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Synthesis and Biological Applications of Schiff Bases: A Short Review

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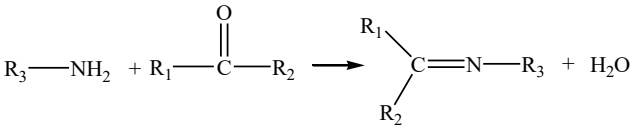
Schiff bases are the bimolecular condensation products of carbonyl compounds and primary amines. Either an aldehyde or ketone can be the carbonyl functional group. Since Schiff bases often contain donor atoms in the forms of -N and -O, they function as ligands. They have good properties, structural resemblances 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 review summarizes the synthesis and biological activities of Schiff bases.

Keywords: Schiff base, Azomethine, Antimicrobial activity, Antiviral activity, Antimalarial activity.

1. Introduction

Azomethines are commonly referred to as Schiff bases since they have a functional group –C=N– Hugo Schiff, a German chemist who had earlier synthesized these compounds in 1864, was honored by their name. Either an aldehyde or ketone can be the carbonyl functional group used in this synthesis. Since Schiff bases often contain donor atoms in the forms of -N and -O, they function as ligands (Aliyu & Sani, 2012; Emara, 2010; Sani & Kurawa, 2016). A fascinating class of ligands known as Schiff bases has found widespread application in the field of coordination chemistry with main group, but it's more stable and more studied with transition metals (Collinson & Fenton, 1996). Schiff bases are commonly used as ligands in coordination chemistry. Because of their fascinating structural characteristics and diverse applications, many researchers have been interested in studying the Schiff bases (Echem *et al.,* 2014; Emara, 2010; Sani *et al.,* 2022).

Schiff bases are often bidentate or tridentate ligands that can chelate with transition metals to produce very stable complexes. The Schiff base exhibits different complexing behaviors based on the nature of the substituents adjacent to imine nitrogen. The Schiff base is formed by a series of addition reactions followed by elimination-based reaction. Scheme 1 illustrates how several different amines have been condensed with aldehydes and ketones to produce Schiff bases.



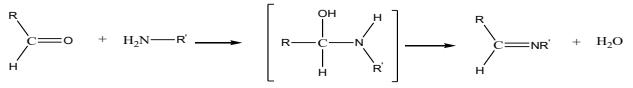
where R_1, R_2 and R_3 may be an aliphatic or an aromatic group

Scheme 1: Systematic route for the synthesis of Schiff base

Schiff bases with alkyl substituents are relatively unstable and easily polymerize, those with aryl substituents that have efficient conjugation are significantly more stable and more readily synthesized.

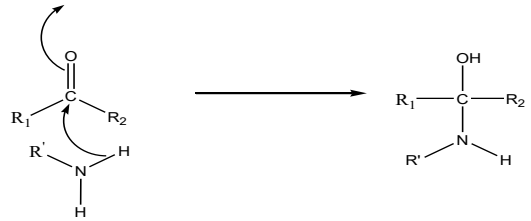
2. Synthesis of Schiff Bases

The first imine synthesis was reported by Hogo Schiff in nineteenth century (Carey & Sundberg, 2007). Subsequently, various techniques for synthesizing imines have been reported. (Chang *et al.,* 2020; Sani *et al.,* 2023). Azeotropic distillation is used in the Schiff's conventional synthesis to condense an amine and a carbonyl molecule. In the process of synthesizing Schiff base, carbinolamine is formed as an intermediate product and then loses a water molecule to form a Schiff base (Scheme 2).



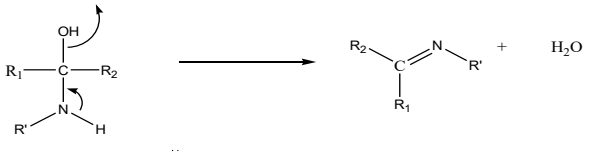
Scheme 2: Systematic route for the synthesis of Schiff base

Mechanistically, an imine is formed in two stages, initially, the carbonyl carbon is attacked by the amine nitrogen, which is a nucleophile (Scheme 3). This is quite similar to hemiacetal and hemiketal formation.



Scheme 3: Nucleophilic attack of amine nitrogen to carbonyl

Scheme 4 shows that when the nitrogen is deprotonated, the electrons in the N-H bond push the oxygen off the carbon, resulting in C=N and water molecule.



