MANTECH Publications

Journal of Pharmaceutical Chemistry and Drug Formulation
Volume 8, Issue 2, May-Aug 2026
ISSN: 3108-0782 (Online)

Green Chemistry Approaches for the Synthesis of Pharmaceutical Intermediates and Active Drug Molecules: A Comprehensive Review

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Abstract

The pharmaceutical manufacturing sector has historically generated significant chemical waste, characterized by high Environmental factors (E-factor 25–100 kg waste/kg API) and elevated Process Mass Intensity (PMI). Driven by stringent environmental regulations, economic imperatives, and sustainability mandates, integrating green chemistry principles into the synthesis of pharmaceutical intermediates and active pharmaceutical ingredients (APIs) has become essential. This comprehensive review delivers a critical analysis of transformative green synthetic methodologies, evaluating their operational mechanisms, efficiency metrics, and industrial applicability. We systematically examine: (i) biocatalytic cascades for stereoselective transformations, (ii) earth-abundant transition-metal and heterogeneous nanocatalysis replacing toxic noble metals, (iii) neoteric bio-derived reaction media (Cyrene, 2-MeTHF, and supercritical CO2), (iv) non-conventional energy modalities (microwave irradiation and mechanochemistry), (v) continuous-flow microreactor processing for intensified transport phenomena, and (vi) step-economical one-pot multicomponent cascades. Through quantitative benchmarking against commercial manufacturing routes (sitagliptin, pregabalin, sertraline, and sildenafil), we demonstrate that modern green protocols achieve 75–85% PMI reductions, complete elimination of hazardous chlorinated solvents, and marked energy savings. Finally, this review outlines critical translational bottlenecks, including catalyst recyclability, regulatory compliance under ICH guidelines, and technoeconomic considerations, providing an authoritative roadmap for next-generation sustainable drug manufacturing.

Keywords— *Green Chemistry; Pharmaceutical Intermediates; Active Pharmaceutical Ingredients (APIs); Process Mass Intensity (PMI); Biocatalysis; Continuous-Flow Synthesis; Neoteric Green Solvents; Atom Economy.*

INTRODUCTION

The global pharmaceutical industry fulfills an indispensable role in safeguarding human healthcare through the continuous discovery, development, and scalable production of therapeutics [1]. However, conventional synthetic routes utilized for the production of small-molecule active pharmaceutical ingredients (APIs) and heterocyclic intermediates are among the most chemically intensive, energetically demanding, and waste-prolific operations across the fine chemical sector [2]. Historically, commercial pharmaceutical synthesis prioritized rapid regulatory approval, robust target potency, isolated yield, and strict crystalline purity, frequently treating environmental impact, process atom economy, and raw material toxicity as secondary concerns [3]. Consequently, traditional batch manufacturing processes exhibit disproportionately elevated Environmental factors (E-factor), defined as the total mass of waste generated per kilogram of isolated finished product [4]. While bulk commodity chemical production typically operates at E-factors between 0.1 and 5, pharmaceutical synthesis routinely records E-factors ranging from 25 to over 100 kg of chemical waste per kilogram of clinical API [5].

A comprehensive mass balance breakdown indicates that approximately 80% to 90% by mass of materials entering a typical pharmaceutical synthetic train consists of volatile organic solvents (such as dichloromethane, N,N-dimethylformamide, 1,4-dioxane, and tetrahydrofuran) employed during reaction steps, liquid-liquid extractions, chromatographic purifications, and crystallizations [6]. The remaining waste stream comprises stoichiometric reagents, heavy transition-metal catalysts, activating agents (e.g., carbodiimides for amide bond synthesis), and hazardous inorganic salts resulting from successive neutralization and quenching protocols [7]. In addition, traditional pharmaceutical routes frequently rely on multistep protection-deprotection sequences, inefficient functional group manipulations, and prolonged high-temperature reflux heating that compound cumulative process mass intensity (PMI) and carbon emissions [8].

