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FULL PAPER

A review of Schiff base-inorganic complexes and recent advances in their biomedicinal and catalytic attributes

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Schiff base-inorganic complexes have significantly contributed to the development of modern drug design due to their significance in a number of multi-discipline study fields. This nearly exhaustive review examines every aspect and characteristic of these complexes, with a focus on a few key biomedical traits. Schiff base, the organic component of these complexes, is formed by the condensation of two important molecules: a carbonyl and a primary amine framework. Organic compounds based on the Schiff base moiety have been demonstrated to have biomedical attributes such as antibacterial, antioxidant, antifungal, antineoplastic, and antiviral properties. In the light of these attributes and the recent advances in the domain of coordinating chemistry, many research outcomes suggest the Schiff base-inorganic complexes as a potential core for medicinally active coordinated compounds and for reaction catalysis. This suggestion is supported by numerous new research findings that document the properties of these complexes as antimicrobial, antioxidant candidates, and efficient promoters in various chemical reactions.

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Introduction

Schiff bases are an extraordinary class of ligands with a wide range of donor atoms and phenomenal coordination modes toward transition metals. These ligands are considered Lewis acids since they contain at least one unshared pair of electrons. The presence of an imine (-C=N-) interconnection in this ligand phenotype has an impact on biological functions. In addition, many Schiff base-derived ligands have been studied in fields other than those related to biology and medicine. The results point to the potential applications of these ligands in various fields, including material science, catalysis, and different industries [1-30].

Salen-based ligands, often known as bis-Schiff bases, are one of the most significant classes of ligands produced from Schiff bases. Any member of this class shares a structural connection with the traditional Salen ligand of the chemical structure illustrated in Figure 1. Salen-based ligands are renowned for their ability to coordinate a broad range of different metals and stabilize them at a multitude of oxidation levels. These ligands are employed as metal deactivators as a result. In addition, numerous complexes based on Salen have been discovered to play a significant role in the catalysis of chemical reactions [31].

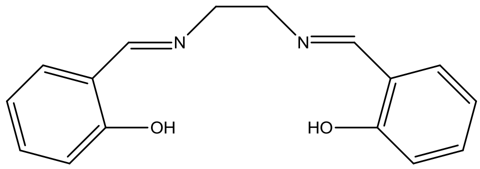

FIGURE 1 The chemical structure of traditional Salen ligand

The salen-based ligands, produced by fusion of various functionalized salicylaldehydes and the primary diamine, are described as versatile ligands for coordination chemistry because their steric and electrical characteristics can be adjusted by modulating various substituents on the building units. This important class of ligands includes donor cores in their structural design, which allow metal ions to reflect different configurations with other ligands. As a result, a wide range of complexes were created by varying the location of metal ions in reference to the Salen-based ligand [32].

The metal chelating activity of the Salen-based ligands with oxygen or nitrogen donor functional groups gives the resulting complexes an interesting kinetic and thermodynamic stability. Nitrogen's contribution to the Schiff base molecular framework gives rise to noteworthy chelating properties, which are useful in many medicinal fields. The salen-based complexes are also crucial components or architectural motifs in recent detectors, nonlinear absorptional devices, solar cells, and the development of bio-inorganic chemistry, catalysis, electromagnetism, and diagnostic imaging [33].

Salen-based ligands are simple to make and can interact with nearly any metal ions to produce the required complexes. The combination of metal ions via imine nitrogen is what makes this possible. Numerous salen-based complexes that have been thoroughly researched have diverse geometries and variable oxidation states. The development of bio-inorganic chemistry and catalysis may be observed in some of them [34].

Along with iron, copper, an essential mineral, helps the body create red blood cells. It makes an important contribution to iron absorption and maintains health blood vessels, bones, nerves, and an effective immune system. Enough copper in the diet may also assist in avoiding heart diseases and osteoporosis, based on the findings of many clinical investigations. Due to its knowledgeable biological properties, copper's coordination chemistry has caught the attention of many researchers. Numerous Schiff base-copper complexes have been successfully employed for studying some biomedical and biomolecular properties [35].

