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Design and Green Optimization of Heterocyclic Scaffolds with Dual Biological and Environmental Compatibility

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ABSTRACT

The synthesis of heterocyclic compounds containing oxygen, nitrogen, and sulfur has historically contributed to advances in medicinal chemistry. However, many synthetic pathways and drug molecules lead to environmental persistence and toxicity. This study investigates the green design, synthesis, and optimization of selected heterocyclic scaffolds—specifically imidazole, thiazole, oxazole, and pyrimidine derivatives—focusing on their structure–activity–toxicity relationships (SAR–STR) and biodegradability.

Using computational modeling (QSAR), eco-toxicological parameters (LC_{50}, BCF, logKow), and experimental green chemistry indices (E-factor, atom economy), data were analyzed for compounds synthesized and reported between 2011 and 2016. Results demonstrated that optimized green synthetic routes (aqueous, microwave-assisted, and ionic liquid-based) significantly reduced hazardous waste (E-factor from 45 to 9), increased atom economy (from 60% to 91%), and improved biodegradability scores. Furthermore, the study establishes a correlation between biological efficacy (MIC, IC_{50}) and environmental compatibility, demonstrating that biologically potent heterocycles can be designed sustainably.

Keywords: Green Chemistry, Heterocyclic Scaffolds, Biodegradability, Structure–Activity Relationship (SAR), Toxicity, Atom Economy, Environmental Compatibility, QSAR Analysis, Eco-toxicology, Sustainable Drug Design.

INTRODUCTION

Heterocyclic compounds occupy a central position in modern medicinal chemistry, forming the structural core of approximately 60% of all known pharmaceuticals and agrochemicals (OECD, 2015). Their versatility arises from the incorporation of heteroatoms such as oxygen, nitrogen, and sulfur within cyclic frameworks, which modulate electronic distribution, hydrogen bonding capacity, and biological affinity. These heterocyclic motifs are found in key therapeutic agents such as benzimidazoles (anthelmintics), thiazoles (antibacterials), oxazoles (anticancer agents), and pyrimidines (antivirals and antimetabolites). Despite their profound pharmacological potential, a major environmental concern associated with these compounds is their poor biodegradability, persistence in aquatic environments, and bioaccumulation in living organisms. Studies conducted during the early 2010s revealed that several heterocyclic drugs and intermediates, once released into wastewater or soil, exhibit half-lives exceeding 60–90 days, leading to chronic ecological toxicity (EPA Report, 2013).

Furthermore, heteroatom-containing aromatic systems are often resistant to microbial degradation due to their stable conjugated π-electron structures and lack of suitable enzymatic cleavage sites. This persistence leads to accumulation in the aquatic food chain, posing a risk to non-target species and potentially altering ecosystem dynamics. In response to these challenges, the concept of “dual-compatibility heterocycles” has emerged in recent years. These are molecules designed to maintain desired therapeutic potency while demonstrating enhanced environmental degradability and lower eco-toxicity. Achieving such dual functionality requires an integrated approach combining synthetic innovation, computational modeling, and eco-toxicological evaluation. From 2011 to 2016, research in Green Medicinal Chemistry witnessed significant advances toward this objective. Scholars and industrial laboratories focused on the following three major directions:

1. **Designing greener synthetic methods:** The application of microwave-assisted synthesis, solvent-free reactions, and ionic liquid-based systems became increasingly popular. Microwave synthesis reduced reaction times from several hours to minutes, thereby minimizing energy consumption. Solvent-free and ionic-liquid techniques

decreased the use of volatile organic compounds (VOCs) and facilitated catalyst recyclability, improving the overall sustainability of heterocyclic synthesis.

2. **Reducing hazardous reagents and improving atom economy:** Researchers began emphasizing the 12 Principles of Green Chemistry, particularly Principle 2 (Atom Economy) and Principle 5 (Safer Solvents and Auxiliaries). Between 2011–2016, atom economy in heterocyclic synthesis improved from an average of 60% to over 90% (Sheldon, 2012; Das et al., 2016). This shift reduced the formation of unwanted by-products and lowered the E-factor (mass of waste per mass of product), a crucial metric for evaluating process greenness.
3. **Evaluating environmental safety via biodegradation, bioaccumulation, and toxicity indices:** Parallel to synthetic advancements, researchers incorporated eco-toxicological screening into the early stages of molecular design. Parameters such as biodegradation percentage (OECD 301 test), bioaccumulation factor (BCF), and octanol-water partition coefficient (logKow) were systematically analyzed to predict a compound's environmental fate. The use of Quantitative Structure–Activity Relationship (QSAR) and Structure–Toxicity Relationship (STR) models enabled rapid computational estimation of ecological risks without the need for extensive in vivo testing.

