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Synthesis, characterization and antimicrobial activity of Schiff base ligand and metal complexes

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This study describes the synthesis of a new Quinoline Schiff base by condensation of 3-formyl-2-hydroxyquinoline-5-carbonitrile and 1-tosylhydrazine. After preparing Schiff base, metal complexes are formed using Cu(II), Ni(II), and Co(II). FT-IR, ^{1}H NMR, ^{13}C NMR, ESI-MS, UV-Visible, XRD spectroscopy have all been able to demonstrate the full synthesis of Schiff base and associated metal complexes. Preparations of compounds with low conductivity have been found to be non-electrolytic. The ligand has O, N, and O binding sites, according to the FT-IR data. According to the magnetic moment of the compounds, the metal complexes of Cu(II), Ni(II), and Co(II) are paramagnetic. The compounds have been tested for their properties against *Bacillus subtilis*, *Escherichia coli*, and *Candida albicans*. It has been found that metal (II) complexes have potent antibacterial and antifungal action in comparison to ciprofloxacin and ketoconazole.

Keywords: Quinoline Schiff base, Spectral properties, Antimicrobial activities

Schiff's bases are an assortment of physiologically active pharmaceutical compounds with a wide variety of pharmacological characteristics that have attracted the interest of medicinal chemists[1]. In an effort to tackle a wide range of illnesses with minimal side effects, several scientists have produced such molecules[2]. Based on these hypotheses, a potential therapeutic route for creating novel, highly effective, physiologically active Schiff's base derivatives has been uncovered[3-5]. There are a wide variety of uses for quinoline and its derivatives in physiology[6]. Studies of quinoline derivatives with biological uses have been described[7]. However, it also demonstrates excellent antibacterial, proliferative, anti-malarial, anti-convulsant, anti-inflammatory, and other actions[7-12]. In addition to apoptosis, cell cycle arrest, suppression of angiogenesis, and disruption of cell migration, this quinoline derivative has been described as an antimicrobial medication[13-16].

Among the heterocyclic compounds that include oxygen. As well as its potential fungicidal, bactericidal, herbicidal, and insecticidal actions, 3-formyl-2-hydroxyquinoline-5-carbonitrile has been found to be a good chelating agent[17-20]. It may also be used as a building block to create many other heterocyclic ring systems. A review of the existing literature shows that there is little investigation into the antibacterial activity of metal complexes based on quinolines[21]. New quinoline Schiff bases and their metal complexes have been synthesized and tested for biological activity in this study.

Results and Discussion

All the required chemicals and solvents were purchased from commercial source with high purity and were used as it is. The progress of the reaction was checked by thin-layer chromatography (TLC). Suitable solvents were used for the recrystallization of products. KBr pellets were used to acquire FT-IR spectra in the range of 4000-400 cm^{-1} using a Nicolet iS10, thermos Scientific, UV spectrophotometer. An internal standard of tetramethylsilane (TMS) was used to record ^{1}H NMR spectra at 400 MHz. Chemical shifts were reported in ppm with respect to TMS, and spectra were acquired at 100 MHz for ^{13}C NMR. At 25°C, the MKl Johnson Matthey model was used to do a Gouy measurement of the magnetic moment. The effective magnetic moment was determined using the formula l_{effe} = 2.828(x mT))1/2B.M. The ESI MS of the prepared compounds was recorded on a Waters Micromass Q-Tof Micro equipped with electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) sources spanning a mass range of 4000 amu in quadruple and 20,000 amu in ToF. The Cu (II) complex EPR spectrum was acquired using a JES - FA200 ESR spectrometer.

