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Recent advances in the design, synthesis, and biological evaluation of pyrazole and imidazole derivatives: Emerging scaffolds in drug discovery and development

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Pyrazole and imidazole are two important nitrogen-containing heterocyclic scaffolds that have attracted considerable attention in medicinal chemistry owing to their broad spectrum of biological activities and structural versatility. These heterocycles are widely incorporated into clinically approved drugs and continue to serve as valuable frameworks for the development of novel therapeutic agents. Recent advances in synthetic methodologies, computational drug design, and biological screening have accelerated the discovery of pyrazole- and imidazole-based compounds with improved pharmacological profiles. This review comprehensively examines recent developments in the design, synthesis, and biological evaluation of pyrazole and imidazole derivatives reported in the literature. Emphasis is placed on modern synthetic approaches, including conventional and green chemistry methodologies, as well as structure-based and ligand-based drug design strategies. The pharmacological activities of these compounds, including antimicrobial, antifungal, anti-inflammatory, antiviral, anticancer, and enzyme inhibitory effects, are critically discussed. Furthermore, structure-activity relationship (SAR) studies, molecular docking investigations, and emerging computational approaches relevant to lead optimization are highlighted. Numerous pyrazole and imidazole derivatives have demonstrated promising biological activities against a variety of therapeutic targets. SAR studies reveal that strategic structural modifications significantly influence potency, selectivity, and pharmacokinetic properties. Recent advances in molecular modeling, artificial intelligence-assisted drug discovery, and hybrid molecule design have facilitated the identification of novel lead compounds with enhanced therapeutic potential. Additionally, sustainable synthetic methodologies have improved the efficiency and environmental compatibility of heterocyclic drug development. Pyrazole and imidazole derivatives remain privileged scaffolds in modern drug discovery due to their remarkable chemical diversity and broad pharmacological applications. Continued integration of medicinal chemistry, computational tools, and innovative synthetic strategies is expected to accelerate the development of safer, more effective, and target-specific therapeutic agents based on these heterocyclic frameworks.

Keywords: Pyrazole, Imidazole, Heterocyclic compounds, Drug discovery, Structure-activity relationship, Molecular docking, Biological evaluation

INTRODUCTION

Nitrogen-containing heterocyclic compounds represent one of the most influential structural classes in contemporary medicinal chemistry, forming the core framework of a substantial proportion of clinically approved small-molecule therapeutics[1,8,13]. Their exceptional structural diversity, tunable electronic properties, synthetic versatility, and ability to establish multiple non-covalent interactions with biological macromolecules have made them indispensable building blocks in modern drug discovery[2,3]. Continuous advances in synthetic organic chemistry, molecular biology, and computational drug

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design have further expanded the therapeutic potential of heterocyclic scaffolds, enabling the development of highly potent and selective drug candidates targeting complex diseases[28]. Among these privileged heterocycles, pyrazole and imidazole have attracted sustained scientific interest because of their remarkable pharmacological versatility, favorable physicochemical characteristics, and broad applicability across diverse therapeutic areas[4,5].

Pyrazole, a five-membered aromatic ring containing two adjacent nitrogen atoms, possesses a unique electronic architecture that facilitates hydrogen bonding, π-π stacking, and other key molecular interactions involved in target recognition and enzyme inhibition[6]. These characteristics have established pyrazole as a versatile pharmacophore in medicinal chemistry, leading to the discovery of compounds exhibiting potent anti-inflammatory, antimicrobial, antiviral, antidiabetic, analgesic, and anticancer activities[7,11,15,32]. The clinical success of several pyrazole-containing drugs, particularly selective cyclooxygenase-2 (COX-2) inhibitors, further underscores the therapeutic significance of this scaffold and continues to inspire the design of structurally optimized analogues with improved efficacy, selectivity, and safety profiles[8,37].

Similarly, imidazole is an aromatic five-membered heterocycle containing two non-adjacent nitrogen atoms whose amphoteric nature and balanced electronic distribution enable diverse interactions with biological targets[9,21]. The imidazole nucleus is naturally present in essential biomolecules such as histidine, where it plays a central role in enzymatic catalysis, proton transfer, and molecular recognition[10]. These intrinsic properties have translated into broad pharmaceutical relevance, with imidazole derivatives demonstrating significant antimicrobial, antifungal, antiviral, antiparasitic, anti-inflammatory, and anticancer activities while serving as key structural motifs in numerous clinically important therapeutic agents[11,38].

The last decade has witnessed remarkable progress in the rational design and optimization of pyrazole- and imidazole-based drug candidates owing to the convergence of medicinal chemistry with computational and data-driven technologies[12,13,54,61]. Structure-based drug design, molecular docking, molecular dynamics simulations, pharmacophore modeling[39], quantitative structure-activity relationship (QSAR) analysis, predictive ADMET assessment, and artificial intelligence (AI)-assisted virtual screening have substantially accelerated lead identification and optimization, allowing the development of compounds with enhanced potency, target selectivity, and pharmacokinetic performance[12,54,56,57,61]. Concurrently[39], hybrid pharmacophore strategies integrating pyrazole or imidazole with complementary bioactive motifs have emerged as an effective approach for generating multitarget-directed ligands capable of addressing multifactorial disorders such as cancer, microbial infections, metabolic diseases, and neurodegenerative conditions[14,25,26].

Parallel advances in synthetic methodology have further strengthened the utility of these heterocyclic frameworks[16,22,23]. In addition to conventional synthetic approaches, environmentally sustainable methodologies-including microwave-assisted synthesis, multicomponent reactions[40], solvent-free protocols, flow chemistry, and green catalytic systems-have enabled rapid, efficient, and scalable access to structurally diverse pyrazole and imidazole libraries while minimizing environmental impact[9,13,15,17,64]. Extensive biological evaluation, supported by detailed structure-activity relationship (SAR) investigations, has provided valuable insights into the molecular determinants governing potency, selectivity, metabolic stability, and target specificity, thereby facilitating the rational optimization of lead compounds for clinical development[18,20,25,46,47].

Despite these significant advances, several challenges continue to hinder the successful clinical translation of pyrazole- and imidazole-based therapeutics[41,43]. Drug resistance, inadequate aqueous solubility, metabolic instability, off-target toxicity, and suboptimal pharmacokinetic properties remain major obstacles during lead optimization and late-stage development[21,24,42,56,57,63].

Addressing these limitations requires an integrated strategy that combines innovative molecular design, sustainable synthetic chemistry, advanced computational modelling, and comprehensive biological evaluation to accelerate the discovery of safer and more effective therapeutics.

Although numerous review articles have summarized the chemistry or pharmacological applications of either pyrazole or imidazole derivatives, most focus on a single scaffold, a specific therapeutic indication[44], or an individual aspect such as synthetic methodology or biological activity[12,45]. Consequently, recent advances in hybrid scaffold design, AI-assisted drug discovery, predictive ADMET modeling, sustainable synthesis, molecular simulations, patent developments, marketed drugs, patent landscape, clinical translation, AI-assisted drug discovery, predictive ADMET modeling, sustainable synthesis, and future research opportunities[34,48]. Therefore, a comprehensive and critically integrated review is timely and necessary. The present review consolidates recent advances in the design, synthesis, biological evaluation, and translational development of pyrazole and imidazole derivatives, with particular emphasis on emerging structure-activity relationship trends, modern computational strategies, green synthetic methodologies[46], clinically relevant molecules, and future research opportunities[50,53.] By integrating these multidisciplinary perspectives, this review aims to provide a valuable resource for medicinal chemists and pharmaceutical researchers engaged in the rational design of next-generation heterocyclic therapeutics[19,25,56].

Unlike previous reviews that focus exclusively on pyrazole chemistry, imidazole chemistry, or individual

pharmacological activities, the present review integrates both privileged scaffolds into a single comprehensive framework[55,58]. It combines recent advances in synthetic methodologies, critical SAR analysis, computational drug discovery, AI-assisted lead optimization, marketed drugs, clinical translation, patent landscape, research gaps, and future perspectives. To the best of our knowledge, this is the first review to comprehensively integrate all of these aspects for pyrazole and imidazole derivatives published during the recent period. Table 1 compares the scope of the present review with recently published reviews, highlighting its broader coverage of synthetic methodologies, SAR analysis, AI-assisted drug discovery, marketed drugs, patent landscape, and clinical translation.

Literature search methodology

The literature included in this review was identified through a structured search of major scientific databases, including PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect, to ensure comprehensive coverage of recent advances in pyrazole- and imidazole-based drug discovery. Publications published between January 2020 and March 2026 were primarily considered, while seminal earlier studies were included where necessary to provide historical context and highlight landmark developments. Search terms included "pyrazole," "imidazole," "pyrazole derivatives," "imidazole derivatives," "medicinal chemistry," "structure-activity relationship (SAR):" "molecular docking," "molecular dynamics," "green synthesis," "hybrid molecules," "artificial intelligence," "drug discovery," "clinical trials," and "patents." Only peer-reviewed articles published in English were included, whereas duplicate records, conference abstracts, editorials, non-English publications, and studies lacking sufficient scientific relevance were excluded. Additional relevant publications were identified through manual screening of reference lists to ensure comprehensive and balanced coverage of recent developments in the field[12,54,61,85].

