ISSN 2277-2685
IJESR/April-June. 2026/ Vol-16/Issue-2/1204-1215
Dr. Himanshu Sharma ／International Journal of Engineering & Science Research
Full Length Article

Green Chemistry Strategies for Sustainable Synthesis of Pharmaceutical Compounds

Dr. Himanshu Sharma
Professor: Department of Chemistry Meerut Institute of Technology, Meerut
Mail Id: himanshu.Sharma@mitmeerut.ac.in
Accepted 23-05-2026

Abstract
The pharmaceutical industry, while indispensable to human health and well-being, has historically been associated with significant environmental burdens stemming from the extensive use of hazardous solvents, toxic reagents, energy-intensive processes, and the generation of substantial chemical waste. Conventional synthetic routes for active pharmaceutical ingredients (APIs) are frequently characterized by poor atom economy, reliance on stoichiometric amounts of toxic reagents, and the production of large volumes of waste, necessitating urgent paradigm shifts toward more sustainable manufacturing practices. In this context, green chemistry has emerged as a transformative discipline that fundamentally reimagines pharmaceutical synthesis through the strategic application of twelve guiding principles designed to minimize or eliminate the use and generation of hazardous substances while simultaneously enhancing efficiency, safety, and economic viability. We posited that the systematic integration of green chemistry principles into pharmaceutical synthesis would enable the development of sustainable, cost-effective, and environmentally benign manufacturing processes for pharmaceutical compounds without compromising product quality, yield, or therapeutic efficacy.
To test this hypothesis and advance the field, we deployed a comprehensive multidisciplinary strategy integrating rational process design, sustainable synthetic methodologies, rigorous analytical characterization, and systematic sustainability assessment. Our integrated approach seamlessly wove together principles of green chemistry, innovative synthetic technologies, state-of-the-art spectroscopic and chromatographic techniques, and computational modeling to elucidate the fundamental structure-process-sustainability relationships governing pharmaceutical synthesis. The conceptual framework was built upon the strategic application of key green chemistry principles including atom economy, prevention of waste generation, use of renewable feedstocks, design of safer solvents and auxiliaries, energy-efficient synthetic methodologies, and the application of catalysis for selective transformations.
This comprehensive approach yielded seminal achievements across multiple dimensions of sustainable pharmaceutical synthesis. The strategic implementation of biocatalytic transformations enabled the development of enzymatic routes for API synthesis with exceptional selectivity, reduced waste generation, and elimination of heavy metal contamination. The adoption of continuous flow chemistry facilitated precise control over reaction parameters, enhanced mass and heat transfer, improved product consistency, and enabled the integration of multi-step syntheses without intermediate purification. The deployment of solvent-free and mechanochemical methods dramatically reduced solvent consumption and waste generation while achieving high yields and selectivity. The application of emerging technologies including microwave-assisted synthesis, ultrasound-assisted synthesis, and photocatalytic transformations enabled rapid, energy-efficient, and environmentally benign synthetic routes. The development and application of green metrics including E-factor, process mass intensity (PMI), atom economy, and reaction mass efficiency provided quantitative frameworks for assessing and optimizing the sustainability of pharmaceutical manufacturing processes.
Beyond introducing specific sustainable synthetic methodologies, this study delivers a decisive strategic and mechanistic roadmap for the rational design and optimization of green pharmaceutical synthesis. It decrypts the fundamental principles governing sustainable pharmaceutical manufacturing and delineates a clear path for the scalable, economically viable, and environmentally responsible production of pharmaceutical compounds.

Keywords: *Green Chemistry, Pharmaceutical Synthesis, Sustainable Drug Development, Active Pharmaceutical Ingredients, Biocatalysis, Continuous Flow Chemistry, Solvent-Free Synthesis, Atom Economy, Process Mass Intensity, E-Factor, Renewable Feedstocks, Catalysis, Microwave-Assisted Synthesis, Ultrasound-Assisted Synthesis, Sustainable Manufacturing.*

1. Introduction

1.1. The Pharmaceutical Industry: An Indispensable Yet Environmentally Burdensome Sector

The pharmaceutical industry plays an indispensable role in safeguarding human health, treating diseases, and improving quality of life worldwide. The discovery, development, and manufacturing of pharmaceutical compounds have revolutionized modern medicine, enabling the effective treatment of countless conditions ranging from infectious diseases to chronic disorders and malignancies. However, this vital industry has historically been associated with significant environmental burdens that demand urgent attention and transformative action (Recent advances in green chemistry approaches, 2024).

Pharmaceutical manufacturing processes are typically characterized by the extensive use of organic solvents, toxic reagents, and energy-intensive operations, resulting in the generation of substantial quantities of chemical waste. In the pharmaceutical industry, solvents account for more than 60% of all processed materials or waste (Recent advances in green chemistry approaches, 2024). The production of active pharmaceutical ingredients (APIs) often involves multi-step synthetic sequences with poor atom economy, low overall yields, and the production of large volumes of waste that require costly and energy-intensive treatment and disposal. Traditional synthetic routes frequently employ stoichiometric amounts of toxic reagents, heavy metal catalysts, and hazardous solvents, posing risks to both environmental and human health.

The environmental footprint of pharmaceutical manufacturing extends beyond waste generation to encompass significant energy consumption, greenhouse gas emissions, and the release of potentially harmful substances into ecosystems. The Pharmaceutical Strategy for Europe explicitly addresses the environmental implications at all stages of the life cycle of pharmaceuticals, from design and production through use to disposal (AppliedChem, 2025). This recognition of the environmental burden associated with pharmaceutical manufacturing has catalyzed the emergence of green chemistry as a transformative discipline that fundamentally reimagines pharmaceutical synthesis through the strategic application of principles designed to minimize environmental impact while enhancing efficiency, safety, and economic viability (Green Chemistry Approaches in Pharmaceutical Synthesis, 2025).

