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Biological Screening and Pharmaceutical Efficiency of Schiff Bases and their Metal Complexes: A Review

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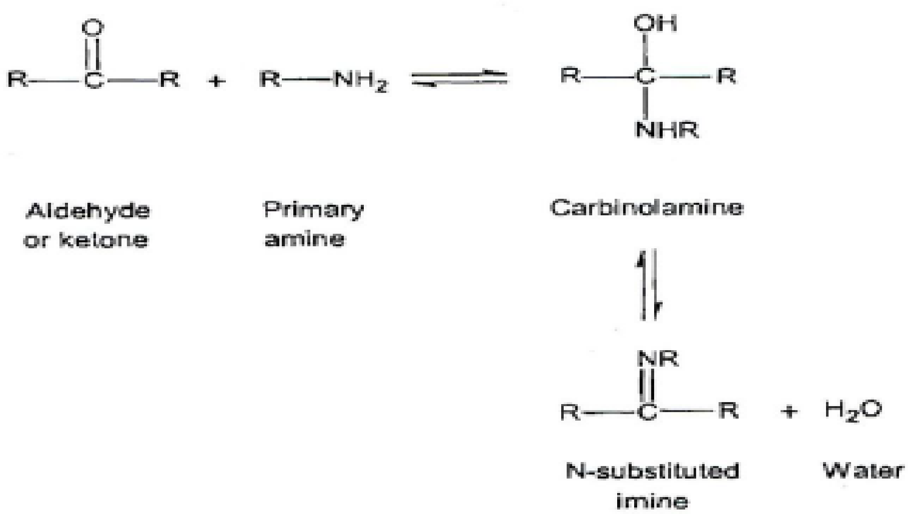
I. INTRODUCTION

The field of combinational bio-inorganic chemistry has recently seen significant advancements, leading to an increase in interest in Schiff base complexes. Many of these metal complexes have been reported to possess the potential to act as core structures for biologically and pharmaceutically important species. This is largely due to the presence of a lone pair of electrons on the nitrogen atom and the electron-donating character of the double bond. These properties have played a crucial role in the development of chemical sciences and have found widespread applications in various fields of chemistry. The synthesis and structural analysis of Schiff base compounds and their metal complexes have garnered significant attention due to their potential pharmacological benefits and the diverse range of bonding modes they exhibit. Schiff bases serve as the basic framework for a large number of organic compounds and have a wide range of applications across various fields. These compounds are excellent ligands, owing to their facile formation and rich coordination chemistry with a wide variety of metal ions. The azomethine group (RHC = N-R1), where R and R1 represent alkyl, aryl, cycloalkyl, or heterocyclic groups, is a common structural feature of these compounds. Schiff bases are condensed products of aldehydes or ketones, and were first reported by German scientist Hugo Schiff in 1864. They are represented by the general structure R'R"C=N-R (as shown in Scheme 1).



Scheme-1.1 General condensation reaction for synthesis of Schiff's base

Schiff base complexes are widely regarded as important stereochemical models in both main group and transition metal coordination chemistry, owing to their diverse structures and ease of preparation [1]. These compounds are a vital class of ligands that coordinate to metal ions via the azomethine nitrogen. In azomethine derivatives, the C=N linkage plays a crucial role in their biological activity. Numerous azomethines have been reported to possess significant antibacterial, antifungal, anticancer, and diuretic activities [2].

Schiff bases have a fascinating application as efficient corrosion inhibitors, owing to their ability to spontaneously form a monolayer on the surface that needs protection. While many commercial inhibitors comprise aldehydes or amines, the Schiff bases tend to function more effectively in several instances, likely due to the C=N bond. The primary interaction between the inhibitor and the metal surface is chemisorption, and the inhibitor molecule must possess centers capable of bonding with the metal surface by electron transfer. These compounds owe their significance to their structural similarity with natural substances, relatively similar synthetic procedures, and synthetic flexibility that allows for the design of suitable structural properties. Schiff bases are well-known intermediates for preparing azetidinone, thiazolidinone, formazone, arylcaetamide, metal complexes, and numerous other derivatives.

