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Exploring The Legacy: The Biological Interactions of Bis Schiff Bases and Their Coordinated Azomethine Derivatives Over Time

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ABSTRACT

Schiff base class of compounds has a double bond between carbon and nitrogen. They form a carbonyl molecule, like an aldehyde or ketone, when combined with a primary amine. A Schiff base is structurally an aldehyde or ketone's nitrogen counterpart where the carbonyl group (CO) has been replaced with an imine or azomethine group. Schiff bases are a significant class of organic compounds with potential applications in many biological fields. They are best recognized for their capacity to generate transition metal complexes. Schiff-base ligands are easily produced and can form complexes with almost any metal ion. The main focus of this review is on the bis Schiff bases, a subclass of Schiff bases identified by the occurrence of two azomethine groups in their structures. These azomethine groups are major contributors to the activity of these compounds, along with substituent effects on key positions. For scientists interested in learning about these particular compounds' potential for specific biological uses, this article provides literature examples of the compounds in question and their biological action processes. A review focusing on the biological applications of Schiff base-derived ligands and their complexes is essential due to the numerous recent publications detailing their antibacterial, antioxidant, and enzyme-inhibitory activities.

Keywords: Schiff Bases, Coordination Complexes, Biomedical Research

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INTRODUCTION

Our goal in this review study is to do a thorough assessment of the literature that has already been written about bis Schiff bases, a unique class of Schiff base compounds that have two azomethine groups in their structures. A significant class of organic compounds, Schiff bases have potential uses in many different processes in biology. They are well-known for their adaptability in building transition metal complexes. As writers, we were conscious of the increasing number of studies in the last several years indicating the growing interest in the biological uses of ligands derived from

Schiff bases and their associated complexes. It became clear that a focused review was necessary, especially one that explored the unique biomedical uses of bis-Schiff bases and clarified their structural characteristics and significant effects on biological processes[1-12].

The importance of Schiff bases in forming complexes with different metal ions and the unique characteristics of bis Schiff bases—namely, the presence of two azomethine groups—are the driving forces behind our review. These structural components are essential to the activities displayed by these compounds, as are the effects of substituents at critical locations. It has been demonstrated that bis-Schiff bases possess antioxidant, antimicrobial, and enzyme-inhibitory qualities, underscoring their biological significance. We identified a significant gap that calls for a comprehensive assessment, given the growing corpus of material in this area. This study will be an invaluable tool for chemists trying to understand the possible uses of bis-Schiff bases in particular biological situations. Our review aims to provide a thorough overview of the various biomedical applications of these compounds as well as to contribute to the understanding of the structural determinants of bis Schiff base activities by presenting examples of these compounds from the literature and clarifying their biological action processes. By filling this gap, we hope that our work will act as a guide for scientists and researchers who are interested in studying the biological possibilities of bis-Schiff bases and their complexes, leading to a better comprehension of their uses in different biological systems[4-10].

Hugo Schiff, a German scientist, first discovered Schiff bases in 1864. Schiff noticed that an aldehyde and amine reaction produced a colored compound, which he eventually recognized as a Schiff base. Schiff bases play a crucial role in biology. They are found in many natural products and are used as intermediates in the synthesis of a variety of pharmaceuticals[1]. Some of the biological properties of Schiff bases include antimicrobial, antifungal, anti-inflammatory, and anticancer activities[1]. Schiff bases can also act as enzyme inhibitors and can be used as molecular probes in biological research. In addition, Schiff bases are important in the field of coordination chemistry, where they can act as ligands for metal ions[2].

In organic chemistry, Schiff bases play a significant role in the synthetic process and are utilized to produce an extensive variety of derivative compounds, some of which are extensively researched for their diverse biological applications[2-7]. Many of these compounds were also thoroughly investigated because of their synthetic adaptability, specificity, and sensitivity to the coordinating metal, as well as because of the azomethine group and structural similarities to genuine biological molecules[1, 2, 6, 8-14]. The azomethine group is considered to be a major contributor to almost all of the characteristic properties of this class of compounds[8]. Under standard laboratory circumstances, a primary amine and an aldehyde molecule can condense in one step to produce a Schiff base. Due to their fragility, aliphatic Schiff bases do have a propensity to polymerize, but Schiff bases made out of aromatic carbonyl are more stable due to a strong conjugation system[15]. Figure 1 depicts a Schiff base's generalized structure.

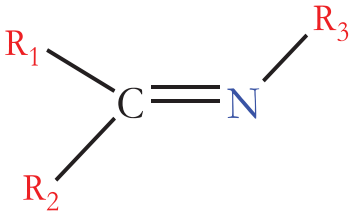

Figure 1: Schiff base generic Lewis structure, R1-3 = Alkyl and/or aryl constituents[8]

The diverse physical and chemical features of Schiff bases are due to the azomethine C=N group, which contains a single pair of electrons. Figure 2 illustrates the general structure of "bis Schiff bases," which are Schiff bases with two C=N groups[8].

