

# Green and Sustainable Synthesis of Bioactive Heterocycles for Antimicrobial Applications: Recent Progress and Future Perspectives

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## Abstract

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## 1. Introduction

Heterocycles are cyclic compounds containing at least one heteroatom and are ubiquitous in medicinal chemistry. Pyridine, pyrimidine, imidazole, pyrazole, triazole, oxazole, thiazole, quinoline, benzimidazole, and related fused systems occur in numerous biologically active molecules because their heteroatoms and aromatic frameworks can establish favorable interactions with enzymes, receptors, nucleic acids, membranes, and metal-containing biological sites [1]–[3]. Their substitutional flexibility also permits systematic structure–activity relationship (SAR) optimization.

The emergence of antimicrobial resistance has intensified the requirement for new antimicrobial chemotypes. The World Health Organization has identified priority bacterial pathogens for which new preventive and therapeutic strategies are urgently required [4]. At the same time, the chemical preparation of candidate heterocycles can impose environmental and economic burdens through long synthetic sequences, stoichiometric reagents, hazardous solvents, and energy-intensive work-up. The principles of green chemistry provide a systematic framework for reducing these impacts [5].

Recent advances in catalytic C–H activation, multicomponent reactions, photoredox catalysis, electrochemistry, mechanochemistry, and flow chemistry provide complementary routes toward more sustainable heterocycle synthesis [6]–[11]. These methods are particularly relevant to antimicrobial medicinal chemistry because rapid analogue generation is essential for identifying meaningful SAR. A further opportunity is the integration of artificial intelligence (AI) with green synthesis. Machine-learning models can prioritize compounds, predict biological activity, suggest synthetic routes, optimize reaction conditions, and balance antimicrobial potency against toxicity and environmental impact. Thus, the future of antimicrobial heterocycle research should combine biological activity with synthetic and environmental performance.

## 2. Green Methods for Heterocycle Construction

Sustainable heterocycle synthesis is not defined by a single reaction type. The overall environmental profile depends on substrate preparation, catalyst loading, solvent quantity and hazard, energy demand, reaction time, purification, waste treatment, and scalability. Consequently, different green technologies should be selected according to the chemistry and intended application.

### 2.1 Catalytic C–H Activation and Cross-Coupling

Direct C–H functionalization can reduce the requirement for prefunctionalized substrates and thereby improve step economy. C–H activation has become a powerful approach for rapid construction and late-stage diversification of heterocycles [6]. Direct arylation, C–H amination, oxidative annulation, and related transformations provide substituted pyridines, indoles, quinolines, and other heterocyclic frameworks. The use of iron, copper, nickel, and other abundant metals is attractive, although catalyst preparation, ligand synthesis, metal recovery, and toxicity must also be evaluated [12].

### 2.2 Multicomponent Reactions

Multicomponent reactions combine three or more building blocks in a single operation and generate structural complexity with fewer isolation steps. Ugi, Biginelli, Hantzsch, Passerini, and related reactions have been widely employed for the synthesis of diverse heterocyclic libraries [7]. Their convergent character, operational simplicity, and

compatibility with one-pot processing make them useful for antimicrobial medicinal chemistry. Water, ethanol, solvent-free media, and mechanochemical conditions can further improve their environmental profile.

### 2.3 Photoredox and Visible-Light Catalysis

Photoredox catalysis enables single-electron and energy-transfer transformations under relatively mild conditions [8]. Visible light can replace conventional chemical oxidants or reductants in selected cyclizations and annulations. Organic dyes and heterogeneous photocatalysts can reduce dependence on precious metals. Nevertheless, a meaningful sustainability assessment should include lamp efficiency, photon utilization, catalyst recovery, reactor design, solvent use, and scale-up.

### 2.4 Electrochemical Synthesis

Electrosynthesis uses electrons as redox reagents and can avoid stoichiometric oxidants or reductants. Electrochemical annulations and dehydrogenative couplings can provide nitrogen-, oxygen-, and sulfur-containing heterocycles under controllable conditions [9]. Paired electrolysis may improve material efficiency by using both anodic and cathodic processes. Scale-up requires attention to electrode materials, current density, cell configuration, electrolyte, mass transfer, and electricity consumption.

### 2.5 Mechanochemistry and Solvent-Free Methods

Mechanochemical synthesis, particularly ball milling, can dramatically reduce solvent use and accelerate condensation and cyclization reactions [10]. High substrate concentration can shorten reaction times and simplify work-up. Limitations include control of milling conditions, heat transfer, contamination from milling media, scale-up, and compatibility with sensitive substrates.