Schiff bases are a highly active class of compounds with diverse biological applications such as antitubercular, anticancer, antibacterial, anti-inflammatory, antifungal, antitumor, diuretic, insecticidal, herbicidal, anthelmintic, anti-HIV, antiproliferative, anticonvulsant, antihypertensive, and antiparasitic activities. Derivatives of Schiff bases have been extensively researched for over a century and have been utilized in various areas, including fine chemicals, analytical reagents, corrosion inhibitors, and ligands. Due to these advantageous properties, coupled with concerns for environmental needs and a strong interest in developing green chemistry, researchers have investigated new sustainable catalysts and environmentally friendly processes that are both economically and technologically feasible.

This review work focuses on recent studies regarding the valuable applications, particularly in biological and pharmaceutical fields, of Schiff's base and its metal complexes. These complexes are formed with various active metals, including main group and transition metals such as Co (II), Mo (II), Sb (II), Ni (II), Cu (II), and Zn (II). The review's main goal is to provide an overview of the recent developments in this area, with a specific focus on the potential applications of these complexes in the biological and pharmaceutical field.

Biological and Pharmaceutical Activeness of Schiff's Bases:

The formation of Schiff base or imine is a crucial reaction in biological chemistry, and it plays a vital role in several biochemical processes. One such example is the chemistry of pyridoxal phosphate (PLP), a derivative of vitamin B6 also known as pyridoxine. The PLP coenzyme forms a Schiff base linkage with enzymes, which is an important step in several enzymatic reactions.

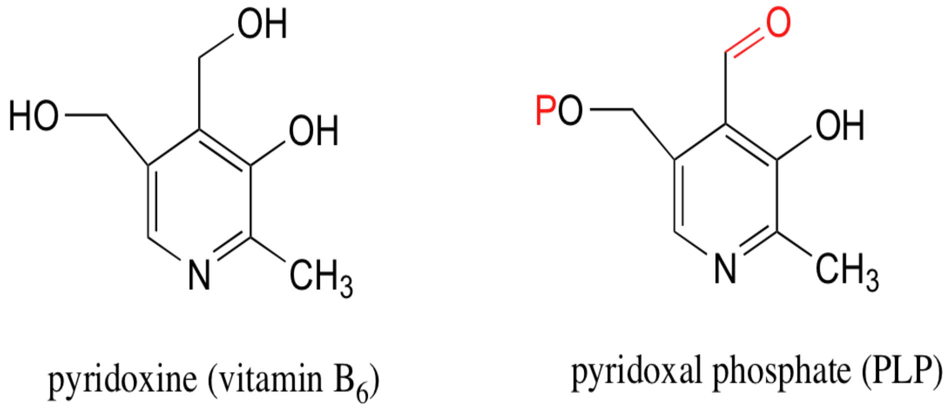
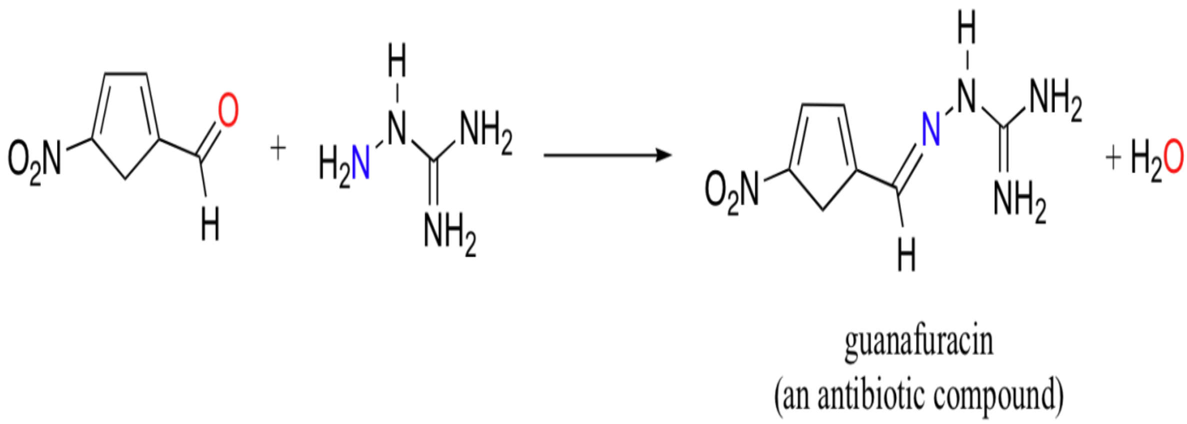


Figure 1.2 Structure of some biologically active Schiff's Bases

Guanafuracin is an antibiotic compound that belongs to the class of hydrazones. It can be synthesized easily by combining equimolar amounts of the appropriate aldehyde and hydrazine.