Chemistry of pyrazole

Pyrazole is a five-membered aromatic diazole heterocycle composed of three carbon atoms and two adjacent nitrogen atoms (N^1 and N^2)[1,7]. Since its first synthesis by Ludwig Knorr in 1883, the pyrazole nucleus has become one of the most important privileged scaffolds in medicinal chemistry owing to its unique electronic properties, synthetic versatility, and broad therapeutic applicability[15,23]. The compact aromatic framework, combined with the presence of

Table 1. Comparison of the scope of the present review with representative recent review articles

Published Review	Year	Pyrazole	Imidazole	Critical SAR	AI-Assisted Drug Discovery	Marketed Drugs / Clinical Status	Patent Landscape	Present Scope
Amino-Pyrazoles in Medicinal Chemistry	2023	✓	✗	✓	Limited	Limited	✗	Scaffold-specific review
Pyrazole: An Emerging Privileged Scaffold in Drug Discovery	2023	✓	✗	✓	Limited	✓	✗	Pyrazole-focused overview
Bioactive Fused Pyrazoles Inspired by 5-Aminopyrazole Derivatives	2025	✓	✗	Limited	✗	Limited	✗	Fused pyrazoles only
Synthetic, Structural and Medicinal Perspective of Imidazole Analogs	2025	✗	✓	✓	Limited	Limited	✗	Imidazole-focused review
Present Review	2026	✓	✓	✓ (Critical analysis)	✓	✓	✓	Integrated review covering synthetic methodologies, SAR, computational drug design, AI, marketed drugs, patents, clinical progress, limitations, and future perspectives

two nitrogen atoms, provides an ideal platform for structural diversification, enabling the rational design of molecules with improved potency, selectivity, and pharmacokinetic characteristics across diverse therapeutic targets[21,60].

The biological significance of pyrazole is largely attributed to its distinctive electronic architecture[19,21]. Aromatic stabilization through the delocalization of six π-electrons imparts excellent chemical stability while preserving sufficient electronic flexibility for structural modification[62,66]. The N^1 atom exhibits pyrrole-like character by contributing its lone pair to the aromatic sextet, whereas the N^2 atom behaves as a pyridine-like nitrogen with a lone pair available for hydrogen bonding and metal coordination[7,67]. This complementary donor-acceptor behavior allows pyrazole derivatives to establish strong interactions with enzymes, receptors, kinases, and nucleic acids, thereby enhancing target recognition and biological activity[68,70]. In addition, prototropic tautomerism arising from proton migration between the two nitrogen atoms influences molecular conformation, receptor binding, and metabolic stability, making tautomer prediction an important consideration during structure-based drug design and computational modeling[47].

The pyrazole scaffold offers multiple sites for chemical functionalization, particularly at the N^1, C^3, C^4, and C^5 positions, allowing systematic optimization of physicochemical and pharmacological properties[2,4]. Strategic incorporation of electron-withdrawing or electron-donating substituents has been widely employed to modulate target affinity, lipophilicity, aqueous solubility, metabolic stability, and pharmacokinetic behavior[7]. Furthermore, fusion of the pyrazole ring with other heterocyclic systems or its incorporation into hybrid pharmacophores has emerged as an effective strategy for developing multitarget-directed ligands with enhanced therapeutic efficacy and reduced resistance[25,26,46].

The synthetic accessibility of pyrazole has further contributed to its widespread application in drug discovery[5,9]. While classical cyclocondensation of hydrazines with 1,3-dicarbonyl compounds remains a cornerstone of pyrazole synthesis, recent advances in microwave-assisted synthesis, multicomponent reactions, transition-metal-catalyzed cyclizations, click chemistry[15], continuous-flow processes, and green synthetic methodologies have enabled the rapid and sustainable generation of structurally diverse pyrazole libraries[12,13]. Coupled with computational approaches such as molecular docking, molecular dynamics simulations, quantitative structure-activity relationship (QSAR) analysis, predictive ADMET modeling, and artificial intelligence-assisted lead optimization, these advances have significantly accelerated the discovery of pyrazole-based drug candidates[47].

The remarkable ability of pyrazole derivatives to engage biological targets through hydrogen bonding, π-π stacking, hydrophobic, and electrostatic interactions has resulted in compounds with potent anti-inflammatory, antimicrobial, antiviral, antidiabetic, and anticancer activities[8,15]. The successful incorporation of the pyrazole pharmacophore into clinically approved drugs further validates its importance in modern medicinal chemistry and highlights its continuing potential for the development of next-generation therapeutics[8,15,47].

Chemistry of imidazole

Imidazole is a five-membered aromatic heterocycle containing three carbon atoms and two non-adjacent nitrogen atoms at the 1- and 3-positions[6]. Owing to its unique electronic properties and widespread occurrence in biologically important molecules such as histidine, histamine, purine nucleotides, and enzyme active sites[10], the imidazole nucleus has emerged as one of the most valuable privileged scaffolds in medicinal chemistry[17]. Its natural biological relevance, combined with excellent synthetic accessibility and structural adaptability[29,] has facilitated the development of numerous therapeutically important compounds across a broad spectrum of disease indications[30,52].

The medicinal importance of imidazole is primarily attributed to its distinctive electronic architecture[10]. The aromatic ring contains six delocalized π-electrons, providing high chemical stability while retaining sufficient electronic flexibility for molecular recognition[17]. The two nitrogen atoms display complementary electronic characteristics: the N^1 atom exhibits pyrrole-like behavior by contributing its lone pair to the aromatic sextet, whereas the N^3 atom behaves as a pyridine-like nitrogen capable of participating in hydrogen bonding and metal coordination[29,30,34]. This amphoteric nature, together with a physiological pKa of approximately 7.0, allows imidazole derivatives to exist in both neutral and protonated forms under physiological conditions, facilitating acid-base catalysis, enzyme inhibition, and strong interactions with a wide range of biological targets, including metalloenzymes, cytochrome P450 enzymes, kinases, and proteases. Furthermore, prototropic tautomerism between the two nitrogen atoms can influence molecular conformation, receptor recognition, and metabolic behavior, making tautomeric considerations increasingly important in molecular docking and structure-based drug design[52]. The basic chemical structures and atom numbering of pyrazole and imidazole are illustrated in Fig. 1.

The imidazole scaffold offers multiple positions for chemical functionalization, enabling systematic optimization of biological activity and drug-like properties. Structural modifications at the N^1, C^2, C^4, and C^5 positions have been widely employed to improve potency, target selectivity, metabolic stability, aqueous solubility, and pharmacokinetic performance. In addition, fusion of the imidazole ring with other heterocyclic