### 2.6 Continuous-Flow Chemistry

Flow chemistry offers precise residence-time control, efficient heat and mass transfer, and safer handling of reactive intermediates. It can reduce solvent volumes and facilitate telescoped sequences without intermediate isolation [11]. Flow photochemistry and electrochemistry are particularly attractive for scalable heterocycle synthesis because light penetration and electrode exposure can be controlled more effectively than in many batch reactors.

## 3. Bioactive Heterocyclic Scaffolds

Nitrogen heterocycles such as imidazoles, pyrazoles, triazoles, pyridines, pyrimidines, quinolines, and benzimidazoles provide versatile platforms for antimicrobial design. Their heteroatoms control polarity and hydrogen bonding, while aromatic surfaces support hydrophobic and  $\pi$ -interactions. Oxygen- and sulfur-containing heterocycles, including oxazoles and thiazoles, can additionally modify polarizability and lipophilicity. Fused heterocycles provide rigid frameworks and can support selective binding to microbial targets [1], [2].

Green methods can be selected according to scaffold requirements. MCRs are attractive for rapid nitrogen-heterocycle libraries, photoredox and electrochemical methods are useful for oxidative annulations, and catalytic C–H functionalization can provide late-stage diversification. Fused systems may benefit from cascade reactions and flow processing [6], [11].

## 4. Green Synthesis and Antimicrobial Drug Discovery

Green synthesis should be integrated with antimicrobial medicinal chemistry rather than applied only after a lead has been identified. A focused library can be designed around a biologically relevant heterocyclic scaffold while simultaneously minimizing reaction steps, hazardous solvents, stoichiometric reagents, and purification.

Antimicrobial evaluation should use standardized procedures and report organism, strain, assay method, inoculum, medium, incubation conditions, concentration units, and controls. MIC is generally more informative for quantitative comparison than inhibition-zone diameter alone. MBC and MFC measurements can provide additional information on bactericidal or fungicidal effects. Reference antimicrobials and appropriate solvent and negative controls are essential.

## 5. Artificial Intelligence for Sustainable Heterocycle Discovery

Artificial intelligence provides an emerging bridge between molecular design and sustainable synthesis. QSAR and machine-learning models can predict antimicrobial activity from molecular descriptors or fingerprints, while graph neural networks can learn from molecular connectivity. Generative models can propose new heterocyclic structures, and reaction-prediction models can identify feasible synthetic pathways [13]–[18].

A practical workflow is: molecular design → activity prediction → toxicity/ADMET filtering → synthetic-accessibility prediction → green retrosynthesis → reaction-condition optimization → synthesis → antimicrobial testing → model updating. Multi-objective optimization is important because a highly active compound may have poor solubility, high toxicity, low synthetic accessibility, or an unfavorable environmental profile.

AI can also reduce experimental waste through active learning. Instead of testing large numbers of randomly selected analogues, a model can identify compounds expected to provide high biological activity or high information gain. Experimental results can then be incorporated into the next design cycle.

## 6. Green Metrics and Life-Cycle Assessment

Sustainability should be evaluated using quantitative metrics rather than yield alone. Atom economy measures the proportion of reactant atoms incorporated into the product, while the E-factor expresses waste generated per mass of product. Process mass intensity (PMI) considers total material input per unit mass of product [19], [20]. Solvent hazard and volume, energy consumption, catalyst loading, purification, and waste treatment should also be reported.

Life-cycle assessment extends the analysis from the reaction vessel to raw-material manufacture, transportation, catalyst production, solvent production, waste treatment, and end-of-life considerations. A reaction with excellent yield can still have a poor environmental profile if it requires hazardous solvents, rare catalysts, or energy-intensive purification. Therefore, cradle-to-gate assessment is preferable when sufficient information is available.

## 7. Antimicrobial Evaluation and SAR

Small changes in heterocyclic substitution can strongly influence antimicrobial potency. Electronic effects, steric effects, hydrogen-bonding capacity, lipophilicity, molecular flexibility, and heteroatom position can all affect target recognition and cellular penetration. Consequently, green synthetic methods that enable rapid analogue generation are valuable for SAR studies.

A rigorous workflow should progress from preliminary screening to MIC determination and, where appropriate, MBC or MFC measurements. Cytotoxicity and selectivity should also be considered. AI-assisted SAR can identify structural features associated with activity and help select the next analogue series. This is particularly useful when the library is designed to explore a defined heterocyclic scaffold rather than broad random chemical space.

