Mushtaq *et al.*
*Future Journal of Pharmaceutical Sciences* (2024) 10:16
https://doi.org/10.1186/s43094-024-00594-5

Future Journal of Pharmaceutical Sciences

REVIEW

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# Pharmaceutical significance of Schiff bases: an overview

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**Abstract**

Schiff bases are a diverse group of organic compounds with great pharmaceutical importance due to the presence of carbon–nitrogen double bonds (–C=N–). These compounds are synthesized by the condensation reaction between a primary amine and an aldehyde or ketone in a suitable solvent such as methanol. These compounds have shown antibacterial, antifungal, antiviral, anti-inflammatory, and antioxidant activities, which have garnered the attention of organic chemists in synthesizing these compounds. Recent advances have been summarized in this review paper mainly including compounds with potential antibacterial, antifungal, and antiviral activities. Synthetic schemes are included to provide a better understanding of the Schiff base synthesis mechanism. This review paper will provide a way forward for the pharmaceutical chemist to synthesize new compounds with potential biological activities.

**Keywords** Schiff bases, Imines, Biological activities, Condensation reaction, Synthesis, Review

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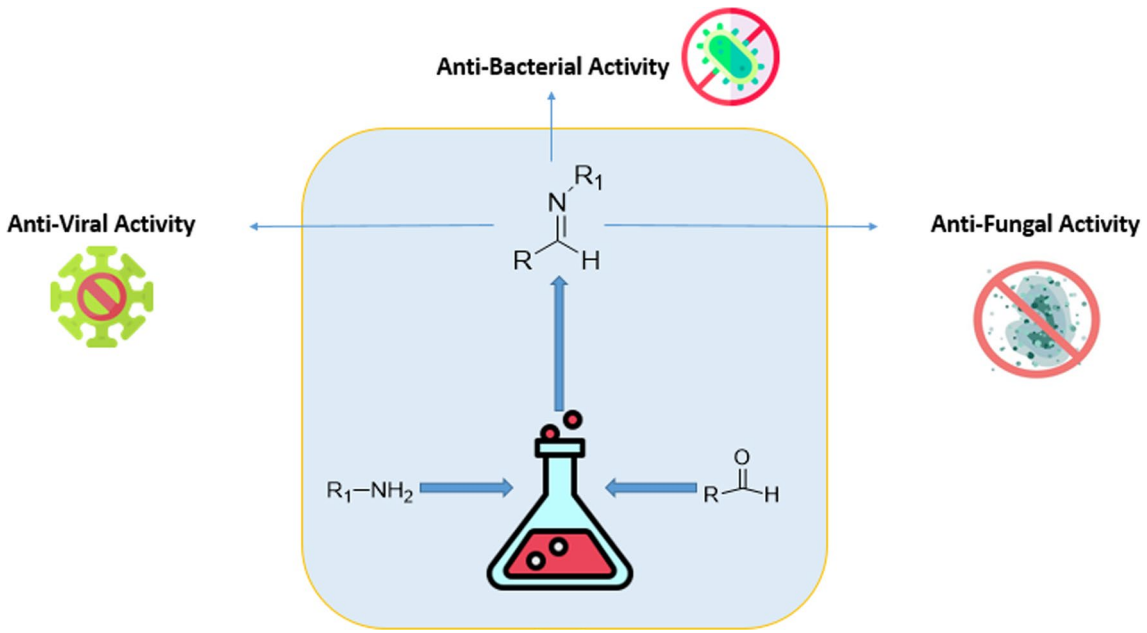
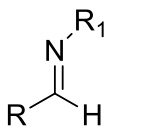
**Graphical abstract**




## Background

Hugo Schiff initially described in 1864, the synthesis of Schiff bases by a condensation reaction between a primary amine and multiple carbonyl compounds [1–6]. These Schiff bases are mostly referred to as the azomethine group represented in organic chemistry as RHC=N–$R^1$ [7, 8]. The corresponding alkyl, aryl, or heterocyclic groups can be the R or $R^1$ in Schiff bases. The Schiff 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 $sp^2$ 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] (Fig. 1).

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]. 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, bioinorganic chemistry, encapsulation processes, supramolecular 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]. 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]. Schiff bases have been shown to possess analytical uses as well. The significance of these bases helps explain the difficult mechanisms inside biological systems and gives proper meaning to the imine group activity. These also provide broad-spectrum activity against several species, including *Candida*, *Plasmopora viticola*, *Trichophyton gypsum*, *Staphylococcus aureus*, *Erysiphe graminis*, *Mycobacterium*, *Albicans*, *Bacillus polymyxa*, and *Escherichia coli* [31–34].




