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Synthesis, spectroscopic, thermal and biological aspects of drug-based copper(II) complexes

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A series of novel complexes of the type $Cu(II)(L_n)_2(H_2O)_2]^{\bullet}xH_2O$ [where $L_n = L_{1-4}$, these ligands being described as: L_1, 2-({4-[6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl]phenylimino}methyl)phenol, $x = 1$; L_2, 2-({4-[6,7-dihydrothieno[3,2-c] pyridin-5(4H)-ylsulfonyl]phenylimino}methyl)-5-(methoxy)phenol, $x = 2$; L_3, 5-chloro-2-({4-[6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl]phenylimino}methyl)phenol, $x = 2$; and L_4, 5-bromo-4-chloro-2-({4-[6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl]phenylimino} methyl)phenol, $x = 1$] was investigated. They were characterized by elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR and electronic spectra, magnetic measurements and thermal studies. The FAB-mass spectrum of $[Cu(II)(L_1)_2(H_2O)_2]^{\bullet}H_2O$ was determined. A magnetic moment and reflectance spectral study revealed that an octahedral geometry could be assigned to all the prepared complexes. Ligands (L_n) and their metal complexes were screened for their *in vitro* antibacterial activity against *Bacillus subtillis, Pseudomonas aeruginosa, Escherichia coli* and *Serratia marcescens* bacterial strains. Kinetic parameters such as order of reaction (n), the energy of activation (E_a), the pre-exponential factor (A), the activation entropy ($\Delta S^{\neq}$), the activation enthalpy ($\Delta H^{\neq}$) and the free energy of activation ($\Delta G^{\neq}$) are reported.

Keywords: Cu(II) complexes; spectroscopic; Freeman-Carroll method; antibacterial activity

Introduction

Compounds 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine and 4-aminobenzene-1-sulfonylchloride are extensively studied compounds owing to their wide spectrum of bioactivities. Despite numerous attempts to develop new structural prototypes in the search for more effective antimicrobials, *N*-benzylidene-4-{6,7-dihydrothieno[3,2-c] pyridin-5(4H)-ylsulfonyl}aniline and its complexes comprise one of the most versatile classes of compounds against microbes and therefore are important components of molecules in drug discovery.

A literature survey revealed that 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine and its various derivatives, such as clopidogrel[1,2] and ticlopidine,[3,4] are acknowledged to show noncytotoxic and complement inhibition properties. A series of substituted 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridines (THTPs) was synthesized and evaluated for human phenylethanolamine *N*-methyltransferase (hPNMT) inhibitory potency and affinity for the α_2-adrenoceptor.[5] Various sulfonamide derivatives of 4-aminobenzene-1-sulfonylchloride like benzo[*d*]-isothiazol-3-one benzenesulfonamides are also well known to have antimicrobial activity.[6] These medicinal properties render the two compounds useful structural units in drug research.

These findings prompted us to synthesize benzylidene derivatives of 4,5,6,7-tetrahydrothieno[3,2-*c*] pyridine as part of our ongoing research program aiming at the synthesis of their various complexes for biological evaluation. Herein, we report the synthesis of a novel series of complexes of *N*-benzylidene-4-{6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl}aniline derivatives and investigation of their antibacterial activity profile. From this point of view, the objective of the present communication comprises the synthesis of a series of new compounds. The synthetic approach is shown in Scheme 1.

Many drugs possess modified pharmacological and toxicological properties when administered in the form of metallic complexes. Probably the most widely studied cation in this respect is Cu(II), since a host of low-molecular-weight copper complexes have been proven beneficial against diseases such as tuberculosis, rheumatoid, gastric ulcers and cancers.[7–10] There is a continuing interest in metal complexes of Schiff bases because of the presence of nitrogen and oxygen donor atoms in the backbones of these ligands. This means that they readily coordinate with a wide range of transition metal ions, yielding stable and intensely colored metal complexes, some of which have been shown to exhibit interesting physical and chemical properties[11–13] and potentially useful biological activities.[14–16]

Thermal analysis techniques are extensively used in studying the thermal behavior of metal complexes.[17–19] Thermogravimetry is a process in which a substance is decomposed in the presence of heat, which causes bonds of the molecules to be broken.[20,21] The present work describes the synthetic, thermal, spectroscopic aspects and anti-bacterial activity of new copper complexes $[Cu(II)(L_n)_2(H_2O)_2]^{\bullet}xH_2O$.

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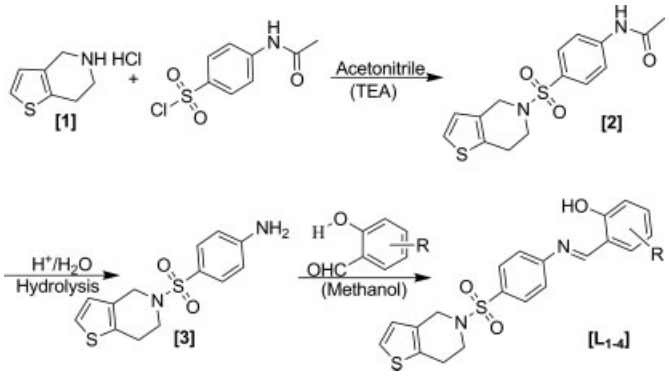


Scheme 1. Synthetic pathway for the preparation of derivatives of 4-(6,7-dihydrothieno[3,2-clpyridin-5(4H)-ylsulfonyl)aniline. Where, R = (L_1)-C_6H_5, (L_2) 4-OCH_3-C_6H_4, (L_3) 4-Cl-C_6H_4, (L_4) 4-Cl-5-Br-C_6H_4.

Materials and Methods

Materials

All the chemicals used were of analytical grade. Salicylaldehyde, ethyl acetoacetate, chloroform, hexane, ethanol, acrtonirile, 4-aminobenzene-1-sulfonylchloride, 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine, cyclohexanone, triethyl amine, dimethyl formamide and $Cu(NO_3)_2^{\bullet}3H_2O$ were purchased from E. Merck (India) Limited, Mumbai. Luria broth and agar-agar were purchased from SRL, India. Acetic acid and Ethylene Diamine Tetra Acetic Acid were purchased from Sigma Chemical Co., India. The organic solvents were purified by the recommended method.[22] The metal contents of the complexes were determined by the EDTA titration technique[23] after treating them with a mixture of $HClO_4$, H_2SO_4 and HNO_3 (1 : 1.5 : 2.5). Elemental analysis was carried out using Perkin Elmer, USA 2400-II CHN analyzer. The magnetic moments were obtained by Gouy's method using mercury tetra-thiocyanatocobaltate(II) as a calibrant ($\chi_g = 16.44 \times 10^{-6}$ c.g.s. units at 20 °C). Diamagnetic corrections were made using Pascal's constant.[24] A simultaneous Thermogravimetry/Derivative Thermogravimetry had been obtained using a model 5000/2960 SDT, TA Instruments, USA. The experiment was performed in a nitrogen atmosphere at a heating rate of 10 °C min^{-1} in the temperature range 50–800 °C, using an Al_2O_3 crucible. The IR spectra were recorded on an Fourier Transform Infrared Spectroscopy Nicolet 400D spectrophotometer using KBr pellets. NMR spectra were recorded on a model Bruker Advance (400 MHz). The FAB mass spectrum was carried out using a Jeol SX-102/DA-6000 mass spectrometer.

