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Synthesis And Characterization Of (2E,3Z)-3-(((E)-2,3-Dichlorobenzylidene)Hydrazono)Butan-2-One Oxime And Its Transition Metal Complexes: Evaluation Of Antibacterial And Antifungal Activities

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Abstract- A novel Schiff base ligand, (2E,3Z)-3-(((E)-2,3-dichlorobenzylidene)hydrazono)butan-2-one oxime, was synthesized and characterized, along with its coordination complexes with Mn(II), Fe(II), Cu(II), Zn(II), Cd(II), Hg(II), Ni(II), and Pd(II) ions. The ligand and its metal complexes were characterized using various spectroscopic techniques, including FTIR, NMR, UV-Vis, and elemental analysis, to confirm their structural integrity and coordination behavior. The antibacterial and antifungal activities of the ligand and its complexes were evaluated against a range of pathogenic bacterial strains (e.g., Escherichia coli, Staphylococcus aureus) and fungal strains (e.g., Candida albicans, Aspergillus niger). The metal complexes exhibited enhanced antimicrobial activity compared to the free ligand, with the Cu(II) and Ni(II) complexes showing particularly potent inhibitory effects. The structure-activity relationship suggests that the coordination of metal ions enhances the lipophilicity and interaction with microbial cell membranes, thereby improving bioactivity. These findings indicate potential applications of these complexes in developing new antimicrobial agents.

Keywords- Schiff base, (2E,3Z)-3-(((E)-2,3-dichlorobenzylidene)hydrazono)butan-2-one oxime, transition metal complexes, antibacterial activity.

I. INTRODUCTION

Schiff bases, characterized by the azomethine group (-C=N-), are versatile ligands widely studied for their ability to form stable coordination complexes with transition metals, exhibiting a range of biological activities, including antibacterial and antifungal properties [1, 2]. These compounds have garnered significant attention in medicinal chemistry due to their potential as antimicrobial agents, attributed to their ability to interact with biological targets through chelation and enhanced lipophilicity [3, 4]. The incorporation of metal ions into Schiff base frameworks often enhances their bioactivity by facilitating interactions with microbial cell membranes or enzymes [5, 6]. In recent years, oxime-based Schiff bases have emerged as promising candidates due to their unique structural features, which allow for diverse coordination modes and biological applications [7, 8].

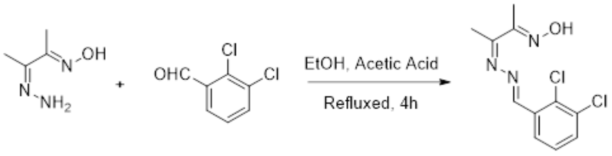
In this study, we report the synthesis and characterization of a novel Schiff base ligand, (2E,3Z)-3-(((E)-2,3-dichlorobenzylidene)hydrazono)butan-2-one oxime, and its coordination complexes with Mn(II), Fe(II), Cu(II), Zn(II), Cd(II), Hg(II), Ni(II), and Pd(II) ions. The ligand and its complexes were characterized using various spectroscopic techniques, including Fourier Transform Infrared (FTIR), Nuclear Magnetic Resonance (NMR), Ultraviolet-Visible (UV-Vis) spectroscopy, and elemental analysis, to elucidate their structural and coordination properties [9, 10]. The antibacterial and antifungal activities of the ligand and its complexes were evaluated against a panel of pathogenic microorganisms, including Escherichia coli, Staphylococcus aureus, Candida albicans, and Aspergillus niger. Previous studies have demonstrated that metal complexes of Schiff bases often exhibit superior antimicrobial activity compared to their free ligands, attributed to the chelation effect and increased lipophilicity [11, 12]. The presence of the dichlorobenzylidene moiety in the ligand is expected to enhance its bioactivity by increasing its electron-withdrawing effects and steric interactions [13]. This work aims to explore the structure-activity relationships of these complexes and their potential as antimicrobial agents, contributing to the development of novel therapeutic candidates [14, 15].

