

Spectral, thermal, biological and multi-heating rate kinetic properties of Cu(II) complexes containing N₂O₂ donor ligands: 1,10-phenanthroline and acyl coumarins

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A series of newly synthesized coumarin-based mixed-ligand copper complexes with 1,10-phenanthroline (Ph) were investigated by means of thermogravimetry, differential thermogravimetry, differential scanning calorimetry (DSC), electronic spectra and magnetic measurements. Structural and spectroscopic properties of neutral bidentate ligands as well as all complexes were studied on the basis of mass spectra, NMR (¹H and ¹³C) spectra, FT-IR spectrophotometry and elemental analyses. IR spectral data suggest tetra-coordinated N₂O₂ bonding of ligand toward metal ion. Dynamic scan of DSC experiments for copper complexes were obtained at different heating rates (2.5–20 °C min⁻¹). Isoconversion methods of Kissinger and Ozawa were used for the determination of the pre-exponential factor (*A*), activation energy (*E_a*) and order of reaction (*n*). Kinetic parameters for second-step degradation obtained by Kissinger's and Ozawa's methods are in good agreement. The results indicate that complexes are much stronger free radical scavenger and antioxidant compounds than ligands. Antimicrobial screening of ligand and its copper compound against *Mycobacterium tuberculosis* shows clear enhancement in antitubercular activity upon copper complexation. Also good antimicrobial activities of the complexes against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhus*, *Aspergillus niger*, *Candida albicans* and *Aspergillus clavatus* have been found compared to its free ligands. Copyright © 2012 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

Keywords: isoconversion methods; 1,10-phenanthroline; antimicrobial; antituberculosis; antioxidant

Introduction

Interest in coumarin chemistry has flourished for many years, also studies of coumarin derivatives have demonstrated a wide range of uses. Coumarin-containing compounds have found important uses as ligands for the synthesis of coordination compounds.^[1,2] The coumarin group can participate in monodentate, didentate or η⁶-arene-binding modes to a metal centre based upon the coumarin/donor atoms present. Coumarins and/or their transition metal complexes represent an important class of compounds, with an extensive range of biological properties^[3] such as anticoagulants,^[4] antibacterial agents,^[5,6] antifungal agents,^[7] biological inhibitors,^[8] chemotherapeutics^[9] and bio-analytical reagents.^[10] Coumarins are also important as photo-chemotherapeutic agents to treat a variety of skin diseases.^[11] They have been also found to exhibit antioxidant,^[12] anticoagulant,^[13] antimutagenic,^[14] cytotoxic,^[15] antiviral,^[16] antithrombotic and vasodilatory^[17] activity. Coumarin and its derivatives have been commercially used as a significant group of organic fluorescent materials, and natural coumarin derivatives are known for their luminescent properties and play a vital role in perfumes, cosmetics, agrochemicals, insecticides, electroluminescent devices, laser dyes and cation/anion sensors, as well as in phosgene detection, along with pharmaceutical industrial production.^[18–22]

1,10-Phenanthroline is a well-known bidentate chelating ligand.^[23] Transition metal complexes of 1,10-phenanthroline and its derivatives are of increasing interest because of their versatile roles in many

fields such as coordination chemistry, analytical chemistry and biological chemistry.^[24] Likewise, study of phenanthroline derivatives has been prompted by current interest in their catalytic, redox, physicochemical, biological properties and novel supramolecular chemistry.^[25–27] In recent years, the study of copper-1,10-phenanthroline complexes has become progressively more important owing to their antimicrobial properties.^[28,29] Furthermore, copper complexes of 1,10-phenanthroline are capable of cleaving DNA.^[30] Copper complexes of nitrogen-donor heterocyclic ligands have been used widely to improve nuclease activity.^[30,31] However, literature survey shows that many mononuclear and polynuclear copper(II) complexes of 1,10-phenanthroline have been synthesized. Mixed ligand complexes including a small number of copper-(o-phen) complexes containing DMF co-ligands have been reported.^[32,33] 1,10-Phenanthroline has been found active against *Mycobacterium tuberculosis*.^[34] Tuberculosis is a well-known disease that has troubled human beings in past times^[35] and still remains a major health problem. The World Health Organization (WHO) estimates that one-third of the population is infected with latent *Mycobacterium tuberculosis* and approximately 3 million people per year die due to this bacillus.^[36]

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In continuation of our preceding work,^[37,38] in the present article we describe synthetic, characteristic, spectroscopic features and thermal aspects of newly synthesized mixed ligand Cu(II) complexes of 1,10-phenanthroline with coumarin derivatives. Antituberculosis, antioxidant and antimicrobial screening have been carried out for all compounds. Isoconversional methods of Kissinger and Flynn–Wall–Ozawa (FWO) were used to evaluate an activation energy and pre-exponential factor.

Experimental

Materials

Salicylaldehyde and ethyl acetoacetate used for the preparation of 3-acetyl coumarin were purchased from E. Merck (India) Ltd, Mumbai. The nitrate of copper metal ion was used as the hydrated salt, e.g. $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$. Benzaldehyde, vanillin, *p*-nitrobenzaldehyde, *p*-chlorobenzaldehyde and *p*-hydroxybenzaldehyde were purchased from Aldrich Chemicals. Catalyst (piperidine) and solvents (chloroform, hexane, ethanol, DMSO) were of analytical grade and were purchased commercially. The organic solvents were purified/dried by a recommended method.^[39]

Physical Measurements

Elemental analysis (C, H, N) was performed using a 2400-II CHN analyzer (PerkinElmer, USA). Analyses of metal ions was carried out by dissolution of the solid complexes in hot concentrated nitric acid, further diluting with distilled water and filtered to remove the precipitated organic ligands. The remaining solution was neutralized with ammonia solution and the metal ions were titrated against EDTA. The melting point of all compounds was measured using the open capillary tube method. FT-IR spectra ($400\text{--}4000\text{ cm}^{-1}$) were recorded with a Spectrum GX-PerkinElmer spectrophotometer using KBr pellets. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra of ligands were recorded on a model Advance 400 Bruker FT-NMR instrument using tetramethylsilane as internal standard and DMSO- d_6 as solvent. The fast atom bombardment (FAB) mass spectrum of the complexes was recorded at SAIF, CDRI, Lucknow with a JEOL SX-102/DA-6000 mass spectrometer at room temperature using argon/xenon as the FAB gas. Electronic spectra (200–1200 nm) were collected using a LAMBDA 19 UV–visible/near-infrared spectrophotometer. Thermal stability and decomposition of the complexes were determined by TG and DTG using a model 5000/2960 SDT (TA Instruments, USA). The experiments were performed in N_2 atmosphere at a heating rate of $20^\circ\text{C min}^{-1}$ in the temperature range 20–800°C. Analysis by differential scanning calorimetry (DSC) was carried out using a DSC-PYRIS-1 (PerkinElmer, USA). DSC analyses of complexes were also evaluated from dynamic scanning experiments at multiple heating rates of 2.5, 5, 10, 15 and $20^\circ\text{C min}^{-1}$ respectively, with the best resolution and comparative results found at a scanning rate of $10^\circ\text{C min}^{-1}$. Sample sizes ranging in mass from 3 to 8 mg were heated in an Al_2O_3 crucible. Magnetic susceptibility measurements were obtained by Gouy's method using mercury tetrathiocyanato cobaltate(II) as a calibrant ($\chi = 16.44 \times 10^{-6}$ c.g.s. units at 20°C). Diamagnetic corrections were made using Pascal's constant.^[40]

