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Review

Versatility of Schiff Base Pharmacophore By green approaches and Its Therapeutics: Updated Mini Review

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Abstract:

Synthesis of bioactive heterocyclic Schiff base and its derivatives is the most noteworthy takes in heterocyclic chemistry. Classical and non-classical methods (microwave irradiation) were used to prepare Schiff bases from primary amines and several substituted benzaldehydes. These methodologies form an energy-efficient and environmentally benign greener synthesis. This review highlights the crucial synthetic route for synthesising various bioactive Schiff base ligands and metal complexes.

Keywords: *Schiff base, microwaves irradiation, green chemistry approach, synthetic route.*

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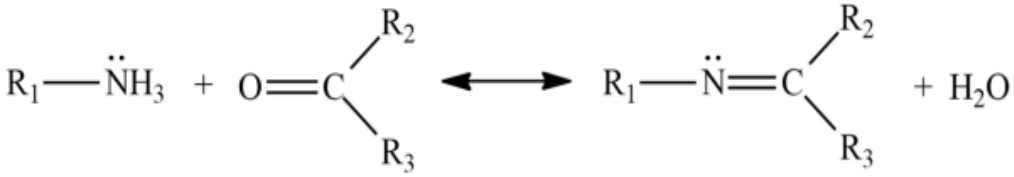
Introduction:

Hugo Schif initially described in 1864, the synthesis of Schif bases by a condensation reaction between a primary amine and multiple carbonyl compounds [1–6]. Tese Schif bases are mostly referred to as the azomethine group represented in organic chemistry as RHC=N–R1 [7, 8]. Te corresponding alkyl, aryl, or heterocyclic groups can be the R or R1 in Schif bases. The Schif bases are mostly referred to as the imines or the azomethine groups in synthetic chemistry [9, 10]. The presence of lone pairs is attributed to its sp2 hybridization as the compound is highly reactive due to carbon and nitrogen atoms. Due to the presence of strong properties like adaptability, simplicity, and functionality, these compounds are of high importance [11, 12].

The significance is of high importance in biological assays that the Schiff bases can form diverse functional groups. An advanced approach to the existing nature of Schiff bases can be helpful nature to tackling the biological gaps and increasing the efficacy of Schiff base drugs [13–17] .

The discovery of Schiff bases dates back to the nineteenth century during which a chemist named “Hugo Schiff” first documented a reaction showing condensation between amines and carbonyl functional groups [13, 18–21].



Scheme1: General scheme for Schiff base reaction.

In contemporary times, this domain of scientific inquiry about Schiff base coordination chemistry has seen significant growth and expansion [22, 23]. The significance of Schiff base complexes in the Fields of material science, biomedical applications, bio inorganic chemistry, encapsulation processes, supra molecular chemistry,

catalysis, and separation, and the generation of molecules with exceptional characteristics and structures has been widely acknowledged and extensively examined in the existing literature [24–27].

