH₃), 15.72 (CH₃), 15.11 (CH₃). Mass spectra (M⁺) at m/z: 522 (75).

C₂₂H₃₅N₆S₄O₇Co (1.6). Yield: 82%; m.p. 263 °C; Anal. Calc. for C₂₂H₃₅N₆S₄O₇Co: C, 46.56; H, 5.64; N, 14.81. Found: C, 46.52; H, 5.60; N, 14.76. IR (KBr discs) ðmax cm⁻¹: 3432 (N−H), 3265 (N−H), 3147 (C−H), 2988 (C−H), 1578 (C=N), 1148 (C−N), 995 (N−N), 927 (C=S), 430 (Cu−N), 320 (Cu−S); ¹H NMR (DMSO-d₆) δH: 10.85 (s, 2H, −N−H), 8.59 (s, 1H, −NH), 6.42 (s, 1H, CH aromatic), 2.63 (s, 3H, −CH₃), 2.52 (s, 3H, −CH₃), 2.43 (s, 3H, −CH₃); ¹³C NMR (DMSO-d₆) (δ): 188.50 (C=S), 145.57 (C=N), 15.85 (CH₃), 15.72 (CH₃), 15.11 (CH₃). Mass spectra (M⁺) at m/z: 568 (74).

2.6. Organism Culture and In Vitro Screening. The antibacterial activity was assessed by the disc diffusion method with minor modifications. The antibacterial cells S. aureus, S. pyogenes, S. typhimurium, and E. coli were subcultured in BHI medium and incubated for 18 h at 37 °C, and then the bacterial cells were suspended, according to the McFarland protocol in saline solution to produce a suspension of about 10⁷ CFU/mL. Serial dilutions of the test compounds, previously dissolved in dimethyl sulfoxide (DMSO), were prepared to final concentrations of 512, 256, 128, 64, 32, 16, 8, 4, 2, and 1 μg/mL to each tube was added 100 μL of a 24 h old inoculum. The MIC, defined as the lowest concentration of the test compound, which inhibits the visible growth after 18 h, was determined visually after incubation for 18 h, at 37 °C, and the results are presented in Table 2. DMSO and chloramphenicol were used as negative and positive controls, respectively.

3. Results and Discussion

Reaction of thiosemicarbazone with CuCl₂, NiCl₂, CoCl₂, Cu(OAc)₂, Ni(OAc)₂, and Co(OAc)₂ gave amorphous solid compounds. All the compounds are isolated in good yields and were stable both in the solid and solution states. Analytical data of these compounds are in good agreement with their composition (see Section 2). The complexes are insoluble in water, methanol, and ethanol and soluble in DMF and DMSO. The structures of the ligand and complexes are presented in Scheme 1 and Figure 1. The chemical structures of all the compounds were confirmed by means of elemental analyses and IR, ¹H NMR, ¹³C NMR, and mass spectra analyses.

3.1. IR Spectral Studies. Assignments of selected characteristic IR band positions provide significant indication for the formation of the thiosemicarbazone and its complexes. The thiosemicarbazone can exist in thione and thiol tautomeric forms shown in Figures 3(a) and 3(b), respectively.

However, the existence of a strong band in the region 945 cm⁻¹ due to ν (C=S) stretch, absence of any band in the region 2528−2675 cm⁻¹ due to ν (C−N) stretch, and the presence of ν (N−H) stretch at 3286 cm⁻¹ in the spectra of the ligand suggest that the thiosemicarbazones remain in their thione form in the solid state.

The downward shift of ν (C=S) band by (18−27) cm⁻¹ in the complexes suggested the coordination of sulfur in thionic form. A strong band at 1585 cm⁻¹ was assigned to ν (C=S) stretch of azomethine linkage in the spectra of free thiosemicarbazone. In the complexes this band shifted to lower frequency by 7−49 cm⁻¹ and this lowering was attributed to the coordination of azomethine nitrogen with metal and formation of M−N band.

3.2. NMR Spectral Analysis. Further evidence for the formation of thiosemicarbazone and its metal complexes was obtained from the ¹H NMR, which provides diagnostic tools for the positional elucidation of the protons. Assignments of the signals are based on the chemical shifts and intensity patterns. The thiosemicarbazone does not show any resonance at ca. 4.0 ppm, attributed to −SH proton resonance,
Table 1: Antibacterial activity of thiosemicarbazone and its metal complexes, positive control chloramphenicol (Chlora.) and negative control (DMSO) measured by the halo zone test (unit, mm).

| Compounds | S. aureus | S. pyogenes | S. typhimurium | E. coli |
|-----------|-----------|-------------|----------------|--------|
| 1         | 9.2 ± 0.3 | 9.0 ± 0.2   | 8.8 ± 0.2      | 8.2 ± 0.5 |
| 1.1       | 17.2 ± 0.2| 17.6 ± 0.3  | 16.8 ± 0.4     | 20.2 ± 0.4 |
| 1.2       | 15.2 ± 0.4| 15.8 ± 0.3  | 15.4 ± 0.3     | 16.8 ± 0.8 |
| 1.3       | 11.6 ± 0.2| 11.2 ± 0.3  | 12.6 ± 0.4     | 11.8 ± 0.4 |
| 1.4       | 12.4 ± 0.4| 11.8 ± 0.2  | 12.2 ± 0.4     | 11.6 ± 0.5 |
| 1.5       | 11.6 ± 0.3| 12.4 ± 0.4  | 13.2 ± 0.4     | 12.6 ± 0.4 |
| 1.6       | 11.2 ± 0.4| 12.2 ± 0.4  | 12.4 ± 0.5     | 13.2 ± 0.2 |
| Chloro.   | 17.0 ± 0.5| 18.2 ± 0.4  | 17.2 ± 0.8     | 20.0 ± 0.2 |
| DMSO      | —         | —           | —              | —      |