Schiff Base

**Fig. 1** General structure of Schiff bases

Furthermore, the Schiff bases are significant in metal complexes due to their unique ability to form a structure holding transition central metals with the reactants of the condensation reaction as illustrated in the literature for metals like Hg(II), Gd(III), Cu(II), Co(II), Ni(II), Zn(II), Y(III), Al(III), Pb(II), and Ag(II) [35–44]. Extensive research has been conducted on Schiff bases due to their significant catalytic characteristics. These compounds exhibit catalytic properties when used in the process of hydrogenating olefins. Biomimetic catalytic processes are applicable in several contexts. One intriguing use of Schiff bases is in their utilization as a very efficient corrosion inhibitor, owing to their inherent capability to autonomously generate a monolayer on the targeted surface for protection. Numerous commercial inhibitors often include aldehydes or amines; nevertheless, it is hypothesized that the enhanced efficacy seen in some instances is attributed to the presence of Schiff bases, likely owing to the presence of the C=N link [45–48]. Chemisorption is the primary mode of combination and the combinatorial mechanism of metals with inhibitors. The inhibitor molecule needs to possess active sites that are capable of establishing chemical connections with the metal surface via the process of electron transfer. In instances of this kind, the metal functions as an electrophile, while the inhibitor assumes the role of a Lewis base. The protective chemical has nucleophilic centers, namely oxygen and nitrogen atoms, that possess unshared electron pairs that are easily accessible for electron sharing. In conjunction with the atoms of the benzene rings, these entities provide several absorption sites for the inhibitor, facilitating the establishment of a stable monolayer [49–51]. The biological features of Schiff bases, including their antibacterial and antifungal activity, have been documented in the literature. Metal complexes have garnered significant attention in the scientific community due to their extensive investigation and exploration, primarily owing to their potential use in anticancer and herbicidal contexts. These organisms function as exemplars for species that have significant biological importance [52–58].

## Main text

### Pharmaceutical significance of Schiff bases

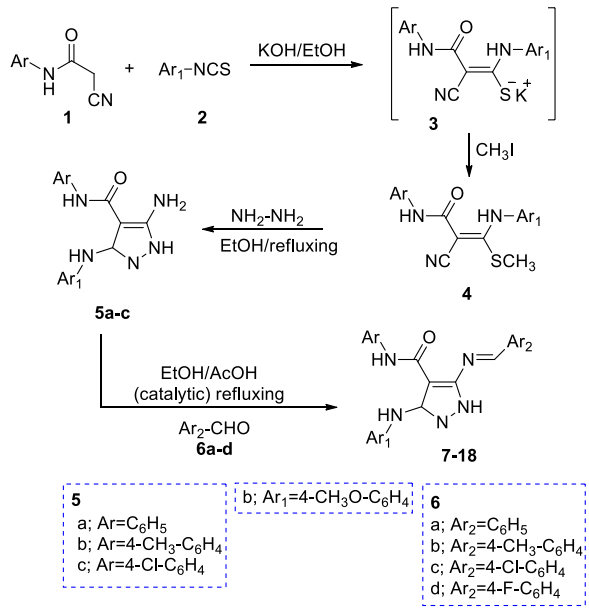
#### *Antibacterial*

Antimicrobials are well recognized as a very effective therapeutic approach in the field of medicine [59]. However, the efficacy of antimicrobials is significantly hindered by the emergence of antibiotic-resistant bacteria. The formation of Schiff bases of amino acids was achieved by the condensation reaction between isatin and several amino acids, including phenylalanine, leucine, cysteine, alanine, valine, and glycine. These amino acids exhibited notable antibacterial efficacy [60, 61]. Schiff bases derived from cellulose are produced by the condensation reaction between p-aminophenol and aldehyde moieties and have shown antibacterial efficacy against, *Staphylococcus aureus*, *Escherichia coli*, and *Enterococcus faecalis* [62].

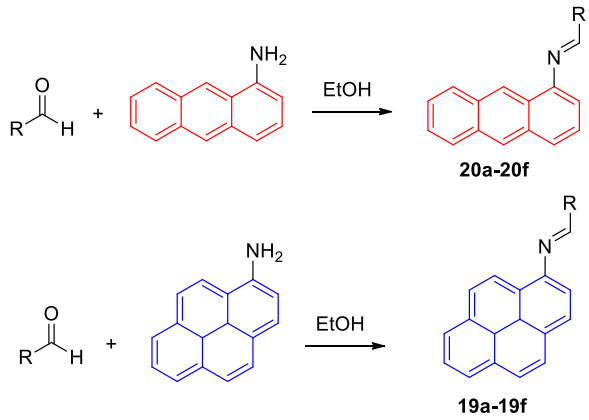
A new collection of aromatic Schiff bases was prepared using a reflux (condensation) reaction between 5-aminopyrazoles and aromatic aldehydes [63]. The synthesis process yielded large quantities of the desired compounds. These Schiff bases were then assessed for their antibacterial efficacy through in vitro experiments against "multi-drug resistant bacteria (MDRB)." In normal circumstances, the majority of the compounds of Schiff bases exhibited superior biological efficacy. Furthermore, the molecular docking investigation revealed that kinase inhibition had a beneficial impact on the activity of dihydrofolate reductase enzymes and *Staphylococcus aureus* DNA gyrase. In addition, the data for drug-likeness indicated that these compounds under investigation satisfy the criteria outlined by Lipinski's rule and exhibit favorable biological drug scores for various activities [64]. The first findings about the Schiff base's effectiveness in combating MDRB have significant potential as a framework for the identification of novel medicines by derivatization or modification (Scheme 1).