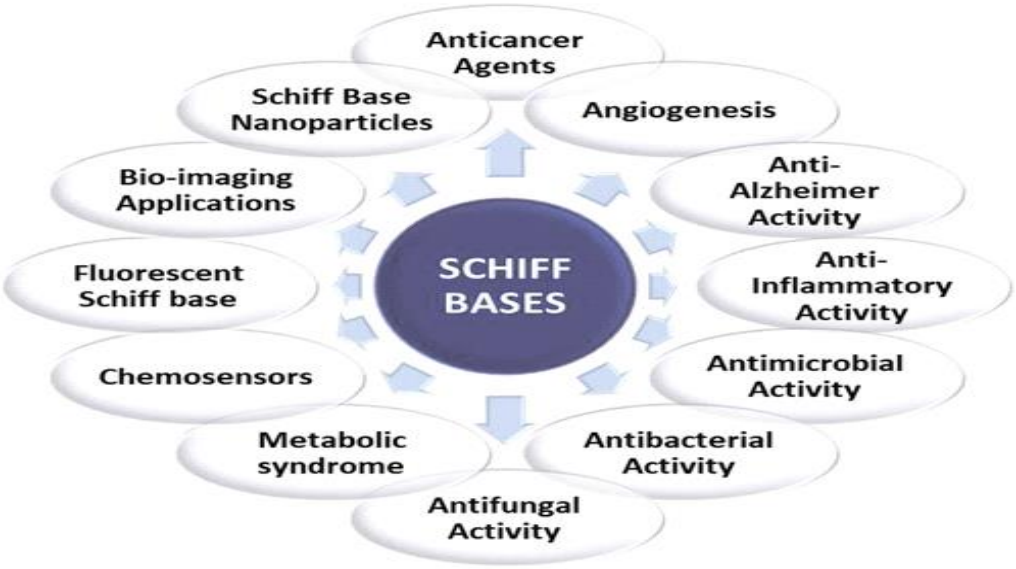
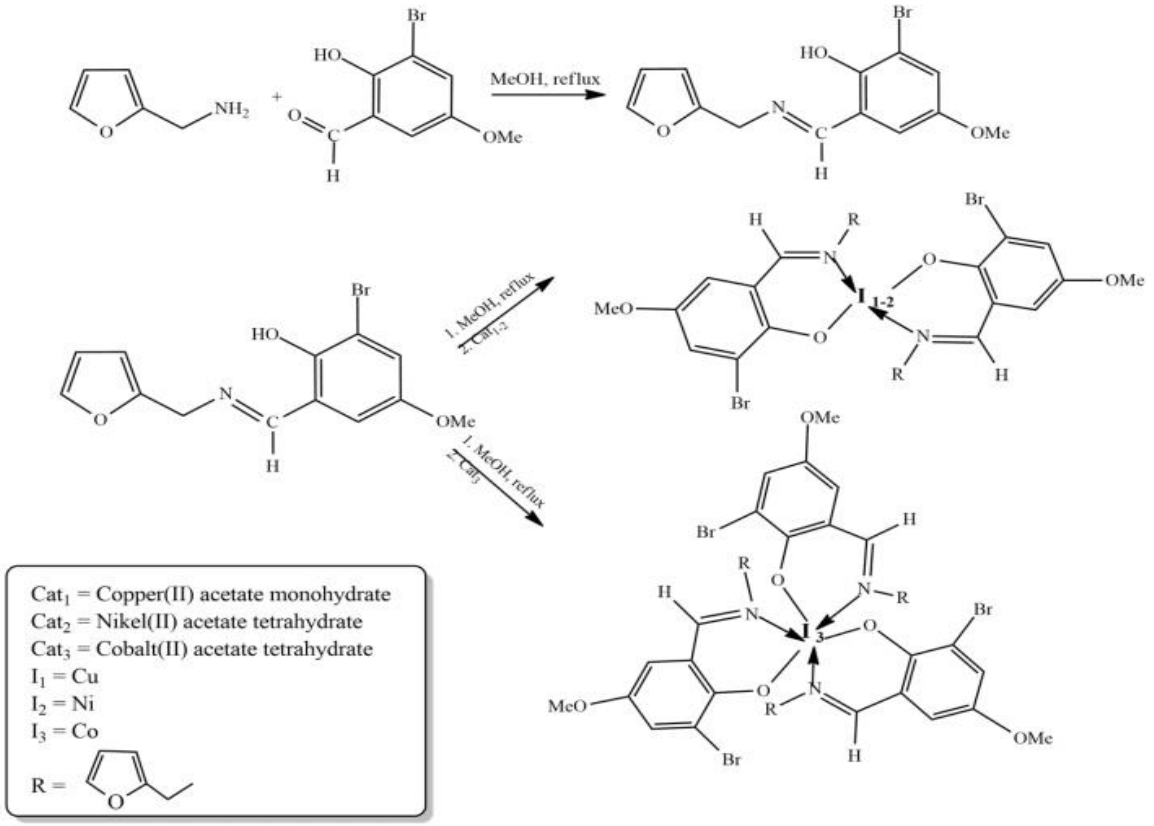


Fig. 1 Schiff Base Different Medicinal Use.