Preparation of *N*-(4-{6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl}phenyl) acetamide (2)

An equimolecular mixture of 4,5,6,7-tetrahydrothieno[3,2-*c*] pyridine hydrochloride (**1**) prepared using a reported method[25,26] (0.01 mol/1.755 g) and 4-acetamidobenzene-1-sulfonyl chloride (0.01 mol/2.335 g) was dissolved in anhydrous acetonitrile (20 ml) using tetra-ethyl amine as base under constant stirring, and the reaction mixture was refluxed for 5 h. After completion of the reaction, it was poured in ice-cold water to obtain a light yellow product (**2**), which was filtered and dried. It was purified by column chromatography and recrystallized from ethanol to give a light yellow crystalline compound. Yield 84.5%; m.p. 180–182 °C. Anal. calcd for $C_{15}H_{16}O_3N_2S_2$ (336): requires C, 53.57; H, 4.76; N, 8.33; S, 19.05%. Found: C, 53.56; H, 4.74; N, 8.32; S, 18.98%. IR (ν_{max}, KBr, cm^{-1}): 3084 (C–H str., aromatic), 1546.7 (C═C asymmetric str.), 1487.5–1469.7 (C═C str. ring), 1224 (C–N str.), 1356–1148 (SO_2, str.), 748.4 (C–H def, aromatic), 721 (C–S–C str., thiophene), 3352, 3378 (-NHCO), 1665 (>C═O of amide). ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): 2.42 (2H, t, proton at C_7), 3.07 (2H, t, proton at C_6), 3.64 (2H, s, proton at C_4), 6.48 (1H, s, -CONH-), 2.45 (3H, s,-$COCH_3$), 6.20–7.46 (6H, m, proton at C_2–H, C_3–H, C_{10}–H, C_{11}–H, C_{13}–H, C_{14}–H). ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): 123.35 (C_2), 123.58 (C_3), 45.57 (C_4), 43.83 (C_6), 24.35 (C_7), 130.38 (C_{3a}), 129.78 (C_{7a}), 131.77 (C_9), 124.43 (C_{10}, C_{14}), 117.54 (C_{11}, C_{13}), 132.30 (C_{12}), 172.46 (-CO- of aceyle group).

Preparation of 4-{6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl}aniline (3)

Compound **3** was prepared by base-catalyzed hydrolysis of 0.01 mol (3.36 g) *N*-(4-{6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl}phenyl) acetamide (**2**) using (25 ml) 10% sodium hydroxide solution. The reaction mixture was then refluxed for 2 h. The solid separated was filtred, dried, purified by column chromatography and recrystallized from ethanol to give white crystalline compound. Yield, 68.7%; m.p. 172–174 °C. Anal. calcd for $C_{13}H_{14}O_2N_2S_2$ (294): requires C, 53.06; H, 4.76; N, 9.52; S, 21.77%. Found: C, 53.04; H, 4.75; N, 9.49; S, 21.74%. IR (ν_{max}, KBr, cm^{-1}): 3082 (C–H str., aromatic), 1542.5 (C═C, asymmetric, str.), 1478.4–1473.5 (C═C str. ring), 1226 (C–N str.), 752.8 (C–H def, aromatic), 724 (C–S–C str., thiophene), 3306 (N–H, amine). ^{1}H-NMR (400 MHz, acetone-d_6), δ (ppm): 2.47 (2H, t, proton at C_7), 3.09 (2H, t, proton at C_6), 3.68 (2H, s, proton at C_4), 6.28–7.56, (6H, m, protons at C_2–H, C_3–H, C_{10}–H, C_{11}–H, C_{14}–H), 11.24 (2H, s, -NH_2). ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): 123.36 (C_2), 123.59 (C_3), 45.58 (C_4), 43.85 (C_6), 24.37 (C_7), 130.39 (C_{3a}), 129.79 (C_{7a}), 131.78 (C_9), 124.45 (C_{10}, C_{14}), 117.55 (C_{11}, C_{13}), 132.32 (C_{12}).

Preparation of Ligands L_{1-4}

An equimolecular mixture of 4-{6,7-dihydrothieno[3,2-c] pyridin-5(4H)-ylsulfonyl}aniline (**3**) (0.01 mol/2.94 g) was refluxed with 2-hydroxy-benzaldehyde and its derivatives, like 2-hydroxy-4-methoxybenzaldehyde, 4-chloro-2-hydroxybenzaldehyde and 5-bromo-4-chloro-2-hydroxybenzaldehyde in ethanol (15 ml), with a few drops of H_2SO_4 as catalyst, on a water bath for 1.5–2 hrs. Excess solvent was removed under vacuum and the solid separated was filtered, dried, purified by column chromatography and recrystallized from ethanol or chloroform. The preparation of ligands is shown in Scheme 1 and the proposed structure is shown in Fig. 1.

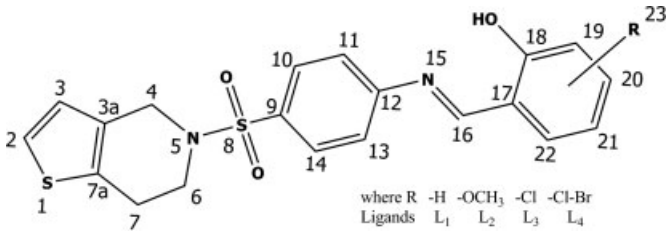


Figure 1. Proposed structure of ligand.

