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Co(II), Ni(II), and Cu(II) complexes with heterocyclic ligand and their biological applications

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In this work are described methods for generating and characterizing mononuclear, heterocyclic ligated Co(II), Ni(II), and Cu(II) and their complexes. The heterocyclic derivative Schiff base (E)-2-(4-bromobenzylideneamino)butanoic acid is produced by reacting 4-bromobenzaldehyde with 2-aminobutanoic acid. Experimental evidence has shown that the Schiff base forms four coordinated mononuclear complexes with the aforementioned metal ions at a 1:2 (metal:ligand) stoichiometry. FT-IR, UV-Vis, ^{1}H and ^{13}C NMR, and mass spectrometry are used to examine the structural modifications of the complexes. Additionally, the Schiff base and its complexes are evaluated for their antibacterial properties, and the findings are explained in detail. Antibacterial and antifungal activity of the metal (II) complexes have been shown to be very high and compared with ciprofloxacin andfluconazole.

Keywords: Analytical data, Schiff base, Antimicrobial activities

Schiff base complexes have become more relevant due to the expanding field of bioinorganic chemistry, since it is well known that many Schiff base complexes may serve as models for physiologically significant species[1]. The Schiff base complexes are studied largely for their potential medical applications and several have been shown to be useful enough to be manufactured into drugs[2]. Medicinal molecules with metal ions in their structural backbone are getting a lot of interest right now[3]. The physiological and catalytic processes of amino acid metal complexes are crucial to the functioning of living systems[4].

The main disadvantages of different ligand systems are their toxicity, air sensitivity, handling issues, and ofcourse high prices[5-8]. Since amino acid Schiff base systems may function as a catalyst in biological and other systems, it may be possible to construct some fascinating amino-acid Schiff base metal complexes and examine their catalytic characteristics[9,10]. Furthermore, the amine and carboxylate moieties in amino acid based systems may form stable chelate complexes with different metal ions[11]. Condensation reactions with aldehydes are often used to alter amino acid characteristics[12]. The heterocyclic group that contains aldehydes has received relatively little attention, despite the fact that modifying and increasing their catalytic characteristics is of interest[13,14].

The creation of novel medicinal drugs relies heavily on indole[15]. Because the presence of hetero atoms can significantly alter the chemical, physical, photo-optical, catalytic, or biological activities of this class of compounds, indole derivatives continue to attract a great deal of attention in coordination and organometallic chemistry[16]. In this study, a heterocyclic Schiff base ligand was produced by reacting 4-bromobenzaldehyde with 2-aminobutanoic acid, and its Co(II), Ni(II), and Cu(II) complexes were also prepared and described structurally[17].

Results and Discussions

Elemental analysis CHN was done using Elementar Vario EL III analyzer and the metal content in the complexes was determined using a thermoelectron IRIS INTREPID II XS PDUO ICP- AES instrument. The KBr pellets used to record the FT-IR spectra were analyzed using a Thermo Nicolet Avatar370 spectrophotometer. Absorption spectra in the UV-Vis range were captured using a Varian Cray 500 spectrometer. The Bruker-Avance III spectrometer was used to acquire ^{1}H NMR spectra with TMS serving as the internal standard. The compound mass spectra were acquired by utilizing acetonitrile and MeOH in a Thermo Fischer Scientific Exactive PDA mass spectrometer. Using a JES-FA200 ESR spectrometer, the solid-state ESR spectra of the Cu(II) complex was obtained at liquid nitrogen temperature (LNT). Using a Brukar D8 advanced spectro photometer, powder XRD patterns of the compounds are acquired. Simultaneous Thermal Analyzer TG-DTA air TGA recordings were taken throughout a temperature range of 100-800°C.