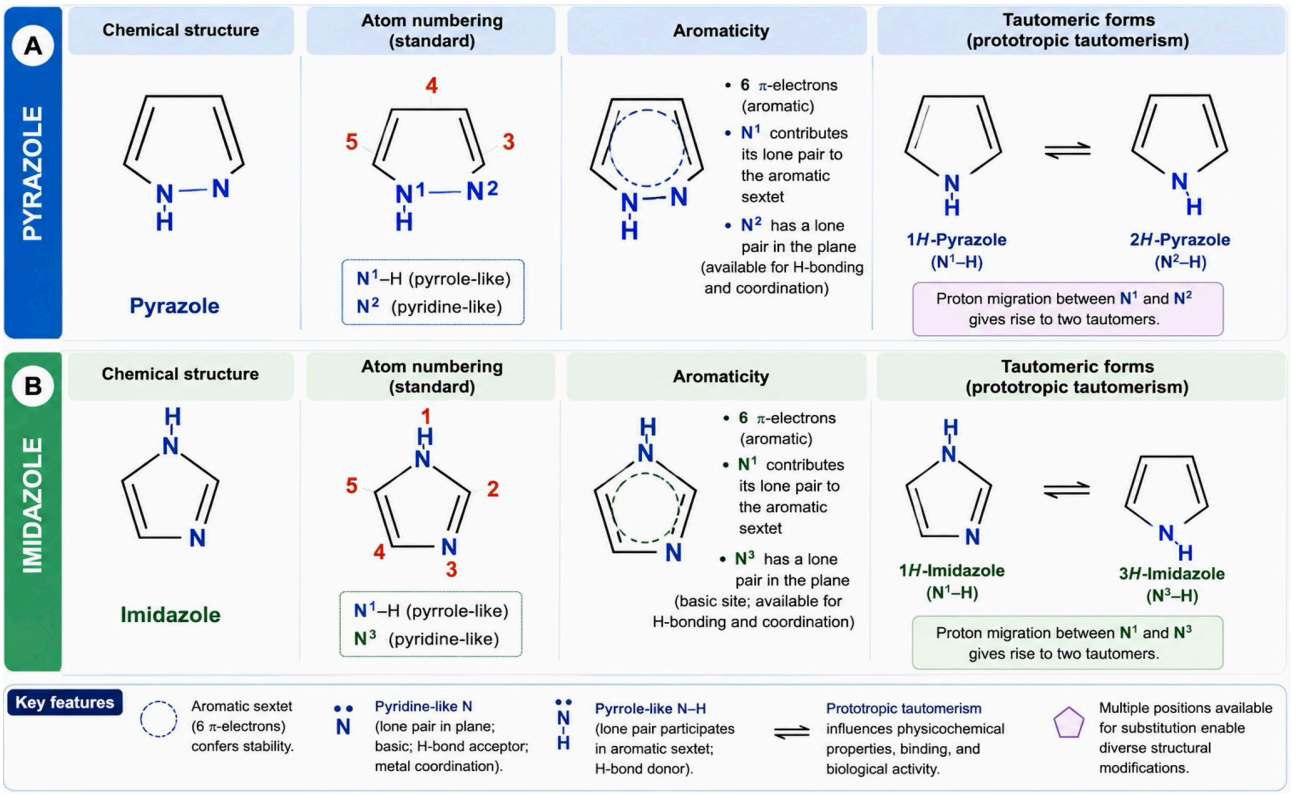

Figure 1. Chemical structures, atom numbering, aromaticity, and tautomeric forms of pyrazole and imidazole

systems has become a successful strategy for generating hybrid molecules with enhanced biological activity and multitarget pharmacological profiles[29,31,34]. The tautomeric forms of pyrazole and imidazole, which influence their physicochemical and biological properties, are presented in Fig. 2.

From a synthetic perspective, imidazole chemistry has evolved considerably beyond conventional cyclocondensation reactions[6,12]. Modern methodologies, including microwave-assisted synthesis, multicomponent reactions, transition-metal-catalyzed transformations, photoredox catalysis, continuous-flow synthesis, mechanochemistry[14], and green synthetic protocols, have significantly improved reaction efficiency, regioselectivity[17], and sustainability while enabling the rapid preparation of structurally diverse imidazole libraries. The integration of these synthetic advances with computational approaches, such as molecular docking, molecular dynamics simulations, quantitative structure-activity relationship (QSAR) analysis, predictive ADMET modelling, and artificial intelligence-assisted lead optimization, has accelerated the discovery of novel imidazole-based therapeutics[32,33].

The ability of imidazole derivatives to establish hydrogen bonding, metal coordination, hydrophobic interactions, and π-mediated contacts underpins their broad pharmacological profile[10]. Consequently, imidazole-containing compounds have demonstrated potent antifungal, antibacterial, antiviral[17], antiparasitic, anti-inflammatory, anticancer, and enzyme inhibitory activities, with several clinically approved drugs validating the scaffold's therapeutic significance[29,30]. Collectively, these characteristics continue to position imidazole as a cornerstone of contemporary medicinal chemistry and an attractive platform for the rational design of next-generation drug candidates[31,52].

Synthetic strategies for pyrazole and imidazole derivatives

The continued success of pyrazole- and imidazole-based drug discovery is closely linked to advances in synthetic organic chemistry that enable the rapid generation of structurally diverse and pharmacologically relevant analogues[5,9]. Owing to their versatile reactivity and multiple sites available for functionalization, both heterocyclic scaffolds can be synthesized and modified through a wide range of conventional and modern synthetic methodologies[6]. While classical cyclocondensation reactions remain the foundation for constructing pyrazole and imidazole rings because of their operational simplicity and broad substrate compatibility, recent developments have significantly expanded the synthetic toolbox available to medicinal chemists[12,14]. Emerging approaches, including microwave-assisted synthesis, multicomponent reactions (MCRs), photoredox catalysis, transition-metal-catalyzed

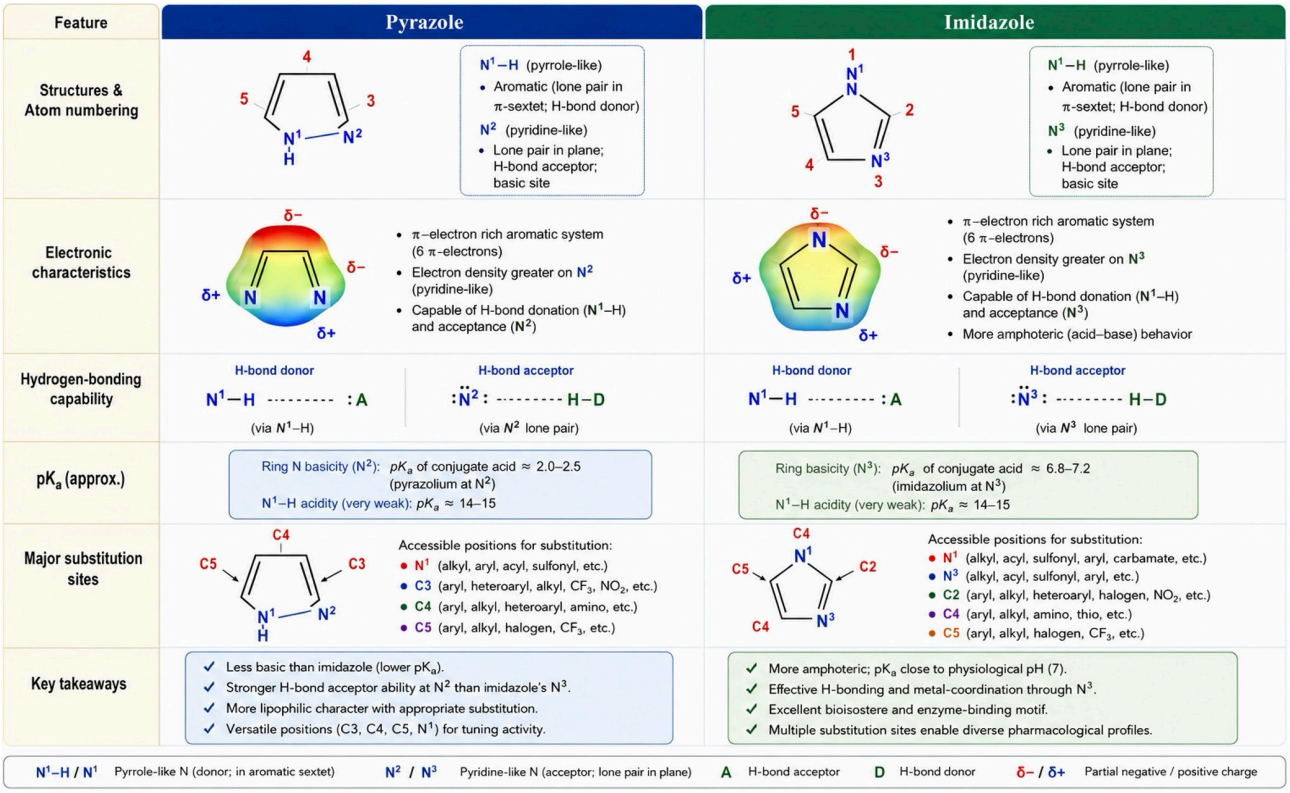

Figure 2. Comparison of electronic properties, hydrogen-bonding characteristics, pKa, and substitution sites of pyrazole and imidazole

transformations, continuous-flow chemistry, and green synthetic methodologies, have substantially improved reaction efficiency, regioselectivity, atom economy, and environmental sustainability[13,15]. These methodologies not only reduce reaction time, energy consumption, and solvent usage but also facilitate the rapid preparation of chemically diverse libraries suitable for high-throughput biological screening and lead optimization[32]. Furthermore, the integration of modern synthetic strategies with computational drug design and structure-based medicinal chemistry has accelerated the identification of novel pyrazole- and imidazole-based therapeutic candidates[64]. The major synthetic approaches employed for the preparation of pyrazole and imidazole derivatives are summarized in Fig. 3.

Modern synthetic strategies for pyrazole and imidazole derivatives

The development of pyrazole- and imidazole-based therapeutics has been greatly facilitated by continuous advances in synthetic organic chemistry[5,9]. Efficient synthetic methodologies are essential for generating structurally diverse heterocyclic libraries, enabling systematic structure-activity relationship (SAR) investigations and rapid lead optimization[14]. Although conventional cyclization reactions continue to provide reliable access to these privileged scaffolds, recent innovations have focused on improving reaction efficiency, regioselectivity, sustainability, and scalability[15]. Modern synthetic approaches also complement computer-aided drug design by allowing the rapid preparation of structurally diverse analogues for biological screening[23,64].

