

## An Investigation into the Macrocyclical Synthesis of Alicyclic Ligands, Their Categorization, and Biological Activity

\*Dr. Ravi Sharma

### Abstract

The development of coordination chemistry was greatly aided by the metal complexes of the Schiff base. Because of their antibacterial, anticancer, analgesic, anti-inflammatory, antifertility, and herbicidal characteristics, several Schiff base complexes have been the subject of substantial investigation. The biological actions of the chelating ligands containing donor atoms N, N, and O are quite diverse, and they are of special interest because they interact with metal ions. Metal ions are known to boost the activity of compounds that are physiologically active when they are present. Salicylaldehyde and other modified salicylaldehydes and amines have been used to study a variety of Schiff bases as ligands, but work on the crucial nuclei of salicylaldehyde and 2-aminobenzimidazole has not been done. There has been a lot of research done on the biological and commercial applications of the Schiff base metal complexes. Complexes of 2-aminobenzimidazole that include various metal ions have been created, characterised physicochemically, and shown to have biological activity. Porphyrins, a common class of macrocyclic compounds, are the subject of this article. They are essential to many biological activities, including the uptake of solar energy (photosynthesis) by plants and the transport of oxygen by animals.

**Keywords:** Analgesic, anti-inflammatory, antifertility, Schiff base

### Introduction

Metal complexes, which have been shown to be physiologically advantageous for chemical synthesis, have received more attention as a result of the developing shift in material chemistry. A wide range of biological activities, such as antibacterial, anti-proliferative, and antioxidant characteristics, are produced by the metal complexes containing N and O. When creating novel therapeutic drugs for all kinds of biological activity, metal has a special role to play.

Small molecules connected to and interacting with DNA often have more biological capability. A group of molecules having a metal centre and heteroatoms, such as N, O, and S, are known as transition metal complexes, and they may interact with nucleic acids by forming H-bonds with them. This is a crucial occurrence for the development of novel medicinal drugs. The use of a validated anti-proliferative medicine for different tumour types is made possible by the pharmacologically active molecules' frequent enhancement of their cleavage activity.

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A number of pharmaceutical capsules include benzil, a powerful inhibitor of human carboxylesterase enzymes involved in carboxylic ester hydrolysis. Pneumococcal pneumonia fatality rates have decreased by 25 to 6% thanks to the usage of pyridine-based compounds in structurally straightforward drugs like isoniazid, ethionamide, bupicomide, and sulpha pyridine (dihydropteroatesynthetase inhibitor). Chemotherapy medications use schiff base ligands made from the pyridine moiety and its copper derivatives. An important role for 2-amino-3-hydroxy pyridine in anti-inflammatory medications.

In our investigation, 2- aminopyridin-3-ol, metal chlorides, and benzil were used to create Schiff base metal complexes based on pyridine. To verify the geometry of the metal complexes, spectrum spectroscopy is used to identify the synthesised compounds. The synthetic compounds have been shown to be effective antibacterial, antioxidant, and anti-carcinogenic agents based on biological research.

### Synthesis of Schiff Base Ligand

To create Schiff's base ligand, 2-amino-3-hydroxy pyridine and benzil are separately diluted in ethanol and combined after three drops of glacial acetic acid and  $K_2CO_3$  are added after 4 hours of refluxing. A crystalline yellow material was the end product. The finished item was cleaned, filtered, and recrystallized from ethanol. The crystalline material was obtained and dried on anhydrous  $CaCl_2$  in a vacuum.