Over the last few decades, numerous academic research studies have concentrated on the intriguing biological applications of Schiff base-derived ligands and their metal complexes, particularly their antioxidant, redox, catalytic, and antimicrobial properties. A review that emphasizes the use of target ligands and their metal complexes is indeed necessary. In polymer science, materials engineering, electrochemistry, isolation procedures, biotechnology, and innovative synthetic pathways, the significance of Schiff base-derived complexes has been thoroughly researched and updated [36].

In general, the metal complexes have relatively higher biological activity than their original ligands. The chemical stability, electron-donating ability, optical nonlinearity, catalytic potential, photochromic properties, and biological potential of the Schiff base-derived complexes are of great interest. The Schiff base-derived complexes derived from amino acids are an intriguing class. Amino acids are dynamically involved in some vital biological processes, and they have the primary amine coordination sites that can combine with molecules that contain carbonyl to create Schiff bases that are simple to integrate with metal ions [37].

The majority of amino acid-based Schiff base ligands and their derived complexes made with the right metals exhibit unique drug-like properties. Ghanghas *et al.* conducted a significant study that investigated amino acid-based Schiff base complexes from last five years. The findings indicated that these complexes have high thermal stability and antibacterial activity. The latter is influenced by the metal ion phenotype, ligand phenotype, complex environment, coordination sites, hydrophilicity/lipophilicity, co-ligand type, and complex concentration [38].

The best candidates for antibacterial drugs are heterocyclic ligands with multiple functions that can communicate with physiological metal ions, which are particular to nucleosides [39]. To gain access to highly conformed states, the ligands intrude on enzymatic binding sites. In a recent study, Ghanghas *et al.* provided an overview of the development of various types of investigations used to enhance the bioactivity of Schiff base-metal complexes, which was extremely helpful in the projection of an innovative category of drugs beginning with the identified complexes. To link the basic activity and its variations to the used ligand and/or metal, the research also examined the antibacterial activity of the Schiff base-derived ligands included in the complexes under study [33].

In recent years, scientists have focused their efforts on developing and studying a new class of ligands with tetramethyldisiloxane linkages connecting the included moieties. The well-known adaptable and lipophilic properties of tetramethyldisiloxane connectors are of genuine importance. Therefore, research activities mainly concentrated on the production of these tetramethyldisiloxane-based ligands and their metal complexes and subsequently investigated their individual roles in reaction catalysis, materials science, bioactivity, and nanoscience [40].

Researchers have focused on the topic of Schiff base-inorganic complexes that begin because of their biological activity, with the leading objective of finding specific and functional drug molecules for treatment of various human diseases. Schiff base-inorganic complex research has received particular attention because it has been found that many of these complexes can be used as candidates because of their biological significance. In this review study, new Schiff base-derived ligands and their related metal complexes are highlighted for their developed biomedical applications, commencing from their exploration in 2016 to the current time. The reviewed attributes for the aforementioned ligands and complexes include their roles as antimicrobials, antioxidants, and chemical reaction promoters.

Anti-pathogenic microorganism attribute

Numerous studies on the use of Schiff base-inorganic complexes as potentially efficient antibacterial agents have been published in recent years, particularly from 2016 to the present. In terms of antibacterial activity, these studies discovered that Schiff base-inorganic complexes outperformed their constructing ligands [41].

The significance of the Schiff base-inorganic complexes for antimicrobial activity and advancements in the study of other types of intriguing topoisomerase complexes as effective antineoplastic agents are highlighted in the recently published review article. After 6 hours of incubation, one of the reviewed research papers discovered that the picolinic acid-copper complex significantly slowed gel electrophoresis, whereas the thiosemicarbazone-copper complex potentially inhibited the overgrowth of *K.*

pneumonia, *S. typhimurium*, and *S. aureus* [42].

