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Recent Advances in the Synthesis Strategies and Antimicrobial Potential of Heterocyclic Metal Complexes: A Review

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Abstract: Heterocyclic metal complexes have garnered significant attention in recent years due to their remarkable structural diversity, chemical stability and broad-spectrum biological activities. Among their various applications, antimicrobial potential—including antibacterial, antifungal and antiviral activity—has emerged as a particularly promising field of study. This review presents a comprehensive overview of recent advances in the synthesis strategies of heterocyclic metal complexes, focusing on both classical and modern synthetic approaches. The review also compiles and compares antimicrobial evaluation data from recent literature to highlight the potential of these complexes as future therapeutic agents.

Keywords: Heterocyclic; Metal; Complexes; Antimicrobial; Activity.

Introduction: -

Heterocyclic compounds are a crucial category of organic compounds characterized by molecular structures that include rings containing at least one element that is not carbon (Mermer et al., 2021). The term "heterocyclic" refers to the existence of a single ring structure inside a compound's structure, including heteroatoms (Borissov et al., 2021; Makhova et al., 2020). Heterocyclic chemistry is an intriguing and important domain of organic chemistry, with both practical and theoretical relevance (Taniguchi, 2021). Heterocyclic molecules are essential in the metabolism of living cells. Their practical applications include a wide array of therapeutic uses as well as various disciplines such as agriculture, photography, biocide formulation and polymer research (Katritzky et al., 2010). The research interest in heterocyclic compounds is fast growing due to intensive synthetic investigations and functional applications. For almost a century, heterocycles have constituted a significant domain of inquiry in organic chemistry. Heterocyclic chemistry is a fundamental aspect of organic chemistry, focusing on heterocyclic molecules that comprise around sixty-five percent of organic science literature. Heterocycles are very prevalent in nature and are essential for the metabolism of living cells. They have significantly contributed to the comprehension of quality-of-life processes and the enhancement of life quality. Recent research has examined an extensive array of biological and pharmacological properties associated with diverse structural derivatives of heterocyclic molecules. Currently, bioinorganic chemists concentrate on heterocyclic ligands and their metal complexes to investigate their pharmacological properties, which is the primary focus of research (Naik et al., 2002). Nitrogen-containing organic compounds and their metal complexes have a broad spectrum of biological activities, including antibacterial, antifungal, anticancer and antiviral effects (Pedrares et al., 2003; El-Asmy et al., 2004; Ekegren et al., 2003). Furthermore, metal ions are crucial in biological processes and the discipline that applies inorganic chemistry to the treatment or detection of diseases is known as medical inorganic chemistry (Thompson, 2011).

The incorporation of metal ions or metal ion-binding agents into biological systems for disease therapy is the primary area of bioinorganic chemistry (Magner, 2005; Orvig and Abrams, 1999; Thompson and Orvig, 2006; Thompson and Orvig, 2003). Metals are characterized by their propensity to readily lose electrons, resulting in the formation of positively charged ions that are often soluble in biological fluids. Metals function in life in their cationic state. Furthermore, these metal ions are crucial components found in the biological intracellular environment of living organisms. Trace elements, with iron, predominantly prevalent in biological systems and most metalloproteins include these elements (Williams et al., 1997; Siegel et al., 2007; Kaim and Rall, 1996). Currently, these metal ions are incorporated in various inorganic pharmaceuticals utilized as treatments for a range of diseases, including antibacterial, antifungal and anticancer applications (Sharma et al., 2013; El-Azab et al., 2013; Eweas et al., 2013; Asif, 2014; Holder, 2012; Ronconi and Sadler, 2007; Schwietert and McCue, 1999; Kraatz and Metzler-Nolte, 2006). Furthermore, N-heterocycles, pyrazolones, benzothiazine and quinazolinone derivatives as ligands influence the complex's environment, hence enhancing its lipophilicity, a critical element in drug design. Therefore, this paper provides an overview of synthesis methodologies and examines anti-microbial potential of heterocyclic metal-ligand complexes, namely, their, antibacterial as well as antiviral and antifungal activities.

