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Role and Efficacy of SBMCs as antimicrobial Agents: A Comprehensive Review

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Abstract

Because of their exceptional biological qualities, especially as antibacterial agents, SBMCs have attracted a lot of attention lately. SBs adaptable ligand structures efficiently combine with metal ions to form stable complexes. They are produced by the condensation of primary amines and carbonyl compounds. Because of their distinct structural and electrical characteristics, these metal complexes exhibit more potent antibacterial action than the metal and free ligands that make them up. The coordination environment, ligand structure, and kind of metal ion present all effect how well SBMCs work against microorganisms. These complexes hinder microbial development by rupturing microbial cell membranes, inhibiting enzymatic function, and producing reactive oxygen species. They are also effective against a wide range of pathogens, such as viruses, fungi, and bacteria, which makes them suitable options for fighting bacterial strains that are resistant to antibiotics. This abstract highlights Schiff base metal complexes' potential for usage in medicinal applications by examining their synthesis, structural features, and antibacterial qualities. Recent developments in their design and assessment of their effectiveness as antimicrobial agents enable new therapeutic methods.

Key words: Schiff base ligand, transition metals, antifungal, antibacterial activities.

1. Introduction

SBMCs are now a vital class of coordination compounds with significant applications in catalysis, medicinal chemistry, and materials research, among other fields. Under some

circumstances, a primary amine interacts with a ketone or aldehyde to make SBs, which are named after the German chemist Hugo Schiff **[1].** These complexes are formed when metal ions align with SBs ligands. As shown in **Fig. 1**, a tetrahedral intermediate is created when an amine nucleophilically approaches the electrophoretic site during the synthesis of a Schiff base.

Because of their biological significance, structural diversity, and flexibility, they are the subject of extensive research **[2].** It is well recognized that metal ions are necessary for life and have a major impact on numerous vital biological functions. They are essential cofactors for many enzymes and aid in the regulation of oxygen transport, electrolyte balance, and electron transfer. They have also been connected to immune system regulation and the host's defence against dangerous invaders. Metals come in a variety of because of the double bond between nitrogen and carbon in their structure, SBs have found several biological uses. The advantageous characteristics of SBMCs extend beyond the azomethine link and include many scaffolds that have strengthened the structure, such as substituted aromatics and aromatic compounds. The resulting biological effects of Schiff bases may be caused by the presence of hydrogen bonds between the existing atoms and functional groups, such as the hydrogen bond between the OH group and the N atom of the azomethine portion and the presence of a nucleophile group **[3].** SBs ligands are easily synthesized and can form complexes with almost any metal ion. Since it is now known that several of these complexes of Schiff bases may serve as mock-ups for physiologically relevant species, interest in these complexes has grown **[4].**

The coordination of transition metal ions and the formation of various enriched metal complexes with a wide range of antibacterial, antiproliferative, antifungal, anticancer, antipyretic, and antimalarial **[5–11]** properties have been demonstrated to be possible with the Schiff bases **(Fig. 2).** Metal complexes have higher biological activity than their ligand counterparts. Schiff base complexes are very interesting because of their optical nonlinearity characteristics, electron-donating ability, stability, catalytic, photochromic, and biological activity. The basis for the activity of SBs is their coordination to metal ions **[12].**

Their synthesis an extensive summary of the function of SBs compounds and their metal complexes in antimicrobial applications is what these paper attempts to provide., structural characteristics, modes of action, and potential to address the present issues with antimicrobial resistance will all be covered.