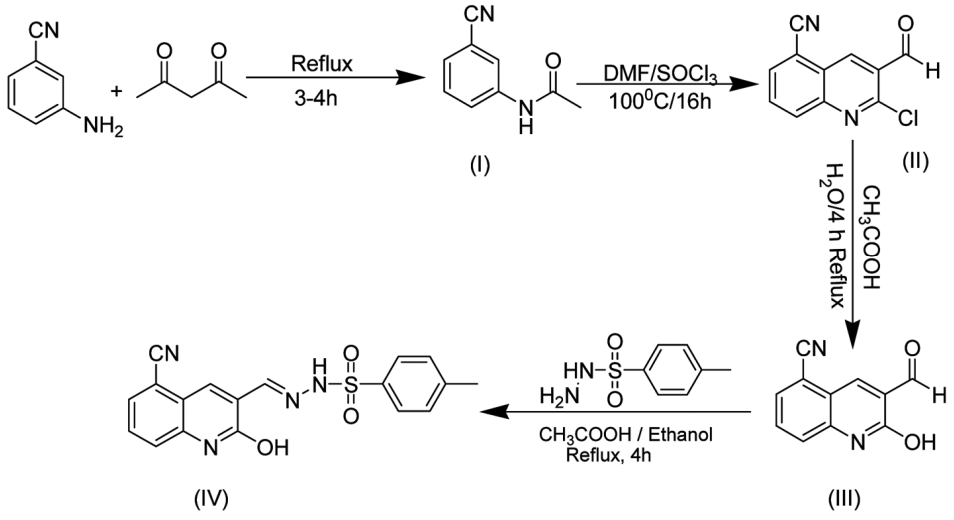
Synthesis of ligand

Synthesis of 2-chloro-3-formylquinoline-5-carbonitrile from 3-aminobenzonitrile was accomplished using the published technique of acylation followed by the Vilsmeier-Haack reaction. The acetic acid was added to the solution of 3-formyl-2-hydroxyquinoline-5-carbonitrile (10 mmol) and water (1 mL). For four hours, the reaction mixture was heated at a steady simmer. The reaction's development was monitored using TLC. After waiting for 4 hours, the reaction material was dumped into very cold water. After collecting the solid, it was filtered and then washed in water. In order to get the pure counterpart, the crude solid was crystallized in ethanol and it lead to second-generation 3-formyl-2-hydroxyquinoline-5-carbonitrile. The acquired intermediates were then incorporated into the completed ligand. In a 15 mL round bottom flask, we combined 1 mmol of 3-formyl-2-hydroxyquinoline-5-carbonitrile, 1 mmol of 1-tosylhydrazine, and 5-10 drops of acetic acid in ethanol. After that, it was refluxed at 70°C for four hours. TLC was used to monitor the reaction in progress using an ethyl acetate:hexane solvent system. With the use of crushed ice and (2×15 ML) of ethyl acetate, the reaction mixture was quenched. The organic extracts underwent a brine solution wash (2×15 mL) and were then dehydrated using anhydrous sodium sulfate. The solvent was subjected to evaporation under decreased pressure in order to extract the matching crude chemicals. The crude chemicals that were acquired were subjected to recrystallization utilizing ethanol as the solvent. The synthetic pathway for ligand production is shown in Scheme 1.