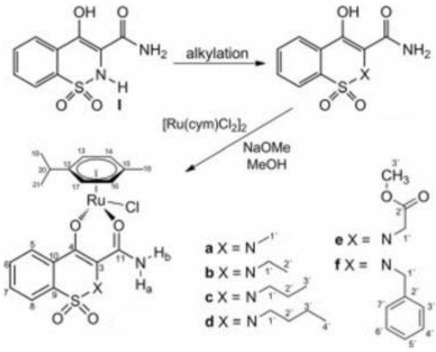
Research Methodology: -

A comprehensive review of existing scientific literature has been conducted to collect and synthesize relevant information on the synthesis strategies and antimicrobial activities of heterocyclic metal-ligand complexes. The selected literature includes journal articles, experimental reports and published works over the last decade, focusing on various metal ions and heterocyclic ligands with documented antimicrobial potential.

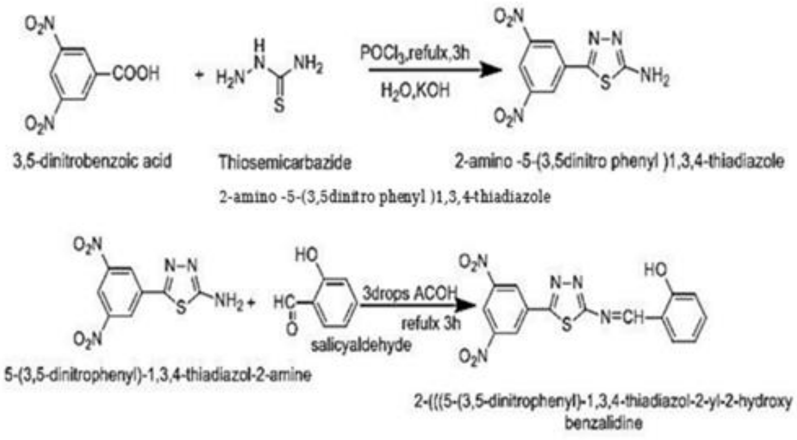
Analysis and Discussion: -

Synthesis Strategies of Heterocyclic Metal Complexes: -

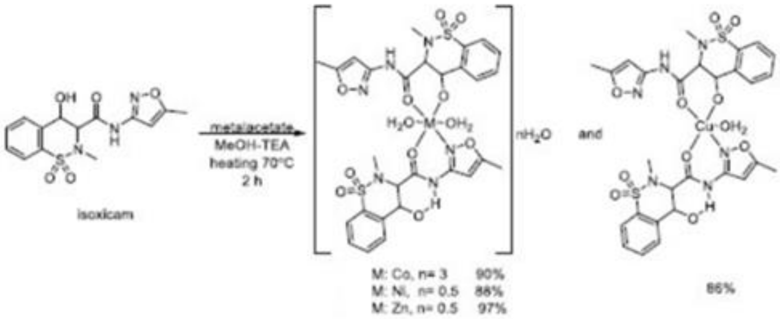
Ashraf et al. (2016) developed Ru(II)(η^6-p-cymene) complexes using 1,2-benzothiazine derivatives for potential anticancer applications. They synthesized a series of 4-hydroxy-2-alkyl-2H-benzo[e][1,2]thiazine-3-carboxamide 1,1-dioxide ligands and their corresponding Ru(II) complexes, demonstrated notable synergistic activity.



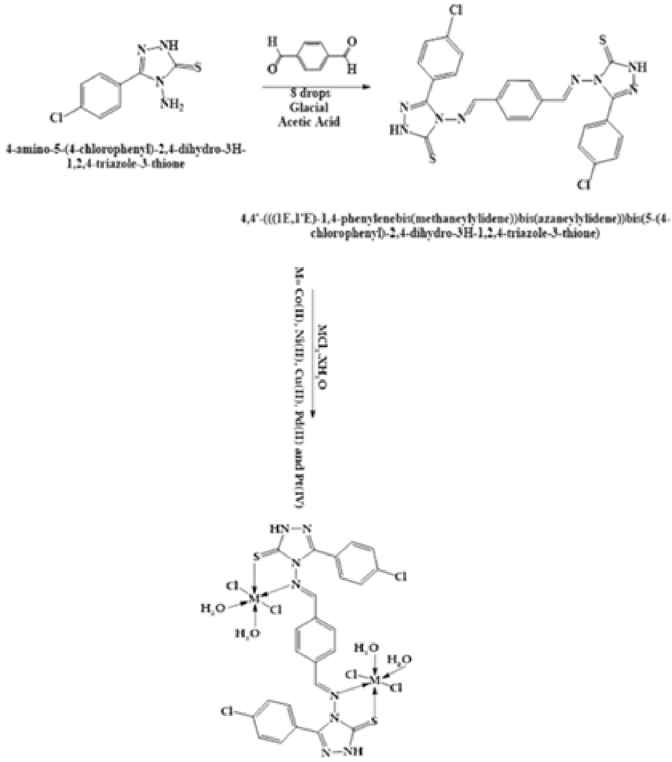
Bader et al. (2019) synthesized a new series of coordination compounds involving transition metal ions such as Co(II), Ni(II), Cu(II), Zn(II) and Cd(II), using a ligand derived from 2-(((5-(3,5-dinitrophenyl)-1,3,4-thiadiazol-2-yl)-2-hydroxybenzylidene). The ligand itself was obtained through a Schiff base condensation reaction between 2-amino-5-(3,5-dinitrophenyl)-1,3,4-thiadiazole and salicylaldehyde. Based on the collected data, the proposed coordination geometries were predominantly octahedral, with the exception of one complex (C1), which exhibited a pyramidal geometry. All complexes were identified as non-electrolytes.



