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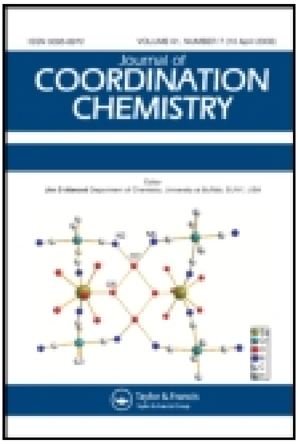

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Synthesis, characterization, DNA cleavage, and in-vitro antimicrobial studies of Co(II), Ni(II), and Cu(II) complexes with Schiff bases of coumarin derivatives

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Synthesis, characterization, DNA cleavage, and *in-vitro* antimicrobial studies of Co(II), Ni(II), and Cu(II) complexes with Schiff bases of coumarin derivatives

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A series of Co(II), Ni(II), and Cu(II) complexes $ML \cdot 3H_2O$ have been synthesized with Schiff bases derived from 3-substituted-4-amino-5-mercapto-1,2,4-triazole and 5-formyl-6-hydroxy coumarin. The complexes are insoluble in common organic solvents but soluble in DMF and DMSO. The measured molar conductance values in DMF indicate that the complexes are non-electrolytes. In view of analytical, spectral (infrared, UV-Vis, ESR, TG, and FAB-mass), and magnetic studies, it has been concluded that all the metal complexes possess octahedral geometry in which ligand is coordinated to metal through azomethine nitrogen, phenolic oxygen, and sulfur *via* deprotonation. The Schiff bases and their complexes have been screened for antibacterial (*Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Salmonella typhi*) and antifungal activities (*Aspergillus niger*, *Aspergillus flavus*, and *Cladosporium*) by the minimum inhibitory concentration method. DNA cleavage is studied by agarose gel electrophoresis.

Keywords: Antimicrobial; DNA; Electrochemical; Formyl coumarin; Transition metal complexes; Spectroscopic studies

1. Introduction

Coumarins comprise a very large class of compounds found throughout the plant kingdom [1, 2]. Coumarin derivatives have diverse applications such as anticoagulants, spasmolytics, anticancer drugs, or as plant-growth-regulating agents [3, 4]. Coumarin nucleus and related derivatives [5, 6] have bioactivities like antibacterial [7], antithrombotic and vasodilatory [8], antimutagenic [9], lipoxygenase and cyclo oxygenase inhibition [10, 11], scavenging of reactive oxygen species and antitumorigenic [12, 13]. Biological activities of some coumarin derivatives are significantly enhanced by binding to metal ions; several reviews summarize advances in various medicinal

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applications of metal complexes of coumarins [14, 15]. The 1,2,4-triazole derivatives have attracted widespread attention due to their diverse biological activities [16, 17] with the metal complexes of Schiff bases derived from 1,2,4-triazole derivatives studied considerably [18–23]. A number of metal complexes with 1,2,4-triazole Schiff bases have been reported from our laboratory [24–27].

Thus, the available literature encouraged us to synthesize and characterize the Co(II), Ni(II), and Cu(II) complexes with newly synthesized Schiff bases derived from 3-substituted-4-amino-5-mercapto-1,2,4-triazole and 5-formyl-6-hydroxy coumarin. The Schiff bases and their metal complexes are screened for their antimicrobial activity and DNA cleavage studies.

2. Experimental

2.1. *Analysis and physical measurements*

Carbon, hydrogen, and nitrogen were estimated using a Elemental Analyzer Carlo Erba EA1108 analyzer. Infrared (IR) spectra of the Schiff bases and their Co(II), Ni(II), and Cu(II) complexes were recorded on a HITACHI-270 IR spectrophotometer. Electronic spectra of the complexes were recorded in HPLC grade DMF and DMSO solvent on a VARIAN CARY 50-BIO UV-spectrophotometer from 200 to 1100 nm. The ^{1}H-NMR spectra of ligands were recorded in $CDCl_3$ on a BRUKER 300 MHz spectrometer at room temperature using TMS as an internal reference. Solutions of 10^{-3} mol L^{-1} were prepared in HPLC grade DMF and DMSO and the experiment was carried out at room temperature. FAB-mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer/data system using argon/xenon (6 KV, 10 Am) as the FAB gas. The accelerating voltage was 10 KV and spectra were recorded at room temperature with *m*-nitrobenzyl alcohol used as the matrix. The mass spectrometer was operated in the +ve ion mode. ESR spectrum was recorded on a Varian-E-4X-band EPR spectrometer with 3000 G at modulation frequency of 100 KHz at room temperature and liquid nitrogen temperature (LNT) using TCNE as "g" marker. Thermogravimetric analyses were measured from room temperature to 1000°C at a heating rate of 10°C min^{-1}. The data were obtained with a T.A. TG/DTG instrument. Molar conductivity measurements were recorded on an ELICO-CM-82 T Conductivity Bridge with a cell having cell constant 0.51 and magnetic moment was carried out by using a Faraday balance.