In a recent study, numerous Schiff base-derived ligands were prepared by condensing various functionalized salicylaldehydes with diamine, using 1,3-bis(3-propyl) tetramethyldisiloxane as a connecter through N_2O_2 coupling mode. The prepared ligands and their copper complexes were investigated as antimicrobial candidates by examining their capacity to inhibit the pathogenic growth of three fungal strains, two gram-positive bacterial strains, and one gram-negative bacterial strain. In the case of the Schiff bases derived from halosalicylaldehyde, the results of this antimicrobial activity study demonstrated a greater performance, pretty close to those of the used standard drugs. The presence of chlorine in the fifth position is what gives the Schiff base-derived ligand made from 5-chlorosalicylaldehyde and its metal complexes the greatest potential as an antimicrobial agent. Some of the prepared compounds were suggested as potential antimicrobial agents based on the outcomes of the antibacterial and antifungal data gathering [43].

Cazacu *et al.* prepared a Schiff base-derived ligand by condensing disiloxane-containing 1,3-bis(3-aminopropyl)-tetramethyl and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde. The resulted in situ ligand was complexed individually with copper, nickel, and manganese. After their evaluation, the prepared complexes have a wide range of intriguing features, with implications in many different fields, including chemical analysis, biology, and industry. In terms of bioactivity, many of these Schiff base-derived complexes showed promising antimicrobial and antitumor properties [44].

It is crucial to pick the right carbonyl and primary amine building blocks when presenting various Schiff base-derived ligand types. Trimethylsilyl-containing homometallic and heterometallic complexes have been shown to be amphiphilic, and depending on the polarity of solvent, they can self-assemble in solution. These distinct properties shape perceptions in solutions and enhance the catalytic activity of complexes on various substrates. In this regard, using a novel trimethylsilyl-propyl-para-aminobenzoate in combination with ortho-vanillin and salicylaldehyde, Zaltariov *et al.* synthesized bidentate Schiff base-derived ligands. Many copper and zinc complexes were created when two moles of these ligands were coordinated; some of these complexes were suggested as potential candidates for bioimaging because of their absorption spectra in the visible region and their green emission. Analysis of the findings from antimicrobial studies revealed that heterometallic complexes exhibit higher bioactivity than the standard controls, Kanamycin, and Caspofungin [45].

In the literature, there are many Schiff base-derived ligands that, as illustrated in Figure 2 and Table 1, have demonstrated hopeful antibacterial activity. The chemical structures of these antibacterial ligands are based on siloxane, curcumin, indole, pyridine, pyridinyl hydrozone, thiosemicarbazone, thiazole, thiazolidione, benzimidazole, isatin, and hydrazide. The antibacterial activity of the homometallic and heterometallic complexes of the aforementioned types of ligands was further investigated. The conclusion revealed that antibacterial activity of these complexes is higher than that of their constituent ligands.

TABLE 1 The Schiff base-derived ligands' fundamental functional groups or backbones, functional substituents (s), and references show promising antibacterial activity

Fundamental functional group or backbone	Functional substituent (s)	Reference
Siloxane	**1**: R1, R2, R3=H **2**: R1, R2=H; R3=NO_2 **3**: R1, R3=Br; R2=H **4**: R1, R2=H; R3=Cl	[43]
Thiosemicarbazone	**5**: R= -Ph-CH_3	[46]
Curcumin	**6**: R= H_2N-CO-NH-NH_2	[47]
Thiazolidione	**7**: R1=Br; R2, R3=NO_2; R4=OH	[48]
Benzimidazole	**8**: R1=NO_2; R2, R5=H; R3=COOH **9**: R1=OH; R2, R5=H; R3=COOH **10**: R1=OCF_3; R2, R5=H; R3=COOH **11**: R1=NO_2; R2, R5=H; R3=SO_3H **12**: R1=OH; R2, R5=H; R3=SO_3H **13**: R1=OCF_3; R2, R5=H; R3=SO_3H	[49]
Thiazole	**14**: R1=NH_2; R2=CN; R3=CH_3	[٥٠]
Hydrazide	**15**: G=NO_2	[51]
Pyridine	**16**: R=OC_2H_5	[52]
Pyridinyl hydrozone	**17**: G=OH	[53]
Isatin	**18**: G=H; **19**: G=F; **20**: G=Cl; **21**: G=CH_3	[54]
Indole	**22**: R=OCH_3	[55]