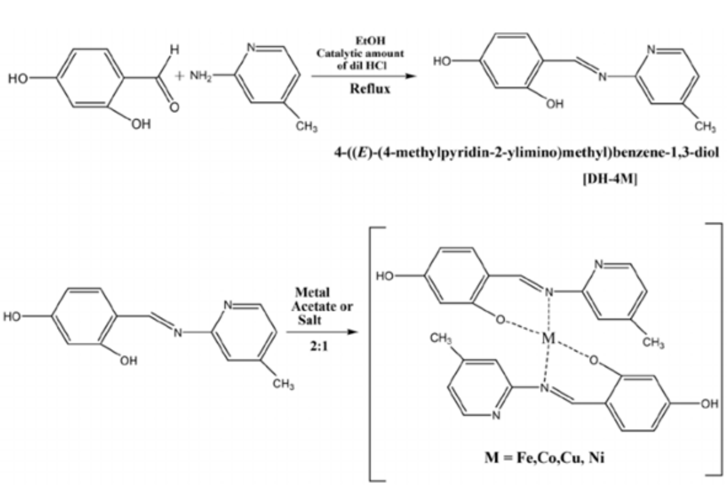
Culita et al. (2019) prepared four metal complexes of Co(II), Ni(II), Zn(II) and Cu(II) by reacting the respective metal acetates with isoxicam in methanol in the presence of triethylamine (TEA) at 70°C.



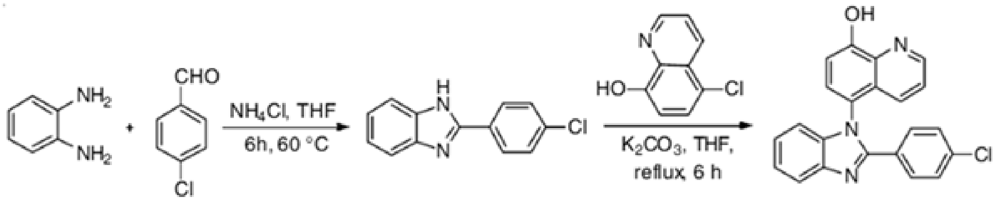
Al-Khazraji (2020) reported the synthesis of a novel Schiff base, 4,4'-(((1E,1'E)-1,4-phenylenebis(methaneylylidene))bis(azaneylylidene))bis(5-(4-chlorophenyl)-4H-1,2,4-triazole-3-thione) (L3), through a condensation reaction between 4-amino-5-(4-chlorophenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione and benzene-1,4-dicarboxaldehyde. This newly synthesized asymmetric Schiff base (L3) was utilized as a ligand to form coordination complexes with Co(II), Ni(II), Cu(II), Pd(II) and Pt(IV) ions in a 1:2 metal-to-ligand molar ratio.



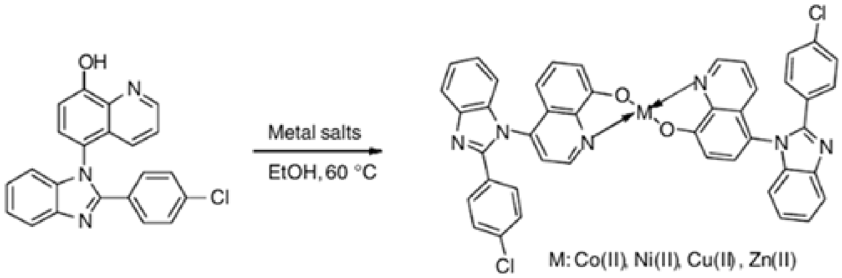
Borase et al. (2021) reported the design and synthesis of novel heterocyclic methyl-substituted pyridine Schiff base transition metal complexes involving Fe(III), Co(III), Cu(II) and Ni(II). These complexes were prepared by reacting metal acetates or metal salts ($FeCl_3$, CoOAc, CuOAc, NiOAc) with a substituted heterocyclic ligand. The structural analysis further suggested that the (N, O) donor atoms of the Schiff base ligand coordinate in a bidentate manner.