The literature has documented the use of Schiff bases derived from salicylaldehydes as agents for regulating plant development, as well as exhibiting antibacterial or antimycotic properties [28–30]. These also provide broad-spectrum activity against several species, including Candida, Plasmoporaviticola, Trichophyton gypsum, Staphylococcus aureus, Erysiphe graminis, Mycobacterium. On the basis of our scientific experience in organic and polymer synthesis in collaboration with colleagues from biological and pharmaceutical sciences, the idea arose to combine in a joint review paper results of research that cover the synthesis of biologically active Schiff bases and their transformation into low- and high-molecular amino-phosphonates with determination and analysis of their biological activity. To the best of our knowledge, such summary material has not been published, and we believe that it will be useful both for those studying and working in the field of organic, polymer and medicinal chemistry, as well as in the design of drugs, macromolecular biodegradable compounds with intrinsic bioactivity, development of therapeutic and diagnostic systems. As mentioned above, Schiff bases comprising heterocyclic moieties are gaining a lot ofinterest due to their ability to act as ligands and to bind multiple biological molecules. Anexample of such a heterocyclic compound is furan—a 5-membered ring containing four carbons and one oxygen. Furan-based offshoots, such as nitrofurantoin, furazolidone, nifuratel and nifurtimox are frequently used in drug research due to the fact that the presence of furanyl moiety in conjugated systems enhances the level of conjugation and improves their solubility and the transport properties.

The use of furan-alternatives in bioorganic chemistry is considered very promising due to their ability to mimic part of the structure of some natural and pharmacological compounds. Vankateswar lu et al. reported the synthesis of a large number of transition metal complexes of various biologically active Schiff bases containing furan as core unit. They demonstrated the obtaining of Cu (II), Ni (II) and Co (III) complexes (Scheme 5). It was proved that the complexes exhibit good antioxidant activity and better antimicrobial activity towards Bacillus thuringiensis, Streptococcus pneumoniae, Escherichia coli and Pseudomonas putida compared to the free ligand [31].

Nowadays, there is an urgent demand for novel antimicrobial agents for a wide application of fields such as hygienic application, hospital, dental surgery equipment, medical devices, health care, water purification system, textiles, storage and food packaging. Mesbah et al. present the synthesis of three new Schiff bases derived from condensation of aldehydes with 4,4-diaminodiphenyl sulfide.



Scheme2: Synthesis of Furan containg Sciff base reaction molecules with different substitution.

According to the literature, not much scientific works have been reported on the preparation of complexes of transition metals with Schiff base derivatives of 2-aminobenzamide providing oxygen and nitrogen donors. Therefore, Tyagi et al. presented in their research the synthesis of a Schiff base derived from the reaction of 2-aminobenzamide with furanmplexes. They were thoroughly characterized by means of different spectroscopic techniques, thermal methods, DFT studies and antimicrobial tests. The authors proved that the newly synthesized Schiff base ligands act as tridentate ligands. Their metal complexes possess higher antimicrobial activity against different bacterial and fungal strains most probably due to azomethine linkage, while also possessing increased activity upon coordination with different metal ions. Thus, the metal complexes could be regarded as candidates for the development of potent antimicrobial drugs. Preparation of Schiff base ligands obtained 2-aminobenzamide and their metal complexes [32].

Microwave synthesis of Schiff Base Derivatives

The microwave heating technique was first proved independently and used in 1984. Microwave heating plays a needful role in recent research because lots of reaction take a long time to complete the same response while microwave heating takes fewer minutes. Microwave-assisted organic synthesis is divided into two major categories that are:

1. Reaction performed in the presence of solvent (DMF, DME, CH2Cl2]

2. Reaction conducted in the absence of solvent Under solvent-free conditions microwave-assisted synthesis is advantageous for reducing pollution to the environment and giving a product with a high yield15. One can avoid toxic and expensive organic solvents using the microwave-assisted synthesis method16. To intensify reaction rates, microwave-assisted synthesis has proved to be an efficient tool and has beforehand been used with good results not only in the solution phase. But also, in solvent phase[17,18] the significance of microwave irradiated reactions is that these reactions take significantly less time and give a high yield. An irradiated time of 5 min is appropriate for most of the responses. In several cases, reactions take less than 5 min. As we can say, the microwave irra-diation

technique saves our time and gives better results than other time-consuming processes. Further studies on microwave-assisted solid-phase synthesis are presently in progress. 20