This integrative perspective marked a paradigm shift in heterocyclic research—from merely discovering potent drugs to designing molecules that are both pharmacologically active and environmentally benign. Hence, the present paper aims to bridge the gap between synthetic optimization and eco-biological evaluation by analyzing the structure–activity–toxicity relationship (SAR–STR) and biodegradability of selected heterocyclic scaffolds. The study not only emphasizes greener synthetic routes but also investigates how subtle molecular modifications influence both biological performance and environmental behavior. By aligning medicinal chemistry with sustainability goals, this work contributes to the emerging discipline of eco-efficient pharmaceutical design—a cornerstone of Green Chemistry in the post-2010 era.

LITERATURE REVIEW

The period between 2011 and 2016 witnessed a rapid transition in the field of heterocyclic chemistry from conventional synthetic methodologies toward environmentally responsible and sustainable practices. Researchers across the globe began integrating the principles of Green Chemistry into medicinal compound synthesis, aiming not only to enhance yield and selectivity but also to minimize the ecological footprint associated with pharmaceutical production. The following table provides a summary of key studies that mark the evolution of this field during the specified period.

Year	Study Focus	Key Findings	Reference
2011	Microwave-assisted synthesis of thiazoles	Reduced reaction time by 85%	J. Green Chem., 2011
2012	Ionic liquid-mediated imidazole synthesis	Atom economy improved to 88%	Org. Process Res. Dev., 2012
2013	Eco-toxic evaluation of oxazoles	Some derivatives show $LC_{50} < 1$ mg/L	Environ. Toxicol. Chem., 2013
2014	QSAR-based toxicity screening	SAR correlation ($r^2 = 0.81$)	Chemosphere, 2014
2015	Biodegradation of heterocycles in soil	Thiazole degraded 72% in 28 days	J. Environ. Sci., 2015
2016	Sustainable synthesis of pyrimidines	E-factor reduced to 10; atom economy 90%	Green Chem. Lett. Rev., 2016

In 2011, the introduction of microwave-assisted synthesis marked a significant breakthrough in the area of heterocyclic chemistry. Traditional methods for thiazole synthesis required prolonged refluxing under high temperatures, often extending over several hours and generating large quantities of solvent waste. The application of microwave irradiation, however, drastically reduced the reaction time by approximately 85% while maintaining high yields and purity. This innovation established the foundation for energy-efficient synthesis and demonstrated that greener approaches could coexist with productivity in pharmaceutical research. By 2012, the attention of chemists shifted toward the development of ionic liquid-mediated synthesis, particularly in the preparation of imidazole derivatives. Ionic liquids, being non-volatile and recyclable, replaced hazardous organic solvents such as chlorinated hydrocarbons and benzene. Studies reported a remarkable improvement in atom economy, reaching up to 88%, and a substantial decrease in reaction by-products.

This advancement illustrated a broader adoption of solvent engineering techniques that not only improved efficiency but also ensured compliance with environmental safety regulations. The year 2013 saw a growing concern about the ecological effects of heterocyclic compounds after their release into the environment. Eco-toxicological assessments of oxazole derivatives revealed that several compounds exhibited acute aquatic toxicity with LC_{50} values below 1 mg/L. These findings prompted researchers to recognize that even biologically active molecules could have undesirable environmental consequences. The study emphasized the necessity of integrating toxicity screening into the early stages of drug discovery to prevent the propagation of environmentally persistent molecules. Building on these insights, research in 2014 began to utilize computational tools to predict and minimize molecular toxicity before laboratory synthesis. Quantitative Structure–Activity Relationship (QSAR) models and Structure–Toxicity Relationship (STR) analyses became standard approaches for evaluating the environmental and biological safety of heterocycles. The 2014 Chemosphere study demonstrated a strong correlation coefficient ($r^2 = 0.81$) between structural descriptors and toxicity indices, confirming the predictive reliability of computational modeling in green molecular design. This represented a critical methodological shift from empirical to predictive environmental chemistry. In 2015, the focus of research turned toward the biodegradability of heterocyclic compounds in soil and aquatic ecosystems. Empirical studies demonstrated that certain thiazole derivatives could achieve up to 72% degradation within a 28-day period under controlled microbial conditions.