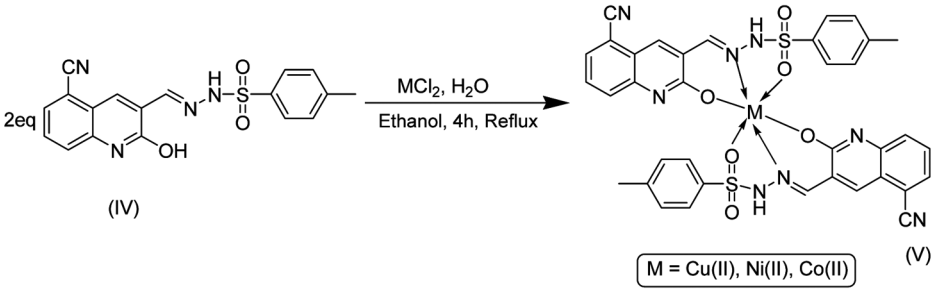
Synthesis of metal complexes

Metal complexes were synthesized by combining a 25 mL hot ethanolic solution of metal salt (0.0015 mol) with a 30 mL hot ethanolic Schiff base solution (0.0030 mol) in a 1:2 ratio for copper (II) chloride ($CuCl_2$), nickel (II) chloride ($NiCl_2$), and cobalt (II) chloride ($CoCl_2$). The reaction mixture was under vigorous stirring for duration of 30 minutes. Subsequently, a small quantity of 5% NaOH solution was introduced into the mixture in order to sustain alkaline conditions, hence maintaining a *p*H value of 8. The reaction mixture underwent reflux for duration of 2 hours, resulting in the formation of a metal complex with a colorful precipitate. The precipitate that was acquired underwent filtration and was afterwards washed with ethanol. It was then subjected to drying in an oven for a duration of 90 minutes at a temperature of 80°C. This process led to the creation of a pure metal complex that corresponds to the initial substance. The reaction and predicted structure of metal complexes are shown in Scheme 2.

The antibacterial activity of test substances against Bacillus subtilis and Escherichia coli was assessed using the agar well diffusion technique. The bacteria were cultivated on agar derived from the Mueller Hinton system. Ciprofloxacin was administered in accordance with the standard practice for the treatment of bacterial infections. The samples were diluted to a concentration of 1 mg/mL in a solution of



Scheme 1 — Synthesis of ligand



Scheme 2 — Synthesis of metal complexes

1 molar (M) dimethylsulfoxide (DMSO). The ligand and [Cu(II)] combination exhibited higher levels of activity, whereas the other compounds had moderate to high levels of activity.

The most effective antifungal drug is ketoconazole. Fungal spores were suspended in sterile PBS at a concentration of 106 cells per milliliter. A sterile swab was immersed into the fungal solution and afterwards rotated on the surface of the agar plate. Prior to their use in the experiment, the plates underwent a 15-minute period of air drying at ambient temperature. Subsequently, the well was filled with a solution containing the test chemical at a concentration ranging from 20 g/mL to 80 g/mL. The plates were incubated at a temperature of 37°C. The assessment of antifungal activity was conducted by quantifying the dimensions of the inhibitory zones after a 48 hr incubation period, measured in millimeters. The ligand and [Cu(II)] combination exhibited higher levels of activity, whereas the other compounds had moderate to high levels of activity (Table 1).

Table 1 — Antimicrobial activities of compounds

Compound	Antimicrobial and antifungal activities of compounds Zone of inhibition (mm)			
	Antibacterial activity		Antifungal activity	
	B. subtilis	E.coli	T. reesei	C. albicans
Ligand	36	34	32	34
Cu(II)	29	33	28	29
Ni(II)	25	26	25	24
Co(II)	28	37	26	39
ciprofloxacin	22	25	-	-
ketoconazole	-	-	23	22

Experimental Section

Synthesis of ligand

1 mmol of 3-formyl-2-hydroxyquinoline-5-carbonitrile, one mmol of 1-tosylhydrazine, and 5-10 drops of acetic acid in ethanol were mixed in a 15 mL round-bottom flask. Then it was refluxed at 70°C for 4 hrs. TLC monitored the reaction in ethyl acetate:hexane. The organic extracts were washed twice with 15 mL of brine and dehydrated with anhydrous sodium sulfate. The solvent was evaporated at reduced pressure to obtain the corresponding crude compounds. Recrystallization in ethanol was performed on the crude compounds.

