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Original Article

Green Synthesis of Schiff Bases Ligand and Biological Evaluation of Their Transition Metal Complexes

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Abstract

The Schiff bases are the bimolecular condensation products of carbonyl compounds and primary amines. Either an aldehyde or ketone can be the carbonyl functional group. Since Schiff bases often contain donor atoms in the forms of -N and -O, they function as ligands. They have good properties, structural resemblances to naturally occurring biological molecules, relatively easy preparation methods, and synthetic flexibility that allows for the design of appropriate structural scaffolds. The majority of Schiff bases exhibit biological properties, including antibacterial, antifungal, antiviral, antimalarial, as well as anticancer activity. This paper summarizes the synthesis and biological activities of Schiff bases.

Keywords: *Schiff bases, Metal complexes, antimicrobial activity, Antiviral activity, Antimalarial activity.*

Introduction:

The Schiff bases, which emerge from the combination of an amino compound and a carbonyl compound, represent a significant category of ligands that bond with metal ions through azomethine nitrogen. They have been the subject of considerable research. In azomethine compounds, the C=N bond is crucial for their biological effectiveness, and various azomethine derivatives have been noted for their impressive properties, including antibacterial, antifungal, anticancer, and diuretic effects [1]. These Schiff bases are utilized in numerous sectors including the food industry, dye production, analytical methods, catalysis, and for their fungicidal, agrochemical, and biological properties. With the rise in cases of deep mycosis, there has been a growing focus on identifying new and more effective antimicrobial agents that exhibit lower toxicity. Schiff-base compounds are recognized as important examples for understanding stereochemistry in coordination chemistry involving main group and transition metals, primarily because they are relatively simple to synthesize and exhibit a range of structures. Many Schiff-base compounds have important biological significance and are comparatively useful analogues of biological molecules. In addition to playing a fundamental role in the development of modern coordination chemistry, they also show up at critical junctures in the development of inorganic biology, catalysis, and optical materials [2].

Compounds containing the imine or azomethine (–C=N–) functional group are known as schiff bases. Originally described by Hugo Schiff, they result from a condensation reaction involving primary amines and carbonyl compounds. Schiff bases are an essential class of organic compounds that are used in many different fields, including analytical, biological, and inorganic chemistry. Due to a variety of biological functions, including anti-inflammatory, pain-relieving, germ-fighting, seizure-preventing, tuberculosis-treating, cancer-fighting, free radical-scavenging, and worm-eliminating activities, their significance has grown in medical and pharmaceutical contexts. Normal cellular processes can be disrupted by the nitrogen atom attached to azomethine forming hydrogen bonds with the active sites of cellular components [3-5].

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Schiff bases have biological functions, but they also function as accelerators, materials used in chemical synthesis, coloring agents, additions for polymer stability, and corrosion-prevention agents. Studies have shown that as compared to their free organic counterparts, metal complexes frequently exhibit increased biological activity. It has been noted that adding transition metals to Schiff bases increases their biological efficacy. Schiff bases have been essential in advancing coordination chemistry, acting as a central component in the development of inorganic biochemistry and materials used for optical purposes. [6]. The condensation reaction of Schiff bases, which involves an amine reacting with a carbonyl group, can be illustrated as shown below (Figure 1).

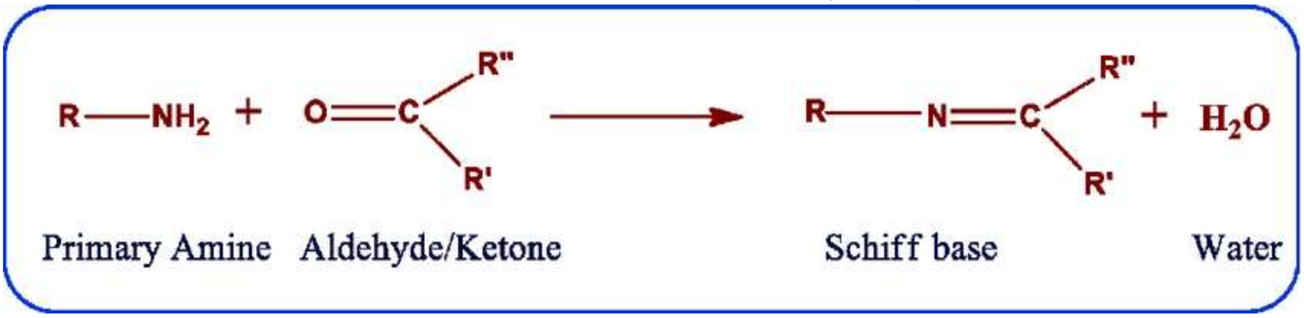

Figure 1. General scheme of formation of Schiff bases.