Classical cyclocondensation methods

Classical cyclocondensation remains the cornerstone for synthesizing pyrazole and imidazole derivatives because of its operational simplicity, broad substrate compatibility, and reproducibility[5,6]. Pyrazoles are commonly prepared through the condensation of hydrazines with 1,3-dicarbonyl compounds, β-diketones, β-ketoesters, or α,β-unsaturated carbonyl compounds, whereas imidazoles are traditionally synthesized using the Debus-Radziszewski reaction involving 1,2-dicarbonyl compounds, aldehydes, and ammonia or primary amines[15]. These well-established methodologies provide moderate-to-high yields and tolerate a wide range of functional groups, making them highly suitable for preparing lead compounds during the early stages of drug discovery[23]. However, their dependence on prolonged heating, larger solvent volumes, and multistep purification has encouraged the development of more efficient synthetic alternatives[49,51].

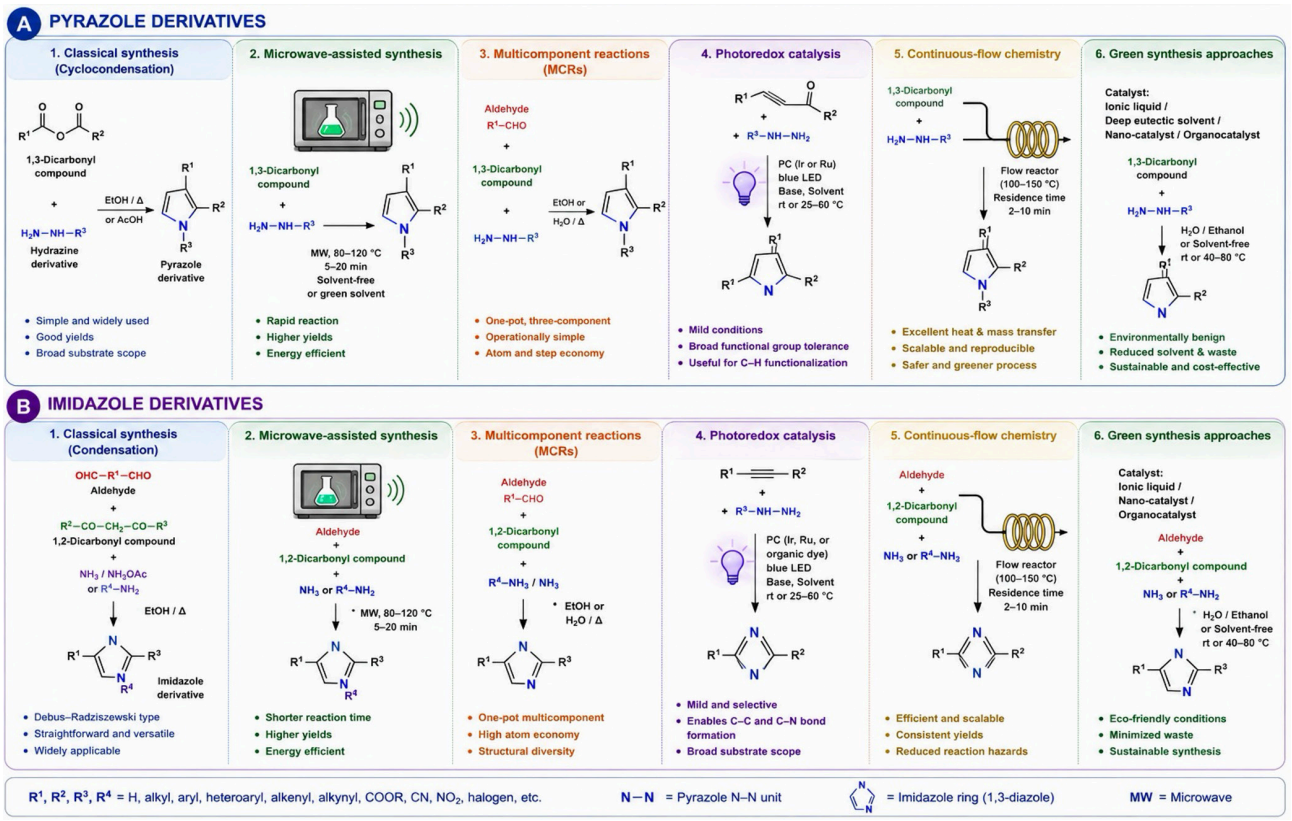

Figure 3. Modern synthetic strategies for pyrazole and imidazole derivatives (classical synthesis, microwave-assisted synthesis, multicomponent reactions, photoredox catalysis, continuous-flow chemistry, and green synthesis)

Microwave-assisted synthesis

Microwave-assisted organic synthesis has become an effective strategy for accelerating the preparation of pyrazole and imidazole derivatives[13,14]. Rapid dielectric heating promotes uniform energy transfer throughout the reaction medium, significantly reducing reaction times from several hours to a few minutes while often improving product yields and regioselectivity[25]. The technology also minimizes side reactions and solvent consumption, thereby enhancing overall synthetic efficiency. Owing to these advantages, microwave-assisted synthesis has become widely adopted for the rapid generation of compound libraries required in medicinal chemistry and high-throughput biological screening[46].

Multicomponent reactions (MCRs)

Multicomponent reactions have emerged as one of the most powerful approaches for constructing structurally complex heterocycles in a single synthetic operation[14,15]. By combining three or more reactants in one pot, MCRs improve atom economy, reduce purification steps, and simplify reaction workflows. Their ability to rapidly generate molecular diversity makes them particularly valuable for the synthesis of pyrazole- and imidazole-based analogues intended for SAR studies. Furthermore, the operational simplicity, scalability, and compatibility with diverse functional groups have established MCRs as indispensable tools for modern medicinal chemistry, where efficient access to chemically diverse libraries is essential for identifying new therapeutic leads[9, 64].

Photoredox catalysis

Photoredox catalysis has recently transformed heterocyclic synthesis by enabling highly selective bond-forming reactions under mild and environmentally benign conditions. Using visible light as a sustainable energy source, photoredox catalysts generate reactive radical intermediates capable of forming C-C and C-N bonds with excellent functional-group tolerance[14]. This strategy enables late-stage functionalization of pyrazole and imidazole scaffolds, facilitating rapid diversification of lead molecules without requiring extensive synthetic redesign. The mild reaction conditions also improve compatibility with sensitive functional groups, making photoredox catalysis an increasingly valuable platform for medicinal chemistry and late-stage drug optimization[23].

Continuous-flow chemistry

Continuous-flow chemistry has emerged as an attractive

alternative to conventional batch synthesis for the preparation of heterocyclic compounds[6,8]. Continuous reactors provide superior control over temperature, mixing, and reaction time, resulting in improved reaction reproducibility, higher product quality, and enhanced safety, particularly for hazardous or highly exothermic transformations[5,13]. The excellent heat and mass transfer characteristics of flow systems facilitate rapid optimization and straightforward scale-up, making this technology highly suitable for industrial drug manufacturing. As pharmaceutical research increasingly emphasizes process intensification and reproducibility, continuous-flow synthesis is becoming an integral component of modern heterocyclic chemistry[14,64].

Green and sustainable synthetic approaches

Sustainability has become a major driving force in contemporary medicinal chemistry, leading to the widespread adoption of environmentally friendly synthetic methodologies[6,15]. Green approaches for the synthesis of pyrazole and imidazole derivatives include solvent-free reactions, aqueous media, recyclable heterogeneous catalysts, ionic liquids, deep eutectic solvents, organocatalysis, and mechanochemical techniques[13-14]. These methodologies reduce hazardous waste, energy consumption, and solvent usage while maintaining high reaction efficiency and product yields. Beyond their environmental benefits, green synthetic strategies frequently offer improved cost-effectiveness and operational simplicity, making them increasingly attractive for both academic research and pharmaceutical manufacturing. Consequently, the integration of sustainable chemistry with advanced synthetic technologies is expected to play a pivotal role in the future development of pyrazole- and imidazole-based therapeutics[57,64].

Critical structure-activity relationship (SAR) analysis

Structure-activity relationship (SAR)[7,25] analysis remains one of the most powerful approaches in medicinal chemistry for understanding how structural modifications influence biological activity[19], target selectivity, and pharmacokinetic behavior[26]. Although numerous pyrazole- and imidazole-based compounds have demonstrated promising pharmacological activities, recent investigations indicate that therapeutic performance depends not only on the heterocyclic scaffold itself but also on the nature, position, and electronic characteristics of substituents[34]. This section critically discusses the major SAR trends that have emerged from recent studies and highlights molecular design strategies that have consistently improved biological activity[46,47].