Yellow Crystals, yeild: 78%, $T_{m.p}$: 167.30-169.32°C, IR (KBr)υ: 3350-3310, 3250–3168 cm^{-1}. ^{1}H NMR spectrum, δ,ppm: 10.68 s (1H, NH), 8.45 m (2H, Ar-H), 8.30 s (1H, CH), 7.99 m (2H, Ar-H), 7.77 m (2H, Ar-H), 7.48 m (2H, Ar-H), 6.78 s (1H, OH), 2.36 s (3H, CH_3); ^{13}C NMR spectrum, δ C,ppm: 163.37, 150.65, 141.68, 138.78, 138.11, 133.67, 132.67, 129.51, 128.58, 125.43, 117.86, 117.63, 117.00, 108.61, 21.13: MS: *m/z* 366.08, Found: 366.27; Anal. Calcd. for $C_{18}H_{14}N_4O_3S$; C 59.01; H 3.85; N 15.29; Found: C 59.05; H 3.88; N 15.32.

The ^{1}H and ^{13}C NMR data of Ligand-1 and complexes 1–3 in DMSO-d_6 is summarized in Table 2. The C=N stretching frequency was seen at 1662 cm^{-1} while the –OH stretching frequency was observed at 3168 cm^{-1} in FT-IR spectra of Schiff base. For metal complexes, however, the C=N stretching frequency peaked at 1654 cm^{-1}, 1622 cm^{-1}, 1647 cm^{-1} for Cu(II), Ni(II), Co(II), respectively. C=N of Schiff base was coordinated with metal ion, as shown by the shift in the FT-IR peak of C = N between Schiff base and its metal complexes. Because the -OH group contributes to bond formation with the central metal ion, the signal found at 3190 cm^{-1} for –OH in Schiff bases disappears entirely in metal complexes. The core metal atom in metal complexes is shown to connect with the Schiff base through O-M and N-M, and several additional peaks were identified in the region of 500-400 cm^{-1} showed in Table 3.

Powder X-ray diffraction (PXRD)

The synthesized compounds were analyzed through powder X-ray diffraction (PXRD) in the 2θ range

Table 2 — ^{1}H and ^{13}C NMR data of Ligand-1 and complexes 1–3 in d_6-DMSO.

	Chemical shift δ (ppm)				
	^{1}H NMR			^{13}C NMR	
Compounds	Aromatic	-OH	-NH-	Quinoline	Aromatic
Ligand	7.48–8.45(m)	6.78	10.68	117.63	117.63-163.37
Cu(II)	7.43–8.24(m)	--	10.62	125.02	122.92–162.42
Ni(II)	7.37–8.35(m)	--	10.63	121.09	126.42–166.52
Co(II)	7.26–8.45(m)	--	10.60	126.09	114.30–163.72

Table 3 — FT-IR stretching frequency of ligand and its metal complexes in cm^{-1}

Compounds	$\nu_{C=N}$	ν_{N-M}	$\nu_{O-M\ (OH)}$	$\nu_{O-M\ (S=O)}$
Ligand	1662	--	--	--
Cu(II)	1654	467	511	435
Ni(II)	1622	466	512	434
Co(II)	1647	463	517	440

Table 4 — XRD spectra of ligand and its metal complexes

Compounds	lattice constants	space group
Ligand	a=14.12600, b=4.98500, and c = 17.55300 Å	P1 2/c 1 (12)
Cu(II)	a =14.45200, b = 18.52600, and c = 12.52300 Å	C1 2 /c 1 (15)
Ni(II)	a = 28.09100, b = 7.98300, and c = 20.15200 Å	C1 2 / c 1 (15)
Co(II)	a = 7.45150, b = 13.97600, and c = 18.92500 Å	P 1 21/c 1 (13)

0-80 at a wavelength of 1.53060 Å and the XRD data is given in Table 4. The ligand and its complexes exhibit a polycrystalline structure where a ≠ b ≠ c and a = b = 90 ≠ λ [22]. The ligand has an important unit cell with lattice constants of a=14.12600, b=4.98500, and c = 17.55300 Å and space group of P1 2/c 1 (12). The space group of Cu(II) complex is C1 2 /c 1 (15), and its unit cell characteristics are a = 14.45200, b = 18.52600, and c = 12.52300 Å. The resulting Ni(II) complex unit cell has the lattice parameters (a, b, c) of C1 2 / c 1 (15), with values of a = 28.0900, b = 7.98300, and c = 20.15200 Å. The lattice parameters of the CO(II) complex are P 1 21/c 1 (13), with a = 7.45150, b = 13.97600, and c = 18.92500 Å.

