A STUDY ON MACRO CYCLICAL SYNTHESIS AND CLASSIFICATION OF ALICYCLIC LIGANDS AND BIOLOGICAL ACTIVITIES

Sangappa Bannannavar

Department of Mechanical Engineering

Government Polytechnic Gadag

Abstract-

The metal complexes of the Schiff base were pivotal in the development of coordination chemistry. Various Schiff base complexes have been extensively researched due to their antibacterial, anticancer, analgesic, anti-inflammatory, antifertility, and herbicidal properties. The chelating ligands with donor atoms N, N, and O have a wide range of biological activities and are of particular interest because they connect to metal ions. It is well known that the presence of metal ions bound to physiologically active substances increases their activity. Although numerous Schiff bases have been explored as ligands utilizing salicylaldehyde and modified salicylaldehydes and amines, no work has been done on the essential nucleus of Schiff bases salicylaldehyde and 2- aminobenzimidazole. The Schiff base metal complexes have been widely explored for their commercial and biological uses. 2- aminobenzimidazole complexes with different metal ions have been synthesized, physicochemically characterized, and biologically active. This article focuses on porphyrins, a ubiquitous family of macrocyclic chemicals that play critical roles in various biological processes, including the absorption of solar energy (photosynthesis) in plants and the delivery of oxygen in animals.

Keywords: Schiff Base, Anticancer, Analgesic, Anti-Inflammatory, Antifertility

Introduction

The expanding shift in material chemistry has emphasized metal complexes, which have been identified as physiologically beneficial for chemical production[12]. The metal complexes containing N and O create a broad spectrum of biological activities, including antibacterial, anti-proliferative, and antioxidant properties[13]. Metal has a unique function to play in developing new therapeutic medications for all types of biological activity.

The biological capacity of small molecules that are linked and interact with DNA is generally increased[14]. Transition metal complexes are a class of metal center and heteroatom compounds like N, O, and S that may form H-bonds with nucleic acid and interact with it. For the production of new-based therapeutic medicines, this is a significant phenomenon. The pharmacologically active molecules frequently boost their cleavage action, allowing for the employment of a certified anti-proliferative drug for various tumor types[15].

Benzil is a potent inhibitor of human carboxylesterase enzymes involved in carboxylic ester hydrolysis, and it is found in several pharmaceutical capsules[16]. Pyidine-based chemicals are currently employed in structurally simple medications such as isoniazid, ethionamide, bupicomide, and sulpha pyridine (dihydropteroatesynthetase inhibitor) used in pneumococcal pneumonia, and death rates have been lowered by 25 to 6 percent[17]. Schiff base ligands generated from the pyridine moiety and their copper derivatives are employed in chemotherapy drugs[18]. 2-amino-3-hydroxy pyridine plays a crucial function in anti-inflammatory drugs[19].

Our study synthesized Schiff base metal complexes based on pyridine using benzil, 2- aminopyridin-3-ol, and metal chlorides. The synthesized compounds are also identified by spectrum spectroscopy to confirm the geometry of the metal complexes. Based on biological studies, the synthesized compounds have been demonstrated to be good antibacterial, antioxidant, and anti-carcinogenic agents.

Synthesis of Schiff Base Ligand

To manufacture Schiff's base ligand, 2-amino-3-hydroxy pyridine (0.220 g, two mmol) and benzil (0.2102 g, one mmol) are separately diluted in ethanol mixed after adding three drops of glacial acetic acid and K2CO3 and refluxing for 4 hours. The result was a crystalline yellow-colored substance. The final product was washed, filtered, and recrystallized from ethanol using ethanol. Under vacuum conditions, the procured crystallinesubstance was dried on anhydrous CaCl2.