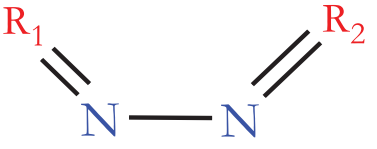

Figure 2: Bis-Schiff base generic Lewis structure, R1-3 = Alkyl and/or aryl constituents[8]

Schiff bases are versatile ligands that can coordinate with a variety of transition metals to form metal complexes. The carbon-nitrogen double bond in Schiff bases provides a site for coordination with the metal ion, which can lead to the formation of stable complexes. Schiff bases can also contain other functional groups, such as phenolic or imidazole groups, which can enhance their coordinating ability by providing additional sites for metal coordination[2, 12-14].

Schiff base metal complexes have a wide range of applications in catalysis, material science, and medicinal chemistry[16]. In catalysis, Schiff base metal complexes are used as catalysts in various chemical reactions, such as oxidation, reduction, and polymerization reactions. The metal ion in the complex can provide the necessary electron transfer for the reaction to occur, while the Schiff base ligand can modulate the reactivity of the metal ion. In material science, Schiff base metal complexes can be used as precursors for the synthesis of metal-containing materials, such as

metal-organic frameworks (MOFs)[16]. MOFs are porous materials with high surface area, which can be used in applications such as gas storage, catalysis, and drug delivery. In medicinal chemistry, Schiff base metal complexes are being investigated as potential anticancer agents[17, 18]. The metal ions in the complex can interact with cellular components, such as DNA, leading to cell death. The Schiff base ligand can also enhance the selectivity and potency of the complex toward cancer cells. Numerous complexes with diverse biological applications that have been produced from two, three, and four-coordinating Schiff bases were revealed by a survey of the literature[2, 6, 10].

DISCUSSION

Many studies and reports have been made about the significant contributions made by Schiff bases and related metal complexes in a variety of medicinal applications, encompassing antimicrobial, antioxidant, enzyme inhibition, etc.[16]. Over the years, they have also received a great deal of attention for their usage in the treatment of conditions like diabetes and HIV/AIDS[9]. They may be utilized to immobilize enzymes, are frequently evaluated as anti-malarial drugs, and are also implicated in the cure of cancer[19-22]. According to numerous studies, Schiff bases' metal complexes exhibit more biological potency than the ligands from which they are generated. Some significant biological aspects were outlined and evaluated in the section after, along with a few carefully chosen instances from the literature.

Antibacterial and Antifungal

It has been established that Schiff bases have strong antibacterial and antifungal properties[23-26]. The antimicrobial properties of Schiff bases are attributed to their ability to disrupt bacterial and fungal cell membranes, leading to cell death. The mechanism of action involves the chelation of essential metal ions, such as iron and copper, which are required for the survival of the microorganisms[24, 25]. This results in the generation of reactive oxygen species, which can cause oxidative damage to the cell membrane and DNA. The presence of functional groups, such as hydroxyl and imidazole groups, in Schiff bases enhances their antimicrobial activity by providing additional sites for interaction with microorganisms[1, 27]. There have also been reports of increased antibacterial and antifungal activity of Schiff base metal complexes than the Schiff base ligands alone, due to the synergistic effect of the metal ion and the ligand. Life-threatening fungal infections and multiple antibiotic resistance in pathogenic microorganisms have raised serious concerns in recent years[28, 29]. The creation of novel antimicrobial medications that effectively attack pathogenic organisms is an urgent medical need in the modern day. In this case, Schiff bases and their derived compounds have been recognized as potentially effective antibacterial agents and have been instrumental in several noteworthy discoveries of novel therapies in this field[23-25, 28].