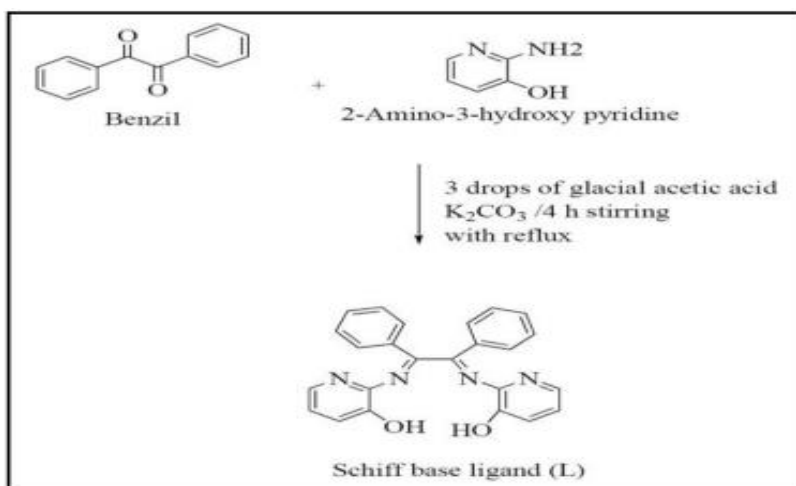


Figure 1: Synthesis of Schiff base ligand

“Yield: 89%. M.F. (C<sub>24</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>); colour: yellow; M.P: 180°C; anal. cal. for [C<sub>24</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>]: C 72.08%, H 4.65%, N 14.10%, found: C 72.01%, H 4.44%, N 14.08%;  $\lambda_{maxcm-1}$  in DMSO 37037 ( $\pi \rightarrow \pi^*$ )

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31,152 ( $n \rightarrow \pi^*$ ) FT-IR (KBr disc  $\text{cm}^{-1}$ ): 1592  $\nu(\text{-C=N})$ , 3437  $\nu(\text{-OH})$ ;  $^1\text{H NMR}$  ( $\text{DMSO-d}_6$ ) ( $\delta$ ): (aromatic) 7.33–8.27 (m), ( $\text{-OH}$ ) 9.63 (s),  $^{13}\text{C NMR}$  ( $\text{DMSO-d}_6$ ) ( $\delta$ ): (aromatic) 127.52, 129.17, 129.70, 129.94, ( $\text{-C=N}$ ) 158.19, ( $\text{-C-OH}$ ) 165.16; ESI-MS: 395 ( $\text{M} + 1$ )."

### Synthesis of Schiff Base

Equimolar amounts of the aromatic aldehyde and 2-aminobenzimidazole were combined with ethanol to create the Schiff base. About 4 hours were spent refluxing the mixture. After the solution concentration was decreased to half its initial volume and maintained for four to five days, deep yellow crystals formed in the reaction mixture. These crystals were filtered, thoroughly washed with the same solvent, and recrystallized with acetone. Analysis was done on the m.p.  $142^\circ\text{C}$  yellow Schiff base product obtained at a yield of 54% (Figure 2).

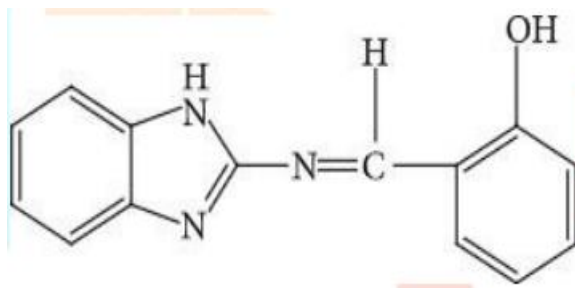


Figure 2: Structure of Schiff base

### Synthesis of the Complex

By conducting conductometric titration using the mono variation approach on a Systronics conductivity metre equipped with a dip form electrode, the ligand-metal ratio needed to create the complex Ab-S-Zn was calculated. 200 mL of pure ethanol was used to dilute 20 mL of a 0.01 M ligand before titrating it against a  $\text{ZnCl}_2$  (0.02 M) solution made in the same solvent. After each addition of the metal salt solution, conductance was measured. The appropriate conductance and the quantity of metal salt used are shown on a graph.

The equivalence point in the graph (L: M) indicates that the complex formation of the ligand with the metal happens at a ratio of 1:1. A 1: 1 (L: M) ratio in the complex was favoured by Turner and Anderson over Job's continuous variation method, which was further supported by conductometric titration.

Separately and together, 0.02 M of Ab-S and 0.02 M of metal salt solutions were made in pure ethanol. The resulting solution had a yellow-green hue. The N/10 NaOH solution was added to the solution, bringing the pH up to 7.5. The light green liquid was collected, refluxed for four hours, and kept for four days. The substance was then filtered, cleaned in the same solvent, dried using a  $\text{CaCl}_2$  fusion, weighed, and subjected to analysis.