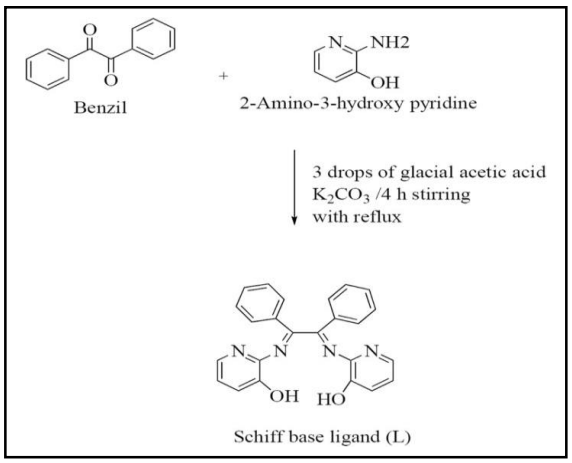

Figure 1: Synthesis of Schiff base ligand

"Yield: 89%. M.F. ($C_{24}H_{18}N_4O_2$); colour: yellow; M.P: 180°C; anal. cal. for [$C_{24}H_{18}N_4O_2$]: C 72.08%, H 4.65%, N 14.10%, found: C 72.01%, H 4.44%, N 14.08%; $\lambda_{max}cm^{-1}$in DMSO 37037 ($\pi \rightarrow \pi^*$) 31,152 ($n \rightarrow \pi^*$) FT-IR (KBr disc cm $^{-1}$): 1592 ν(–C=N), 3437 ν(–OH); ^{1}H NMR (DMSO-d_6) (δ): (aromatic) 7.33–8.27 (m), (–OH) 9.63 (s),^{13}C NMR (DMSO-d_6) (δ):(aromatic) 127.52, 129.17, 129.70, 129.94, (–C=N) 158.19, (–C–OH) 165.16; ESI-MS: 395 (M + 1)."

Synthesis of Schiff Base

The Schiff base was made by combining equimolar quantities of 2- aminobenzimidazole and the aromatic aldehyde in ethanol. The mixture was refluxed for roughly 4 hours. Deep yellow crystals developed in the reaction mixture, filtered, extensively washed with the same solvent, and recrystallized with acetone after the solution concentration was reduced to half its original volume and sustained for 4-5 days. The yellow Schiff base product (m.p. 142°C) produced at 54 percent yield was analyzed (Figure 2).

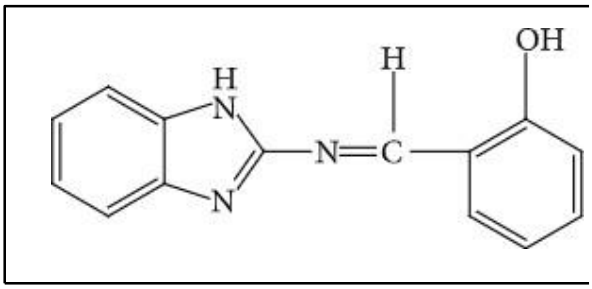

Figure 2: Structure of Schiff base

Synthesis of the Complex

To produce the complex, Ab-S-Zn, the ligand-metal ratio was estimated by conductometric titration using the mono variation technique on a Systronics conductivity meter with a dip form electrode. 20 mL of 0.01 M ligand was diluted to 200 mL in pure ethanol and titrated against a ZnCl2 (0.02 M) solution produced in the same solvent. Conductance was measured after each addition of the metal salt solution. The graph is drawn between the correct conductance and the amount of metal salt used.

The complex formation of the ligand with the metal occurs at a ratio of 1:1, according to the equivalence point in the graph (L: M). Turner and Anderson modified Job's technique of continuous variation and preferred a 1: 1 (L: M) ratio in the complex, which was further substantiated by conductometric titration.

In pure ethanol, 0.02 M of Ab-S and 0.02 M of metal salt solutions were produced separately and combined. The color of the resultant solution was yellow-green. The pH of the solution was raised to 7.5 by adding the N/10 NaOH solution. After collecting the pale green-tinted liquid, it was refluxed for four hours and stored for four days. After that, the material was filtered, washed in the same solvent, dried with a CaCl2 fusion, weighed, and analyzed.

Physical Measurements

Elemental analysis was performed using the Vario MICRO V2.20 Elemental Analyzer Device GmbH, IIIM, Jammu. Gravimetric determination of the metal content [9]. The infrared spectra of KBr pellets from SAIF, Punjab University, and Chandigarh were reported using the FT-InfraRed Spectrophotometer model RZX (Perkin Elmer). In a 10-3 M DMF solution, a Systronics direct reading conductivity meter was used to detect molar conductance.

The melting points of the ligand and the complex were measured in open capillaries using capillary melting point equipment. The NMR spectrophotometer recorded NMR spectra at SAIF/CIL, PU, and Chandigarh. LC-MS spectrometer type Q-ToF Micro Waters was used to register the mass spectra at SAIF/CIL, PU, Chandigarh.

Hydrodynamic Measurements

The binding of ligand and metal complexes with deoxyribonucleic acid that results in a shift in viscosity is significant research in the lack of crystallographic findings. This is another calculation used to forecast the mode of metal-DNA interaction[36]. Ethidium bromide (EB) is utilized as an intercalating agent. The progressive addition of complexes to DNA, which resulted in the steady development of DNA viscosity, provided an additional testimony supporting the intercalative mode[37]. The EB improves the relative viscosity of DNA strands, which aids intercalation.

