Int. J. Sci. R. Tech., 2026 3(5)
A Multidisciplinary peer-reviewed Journal
www.ijsrtjournal.com [ISSN: 2394-7063]

Original Article

Green Synthetic Approaches For Bioactive Heterocyclic Compounds: Recent Advances And Pharmaceutical Applications

Vaishnavi Jadhav*

Pharmaceuticals Chemistry, Gurunathappa Bavage Knowledge City At Post Hasegaon, TQ Ausa, Dist Latur, Maharashtra 413531

ABSTRACT

Bioactive heterocyclic compounds constitute one of the most important classes of organic molecules in medicinal chemistry due to their wide spectrum of pharmacological activities and extensive applications in drug discovery. Numerous clinically approved drugs contain nitrogen-, oxygen-, and sulfur-containing heterocyclic scaffolds that exhibit anticancer, antimicrobial, antiviral, anti-inflammatory, antidiabetic, and central nervous system activities. However, conventional synthetic methods employed for heterocyclic synthesis are often associated with hazardous solvents, toxic reagents, high energy consumption, and significant environmental pollution. Consequently, the development of sustainable and environmentally benign synthetic methodologies has become increasingly important in modern pharmaceutical research. The present review highlights recent advances in green synthetic approaches for bioactive heterocyclic compounds with special emphasis on environmentally friendly methodologies and pharmaceutical applications. Various green synthetic techniques including microwave-assisted synthesis, ultrasound-assisted synthesis, solvent-free synthesis, multicomponent reactions, ionic liquids, nanocatalysis, biocatalysis, photocatalysis, electrochemical synthesis, and flow chemistry have been critically discussed. The advantages of these approaches such as reduced reaction time, improved yield, enhanced atom economy, lower toxicity, catalyst recyclability, and reduced waste generation are also summarized. Furthermore, recent developments from 2020–2026 including AI-assisted green synthesis, hybrid catalytic systems, sustainable drug synthesis strategies, and emerging green medicinal chemistry trends have been reviewed. Comparative analysis between conventional and green synthetic methods demonstrates the superior environmental and economic benefits of sustainable synthesis. The review also discusses industrial applications, pharmaceutical relevance, regulatory perspectives, current limitations, scale-up challenges, and future opportunities in green heterocyclic synthesis. Overall, green synthetic methodologies provide efficient, sustainable, and economically viable alternatives for the synthesis of bioactive heterocyclic compounds and are expected to play a major role in future pharmaceutical manufacturing and environmentally responsible medicinal chemistry.

Keywords: Bioactive heterocyclic compounds, Green chemistry, Sustainable synthesis, Microwave-assisted synthesis, Nanocatalysis; Biocatalysis, Flow chemistry, Photocatalysis, Medicinal chemistry, Pharmaceutical applications.

INTRODUCTION

1.1 Introduction to Heterocyclic Compounds

Heterocyclic compounds are cyclic organic molecules containing at least one heteroatom such as nitrogen, oxygen, or sulfur within the ring structure. These compounds represent one of the most significant classes of organic molecules due to their broad occurrence in natural products, pharmaceuticals, agrochemicals, and biologically active substances [1]. The incorporation of heteroatoms into cyclic frameworks modifies the physicochemical and biological properties of the molecules, thereby enhancing their therapeutic potential and chemical reactivity [2].

Heterocyclic scaffolds are widely distributed in medicinally important molecules because of their ability to interact effectively with biological targets through hydrogen bonding, dipole interactions, and hydrophobic interactions [3]. Nitrogen-containing heterocycles such as pyridine, pyrimidine, quinoline,

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

indole, and imidazole are particularly important owing to their extensive pharmacological activities [4]. Similarly, oxygen- and sulfur-containing heterocycles including furan, coumarin, thiophene, and thiazole exhibit diverse biological and industrial applications [5].

Several clinically important drugs contain heterocyclic nuclei, including Diazepam, Fluconazole, and Imatinib, highlighting the importance of heterocyclic chemistry in modern therapeutics [6].

Class	Examples	Biological Activities
Nitrogen-containing heterocycles	Pyridine, Pyrimidine, Indole	Anticancer, Antimicrobial
Oxygen-containing heterocycles	Furan, Coumarin	Anti-inflammatory, Antioxidant
Sulfur-containing heterocycles	Thiophene, Thiazole	Antibacterial, Antiviral

Table 1. Classification of Bioactive Heterocyclic Compounds

1.2 Importance in Medicinal Chemistry

Heterocyclic compounds occupy a central position in medicinal chemistry because they serve as essential structural frameworks in the synthesis and design of bioactive molecules. It has been estimated that nearly 75% of approved small-molecule drugs contain one or more heterocyclic rings, emphasizing their pharmaceutical relevance [7].

The presence of heteroatoms within cyclic systems enhances important drug-like properties such as solubility, lipophilicity, metabolic stability, and receptor-binding affinity [8]. Due to these advantages, heterocyclic compounds exhibit a broad spectrum of biological activities including anticancer, antimicrobial, antiviral, anti-inflammatory, antidiabetic, antihypertensive, and central nervous system activities [9].

In medicinal chemistry, heterocyclic moieties are commonly used to improve molecular selectivity and optimize structure–activity relationships (SAR). For example, pyrimidine derivatives are extensively used in antiviral and anticancer drugs, whereas indole-containing compounds possess significant anti-inflammatory and neurological activities [10]. Consequently, heterocyclic chemistry remains a fundamental component of modern drug discovery and pharmaceutical research.

1.3 Role of Heterocyclic Compounds in Drug Discovery

The contribution of heterocyclic compounds to drug discovery has increased tremendously due to advancements in synthetic chemistry, molecular biology, and computational drug design. Heterocyclic scaffolds provide versatile platforms for generating structurally diverse molecules that can interact efficiently with biological targets [11].

Nitrogen-containing heterocycles are extensively employed in kinase inhibitors, antimicrobial agents, antitubercular drugs, and anticancer therapeutics because of their favorable electronic and steric characteristics [12]. Additionally, fused heterocyclic systems have demonstrated remarkable therapeutic potential against chronic and infectious diseases [13].

Heterocyclic compounds also play a crucial role in combinatorial chemistry and fragment-based drug discovery owing to their synthetic flexibility and tunable pharmacokinetic properties [14]. Furthermore, molecular docking and computational screening techniques have accelerated the identification of novel heterocyclic lead compounds with enhanced efficacy and reduced toxicity [15].

The increasing prevalence of drug-resistant microbial strains and chronic diseases has further stimulated the search for novel heterocyclic molecules possessing improved therapeutic profiles and safety characteristics.

1.4 Limitations of Conventional Synthetic Methods

Despite the pharmaceutical significance of heterocyclic compounds, conventional synthetic methods often suffer from several environmental and operational limitations. Traditional synthesis frequently utilizes toxic organic solvents, hazardous reagents, harsh reaction conditions, prolonged reaction times, and non-recyclable catalysts [16].

Conventional heterocyclic synthesis generally produces large quantities of chemical waste and undesirable by-products, contributing to environmental pollution and increased manufacturing costs [17]. Moreover, the extensive use of volatile organic compounds (VOCs) poses serious risks to both human health and environmental safety [18].

Many classical synthetic approaches also exhibit poor atom economy, low selectivity, and high energy consumption due to the requirement for reflux conditions and multistep purification procedures [19]. Such drawbacks limit the sustainability and industrial applicability of conventional synthetic methodologies.

As environmental regulations become increasingly stringent, there is a growing demand for eco-friendly and sustainable alternatives for pharmaceutical synthesis.

Parameter	Conventional Synthesis	Green Synthesis
Solvents	Toxic organic solvents	Eco-friendly solvents
Energy Consumption	High	Low
Reaction Time	Longer	Shorter
Waste Generation	High	Minimal
Environmental Impact	Significant	Reduced

Table 2. Comparison Between Conventional and Green Synthetic Methods

1.5 Need for Green Chemistry in Pharmaceutical Synthesis

Green chemistry has emerged as an efficient and sustainable strategy for reducing the environmental impact associated with chemical manufacturing. The primary objective of green chemistry is to design safer chemical processes that minimize or eliminate the generation of hazardous substances during synthesis [20].

In heterocyclic synthesis, green chemistry approaches include microwave-assisted synthesis, ultrasound-assisted synthesis, solvent-free reactions, multicomponent reactions, ionic liquids, deep eutectic solvents, nanocatalysis, and biocatalysis [21]. These methodologies significantly reduce reaction time, waste generation, energy consumption, and toxic emissions while improving product yield and selectivity [22].

The pharmaceutical industry has increasingly adopted green synthetic technologies to achieve sustainable manufacturing and comply with environmental safety regulations. Green chemistry not only enhances environmental compatibility but also offers economic advantages through simplified work-up procedures, lower operational costs, and improved scalability [23].

