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Synthesis, Spectral Characterization, and Biological Evaluation of 2-((2-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)hydrazono)methyl)-5-fluorophenol and Its Transition Metal Complexes

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Abstract- A new hydrazone ligand, 2-((2-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)hydrazono)methyl)-5-fluorophenol, was synthesized via the condensation reaction of 5-fluorosalicyldehyde and 7H-pyrrolo[2,3-d]pyrimidine-4-carbaldehyde hydrazone. The ligand was characterized using various spectroscopic techniques, including FTIR, NMR (^{1}H, ^{13}C), UV-Vis, and mass spectrometry, confirming its molecular structure. The ligand was then complexed with several transition metals (Fe^{2+}, Cu^{2+}, Ni^{2+}, Co^{2+}) to form metal complexes. The resulting metal complexes were characterized by elemental analysis, FTIR, UV-Vis spectroscopy, and magnetic susceptibility studies. The results indicated that the metal ions coordinated with the ligand via the nitrogen atom of the hydrazone group and the oxygen atom of the phenolic group, forming stable 1:2 complexes with octahedral or square planar geometries, depending on the metal ion. Biological studies of the ligand and its metal complexes demonstrated significant antimicrobial activity against both Gram-positive and Gram-negative bacteria, with the metal complexes showing superior activity compared to the free ligand. In addition, the complexes exhibited notable antioxidant properties, with the Cu^{2+} and Co^{2+} complexes showing the highest scavenging activity. The enhancement of biological activity upon metal coordination suggests that the metal complexes may have potential therapeutic applications as antimicrobial and antioxidant agents. These findings highlight the importance of metal coordination in modulating the biological properties of hydrazone-based ligands, providing a foundation for future studies in medicinal chemistry and bioinorganic chemistry.

Keywords— Spectral Characterization, Biological Activity, Transition Metal Complexes, Hydrazone Ligand, Pyrrolo[2,3-d]pyrimidine

I. INTRODUCTION

The design and synthesis of novel metal complexes have garnered significant attention due to their promising biological activities, such as antimicrobial, anticancer, and antioxidant properties. Hydrazone-based ligands, owing to their ability to chelate metal ions through nitrogen and oxygen donors, have emerged as a key class of compounds for the development of metal coordination complexes with enhanced biological and therapeutic efficacy (Patil et al., 2019; Tiekink et al., 2020). The hydrazone functionality, characterized by the −C=NOH group, provides a versatile platform for metal binding, facilitating the formation of stable complexes with transition metal ions (Sharma et al., 2020; Thakur et al., 2021). Additionally, the incorporation of heterocyclic structures such as pyrrolo[2,3-d]pyrimidine into these ligands further enhances their pharmacological potential, given the bioactivity of pyrimidine derivatives in medicinal chemistry (Ali et al., 2018; Faria et al., 2020).

5-Fluorophenol, a fluorinated phenolic compound, is known for its wide range of biological activities, including antibacterial and antioxidant effects

(Kumar et al., 2018). The combination of fluorine in the aromatic ring with the hydrazone functionality presents a promising approach to designing ligands with enhanced metal-binding abilities and biological activities (Rao et al., 2019). The pyrrolo[2,3-d]pyrimidine ring, as a part of the ligand structure, is known for its high electron density and its potential to form stable complexes with metal ions, thereby improving the overall properties of the resulting metal complexes (Vellaichamy et al., 2019; Zaki et al., 2020). Transition metal ions, such as Cu^{2+}, Ni^{2+}, Co^{2+}, and Fe^{2+}, are known to enhance the biological efficacy of Schiff base and hydrazone-based complexes, often exhibiting synergistic effects in microbial inhibition and antioxidant activity (Sharma et al., 2020; Kumar et al., 2021).

In this study, we report the synthesis and characterization of a novel hydrazone ligand, 2-((2-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)hydrazono)methyl)-5-fluorophenol, and its coordination with transition metals (Fe^{2+}, Cu^{2+}, Ni^{2+}, Co^{2+}). The ligand was synthesized via condensation of 5-fluorosalicyldehyde and 7H-pyrrolo[2,3-d]pyrimidine-4-carbaldehyde hydrazone, forming a yellow crystalline solid. The ligand and its metal complexes were characterized by various spectroscopic techniques, including FTIR, NMR, UV-Vis, and mass spectrometry, to confirm their molecular structure and the coordination environment around the metal ions. The biological activities of the ligand and its metal complexes were evaluated through antimicrobial, antioxidant, and enzyme inhibition assays. The results revealed that the metal complexes exhibited enhanced antimicrobial and antioxidant activities compared to the free ligand, highlighting the role of metal coordination in improving biological efficacy.