In the creation of Schiff bases, nucleophilic amines engage with electrophilic carbonyl substances througha hemiaminal structure through a nucleophilic addition process, which is subsequently dehydrated to produce imine derivatives. In the first step of the process, the amine combines with a ketone or an aldehyde to create carbinolamine, a transitory addition product. After that, either an acid or a base can catalyze the dehydration of carbinolamine. When carbinolamine is exposed to an acid catalyst, it takes part in a dehydration reaction since it is categorized as an alcohol (Figure 2).

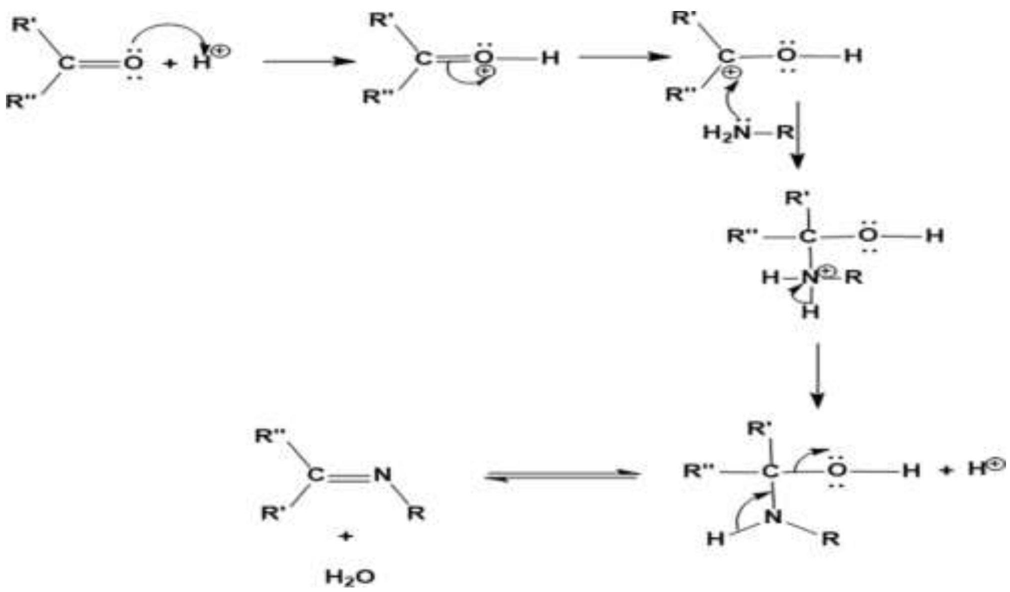

Figure 2. Mechanistic explanation of the formation of Schiff base.

This document focuses on the creation and biological function of Schiff base ligands and their complexes with transition metals.

2. Synthetic methods of Schiff bases:

Because of their biological and pharmacological characteristics, Schiff base ligands which are made up of molecules with imine groups have become more well-known. As models for biological processes, they belong to an interesting class of chelating agents that can attach to metal ions in a complex. The synthesis of Schiff bases has been the subject of numerous studies [7]. These compounds have been synthesized utilizing both traditional and environmentally friendly methods (Figure 3).