Synthesis of (E)-2-(4-bromobenzylideneamino) butanoic acid

A solution of 2-aminobutanoic acid (1.0312 g, 10 mmol) in ethanol (10 mL) was gradually added, while stirring continuously, to an alcoholic solution (20 mL) containing KOH (0.5610 g, 10 mmol). After 30 minutes of magnetic stirring, the solution was filtered. The filtrate was added dropwise to a solution of 4-bromobenzaldehyde (1.4516 g, 10 mmol) in EtOH (20 mL), which was then refluxed for 5 hours while being constantly stirred. To take out the potassium ions from the aforementioned reaction mixture, two drops of concentrated HCl were added. After that, we took half of the solution and stored it at RT for a week. The yellow crystals were produced by a recrystallization process using MeOH. Scheme 1a displays the synthetic procedure for the Schiff base.

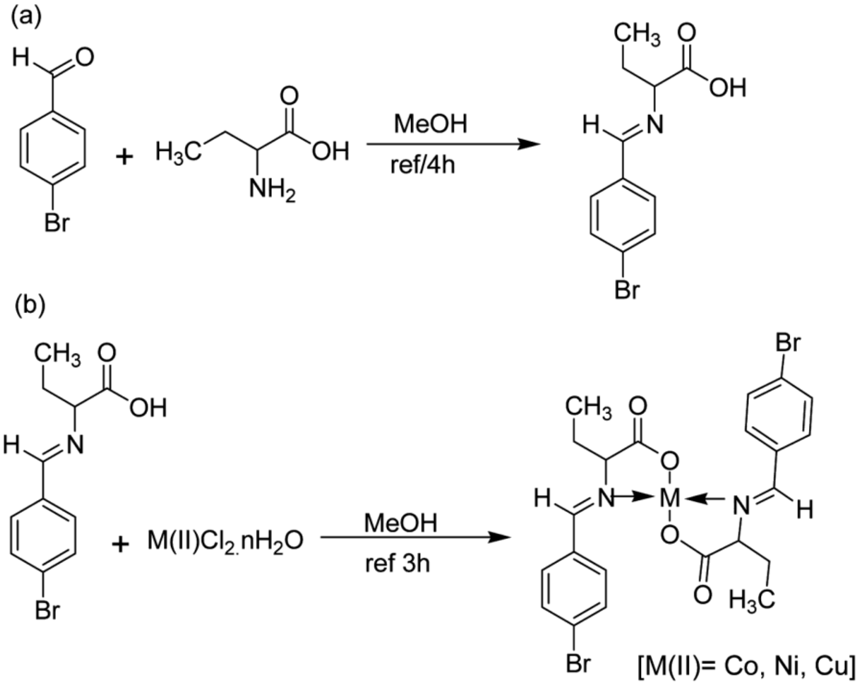
Synthesis of Metal complex

To a mixture of (E)-2-(4-bromobenzylideneamino)butanoic acid (10 mmol) in MeOH (20 mL), 5 mmol each of cobalt chloride, nickel chloride, and copper chloride, dissolved in EtOH (15 mL), was added slowly while magnetically stirring 4 hours, the aforesaid solution was agitated while in a reflux condition. The melting point and purity of the resulting product were determined after it had been filtered, washed many times with EtOH, and then dried in a vacuum over anhydrous $CaCl_2$. Scheme 1b shows the synthesis pathway to metal complexes.

Anti Microbiological studies

Disk diffusion technique with nutrient agar medium was used to test the antibacterial property of the prepared compounds against *Bacillus subtilis* (*B. subtilis*), *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*). *Aspergillus niger* (*A. niger*) and *Candida albicans* (*C. albicans*) were used in a test of the compounds antifungal properties on Potato dextrose agar medium.

The test microorganism is introduced at a constant concentration onto the agar plates. The necessary concentration of the test substance is then deposited on the agar surface in the form of filter paper discs (approx. 6 mm in diameter). The Petri dishes are kept in an incubator. Measurements of the diameters of the inhibition growth zones were made in millimeters (mm), and the minimum inhibitory concentration (MIC) was calculated and compared with the standards, Ciprofloxacin and Fluconazole.