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### Physical Measurements

The Vario MICRO V2.20 Elemental Analyzer Device GmbH was used to conduct the elemental analysis. Metal content may be determined gravimetrically. The FT-InfraRed Spectrophotometer model RZX (Perkin Elmer) was used to record the infrared spectra of KBr pellets. A Systronics direct reading conductivity metre was used to determine molar conductance in a 10<sup>-3</sup> M DMF solution. Using capillary melting point apparatus, the melting points of the ligand and the complex were determined in open capillaries.

The NMR spectrophotometer captured NMR spectra at University, and SAIF/CIL. The mass spectra were registered at SAIF/CIL, PU, using an LC-MS spectrometer of type Q-ToF Micro Waters.

### Hydrodynamic Measurements

In the absence of crystallographic evidence, the binding of ligand and metal complexes with deoxyribonucleic acid that causes a change in viscosity is important study. Another computation to predict the manner of metal-DNA interaction is this one. The intercalating agent is ethidium bromide (EB). Another argument in favour of the intercalative mode is the gradual addition of complexes to DNA, which led to the constant increase in DNA viscosity. Intercalation is facilitated by the EB's improvement of the relative viscosity of DNA strands.

Contrarily, partial and unconventional intercalatory chemicals have the ability to damage double-strand DNA and lessen its viscosity. The results were quite similar to the way that complexes and DNA strands intercalate. Viscosity values are unaffected if the binding mechanism is electrostatic and groove binding. It has been shown that synthetic compounds may attach to a DNA base pair, expanding the DNA loop and raising the relative viscosity of the DNA solution. Plotting  $(A/T)^{1/3}$  against  $[\text{Complex}]/[\text{DNA}]$ , where yes and no indicate the presence and absence of DNA solution complexes, respectively, yields the viscosity of the compounds in this experiment.

### Anti-bactericidal/Fungicidal Activity

Antimicrobial function is the process by which a disease that causes pathogenesis is stopped or avoided. In this work, the anti-pathogenic efficacy of the synthesised compounds against the selected bacteria is evaluated using the micro-dilution method. Using biochemical and morphological changes, the generated compounds may be examined for resistance to infections. The capability of action was measured using MIC values. Less doses of the medication are needed to stop the organism from developing if the MIC value is lower. Complexes in this investigation showed a lower MIC score than ligands, which suggested stronger antibacterial agents.

Figure1.11: The antibacterial activity of the synthesized compounds

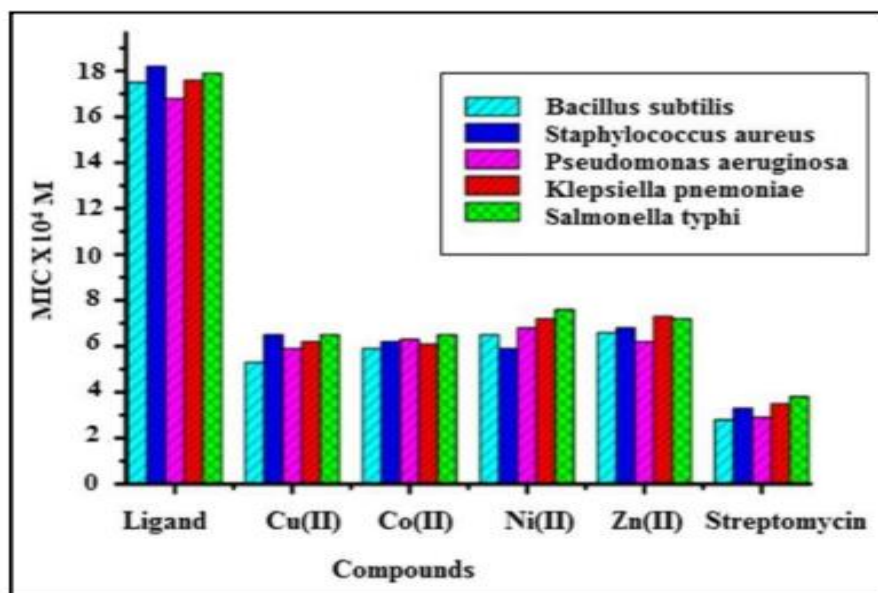
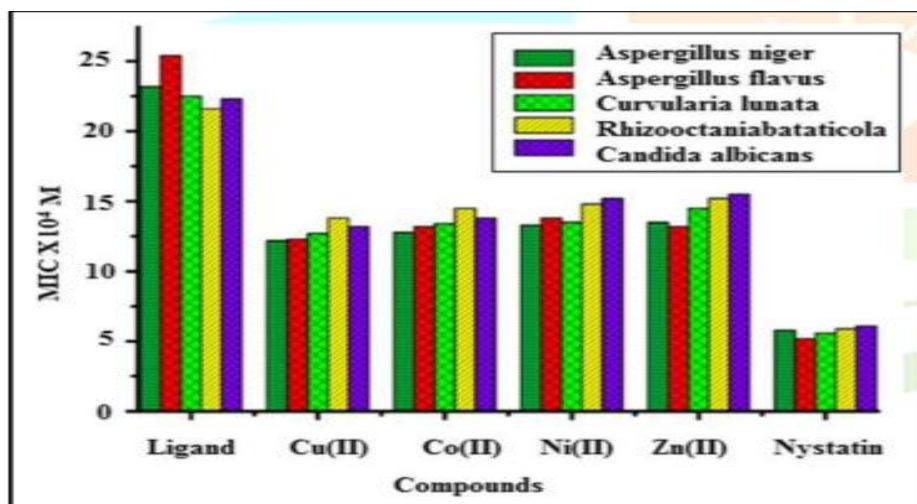