Recent advancements in nanotechnology, photocatalysis, electrochemical synthesis, and continuous flow chemistry have further expanded the scope of sustainable heterocyclic synthesis, making green chemistry an indispensable component of modern pharmaceutical manufacturing [24].

1.6 Aim and Scope of the Review

The present review aims to provide a comprehensive overview of recent advancements in green synthetic approaches for bioactive heterocyclic compounds and their pharmaceutical applications. The review focuses on environmentally friendly methodologies such as microwave-assisted synthesis, ultrasound-assisted synthesis, solvent-free reactions, multicomponent reactions, nanocatalysis, biocatalysis, photocatalysis, and electrochemical synthesis.

Additionally, the review discusses the biological significance and therapeutic importance of heterocyclic compounds in medicinal chemistry. Comparative analysis between conventional and green synthetic methodologies is also presented to highlight the advantages of sustainable approaches in terms of efficiency, environmental safety, and industrial applicability.

Furthermore, recent developments reported between 2020 and 2026 are critically summarized to provide updated insights into sustainable pharmaceutical synthesis. Overall, this review aims to serve as a valuable scientific resource for researchers working in the fields of green chemistry, medicinal chemistry, and heterocyclic drug development.

2. BIOACTIVE HETEROCYCLIC COMPOUNDS

2.1 Classification of Heterocyclic Compounds

Heterocyclic compounds are cyclic organic molecules that contain at least one heteroatom such as nitrogen, oxygen, or sulfur within their ring structure. These compounds constitute one of the most significant classes of organic molecules because of their wide occurrence in natural products, pharmaceuticals, agrochemicals, dyes, and biologically active materials [25]. The incorporation of heteroatoms into cyclic frameworks alters the electronic distribution, polarity, and physicochemical properties of molecules, thereby enhancing their biological activity and pharmaceutical utility [26].

Heterocyclic compounds are broadly classified according to the type of heteroatom present in the ring system. Nitrogen-containing heterocycles are the most extensively investigated class owing to their diverse therapeutic applications, followed by oxygen-containing and sulfur-containing heterocycles [27]. These compounds serve as important pharmacophores in medicinal chemistry because they can efficiently interact with enzymes, receptors, nucleic acids, and other biological targets [28].

Class	Examples	Major Biological Activities
Nitrogen-containing heterocycles	Pyridine, Pyrimidine, Quinoline, Imidazole, Indole	Anticancer, Antimicrobial, CNS activity
Oxygen-containing heterocycles	Furan, Coumarin	Anti-inflammatory, Antioxidant
Sulfur-containing heterocycles	Thiophene, Thiazole	Antibacterial, Antiviral

Table 3: Classification of Important Bioactive Heterocyclic Compounds

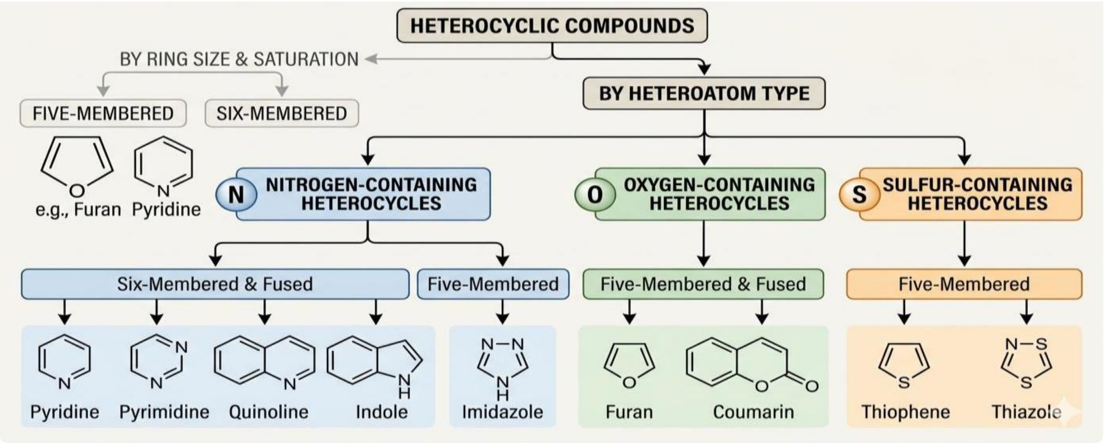

Figure 1: Structural Classification of Bioactive Heterocyclic Compounds

2.1.1 Nitrogen-Containing Heterocycles

Nitrogen-containing heterocycles represent one of the most pharmacologically important classes of organic compounds due to their remarkable biological and therapeutic properties [29]. The nitrogen atom contributes electron density and hydrogen-bonding capability, thereby improving receptor binding affinity and pharmacological activity [30].

Pyridine:

Pyridine is a six-membered aromatic heterocycle containing one nitrogen atom in the ring structure. Pyridine derivatives exhibit broad pharmacological activities including antimicrobial, anticancer, anti-inflammatory, and antihypertensive properties [31]. Pyridine-containing compounds are widely employed in medicinal chemistry because of their metabolic stability and excellent bioavailability.

Pyrimidine:

Pyrimidine is an aromatic six-membered heterocyclic ring containing two nitrogen atoms at positions 1 and 3. Pyrimidine derivatives are structurally related to nucleic acid bases and therefore play an essential role in biological systems [32]. Several clinically important antiviral and anticancer agents contain pyrimidine scaffolds because of their ability to inhibit nucleic acid biosynthesis and cellular proliferation [33].

Quinoline:

Quinoline is a fused bicyclic heterocycle composed of benzene and pyridine rings. Quinoline derivatives exhibit diverse biological activities including antimalarial, antibacterial, anticancer, anti-inflammatory, and antiviral activities [34]. Due to their favorable pharmacokinetic properties, quinoline-based molecules are extensively utilized in modern drug discovery programs.

Imidazole:

Imidazole is a five-membered aromatic heterocycle containing two nitrogen atoms. Imidazole derivatives possess significant antifungal, antibacterial, antiviral, anticancer, and anti-inflammatory activities [35]. Therapeutically important compounds such as Metronidazole and Ketoconazole contain imidazole moieties.

Indole:

Indole is a bicyclic aromatic heterocycle consisting of a benzene ring fused with a pyrrole ring. Indole derivatives are widely recognized for their anticancer, antimicrobial, antioxidant, anti-inflammatory, and neurological activities [36]. The indole scaffold is considered a privileged structure in medicinal chemistry because of its widespread occurrence in biologically active natural products and pharmaceutical agents.

2.1.2 Oxygen-Containing Heterocycles

Oxygen-containing heterocycles exhibit considerable pharmaceutical and industrial importance owing to their unique electronic properties and broad biological activities [37]. These compounds are extensively utilized in the synthesis of therapeutic agents and natural products.

Furan:

Furan is a five-membered aromatic heterocycle containing one oxygen atom. Furan derivatives possess diverse biological activities including antimicrobial, anticancer, antioxidant, and anti-inflammatory properties [38]. Furan-containing molecules are frequently used in pharmaceutical and agrochemical industries because of their favorable biological profiles.

Coumarin:

Coumarin is a benzopyrone derivative composed of fused benzene and α-pyrone rings. Coumarin derivatives exhibit anticoagulant, antimicrobial, antioxidant, anticancer, antiviral, and anti-inflammatory activities [39]. Due to their excellent pharmacological potential, coumarin-based compounds continue to attract significant attention in medicinal chemistry research.

2.1.3 Sulfur-Containing Heterocycles

Sulfur-containing heterocycles are important classes of biologically active compounds widely utilized in pharmaceutical chemistry [40]. The sulfur atom contributes enhanced lipophilicity and electronic flexibility, thereby improving biological interactions and therapeutic efficacy.

Thiophene:

Thiophene is a sulfur-containing aromatic five-membered heterocycle exhibiting antibacterial, anticancer, anti-inflammatory, anticonvulsant, and antioxidant activities [41]. Thiophene derivatives are widely investigated because of their excellent pharmacological and physicochemical properties.

Thiazole:

Thiazole is a five-membered aromatic heterocycle containing both sulfur and nitrogen atoms within the ring structure. Thiazole derivatives exhibit broad biological activities including antimicrobial, anticancer, anti-inflammatory, antiviral, and antitubercular properties [42]. Several approved drugs contain thiazole nuclei because of their potent therapeutic effects.

2.2 Biological Activities of Heterocyclic Compounds

Heterocyclic compounds exhibit diverse biological activities owing to their structural versatility and ability to interact efficiently with various biological targets [43]. These compounds have become indispensable in medicinal chemistry and pharmaceutical research because they improve receptor selectivity, metabolic stability, and therapeutic efficacy.

2.2.1 Anticancer Activity

Numerous heterocyclic compounds exhibit potent anticancer activity by inhibiting tumor cell proliferation, inducing apoptosis, and targeting specific signaling pathways associated with cancer progression [46]. Quinoline, indole, pyrimidine, and thiazole derivatives are extensively investigated as anticancer agents due to their remarkable cytotoxic and kinase inhibitory properties.