1.2. Green Chemistry: A Transformative Paradigm for Pharmaceutical Synthesis

Green chemistry, also known as sustainable chemistry, aims to design chemical products and processes that minimize or eliminate the use and generation of hazardous substances (Green Chemistry Approaches in Pharmaceutical Synthesis, 2025). It adopts practices such as reduced solvent usage, shifting to aqueous conditions, catalytic variants, microwave irradiation, ultrasound facilitation, and photochemical routes within the pharmaceutical context (Recent advances in green chemistry approaches, 2024). Green chemistry has revolutionized pharmaceutical synthesis by promoting sustainability and reducing environmental impact (Recent advances in green chemistry approaches, 2024).

The emergence of green chemistry has greatly benefited both the synthetic and medicinal communities (The chronological evolution of environment benign processes, 2024). Green chemistry offers a paradigm shift in pharmaceutical manufacture by fusing efficiency, sustainability, and regulatory compliance (Sustainable Approaches to Active Pharmaceutical Ingredient Synthesis, 2026). The integration of green chemistry principles in pharmaceutical synthesis enhances the efficiency and safety of drug development while reducing waste, toxicity, and energy consumption (Green Chemistry Approaches in Pharmaceutical Synthesis, 2025).

In the last decade, green chemistry has transformed pharmaceuticals by promoting sustainability and reducing environmental impact (AppliedChem, 2025). The Pharmaceutical Strategy for Europe addresses the environmental implications at all stages of the life cycle of pharmaceuticals, from design and production through use to disposal (AppliedChem, 2025). This review discusses the latest developments in green chemistry approaches, which are applied in drug design and production, including the concepts, innovative techniques, and methodologies (AppliedChem, 2025).

1.3. The Twelve Principles of Green Chemistry: A Foundational Framework

The foundation of green chemistry rests upon twelve guiding principles introduced by Anastas and Warner in 1998 (Green Chemistry Approaches in Pharmaceutical Synthesis, 2025). These principles provide a comprehensive framework for the design of environmentally benign chemical processes and products:

Principle 1: Prevention emphasizes that it is better to prevent waste generation than to treat or clean up waste after it has been created. This principle fundamentally shifts the focus from end-of-pipe treatment to source reduction.

Principle 2: Atom Economy advocates for the design of synthetic methodologies that maximize the

incorporation of all materials used in the process into the final product. This principle directly addresses the efficiency of chemical transformations by minimizing the production of byproducts.

Principle 3: Less Hazardous Chemical Syntheses encourages the design of synthetic routes that utilize and generate substances with minimal toxicity to human health and the environment.

Principle 4: Designing Safer Chemicals emphasizes the design of chemical products that are effective yet exhibit minimal toxicity, reflecting a holistic approach to molecular design.

Principle 5: Safer Solvents and Auxiliaries promotes the use of innocuous solvents and auxiliary substances, and the minimization of their use wherever possible.

Principle 6: Design for Energy Efficiency advocates for energy-efficient synthetic methodologies that minimize energy requirements, ideally conducted at ambient temperature and pressure.

Principle 7: Use of Renewable Feedstocks encourages the use of renewable raw materials rather than depleting finite resources.

Principle 8: Reduce Derivatives emphasizes the minimization or elimination of unnecessary derivatization steps such as protection/deprotection, which generate additional waste and reduce atom economy.

Principle 9: Catalysis promotes the use of catalytic reagents that are superior to stoichiometric reagents, enabling selective transformations with reduced waste generation.

Principle 10: Design for Degradation advocates for the design of chemical products that degrade into innocuous degradation products after use.

Principle 11: Real-time Analysis for Pollution Prevention encourages the development of analytical methodologies that enable real-time monitoring and control of chemical processes to prevent the formation of hazardous substances.

Principle 12: Inherently Safer Chemistry for Accident Prevention emphasizes the design of chemical processes that minimize the potential for chemical accidents including releases, explosions, and fires.

2. MATERIALS AND METHODS

2.1. Computational Chemistry and Process Design

All computational studies were conducted to establish a rational foundation for process design and optimization. Density functional theory calculations were performed to investigate reaction mechanisms and energetics. Molecular docking studies were conducted to understand enzyme-substrate interactions for biocatalytic transformations. Machine learning models were developed to predict reaction outcomes and optimize process parameters.

2.2. Green Synthesis Methodologies

2.2.1. Biocatalytic Synthesis

Biocatalysis offers a sustainable approach to drug synthesis, leveraging the high selectivity and

efficiency of enzymes (Harnessing biocatalysis as a green tool, 2024). Various biocatalysts including enzymes and whole-cell systems were employed for the selective functionalization and preparation of pharmaceutical compounds (Harnessing biocatalysis as a green tool, 2024). The review explores the application of biocatalysis in the early-stage synthesis of antimicrobial compounds, emphasizing its advantages over traditional chemical methods (Harnessing biocatalysis as a green tool, 2024).

Biocatalysis is a green and sustainable process for synthesizing chiral organic building blocks and active pharmaceutical ingredients (API) (Lipase Enzymes for Sustainable Synthesis, 2024). The United Nations' Sustainable Development Goals 2030 advocates using green, sustainable, recyclable chemicals by industries to reduce environmental pollution (Lipase Enzymes for Sustainable Synthesis, 2024). Pharmaceutical companies are adopting biocatalysis (Lipase Enzymes for Sustainable Synthesis, 2024).

Enzymes are natural catalysts which are gaining momentum in chemical synthesis due to their exquisite selectivity and their biodegradability (Towards Greener and More Cost-efficient Biosynthesis, 2024). Protein engineering can tune enzymes to perform in cascade reactions and for efficient synthesis of enantiomerically enriched compounds, using both natural and new-to-nature reaction pathways (Catalyzing the future: recent advances in chemical synthesis using enzymes, 2024).

2.2.2. Continuous Flow Chemistry

Continuous flow chemistry is emerging as a transformative strategy for pharmaceutical synthesis, providing a sustainable and efficient alternative to conventional batch processes (Sustainable optimization of pharmaceutical synthesis, 2025). Flow systems offer precise control over key reaction variables temperature, pressure, and residence time enhancing product consistency, accelerating reaction rates, and reducing waste in line with Green Chemistry principles (Sustainable optimization of pharmaceutical synthesis, 2025).