2.2. *Methods*

All chemicals used were of reagent grade. 6-Hydroxy coumarin [28], thiocarbohydrazide [29], 5-formyl-6-hydroxy coumarin [30, 31], and 3-substituted-4-amino-5-mercapto-1,2,4-triazole [29, 32] have been synthesized according to the published procedure.

2.3. *Synthesis of Schiff bases (I and II)*

The Schiff bases have been synthesized by refluxing hot ethanolic solution (30 mL) of 3-substituted-4-amino-5-mercapto-1,2,4-triazole (0.01 mol) and hot ethanolic solution

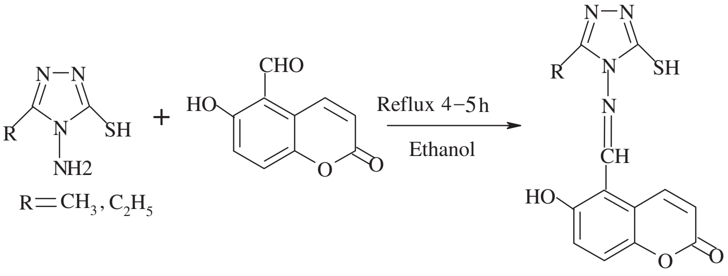

Figure 1. Synthesis of I and II.

(30 mL) of 5-formyl-6-hydroxy coumarin (0.01 mol) for 4–5 h with addition of four to five drops of hydrochloric acid (figure 1). The precipitate formed during reflux was filtered, washed with cold EtOH, and recrystallized from hot EtOH.

2.4. *Synthesis of Co(II), Ni(II), and Cu(II) complexes (1–6)*

An alcoholic solution (45 mL) of Schiff bases (2 mmol) was mixed with an alcoholic solution (5 mL) of 1 mmol of $CoCl_2 \cdot 6H_2O/NiCl_2 \cdot 6H_2O/CuCl_2 \cdot 2H_2O$ and refluxed on a water bath for 2 h. Then, to the reaction mixture 2 mmol of sodium acetate was added and reflux was continued for 3 h. The separated complex was filtered, washed thoroughly with water, ethanol, ether, and finally dried in vacuum over fused $CaCl_2$.

3. Pharmacology

3.1. *DNA cleavage experiments*

3.1.1. Preparation of culture media. DNA cleavage experiments were done according to the method reported [33].

3.1.2. Isolation of DNA. The fresh bacterial culture (1.5 mL) is centrifuged to obtain the pellet which is then dissolved in 0.5 mL of lysis buffer (100 mmol L^{-1} tris pH 8.0, 50 mmol L^{-1} EDTA, 10% SDS). To this 0.5 mL of saturated phenol was added and incubated at 55°C for 10 min, centrifuged at 10,000 rpm for 10 min and to the supernatant, equal volume of chloroform : isoamyl alcohol (24 : 1) and 1/20th volume of 3 mol L^{-1} sodium acetate (pH 4.8) was added. This was again centrifuged at 10,000 rpm for 10 min, and to the supernatant, three volumes of chilled absolute alcohol was added. The precipitated DNA was separated by centrifugation and the pellet was dried and dissolved in TAE buffer (10 mmol L^{-1} tris pH 8.0, 1 mmol L^{-1} EDTA) and stored cold.

3.1.3. Agarose gel electrophoresis. Cleavage products were analyzed by agarose gel electrophoresis [30].

3.1.4. *In-vitro* antibacterial and antifungal assay. The biological activities of synthesized Schiff bases and their complexes have been studied by agar and potato dextrose agar diffusion methods. The antibacterial and antifungal activities were done at 10, 30, 50, and 100 $\mu g\,mL^{-1}$ concentrations in DMF by using four bacteria (*Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Salmonella typhi*) and three fungi (*Aspergillus niger*, *Aspergillus flavus*, and *Cladosporium*) by the MIC method [34]. These bacterial strains were incubated for 24 h at 37°C and fungal strains were incubated for 48 h at 37°C. Standard antibacterial (Gentamycin) and antifungal drugs (Fluconozole) were used for comparison under similar conditions.