Scheme 4: Formation of Imine

Water generated in the system is subsequently remove using molecular sieves. (Westheimer & Taguchi, 1971). Using dehydrating solvents like trimethyl orthoformate or tetramethyl orthosilicate, an in-situ technique for water removal was developed in the 1990s (Lu & Wei, 1997). Chakravarty and Banerjee, 2012, state that the use of strongly nucleophilic amines and highly electrophilic carbonyl compounds is essential for these approaches to be effective. As a substitute, they suggested using compounds that operate as Lewis or Bronsted-Lowry acids to activate the aldehyde's carbonyl group, trigger amines' nucleophilic attack, and dehydrate the system until water is removed (Chakravarty & Banerjee, 2012).

3. Biological Activities of Schiff bases

The recognition that many of these Schiff bases may serve as models for biologically significant species has led to a rise in interest in Schiff bases as a result of developments in the field of bio-inorganic chemistry (Sani & Kurawa, 2016). Transition metal ions are essential for a plethora of diverse biological functions. Additionally, when the biologically active ligand is coordinated to a transition metal ion, the activity might be enhanced. Schiff base metal complexes that derived from heterocyclic compounds that have oxygen, sulfur, nitrogen, or both as ligand atoms are interesting because they can serve as basic structural models for more complex biological systems (Sakıyan *et al.,* 2004; Sani, 2022). The development of novel, more affordable, and more potent analogues of compounds with established biological activity is a major area of pharmaceutical research. By altering the parent structures, it is possible to reduce the toxicity or side effects of the parent drug while simultaneously increasing the activity of the potent analogs.

The physicochemical properties of metal complexes derived from Schiff bases containing N and S chelating ligands have attracted a lot of attention because of their remarkable biological and pharmacological activity. The N and S atoms have a major impact on the coordination of metals at the active sites of several metallobiomolecules (Sakıyan *et al.,* 2004; Sani *et al.,* 2018; Yeap *et al.,* 2012).

3.1 Antibacterial Activity

Multiple antibiotic-resistant bacteria are directly linked to an increase in the mortality rate related to infectious diseases. This problem is mostly caused by the lack of effective treatments (Alekshun & Levy, 2007; Baquero, 1997). Researchers undoubtedly needs to focus on developing novel and more effective antibacterial drugs with unique modes of action (Rice, 2006; Sani *et al.,* 2019).

Schiff bases are said to function as effective antimicrobial agents. For instance, N-(salicylidene)-2-hydroxyaniline (Figure 1), has a MIC value of 8 µg/ml and is effective against Mycobacterium TB H37Rv. Experiments were conducted to investigate the compound's selectivity using J774 macrophages. The chemical did not show any cytotoxic effects on J774 macrophages, even at concentrations up to 1000 µg/ml. Nearly 80% of macrophage cells were alive in these experimental settings, demonstrating the compound's strong selectivity (Souza *et al.,* 2007).

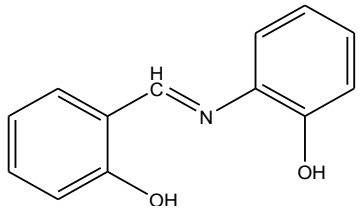


Figure 1: N-(salicylidene)-2-hydroxyaniline

It has been reported that a number of Schiff bases with antibacterial properties have been synthesized via condensation of 5-chloro-salicylaldehyde with primary amines. The most effective derivative against at least one of the assessed bacterial species was 5-chloro-salicylaldehyde-Shiff base (Figure 2). According to (Shi *et al.,* 2007), the strain of *Pseudomonas Fluorescence* was the most susceptible to compounds with MIC values ranging from 2.5 to 5.2 µg/ml.

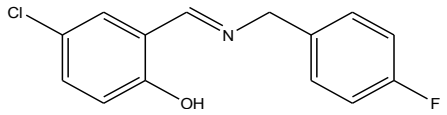


Figure 2: 5-chloro-salicylaldehyde-Shiff base derivative

The Schiff base compound was synthesized by solvent-assisted mechanochemical synthesis from 2-hydroxy-3-methoxybenzaldehyde and o-phenylenediamine, with a small addition of dimethylformamide as a liquid-assisted solvent (Figure 3). The Schiff base exhibited moderate antibacterial activity against *Staphylococcus aureus and Escherichia coli*, with corresponding inhibition zones of 14 mm and 11 mm at higher concentrations (Sani *et al.,* 2022).