Synthesis of Ligands ($\text{L} = \text{L}^1\text{--}\text{L}^5$)

Neutral bidentate ligands were synthesized using Claisen–Schmidt condensation by a reported method.^[41] The Characterization data of ligand L^2 and L^5 (Mass, $^1\text{H NMR}$, $^{13}\text{C NMR}$, IR) is given in Supplementary material ($\text{S}_1\text{--}\text{S}_4$ and $\text{S}_6\text{--}\text{S}_9$).

3-(3-Phenyl-acryloyl)-2H-chromen-2-one (L^1)

An ethanolic (50 ml) solution of 3-acetyl coumarin (0.01 M) and benzaldehyde (0.01 M) was placed in a three-neck round-bottom flask. A catalytic amount of piperidine (1.0 ml) was added in reaction mass and the mixture was stirred for 10 min at room temperature. After a clear solution was obtained the reaction mixture was refluxed in a water bath for 6 h. Completion of the reaction was monitored by thin-layer chromatography using mobile-phase ethyl acetate–hexane (7:3). After completion of the reaction, the mixture was allowed to come at room temperature. A solid product separated out which was filtered off, washed with cold ethanol and dried in air. It was recrystallized from ethanol. Yield 77%; m.p. 142°C . Anal. Calcd for $\text{C}_{18}\text{H}_{12}\text{O}_3$ (%): C, 78.25; H, 4.38. Found: C, 78.20; H, 4.32. $^1\text{H NMR}$ (DMSO- d_6 400 MHz): δ 6.80 (1H, m, $\text{C}_6=\text{H}$), 7.11–7.63 (8H, m, aromatic protons), δ 7.77 (1H, d, $J=7.6$, $\text{CH}=\text{CH}=\text{H}$ protons), δ 7.83 (1H, d, $J=7.6$, $\text{CH}=\text{CH}=\text{H}$ protons), δ 8.49 (1H, s, $\text{C}_4=\text{H}$). $^{13}\text{C NMR}$ (DMSO- d_6 100 MHz): δ 113.6 (C-4a), 117.1 (C-8), 118.9 (C-10, $=\text{CO}=\text{CH}=\text{H}$), 124.7, 125.3, 126.0, 127.4, 128.8, 129.7, 133.6, 134.2, (eight different types of aromatic carbons), 146.9 (C-11, $=\text{CH}=\text{CH}=\text{H}$), 147.3 (C-4), 152.2 (C-8a), 159.3 (C=O, lactone carbonyl of coumarin), 189.5 (C=O, α,β -unsaturated ketone). ESI-MS (m/z): 276.07, FT-IR (KBr, cm^{-1}): 1610, ν (C=O, α,β -unsaturated ketone), 1740, ν (C=O, lactone carbonyl of coumarin).

3-(3-(4-Chlorophenyl)acryloyl)-2H-chromen-2-one (L^2)

L^2 was synthesized by same method used for L^1 by using *p*-chlorobenzaldehyde as a substitute of benzaldehyde. Yield 70%; m.p. 223°C . Anal. Calcd for $\text{C}_{18}\text{H}_{11}\text{ClO}_3$ (%): C, 69.58; H, 3.57. Found: C, 69.40; H, 3.36. $^1\text{H NMR}$ (DMSO- d_6 400 MHz): δ 6.86 (1H, m, $\text{C}_6=\text{H}$), δ 7.12 (2H, d, $J=7.2$, *p*-substituted phenyl ring), δ 7.23 (1H, m, aromatic protons), δ 7.39 (2H, m, aromatic proton), δ 7.63 (2H, d, $J=7.2$, *p*-substituted phenyl ring), δ 7.88 (1H, d, $J=7.8$, $\text{CH}=\text{CH}=\text{H}$ protons), δ 7.90 (1H, d, $J=7.8$, $\text{CH}=\text{CH}=\text{H}$ protons), δ 8.52 (1H, s, $\text{C}_4=\text{H}$). $^{13}\text{C NMR}$ (DMSO- d_6 100 MHz): δ 114.8 (C-4a), 116.5 (C-8), 118.6 (C-10, $=\text{CO}=\text{CH}=\text{H}$), 124.2, 125.1, 126.2, 127.9, 129.8, 130.0, 133.5, 134.6 (eight different types of aromatic carbons), 147.1 (C-11, $=\text{CH}=\text{CH}=\text{H}$), 147.6 (C-4), 151.5 (C-8a), 159.7 (C=O, lactone carbonyl of coumarin), 190.2 (C=O, α,β -unsaturated ketone). ESI-MS (m/z): 310.6, 312.7. FT-IR (KBr, cm^{-1}): 1618, ν (C=O, α,β -unsaturated ketone), 1742, ν (C=O, lactone carbonyl of coumarin).

3-(3-(4-Nitrophenyl)acryloyl)-2H-chromen-2-one (L^3)

L^3 was synthesized by the same method used for L^1 by using *p*-nitrobenzaldehyde as a substitute for benzaldehyde. Yield 68%; m.p. 171°C . Anal. Calcd for $\text{C}_{18}\text{H}_{11}\text{NO}_5$ (%): C, 67.34; H, 3.45; N, 4.39. Found: C, 67.29; H, 3.37; N, 4.36. $^1\text{H NMR}$ (DMSO- d_6 400 MHz): δ 6.90 (1H, m, $\text{C}_6=\text{H}$), δ 7.14 (2H, d, $J=7.2$, *p*-substituted phenyl ring), δ 7.25 (1H, m, aromatic protons), δ 7.45 (2H, m, aromatic proton), δ 7.78 (2H, d, $J=7.2$, *p*-substituted phenyl ring), δ 7.86 (1H, d, $J=7.2$, $\text{CH}=\text{CH}=\text{H}$ protons), δ 7.91 (1H, d, $J=7.2$, $\text{CH}=\text{CH}=\text{H}$ protons), δ 8.53 (1H, s, $\text{C}_4=\text{H}$). $^{13}\text{C NMR}$ (DMSO- d_6 100 MHz): δ 114.1 (C-4a), 116.3 (C-8), 118.5 (C-10, $=\text{CO}=\text{CH}=\text{H}$), 124.9, 125.7, 126.9, 127.1, 129.5, 130.6, 134.8 (seven different types of aromatic carbons), 146.8 (C-11, $=\text{CH}=\text{CH}=\text{H}$), 147.2 (C-4), 148.7 (C-17, carbon attached to phenolic NO_2), 154.7 (C-8a), 159.6 (C=O, lactone carbonyl of coumarin), 189.7 (C=O, α,β -unsaturated ketone). ESI-MS (m/z): 321.4, FT-IR (KBr, cm^{-1}): 1614, ν (C=O, α,β -unsaturated ketone), 1738, ν (C=O, lactone carbonyl of coumarin), 1523 (ArNO_2 , asymmetric), 1347 (ArNO_2 , symmetric).