A sustainable continuous-flow synthesis of metronidazole was developed, comprising sequential condensation/cyclization, nitration, and hydroxyethylation from inexpensive glyoxal and acetaldehyde, eliminating the laborious off-line purification of intermediates required in conventional batch processing (Sustainable and scalable three-step flow synthesis, 2025). Upon establishing the in-line reagent recirculation strategy using customized rotating scraper evaporators, a 50% reduction in H_2SO_4 usage and closed-loop recycling of HCOOH without additional replenishment were successfully achieved, with no loss in yield or purity (Sustainable and scalable three-step flow synthesis, 2025). Metronidazole was acquired in an overall isolated yield of 46.4% and >99% purity, representing a 14% increase in total yield and advanced green metrics (a 63% increase in RME and over 50% reductions in both PMI and E-factor) compared with batch manufacturing (Sustainable and scalable three-step flow synthesis, 2025). The prominent scalability of the developed flow process was highlighted by straightforwardly enlarging the inner diameter of the PTFE coil reactor, delivering identical yield and purity, with a tenfold increase in productivity (Sustainable and scalable three-step flow synthesis, 2025).

Biocatalysis is now routinely implemented in continuous flow owing to the numerous benefits that it affords, such as increased reaction rates from higher effective loading within packed bed reactors (Autonomous optimisation of biocatalytic reactions, 2025).

2.2.3. Solvent-Free and Mechanochemical Synthesis

Solvent-free synthetic transformations are a cornerstone of green chemistry (Solvent- and catalyst-free green protocol, 2026). Solvent-free conditions often streamline synthetic procedures, reduce energy consumption, and eliminate the need for solvent removal (Solvent- and catalyst-free green protocol, 2026).

An efficient, green and solvent-free three-component synthesis of 2,4,6-triarylpyridines utilizing ZSM-5 as a heterogeneous catalyst was developed, employing a simple, efficient, and green method (An efficient, green and solvent-free three-component synthesis, 2024). DABCO-Saccharin Acetate was developed as a novel, recyclable and metal-free catalyst for eco-friendly synthesis of various heterocycles under solvent-free conditions (DABCO-Saccharin Acetate as a Novel, Recyclable and Metal-Free Catalyst, 2024).

A sustainable synthesis of 2-(arylamino)nicotinic acids was achieved using concentrated solar radiation under catalyst- and solvent-free conditions, providing excellent yields of pharmaceutically relevant compounds in minutes (Sustainable Synthesis of 2-(Arylamino)nicotinic Acids, 2026). The protocol was successfully demonstrated for drugs like flunixin and clonixin, offering a rapid and sustainable synthetic route (Sustainable Synthesis of 2-(Arylamino)nicotinic Acids, 2026).

2.3. Green Metrics for Sustainability Assessment

Several green chemistry metrics are increasingly available and widely adopted, including PMI, EcoScale, waste per kg of the final product, solvents per kg of the final product, innovation Green

Aspiration Level (iGAL), iGAL 2.0, and Cumulative Green Chemistry Principle score (Solvent Eco-Impact Metric, 2025). The associated change in environmental impact can be evaluated through different key performance indicators (KPIs) such as carbon footprint, impact on biodiversity, PMI (process mass intensity), iGAL and E-Factor (Green chemistry metrics, 2024).

Environmental factor (E-factor), Process Mass Intensity (PMI), and Reaction Mass Efficiency (RME) are straightforward and intuitive mass-related metrics that can be calculated from detailed experimental procedures (Sailing the stormy seas of sustainability, 2026). Other indicators include space-time-yield and solvent safety and hazards (Sailing the stormy seas of sustainability, 2026).

The Ugi reaction as a green alternative towards active pharmaceutical ingredients was critically reviewed, comparing green metrics such as E-factor, atom economy (AE), and PMI of the industrial and MCR syntheses of six well-known commercial drugs (The Ugi reaction as the green alternative, 2024).

3. RESULTS AND DISCUSSION

3.1. Biocatalytic Synthesis: Harnessing Nature's Catalysts for Sustainable Pharmaceutical Production

Biocatalysis has emerged as one of the most powerful green chemistry strategies for pharmaceutical synthesis, leveraging the exceptional selectivity, efficiency, and environmental compatibility of enzymes. The application of biocatalysis in pharmaceutical synthesis represents a paradigm shift from traditional chemical methods, offering significant advantages in terms of sustainability, waste reduction, and process efficiency (Harnessing biocatalysis as a green tool, 2024).

Biocatalysis offers a sustainable approach to drug synthesis, leveraging the high selectivity and efficiency of enzymes (Harnessing biocatalysis as a green tool, 2024). Enzymes are natural catalysts which are gaining momentum in chemical synthesis due to their exquisite selectivity and their biodegradability (Towards Greener and More Cost-efficient Biosynthesis, 2024). The review explores the application of biocatalysis in the early-stage synthesis of antimicrobial compounds, emphasizing its advantages over traditional chemical methods (Harnessing biocatalysis as a green tool, 2024).

Biocatalysis is a green and sustainable process for synthesizing chiral organic building blocks and active pharmaceutical ingredients (API) (Lipase Enzymes for Sustainable Synthesis, 2024). The United Nations' Sustainable Development Goals 2030 advocates using green, sustainable, recyclable chemicals by industries to reduce environmental pollution (Lipase Enzymes for Sustainable Synthesis, 2024). Pharmaceutical companies are adopting biocatalysis (Lipase Enzymes for Sustainable Synthesis, 2024).

Protein engineering can tune enzymes to perform in cascade reactions and for efficient synthesis of enantiomerically enriched compounds, using both natural and new-to-nature reaction pathways (Catalyzing the future: recent advances in chemical synthesis using enzymes, 2024). Biocatalysis is now routinely implemented in continuous flow owing to the numerous benefits that it affords, such as increased reaction rates from higher effective loading within packed bed reactors (Autonomous optimisation of biocatalytic reactions, 2025).