Table 2: Minimum inhibition concentration (MIC) of thiosemicarbazone and its metal complexes.

| Bacterial strain | MIC (µg/mL⁻¹) | compound | Positive control |
|------------------|---------------|----------|------------------|
| S. aureus        | 512           | 32       | 64               | 321264 |
| S. pyogenes      | 512           | 32       | 64               | 3212825 |
| S. typhimurium   | 128           | 32       | 32               | 256128128 |
| E. coli          | 128           | 32       | 32               | 2561286432 |

3.3. FAB Mass Analysis. Characteristic peaks were observed in the mass spectra of thiosemicarbazone and its metal complexes, which followed the similar fragmentation patterns. The spectrum of thiosemicarbazone shows a molecular ion peak (M⁺) at m/z = 228 and its complexes do the following: Cu(II) (1.1 and 1.2) shows a molecular ion peak (M⁺) at m/z = 515 and 563, Ni(II) (1.3 and 1.4) shows a molecular ion peak (M⁺) at m/z = 521–568, and Co(II) (1.5 and 1.6) shows a molecular ion peak (M⁺) at m/z = 522 and 569.

3.4. Antimicrobial Activity: Disc Diffusion. The in vitro antibacterial activity of thiosemicarbazone and its metal complexes (1–1.6) was assayed by the disk diffusion method using cultures of S. aureus, S. pyogenes, S. typhimurium, and
Figure 2: Cyclic voltammogram of ligand and its metal complexes.
E. coli. Chloramphenicol (30 mg) was used as the standard drug, whereas a DMSO-wetted disk was used as negative control [25]. The results showed that compounds 2 and 3 are better at inhibiting the growth of both types of the bacteria (Gram-positive and Gram-negative) as compared to chloramphenicol. Results are summarized in Tables 1 and 2.

3.5. Electrochemical Studies. Generally the electrochemical properties of the complexes depend on a number of factors such as chelate ring size, axial ligation degree, distribution of unsaturation, substitution pattern in the chelate ring, charge type, and coordination number [30, 31]. The redox behaviors of thiosemicarbazone and its complexes have been investigated by cyclic voltammetry in the range from +1.6 to −2.0 V. The cyclic voltammograms of the complexes show metal centered processes and waves corresponding to the ligand. Repeated scans, as well as different scan rates, showed that dissociation does not take place in these complexes. The electrochemical data of the complexes is given in Table 3 and the representative cyclic voltammograms for the behaviors of the complexes are shown in Figure 2. The cyclic voltammogram of the ligand 1 in DMF shows an irreversible anodic wave in the positive range (0.989 V) and irreversible cathodic wave in the negative range (−0.50 V), which can be attributed to the redox behaviors of the imine or thioamide groups present in the ligand [32]. In metal chlorides (1.1, 1.3, and 1.5), addition to the peaks of ligand, exhibits a single quasireversible anodic wave and a single irreversible cathodic wave. In the positive range 0 to +1.00 V, a redox couple associated with the M(III)/M(II) process can be observed. The peak of the M(III)/M(II) couple is similar to the values reported earlier [33]. The redox process is quasireversible in nature as is evident from the criteria: the \( E_{1/2} \) values are independent of scan rate; the \( \Delta E_p \) slightly increases with increasing scan rate (50–600 mV s\(^{-1}\)) and is always greater than 60 mV. Cyclic voltammogram of acetate complex is shown in Figure 2 (1.2, 1.4, and 1.6). The complex exhibited two quasireversible peaks. Cyclic voltammogram displays two reduction peaks with an associated oxidation peak in the range of 0.20–0.85 V and 0.25–0.59 V. However, the peak current increases with the increase of the square root of the scan rates. This establishes the electrode process as diffusion controlled.

### Table 3: Electrochemical properties of the compounds 1–1.6.

| Compounds | Epa | Epc | \( \Delta E_p \) |
|-----------|-----|-----|-----------|
| 1         | 0.989 | 0.50 | 0.39 |
| 1.1       | 0.40  | −0.60 | 0.45 |
| 1.2       | 0.26, 0.65 | 0.32, −0.52 | 0.45 |
| 1.3       | 0.32, 0.73 | 0.41, −0.39 | 0.40 |
| 1.4       | 0.29, 0.84 | 0.34, −0.59 | 0.78 |
| 1.5       | 0.33, 0.69 | −0.36 | 0.61 |
| 1.6       | 0.32, 0.79 | 0.29, −0.43 | 0.65 |

4. Conclusion

This research examined the synthesis, characterization, and antibacterial activity of novel thiosemicarbazone and its Cu(II), Ni(II), and Co(II) complexes. The thiosemicarbazone were obtained by the thiosemicarbazide with 3-acetyl-2,5-dimethylthiophene. In vitro antibacterial activity of these compounds was tested by the disk diffusion microdilution assay against two Gram-positive and Gram-negative bacteria. The results showed that chloro containing Cu(II) metal complex is better antibacterial agent as compare to chloramphenicol.

### Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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