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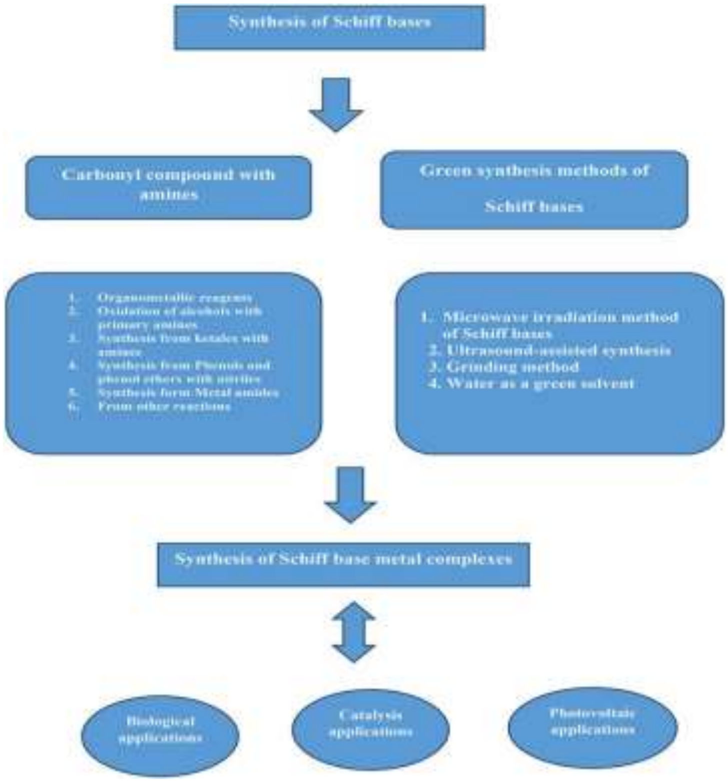

Figure 3. Synthetic methods of Schiff bases.

Heating is often essential in various condensation reactions, and standard reaction conditions generally require the reactants to be heated in metal, oil, or sand baths for extended periods, sometimes lasting hours or even days. The typical approach includes either refluxing or stirring different aldehydes or ketones with assorted primary amines. When compared to conventional synthetic methods, green chemistry offers significant economic and ecological benefits. It implies that developments in green chemistry have increased the demand for organic synthesis, which calls for the discovery of special reaction conditions in order to reduce the usage of hazardous solvents or toxic materials. Compared to conventional methods, green approaches should improve selectivity, reduce reaction times, and facilitate product separation. Solvent-free or minimal solvent conditions have been used in the microwave-assisted synthesis of Schiff bases, which has significantly reduced reaction times, increased conversion rates, and occasionally improved selectivity. Since the development of solvent-free microwave techniques for Schiff base synthesis, this approach has become the most well-known and simple method for these reactions, and it can be used in many other situations. The utilization of microwave-assisted synthesis for various Schiff bases and their derivatives has been documented by numerous researchers.

3. Biological Evaluation of Schiff Base and Their Transition Metal Complexes:

Usually acting as bidentate or tridentate ligands, the Schiff bases can form extremely stable complexes with transition metals. Schiff base reactions are helpful for creating carbon-nitrogen bonds in the field of organic synthesis..

3.1 Antibacterial Activity:

Hakan Arslan *et al.* synthesized five thiourea derivatives ligand and their Ni^{2+} and Cu^{2+} complexes. Those Compounds were assessed for their antibacterial effectiveness in vitro utilizing Gram-positive bacteria (including two standard strains of *Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis, Streptococcus pyogenes, Bacillus cereus* alongside Gram-negative bacteria *Escherichia coli, Pseudomonas aeruginosa, Enterobacter cloacae, Proteus vulgaris, Enterobacter aerogenes.* [8].

Yu-Ye Yu and colleagues created Mn(II), Co(II), Ni(II), Cu(II), and Cd(II) complexes utilizing the Schiff base ligand 2-[(4-methylphenylimino)methyl]-6-methoxyphenol, which was created by mixing p-toluidine with o-vanillin (2-hydroxy-3-methoxybenzaldehyde). They tested this Schiff base ligand's and its complexes' antibacterial qualities in vitro against microorganisms like *Bacillus subtilis, Staphylococcus aureus,* and *Escherichia coli.* [9,10].

Sohail Saeed and his team synthesized nickel(II) and copper(II) complexes from N-(alkyl (aryl) carbamothioyl)-4-nitrobenzamide, which were then subjected to antibacterial screening against *S. aureus, S. epidermidis, E. faecalis, E. coli, E. cloacae, and P. vulgaris* using the broth microdilution method. [11,12].