2-[(4-{6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl}phenylimino)methyl]phenol ***L_1***

Yellow crystalline compound. Yield, 62.4%; m.p. 186–188 °C, IR (ν_{max}, KBr, cm^{-1}): 3075 (C–H str., aromatic), 1484–1474.8 (C=C str. ring), 1226 (C–N str.), 736 (C–S–C, str., thiophene), 1643 (-N=CH-), 3410 (O–H). ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): 2.50 (2H, t, proton at C_7), 3.13(2H, t, proton at C_6), 3.70 (2H, s, proton at C_4), 4.96 [1H,s, proton at C_{16}(-N=CH-)], 6.37–7.66 (10H, m, protons at C_2–H, C_3–H, C_{10}–H, C_{11}–H, C_{13}–H, C_{14}–H, C_{19}–H, C_{20}–H, C_{21}–H, C_{22}–H), 9.55 (1H, s, proton-OH). ^{13}C-NMR (400 MHz, DMSO-d_6), δ, (ppm): 123.37 (C_2), 123.62 (C_3), 45.60 (C_4), 43.84 (C_6), 24.36 (C_7), 130.42 (C_{3a}), 129.78 (C_{7a}), 131.80 (C_9), 124.46 (C_{10}, C_{14}), 117.57 (C_{11}, C_{13}), 132.32 (C_{12}), 157.07 (C_{16}), 113.19 (C_{17}), 157.16 (C_{18}), 103.21 (C_{19}), 129.22 (C_{20}), 115.04 (C_{21}), 128.84 (C_{22}).

2-[(4-{6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl}phenylimino]methyl)-5-(methoxy)phenol ***L_2***

Orange-colored crystalline compound. Yield, 58.64%; m.p. 208–210 °C, IR (ν_{max}, KBr, cm^{-1}): 3079 (C–H str., aromatic), 1487–1476 (C=C str. ring), 1229 (C–N str.), 738 (C–S–C, str., thiophene), 1640 (-N=CH-), 3413 (O–H). ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): 2.31 (3H, s, C_{23}, -OCH_3), 2.54 (2H, t, proton at C_7), 3.17(2H, t, proton at C_6), 3.74 (2H, s, proton at C_4), 4.98 [1H, s, proton at C_{16} (-N=CH-)], 6.39–7.69 (10H, m, protons at C_2–H, C_3–H, C_{10}–H, C_{11}–H, C_{13}–H, C_{14}–H, C_{19}–H, C_{20}–H, C_{21}–H, C_{22}–H), 9.59 (1H, s, proton-OH). ^{13}C-NMR (400 MHz, acetone-d_6), δ (ppm): 23.36 (C_2), 123.63 (C_3), 45.60 (C_4), 43.85 (C_6), 24.35 (C_7), 130.41 (C_{3a}), 129.79 (C_{7a}), 131.81 (C_9), 124.47 (C_{10}, C_{14}), 117.56 (C_{11}, C_{13}), 132.33 (C_{12}), 157.09 (C_{16}), 113.20 (C_{17}), 157.18 (C_{18}), 103.22 (C_{19}), 129.43 (C_{20}), 118.6 (C_{21}), 128.83 (C_{22}).

5-Chloro-2-[(4-{6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl}phenylimino) methyl]phenol ***L_3***

Orange-yellow crystalline compound. Yield, 64.5%; m.p. 168–170 °C, IR (ν_{max}, KBr, cm^{-1}): 3077 (C–H str., aromatic), 1484–1476 (C=C str. ring), 1226 (C–N str.), 737 (C–S–C, str., thiophene), 1643 (-N=CH-), 3423 (O–H). ^{1}H-NMR (400 MHz, DMSO-d_6), δ(ppm): 2.48 (2H, t, proton at C_7), 3.10 (2H, t, proton at C_6), 3.68 (2H, s, proton at C_4), 4.93 [1H,s, proton at C_{16} (-N=CH-)], 6.34–7.63 (10H, m, protons at C_2–H, C_3–H, C_{10}–H, C_{11}–H, C_{13}–H, C_{14}–H, C_{19}–H, C_{20}–H, C_{21}–H, C_{22}–H), 9.52 (1H, s, proton-OH). ^{13}C-NMR (400 MHz, acetone-d_6), δ (ppm): 123.38 (C_2), 123.64 (C_3), 45.63 (C_4), 43.82 (C_6), 24.37 (C_7), 130.43 (C_{3a}), 129.77 (C_{7a}), 131.82 (C_9), 124.47 (C_{10}, C_{14}), 117.58 (C_{11}, C_{13}), 132.33 (C_{12}), 157.09 (C_{16}), 113.17 (C_{17}), 157.18 (C_{18}), 103.22 (C_{19}), 115.05 (C_{21}), 129.26 (C_{20}), 128.83 (C_{22}).

5-Bromo-4-chloro-2-[(4-{6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl}phenyl- imino)methyl]phenol ***L_4***

Dark yellow crystalline compound. Yield, 58.6%; m.p. 208–210 °C. IR (ν_{max}, KBr, cm^{-1}): 3074 (C–H str., aromatic), 1486 (C=C str. ring), 1230 (C–N str.), 738 (C–S–C, str., thiophene), 1630 (-N=CH-), 3468 (O–H). ^{1}H-NMR (400 MHz, DMSO-d_6), δ (ppm): 2.46 (2H, t, proton at C_7), 3.09(2H, t, proton at C_6), 3.66 (2H, s, proton at C_4), 4.92 [1H, s, proton at C_{16} (-N=CH-)], 6.33–7.62 (10H, m, protons at C_2–H, C_3–H, C_{10}–H, C_{11}–H, C_{13}–H, C_{14}–H, C_{19}–H, C_{20}–H, C_{21}–H, C_{22}–H), 9.51 (1H, s, proton-OH). ^{13}C-NMR (400 MHz, DMSO-d_6), δ (ppm): 123.39 (C_2), 123.69 (C_3), 45.65 (C_4), 43.86 (C_6), 24.37 (C_7), 130.45 (C_{3a}), 129.77 (C_{7a}), 31.83 (C_9), 124.48 (C_{10}, C_{14}), 117.59 (C_{11}, C_{13}), 132.34 (C_{12}), 157.09 (C_{16}), 113.20 (C_{17}), 157.17 (C_{18}), 103.23 (C_{19}), 129.25 (C_{20}), 115.07 (C_{21}), 128.87 (C_{22}).

General procedure for synthesis of Cu(II) complexes

An ethanolic solution (25 ml) of $Cu(NO_3)_2^{\bullet}3H_2O$ (10 mmol) was added to an ethanolic solution (50 ml) of ligand (L_n) (20 mmol); the pH was adjusted to 4.5–6.0 with dilute sodium hydroxide solution. The resulting solution was refluxed for 5 h and then heated over a steam bath to evaporate up to half of the volume. The reaction mixture was then kept overnight at room temperature. A colored crystalline product was obtained. The obtained product was washed with ether and dried in vacuum desiccators. The suggested structure is shown in Fig. 2 and analytical and physical data are shown in Table 1.

Antibacterial Studies

Preparation of stock solution

A stock solution of 10 mg ml^{-1} was made by dissolving compound in the minimum amount of Dimethyl Sulfoxide and making it up with double-distilled water.

Preparation of agar plates

The media was made up by dissolving bacteriological agar (20 g) and Luria broth (20 g) (SRL, India) in 1:l distilled water. The mixture was autoclave for 15 min at 120 °C and then dispensed into sterilized Petri dishes, allowed to solidify and then used for inoculation.