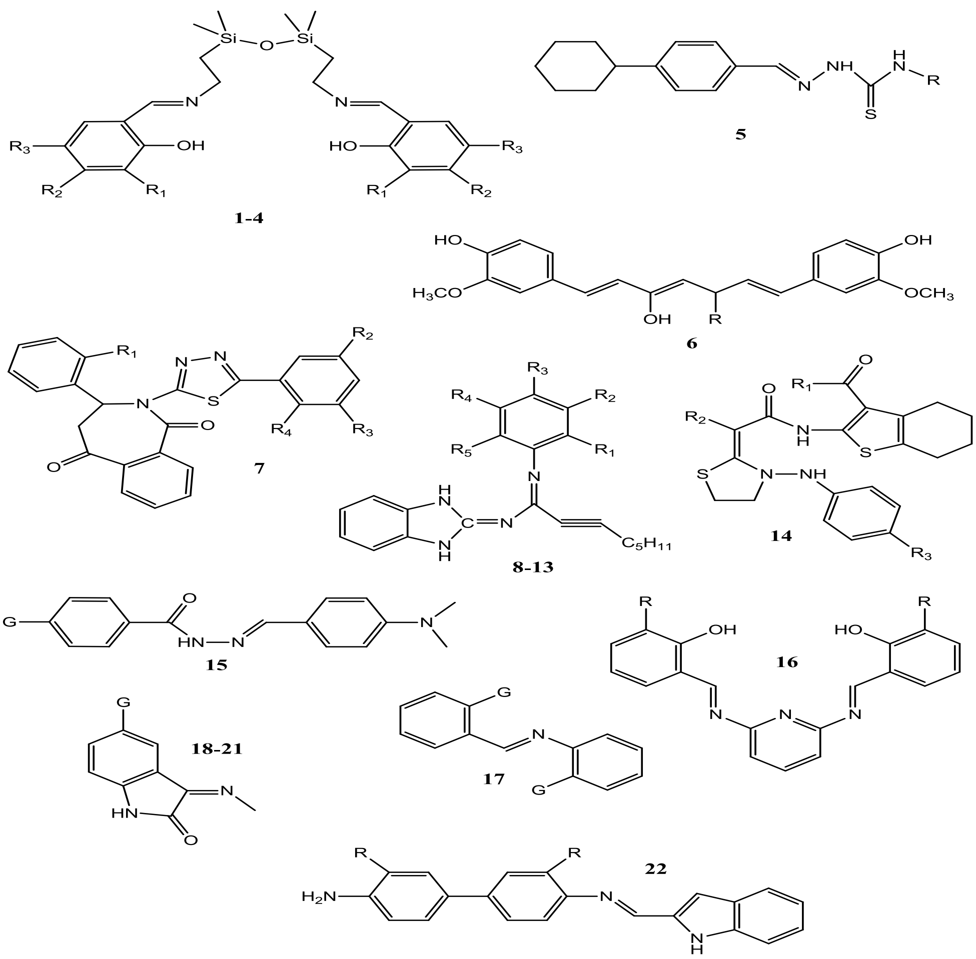

FIGURE 2 The chemical frameworks of Schiff base-derived ligands demonstrated hopeful antibacterial activity

Various published research studies have found a significant rise in systemic and fatal fungus infections[56]. Multiple studies have shown that the most serious fungal infections are caused by species of Candida and Aspergillus. Therefore, it is crucial to advance new antifungal candidates with higher efficacy and lower resistance. Several time-consuming and tedious studies have been conducted, and some Schiff base-derived ligands have proven to be effective antifungal compounds. The researchers also emphasized the presence of various groups, including naphthyl, halogen, and methoxy, which improve the ligand's fungicidal activity. Despite the widespread distribution of pathogenic fungi, the spectacular power of developing antifungal drugs in metal complex domain is amplified by new pieces of literature [57].