The reaction included the utilization of heteroaromatic aldehydes, which were separately reacted with aminoanthracene and aminopyrene. As a result, new Schiff base derivatives 19a–19f and 20a–20f were produced with high yields [65]. The novel synthesized compounds were subjected to several tests to evaluate their reducing power, metal chelating, DNA binding abilities, antibacterial, and free radical scavenging [66]. The radical scavenging activity of the series of compounds was much superior to that of the 19 series compounds. The compound 19c exhibited the greatest metal chelating activity. In three antioxidant test methods, the standards demonstrated greater antioxidant activity compared to the DMSO solution of chemicals. Furthermore, it was shown that both compounds exhibited potential bacterial resistance activity against the employed microorganisms. Additionally, both compounds had a strong affinity for binding to CT-DNA. The findings of this research suggest that the recently examined compounds possess the ability to attach to DNA, making them promising candidates for cancer therapy. However, it is recommended that their structural composition be further modified in further investigations [67, 68] (Scheme 2).

A total of twelve Schiff bases (21a–27a, 21b–25b) were synthesized by the reaction of isatin and 5-bromoisatin with various anilines as shown in Scheme 3. The synthesis process used green chemistry principles,




**Scheme 1** Synthesis of Schiff Bases **7–18** [63]

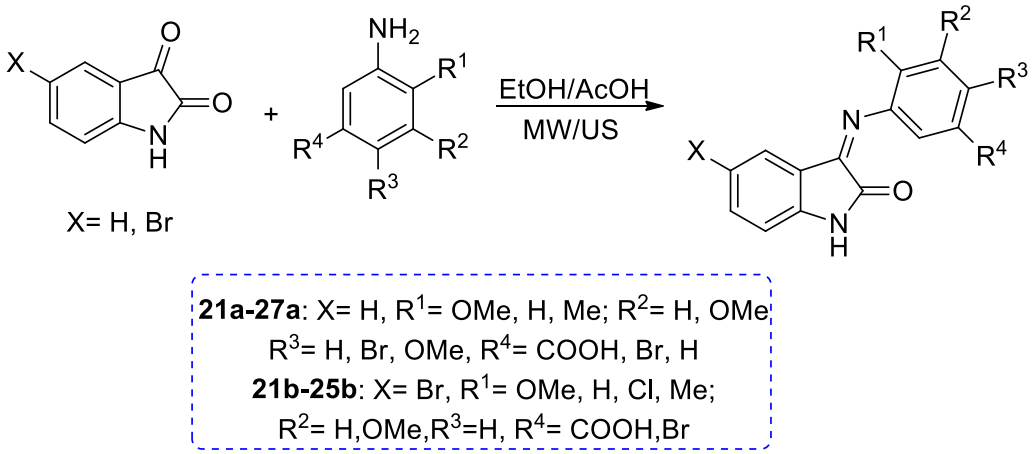



**Scheme 2** Synthesis of anthracene- and pyrene-based Schiff base derivatives [65]

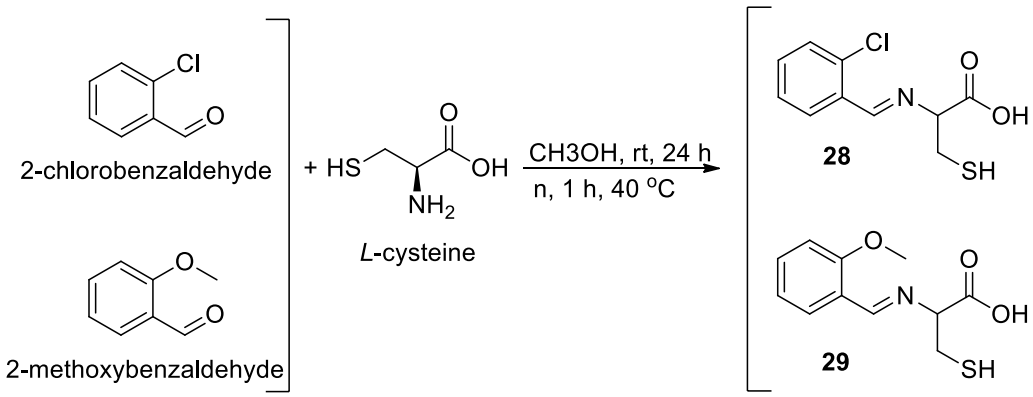
specifically using microwave (MW) and ultrasonic (US) assistance. The antimicrobial efficacy of each chemical was assessed against a total of nine bacterial strains, including both standard and clinical isolates, using the Agar-well diffusion technique. The minimum inhibitory concentration against *Pseudomonas aeruginosa* for 21a and 21b was found to be 78 µg/mL, which is the lowest value obtained. The identification of all synthesized substances was accomplished by the use of multiple characterization techniques including ultra-violet spectroscopy, proton nuclear magnetic resonance, infrared spectroscopy, caron-13 nuclear magnetic resonance, and microanalysis. The antibacterial activity for newly synthesized Schiff bases was rationalized by using the "Molecular Electrostatic Potential Surface (MEPS) analysis" and "Quantitative Structure–Activity Relationship (QSAR)." The findings of the QSAR analysis, which included density functional theory (DFT)-based, steric, and hydrophobic descriptors, indicate that compounds exhibiting higher hydrophobicity and lower dipole moment have antibacterial properties against "*Klebsiella pneumoniae* ATCC700603" [69].

