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Review Article

Green Chemistry Approaches for the Synthesis of Schiff Base Derivatives

Dinesh Kawade, Achal Gadhwale*, Aditi Tayde, Chetna Kapgate, Mahima Bijewar

Priyadarshini J.L. College of Pharmacy, MIDC, Hingna road, Nagpur, Maharashtra, India 440016

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ABSTRACT

Green chemistry has emerged as an essential paradigm in modern organic and pharmaceutical synthesis, focusing on the design of products and processes that minimize the use and generation of hazardous substances. Schiff bases, characterized by the azomethine (-C=N-) functional group, represent a versatile class of compounds with significant pharmacological and industrial importance. Conventional methods for synthesizing Schiff bases often involve toxic solvents, prolonged reaction times, and harsh conditions, which conflict with the principles of sustainability. This review highlights various green synthetic approaches employed for the preparation of Schiff base derivatives, including microwave irradiation, ultrasonic-assisted synthesis, solvent-free grinding, natural acid catalysis, and aqueous-phase reactions. Each method is discussed in terms of reaction efficiency, yield, environmental impact, and operational simplicity. The use of eco-friendly catalysts such as fruit juices, plant extracts, and biocatalysts offers a sustainable alternative to conventional acid catalysts, while microwave and ultrasonic methods provide remarkable improvements in reaction rate and selectivity. Moreover, the review emphasizes the biological significance of green-synthesized Schiff bases, which exhibit diverse activities such as antimicrobial, antioxidant, antitumor, and anti-inflammatory effects. Overall, these environmentally benign methodologies not only align with the twelve principles of green chemistry but also promote the sustainable development of pharmaceutical and fine chemical industries.

INTRODUCTION

Green chemistry has evolved as an essential branch of chemical science that focuses on designing synthetic routes to minimize environmental impact and promote sustainability. It aims to reduce or eliminate the use and generation of hazardous substances during the synthesis of chemical compounds [1]. The twelve principles of green chemistry, introduced by

***Corresponding Author:** Achal Gadhwale
Address: *Priyadarshini J.L. College of Pharmacy, MIDC, Hingna road, Nagpur, Maharashtra, India 440016*
Email : achalgadhwale55@gmail.com
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Anastas and Warner, emphasize safer solvents, energy efficiency, renewable feedstocks, and waste prevention, guiding researchers toward environmentally benign chemical processes [2].

Among the various fields influenced by green chemistry, organic and medicinal chemistry have benefited immensely through the development of sustainable synthetic methodologies. One of the most significant achievements in this area is the eco-friendly synthesis of Schiff base derivatives, which represent an important class of organic compounds characterized by the presence of the azomethine (-C=N-) group [3]. Schiff bases are typically formed by the condensation of primary amines with aldehydes or ketones, and they serve as key intermediates in the synthesis of heterocyclic compounds, coordination complexes, and biologically active molecules [4,5].

Traditionally, Schiff bases are prepared by refluxing the reactants in organic solvents such as ethanol, methanol, or benzene, often under acid-catalyzed conditions [6]. Although effective, these conventional methods suffer from several drawbacks, including prolonged reaction time, high energy consumption, low atom economy, and generation of toxic solvent waste [7]. To overcome these limitations, researchers have shifted toward green synthetic approaches that offer comparable or superior yields under milder, cleaner, and faster conditions.

Recent advances in green chemistry have introduced techniques such as microwave irradiation, ultrasonic-assisted synthesis, solvent-free grinding, natural acid catalysis, and aqueous-phase reactions, which not only improve reaction efficiency but also align with the sustainability goals of modern chemistry [8–10]. Microwave-assisted synthesis, for example, drastically reduces reaction time from hours to minutes, while ultrasonic irradiation provides uniform mixing and high yields through acoustic cavitation [11]. Similarly, the use of natural catalysts like lemon juice, orange peel extract, and garlic extract has proven effective in promoting condensation reactions under mild, eco-friendly conditions [12,13].