In a different study, homometallic complexes of cadmium, nickel, zinc, copper, manganese, iron, and chromium as well as Schiff base-derived ligands were created and used for *in vitro* tests to establish their antimicrobial activity against numerous strains of pathogenic bacteria and fungi. The novel coronavirus protein sites were used in this study to lead the screening potential of drugs using molecular docking, and the research was set up for molecular modeling without verification via dynamic simulation [58].

Finally, various Schiff base-derived ligands of 4-(benzyloxy)-2-hydroxybenzaldehyde and their zinc, copper, nickel, and cobalt complexes were synthesized by Devi *et al*. The *in vitro* antifungal activity of these ligands and their inorganic complexes versus *C. albicans* was comparable to that of the conventional medicaments. The results are further documented by an *in silico* study using *C. albicans* sterol 14-α-demethylase. The researchers concluded that the prepared ligands and their inorganic complexes in general, and copper complexes in particular, could be used as orally active antifungal agents [59].

Free-radical quenching attribute

Finding compounds with antioxidant potential has sparked a great deal of attention. The synthetic antioxidants are more widely used since they are more potent and less costly than isolated natural antioxidants, which are recognized to be the most expensive. To effectively act as quenchers of oxygen-related radicals acting as antioxidants, some metal complexes have been researched [60].

Two groups of researchers, Uddin *et al.* and Borase *et al.*, prepared numerous Schiff bases derived from condensing various benzohydrazides, thiocarbohydrazides, hydroxyquinolines, sulfanilamides, and diamines with different functionalized ketones or aldehydes. The prepared ligands were coordinated to create many Schiff base-inorganic complexes of ruthenium, cadmium, platinum, nickel, iron, copper, zinc, and cobalt. The created ligands and their inorganic complexes with nitro or methyl functional groups presented a higher free-radical quenching attribute than the ones with 4-OH groups [61,62].

Kizilkaya *et al.* synthesized a number of heterocyclic Schiff base-derived ligands by refluxing a methanolic solution of 4-amino-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2H)-one with various functionalized aldehydes. The free-radical quenching attribute of the prepared ligands was assessed by analyzing their examination scores using three traditional antioxidant assays, named reducing power, DPPH, and ABTS. The results inspired the authors to recommend that the compounds, with the chemical structures illustrated in Figure 3, have the potential to act as antioxidant candidates [1].

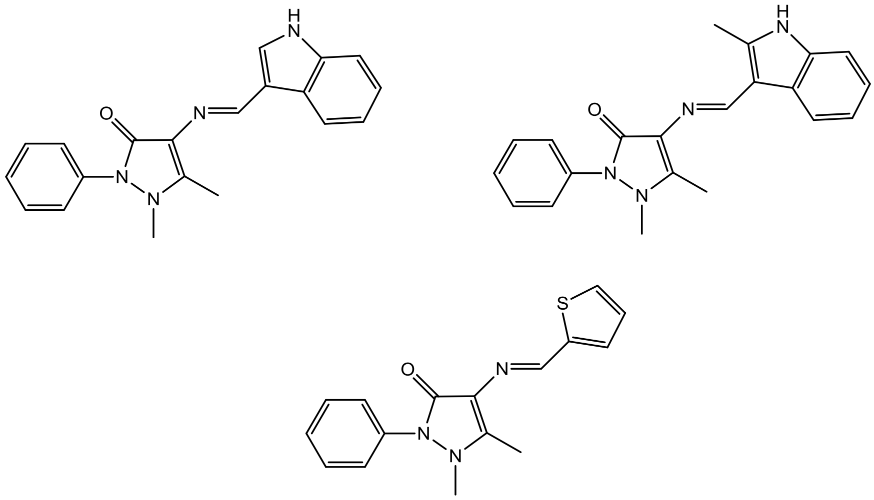

FIGURE 3 The chemical structure of heterocyclic Schiff base-derived ligands prepared by Kizilkaya *et al*.

