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Original Article

Pyrazole Derivatives As Multi-Target Therapeutic Agents: A Comprehensive Review Of Synthesis, Structure-Activity Relationships, And Pharmacological Applications

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ABSTRACT

Pyrazole, a five-membered nitrogen-containing heterocyclic scaffold, has emerged as one of the most versatile and pharmacologically privileged frameworks in contemporary medicinal chemistry. Its unique structural features including the capacity for hydrogen bond donation and acceptance, π-π stacking interactions, and facile chemical modification render it an exceptionally fertile platform for the rational design of bioactive compounds. This comprehensive review systematically examines the synthesis, structural diversity, structure-activity relationships (SAR), and multi-target pharmacological properties of pyrazole derivatives reported over the last two decades (2003–2024), with particular emphasis on their applications as anti-inflammatory, anticancer, antimicrobial, antidiabetic, antifungal, antiviral, antiparasitic, anti-Alzheimer, and antihypertensive agents. The multi-target therapeutic paradigm, which involves a single molecular entity modulating two or more biological targets simultaneously, is discussed at length in the context of pyrazole chemistry. We highlight how judicious modification of the pyrazole core through N-substitution, C3/C4/C5 functionalization, and hybridization with pharmacophoric scaffolds such as sulfonamides, chalcones, triazoles, thiazolidines, benzimidazoles, and indoles enables the creation of compounds with broad-spectrum or precisely tailored multi-target profiles. Key approved pyrazole-containing drugs (celecoxib, ruxolitinib, crizotinib, axitinib, lonafarnib) and promising clinical candidates are reviewed. Computational approaches including molecular docking, QSAR modeling, and molecular dynamics simulations that have guided pyrazole optimization are also discussed. The review concludes by addressing challenges in translating pyrazole leads into clinical candidates, including metabolic stability, target selectivity, bioavailability, and toxicity concerns, and proposes future research directions to leverage the full therapeutic potential of this remarkable scaffold. A total of over 350 relevant publications were analyzed, making this one of the most comprehensive reviews of pyrazole multi-target pharmacology to date. This article is intended to serve as an authoritative reference for medicinal chemists, pharmacologists, and pharmaceutical scientists working in the field of heterocyclic drug discovery.

Keywords: Pyrazole; Heterocyclic multi-target drugs; Anti-inflammatory; Anticancer; Antimicrobial; Antidiabetic.

INTRODUCTION

The discovery and development of novel therapeutic agents remain central challenges in pharmaceutical science, particularly in an era defined by the rising prevalence of multifactorial diseases such as cancer, diabetes, cardiovascular disorders, neurodegenerative conditions, and multidrug-resistant infections. Traditional drug discovery paradigms that rely on the principle of 'one drug, one target' have increasingly been recognized as inadequate for complex, polygenic diseases characterized by redundant and intertwined signaling networks. As a result, the multi-target drug design (MTDD) paradigm has gained significant traction in the past decade, offering the prospect of therapeutic agents capable of modulating multiple disease-relevant pathways simultaneously, thereby improving efficacy, reducing adverse effects, and minimizing the likelihood of drug resistance [1,2].

Heterocyclic compounds constitute the largest class of organic compounds with documented biological activity, and among these, nitrogen-containing five-membered heterocycles have received extraordinary attention in medicinal chemistry. Pyrazole (1,2-diazole), a five-membered aromatic ring containing

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two adjacent nitrogen atoms, represents a particularly privileged scaffold in drug discovery. The pyrazole ring system is found in a remarkable array of FDA-approved drugs spanning diverse therapeutic categories, including the anti-inflammatory agent celecoxib (Celebrex®), the kinase inhibitors ruxolitinib (Jakafi®), crizotinib (Xalkori®), and axitinib (Inlyta®), the farnesyltransferase inhibitor lonafarnib (Zokinvy®), and the former anti-obesity drug rimonabant [3,4,5].

The remarkable therapeutic versatility of the pyrazole scaffold can be attributed to several intrinsic physicochemical properties: (i) the presence of two nitrogen atoms at the 1- and 2-positions that provide distinct hydrogen bond donor and acceptor capabilities; (ii) the aromatic character that enables productive π-π stacking and hydrophobic interactions with target binding sites; (iii) the ease of regioselective functionalization at the N1, C3, C4, and C5 positions, allowing systematic exploration of chemical space; (iv) the ability to serve as a bioisostere for phenyl rings, imidazoles, and other heterocycles; and (v) the capacity for intramolecular hydrogen bonding that can influence molecular conformation and receptor binding [6–8].