Both thiazoles and benzothiazoles are heterocyclic compounds that contain nitrogen and sulfur atoms in their rings, respectively. These heterocycles have been reported to possess antimicrobial activity on their own, and when combined with Schiff base moieties, the resulting compounds exhibit enhanced activity[30, 31]. The mechanism of action of thiazole and benzothiazole, which contain Schiff bases, involves the chelation of essential metal ions in the microorganisms, which disrupts the membrane and cell wall integrity. This results in the leakage of intracellular components and eventually leads to cell death[32]. Studies have shown that thiazole and benzothiazole containing Broad-spectrum antibacterial activity of Schiff bases have been found against fungi and both gram-positive and gram-negative bacteria[30, 32]. They have also been found to be effective against multidrug-resistant strains of microorganisms. Methoxy, halogen, and napthyl groups increase the fungicidal action of these drugs against *Curvularia*[9]. Physiological action against *A. niger* has been shown by pyrandione Schiff bases. When applied to *Candida albicans*, *Trichophyton rubrum, T. mentagrophytes, A. niger*, and *Micosporum gypsum*, some Schiff bases of quinazolinones have antifungal action. The antifungal activity of furfurglidene nicotinamide Schiff base is demonstrated against *Alternaria solani, Collectotrichum capsici*, and *A. niger*[1, 27, 33-36]. "N-(Salicylidene)-2-hydroxyaniline", is discovered to be potent against Mycobacterium tuberculosis[37]. The "[(2-hydroxy-1-naphthaldehyde)-3-isatin]-bis hydrazone", has been documented to have antibacterial effects against *E. coli, V. cholera, B. magaterium, and S. aureus*[1,10]. M. Saranagapani et al. have described an array of "-isatin aldehyde, N, N-thiocarbohydrazone" compounds that have strong antibacterial properties against a range of gram-positive and gram-negative bacteria, such as *B. subtilis, S. aureus, E. coli, and P. aeruginosa*. Also, it was shown that these compounds were effective against a few fungi, including *C. albicans, P. notatum, and A. niger*[38]. Bis Schiff base, "bis (2-aminobenzaldehyde) malonyldihydrazone" and "5-(benzylideneamino)-1H-imidazole-4-carboxamide", have been documented to be effective antibacterial agents against some fungi and *S. aureus*[10,30].

Several studies have reported that Schiff base metal complexes demonstrate significant antibacterial properties against fungus and bacteria. These metal complexes are generally found to have higher biological activity than their parent ligands. The occurrence of metal centers within these complexes is thought to be responsible for this increase in antibacterial capability, which imparts greater lipophilicity and enables the molecule to better interact with the microbial cell membranes and disrupt their normal cellular processes2. Moreover, the metal ion can facilitate the delivery

of the Schiff base ligand to the target cells, resulting in enhanced uptake and bioactivity. In addition, the metal center in these complexes can also act as a redox-active site, generating reactive oxygen species that can cause oxidative damage to the microbial cells[1, 2]. Additionally, Schiff base-derived transition metal complexes have demonstrated promise in the fight against multidrug-resistant microbes, providing a promising avenue for the development of new antimicrobial agents[1, 2, 9, 27, 39].

Complexes of Co^{+2}, Ni^{+2}, Cu^{+2}, and Mn^{+2} of bis Schiff base derived from isatin have reportedly been active against a few bacteria and some fungi[1, 34]. Similar bivalent complexes of "[(2-hydroxy-1-naphthaldehyde)-3-isatin]-bishydrazone", have been documented in the literature to possess greater bactericidal properties than the ligand from which they are synthesised[1]. Venkatesh et al.[40] have also described the potent antimicrobial activity of bivalent Cu and Zn complexes of a Schiff base "(E)- 4-(1-(2, 4-dihydroxyphenyl)-ethylidene amino) benzenesulfonamide". Kuruba Siddappa et al. have described bivalent complexes of Co, Ni, Zn, Cd, Cu, and Hg of "5-bromo-3-((8-hydroxy-2-methylquinolin-7-yl) methylene) hydrazono) indolin-2-one". Reportedly all the complexes were better microbicidal agents than the parent ligand especially against *S. aureus, B. subtilis, P. aeruginosa, A. niger, and C. albicans,* etc.[15]. The antimicrobial potential of the palladium complexes was measured against gram-negative *Proteus vulgaris and Klebsiella pneumonia, gram-positive S. aureus and B. subtilis,* and fungi culture of *Candida albicans*. P. Kavitha et al. found that five bivalent Pd complexes of "3-formyl chromone" had antimicrobial and antifungal properties. They additionally stated that the palladium complexes had greater microbial inhibition actions than the Schiff base ligands[4]. Two bivalent zinc complexes of "4-pyridine carboxylic acid [(2-hydroxyphenyl) methylene] hydrazide" and "4-pyridine carboxylic acid [(2-hydroxy-5-methoxyphenyl) methylene] hydrazide," have been reported by M.K. Prasanna et al. to be effective against the fungus *Aspergillus flavus*[24].

Chelation has been shown in multiple studies to enhance the antibacterial action of metal complexes. This effect is thought to be brought about by the complexes' increased lipophilicity, which is the outcome of the metal and ligands partially sharing electron density. Chelation is characterized by coordinate bonding, which makes the metal centerless polar by delocalizing electrons across the chelating ring and reducing its polarity[2, 8]. This enhances the lipophilicity of the complex, facilitating its penetration of the cell membrane's lipid layer, where major membrane constituents such as aminophospholipids and cysteinyl ligands are also competing for metal ion interactions. Possible metal interaction sites with generally increased electron density are shown in Figure 3, which electropositive metal centers can readily accept, leading to the disintegration of the plasma membrane[1]. The interaction between metal ions and lipids favors cell membrane breakdown, allowing the complex to disrupt normal cellular processes and ultimately leading to cell death[26, 28, 41-43]. It is worth noting that the increase in antimicrobial activity upon chelation is dependent on the type of metal center and the used coordinating ligand, together with the target microorganism.