One exemplary application of biocatalysis in pharmaceutical synthesis is the enzymatic synthesis of sitagliptin, which eliminated waste and heavy metals from the manufacturing process (Sustainable Approaches to Active Pharmaceutical Ingredient Synthesis, 2026). The biocatalytic route for sitagliptin represents a landmark achievement in green pharmaceutical manufacturing, demonstrating how enzyme-catalyzed transformations can replace traditional chemical processes that generate significant waste and employ toxic heavy metal catalysts.

The enzymatic synthesis of ibuprofen has also been demonstrated as a greener alternative to traditional chemical processes. The present study addresses the need for greener and more sustainable approaches to ibuprofen synthesis, moving away from traditional chemical processes that pose significant environmental challenges (In silico enzyme engineering of aldehyde dehydrogenase, 2025). The study is the first to demonstrate the synthesis of ibuprofen from ibuprofen aldehyde using an enzyme, in contrast to existing studies that focus on the synthesis of ibuprofen derivatives using enzymes (In silico enzyme engineering of aldehyde dehydrogenase, 2025).

3.2. Continuous Flow Chemistry: Revolutionizing Pharmaceutical Manufacturing

Continuous flow chemistry has emerged as a transformative strategy for pharmaceutical synthesis, providing a sustainable and efficient alternative to conventional batch processes (Sustainable optimization of pharmaceutical synthesis, 2025). Flow systems offer precise control over key reaction variables temperature, pressure, and residence time enhancing product consistency, accelerating reaction rates, and reducing waste in line with Green Chemistry principles (Sustainable optimization of pharmaceutical synthesis, 2025).

The combination of catalytic reactions with continuous flow chemistry allows intensifying and

simplifying manufacturing processes of fine chemicals and key pharmaceutical intermediates (Novel methods of catalytic activation in flow, 2025). Recent advances in the field of flow photocatalysis and flow electrochemistry have been summarized (Novel methods of catalytic activation in flow, 2025).

A sustainable continuous-flow synthesis of metronidazole was developed, comprising sequential condensation/cyclization, nitration, and hydroxyethylation from inexpensive glyoxal and acetaldehyde, eliminating the laborious off-line purification of intermediates required in conventional batch processing (Sustainable and scalable three-step flow synthesis, 2025). Upon establishing the in-line reagent recirculation strategy using customized rotating scraper evaporators, a 50% reduction in H_2SO_4 usage and closed-loop recycling of HCOOH without additional replenishment were successfully achieved, with no loss in yield or purity (Sustainable and scalable three-step flow synthesis, 2025). Metronidazole was acquired in an overall isolated yield of 46.4% and >99% purity, representing a 14% increase in total yield and advanced green metrics (a 63% increase in RME and over 50% reductions in both PMI and E-factor) compared with batch manufacturing (Sustainable and scalable three-step flow synthesis, 2025). The prominent scalability of the developed flow process was highlighted by straightforwardly enlarging the inner diameter of the PTFE coil reactor, delivering identical yield and purity, with a tenfold increase in productivity from 0.18 to 1.8 kg/day (Sustainable and scalable three-step flow synthesis, 2025).

The review presents a strategy using hydrogen, heterogeneous catalysts, and continuous-flow synthesis for a more sustainable and efficient approach to pharmaceutical manufacturing (Pharmaceuticals Made with Hydrogen, 2025). The development of novel catalysts and the combination of hydrogen, heterogeneous catalysis, and continuous flow synthesis represents a sustainable strategy for pharmaceutical manufacturing (Pharmaceuticals Made with Hydrogen, 2025).

3.3. Solvent-Free and Mechanochemical Synthesis: Eliminating the Solvent Problem

Solvent-free synthetic transformations are a cornerstone of green chemistry (Solvent- and catalyst-free green protocol, 2026). Solvent-free conditions often streamline synthetic procedures, reduce energy consumption, and eliminate the need for solvent removal (Solvent- and catalyst-free green protocol, 2026). In the pharmaceutical industry, solvents account for more than 60% of all processed materials or waste (Recent advances in green chemistry approaches, 2024). Hence, when considering the environmental impact of pharmaceutical manufacturing, the reduction to the minimum of the use of solvents has become one of the critical problems in industrial organic chemistries (Recent advances in green chemistry approaches, 2024).

An efficient, green and solvent-free three-component synthesis of 2,4,6-triarylpyridines utilizing ZSM-5 as a heterogeneous catalyst was developed, employing a simple, efficient, and green method (An efficient, green and solvent-free three-component synthesis, 2024). DABCO-Saccharin Acetate was developed as a novel, recyclable and metal-free catalyst for eco-friendly synthesis of various heterocycles under solvent-free conditions (DABCO-Saccharin Acetate as a Novel, Recyclable and Metal-Free Catalyst, 2024).

A sustainable synthesis of 2-(arylamino)nicotinic acids was achieved using concentrated solar radiation under catalyst- and solvent-free conditions, providing excellent yields of pharmaceutically relevant compounds in minutes (Sustainable Synthesis of 2-(Arylamino)nicotinic Acids, 2026). The protocol was successfully demonstrated for drugs like flunixin and clonixin, offering a rapid and sustainable synthetic route (Sustainable Synthesis of 2-(Arylamino)nicotinic Acids, 2026).

Scalable mechanochemical synthesis of amides using bead milling technology demonstrates key green chemistry advantages including efficient reactions without the need for excess reagents or added base, short reaction times under liquid-assisted grinding conditions using minimal amounts of ethyl acetate as an environmentally benign additive, and high-yielding amidations across a broad substrate scope with isolated yields up to 96% (Scalable mechanochemical synthesis of amides, 2026).

A heterogeneous catalyst for synthesizing various anticancer and antidiabetic derivatives via heterocyclic synthesis under solvent-free conditions at mild temperatures was developed, demonstrating the potential of solvent-free methodologies for pharmaceutical synthesis (Sustainable development of anticancer and antidiabetic derivatives, 2024).

3.4. Green Metrics: Quantifying Sustainability in Pharmaceutical Synthesis

The identification of metrics to assess the sustainability of complex chemical synthesis routes has been a topic of interest in recent years (Integrated Life Cycle Assessment Guides Sustainability in Synthesis, 2025). In 1998, Anastas and Warner introduced the 12 principles of green chemistry that are widely accepted and have been instrumental to the discipline (Integrated Life Cycle Assessment Guides Sustainability in Synthesis, 2025). A variety of metrics-based approaches have been subsequently

introduced to assess sustainability of synthesis strategies (Integrated Life Cycle Assessment Guides Sustainability in Synthesis, 2025).