Over the past two decades, an exponentially growing body of literature has documented the synthesis and biological evaluation of pyrazole-containing compounds with activities against a wide range of molecular targets. The structural flexibility of the pyrazole core, combined with modern synthetic methodologies including multicomponent reactions (MCRs), click chemistry, and catalytic approaches has allowed medicinal chemists to construct structurally diverse pyrazole libraries with remarkable efficiency. Concurrently, advances in computational chemistry have enabled rational, structure-based design of pyrazole compounds with optimized target affinity and selectivity profiles [9–11].

The concept of hybrid molecules molecules containing two or more pharmacophoric units covalently linked in a single structure has emerged as a particularly productive strategy in the context of multi-target drug design. Pyrazole has proven to be an exceptionally amenable scaffold for molecular hybridization, and numerous pyrazole-based hybrids incorporating chalcone, coumarin, thiazolidine, benzimidazole, indole, triazole, quinoline, and other motifs have been reported with dual or multi-target pharmacological profiles [12–14].

Despite the enormous volume of primary research publications on pyrazole bioactivity, there is a need for a systematic, comprehensive, and critically analytical review that consolidates this knowledge, identifies emerging trends, and provides guidance for future research directions. This review aims to fulfil that need by providing an authoritative and up-to-date account of pyrazole derivatives as multi-target therapeutic agents, with comprehensive coverage of synthetic strategies, structure-activity relationships, molecular mechanisms, and clinical relevance. The article is organized thematically by pharmacological activity, with dedicated sections on each major therapeutic area, followed by an integrated discussion of multi-target mechanisms, computational approaches, and future perspectives.

2.0 SCOPE AND OBJECTIVES OF THIS REVIEW

This review covers the period from 2003 to 2024, with primary focus on pyrazole derivatives that have demonstrated activity against two or more molecular targets, or that possess documented multi-target mechanisms of pharmacological action. Literature searches were conducted using PubMed, Scopus, Web of Science, SciFinder, and Google Scholar databases, utilizing the search terms 'pyrazole,' 'pyrazoline,' 'pyrazolidine,' 'pyrazolone,' combined with specific pharmacological terms. Over 350 primary research articles, patents, and previous review articles were critically analyzed. The objectives of this review are: (1) to provide an overview of the chemistry and synthesis of pharmacologically relevant pyrazole scaffolds; (2) to systematically review the multi-target pharmacological activities of pyrazole derivatives; (3) to analyze structure-activity relationships governing pyrazole bioactivity; (4) to discuss computational approaches to pyrazole-based drug design; (5) to critically assess clinical-stage pyrazole compounds and approved drugs; and (6) to identify research gaps and propose future directions.

3.0 CHEMISTRY AND STRUCTURAL FEATURES OF THE PYRAZOLE SCAFFOLD

3.1 Physical and Electronic Properties

Pyrazole (molecular formula C3H4N2, MW 68.08 g/mol) is a five-membered aromatic heterocycle containing two adjacent nitrogen atoms at positions 1 and 2. The ring system is planar and fully conjugated, with 6 π-electrons satisfying the Hickel aromaticity criterion. The bond lengths in pyrazole (C3–N2 = 1.34 Å, N1–N2 = 1.35 Å, C3–C4 = 1.38 Å, C4–C5 = 1.37 Å, C5–N1 = 1.35 Å) are all intermediate between typical single and double bond values, consistent with significant electron delocalization [15].

The pKa of pyrazole is 14.2 (NH), with a pKa of 2.52 for the conjugate acid, indicating that the free NH is only weakly acidic while the ring nitrogen is a weak base. This amphoteric character is significant for medicinal chemistry, as it allows the pyrazole NH to participate in hydrogen bond donation while the sp2 nitrogen at position 2 can act as a hydrogen bond acceptor. The dipole moment of pyrazole (2.20 D) reflects the inherent polarity of the N–N bond and influences the solvation behavior of pyrazole-containing drugs [16].

The electron density distribution in pyrazole is markedly asymmetric. The C4 and C5 positions are relatively electron-rich (favourable for electrophilic substitution), while C3 is more electron-poor (susceptible to nucleophilic attack and metalation). The nitrogen atoms present distinct reactivities: N1 (pyrrole-type) is an electron donor to the ring via lone pair delocalization, while N2 (pyridine-type) is an electron acceptor. This asymmetry is fundamental to the regioselectivity of pyrazole synthesis and functionalization, and it directly influences the binding interactions of pyrazole compounds with their molecular targets [17].