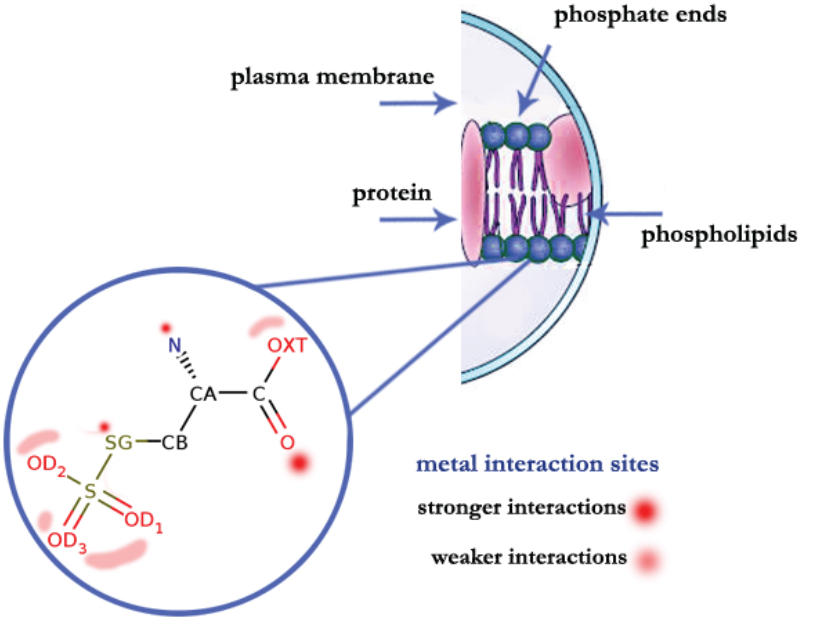

Figure 3: components of the cell membrane that interact with metal ions and have electron-rich groups.

In the modern era of microbial resistance, bacterial resistance is an important element to consider when developing antimicrobial medications that contain metals, such as metal complexes of Schiff bases. Metal-resistant bacteria are those that have developed resistance to heavy metals such as copper, silver, zinc, and cadmium. These bacteria have evolved mechanisms to detoxify and expel these metals from their cells, which can also confer resistance to other antimicrobial agents[13]. In terms of antimicrobial activity, the resistance mechanisms developed by metal-resistant bacteria can also contribute to resistance to antimicrobial agents. For example, some antimicrobial agents work by disrupting the bacterial cell membrane, but metal-resistant bacteria may have developed efflux pumps to remove the antimicrobial agent from the cell before it can cause damage. In addition, exposure to heavy metals can select bacteria with multiple resistance mechanisms, including resistance to antimicrobial agents13. This is because genes for metal resistance and antimicrobial resistance can be located on the same mobile genetic elements, such as plasmids or transposons, which can be easily transferred between bacteria. Therefore, the presence of metal-resistant bacteria in an environment may indicate a higher likelihood of antimicrobial resistance, and antimicrobial agents may be less effective against these bacteria due to their multiple resistance mechanisms. It is important to consider the potential for cross-resistance when selecting antimicrobials against metal-resistant bacteria[13].

Antioxidant

Given their capacity to neutralize free radicals and avert oxidative damage, Schiff bases have been proven to have antioxidant potential. Biomolecules including lipids, proteins, and DNA can sustain oxidative damage due to the presence of extremely reactive molecules called free radicals. This oxidative damage is associated with a range of illnesses, such as neurological problems, cancer, and cardiovascular disease[2, 8, 44, 45]. The antioxidant mechanism of Schiff bases entails giving the free radical an electron or hydrogen atom thereby neutralizing its reactivity and preventing it from causing oxidative damage. The presence of electron-donating groups, such as phenolic or amino groups, in Schiff bases enhances their antioxidant activity by providing additional sites for free radical scavenging[8, 45].

Additionally, it has been shown that metal complexes of Schiff bases have more antioxidant capacity than the Schiff base ligands themselves. The metal ion in the complex can act as a redox-active site, generating reactive species that can enhance the antioxidant potential of the complex. The metal ion can also stabilize the Schiff base ligand by forming coordination bonds, preventing its degradation, and enhancing its antioxidant activity[2]. Overall, the antioxidant potential of Schiff bases and their metal complexes makes them promising candidates for the development of new antioxidant agents for the prevention and treatment of diseases associated with oxidative stress.