Procedure of inoculation

The target microorganism cultures were prepared separately in 15 ml of liquid Luria broth medium for activation. Inoculation was done with the help of a micropipette with sterilized tips; 100 µl of activated strain was placed onto the surface of an agar plate and spread evenly over the surface by means of a sterile bent glass rod. Then two wells with a diameter of 10 mm were made using a sterilized borer in each plate.

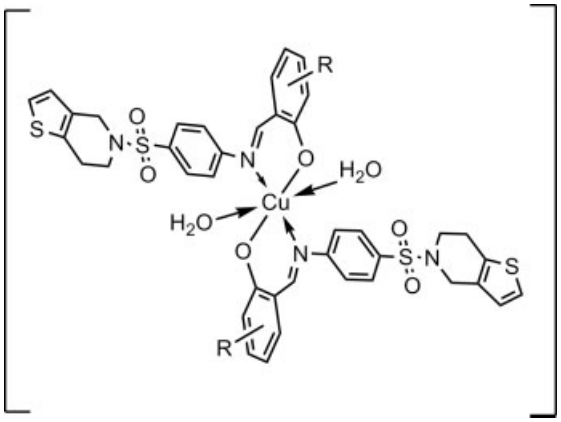


Figure 2. The suggested structure of metal complexes, where R = H, 4-OCH_3, 4-Cl-5-Br.

Application of disks

Sterilized stock solutions (10 mg ml^{-1}) were used for the application in the well of earlier inoculated agar plates. When the disks were applied, they were incubated at 30 °C (Gram-positive) and 37 °C (Gram-negative) for 24 h. The zone of inhibition was then measured (in mm) around the disk. The control experiments were performed with only the equivalent volume of solvents without added test compounds and the zone of inhibition was measured (in mm). All experiments were performed using ciprofloxacin as the standard drug.[27]

Thermal Studies

The thermodynamic activation parameters of the decomposition process of the metal complexes such as energy of activation (E_a) and order of reaction (n) were evaluated graphically employing the Freeman–Carroll method[28] using the following relation:

$$[(-E_a/2.303R)\Delta(1/T)]\Delta \log W_r = -n + \Delta \log(dW/dt)\Delta \log W_r \quad (1)$$

where T is the temperature in K, R is the gas constant, $W_r = W_c - W$ (W_c is the weight loss at the completion of the reaction and W is the total mass loss up to time t) and E_a and n are the energy of activation and order of reaction respectively. A typical curve of $[\Delta \log(dW/dt) = \Delta \log W_r]$ vs $[\Delta(1/T)/\Delta \log W_r]$ for the Cu(II) complex is shown in Fig. 3. The slope of the plot gave the value of $E_a = 2.303R$ and the order of reaction (n) was determined from the intercept. The linear relationship confirmed that the assumed order of $n = 1$ is correct.

Results and Discussion

The analytical and physical data of the ligands $\mathbf{L_{1-4}}$ and their complexes are listed in Table 1. The following reaction describes the formation of the complexes:

$$Cu(NO_3)_2^{\bullet}3H_2O + L \longrightarrow [Cu(L)_2(H_2O)_2]^{\bullet}xH_2O + 2HNO_3 + nH_2O$$

where L = $\mathbf{L_{1-4}}$; $x = 1, 2, 2, 1$ and $n = 2, 1, 1, 2$, respectively.

All the complexes were insoluble in all common organic solvents, such as acetone, ethanol, chloroform, methanol, benzene and dimethyl formamide, but were least soluble in dimethyl sulfoxide.

IR Spectra

The important infrared spectral bands and their tentative assignments for the synthesized metal complexes are summarized in Table 2. All the ligands ($\mathbf{L_{1-4}}$) in the present investigation exhibit a broad band centered at 1355–1370 cm^{-1} (SO_2, asymmetric str.), and a second band at 1145–1163 cm^{-1} (SO_2, symmetric str.) shows the presence of the SO_2 group.[29,30] The band at 1638–1648 cm^{-1} present in all the ligand molecules indicates -N=CH- stretching. Also, all the ligands ($\mathbf{L_{1-4}}$) exhibit a broad band centered at 3428–3410 cm^{-1}, which is assigned to ν(O–H) for the free hydroxyl group on benzilidine ring at *ortho* position,

Table 1. Physical and analytical data of the ligand and its metal complexes

Empirical formula of ligand/metal complexes	Color	Yield (%)	Molecular weight	Analysis found %/(calcd. %) C	H	N	S	Cu	μ_{eff} (B.M.)
$\mathbf{L_1}$ ($C_{20}H_{18}N_2S_2O_3$)	Pale Yellow	62.4	398.50	60.28 (60.29)	4.55 (4.57)	7.03 (7.06)	16.09 (16.07)	–	–
$\mathbf{L_2}$ ($C_{21}H_{20}N_2S_2O_4$)	Dark yellow	58.6	428.52	58.86 (58.81)	4.70 (4.72)	6.54 (6.56)	14.97 (14.95)	–	–
$\mathbf{L_3}$ ($C_{20}H_{17}N_2S_2O_3Cl$)	Brown	64.5	432.94	55.48 (55.52)	3.96 (3.95)	6.47 (6.49)	14.81 (14.79)	–	–
$\mathbf{L_4}$ ($C_{20}H_{16}N_2S_2O_3ClBr$)	Light brown	58.6	511.84	46.93 (46.95)	3.15 (3.13)	5.47 (5.50)	12.53 (12.52)	–	–
$[Cu(\mathbf{L_1})_2(H_2O)_2]^{\bullet}H_2O$ ($C_{40}H_{40}CuO_9N_4S_4$)	Dark brown	69.4	912.57	52.65 (52.61)	4.42 (4.38)	6.14 (6.16)	14.05 (14.04)	6.96 (6.94)	1.79
$[Cu(\mathbf{L_2})_2(H_2O)_2]^{\bullet}2H_2O$ ($C_{42}H_{46}CuO_{12}N_4S_4$)	Dark brown	76.8	990.64	50.92 (50.94)	4.68 (4.65)	5.66 (5.67)	12.95 (12.94)	6.41 (6.45)	1.93
$[Cu(\mathbf{L_3})_2(H_2O)_2]^{\bullet}2H_2O$ ($C_{40}H_{40}CuO_{10}N_4S_4Cl_2$)	Dark brown	58.3	999.48	48.07 (48.05)	4.03 (4.07)	5.61 (5.63)	12.83 (12.82)	6.36 (6.34)	1.77
$[Cu(\mathbf{L_4})_2(H_2O)_2]^{\bullet}H_2O$ ($C_{40}H_{36}CuO_9N_4S_4Br_2Cl_2$)	Dark brown	64.7	1139.26	42.17 (42.15)	3.19 (3.16)	4.92 (4.96)	11.26 (11.24)	5.58 (5.57)	1.98