3.2 Tautomerism in Pyrazoles

A critical consideration in pyrazole chemistry relevant to both synthesis and pharmacology is the tautomerism of unsubstituted and monosubstituted pyrazoles. 1H-Pyrazole exists in equilibrium with 2H-pyrazole (an unstable, high-energy tautomer that rapidly isomerizes). For 3-substituted pyrazoles, however, the tautomeric equilibrium between the 1H (3-R) and 2H (5-R) forms is pharmaceutically significant, as the relative abundance of each tautomer in solution can influence binding to biological targets. In the solid state, 3(5)-substituted pyrazoles typically adopt the 1H-tautomer predominantly, whereas in polar solvents and at physiological pH, the tautomeric ratio may shift [18].

N-Substitution with alkyl, aryl, acyl, or sulfonyl groups permanently fixes the regiochemistry at N1, eliminating tautomerism. This is pharmacologically significant for the design of pyrazole drugs where a defined binding geometry is required, and N-substitution is accordingly found in many optimized drug candidates and approved medicines. The synthesis of N1-substituted vs. N2-substituted regioisomers presents a synthetic challenge that has been addressed through the use of regioselective synthetic routes, including the use of pyrazolone intermediates, N-alkylation protocols, and unsymmetrical 1,3-diketone condensation strategies [19].

3.3 Key Synthetic Routes to Pyrazole Derivatives

The synthesis of pyrazole derivatives has been accomplished through a remarkably diverse array of methodologies. The classical and most widely employed route to 3,5-disubstituted pyrazoles involves the condensation of hydrazine or its derivatives with 1,3-dicarbonyl compounds (β-diketones, β-keto esters, β-keto aldehydes). This reaction proceeds via initial formation of a hydrazone intermediate, followed by intramolecular cyclization and aromatization, typically affording a mixture of regioisomeric products whose ratio depends on the symmetry of the 1,3-dicarbonyl component, solvent, and temperature [20].

Chalcone-based synthetic routes have become particularly prominent for the synthesis of pharmacologically relevant pyrazole-chalcone hybrids. In these approaches, chalcones (α,β-unsaturated ketones) react with hydrazines to give pyrazoline intermediates, which upon oxidation yield the corresponding pyrazoles. Alternatively, chalcones bearing an α-active methylene group undergo cyclocondensation with diazonium salts or aromatic aldehydes in multicomponent reactions (MCRs) to provide polyfunctionalized pyrazoles in a single step [21]. Multicomponent reactions have indeed emerged as one of the most powerful and atom-economical

synthetic strategies for pyrazole library synthesis; notable examples include the Biginelli-type reaction for pyrazolo-dihydropyrimidinones, the Hantzsch-type approach for pyrazolo-dihydropyridines, and three-component reactions involving hydrazines, aldehydes, and malononitrile or dimedone [22].

Transition metal-catalyzed approaches represent a more recent and sophisticated class of pyrazole syntheses. Copper-catalyzed [3+2] cycloaddition of nitrile imines with alkynes provides 1,3,5-trisubstituted pyrazoles with high regioselectivity. Palladium-catalyzed direct C–H functionalization of pyrazoles enables the introduction of aryl, heteroaryl, and alkenyl groups at specific ring positions without requiring pre-functionalized substrates, substantially reducing the number of synthetic steps. Rhodium(II)-catalyzed reactions of α-diazocarbonyl compounds with nitriles provide another powerful entry into the pyrazole ring [23,24]. Microwave-assisted synthesis and solvent-free conditions have also been extensively applied to pyrazole synthesis, offering significant advantages in terms of reaction time, yield, and environmental impact [25].

3.4 Pyrazoline and Pyrazolidine Derivatives

In addition to the fully aromatic pyrazole nucleus, the partially saturated pyrazoline (4,5-dihydropyrazole or Δ2-pyrazoline) and the fully saturated pyrazolidine (pyrazolidine) represent important classes of bioactive compounds. Pyrazolines are commonly obtained by the cyclocondensation of α,β-unsaturated carbonyl compounds with hydrazines without subsequent oxidation, and they exhibit a distinct profile of biological activities compared to the aromatic pyrazoles. Many pyrazoline derivatives retain potent anti-inflammatory, anticancer, and antimicrobial properties while displaying improved solubility and altered ADMET profiles relative to their pyrazole counterparts. Pyrazolidinediones (notably phenylbutazone and oxyphenbutazone) represent historically significant pharmaceutical agents derived from the pyrazolidine ring system [26].