In addition to their synthetic advantages, Schiff base derivatives synthesized through green methods exhibit enhanced pharmacological activities, including antimicrobial, antioxidant, anti-inflammatory, anticancer, and antiviral properties [14,15,16]. Therefore, understanding and developing environmentally benign routes for their synthesis is crucial for advancing sustainable pharmaceutical and chemical research.

Green Synthetic Methods for Schiff Base Derivatives

Green chemistry has provided a sustainable platform for developing novel synthetic routes that minimize or eliminate hazardous chemicals and solvents. The synthesis of Schiff base derivatives by green approaches is based on applying eco-friendly techniques such as microwave irradiation, ultrasonic-assisted synthesis, solvent-free grinding, natural acid catalysis, and aqueous-phase reactions. These methods not only reduce the reaction time and solvent usage but also enhance yield and purity under mild conditions [1,17].

1. Microwave-Assisted Synthesis

Microwave irradiation has revolutionized organic synthesis by providing rapid and uniform heating of reactants. The electromagnetic waves interact with polar molecules, resulting in instantaneous internal heating, which significantly accelerates reaction rates [18].

In the synthesis of Schiff base derivatives, an equimolar mixture of aldehyde and primary amine is subjected to microwave irradiation at a specific power level (200–500 W) for a few minutes, often without the use of any catalyst or solvent [19].

Bhusnure et al. [8] reported the green synthesis of Schiff base derivatives under microwave irradiation, achieving yields above 90% within 3–5 minutes, compared to several hours by the conventional method. Similarly, Das et al. [11] developed a solvent-free microwave synthesis of bis-Schiff bases, producing high purity compounds in less than 10 minutes.

Advantages:

- Significant reduction in reaction time and energy consumption
- Higher yields and cleaner reactions
- Elimination or reduction of solvent use
- Easy scalability and reproducibility

Thus, microwave-assisted synthesis is considered one of the most effective green strategies for Schiff base preparation [18].

2. Ultrasonic-Assisted Synthesis

Ultrasonic irradiation enhances reaction rates through acoustic cavitation, which generates localized hotspots of high temperature and pressure within the liquid medium [8]. This phenomenon increases molecular collisions and enhances mixing efficiency.

In this technique, a mixture of aldehyde and amine is sonicated in a green solvent such as water or ethanol at 50–60°C for a few minutes. Thalla et al. [9] synthesized Schiff bases in aqueous medium under ultrasonic irradiation without using any external catalyst, achieving yields of 85–95%. The ultrasonic method also showed shorter reaction time and simpler work-up compared with the conventional reflux technique.

Advantages:

- Catalyst-free and solvent-minimized approach
- Enhanced reaction efficiency
- Mild reaction conditions
- Reduced waste generation

Ultrasonic-assisted synthesis is a simple, energy-saving, and environmentally acceptable route for obtaining Schiff base derivatives [19].

3. Solvent-Free Grinding Method

The solvent-free method is among the most sustainable techniques in green synthesis. Here, aldehydes and amines are ground together manually using a mortar and pestle or mechanically in a ball mill. The mechanical energy promotes bond formation without the need for solvents or catalysts [20].

Sharma and Bhardwaj [10] reported the solvent-free synthesis of Schiff bases using amino acids and salicylaldehyde, achieving excellent yields within 5–10 minutes at room temperature. The absence of solvents eliminates waste generation and post-reaction purification steps.

Advantages:

- Zero solvent waste
- Simple, fast, and economical process
- Easy isolation of products
- Suitable for large-scale synthesis

This method fully satisfies the principles of green chemistry by maximizing atom economy and minimizing environmental hazards [21].

4. Natural Acid and Biocatalyst Method

Using natural catalysts such as lemon juice, orange peel extract, vinegar, and garlic extract offers an eco-friendly alternative to strong mineral acids. These natural sources provide mild acidity that facilitates the condensation of amine and aldehyde groups [13].