Structure-activity relationships of pyrazole derivatives

The pyrazole nucleus provides four principal positions (N^1, C^3, C^4, and C^5) for structural modification[1,19], enabling systematic optimization of potency, selectivity, and pharmacokinetic properties. Rather than acting independently[7], substituents influence activity through electronic effects, steric interactions, lipophilicity, hydrogen-bonding capacity[21], and conformational flexibility[26]. Consequently, successful lead optimization generally requires balancing these factors according to the biological target[47].

Influence of electron-withdrawing groups[19,26]: Electron-withdrawing substituents[25] are among the most frequently employed modifications in pyrazole medicinal chemistry because they alter electron distribution while improving metabolic stability and target affinity[46,65].

Trifluoromethyl ($-CF_3$): The trifluoromethyl group has consistently emerged as one of the most beneficial substituents in pyrazole derivatives[26]. Its strong electron-withdrawing nature increases lipophilicity, enhances membrane permeability, and reduces susceptibility to oxidative metabolism[46]. These properties frequently translate into improved oral bioavailability and prolonged biological activity. In addition, the $-CF_3$ group occupies hydrophobic pockets within enzyme active sites, strengthening van der Waals interactions and improving binding affinity[65]. Pyrazole derivatives containing para- or meta-trifluoromethyl substituents often demonstrate superior anticancer, anti-inflammatory, and antimicrobial activities compared with unsubstituted analogues[84].

Fluoro (-F): Fluorine substitution provides a subtle yet highly effective means of improving biological activity[46]. Because fluorine is similar in size to hydrogen but possesses high electronegativity, it can modulate electronic properties without introducing significant steric hindrance. Fluorination often enhances metabolic stability by blocking oxidative metabolism and can strengthen ligand-protein interactions through favorable electrostatic effects[65]. Para-fluoro substitution has frequently been associated with increased kinase inhibition and improved receptor selectivity[84].

Chloro (-Cl) *and bromo* (-Br): Halogen substituents such as chlorine and bromine generally increase hydrophobicity and facilitate stronger interactions with hydrophobic amino acid residues[8]. Larger halogens may also participate in halogen bonding, thereby improving target recognition[46]. While chloro substitution often enhances antimicrobial and antifungal activity[65], excessive steric bulk resulting from multiple halogen substitutions may reduce aqueous solubility and negatively affect pharmacokinetic properties[74]. Therefore, careful optimization of halogen type and substitution pattern is essential.

Influence of electron-donating groups[1]: Electron-

donating substituents frequently enhance biological activity by improving hydrogen-bonding interactions or altering electron density within the aromatic system[26,47].

Hydroxyl (-OH): Hydroxyl groups increase molecular polarity and enable additional hydrogen-bond formation with amino acid residues[46]. In many enzyme inhibitors, strategically positioned hydroxyl substituents improve binding affinity and aqueous solubility[47]. However, excessive hydroxylation may reduce membrane permeability and oral absorption because of increased polarity.

Methoxy ($-OCH_3$): Methoxy groups represent one of the most versatile substituents in pyrazole chemistry[26]. Besides donating electron density, they contribute moderate lipophilicity while serving as hydrogen-bond acceptors[46]. Numerous studies have reported that para-methoxy substitution improves anti-inflammatory and anticancer activity by optimizing interactions within hydrophobic binding pockets[84].

Amino ($-NH_2$): The amino group provides both hydrogen-bond donor and acceptor capabilities, enabling stronger interactions with catalytic residues[1]. Amino-substituted pyrazoles frequently demonstrate improved enzyme inhibition and enhanced target selectivity[21]. Nevertheless, primary amino groups may undergo rapid metabolic transformation; consequently, medicinal chemists often employ protected or substituted amino analogues to improve pharmacokinetic stability[46].

Nitro group ($-NO^2$): Nitro substituents substantially modify electron distribution and frequently enhance antimicrobial and antiparasitic activity through increased electrophilicity[8]. However, nitro groups are also associated with potential toxicity and metabolic activation to reactive intermediates[47]. Consequently, recent medicinal chemistry has increasingly replaced nitro groups with safer bioisosteres that preserve biological activity while reducing toxicity risk[65].

N-substitution: Modification of the pyrazole nitrogen atom profoundly influences biological behavior[21]. N-alkylation generally increases lipophilicity and membrane permeability but may reduce hydrogen-bond donor capacity[22]. Conversely, N-acylation and N-sulfonylation can improve target selectivity by introducing additional hydrogen-bond acceptors and modifying molecular conformation[46]. Optimal N-substitution, therefore, depends on the requirements of the intended biological target rather than following a universal strategy.

Ring fusion: Fusion of the pyrazole ring with other aromatic or heterocyclic systems restricts conformational flexibility and often enhances receptor complementarity[2]. Fused pyrazole derivatives commonly exhibit improved metabolic stability and stronger π-π interactions with aromatic residues within protein active sites[25]. Such compounds have demonstrated considerable promise as kinase inhibitors and anticancer agents[26].

Bioisosteric replacement: Bioisosteric modification has become an important strategy for optimizing pyrazole derivatives[46]. Replacement of phenyl rings with pyridine, pyrimidine, or thiophene rings can improve aqueous solubility and introduce additional hydrogen-bonding interactions without substantially altering molecular geometry[56]. Similarly, replacement of metabolically labile functional groups with more stable bioisosteres frequently enhances pharmacokinetic performance while maintaining biological activity[59].

Hybrid molecule design: Hybrid pharmacophore design has emerged as one of the most productive approaches in recent medicinal chemistry[25,27]. Incorporation of the pyrazole scaffold into quinoline, triazole, indole, coumarin, benzimidazole, pyridine, or chalcone frameworks often produces synergistic biological activity by simultaneously interacting with multiple therapeutic targets. Such hybrid molecules have shown considerable promise in overcoming multidrug resistance and improving therapeutic efficacy[26,46].

Molecular docking and target selectivity: Recent molecular docking and molecular dynamics studies provide mechanistic insight into the SAR of pyrazole derivatives[12]. Highly active compounds consistently establish multiple hydrogen bonds together with hydrophobic[26] and π-π interactions[46] within enzyme active sites. The orientation of substituents frequently determines whether the ligand occupies catalytic or allosteric binding pockets, thereby influencing potency and selectivity. Consequently, computational methods have become indispensable for predicting favorable substitution patterns prior to synthesis[47].

Structure-activity relationships of imidazole derivatives

The medicinal chemistry of imidazole derivatives follows similar design principles but is strongly influenced by the amphoteric nature of the imidazole ring and its ability to coordinate metal ions[10,17]. Because the imidazole nucleus readily participates in hydrogen bonding[29,30], proton transfer, and metal coordination, relatively small structural modifications often produce substantial changes in biological activity[34,52].

Halogen substitution: Fluoro-, chloro-, and bromo-substituted imidazole derivatives[10] generally display improved antimicrobial, antifungal, and anticancer activities. Halogen atoms enhance lipophilicity and facilitate stronger hydrophobic interactions with protein targets[29,30]. In antifungal agents, halogenated aromatic rings frequently improve binding within the hydrophobic cavity of lanosterol 14α-demethylase (CYP51): resulting in enhanced inhibition of ergosterol biosynthesis[31,34].

Hydroxyl and methoxy substituents: Hydroxyl and methoxy groups enhance hydrogen-bonding interactions and often improve receptor affinity[10]. Para-methoxy

substitution is particularly effective in anti-inflammatory and anticancer derivatives because it balances electronic effects with lipophilicity[29]. Hydroxyl groups improve aqueous solubility but require careful optimization to avoid reduced membrane permeability[31].

Amino substitution: Introduction of amino substituents frequently enhances interactions with catalytic residues and increases enzyme inhibitory activity[17]. However, amino-containing derivatives may exhibit reduced metabolic stability[29], emphasizing the importance of balancing potency with pharmacokinetic performance[32].

Nitro substitution: Nitro-substituted imidazole derivatives remain valuable in antimicrobial and antiparasitic therapy because intracellular reduction of the nitro group generates reactive intermediates that damage microbial DNA[29]. Despite this established mechanism, concerns regarding mutagenicity have encouraged the development of safer nitro bioisosteres and alternative electron-withdrawing substituents[30].

N-substitution: N-alkylation[32], N-acylation, and N-arylation substantially influence biological activity by altering lipophilicity, hydrogen-bonding capacity[33], and molecular conformation. Appropriate N-substitution often improves target selectivity while reducing nonspecific protein binding and enhancing pharmacokinetic properties[34].

Ring fusion and hybrid molecules: Fusion of imidazole with benzimidazole, quinoline, triazole, pyrazole, indole, or pyridine scaffolds[14] has generated numerous compounds exhibiting superior potency compared with their parent molecules[17]. Hybridization enables simultaneous modulation of multiple signaling pathways and represents an increasingly important strategy for developing multi-target-directed therapeutics[34,35].