Scheme 1 — The synthesis of (a) Schiff bases and (b) metal complexes

Most of the complexes have very good activity against the gram-negative bacteria *E. coli*, and this suggests that they may have a future as antitumor agents, as gram-negative bacteria are used as quantitative microbiological methods for testing beneficial and important drugs in both clinical and experimental tumor chemotherapy.

The metal complex [Cu(II)] has the highest antimicrobial efficacy, against two species, it is more effective than the standard of excellence medication ciprofloxacin and is with the effectiveness of fluconazole. This is because the chelation effect could interfere with the function of metal-dependent proteins, which in turn disturbs the equilibrium of microbial cells and ultimately prevents them from receiving the nutrients they need to grow and multiply (Table 1).

Experimental Section

Characterization of Schiff base ligand

FT-IR spectra

The IR spectra of the free Schiff base ligand validates the synthesis of the hypothesized SB ligand by showing that stretching frequency bands identified at 1632 and 1422 cm^{-1} might be attributed to carboxyl asymmetric $\nu_{as}(COO^{-})$ and symmetric $\nu_{sy}(COO^{-})$ vibrations. The azomethine group is distinguished by the formation of a new, strong stretching frequency band around 1640 cm^{-1}. Spectra of C-Br and OH exhibited stretching vibrations at 690 and 3282 cm^{-1}, respectively (Table 2).

Mass spectra

The molecular ion peak at *m/z* 269.01 in the mass spectrum of (E)-2-(4-bromobenzylideneamino) butanoic acid corresponds with its molecular formula, [$C_{11}H_{12}BrNO_2$]. The [M+1] peak at *m/z* 269 is also seen in the (E)-2-(4-bromobenzylideneamino) butanoic acid mass spectrum. The fragment $[C_8H_8BrN]^+$ has a base peak at *m/z* 196.98. The fragmentation of the SB ligand molecule *via* the breaking of distinct bonds within the molecule by sequential degradation is responsible for the appearance of the various peaks in the mass spectrum of (E)-2-(4-bromobenzylideneamino)butanoic acid.

Absorption spectra

Absorption or UV-Vis spectrum of Schiff base (E)-2-(4-bromobenzylideneamino)butanoic is available in Supplementary Information. The C=N chromophore's π-π* transition is responsible for the strong absorption band in the spectrum seen at 325 nm.

^{1}H and ^{13}C NMR spectra of ligand

In the spectrum of free Schiff base ligand, the characteristic signal for aldehydic proton at δ 11.5 ppm was observed. –OH proton was observed at δ 6.40 ppm. The C=N carbon was observed in ^{13}C at 161.59 ppm. Which confirms the formation of Schiff base ligand.

Thermal studies

The Schiff base ligand is stable up to 260°C, as shown by its thermogram, and its degradation is an a single-step process. The endothermic peak between 60 and 100°C in the thermograms were not recorded for the sample it provides compelling evidence for the absence of uncoordinated water molecules.

Characterization of complexes

All of the metal complexes are soluble in organic solvents including MeOH, DMF, and DMSO, and

Table 1 — Antimicrobial activities of ligand and metal complexes

Ligand/Complex	Antibacterial			Antifungal	
	B. subtilis	*S. aureus*	*E. coli*	*A. niger*	*C. albicans*
[$C_{11}H_{12}BrNO_2$]	30	25	36	30	29
[$C_{22}H_{22}Br_2CoN_2O_4$]	32	31	40	30	28
[$C_{22}H_{22}Br_2NiN_2O_4$]	31	29	37	28	26
[$C_{22}H_{22}Br_2CuN_2O_4$]	30	32	35	33	30
Ciprofloxacin	15	20	26	–	–
Fluconazole	–	–	–	25	20

