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Review Article

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Biological activities of metal complexes with Schiff base

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Abstract: Schiff bases are a class of synthetic compounds that form when primary amines combine with aldehydes or ketones. These compounds are incredibly important across various fields, such as biology, catalysis, and optics, due to their diverse features. One notable aspect is their ability to form complexes with transition metals, which opens up a wide range of potential uses, particularly in human systems. In the human body, Schiff base metal complexes display a range of biological actions, including antibacterial, antifungal, anticancer, and antimalarial properties. The versatility of Schiff bases in reacting with different transition metals gives these complexes intriguing potential for addressing biological issues and treating diseases. This article explores various examples of Schiff bases, metal complexes, and their associated ligands, highlighting their usefulness in a variety of biological applications. The potential of Schiff base metal complexes as valuable agents in resolving medical difficulties and advancing biomedical research is emphasized.

Keywords: Schiff bases; metal complexes; biological activity; antibacterial properties; biomedical applications

1 Introduction

Metal ions play vital roles in biological functions, and medical inorganic chemistry is a branch of science that deals with the use of inorganic chemistry in medicine or illness diagnostics.[1–3] Considering the contributions of various medications that have become fundamental components of contemporary pharmacopeia, as well as breakthroughs in our understanding of inorganic chemical biology, medical inorganic chemistry is still regarded as a developing field.[4] This is partly owing to the field qualitative character, which lacks a set of norms such as Lipinski's rule.[5] Metal complexes are an exceedingly flexible and dependable technique for the synthesis of better pharmaceutical molecules. The chemical characteristics of these complexes may be accurately tuned by adjusting the metal center oxidation state and selecting the best ligands for each application. It is not unexpected that the difficulty of developing new and better metal-based medications is closely related to the creation of innovative and improved ligands for the functional metal element. Metals are known for their ability to quickly lose electrons, producing ions with a positive charge that are easily dissolved in biological liquids. Metals perform their biological functions in this cationic state. Metal ions are electron-poor. Unlike most biological elements, electron-rich materials include proteins and DNA. Metal ions bind and interact with biological molecules due to the attraction between their opposing charges.[6–8] The identical idea works for metal ions affinity for numerous tiny ions and molecules required for life, like oxygen. Given the wide range of metal interactions in life, it is not surprising that natural evolution has incorporated various metals into important biological processes. Metals play diverse roles, such as transporting oxygen throughout the body and facilitating electron movement. Hemoglobin, for example, is an iron-containing protein that interacts with oxygen and distributes this vital chemical to bodily tissues. Similarly, calcium-based minerals form the foundation of bones, providing the skeletal structure for the human body. Additionally, metals such as iron, copper, manganese, and zinc are incorporated into protein catalysts known as metalloenzymes, which support a wide

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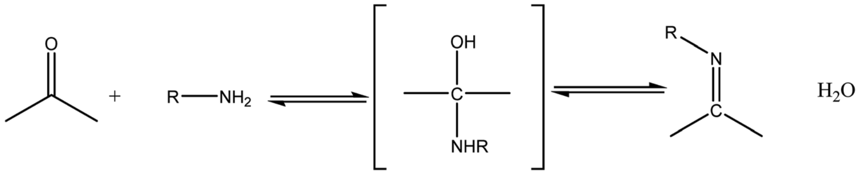


Figure 1: Synthesis of the general reaction of Schiff base compounds.[33]

array of essential chemical reactions necessary for life. The complexes of metals currently being used in clinical settings, This encourages ongoing research for novel metalloid medicines such as metal-based anti-biotic, anti-bacterial,[9] antipyretic, antibacterial,[9] antiviral,[10] anxiolytic,[11] antifungal,[12] anti-inflammatory,[13,14] ant proliferative,[15] analgesic, anxiolytic.[11] Metal complexes combining various metals with Schiff Base showed an extensive range of activities,[16,17] as well as catalytic uses [18] in which Metals can be represented by Mo,[19] Pd,[20] Ni,[21] Zr,[22–24] Zn,[25,26] Ru,[27] Cu,[28] Ni,[21] Mn,[29] and Cu.[30–32] A primary amine reacts with the carbonyl group of an aldehyde (RHC=O) or ketone (R2C=O) to form Schiff base compounds (Figure 1).

Schiff bases are compounds consisting of a carbon double bonded to a nitrogen atom (C–N), commonly referred to as azomethine or imine. The presence of this functional group is essential for their involvement in complex reactions and biological activity.[34–37] The purpose of this review is to analyze the biological activity of Schiff base complexes and ligands with biological activities.