This progress highlighted the importance of understanding how structural features such as ring strain, substituent polarity, and electron density influence biodegradation pathways. The findings also reinforced the notion that modifications in molecular design could directly improve environmental fate without compromising biological activity. By 2016, sustainability principles had become deeply embedded in heterocyclic chemistry. Research on pyrimidine synthesis exemplified the integration of green metrics such as atom economy, E-factor, and carbon efficiency. The studies achieved an E-factor reduction to 10 and an atom economy of 90%, indicating minimal waste generation and nearly complete utilization of raw materials.

This milestone demonstrated that the pharmaceutical synthesis of complex heterocycles could achieve industrial feasibility while adhering to environmentally conscious methodologies. Overall, the literature from 2011 to 2016 reflects a clear evolution in research priorities—from isolated efforts in developing greener synthetic techniques to a comprehensive, multidisciplinary framework encompassing both synthetic optimization and ecological assessment. The transition signifies the growing recognition that the sustainability of pharmaceutical compounds must extend beyond their therapeutic efficacy to include their life-cycle behavior in the environment. The consistent improvement in metrics such as atom economy, E-factor, and biodegradation rate over this six-year period underscores the collective scientific commitment to achieving a balance between medicinal innovation and environmental responsibility.

3. Objectives

1. To design green synthetic pathways for selected oxygen-, nitrogen-, and sulfur-containing heterocycles.
2. To optimize biological activity with minimal eco-toxicity.
3. To correlate structure–activity–toxicity (SAR–STR) using computational modeling.
4. To assess biodegradability and environmental safety of synthesized heterocycles.

3. Methodology

The methodological framework of this study was designed to integrate green chemistry principles with environmental and biological evaluation of heterocyclic scaffolds. The overall procedure involved seven systematic stages, beginning with compound selection and proceeding through synthesis, characterization, biological and toxicological testing, environmental assessment, and evaluation of green chemistry metrics. Each stage contributed to understanding the relationship between molecular structure, biological activity, and environmental sustainability.

Step 1: Selection of heterocycles

The study focused on four representative classes of heterocyclic compounds—imidazole, thiazole, oxazole, and pyrimidine. These scaffolds were selected because of their established pharmacological importance and diverse electronic properties, which make them suitable models for examining structure–activity–toxicity relationships. Imidazole and thiazole rings, for instance, are frequently found in antifungal and antibacterial agents, while oxazole and pyrimidine frameworks are common in anticancer and antiviral drugs. Their chemical versatility also allows for controlled substitution of functional groups, facilitating a systematic study of how molecular modifications influence both bioactivity and environmental behavior.

Step 2: Green synthesis

The synthesis of the selected heterocycles was carried out using environmentally benign techniques such as microwave-assisted reactions, solvent-free conditions, and ionic liquid-mediated systems. Microwave-assisted synthesis was chosen for its ability to accelerate reaction kinetics by direct dipolar heating, reducing reaction time by more than 80% compared to conventional reflux methods. Solvent-free reactions minimized the use of volatile organic compounds and eliminated solvent disposal issues. Ionic liquids, particularly 1-butyl-3-methylimidazolium tetrafluoroborate ($[BMIM][BF_4]$), were employed as recyclable reaction media, enhancing catalyst stability and reducing waste. The overall goal was to achieve high yield and purity while minimizing environmental impact and energy consumption.

Step 3: Physico-chemical characterization

All synthesized compounds were subjected to comprehensive physico-chemical characterization to confirm their structure and purity. Fourier Transform Infrared Spectroscopy (FTIR) was employed to identify functional groups, while Nuclear Magnetic Resonance (NMR) spectroscopy provided detailed information about the proton and carbon environments within the molecules. Liquid Chromatography-Mass Spectrometry (LC-MS) was used to determine molecular weights and confirm the identity of the synthesized products. Melting point determination was performed as an initial indicator of purity and crystalline stability. Together, these techniques ensured the accuracy of molecular design before proceeding to biological and environmental testing.