Table 2 — IR spectral bands of ligand and its complexes

Ligand/Complex	IR bands, wavenumber (cm^{-1})				
	ν(C=N)	$\nu_{asy}(COO^{-})$	$\nu_{sy}(COO^{-})$	ν(M-O)	ν(M-N)
[$C_{11}H_{12}BrNO_2$]	1640	1632	1422	–	–
[$C_{22}H_{22}Br_2CoN_2O_4$]	1625	1640	1466	519	420
[$C_{22}H_{22}Br_2NiN_2O_4$]	1621	1620	1418	542	448
[$C_{22}H_{22}Br_2CuN_2O_4$]	1631	1620	1422	560	462

they are stable at RT. All of the complexes had melting points between 315 and 320°C and a yield of 78 to 72%. Table 3 displays the analytical results for the complexes [Co(II)], [Ni-(II)], [Cu-(II)]. In the case of Schiff base ligand and its complexes, the molecular formula provided is consistent with analytical evidence. In addition, the stoichiometry of all the metal complexes is ML2, or 1:2 metal to ligand.

FT-IR spectra

Infrared (IR) spectra of [Co(II)], [Ni-(II)], [Cu-(II)] are shown. The 1640 cm^{-1} band in the infrared spectra of free Schiff base ligand may be ascribed to vibrations in the azomethine group. The band changed from 1625, 1621, and 1631 cm^{-1}, respectively, indicating that nitrogen from azomethine coordinated with the metal ion. The finding of a new band at 430-450 cm^{-1} that may be attributed to (M-N) stretching frequencies provides more support for this theory. In the spectra of complexes, the band owing to O-H stretching vanished, and lower shifting was detected for the carboxyl asymmetric $\nu_{asy}(COO^{-})$ and symmetric $\nu_{sy}(COO^{-})$ stretching bands at 1632-1640 and 1422-1446 cm^{-1}, respectively. The appearance of a weak band between 519 and 570 cm^{-1} has been attributed to the v(M-O) vibration. This analysis suggests that ligand acts as a bidentate Schiff base ligand, with the oxygen atom of the carboxyl group of ligand and the nitrogen atoms of the imine groups of the azomethine linkage coordinating the metal ion. Table 3 displays the IR spectra of ligand and its complexes, including several very useful bands.

^{1}H and ^{13}C NMR spectra of metal complexes

After coordination, the azomethine proton showed a downfield shift, and the chemical shift value improved to 11.5 ppm. The observed increase in the δ value provides more evidence of the coordination between the azomethine nitrogen and the metal. The observed increase in the δ value provides more evidence of the coordination between the azomethine nitrogen and the metal. The spectra of exhibited multiplet signals within the region of 7.38 to 7.59 ppm, which may be ascribed to the presence of aryl CH protons. The –OH proton which is exhibited at range 6.40 ppm in the ligand which was absent in the metal complex. This signal disappears in the spectrum of the [Zn-(II)] complex, indicating that the COOH moiety plays a role in chelation after deprotonation.Therefore, the IR spectral data provides the mode of chelation, and the ^{1}H NMR spectral data further supports this mode. The ^{13}C spectra of aryl carbons which were shown at δ 128-134 ppm.

Table 3 — Analytical data of metal complexes

Complexes	λ max (nm)	Transitions	Geometry
$[C_{22}H_{22}Br_2CoN_2O_4]$	550	$^4A_2\ (F)\rightarrow{}^4T_1(F)$	Tetrahedral
$[C_{22}H_{22}Br_2NiN_2O_4]$	620	$^3T_1\rightarrow{}^3T_1(P)$	Tetrahedral
$[C_{22}H_{22}Br_2CuN_2O_4]$	630	$^2B_{1g}\rightarrow{}^2A_{1g}$	Square planar

Mass spectra

The molecular ion peak at *m/z* 594.93, 593.93, and 598.92 in the mass spectra of the [Co-(II)], [Ni-(II)], and [Cu-(II)] complexes, respectively is compatible with the hypothesized molecular formula and verifies a 1:2 metal to ligand ratio. The *m/z* 186 peak detected in the cobalt complex may be attributed to the fragment $[C_{12}H_{14}N_2]$ produced after the breakage of M-O and M-N bonds and the elimination of $[CO_2\bullet]$ from the initial fragment $[C_{11}H_{12}BrNO_2]$. An additional [M+1] peak, at *m/z* 595.93, was seen in the mass spectrum. The fragment $[C_8H_8BrN]$ may be ascribed to the base peak at *m/z* 196.98 in the LC-MS spectra obtained for the [Ni-(II)] complex.