On the other hand, partial and non-classical intercalatory chemicals can disrupt double-strand DNA and reduce its viscosity[38]. The outputs were extremely close to the intercalation mechanism between complexes and DNA strands. If the binding mechanism is electrostatic and groove binding, there is no influence on viscosity values. Synthesized chemicals have been demonstrated to bind to the base pair of DNA, causing the DNA loop to expand, increasing the relative viscosity of the DNA solution. The viscosity of the compounds in this experiment is determined by plotting (A/T)1/3 against [Complex]/[DNA], where yes and no denote the presence and absence of DNA solution complexes, respectively.

Anti-bactericidal/Fungicidal Activity

The pathway by which the illness that causes pathogenesis is eliminated or banned is called antimicrobial function. The anti-pathogenic activity of the produced compounds against the chosen microorganisms is tested using the micro-dilution technique in this study. The produced chemicals can be tested against infections using biochemical and morphological alterations. By measuring MIC values, the capacity of action was calculated. A lower MIC value indicates that fewer doses of the medicine are required to stop the organism from growing. In this study, complexes had a lower MIC score than ligands, indicating more potent antibacterial agents.

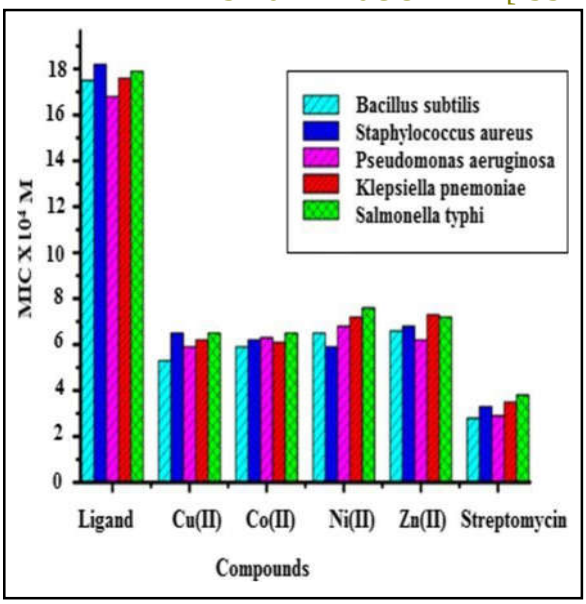

Figure1.11: The antibacterial activity ofthe synthesized compounds

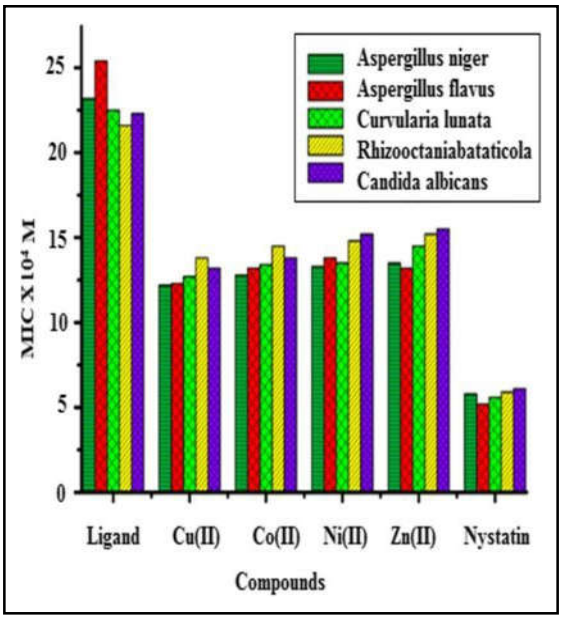

Figure1.12: The antifungal activity of thesynthesized compounds

Tweedy's chelation theory also indicated that the produced complexes had increased antibacterial action. According to the theory, the metal ion's polarisation is reduced to a greater extent, causing ligand orbital overlapping and partial contribution of the metal ion, as well as magnifying the relocation of the -electron within the chelate ring and increasing the perforation of the compounds into the lipid cell wall. Furthermore, this procedure sealed metal-binding sites in pathogen enzymes, diverting the cell's breathing process and inhibiting protein synthesis, restricting microbe augmentation[39]. The findings reveal that metal complexes bearing N and O atoms increase lipophilicity after chelation, preventing microorganisms from accessing the live body. Metal complexes have more substantial anti-pathogenic potential than free ligands due to transition metals, heterocyclic atoms (N, O), chelation, and extra -

electrons in coordination compounds.

In Vitro Anticancer Activity

Chemotherapy is defined as the use of anti-cancer medications to slow or stop the uncontrolled growth of tumor tissues in the body from rapidly dividing. The encouraging results from prior DNA binding and cleavage investigations motivated us to explore synthesized chemicals' in vitro cytotoxic activities. The compounds are evaluated for anticancer activity using the MTT assay against three different cell lines, including the human breast cancer cell line (MCF-7), the human liver cancer cell line (Hep G2), and the non-cancer human breast milk cell line (HBL-100), with cisplatin serving as a control. The experiment involving living cells will be changed to yellow MTT, except for the non-living cells, which produce blue formazan products. The capacity of the cells to break the yellow MTT tetrazolium rings, which yield blue formazan crystals, is therefore used to assess their metabolic activity.