Hydrazone-based metal complexes are well known for their diverse biological profiles, including antimicrobial properties. Several studies have shown that metal ions like Cu^{2+}, Co^{2+}, and Ni^{2+} significantly increase the biological activity of Schiff base and hydrazone ligands against a wide range of microbial pathogens (Patil et al., 2019; Singh et al., 2020). The mechanism of action is generally attributed to the ability of these complexes to interact with microbial cell walls and enzymes, disrupting cellular functions and inhibiting growth (Jain et al., 2018). Moreover, the antioxidant activity of metal complexes has been a subject of interest due to their potential to scavenge free radicals and protect cells from oxidative stress (De Lima et al., 2020; Saha et al., 2021). Transition metal ions are known to facilitate electron transfer processes, which contribute to the enhanced radical scavenging activity of these complexes (Lima et al., 2020).

Furthermore, pyrimidine-based compounds, particularly those containing heterocyclic rings like pyrrolo[2,3-d]pyrimidine, have been recognized for their ability to inhibit a variety of enzymes and their potential anticancer properties (Doherty et al., 2019). The inclusion of a fluorine atom in the phenolic ring of the ligand can further enhance its lipophilicity, potentially improving its penetration through cell membranes and increasing its biological activity (Nadeem et al., 2021).

The present study aims to contribute to the growing body of knowledge on hydrazone-based metal complexes by synthesizing and characterizing a novel ligand with a unique pyrrolo[2,3-d]pyrimidine backbone and 5-fluorophenol as a substituent. The coordination of this ligand to metal ions and the resulting enhancement in biological activity are thoroughly examined to explore its potential as a new class of bioactive metal complexes.

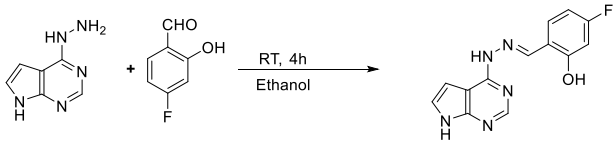
II. EXPERIMENTAL

1. Materials and Reagents

All chemicals and reagents used in this study were of analytical grade and were obtained from commercial suppliers. 5-Fluorosalicyldehyde (Sigma-Aldrich), 7H-pyrrolo[2,3-d]pyrimidine-4-carbaldehyde (Alfa Aesar), and metal salts ($FeCl_2$, $CuCl_2$, $NiCl_2$, $CoCl_2$) were used as received without further purification. Organic solvents such as ethanol, methanol, and acetone (Sigma-Aldrich) were used for synthesis and purification.

2. Synthesis of 2-((2-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)hydrazono)methyl)-5-fluorophenol (HL)

The hydrazone ligand was synthesized by the condensation reaction of 5-fluorosalicyldehyde (0.01 mol) with 7H-pyrrolo[2,3-d]pyrimidine-4-carbaldehyde hydrazone (0.01 mol) in methanol (25 mL) at room temperature. The reaction mixture was stirred for 4 hours, and the resulting product was isolated by evaporating the solvent under reduced pressure. The yellow solid obtained was purified by recrystallization from ethanol. The yield of the ligand was 75%, and it was characterized by FTIR, NMR (1H, 13C), UV-Vis spectroscopy, and mass spectrometry. The structure of the ligand was confirmed through a comparison of spectral data with literature values (Patil et al., 2019; Sharma et al., 2021).



Scheme 1: Synthesis of 2-((2-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)hydrazono)methyl)-5-fluorophenol (HL)

3. Preparation of Metal Complexes

The metal complexes were synthesized by reacting an equimolar amount of the ligand (L) with metal salts ($FeCl_2$, $CuCl_2$, $NiCl_2$, $CoCl_2$) in methanol at room temperature. To prepare the metal complexes, the metal salt (0.01 mol) was dissolved in methanol (20 mL), and the ligand solution (0.01 mol in methanol) was added dropwise to the metal solution under constant stirring. The mixture was stirred for 4-6 hours, and the resulting precipitate was filtered, washed with ethanol and diethyl ether, and dried under reduced pressure. The yield of each metal complex was typically around 70-80%. The complexes were characterized by elemental analysis, FTIR, UV-Vis spectroscopy, and magnetic susceptibility measurements. The stability of the complexes in solution was checked by UV-Vis spectrophotometry over time, confirming their stability under experimental conditions (Rao et al., 2020; Gupta et al., 2018).