Computational insights: Recent docking and molecular dynamics studies demonstrate that highly active imidazole derivatives establish stable hydrogen-bond networks while coordinating essential metal ions within enzyme active sites[12]. Computational approaches have therefore become integral to the rational optimization of potency, selectivity, and ADMET characteristics before experimental synthesis[31,34].

Emerging SAR trends and future directions

Analysis of recent literature reveals several consistent trends[12]. Moderate lipophilicity combined with balanced hydrogen-bonding capacity generally produces optimal biological activity[25,26]. Electron-withdrawing groups such as trifluoromethyl and fluorine frequently improve potency and metabolic stability, whereas methoxy and amino substituents strengthen target recognition through hydrogen-bond formation[34]. Hybrid pharmacophore design, bioisosteric replacement, and conformational restriction through ring fusion have emerged as particularly successful lead optimization strategies[46,47]. Increasingly, these approaches are being integrated with molecular docking, molecular dynamics simulations, predictive ADMET modeling, and artificial intelligence-assisted molecular design to accelerate the discovery of pyrazole- and imidazole-based therapeutics with improved efficacy[56], selectivity, and clinical translation potential[57]. The major structure–activity relationship trends observed for pyrazole and imidazole derivatives are summarized in Table 2.

Biological evaluation

The remarkable therapeutic versatility of pyrazole and imidazole derivatives is primarily attributed to their favorable electronic properties and their ability to establish hydrogen-bonding, π-π stacking, hydrophobic[7], and electrostatic interactions[8] with diverse biological targets. Consequently, these privileged scaffolds have been extensively explored for the treatment of cancer[10], inflammatory disorders[12], microbial infections[19], viral diseases[26], metabolic disorders[29], and neurological conditions[31]. Advances in medicinal chemistry, structure-activity relationship (SAR) studies, and computational drug design have further accelerated the optimization of these heterocyclic frameworks for improved potency, selectivity, and pharmacokinetic performance[36,47].

Anticancer activity

Pyrazole and imidazole derivatives have demonstrated significant anticancer potential by modulating multiple signaling pathways involved in tumor growth and progression[7]. Their anticancer activity is commonly associated with inhibition of protein kinases[12], histone deacetylases[19], topoisomerases[25], and tubulin polymerization[26], leading to cell-cycle arrest, apoptosis, and suppression of angiogenesis[31]. SAR studies indicate that strategic substitution with electron-withdrawing groups and hybridization with other bioactive pharmacophores frequently enhances target affinity and antiproliferative activity[46]. Although numerous derivatives exhibit potent in vitro activity, further optimization of pharmacokinetic properties and in vivo efficacy remains necessary for successful clinical translation[47].

Anti-inflammatory activity

Pyrazole derivatives are well recognized for their anti-inflammatory and analgesic properties, primarily through selective inhibition of cyclooxygenase-2 (COX-2) and modulation of inflammatory mediators such as NF-κB[8,15], TNF-α, and interleukins[19,25]. Rational structural modification has improved COX-2 selectivity while reducing gastrointestinal toxicity[26,] highlighting the importance of SAR-guided lead optimization[46].

Table 2. Representative structure–activity relationship (SAR) trends of pyrazole and imidazole derivatives

Compound Series	Key Structural Modification	Observed SAR Effect	Biological Activity
Pyrazole derivatives	Halogen substitution at C-3	Enhanced lipophilicity and target binding affinity	Increased anticancer activity
Pyrazole derivatives	Electron-withdrawing groups (CF_3, CN, NO_2) at C-3/C-5	Improved receptor/enzyme interactions	Enhanced antimicrobial and anti-inflammatory activity
Pyrazole derivatives	Aromatic/heteroaromatic substitution	Stronger π–π stacking interactions	Improved anticancer and enzyme inhibitory activity
Pyrazole derivatives	N-1 substitution	Improved membrane permeability and metabolic stability	Enhanced pharmacokinetic profile
Imidazole derivatives	Aryl substitution at C-2/C-4/C-5	Increased hydrophobic interactions with fungal targets	Improved antifungal activity
Imidazole derivatives	Halogenated phenyl groups	Enhanced target affinity and potency	Increased antimicrobial activity
Imidazole derivatives	N-1 alkyl/aryl substitution	Improved bioavailability and cellular uptake	Enhanced biological activity
Imidazole derivatives	Hydrogen-bond donor/acceptor groups	Stronger ligand–target interactions	Improved enzyme inhibition and anticancer activity
Pyrazole–Imidazole hybrids	Dual pharmacophore incorporation	Multi-target engagement	Enhanced anticancer and antimicrobial activity
Hybrid derivatives	Conjugation with bioactive scaffolds	Improved potency and selectivity	Broad-spectrum therapeutic activity

Antimicrobial activity

Both scaffolds exhibit broad-spectrum antibacterial[10] and antifungal activity by targeting essential microbial enzymes[17,] disrupting membrane integrity[29,] or interfering with nucleic acid synthesis[30]. Imidazole derivatives remain particularly important as inhibitors of lanosterol 14α-demethylase (CYP51): a validated antifungal target[31,34]. Hybrid scaffold design has further expanded antimicrobial potency against multidrug-resistant pathogens[74].

Antiviral activity

Recent studies have identified pyrazole- and imidazole-based compounds as promising antiviral agents through inhibition of viral proteases[7,12], polymerases[17,26], and other enzymes required for viral replication[31]. Continued SAR optimization and computational screening are expected to facilitate the discovery of broad-spectrum antiviral therapeutics[54].

Antidiabetic activity

Several pyrazole and imidazole derivatives have demonstrated antidiabetic activity by inhibiting α-glucosidase[19,26], α-amylase[31], dipeptidyl peptidase-4 (DPP-4), and protein tyrosine phosphatase 1B (PTP1B)[47]. Structural modifications that enhance enzyme selectivity and metabolic stability have produced promising lead compounds with improved glucose-lowering potential[65].

CNS disorders

The ability of these heterocycles to interact with monoamine oxidases, γ-aminobutyric acid (GABA) receptors[17], phosphodiesterases[26], and acetylcholinesterase has stimulated their investigation for neurological disorders, including epilepsy[31], depression, Alzheimer's disease, and Parkinson's disease[54,61]. Nevertheless, improving blood-brain barrier permeability and minimizing off-target effects remain important challenges.

Other pharmacological activities

Beyond these applications[17], pyrazole and imidazole derivatives have shown promising antitubercular[26], antiparasitic[29], antioxidant[31], antihypertensive[46], and enzyme inhibitory activities. Their broad pharmacological profile, combined with advances in synthetic chemistry, computational modelling, and hybrid pharmacophore design[47], continues to support the development of next-generation therapeutics with enhanced efficacy, selectivity, and clinical potential[54]. Representative synthetic routes for the preparation of pyrazole and imidazole derivatives are shown in

Fig. 4. Representative pyrazole and imidazole derivatives, together with their therapeutic targets, biological activities, and key SAR findings, are summarized in Table 3.

Clinical translation

The successful translation of pyrazole- and imidazole-based compounds from laboratory research to clinical practice highlights their importance as privileged scaffolds in modern drug discovery[8,10]. Owing to their favorable physicochemical properties, synthetic versatility, and ability to modulate diverse biological targets, several derivatives have progressed beyond preclinical evaluation to become marketed drugs or advanced clinical candidates[17,26]. Their therapeutic applications span oncology, inflammation[29], infectious diseases[31], cardiovascular disorders, metabolic diseases[63], and central nervous system disorders.

Among marketed drugs, celecoxib remains one of the most successful pyrazole-based selective COX-2 inhibitors for the treatment of inflammatory disorders, whereas crizotinib demonstrates the clinical value of pyrazole-containing kinase inhibitors in targeted cancer therapy[17]. Likewise, sildenafil has established the therapeutic utility of pyrazole derivatives in pulmonary arterial hypertension and erectile dysfunction[29]. Imidazole-containing drugs such as ketoconazole, clotrimazole, miconazole, and metronidazole continue to play indispensable roles in the management of fungal, bacterial, and protozoal infections through well-defined molecular mechanisms[29,31].

In parallel with these approved agents, numerous pyrazole- and imidazole-based compounds are undergoing preclinical optimization and clinical evaluation for cancer, antimicrobial resistance[12], metabolic disorders, and neurological diseases[26]. Recent advances in structure-based drug design, artificial intelligence-assisted lead optimization, predictive ADMET modelling[31,] and biomarker-guided drug development have accelerated the identification of candidates with improved potency, selectivity, and pharmacokinetic profiles. Nevertheless, despite encouraging biological activity, many lead compounds continue to face challenges related to aqueous solubility, metabolic stability, toxicity, and limited clinical efficacy[54,57]. Addressing these limitations through rational molecular optimization, hybrid pharmacophore design, and precision medicine approaches is expected to improve clinical success rates[61]. Collectively, the growing number of approved drugs and emerging clinical candidates underscores the considerable translational potential of pyrazole and imidazole scaffolds for the development of next-generation therapeutics[63].