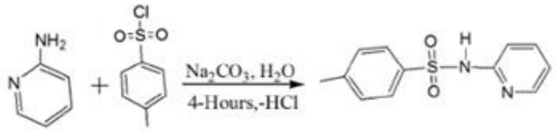
Krishna et al. (2021) developed a heterocyclic ligand, specifically 5-(2-(4-chlorophenyl)-1H-benzo[d]imidazol-1-yl)quinolin-8-ol, along with its metal complexes involving Co(II), Ni(II), Cu(II) and Zn(II) ions. Spectral data indicated that the ligand behaves as a bidentate donor, coordinating through a nitrogen atom and a deprotonated oxygen atom. The geometry of the resulting complexes was found to differ based on the metal ion: Cu(II) and Ni(II) complexes exhibited square planar geometry, while Co(II) and Zn(II) complexes displayed tetrahedral coordination geometry.



Synthesis of ligand



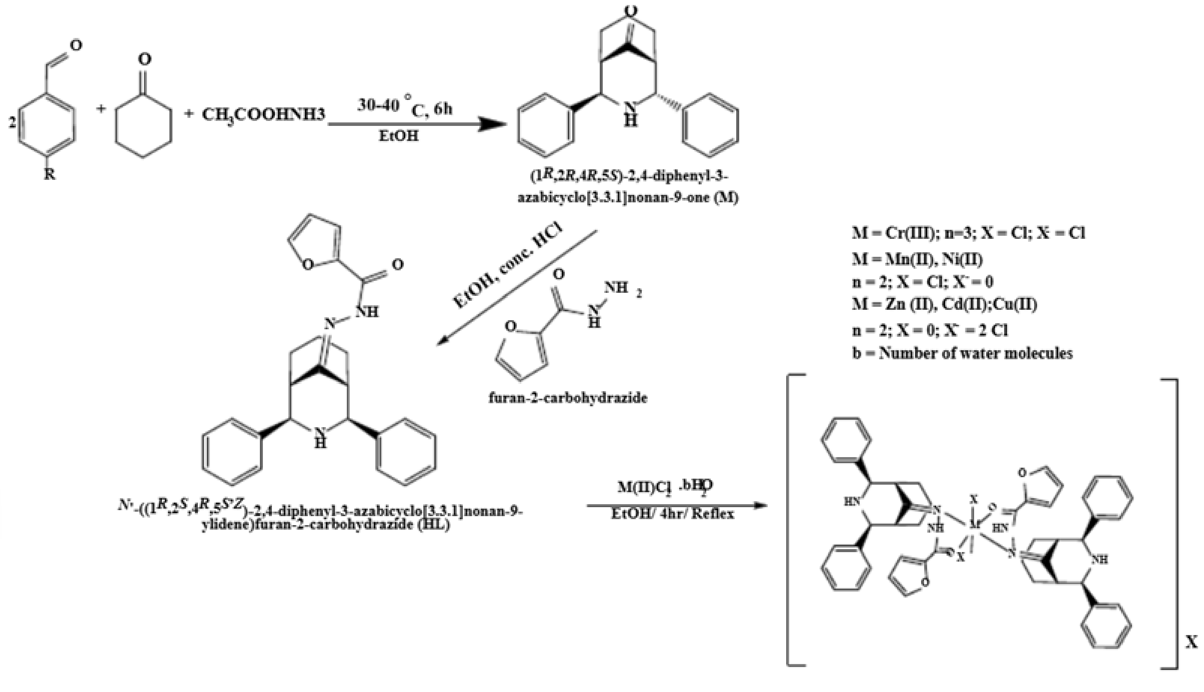
Orie et al. (2021) investigated the synthesis, structural characterization and biological properties of metal complexes derived from a heterocyclic sulphonamide based on aminopyridine. The sulphonamide ligand was obtained through the reaction of 2-aminopyridine with tosyl chloride in an aqueous alkaline medium at room temperature. Iron(II) and copper(II) complexes of the synthesized ligand were subsequently prepared and purified using appropriate recrystallization techniques. Shifts observed in the IR absorption bands of the sulphonamide derivatives upon complexation—either to higher or lower wavenumbers—suggested coordination of the azomethine nitrogen with the metal ions.