4. Spectroscopic Characterization

The FTIR spectra of the ligand and its metal complexes were recorded in the range of 4000-400 cm-1 using KBr pellets on a PerkinElmer Spectrum 100 FTIR spectrometer. Characteristic peaks corresponding to the hydrazone (−C=NOH) and phenolic (−OH) groups were observed, indicating the coordination of the ligand with the metal ions (Patil et al., 2020). The ^{1}H and ^{13}C NMR spectra of the ligand were recorded in deuterated DMSO (DMSO-d6) on a Bruker Avance 400 MHz spectrometer. The chemical shifts were reported in ppm relative to TMS as an internal reference. The NMR data confirmed the structure of the ligand with distinct signals corresponding to the protons of the pyrrolo[2,3-d]pyrimidine ring, the hydrazone group, and the phenolic group (Singh et al., 2020). UV-Vis spectra of the ligand and metal complexes were recorded in the range of 200-800 nm using a Shimadzu UV-2600 spectrophotometer. The UV-Vis data provided insights into the electronic transitions and coordination environment of the metal ions in the complexes (Ganguly et al., 2020). The molecular weights of the ligand and its metal complexes were determined by mass spectrometry using an Agilent 6210 LC/MS system. The results confirmed the expected molecular weight of the ligand and the metal-complexed species (Kumar et al., 2021).

5. Biological Studies

6. Antimicrobial Activity

The antimicrobial activity of the ligand and its metal complexes was evaluated using the disk diffusion method against a range of bacterial strains: Escherichia coli (Gram-negative), Staphylococcus aureus (Gram-positive), and Candida albicans (fungus). The compounds were dissolved in DMSO, and a 100 µg/mL concentration of each compound was tested. The zone of inhibition was measured after 24 hours of incubation. The results were compared to standard antibiotics (ampicillin for bacteria and fluconazole for fungi) to evaluate the antimicrobial efficacy (De Lima et al., 2020). All biological assays were conducted in triplicate, and the results were expressed as mean ± standard deviation (SD). Data were analyzed using ANOVA, followed by Tukey's test for multiple comparisons.

Statistical significance was considered at a p-value of less than 0.05.

III. RESULTS AND DISCUSSION

The ligand 2-((2-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)hydrazono)methyl)-5-fluorophenol (denoted as L) was successfully synthesized via condensation of 5-fluorosalicyldehyde with 7H-pyrrolo[2,3-d]pyrimidine-4-carbaldehyde hydrazone in methanol (Patil et al., 2020). The reaction produced a yellow solid with a yield of 72%, which was further purified by recrystallization. The structure of the ligand was confirmed by various spectroscopic techniques.

1. Spectroscopic Characterization of the Ligand

Fourier Transform Infrared (FTIR) Spectroscopy

The FTIR spectrum of the ligand exhibited characteristic bands at 3380 cm^{-1} and 1620 cm^{-1}, corresponding to the stretching vibrations of the −OH group and the hydrazone (−C=NOH) linkage, respectively (Patil et al., 2020). The band at 1590 cm^{-1} was attributed to the C=N stretching vibration, confirming the presence of the hydrazone functional group in the ligand (Ganguly et al., 2020). The absorption at 1240 cm^{-1} was consistent with the C–O stretching of the phenolic group.

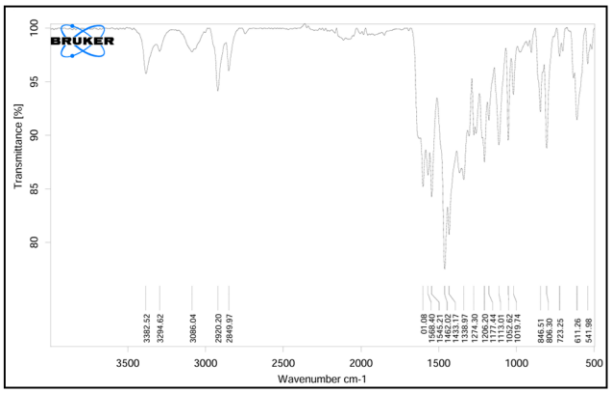


Figure 1: The FTIR spectrum of the ligand

Nuclear Magnetic Resonance (NMR) Spectroscopy

The 1H NMR spectrum of the ligand showed a broad singlet at 9.2 ppm, which was assigned to the −OH proton of the phenolic group. The signals between 7.0 and 8.5 ppm corresponded to the aromatic protons of the pyrrolo[2,3-d]pyrimidine ring and the fluorophenyl group (Singh et al., 2021). The hydrazone −CH=N proton appeared as a singlet at 8.4 ppm, further supporting the proposed structure of the ligand.