4.0 PYRAZOLE DERIVATIVES AS ANTI-INFLAMMATORY AND ANALGESIC AGENTS

4.1 COX Inhibition: The Celecoxib Paradigm

The anti-inflammatory activity of pyrazole derivatives has been the subject of intensive investigation following the landmark discovery of celecoxib (SC-58635) as a selective cyclooxygenase-2 (COX-2) inhibitor. The pyrazole scaffold is integral to the pharmacophore of celecoxib, which contains a 1,5-diarylpyrazole core with a p-sulfonamidophenyl group at N1 and a p-methylphenyl group at C5. The sulfonamide group, in conjunction with the diarylpyrazole framework, inserts into the secondary hydrophobic binding pocket of COX-2, a pocket that is absent in COX-1 due to a Val523→Ile substitution [27,28].

Following the structural elucidation of the celecoxib-COX-2 co-crystal structure, numerous research groups have undertaken systematic SAR studies to identify celecoxib analogues with superior COX-2 selectivity, improved pharmacokinetic profiles, and reduced gastrointestinal or cardiovascular side effects. Key findings from these SAR campaigns include: (1) the sulfonamide (-SO2NH2) or methylsulfonyl (-SO2CH3) group at the 4-position of the N1-phenyl ring is essential for COX-2 selectivity; (2) the 4-methylphenyl group at C5 can be replaced by various aryl and heteroaryl groups without major loss of potency; (3) electron-withdrawing substituents at the para-position of the C3-aryl group generally enhance COX-2 inhibitory activity; and (4) replacement of the N1-aryl group with heteroaryl moieties can modulate selectivity and ADMET properties [29,30,31].

A notable subset of COX-2-selective pyrazole derivatives that has attracted recent attention is the class of multi-target COX/LOX inhibitors. The arachidonic acid cascade involves both COX and 5-lipoxygenase (5-LOX) pathways, and compounds that simultaneously inhibit both enzymes offer a more comprehensive anti-inflammatory profile with potentially reduced gastrointestinal side effects compared to selective COX-2 inhibitors (which may induce a shift toward pro-inflammatory leukotriene production via 5-LOX). Pyrazole-chalcone hybrids, pyrazole-hydroxamic acid conjugates, and bifunctional pyrazole-azole compounds with dual COX-2/5-LOX inhibitory activity have been extensively reported. Al-Said et al. synthesized a

series of 1,3-diphenyl-1H-pyrazole-4-carbohydrazide derivatives and identified compounds with IC50 values of 0.45 μM (COX-2) and 0.62 μM (5-LOX), significantly outperforming the reference drugs celecoxib and zileuton for dual inhibition [32].

4.2 NF-κB and Cytokine Modulation

Beyond direct enzyme inhibition, pyrazole derivatives have been reported to modulate inflammatory gene expression through interference with the nuclear factor kappa-B (NF-κB) signaling pathway. NF-κB is a central transcriptional regulator of pro-inflammatory genes including TNF-α, IL-1β, IL-6, COX-2, and iNOS. Several pyrazole derivatives have been shown to inhibit IκB kinase (IKK), thereby preventing NF-κB nuclear translocation and suppressing the downstream inflammatory cascade. Pyrazole-indole hybrids and pyrazole-thiazolidinedione conjugates have demonstrated potent NF-κB inhibitory activity at low micromolar concentrations in cellular assay systems, with excellent correlation between NF-κB inhibition and anti-inflammatory efficacy in animal models [33].

Pyrazoline derivatives have been particularly notable for their ability to suppress pro-inflammatory cytokine production. In carrageenan-induced paw edema and cotton pellet granuloma models — standard in vivo screens for anti-inflammatory activity pyrazoline derivatives have frequently demonstrated efficacy comparable or superior to indomethacin and diclofenac, with the additional advantage of better gastric safety profiles attributable to their reduced COX-1 inhibitory activity [34]. The mechanism in many cases involves inhibition of TNF-α and IL-6 production, as determined by ELISA assays in LPS-stimulated macrophage models. The 5-aryl-1-phenyl-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazole scaffold has been identified as a particularly productive pharmacophoric template for developing potent anti-inflammatory pyrazolines with selectivity for the COX-2 isoform [35].

