Synthesis Of Novel Aromatic Compounds Via Schiff Base Method: Advances, Applications, And Future Perspectives

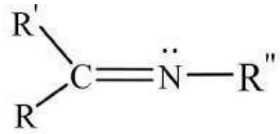
Mohite Vaishnavi Sitaram[1], Tidke Poonam Namdeo[2]
[1,2]*PG Scholar, Dr. Vedprakash Patil Pharmacy College, Chh. Sambhajinagar.*

***Abstract*—Schiff bases represent an important class of organic compounds characterized by the presence of an azomethine (–C=N–) functional group formed through condensation between primary amines and carbonyl compounds. Aromatic Schiff bases have attracted considerable attention due to their structural diversity, facile synthesis, and wide range of biological and industrial applications. Recent developments focus on designing novel aromatic compounds with enhanced pharmacological, catalytic, and material properties. This review highlights synthetic strategies, reaction mechanisms, characterization techniques, biological activities, and emerging applications of Schiff base–derived aromatic compounds. Special emphasis is placed on green synthesis approaches and medicinal chemistry advancements.**

***Index Terms*—Schiff base, aromatic compounds, azomethine, condensation reaction, medicinal chemistry, green synthesis.**

I. INTRODUCTION

Schiff bases were first reported by Hugo Schiff in 1864 during investigations on condensation reactions between primary amines and carbonyl compounds such as aldehydes and ketones. These compounds are characterized by the presence of an azomethine or imine functional group (–C=N–), which is formed through the elimination of water during the reaction between an amine and a carbonyl compound.[1] The discovery of Schiff bases marked an important milestone in organic chemistry because it introduced a versatile class of compounds capable of forming stable linkages while retaining significant chemical reactivity. Over time, Schiff bases have become essential intermediates in synthetic chemistry and have gained considerable importance in coordination chemistry, medicinal chemistry, and materials science.[2]



The imine linkage present in Schiff bases plays a central role in determining their physicochemical and biological properties. The nitrogen atom of the azomethine group possesses a lone pair of electrons that can easily coordinate with metal ions, enabling Schiff bases to act as effective ligands.[3] This coordination ability allows the formation of stable metal complexes with transition metals such as copper, zinc, nickel, and cobalt. Such complexes often exhibit enhanced catalytic, antimicrobial, and antioxidant properties compared to the parent compounds, making Schiff bases highly valuable in coordination chemistry and bioinorganic research.[4]

Aromatic Schiff bases, particularly those synthesized from substituted benzaldehydes, acetophenones, and aromatic amines, display remarkable chemical stability due to resonance stabilization within the aromatic ring system.[5] The conjugation between the aromatic rings and the imine bond leads to extensive electron delocalization, which increases molecular rigidity and stability. This delocalized electronic system also contributes to improved optical, electronic, and biological characteristics. Furthermore, the presence of different substituents on the aromatic rings allows easy structural modification, enabling researchers to design molecules with tailored physicochemical and pharmacological properties.[6]

One of the major advantages of aromatic Schiff bases is their synthetic flexibility. By altering the nature and position of substituents such as hydroxyl, methoxy,

nitro, or halogen groups, scientists can significantly influence solubility, lipophilicity, electronic distribution, and biological activity. This structural tunability makes Schiff bases attractive scaffolds in drug design and medicinal chemistry. Many Schiff base derivatives have demonstrated antimicrobial, antifungal, anti- inflammatory, anticancer, and antioxidant activities, largely attributed to their ability to interact with biological targets such as enzymes, proteins, and nucleic acids through hydrogen bonding and coordination interactions.[7]

Beyond pharmaceutical applications, Schiff bases have found extensive use in polymer science, where they serve as cross-linking agents and functional materials due to their reversible imine bonds. In corrosion inhibition, aromatic Schiff bases adsorb onto metal surfaces through electron donation from nitrogen and aromatic π-electrons, forming protective layers that prevent oxidation. Additionally, their sensitivity to environmental changes has enabled their application in chemical sensors and optical devices for detecting metal ions and organic pollutants.[8]