According to the processes shown in Scheme 4, chlorobenzene aldehydes were reacted with amino derivatives like L-cysteine by condensing the reactants in a solvent methanol to produce Schiff base **28**, and methoxybenzene aldehydes were reacted with the amino mercapto acids by condensing in a solvent methanol to produce Schiff base **29**. The yields for compounds 1 and 2 were outstanding (77% and 85%, respectively) [70]. TLC was used to evaluate the reaction's progression and the purity of the synthesized compounds. The stationary phase used was of silica gel and the mobile phase was of methanol which ascended higher in the chromatogram. FT-IR, 13C, and 1H, NMR spectroscopy were used to characterize the synthesized compounds 28 and 29. With compound **28** having more antibacterial activity than compound **29**, the newly synthesized Schiff bases demonstrated action against the aforementioned microbes. The Schiff base 1 is a little reactive and more stable in a biological environment according to the estimated global chemical reactivity indices. However, further research will be needed in the future to fully understand the mechanism of these chemicals' antibacterial effects [71].

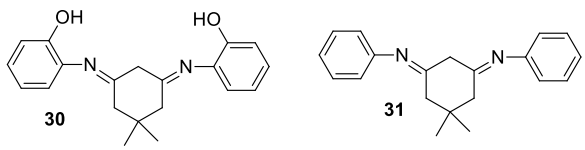
Schiff base compounds have broad use across several domains, including organic, inorganic, analytical, and biological disciplines. In the contemporary period, pharmacology applications have exceptional potential and are extensively used within the pharmaceutical sector. A recent study based on the antibacterial activity of Schiff bases was carried out by reacting the compounds in a way to produce two main compounds named DmChDp (2,2′-(5,5-dimethylcyclohexane-1,3-diylidene)bis(azan-1-yl-1-ylidene)diphenol) and the DmChDa (N,N′-(5,5-dimethylcyclohexane-1,3-diylidene)dianiline). These newly synthesized Schiff bases have gained a lot of attention due to their diverse and significant antibiological activities against the strains of *Staphylococcus aureus*. The ligand interactions were also studied to understand the pro-drug-like features that aided in the efficacy of the final products. The characterization techniques included the docking process and the analysis using traditional spectroscopic techniques. The biological activities were evaluated against the six given proteins derived from *S. aureus*. The newly formed Schiff bases showed a great




**Scheme 3** Synthetic route of Schiff bases of isatin [69]



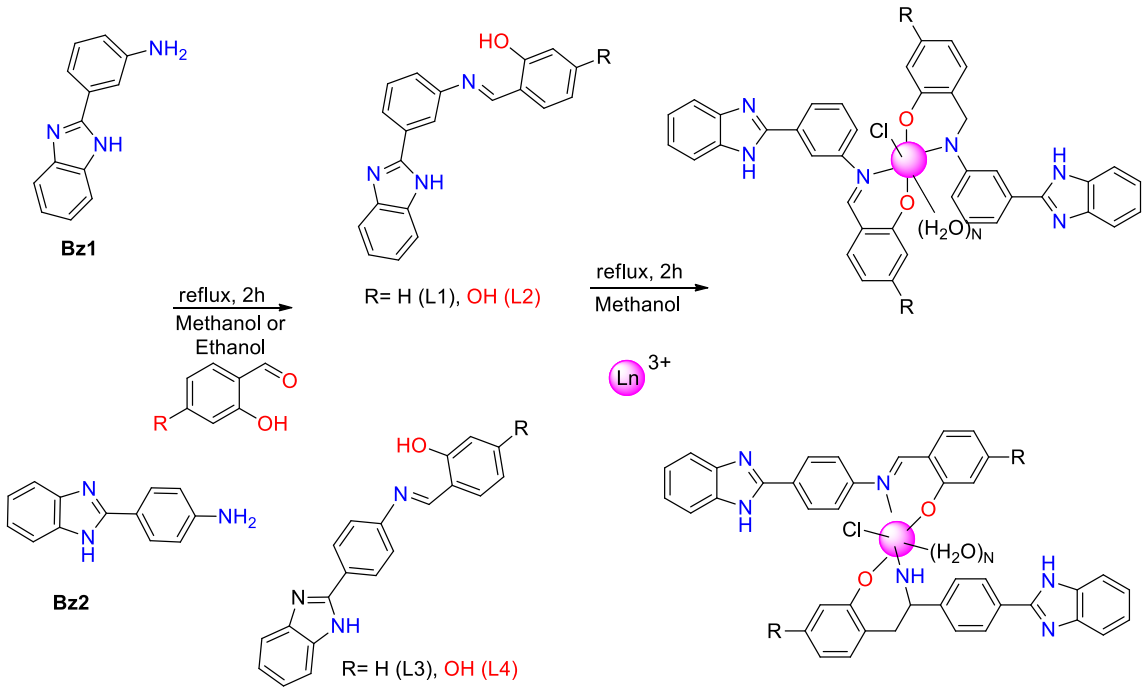

**Scheme 4** Synthesis of Schiff compounds [70]




**Scheme 5** Structure of 30) DmChDp 31) DmChDa Schiff bases [17]

inhibitory effect for bacteria and helped in increasing the efficiency of drugs [17] (Scheme 5).