2.2.2 Antimicrobial Activity

Heterocyclic compounds demonstrate broad-spectrum antimicrobial activity against various bacterial and fungal pathogens [47]. Imidazole, quinoline, and thiazole derivatives interfere with microbial cell membrane integrity, nucleic acid synthesis, and essential metabolic pathways, thereby exhibiting potent antibacterial and antifungal effects.

2.2.3 Antiviral Activity

Several heterocyclic compounds possess antiviral activity against RNA and DNA viruses [48]. Pyrimidine and quinoline derivatives are particularly important because of their ability to inhibit viral replication enzymes and interfere with viral nucleic acid synthesis.

2.2.4 Anti-inflammatory Activity

Heterocyclic compounds such as coumarin, indole, and thiophene derivatives exhibit anti-inflammatory activity through inhibition of inflammatory mediators and cyclooxygenase enzymes [49]. These compounds have shown promising therapeutic potential in inflammatory disorders and autoimmune diseases.

2.2.5 Antidiabetic Activity

Various heterocyclic compounds exhibit significant antidiabetic activity by improving insulin sensitivity and inhibiting carbohydrate-metabolizing enzymes [50]. Thiazole and pyridine derivatives have emerged as promising therapeutic agents for diabetes management.

2.2.6 CNS Activity

Several heterocyclic scaffolds possess central nervous system (CNS) activity due to their interactions with neurotransmitter receptors and enzymes [51]. Indole and pyridine derivatives are extensively utilized in the development of anxiolytic, antidepressant, antipsychotic, and anticonvulsant agents.

3. GREEN CHEMISTRY IN HETEROCYCLIC SYNTHESIS

3.1 Concept of Green Chemistry

Green chemistry refers to the design of chemical products and processes that minimize or eliminate the use and generation of hazardous substances [52]. The concept was introduced to reduce environmental pollution, improve process efficiency, and promote sustainable chemical manufacturing [53]. In heterocyclic synthesis, green chemistry focuses on the use of eco-friendly solvents, recyclable catalysts, energy-efficient methods, and waste reduction strategies [54].

Green synthetic approaches such as microwave-assisted synthesis, ultrasound irradiation, solvent-free reactions, and biocatalysis have gained significant attention because they reduce toxic waste generation and improve reaction efficiency [55]. These methods play an important role in sustainable pharmaceutical synthesis and environmentally benign industrial processes.

Green Concept	Application in Heterocyclic Synthesis
Waste prevention	Reduction of by-products
Safer solvents	Water, ethanol, ionic liquids
Energy efficiency	Microwave and ultrasound synthesis
Catalysis	Nanocatalysts and biocatalysts
Renewable resources	Sustainable feedstocks

Table 4: Major Concepts of Green Chemistry in Heterocyclic Synthesis

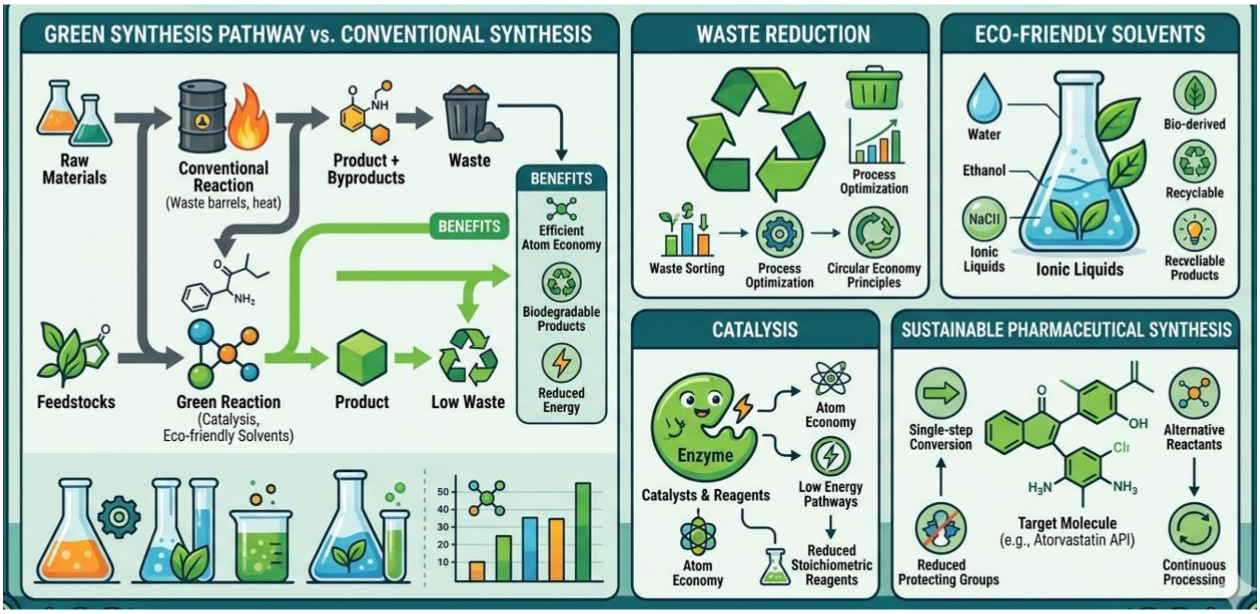

Figure 2: Concept and Applications of Green Chemistry

3.2 Principles of Green Chemistry

The principles of green chemistry were developed to encourage environmentally safe and sustainable chemical processes [56]. These principles emphasize waste prevention, atom economy, safer solvents, renewable feedstocks, catalysis, and energy-efficient synthesis [57].

Among the twelve principles, atom economy, catalytic reactions, safer reaction conditions, and reduction of hazardous substances are particularly important in heterocyclic synthesis [58]. The application of these principles significantly improves process sustainability and reduces environmental impact.

3.3 Green Chemistry Metrics

Green chemistry metrics are quantitative tools used to evaluate the environmental efficiency and sustainability of chemical processes [59]. These metrics help compare conventional and green synthetic methods in terms of waste generation, resource utilization, and reaction efficiency.

Atom Economy

Atom economy measures the incorporation efficiency of reactant atoms into the desired final product [60]. Higher atom economy indicates minimal waste generation and improved sustainability. Multicomponent reactions and one-pot syntheses generally exhibit excellent atom economy.

E-factor

The environmental factor (E-factor) represents the amount of waste generated per unit mass of product formed [61]. Lower E-factor values indicate greener and more environmentally friendly chemical processes.

Carbon Efficiency

Carbon efficiency evaluates the conversion of carbon atoms from reactants into useful products [62]. High carbon efficiency reduces carbon loss and improves the sustainability of pharmaceutical synthesis.

3.4 Advantages of Green Synthetic Approaches

Green synthetic approaches offer several advantages over conventional synthetic methods including reduced waste generation, lower energy consumption, shorter reaction times, improved yields, and minimal environmental pollution [63]. These approaches also reduce the use of hazardous solvents and toxic reagents, thereby enhancing laboratory safety and industrial sustainability [64].

Microwave-assisted synthesis, solvent-free reactions, and nanocatalysis significantly improve reaction efficiency and selectivity while minimizing operational costs [65]. Consequently, green chemistry has become an essential component of sustainable pharmaceutical manufacturing and modern heterocyclic synthesis.

4. GREEN SYNTHETIC APPROACHES FOR HETEROCYCLIC COMPOUNDS:

4.1 Microwave-Assisted Synthesis:

Microwave-assisted synthesis is an important green synthetic technique widely used for the preparation of heterocyclic compounds because it provides rapid heating, shorter reaction time, and higher product yield [66]. The method is based on dielectric heating, where microwave energy interacts with polar molecules and ions present in the reaction medium [67]. Uniform internal heating accelerates reaction kinetics and improves reaction efficiency [68]. Microwave synthesis is extensively applied for the synthesis of pyrimidine, quinoline, imidazole, and indole derivatives possessing antimicrobial and anticancer activities [69]. The major advantages of this technique include reduced solvent usage, low energy consumption, eco-friendly conditions, and improved reaction yield.

4.2 Ultrasound-Assisted Synthesis:

Ultrasound-assisted synthesis utilizes ultrasonic waves to promote chemical reactions under mild and environmentally friendly conditions [70]. The technique operates through acoustic cavitation, where formation and collapse of microscopic bubbles generate localized high temperature and pressure, thereby accelerating reaction rates [71]. Ultrasound-assisted methods are widely applied in the synthesis of imidazole, pyridine, and thiazole derivatives with improved yield and reduced reaction time [72].

4.3 Solvent-Free Synthesis:

Solvent-free synthesis is considered an environmentally benign approach because it eliminates the use of hazardous organic solvents during chemical reactions [73]. Mechanochemical methods such as grinding and milling provide mechanical energy to facilitate chemical transformations [74]. Grinding techniques improve reactant interaction and minimize waste generation, making the process economical and sustainable for heterocyclic synthesis [75].