4. Results and discussion

The Schiff bases (I & II) form octahedral complexes (**1**–**6**) (table 1) with $CoCl_2 \cdot 6H_2O$/$NiCl_2 \cdot 6H_2O$/$CuCl_2 \cdot 2H_2O$ in ethanol. All the Co(II), Ni(II), and Cu(II) complexes are colored (table 1), stable, and non-hygroscopic. These complexes are insoluble in common organic solvents but soluble in DMF and DMSO. Elemental analyses show that the Co(II), Ni(II), and Cu(II) complexes have 1 : 1 stoichiometry, $ML \cdot 3H_2O$, where "L" stands for a deprotonated ligand (figure 1) and exhibits thiol–thione tautomerism (figure 2). The molar conductance values are too low to account for any dissociation of the complexes in DMSO, indicating the non-electrolytic nature of the complexes in DMSO (table 1).

4.1. *IR spectral studies*

Prominent IR spectral data of the Schiff bases and their Co(II), Ni(II), and Cu(II) complexes are presented in Supplementary table S1. IR spectra of the Schiff bases show characteristic bands due to ν(NH) and ν(SH) at 3176–3143 and 2747–2760 cm^{-1}, respectively [35]. The characteristic high-intensity band at 1610–1602 cm^{-1} is assigned to ν(CH=N) [36] and a band around 1115–1099 cm^{-1} is assigned to ν(C=S) [37]. A high-intensity band at 1284–1259 cm^{-1} and a band at 1709–1715 cm^{-1} are assigned to phenolic ν(C–O) and ν(C=O) [38], respectively.

In comparison with the spectra of the Schiff bases, **1**–**6** exhibited ν(C=N) at 1578–1594 cm^{-1} indicating that the nitrogen of azomethine is coordinated [36, 38, 39]. Deprotonation of the thiol is indicated by the absence of a band at ~2672 cm^{-1} in all the metal complexes, due to ν(S–H), indicating that the metal is coordinated through sulfur. This is further supported by the band at 786–769 cm^{-1} in the metal complexes due to ν(C–S). A medium to high-intensity band at 1320–1333 cm^{-1} due to phenolic ν(C–O) indicates coordination of phenolic oxygen *via* deprotonation. The shift of ν(C–O) in the metal complexes may be due to the expected high mesomeric interaction in the complex that is probably activated by the presence of the metal ion. New bands at 489–473 cm^{-1} in spectra of the complexes are assigned to M–N stretching frequencies [40] and at 379–385 cm^{-1} to ν(M–O). Bands at 348–336 cm^{-1} in spectra of the complexes are assigned to metal–sulfur bonds.

Table 1. Elemental analyses of Schiff bases and their Co(II), Ni(II), and Cu(II) complexes along with molar conductance and magnetic moment data.

Comp. No.	Empirical formula	Color/Yield %	M% Found	M% Calcd	C% Found	C% Calcd	H% Found	H% Calcd	N% Found	N% Calcd	Molar conductance (Ω^{-1} cm^2 mol^{-1})	μ_{eff} (BM)
I	$C_{13}H_{10}N_4O_3S$	74	–	–	51.48	51.65	3.22	3.31	18.42	18.54	–	–
II	$C_{15}H_{14}O_3N_4S$	76	–	–	54.32	54.87	2.65	2.85	17.07	17.07	–	–
1	$Co(C_{13}H_8N_4O_3S)3H_2O$	Brown/71	14.24	14.28	37.72	37.77	3.34	3.38	13.55	13.55	21.8	4.82
2	$Co(C_{15}H_{12}N_4O_3S)3H_2O$	Brown/69	13.41	13.43	41.12	41.00	4.09	4.10	12.70	12.75	17.25	4.65
3	$Ni(C_{13}H_8N_4O_3S)3H_2O$	Yellowish green/68	14.02	14.07	37.82	37.86	3.32	3.39	13.52	13.59	22.88	3.52
4	$Ni((C_{15}H_{12}N_4O_3S)3H_2O$	Yellowish green/69	13.22	13.24	41.13	41.09	4.04	4.10	12.74	12.78	27.64	3.43
5	$Cu(C_{13}H_8N_4O_3S_)3H_2O$	Dark green/66	15.01	15.10	37.44	37.41	3.28	3.35	13.39	13.42	18.4	1.76
6	$Cu(C_{15}H_{12}N_4O_3S)3H_2O$	Dark green/69	14.18	14.22	40.44	40.63	4.01	4.06	12.55	12.64	21.16	1.78

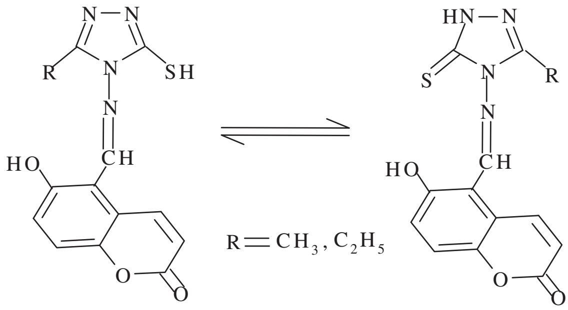

Figure 2. Thiol–thione tautomerism of Schiff bases.