3-(3-(4-Hydroxy-3-methoxyphenyl)acryloyl)-2H-chromen-2-one (L^4)

L^4 was synthesized by same method used for L^1 by using vanillin as a substitute for benzaldehyde. Yield 79%; m.p. 230°C. Anal. Calcd for $C_{19}H_{14}O_5$ (%): C, 70.80; H, 4.38. Found: C, 70.77; H 4.31. 1H NMR (DMSO- d_6 400 MHz): δ 3.86 (3H, s, =OCH₃), δ 6.91 (1H, m, C₆=H), 7.12–7.79 (6H, m, aromatic protons), δ 7.89 (1H, d, $J=7.6$, CH=CH= protons), δ 7.93 (1H, d, $J=7.6$, CH=CH= protons), δ 8.56 (1H, s, C₄=H), δ 11.62 (1H, s, =OH). ^{13}C NMR (DMSO- d_6 100 MHz): δ 34.9 (C-18, OCH₃), 111.5 (C-13), 114.6 (C-16), 115.1 (C-4a), 116.4 (C-8), 118.0 (C-10, =CO=CH=), 124.2, 125.8, 127.6, 129.4, 130.4, 134.5 (six different types of aromatic carbons), 147.2 (C-11, =CH=CH=), 147.4 (C-4), 148.8 (C-14), 151.7 (C-17, carbon attached to phenolic OH), 155.6 (C-8a), 158.8 (C=O, lactone carbonyl of coumarin), 190.4 (C=O, α,β -unsaturated ketone). ESI-MS (m/z): 322.6. FT-IR (KBr, cm^{-1}): 3466, ν (O=H, stretching), 1620, ν (C=O, α,β -unsaturated ketone), 1743, ν (C=O, lactone carbonyl of coumarin), 1241 (C=O=C, asymmetric), 1039 (C=O=C, symmetric).

3-(3-(4-Hydroxyphenyl)acryloyl)-2H-chromen-2-one (L^5)

L^5 was synthesized by the same method used for L^1 by using *p*-hydroxybenzaldehyde as a substitute for benzaldehyde. Yield 72%; m.p. 210°C. Anal. Calcd. for $C_{18}H_{12}O_4$ (%): C, 73.97; H, 4.02. Found: C, 73.90; H, 4.14. 1H NMR (DMSO- d_6 400 MHz): δ 6.86 (2H, d, $J=7.8$, *p*-substituted phenyl ring), δ 6.88 (1H, d, $J=16$, CH=CH= protons), δ 7.23 (1H, m, aromatic protons), δ 7.40 (2H, d, $J=7.8$, *p*-substituted phenyl ring), δ 7.63–7.74 (3H, m, three aromatic protons), δ 7.90 (1H, d, $J=16$, CH=CH= protons), δ 8.53 (1H, s, C₄=H), δ 9.58 (1H, s, =OH). ^{13}C NMR (DMSO- d_6 100 MHz): δ 114.4 (C-4a), 116.7 (C-8), 118.3 (C-10, =CO=CH=), 124.5, 125.0, 127.0, 127.5, 129.9, 130.2, 134.4 (seven different types of aromatic carbons), 147.1 (C=11, =CH=CH=), 147.5 (C-4), 151.7 (C-17, carbon attached to phenolic OH), 155.3 (C-8a), 159.2 (C=O, lactone carbonyl of coumarin), 190.8 (C=O, α,β -unsaturated ketone). ESI-MS (m/z): 292.4. FT-IR (KBr, cm^{-1}): 3484, ν (O=H, stretching), 1622, ν (C=O, α,β -unsaturated ketone), 1745, ν (C=O, lactone carbonyl of coumarin), 1245 (C=O=C, asymmetric), 1044 (C=O=C, symmetric).

Synthesis of Complexes (C = C^1 – C^5) $[Cu(L^1)(Ph)(OH)_2] \cdot 2H_2O$ (C^1)

An aqueous solution of $Cu(NO_3)_2 \cdot 3H_2O$ (10 mM, 100 ml) was added to an ethanolic solution of ligand L^1 (10 mM, 100 ml), followed by addition of an ethanolic solution of 1,10-phenanthroline

(10 mM, 100 ml); the pH was adjusted to 6.0 with diluted NaOH solution. The resulting solution was refluxed for 8 h and then heated over a steam bath to evaporate up to half of the volume. The reaction mixture was kept overnight at room temperature. A fine colored crystalline product was obtained. The obtained product was washed with ether and dried over vacuum desiccators. The general synthetic route of complexes (C) is shown in Scheme 1.

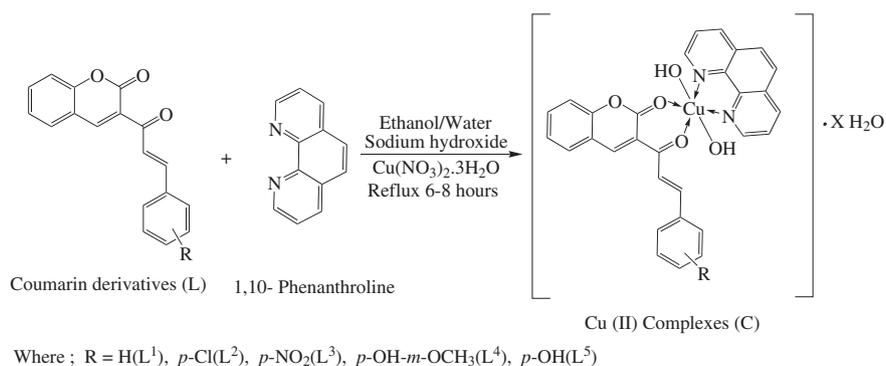
Complexes C^2 – C^5 were synthesized according to same method as C^1 ; their analytical and physicochemical parameters are summarized in Table 1.