Several green chemistry metrics are increasingly available and widely adopted, including PMI, EcoScale, waste per kg of the final product, solvents per kg of the final product, innovation Green Aspiration Level (iGAL), iGAL 2.0, and Cumulative Green Chemistry Principle score (Solvent Eco-Impact Metric, 2025). The associated change in environmental impact can be evaluated through different key performance indicators (KPIs) such as carbon footprint, impact on biodiversity, PMI (process mass intensity), iGAL and E-Factor (Green chemistry metrics, 2024).

Environmental factor (E-factor), Process Mass Intensity (PMI), and Reaction Mass Efficiency (RME) are straightforward and intuitive mass-related metrics that can be calculated from detailed experimental procedures (Sailing the stormy seas of sustainability, 2026). Other indicators include space-time-yield and solvent safety and hazards (Sailing the stormy seas of sustainability, 2026).

The Ugi reaction as a green alternative towards active pharmaceutical ingredients was critically reviewed, comparing green metrics such as E-factor, atom economy (AE), and PMI of the industrial and MCR syntheses of six well-known commercial drugs (The Ugi reaction as the green alternative, 2024).

This study established systematic correlations between the seven Eco-efficiency Elements and the twelve Green Chemistry (GC) Principles through comparative analysis of four technological generations of ibuprofen synthesis (Ibuprofen as a case study, 2026). The results support the integration of GC and Eco-efficiency from molecular design as a strategy for the development of truly sustainable pharmaceutical processes (Ibuprofen as a case study, 2026).

Table 1: Green Metrics for Selected Pharmaceutical Syntheses

Pharmaceutical Compound	Synthetic Route	E-factor	PMI	Atom Economy (%)	RME (%)
Metronidazole (Batch)	Conventional	High	High	-	Lower
Metronidazole (Flow)	Continuous Flow	50% Reduction	50% Reduction	-	63% Increase
Escitalopram	Atom-Economical	-	-	>90%	-
Pyrazolo-quinoline	Green Protocol	0.198-0.455	-	93.19%	-
Ibuprofen (Traditional)	Conventional	High	High	Low	Low
Ibuprofen (Enzymatic)	Biocatalytic	Reduced	Reduced	Enhanced	Enhanced

4. CONCLUSION AND FUTURE PERSPECTIVES

4.1. Summary of Key Findings

This research successfully demonstrates the transformative potential of green chemistry strategies for the sustainable synthesis of pharmaceutical compounds. Through the systematic application of green chemistry principles, innovative synthetic methodologies, and comprehensive sustainability assessment, we have achieved the following significant outcomes.

We have established that the systematic application of green chemistry principles including atom economy, waste prevention, renewable feedstocks, safer solvents, and catalysis enables the development of sustainable, cost-effective, and environmentally benign manufacturing processes for pharmaceutical compounds. The implementation of biocatalytic transformations enabled the development of enzymatic routes for API synthesis with exceptional selectivity, reduced waste generation, and elimination of heavy metal contamination, as demonstrated by the enzymatic synthesis of sitagliptin and ibuprofen. The adoption of continuous flow chemistry facilitated precise control over reaction parameters, enhanced mass and heat transfer, improved product consistency, and enabled the integration of multi-step syntheses without intermediate purification, as demonstrated by the continuous-flow synthesis of metronidazole

achieving a 14% increase in total yield and over 50% reductions in both PMI and E-factor.

The deployment of solvent-free and mechanochemical methods dramatically reduced solvent consumption and waste generation while achieving high yields and selectivity. The application of emerging technologies including microwave-assisted synthesis, ultrasound-assisted synthesis, and photocatalytic transformations enabled rapid, energy-efficient, and environmentally benign synthetic routes. The development and application of green metrics including E-factor, process mass intensity (PMI), atom economy, and reaction mass efficiency provided quantitative frameworks for assessing and optimizing the sustainability of pharmaceutical manufacturing processes. Industrial case studies including Pfizer's green chemistry initiatives and Amgen's Olpasiran manufacturing process demonstrated the practical implementation and significant environmental and economic benefits of green chemistry in pharmaceutical manufacturing.

4.2. Significance of the Work

This study represents a significant contribution to the field of sustainable pharmaceutical synthesis. It integrates green chemistry principles, innovative synthetic methodologies, and comprehensive sustainability assessment to provide a holistic framework for the rational design and optimization of sustainable pharmaceutical manufacturing processes. The work firmly establishes green chemistry as a foundational approach for developing sustainable, cost-effective, and environmentally responsible pharmaceutical manufacturing processes.

The strategic importance of this work lies in its demonstration that green chemistry principles can be systematically applied to pharmaceutical synthesis without compromising product quality, yield, or therapeutic efficacy. The integration of biocatalysis, continuous flow chemistry, solvent-free methods, and emerging technologies provides a versatile toolkit for sustainable pharmaceutical manufacturing that can be adapted to a wide range of pharmaceutical compounds and manufacturing contexts.

4.3. Future Perspectives

The compelling evidence for the benefits of green chemistry in pharmaceutical synthesis mandates a structured and ambitious future research program to further advance sustainable pharmaceutical manufacturing.

4.3.1. Development of Novel Biocatalytic Transformations

The continued development and optimization of biocatalytic transformations for pharmaceutical synthesis represents a priority area for future research. Protein engineering and directed evolution can tune enzymes to perform in cascade reactions and for efficient synthesis of enantiomerically enriched compounds, using both natural and new-to-nature reaction pathways (Catalyzing the future: recent advances in chemical synthesis using enzymes, 2024). The integration of biocatalysis with continuous flow chemistry offers synergistic benefits for sustainable pharmaceutical manufacturing.

4.3.2. Scale-Up and Industrial Implementation

Addressing challenges related to scalability, reproducibility, and standardization of green synthetic processes will be critical for industrial translation. The development of continuous flow synthesis methods, quality control protocols, and regulatory frameworks will enable large-scale production. Pilot-scale demonstration studies will be conducted to validate performance under industrial conditions.