In brief, a series of new lanthanide complexes were synthesized by the use of Schiff base ligands, together with a "benzimidazole moiety." These complexes were thoroughly characterized by utilizing several analytical methodologies, ensuring their unambiguous identification and understanding. Initial experiments for the compounds were performed to assess various pharmacological uses of the substances under investigation. These assessments were undertaken using a range of bioassays, including tests for antiproliferative activity, antiparasitic activity, and antibacterial activity. The findings indicate that the biological activities of the compounds are influenced by structural modifications. Specifically, ligands L1 and L2, along with their metal complexes, demonstrated minimum inhibitory concentration (MIC) values in comparison with ligands L3 and L4 and their respective complexes. This disparity in MIC values may be attributed to substitutions on the "aminophenol ring." In a similar vein, it was shown that the compounds had an impact on the fluidity of the cell membrane by modifying the hydrophobic region inside the lipid bilayer. This observation suggests a possible correlation between such alterations and the potential therapeutic uses of these compounds. The aforementioned result has the potential to serve as a valuable point of reference in future endeavors aimed at the advancement of novel pharmacological medicines. Ongoing investigations in the laboratory are now exploring the impact of the alterations on the molecular architecture.




**Scheme 6** Synthesis of Lanthanide complex Schiff bases [72]

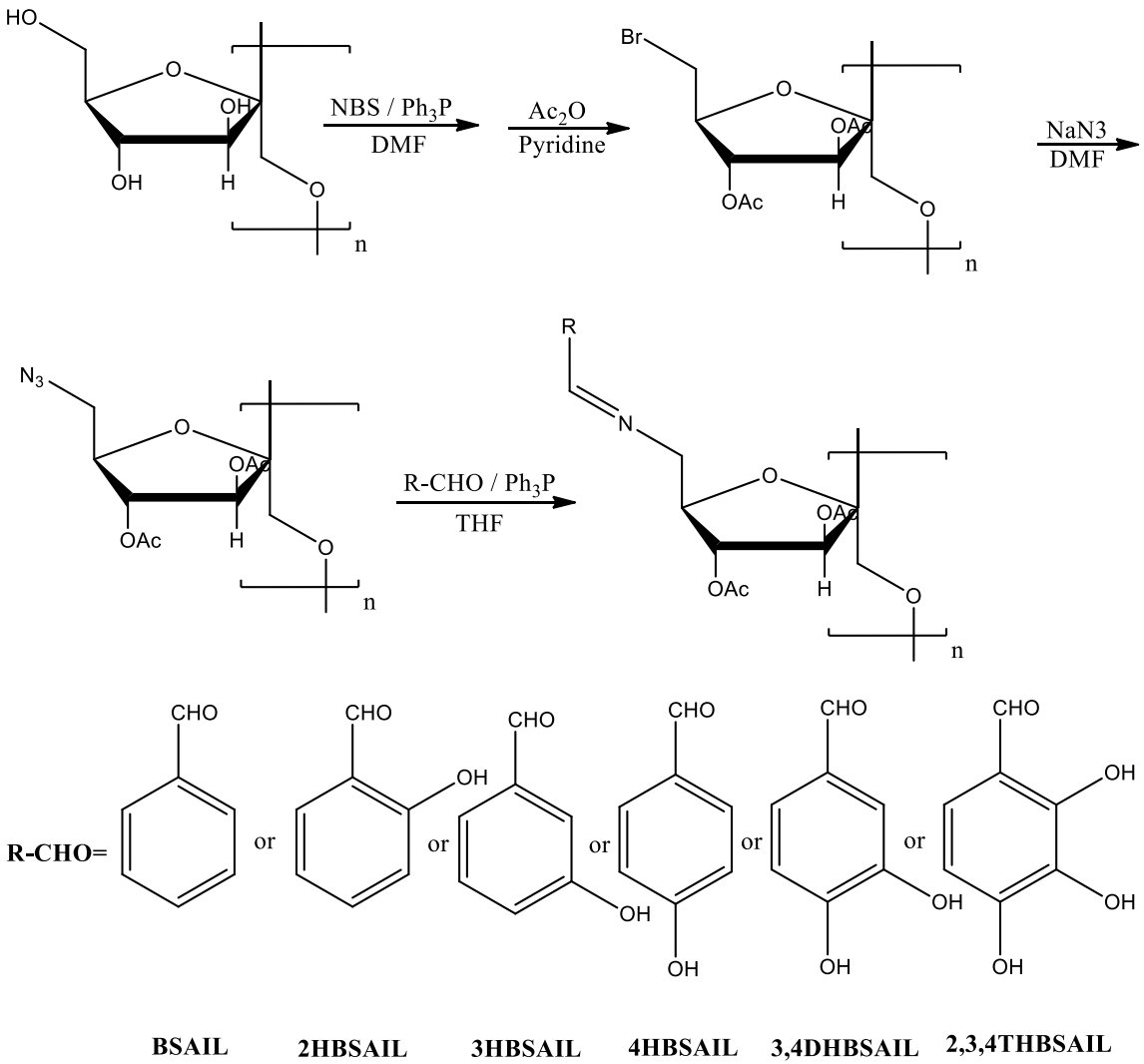
This research aimed to provide deeper insights into the mechanism of action associated with these particular molecules [72] (Scheme 6).

