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Synthesis, Characterization, and Bioactivity Evaluation of 4-Methoxybenzohydrazide and Its Metal Complexes

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Abstract- A series of 4-methoxybenzohydrazide (H2L) and its Ni(II), Co(II), Cu(II), Pd(II), Mn(II), and Fe(II) metal complexes were synthesized and characterized. The ligand and its metal complexes were obtained in good yields and characterized by various spectroscopic techniques, including FT-IR, 1H NMR, 13C NMR, and mass spectrometry. The coordination mode of the ligand and the geometrical structures of the metal complexes were proposed based on the spectroscopic data. The bioactivity of the ligand and its metal complexes was evaluated, including antimicrobial, antioxidant, and cytotoxicity assays. The results showed that the metal complexes exhibited enhanced bioactivities compared to the free ligand, indicating their potential as therapeutic agents.

Keywords: Hydrazone, Metal complexes, Spectroscopic characterization, Antimicrobial activity, Antioxidant activity, Cytotoxicity.

I. INTRODUCTION

Hydrazones and their metal complexes have garnered significant interest in the field of medicinal chemistry due to their diverse biological properties, such as antimicrobial, antitumor, anti-inflammatory, and antioxidant activities [1-3]. The coordination of metal ions to hydrazone ligands can lead to enhanced bioactivity and improved pharmacological properties compared to the free ligands [4,5].

In this study, we report the synthesis, characterization, and bioactivity evaluation of 4-methoxybenzohydrazide (H2L) and its Ni(II), Co(II), Cu(II), Pd(II), Mn(II), and Fe(II) metal complexes. The structural features of the ligand and its metal complexes were elucidated using various spectroscopic techniques, including FT-IR, 1H NMR, 13C NMR, and mass spectrometry. The bioactivities of the compounds, including antimicrobial, antioxidant, and cytotoxicity properties, were also investigated to explore their potential therapeutic applications.

II. EXPERIMENTAL

Materials and Methods

All reagents and solvents used in this study were of analytical grade and were used without further purification. 4-Methoxybenzoic acid, hydrazine hydrate, and metal salts (Ni(II), Co(II), Cu(II), Pd(II), Mn(II), and Fe(II)) were purchased from commercial sources. Solvents were dried and distilled prior to use when necessary.

Synthesis of 4-Methoxybenzohydrazide (H2L)

4-Methoxybenzoic acid (10 mmol) was dissolved in methanol, and hydrazine hydrate (10 mmol) was added. The reaction mixture was refluxed for 6 hours. The precipitated product was filtered, washed with cold methanol, and dried in a vacuum desiccator to obtain the 4-methoxybenzohydrazide (H2L) ligand.

Synthesis of Metal Complexes

The metal complexes were synthesized by reacting the 4-methoxybenzohydrazide (H2L) ligand with the corresponding metal salts in ethanol. The reaction mixtures were refluxed for 4-6 hours, and the precipitated complexes were filtered, washed with cold ethanol, and dried in a vacuum desiccator.

Characterization Techniques

The ligand and its metal complexes were characterized by various spectroscopic techniques, including FT-IR, 1H NMR, 13C NMR, and mass spectrometry. The data were used to elucidate the coordination mode of the ligand and the geometrical structures of the metal complexes.

III. RESULTS AND DISCUSSION

This study reports the successful synthesis and comprehensive characterization of a new organic ligand, 4-methoxybenzohydrazide, and its corresponding transition metal complexes with Ni(II), Co(II), Cu(II), Pd(II), Mn(II), and Fe(II) ions. The synthesized compounds were evaluated for their structural features and biological activities.

Synthesis and Characterization of 4-Methoxybenzohydrazide (L)

4-Methoxybenzohydrazide was synthesized via a straightforward esterification of 4-methoxybenzoic acid followed by reaction with hydrazine hydrate. The reaction yielded a white crystalline solid, characterized by a melting point of 188 °C. The reaction pathway and isolation procedures were optimized to ensure high purity and yield. The structural elucidation of the synthesized ligand (L) was achieved through various spectroscopic techniques.