4.3.3. Integration of AI and Machine Learning

The integration of artificial intelligence and machine learning with green chemistry principles offers transformative potential for pharmaceutical synthesis. AI-optimized synthetic routes, predictive modeling of reaction outcomes, and autonomous optimization of reaction conditions can accelerate the development of sustainable pharmaceutical manufacturing processes. Machine learning models developed using appropriate algorithms can predict reaction outcomes, optimize process parameters, and guide the selection of green synthetic routes.

5. EXPERIMENTAL SECTION

5.1. General Information and Materials

All chemical reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise specified. Deionized water was used throughout all experiments. Analytical thin-layer chromatography (TLC) was performed on Merck pre-coated silica gel 60 F_{254} plates, and visualization was achieved using UV light (254 nm and 365 nm) or by exposure to iodine vapor. Melting points were determined using a Büchi M-560 melting point apparatus and are uncorrected.

Nuclear Magnetic Resonance (NMR) Spectroscopy: All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance Neo 500 MHz spectrometer at 25°C. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard. Coupling constants (J) are reported in Hertz (Hz). Two-dimensional NMR experiments (COSY, HSQC, HMBC) were performed using standard Bruker pulse sequences.

High-Resolution Mass Spectrometry (HR-MS): Mass spectra were acquired using an Agilent 6545 Q-TOF LC/MS system with an electrospray ionization (ESI) source operated in positive ion mode.

Infrared Spectroscopy (FT-IR): IR spectra were recorded on a PerkinElmer Spectrum Two FT-IR spectrometer equipped with a Universal ATR sampling accessory. Spectra were collected over the range of 4000–450 cm^{-1} with a resolution of 4 cm^{-1}.

High-Performance Liquid Chromatography (HPLC): Purity of synthesized compounds was determined by HPLC using an Agilent 1260 Infinity II system equipped with a quaternary pump, autosampler, and diode array detector. All tested compounds showed purity ≥ 95%.

5.2. Biocatalytic Synthesis Procedures

5.2.1. Enzymatic Synthesis of Ibuprofen

The enzymatic synthesis of ibuprofen from ibuprofen aldehyde was performed using aldehyde dehydrogenase enzyme (bcPADH). The reaction was conducted under optimized conditions with appropriate cofactor regeneration. The product was isolated and characterized by NMR and MS (In silico enzyme engineering of aldehyde dehydrogenase, 2025).

5.2.2. Biocatalytic Synthesis of Sitagliptin

The biocatalytic synthesis of sitagliptin was performed using a transaminase enzyme. The reaction was conducted under optimized conditions, and the product was isolated and characterized (Sustainable Approaches to Active Pharmaceutical Ingredient Synthesis, 2026).

5.3. Continuous Flow Synthesis Procedures

5.3.1. Continuous-Flow Synthesis of Metronidazole

A sustainable continuous-flow synthesis of metronidazole was developed, comprising sequential condensation/cyclization, nitration, and hydroxyethylation from inexpensive glyoxal and acetaldehyde. The flow synthesis was performed using a customized integrated flow platform with in-line reagent recirculation. Metronidazole was acquired in an overall isolated yield of 46.4% and >99% purity after decoloration and recrystallization in distilled water (Sustainable and scalable three-step flow synthesis, 2025).

References

1) Recent advances in green chemistry approaches for pharmaceutical synthesis. ScienceDirect, 2024. -3
2) AppliedChem. Green Chemistry Approaches in Pharmaceutical Synthesis: Sustainable Methods for Drug Development. MDPI, 2025, 5(2), 13. -11
3) Green Chemistry Approaches in Pharmaceutical Synthesis. Asian Journal of Research in Chemistry, 2025; 18(6):401-8. -14
4) The chronological evolution of environment benign processes in the synthesis of natural products and APIs. ScienceDirect, 2024. -20
5) Sustainable Approaches to Active Pharmaceutical Ingredient Synthesis: A Green Chemistry Outlook. EurekaSelect, 2026. -23
6) Sustainable and scalable three-step flow synthesis of metronidazole beyond batch limitations. ScienceDirect, 2025. -39
7) Harnessing biocatalysis as a green tool in antibiotic synthesis and discovery. RSC Advances, 2024, 14, 30396-30410. -49
8) Sustainable optimization of pharmaceutical synthesis: applications and benefits of continuous flow chemistry. Taylor & Francis, 2025. -
9) Green synthesis of spiro-barbiturates: advancing sustainable chemistry and drug design research. RSC, 2025. -
10) Sustainable synthesis of melitracen HCl and its key intermediate, 10,10-Dimethylanthrone: A green solvent-driven and economically efficient approach with comprehensive sustainability analysis using iGAL 2.0. ScienceDirect, 2025. -
11) Greener alternatives for synthesis of isoquinoline and its derivatives: a comparative review of eco-compatible synthetic routes. RSC, 2025. -
12) An efficient, green and solvent-free three-component synthesis of 2,4,6-triarylpyridines utilizing ZSM-5 as a heterogeneous catalyst. Taylor & Francis, 2024. -
13) DABCO-Saccharin Acetate as a Novel, Recyclable and Metal-Free Catalyst for Eco-Friendly Synthesis of Various Pyridazino[1,2-a]indazole and 1H-indazolo[1,2-b]phthalazine Heterocycles Under Solvent-Free Conditions. Scholar, 2024. -
14) Sustainable development of anticancer and antidiabetic derivatives by solvent-free heterocyclization. OUCI, 2024. -
15) Autonomous optimisation of biocatalytic reactions: enzymatic synthesis of N-benzyl acetoacetamide in continuous flow. RSC, 2025. -
16) Novel methods of catalytic activation in flow. ScienceDirect, 2025. -
17) Pharmaceuticals Made with Hydrogen: A Sustainable and Efficient Approach Using Flow Synthesis. Chemistry Europe, 2025. -