Scheme 1.3 Synthesis of a Schiff's Base based antibiotic

Schiff bases are considered a versatile class of compounds due to their structural similarities with natural biological substances, relatively simple synthesis procedures, and synthetic flexibility which allows for the design of suitable structural properties. They are known to be intermediate compounds in the preparation of azetidinone, thiazolidinone, formazone, arylacetamide, metal complexes, and other derivatives [3].

Schiff bases are known for their unique properties such as high thermal stability, unusual magnetic behavior, significant biological activities, synthetic flexibility, coordination capabilities, and medicinal value [4]. These compounds have been extensively studied for more than a century and have been used in various fields, including magnetochemistry, non-linear optics, photophysical studies, catalysis, materials chemistry, chemical analysis, and oxygen absorption and transport [5].

The use of metal complexes of transition elements with heterocyclic ligands, particularly those that contain nitrogen and sulfur, has a wide range of applications in various fields such as biology and anti-herbicidal activities. Thioamide ligands and their metal complexes are well-known and have gained increasing attention recently. Sulphur and nitrogen donor ligands are also utilized as effective pesticides. Schiff bases, which are extensively studied, are a key element for the development of coordination chemistry, inorganic biochemistry, catalysis, and optical chemistry. Metal complexes synthesized from Schiff bases have been widely studied due to their industrial, antifungal, and biological applications. These complexes are also used in the food and dye industries and analytical chemistry. A significant number of Schiff base complexes have potential biological significance and can be used as successful models of biological compounds, possessing diverse biological applications, such as antiparasitic activities.

Summarisation of recent developments with application of Schiff base-metal complexes

(i) Antimicrobial Activities of Schiff's bases:
Schiff base metal complexes have been found to exhibit remarkable antibacterial activity. For instance, the Schiff base 4-chloro-2-(2-morpholinoethylimino)methylphenolatomethanolchloro and its Zn(II) complex were observed to display significant activity against two Gram-negative bacterial strains, namely E. coli and P. fluorescence [6]. Additionally, bidentate complexes of benzofuran-2-carbohydrazide and benzaldehyde [BPMC] with Zn (II) and Ni (II) and Zn(II) complexes of 3,4-dimethoxybenzaldehyde [BDMeOPMC] exhibited higher activity against S. aureus in comparison to the free ligands [7].

(ii)Antifungal Activities of Schiff's bases:
Studies have revealed that Schiff base complexes of Co(II), Ni(II), and Cu(II) possess exceptional antifungal activities compared to free ligands [8]. In a related study, Fujiwara et al. investigated the antifungal activity of neutral complexes of Co(II), Ni(II), Cu(II), and Zn(II) with Schiff bases obtained from 3-nitrobenzylidene-4-aminoantipyrine and aniline/p-nitroaniline aniline [9]. The introduction of an electron-withdrawing nitro group in the phenyl ring led to increased inhibition [10].

(iii)Antitumor and Cytotoxic Activities of Schiff's bases:
Schiff's base metal complexes have also been found to exhibit potent cytotoxic and antitumor activities [11]. For instance, a tridentate Schiff's base obtained from the condensation of S-benzyldithiocarbazate with salicyldehyde, and its Zn, Sb, and Cu complexes, displayed significant cytotoxic properties. The complexes were highly active against the leukemic cell line (HL-60) [12].

(iv) Schiff's base as Insecticides
Schiff's bases derived from sulfanethiadizole and salicylaldehyde or thiophene-2-aldehydes, and their corresponding complexes, have been observed to exhibit toxicities against insects [13]. Moreover, Schiff's bases of thiadiazole derivatives with salicylaldehyde, and their Mo(II) metal complexes, were found to display insecticidal activities against bollworms and promote cell survival rates of mung bean sprouts [14].