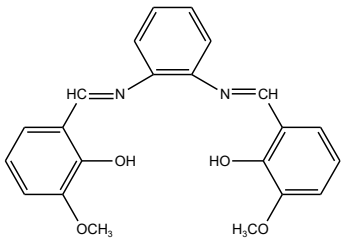


Figure 3: 6,6'-Dimethoxy-2,2'-[1,2-Phenylenebis(nitrilomethylidyne)] bis-phenol

Another investigation of Schiff base derived from two starting materials: p-anisaldehyde and p-anisalcefuroxime was reported by Hoque et al., 2025. The study examined the antibacterial properties of these compounds against gram-positive and gram-negative bacterial strains demonstrating promising antibacterial properties. This suggests that the Schiff base ligand have the potential to be developed into effective antibacterial agents. The study's results are consistent with the known properties of Schiff bases, which are often highly effective in biological applications due to their favourable biocompatibility, low toxicity, and ability to interact with biomolecules.

Ibrahim *et al.* (2021) synthesized a novel Schiff base by condensing 2-hydroxy-1-naphthaldehyde with 4-iodoaniline. The resulting compound, depicted in Figure 4, was evaluated for its antibacterial efficacy against common pathogens, including *Staphylococcus aureus*, *Escherichia coli*, and *Salmonella typhi*, using the disc diffusion method. While the compound exhibited some antibacterial activity, the inhibition zones observed (11-18 mm) were considered moderate (Ibrahim *et al.,* 2021).

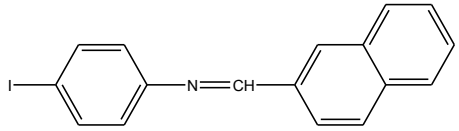


Figure 4: (4-Iodophenyl)-naphthalen-2-ylmethyleneamine

It has also been reported that Schiff bases made from isatin have antibacterial properties (Pandeya *et al.,* 1999). Out of the twenty-eight clinically relevant bacteria used in the research, the isatin-derived Schiff base depicted in Figure 5, exhibited the strongest antibacterial activity against all the tested pathogens

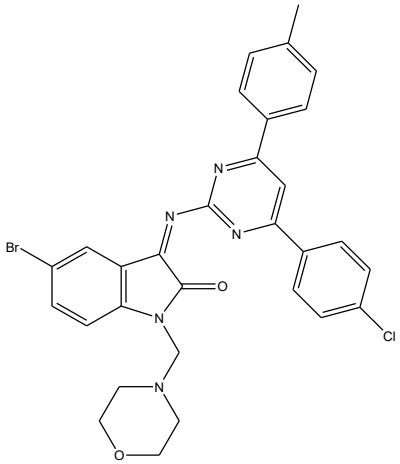


Figure 5: Isatin-derived Schiff base

3.2 Antifungal Activity

Fungi are abundant in nature and can be found in soil, on plants, in saline water, and on other surfaces (Blackwell, 2011). These are important plant pathogens that are mostly responsible for crop damage and food spoiling. In addition to being a part of the natural flora of animals, fungi are incredibly adaptable organism that can cause a wide range of infections (Sundriyal *et al.,* 2006). (Nucci & Marr, 2005). (Martins *et al.,* 2008).

Studies have highlighted a concerning rise in systemic fungal infections, emphasizing that these infections can extend beyond superficial tissues (Sundriyal *et al.*, 2006). This is largely attributed to the increasing number of individuals at risk, including the elderly, immunocompromised patients, those undergoing major surgeries, individuals with AIDS or cancer, and recipients of solid organ or hematopoietic stem cell transplants (Nucci & Marr, 2005). Given this alarming trend, there is an urgent need to discover and develop more potent antifungal agents. Martins *et al.,* 2008 and several Schiff bases have garnered attention as promising candidates for antifungal therapy.

A number of cruciferous crops, including broccoli, mustard, cauliflower, cabbage, rape, turnip, and radish, are severely impacted by phytopathogenic fungi such as *Alternaria brassicae* and *Alternaria brassicicola*. Rehman et al., 2004 reported that N-(Salicylidene)-2-hydroxyaniline inhibited the growth of these fungi at a 500 ppm concentration by 67–68%.

Domb *et al.* (1996) developed an innovative method to synthesize a Schiff base derivative of nystatin

dextran, as illustrated in Figure 6. This modification significantly enhanced the water solubility of nystatin. At a concentration of 20 µg/ml, the synthesized compound effectively inhibited the growth of *Cryptococcus neoformans* and *Candida albicans*. Notably, free nystatin required a higher concentration of 10 µg/ml to achieve a comparable inhibitory effect.