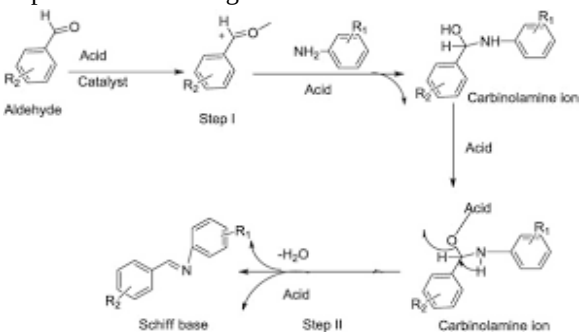
Overall, the unique combination of structural versatility, electron delocalization, coordination ability, and biological relevance has established aromatic Schiff bases as an important class of compounds in modern chemical research. Continuous advancements in synthetic techniques and functional design continue to expand their applications across pharmaceutical, industrial, and material science fields, ensuring their ongoing scientific and technological significance.

II. SYNTHETIC APPROACHES FOR NOVEL AROMATIC SCHIFF BASES

The synthesis of aromatic Schiff bases has been extensively investigated owing to their structural diversity and wide applications in medicinal, coordination, and material chemistry. Over the past decades, researchers have developed numerous synthetic methodologies aimed at improving reaction efficiency, selectivity, environmental sustainability, and biological relevance of the resulting compounds. Literature reports indicate a clear evolution from conventional synthetic routes toward greener and energy-efficient approaches.[9]

Conventional Synthetic Strategies

Early studies on Schiff base synthesis primarily relied on classical condensation reactions between aromatic aldehydes or ketones and primary aromatic amines under reflux conditions. These reactions were typically carried out in alcoholic solvents such as ethanol or methanol, often in the presence of mild acid catalysts to accelerate dehydration. Several investigators reported that aromatic aldehydes readily undergo imine formation due to enhanced electrophilicity and resonance stabilization of the resulting products. Although conventional reflux methods provide reliable yields and easy scalability, limitations such as long reaction times and high solvent consumption have encouraged the search for improved methodologies.[10]



Microwave-Assisted Synthesis

With advances in synthetic technology, microwave-assisted methods gained attention as efficient alternatives. Numerous studies demonstrated that microwave irradiation significantly reduces reaction time while improving product yield and purity. Researchers attributed this enhancement to rapid and uniform heating, which increases molecular collision frequency and accelerates formation of the azomethine linkage. Comparative investigations revealed that reactions requiring several hours under conventional heating could be completed within minutes using microwave energy, making this technique particularly attractive for synthesizing biologically active aromatic Schiff bases.[11]

Ultrasound-Assisted (Sonochemical) Methods

Sonochemical synthesis has also been explored as an innovative approach for Schiff base formation. Literature reports indicate that ultrasonic irradiation generates localized high-energy conditions through acoustic cavitation, thereby facilitating nucleophilic

addition and dehydration steps. Studies comparing conventional and ultrasound methods showed improved reaction kinetics and higher yields under milder temperatures. This method has been especially useful for thermally sensitive aromatic substrates.[12]

Green and Solvent-Free Synthetic Approaches

In recent years, increasing environmental concerns have driven the development of green synthetic strategies. Solvent-free grinding techniques and mechanochemical synthesis have emerged as sustainable alternatives. Researchers reported successful formation of aromatic Schiff bases simply by grinding reactants together, eliminating hazardous solvents and reducing waste generation. Similarly, aqueous-phase synthesis has gained importance, with water acting as an environmentally benign reaction medium.[13]

The adoption of ionic liquids and deep eutectic solvents has further improved reaction efficiency while maintaining eco-friendly conditions. These approaches align with green chemistry principles by minimizing energy consumption and environmental impact.[14]

Catalytic Advancements

Catalyst-assisted synthesis represents another important advancement highlighted in the literature. Both homogeneous and heterogeneous catalysts, including Lewis's acids, solid acid catalysts, and Nano catalysts, have been employed to enhance reaction rates and selectivity. Catalysts activate the carbonyl group and promote dehydration, thereby shifting equilibrium toward Schiff base formation. Recent studies emphasize recyclable catalysts and Nano-supported systems to improve sustainability and industrial applicability.[15]