The literature provides a wealth of examples demonstrating Schiff bases' capacity to scavenge free radicals and act as antioxidants in a variety of in vitro and in vivo settings. The compounds "[(3-Bromobenzylidene)-amino] phenol" [31], a bromo Schiff base "(E)-4-(3,4-dihydroxybenzylideneamino)-2,3-dimethyl-1-phenyl-1,2-dihydropyrazol-5-one"[46], "(E)-N'-(4-nitrobenzylidene)-4-chlorobenzohydrazide" to name a few, have been reported in the reviewed literature for excellent antioxidant activity[47].

Kuruba Siddappa et al. have described bivalent complexes of "5-bromo-3-((8-hydroxy-2-methylquinolin-7-yl) methylene) hydrazono) indolin-2-one". Reportedly Co^{+2}, Ni^{+2}, Zn^{+2}, and Cu^{+2} complexes were better antioxidants than the parent ligands, while cadmium and mercury complexes were found to moderate 2,2-diphenyl-1 picrylhydrazyl (DPPH) radical scavengers compared to standard ascorbic acid15.
Some M+2 complexes have been shown to exhibit antioxidant action by Kumar et al. "8-((2-(2,4-dinitrophenyl) hydrazone) methyl)-7-hydroxy-4-methyl-2H-chromen-2-one". Because the complexes have a greater ability to scavenge free radicals, it has been shown that complexation increases the antioxidant activity[48]. M.L. Sundararajan et al. listed a few bivalent transition metal compounds of "2-((E)-(benzo[d] [1,3] dioxolane-6-amino) methyl)-4-bromophenol" had significantly more antioxidant capacity than the unbound ligand. It has been stated that of all the complexes, the Cd and Hg complexes are the most active[3]. K. Balan et al. (2017) have described a bivalent Zn complex of N_2O_2 derived Schiff base ligand with free radical scavenging potential to be nearly equivalent to the standards, against both hydroxyl and DPPH radicals. For both scenarios, the activity was reportedly being dose-dependent[3].

A lot of research has been done on the medium-to-strong free radical scavenging properties of Schiff bases, particularly those with hydroxyl and amino groups [44, 49]. The typical process of quenching free radicals by Schiff bases, such as DPPH•, is depicted in Figure 4 by giving hydrogen atoms to the free radicals. However, it has been noted that metal complexes containing Schiff bases have less antioxidant action. This is likely due to the hydroxyl groups' deprotonation upon coordination, which prevents them from being able to provide hydrogens to free radicals. The remaining substitutions on different places within the ligands are useful since they do not take part in complexation and can thus provide hydrogen, which enables them to hunt down free radicals. This assumption was confirmed by several studies examined for this review. It was found that

while Schiff bases with multiple OH groups were able to retain a reasonable level of antioxidant capacity even when coordinated to metals, Schiff bases with only one OH group demonstrated reduced inhibition if coordinated to metals[2, 44].