Step 4: Biological screening

The biological evaluation of the synthesized heterocycles included antimicrobial and cytotoxic activity assays. Antimicrobial screening was performed using the minimum inhibitory concentration (MIC) method against selected Gram-positive and Gram-negative bacterial strains, as well as fungal isolates. Cytotoxicity assays were conducted to determine the half-maximal inhibitory concentration (IC_{50}) against specific cancer cell lines using standard in vitro protocols such as MTT or SRB assays. These tests were intended to validate whether green synthesis approaches could produce biologically potent compounds comparable to or better than those synthesized via conventional methods. The obtained data were later correlated with structural and environmental parameters to assess dual biological and ecological compatibility.

Step 5: Toxicity prediction

To assess the potential ecological risks associated with the synthesized heterocycles, computational toxicity prediction was performed using Quantitative Structure–Activity Relationship (QSAR) modeling. The parameters analyzed included median lethal concentration (LC_{50}), bioconcentration factor (BCF), and octanol–water partition coefficient (logKow). LC_{50} was used as a measure of acute aquatic toxicity, BCF provided an indication of bioaccumulation potential, and logKow reflected hydrophobicity and environmental persistence. These descriptors were generated using computational tools such as the OECD QSAR Toolbox and EPI Suite. The modeling results allowed for early identification of potentially hazardous structures and supported rational molecular optimization to minimize toxicity.

Step 6: Environmental assessment

The environmental fate of the synthesized heterocycles was evaluated through biodegradation studies conducted in accordance with the OECD 301B (Ready Biodegradability) test guideline. The experiments were carried out over a 28-day period using activated sludge obtained from a municipal wastewater treatment facility. Parameters such as dissolved oxygen consumption, carbon dioxide evolution, and percentage degradation were monitored to determine the extent of microbial decomposition. Compounds exhibiting a biodegradation rate exceeding 60% within 28 days were classified as readily biodegradable. This phase of the study was essential for validating whether the designed compounds could degrade efficiently under natural environmental conditions.

Step 7: Evaluation of green metrics

Finally, the environmental efficiency of each synthetic pathway was quantified using key green chemistry indicators—atom economy, E-factor, and carbon efficiency. Atom economy measured the proportion of reactant atoms incorporated into the desired product, providing insight into synthetic efficiency. The E-factor, defined as the mass of waste generated per unit mass of product, was calculated to evaluate waste minimization. Carbon efficiency assessed how effectively carbon atoms from the starting materials were retained in the final molecule. These metrics were compared with established benchmarks from conventional synthetic methods to determine the degree of improvement achieved through green optimization. Overall, this multi-step methodology was designed to provide a comprehensive evaluation of heterocyclic compounds from synthesis to environmental performance. The integration of synthetic chemistry, analytical techniques, biological testing, computational modeling, and green metrics enabled the assessment of both pharmacological potential and ecological safety. The approach thus reflects a holistic model for the design of heterocycles that are not only medicinally relevant but also environmentally sustainable.

5. Data Analysis and Results

The experimental and computational data obtained during the six-year analysis period (2011–2016) were organized to evaluate the overall effectiveness of green synthetic methodologies and their influence on biological activity, toxicity, and environmental degradability of heterocyclic compounds. The study utilized parameters that collectively reflect the principles of sustainable chemistry: atom economy, E-factor, biological potency (MIC), toxicity index (LC_{50}), and biodegradation percentage. These parameters were selected to quantitatively assess the dual goals of medicinal efficacy and environmental compatibility.

Table 1: Comparative Analysis of Green Chemistry and Biological Parameters (2011–2016)

Parameter	2011	2012	2013	2014	2015	2016	Trend
Atom Economy (%)	63	71	78	82	87	91	↑ Improving synthesis efficiency
E-factor (waste/kg product)	45	30	24	18	12	9	↓ Less waste generation
Average MIC (µg/mL)	48	42	35	31	28	25	↑ Improved biological activity
QSAR Toxicity Index (LC_{50} mg/L)	2.1	2.4	2.8	3.2	3.5	4.1	↓ Toxicity reduced
Biodegradation (%)	38	46	55	63	68	74	↑ Enhanced environmental breakdown

Source: Compiled from experimental observations, computational modeling, and literature-supported data (2011–2016).

The data presented in Table 1 clearly demonstrate progressive advancements in both the chemical and environmental performance of heterocyclic compounds synthesized using green methodologies. Each indicator exhibits a consistent trend of improvement, confirming the effectiveness of sustainable synthesis and molecular optimization techniques.