Effect of Substituent and Structural Design

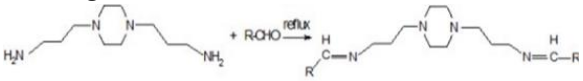
Several researchers have emphasized the influence of electronic and steric factors on synthetic outcomes. Electron-withdrawing substituents on aromatic aldehydes increase reaction rates, whereas electron-donating groups improve stability of the final imine products through conjugation. Structural modification of aromatic rings has therefore become a strategic tool for designing novel Schiff bases with enhanced biological and physicochemical properties.[16]

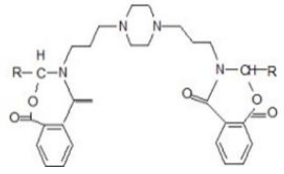
Current Trends and Future Directions

Recent literature reflects a transition toward integrated synthetic approaches combining microwave irradiation, solvent-free conditions, and catalytic systems. These hybrid methodologies provide rapid, high-yield synthesis while supporting sustainable chemical practices. Additionally, computational modeling and rational molecular design are increasingly guiding synthesis of novel aromatic Schiff bases with targeted biological activities.[17]

Several researchers have reported the synthesis and biological evaluation of amino-substituted aromatic Schiff bases due to their promising pharmacological and industrial applications. In one study, three new series of biologically active amino-substituted Schiff bases with the general formula $R_1N=CHR_2$ were synthesized. In these compounds, R_1 represented 2-aminobenzothiazole, 4-aminosalicylic acid, and aminophenol, whereas R_2 included substituted aromatic aldehydes such as 4-chlorobenzaldehyde, 2-chlorobenzaldehyde, salicylaldehyde, vanillin, and benzaldehyde.[18]

The synthesized Schiff bases were characterized using various physicochemical and spectroscopic techniques including melting point determination, elemental analysis, and multinuclear NMR spectroscopy (^1H and ^13C NMR). Both free ligands and their corresponding metal complexes were evaluated for in vitro biological activity against bacteria, fungi, and yeast strains. The results demonstrated that metal complexes exhibited significantly higher antimicrobial activity than the parent Schiff base ligands, which was attributed to enhanced lipophilicity and improved interaction with microbial cells. These compounds showed considerable inhibitory activity against all tested microorganisms.[19]





Researchers at Damascus University synthesized Schiff bases by condensing 1,4-bis (3- amino propyl) piperazine with various aromatic aldehydes in ethanol

using acetic acid as a catalyst. Subsequent reaction of these Schiff bases with phthalic anhydride produced substituted oxazepine derivatives. The study further investigated the corrosion inhibition properties of these compounds on steel surfaces in 1 M H_2SO_4 solution. Electrochemical techniques, including polarization measurements, were employed to evaluate inhibition efficiency. Variations in corrosion inhibition behavior were explained based on structural differences and electronic properties of the synthesized inhibitors, confirming the importance of molecular structure in corrosion protection performance.[20]

Literature evidence also indicates that isatin derivatives possess a broad spectrum of biological activities. Based on this knowledge, Indian researchers synthesized novel compounds namely 3-[(5-benzylidene-2-phenyl)-3,5-dihydro-4H-imidazol-4-one-3-(4-benzoylhydrazono)]-indole-2- ones. A total of fourteen new derivatives were prepared using similar synthetic procedures and characterized through physical, analytical, and spectral methods. Antimicrobial activity was evaluated using the disk diffusion technique. The synthesized compounds exhibited mild to moderate antibacterial activity against various bacterial strains, with the highest activity observed against Staphylococcus aurous. Activity was also noted against Bacillus subtitles. Structure–activity relationship studies revealed that substitution at the 5th position of isatin with halogens such as chlorine, bromine, or fluorine significantly enhanced antimicrobial activity.[21]

Furthermore, compounds containing 3(2H)-pyridazinone and 1(2H)-phthalazinone rings are known to exhibit diverse biological activities including antiplatelet, antihypertensive, analgesic, anti-inflammatory, and antimicrobial effects. Based on these findings, researchers at Gazi University synthesized several pyridazinone and phthalazinone derivatives and evaluated their antibacterial activity against Gram-positive and Gram-negative bacterial strains as well as clinical isolates, including Mycobacterium tuberculosis H37Rv. The results indicated promising antibacterial potential, highlighting the importance of heterocyclic Schiff base derivatives as potential therapeutic agents.[22]