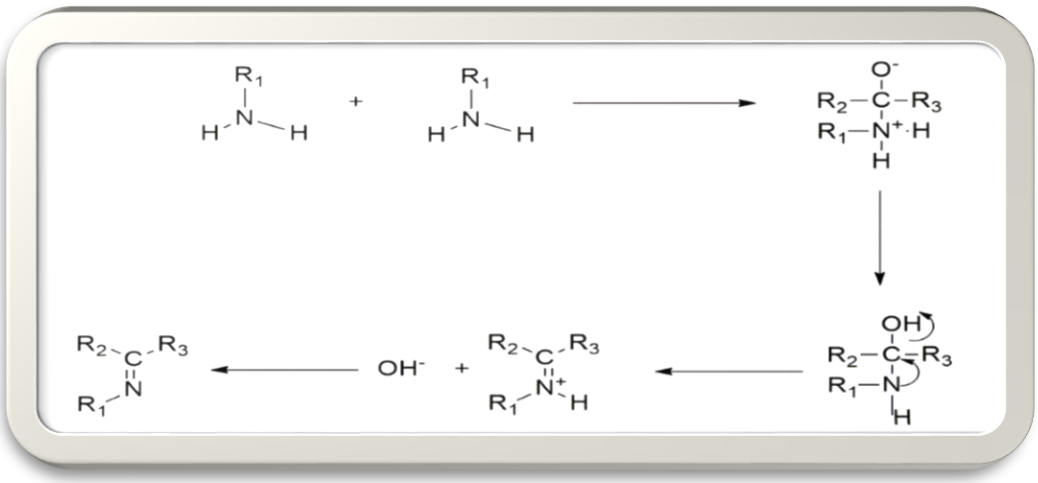


Fig. 1 Mechanism for formation of SBs

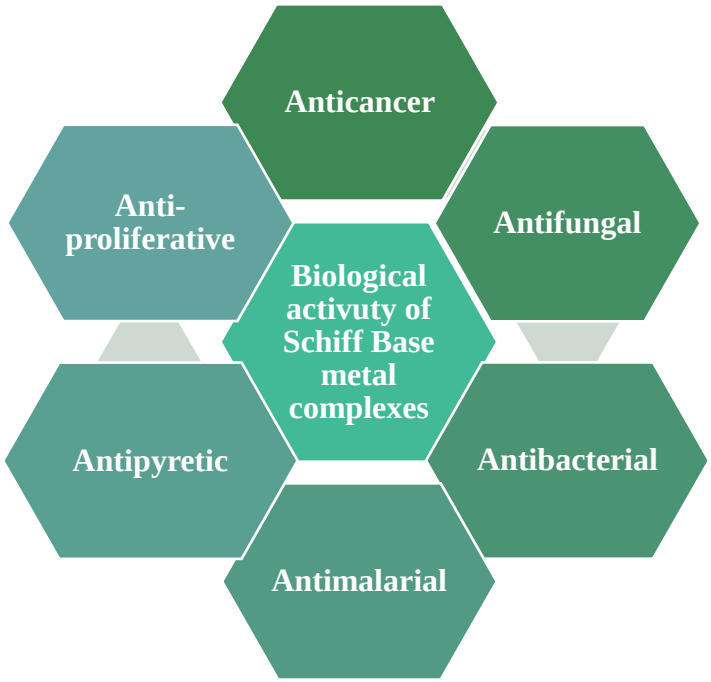


Fig. 2 Biological activity of SBMs

2. Mechanism of action of Antimicrobial activity

The mechanisms of resistance to antimicrobial drugs are examined in order to study their effects. Antimicrobial medications that target vital bacteria functions have little to no effect on host functioning. Every antimicrobial medication works via a different mode of action **[13–14]**. These mechanisms, which include the following, can be categorized according to the bacterial structures or functions they target.

(a) Interaction with Cell Membranes

SBs increase permeability by interacting with proteins and phospholipids to disrupt microbial cell membranes. As a result, essential cell constituents such as proteins, ions, and nucleotides leak out, ultimately resulting in cell death.

(b) Inhibition of Enzymatic Activity

In order to bind to microbial enzymes, SBs must have the azomethine (-C=N-) group. By blocking the action of enzymes by forming stable complexes with their active sites, SBs interfere with vital metabolic activities required for microbial survival.

(c) Generation of Reactive Oxygen Species (ROS)

SBM exhibiting redox activity generate reactive oxygen species (ROS), including hydrogen peroxide, superoxide anions, and hydroxyl radicals. These ROS damage proteins, lipids, and DNA, which results in oxidative stress and death in microorganisms.

(d) DNA Intercalation and Damage

Transcription and replication are inhibited by Schiff bases and their complexes' capacity to intercalate into microbial DNA. Metal compounds enhance this activity and kill microorganisms by encouraging DNA cleavage through redox reactions or direct contact.