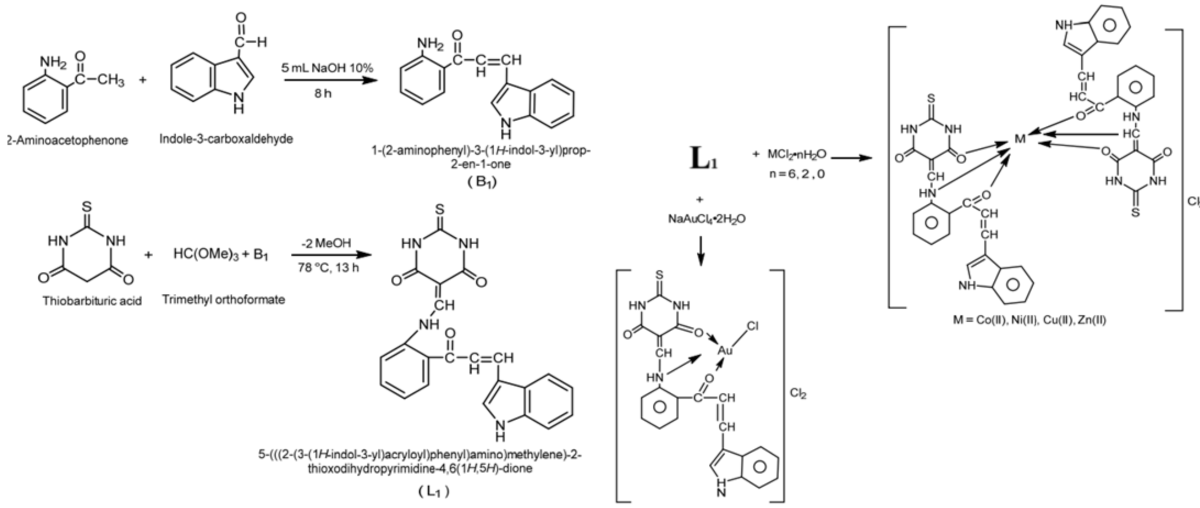
$M^{2+} + L_A \rightarrow [M(L_A)_2]$ L_A= Methyl-N-(pyridin-2-yl)benzene sulphonamide

$M^{2+} = Fe^{2+}, Cu^{2+}$

Khaleel and Al-Rubaye (2024) described the synthesis of a Schiff base ligand containing N_2O_2 donor atoms, derived from a hydrazine moiety, along with its coordination complexes with various metal ions.



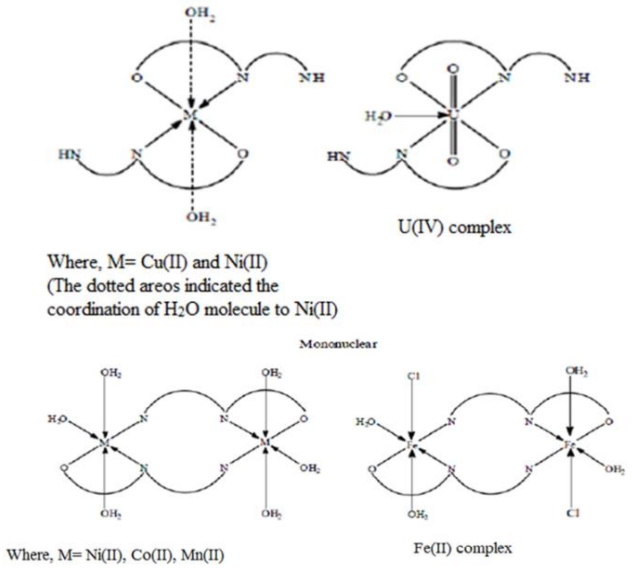
Hilal and Kareem (2025) reported the synthesis of a novel ligand, 5-(((2-(3-(1H-indol-3-yl)acryloyl)phenyl)amino)methylene)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (L1), through a one-pot, three-component reaction utilizing thiobarbituric acid as the starting material. This ligand, featuring two carbonyl functional groups, was subsequently used to prepare metal complexes with Co(II), Ni(II), Cu(II), Zn(II) and Au(III). Based on the collected data, L1 was found to coordinate with Co(II), Ni(II), Cu(II) and Zn(II) ions in an octahedral geometry, whereas it adopted a square planar configuration with the Au(III) ion.