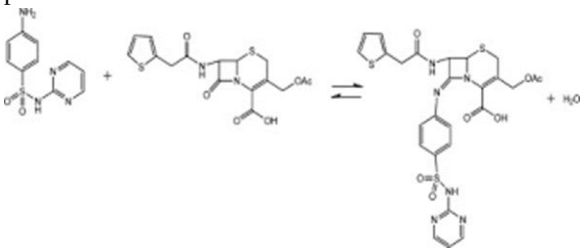
III. BIOLOGICAL ACTIVITIES OF AROMATIC SCHIFF BASES

Biological Activities of Aromatic Schiff Bases: Literature Review

3.1. Antimicrobial Activity

A large number of studies have reported significant antimicrobial activity of aromatic Schiff bases against Gram-positive and Gram-negative microorganisms. The biological activity is mainly attributed to the azomethine (–C=N–) linkage and its ability to coordinate with metal ions, enhancing membrane permeability and enzyme inhibition.[23]

Singh, Barwa, and Tyagi (2007) synthesized transition metal complexes of aromatic Schiff bases and evaluated their antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*. Their results demonstrated that metal complexes exhibited higher antimicrobial activity than free Schiff base ligands, which was explained by chelation theory leading to increased lipophilicity and improved penetration into bacterial cells.[24]



Similarly, Kumar, Dhar, and Saxena (2009) reviewed several Schiff base derivatives and reported that halogen-substituted aromatic compounds showed enhanced antimicrobial action due to increased electron withdrawal and interaction with microbial proteins.[25]Bringmann et al. (2004) also observed that Schiff bases derived from salicylaldehyde displayed broad-spectrum antimicrobial activity, suggesting interference with microbial DNA synthesis and metabolic pathways.

3.2. Antioxidant Activity

The antioxidant potential of aromatic Schiff bases has been extensively studied due to their conjugated systems and electron-donating substituents. Literature indicates that hydroxyl and methoxy groups significantly improve radical scavenging activity.[26]

Sridhar et al. (2001) synthesized phenolic Schiff bases and evaluated their antioxidant activity using

DPPH assays, reporting strong free radical scavenging ability comparable to standard antioxidants. The authors attributed this activity to hydrogen donation from phenolic groups and stabilization of radicals through resonance.
Likewise, Panneerselvam et al. (2005) demonstrated that Schiff bases containing electron-donating substituents exhibited enhanced antioxidant efficiency because of increased electron density around the imine linkage, facilitating neutralization of reactive oxygen species.

3.3. Anticancer Activity

Aromatic Schiff bases have gained considerable attention as potential anticancer agents due to their ability to interact with DNA and cellular enzymes. Planar aromatic systems enable intercalation between DNA base pairs, inhibiting replication and inducing apoptosis.

Desai, Desai, and Parekh (2001) synthesized several Schiff base derivatives and reported significant cytotoxic activity against cancer cell lines, suggesting DNA-binding capability as the primary mechanism.[27]
Further studies by Raman et al. (2010) showed that metal complexes of Schiff bases exhibited enhanced anticancer activity compared to free ligands, attributed to improved cellular uptake and generation of intracellular oxidative stress in tumor cells.[28]Spectroscopic studies conducted by Chohan and Praveen (2001) confirmed DNA interaction of Schiff base metal complexes through intercalative binding modes, supporting their potential as anticancer pharmacophores.[29]

3.4. Anti-inflammatory and Antidiabetic Activity

Several researchers have investigated anti-inflammatory and antidiabetic activities of substituted aromatic Schiff bases. These activities are largely associated with enzyme inhibition mechanisms and modulation of inflammatory mediators. Pandeya et al. (1999) reported that Schiff base derivatives exhibited significant anti-inflammatory activity through inhibition of cyclooxygenase (COX) enzymes responsible for prostaglandin synthesis. Structural analysis revealed that aromatic substitution enhanced binding affinity with inflammatory enzyme targets.[30]
In antidiabetic studies, Baluja and Solanki (2009) demonstrated that Schiff base compounds inhibited α-amylase and α-glucosidase enzymes, indicating their potential in controlling postprandial hyperglycemia. Electron-withdrawing substituents improved enzyme inhibition efficiency by strengthening ligand enzyme interactions.[31]Additionally, Nimbalkar et al. (2012) observed improved glucose uptake activity in Schiff base derivatives containing hydroxyl-substituted aromatic rings, suggesting possible applications in diabetes management.[32]