(e) Metal Ion Release and Toxicity

Metal ions that are coupled with Schiff bases may be released by the microbial cell under healthy conditions. These ions, such as Cu^{2+}, Zn^{2+}, or Ag^{+} interfere with microbial metabolism and electron transport, leading to detrimental consequences that either halt the growth of the microbe or result in its death.

(f) Chelation Therapy

Essential metal ions are chelated by SBs, which function as ligands in microbial cells, depriving them of cofactors required for metabolic and enzymatic processes. Growth and function of microorganisms are hampered by this shortage.

(g) Synergistic Effects with Metal Complexes

The combination of metal ions and SBs increases lipophilicity, which facilitates the molecule's entry into microbial cells. The efficacy is often increased by this synergistic action compared to unbound Schiff bases.

3. Structural Factors Influencing Antimicrobial Activity

Several structural factors influence the antimicrobial activity of Schiff base metal complexes:

(a) **Chemical and Electronic Effects:** The stability and reactivity of the complex are influenced by the donor atoms in the Schiff base ligand as well as the size and shape of the metal ion. The antibacterial action can be increased by a stiff ligand or a bigger metal ion.

(b) **The Ligand's nature:** The lipophilicity, solubility, and general bioactivity of the complex can be influenced by the kind of functional groups—such as hydroxyl, methoxy, or halogen groups—that are affixed to the Schiff base ligand.

(c) **Coordination Geometry:** The interaction with microbial cells and the effectiveness of antimicrobial activity can be affected by the coordination environment of the metal ion in the Schiff base complex, such as square planar, octahedral, or tetrahedral geometry.

4. Schiff Base metal complexes and their Antimicrobial activity

A bidentate Schiff base N_2O_2 donor ligand, namely (E)-2-bromo-4-chloro-6-[(2,6-dimethylphenylimino) methyl] phenol (HL), was used to create a mononuclear Cu (II) complex **(Fig. 3).** Its photophysical characteristics, including as UV-Vi's absorption and fluorescence spectra, were thoroughly investigated. Moreover, X-ray diffraction was used to examine its powder form **[15].** The produced compounds' antibacterial efficacy was assessed against *E. coli, P. aeruginosa*, and *S. aureus*. Interestingly, the minimum inhibitory concentration (MIC) of the copper complex against E. coli was 1.25 mmol L^{-1}.

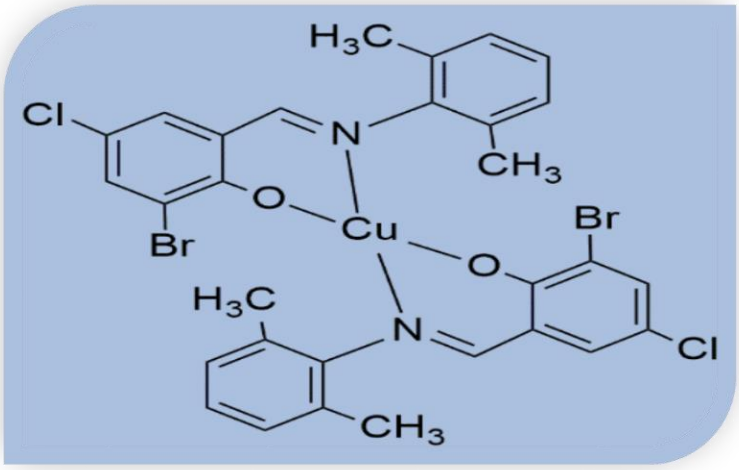


Fig. 3 Structure of Cu (II) complex with N_2O_2 donor ligand

Co (II), Ni (II), Cu (II), and Zn (II) complexes **(Fig. 4)** of Schiff base ligand were described by Devi et al. [**16]** and were created by reacting satin with bromo and nitro derivatives of aminophenol. IR, UV-Vis, NMR, and ESR were among the spectroscopic and analytical techniques used to describe the produced compounds. The results showed that the complexes had an octahedral geometry. Gram-positive bacteria like B. subtilis and M. luteus, Gram-negative bacteria like *P. aeruginosa* and *P. Mendocino*, and fungi like *V. dahliae*, *C. herbarium,* and *T. soudanense* were all tested for the compounds' in vitro antimicrobial activity. The agar plate disc diffusion method was used to measure the biological activity. The findings demonstrated that the antibacterial activity of the transition metal complexes was higher than that of the comparable Schiff base ligands.