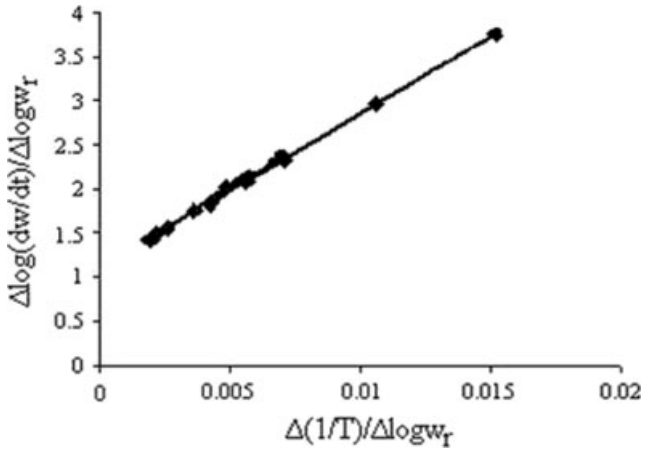


Figure 3. Freeman–Carroll plot for the metal complex $[Cu(\mathbf{L_3})(H_2O)_2]^{\bullet}2H_2O$.

which was further confirmed by ^{1}H-NMR and ^{13}C-NMR studies in the solution state.

Comparing the main IR frequencies of Cu(II) cyclic complexes with that of the free ligand (Table 2), the following results were found. The broad band around 3420 cm^{-1} observed in the case of ligands was shifted at 3440 cm^{-1}, which was attributed to υ(O–H) of coordinated water molecules.

This was further supported by the bands observed in the regions 3418–3437, 1278–1295, 865–875 and 705–710 cm^{-1}, which are attributed to -OH stretching, bending, rocking and wagging vibrations, respectively, due to the presence of water molecules.[31,32] The presence of a rocking band indicates the coordination nature of the water molecule.[33] The presence of coordinated water were further supported by TG analysis. In addition, the shifting of the band around 1640 cm^{-1} for free -N═CH- to the higher frequency of 1665 cm^{-1} in metal complexes clearly indicates the coordination of the ligands with Cu metal in these complexes.[34–36] The weak bands are attributed to the υ(Cu–O) and υ(Cu–N) stretching frequencies.[37]

In the far-IR region, two new bands around 520 and 775 cm^{-1} in the complexes were assigned to ν(Cu–O) coordination of the hydroxyl group and ν(Cu–N) coordination of the N lone pair of Schiff's base, respectively. All these data confirm the fact that 2-[(4-{6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl}phenylimino)methyl]phenol ($\mathbf{L_{1-4}}$) behaves as a bidentate ligand, forming a metal complex.

^{1}H-NMR and ^{13}C-NMR Spectra of the Ligands ($\mathbf{L_{1-4}}$)

Structural analyses of the ligands were carried out using ^{1}H-NMR and ^{13}C-NMR acquired on a Bruker 400 MHz NMR spectrometer using DMSO-d_6 as the solvent. The data are presented in the Experimental Section.

In the case of ^{1}H-NMR spectra for all the ligands, a peak was observed as a triplet centered at 2.50 δ (^3J = 5.6 Hz) and 3.13 δ (^3J = 5.6 Hz), each integrating for two protons on C_7 and C_6 respectively. A singlet observed at 3.70 δ is due to two protons attached at C_4. A peak observed as a singlet at 4.96 δ is due to a proton attached to C_{16} (-N═CH-). A total of 10 aromatic protons were observed in the region 6.37–7.66δ. The most downfield signal observed at 9.55 δ as a singlet is due to a hydroxyl proton (-OH), confirmed by D_2O exchange experiment.

The ^{13}C-NMR spectrum showed 19 nonequivalent carbon signals. The signals at 24.36δ, 43.84δ and 45.60δ are due to C_7, C_6 and C_4, respectively. This was confirmed by the DEPT-135 spectrum, in which these signals were inverted. A signal observed at 157.16δ is due to C_{16} (-N═CH-). The aromatic carbons appeared between 103.19 and 157.16δ.

The Thermal Behavior of the Prepared Metal Complexes

Thermal data and kinetic parameters of the metal complexes are given in Tables 3 and 4, respectively. Typical TG/DTG and Differential Scanning Calorimetry curves of the metal complex $[Cu(II)(\mathbf{L_3})_2(H_2O)_2]^{\bullet}xH_2O$ (where x = 2) and $[Cu(II)(\mathbf{L_1})_2(H_2O)_2]^{\bullet}xH_2O$ (where x = 2) are presented in Figs 4 and 5, respectively.

$$[Cu(II)(L_3)_2(H_2O)_2]xH_2O \xrightarrow[\text{Removal of lattice water molecules + coordinated water molecule}]{50\text{-}260^{\circ}C} [Cu(II)(L_3)_2] + 2H_2O + xH_2O$$

where x = 2;

$$Cu(II)(L_3)_2] \xrightarrow[\text{removal of Ligand } (L_3) \text{ molecules}]{260\text{-}760^{\circ}C} \text{Metal residue}$$

where metal residue = CuO.

The thermodynamic activation parameters of the decomposition process of dehydrated complexes such as activation entropy

Table 2. The characteristic IR bands of ligand ($\mathbf{L_{1-4}}$) and their metal complexes

Compounds	ν (O–H)	ν (C═N)	ν (S–N)	ν (O═S═O) Antisymmetric	ν (O═S═O) Symmetric	$\Delta\nu$	ν (Cu–O)	ν (Cu–N)
$C_{20}H_{18}N_2S_2O_3$	3410	1643	276	1370	1168	202	–	–
$C_{21}H_{20}N_2S_2O_4$	3428	1638	264	1358	1148	210	–	–
$C_{20}H_{17}N_2S_2O_3Cl$	3418	1645	270	1361	1143	218	–	–
$C_{20}H_{16}N_2S_2O_3ClBr$	3436	1648	259	1372	1152	220	–	–
$[Cu(\mathbf{L_1})_2(H_2O)]$ ($C_{40}H_{38}CuO_8N_4S_4$)	–	1664	274	1367	1164	203	519	778
$[Cu(\mathbf{L_2})_2(H_2O)]$ ($C_{42}H_{42}CuO_{10}N_4S_4$)	–	1658	263	1355	1146	209	517	767
$[Cu(\mathbf{L_3})_2(H_2O)]$ ($C_{40}H_{36}CuO_8N_4S_4Cl_2$)	–	1672	268	1359	1141	218	522	772
$[Cu(\mathbf{L_4})_2(H_2O)]$ ($C_{40}H_{34}CuO_8N_4S_4Br_2Cl_2$)	–	1668	257	1368	1150	220	518	769