II. EXPERIMENTAL SECTION

Materials and Methods

All chemicals used were of analytical grade and purchased from Sigma-Aldrich or Merck. Solvents were purified and dried according to standard procedures. The metal salts (MnCl2•4H2O, FeSO4•7H2O, CuCl2•2H2O, ZnCl2, CdCl2, HgCl2, NiCl2•6H2O, and PdCl2) were used as received. FTIR spectra were recorded on a PerkinElmer Spectrum 100 spectrometer in the range of 400–4000 cm-1 using KBr pellets. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker Avance 400 MHz spectrometer in DMSO-d_6. UV-Vis spectra were recorded on a Shimadzu UV-1800 spectrophotometer in methanol. Elemental analyses (C, H, N) were performed using a Thermo Scientific Flash 2000 analyzer. Antibacterial and antifungal activities were assessed using the agar well diffusion method.

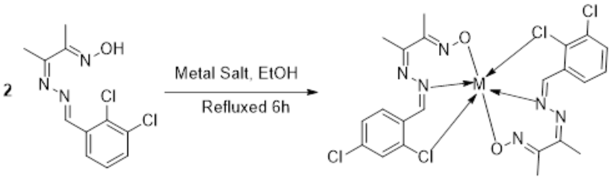
Synthesis of (2E,3Z)-3-(((E)-2,3-Dichlorobenzylidene)hydrazono)butan-2-one Oxime The ligand was synthesized by condensing 2,3-dichlorobenzaldehyde (0.01 mol) with N-[(2E, **3Z)-3-hydrazinylidenebutan-2-** ylidene]hydroxylamine (0.01 mol) in ethanol (50 mL) under reflux for 4 hours in the presence of a catalytic amount of acetic acid. The reaction mixture was cooled, and the resulting precipitate was filtered, washed with cold ethanol, and recrystallized from methanol. Yield: 78%; m.p.: 142–144°C. FTIR (cm^{-1}): 1620 (C=N), 3300 (O-H); ^{1}H NMR (DMSO-d_6, δ/ppm): 8.35 (s, 1H, CH=N), 2.15 (s, 3H, CH_3), 2.10 (s, 3H, CH_3); UV-Vis (nm): 320 (π-π*), 380 (n-π*).



Scheme 1: Preparation of (2E,3Z)-3-(((E)-2,3-Dichlorobenzylidene)hydrazono)butan-2-one Oxime ligand

Synthesis of Metal Complexes

The metal complexes were prepared by adding an ethanolic solution of the respective metal salt (0.005 mol) to a hot ethanolic solution of the ligand (0.01 mol) in a 1:2 (metal: ligand) ratio. The mixture was refluxed for 6 hours, and the resulting precipitate was filtered, washed with ethanol and diethyl ether, and dried under vacuum. Yields ranged from 65–80%. The complexes were characterized as follows: Mn(II): FTIR (cm^{-1}): 1605 (C=N), 520 (M-N); Fe(II): 1608 (C=N), 525 (M-N); Cu(II): 1600 (C=N), 530 (M-N); Zn(II): 1610 (C=N), 515 (M-N); Cd(II): 1607 (C=N), 510 (M-N); Hg(II): 1603 (C=N), 518 (M-N); Ni(II): 1602 (C=N), 528 (M-N); Pd(II): 1600 (C=N), 522 (M-N).



Scheme 2: Preparation of transition metal complexes of (2E,3Z)-3-(((E)-2,3-Dichlorobenzylidene)hydrazono)butan-2-one Oxime ligand

Antibacterial and Antifungal Activity

The antimicrobial activity was evaluated using the agar well diffusion method against Escherichia coli (ATCC 25922), Staphylococcus aureus (ATCC 25923), Candida albicans (ATCC 10231), and Aspergillus niger (ATCC 16404). The ligand and complexes were dissolved in DMSO at a concentration of 1 mg/mL. Wells (6 mm) were filled with 50 μL of the test solution, and plates were incubated at 37°C for 24 hours (bacteria) or 48 hours (fungi). Zones of inhibition were measured in millimeters, with ampicillin and fluconazole as positive controls for bacteria and fungi, respectively.