Marketed drugs and clinical candidates

The successful clinical translation of pyrazole- and

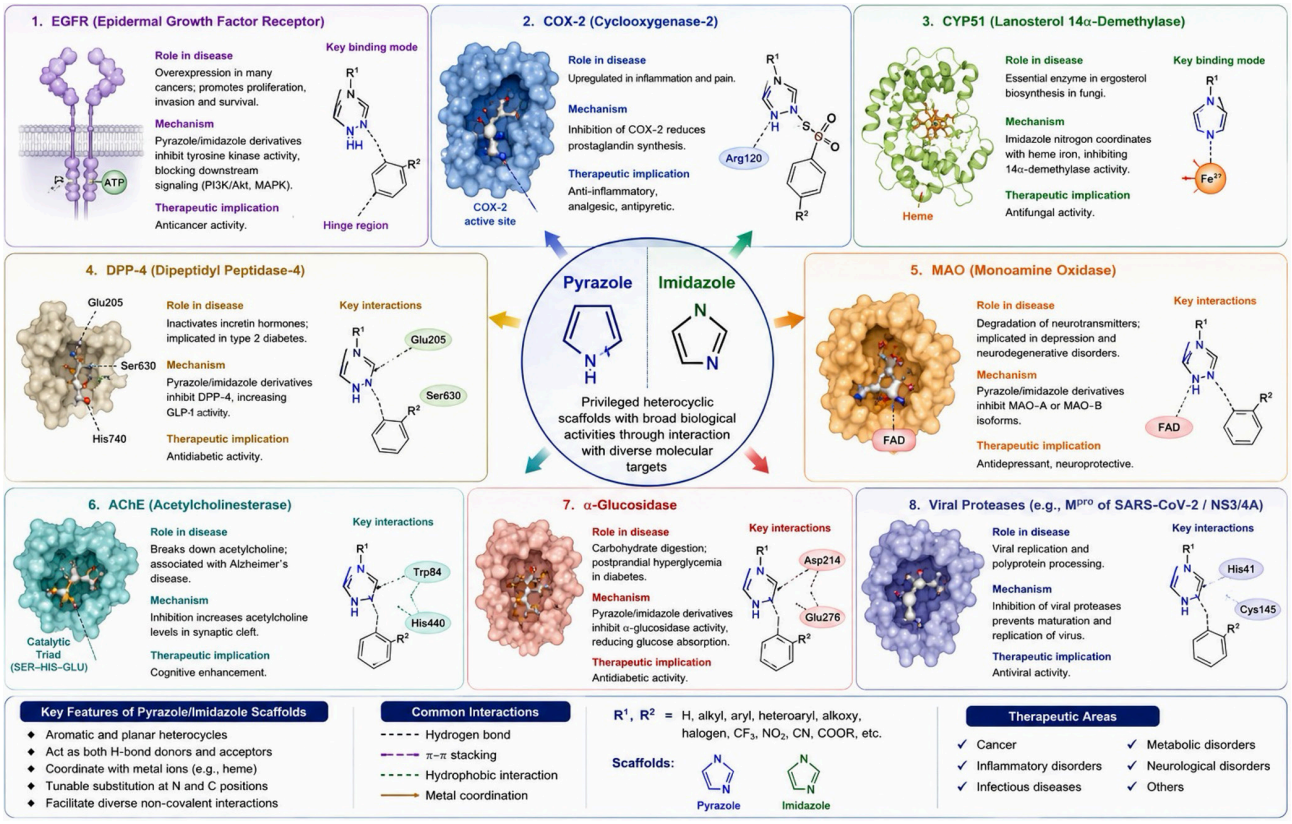

Figure 4. Major molecular targets and therapeutic applications

Table 3. Representative pyrazole and imidazole derivatives, therapeutic targets, biological activities, and key SAR findings

Scaffold	Representative Compound (Example)	Structure	Therapeutic Target(s)	Biological Activity (IC_{50}/MIC/EC_{50})	Key SAR Findings	Reference
Pyrazole derivatives	Celecoxib (COX-2 inhibitor)	Insert chemical structure	COX-2	IC_{50} = 40 nM (selective for COX-2)	• Sulfonamide moiety essential for COX-2 binding. • Para-amino group increases activity. • Bulky substituents at N1 enhance selectivity.	(1,2)
	Crizotinib (anticancer agent)	Insert chemical structure	ALK, ROS1, MET	IC_{50} = 11 nM (ALK)	• Pyrazole ring crucial for hinge binding. • Halogens at C4 improve potency. • Morpholine side chain enhances solubility.	(3,4)
	Pyrazinamide (antitubercular)	Insert chemical structure	Pyrazinamidase (RncA)	MIC = 12.5 μg/mL (M. tuberculosis)	• Carboxamide group important for activity. • Electron-withdrawing substituents at C3 beneficial. • Improves penetration in mycobacterial cell wall.	(5,6)
	Compound 4b (antifungal)	Insert chemical structure	CYP51 (14α-demethylase)	IC_{50} = 0.23 μM (Candida albicans)	• Halogen substitution increases lipophilicity. • Hydroxyl group enhances heme binding. • N1-aryl substitution improves spectrum.	(7)
Imidazole derivatives	Ketoconazole (antifungal)	Insert chemical structure	CYP51 (14α-demethylase)	IC_{50} = 0.02 μM (C. albicans)	• Imidazole N coordinates with heme iron. • Dioxolane ring increases lipophilicity. • Dichloro substitution improves potency.	(8,9)
	Metronidazole (antiprotozoal/ antibacterial)	Insert chemical structure	DNA damage (anaerobic activation)	MIC = 0.5–2 μg/mL	• Nitro group essential after reduction. • Hydroxyethyl chain improves solubility. • N1 substitution affects potency.	(10)
	Losartan (antihypertensive)	Insert chemical structure	AT1 receptor	IC_{50} = 8 nM	• Biphenyl-tetrazole essential. • Imidazole ring anchors via H-bonding. • Butyl chain length influences activity.	(11,12)
	Compound 9k (anticancer)	Insert chemical structure	EGFR kinase	IC_{50} = 0.15 μM (A549 cells)	• Electron-withdrawing CF3 improves potency. • N1-alkyl/aryl substitution improves selectivity. • Planar aryl groups favor EGFR binding.	(13)
	Compound 6f (antidiabetic)	Insert chemical structure	α-Glucosidase	IC_{50} = 1.8 μM	• Electron-donating groups improve binding. • Aromatic substituents enhance hydrophobic interactions. • Optimal linker length increases activity.	(14)

imidazole-based compounds highlights the importance of these heterocyclic scaffolds as privileged structures in contemporary drug discovery. Owing to their favorable physicochemical properties, synthetic versatility, and ability to modulate diverse biological targets, numerous derivatives have progressed from experimental leads to approved therapeutics or advanced clinical candidates[61]. Representative pyrazole-containing drugs include celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor widely used for inflammatory disorders, crizotinib, an ALK/ROS1/MET kinase inhibitor for non-small cell lung cancer, sildenafil, a phosphodiesterase-5 (PDE5) inhibitor for pulmonary arterial hypertension and erectile dysfunction, and fezolinetant, a neurokinin-3 receptor antagonist recently approved for the treatment of menopausal vasomotor symptoms. Likewise, clinically important imidazole derivatives such as ketoconazole, clotrimazole, miconazole, and metronidazole remain indispensable agents for the management of fungal, bacterial, and protozoal infections. Beyond these marketed drugs, numerous pyrazole- and imidazole-based molecules are currently undergoing preclinical optimization and clinical evaluation as kinase inhibitors, enzyme modulators, and multitarget therapeutics for cancer, infectious diseases, metabolic disorders, and neurological conditions. Advances in structure-based drug design, predictive ADMET modeling, and artificial intelligence-assisted lead optimization continue to accelerate the discovery of clinically promising candidates with improved efficacy, selectivity, and pharmacokinetic performance[63].

In addition to marketed drugs, several pyrazole- and imidazole-based compounds are currently undergoing early-stage clinical evaluation for oncology, inflammatory disorders, and infectious diseases. Many of these investigational agents function as selective kinase inhibitors, enzyme modulators, or receptor antagonists, reflecting the expanding therapeutic versatility of these privileged scaffolds. Although relatively few candidates have progressed to late-stage clinical trials, continued advances in medicinal chemistry, biomarker-guided drug development, and AI-assisted lead optimization are expected to accelerate their clinical translation and improve the success rate of future therapeutic candidates[15,32,54,61]. Representative marketed drugs and clinical candidates containing pyrazole or imidazole scaffolds are summarized in Table 4.