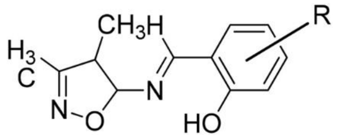
In conclusion, these studies collectively highlight the growing versatility in synthetic approaches—ranging from Schiff base condensation and one-pot multi-component reactions to metal acetate coordination in various solvents—enabling the design of heterocyclic ligands with tailored donor atoms and geometries that facilitate stable complexation with a wide range of transition and noble metal ions, ultimately influencing their structural characteristics.

Antimicrobial Activity of Heterocyclic Metal Complexes: -

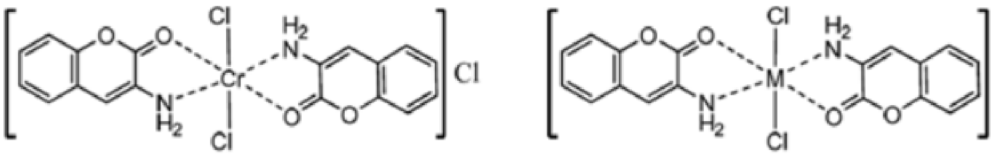
Antibiotics are chemical agents that inhibit the growth of bacteria and fungi, even at low concentrations, and are essential in the treatment of infectious diseases. Fungal infections commonly affect the skin, hair and nails, and antifungal drugs act either by directly killing pathogens or disrupting fungal cell membranes. Antibacterial agents typically interfere with vital bacterial processes like cell wall synthesis or protein production. However, rising antibiotic resistance has prompted the search for new agents, including metal-based compounds. Viruses, which rely on host cells for replication, are treated with antiviral drugs that target specific stages of their life cycle. Recent studies show that heterocyclic metal-ligand complexes possess promising antibacterial, antifungal and antiviral activities, offering a potential route for developing next-generation antimicrobial agents. In this line, Al-Shaalan (2011) synthesized a Schiff base hydrazone ligand (HL) through the condensation of 7-chloro-4-quinoline with o-hydroxyacetophenone. The ligand was reacted with metal ions such as Cu(II), Ni(II), Co(II), Mn(II), UO_2(VI) and Fe(III), leading to the formation of both mono- and binuclear complexes. The antimicrobial potential of HL and its metal complexes was evaluated. The results revealed that the synthesized compounds exhibited significant antibacterial activity.



Chityala et al. (2011) investigated a series of Cu(II) complexes formed with Schiff bases. Biological evaluation revealed that both the Schiff bases and their corresponding metal complexes exhibited noteworthy antimicrobial activity, with the metal complexes showing superior potency. Additionally, the cytotoxic effects of the Cu(II) complexes on human cervical carcinoma (HeLa) cells were assessed using the MTT assay, demonstrating significant biological relevance.

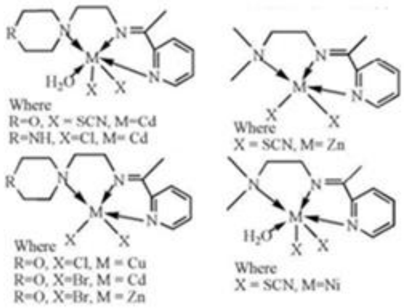


In a study by Kadhum et al. (2011), 3-aminocoumarin (L) was synthesized and utilized as a ligand to form metal complexes with Cr(III), Ni(II) and Cu(II) ions. Biological assays demonstrated that these complexes possess noteworthy antimicrobial activity against selected microbial strains.

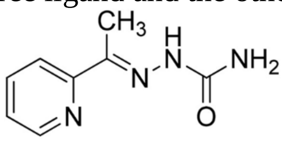


M = Ni and Cu

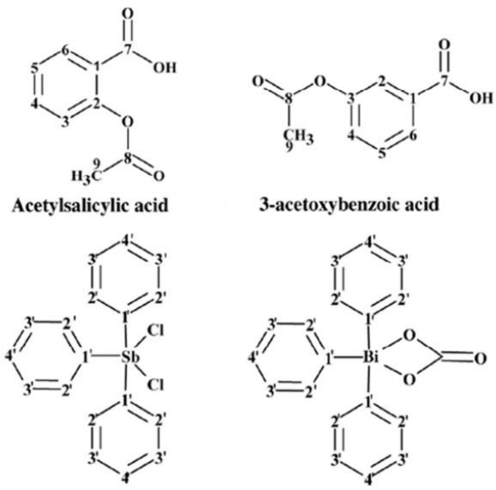
Gwaram et al. (2012) investigated a series of metal complexes formed with Schiff bases derived from 2-acetylpyridine. The antibacterial potential of these complexes indicated that the complexes exhibited the strongest antibacterial activity; weaker effects were observed against *A. baumannii* and *P. aeruginosa*.