Antimicrobial Studies

The *in vitro* antimicrobial activity of all the synthesized compounds was assessed against 24 h old cultures of microorganisms *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhus*, *Aspergillus niger*, *Candida albicans* and *Aspergillus clavatus* by the broth dilution method.^[42] The serial broth micro-dilution method was adopted as a reference method. 2% Luria broth solution was prepared in distilled water; the pH of the solution was adjusted to 7.4 ± 0.2 at room temperature and sterilized by autoclaving at 15 lb pressure for 20 min. The tested microorganism strains were made in the Luria broth and incubated at 37°C overnight. Sample solutions were prepared in DMSO for different concentrations. Standard solutions of streptomycin (antibacterial drug) and nystatin (antifungal drug) were prepared in DMSO. Serial dilutions of test compounds were inoculated in broth; to this a standardized microorganism suspension was added. Each test tube was incubated at 35°C for 24 h. At the end of the incubation period tubes were examined for turbidity. Turbidity in the test tubes indicated that microorganism growth was not inhibited by the antibiotic contained in the medium at the test concentration. All samples were carried out in triplicate.

Antituberculosis Studies

All the synthesized compounds (L^1 – L^5 and C^1 – C^5) were examined for antituberculosis activity against *Mycobacterium tuberculosis* H37Rv strain using the Lowenstein–Jensen medium method.^[43] Isoniazid, rifampicin and ethambutol were used as the standard drug. Dilutions of standard drugs were prepared in DMSO to obtain concentrations of 25, 12.5, 6.25, 3.12 and 0.25 $\mu g ml^{-1}$. Stock solutions of synthesized compounds were prepared in DMSO for a concentration of 150 $\mu g ml^{-1}$. Further dilutions were prepared in DMSO to obtain concentrations such as 150, 100, 90, 80, 70, 60, 50,



Scheme 1. General synthetic route of complexes (C).

Table 1. Analytical and physicochemical parameters of synthesized compounds

Compound (empirical formula)	Elemental analyses (% found (required))				m.p. (°C)	Yield (%)	Molecular mass	μ_{eff} (BM)
	C	H	N	Cu(II)				
[Cu(L ¹)(Ph)(OH) ₂] ₂ H ₂ O C ₃₀ H ₂₆ CuN ₂ O ₇ /(C ¹)	60.90 (61.06)	4.30 (4.44)	4.56 (4.75)	10.54 (10.77)	>350	65	590.08	1.80
[Cu(L ²)(Ph)(OH) ₂] ₃ H ₂ O C ₃₀ H ₂₇ ClCuN ₂ O ₈ /(C ²)	55.95 (56.08)	4.12 (4.24)	4.24 (4.36)	9.70 (9.89)	>350	77	642.54	1.82
[Cu(L ³)(Ph)(OH) ₂] ₂ H ₂ O C ₃₀ H ₂₃ CuN ₃ O ₈ /(C ³)	58.26 (58.39)	3.65 (3.76)	6.70 (6.81)	10.22 (10.30)	>350	60	617.06	1.79
[Cu(L ⁴)(Ph)(OH) ₂] ₃ H ₂ O C ₃₁ H ₃₀ CuN ₂ O ₁₀ /(C ⁴)	56.72 (56.92)	4.46 (4.62)	4.19 (4.28)	9.58 (9.71)	>350	70	654.12	1.82
[Cu(L ⁵)(Ph)(OH) ₂] ₂ H ₂ O C ₃₀ H ₂₆ CuN ₂ O ₈ /(C ⁵)	59.26 (59.45)	4.16 (4.32)	4.42 (4.62)	10.32 (10.48)	>350	72	606.08	1.77

40, 30, 20 and 10 $\mu\text{g ml}^{-1}$. 1.0 ml of each concentration was used for the study, to which 9.0 ml Lowenstein–Jensen medium was added. A sweep from *M. tuberculosis* H37RV strain culture was discharged with the help of a nichrome wire loop having 3 mm external diameter into a vial containing 4 ml sterile distilled water. The vial was shaken for 5 min. Using a nichrome wire loop the suspension was then inoculated on the surface of each test compound containing L-J media. Further test media were incubated for 2 weeks at 37°C. Readings were taken after incubation for 2 weeks. Readings for standard drugs were also carried out by the same method.

Radical-Scavenging Activity

1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical and 2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) cationic radical activities of compounds were investigated out using reported methods.^[44,45] For determination of the reducing activity of the stable radical DPPH, various concentrations of compounds were added to a solution of DPPH in methanol (125 μM , 2 ml) and the final volume was made up to 3 ml with water. The solution was shaken and incubated at 37°C for 30 min at room temperature. The absorbance at 515 nm was measured by a spectrophotometer. ABTS radical cation was produced by reacting ABTS stock solution with 2.45 mM potassium persulfate and allowing the mixture to stand in the dark for 12–16 h. The methanolic solution of ABTS radical was then reacted with the compound for 2 h in the dark and the absorbance was measured at 734 nm using a spectrophotometer.

The tests were run in triplicate and various concentrations of the complexes were used to fix a concentration at which each

complex showed approximately 50% activity. Scavenging activity was calculated using the equation (%) activity = $100(A_c - A_s)/A_c$, where A_c is the absorbance of the control reaction and A_s is the absorbance in the presence of the sample.

Results and Discussion

Chemistry

Neutral bidentate ligands of coumarins were prepared with a 1:1 molar ratio of 3-acetyl coumarin and different aromatic aldehydes in ethanol using piperidine as catalyst. All ligands were confirmed for their purity by melting points, elemental analyses and other spectral studies. All the complexes (C) were obtained by the reaction of two ligands and metal nitrate with a 1:1:1 molar ratio in ethanol. The synthesized complexes were characterized by elemental analysis, FT-IR, electronic spectra, FAB mass spectroscopy, and thermal and magnetic studies. The complexes were colored and stable in air. They were insoluble in water and in most organic solvents but partially soluble in DMSO.

IR Spectra

Important infrared spectral bands and their assignments for the synthesized compounds were recorded as KBr disks; they are presented in Table 2. The IR data of the free ligands and its metal complexes were carried out within the IR range 400–4000 cm^{-1} . The IR spectrum of complex C² and C⁵ is given in supplementary material (S₅ and S₁₀).