2 Mononuclear SBs complexes

Saritha and Metilda[38] explored the anti-inflammatory and antibacterial properties of a novel Schiff Base ligand generated from curcumin and semi-carbazide, along with its corresponding transition metal complexes, including Co(II), Mn(II), Cu(II), Zn(II) and Ni(II). The anti-microbial effectiveness was tested against a range of bacteria (*Staphylococcus aureus*, *Escherichia coli*, *K. Bacillus subtilis*, *Pseudomonas aeruginosa*, and pneumonia) and fungi (*A. niger* and *Candida albicans*). Applying the agar well diffusion technique. Comparative analysis with nystatin revealed that the Zn complex Zn(HMHC)$_2$].H$_2$O. Figure 2 showed superior efficacy against *B. subtilis* K. and pneumonia bacteria, as well as against fungus.[35] Overtone's concept[39] and Tweedys Chelation theory[40] were used to explain the complexes increased activity. Furthermore, the anti-inflammatory activity of complexes was investigated utilizing the blocking of albumin denaturation technique, according to a slightly modified literature protocol.[41] Figure 2 inhibited heat-induced albumin denaturation at various doses, with the highest inhibition of 92.2 % at 100 g/mL, compared with diclofenac sodium (100 % inhibition).

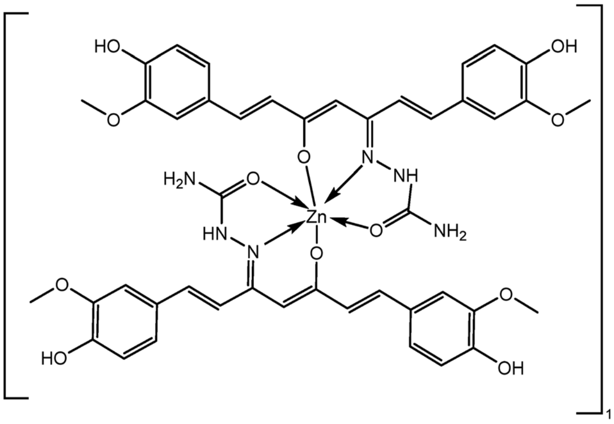
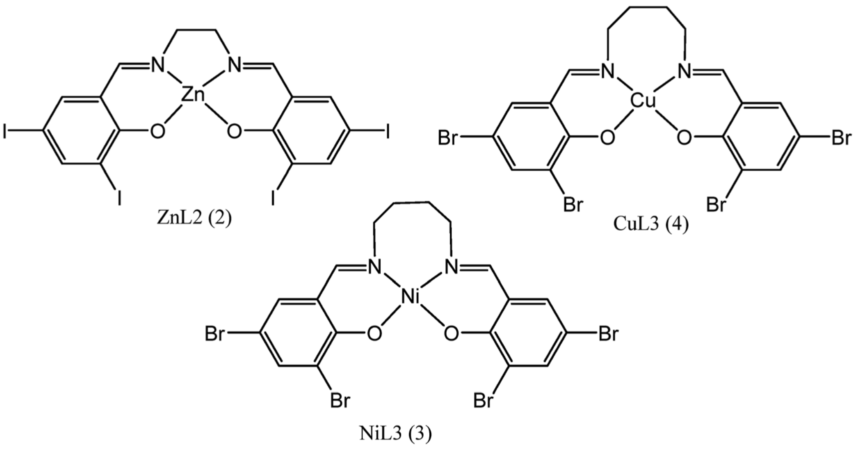


Figure 2: The Zn complex [Zn(HMHC)2].H2O.

Kargar and co-workers[42] Utilizing the disc-based diffusion technique, antibacterial activity was determined versus two Gram-positive (*Bacillus cereus* and *S. aureus*) and 2 Gram-negative (*P. aeruginosa* and *E. coli*) bacterial strains. The complexes demonstrated efficiency against all the bacteria examined compared to the standards, erythromycin, and ampicillin (Figure 3). Complex 3 exhibiting the highest activity, underwent examination using single crystal X-ray diffraction, revealing its adoption of slightly distorted octahedral geometries surrounding Ni(II).