New tin-diorganotin complexes with the general formula R_2SnL were made by Devi and Pachwania. The *in vitro* antibacterial property against various bacterial and fungal pathogens was carried out using the multidilution technique to investigate the biomedical characteristics of these complexes. In addition, the antioxidant potential of complexes was determined by their ability to capture the DPPH radical. According to the findings, the complex with two phenyl rings and the structure shown in Figure 4 has the best antimicrobial and antioxidant activities when compared with the other tin-based complexes that have been created [63].

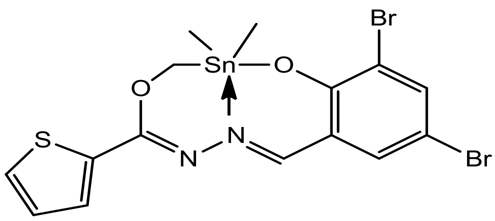

FIGURE 4 The chemical structure of the best Schiff base-tin complex prepared by Devi and Pachwania

In a different study, Devi *et al.* created 16 new Schiff base-inorganic complexes. The organic part of the prepared complexes was synthesized by condensing 4-(benzyloxy)-2-hydroxybenzaldehyde with various congeners of aminophenol, while the inorganic part was represented by the metals nickel, copper, cobalt, and zinc. The antioxidant attribute of the prepared ligands and their corresponding complexes was monitored by following the ability of the test entity to decolorize the DPPH-purple color. The findings revealed that the Schiff base-inorganic complexes exhibited more antioxidant activity than their corresponding Schiff base-derived ligands under the test conditions. Furthermore, the copper-based complexes showed the best capacity as antioxidant candidates among the other complexes [64].

Aidi *et al.* have prepared two macrocyclic Schiff base-derived ligands of the symmetrical type by condensing 2-hydroxy-3-methoxybenzaldehyde and 2-hydroxybenzaldehyde with polyamine. The resultant ligands were coordinated with copper and cobalt metals, affording different Schiff base-inorganic complexes. The ability of the created complexes to trap DPPH radicals and inhibit the growth of pathogenic bacterial strains was evaluated *in vitro*. The findings recommended that, in view of tested biomedical activities and in comparison with the positive controls, vitamin C and various antibiotics, these complexes may open new windows for developing potent therapeutic agents to handle pathogenic infections and oxidative stress-related diseases [65].

Finally, Soroceanu *et al.* synthesized and tested four Schiff base-copper complexes, as illustrated in Figure 5, for bioactivity. The organic part was synthesized by condensing 1,3-bis(3-aminopropyl) tetramethyldisiloxane with four different aldehydes, which are 5-chloro-2-hydroxybenzaldehyde, 2-hydroxy-5-nitrobenzaldehyde, 3,5-di-bromo-2-hydroxybenzaldehyde, and 2-hydroxybenzaldehyde. The bioactivity potential of the prepared copper complexes was assessed against three pathogenic (*Alternaria alternate*, *Penicillium chrysogenum*, and *Aspergillus flavus*) and two highly infective strains of bacteria (Bacillus spp., and *Pseudomonas aeruginosa*). The capacity of these Schiff base-copper complexes to enhance the antioxidant property of spirulina extract was further evaluated. Among all the investigated complexes, the one derived from 5-chlorosalicylaldehyde demonstrated the best antifungal, antibacterial, and antioxidant-enhancing properties [43].