Electronic spectra

Schiff base electronic spectrum was obtained in 10^{-3}M DMSO and the results are given in Table 5. The Schiff base heterocyclic moiety and azomethine group are responsible for the observed transition bands at 317 and 376 nm for the π→π* and n→π* transitions, and for Cu(II) π→π* and n→π* bands at 324.5 and 389.5, n→π*and π→π*, π→π* and n→π* transition bands were found at 320.5 and 380 nm and at 329.5 and 386.5 nm, for Ni(II), and Co(II) metal complexes, respectively. Coordination of a Schiff base with a central metal ion caused a shift in the transition band to longer wavelengths in metal complexes. As their strength was amplified, these

Table 5 — Ligands and metals electronic spectra and magnetic moments

Compound	λ max n.m	μ eff /B.M	Assignment
Ligand	317	-	π→π*
	376		n→π*
Cu(II)	324.5	1.73	π→π*
	389.5		n→π*
Ni(II)	320.5	3.25	n→π*
	380.5		π→π*
Co(II)	329.5	4.85	π→π*
	386.5		n→π*

bands changed to larger wave lengths in the metal complexes. This change might result from a metal ion accepting a lone pair of electrons from a nitrogen atom in a Schiff base combination containing azomethine. The metal complexes Cu (II), Ni (II), and Co (II) were all found to be paramagnetic when their magnetic moment susceptibility was measured at ambient temperature. For the Cu (II) complex, a magnetic moment of 1.73, 3.25, 4.85 B. M. was measured. And for Ni(II) the first decomposition starts at 170 and last decomposition at 800, for Cu(II) and Co(II) the last decomposition at 1000 and 800.

Element analysis was used to determine the precise elemental structure of the ligand and its metal complexes. Complete formation of compounds is indicated by a perfect match between analytical data for composing carbon, nitrogen, hydrogen,

Table 6 — Melting points, elemental analytical data (%) and m/z value of Ligand and complexes 1–3

Compounds	Physical Appearance	Melting Point(^{0}C)	Elemental (%)				(M)metal	m/z
			C	H	N	S		
Ligand	Yellow	167-169	59.01 (59.05)	3.85 (3.88)	15.29 (15.32)	8.75 (8.76)	-	366.84
Cu(II)	Green	276–278	54.43 (54.45)	3.30 (3.32)	14.11 (14.13)	8.07 (8.10)	8.00 (8.12)	793.15
Ni(II)	Green	>300	54.77 (54.78)	3.22 (3.25)	14.19 (14.21)	8.12 (8.15)	7.43 (7.45)	788.53
Co(II)	Brown	>300	54.75 (54.82)	3.32 (3.35)	14.19 (14.22)	8.12 (8.15)	14.19 (14.21)	789.27

and sulphur in ligand and metal complexes and the actual composition of ligand and metal complexes. Table 6 displays the findings in tabular form.

Conclusion

The physical and analytical properties of newly developed metal complexes of a Schiff base are studied, and the findings accord well with those of synthesized molecules. Cu(II), Co(II) and Ni(II) complexes supported by spectroscopic, ^{1}H NMR, ^{13}C NMR, FT-IR, Mass and magnetic moment and electronic data. In *in vitro* antimicrobial assays, all complexes demonstrated much greater activity than the ligand alone. The Ligand, Cu(II), Co(II) complex showed the highest activity against both E. coli, B. subtilis, T. reesei and C. albicans with a MIC value of 20-80 g mL^{-1}. In this context, we highlight our efforts to identify more substituted analogues exhibiting excellent biological activity.

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Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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