Absorption spectra

The geometry of complexes was assigned using the absorption spectral measurements based on the locations and numbers of d-d transition peaks. An absorption band at 550 nm, caused by the $^4A_2(F)\rightarrow{}^4T_1(F)$ transition, was seen in the visible part of the electronic spectrum of the [Co-(II)] complex. Because of this number, tetrahedral construction of the complex is preferable. At 620 nm, nickel complex has d-d transition bands in its electronic spectrum. Assignable to a $^3T_1\rightarrow{}^3T_1(P)$ broad absorption band. Broadband at 630 nm was detected for the [Cu-(II)] complex, which has a square planar shape as indicated by the assignment to the $^2B_{1g}\rightarrow{}^2A_{1g}$ transition. Table 3 displays the important electronic spectrum data assignments of metal complexes.

Thermal studies

At temperatures between 260 and 290°C, the thermogram of metal complexes showed no indication of weight loss, indicating stability and the lack of water molecules in the complexes. Thermo gravimetric analysis of the complexes indicated that melting and partial breakdown of (E)-2-(4-bromobenzylideneamino)butanoic acid may account for the 22.5-29% weight loss seen at temperatures between 260 and 360°C. At the second stage of disintegration, between 370 and 560°C, the resulting complexes lost 30 to 40 percent of their original mass. Mass loss of 7.2% to 7.5% is considered the bare minimum after total disintegration. metal oxide residue in the complexes, which became visible after heating to 760°C. At temperatures below 760–800°C, the TGA curve of the complex expands, indicating that the completely organic portion of the chelate decomposes, leaving just the metallic oxide. TG curves of [Co-(II)], [Ni-(II)] and [Cu-(II)]are shown.

X-ray diffraction studies

In X-ray diffraction examination, the crystalline structure of the [Co-(II)], [Ni-(II)] and [Cu-(II)] complexes was clearly shown. The structure and particle size of the produced ligand complexes may be determined with the use of powder X-ray diffraction analysis. The cubic crystal structure for these compounds is confirmed by X-ray diffraction study of the its cobalt(II)complex. Ligand has unit cell dimensions a=b=c=17.69, $\alpha=\beta=\gamma=90$ and [Co(II)] has unit cell dimensions a=b=c=17.19, $\alpha=\beta=\gamma=90$, [Ni(II)] has unit cell dimensions a=b=c=17.39, $\alpha=\beta=\gamma=90$, and [Cu(II)] has unit cell dimensions a=b=c=18.29, $\alpha=\beta=\gamma=90$. Diffractograms showed that complex formation occurred at $2\theta = 14.56°$ and 26.04° for [Cu(II)], 14.17 and 16.35 for [Co(II)], 14.00 and 24.54 for [Ni(II)]. The XRD pattern reveals that the compounds are crystalline.

Conclusion

Spectroscopic research, along with thermal and magnetic moment data, favours tetrahedral geometries for Co(II), Ni(II) complexes, whereas Cu(II) complexes are found in a square planar environment. All of the complexes were shown to have much higher activity than the ligand *in vitro* antimicrobial tests. The complex [Co-(II)] had the greatest activity among the tested complexes, with a MIC value of 16 µg $\mathrm{mL^{-1}}$ against both *E. coli* and *B. subtilis*. Here, we emphasize our attempts to discover further substituted analogues with remarkable biological activity.

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Conflict of Interest

The authors have confirmed that there is no conflict of interest.

Supplementary Information

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

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