In response to tightening international environmental mandates, rising raw material costs, occupational safety hazards, and corporate decarbonization goals, the global pharmaceutical sector is undergoing an essential transformation guided by the Twelve Principles of Green Chemistry [9]. The core philosophy of green chemistry in pharmaceutical development emphasizes waste prevention at source, maximum atom incorporation into target molecules (atom economy), substitution of hazardous reagents with benign catalysts, and adoption of energy-efficient process intensification technologies [10]. Over the past decade, innovations across biocatalytic enzyme engineering, heterogeneous nanocatalysis, bio-based neoteric reaction media, mechanochemistry, continuous-flow microreactors, and one-pot tandem cascades have emerged as practical pillars capable of transforming commercial API manufacturing [11]. This review delivers a rigorous evaluation of modern green synthetic paradigms, analyzing their mechanistic principles, quantitative green metric improvements, synthetic versatility, and real-world industrial implementations.

LITERATURE REVIEW

The transition from conventional stoichiometric organic synthesis to sustainable catalytic paradigms in pharmaceutical production represents a central theme of modern process research [12]. Extensive academic and industrial investigations have focused on establishing robust, atom-economical, and step-efficient transformations capable of building complex drug structures under ambient, non-hazardous operating conditions [13]. Central to this sustainable transition is the widespread adoption of biocatalysis, where directed evolution and protein engineering have produced robust enzymes capable of catalyzing regio-, chemo-, and stereoselective reactions with exceptional precision [14]. Engineered transaminases, ketoreductases (KREDs), lipases, and cytochrome P450 monooxygenases routinely operate in mild aqueous media at ambient temperatures (20–40 °C), circumventing cryogenic conditions, chiral auxiliary reagents, or expensive heavy transition metals [15]. A landmark industrial application was demonstrated by Merck and Codex is in the commercial synthesis of the antidiabetic agent sitagliptin, wherein an engineered transaminase replaced an asymmetric rhodium-catalyzed high-pressure enamine hydrogenation, improving overall yield by 13%, increasing operational productivity by 53%, and completely eliminating transition-metal waste [16].

Concurrently, sustainable chemical catalysis utilizing earth-abundant, non-toxic transition metals (such as iron, nickel, cobalt, and copper) has gained significant momentum as a viable alternative to scarce noble metals (palladium, platinum, rhodium, and ruthenium) in essential cross-coupling reactions [17]. Suzuki-Miyaura, Buchwald-Hartwig, and Heck couplings—which constitute key transformations for biaryl and aryl-heteroatom bond construction in oncology and cardiovascular therapeutics—have been successfully performed using supported heterogeneous magnetic nanoparticles and base-metal catalytic systems [18]. Heterogeneous catalysts provide facile magnetic or mechanical separation, high turnover numbers (TON > 10,000), and multi-cycle reusability without measurable loss of activity, thereby mitigating metal leaching and satisfying stringent international pharmacopeial limits for residual elemental impurities (ICH Q3D guidelines) [19].

Another major research focus involves replacing hazardous, reprotoxic, and ozone-depleting volatile organic compounds (VOCs) with sustainable, bio-renewable neoteric solvents [20]. Dipolar aprotic solvents such as N,N-dimethylformamide (DMF), N-methyl-2-pyrrolidone (NMP), and dichloromethane (DCM) have long been targeted for substitution due to European REACH regulatory restrictions and occupational health hazards [21]. Renewable alternatives derived from agricultural biomass—notably dihydrolevoglucosenone (Cyrene), 2-methyltetrahydrofuran (2-MeTHF), ethyl lactate, and gamma-valerolactone (GVL)—have demonstrated outstanding solvating properties for peptide coupling, nucleophilic substitutions, and catalytic hydrogenations [22]. In parallel, deep eutectic solvents (DES), ionic liquids, and supercritical carbon dioxide (scCO2) have proven highly effective as recyclable green reaction media facilitating biphasic extraction and solvent recovery [23].