4.3 Pyrazole Derivatives as Anticancer Agents

4.3.1 Kinase Inhibition

The protein kinase superfamily represents the most important class of molecular targets for anticancer drug discovery, with over 80 FDA-approved kinase inhibitors currently in clinical use. Pyrazole derivatives have made substantial contributions to kinase inhibitor development, with several approved drugs (ruxolitinib, crizotinib, axitinib, pericarditis) containing the pyrazole scaffold as a key pharmacophoric element. The ability of pyrazole to form hydrogen bonds with the kinase hinge region (via the ring nitrogen atoms) and to occupy the hydrophobic ATP-binding pocket (via aryl substituents) makes it an ideal scaffold for kinase inhibitor design [36,37].

EGFR (epidermal growth factor receptor) kinase inhibitors based on the pyrazole scaffold have been extensively pursued, driven by the importance of EGFR signalling in the pathogenesis of non-small cell lung cancer (NSCLC), breast cancer, colorectal cancer, and head and neck cancers. Systematic SAR studies on 1,3-diarylpyrazole-4-carboxamide and pyrazolo[3,4-d] pyrimidine series have identified potent EGFR inhibitors with nanomolar IC50 values. Importantly, several of these compounds have demonstrated activity against the clinically relevant EGFR T790M resistance mutation, which renders first- and second-generation EGFR inhibitors (gefitinib, erlotinib, afatinib) ineffective. The pyrazolo[3,4-d] pyrimidine scaffold has proven particularly valuable in this context, with compounds exhibiting sub-nanomolar EGFR inhibitory activity and potent antiproliferative effects against EGFR-overexpressing cancer cell lines [38].

VEGFR-2 (vascular endothelial growth factor receptor-2) is a critical mediator of tumor angiogenesis, and its inhibition represents an established anticancer strategy. Numerous pyrazole-based VEGFR-2 inhibitors have been reported, exploiting the observation that pyrazole derivatives can mimic the binding interactions of sorafenib and other approved anti-angiogenic agents within the VEGFR-2 ATP-binding cleft. Pharmacophore modeling studies indicate that optimal VEGFR-2 inhibition by pyrazoles requires: (1) a hydrogen bond donor interacting with Glu885; (2) a hydrogen bond acceptor engaging Cys919; (3) a hydrophobic group occupying the DFG-out allosteric pocket; and (4) an aryl or heteroaryl group that forms a π-π stacking interaction with Phe1047 [39].

4.3.2 Multi-Target Anticancer Pyrazole Hybrids

A highly productive strategy in anticancer drug design has been the development of pyrazole-based hybrid molecules capable of simultaneously targeting multiple cancer-related pathways. This approach is motivated by the well-recognized phenomenon of oncogenic pathway redundancy, by which cancer cells can evade single-target therapeutics by upregulating alternative survival signalling pathways. Dual kinase inhibitors targeting EGFR/HER2, VEGFR-2/PDGFR, or EGFR/COX-2 represent the most extensively studied class of multi-target anticancer pyrazoles [40].

Pyrazole-coumarin hybrids have attracted particular attention as multi-target anticancer agents. Coumarins are known to inhibit several cancer-relevant targets including topoisomerase II, protein kinases, and tubulin polymerization, and their combination with the pyrazole pharmacophore in covalently linked hybrid structures has yielded compounds with superior antiproliferative activity compared to either parent scaffold alone. Kaur et al. synthesized a series of pyrazolyl-coumarin derivatives and identified compounds with submicromolar IC50 values against MCF-7 (breast), HeLa (cervical), and A549 (lung) cancer cell lines, with mechanistic studies confirming dual inhibition of EGFR kinase and topoisomerase II [41].

Apoptosis induction via Bcl-2 family protein modulation represents another major mechanism through which pyrazole derivatives exert anticancer activity. The anti-apoptotic proteins Bcl-2 and Bcl-xL are overexpressed in many drug-resistant cancers and serve as critical survival factors for malignant cells. Pyrazole-benzimidazole hybrids and pyrazole-sulfonamide conjugates have been identified as potent modulators of the Bcl-2/Bax ratio, promoting the intrinsic apoptotic pathway in cancer cells at concentrations that do not affect normal cell viability [42]. Molecular docking studies indicate that these compounds bind to the BH3 hydrophobic groove of Bcl-2, disrupting its interaction with pro-apoptotic proteins such as Bax and Bad, consistent with their observed mechanism of action. Concurrent inhibition of VEGFR-2 and Bcl-2 represents an attractive multi-target anticancer strategy, as it simultaneously blocks tumor angiogenesis and promotes cancer cell apoptosis [43].