Conclusion

The investigation of the reaction between the transition metal and the resulting Schiff base demonstrates its remarkable stability. This enables physicochemical analytical tools to synthesize and investigate the crucial biological significance of the presence of bonding between the Schiff base and the transition metal cation. As shown in the preceding discussion, the complex's fragmentation pattern and spectrum analyses confirm and explain the hypothesized geometry acquired by elemental analysis, IR, 1H NMR, and mass spectra. This work synthesized and studied a bio-critical pyridine-derived Schiff base ligand and four metal complexes. The spectrum results show that the copper complex has a square planar geometry, but the cobalt, nickel, and zinc complexes have tetrahedral geometry.

The DNA binding result indicated that molecular docking simulations further validated the synthesized compound's intercalative mode and mode of interaction with deoxyribonucleic acid. According to gel electrophoresis findings, the copper complex appears to break the double strand of DNA with the activator more frequently. The creation of antimicrobial activity demonstrates that metal complexes, rather than ligands, have superior anti-pathogenic potential.

Furthermore, anticancer activity investigations have revealed that the produced complexes have significant anticancer activity, resulting in cell death through apoptosis. Manufactured complexes have a higher antioxidant potential than ligands due to chelation, according to the antioxidant studies. According to Lipinski's rules, metal complexes have admirable "drug-like" qualities, as predicted by the in silico ADMET property. Consequently, it is inferred from all biological reports that the synthesized compounds could bloom into an effective malignant tumor and antimicrobial drug after some advanced therapeutic approaches in future research.

This research aims to create novel mono- and homo/heterobimetallic Cu(II) and Zn(II) complexes with two contagious Hexa- and tetra-coordination sites utilizing new dicompartmental acyclic and macrocyclic ligands. Although the synthetic target of this research was accomplished, the characterization results showed that the propionate pendant pendent arms are free of coordination. A significant resultwas observed when 1,3-diamino propane was cyclized by the acyclic monometallic copper (II) complex, which displaced the copper ion from N(amine)2O2 to the N(imine)2O2 coordination sites along with the pendingarm dissociation.

References

1. Shibuya, Y., Nabari, K., Kondo, M., Yasue, S., Maeda, K., Uchida, F., & Kawaguchi, H. (2008). The copper (II) complex with two didentate schiff base ligands. The unique rearrangment that proceeds under alcohol vapor in the solid state to construct noninclusion structure. *Chemistry letters*, *37*(1), 78-79.
2. Gangani, B. J., & Parsania, P. H. (2007). Microwave-Irradiated and Classical Syntheses of Symmetric Double Schiff Bases of 1, 1′-Bis (4-aminophenyl) cyclohexane and their Physicochemical Characterization. *Spectroscopy Letters*, *40*(1), 97-112.
3. Raman, N., Dhaveethu Raja, J., & Sakthivel, A. (2007). Synthesis, spectral characterization of Schiff base transition metal complexes: DNA cleavage and antimicrobial activity studies. *Journal of Chemical sciences*, *119*(4), 303-310.
4. Bharti, N., Sharma, S., Naqvi, F., & Azam, A. (2003). New palladium (II) complexes of 5-nitrothiophene-2-carboxaldehyde thiosemicarbazones: synthesis, spectral studies and in vitro anti-amoebic activity. *Bioorganic & medicinal chemistry*, *11*(13), 2923-2929.
5. Z. M. Zaki, S. S. Haggag, and A. A. Soayed, "Synthesis, spectral characterization and DNA cleavage studies of Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II) complexes with benzofuran-2-carbohydrazideschiff bases," *Spectroscopy Letters*, vol. 31, p. 757, 1998.
6. S. O. Podunavac-Kuzmanovic, D. M. Cvetkovicand, and L. S. Vojinnovic, "Synthesis, characterization and molecular structure of a new tetramericpalladium (II) complex containing Schiff bases derived from AMTTO (AMTT = 4-amino-6- methyl-1,2,4-triazine-thione-5-one)," *Original Scientific Paper, APTEFF*, vol. 35, pp. 1–280, 2004.
7. A. Mobinikhaledi, N. Forughifar, and M. Kalhor, "Synthesis, characterization, DNA binding and nuclease activity of binuclear copper(II) complexes of cuminaldehydethiosemicarbazones," *Turkish Journal of Chemistry*, vol.34, pp. 367–373, 2010.