4.4 Multicomponent Reactions (MCRs):

Multicomponent reactions involve the simultaneous reaction of three or more reactants in a single reaction vessel to produce structurally complex heterocyclic compounds [76]. One-pot synthesis reduces purification steps, saves energy, and minimizes waste generation [77]. MCRs are highly atom-efficient because most of the reactant atoms are incorporated into the final product, making them valuable green synthetic strategies [78].

4.5 Ionic Liquids and Deep Eutectic Solvents:

Ionic liquids and deep eutectic solvents are emerging as environmentally friendly alternatives to volatile organic solvents in heterocyclic synthesis [79]. These solvent systems possess low vapor pressure, high thermal stability, and excellent solvation properties [80]. Additionally, they can often be recycled and reused multiple times without significant loss of efficiency, thereby supporting sustainable synthesis [81].

4.6 Nanocatalysis:

Nanocatalysis has become an important green approach due to the high surface area and excellent catalytic activity of nanoparticles [82]. Metal nanoparticles such as silver, gold, and palladium nanoparticles are extensively utilized in heterocyclic synthesis [83]. Magnetic nanocatalysts facilitate easy catalyst separation and recovery using external magnetic fields [84]. The reusability of nanocatalysts significantly reduces catalyst waste and operational cost [85].

4.7 Biocatalysis and Enzyme-Mediated Synthesis:

Biocatalysis utilizes enzymes and biological catalysts for sustainable chemical transformations under mild reaction conditions [86]. Enzymes exhibit high selectivity and catalytic efficiency, making them valuable in heterocyclic synthesis [87]. Most biocatalytic reactions are performed in aqueous media under ambient temperature and pressure, thereby reducing environmental impact and improving process safety [88].

4.8 Photocatalytic Methods:

Photocatalytic synthesis utilizes light energy to promote chemical transformations in an environmentally sustainable manner [89]. Visible-light synthesis enables energy-efficient preparation of heterocyclic compounds under mild conditions [90]. Photoredox catalysis facilitates electron transfer reactions that improve selectivity and reaction efficiency in organic synthesis [91].

4.9 Electrochemical Synthesis:

Electrochemical synthesis is a sustainable method that utilizes electric current to drive oxidation and reduction reactions without hazardous chemical reagents [92]. Electro-organic reactions reduce the requirement for toxic oxidizing and reducing agents [93]. These methods minimize chemical waste and improve selectivity in heterocyclic synthesis [94].

4.10 Flow Chemistry and Continuous Processing:

Flow chemistry involves continuous movement of reactants through reactors under controlled conditions [95]. Continuous processing improves heat transfer, reaction control, and process safety while minimizing waste generation [96]. Due to its scalability and efficiency, flow chemistry is increasingly applied in pharmaceutical industries for sustainable heterocyclic synthesis [97].

Method	Major Advantages
Microwave synthesis	Rapid heating, high yield
Ultrasound synthesis	Mild reaction conditions
Solvent-free synthesis	Reduced toxicity
Multicomponent reactions	High atom economy
Nanocatalysis	Reusable catalysts
Biocatalysis	Eco-friendly reactions
Flow chemistry	Industrial scalability

Table 5: Green Synthetic Approaches and Their Advantages

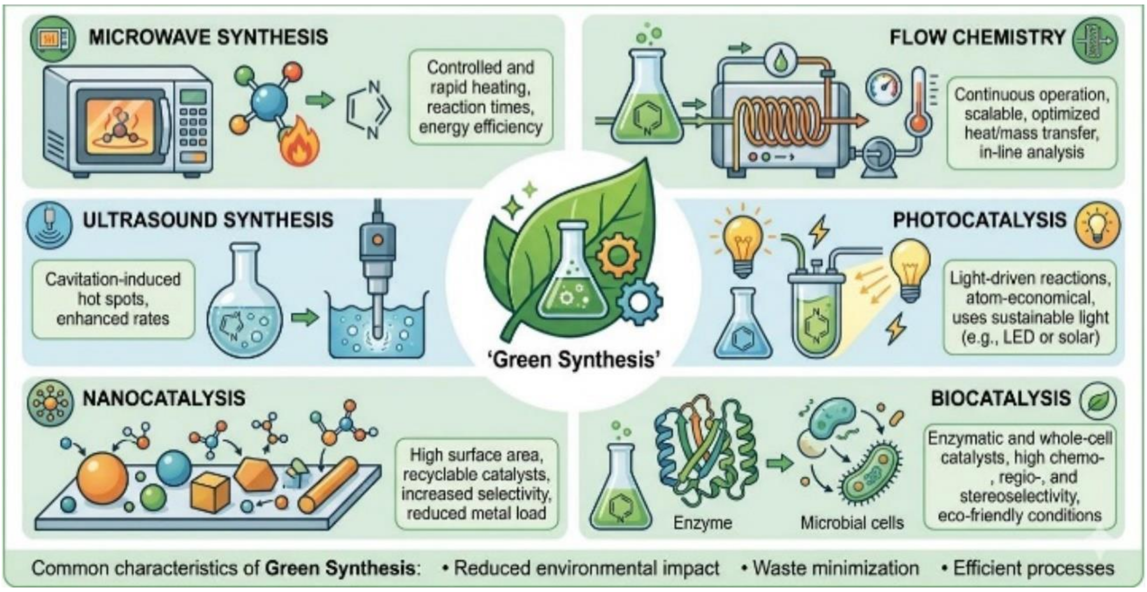

Figure 3: Green Synthetic Approaches for Heterocyclic Compounds

5. RECENT ADVANCES (2020–2026):

5.1 Recent Catalytic Developments

Recent years have witnessed significant advancements in green catalytic systems for heterocyclic synthesis, particularly involving transition-metal catalysis, photocatalysis, electrocatalysis, and organocatalysis [98]. Modern catalytic approaches provide improved selectivity, reduced reaction time, and enhanced atom economy under environmentally benign conditions. Metal-catalyzed cyclization reactions have become highly effective for constructing nitrogen-containing heterocycles with pharmaceutical importance [99]. Additionally, electrochemical and photoredox catalytic systems are increasingly utilized because they minimize the requirement for hazardous oxidizing and reducing agents [100].

5.2 AI-Assisted Green Synthesis

Artificial intelligence (AI) has emerged as a promising tool in sustainable chemical synthesis and catalyst optimization [101]. AI-based retrosynthetic analysis assists in predicting efficient synthetic pathways with reduced waste generation and improved process efficiency [102]. Machine learning models are also being applied in catalyst design, reaction optimization, and green solvent selection, thereby accelerating sustainable drug development and heterocyclic synthesis [103].

5.3 Hybrid Catalytic Systems

Hybrid catalytic systems combining photocatalysis, nanocatalysis, electrocatalysis, and biocatalysis have gained considerable attention in recent years [104]. These integrated systems improve catalytic efficiency, selectivity, and recyclability while minimizing environmental impact. Hybrid catalysts are increasingly utilized in multicomponent and one-pot heterocyclic syntheses because they provide sustainable and energy-efficient reaction conditions [98].

5.4 Sustainable Drug Synthesis Approaches

Sustainable pharmaceutical synthesis focuses on minimizing toxic reagents, reducing solvent consumption, and improving energy efficiency [105]. Green methodologies such as flow chemistry, microwave-assisted synthesis, solvent-free reactions, and biocatalysis are now widely employed in the synthesis of bioactive heterocyclic drugs [106]. Continuous processing and recyclable catalytic systems have further improved industrial-scale sustainable drug manufacturing.

5.5 Novel Green Methodologies Reported in Literature

Several novel green methodologies reported between 2020 and 2026 include visible-light photocatalysis, electrochemical heterocyclic synthesis, deep eutectic solvent systems, and catalyst-free multicomponent reactions [107]. Recent studies have also demonstrated the use of carbon dioxide as a sustainable C1 source for heterocyclic synthesis through photochemical and electrochemical approaches [108]. These innovative methodologies significantly reduce waste generation and enhance the sustainability of pharmaceutical synthesis.