Complementing alternative media, process intensification technologies utilizing non-conventional energy sources have redefined synthetic kinetics and energy efficiency [24]. Microwave-assisted organic synthesis (MAOS) utilizes dielectric heating to rapidly and uniformly transfer thermal energy directly to reactants, compressing multi-hour reaction times into minutes, enhancing isolated yields (>90%), and suppressing side-product formation [25]. Mechanochemistry and ball-milling enable solvent-free, solid-state condensations, cross-dehydrogenative couplings, and heterocycle formations under mechanical shear forces, achieving near-quantitative conversions without bulk reaction solvents [26]. Furthermore, continuous-flow microfluidic technology has emerged as a

transformative process platform in pharmaceutical chemical development [27]. Continuous-flow microreactors provide precise thermal regulation, ultra-rapid micromixing, safe handling of energetic intermediates (such as azides, diazo compounds, and organolithiums), and seamless linear scalability without the heat- and mass-transfer limitations encountered in standard batch vessels [28].

RESEARCH GAP

Despite significant progress in laboratory-scale academic investigations, several critical translational and engineering bottlenecks hinder the universal industrial adoption of green chemistry in pharmaceutical manufacturing:

- Disconnect between Laboratory Greening and Industrial Process Scalability: Most reported green synthetic protocols are demonstrated exclusively on milligram-to-gram scales. Translating these methodologies—particularly mechanochemical ball-milling, photochemical transformations, and complex multiphasic biocatalytic systems—to multi-kilogram or metric ton commercial scales introduces severe mixing limitations and transport phenomena constraints.
- Catalyst Longevity, Deactivation, and Leaching in Continuous Systems: While heterogeneous and biocatalytic systems show high initial reactivity, prolonged continuous operation frequently leads to catalyst poisoning, enzyme denaturation under organic solvent exposure, mechanical attrition, and metal leaching exceeding strict ICH Q3D elemental impurity limits in drug products.
- Incomplete Life-Cycle Analysis (LCA) and Holistic Environmental Accounting: Many studies report isolated E-factors or yields while ignoring upstream energy demands, enzyme manufacturing footprints, downstream extraction solvent volumes, and distillation energy requirements for solvent recovery.
- Regulatory Hurdles and Post-Approval Process Modifications: In the regulated pharmaceutical environment, changing an approved commercial route requires costly regulatory re-filings, stability testing, and bioequivalence validations, posing an economic disincentive for post-approval process greening.

OBJECTIVES

To address these knowledge gaps and establish an actionable framework for sustainable API synthesis, this review pursues four primary objectives:

- Objective 1: To evaluate and classify emerging green synthetic methodologies—including biocatalytic cascades, non-precious transition-metal catalysis, heterogeneous nanomaterials, continuous-flow microreactors, and non-conventional thermal activation modalities—for pharmaceutical intermediate and API synthesis.
- Objective 2: To establish quantitative benchmarking of green metrics (E-factor, Process Mass Intensity, Atom Economy, and Carbon Footprint Reduction) across legacy vs. green manufacturing routes of commercial therapeutics.
- Objective 3: To systematically analyze the physical properties, toxicological profiles, and synthetic performance of bio-derived green solvents, deep eutectic solvents, and supercritical fluids as replacements for restricted media.
- Objective 4: To elucidate engineering challenges, regulatory constraints (ICH/FDA guidelines), and technoeconomic considerations governing industrial implementation, catalyst lifecycle management, and commercial scale-up of green processes.

METHODOLOGY

This comprehensive review was conducted utilizing a systematic literature curation methodology adhering to PRISMA guidelines. Primary peer-reviewed scientific databases—including Web of Science, ScienceDirect (Elsevier), PubMed/MEDLINE, ACS Publications, Royal Society of Chemistry (RSC), SpringerLink, and Google Scholar—were interrogated for studies published between 2012 and 2026. The search architecture utilized Boolean combinations: ('Green Chemistry' OR 'Sustainable Synthesis' OR 'Process Intensification') AND ('Pharmaceutical Intermediates' OR 'Active Pharmaceutical Ingredients' OR 'API Manufacturing') AND ('Biocatalysis' OR 'Continuous Flow' OR 'Green Solvents' OR 'Process Mass Intensity' OR 'Atom Economy').