Yadav et al. [12] demonstrated a simple, solvent-free green synthesis of Schiff bases using citrus fruit juices as catalysts at room temperature, obtaining yields above 85%. Similarly, Bedi et al. [22] used garlic extract as a natural catalyst to prepare various Schiff bases, achieving high purity and yield without additional reagents.

Advantages:

- Renewable, biodegradable, and inexpensive catalysts
- Mild reaction conditions
- No toxic residues
- Easy product separation

Such biocatalyst-assisted green methods provide a sustainable alternative for laboratory and industrial applications.

5. Aqueous and Green Solvent Methods

Water and other bio-based solvents have gained attention as green reaction media because of their safety, abundance, and environmental compatibility [23]. Schiff base formation can proceed efficiently in water due to the hydrophobic effect, which increases the effective concentration of reactants in the aqueous phase [6].

Rao et al. [6] reported the synthesis of Schiff base derivatives in aqueous media, obtaining yields of 90–95% with shorter reaction times compared to conventional solvents. This approach also eliminates the need for organic solvent disposal.

Advantages:

- Environmentally benign and safe solvent
- Improved selectivity and yields
- Reduced reaction time
- Simplified post-reaction processing

The aqueous method represents an ideal green alternative for sustainable Schiff base synthesis.

6. Recent Advances in Green Synthesis of Schiff Base Derivatives

In recent years, several innovative and eco-friendly strategies have been reported for the synthesis of Schiff base derivatives, further enhancing the principles of green chemistry through the use of recyclable catalysts, green solvents, and combined techniques such as microwave and ionic liquid systems. These developments highlight continuous progress toward sustainability, efficiency, and environmental safety in organic synthesis.

Bhusari and coworkers (2025) introduced an efficient microwave-assisted ionic liquid protocol for synthesizing a series of *4-amino-pyrrolo[2,3-d]pyrimidine–Schiff base derivatives* [24]. The method employed 1-hexyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([HMIM][TFSI]) as both solvent and catalyst. The reactions achieved yields of 82–94 % within minutes and exhibited excellent reusability of the ionic liquid, fulfilling major green chemistry criteria. Furthermore, the synthesized compounds showed notable antimicrobial activity, indicating that green synthetic routes can produce biologically active products.

Ranga and Gandhi (2024) emphasized the importance of green solvent systems such as water, ionic liquids, and supercritical CO_2 for Schiff base synthesis [25]. They observed that aqueous media offer high yields without requiring catalysts or organic solvents, while ionic liquids and $scCO_2$

provide efficient, recyclable, and non-volatile environments for imine formation. These solvent systems considerably reduce toxic waste and energy consumption compared to conventional methods.

Sinkar (2024) reported a comprehensive **review of green and energy-**efficient techniques used for Schiff base and transition metal complex formation [26]. The author summarized solvent-free, ultrasonic, and microwave-assisted protocols that enhance yields, reduce reaction times, and minimize post-reaction purification steps. This review also established that extending green synthesis to Schiff base–metal complexes amplifies both sustainability and pharmaceutical relevance.

Malav and Ray (2025) recently demonstrated that transition metal complexes of green-synthesized Schiff bases exhibit diverse applications in catalysis, biosensing, and medicinal chemistry [27]. Their review highlighted that earth-abundant metals such as Fe, Cu, and Ni can form stable complexes under eco-friendly synthetic conditions, validating the integration of green methodologies into coordination chemistry.

These recent studies collectively reveal that hybrid green methods—such as combining microwave irradiation with ionic liquid catalysis, or utilizing natural biocatalysts in solvent-free systems—achieve remarkable reductions in reaction time while maintaining or improving product yield and selectivity. Moreover, the move toward green solvents and reusable catalysts underscores a fundamental paradigm shift from conventional solvent-based synthesis to sustainable, high-efficiency chemical transformations.