(v) Schiff's base as Plant Growth Regulator
Schiff's bases have demonstrated remarkable activities on plant hormones, such as auxins, with effects on root growth [15]. Additionally, Schiff's bases of thiodiazole have been shown to exhibit good plant growth regulator activity towards auxin and cytokine [16]. N-acetylated compounds have been found to display growth inhibitory activity with seedlings of wheat, rye, and barley [17]. Furthermore, Schiff's bases of ester and carboxylic acid have shown remarkable activity as plant growth hormones [18]. In addition to these, various Schiff's bases possess anti-inflammatory, allergic inhibitors reducing activity, radical scavenging, analgesic, and anti-oxidative properties [19].

(vi) Schiff's base as Catalysts

Many metal ion Schiff base complexes have exhibited high catalytic activity and have played a significant role in various reactions, enhancing yield and product selectivity. These complexes have been shown to be efficient catalysts in both homogeneous and heterogeneous reactions, with their activity varying based on factors such as the type of ligands, coordination sites, and metal ions. Additionally, chiral Schiff base complexes have been found to be more selective in various reactions such as oxidation, hydroxylation, aldol condensation, and epoxidation [20].

Furthermore, metal complexes of Schiff's bases have also shown good catalytic activity. For example, various metal complexes of Schiff's bases derived from hydroxybenzaldehyde have been utilized in the oxidation of cyclohexane into cyclohexanol and cyclohexanone in the presence of hydrogen peroxide [21]. Ni(II) complexes with bidentate(NN) ligands have been demonstrated to be efficient catalyst precursors for olefin oligomerisation in the presence of an activator [22].

(vii) Schiff's base as Dying agents

Schiff's base metal complexes containing Azo groups are widely used as effective dyeing agents in various industries such as textile, leather, and food packaging. Research studies have indicated that these metal complexes exhibit excellent dyeing properties [23]. For example, chromium azomethine complexes, cobalt complex Schiff's base, and unsymmetrical complex 1:2 chromium [24] dyes provide fast and long-lasting colors to materials such as leather, wool, and food packaging. Additionally, the cobalt complex of Schiff's base, which is prepared using salicylaldehyde and diamine, exhibits exceptional light resistance and storage stability, and remains stable even when exposed to acidic gases such as CO_2 [25].

Schiff bases have demonstrated potential for diverse applications, including serving as catalysts, intermediates in organic synthesis, dyes, pigments, polymer stabilizers, and corrosion inhibitors [26]. Numerous studies have suggested that metal complexes of Schiff's base exhibit greater potency compared to the corresponding free organic ligands [27]. Transition metal complexes, such as those containing 1,10-phenanthroline and 2,2-bipyridine, have been utilized in petroleum refining [28]. Moreover, zinc (II) complexes with Schiff's base chelating ligands have shown promise as effective emitting layers [29]. Furthermore, the derivatives of N_2S_2-Schiff's base ligands complexed with zinc (II) and cadmium (II) represent a new class of luminescent compounds that can be fine-tuned for their emission wavelength by careful substituent derivatization on the pendent phenyl rings [30].

Due to the favorable properties and numerous applications of Schiff's bases, as well as the growing interest in green chemistry, there is a strong need for the development of sustainable catalysts and environmentally friendly processes for their synthesis [31]. The aim is to create cost-effective and technologically feasible methods that meet environmental demands and minimize the ecological impact of the manufacturing process. As a result, various studies have been conducted in this regard to explore new approaches for synthesizing Schiff's bases that are both sustainable and environmentally benign.

II. CONCLUSIONS

The primary objective of coordination chemists is to explore new complexes that have potential applications. One of the foremost priorities of researchers is to develop new, eco-friendly, precise, and efficient methods for synthesizing biologically active derivatives of Schiff base using green synthesis protocols that avoid the use of toxic chemicals. Schiff bases are ideal chelating agents and have multidisciplinary applications due to their relative ease of preparation, synthetic flexibility, and unique C=N group properties. Furthermore, these compounds have demonstrated remarkable activity against a wide range of organisms and have medicinal significance, making them useful in pharmacology and drug design. The present study aims to provide a concise summary of recent advancements in the synthesis of biologically active Schiff base derivatives based on reported work in the literature.

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