### Antifungal

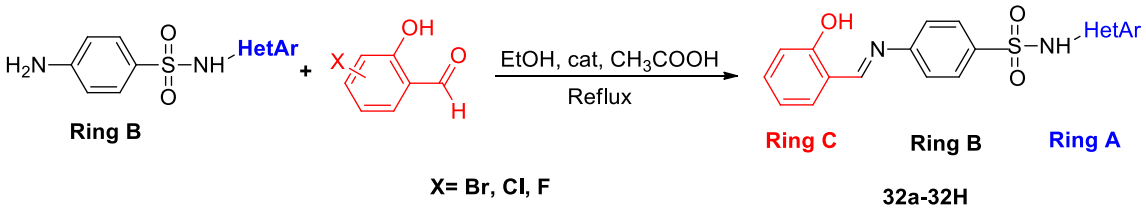
The recent work included the chemical modification using diabetic insulin structure by the Schiff bases introduction onto the main chain of the reactant. Approximately six different derivatives of the insulin were produced by a simple method, and structures were characterized using FT-IR, proton NMR, and carbon-13 NMR spectroscopic techniques [73]. 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 [15, 74]. 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 [75, 76] (Scheme 7).

The synthesis of Schiff base derivatives of sulfa drugs involved the condensation of commercially available sulfa drugs, namely sulfamethoxazole, sulfamethazine, and Sulfamethoxypyridazine, with suitable "substituted aromatic aldehydes." A variety of solvents with different levels of polarity were used to optimize the reaction conditions. Ultimately, a solvent combination consisting of ethanol and a small amount of acetic acid was determined to be the most suitable for the condensation processes, as shown in Scheme 8. In all instances, a stoichiometric amount of "sulfonamides and substituted aromatic aldehydes" was used, resulting in reaction yields ranging from 35 to 92%. The purification of the compounds was conducted using either recrystallization or liquid column chromatography before their characterization. It was ensured that all compounds had a minimum purity of 95% before they were deemed suitable for microbiological examination [77].

The present work effectively synthesized a range of chitosan derivatives containing active halogenated aromatic

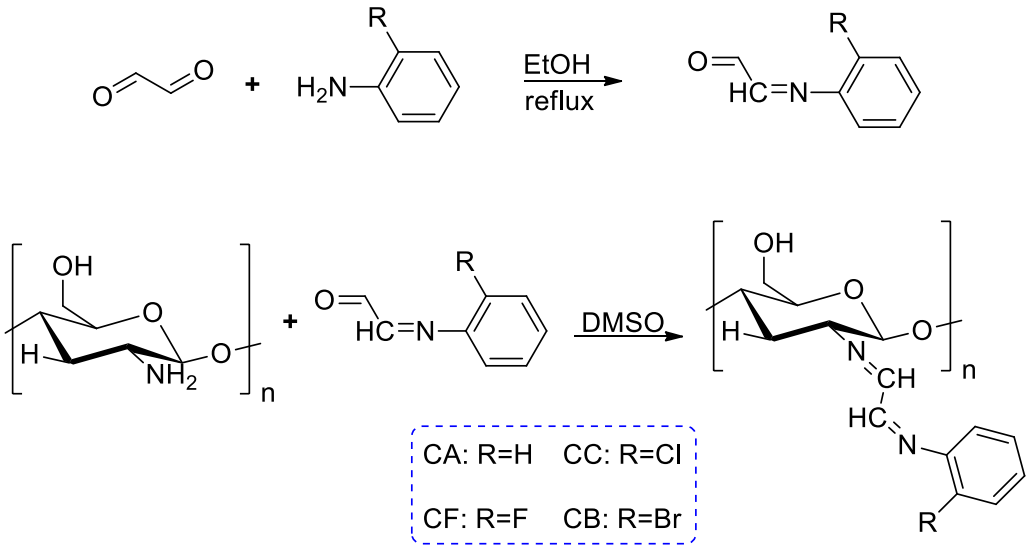



**Scheme 7** Synthesis of Schiff bases [73]




**Scheme 8** Reaction condition for the synthesis of Schiff base derivatives (**32a-32h**) of aminobenzenesulfonamied [77]