Maia and colleagues[43] documented the method for the synthesis of a nickel(II) chloride Schiff Base compound, designated as (Ni(L2), and have examined its anti-microbial properties contrary to a range of strains, such as leishmania, *E. coli* (derived from a urine culture), *P. aeruginosa* (obtained from a rectal swab), and multi-resistant *S. aureus* (isolated from a catheter tip). According to the study, this complex exhibited significant activity at a concentration of 256 µg/mL, inhibiting the growth of *P. aeruginosa* strains. It did not, however, show any appreciable activity against strains of *E. coli* and *S. aureus*. The impact of Figure 4 on the antibiotic's effectiveness against strains that are resistant to multiple resistances was also examined in this study. Interestingly, Figure 4 improved the efficiency of gentamicin against *S. aureus* by lowering the minimum inhibitory concentration (MIC) from 50.8 to 16 µg/mL. This means that 68.5 % less gentamicin was needed to achieve the same

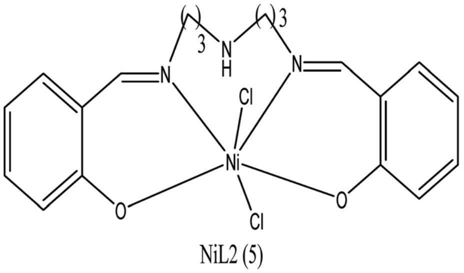


ZnL2 (2)

CuL3 (4)

NiL3 (3)

Figure 3: Structures of antimicrobial activity by Kargar et al.[42]



NiL2 (5)

Figure 4: Ni(L2) complex with antimicrobial activity.

effect on the strain. Similarly, there was a decrease of approximately 20.6 % for *E. coli*. Additionally, Figure 4 enhanced amikacin's anti-*E. coli* activity, resulting in a 37 % decrease. However, when combined with the complex, both gentamicin and amikacin experienced a reduction in their antimicrobial activity. Furthermore, promising results were observed in the fight against Leishmania.

Kulandaisamy A. and Palanimurugan A. created new transition metal complexes by combining benzylidene *para*-nitroaniline and 2,2-bipyridyl with a mixed SBs ligand. The resulting complexes were ZN(II), Cu(II), Co(II), Ni(II), and VO(II). Upon characterization using spectroscopic techniques, it was determined that all the complexes exhibited a square planar geometry, except for the VO(II) complex, which displayed a square pyramidal geometry (see Figure 5). Molar conductivity and magnetic susceptibility measurements were conducted to assess the electrolytic behavior and monomeric structure of the complexes. A quasi-reversible peak was detected through cyclic voltammetry analysis of the Copper(II) complex in acetonitrile solution. The characteristics of its oxidation and reduction were documented. The biological activity of the resulting compounds was evaluated against several bacteria, including Salmonella typhi, *B. subtilis*, *E. coli*, *Klebsiella pneumonia*, and *S. aureus*.

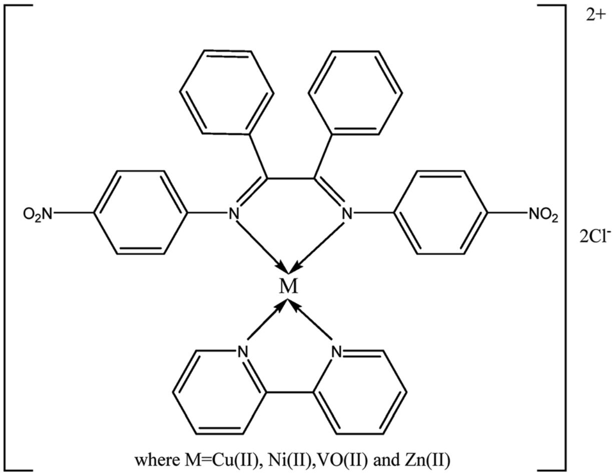


Figure 5: The square pyramidal geometry of VO(II) complex.

In comparison to the ligand, the anti-microbial evaluation of the complexes showed encouraging outcomes. Because of its increased lipophilicity, the zinc (II) complex exhibited superior anti-microbial properties when compared to the other complexes.[44] In their research, Tyula and colleagues[45] examined Schiff base (SB) complexes containing various metals (Cd2+, Zn2+, and Hg2+) to determine their anti-bacterial properties. They conducted a detailed structural analysis specifically on the cadmium (II) complex, referred to as $[Cd(H_2L)].2H_2O$ (Figure 6). H4L represents N,N,N′,N′-tetrakis(5-bromosalicylidene) N,N,N′, N-tetrakis (2-aminoethyl) ethylenediamine. The analysis involved single-crystal X-ray crystallography, Hirshfeld surface analysis, and the comparison of two-dimensional fingerprint graphs. The anti-bacterial effectiveness of these complexes was assessed using the disc diffusion technique against three Gram-positive bacteria (*Staphylococcus epidermidis*, *Enterococcus faecalis*, and *S. aureus*) and three Gram-negative bacteria (*K. pneumoniae*, *P. aeruginosa*, and *E. coli*).