Elzahany and coworkers developed several transition metal complexes incorporating Schiff bases derived from 2-formylindole, salicylaldehyde, and N-amino Rhodanine. The characterization of the Schiff base ligands involved elemental analysis, IR, Mass, 1H NMR, and electronic spectral data. Both the free ligands and their associated metal complexes underwent antimicrobial testing against *Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa,*

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Staphylococcus aureus, and Candida albicans. Findings showed that the ligands were inactive, while their complexes exhibited enhanced activity against the same pathogens under similar experimental conditions. [13,14].

3.2 Antifungal Activity:

Sakhare *et al* also reported the Synthesis of a Schiff base ligand was achieved through the reaction of 2-amino-4,6-dimethylpyrimidine and 5-nitrosalicylaldehyde. The ligand was evaluated for its antifungal and antibacterial properties against Aspergillus niger, Penicillium chrysogenum, Fusarium moneliforme, Aspergillus flavus, as well as *Escherichia coli, Salmonella typhi, Staphylococcus aureus, and B. subtilis* at concentrations of 1% and 2% in DMSO. This was then compared to the effectiveness of established antibiotics such as *Griseofulvin and Penicvolume.* The findings showed that the ligand demonstrated significant antifungal and antibacterial effects. [15,16].

In a separate research conducted by Panneerselvam and colleagues revealed that 2-methoxy-4-[(4-morpholin-4-ylphenylimino)-methyl]-phenol, given at a concentration of 30 µg/ml, significantly suppressed the proliferation of both Candida albicans and Aspergillus niger. While researchinvestigating the antifungal properties of Schiff bases against phytopathogenic fungi has been relatively limited, these findings underscore their potential as promising agents in this area.

The growth of Aspergillus niger and Candida albicans were inhibited using 2-methoxy-4-[(4-morpholin-4-yl-phenylimino)-methyl]-phenol (Figure 4) at 30 µg/ml. Generally, not much research has been done to assess how Schiff bases affect the growth of phytopathogenic fungi, and more needs to be done in this area [17,18].

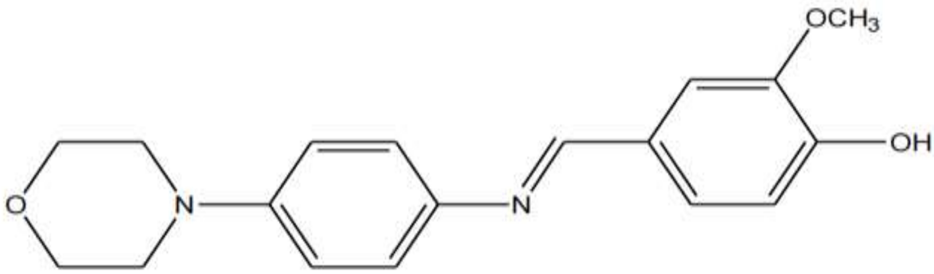

Figure 4: 2-methoxy-4-[(4-morpholin-4-ylphenylimino)-methyl]-phenol.

3.3 Antiviral Activity:

According to Wang proposed that salicylaldehyde Schiff bases obtained from 1-amino-3-hydroxyguanidine tosylate may act as valuable frameworks for creating new antiviral medicines. Of these substances, the Schiff base illustrated in (Figure 5) exhibited strong antiviral effects against mouse hepatitis virus (MHV), suppressing viral proliferation by 50% at an impressively low concentration of 3.2 µM. [19,20].