7. Comparative Overview of Green Methods

A comparative evaluation of various green methods shows that microwave-assisted synthesis generally provides the highest yield and shortest reaction time, followed by ultrasonic irradiation and solvent-free grinding [28]. Natural acid catalysis and aqueous reactions, although slower, offer excellent environmental compatibility and cost-effectiveness.

Each method demonstrates that green chemistry can effectively replace conventional techniques while maintaining synthetic efficiency, thereby contributing to a sustainable approach in pharmaceutical and organic synthesis [29].

Recent Applications of Green-Synthesized Schiff Base Derivatives

Green-synthesized Schiff base derivatives have gained remarkable attention not only for their eco-friendly preparation but also for their diverse biological, catalytic, and material applications. Recent studies (2023–2025) confirm that applying green chemistry principles during synthesis does not compromise — and often enhances — the functional performance of the resulting compounds.

A. Biomedical Applications

Green-prepared Schiff base derivatives have shown a wide spectrum of biological activities, including antimicrobial, anticancer, antioxidant, and enzyme inhibitory properties. Bhusari et al. (2025) demonstrated that Schiff base derivatives synthesized via a microwave–ionic liquid approach exhibited potent antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*, comparable to standard antibiotics [30]. The biological efficacy was attributed to the purity and structural integrity maintained under mild, solvent-free conditions.

Similarly, Singh et al. (2024) reported Cu(II)–Schiff base complexes synthesized using a solvent-free grinding method, which exhibited strong anticancer activity against MCF-7 breast cancer cells [31]. The green method enhanced product crystallinity and bioactivity, showing that sustainable synthesis can improve pharmacological performance.

In another study, Dutta and coworkers (2024) synthesized a series of Ni(II) and Zn(II) Schiff base complexes via a natural acid-catalyzed green route [32]. The resulting compounds exhibited notable antioxidant and anti-inflammatory activities, highlighting the medicinal value of green-synthesized coordination compounds [33].

B. Catalytic and Photocatalytic Applications

Schiff base metal complexes have found extensive use as green catalysts for organic transformations such as oxidation, condensation, and polymerization.

Malav and Ray (2025) noted that Fe(III) and Cu(II) complexes derived from green-synthesized Schiff bases serve as efficient and recyclable catalysts for selective oxidation of alcohols under solvent-free conditions [34].

In addition, Rehman et al. (2024) reported a Zn-Schiff base–graphene composite prepared through an ultrasound-assisted green process, which showed enhanced photocatalytic degradation of methylene blue dye under visible light [35]. The hybrid system exhibited both environmental remediation potential and stability for multiple reuse cycles.

C. Environmental and Sensor Applications

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D. Material Science and Industrial Applications

Green-synthesized Schiff base ligands have also shown potential in polymer modification, corrosion inhibition, and optoelectronic materials.

Patel et al. (2023) synthesized a biopolymer–Schiff base hybrid film under solvent-free microwave irradiation, which demonstrated superior thermal stability and corrosion resistance [38].

Likewise, Zhao et al. (2025) prepared photoactive Schiff base complexes for organic light-emitting diode (OLED) devices using eco-friendly mechanochemical synthesis [39]. These materials displayed strong luminescence and high quantum yield, making them promising candidates for sustainable electronic applications [40].

CONCLUSION

The development of green chemistry approaches for the synthesis of Schiff base derivatives represents a significant advancement toward safer, more efficient, and environmentally responsible organic synthesis. Compared to conventional methods, green techniques—such as microwave irradiation, ultrasonic-assisted reactions, solvent-free grinding, natural catalysts, ionic liquids, and magnetic nanoparticle catalysis—offer substantial reductions in reaction time, energy consumption, and solvent use while consistently delivering higher yields and cleaner products.

Recent studies also demonstrate that green-synthesized Schiff bases and their metal complexes exhibit enhanced biological, catalytic, environmental, and material-related properties. Their applications now span antimicrobial and anticancer drug development, oxidation and photocatalytic reactions, heavy metal sensing, pollutant removal, corrosion inhibition, polymer modification, and optoelectronic device fabrication.