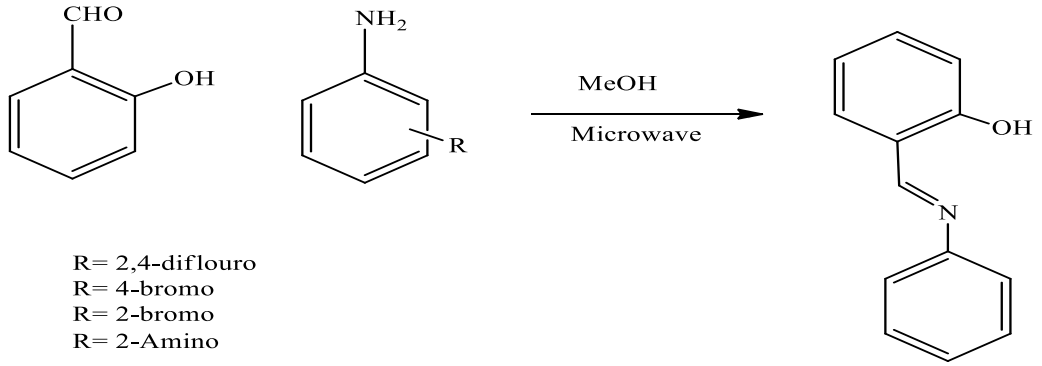
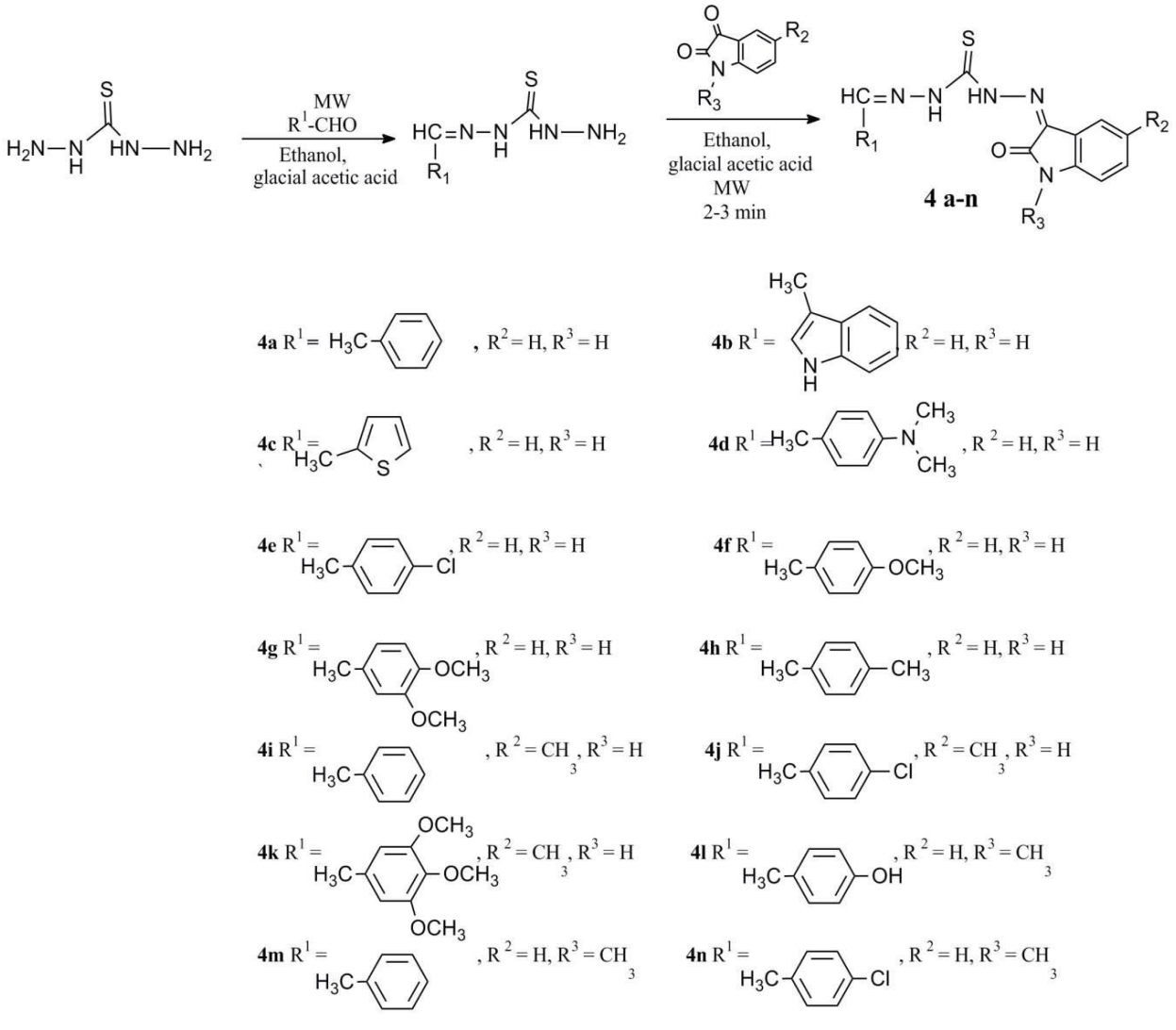