Table 3. Thermo-analytical data of the Metal complexes

Compounds	TG range (°C)	DTG_{max} (°C)	DSC_{max} (°C)	Mass loss (%), observed (calcd)	Assignment
$[Cu(\mathbf{L_1})_2(H_2O)_2]^{\bullet}H_2O$	50–240	60–68	61.56	7.17 (7.26)	Loss of one lattice + two coordinated water molecules
	240–720	496.76	149.60	82.09 (82.03)	Removal of ($\mathbf{L_1}$) ligand molecule
				89.26*(89.29)	Leaving CuO residue
$[Cu(\mathbf{L_2})_2(H_2O)_2]^{\bullet}2H_2O$	50–130	68.74	84.48	4.88 (4.76)	Loss of two lattice water molecules
	130–280	–	160.34	4.61 (4.76)	Loss of two coordination water molecules
	280–760	474.54	–	82.69 (82.58)	Removal of ($\mathbf{L_2}$) ligand molecule
				92.18*(92.10)	Leaving free CuO residue
$[Cu(\mathbf{L_3})_2(H_2O)_2]^{\bullet}2H_2O$	50–260	67.96	155.99	9.36 (9.51)	Loss of two lattice + two coordinated water molecules
	260–760	432.78	–	80.62 (80.57)	Removal of ($\mathbf{L_3}$) ligand molecule
				89.98*(90.08)	Leaving CuO residue
$[Cu(\mathbf{L_4})_2(H_2O)_2]^{\bullet}H_2O$	50–130	64.50	58.91	2.28 (2.45)	Loss of one lattice water molecule
	130–260	–	143.44	4.85 (4.90)	Loss of two coordination water molecules
	260–260	429.89		81.94 (81.80)	Removal of ($\mathbf{L_4}$) ligand molecule
				89.07 (89.15)	Leaving CuO residue

Table 4. Kinetic parameters of the Metal complexes

Compounds	TG range (°C)	E_a (kJ mol^{-1})	n	A (s^{-1})	$\Delta S^{\#}$ (J K^{-1} mol^{-1})	$\Delta H^{\#}$ (J K^{-1} mol^{-1})	$\Delta G^{\#}$ (J K^{-1} mol^{-1})
$[Cu(\mathbf{L_1})_2(H_2O)_2]^{\bullet}H_2O$	50–260	3.36	0.00	0.12	−102.38	0.59	34.75
	260–760	69.88	1.00	0.79×10^4	−94.45	63.49	136.09
$[Cu(\mathbf{L_2})_2(H_2O)_2]^{\bullet}2H_2O$	50–130	3.18	0.00	0.15	−102.02	0.97	141.00
	130–280	4.90	1.49	0.12	−101.98	1.28	35.83
	280–760	101.02	1.00	0.26×10^6	−93.00	94.83	45.46
$[Cu(\mathbf{L_3})_2(H_2O)_2]^{\bullet}2H_2O$	50–260	3.80	0.00	0.15	−102.00	0.96	106.58
	260–760	81.40	1.00	0.21×10^6	−93.60	75.50	35.80
$[Cu(\mathbf{L_4})_2(H_2O)_2]^{\bullet}H_2O$	50–130	3.52	0.00	0.13	−102.25	0.73	35.13
	130–260	5.19	1.50	0.11	−101.98	1.36	48.34
	260–780	45.35	1.00	0.26×10^3	−95.67	39.52	106.58

($\Delta S^{\#}$), pre-exponential factor (A), activation enthalpy ($\Delta H^{\#}$) and free energy of activation ($\Delta G^{\#}$) were calculated using the reported equations.[38,39]

According to the kinetic data obtained from DTG curves, all the metal complexes have negative entropy, which indicates that the studied metal complexes have more ordered systems than the reactants.[40] The kinetic parameters, especially energy of activation (E_a), are helpful in assigning the strength of the metal complexes. The calculated E_a values of the investigated complexes, i.e. the stage of the formation of volatile gas products, are relatively high, which indicates that the ligand is strongly bonded to the metal ion.[41] The calculated E_a values of the investigated metal complexes for the first dehydration step are in the range 3.36–3.81 kJ mol^{-1} (Table 4).

Magnetic Moments and Electronic Spectra

The information regarding the geometry of the metal complexes was obtained from their electronic spectral data and magnetic moments. Copper (II) complex d^9 systems are known for their varieties of structures owing to their different coordination numbers. A six-coordinated copper (II) complex possesses distorted octahedral geometry. The spectra of copper complexes are very difficult to assign, even with relatively simple ligands because of the breadth of absorption band even at low temperatures. The different coordination numbers have a wide range of geometry. The copper(II) complexes exhibit magnetic moments of 1.79, 1.93, 1.77 and 1.98 BM (Bohr magneton), respectively. These values are close to the spin-allowed values expected for an $S = 1/2$ system (1.73 BM) and may be indicative of an octahedral geometry around the copper(II) ions. The copper (II) complexes display a broad band at ca. 15 000 cm^{-1} due to the $^2E_g \rightarrow {}^2T_{2g}$ transition.[42]

FAB Mass Spectra

In the mass spectra of $[Cu(\mathbf{L_1})_2(H_2O)_2]^{\bullet}H_2O$, the peak at m/z = 893 stands for the molecular ion peak of complex (without water of crystallization). The proposed fragmentation pattern of $[Cu(\mathbf{L_1})_2(H_2O)_2]^{\bullet}H_2O$ is given in Scheme 2. The measured molecular weights were consistent with expected values, and the mass spectrum of $[Cu(\mathbf{L_1})_2(H_2O)_2]^{\bullet}H_2O$ complex is shown in Fig. 6.