4.2. ^{1}H NMR and ^{13}C NMR spectrum of Schiff bases

In the ^{1}H NMR spectrum of I, the NH is at 13.82 ppm (s, 1H). A signal at 8.48 ppm (s, 1H) and a signal at 10.43 ppm (s, 1H) are assigned to –CH=N and phenolic –OH, respectively. Signals at 7.10–7.88 ppm (m, 4H) and a sharp signal at 3.01 ppm (s, 1H) are due to aromatic protons and SH, respectively (Supplementary table S2).

The ^{13}C NMR spectrum of Schiff base exhibits signals at 118.4, 119.7, 122.2 128.5, and 147.5, 155.4 ppm corresponding to aromatic carbons. The azomethine (–HC=N) carbon shows a peak at 160.5 ppm (Supplementary table S2).

4.3. Electronic spectra and magnetic studies

Co(II) complexes exhibit bands at 8000–10,000 and 18,000–20,000 cm^{-1} corresponding to transitions $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ (ν_1) and $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ (ν_3), respectively. In this study, the brownish Co(II) complexes show absorption bands at 9371–9377 and 18,345–18,367 cm^{-1} corresponding to ν_1 and ν_3, respectively, characteristic of high-spin octahedral Co(II) complexes [41]. However, ν_2 is not observed because of its proximity to the strong ν_3 transition. The ligand field parameters calculated are presented in Supplementary table S3. The lower β values (0.684 and 0.690) indicate considerable covalence in metal–ligand bonding. The magnetic measurement for Co(II) complexes exhibit magnetic moment values of 4.82–4.65 BM which agree with the octahedral range of 4.3–5.2 BM [42].

The greenish Ni(II) complex **3** exhibited three bands at 10,523, 16,463, and 26,678 cm^{-1} which are attributed to the $^3A_{2g} \rightarrow {}^3T_{2g}$ (ν_1), $^3A_{2g} \rightarrow {}^3T_{1g}(F)$ (ν_2), and $^3A_{2g} \rightarrow {}^3T_{1g}$ (P) (ν_3) transitions, respectively, indicating an octahedral geometry around Ni(II) [43]. The value of ν_2/ν_1 is 1.54 and μ_{eff} is 3.13, within the range of 2.8–3.43 BM [44], suggesting octahedral Ni(II). The values of the nephelauxetic parameter, β, indicate low covalent character of the metal–ligand σ bonds. Hence, the ligand field parameters correlate the electronic spectral and magnetic properties.

Electronic spectra of Cu(II) complexes display two prominent bands. A low-intensity broad band at 16,567 cm^{-1} is assigned to $^2E_g \rightarrow {}^2T_{2g}$ transition and another high-intensity band at 25,611 cm^{-1} is due to symmetry forbidden ligand → metal charge transfer. On the basis of electronic spectra, distorted octahedral geometry around Cu(II) ion is suggested [45]. The Cu(II) complexes showed magnetic moments 1.76–1.78 BM, slightly higher than the spin-only value of 1.73 BM expected for one unpaired electron, consistent with an octahedral geometry [46].

4.4. *FAB-mass spectral studies*

Representative FAB-mass spectrum of I is depicted in Supplementary figure S1. The spectrum showed a molecular ion peak at m/z 302 which is equivalent to its molecular weight. Fragment ion peaks at m/z 285 and 111 are due to cleavage of OH and $C_{10}H_6O_3$, respectively. For II the molecular ion peak is observed at m/z 328 which is ascribed to $C_{15}H_{14}O_3N_4S$.

The FAB-mass spectra of Co(II) (**1**), Ni(II) (**3**), and Cu(II) (**5**) complexes of Schiff base I showed molecular ion peaks M^+ at m/z 413, 412, and 417, equivalent of their molecular weight. All the fragments of the species $[MHL]^+$ undergoes demetallation to form the species $[L + H]^+$ fragment ion peak at m/z 302. Representative FAB mass spectrum of **3** is depicted in Supplementary figure S2. In the case of **2**, **4**, and **6** of Schiff base II, the FAB-mass spectra showed molecular ion peaks at m/z 439, 438, and 443, respectively, equivalent to their molecular weights. The complexes undergo demetallation to form $[L + H]^+$ and gave the fragment ion peak at m/z 328.