Fig.3 Synthesis of substituted aromatic amine Schiff base derivatives



Scheme 4: Synthesis of β-Isatin aldehyde-N,N'-thiocarbohydrazone Schiff base derivatives**.**

Pharmacological Response :

Antifungal

The recent work included the chemical modification using diabetic insulin structure by the Schiff bases introduction onto the main chain of the reactant. Approximately six different derivatives of the insulin were produced by a simple method, and structures were characterized using FT-IR, proton NMR, and carbon-13 NMR spectroscopic techniques [39]. The structures exhibited variations in the quantity and positional substitution benzene ring using the phenoxide ions or phenolic groups. Following this, further research was conducted to investigate their biological properties, specifically focusing on their antioxidant and antifungal actions. The assessment of antioxidant activity included the determination of scavenging capacities toward superoxide radicals, hydroxyl radicals, and DPPH radicals in addition to antioxidant activities. These activities were of inulin which has shown a considerable enhancement in comparison with that of inulin. In addition, the in vitro evaluation of antifungal activity against three types of plant pathogenic fungus was conducted using the mycelium growth rate technique [40]. The antifungal activity of the inulin derivatives was found to be much higher when compared to that of pure inulin. The biological activity of the inulin derivatives was influenced by many parameters, such as the degree of substitution (DS), as well as the quantity and location of phenolic hydroxyl groups. The products elucidated in this manuscript show significant promise as biomaterials characterized by favorable bioactivity and biocompatibility. Further investigation of the structure–activity link is warranted in future research endeavors [41,42].