Recent Advancement	Major Benefit
AI-assisted synthesis	Reaction optimization
Hybrid catalysis	Improved efficiency
Photoredox catalysis	Mild reaction conditions
Electrochemical synthesis	Reduced chemical waste
Flow chemistry	Industrial scalability
Deep eutectic solvents	Green solvent system

Table 6: Recent Advances in Green Heterocyclic Synthesis (2020–2026)

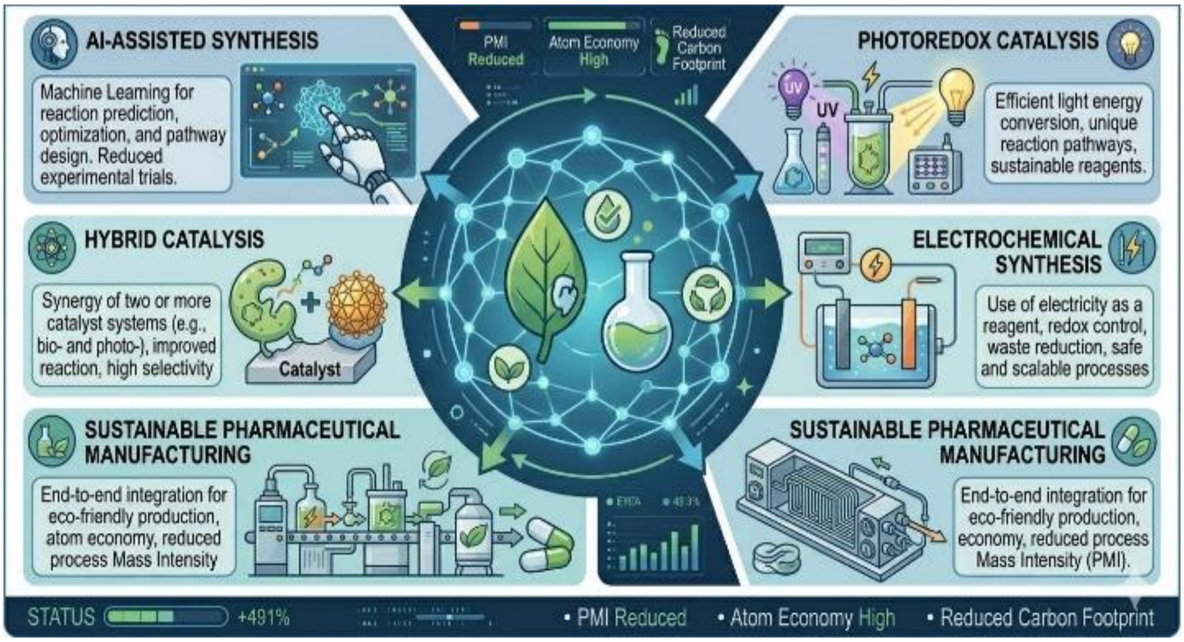

Figure 4: Recent Green Technological Advances in Heterocyclic Synthesis

6. PHARMACEUTICAL APPLICATIONS

6.1 Heterocyclic Drugs in Clinical Use

Heterocyclic compounds play an essential role in modern drug discovery and pharmaceutical therapy due to their diverse biological activities and favorable pharmacological properties [109]. A large number of clinically approved drugs contain heterocyclic scaffolds because these structures enhance receptor binding, metabolic stability, and therapeutic efficacy [110]. Nitrogen-, oxygen-, and sulfur-containing heterocycles are widely utilized in antimicrobial, anticancer, anti-inflammatory, and central nervous system drugs.

Examples

- Fluconazole is a triazole-containing antifungal drug used for the treatment of fungal infections [111].
- Diazepam contains a benzodiazepine heterocyclic scaffold and is widely prescribed

for anxiety, seizures, and muscle spasms [112].

- Celecoxib is a pyrazole-containing anti-inflammatory drug used in arthritis and pain management [113].
- Imatinib contains heterocyclic pharmacophores and is extensively used in chronic myeloid leukemia therapy [114].

6.2 Green Synthesis in Pharmaceutical Manufacturing

Green synthesis has become increasingly important in pharmaceutical manufacturing because it reduces toxic waste generation, energy consumption, and environmental pollution [115]. Techniques such as microwave-assisted synthesis, flow chemistry, biocatalysis, and solvent-free reactions are now widely adopted in industrial drug synthesis [116]. The implementation of green methodologies improves process efficiency, safety, and sustainability while lowering manufacturing costs.

6.3 Industrial Applications

Green synthetic approaches are extensively applied in pharmaceutical industries for large-scale production of heterocyclic compounds [117]. Continuous flow processing, recyclable catalysts, and eco-friendly solvents have improved industrial productivity and minimized hazardous waste generation [118]. Nanocatalysis and biocatalysis are also gaining industrial importance because of their high selectivity and catalyst recyclability.

6.4 Regulatory and Environmental Perspectives

Regulatory agencies and environmental organizations strongly encourage the implementation of green chemistry principles in pharmaceutical production [119]. Guidelines focusing on waste minimization, safer solvents, sustainable manufacturing, and reduction of hazardous chemicals have promoted environmentally responsible drug synthesis [120]. Green pharmaceutical manufacturing not only reduces environmental impact but also improves compliance with international sustainability standards.

Drug	**Heterocyclic Scaffold**	**Therapeutic Application**
Fluconazole	Triazole	Antifungal
Diazepam	Benzodiazepine	Anxiolytic
Celecoxib	Pyrazole	Anti-inflammatory
Imatinib	Pyrimidine derivative	Anticancer

Table 7: Pharmaceutical Applications of Heterocyclic Compounds

7. COMPARATIVE ANALYSIS

7.1 Conventional vs Green Synthetic Methods

Conventional synthetic methods used for heterocyclic synthesis generally involve hazardous organic solvents, toxic reagents, high energy consumption, and prolonged reaction times [121]. These methods often generate large amounts of chemical waste and may negatively impact the environment. In contrast, green synthetic approaches focus on eco-friendly solvents, recyclable catalysts, energy-efficient techniques, and waste minimization [122]. Green methods such as microwave-assisted synthesis, solvent-free reactions, and flow chemistry provide improved sustainability, higher efficiency, and safer reaction conditions.

7.2 Comparison Based on Different Parameters

Green synthetic approaches are increasingly preferred over conventional methods because they offer significant advantages in terms of yield, reaction time, toxicity reduction, operational cost, energy efficiency, and environmental safety [123].

Yield

Green synthetic methods generally provide higher product yield because of improved reaction selectivity and optimized catalytic conditions [124].

Reaction Time

Techniques such as microwave-assisted and ultrasound-assisted synthesis significantly reduce reaction time compared to conventional heating methods [125].

Toxicity

Green synthesis minimizes the use of hazardous solvents and toxic reagents, thereby improving laboratory and environmental safety [126].

Cost

Although some green technologies require initial investment, reduced solvent consumption, catalyst recyclability, and energy savings lower the overall production cost [127].

Energy Consumption

Modern green approaches such as microwave synthesis and flow chemistry consume less energy due to efficient heat transfer and controlled reaction conditions [128].

Environmental Impact

Green chemistry significantly reduces waste generation, pollution, and carbon emissions, making pharmaceutical synthesis more sustainable [129].

7.3 Comparative Tables and Case Studies

Several studies have demonstrated the superiority of green synthetic methods over conventional techniques in heterocyclic synthesis [130]. Microwave-assisted synthesis of imidazole and pyrimidine derivatives has shown shorter reaction times and higher yields compared to traditional reflux methods [131]. Similarly, solvent-free multicomponent reactions have demonstrated improved atom economy and reduced waste generation [132].

Parameter	Conventional Methods	Green Synthetic Methods
Reaction Time	Longer	Shorter
Product Yield	Moderate	Higher
Solvent Use	Toxic organic solvents	Eco-friendly solvents
Energy Consumption	High	Low
Waste Generation	More	Minimal
Environmental Impact	Harmful	Sustainable

Table 8: Comparison Between Conventional and Green Synthetic Methods

8. CHALLENGES AND FUTURE PERSPECTIVES

8.1 Limitations of Current Green Methods

Despite significant advancements, several limitations are associated with current green synthetic approaches for heterocyclic compounds [133]. Some green methodologies require expensive catalysts, specialized equipment, or complex optimization procedures. In certain cases, green reactions may exhibit limited substrate compatibility and lower scalability compared to conventional methods [134]. Additionally, recovery and recycling of catalysts and solvents may sometimes reduce process efficiency.

8.2 Scale-Up Challenges

Scale-up of green synthetic methods from laboratory level to industrial production remains a major challenge [135]. Techniques such as microwave-assisted synthesis and photochemical reactions often face difficulties in maintaining uniform energy distribution during large-scale operations [136].

Continuous monitoring, reactor design, and process optimization are essential for achieving efficient industrial-scale green synthesis.

8.3 Industrial Adaptation Issues

Although green chemistry offers numerous environmental and economic benefits, industrial adaptation is sometimes limited by high initial investment costs and infrastructure requirements [137]. Pharmaceutical industries may require modification of existing manufacturing systems to accommodate green technologies such as flow chemistry, nanocatalysis, and biocatalysis [138]. Regulatory validation and process standardization also remain important challenges for industrial implementation.

8.4 Future Scope of Sustainable Pharmaceutical Synthesis

The future of sustainable pharmaceutical synthesis is expected to focus on waste-free reactions, renewable feedstocks, recyclable catalysts, and energy-efficient technologies [139]. Green approaches such as continuous flow processing, artificial intelligence-assisted synthesis, electrochemical synthesis, and biocatalysis are likely to play a major role in next-generation pharmaceutical manufacturing [140]. Increasing global emphasis on environmental sustainability will further accelerate the development of eco-friendly heterocyclic synthesis.