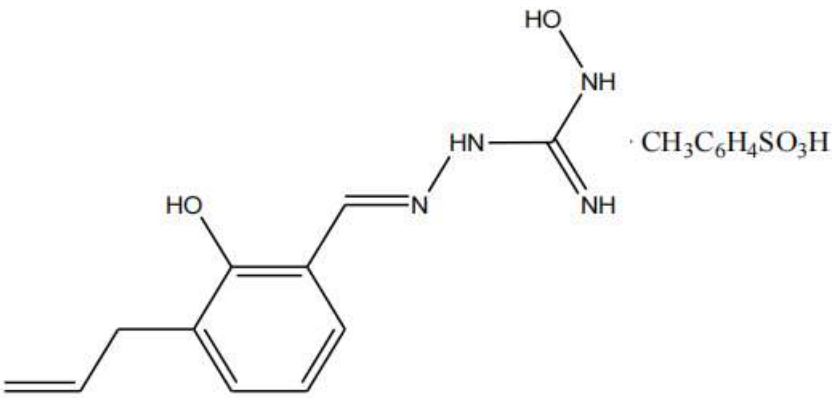

Figure 5: 1-amino-3-hydroxyguanidine tosylate derived Schiff base

3.4 Antimalarial Activity:

Malaria, despite being a neglected disease, remains a significant public health burden. Approximately 500 million individuals are affected annually, with 1-3 million fatalities, primarily among children in subSaharan Africa. Malaria is prevalent in over 100 countries across Africa, Asia, Oceania, and Latin America. Four species of Plasmodium are the primary causative agents of malaria in humans: *P. vivax, P. falciparum, P.malariae, and P. ovale.* Female Anophelesmosquitoes serve as the primary vectors for *Plasmodium transmission* [21,22].

Bringmann *et al.*, Schiff bases have emerged as promising molecules for the development of antimalarial drugs. Plants belonging to the Ancistrocladaceae and Dioncophyllaceae families produce ancistrocladidine, a secondary metabolite containing an imine group. This compound has demonstrated efficacy against *Plasmodium falciparum strains* K1 and 3D7. Bringmann et al. reported Minimum inhibitory concentrations, or MIC values, were determined to be 0.3 and 1.9 µg/ml for ancistrocladidine when tested against P. falciparum K1 and 3D7, respectively [23,24] .

Dong et al., Rathelot synthesized Schiff base-functionalized 5-nitroisoquinolines and evaluated their in vitro efficacy against a Plasmodium falciparum strain resistant to chloroquine (ACC Niger). Among the synthesized derivatives, the Schiff base depicted in Figure 13 demonstrated the highest antimalarial potency. This compound exhibited an IC50 value of 0.7 µg/ml against P. falciparum growth, which is comparable to chloroquine's IC50 value of 0.1 µg/ml under identical experimental conditions [25-27].

3.5 Anticancer Activity:

Uncontrollable growth, invading, and sometimes metastasis of a group of cells are features of a
family of disorders called malignant neoplasms or cancer. It is the most serious public health issue facing the world. After cardiovascular diseases, it is the second most common cause of death for human worldwide in both developed and developing countries Bandgar et al., Currently, chemotherapy and surgery are the main treatments for cancer, however, the efficaciousness of the available chemotherapeutic drugs is inadequate and they have several side effects. One of the major efforts over the last halfcentury has been the development of more potent drugs to treat cancer patients. Many derivatives of Schiff bases have been linked to anticancer properties in recent years [28-30].

Xu *et al*., Five ternary complexes of rare earth ions, incorporating salicylaldehyde, L-phenylalanine, and o-phenanthroline, were investigated for their anticancer potential. The complexes were evaluated for their ability to induce apoptosis and inhibit the growth of K562 tumor cells using methyl thiazolyl tetrazolium colorimetry and flow cytometry. The study revealed a dose-dependent increase in inhibition ratio, suggesting a strong positive correlation between drug dosage and anticancer activity. Overall, all of these complexes demonstrated promising anticancer effects against K562 tumor cells [31].

Li *et al*.,Many platinum(II) complexes derived from Amino acid Schiff bases have been identified as having potential anticancer effects. The relationship between these substances and salmon sperm DNA was investigated, revealing their in vitro anticancer activity against cell lines HL-60, KB, BGC-823, and Bel-7402 through the MTT assay. Of the Pt(II) complexes formed from reduced amino acid Schiff bases, the compound illustrated in Figure 14 showed similar cytotoxicity on the Bel-7402 cell line and exceeded cisplatin in effectiveness against the BGC-823 and HL-60 cell lines. [32].

Conclusion:

The structural diversity of the Schiff bases has led to rapid developments in their chemistry, particularly those derived from aldehydes and amines. Schiff bases have many synthetic applications in organic chemistry. The development in the field of antibacterial, antifungal, antiviral, antimalarial and anticancer activities has boosted interest in the study of Schiff bases, as it has been discovered that many of them exhibit biological activity. In this paper, the biological functions of certain Schiff bases have been assessed.

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Conflicts of interest:

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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