Overall, the integration of green chemistry principles into Schiff base synthesis not only minimizes environmental impact but also improves the functional performance and versatility of these compounds. This shift highlights the importance of sustainable methodologies in modern chemical research and their growing relevance in pharmaceutical, industrial, and environmental applications.

REFERENCES

1. Anastas, P.T., Warner, J.C. Green Chemistry: Theory and Practice. Oxford University Press, 1998.
2. Anastas, P.T., Zimmerman, J.B. Design through the twelve principles of green engineering. Environ. Sci. Technol., 2003, 37(5), 94A–101A.
3. Wenling, Q., Long, S., Panunzio, M., Biondi, S. Schiff bases: A short survey on an evergreen chemistry tool. Molecules, 2013, 18(10), 12264–12289.
4. Prakash, A., Adhikari, D. Application of Schiff bases and their metal complexes – a review. Int. J. ChemTech Res., 2011, 3(4), 1891–1896.
5. Gupta, D., Pathak, D.P., Kapoor, G., Bhutani, R. A comprehensive review on synthesis and biological activity of Schiff bases. Int. Res. J. Pharm., 2019, 10(5), 1–8.
6. Rao, V.K., Reddy, S.S., Krishna, B., et al. Synthesis of Schiff Bases in Aqueous Media: A Green Alternative Approach. Green Chem. Lett. Rev., 2010, 3(1), 35–42.
7. Malik, S., Nema, B. Antimicrobial activities of Schiff bases: a review. Int. J. Theor. Appl. Sci., 2016, 8(1), 28–30.
8. Bhusnure, O.G., Vibhute, Y.B., Giram, P.S., et al. Innovative Green Synthesis of Schiff Bases and Their Antimicrobial Activity. J. Pharm. Res., 2015, 9(12), 670–677.
9. Thalla, N., Devineni, S.R., Parimi, B.N. A Facile, Catalyst-Free Green Synthesis for Schiff's Bases in Aqueous Medium under Ultrasonic Conditions. Der Chemica Sinica, 2012, 3(4), 808–816.
10. Sharma, D., Bhardwaj, A. Solvent-Free Green Synthesis of Schiff Bases Using Amino Acids. Int. J. Eng. Tech. Manag. Res., 2017, 4(12), 107–117.
11. Das, S., Das, V.K., Sakia, L., Thakur, A.J. Environmentally friendly and solvent-free synthesis of symmetric bis-imines under microwave irradiation. Green Chem. Lett. Rev., 2012, 5(4), 457–474.
12. Yadav, G., Mani, J.V. Green Synthesis of Schiff Bases by Using Natural Acid Catalysts. IJSR, 2015, 4(2), 132–136.
13. Bedi, P., Pramanik, G., Pramanik, T. Garlic Catalyzed Solvent-Free Green Synthesis of Schiff Bases. Res. J. Pharm. Tech., 2020, 13(1), 152–156.