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




**Scheme 9** Synthesis pathway for double Schiff bases of Chitosan [78]

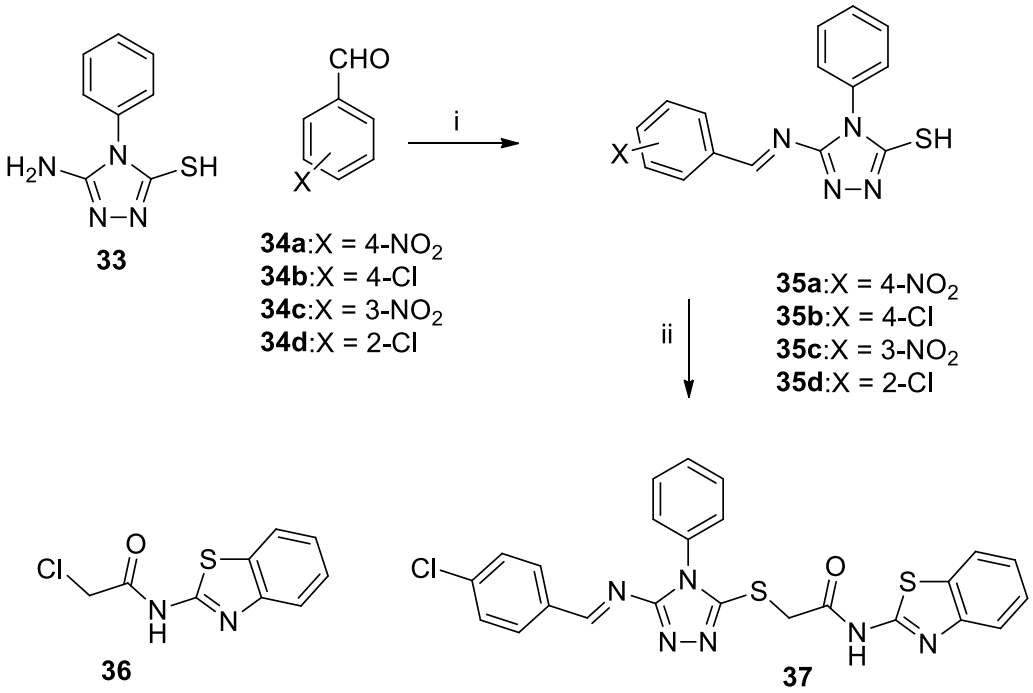
derivatives was much higher than that of chitosan, particularly at a concentration of 1.0 mg/mL. The chitosan derivatives with dual Schiff bases, including halogenated benzene moieties, exhibited inhibitory indices of 95% at a concentration of 1.0 mg/mL against *Botrytis cinerea*. This high inhibitory 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 [78] (Scheme 9).

## Antiviral

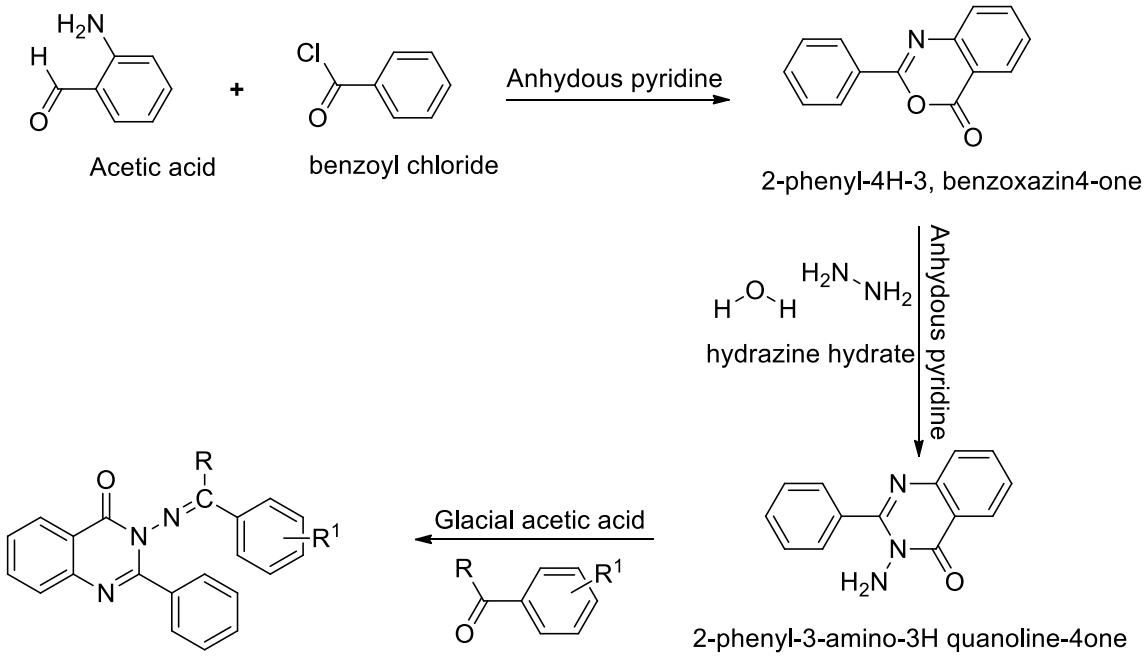
In this study, a series of novel Schiff base ligands were synthesized by reacting 5-amino-4-phenyl-4H-1,2,4-triazole-3-thiol **33** with various substituted benzaldehydes (**34a-34d**). Additionally, metal complexes of these ligands with Cu(II), Fe(II), Au(III), and Mn(II) were also prepared. The synthesis 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 cytopathogenicity 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 [79] (Scheme 10).