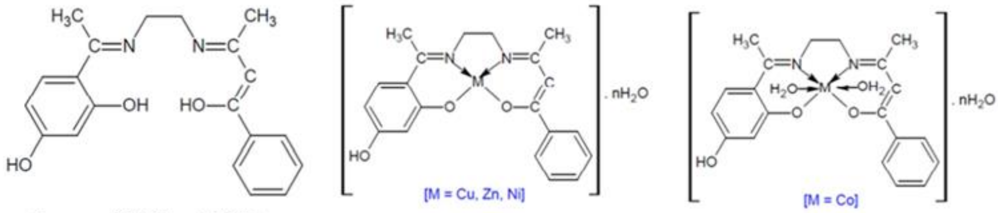
Shaabani et al. (2013) synthesized a Schiff base ligand, methyl 2-pyridyl ketone semicarbazone (HL), through the condensation of methyl 2-pyridyl ketone with semicarbazide. This ligand was then utilized to prepare a series of novel binuclear Cu(II) complexes. The antimicrobial properties of the ligand and its Cu(II) complexes (1–3) were evaluated. Among the tested compounds, complex given below exhibited superior antimicrobial activity compared to both the free ligand and the other complexes.



Islam et al. (2014) reported the synthesis and characterization of two novel organoantimony(V) and two organobismuth(V) complexes of the general formula ML_2, where the ligand (L) was either acetylsalicylic acid (HL_1) or 3-acetoxybenzoic acid (HL_2) and the metal center (M) was either triphenylantimony(V) (M_1) or triphenylbismuth(V) (M_2). All metal complexes demonstrated both antileishmanial and antibacterial activities, with bismuth-based complexes showing superior performance. Interestingly, while coordination with the bismuth(V) center reduced antileishmanial activity, it significantly enhanced antibacterial efficacy.



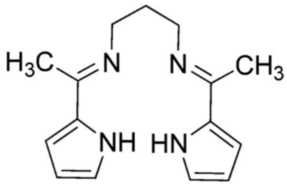
Ejidike and Ajibade (2015) prepared Co(II), Ni(II), Zn(II) and Cu(II) complexes using the Schiff base ligand (3E)-3-[(2-{(E)-[1-(2,4-dihydroxyphenyl)ethylidene]amino}ethyl)imino]-1-phenylbutan-1-one ($DEPH_2$). The ligand and its corresponding metal complexes were evaluated for antibacterial activity against both Gram-positive and Gram-negative bacterial strains. Significant activity was observed.



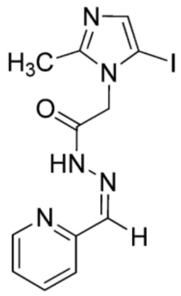
Structure of Schiff base (DEPH₂).

Where n = 2 for Cu(II), Co(II) and Zn(II); n = 3 for Ni(II)

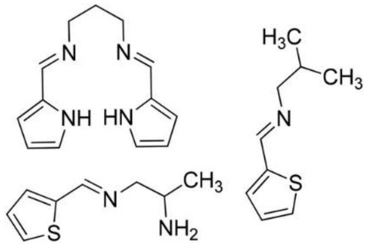
Zafar et al. (2015) synthesized a series of Schiff base metal complexes, denoted as $MLCl_2$ [where M = Fe(II), Co(II), Ni(II), Cu(II) and Zn(II)], using a template method involving 2-acetylpyrrole and 1,3-diaminopropane in a 1:2:1 molar ratio with the respective metal ions. The antibacterial efficacy of the complexes was evaluated. Among the series, the copper(II) complex [$CuLCl_2$] exhibited the most potent antibacterial activity, nearly comparable to that of ciprofloxacin, a standard antibiotic. Other metal complexes also demonstrated notable antibacterial effects.