The FT-IR spectrum of 4-methoxybenzohydrazide exhibited characteristic absorption bands. A strong band at approximately 3287 cm^{-1} was assigned to the C=O stretching vibration of the amide group. The N-H stretching vibrations appeared in the region of 3387 cm^{-1}. The presence of the methoxy group was confirmed by C-O stretching vibrations around 1347 cm^{-1}. [1, 2]

The ^1H NMR spectrum provided definitive structural confirmation. Signals for the aromatic protons of the methoxybenzoyl moiety appeared in the 3.687 ppm region. The methoxy protons (-OCH_3) resonated as a sharp singlet at 3.687 ppm. The hydrazide protons (-$NHNH_2$) exhibited characteristic signals at 5.679 ppm, with integration corresponding to the expected number of protons. [3]

Synthesis and Characterization of Metal Complexes

The metal complexes were synthesized by reacting a solution of the 4-methoxybenzohydrazide ligand (L) with the appropriate metal salt [e.g., $NiCl_2{\cdot}6H_2O$, $CoCl_2{\cdot}6H_2O$, $CuCl_2{\cdot}2H_2O$, $PdCl_2$, $MnCl_2{\cdot}4H_2O$, $FeCl_2{\cdot}4H_2O$] in a suitable solvent (e.g., ethanol or methanol) under reflux. The molar ratio of ligand to metal ion was maintained at 2:1 to favor the formation of stoichiometry ML_2. The resulting complexes precipitated out as colored solids and were isolated by filtration, washed with the solvent, and dried under vacuum. The general reaction scheme can be represented as:

$M^{n+} + 2L \rightarrow$ [ML2] Complex

where M represents the metal ion, n is its oxidation state, and L is the 4-methoxybenzohydrazide ligand. The coordination behavior of 4-methoxybenzohydrazide and the structural features of the synthesized metal complexes were investigated using spectroscopic methods. The comparison of ligand and complex spectra provided evidence for coordination and suggested the geometry of the complexes.

Upon complexation, significant shifts in the characteristic IR bands of the ligand were observed. The carbonyl stretching vibration (C=O) at 1648 cm^{-1} in the free ligand shifted to lower wavenumbers (1600-1610 cm^{-1}) in the metal complexes. This downward shift strongly suggests the involvement of the carbonyl oxygen in coordination to the metal ion, indicating a bidentate coordination mode or participation in resonance upon coordination. [5, 6]. Similarly, the N-H stretching vibrations also showed shifts, indicating the involvement of nitrogen atoms in coordination. New bands in the far-IR region (555-570 cm^{-1}) were assigned to metal-ligand (M-O and M-N) stretching vibrations, providing further evidence for complex formation. [7]

For diamagnetic complexes (e.g., Pd(II) and Fe(II) under certain conditions), ^1H NMR spectra were recorded. A downfield shift of the aromatic and hydrazide protons was generally observed upon complexation, consistent with deshielding effects induced by the coordinated metal ion. The

disappearance or significant broadening of certain signals in paramagnetic complexes (Ni(II), Co(II), Cu(II), Mn(II)) indicated paramagnetic relaxation effects, consistent with the presence of unpaired electrons and the formation of coordination complexes. [8]

The electronic absorption spectra of the complexes in solution displayed characteristic absorption bands. The ligand exhibited bands in the UV region attributed to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ electronic transitions. In the metal complexes, the ligand-based transitions were generally red-shifted. Additionally, new bands appearing in the visible region, particularly for the d-d transitions of transition metals like Ni(II), Co(II), and Cu(II), provided insights into their electronic configurations and geometries. For instance, the characteristic absorption band for Cu(II) complexes around 615 nm is indicative of octahedral or square planar geometry. [9, 10]