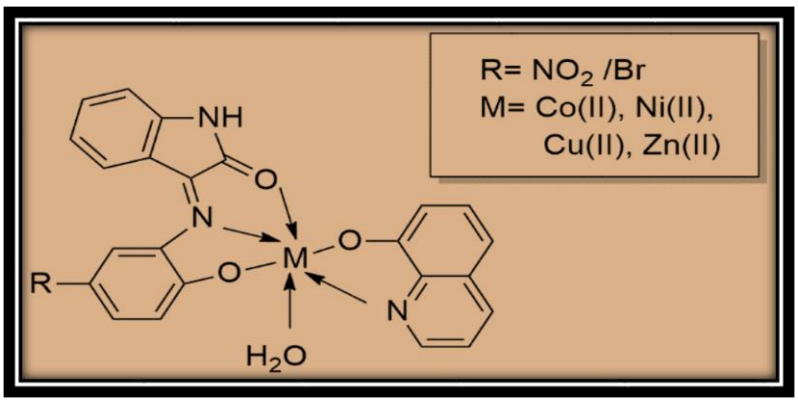


Fig. 4 Co (II), Ni (II), Cu (II), and Zn (II) complexes

In addition to its $CoCl_2$, $PdCl_2$, $CuCl_2$, and $ZnCl_2$ complexes, tridentate and dideprotonable Schiff bases (H3L1–H3L4) with three hydroxyl groups were synthesized **[17].** In addition to a detailed characterization of these compounds, the keto-enol tautomerization of the Schiff bases was covered. The produced compounds' antifungal and antibacterial properties were assessed. With MIC values of 4.87, 4.87, and 9.75 µg/mL, respectively, $[Zn(H_2L_1)Cl]\cdot 4H_2O$ (Fig 5) showed noteworthy superior efficacy against *C. albicans*, *C. parapsilosis*, and *C. tropicalis.* Furthermore, H_3L_1, H_3L_2, and H_3L_3 demonstrated selectivity by being highly efficient against *S. aureus* while being inactive against other pathogens.

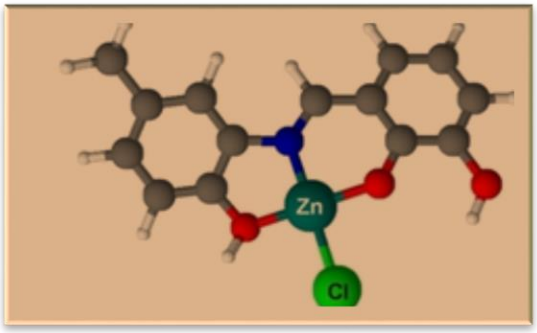


Fig. 5 Crystal structure of $[Zn(H_2L_1)\ Cl]\cdot 4H_2O$ complex

Mn(II), Fe(II), and Co(II) complexes of Schiff base **(Fig. 6)** were reported by Basir and Siraj **[18]** and were made by condensation of 2-thiophenecarboxaldehyde and ethylenediamine. Melting point/decomposition temperature analysis, solubility tests, molar conductance, magnetic susceptibility, elemental analysis, infrared spectroscopy, and UV-visible spectrophotometry were used to describe each complex. *In vitro* antibacterial activity of the Schiff base and its metal complexes was assessed against two pathogenic fungi i.e. *Aspergillus niger* and *Aspergillus fflavus and*three harmful bacteria i.e. *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Escherichia coli*. The metal complexes showed somewhat larger inhibition zones (6–17 mm), but the Schiff base showed modest antibacterial activity with inhibition zones ranging from 6–14 mm. Their action, however, was less than that of the control medications, which displayed 18–30 mm inhibitory zones.