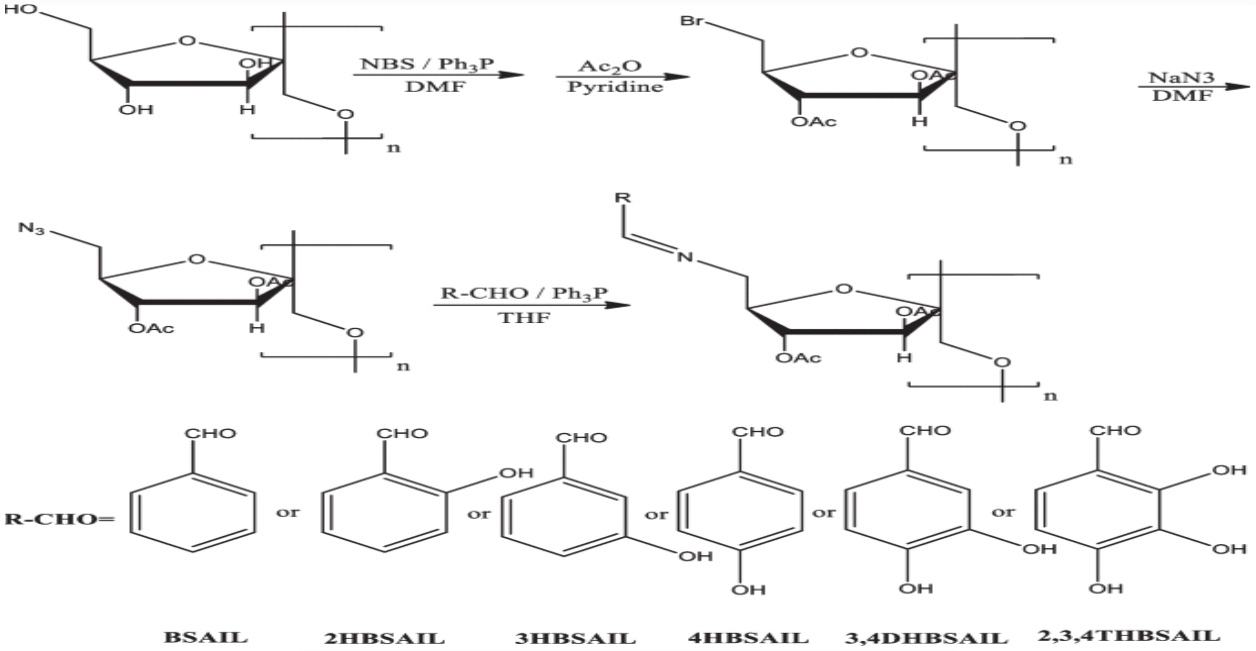
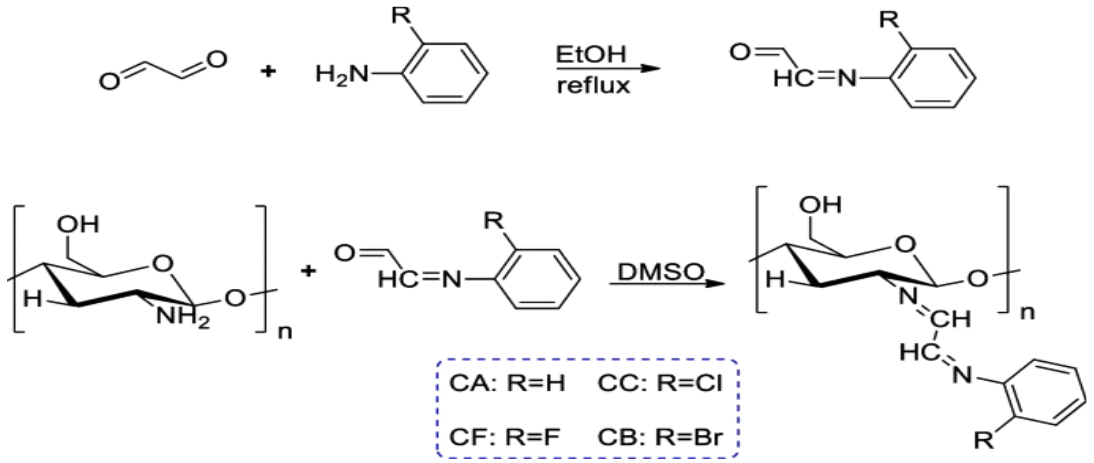


Fig. 5 Synthesis pathway for double Schiff bases of Chitosan.

The present work effectively synthesized a range of chitosan derivatives containing active halogenated aromatic imines by the formation of Schiff bases, resulting in high degrees of substitution. The structural characterization of the sample was conducted via the use of elemental analysis, solid-state 13C nuclear magnetic resonance (NMR) spectroscopy, and Fourier transforms infrared (FT-IR) spectroscopy. Additionally, an examination was conducted to assess the antifungal efficacy against three prevalent plant pathogenic fungi, namely *Botrytis cinerea*, *Fusarium oxysporum* f. sp. *cucumerinum*, and *Fusarium oxysporum* f. sp. *niveum*, by in vitro hyphal measurements. The findings of the study indicate that the antifungal activity of double Schiff bases of chitosan derivatives was much higher than that of chitosan, particularly at a concentration of 1.0 mg/mL.

The chitosan derivatives with dual Schiff bases, including halogenated benzene moieties, exhibited inhibitory indices of 95% at a concentration of 1.0 mg/mL against *Botrytis cinerea*. This high inhibitory activity may be attributed to the higher electron-withdrawing nature of the halogen substituents. The increased degree of substitution was shown to have a good impact on enhancing the antifungal activity. This work presents a pragmatic approach for

the synthesis of novel double Schiff bases of chitosan derivatives including halogeno-benzenes, with the potential for further development as potent antifungal drugs[42].