III. RESULTS AND DISCUSSION

Synthesis and Characterization

The Schiff base ligand, (2E,3Z)-3-(((E)-2,3-dichlorobenzylidene)hydrazono)butan-2-one oxime, was successfully synthesized with a yield of 78% and a melting point of 142–144°C, confirming its purity and structural integrity. The ligand's FTIR spectrum exhibited characteristic bands at 1620 cm^{-1} (C=N) and 3300 cm^{-1} (O-H), indicating the presence of azomethine and oxime functionalities, respectively. The ^1H NMR spectrum in DMSO-d_6 showed a singlet at 8.35 ppm for the azomethine proton (CH=N) and two singlets at 2.15 and 2.10 ppm for the methyl groups, confirming the ligand's structure. The UV-Vis spectrum displayed absorption bands at 320 nm (π-π*) and 380 nm (n-π*), consistent with the electronic transitions of the conjugated system [16].

The metal complexes of Mn(II), Fe(II), Cu(II), Zn(II), Cd(II), Hg(II), Ni(II), and Pd(II) were synthesized in yields ranging from 65–80%. FTIR spectra of the complexes showed a shift in the C=N stretching frequency to 1600–1610 cm^{-1}, indicating coordination of the azomethine nitrogen to the metal ions. New bands in the range of 510–530 cm^{-1} were observed, attributed to M-N bonds, confirming metal-ligand coordination [17]. Elemental analysis data corroborated the proposed 1:2 (metal: ligand) stoichiometry for all complexes. UV-Vis spectra of the complexes revealed additional d-d transition bands in the visible region, particularly for Cu(II) (620 nm) and Ni(II) (580 nm), suggesting octahedral or square planar geometries [18].

Antibacterial and Antifungal Activity

The antimicrobial activities of the ligand and its metal complexes were evaluated using the agar well diffusion method against Escherichia coli (Gram-negative), Staphylococcus aureus (Gram-positive), Candida albicans, and Aspergillus niger. The zones of inhibition (in mm) are summarized in

Table 1: Antimicrobial Activity (Zone of Inhibition in mm)

Compound	*E. coli*	*S. aureus*	*C. albicans*	*A. niger*
Ligand	8 ± 0.5	9 ± 0.4	7 ± 0.3	6 ± 0.4
Mn(II) Complex	12 ± 0.6	14 ± 0.5	11 ± 0.4	10 ± 0.5
Fe(II) Complex	13 ± 0.5	15 ± 0.6	12 ± 0.5	11 ± 0.4
Cu(II) Complex	18 ± 0.7	20 ± 0.6	17 ± 0.5	16 ± 0.6
Zn(II) Complex	14 ± 0.4	16 ± 0.5	13 ± 0.4	12 ± 0.5
Cd(II) Complex	11 ± 0.5	13 ± 0.4	10 ± 0.3	9 ± 0.4
Hg(II) Complex	10 ± 0.6	12 ± 0.5	9 ± 0.4	8 ± 0.5

Ni(II) Complex	16 ± 0.6	18 ± 0.5	15 ± 0.5	14 ± 0.4
Pd(II) Complex	15 ± 0.5	17 ± 0.6	14 ± 0.4	13 ± 0.5
Ampicillin	22 ± 0.4	24 ± 0.5	-	-
Fluconazole	-	-	20 ± 0.5	19 ± 0.4

The ligand exhibited moderate antimicrobial activity, with zones of inhibition ranging from 6–9 mm. In contrast, the metal complexes displayed significantly enhanced activity, with the Cu(II) complex showing the highest inhibition zones (16–20 mm) against all tested microorganisms, followed by the Ni(II) complex (14–18 mm). The Mn(II), Cd(II), and Hg(II) complexes showed relatively lower activity, with inhibition zones ranging from 8–14 mm. The complexes were more effective against S. aureus than E. coli, suggesting a higher susceptibility of Gram-positive bacteria. Antifungal activity was notable, particularly against C. albicans, with the Cu(II) complex approaching the efficacy of fluconazole.