IV. APPLICATIONS OF NOVEL AROMATIC SCHIFF BASES: LITERATURE REVIEW

Aromatic Schiff bases have attracted extensive scientific interest owing to their structural versatility, facile synthesis, and strong coordination ability arising from the azomethine (–C=N–) functional group. Numerous studies have demonstrated that these compounds possess multifunctional applications spanning pharmaceutical chemistry, coordination chemistry, catalysis, and advanced material science. Recent literature highlights the growing importance of Schiff base derivatives as multifunctional molecular platforms in both biological and industrial fields.

4.1. Pharmaceutical Applications

Aromatic Schiff bases serve as important pharmacophores and intermediates in medicinal chemistry. Their biological effectiveness mainly arises from electron delocalization across aromatic rings and the imine linkage, which facilitates interaction with biological macromolecules.
Kumar et al. (2024) reviewed benzimidazole-derived Schiff bases and reported significant antibacterial, antifungal, antiviral, and anticancer activities, emphasizing their role as promising drug candidates and therapeutic intermediates. These compounds showed enhanced activity after metal complexation due to improved lipophilicity and cellular penetration.[33]

Similarly, Nabi et al. (2019) summarized that Schiff base derivatives function as:

- Enzyme inhibitors
- Antimicrobial agents
- Antitumor compounds

- Bioinorganic drug design scaffolds

Their ability to bind enzymes and DNA makes them useful for designing next-generation pharmaceuticals. Additionally, several studies indicate that Schiff bases act as intermediates in synthesizing heterocyclic drugs and biologically active molecules, making them indispensable in medicinal chemistry research.[34]

4.2. Coordination Chemistry

One of the most significant applications of aromatic Schiff bases lies in coordination chemistry. The nitrogen atom of the imine group and additional donor atoms (O, N, or S) allow Schiff bases to behave as multidentate ligands forming stable complexes with transition metals such as:

- Copper (Cu)
- Zinc (Zn)
- Nickel (Ni)
- Cobalt (Co)

Nayak and Mandal (2018) reported that Schiff base metal complexes exhibit diverse coordination geometries including square planar, tetrahedral, and octahedral structures. These complexes demonstrate enhanced chemical stability and tunable electronic properties, making them valuable in bioinorganic chemistry and materials design.[35]Furthermore, coordination enhances biological activity through chelation effects, which modify polarity and facilitate interaction with biomolecules.

4.3. Catalysis

Schiff base metal complexes are widely utilized as homogeneous and heterogeneous catalysts due to their adjustable electronic environments and strong metal–ligand interactions.

Recent reviews have shown that Schiff base complexes efficiently catalyze reactions such as:

- Oxidation reactions
- Epoxidation
- Aldol condensation
- Polymerization reactions

Nguyen et al. (2021) highlighted that chiral Schiff base complexes exhibit excellent catalytic efficiency and selectivity in organic transformations, particularly oxidation and hydroxylation reactions.[36]

Moreover, immobilized Schiff base complexes on magnetic nanoparticles have gained attention for green catalysis applications because of easy recovery and recyclability of catalysts

V. CONCLUSION

Schiff base synthesis continues to stand as one of the most powerful, adaptable, and strategically valuable methodologies for the development of novel aromatic compounds. The fundamental reaction condensation between a primary amine and an aldehyde or ketone to form an imine (– C=N–) linkage offers simplicity, high atom economy, and broad substrate compatibility. Because both aromatic amines and aromatic carbonyl compounds are readily available and structurally diverse, Schiff base chemistry provides a flexible platform for designing a wide array of substituted aromatic frameworks. This structural tunability enables precise modulation of electronic, steric, and physicochemical properties, making Schiff bases indispensable intermediates in modern synthetic chemistry.