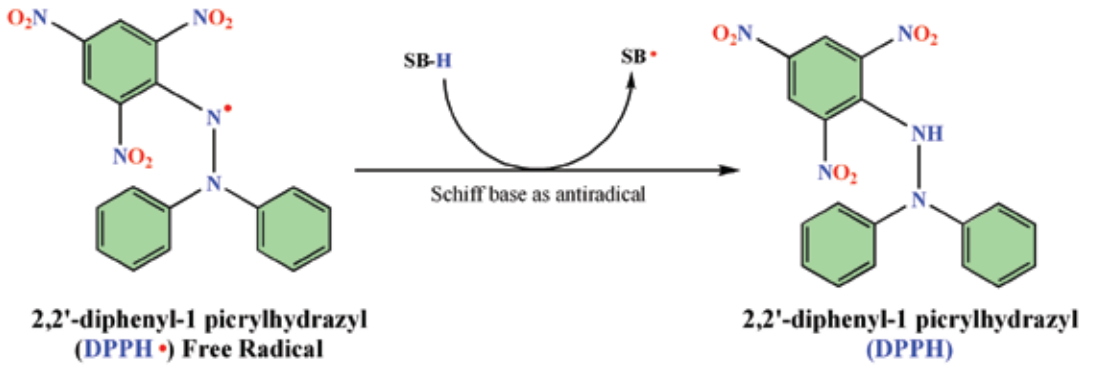

Figure 4: **As an anti-radical agent, Schiff base, *(SB = Schiff base)***

a-Glucosidase Inhibition

Alpha-glucosidase is an essential enzyme in the conversion of complex carbohydrates into simple sugars. Inhibitors of alpha-glucosidase are a class of compounds that can reduce the rate of carbohydrate digestion and absorption, which can be beneficial in the management of type [2] diabetes and other related metabolic disorders. It has been discovered that Schiff bases and their transition metals have considerable alpha-glucosidase inhibitory action, making them suitable therapeutics for the management of diabetes. These compounds work by attaching to alpha-active glucosidase's site and inhibiting the enzyme from hydrolyzing complex carbs into simple sugars[8,50, 51]. Moreover, it has been discovered that Schiff bases and associated transition metals possess anti-glycation qualities. The production of advanced glycation end products is the result of the non-enzymatic process of glycation, which includes the covalent interaction of reducing sugars with amino protein chains (AGEs). Diabetes, vascular dementia, and cardiovascular disease are just a few of the chronic diseases that have been linked to AGEs. Schiff bases and related metal complexes' capacity to consume free radicals as well as avoid the production of AGEs is primarily responsible for their anti-glycation characteristics. Specifically, these compounds can trap reactive carbonyl species (RCS) and inhibit their interaction with amino groups of proteins, which is a key step in the formation of AGEs. In general, Schiff bases and their metal complexes possess both alpha-glucosidase inhibitory activity and anti-glycation properties, which makes them excellent candidates for the development of innovative therapeutic medicines for the treatment of metabolic disorders such as diabetes[50, 51].

The compound "4-[(E)-benzylideneamino]-5-(4-chloro-2-methyl-phenyl)-4H-1,2,4-triazole-3-thiol" exemplifies Schiff bases as -glucosidase inhibitors, and literature evidence indicates that Schiff bases also exhibit strong -glucosidase inhibition and anti-glycation actions[52]. Excellent β-glucuronidase inhibitory activity has been shown for a series of phenoxy acetohydrazide Schiff base analogs by Khalid et al. Here are two examples that demonstrated greater a-glucuronidase inhibitory activity than the reference, D-saccharic acid-1,4-lactone[51]. Certain oxo-vanadium IV complexes with notably greater a-glucosidase inhibitory activity than the typical acrabose compound have been identified by Mishra et al. It was discovered that these complexes could reduce blood glucose levels by 12%, but the control group could only achieve a reduction of roughly 35%[50]. The biological activities of a Zn^{+2} complex of a Schiff base ligand named "bis(3-acetyl-5-methyl-pyran-2,4-dione) ethylenediamine" have been reported by K. Balan et al. Additionally, this combination demonstrated promising dose-dependent -glucosidase inhibitory action[3].

For the most part, when it comes to a-glucosidase inhibitors, Schiff bases and their metal complexes often belong to the "non-glycosidic derivative" category and function similarly, meaning that compounds with substituent groups that strengthen the hydrophobic connections with the enzyme are more effective. Figure 5 illustrates inhibition in a basic way.

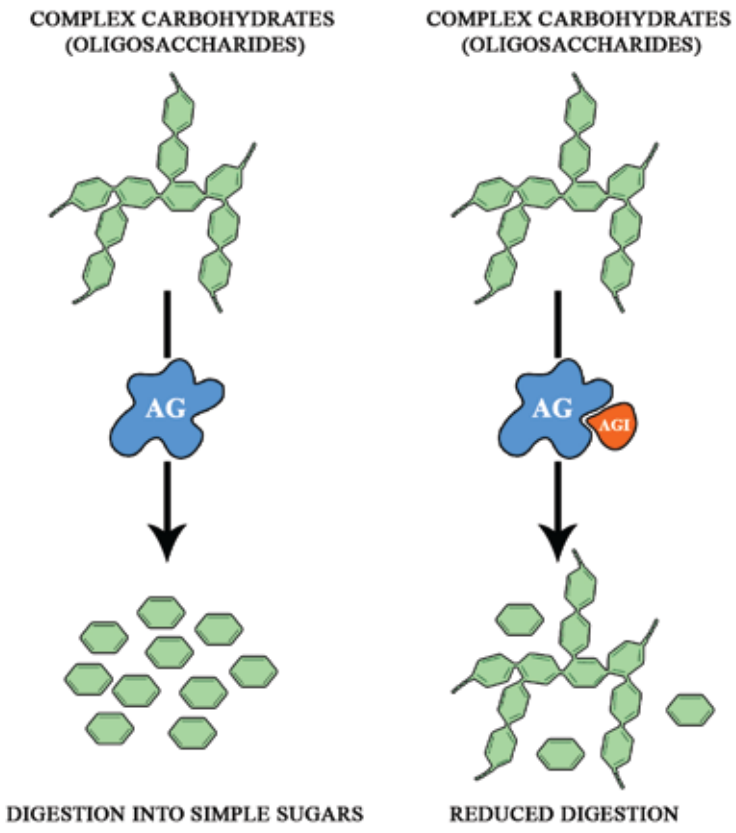

Figure 5: Schiff base acting as alpha-glucosidases inhibitor[8]