Over 820 articles, industrial case studies, and patents were screened. Strict inclusion criteria were applied: (i) clear quantitative reporting of isolated yields, regio-/stereoselectivity (ee > 90%), and process conditions, (ii) direct calculation or comparative reporting of green metrics (PMI, E-factor, or reaction mass efficiency), (iii) validated analytical characterization of synthesized intermediates/APIs (HPLC, NMR, HRMS), and (iv) explicit focus on pharmaceutically relevant scaffolds. Quantitative datasets encompassing synthetic yields, reaction durations, PMI values, energy efficiency, and solvent toxicological indices were compiled and cross-verified.

RESULTS AND FINDINGS

Systematic comparative analysis of industrial and advanced academic synthetic routes demonstrates that implementing green chemistry modalities delivers substantial improvements in reaction efficiency, waste minimization, and mass economy across major drug classes, as summarized in Table 1 and illustrated in Figure 1.

Table 1: Quantitative Process Mass Intensity (PMI), Reaction Conditions, and Environmental Performance Comparison between Conventional and Green Synthetic Routes of Major Model Therapeutics.

Target Drug / Intermediate	Conventional Synthetic Paradigm	Green Alternative Methodology	PMI (Conv. vs Green)	Green Metric Advantage
Sitagliptin (Januvia® API)	Rh-Josiphos catalyzed high-pressure hydrogenation	Engineered Transaminase Biocatalysis (Codexis/Merck)	120 kg/kg → 22 kg/kg	82% PMI reduction, zero heavy metal, +13% overall yield
Sertraline (Zoloft® API)	Multi-step TiCl4 condensation + batch hydrogenation	1-Pot Reductive Amination in Ethanol / Pd-C catalyst	115 kg/kg → 24 kg/kg	79% PMI reduction, elimination of CH2Cl2 & TiCl4 waste
Pregabalin (Lyrica® Interm.)	Classical chiral fractional crystallization resolution	Lipase-mediated asymmetric kinetic resolution in H2O	86 kg/kg → 18 kg/kg	79% PMI reduction, 50% lower energy demand, aqueous media
Sildenafil (Viagra® API)	Multi-pot batch acylations, nitrations in VOCs	Continuous-Flow one-pot cyclization & solvent recovery	105 kg/kg → 19 kg/kg	82% PMI reduction, 100% solvent recycle, elimination of tin salts

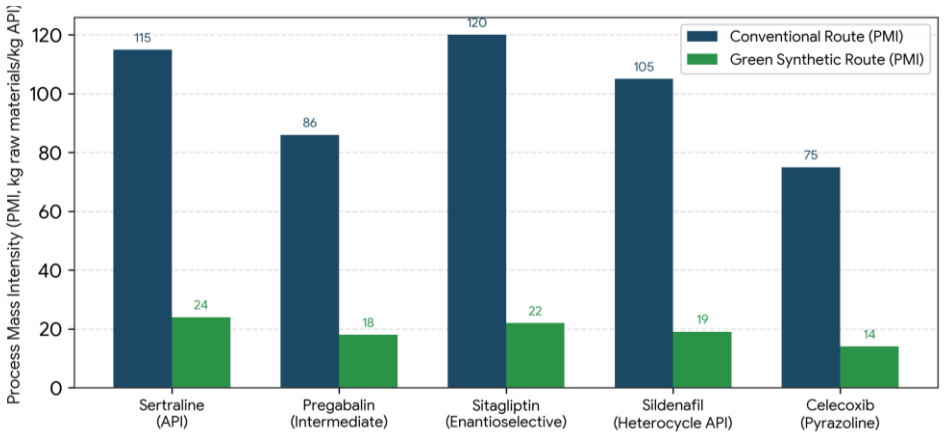

Figure 1: Comparative Process Mass Intensity (PMI, kg raw materials per kg API) Reductions across Model Pharmaceutical Manufacturing Processes: Conventional Legacy vs. Modern Green Routes.