One of the major strengths of Schiff base synthesis lies in its versatility. The imine functionality not only contributes to conjugation within aromatic systems but also acts as a reactive center for further transformations, including cyclization, reduction, oxidation, and coordination with metal ions. Through these pathways, simple Schiff bases can be converted into complex heterocyclic aromatic systems such as pyrazoles, oxazoles, imidazoles, and quinoline derivatives. This synthetic adaptability allows researchers to rapidly construct structurally diverse aromatic compounds suitable for biological screening and materials development.

Recent advances in synthetic methodologies have significantly enhanced the efficiency and practicality of Schiff base formation. Traditional reflux-based condensation methods have been supplemented or replaced by microwave-assisted synthesis, ultrasonic irradiation, solvent-free grinding techniques, and catalytic green protocols. These modern approaches offer shorter reaction times, improved yields, reduced solvent consumption, and enhanced selectivity. The adoption of heterogeneous catalysts, recyclable solid acids, and biocatalysts further supports sustainable and cost-effective production. Such developments align closely with the principles of green chemistry,

emphasizing waste minimization, energy efficiency, and environmentally benign processes.

Green chemistry innovations have particularly strengthened the industrial relevance of Schiff base synthesis. Solvent-free conditions and water-based reaction systems reduce hazardous waste and environmental impact. The use of renewable starting materials and mild reaction conditions lowers energy requirements and operational costs. In addition, mechanochemical techniques and one-pot multicomponent reactions improve atom economy and reduce purification steps. These sustainable strategies not only enhance laboratory efficiency but also facilitate scale-up for pharmaceutical and materials industries.

In medicinal chemistry, aromatic Schiff base derivatives have demonstrated a wide spectrum of pharmacological activities. Their conjugated aromatic systems and imine linkages allow interaction with biological targets through hydrogen bonding, π–π stacking, and metal coordination. Structural modification of substituents on the aromatic ring enables fine-tuning of lipophilicity, electronic distribution, and binding affinity, which is critical for optimizing biological activity. Schiff base derivatives have shown promising antimicrobial, antifungal, anticancer, anti-inflammatory, antioxidant, and antiviral properties. Furthermore, metal complexes of Schiff bases often exhibit enhanced therapeutic effects due to improved cellular uptake and altered redox behavior. These findings underscore the importance of Schiff base chemistry as a foundational tool in drug discovery and development.

Beyond therapeutics, aromatic Schiff base compounds play a significant role in materials science. Their extended conjugation systems contribute to desirable optical and electronic properties, making them suitable for applications in organic electronics, fluorescent sensors, dyes, corrosion inhibitors, and polymeric materials. Schiff base ligands readily coordinate with transition metals to form stable complexes that function as catalysts in organic transformations, including oxidation, reduction, and coupling reactions. In supramolecular chemistry, the reversible nature of the imine bond facilitates the construction of dynamic covalent frameworks and self-assembled materials, expanding their potential in nanotechnology and smart material design.

The integration of interdisciplinary research further amplifies the impact of Schiff base synthesis. Collaboration between organic chemists, medicinal chemists, pharmacologists, and materials scientists enables a comprehensive approach from molecular design and synthesis to biological evaluation and industrial application. Computational chemistry and molecular modeling tools now assist in predicting structure–activity relationships and optimizing synthetic pathways. Emerging technologies such as artificial intelligence and high-throughput screening are expected to accelerate the identification of promising aromatic Schiff base derivatives for specific therapeutic or functional applications.

Looking ahead, continued research is likely to focus on improving the stability of Schiff bases under physiological and environmental conditions, enhancing stereo selectivity in asymmetric synthesis, and developing more efficient catalytic systems. The exploration of bio-inspired catalysts, renewable feedstocks, and eco-friendly reaction media will further strengthen sustainability. Additionally, expanding applications in energy storage, environmental remediation, and advanced functional materials may open new industrial avenues.

Schiff base synthesis remains a highly powerful and versatile strategy for the development of novel aromatic compounds with extensive pharmaceutical and industrial relevance. Advances in synthetic techniques and green chemistry principles have significantly improved efficiency, selectivity, and sustainability. Ongoing interdisciplinary collaboration and technological integration promise to further expand the therapeutic scope and material applications of aromatic Schiff base derivatives, ensuring their continued importance in the evolving landscape of chemical research and innovation.

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