The IR spectrum of compounds L⁴ and L⁵ showed a strong OH stretching band between 3470 and 3510 cm^{-1} , while spectra of

Table 2. FT-IR data of synthesized compounds

Ligands (L ¹ –L ⁵) and complexes (C ¹ –C ⁵)	$\nu(\text{O}=\text{H})^{\text{br}}$ (cm^{-1})	$\nu(\text{C}=\text{N})^{\text{w}}$ (cm^{-1})	α,β -Unsaturated $\nu(\text{C}=\text{O})^{\text{s}}$ (cm^{-1})	Lactone carbonyl $\nu(\text{C}=\text{O})^{\text{s}}$ (cm^{-1})	$\nu(\text{Cu}=\text{N})^{\text{w}}$ (cm^{-1})	$\nu(\text{Cu}=\text{O})^{\text{w}}$ (cm^{-1})
L ¹	—	—	1610	1740	—	—
L ²	—	—	1618	1742	—	—
L ³	—	—	1614	1738	—	—
L ⁴	3466	—	1620	1743	—	—
L ⁵	3484	—	1622	1745	—	—
[Cu(L ¹)(Ph)(OH) ₂] ₂ H ₂ O	3439	1558	1600	1728	548	456
[Cu(L ²)(Ph)(OH) ₂] ₃ H ₂ O	3434	1557	1610	1732	549	456
[Cu(L ³)(Ph)(OH) ₂] ₂ H ₂ O	3433	1555	1603	1727	549	459
[Cu(L ⁴)(Ph)(OH) ₂] ₃ H ₂ O	3441	1559	1609	1734	550	457
[Cu(L ⁵)(Ph)(OH) ₂] ₂ H ₂ O	3443	1558	1612	1740	551	458

^sstrong; ^wweak; ^{br}broad.

the mixed-ligand Cu(II) complexes revealed a broad band in the region $3400\text{--}3450\text{ cm}^{-1}$ due to stretching vibration of the OH group, indicating formation of complexes. However, bands at ~ 850 and $\sim 715\text{ cm}^{-1}$ were due to rocking and wagging vibration of the OH group, respectively.^[46] The IR spectrum of the free ligand showed very strong bands at ~ 1633 and $\sim 1598\text{ cm}^{-1}$ due to the stretching frequency of the C=N present in the 1,10-phenanthroline moiety. These bands were shifted to lower frequencies upon complexation through the metal ions ($\sim 30\text{--}38\text{ cm}^{-1}$), indicating participation of the eneamino nitrogen group in coordination. The IR spectra of the ligands showed ~ 1618 and $\sim 1742\text{ cm}^{-1}$ bands corresponding to α,β -unsaturated ketone and lactone carbonyl ketone, respectively; on complexation these peaks shifted to a lower frequency, ~ 1610 and $\sim 1732\text{ cm}^{-1}$, due to complex formation. The complexation was further confirmed by bands found at ~ 549 and $\sim 456\text{ cm}^{-1}$ due to Cu=N and Cu=O, respectively.^[47,48]

Electronic Spectra and Magnetic Measurement

Electronic spectral data along with magnetic susceptibility measurements gave adequate support in discovering the geometry of the metal complexes. The electronic spectra of complexes were recorded in DMF solution with a scan range of 200–1200 nm. The electronic spectra of complex **C** is given in supplementary material (S₁₁). Normal octahedral geometry was found for Cu(II),^[49,50] despite the known preference for Jahn–Teller distortions in cases of trigonal and octahedral geometry. A very weak low-intensity absorption band associated with d–d transition for Cu(II) complexes at 465 and 532 nm indicated typical octahedral transition.^[51] However, many copper compounds show temperature-dependent geometric distortions, and single copper ions in a host lattice of regular symmetry may exhibit interesting spectroscopic properties.^[52]

In the electronic spectra of the metal complexes, wide-range bands were observed due to either the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ of C=N chromophore or charge transfer transition arising from π electron interactions between the metal and ligand, involving either a metal-to-ligand or ligand-to-metal electron transfer.^[53] Furthermore, the electronic spectra of six coordinate copper(II) complexes showed either D_{4h} or C_{4v} symmetry, the E_g and T_{2g} level of ²D free ion term splitting into B_{1g}, A_{1g}, B_{2g} and E_g levels, respectively, under the influence of the distortion, causing two transitions such as ²B_{1g} → ²B_{2g} and ²B_{1g} → ²A_{1g}. This supports the distorted octahedral copper(II) complex, which was usual in the d⁹ system.^[54] The electronic spectra of copper(II) complexes (**C**¹–**C**⁵) display three prominent bands. A low-intensity broad band in the region $16\,900\text{--}17\,800\text{ cm}^{-1}$ was assigned to the 10 Dq band corresponding to ²E_g → ²T_{2g} transition.^[55] In addition, there was a high-intensity band in the region $23\,000\text{--}27\,000\text{ cm}^{-1}$. This band was due to symmetry-forbidden ligand → metal charge transfer transition.^[56] The band above $27\,000\text{ cm}^{-1}$ was assigned as ligand band. Hence distorted octahedral geometry around Cu(II) ion was suggested on the basis of electronic spectra,^[57] which was further confirmed by its magnetic moment value 1.77–1.82 BM, which falls within the range normally observed for octahedral Cu(II) complexes.^[58] Thus the electronic spectral data and magnetic moment data support the octahedral geometry for all complexes.

Thermal Studies of Cu(II) Complexes

Thermal behavior of the complexes was studied by TG and DTG (Fig. 1), while the thermal decomposition data for all complexes

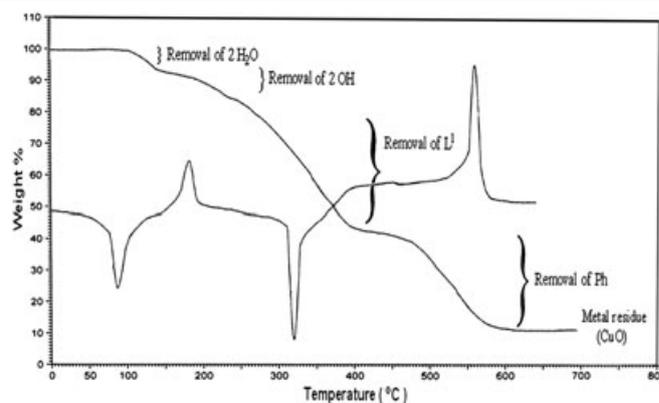


Figure 1. TG and DTG curve of complex $[\text{Cu}(\text{L}^1)(\text{Ph})(\text{OH})_2]\cdot 2\text{H}_2\text{O}$.

are summarized in Table 3. The thermal decomposition occurs in four steps as per supplementary material (S₁₂). According to the mass losses, all the compounds decompose progressively by the following degradation pattern for the complex. Thermal decomposition started by a dehydration process and was accompanied by endothermic effect between 80 and 130°C due to loss of two lattice water molecules in the first step. The observed mass loss was 6.08%, which was nearly equal to the theoretical value 6.45%. The loss of 2 mol lattice water molecules was first order. In the second step, exothermic decomposition between 180 and 230°C corresponds to loss of two hydroxyl molecules. The observed mass loss was 5.45%, which was nearly equal to the theoretical value of 5.75%. The next two steps were endothermic and exothermic, associated with elimination of coordinated ligand as well as 1,10-phenanthroline, respectively. As temperature increases the intermediate complexes $[\text{Cu}(\text{L}^1)(\text{Ph})]$ (230–400°C) and $[\text{Cu}(\text{Ph})]$ (460–600°C) convert to CuO residue of fragments. The observed mass loss for the third and fourth stages was 46.88% and 30.73%, respectively. The final solid product of decomposition was CuO, accompanied by a broad exothermic effect at 600°C.