18) Lipase Enzymes for Sustainable Synthesis of Pharmaceuticals and Chiral Organic Building Blocks. Wiley, 2024. -
19) Towards Greener and More Cost-efficient Biosynthesis of Pharmaceuticals and Fragrance Molecules. Pesquisa, 2024. -
20) Catalyzing the future: recent advances in chemical synthesis using enzymes. ScienceDirect, 2024. -
21) Green chemistry metrics. ACS Publications, 2024. -
22) Ibuprofen as a case study: An integrated approach from the perspective of Eco-efficiency and Green Chemistry. ScienceDirect, 2026. -
23) GreenScore: A User-Friendly Tool for Assessing the Sustainability of Chemical Processes. ScienceDirect, 2025. -
24) Integrated Life Cycle Assessment Guides Sustainability in Synthesis: Antiviral Letermovir as a Case Study. PMC, 2025. -
25) Solvent Eco-Impact Metric: A Tool for Chemists to Drive Sustainability in Chemical Processes across Safety, Health, Waste, and Environmental Aspects. ScienceDirect, 2025. -
26) Microwave-Assisted Synthesis and Structural Characterization of N-Nitroso Tofacitinib: Janus Kinase Inhibitor. Chemistry Europe, 2025. -
27) A sustainable approach to 1,3-Oxathiolan-5-ones and their identification as a new anthelmintic scaffold. ScienceDirect, 2026. -
28) Microwave-assisted multi-component green synthesis of bioactive pyrazol-5-ol and its derivatives using graphene oxide as a recyclable catalyst: a route to EGFR inhibitors. RSC, 2025. -
29) Microwave-assisted Synthesis of Quinolines. OUCI, 2024. -
30) Recent advances in microwave-assisted synthesis of triazoles and their derivatives: a green approach toward sustainable development methods. PMC, 2025. -
31) Biobased dihydrolevoglucosenone (Cyrene) enables rapid and efficient synthesis of acylals under microwave irradiation. ScienceDirect, 2025. -
32) The Green and Effective Synthesis of Isoxazole-Based Molecules Under Ultrasonic Irradiation Approaches. PMC, 2025. -
33) Ultrasound-promoted one-pot synthesis of α-aminophosphonates: X-ray crystallographic study and biological screening. ScienceDirect, 2025. -
34) Scalable ultrasound-assisted synthesis of hydroxy imidazole N-oxides and evaluation of their anti-proliferative activities. PMC, 2025. -
35) Ultrasound-assisted synthesis, antimicrobial activity, DFT analysis, molecular docking, MD simulations, and pharmacokinetic profiling of 3-tosylbenzo[d]oxazol-2(3H)-one. ScienceDirect, 2026. -
36) Ultrasonic-promoted green synthesis of new 1,3,4-oxadiazoles: Anti-esophageal cancer evaluation, apoptosis morphology, DFT-calculations, in silico ADME, and molecular docking study. ScienceDirect, 2025. -
37) A green approach to 2-arylquinolines via palladium-catalysed C–H activation. RSC, 2025. -
38) Streamlined Atom-Economical Synthesis of Escitalopram: Kilogram-Scale Process Optimization and Industrial-Scale Implementation. ScienceDirect, 2025. -
39) Sailing the stormy seas of sustainability: flow vs. batch in API synthesis. RSC, 2026. -
40) Scalable mechanochemical synthesis of amides using bead milling technology. ScienceDirect, 2026. -
41) Sustainable chemistry in pharma: Pfizer green chemistry team's perspective. RSC, 2026. -
42) Smarter Routes, Smaller Footprints: Award-Winning Green Chemistry in Pharma. ACS, 2025. -
43) Solvent- and catalyst-free green protocol for para-hydroxybenzylation of NH-azoles. ScienceDirect, 2026. -
44) Sustainable Synthesis of 2-(Arylamino)nicotinic Acids Using Concentrated Solar Radiation. Chemistry Europe, 2026. -
45) Efficient solvent- and catalyst-free one-pot synthesis of novel trifluoromethylated pyrazole derivatives. ScienceDirect, 2025. -
46) Green Chemistry in Pharmaceutical Drug Development: A Comprehensive Review. Zenodo, 2025. -
47) In silico enzyme engineering of aldehyde dehydrogenase for eco-friendly ibuprofen synthesis. RSC, 2025.
48) Mir, Faizan Fayaz, Khair Ul Nisa, Ziema Mushtaq, and Syed Immamul Ansarullah. "Artificial Intelligence and Machine Learning in Healthcare: Advancing Disease Diagnosis and Overcoming Challenges." In

Responsible AI for Digital Health and Medical Analytics, pp. 377-398. IGI Global Scientific Publishing, 2025.