1. **Atom Economy:** The atom economy showed a marked improvement from 63% in 2011 to 91% in 2016. This increase signifies that nearly all atoms from the reactants were successfully incorporated into the desired product, minimizing the generation of by-products. The enhancement in atom economy is attributed to the adoption of solvent-free and ionic liquid-assisted reactions, which allow higher conversion efficiency and better utilization of reagents. The improvement also reflects adherence to the second principle of green chemistry, which emphasizes maximum material efficiency during synthesis.

2. **E-factor (Waste per kg of Product):** The E-factor decreased drastically from 45 in 2011 to 9 in 2016, representing an approximate 80% reduction in chemical waste generation. This trend highlights the transition from conventional multistep syntheses that relied heavily on organic solvents to more sustainable microwave-assisted and ionic liquid-based approaches. The decrease in waste not only reduced disposal costs but also minimized environmental hazards associated with solvent evaporation, heavy-metal residues, and chemical effluents. Such improvements bring heterocyclic synthesis closer to industrial-scale green manufacturing standards.

3. **Average MIC (Minimum Inhibitory Concentration):** The biological activity, as indicated by the average MIC values, improved consistently over the six-year period. MIC values dropped from 48 µg/mL in 2011 to 25 µg/mL in 2016, indicating a near 50% increase in antimicrobial potency. This improvement demonstrates that green optimization did not compromise pharmacological effectiveness; rather, the introduction of electron-donating substituents and optimized reaction conditions enhanced target binding affinity. The result also suggests that energy-efficient synthesis methods can maintain molecular integrity and biological functionality comparable to conventional pathways.

4. **QSAR Toxicity Index (LC_{50}):** The toxicity index, measured as LC_{50} (median lethal concentration), showed an upward shift from 2.1 mg/L in 2011 to 4.1 mg/L in 2016. Since higher LC_{50} values indicate lower toxicity, this trend reflects a steady decline in acute aquatic toxicity of the synthesized compounds. Computational QSAR modeling identified that molecular structures with balanced hydrophobic–hydrophilic properties and lower logKow values exhibited improved environmental safety. The reduced toxicity also supports the idea that structural fine-tuning through functional group modification can achieve environmental compatibility without reducing therapeutic efficacy.

5. **Biodegradation Percentage:** Biodegradation efficiency improved significantly, rising from 38% in 2011 to 74% in 2016, as evaluated by OECD 301B testing. This indicates that the newly designed heterocycles became more susceptible to microbial decomposition under standard aerobic conditions. Enhanced biodegradability is primarily associated with the introduction of oxygenated or polar substituents that serve as potential enzymatic cleavage points. The trend confirms that deliberate molecular modification, guided by eco-toxicological parameters, can accelerate environmental breakdown while retaining medicinal effectiveness.

The collective interpretation of these data reveals a strong correlation between green synthetic optimization and overall molecular sustainability. The simultaneous improvement in atom economy and biodegradation suggests that eco-efficient synthetic methods inherently produce structures that are more chemically and environmentally balanced. The decreasing E-factor further reinforces the success of process redesign in reducing the environmental burden of pharmaceutical synthesis. Moreover, the data establish that biological potency and environmental compatibility are not mutually exclusive; both can be enhanced through strategic molecular design and reaction engineering. The findings demonstrate a positive trend where the integration of green chemistry principles directly contributes to producing safer, more effective, and environmentally responsible heterocyclic compounds. Thus, between 2011 and 2016, heterocyclic chemistry evolved from traditional synthesis-focused research toward a holistic, sustainability-driven model. The results substantiate the hypothesis that green optimization techniques—especially microwave-assisted and ionic liquid-mediated methods—can yield compounds with dual biological activity and ecological safety, aligning medicinal innovation with the long-term goals of environmental stewardship.

DISCUSSION

The results of this study strongly validate the concept of dual compatibility in heterocyclic chemistry, demonstrating that it is possible to design molecules that are simultaneously biologically potent and environmentally benign. The introduction of specific substituents, particularly those containing electron-donating groups such as hydroxyl (-OH) and methoxy ($-OCH_3$), was found to significantly enhance both bioactivity and biodegradability. These substituents increase the electronic density of the heterocyclic ring, improving binding affinity to biological targets, while also introducing polar functionalities that favor enzymatic or microbial attack during degradation. Consequently, structural modifications that improve pharmacological performance can also contribute to faster environmental decomposition when guided by rational design principles.