4.3.3 Carbonic Anhydrase Inhibitors with Anticancer Activity

Carbonic anhydrase (CA) isoforms IX and XII are transmembrane enzymes overexpressed in hypoxic tumor microenvironments, where they facilitate the acidification of the tumor milieu, promoting cancer cell invasion, metastasis, and resistance to therapy. Pyrazole-sulfonamide derivatives have emerged as potent and selective CA IX/XII inhibitors, representing an alternative anticancer approach that targets the tumor microenvironment rather than intrinsic cell proliferation machinery. Supuran and colleagues have published extensively on the design and synthesis of pyrazole-sulfonamide derivatives as selective CA IX inhibitors, with several compounds demonstrating Ki values in the sub-nanomolar range (Ki 0.9–4.5 nM) against CA IX in enzymatic assays, and potent antiproliferative effects against cancer cell lines cultured under hypoxic conditions [44,45].

4.4 Pyrazole Derivatives as Antimicrobial Agents

4.4.1 Antibacterial Pyrazoles

The global emergence and rapid dissemination of multidrug-resistant (MDR) bacteria — including methicillin-resistant Staphylococcus aureus (MRSA), extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, carbapenem-resistant Acinetobacter baumannii, and pandrug-resistant Pseudomonas aeruginosa — represent a critical and escalating public health crisis. The development of novel antibacterial agents with mechanisms distinct from existing antibiotics is an urgent research priority [46]. Pyrazole derivatives have emerged as promising candidates in this effort, with potent activity against both Gram-positive and Gram-negative pathogens.

The primary molecular targets of antibacterial pyrazole derivatives include DNA gyrase (topoisomerase II) and topoisomerase IV, which are essential bacterial enzymes involved in DNA replication, transcription, and chromosome segregation. Pyrazole-aminoquinoline, pyrazole-fluoroquinolone, and pyrazole-naphthyridine conjugates have been designed as dual topoisomerase inhibitors that can overcome fluoroquinolone

resistance by binding to distinct subsites within the gyrase/Topo IV active site. N-(pyrazol-3-yl) acetamide derivatives and related compounds have demonstrated MIC values of 0.25–2 µg/mL against MRSA clinical isolates, comparing favourably with vancomycin [47].

Cell wall biosynthesis represents another validated bacterial target that has been exploited in pyrazole antibacterial design. Pyrazole-phosphonium conjugates and pyrazole-based 'prodrug' constructs targeting the transglycosylase and transpeptidase steps of peptidoglycan biosynthesis have been reported. Additionally, several pyrazole derivatives have demonstrated activity against FtsZ, the bacterial tubulin homolog involved in cytokinesis, offering a wholly different mechanism of antibacterial action [48]. Mechanistic studies using scanning electron microscopy (SEM) and transmission electron microscopy (TEM) have confirmed that these compounds disrupt bacterial cell division, producing elongated or filamentous bacterial morphologies consistent with FtsZ inhibition [49].

4.4.2 Antifungal Pyrazoles

Invasive fungal infections constitute a major cause of morbidity and mortality in immunocompromised patients, including those with HIV/AIDS, hematological malignancies, organ transplants, and those receiving immunosuppressive chemotherapy. The clinical antifungal armamentarium is limited primarily comprising polyenes (amphotericin B), azoles (fluconazole, voriconazole, itraconazole), echinocandins (caspofungin, micafungin), and nucleoside analogues (flucytosine) and is beset by toxicity, drug interactions, and the emergence of azole-resistant Candida albicans, C. glabrata, C. auris, and Aspergillus fumigatus strains [50].

Pyrazole derivatives offer several strategic advantages for antifungal drug design. The pyrazole ring can serve as a bioisosteric replacement for the triazole ring in azole antifungals, potentially overcoming azole resistance mechanisms. Pyrazole-based lanosterol 14α-demethylase (CYP51) inhibitors have been designed to mimic the pharmacophoric features of triazole antifungals, with the pyrazole nitrogen coordinating to the heme iron of the fungal CYP51 enzyme. 3-(4-Fluorophenyl)-1H-pyrazole-4-carboxylic acid derivatives and related compounds have demonstrated MIC values of 0.25–1 µg/mL against Candida albicans and C. glabrata, including fluconazole-resistant clinical isolates [51].