The first decomposition step was a dehydration process with an endothermic effect on the DTG curve at 90°C, while increasing temperature of $[\text{Cu}(\text{L}^1)(\text{Ph})(\text{OH})_2]$ and $[\text{Cu}(\text{L}^1)(\text{Ph})]$ shows exothermic and endothermic effects at 180°C and 320°C respectively. An exothermic DTG peak at 550°C was associated with elimination of 1,10-phenanthroline. The final residue was predicted as copper oxide.

Kinetic Measurement by Isoconversion Methods

The dynamic scanning method was superior for investigation of the kinetics at the start and end of the reaction. The kinetic parameters can easily be interpreted by a comparison of measurements at different heating rates.^[59] Multiple dynamic DSC experiments of all complexes were carried out at heating rates of 2.5, 5, 10, 15 and 20°C min⁻¹, respectively; second-step decomposition DSC scans of complex **C**¹ at multiple heating rates are given in Fig. 2. An isoconversional method presumes the activation energy and pre-exponential factor are both functions of the degree of heat flow; this can be used to investigate the multi-heating rate scan data.^[60] Similarly, this approach was useful in estimating the order of reaction (*n*). Results obtained from multi-heating rate dynamic scan experiments were examined by Kissinger's^[61,62] and Ozawa's^[63,64] approaches to determine kinetic parameters. Kissinger's approach works on the principle that peak temperature is a function of the heating rate. In the case of all complexes the exothermic peak temperature

Table 3. Thermoanalytical data (TG and DTG) of Cu(II) complexes

Complex	TG range (°C)	DTG _{max} (°C)	Mass loss (% calcd (obs.))	Assignment
[Cu(L ¹)(Ph)(OH) ₂] ₂ H ₂ O	80–130	90	6.45 (6.08)	Loss of 2 lattice water molecules
	180–230	180	5.75 (5.45)	Loss of 2 hydroxyl molecules
	230–400	320	46.88	Removal of L ¹ ligand
	460–600	550	30.73	Removal of 1,10-phenanthroline ligand
			10.19 (10.86)	Leaving CuO residue
[Cu(L ²)(Ph)(OH) ₂] ₃ H ₂ O	70–120	82	9.71 (9.52)	Loss of 3 lattice water molecules
	150–200	160	5.95 (5.76)	Loss of 2 hydroxyl molecules
	210–380	310	42.50	Removal of L ² ligand
	480–650	620	32.20	Removal of 1,10-phenanthroline ligand
			9.64 (10.02)	Leaving CuO residue
[Cu(L ³)(Ph)(OH) ₂] ₂ H ₂ O	80–150	98	3.18 (2.90)	Loss of 1 lattice water molecules
	150–190	157	5.30 (5.08)	Loss of 2 hydroxyl molecules
	210–370	305	50.16	Removal of L ³ ligand
	500–680	600	30.02	Removal of 1,10-phenanthroline ligand
			11.34 (10.84)	Leaving CuO residue
[Cu(L ⁴)(Ph)(OH) ₂] ₃ H ₂ O	80–140	97	8.48 (8.23)	Loss of 3 lattice water molecules
	140–180	165	5.68 (5.48)	Loss of 2 hydroxyl molecules
	250–380	335	45.00	Removal of L ⁴ ligand
	520–660	627	31.10	Removal of 1,10-phenanthroline ligand
			9.74 (10.19)	Leaving CuO residue
[Cu(L ⁵)(Ph)(OH) ₂] ₂ H ₂ O	70–130	90	6.45 (5.98)	Loss of 2 lattice water molecules
	150–210	170	5.75 (5.32)	Loss of 2 hydroxyl molecules
	220–370	310	48.40	Removal of L ⁵ ligand
	480–660	622	30.20	Removal of 1,10-phenanthroline ligand
			9.20 (10.01)	Leaving CuO residue

was shifted to a higher temperature with increase in heating rate. According to Kissinger's approach, the maximum reaction rate $d\alpha/dt$ occurs at T_p , where $d^2\alpha/dt^2 = 0$, and the kinetic equation (1) can be expressed through the following first-order reaction:

$$\ln\left(\frac{\beta}{T_p^2}\right) = \ln\left(\frac{AR}{E_a}\right) - \frac{E_a}{RT_p} \quad (1)$$

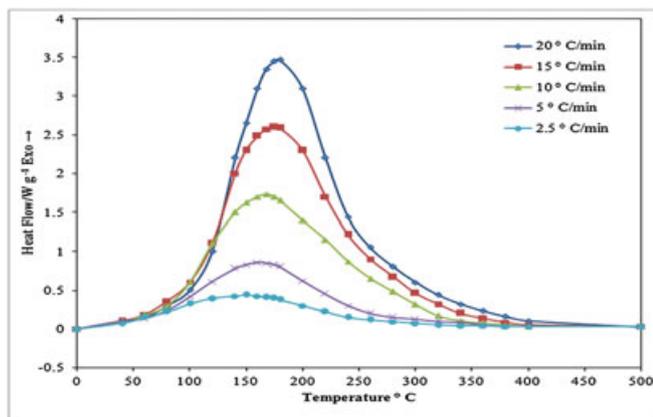
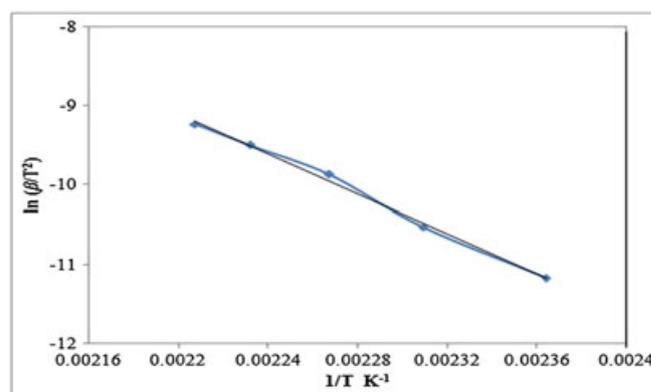
where T_p is the peak temperature of the DSC curve, β represents the heating rate and R is the gas constant. This equation was utilized with a sensible estimation even to an n th order but it was not a considerable order. The reaction progressed under appropriate conditions when thermal equilibrium was constantly maintained. A plot of $\ln(\beta/T_p^2)$ versus $1/T_p$ gives a straight line with a slope

equal to $-E_a/R$, as shown in Fig. 3. The value of activation energy was calculated from slope, while the value of the pre-exponential factor A was found from the intercept.