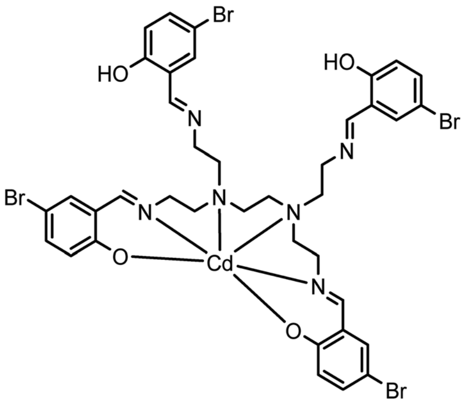


Figure 6: Cadmium (II) complex with antimicrobial activity.

The Hg(II) compound, as shown in Figure 7, exhibited the highest efficacy with moderate antibacterial effects. It effectively inhibited the growth of *E. faecalis*, *S. epidermidis*, and *P. aeruginosa*, surpassing the standard sulfisoxazole. All complexes demonstrated impressive activity against *P. aeruginosa*, as quantified by the percentage of inhibition, with a range of 120 %–200 %. Additionally, the Hg complex displayed remarkable activity against *E. faecalis* and *S. epidermidis*, with 120 %–140 % inhibition, and noteworthy activity against *E. coli*, with 90 % inhibition.

In 2021, Abu-Dief and colleagues[46] conducted a study to examine the antimicrobial properties of various metal complexes (Pd(II), Cr(III), VO(II), and Zn(II)) combined with a Schiff base derivative (HNP). The Schiff base derivative, known as HNP, is represented by the chemical formula 1-(pyrimidin-2-yliminomethyl)-naphthalen-2-ol. The researchers tested these metal complexes against two Gram-negative bacteria (*E. coli* and Serratiamarcescens), one Gram-positive bacterium (*Micrococcus luteus*), and three fungal species (*Geotrichum candidum*, *Aspergillus flavus*, and *Fusarium oxysporum*). Interestingly, the HNPPd complex, as shown in Figure 8, exhibited significant inhibition comparable to conventional antibiotics such as fluconazole against *A. flavus* and ofloxacin against bacteria. Furthermore, the researchers investigated the antiproliferative effects of these complexes on three human cancer cell lines: human colon cancer and human hepatocellular carcinoma. Figure 8 indicated promising antiproliferative properties, as it inhibited the growth of tumor cells in a manner similar to vinblastine.

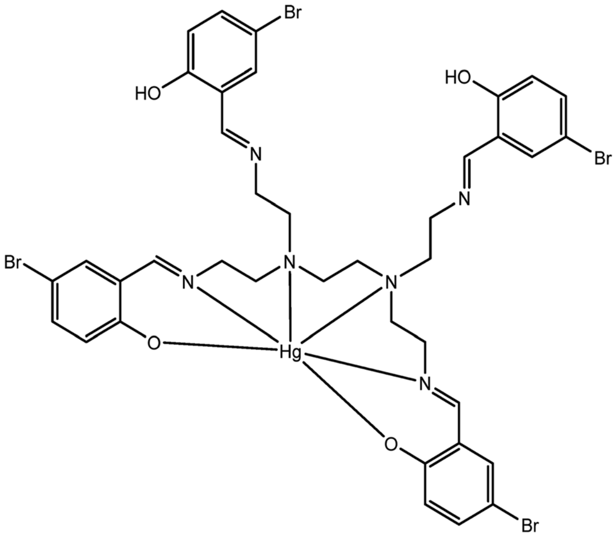
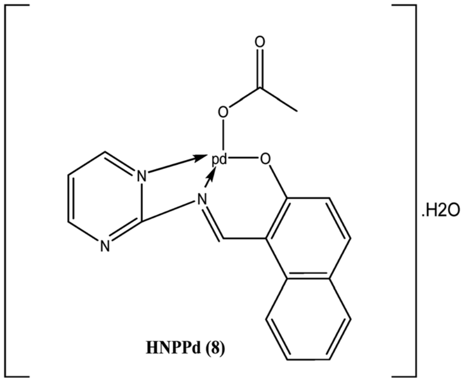


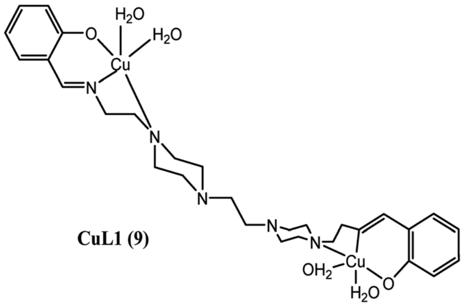
Figure 7: Hg(H2L) complex with antibacterial effects.