The ability of the inhibitor to generate hydrogen bonds that bind to the catalytic site of a-glucosidase throughout the inhibitory action is another mechanism of the inhibition that has been documented. In the inhibitory process, hydrogen bonds are created between an inhibitor's hydrogen bond donor and an enzyme residue's hydrogen bond acceptor, or the other way around[53]. It is commonly stated that the complexes outperform their respective ligands as inhibitors. Either of the two causes or even more of a combination effect, have been suggested as the cause of the increase in inhibitory potency. The coordinated compounds' many substituent groups, such as methyl, chloro, methoxy, hydroxyl, and –N(CH^3)^2, are the first. The inhibitory potential is directly impacted by the substituent groups' electron-donating or electron-withdrawing characteristics[54]. Significantly stronger inhibitors are substituent groups that remove electrons [55, 56]. Second, chelation results in a decrease in the polarity for the metallic ions, increasing the complex's lipophilicity and raising the likelihood that the inhibitor will interact with the enzyme[43]. Additionally, it has been shown that a-glucosidase can stabilize the inhibitor by coordinating with the core metallic ions of the complexes if the creation of such a link is advantageous[57]. Furthermore, whenever there is a possibility of these interactions, it is discovered that the influence of hydrogen bonding at the active site of the enzyme is helpful to the inhibition. The substituent groups might affect the candidate inhibitor's ability to donate or accept hydrogen bonds. For example, the phenyl hydroxyl and chloro groups might be more effective at accepting hydrogen bonds from the right donors at the enzyme's protein side chains than the other groups[54].

Urease Inhibition

The metalloenzyme urease, which contains nickel, catalyzes the conversion of urea into carbon dioxide and ammonia. Ammonia is a toxic molecule in biological systems, particularly in high concentrations. It is formed when urea is broken down in the liver through the process of deamination. In the liver, ammonia is converted to urea and excreted by the kidneys[45]. However, if the liver is damaged or if there is an excess of ammonia production, ammonia can build up in the body and cause toxicity. Urease inhibition is an important strategy to cure of infection triggered by urease-producing species, such as *Helicobacter pylori*, which can contribute to the toxicity of ammonia in a biological system. When *H. pylori* colonizes the stomach, it can increase the production of ammonia, leading to local inflammation and damage to the gastric mucosa[21]. The increased levels of ammonia produced by *H. pylori* can also lead to systemic toxicity. Studies have shown that *H. pylori* infection is associ-

ated with an increased risk of developing liver cirrhosis, which is characterized by liver damage and impaired function. The presence of H. pylori in the gastrointestinal tract has also been connected to the onset of hepatic encephalopathy, which is a disorder marked by a liver disease-related impairment in brain function, which is in part caused by the elevated levels of ammonia produced by the bacteria[21]. In addition, H. pylori infection has been linked to an increased risk of developing gastric cancer, and it has been suggested that the toxicity of ammonia produced by the bacteria may contribute to the carcinogenic effects. This is because high levels of ammonia can cause DNA damage and induce oxidative stress, which can lead to mutations and the development of cancer.

Several dangerous pathogenic bacterial strains, like Helicobacter pylori, depend on the enzyme urease to survive. Despite numerous attempts, it has been difficult to develop effective urease inhibitors that don't have any negative effects on the human host[58]. Schiff bases and their metal complexes have been found to possess significant urease inhibition activities, which makes them potential therapeutic agents for the treatment of such infections. The mechanism of urease inhibition by Schiff bases and their metal complexes involves the binding of these compounds to the active site of urease, thereby preventing the enzyme from hydrolyzing urea into ammonia and carbon dioxide. This leads to a decrease in the concentration of ammonia, which is toxic to host cells and promotes the survival of urease-producing bacteria. Several studies have reported the urease inhibition activities of Schiff bases and their metal complexes. For example, some copper and nickel complexes of Schiff bases have been found to exhibit potent urease inhibition activities in vitro, with IC50 values in the micromolar range. Similarly, some palladium and platinum complexes of Schiff bases have also been reported to possess significant urease inhibition activities. Therefore, these properties of this set of compounds make them potential therapeutic agents for the treatment of infections caused by urease-producing bacteria[19, 21, 45, 59].