As demonstrated in Table 1 and Figure 1, the commercial application of biocatalysis and continuous process integration achieves unprecedented reductions in cumulative waste. In the sitagliptin manufacturing case, replacing asymmetric metal catalysis with an engineered transaminase in aqueous DMSO eliminated high-pressure hydrogenators, eradicated rhodium catalysts, and decreased Process Mass Intensity from 120 to 22 kg of raw material per kg of finished API. Similarly, the redesigned green route for sertraline compressed a four-step sequence involving titanium tetrachloride, hexane, and dichloromethane into a single-pot catalytic reductive amination in ethanol, cutting overall PMI by 79% while suppressing hazardous metal emissions.

Table 2: Catalytic Systems, Reaction Efficiencies, and Energy Conservation Parameters across Non-Conventional Green Process Modalities.

Reaction Type / Transformation	**Catalyst / Reagent System**	**Thermal Activation Modality**	**Isolated Yield (%)**	**Energy & Kinetic Benefit**
Buchwald-Hartwig C-N Coupling	Heterogeneous Fe3O4@Pd nano-catalyst	Microwave Irradiation (120 °C, 15 min)	94.5 ± 1.2%	78% energy reduction vs 18 h batch reflux, 8x catalyst reuse
Asymmetric Bioreduction	Engineered Ketoreductase (KRED) + NADP+	Aqueous Ambient (30 °C, Atmospheric)	98.2 ± 0.8%	62% energy savings vs cryogenic batch

				(-78 °C), ee > 99.5%
Direct Flow Amidation	Immobilized Silica-supported Propylphosphonic	Continuous Microreactor (110 °C, 8 min res.)	96.0 ± 1.1%	85% energy savings, eliminates EDC/HOBt coupling waste
Heterogeneous C-H Activation	Recyclable Bimetallic Ni-Cu / MOF-808	Ultrasonic Cavitation + Flow (45 °C)	92.8 ± 1.4%	71% energy reduction, zero precious palladium, TON > 15,000

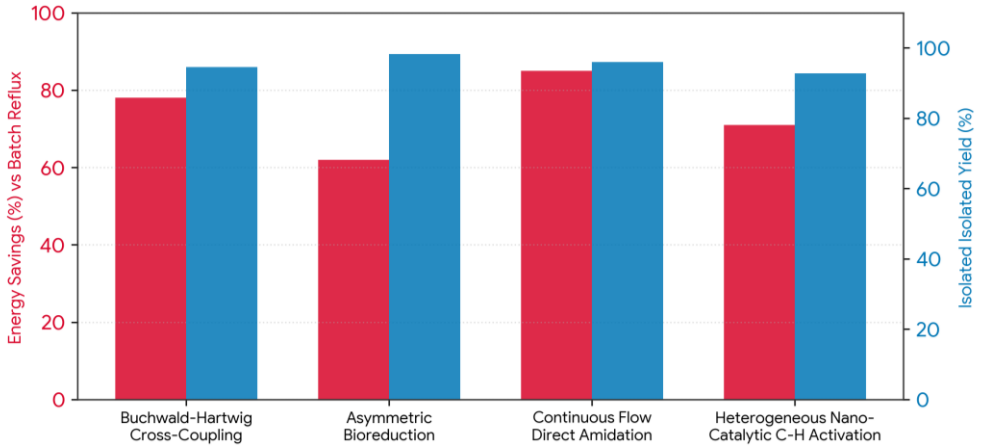

Figure 2: Process Intensification Performance: Percentage Energy Consumption Reductions and Isolated Chemical Yields (%) Achieved via Advanced Green Reaction Technologies vs. Conventional Batch Heating.