HNPPd (8)

Figure 8: HNPPd complex with antiproliferative.

Keypour and colleagues[47] researched both mononuclear and binuclear complexes, examining their cytotoxic effects against cell lines of lung and breast adenocarcinoma cancer using the test known as MTT. According to their research, binuclear complexes were generally found to be more cytotoxic than mononuclear complexes. In particular, the complexes of Figures 9 and 10 turned out to be the most effective.



CuL1 (9)

Figure 9: Binuclear CuL1 metal complex with SBs.

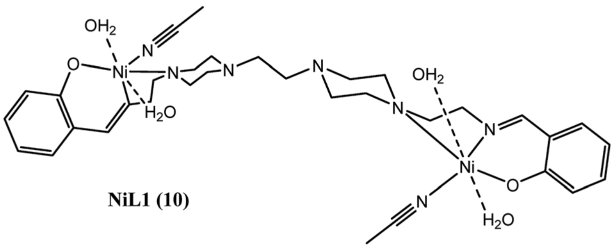

NiL1 (10)

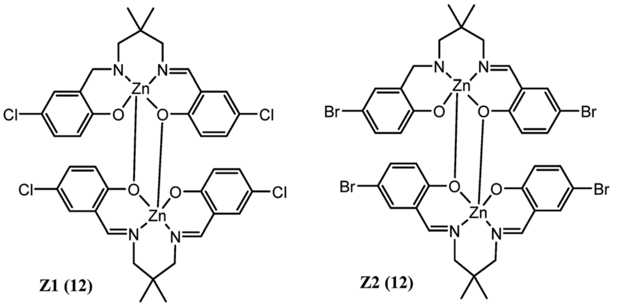
Figure 10: Binuclear NiL1 metal complex with SBs.

3 Binuclear SBs complexes

Binuclear complexes incorporating Schiff bases catalytic qualities have been the subject of much research.[48–50] as well as their applications in fluorescence and luminescence studies,[51,52] Additionally, their potential antimicrobial activities have been documented.[53,54] Recently, there has been interest in exploring binuclear Schiff base complexes for the treatment of COVID-19,[55] supported by molecular modeling investigations.[56] Kargar and colleagues[54] researched two binuclear zinc(II) Schiff base complexes, denoted as Figure 11. They assessed the antibacterial effects of these complexes against both Gram-positive bacteria (*B. cereus* and *S. aureus*) and Gram-negative bacteria (*E. coli* and *P. aeruginosa*) by applying the diffusion technique in an agar well. While the complexes demonstrate activity against Gram-positive bacteria, their effectiveness was observed to be less potent compared to the standard antibiotic, chloramphenicol.

Li and colleagues[57] conducted a study focusing on a binuclear complex of bismuth(III) formed with (E)-N'-(2-hydroxy-4-methoxybenzylidene)isonicotinohydrazide (Figure 12) and evaluated its anti-microbial properties toward two Gram-positive bacteria (*B. subtilis* and *S. aureus* Newman) and two Gram-negative bacteria (*P. aeruginosa* and *E. coli*) acquired from the China General Microbiological Culture Collection Center (CGMCC, China, Beijing). The antimicrobial efficacy of the complex was compared to three standard antibiotics: tetracycline, kanamycin, and vancomycin. Remarkably, the complexes showed significant efficacy in combating *S. aureus*, similar to vancomycin. Furthermore, antiproliferative studies were conducted on human gastric cancer cell lines using the Cell Counting Kit No. 8. The compound demonstrated efficacy comparable to conventional doxorubicin.

A binuclear Cu(II) complex with a -phenoxo N2O4 SBs ligand was described by Jahromi and co-authors.[58] It is designated as {CuII2L(m1,1-NO3)(m-OH)(NO3)(H2O) (Figure 13), where L = [2,6-bis[N-(2-pyridylethyl)formidoyl]-4-methylphenol. The complex structure was determined, revealing two Cu(II) ions in a deformed six-coordinated environment. Various analytical techniques were used to investigate the complex's interaction with


Z1 (12)

Z2 (12)

Figure 11: Two bi-nuclear zinc(II) Schiff base complexes.