4.5. *ESR spectra of 5*

The ESR spectra of **5** were recorded in DMSO at LNT and at room temperature (RT). At RT one intense isotropic absorption band in the high field region is observed; however, at LNT four well-resolved peaks in low field region are observed with $g_{\|}$ and $g_{\perp}$ of 2.07 and 2.06, respectively. The trend $g_{\|} > g_{\perp} > 2.0023$ observed for the complex indicates that the unpaired electron is localized in the $d_{x^2-y^2}$ orbital of Cu(II), characteristic for axial symmetry [47]. The g_{av} was 2.01. Thus, the results confirm that Cu(II) complexes possess distorted octahedral geometry.

4.6. *Thermal studies of metal complexes*

The thermal behavior of Co(II), Ni(II), and Cu(II) complexes has been studied as a function of temperature. The thermal behaviors of all the complexes are almost the same and only **1**, **3**, and **5** will be discussed here.

Supplementary figure S3 represents the TG/DTG spectrum of **1**. The thermal decompositions of **1**, **3**, and **5** take place in three steps as indicated by DTG peaks at 197–199, 281–285, and 340–345 corresponding to the mass loss of coordinated water, triazole, and coumarin. Finally, the metal complexes decompose gradually with the formation of metal oxide above 500°C. The nature of proposed chemical change with temperature range and the percentage of metal oxide are presented in Supplementary table S4.

5. Pharmacological results

5.1. In-vitro *antibacterial and antifungal activity*

A number of authors [14, 15, 48, 49] have investigated the biological properties of transition metal complexes of coumarin derivatives. The antibacterial studies inferred that the Schiff bases were highly active against *P. aeruginosa* and *S. typhi*, moderately active against *S. aureus* and *E. coli*. Complexes **1**–**6** show antibacterial activity against all the bacterial strains (Supplementary table S5). For antifungal activity, the Schiff bases and their Co(II), Ni(II), and Cu(II) complexes were highly active. Higher antimicrobial activity of the metal complexes compared to Schiff bases is due to change in structure due to coordination and chelating tends to make metal complexes more powerful and potent bacteriostatic agents, thus inhibiting the growth of the microorganisms [50, 51]. Similar observations were found by Alghool [52], who studied the biological activity of the ligand derived from 7-hydroxy-4-methylcoumarin and diazonium salts, obtained by diazotization of aniline and their Cu(II), Co(II), Ni(II), Cd(II), and Zn(II) complexes. Azza and co-workers [53] studied a series of solvatochromic-copper(II)-mixed ligand complexes of 3-acetylcoumarin, screened for antimicrobial activities against *E. coli*, *Azotobacter*, *A. niger,* and *F. oxysporium*. In both cases metal complexes exhibited higher activities than the respective ligands in line with our studies.

The minimum inhibitory concentration (MIC) of some selected compounds, which showed significant activity against selected bacterial and fungi species, were determined. The results indicated that these compounds were active in inhibiting growth of the tested organisms at $10\,\mu g\,mL^{-1}$ (Supplementary table S6).

5.2. *DNA cleavage activity*

The representative Schiff base I and **1**, **3**, and **5** were studied for their DNA cleavage activity by agarose gel electrophoresis against DNA of *A. niger* (Supplementary figure S4). DNA-binding studies are important for the design and construction of new and more efficient drugs targeted to DNA [54]. The electrophoresis clearly revealed that I and its metal complexes act on DNA as there was molecular weight difference between the control and the treated DNA. The difference was observed in the bands of Lanes 1–4 compared to the control DNA of *A. niger*. The control DNA alone does not show any apparent cleavage whereas I, **1**, **3**, and **5** do. The nature of reactive intermediates involved in DNA cleavage by the complexes is not clear. The results indicate the important role of metal in these DNA cleavage reactions. As the compounds cleave DNA, it can be concluded that they inhibit the growth of the pathogenic organism by cleaving the genome.

6. Conclusion

New Schiff bases are tridentate, coordinating to metal through azomethine nitrogen, phenolic oxygen, and sulfur *via* deprotonation. The Schiff bases and their metal complexes were active against some antibacterial and antifungal species; activity is significantly increased on coordination. The DNA cleavage studies revealed that the complexes show non-specific cleavage of DNA.

All these observations put together lead us to propose the structures shown in Supplementary figure S5.

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