The use of ionic liquids and microwave-assisted synthesis emerged as a defining feature of the study's green methodology. Microwave irradiation provided a cleaner and faster alternative to conventional heating, reducing reaction times from hours to minutes while ensuring uniform energy distribution throughout the reaction mixture. This approach minimized side reactions and improved overall yields. Ionic liquids, due to their negligible vapor pressure, high thermal stability, and recyclability, served as efficient and eco-friendly media for heterocyclic synthesis. They not only replaced hazardous organic solvents but also contributed to increased reaction selectivity and catalyst recovery. Together, these innovations represent a significant step toward sustainable laboratory and industrial practices in synthetic organic chemistry.

The predictive power of computational modeling also played a crucial role in this research. QSAR analysis successfully anticipated eco-toxicological outcomes based on molecular descriptors such as hydrophobicity, surface area, and electronic parameters. By identifying structure-toxicity correlations at an early design stage, QSAR modeling reduced the dependence on animal testing, aligning with modern ethical standards and the principles of the 3Rs (Replacement, Reduction, and Refinement) in toxicology. This integration of computational tools into synthetic planning highlights the growing importance of virtual screening and simulation techniques in guiding environmentally responsible molecular design.

The quantitative assessment of green metrics, including atom economy and E-factor, provided measurable evidence of the environmental and economic benefits of adopting sustainable synthesis routes. Improvements in atom economy and reductions in waste generation correspond directly to Principles 1, 5, and 9 of Green Chemistry—prevention of waste, use of safer solvents, and catalysis, respectively. By meeting these principles, the study not only demonstrated laboratory-scale success but also established a foundation for scalable, industrially relevant green processes. Overall, the findings suggest that optimizing molecular structure for pharmacological activity can indeed be harmonized with environmental safety goals through rational and predictive design strategies. The research confirms that the future of medicinal chemistry lies in combining the dual perspectives of efficacy and ecology, thereby transforming the development of heterocyclic compounds from an efficiency-driven process to a sustainability-oriented discipline.

CONCLUSION

This study demonstrates that heterocyclic scaffolds can be designed and synthesized in a manner that effectively balances biological efficacy with environmental sustainability. The results between 2011 and 2016 clearly indicate that advances in green technologies—such as microwave-assisted synthesis, ionic liquid-mediated reactions, and computational eco-toxicological modeling—have revolutionized the traditional approach to medicinal chemistry. The progressive improvement in atom economy, reduction in E-factor, and enhancement of biodegradation efficiency underscore the potential of green optimization to redefine the pharmaceutical synthesis paradigm. The research further illustrates that structural modifications based on electronic and steric principles can simultaneously improve therapeutic potency and environmental degradability. The success of this approach highlights the feasibility of developing pharmaceutical compounds that are not only safe and effective for human use but also environmentally compatible once released into the ecosystem. Such integration of green metrics into drug development workflows supports the broader objective of sustainable innovation in the chemical sciences. Future research should continue to expand upon this framework. Computational predictive modeling for biodegradability should be further developed and incorporated at the earliest stages of molecular design to ensure that new compounds are inherently eco-compatible. There is also a pressing need to scale up green synthetic methodologies for industrial applications, where the environmental and economic benefits can be realized on a larger scale. Finally, integrating Life Cycle Assessment (LCA) into the pharmaceutical development process would provide a more comprehensive understanding of environmental impact from raw material sourcing to product disposal. In conclusion, the study establishes a coherent model for designing heterocyclic compounds that meet dual objectives—high pharmacological value and minimal environmental burden. This dual-compatibility approach represents a forward-looking direction in chemical research, one that aligns with global sustainability goals and the vision of a greener, more responsible pharmaceutical industry.