Research on Schiff bases in the literature has shown that they can also inhibit urease, and several Schiff bases have been found to have respectable urease inhibitory activity. We discovered a few Schiff bases that have sufficient inhibitory power as urease inhibitors. Hanif, M., et al., have reported four Schiff bases promising urease inhibitors: "5-(4-Chlorobenzyl)-1,3,4-oxadiazole-2(3H)-thione", "5-(4-Methoxyphenethyl)-1,3,4-oxadiazole-2(3H)-thione", "5-(2-Methoxyphenethyl)-1,3,4-oxadiazole-2(3H)-thione", "5-(4-Methoxybenzyl)-1,3,4-oxadiazole-2(3H)-thione"[45]. A Cu^{+2} compound of "(E)-2-((2-chlorobenzylimino) methyl)-4,6-dibromophenol" Schiff base has been reported by W. Chen et al. to have potent inhibitory activity against jack bean urease. Moreover, compounds of Co^{+2}, Ni^{+2}, and Zn^{+2} with strong urease inhibition properties have been discovered[60]. Certain poly-nuclear Cd+2 complexes with potent urease inhibitory actions have been reported by Zhong-Lu You et al. The Cd+2 complex of "N-methyl-N-(1-pyridin-2-ylmethylidene) ethane-1,2-diamine" is one example of such a compound[61]. Several current research indicate that certain Cu^{+2} compounds that were driven from the Schiff base exhibit good urease inhibitory capabilities[62-70].

Transition metals, including copper, have been suggested to be effective urease inhibitors by either binding to functional groups within the enzyme or distorting its active site[65, 69]. A simplified mechanism of inhibition is shown in Figure 6.

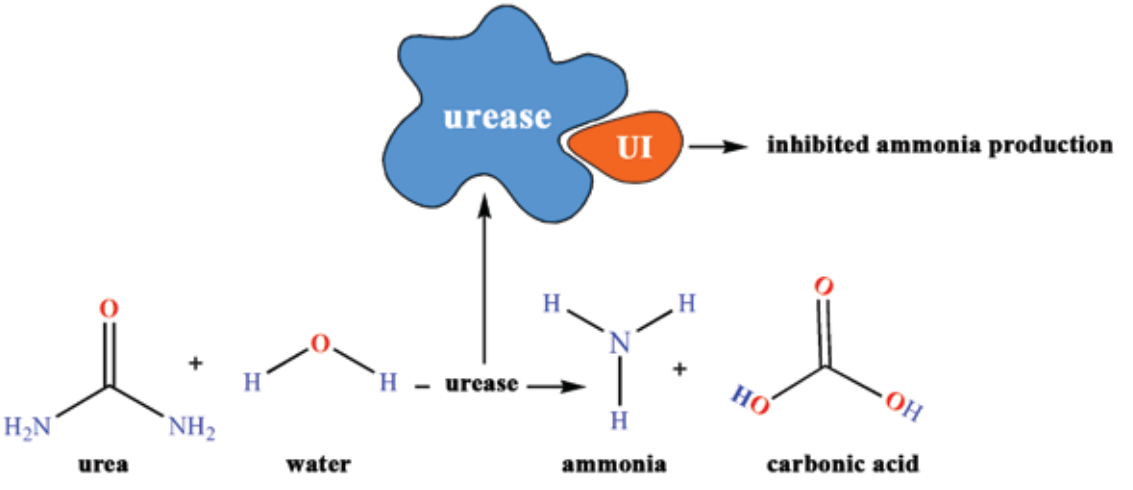

Figure 6: Schiff base acting as urease inhibitor[19, 59]

It has been documented that metals other than copper can bind to protein functional groups including thiol groups and N- and O-containing groups[68, 70] but copper ions have been shown to frequently distort the enzyme's active site, thereby inhibiting its ability to catalyze the hydrolysis of urea[62, 63, 65, 68]. In addition to copper ions alone, copper complexes have also been studied for their urease inhibition potential. The functional groups and other substituent moieties present in the ligands of these complexes can contribute to their inhibitory activity by steadying interactions with the enzyme, like binding in the active site of nickel ions[66]. The efficiency of inhibition is also thought to be influenced by stem effects, with less bulky groups in the complexes preferring higher inhibitory capacity[62, 65, 68].

CONCLUSION

This review has demonstrated that the wide spectrum of biological activities exhibited by Schiff bases can be attributed to their azomethine groups. Particularly, the electron donor atoms, like oxygen and nitrogen, are important in establishing coordination covalent connections with metal ions, which facilitates the synthesis of transition metal complexes with important biological functions, and in regulating the biological response of these compounds. Research has demonstrated that as compared to their parent ligands, these metal complexes display enhanced biological activity, especially about antibacterial qualities. This increase in activity is thought to be caused by a decrease in the polarity of metal ions after chelation. This makes it easier for the complexes to pass through the lipid barrier of cell membranes and interfere with regular biological processes. In the context of enzyme inhibition, multiple processes could be at play. Complexes can alter the functional portion of the protein, create hydrogen bonds with the receptor, or change the ligands in a complex to affect its overall activity. To completely comprehend the different mechanisms that underlie the biological actions of Schiff bases and their metal complexes, more investigation is required. These mechanisms may have significant ramifications for the creation of novel therapeutic medicines.

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CONFLICT OF INTEREST

The authors declares that there are not conflict of interest of any kind.

AUTHORS CONTRIBUTION

Both authors of this paper contributed equally during the research and writing of the manuscript.

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