Table 4. Clinical translation of representative pyrazole and imidazole derivatives

Compound	Scaffold	Therapeutic Target	Clinical Status	Major Indication
Celecoxib	Pyrazole	COX-2	Marketed	Osteoarthritis, rheumatoid arthritis, pain
Crizotinib	Pyrazole	ALK, ROS1, MET	Marketed	Non-small cell lung cancer
Sildenafil	Pyrazole-containing	PDE5	Marketed	Erectile dysfunction, pulmonary arterial hypertension
Fezolinetant	Pyrazole	Neurokinin-3 receptor (NK3R)	Marketed	Moderate-to-severe vasomotor symptoms (menopause)
Ketoconazole	Imidazole	CYP51 (14α-demethylase)	Marketed	Systemic fungal infections
Clotrimazole	Imidazole	CYP51	Marketed	Superficial fungal infections
Miconazole	Imidazole	CYP51	Marketed	Candidiasis and dermatophytosis
Metronidazole	Imidazole	DNA damage in anaerobic microorganisms	Marketed	Anaerobic bacterial and protozoal infections
Novel pyrazole derivatives	Pyrazole	Kinases, HDACs, COX-2	Preclinical/ Clinical evaluation	Cancer, inflammation
Novel imidazole hybrids	Imidazole	CYP51, EGFR, MAO, DPP-4	Preclinical/ Clinical evaluation	Infectious, metabolic and neurological disorders

Patent landscape

The growing number of patent applications involving pyrazole and imidazole derivatives reflects their continued importance as privileged scaffolds in pharmaceutical research. Recent patents have focused on improving target selectivity[54], overcoming drug resistance, optimizing pharmacokinetic properties, and developing hybrid molecules with enhanced biological activity. In addition to novel chemical entities, patent activity increasingly encompasses green synthetic methodologies, AI-assisted lead optimization, and multitarget-directed ligands. These innovations demonstrate the strong commercial potential of pyrazole- and imidazole-based therapeutics and highlight ongoing efforts to translate medicinal chemistry discoveries into clinically useful drugs[65,69]. Recent representative patents involving pyrazole and imidazole

derivatives, together with their therapeutic targets and applications, are summarized in Table 5.

Limitations and research gaps

Despite remarkable progress in the design and biological evaluation of pyrazole- and imidazole-based compounds[21], several challenges continue to hinder their successful translation into clinically useful therapeutics[24]. One of the major concerns is the emergence of drug resistance[26], particularly in cancer and infectious diseases, where continuous genetic mutations and adaptive cellular mechanisms often reduce the long-term efficacy of targeted agents[42,80,82]. Consequently, the development of multi-target or resistance-modulating derivatives has become an important area of investigation[63,81,83].

Another significant limitation is achieving high target selectivity while minimizing off-target interactions. Although structural modifications and hybrid pharmacophore strategies have improved biological potency[56,79], many lead compounds still exhibit limited selectivity, increasing the risk of adverse effects. Furthermore, poor aqueous solubility, insufficient membrane permeability, and suboptimal pharmacokinetic (PK) properties, including rapid metabolism and low oral bioavailability, frequently compromise therapeutic efficacy[57]. These issues often necessitate additional optimization through prodrug design, formulation strategies, or rational molecular modification[63].

Toxicity also remains a major obstacle during drug development[24,78]. Several promising derivatives demonstrate excellent in vitro potency but fail during preclinical evaluation because of hepatotoxicity, cardiotoxicity, or unfavorable safety profiles. Similarly, many published studies rely primarily on enzyme-based assays or cultured cell lines, with relatively few comprehensive in vivo investigations to confirm efficacy, pharmacokinetics, long-term safety, and therapeutic outcomes[42,57,77]. This gap limits confidence in the translational potential of many reported compounds.

Another important research gap is the limited application of biomarker-guided drug design and patient stratification[12,54], which are increasingly recognized as essential components of precision medicine[57,76]. Integrating molecular biomarkers with artificial intelligence-assisted drug discovery, predictive ADMET modeling, and systems pharmacology could substantially improve lead optimization and clinical success rates[61]. Therefore, future research should emphasize multidisciplinary approaches that combine medicinal chemistry, computational modeling, pharmacology, and

Table 5. Representative patents involving pyrazole and imidazole derivatives (2020–2025)[85,86,87,88,89,90,91,92]

Patent publication	Applicant / Assignee	Compound class	Molecular target / Mechanism	Year	Therapeutic area
WO2021041276A1	Taiho Pharmaceutical Co., Ltd.	Heterocyclic pyrazole derivatives	Type III receptor tyrosine kinases (e.g., FLT3/KIT family)	2021	Cancer (Google Patents)
US20200290998A1	(Published PCT application)	Novel imidazole–pyrazole derivatives	Antibacterial agents	2020	Bacterial infections (Justia Patents)
US20230295123A1	(Continuation of PCT application)	Novel imidazole–pyrazole derivatives	Antibacterial agents	2023	Drug-resistant bacterial infections (Justia Patents)
WO2021197464A1	Jiangsu Hengrui Medicine Co., Ltd.	Fused imidazole derivatives	Protein kinase/enzyme modulation	2021	Metabolic disorders and oncology (PubChem)
WO2022251188A2	Blueprint Medicines Corporation	Imidazole-containing kinase inhibitors	ALK2 kinase	2022	Rare genetic disorders / oncology (Google Patents)
WO2020247447A1 (family of US12275744B2)	Hager Biosciences LLC	Pyrazole–imidazole derivatives	Orexin receptor antagonists	2020	Neurological and psychiatric disorders (PubChem)
US12310963B2	Tarapeutics Science Inc.	Pyrazole derivatives	PDGFRα/PDGFRβ kinase inhibitors	2025	Cancer (PubChem)
US12275744B2	Hager Biosciences LLC	Pyrazole–imidazole derivatives	Orexin receptor antagonists	2025	Sleep and neurological disorders (MTEC)

translational studies to develop pyrazole- and imidazole-based therapeutics with improved efficacy, safety, pharmacokinetic performance, and greater potential for successful clinical translation[63].

Future perspectives

The continued evolution of medicinal chemistry and computational technologies is expected to significantly expand the therapeutic potential of pyrazole and imidazole derivatives[12,71]. Artificial intelligence (AI)-driven drug discovery, machine learning algorithms, and generative molecular design are transforming lead identification by enabling rapid prediction of biological activity, target selectivity, and pharmacokinetic behavior[54,72]. These computational advances, when integrated with predictive ADMET modeling and structure-based drug design, are likely to accelerate the development of safer and more effective candidates[61,73].

Emerging therapeutic strategies such as proteolysis-targeting chimeras (PROTACs): molecular glues, and covalent inhibitors offer promising opportunities to exploit pyrazole and imidazole scaffolds for previously undruggable targets[14,15,75]. In parallel, the design of hybrid pharmacophores capable of simultaneously modulating multiple disease-associated pathways may provide improved efficacy while reducing the likelihood of drug resistance[54]. Sustainable medicinal chemistry will also play an increasingly important role, with green synthetic methodologies, including solvent-free reactions, recyclable catalysts[61], continuous-flow chemistry, and energy-efficient processes[64], supporting environmentally responsible drug development.

Furthermore, advances in genomics, biomarker discovery[12], and systems pharmacology are paving the way for precision medicine and personalized therapeutic strategies, enabling treatments tailored to individual patient profiles[54,57]. The integration of these multidisciplinary approaches is expected to facilitate the rational design of next-generation pyrazole- and imidazole-based therapeutics with enhanced efficacy, safety, and clinical applicability[61,63].

Conclusions

Pyrazole and imidazole remain among the most versatile and extensively investigated nitrogen-containing heterocyclic scaffolds in medicinal chemistry because of their favorable electronic characteristics, structural diversity, and broad pharmacological potential. This review has comprehensively summarized recent advances in their chemistry, modern synthetic methodologies, structure-activity relationships, biological evaluation, clinical translation, and emerging applications in drug discovery. The growing number of marketed drugs and promising lead compounds highlights the significant contribution of these scaffolds to the development of therapeutics for cancer, inflammatory disorders, infectious diseases, metabolic abnormalities, and neurological conditions.

Despite substantial progress, important challenges related to drug resistance, target selectivity, pharmacokinetic limitations, toxicity, and clinical translation continue to influence the successful development of new drug candidates. Addressing these issues will require the integration of rational molecular design, advanced computational approaches, sustainable synthetic methodologies, and comprehensive biological evaluation. Future research combining artificial intelligence, biomarker-guided drug discovery, hybrid pharmacophore strategies, and precision medicine is expected to accelerate the discovery of innovative therapeutics. Collectively, pyrazole and imidazole scaffolds will continue to serve as valuable platforms for the development of safer, more selective, and clinically effective drugs across diverse therapeutic areas.

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