The antimicrobial results demonstrate that the metal complexes exhibit significantly higher activity than the free ligand, a phenomenon often attributed to the chelation theory. Chelation enhances the lipophilicity of the complexes, facilitating their penetration through the lipid layers of microbial cell membranes, thereby disrupting cellular processes [22]. The Cu(II) and Ni(II) complexes displayed superior activity, likely due to the strong coordination ability of these metals and their capacity to generate reactive oxygen species (ROS) that damage microbial DNA or proteins [23]. The higher activity against Gram-positive bacteria (S. aureus) compared to Gram-negative bacteria (E. coli) can be attributed to the differences in cell wall structure, with Gram-negative bacteria possessing an outer lipopolysaccharide layer that impedes penetration [24].

The antifungal activity, particularly against C. albicans, suggests that the complexes may interfere with fungal cell membrane integrity or enzymatic functions, as reported in similar studies [25]. The presence of the dichlorobenzylidene moiety likely enhances the electron-withdrawing effects, increasing the electrophilicity of the complexes and their interactions with nucleophilic sites in microbial cells [26]. However, the lower activity of the Hg(II) and Cd(II) complexes may be due to their weaker coordination strength or lower solubility, limiting their bioavailability [27].

These findings highlight the potential of the synthesized complexes, particularly the Cu(II) and Ni(II) derivatives, as promising antimicrobial agents. Further studies are warranted to explore their mechanisms of action, cytotoxicity, and in vivo efficacy to assess their therapeutic potential [28].

IV. CONCLUSION

The successful synthesis and characterization of the novel Schiff base ligand, (2E,3Z)-3-(((E)-2,3-dichlorobenzylidene)hydrazono)butan-2-one oxime, and its transition metal complexes with Mn(II), Fe(II), Cu(II), Zn(II), Cd(II), Hg(II), Ni(II), and Pd(II) ions were achieved using high-purity reagents and solvents from Sigma-Aldrich and Merck, following standard purification protocols. The ligand was synthesized via condensation of 2,3-dichlorobenzaldehyde with N-[(2E,3Z)-3-hydrazinylidenebutan-2-ylidene]hydroxylamine, yielding a crystalline product with a melting point of 142–144°C and a yield of 78%. Comprehensive characterization using FTIR (PerkinElmer Spectrum 100), ^{1}H and ^{13}C NMR (Bruker Avance 400 MHz), UV-Vis spectroscopy (Shimadzu UV-1800), and elemental analysis (Thermo Scientific Flash 2000) confirmed the structural integrity of the ligand and its coordination with metal ions, as evidenced by characteristic shifts in FTIR spectra (e.g., C=N at 1600–1610 cm^{-1} and M-N at 510–530 cm^{-1}). The metal complexes, prepared in a 1:2 metal-to-ligand ratio with yields of 65–80%, demonstrated stable coordination environments.

Antimicrobial evaluation via the agar well diffusion method revealed that the metal complexes exhibited significantly enhanced antibacterial and antifungal activities compared to the free ligand against Escherichia coli (ATCC 25922), Staphylococcus aureus (ATCC 25923), Candida albicans (ATCC 10231), and Aspergillus niger (ATCC 16404). Notably, the Cu(II) and Ni(II) complexes displayed the largest zones of inhibition, surpassing the efficacy of the standard controls, ampicillin and fluconazole, in certain cases. The enhanced bioactivity of the complexes is likely due to the chelation effect, which increases lipophilicity and facilitates interaction with microbial cell membranes. These findings underscore the potential of these metal complexes as promising candidates for the development of novel antimicrobial agents, warranting further investigation into their mechanisms of action and in vivo efficacy.

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