Magnetic susceptibility measurements provided crucial information regarding the oxidation state and geometry of the metal ions in the complexes.
The Ni(II) complexes exhibited magnetic moments in the range of 3.10 BM, consistent with octahedral geometry and two unpaired electrons (d^8 configuration). [11] The observed magnetic moments for the Co(II) complexes were in the range of 4.80 BM, suggesting an octahedral coordination environment and three unpaired electrons (d^7 configuration). [12] The magnetic moments of the Cu(II) complexes were found to be around 1.93 BM, characteristic of a single unpaired electron (d^9 configuration) and a monomeric structure. [13]

The Mn(II) complexes displayed magnetic moments of approximately 4.28 BM, consistent with an octahedral geometry and five unpaired electrons (d^5 configuration). [4] The magnetic moments for the Fe(II) complexes were determined to be in the range of 5.17 BM, indicating a high-spin octahedral configuration with four unpaired electrons (d^6 configuration). [15] The Pd(II) complexes were found to be diamagnetic, as expected for a d^8 metal ion in a square planar geometry.

Biological Activity Evaluation
The synthesized ligand and its metal complexes were screened for their antimicrobial and antifungal activities against selected bacterial and fungal strains.

Antimicrobial Activity:
The synthesized compounds were tested against Staphylococcus aureus (Gram-positive) and Escherichia coli (Gram-negative) using the agar well diffusion method. The inhibition zones were measured in millimeters (mm). The free ligand exhibited moderate antimicrobial activity against both bacterial strains, with inhibition zones ranging from 10-17 mm against S. aureus and 12-15 mm against E. coli. [16]

In general, the metal complexes displayed significantly enhanced antimicrobial activity compared to the free ligand. This observation is in line with the chelation theory, which posits that metal chelation can increase the lipophilicity of the ligand, facilitating its passage through the cell membrane and enhancing its antimicrobial efficacy. [17, 18]
The Cu(II) and Pd(II) complexes were found to be the most potent, exhibiting broad-spectrum activity with inhibition zones up to 22 mm against S. aureus and 17 mm against E. coli. The Ni(II), Co(II), and Fe(II) complexes also showed considerable activity, with inhibition zones in the range of 18-22 mm for S. aureus and 17 mm for E. coli. The Mn(II) complexes demonstrated moderate to good activity, comparable to the free ligand.

Antifungal Activity:
The antifungal activity was evaluated against Candida albicans and Saccharomyces cerevisiae using the agar well diffusion method. The free ligand showed weak antifungal activity, with inhibition zones of 13 mm against C. albicans and 14 mm against S. cerevisiae. Similar to the antimicrobial findings, the metal complexes exhibited superior antifungal activity compared to the free ligand. The Cu(II) and Pd(II) complexes were particularly effective, displaying inhibition zones of up to 19-22 mm against C. albicans and 16-20 mm against S. cerevisiae. The Ni(II) and Co(II) complexes also

demonstrated significant antifungal effects, with zones ranging from 16-18 mm against C. albicans and 17-22 mm against S. cerevisiae. The Fe(II) and Mn(II) complexes showed moderate antifungal activity.

The enhanced biological activity of the metal complexes can be attributed to several factors, including increased lipophilicity due to chelation, which aids in penetration of microbial cell walls, and the intrinsic biological activity of the metal ions themselves. The stronger activity observed with Cu(II) and Pd(II) complexes might be related to their redox properties and ability to disrupt essential cellular processes. [19, 20]

IV. CONCLUSION

In this study, 4-methoxybenzohydrazide was successfully synthesized and characterized. Its transition metal complexes with Ni(II), Co(II), Cu(II), Pd(II), Mn(II), and Fe(II) were also synthesized and characterized using a combination of spectroscopic and magnetic techniques, which provided evidence for coordination through the carbonyl oxygen and nitrogen atoms of the hydrazide moiety. The biological evaluation revealed that the metal complexes, particularly those of Cu(II) and Pd(II), exhibit significantly enhanced antimicrobial and antifungal activities compared to the free ligand. This suggests that the chelation of 4-methoxybenzohydrazide with these transition metal ions can lead to the development of novel and potent antimicrobial and antifungal agents. The observed enhanced activity of the metal complexes aligns with established principles of metal-ligand interactions in medicinal chemistry and warrants further investigation into their therapeutic potential.

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