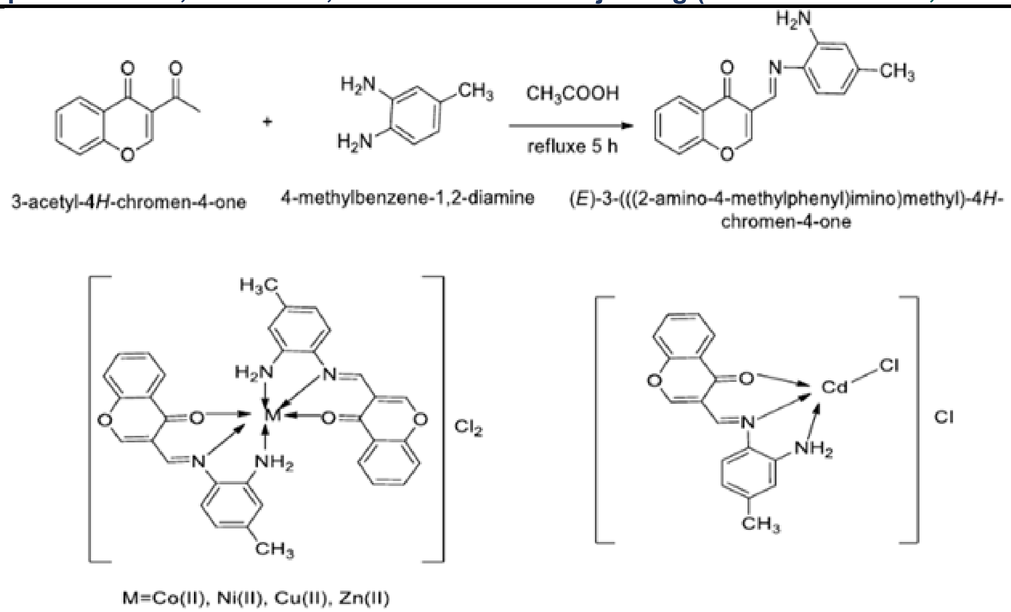
Wani et al. (2016) developed an imidazole-based ligand, which was subsequently complexed with Cu(II), Co(II) and Ni(II) salts to yield mononuclear metal complexes designated as IHC1, IHC2 and IHC3, respectively, with the general molecular formula [$M(L)_2$]. Spectral and physical analysis confirmed that the complexes exhibit an octahedral geometry. The ligand and its corresponding metal complexes were tested for antifungal activity against three *Candida* strains by determining their MIC and MFC. The results indicated that all synthesized compounds demonstrated significant antifungal activity, with the Cu(II) complex (IHC1) showing the highest potency. Confocal scanning laser microscopy revealed that the mechanism of antifungal action likely involves disruption of the fungal cell membrane.



Bandhopadhyay et al. (2017) synthesized and characterized three novel cobalt(III) Schiff base complexes: $[Co(L1)(N3)]_2$ (1), $[Co(L2)_2(N3)_2]NO_3$ (2) and $[Co(L3)_2(N3)_2]ClO_4$ (3), where H_2L1 is N,N′-propane-1,3-diylbis[1-(pyrrol-2-yl)methanimine], L2 is 1-[(thiophen-2-ylmethylidene)amino]propan-2-amine and L3 is 1-[(3-methylthiophen-2-ylmethylidene)amino]propan-2-amine. Structural analysis revealed that all three complexes feature a CoN_6 coordination environment, with cobalt(III) adopting a distorted octahedral geometry. The antibacterial potential of the complexes, as well as their corresponding Schiff base ligands, was evaluated against selected Gram-positive and Gram-negative bacterial strains. The results were quite significant in terms of activity.



Salim et al. (2025) produced complexes of Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) using the ligand 3-(((2-amino-4-methylphenyl)imino)methyl)-4H-chromen-4-one. The antimicrobial properties of the synthesized complexes were evaluated against two bacterial strains: *E.a coli* and *S. aureus*. Significant results were observed in terms of antibacterial activity.



In conclusion, these findings strongly support the view that heterocyclic metal-ligand complexes, particularly those involving transition metals and Schiff base ligands, exhibit potent and often enhanced antimicrobial activity—encompassing antibacterial, antifungal and even antiviral activity—thus positioning them as promising candidates in the development of next-generation antimicrobial agents.

Conclusion: This study presents a review of the pharmacological properties of selected metal complexes, highlighting the growing significance of bioinorganic chemistry in the field of medicine. The development of innovative metal-based therapeutic and diagnostic agents is increasingly influencing contemporary medical practice. Progress in bioinorganic chemistry plays a crucial role in enhancing compound design, minimizing toxic side effects and elucidating mechanisms of action. The review suggests that pharmacologically active metals offer promising potential as a foundation for the development of new therapeutic approaches in medical treatment.

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