## 8. Challenges and Limitations

Important limitations remain. Some catalytic methods have restricted substrate scope, while photochemical and electrochemical procedures may require specialized equipment for scale-up. Mechanochemical methods can be sensitive to milling parameters. Alternative solvents and catalysts may also present cost, toxicity, recovery, or supply-chain challenges [21].

Green metrics are often reported inconsistently, making direct comparisons difficult. Yield alone is inadequate. AI introduces additional issues including small datasets, assay heterogeneity, biased training data, data leakage, overfitting, limited interpretability, and inaccurate synthetic-accessibility predictions. These problems require careful structure curation, scaffold-based validation, applicability-domain analysis, and experimental confirmation.

**Table 1. Sustainable approaches for antimicrobial heterocycle synthesis**

| Method           | Principal application           | Sustainability advantage                        | Key limitation                        |
|------------------|---------------------------------|-------------------------------------------------|---------------------------------------|
| C–H activation   | Direct functionalization        | Reduced prefunctionalization and step count     | Catalyst/directing-group requirements |
| MCRs             | Library synthesis               | Convergent assembly and fewer isolations        | Substrate scope/selectivity           |
| Photoredox       | Cyclization/annulation          | Mild conditions; light-driven activation        | Photon efficiency and scale-up        |
| Electrosynthesis | Oxidation/reduction             | Electrons replace stoichiometric redox reagents | Cell/electrode optimization           |
| Mechanochemistry | Condensation/cyclization        | Very low or no solvent                          | Scale-up and mixing                   |
| Flow chemistry   | Continuous/telescoped synthesis | Heat/mass transfer and process safety           | Equipment/process development         |

**Table 2. AI-assisted opportunities in sustainable antimicrobial heterocycle discovery**

| AI component          | Input                             | Potential output                  |
|-----------------------|-----------------------------------|-----------------------------------|
| QSAR/ML               | Structures and activity data      | Predicted antimicrobial potency   |
| Graph neural networks | Molecular graphs                  | Nonlinear SAR/activity prediction |
| Generative AI         | Scaffold and property constraints | Novel heterocyclic candidates     |
| Retrosynthesis        | Target molecule                   | Candidate synthetic routes        |
| Reaction optimization | Experimental reaction data        | Optimized conditions              |
| ADMET models          | Molecular structures              | Toxicity/PK prioritization        |
| Active learning       | Experimental and predicted data   | Next best compound/experiment     |

## 9. Future Perspectives

Future sustainable antimicrobial discovery will increasingly combine green chemistry, AI, continuous processing, and microbiology. Earth-abundant catalysts and organocatalysts should be developed with broad functional-group tolerance and low loading. Flow photochemistry and electrochemistry can support continuous library generation [11]. Protecting-group-free and telescoped sequences can further reduce solvent and purification requirements.

AI provides an opportunity for multi-objective optimization of antimicrobial potency, selectivity, synthetic accessibility, solvent impact, energy demand, and waste. Generative models can propose structures under synthetic constraints, while reaction-prediction models can identify alternative routes when an initial pathway is inefficient [14]–[18]. The long-term vision is a closed-loop system in which AI-guided design, green retrosynthesis, automated or high-throughput synthesis, antimicrobial testing, environmental assessment, and model retraining operate iteratively.

## 10. Conclusions

Green and sustainable synthesis of bioactive heterocycles has direct relevance to the discovery and manufacture of antimicrobial agents. C–H activation, multicomponent reactions, photoredox catalysis, electrochemical synthesis, mechanochemistry, and flow processing provide complementary approaches for reducing waste and improving process efficiency. Their sustainability should be evaluated through atom economy, E-factor, PMI, solvent impact, energy demand, and life-cycle considerations. The integration of AI with green heterocycle chemistry represents a particularly promising next step. Machine learning can prioritize biologically promising structures, generative models can explore chemical space, retrosynthesis tools can assess synthetic feasibility, and active learning can minimize unnecessary experiments. However, computational predictions must be experimentally validated through reproducible synthesis and standardized antimicrobial testing. The convergence of AI, sustainable synthesis, medicinal chemistry, and microbiology

therefore offers a realistic route toward antimicrobial candidates that are not only potent but also synthetically efficient, scalable, and environmentally responsible.

### Conflict of interest

The author affirms that he has no conflicts of interest related to this work's publication. The research, analysis, findings interpretation, and paper preparation were not impacted by any financial, personal, or professional interactions.

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