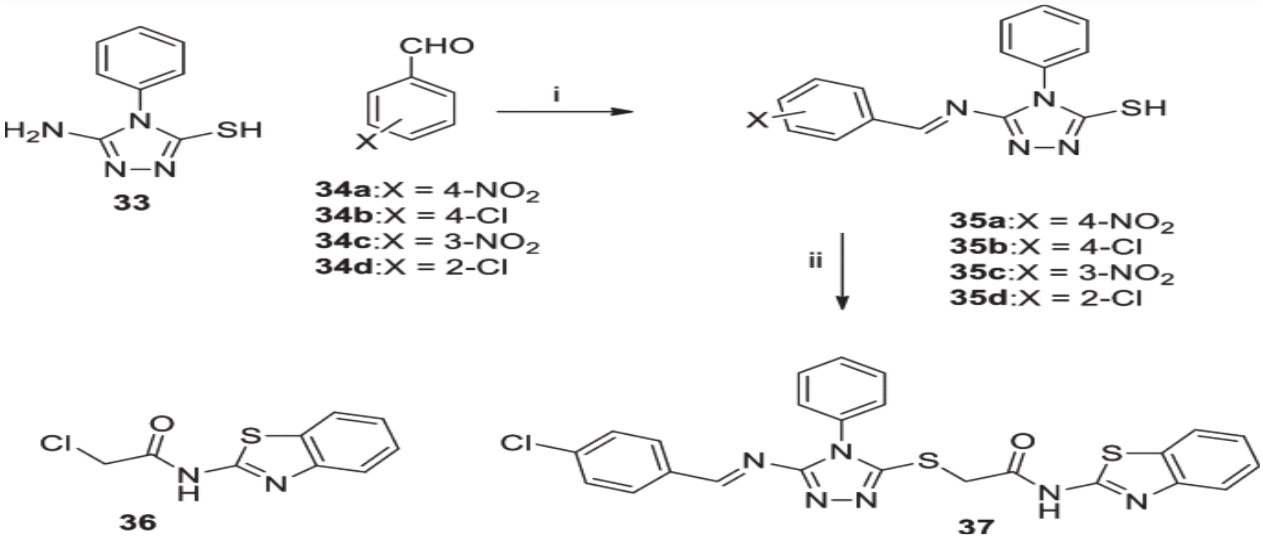


Scheme 5: Schiff base reaction chitosen derivatives.

Antiviral

In this study, a series of novel Schiff base ligands were synthesized by reacting 5-amino-4-phenyl-4H-1,2,4-triazole-3-thiol **33** with various substituted benzaldehydes. Additionally, metal complexes of these ligands with Cu(II), Fe(II), Au(III), and Mn(II) were also prepared. The synthesis of a novel benzothiazole derivative (**37**) was achieved by the reaction between the reactant compound and N-(benzothiazol-2-yl)-2-chloroacetamide through coupling.

The spectral qualities of the subject were examined. The anti-HIV-1 and HIV-2 activity of the recently developed and synthesized Schiff base ligands and their corresponding metal complexes were evaluated by the analysis of their ability to suppress "HIV-induced cytopatho-genicity in MT-4 cells." Compounds **37** exhibited significant inhibitory activity in cell culture against HIV1, with EC50 values of 12.2 µg/mL (selectivity index (SI) = 4) and > 2.11 µg/mL (SI = > 1), respectively. Compound 11 also demonstrated inhibition against HIV-2, with an EC50 value above 10.2 µg/mL and a selectivity index of 9. This finding suggests that compound **37** has promise as a potential candidate for further refinement and enhancement.



Conclusion

The pharmaceutical significance of Schiff bases has gained a lot of attention and this review focuses on giving an insight into the antibacterial, antifungal, and antiviral activities. The Schiff base-derived antibacterial drugs showed significant activities against bacteria by structural modifications while anti fungal drugs proved to treat skin diseases mainly. The antiviral Schiff base drugs are currently being used against viral diseases such as influenza, herpes

simplex, and HIV. The given literature also explains the mechanism by which the different products are synthesized and their potential activating groups. Furthermore, activities detail for various microorganisms is given which will help chemists to evaluate further compounds. The inhibitory effects of given compounds are also discussed. Overall, this review is a thoughtful and promising contribution to the field of Schiff bases that will bring positive outcomes in the future.

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