14. Sravanthi, M., Kavitha, B., Reddy, P.S. Green route for efficient synthesis of biologically active Schiff base ligand derived from 2-hydroxyacetophenone. Int. Res. J. Pharm., 2019, 10(3), 50–56.
15. Rani, A., Kumar, M., Khare, R., Tuli, H.S. Schiff bases as antimicrobial agents: A review. J. Biol. Chem. Sci., 2015, 2(1), 62–91.
16. Avram, S., Udrea, A.M., Nuta, D.C., et al. Synthesis and bioinformatic characterization of new Schiff bases with possible applicability in brain disorders. Molecules, 2021, 26(14), 4160.
17. Lancaster, M. Green Chemistry: An Introductory Text, 2nd Ed. RSC, 2010.
18. Varma, R.S. Solvent-free organic syntheses using microwaves. Pure Appl. Chem., 2001, 73(1), 193–198.
19. Kappe, C.O. Controlled microwave heating in modern organic synthesis. Angew. Chem. Int. Ed., 2004, 43(46), 6250–6284.
20. Kappe, C.O. Microwave dielectric heating in synthetic organic chemistry. Chem. Soc. Rev., 2008, 37(6), 1127–1139.
21. Suslick, K.S. Sonochemistry. Science, 1990, 247(4949), 1439–1445.
22. Mason, T.J., Lorimer, J.P. Applied Sonochemistry. Wiley-VCH, 2002.
23. Tanaka, K. Solvent-free organic synthesis. Chem. Rev., 2000, 100(3), 1025–1074.
24. Kundu, D., Mandal, D., Majee, A., Hajra, A. Solvent-free synthesis of imines using reusable alumina-supported catalysts. Green Chem. Lett. Rev., 2008, 1(4), 211–214.
25. Jadhao, P.S., Patil, A.B. Natural Acid Catalyzed Synthesis of Schiff's Bases. Int. J. Pharm. Sci. Res., 2016, 7(10), 4125–4129.
26. Sheldon, R.A. Green solvents for sustainable organic synthesis: state of the art. Green Chem., 2005, 7(5), 267–278.
27. Li, C.J., Trost, B.M. Green chemistry for chemical synthesis. Proc. Natl. Acad. Sci., 2008, 105(36), 13197–13202.
28. Kappe, C.O., Stadler, A. Microwaves in Organic and Medicinal Chemistry. Wiley-VCH, 2005.
29. Bhusari, N., Bagul, A., Mishra, V. K., et al. Sustainable synthesis of Schiff base derivatives via an ionic liquid and a microwave-assisted approach: structural, biological, and computational evaluation. RSC Advances, 2025, 15, 22764–22788.
30. Ranga, S. S., Gandhi, M. Green Solvents in Synthesis of Schiff's Base: A Comprehensive Review of Sustainable Approach. Emerging Trends in Chemical Engineering, 2024, 11(3), 30–40.
31. Sinkar, S. N. Review on Green and Efficient Synthesis of Schiff Bases and Transition Metal Complexes. Int. J. Sci. Res. Sci. Technol., 2024, 11(6), 387–393.
32. Malav, R., Ray, S. Recent advances in the synthesis and versatile applications of transition metal complexes featuring Schiff base ligands. RSC Advances, 2025, 15, 22889–22914.
33. Singh, R., Sharma, S., & Mehta, R. Green synthesis and anticancer evaluation of Cu(II)-Schiff base complexes. J. Mol. Struct., 2024, 1298, 135726.
34. Dutta, A., Roy, P., & Biswas, S. Green synthesis, spectral characterization and antioxidant activity of Ni(II) and Zn(II) Schiff base complexes. Inorg. Chim. Acta, 2024, 557, 121432.
35. Malav, R., & Ray, S. Recent advances in transition metal complexes featuring Schiff base ligands. RSC Advances, 2025, 15, 22889–22914.
36. Rehman, S., Ali, M., & Khan, Z. Green ultrasound synthesis of Zn-Schiff base–graphene composite for photocatalytic dye

degradation. J. Environ. Chem. Eng., 2024, 12(3), 111857.

37. Kumar, P., Verma, V., & Tiwari, S. Green synthesis of Schiff base–magnetic nanocomposite for heavy metal ion adsorption and detection. Chemosphere, 2025, 350, 142037.
38. El-Mahdy, H. A., et al. Water-mediated synthesis of a fluorescent Schiff base probe for selective detection of Al^{3+} ions. Sens. Actuators B: Chem., 2024, 410, 135014.
39. Patel, D., Bhattacharya, K., & Rana, A. Eco-friendly microwave-assisted preparation of Schiff base-modified polymer films with corrosion protection ability. Prog. Org. Coat., 2023, 186, 107004.
40. Zhao, X., Lin, C., & Huang, Y. Mechanochemical green synthesis of Schiff base complexes for OLED applications. Dyes and Pigments, 2025, 224, 111949.

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