A novel series comprising 3-(benzylideneamino) compounds has been developed. The synthesis of 2-phenylquinazoline-4(3H)-ones included the production of Schiff bases from 3-amino compounds. The reaction of -2-phenyl quinazoline-4(3)H-one with several carbonyl compounds that have been replaced. The chemical structures of the compounds were determined by the use of spectrum analysis. The cytotoxicity and antiviral activity of the tested compounds were assessed against a range of viruses, including influenza B virus, influenza A H3N2 subtype, influenza A H1N1 subtype, vaccinia virus, feline herpes virus, herpes simplex virus-1 TK-KOS ACVr, Punta Toro virus, herpes simplex virus-2 (G), para influenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4, vesicular stomatitis virus, respiratory syncytial virus herpes simplex virus-1 (KOS), and feline coronavirus (FIPV). A compound formed exhibited superior antiviral efficacy against all evaluated viral strains [80] (Scheme 11).

This study presents a unique way to synthesize novel prodrugs such as abacavir using nitrogen substitution using different ketone and substituted benzaldehyde derivatives. The results of the in vitro experiments demonstrated that compound (3-(2-(4-methylaminobenzylideneamino)-6-(cyclopropylamino)-9H-purin-9-yl)cyclopentyl)methanol (**38c**) exhibited the highest level of effectiveness against

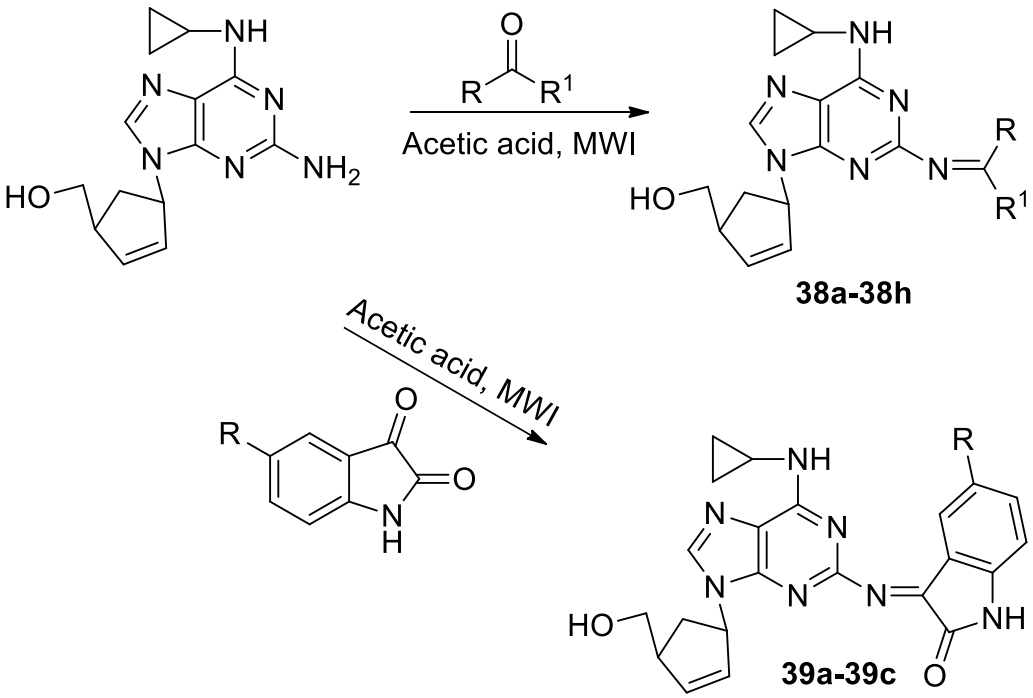



**Scheme 10** Reagents and conditions i) EtOH, reflux, 2h; ii) **36**, $K_2CO_3$, acetone, 20 °C, then flux [79]




**Scheme 11** Synthetic route for the title compounds [80]

HIV, as shown by its EC50 value of 0.05 lM. Furthermore, the compound had an EC50 value above 100 lM, resulting in a selectivity index greater than 2000. Compound **38c** exhibited a much higher potency compared to the original medication, with a 32-fold increase in activity as shown by its EC50 value of 1.6 lM. At a pH of 7.4 and a temperature of 37 °C, the hydrolytic half-life (t1/2) exhibited a range of 120 to 240 min [81] (Scheme 12).




**Scheme 12** Synthesis of Schiff bases derivatives of Abacavir [81]

## 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 antifungal 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.

**Abbreviations**

| | |
|---|---|
| MDRB | Multi-drug resistant bacteria |
| DMSO | Dimethyl sulfoxide |
| MW | Microwave |
| IR | Infrared |
| NMR | Nuclear magnetic resonance |
| MEPS | Molecular electrostatic potential surface |
| QSAR | Quantitative structure–activity relationship |
| DmChDp | 2,2′-(5,5-Dimethylcyclohexane-1,3-diylidene)bis(azan-1-yl-1-ylidene)diphenol |
| DmChDa | N,N′-(5,5-dimethylcyclohexane-1,3-diylidene)dianiline |
| EC50 | Half maximal effective concentration |
| CT-DNA | Circulating tumor DNA |

**Acknowledgements**
Not applicable.

**Author contributions**
IM contributed to the design of the study and drafted the paper; AA contributed to drafting the paper and critical revision of the article; all authors have read and approved the final manuscript.

**Funding**
This work was not supported by any funding agencies.

**Availability of data and materials**
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
The authors declare no conflict of interest.

**Competing interests**
The authors declare that they have no competing interests.

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Received: 18 September 2023 Accepted: 6 February 2024
Published online: 12 February 2024

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