The isoconversional Flynn–Wall–Ozawa method is an integral method which furnishes a basic correlation between the activation energy, heating rate and isoconversion temperature, as shown in equation (2):

$$\log\beta = \frac{0.4567E_a}{RT_i} + A' \quad (2)$$

where, for each degree of conversion, A' is a constant that can be expressed as in equation (3):

**Figure 2.** Dynamic scan DSC curve of complex C¹.**Figure 3.** Kissinger's approach to determine kinetic parameters for complex C¹.

$$A' = \log\left(\frac{AE_a}{g(\alpha)R}\right) - 2.315 \quad (3)$$

where E_a is the activation energy, A is the pre-exponential factor, R is the gas constant, β is the heating rate, α is the degree of conversion, $g(\alpha)$ is an integral function of conversion and $f(\alpha)$ is the differential function of conversion. For each degree of conversion α , the plot of $\log \beta$ versus $1/T$ obtained at different heating rates should be a straight line which gives a slope proportional to the corresponding activation energy E_a and an intercept corresponding to the pre-exponential factor A shown in Fig. 4.

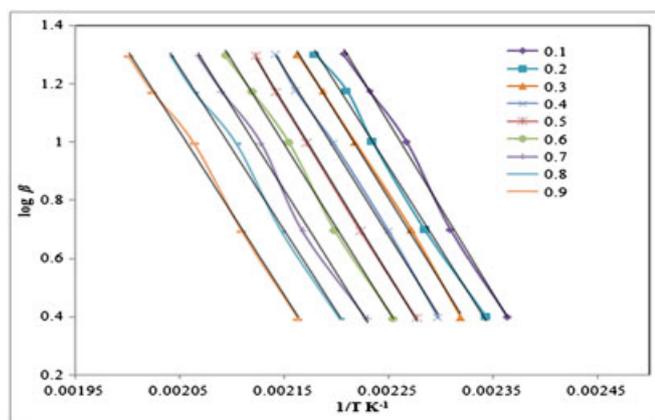


Figure 4. Kinetic parameters of complex C^1 using Ozawa's approach.

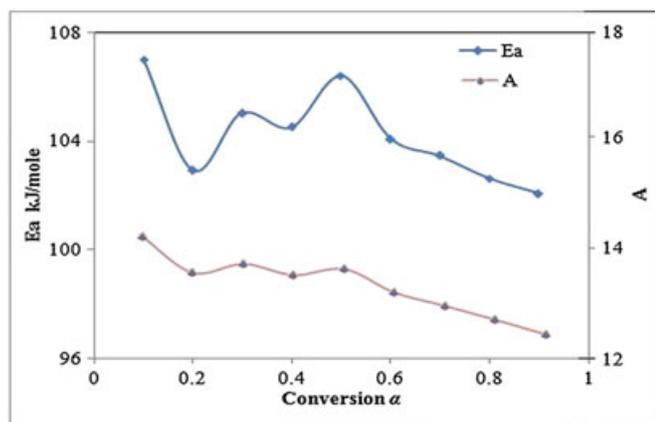


Figure 5. Linear relationship between α , E_a and A for complex C^1 : Ozawa's approach.

The relationship between activation energy and conversion was measured through the whole reaction. The activation energy at the beginning decreased with increasing value of conversion, reaching a minimum value at around 20% conversion. The activation energy then increased up to 60% conversion, prior to decreasing again at high conversions. From plots of both methods, the experimental data agreed reasonably well throughout most of the temperature range but deviated significantly in the high-temperature regions. The factor A showed a similar progression to E_a with conversion as per the plot shown in Fig. 5, which suggested a linear relationship between activation energy and the pre-exponential factor. The analytically calculated results from Kissinger's method are shown in Table 4. Ozawa's method gives an average activation energy value of complexes C^1 and C^5 of 104.24 and 122.02 kJ mol^{-1} , respectively, which is slightly lower than that obtained from Kissinger's method. Kissinger's and Ozawa's methods likewise show an outstanding linear relationship between kinetics parameters based on the experimental data.

FAB Mass Spectra

The FAB mass spectrum of complex $[\text{Cu}(\text{L}^1)(\text{Ph})(\text{OH})_2] \cdot 2\text{H}_2\text{O}$ (Fig. 6) reveals an isotropic peak at m/z 553 for the complex without water of crystallization, whereas several peaks are observed at 519.07, 445.06, 467.04, 344.02, 307.0, 292.09, 289.0, 243.98, 154.0, 137.0 and 136.0 m/z values. Thus the m/z of all the fragments of the complex with relative intensity confirms the stoichiometry of the complex. The mass fragmentation scheme of complex C^1 is given in supplementary material (S_{13}).

Antimicrobial

From the *in vitro* screening results, the ligands (L^2 , L^5) were found significantly active against all the bacteria and results are compatible with 1,10-phenanthroline (Table 5). Ligand L^4 showed moderate activity, while Ligands L^1 and L^3 showed poor activity against all bacteria compared with the standard drugs. All the Cu(II) complexes showed enhanced activity compared to ligands, while Cu(II) complexes (C^5 and C^2) showed an excellent minimum inhibitory concentration (MIC) of 20 and 30 $\mu\text{g ml}^{-1}$, respectively. Furthermore, all the metal complexes showed good antifungal activity then free ligands as well as compares to standard drug Nystatin. The microbial studies suggest that all the complexes possess good antimicrobial activity compared to its free ligands. The results are summarized in Table 5.

Interestingly, compound L^5 and C^5 containing A hydroxyl group at the 4-position on the phenyl ring have been found active against all the employed strains, but addition of the methoxy group at the 3-position of the phenyl ring (compounds

Table 4. Kinetic parameters of Cu(II) complexes by Kissinger's approach

Heating rate ($^{\circ}\text{C min}^{-1}$)	T_p ($^{\circ}\text{C}$) for C^1	Kissinger values for C^1		T_p ($^{\circ}\text{C}$) for C^5	Kissinger values for C^5	
		E_a (kJ mol^{-1})	$\ln A$		E_a (kJ mol^{-1})	$\ln A$
20	180	105.25 \pm 0.5	21.28 \pm 0.1	170	126.62 \pm 0.3	27.95 \pm 0.1
15	175			166		
10	168			160		
5.0	160			153		
2.5	150			146		

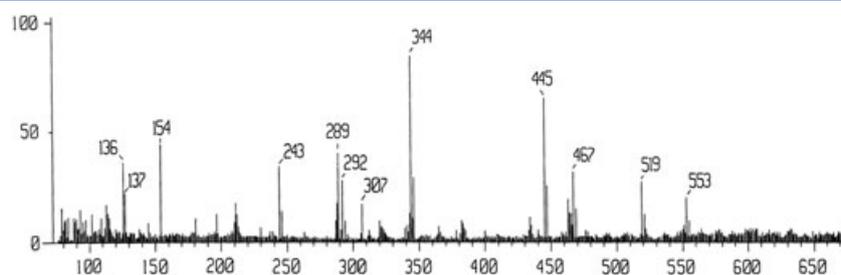


Figure 6. FAB mass spectra of complex $[\text{Cu}(\text{L}^1)(\text{Ph})(\text{OH})_2] \cdot 2\text{H}_2\text{O}$.