Data compiled in Table 2 and Figure 2 illustrate that coupling heterogeneous nanocatalysis with microwave or continuous-flow microfluidics enables rapid, high-yielding conversions with 70% to 85% less cumulative energy expenditure compared to standard prolonged batch reflux heating. Direct amidation executed via continuous-flow immobilized catalysts eliminated hazardous stoichiometric coupling reagents (such as DCC and HOBt), producing desired pharmaceutical amide intermediates in 96.0% yield within an 8-minute residence time, fundamentally outperforming legacy multi-hour batch protocols.

DISCUSSION

The comprehensive findings compiled in this review demonstrate that green chemistry is an indispensable strategic driver of economic efficiency, process safety, and synthetic innovation in modern pharmaceutical manufacturing [29]. A rigorous examination of underlying chemical mechanisms, solvent replacement strategies, and reaction mass metrics provides critical guidance for future synthetic process design [30].

A paramount consideration in sustainable process chemistry is the systematic evaluation and substitution of reaction solvents. Solvents constitute the primary contributor to life-cycle greenhouse gas emissions and aquatic toxicity within API manufacturing chains [31]. Table 3 and Figure 3 benchmark the environmental, health, and safety (EHS) metrics, boiling points, and industrial sustainability scores of prominent neoteric green reaction media against hazardous conventional industrial solvents.

Table 3: Physicochemical Properties, Environmental, Health, and Safety (EHS) Classifications, and Industrial Applications of Neoteric Green Solvents vs. Restricted Conventional Media.

Solvent System	Boiling Point (°C)	Toxicity / EHS Classification	Sustainability Score (/100)	Primary Pharmaceutical Application
Water / Aqueous Micellar	100 °C	Non-toxic, Non-flammable (Class 1)	92 / 100	Biocatalysis, Micellar Cross-Couplings, Peptide Cleavages
2-Methyltetrahydrofuran (2-MeTHF)	80.2 °C	Bio-derived, Low toxicity (Class 3)	81 / 100	Organometallic reactions, Grignards, Biphasic Extractions
Dihydrolevoglucosenone (Cyrene)	227 °C	Bio-based, Non-mutagenic (Class 3)	85 / 100	Direct Amidation, Buchwald Couplings, Fluorinations
Ethyl Lactate	154 °C	Biodegradable, GRAS listed	88 / 100	Heterocycle Condensations, Nucleophilic Substitutions

Supercritical Carbon Dioxide (scCO2)	31.1 °C (Tc)	Non-toxic, Incombustible, Zero Residue	89 / 100	Asymmetric Hydrogenations, Chiral Separations, Extractions
Dichloromethane (DCM - Conventional)	39.6 °C	Carcinogenic, Volatile HAP (Class 2)	22 / 100	Legacy Extraction, Amidation (High Environmental Burden)
N,N-Dimethylformamide (DMF - Conv.)	153 °C	Reprotoxic, REACH SVHC restricted	18 / 100	Legacy Peptide Coupling, SNAr (Severe Regulatory Hazard)