8.5 Emerging Trends in Green Medicinal Chemistry

Recent trends in green medicinal chemistry include visible-light photocatalysis, carbon dioxide utilization, deep eutectic solvents, and hybrid catalytic systems [141]. Artificial intelligence and machine learning are also emerging as powerful tools for reaction prediction, catalyst optimization, and sustainable drug design [142]. These innovative approaches are expected to improve efficiency, reduce environmental impact, and support the development of safer pharmaceutical products.

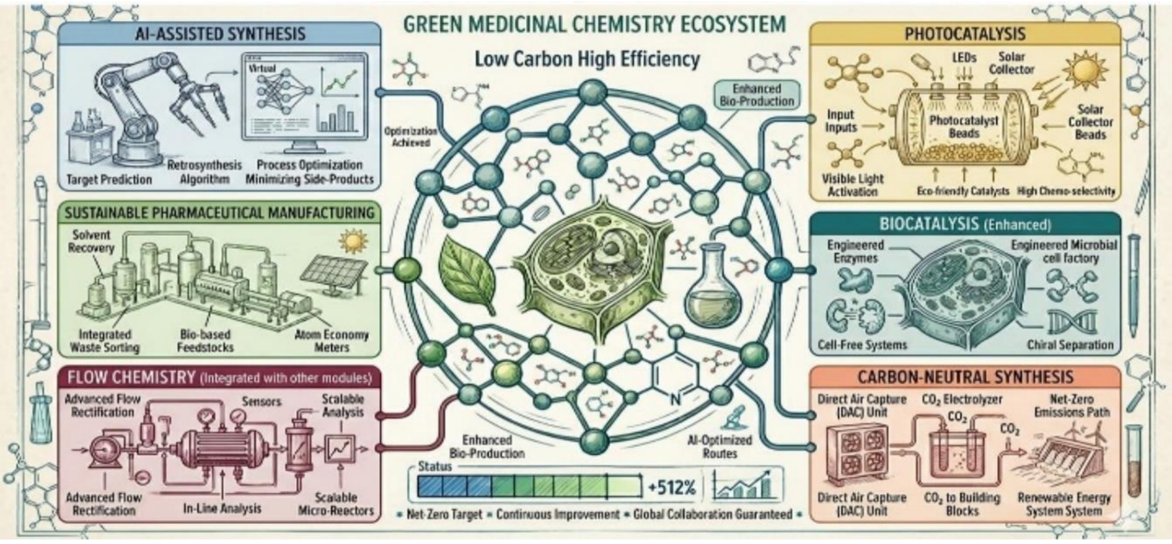

Figure 5: Future Perspectives of Green Medicinal Chemistry

CONCLUSION

Green synthetic approaches for bioactive heterocyclic compounds have emerged as highly important strategies in modern medicinal chemistry and sustainable pharmaceutical synthesis. Heterocyclic compounds continue to play a major role in drug discovery due to their wide range of biological activities including anticancer, antimicrobial, antiviral, anti-inflammatory, antidiabetic, and central nervous system activities. Conventional synthetic methods, although effective, are often associated with toxic solvents, high energy consumption, hazardous waste generation, and environmental pollution [145]. Therefore, the development of environmentally friendly synthetic methodologies has become essential for sustainable pharmaceutical manufacturing.

The present review highlights various green synthetic approaches including microwave-assisted synthesis, ultrasound-assisted synthesis, solvent-free synthesis, multicomponent reactions, nanocatalysis, biocatalysis, photocatalysis, electrochemical synthesis, and flow chemistry. These techniques offer several advantages such as reduced reaction time, improved product yield, lower toxicity, enhanced atom economy, energy efficiency, and minimized environmental impact. Recent advancements involving artificial intelligence-assisted synthesis, hybrid catalytic systems, and sustainable industrial processing have further strengthened the role of green chemistry in heterocyclic drug synthesis.

Green chemistry has significantly contributed to the development of safer, cost-effective, and sustainable pharmaceutical processes. The integration of recyclable catalysts, eco-friendly solvents, renewable feedstocks, and continuous processing technologies has improved industrial applicability and environmental safety. Furthermore, increasing regulatory emphasis on sustainable manufacturing is expected to accelerate the adoption of green methodologies in pharmaceutical industries worldwide.

In the future, sustainable pharmaceutical synthesis is expected to focus on carbon-neutral processes, artificial intelligence-driven reaction optimization, renewable energy utilization, and highly selective catalytic systems. Emerging technologies such as photoredox catalysis, electrochemical synthesis, deep eutectic solvents, and biocatalytic transformations are likely to play a major role in next-generation medicinal chemistry. Overall, green synthetic approaches provide a promising pathway toward environmentally responsible and economically sustainable heterocyclic drug development.

REFERENCES

1. Joule JA, Mills K. Heterocyclic Chemistry. 5th ed. Oxford: Wiley-Blackwell; 2010.
2. Katritzky AR, Ramsden CA, Scriven EFV, Taylor RJK. Comprehensive Heterocyclic Chemistry III. Oxford: Elsevier; 2008.
3. Vitaku E, Smith DT, Njardarson JT. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. J Med Chem. 2014;57(24):10257-74.
4. Gupta RR, Kumar M, Gupta V. Heterocyclic Chemistry. Berlin: Springer; 1998.
5. Eicher T, Hauptmann S, Speicher A. The Chemistry of Heterocycles. 3rd ed. Weinheim: Wiley-VCH; 2012.
6. Brown DG, Boström J. Analysis of past and present synthetic methodologies on medicinal chemistry: where have all the new reactions gone? J Med Chem. 2016;59(10):4443-58.
7. Taylor AP, Robinson RP, Fobian YM, Blakemore DC, Jones LH, Fadeyi O. Modern advances in heterocyclic chemistry in drug discovery. Org Biomol Chem. 2016;14(28):6611-37.
8. Kerru N, Gummidi L, Maddila S, Gangu KK, Jonnalagadda SB. A review on recent advances in nitrogen-containing molecules and their biological applications. Molecules. 2020;25(8):1909.
9. Chhajed SS, Padwal MS, Dighe NS, Pattan SR. Recent advances in the synthesis and biological applications of heterocyclic compounds. Int J Pharm Sci Rev Res. 2019;58(2):45-56.
10. Heravi MM, Zadsirjan V. Prescribed drugs containing nitrogen heterocycles: an overview. RSC Adv. 2020;10:44247-511.
11. Dömling A, Wang W, Wang K. Chemistry and biology of multicomponent reactions. Chem Rev. 2012;112(6):3083-135.
12. Baell JB, Holloway GA. New substructure filters for removal of pan assay interference compounds (PAINS). J Med Chem. 2010;53(7):2719-40.
13. Roughley SD, Jordan AM. The medicinal chemist’s toolbox: an analysis of reactions used in the pursuit of drug candidates. J Med Chem. 2011;54(10):3451-79.
14. Lionta E, Spyrou G, Vassilatis DK, Cournia Z. Structure-based virtual screening for drug discovery. Curr Top Med Chem. 2014;14(16):1923-38.
15. Keri RS, Patil MR, Patil SA, Budagumpi S. A comprehensive review in current developments of benzothiazole-based molecules in medicinal chemistry. Eur J Med Chem. 2015;89:207-51.
16. Anastas PT, Warner JC. Green Chemistry: Theory and Practice. New York: Oxford University Press; 1998.