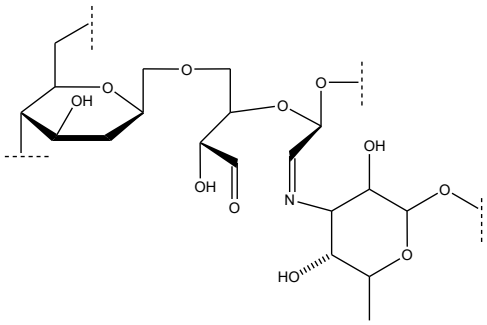
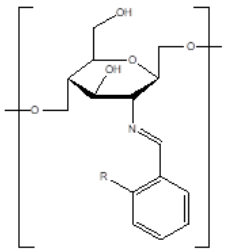


Figure 6: Nystatin-dextran-derived Schiff base

Chitosan-derived Schiff bases (Figure 7) have antifungal properties. When applied at 1000 ppm, they inhibited the growth of *Colletotrichum lagenarium* and *Botrytis cinerea* by 35-8% and 26-33%, respectively (Guo et al., 2007).



[R = OH or H]

Figure 7: Chitosan Derived Schiff Base

A Schiff base ligand was synthesized using a mechanochemical approach by condensing 2-hydroxy-1-naphthaldehyde and 2-aminobenzothiazole (Figure 8). The Schiff base ligand has been tested for antifungal activity against various fungal infections (*Candida albican and Aspergillus fumigatus*) using the agar well diffusion method. The synthetic Schiff base was discovered to be effective against *Aspergillus fumigatus* (Sani & Siraj, 2021)

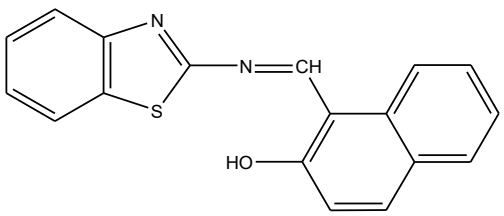


Figure 8: 1-(Benzothiazol-2-yliminomethyl)-naphthalen-2-ol

Sakhare (2025) also reported the synthesis of Schiff base ligand via condensation of 2-amino-4,6-dimethylpyrimidine and 5-nitrosalicylaldehyde. The ligand was screened for its antifungal and antibacterial activities against *Aspergillus niger*, *Penicillium chrysogenum*, *Fusarium moneliforme, Aspergllus flavus*, and *Escherichia coli, Salmonella typhi, Staphylococcus aureus*, and *B. subtilis* at the concentrations 1% and 2% in DMSO and was compared with known antibiotics viz Griseofulvin and Penicvolume. The results indicated that the ligand exhibited good antifungal and antibacterial activities.

In a separate study, (Panneerselvam *et al.,* 2005) demonstrated that 2-methoxy-4-[(4-morpholin-4-yl-phenylimino)-methyl]-phenol, when administered at a concentration of 30 µg/ml, effectively inhibited the growth of both *Candida albicans* and *Aspergillus niger*. While research investigating 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 9) 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 (Panneerselvam *et al.,* 2005).

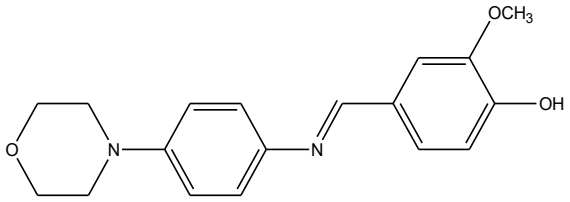


Figure 9: 2-methoxy-4-[(4-morpholin-4-yl-phenylimino)-methyl]-phenol.

3.3 Antiviral Activity

Viral diseases such as smallpox, polio, and rubella might be completely eradicated by vaccines. Nevertheless, the disadvantage of vaccination strategies has been the development of virus-related and hepatitis C immunodeficiency diseases (De Clercq, 2002). Treatment for viral diseases must be started right once in order to prevent fatal outcomes in patients with impaired immune systems. Because viruses mutate so frequently, it is likely that existing antiviral agents will never be completely effective despite the vast array of therapeutic choices available for viral diseases. A multitude of adverse effects could also be present.

According to Wang (Wang *et al.,* 2010) proposed that salicylaldehyde Schiff bases derived from 1-amino-3-hydroxyguanidine tosylate could serve as promising scaffolds for the development of novel

antiviral drugs. Among these compounds, the Schiff base depicted in Figure 10 demonstrated potent antiviral activity against mouse hepatitis virus (MHV), inhibiting viral growth by 50% at a remarkably low concentration of 3.2 μM (Bringmann et al., 2004; Sriram et al., 2006).