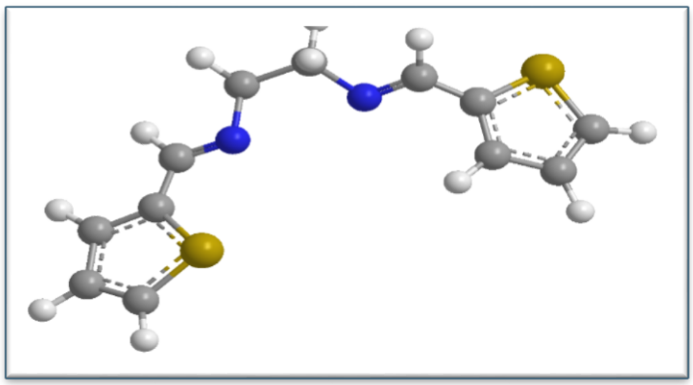


Fig. 6 Structure of Schiff base

Through equimolar reactions of 3-aminopyridine with o- and p-vanillin, two physiologically active Schiff bases were produced **(Fig. 7).** In the presence of trimethylamine, these Schiff bases were then reacted with cobalt acetate, cobalt chloride, or cobalt chloride utilizing a 2:1 molar ratio of Schiff base to cobalt salt. The produced Schiff bases and their cobalt(II) complexes were examined by means of mass spectrometry, FTIR, diffuse reflectance, and UV–

visible spectroscopy in methanol. The Schiff bases' bidentate coordination with the cobalt core during complex formation was validated by FTIR analysis. A deformed tetrahedral geometry was suggested for the Co(II) complexes based on spectrum analyses. The Schiff bases and their cobalt(II) complexes were tested for their antibacterial properties against strains of *Pseudomonas aeruginosa*, *Escherichia coli, Staphylococcus aureus,* and the fungus *Aspergillus niger* that were isolated in a lab. In contrast to the free Schiff bases, the cobalt complexes showed more biological activity, according to the data **[19].**

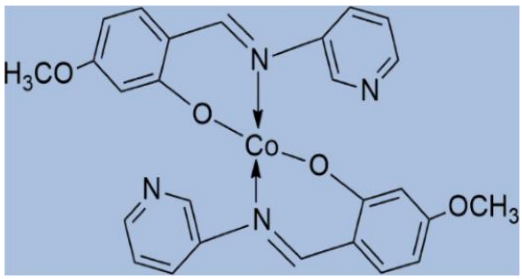


Fig. 7 Cobalt(II) complex of Schiff base derived from *p-vanillin* and 3-aminopyridine

The antibacterial qualities of copper complexes have been the subject of several investigations throughout the last five years. Key instances of iron's and related elements' antibacterial uses are noteworthy for context, even though they are better addressed separately. Kaushal et al. **[20]** synthesized and studied a variety of 2-acetylpyridine-N-substituted thiosemicarbazones of copper (II) **(Fig. 8),** showing notable efficacy against *Candida albicans*, *Klebsiella pneumoniae*, and methicillin-resistant *Staphylococcus aureus* (MRSA). With minimum inhibitory concentrations (MICs) between 0.5 and 5 µg/mL, these complexes demonstrated effectiveness similar to that of common antimicrobials such as gentamicin and amphotericin. The study also investigated the connection between the antibacterial efficacy of halogens (X) and the structural alterations of the R groups.

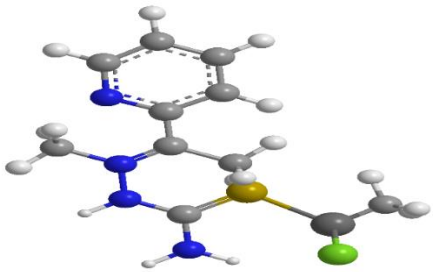


Fig. 8 Cu(II) complex of 2-acetylpyridine-N-substituted thiosemicarbazonates

Chandra et al. **[21**] produced a cobalt(II) complex with a tetradentate nitrogen donor [N_4] macrocyclic ligand, 6,15-dimethyl-8,17-diphenyl-7,16-

dihydrodibenzo[b,i][1.4.8.11]tetraazacyclotetradecine. Its structure was detailed using spectroscopic methods like infrared, ^{1}H-NMR (for the ligand), electronic spectrum studies, magnetic susceptibility tests, molar conductance, and elemental analysis. The substance in **Fig. 9** was not an electrolyte, according to these investigations. Tests for fungicidal efficacy against two dangerous fungi were used to further evaluate the ligands and its cobalt (II) complex's capacity to inhibit fungal growth.