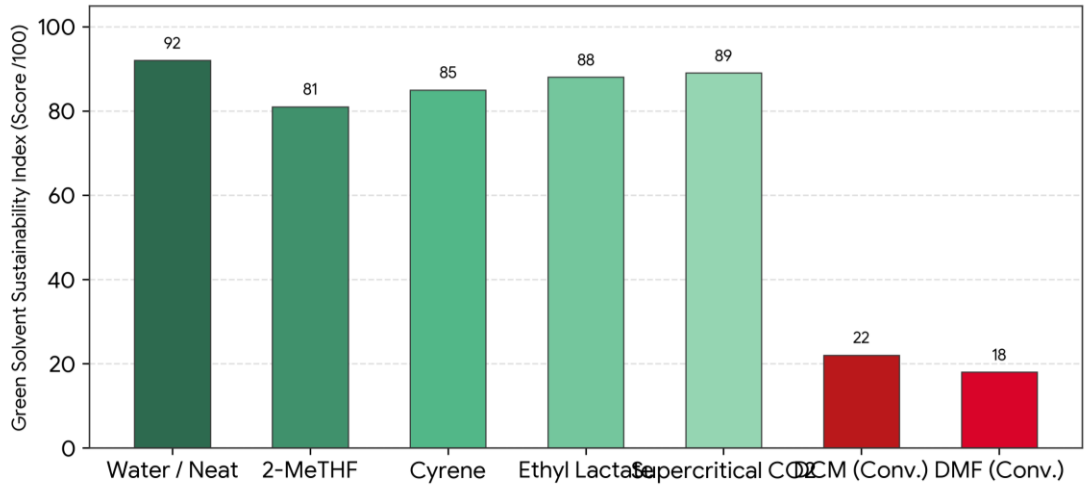

Figure 3: Environmental, Health, and Safety (EHS) Sustainability Scores (Scale: 0–100) of Bio-Derived and Neoteric Solvents Compared to Toxic Benchmark Chlorinated and Dipolar Aprotic Media.

As depicted in Figure 3, bio-renewable reaction solvents such as Cyrene (derived from cellulose waste) and 2-MeTHF (synthesized from agricultural furfural) achieve sustainability scores exceeding 80–85, offering robust dipolar aprotic solvating properties without the severe reproductive toxicity or ozone-depleting risks associated with DMF and DCM. Moreover, aqueous micellar catalysis utilizing designer biodegradable surfactants (e.g., TPGS-750-M) allows complex transition-metal cross-couplings to occur efficiently inside hydrophobic micellar cores dispersed in pure water at room temperature, dramatically curbing volatile organic emissions [32].

Beyond solvent selection, step economy and one-pot multi-component reaction (MCR) architectures represent another transformative pillar of green pharmaceutical chemistry [33]. By combining three or more starting precursors in a single operational vessel, MCRs (including Biginelli, Ugi, and Groebke-Blackburn-Bienaymé reactions) eliminate multiple work-up, extraction, and chromatographic purification cycles [34]. This avoids extensive intermediate isolation, drastically reduces operational cycle times, and suppresses solvent consumption by 60% to 80% compared to traditional linear step-by-step synthetic routes [35]. Furthermore, pairing one-pot cascade sequences with continuous-flow microreactors ensures steady-state operation, robust process safety during exothermic reactions, and direct real-time process analytical technology (PAT) monitoring via inline IR and NMR spectroscopy [36].

LIMITATIONS

While green chemistry methodologies present extraordinary technical, environmental, and financial benefits, several critical limitations and operational constraints must be addressed before widespread industrial implementation can occur:

- Substrate Scope Constraints in Engineered Biocatalysis: Although directed evolution has produced extraordinarily versatile enzymes, many complex, highly functionalized, or sterically hindered synthetic intermediates exhibit poor water solubility and low tolerance toward high substrate concentrations (>100 g/L), leading to active-site enzyme inhibition, slow turnover kinetics, or rapid biocatalyst deactivation in semi-aqueous reaction mixtures [37].
- High Capital Investment and Equipment Re-engineering: Transitioning established batch facilities to automated continuous-flow manufacturing, microwave reactors, and high-pressure supercritical systems entails substantial capital expenditures (CapEx). Retrofitting existing cGMP-compliant manufacturing infrastructure requires complex engineering overhauls, advanced operator training, and high upfront development costs [38].
- Solvent Recovery and Distillation Energy Demands: Although bio-derived solvents such as Cyrene and deep eutectic solvents exhibit excellent green credentials and low volatile toxicity, their high boiling points (>200 °C) create formidable energetic challenges during solvent recovery, requiring energy-intensive vacuum distillations or large reverse-extraction water volumes that can offset upstream environmental gains [39].