Antibacterial Results

The increase in antimicrobial activity may be considered in light of Overtone's concept[43] and Tweedy's chelation theory.[44]

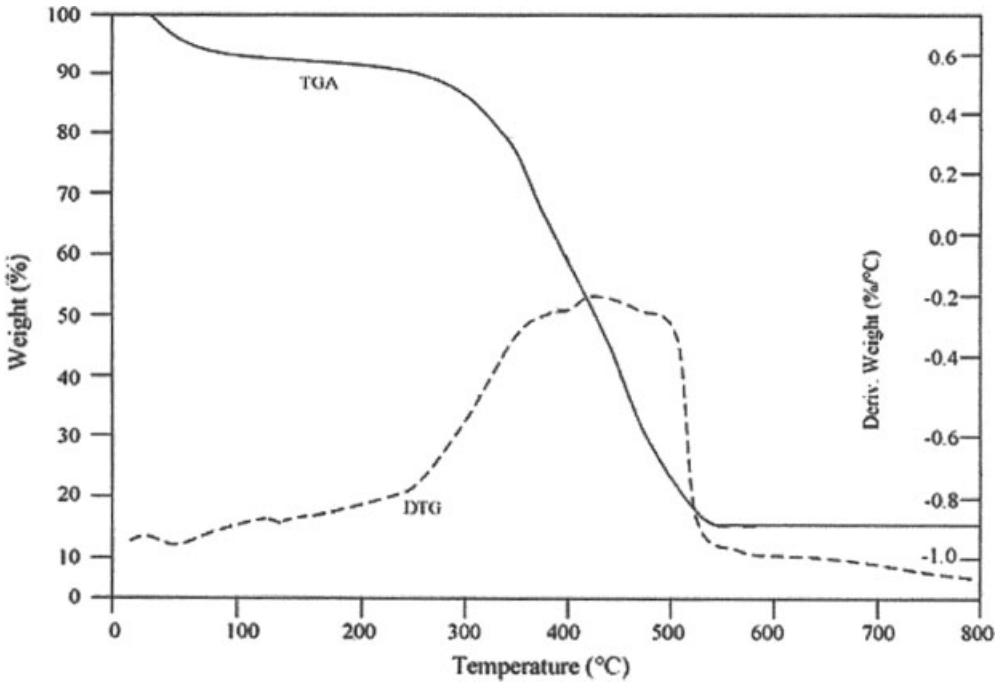


Figure 4. TGA/DTG curves of $[Cu(II)(\mathbf{L_3})(H_2O)_2]^{\bullet}2H_2O$.

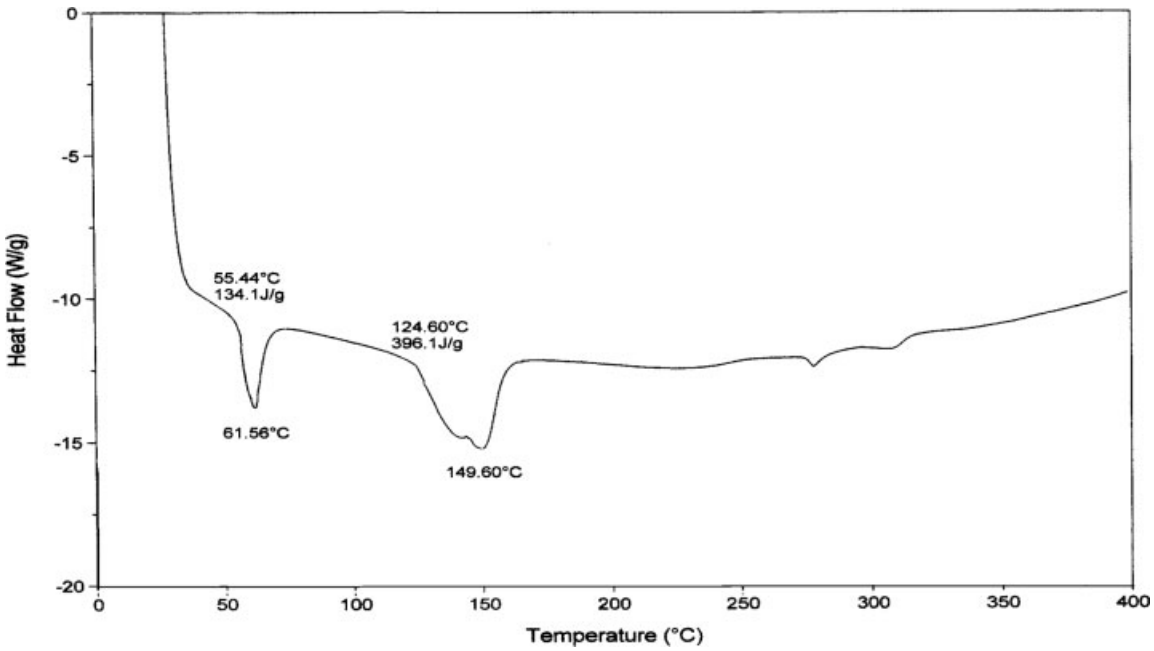
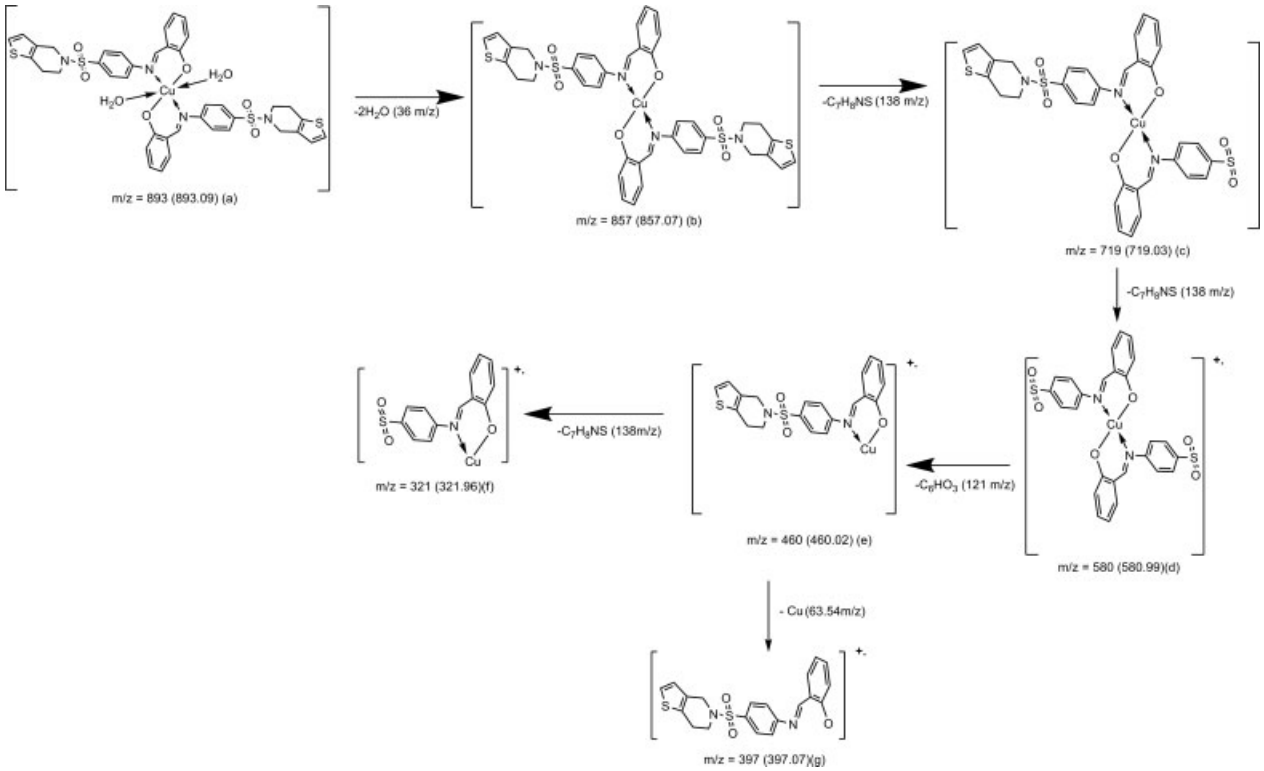


Figure 5. DSC curve of $[Cu(II)(\mathbf{L_1})(H_2O)_2]^{\bullet}xH_2O$.