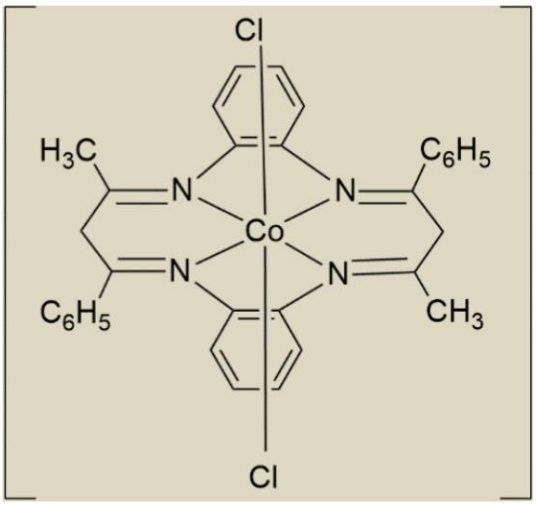
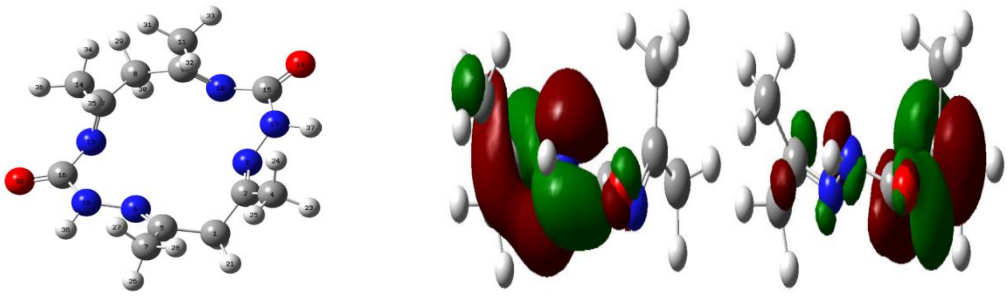


Fig. 9 Co(II) complex of tetradentate macrocyclic ligand

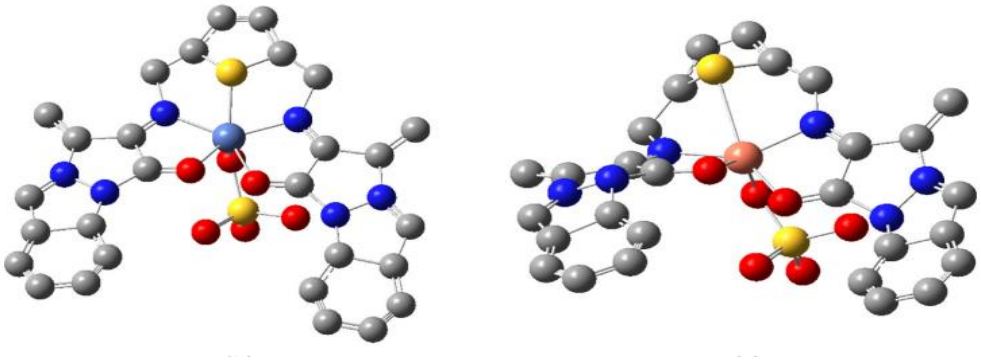
Ni(II), Pd(II), Pt(IV), and Cu(II) complexes of a Schiff base azamacrocyclic ligand, 5,7,12,14-tetramethyl-1,2,4,8,10,11-hexaazacyclotetradeca-4,7,11,14-tetraene-3,9-dione **(Fig. 10a).** were synthesized and described by Gautam et al**. [22].** Using the 6-31g(d,p) basis set, the shape of ligand (L) was completely optimized with regard to energy **(Fig. 10b).** Using streptomycin and chlorothalonil as standards, antimicrobial and antifungal activity were evaluated *in vitro* against bacteria (*Sarcina lutea and Escherichia coli)* and fungus (*Aspergillus species)* using the Agar Plate and disc diffusion procedures. Because the chelation effect increases bioactivity, the results showed that metal chelates were more active than the ligand alone, especially for Cu complexes.