17. Sheldon RA. Fundamentals of green chemistry: efficiency in reaction design. Chem Soc Rev. 2012;41(4):1437-51.
18. Clark JH, Tavener SJ. Alternative solvents: shades of green. Org Process Res Dev. 2007;11(1):149-55.
19. Poliakoff M, Fitzpatrick JM, Farren TR, Anastas PT. Green chemistry: science and politics of change. Science. 2002;297(5582):807-10.
20. Li CJ, Trost BM. Green chemistry for chemical synthesis. Proc Natl Acad Sci U S A. 2008;105(36):13197-202.
21. Kappe CO. Controlled microwave heating in modern organic synthesis. Angew Chem Int Ed Engl. 2004;43(46):6250-84.
22. Sheldon RA. The E factor 25 years on: the rise of green chemistry and sustainability. Green Chem. 2017;19:18-43.
23. Clark JH. Green chemistry: challenges and opportunities. Green Chem. 1999;1(1):1-8.
24. Sheldon RA. Green and sustainable manufacture of chemicals from biomass: state of the art. Green Chem. 2014;16:950-63.
25. Almansour AI, Arumugam N, Kumar RS, Periyasami G. Recent advances in biologically active heterocyclic compounds. Bioorg Chem. 2020;95:103520.
26. Khan I, Ibrar A, Abbas N, Saeed A. Recent advances in the structural library of functionalized quinolines and their medicinal applications: a review. Eur J Med Chem. 2014;76:193-244.
27. Gomtsyan A. Heterocycles in drugs and drug discovery. Chem Heterocycl Compd. 2012;48(1):7-10.
28. Dua R, Shrivastava S, Sonwane SK, Srivastava SK. Pharmacological significance of synthetic heterocycles scaffold: a review. Adv Biol Res. 2011;5(3):120-44.
29. Vitaku E, Smith DT, Njardarson JT. Analysis of nitrogen heterocycles in FDA-approved pharmaceuticals. J Med Chem. 2014;57(24):10257-74.
30. Kerru N, Gummidi L, Maddila S, Gangu KK, Jonnalagadda SB. Green synthesis and medicinal applications of nitrogen-containing heterocycles. Molecules. 2020;25(8):1909.
31. Patel NB, Shaikh FM. Synthesis and antimicrobial activity of pyridine derivatives. Saudi Pharm J. 2010;18(3):129-36.
32. Sharma V, Chitranshi N, Agarwal AK. Significance and biological importance of pyrimidine in the microbial world. Int J Med Chem. 2014;2014:202784.
33. US Patent US20130267465A1. Pyrimidine derivatives and their pharmaceutical applications. United States Patent Office; 2013.
34. Musiol R. An overview of quinoline as a privileged scaffold in cancer drug discovery. Expert Opin Drug Discov. 2017;12(6):583-97.
35. Zhang L, Peng XM, Damu GLV, Geng RX, Zhou CH. Comprehensive review on the medicinal chemistry of imidazole derivatives. Med Res Rev. 2014;34(2):340-437.
36. Kumari A, Singh RK. Medicinal chemistry of indole derivatives: current to future therapeutic prospectives. Bioorg Chem. 2019;89:103021.
37. Nepali K, Lee HY, Liou JP. Coumarin-based anticancer agents: recent developments. Future Med Chem. 2019;11(15):1953-76.
38. Bhardwaj A, Kaur J, Wuest M, Wuest F. Furan derivatives as bioactive agents. Mini Rev Med Chem. 2015;15(11):870-83.
39. Borges F, Roleira F, Milhazes N, Santana L, Uriarte E. Simple coumarins and analogues in medicinal chemistry. Curr Med Chem. 2005;12(8):887-916.
40. Siddiqui N, Arshad MF, Ahsan W, Alam MS. Thiazoles: a valuable insight into medicinal chemistry. Int J Pharm Sci Drug Res. 2009;1(3):136-43.
41. Mishra R, Jha KK, Kumar S, Tomer I. Thiophene: a biologically active scaffold. Der Pharma Chem. 2011;3(4):38-54.
42. Chhabria MT, Patel S, Modi P, Brahmkshatriya PS. Thiazole derivatives and their biological activities. Curr Top Med Chem. 2016;16(26):2841-62.
43. Kaur R, Rani V, Abbot V, Kapoor Y, Konar D, Kumar K. Heterocyclic compounds in medicinal chemistry. Eur J Med Chem. 2017;126:767-809.
44. Patel RV, Kumari P, Rajani DP, Chikhalia KH. Medicinal significance of heterocyclic scaffolds. Eur J Med Chem. 2013;67:47-57.
45. Ahmad S, Alam O, Naim MJ, Shaquiquzzaman M, Alam MM, Iqbal M. Biological potential of

heterocyclic compounds. Med Chem Res. 2018;27:2789-821.

46. Nepali K, Sharma S, Sharma M, Bedi PMS, Dhar KL. Heterocyclic anticancer agents: current developments and future perspectives. Eur J Med Chem. 2014;77:422-87.
47. Kaur H, Kumar S, Vishwakarma P, Sharma M, Saxena KK, Kumar A. Antimicrobial heterocycles: recent advances. Eur J Med Chem. 2018;151:401-33.
48. De Clercq E. Strategies in the design of antiviral drugs. Nat Rev Drug Discov. 2002;1(1):13-25.
49. Kumari A, Singh RK. Anti-inflammatory heterocyclic compounds in medicinal chemistry. Bioorg Chem. 2019;89:103021.
50. Patel RV, Park SW. Heterocyclic compounds as antidiabetic agents. Mini Rev Med Chem. 2013;13(11):1579-601.
51. Gupta SP. QSAR studies on CNS-active heterocyclic compounds. Chem Rev. 2013;113(7):5049-87.
52. Anastas PT, Warner JC. Green Chemistry: Theory and Practice. New York: Oxford University Press; 1998.
53. Clark JH. Green chemistry: challenges and opportunities. Green Chem. 1999;1(1):1-8.
54. Sheldon RA. Fundamentals of green chemistry: efficiency in reaction design. Chem Soc Rev. 2012;41(4):1437-51.
55. Li CJ, Trost BM. Green chemistry for chemical synthesis. Proc Natl Acad Sci U S A. 2008;105(36):13197-202.
56. Poliakoff M, Fitzpatrick JM, Farren TR, Anastas PT. Green chemistry: science and politics of change. Science. 2002;297(5582):807-10.
57. Lancaster M. Green Chemistry: An Introductory Text. 3rd ed. Cambridge: Royal Society of Chemistry; 2016.
58. Kappe CO. Controlled microwave heating in modern organic synthesis. Angew Chem Int Ed Engl. 2004;43(46):6250-84.
59. Sheldon RA. The E factor 25 years on: the rise of green chemistry and sustainability. Green Chem. 2017;19:18-43.
60. Trost BM. The atom economy—a search for synthetic efficiency. Science. 1991;254(5037):1471-77.
61. Sheldon RA. Metrics of green chemistry and sustainability: past, present, and future. ACS Sustain Chem Eng. 2018;6(1):32-48.
62. Constable DJC, Curzons AD, Cunningham VL. Metrics to green chemistry— which are the best? Green Chem. 2002;4(6):521-27.
63. Tanaka K. Solvent-Free Organic Synthesis. 2nd ed. Weinheim: Wiley-VCH; 2009.
64. Horváth IT, Anastas PT. Innovations and green chemistry. Chem Rev. 2007;107(6):2169-73.
65. Cintas P, Luche JL. Green chemistry and sonochemistry. Green Chem. 1999;1(3):115-25.
66. Kappe CO. Controlled microwave heating in modern organic synthesis. Angew Chem Int Ed Engl. 2004;43(46):6250-84.
67. Lidström P, Tierney J, Wathey B, Westman J. Microwave assisted organic synthesis—a review. Tetrahedron. 2001;57(45):9225-83.
68. Hayes BL. Microwave Synthesis: Chemistry at the Speed of Light. Matthews: CEM Publishing; 2002.
69. Dallinger D, Kappe CO. Microwave-assisted synthesis in medicinal chemistry. Chem Rev. 2007;107(6):2563-91.
70. Mason TJ, Lorimer JP. Applied Sonochemistry. Weinheim: Wiley-VCH; 2002.
71. Cintas P, Luche JL. Green chemistry and sonochemistry. Green Chem. 1999;1(3):115-25.
72. Cravotto G, Cintas P. Power ultrasound in organic synthesis. Chem Soc Rev. 2006;35(2):180-96.
73. Tanaka K. Solvent-Free Organic Synthesis. Weinheim: Wiley-VCH; 2009.
74. James SL, Adams CJ, Bolm C, et al. Mechanochemistry: opportunities for cleaner synthesis. Chem Soc Rev. 2012;41(1):413-47.
75. Kaupp G. Solid-state molecular syntheses without auxiliaries. CrystEngComm. 2003;5:117-33.
76. Dömling A, Wang W, Wang K. Multicomponent reactions. Chem Rev. 2012;112(6):3083-135.
77. Zhu J, Bienaymé H. Multicomponent Reactions. Wiley-VCH; 2005.
78. Ramón DJ, Yus M. Asymmetric multicomponent reactions. Angew Chem Int Ed Engl. 2005;44(11):1602-34.
79. Welton T. Ionic liquids in catalysis. Coord Chem Rev. 2004;248(21-24):2459-77.
80. Smith EL, Abbott AP, Ryder KS. Deep eutectic solvents and their applications. Chem Rev. 2014;114(21):11060-82.