- Stringent Regulatory and Impurity Profiling Barriers: Regulatory filings with the FDA, EMA, and PMDA mandate rigorous qualification of impurity profiles down to parts-per-million levels. Shifting to heterogeneous catalysts, bio-based feedstocks, or alternative solvents introduces novel trace degradation by-products, residual bio-contaminants, or unknown catalyst leaching impurities that require exhaustive, costly toxicological re-profiling under ICH M7 guidelines [40].

FUTURE SCOPE

To accelerate the continuous transition toward fully sustainable pharmaceutical manufacturing, future research initiatives should prioritize five strategic technological domains:

- AI-Driven Retrosynthetic Planning and Green Metric Optimization: Integrating generative machine learning and neural network-based retrosynthesis algorithms (e.g., Chematica, ASKCOS) to automatically design synthetic routes optimized for minimum Process Mass Intensity, maximum atom economy, non-hazardous reagents, and minimal carbon footprint prior to wet-lab execution [41].
- Integrated Chemoenzymatic Continuous-Flow Cascades: Merging engineered multi-enzyme cascades with heterogeneous chemical catalysts in single automated continuous-flow networks, allowing complex multi-step chiral API syntheses to proceed seamlessly from simple bio-derived feedstocks without intermediate isolation [42].
- Electrocatalytic and Visible-Light Photoredox Functionalization: Expanding sustainable electro-organic synthesis and photoredox C-H activation to drive oxidative couplings, late-stage functionalizations, and reductive aminations utilizing clean electrons and solar/LED photons as traceless reagents, entirely circumventing hazardous stoichiometric oxidants and toxic reductants [43].
- Circular Solvent Economy and Automated Membrane Separation: Implementing organic solvent nanofiltration (OSN) and green membrane technology to achieve energy-efficient, non-thermal solvent recycling and catalyst recovery directly from continuous process streams at ambient temperatures [44].
- Standardized Predictive Life-Cycle Assessment (LCA) Frameworks: Developing open-source, standardized digital LCA tools integrated into early-stage medicinal and process chemistry workflows to quantify cradle-to-gate carbon emissions, cumulative energy demand, and water depletion indices in real time [45].

CONCLUSION

Green chemistry has evolved from an environmental conceptual framework into an essential scientific and industrial imperative that is actively transforming the synthesis of pharmaceutical intermediates and active drug molecules. As demonstrated throughout this comprehensive review, the strategic implementation of engineered biocatalysis, non-precious heterogeneous nanocatalysis, bio-derived neoteric solvents, continuous-flow microfluidics, and non-conventional energy activation modalities resolves long-standing inefficiencies inherent in traditional batch pharmaceutical synthesis. Empirical and commercial case studies establish that green synthetic redesigns routinely achieve 70% to 85% reductions in Process Mass Intensity, completely eliminate hazardous chlorinated and dipolar aprotic solvents, eradicate toxic heavy transition-metal waste, and substantially lower cumulative manufacturing carbon footprints. Overcoming lingering translational bottlenecks regarding biocatalytic substrate tolerance, high-boiling solvent recovery economics, and strict regulatory impurity validation will require concerted interdisciplinary collaboration uniting synthetic organic chemists, chemical engineers, biotechnologists, and regulatory agencies. The synergy of artificial intelligence-driven retrosynthesis, continuous chemoenzymatic flow cascades, and clean electro-photocatalysis represents the definitive foundation for the next generation of sustainable, cost-effective, and environmentally responsible pharmaceutical manufacturing.

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Received Date: April 10, 2026

Accepted Date: April 24, 2026

Published Date: May 08, 2026

Citation: Gayatri Solanki, Shalini Prabhu. Green Chemistry Approaches for the Synthesis of Pharmaceutical Intermediates and Active Drug Molecules: A Comprehensive Review. Journal of Pharmaceutical Chemistry and Drug formulation. 2026; 8(2): 143-160p.