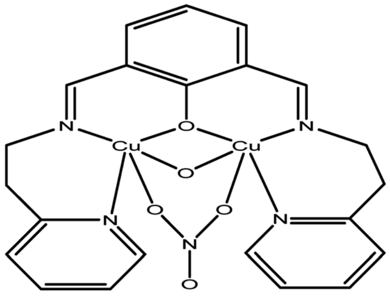

$CuII\ 2L\ (m_1,\ 1\text{-}NO_3)(m\text{-}OH)(NO_3)(H_2O)$

Figure 13: A binuclear Cu(II) complex with a -phenoxo N2O4 SBs ligand.

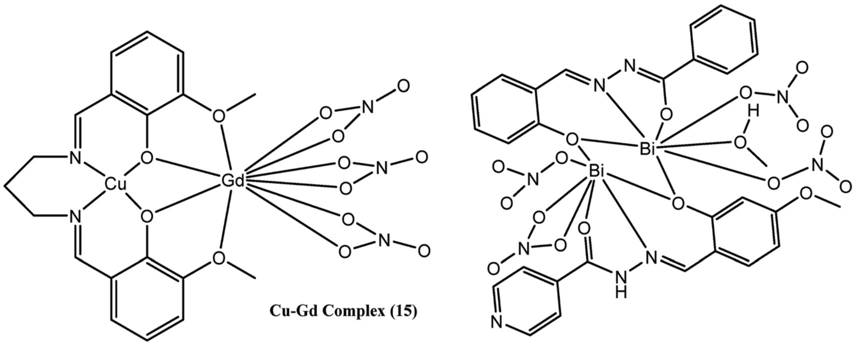

Cu-Gd Complex (15)

Figure 12: Cu–Gd and Bi2(HL)2(NO3)4 complexes with anti-microbial properties.

FS-DNA/BSA. Results from binding competition assays with ethidium bromide and ultraviolet-visible absorption suggested that the complex interacts with DNA through an intercalation mechanism. Initially, the complex exhibited moderate luminescence in a Tris buffer solution. However, as the concentration of DNA increased, the fluorescence intensity noticeably rose, almost doubling, and resulted in intense green fluorescence that was visible to the naked eye. This behavior indicates that the compound serves as a “light switch” for DNA in aqueous environments.

The anti-proliferative impact of the compound was assessed versus three lines of cells- HeLa, MCF-7 and LNCaP – using the (MTT) test, revealing a time-dependent reduction in cell proliferation following treatment with the complex. Furthermore, the complex efficiency was evaluated for its catecholase activity in catalyzing the oxidation of {3,5-di-tert-butylcatechol} (3,5-DTBC) to 3,5-ditert-butylquinone (3,5-DTBQ) in both DMF and acetonitrile solvents using the UV-visible technique. particularly, the complex exhibited significant activity in facilitating the oxidation of 3,5-DTBC to 3,5-DTBQ specifically in acetonitrile. Keshavarzian and colleagues[59] conducted research focusing on a di-metallic compound consisting of Copper (II) and Gadolinium (III), denoted as the [Cu(II)-Gd(III)] Schiff base (Figure 14). The complex binding affinity FS-DNA was examined. Using various analytical methods, intercalation as the principal binding method. Furthermore, the study examined the relationship between the compound and BSA (bovine serum albumin), which revealed a strong complexation. The anti-proliferative efficacy of the compound was then evaluated using the MTT assay on various cancer cell lines, including HeLa, LNCaP, and MCF-7. Additionally, the mechanism and kinetics of the complex’s catalytic action in the oxidation process of (3,5-di-tert butylcatechol) were investigated at a temperature of 298 K. In the DMF medium, the compound demonstrated a modest level of catalytic activity in facilitating the catecholase process.

Jahromi and colleagues[58] investigated a bi-nuclear water soluble Copper (II) compound, denoted as {CuII2L(m1,1-NO3)(m-OH)(NO3)(H2O) (Figure 15), where L = [2,6-bis{N-(2-pyridylethyl) formidoyl}-4-methylphenol], featuring a _-phenoxo N2O4 Schiff base ligand. The structure analysis revealed bi-nuclear Copper (II) ions situated in a distorted A six coordinated setting. The complex relationship with FS-DNA/BSA was investigated by a variety of analytical methods, providing evidence of its relationship with DNA by absorbing ultraviolet (UV) light and an ethidium bromide binding competition testing that points to an incorporation mechanism. The complex originally showed rather moderate luminescence in a this buffer solution, but when the concentration of DNA increased, there was a noticeable rise in fluorescence intensity, almost doubling, along with intense green fluorescence that was apparent to the unaided eye. This behavior implies that in aquatic conditions, the complex functions as a “light button” for DNA. Furthermore, the anti-proliferative effect of the compound was assessed against three cell lines – MCF-7, HeLa, and LNCaP – using the MTT test, indicating a time-dependent reduction in cell proliferation following treatment with the complex. Additionally, the effectiveness of the compound was examined for its ability to catalyze the conversion of 3,5-di-tertiary-butylcatechol (3,5-DTBC) to 3,5-di-tertiary-butylquinone (3,5-DTBQ) in DMF and acetonitrile using the UV–vis technique. The compound demonstrated notable efficacy in promoting the oxidation of 3,5-DTBC to 3,5-DTBQ, specifically in acetonitrile.