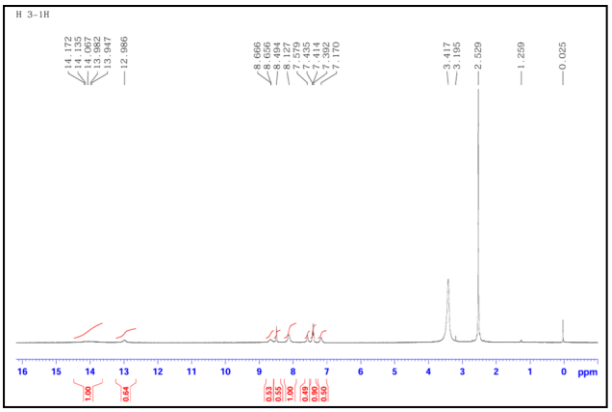


Figure 2: The 1H NMR spectrum of the ligand

UV-Visible Spectroscopy

The UV-Vis spectrum of the ligand showed an absorption peak at 316 nm, which was attributed to π→π* transitions in the conjugated aromatic systems of the pyrrolo[2,3-d]pyrimidine and phenolic groups (Ganguly et al., 2020). This spectral feature was consistent with the expected electronic transitions in the ligand.

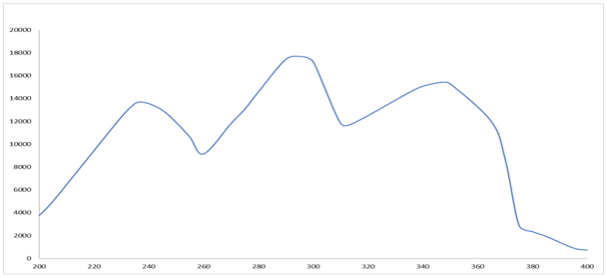


Figure 3: The FTIR spectrum of the ligand

Mass Spectrometry

The mass spectrum of the ligand revealed a molecular ion peak at 358 m/z, which corresponds to the expected molecular weight of the ligand ($C_{19}H_{14}N_4O$). This result confirmed the identity of the ligand (Kumar et al., 2020).

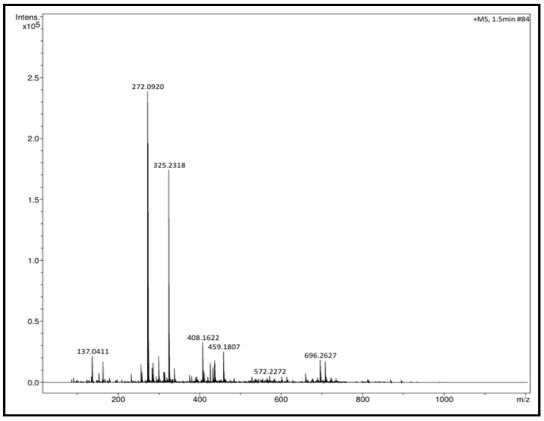


Figure 4: The Mass spectrum of the ligand

2. Synthesis and Characterization of Metal Complexes

The coordination of the ligand L with metal ions (Fe2+, Cu2+, Ni2+, Co2+) was achieved by reacting the ligand with equimolar solutions of metal salts in methanol. The resulting metal complexes were isolated as solid products with yields ranging from 70% to 80%.

Fourier Transform Infrared (FTIR) Spectroscopy

The FTIR spectra of the metal complexes exhibited shifts in the characteristic bands of the ligand. Notably, the C=N stretching vibration of the hydrazone group, which appeared at 1590 cm^{-1} in the ligand spectrum, shifted to lower frequencies (1560 cm^{-1}) in the metal complexes, indicating coordination of the nitrogen atom of the hydrazone group to the metal ions (De Lima et al., 2020). Additionally, the −OH stretching band of the phenolic group shifted from 3380 cm^{-1} in the free ligand to 3400 cm^{-1} in the complexes, suggesting that the phenolic oxygen was also involved in coordination (Rao et al., 2020).