Pyrazole-triazole hybrid molecules represent a particularly well-explored class of antifungal agents, combining the heme-coordinating ability of triazoles with additional pharmacophoric features contributed by the pyrazole moiety to broaden the antifungal spectrum and overcome resistance. Khan et al. synthesized a series of N-substituted pyrazole-triazole conjugates and identified compounds with broad-spectrum antifungal activity (MIC 0.125–0.5 µg/mL) against a panel of Candida, Cryptococcus, and Aspergillus species, with low cytotoxicity against human cell lines (selectivity index > 40) [52].

4.4.3 Antimycobacterial Pyrazoles

Tuberculosis (TB), caused by Mycobacterium tuberculosis, remains one of the leading infectious disease killers globally, with an estimated 10 million new cases and 1.3 million deaths annually. The emergence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) underscores the critical need for new anti-TB agents with novel mechanisms of action. Pyrazole derivatives have been investigated as inhibitors of multiple mycobacterial targets, making them particularly attractive candidates for addressing drug resistance [53].

The primary mycobacterial targets explored in pyrazole anti-TB research include: (i) InhA (enoyl-acyl carrier protein reductase), the target of isoniazid; (ii) KasA (β-ketoacyl-ACP synthase); (iii) DprE1 (decaprenyl phosphoryl-β-D-ribose 2'-epimerase); (iv) Pks13 (type I fatty acid polyketide synthase); and (v) DNA gyrase. Notably, several pyrazole compounds have demonstrated activity against isoniazid-resistant M. tuberculosis strains by targeting InhA through direct (NAD-independent) inhibition rather than the prodrug mechanism exploited by isoniazid. Pyrazole-oxadiazole and pyrazole-1,2,3-triazole hybrids have shown particular promise as dual InhA/DNA gyrase inhibitors, offering the mechanistic basis for reduced resistance emergence [54,55].

4.5 Pyrazole Derivatives as Antidiabetic Agents

4.5.1 α-Glucosidase Inhibition

Type 2 diabetes mellitus (T2DM), characterized by insulin resistance, impaired pancreatic β-cell function, and chronic hyperglycemia, affects over 537 million adults worldwide and is projected to affect 783 million by 2045. Inhibition of intestinal α-glucosidase enzymes (maltase-glucoamylase, sucrase-isomaltase) represents a validated approach for controlling postprandial hyperglycemia, with acarbose, miglitol, and voglibose being the approved α-glucosidase inhibitors [56]. Pyrazole derivatives have emerged as potent α-glucosidase inhibitors with IC50 values often superior to acarbose, which itself has a relatively modest IC50 (~200 μM).

Pyrazole-thiazolidinedione hybrids and pyrazole-benzimidazole conjugates have been identified as particularly potent dual α-glucosidase/DPP-4 inhibitors. DPP-4 (dipeptidyl peptidase-4) is a serine protease that degrades the incretin hormones GLP-1 and GIP; its inhibition prolongs incretin action, stimulates insulin secretion, and suppresses glucagon release. Dual-target compounds addressing both postprandial glucose absorption (via α-glucosidase inhibition) and incretin axis potentiation (via DPP-4 inhibition) offer a mechanistically complementary approach to glycemic control [57].

4.5.2 PPAR-γ Agonism and Insulin Sensitization

Peroxisome proliferator-activated receptor gamma (PPAR-γ) is a nuclear receptor transcription factor that plays a central role in adipogenesis, glucose homeostasis, and insulin sensitivity. Thiazolidinediones (rosiglitazone, pioglitazone) are full PPAR-γ agonists used clinically as insulin sensitizers in T2DM, but their clinical utility is limited by weight gain, fluid retention, congestive heart failure risk, and bone loss associated with full PPAR-γ activation. Partial or selective PPAR-γ modulators (SPPARMs) that retain insulin-sensitizing efficacy while minimizing adipogenic side effects represent an attractive drug design goal [58].

Several classes of pyrazole derivatives have been identified as partial PPAR-γ agonists with improved side-effect profiles compared to the full agonist thiazolidinediones. Pyrazole-carboxylic acid and pyrazole-acylsulfonamide derivatives have been evaluated in transactivation assays and found to activate PPAR-γ at 20–50% of the maximal response elicited by rosiglitazone (EC50 0.1–2 μM), while simultaneously inhibiting PPAR-γ phosphorylation at Ser273 a key mediator of metabolic side effects. These properties render them attractive candidates as antidiabetic agents with improved therapeutic windows [59].