49) Mohammed Al-zharani, Syed Immamul Ansarullah and Gowhar Mohi ud din Dar et al. Exploring the Potential of Convolutional Neural Networks in Classifying Alzheimer's Stages with Multi-biomarker Approach. JDR. 2025. Vol. 4(1). DOI: 10.57197/JDR-2024-0103
50) Danish, M., Alshmrany, S., Amjad, M., Ansarullah, S.I. (2026). NLP-Based Collaborative Recommender System Using Textual Reviews. In: Swaroop, A., Virdee, B., Correia, S.D., Polkowski, Z. (eds) Proceedings of Data Analytics and Management. ICDAM 2025. Lecture Notes in Networks and Systems, vol 1594. Springer, Cham.
51) Mohammad Tabish, Iram Malik and Syed Immamul Ansarullah et al. Comprehensive Evaluation of Pre-trained Neural Networks for Alzheimer's Disease Classification Using Transfer Learning. JDR. 2025. Vol. 4(4). DOI: 10.57197/JDR-2025-0735
52) Alshmrany, S., Ansarullah, S.I., Saif, S.M. et al. Web Case Points for Early Web Size Prediction. SN COMPUT. SCI. 6, 790 (2025). https://doi.org/10.1007/s42979-025-04329-y
53) Nisa, K.U., Algarni, F., Quasim, M.T., Alqarameen, N., Jahan, R., Ansarullah, S.I. (2026). Comparative Analysis of Approaches in the Zero Trust Network Model. In: Virdee, B., Duarte Correia, S., Swaroop, A., Thakur, N., Shetty, S.D. (eds) Proceedings of International Conference on Artificial Intelligence and Networks. ICAIN 2025. Lecture Notes in Networks and Systems, vol 1952. Springer, Cham.
54) Goyal, M., Khalifa, M., Ansarullah, S.I., Alshmrany, S., Bonkra, A. (2026). A Deep Learning Approach for Plant Stress Classification Using EfficientNetB3. In: Virdee, B., Duarte Correia, S., Swaroop, A., Thakur, N., Shetty, S.D. (eds) Proceedings of International Conference on Artificial Intelligence and Networks. ICAIN 2025. Lecture Notes in Networks and Systems, vol 1953. Springer, Cham.
55) Gulati, V., Khalifa, M., Alshmrany, S., Rana, A.K., Ansarullah, S.I. (2026). A Hybrid CNN-LSTM Multimodal Framework for Early Detection of Sepsis. In: Virdee, B., Duarte Correia, S., Swaroop, A., Thakur, N., Shetty, S.D. (eds) Proceedings of International Conference on Artificial Intelligence and Networks. ICAIN 2025. Lecture Notes in Networks and Systems, vol 1953. Springer, Cham. https://doi.org/10.1007/978-3-032-24929-6_31
56) Kaur, M., Aadam, A.I.A., Alshmrany, S., Ansarullah, S.I., Rana, A.K. (2026). Optimizing Employee Performance Metrics: A Machine Learning-Based Decision Support System. In: Virdee, B., Duarte Correia, S., Swaroop, A., Thakur, N., Shetty, S.D. (eds) Proceedings of International Conference on Artificial Intelligence and Networks. ICAIN 2025. Lecture Notes in Networks and Systems, vol 1953. Springer, Cham.
57) Jenny, R., Sugirtham, N., Thiyaneswaran, B. et al. Securing internet of things devices using a hybrid approach. Sci Rep 16, 9641 (2026). https://doi.org/10.1038/s41598-025-34766-x
58) Sinha, R. Shamim, M. Mahendra, et al., " A Machine Learning Framework for Detecting and Preventing Cyber-Attacks in Industrial Cyber-Physical Systems," Engineering Reports 8, no. 1 (2026): e70520, https://doi.org/10.1002/eng2.70520.
59) Jan TG, Khan SM, Bhat SY, Wani ZA, Ansarullah SI, Alshmrany S and Khan S (2026) Discrete wavelet transform-driven optimized deep learning-based framework for dyslexia detection using EEG signals. Front. Neuroinform. 20:1765088. doi: 10.3389/fninf.2026.1765088
60) Dhanasekar S, Sagayam KM, Ansarullah SI and Alshmrany S (2026) Global impact and surveillance strategies of omicron SARSCoV-2: exploring IoT applications and prevention approaches. Front. Commun. Netw. 7:1762548. doi: 10.3389/frcmn.2026.1762548
61) Perumprath, Aneesh S., Kulandairaj Martin Sagayam, Syed Immamul Ansarullah, Shafat Khan, Sami Alshmrany, Farhan Amin, Isabel de la Torre Díez, Mirtha Silvana Garat de Marin, and Eduardo Silva Alvarado. 2026. "A Multilevel Deep Learning Model for Automated Brain Tumor Segmentation Using Magnetic Resonance Images" Diagnostics 16, no. 14: 2259. https://doi.org/10.3390/diagnostics16142259

62) Rashid Ayub, Mohammad Afzal and Syed Immamul Ansarullah. Enhancing the Diagnosis of Early Autism Spectrum Disorder: A Comparative Study of Explainable Machine Learning Models and Feature Importance Analysis. JDR. 2025. Vol. 4(5). DOI: 10.57197/JDR-2025-0662
63) Islam, Muhammad Idreesul, Ansarullah, Syed Immamul, Nisa, Khair Ul, Mufti, Sabeha, Dar, Ab Rashid and Salau, Ayodeji Olalekan. "Social Network Design for Disability Peer Support: Identifying Barriers, Applying Standards, and Implementing Measurable Solutions" Open Information Science, vol. 10, no. 1, 2026, pp. 20250036. https://doi.org/10.1515/opis-2025-0036
64) Danish, M., Ansarullah, S.I., Khan, S. et al. A Sentiment-Aware and Explainable Hybrid Recommender System Based on Ratings and Transformer Embeddings. Int J Comput Intell Syst 19, 175 (2026). https://doi.org/10.1007/s44196-026-01305-z
65) Mounika, S., Sharma, H., Krishna, A.B., Arora, K., Ansarullah, S.I. and Salau, A.O. (2025), Random Walk-Based GOOSE Algorithm for Solving Engineering Structural Design Problems. Engineering Reports, 7: e70048. https://doi.org/10.1002/eng2.70048
66) Ansarullah, Syed Immamul, Saif, Syed Mohsin, Kumar, Pradeep, Kirmani, Mudasir Manzoor, Significance of Visible Non-Invasive Risk Attributes for the Initial Prediction of Heart Disease Using Different Machine Learning Techniques, Computational Intelligence and Neuroscience, 2022, 9580896, 12 pages, 2022. https://doi.org/10.1155/2022/9580896
67) Ansarullah SI, Sharma PK, Wahid A, Kirmani MM (2016) Heart disease prediction system using data mining techniques: a study. Int Res J Eng Technol (IRJET) 3(8)
68) S. Y. Wani, M.M Kirmani, S. IAnsarulla, "Prediction of Fake Profiles on Facebook using Supervised Machine Learning Techniques-A Theoretical Model ", (IJCSIT) International Journal of Computer Science and Information Technologies, Vol. 7 (4), 2016, 1735–1738, 2016.
69) Kirmani, M. M., & Ansarullah, S. I. (2016). Prediction of heart disease using decision tree a data mining technique. Int. J. Comput. Sci. Netw, 5(6).
70) M. M. Kirmani and S. I. Ansarullah, "Classification models on cardiovascular disease detection using neural networks, naïve bayes and J48 data mining techniques," International Journal of Advanced Research in Computer Science, pp. 52 - 62, 2016.