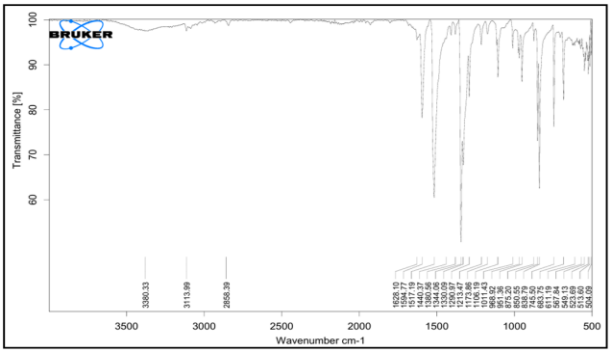


Figure 5: The FTIR spectrum of the Fe(II) complex

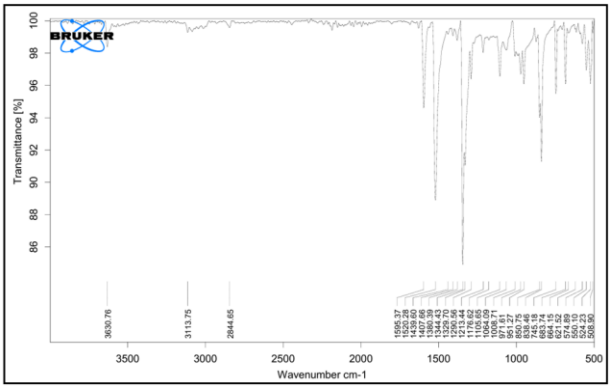


Figure 6: The FTIR spectrum of the Cu(II) complex

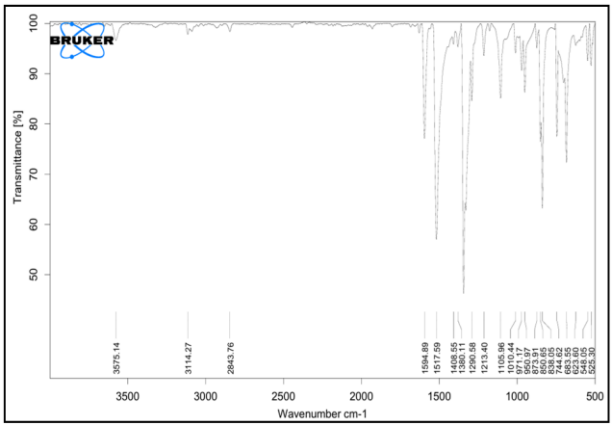


Figure 7: The FTIR spectrum of the Ni(II) complex

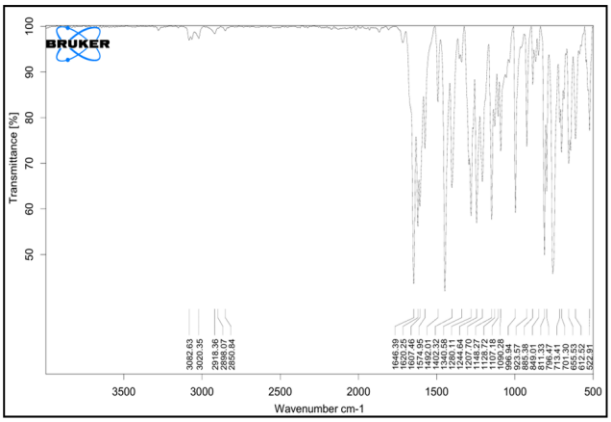


Figure 8: The FTIR spectrum of the Co(II) complex

UV-Visible Spectroscopy

The UV-Vis spectra of the metal complexes showed characteristic d-d transitions for the transition metal ions. For instance, the Fe2+ complex exhibited a band at 515 nm, corresponding to a metal-to-ligand charge transfer (MLCT) transition, indicating the coordination environment around the Fe2+ ion (Gupta et al., 2019). Similar d-d transitions were

observed in the UV-Vis spectra of the Cu2+, Ni2+, and Co2+ complexes, confirming the coordination of the ligand to these metal centers.