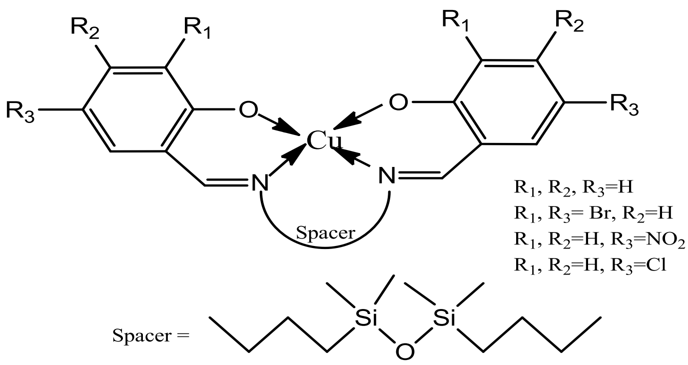

FIGURE 5 The representation of four Schiff base-copper complexes prepared by Soroceanu *et al.*

Reaction catalytic attribute

Schiff base-derived ligands and their corresponding complexes with transition metals are a class of highly desirable composites among numerous promoters frequently used in different synthetic experiments because of their ease of acquisition and the abundance of metallic ions that can be integrated into the cooperative sphere. Various functional moieties can be added due to the general structural framework of these ligands, and thus their complexes. This chemical adaptability could be used to increase the covalent stability of such promoters on a substrate. On this subject, outstanding research has been published, like that conducted by Castro-Osma *et al.* [66].

Racles *et al.* prepared four hydrophobic Schiff base-derived ligands and their corresponding cobalt and copper complexes. Under various conditions, the 12 prepared composites' catalytic functions in two chemical reactions, including the photocatalytic degradation of Congo red and the alkaline degradation of H_2O_2, were investigated. The study findings are similar to those discovered for other electrocatalysts in photoreactors or with H_2O_2 in terms of coefficients and performance [67]. A Fenton-like methodology was used to evaluate the best catalyst, and it was discovered that the H_2O_2 introduction multiplies the rate coefficient and boosts efficiency to 97%. On the other side, it was found that without adding H_2O_2, the prepared compounds, especially the cobalt-based complexes, afforded greener water after the residual water from Congo red photodegradation was investigated by electron-spray ionization mass spectrometry [68].

Many polymeric Schiff base-derived complexes of zinc, copper, nickel, cobalt, and manganese were prepared by Maharana *et al*. The catalytic impact of the prepared complexes was investigated by following their capacity to accelerate alkene peroxidation. α-pinene, α-methyl styrene, cyclooctene, linear alkenes, Z-stilbene, verbenone, E-stilbene, styrene, cyclohexene, and limonene are among the alkenes used. Because of their unique characteristics when compared with unsupported motivators, the research findings indicated that complexes retrieved from the first-row transition metals for alkene peroxidation have been shown to be very intriguing and notable to material and catalytic scientists. The authors further provided difficulties and chances for further research]69].

Conclusion

The Schiff base-derived ligands are an important class of bioactive substances because of their ability to form complexes with various kinds of metal ions and their biomedical characteristics. Because of their numerous biological application fields and possible benefits in the development of novel, intriguing therapeutic agents, and organic-inorganic complexes have attracted an increasing amount of curiosity in recent years. However, it remains necessary to investigate the biomedical uses of pre-synthesized organic-inorganic complexes and to create new complexes with superior features in response. In-depth research on Schiff base-inorganic complexes in the anti-pathogenic microorganism field has revealed that they have antibacterial activity against pathogenic gram-positive and gram-negative types of bacteria as well as potential antifungal properties. The following is a summary of the most recent research on antibacterial candidate Schiff base-derived ligands and their metallic complexes. It is encouraging to observe that the Schiff base-inorganic complexes have higher anti-pathogenic microbial and free radical quenching properties than their Schiff base-derived ligand counterparts. The information analyzed here needs to be considered to accelerate the creation of new metal complexes with improved potentials for these attributes. Finally, after reviewing the listed studies, the authors draw the conclusion that it is anticipated that this brief overview presentation will be extremely helpful for inorganic chemistry researchers who are operating with Schiff base-inorganic complexes or who are just getting started in this fascinating domain.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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