In 2018, Nuray Y. and colleagues synthesized SBs by reacting 5-chlorosalicylaldehyde with 2-aminopyridine. They used spectroscopy and X-ray data to examine the composition of the molecule. The geometry of the Schiff base was verified using single-crystal X-ray data, which aligned well with computational predictions from density functional theory. The compound’s antimicrobial properties were assessed against various bacteria (including, *B. cereus* NRRL,

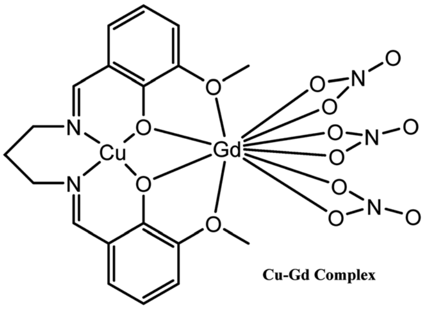


Figure 14: A binuclear [Cu(II)-Gd(III)] Schiff base complex.

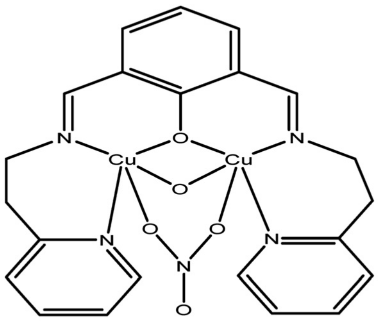


Figure 15: A bi-nuclear copper (II) ions situated in a distorted: a six coordinated setting.

E. faecalis, *E. coli*, *E. coli*, *S. aureus*, and *P. aeruginosa*) and fungi (such as *Candida tropicalis* and *C. albicans*) using the broth microdilution test to determine minimum inhibitory concentrations. Additionally, the relationship between the SBs compound and calf thymus DNA was examined through UV–Vis spectroscopy, revealing an electrostatic binding affinity. By altering the degrees of addition, the colorimetric sensitivity of the SBs complex to various anions was examined.[60] The SB ligand complex (Figure 16).

de Fátima and colleagues authored a concise review focusing on SBs ligands and their transition metal complexes as potential anti-urease agents. Specifically, Cu(II) complexes with SBs hydrazone ligands exhibit inhibiting action of urease. Within these structures, the Cu(II) ion acts by polymerizing the protein, thereby enhancing its activity. The mechanism involves the prevention of thiol group formation, which usually forms the ureolytic site by binding to histidine in the protein. The complex structures exhibit a variety of geometries, such as octahedral, square planar, and tetrahedral, due to the strong Lewis acid activity of the copper ion and its electronic configuration. Together with other donor atoms found in the Schiff base, the imine group's nitrogen plays a major role in the coordination of these Figure 17.[61]

Lei et al. [62] investigated the Schiff base ligand H2L, (E)-N'-(2-hydroxy-3-methoxybenzylidene) isonicotinic-hydrazide, they examined binuclear bismuth(III) complex, [Bi2(HL) 2(NO3)4 (Figure 18), and evaluated its antibacterial efficacy against Schizo-saccharomyces pombe using bio-microcalorimetry. The complex was shown to have a binuclear molecule by X-ray crystallographic study. Two tetradentate O3N-donor ligands and two nitrate ions, or a total of nine coordination sites, coordinated each bismuth(III) ion. The anti-microbial properties of the compound proved to be notably superior to that of isoniazid, a standard reference, as evidenced by a comparison of their respective values. The binuclear nature of the complex presents intriguing possibilities for both chemical and biological investigations, surpassing the mononuclear counterparts in significance.

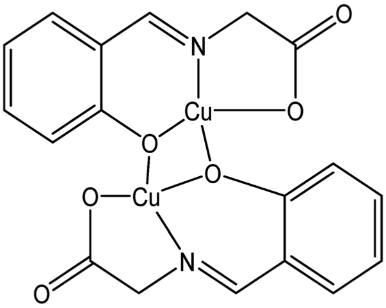


Figure 16: Urease inhibitor complex with Schiff base.