Table 5. Antimicrobial activity of compounds

Compound	Minimum inhibitory concentration ($\mu\text{g ml}^{-1}$)						
	Gram-positive		Gram-negative		Fungicidal		
	<i>B. Subtilis</i> (MTCC 441)	<i>S. aureus</i> (MTCC 96)	<i>E. coli</i> (MTCC 443)	<i>S. typhi</i> (MTCC 531)	<i>C. albicans</i> (MTCC 227)	<i>A. niger</i> (MTCC 282)	<i>A. clavatus</i> (MTCC 1323)
L¹	350	450	350	450	150	200	350
L²	250	300	200	250	150	150	200
L³	450	500	450	450	350	300	450
L⁴	300	350	300	350	250	150	250
L⁵	200	250	200	200	150	100	150
C¹	80	100	100	200	100	150	250
C²	30	40	40	70	100	100	150
C³	100	150	150	250	250	200	250
C⁴	50	50	70	90	150	100	200
C⁵	20	30	30	50	100	100	100
1,10-Phenanthroline	50	75	75	100	50	50	75
Streptomycin	<25	<25	<25	<25	—	—	—
Nystatin	—	—	—	—	100	100	100

L⁴ and **C⁴**, and (un)substituted (**C¹**) resulted in a decrease of activity towards all the employed strains. It has been observed that the complex having hydroxyl substitution at the 4-position on the phenyl ring showed better antimicrobial potency than (un)substitution and substitution at other positions. Further, complexes **C⁵** and **C²** with electron-donating groups at the 4-position on the phenyl ring displayed good inhibitory action against most of the employed strains compared with electron-donating groups at the 3-position (**C⁴**), (un)substitutions (**C¹**), and electron-negative group at the 4-position (**C³**) on the phenyl ring.

Compound **C⁵** was found to be the most active against all the microorganism due to the presence of a hydroxyl group in the free ligand. Although the range of functionalities on the aromatic ring of the coumarin core is more significant in the presence of a hydroxyl group on the aromatic ring, antimicrobial activity was shown for the subsequent Cu(II) complexes. Metal complexes of other hydroxylated derivatives of coumarin were earlier shown to have excellent antimicrobial activity. Examples include Cu(II) and Ni(II) complexes of 4-hydroxycoumarins.^[65] In a previous study of the antimicrobial activity of catechols, the position and number of hydroxyl groups on the aromatic ring were responsible for their relative toxicity towards microorganisms, with increasing hydroxylation resulting in enhanced antimicrobial activity.^[66] The mechanism suggested to be responsible for catechol toxicity to microorganisms include enzyme inhibition by the oxidized compounds, possibly through sulphhydryl groups or by non-specific interactions with proteins. The results indicate that

substitution of the hydroxyl groups on the aromatic ring of the coumarin ligand play a vital role in increasing the antimicrobial activity of Cu(II) complexes.

Antituberculosis

The encouraging results from the antibacterial studies prompted us to attempt preliminary screening of complexes for their *in vitro* antituberculosis activity, expressed as MIC. Compounds were assayed for their inhibitory activity toward *M. tuberculosis* H37Rv (MTCC200). The MIC as well as percent inhibition of growth were determined for all compounds, including standard drugs (Table 6). Isoniazid, rifampicin and ethambutol were used as standard drugs for comparison purposes. From reviewing the activity data of ligands (**L**), **L²** and **L⁵** showed good activity, while **L¹**, **L³** and **L⁴** showed moderate activity. In conclusion, all complexes showed clear enhancement in antitubercular activity compared to their free ligands. The most effective compound (**C⁵**) was significantly enhanced at MIC (30 $\mu\text{g ml}^{-1}$), which effected 86% inhibition of growth.

Antioxidant

The antioxidant *in vitro* assays of compounds were evaluated using DPPH radicals and ABTS cationic radicals. The radicals are either oxidized or reduced by scavengers. IC₅₀ values of the

Table 6. Antituberculosis and antioxidant activity of compounds

Compound	Antituberculosis		Antioxidant	
	MIC ($\mu\text{g ml}^{-1}$) <i>M. tuberculosis</i> (MTCC 200)	% Inhibition	DPPH radical	ABTS cationic
L ¹	100	22	162.5	75.0
L ²	60	54	140.5	64.1
L ³	>150	05	150.8	67.3
L ⁴	100	40	135.7	60.2
L ⁵	50	60	157.2	82.9
C ¹	80	52	41.0	9.0
C ²	30	75	35.6	5.6
C ³	>150	20	38.1	6.8
C ⁴	70	64	32.2	4.9
C ⁵	30	86	45.5	12.5
Isoniazid	0.25	99	—	—
Rifampicin	25	95	—	—
Ethambutol	3.125	99	—	—

ligands (L) on DPPH and ABTS cationic radicals are shown in Table 6. From reviewing the antioxidant activity data it is clear that all the complexes possess potent free radical-scavenging activity. The results indicate that synthesized complexes are much stronger free radical scavengers and antioxidant compounds than the ligands.

Further, the results obtained against the two different radicals confirmed that the complexes are more effective in capturing the formation of the ABTS than the DPPH radicals. In addition, the results obtained suggested that the metal complexes possess excellent antioxidant activities compared to standard antioxidants such as butylated hydroxytoluene (BHT) ($18.27 \mu\text{g ml}^{-1}$) and Trolox ($5.23 \mu\text{g ml}^{-1}$).

Conclusion

Thermal studies (TG, DTG and DSC) carried out on the studied mixed ligand Cu(II) complexes shows the presence of lattice water molecules in the respective compounds. This has also suggested an octahedral geometry for the complexes, which was further confirmed using electronic spectroscopy and magnetic moment measurements. IR spectral data suggest tetra-coordinated N_2O_2 bonding of the ligand towards the metal ions, two nitrogen atoms from ene-amino and two oxygen atoms from the 1,3-diketone group of the coumarin. Activation energy and pre-exponential factor obtained using first-order reaction of Kissinger's as well as Ozawa's method are in good agreement.

All the complexes showed enhancement in activity against *M. tuberculosis* due to the coordination of metal ion. Amongst all these compounds C² and C⁵ showed very good activity against *M. tuberculosis* with reference to rifampicin as standard drug. Also, in the case of antibacterial and antifungal activities, metal complexes exhibited higher biocidal activity as compared to the free ligands and were compatible with the standard drug. The observed lower IC_{50} values in antioxidant assays showed that these complexes have the potential antioxidant capacity to eliminate the radicals.

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