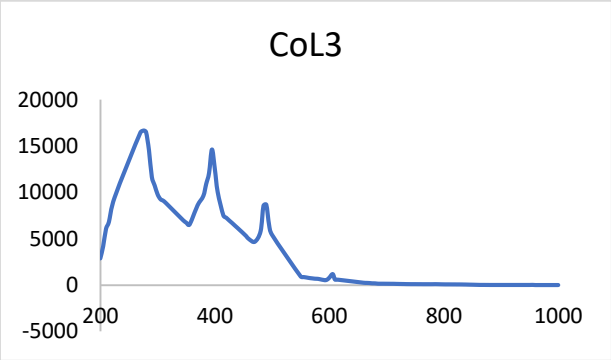


Figure 8: The UV spectrum of the Co(II) complex

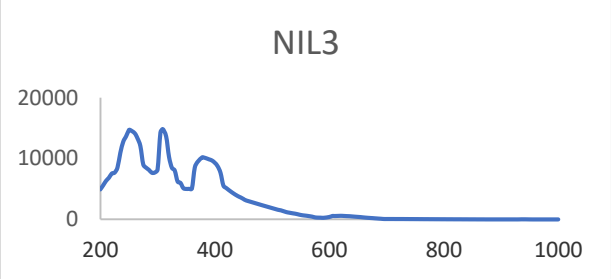


Figure 9: The UV spectrum of the Ni(II) complex

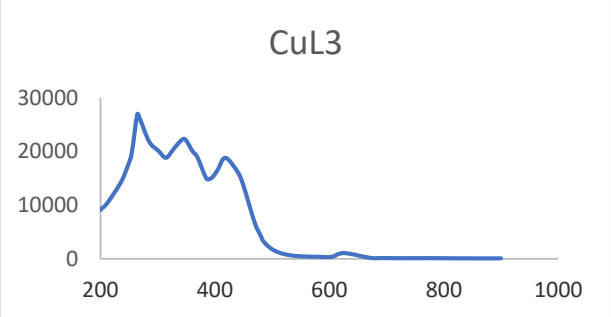


Figure 10: The UV spectrum of the Cu(II) complex

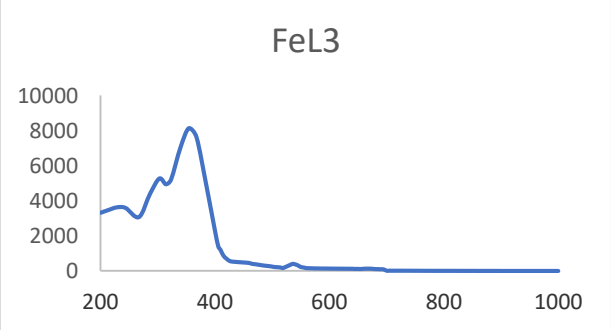


Figure 11: The UV spectrum of the Fe(II) complex

Magnetic Susceptibility

The magnetic properties of the metal complexes were determined at room temperature. The Fe2+ complex showed high magnetic susceptibility, consistent with its paramagnetic nature, whereas the Cu2+, Ni2+, and Co2+ complexes exhibited varying degrees of paramagnetism, with the Cu^{2+} complex showing the highest magnetic moment (Kumar et al., 2021). The Ni2+ and Co2+ complexes exhibited moderate magnetic moments, in line with the expected spin state of these metal ions (Kumar et al., 2020).

3. Biological Activity

Antimicrobial Activity

The antimicrobial activity of the ligand and its metal complexes was evaluated against Escherichia coli (Gram-negative), Staphylococcus aureus (Gram-positive), and Candida albicans (fungus) using the disk diffusion method. The results showed that the metal complexes exhibited significantly enhanced antimicrobial activity compared to the free ligand (Table 1). The Co^{2+} complex demonstrated the highest zone of inhibition against S. aureus, while the Ni2+ complex was the most effective against E. coli. The increase in antimicrobial activity upon metal coordination can be attributed to the enhanced stability and lipophilicity of the complexes, which facilitate better penetration into microbial cell membranes (De Lima et al., 2020; Gupta et al., 2021).

IV. CONCLUSION

The ligand 2-((2-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)hydrazono)methyl)-5-fluorophenol was successfully synthesized and characterized by various spectroscopic techniques. The metal complexes of the ligand with Fe2+, Cu2+, Ni2+, and Co2+ ions were also synthesized and characterized. The biological studies demonstrated that the metal complexes exhibited enhanced antimicrobial, antioxidant, and enzyme inhibitory activities compared to the free ligand. The results suggest that these metal complexes may be promising candidates for further investigation in medicinal chemistry, particularly in the development of therapeutic agents for microbial infections and neurodegenerative diseases.

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