According to Overtone's concept of cell permeability, the lipid membrane that surrounds the cell favors the passage of only lipid-soluble materials, which indicates that liposolubility is an important factor controlling the antimicrobial activity. On chelation, the polarity of the metal ion will be reduced to a greater extent owing to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further, it increases the delocalization of π-electrons over the whole chelate ring and enhances the lipophilicity of the complexes. This increased lipophilicity enhances the penetration of the metal chelate into lipid membranes and blocks the metal binding sites in the enzymes of microorganisms. These metalchelates also disturb the respiration process of the cell and thus block the synthesis of proteins, which restricts further growth of the organisms.

Furthermore, the mode of action of the compounds may involve the formation of a hydrogen bond through the azomethine/carbonyl/amine group with the active center of cell constituents resulting in interference with the normal cell process.[45] Metal complexes exhibit higher biocidal activity as compared with



Scheme 2. The suggested fragmentation pattern of $[Cu(L_1)(H_2O)_2].H_2O$.

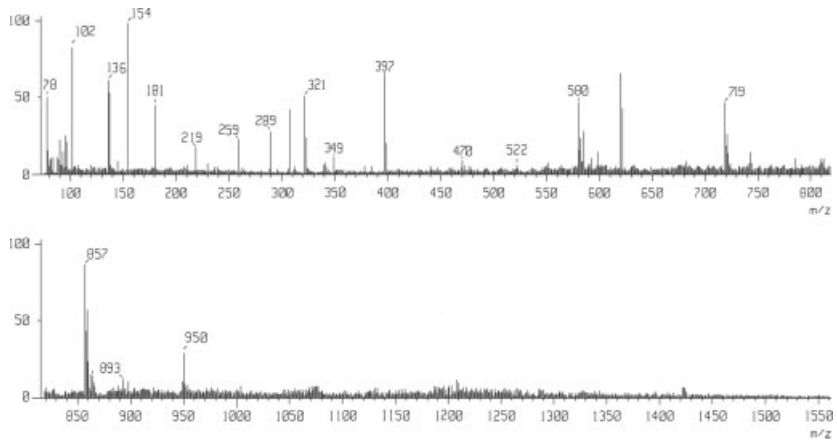


Figure 6. Fab mass spectra of metal complex $[Cu(II)(\mathbf{L_1})(H_2O)_2]^{\bullet}H_2O$.

the free ligands, metal salts and control dimethyl sulfoxide. From the comparative analysis shown in Fig. 7, it is observed that all the metal complexes are more potent biocidals than the ligands $\mathbf{L_{1-4}}$. The zone of inhibition was measured (in mm) around the disk and the results are represented in Table 5. From the graph it is clear that Cu(II) is highly active among the complexes of the respective metal.

Conclusion

All the synthesized compounds were screened for their biocidal activity. The metal complexes exhibited strong activities against two Gram-negative (*Escherichia coli, Serratia marcescens*) and two Gram-positive (*Bacillus subtillis, Pseudomonas aeruginosa*) microorganisms. In comparison with both the ligands and the metal salt, the Cu(II) metal complexes were more active against one or more bacterial strains, thus introducing a novel class of metal-based bactericidal agents.

The information regarding geometry of the metal complexes was obtained from their electronic and magnetic moment values. Magnetic moment values indicate that Cu(II) metal complexes are high-spin, lacking exchange interactions. The studies reveal that an octahedral geometry can be assigned to metal complexes.

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One of the authors, D. J. Patel, is thankful to UGC (New Delhi) for awarding a meritorious scholarship. The authors are

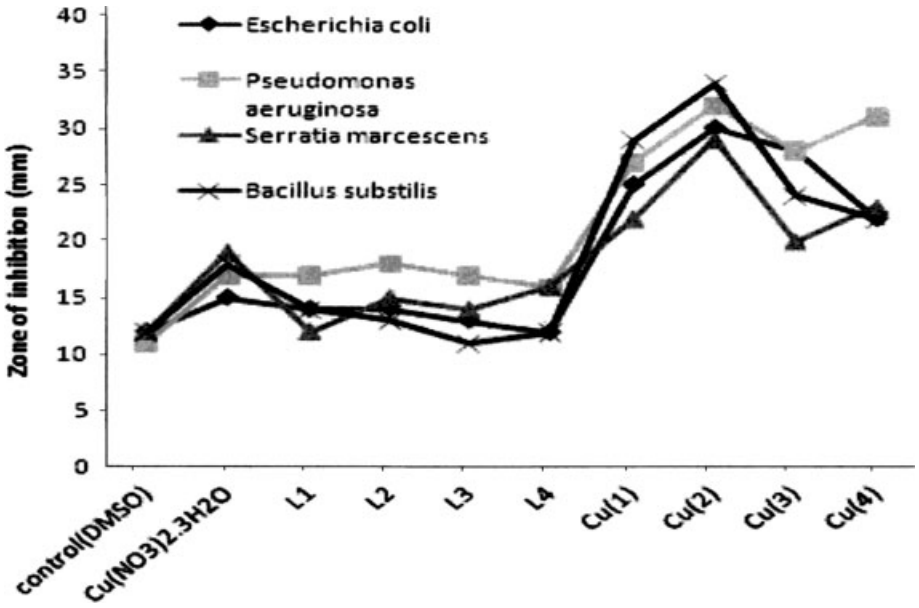

Figure 7. Comparative analysis of ligand and its metal complexes.

Table 5. Agar plate technique

	Zone of inhibition (mm)			
	Gram-negative		Gram-positive	
Compound	*Escherichia coli*	*Serratia marcescens*	*Pseudomonas aeruginosa*	*Bacillus substilis*
Control (DMSO)	12	11	12	12
$Cu(NO_3)_2^{\bullet}3H_2O$	15	17	19	18
Ciprofloxacin	35	44	52	44
L_1	14	17	12	14
L_2	14	18	15	13
L_3	13	17	14	11
L_4	12	16	16	12
Cu(1)	25	27	22	29
Cu(2)	30	32	29	34
Cu(3)	28	28	20	24
Cu(4)	22	31	23	22

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