Figure1.12: The antifungal activity of the synthesized compounds



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According to Tweedy's chelation hypothesis, the complexes that were created had stronger antibacterial effects.

The theory states that the metal ion's polarisation is diminished more, leading to ligand orbital overlap and partial metal ion contribution, as well as amplifying the relocation of the  $\pi$ -electron within the chelate ring and increasing the perforation of the compounds into the lipid cell wall.

Additionally, by blocking protein synthesis and sealing metal-binding sites in pathogen enzymes, this method restricted the growth of microbes. The results show that following chelation, metal complexes with N and O atoms become more lipophilic, preventing germs from entering the human body. Due to transition metals, heterocyclic atoms (N, O), chelation, additional electrons in coordination compounds, and transition metals themselves, metal complexes have more anti-pathogenic potential than free ligands.

### Conclusion

The analysis of the transition metal's reactivity with the resultant Schiff base reveals the exceptional stability of the material. Due to the existence of bonding between the Schiff base and the transition metal cation, physicochemical analytical methods can now synthesise and examine the important biological importance of this. As was discussed above, the complex's fragmentation pattern and spectrum studies support and provide an explanation for the assumed geometry discovered by elemental analysis, IR,  $^1\text{H}$  NMR, and mass spectra. In this study, four metal complexes and a bio-critical Schiff base ligand generated from pyridine were synthesised and investigated. The cobalt, nickel, and zinc complexes have tetrahedral geometry, according to the spectrum data, whereas the copper complex has a square planar shape.

The DNA binding result demonstrated that molecular docking simulations further supported the intercalative mode and mode of interaction with deoxyribonucleic acid of the synthesised chemical. The copper complex seems to more commonly break the double strand of DNA with the activator, according to gel electrophoresis results. The generation of antibacterial activity proves that metal complexes have greater anti-pathogenic potential than ligands.

Additionally, studies on anticancer activity have shown that the generated complexes have strong anticancer potential, causing cell death by apoptosis. The antioxidant investigations have shown that manufactured complexes have a stronger antioxidant capacity than ligands owing to chelation. Lipinski's criteria state that metal complexes exhibit admirable "drug-like" characteristics, as shown by the *in silico* ADMET property. The conclusion drawn from the available biological data is that the synthesised chemicals may develop into potent antibacterial and malignant tumour treatments with some sophisticated therapeutic strategies in the future.

The objective of this study is to develop novel dicompartmental acyclic and macrocyclic Cu(II) and Zn(II) complexes with two contiguous Hexa- and Tetra-coordination sites. The propionate pendant pendent arms were found to be devoid of coordination, despite the fact that the research's synthetic

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goal had been met. A noteworthy outcome was seen when the copper (II) ion was transferred from the N(amine)<sub>2</sub>O<sub>2</sub> coordination sites to the N(imine)<sub>2</sub>O<sub>2</sub> coordination sites during the cyclization of 1,3-diamino propane by the acyclic monometallic copper (II) complex.

**\*Associate Professor  
Department of Chemistry  
SMPBJ Govt. College Sheoganj  
Sirohi (Raj.)**

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