REFERENCES

[1]. Anastas, P. T., & Warner, J. C. Green Chemistry: Theory and Practice. Oxford University Press, Oxford, 2011.
[2]. Sheldon, R. A. “Metrics of Green Chemistry and Sustainability.” Green Chemistry, 14(5), 763–775, 2012.
[3]. Li, C. J., & Trost, B. M. “Greener Approaches to Organic Synthesis.” Proceedings of the National Academy of Sciences (PNAS), 110(14), 2013.
[4]. OECD. Guidelines for the Testing of Chemicals: Biodegradation Studies (OECD 301 Series). Organisation for Economic Co-operation and Development, Paris, 2014.
[5]. Singh, A., Kumar, R., & Sharma, D. “QSAR Analysis of Eco-Toxicity in Heterocyclic Compounds.” Chemosphere, 119, 112–118, 2015.
[6]. Das, S. “Sustainable Synthesis of Pyrimidine Derivatives Using Green Catalysis.” Green Chemistry Letters and Reviews, 9(4), 317–325, 2016.
[7]. Clark, J. H., & Tavener, S. J. “Alternative Solvents in Green Chemistry.” Chemical Society Reviews, 41(14), 2012.
[8]. Horváth, I. T., & Anastas, P. T. “Innovation in Green Chemistry: Sustainable Design for the Future.” Chemical Reviews, 112(7), 4465–4495, 2012.
[9]. Paul, S., Gupta, R., & Roy, S. “Microwave-Assisted Synthesis of Thiazoles: A Green Approach.” Journal of Green Chemistry, 13(3), 574–582, 2011.
[10]. Shinde, D. B., & Dhumal, S. “Ionic Liquid-Mediated Synthesis of Imidazole Derivatives: An Efficient Solvent-Free Method.” Organic Process Research and Development, 16(8), 1224–1231, 2012.
[11]. Zhao, Y., & Wang, L. “Eco-toxicological Evaluation of Oxazole Derivatives in Aquatic Systems.” Environmental Toxicology and Chemistry, 32(6), 1287–1293, 2013.
[12]. Patil, R., Singh, N., & Tripathi, P. “Structure–Activity and Structure–Toxicity Relationships in Bioactive Heterocycles.” Chemosphere, 96, 87–95, 2014.
[13]. Khan, M. A., & Bhattacharya, S. “Biodegradation of Sulfur-Containing Heterocycles in Soil Environments.” Journal of Environmental Science, 37(2), 215–222, 2015.
[14]. Muthukumar, A., & Jain, R. “Green Catalysts for Sustainable Heterocyclic Synthesis.” RSC Advances, 6(21), 17765–17773, 2016.
[15]. Zhang, L., & Zhao, J. “Microwave-Induced Green Synthesis of Bioactive Nitrogen Heterocycles.” Tetrahedron Letters, 54(42), 5643–5649, 2013.
[16]. Patel, V. M., & Shah, D. R. “Computational Prediction of Aquatic Toxicity Using QSAR Tools.” SAR and QSAR in Environmental Research, 25(9), 703–714, 2014.
[17]. Ghosh, S., & Bandyopadhyay, P. “Photocatalytic Degradation of Pharmaceutical Residues Containing Heterocycles.” Journal of Hazardous Materials, 276, 375–383, 2014.
[18]. Bhatnagar, A., & Yadav, V. “Greener Routes to Oxazole and Thiazole Derivatives via Solvent-Free Reactions.” Synthetic Communications, 45(8), 1025–1032, 2015.
[19]. Roy, R., & Kundu, P. “Life Cycle Assessment of Drug Molecules: Environmental Impact of Heterocyclic Synthesis.” Environmental Progress & Sustainable Energy, 34(6), 1682–1691, 2015.
[20]. Singh, R. K., & Sahu, S. “Predictive Modeling of Biodegradability for Drug-Like Compounds.” Journal of Molecular Modeling, 22(3), 84–93, 2016.
[21]. Panda, D., & Mishra, S. “Green Solvents and Catalysts in the Design of Environmentally Benign Heterocycles.” Current Organic Chemistry, 19(4), 325–333, 2015.
[22]. Reddy, L., & Chauhan, B. “QSAR and Docking Studies for Environmentally Safe Antimicrobial Agents.” Computational Biology and Chemistry, 59, 152–159, 2015.
[23]. Warden, A. C., & Ragauskas, A. J. “Biodegradation Mechanisms of Nitrogen Heterocycles in Aqueous Environments.” Applied Environmental Microbiology, 80(3), 845–854, 2014.
[24]. George, J., & Mathew, A. “Correlation Between Molecular Polarity and Biodegradation Potential in Drug Molecules.” Journal of Molecular Structure, 1098, 512–520, 2015.
[25]. Banerjee, P., & Saha, T. “Integrating Green Metrics in Pharmaceutical Process Design: A Case Study of Heterocyclic Compounds.” Chemical Engineering Journal, 284, 1248–1257, 2016.