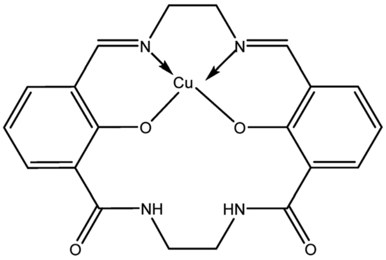


Figure 17: Cu(II) transition metal complexes Schiff base ligands.

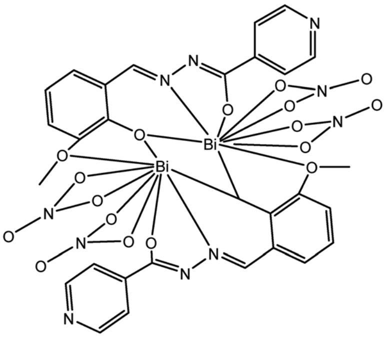


Figure 18: A binuclear bismuth(III) complex with anti-microbial properties.

Arslan and colleagues[63] produced five ligands derived from thiourea and the matching Cu2+ and Ni2+ complexes. The *in vitro* anti-bacterial properties of these complexes were tested against a variety of bacteria, including Gram-negative (*Enterobacter aerogenes*, *P. aeruginosa*, *Proteus vulgaris*, *Enterobacter cloacae*, and *E. coli*) and Gram-positive (two standard strains of, *S. epidermidis*, *B. cereus*, *S. aureus*, *Streptococcus pyogenes*, and *E. faecalis*). Saeed and colleagues synthesized nickel(II) and copper(II) complexes of N-(alkyl or aryl carbamothioyl)-4-nitrobenzamide and evaluated their antibacterial efficacy against *S. aureus*, *S. epidermidis*, *E. faecalis*, *E. coli*, *E. cloacae*, and *P. vulgaris* using the broth microdilution method.[64] Obaleye et al. examined the antimicrobial properties of a Ni(II) complex of Mefloquine Hydrochloride.[65] Lead (II) complexes of metals containing steroidal thiosemicarbazones were created by Asiri and Khan, who evaluated their antibacterial efficacy *in vitro* contrary to a range of bacterial species. The results showed that when compared to steroidal thiosemicarbazones, the steroidal complexes showed better inhibition against both Gram-positive and Gram-negative bacteria.[66] Budakoti utilized 1-N-substituted thiocarbamoyl-3,5-diphenyl-2-pyrazoline derivatives to create novel palladium (II) structures and investigated their biological activity *in vitro*.[67] Abdul Amir H. and colleagues synthesized 3-Aminocoumarin and employed it as a ligand to create complexes with Ni(II), Cu(II) *and* Cr(III).[68] The ligand and its metal (Figure 19) underwent screening for anti-bacterial

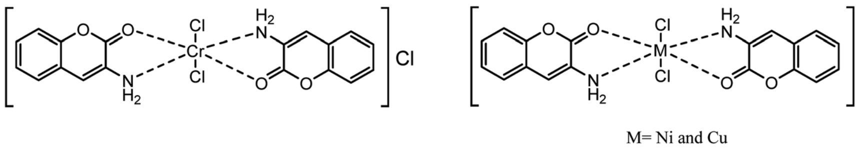


Figure 19: Nickel(II) and copper(II) complexes antibacterial efficacy.

properties contrary to both Gram-negative and Gram-positive bacteria.

4 Conclusions

The study of medicinal inorganic chemistry offers an intriguing avenue for discovering new medicines by modifying metal complexes to enhance their efficacy in disease treatment. Although this field is still in its infancy, it holds significant potential for generating novel ideas and making substantial progress. Metal ions possess a unique ability to interact with crucial molecules in our bodies, playing a vital role in maintaining our well-being. Nature has ingeniously incorporated metals into various essential biological processes, underscoring their importance. Notably, metal complexes, particularly those with Schiff bases, have shown promise in combating infections and mitigating inflammation. Schiff bases possess an azomethine group, a distinctive component that enables them to effectively work with metal ions in combating diseases. Further exploration of Schiff base complexes and their constituents could pave the way for the development of improved medications. By comprehending the intricacies of the interactions between metal ions and biological molecules, we can make significant strides in disease treatment and patient care. This review consolidates recent studies on Schiff base metal complexes, with a particular focus on their role in fighting infections, a critical aspect in addressing antibiotic resistance.

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Informed consent: Not applicable.
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Conflict of interest: The authors state no conflict of interest.
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Data availability: Not applicable.

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