81. Abbott AP, Capper G, Davies DL, et al. Novel solvent properties of choline chloride/urea mixtures. Chem Commun. 2003;(1):70-71.
82. Polshettiwar V, Varma RS. Green chemistry by nano-catalysis. Green Chem. 2010;12:743-54.
83. Astruc D. Nanoparticles and catalysis. Wiley-VCH; 2008.
84. Lu AH, Salabas EL, Schüth F. Magnetic nanoparticles and applications. Angew Chem Int Ed Engl. 2007;46(8):1222-44.
85. Nasrollahzadeh M, Sajadi SM, Atarod M, et al. Green nanotechnology in organic synthesis. Elsevier; 2019.
86. Sheldon RA, Woodley JM. Role of biocatalysis in sustainable chemistry. Chem Rev. 2018;118(2):801-38.
87. Bornscheuer UT, Kazlauskas RJ. Hydrolases in Organic Synthesis. Wiley-VCH; 2006.
88. Patel RN. Biocatalysis for pharmaceuticals. Bioorg Med Chem. 2018;26(6):1252-74.
89. Ravelli D, Protti S, Fagnoni M. Photogenerated intermediates in synthesis. Chem Rev. 2016;116(17):9850-913.
90. Marzo L, Pagire SK, Reiser O, König B. Visible-light photocatalysis in synthesis. Angew Chem Int Ed Engl. 2018;57(32):10034-72.
91. Prier CK, Rankic DA, MacMillan DWC. Visible light photoredox catalysis. Chem Rev. 2013;113(7):5322-63.
92. Yan M, Kawamata Y, Baran PS. Organic electrochemical methods. Chem Rev. 2017;117(21):13230-319.
93. Horn EJ, Rosen BR, Baran PS. Synthetic organic electrochemistry. ACS Cent Sci. 2016;2(5):302-8.
94. Möhle S, Zirbes M, Rodrigo E, et al. Electrochemical synthesis of organic products. Angew Chem Int Ed Engl. 2018;57(21):6018-41.
95. Plutschack MB, Pieber B, Gilmore K, Seeberger PH. Flow chemistry. Chem Rev. 2017;117(18):11796-893.
96. Porta R, Benaglia M, Puglisi A. Flow chemistry in pharmaceuticals. Org Process Res Dev. 2016;20(1):2-25.
97. Pastre JC, Browne DL, Ley SV. Flow chemistry synthesis of natural products. Chem Soc Rev. 2013;42(23):8849-69.
98. Shen X, Hong G, Wang L. Recent advances in green multi-component reactions for heterocyclic compound construction. Org Biomol Chem. 2025;23:2059-78.
99. Zhang X, Bi W, Cao Z, Shen J, Chen B. Recent developments in the metal-catalyzed synthesis of nitrogenous heterocyclic compounds. Molecules. 2024;29(22):5458.
100. Hashmi SZ, Bareth D, Dwivedi J, Kishore D, Alvi PA. Green advancements towards the electrochemical synthesis of heterocycles. RSC Adv. 2024;14:1-25.
101. Zhong Z, Song J, Feng Z, Liu T, Jia L, Yao S, et al. Recent advances in artificial intelligence for retrosynthesis. arXiv. 2023;2301.05864.
102. Coley CW, Eyke NS, Jensen KF. Autonomous discovery in the chemical sciences part I: progress. Angew Chem Int Ed Engl. 2020;59(51):22858-93.
103. Lai NS, Tew YS, Zhong X, Yin J, Li J, Yan B, et al. An artificial intelligence workflow for catalyst design and optimization. arXiv. 2024;2402.04557.
104. Garg A, Rendina D, Bendale H, Akiyama T, Ojima I. Recent advances in catalytic asymmetric synthesis. Front Chem. 2024;12:1398397.
105. Sheldon RA. Green and sustainable manufacture of chemicals from biomass: state of the art. Green Chem. 2014;16(3):950-63.
106. Porta R, Benaglia M, Puglisi A. Flow chemistry: recent developments in the synthesis of pharmaceutical products. Org Process Res Dev. 2016;20(1):2-25.
107. Javahershenas R, Makarem A, Klika KD. Recent advances in microwave-assisted multicomponent synthesis of spiro heterocycles. RSC Adv. 2024;14:1-30.
108. Xie YY, Pan YM. Advances in photochemical/electrochemical synthesis of heterocyclic compounds from carbon dioxide. Green Chem. 2024;26:9599-9618.
109. Vitaku E, Smith DT, Njardarson JT. Analysis of the structural diversity of heterocycles in FDA-approved drugs. J Med Chem. 2014;57(24):10257-74.
110. Gomtsyan A. Heterocycles in drugs and drug discovery. Chem Heterocycl Compd. 2012;48(1):7-10.
111. Richardson K, Cooper K, Marriott MS, Tarbit MH, Troke PF, Whittle PJ. Discovery and

mode of action of fluconazole. Rev Infect Dis. 1990;12(Suppl 3):S267-71.

112. Sternbach LH. The benzodiazepine story. J Med Chem. 1979;22(1):1-7.

113. Penning TD, Talley JJ, Bertenshaw SR, Carter JS, Collins PW, Docter S, et al. Synthesis and biological evaluation of celecoxib. J Med Chem. 1997;40(9):1347-65.

114. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, et al. Efficacy and safety of imatinib in chronic myeloid leukemia. N Engl J Med. 2001;344(14):1031-37.

115. Sheldon RA. Green chemistry and resource efficiency: towards a green economy. Green Chem. 2016;18:3180-83.

116. Pastre JC, Browne DL, Ley SV. Flow chemistry syntheses of natural products and pharmaceuticals. Chem Soc Rev. 2013;42(23):8849-69.

117. Dunn PJ. The importance of green chemistry in process research and development. Chem Soc Rev. 2012;41(4):1452-61.

118. Porta R, Benaglia M, Puglisi A. Flow chemistry in industrial pharmaceutical synthesis. Org Process Res Dev. 2016;20(1):2-25.

119. Constable DJC, Jimenez-Gonzalez C, Henderson RK. Perspective on solvent use in pharmaceutical manufacturing. Org Process Res Dev. 2007;11(1):133-37.

120. Jimenez-Gonzalez C, Poechlauer P, Broxterman QB, Yang BS, am Ende D, Baird J, et al. Key green engineering research areas for sustainable manufacturing. Org Process Res Dev. 2011;15(4):900-11.

121. Anastas PT, Warner JC. Green Chemistry: Theory and Practice. Oxford University Press; 1998.

122. Sheldon RA. Fundamentals of green chemistry: efficiency in reaction design. Chem Soc Rev. 2012;41(4):1437-51.

123. Clark JH. Green chemistry: challenges and opportunities. Green Chem. 1999;1(1):1-8.

124. Poliakoff M, Fitzpatrick JM, Farren TR, Anastas PT. Green chemistry: science and politics of change. Science. 2002;297(5582):807-10.

125. Kappe CO. Controlled microwave heating in modern organic synthesis. Angew Chem Int Ed Engl. 2004;43(46):6250-84.

126. Horváth IT, Anastas PT. Innovations and green chemistry. Chem Rev. 2007;107(6):2169-73.

127. Dunn PJ. Benefits of green chemistry in pharmaceutical manufacturing. Chem Soc Rev. 2012;41(4):1452-61.

128. Porta R, Benaglia M, Puglisi A. Flow chemistry in pharmaceutical synthesis. Org Process Res Dev. 2016;20(1):2-25.

129. Sheldon RA. Green and sustainable manufacture of chemicals from biomass. Green Chem. 2014;16(3):950-63.

130. Dallinger D, Kappe CO. Microwave-assisted synthesis in medicinal chemistry. Chem Rev. 2007;107(6):2563-91.

131. Cravotto G, Cintas P. Power ultrasound in organic synthesis. Chem Soc Rev. 2006;35(2):180-96.

132. Dömling A, Wang W, Wang K. Multicomponent reactions in green synthesis. Chem Rev. 2012;112(6):3083-135.

133. Sheldon RA. The E factor 25 years on: green chemistry and sustainability. Green Chem. 2017;19:18-43.

134. Li CJ, Trost BM. Green chemistry for chemical synthesis. Proc Natl Acad Sci U S A. 2008;105(36):13197-202.

135. Plutschack MB, Pieber B, Gilmore K, Seeberger PH. The hitchhiker's guide to flow chemistry. Chem Rev. 2017;117(18):11796-893.

136. Kappe CO, Dallinger D. Controlled microwave heating in modern organic synthesis. Nat Rev Drug Discov. 2006;5(1):51-63.

137. Dunn PJ. Green chemistry in the pharmaceutical industry. Chem Soc Rev. 2012;41(4):1452-61.

138. Porta R, Benaglia M, Puglisi A. Continuous processing in pharmaceutical synthesis. Org Process Res Dev. 2016;20(1):2-25.

139. Sheldon RA, Woodley JM. Role of biocatalysis in sustainable chemistry. Chem Rev. 2018;118(2):801-38.

140. Coley CW, Eyke NS, Jensen KF. Autonomous discovery in chemical sciences. Angew Chem Int Ed Engl. 2020;59(51):22858-93.

141. Marzo L, Pagire SK, Reiser O, König B. Visible-light photocatalysis in organic synthesis.

Angew Chem Int Ed Engl. 2018;57(32):10034-72.

142. Zhong Z, Song J, Feng Z, Liu T, Jia L, Yao S, et al. Recent advances in artificial intelligence for retrosynthesis. arXiv. 2023;2301.05864.

HOW TO CITE: Vaishnavi Jadhav*, Green Synthetic Approaches For Bioactive Heterocyclic Compounds: Recent Advances And Pharmaceutical Applications, Int. J. Sci. R. Tech., 2026, 3 (6), 372-391. https://doi.org/10.5281/zenodo.20555904