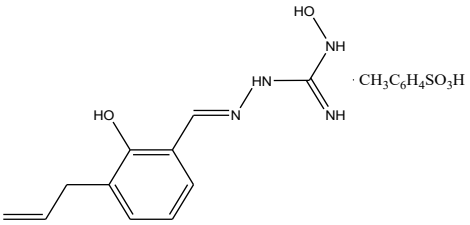


Figure 10: 1-amino-3-hydroxyguanidine tosylate-derived Schiff base

Sriram reported the synthesis and antiviral activity of a novel Schiff base derived from abacavir (Figure 11). This compound represents a promising addition to the class of abacavir prodrugs. Abacavir, a nucleoside analog, inhibits the activity of reverse transcriptase and is used to treat HIV and AIDS. The synthesized Schiff base demonstrated significant antiviral efficacy against human immunodeficiency virus-type 1 (HIV-1). Its effective concentration (EC50) for 50% protection of human leukemic cells (CEM) against HIV-1 cytopathic effect was less than 6 μM, making it the most potent Schiff base within the series at a concentration of 50 nM.. According to Sriram *et al.* (2006), Sriram suggested that this compound could serve as a promising lead compound for the development of novel anti-HIV-1 drugs. Its low toxicity to CEM cells at concentrations below 100 μM suggests a favorable therapeutic window (Sriram et al., 2006).

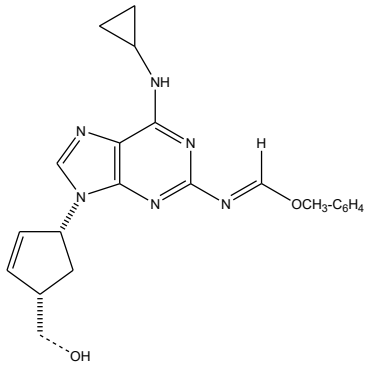


Figure 11: Abacavir-derived Schiff base

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 sub-Saharan Africa (Guo *et al.,* 2007). 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 *Anopheles* mosquitoes serve as the primary vectors for *Plasmodium* transmission (Kayser *et al.,* 2003).

Schiff bases have emerged as promising molecules for the development of antimalarial drugs. Plants belonging to the Ancistrocladaceae and Dioncophyllaceae families produce ancistrocladidine (Figure 12), a secondary metabolite containing an imine group. This compound has demonstrated efficacy against *Plasmodium falciparum* strains K1 and 3D7. Bringmann *et al.* (2004) reported minimum inhibitory concentrations (MIC values) of 0.3 and 1.9 μg/ml for ancistrocladidine against *P. falciparum* K1 and 3D7 respectively (Bringmann *et al.,* 2004).

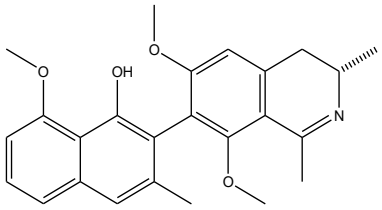


Figure 12: Ancistrocladidine

Rathelot synthesized Schiff base-functionalized 5-nitroisoquinolines and evaluated their in vitro activity against a chloroquine-resistant *Plasmodium falciparum* strain (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 (Dong et al., 2010; Rathelot *et al.,* 1995).

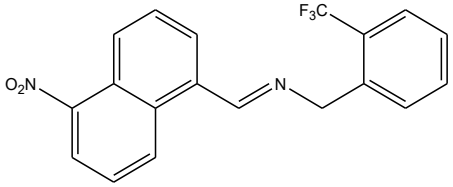


Figure 13: Schiff base-functionalised 5-nitroisoquinolines

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 (Devita *et al.,* 2004). 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.,* 2010). 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 half-century 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.

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 (Xu *et al.,* 2008).

Many platinum(II) complexes derived from amino acid Schiff bases have been reported to exhibit anticancer properties. The interaction of these compounds with salmon sperm DNA was examined, and their in vitro anticancer activity against HL-60, KB, BGC-823, and Bel-7402 cell lines was confirmed using the MTT assay. Among the Pt(II) complexes of reduced amino acid Schiff bases, the compound depicted in Figure 14 displayed comparable cytotoxic effects against the Bel-7402 cell line and surpassed cisplatin in its efficacy against BGC-823 and HL-60 cell lines (Li *et al.,* 2013).

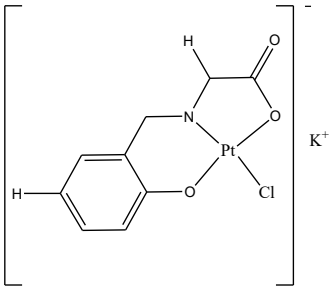


Figure 14: Pt(II) Complex of reduced amino acid Schiff base

4. 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 activities of some Schiff bases have been reviewed.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

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