(a) **(b)**

Fig.10 (a) Structure of Schiff base ligand (**b)** HOMO and LUMO plot for Schiff base ligand .

4-aminoantipyrine and its Ni(II) and Cu(II) complexes **(Fig. 11)** were used to create and describe a Schiff base ligand by Tyagi et al. **[23].** To find the minimum inhibitory concentration (MIC), the antifungal activity of these compounds was assessed against *Phoma sorghina*, *Aspergillus niger*, and *Fusarium oxysporum* using the serial dilution method. DMSO was used as the control, and bavistin was used as the usual medication. The majority of the complexes exhibited modest antifungal activity, with increasing activity upon metal coordination, as explained by the chelation theory and Overtone's idea **[24–29].**



(a) **(b)**

Fig. 11 Geometry optimized structure of complexes **(a)**) $[NiL(SO_4)]$ **(b)** $[CuL(SO_4)]$

Co(II) complexes with particular amino acids were created from an N-salicylidene derivative that had amine and nitro groups **[30].** The biological activity of these complexes against different bacteria strains was examined. The findings showed that the metal complexes had more potent antibacterial qualities than the Schiff base ligand in its free form.

5. Challenges and Future Directions

Enhancing the bioavailability, stability, and selectivity of Schiff base transition metal complexes in biological systems is the main goal of the problems and future directions in their antibacterial activity **[30–32].** Although these complexes have potential as antibacterial agents, a number of obstacles must be overcome to maximize their therapeutic potential. Optimizing the metal-ligand coordination to attain greater stability and solubility, which would increase their efficacy in biological settings, is one major problem **[33].** Furthermore, in order to improve their interaction with microbial membranes and their capacity to infiltrate and destroy microbial cells, Schiff base metal complexes frequently need to have their molecular structure

adjusted. Changes to the ligand structure and the selection of metal ions, which are essential to the complex's bioactivity, can accomplish this. In order to enhance medication delivery systems, guarantee targeted action, and reduce adverse effects, future research should concentrate on integrating these complexes with contemporary nanotechnology. Additionally, creating hybrid molecules that mix Schiff base metal complexes with other medicinal substances may improve their antibacterial effectiveness by producing synergistic effects **[34–35].**

6. Conclusion

In the fight against infectious diseases, Schiff base transition metal complexes have shown great promise as antibacterial agents and present a viable substitute for conventional antibiotics. By enhancing their biological activity, transition metals including copper, nickel, cobalt, and zinc can be coordinated with Schiff base ligands to improve their solubility, stability, and antibacterial efficiency. These complexes demonstrate their versatility as antimicrobial agents by demonstrating activity against a wide range of pathogens, including fungi and both Gram-positive and Gram-negative bacteria. The chelation of metal ions, which may improve the complex's capacity to interact with microbial cell membranes and enzymes and impede microbial development, is one of the mechanisms contributing to the increased antibacterial efficacy of Schiff base metal complexes. Several complexes exhibit action that is on par with or better than that of traditional antibacterial medicines, and this chelation effect frequently results in improved potency when compared to free Schiff base ligands. These complexes have intriguing features, but there are obstacles that must be overcome before they may be widely used in therapeutic settings. To improve their stability, selectivity, and bioavailability in biological systems, their architectures are optimized. Additionally, in order to guarantee safety in human uses, its possible toxicity needs to be carefully assessed.

Schiff base metal complexes may be able to treat resistant bacterial and fungal strains more successfully if they are combined with cutting-edge drug delivery technologies like nanoparticles or hybrid materials. To sum up, Schiff base transition metal complexes have a lot of potential for creating novel antibacterial medicines, especially as substitutes to fight antibiotic resistance. To fully realize their therapeutic potential, more research into their structural alterations, modes of action, and clinical uses is necessary. Schiff base metal complexes could play a key role in future antimicrobial treatments as coordination chemistry, nanotechnology, and drug delivery methods continue to progress.

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