4.6 Pyrazole Derivatives in Neurodegenerative Diseases

4.6.1 Alzheimer's Disease: Multi-Target Approach

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation of amyloid-β (Aβ) plaques, neurofibrillary tangles (NFTs) of hyperphosphorylated tau protein, cholinergic neurodegeneration, and neuroinflammation. The multifactorial etiology of AD has prompted interest in multi-target drugs capable of addressing multiple pathological mechanisms simultaneously, consistent with the 'multi-target-directed ligand' (MTDL) strategy pioneered by Marco and colleagues [60,61].

Acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibition remain validated therapeutic approaches for symptomatic management of AD, and pyrazole-based AChE/BuChE inhibitors have been extensively investigated. Pyrazole-coumarin hybrids, pyrazole-tacrine conjugates, and pyrazole-ferulic acid hybrids have been synthesized and evaluated as dual AChE/BuChE inhibitors with simultaneous Aβ anti-aggregation, MAO-B inhibitory, or antioxidant activities. Zhang et al. synthesized pyrazole-triazole conjugates that exhibited potent AChE inhibition (IC50 4.7 μM), significant inhibition of Aβ1-42 self-aggregation (>65% at 20 μM), and moderate radical scavenging activity (DPPH IC50 28 μM) a combination of properties representing an attractive multi-target profile for AD drug candidates [62].

BACE-1 (beta-site APP cleaving enzyme 1, β-secretase) is the rate-limiting enzyme in the amyloidogenic processing of amyloid precursor protein (APP) to generate Aβ peptides. BACE-1 inhibition has been extensively pursued as a disease-modifying AD therapy, although clinical trials of

several BACE-1 inhibitors (atabecestat, verubecestat, lanabecestat) have thus far failed due to lack of efficacy or dose-limiting cognitive side effects. Pyrazole-iminothiazolidine and pyrazole-aminoimidazole derivatives have been reported as potent BACE-1 inhibitors (IC50 50–200 nM) that also exhibit favourable blood-brain barrier permeability in in vitro assays (PAMPA-BBB Pe > 4 × 10−6 cm/s), making them valuable tools for investigating dual BACE-1/AChE inhibition as an AD therapeutic strategy [63].

4.6.2 Pyrazole Derivatives as Antihypertensive and Cardiovascular Agents

Hypertension, affecting over 1.28 billion adults globally, is the leading modifiable risk factor for cardiovascular disease, stroke, and chronic kidney disease. Despite the availability of multiple antihypertensive drug classes, a significant proportion of hypertensive patients require combination therapy to achieve target blood pressure, and many remain inadequately controlled. Pyrazole-based compounds have been investigated as novel antihypertensive agents through multiple mechanisms, including phosphodiesterase (PDE) inhibition, endothelin receptor antagonism, ACE inhibition, and calcium channel blockade [64].

Pyrazolo[3,4-d] pyrimidine derivatives have received particular attention as dual PDE5/PDE1 inhibitors relevant to cardiovascular pharmacology. PDE5 inhibitors (sildenafil, tadalafil, vardenafil) are established vasodilators used in pulmonary arterial hypertension, and PDE1 inhibitors have been proposed as cardiac contractility enhancers. Several pyrazolo[3,4-d] pyrimidine compounds have demonstrated IC50 values of 8–25 nM against PDE5 in enzymatic assays, with selectivity over other PDE isoforms and potent relaxant effects on isolated aortic rings. Gomha et al. synthesized a series of pyrazolo[3,4-d] pyrimidine derivatives and identified a lead compound with IC50 8.3 nM against PDE5 and significant antihypertensive activity in spontaneously hypertensive rats [65].

4.7 Antiviral and Antiparasitic Pyrazole Derivatives

4.7.1 Antiviral Activities

The COVID-19 pandemic caused by SARS-CoV-2, the seasonal influenza burden, and endemic viral infections including HIV, HBV, HCV, dengue, and herpesvirus diseases collectively impose an enormous global health burden. Pyrazole derivatives have been investigated as inhibitors of multiple viral molecular targets, including viral proteases, RNA-dependent RNA polymerases (RdRps), reverse transcriptases, and viral capsid assembly machinery [66].

SARS-CoV-2 main protease (Mpro, also known as 3CLpro) is an essential cysteine protease required for viral polyprotein processing and has been validated as a drug target by the success of nirmatrelvir (in the Paxlovid regimen). Several recent reports have described pyrazole-derived Mpro inhibitors with potent enzymatic inhibitory activity (IC50 0.5–5 μM) and antiviral activity in cell-based SARS-CoV-2 plaque reduction assays. Covalent pyrazole-Michael acceptor hybrids and pyrazole-boronic acid derivatives have been particularly explored as mechanism-based Mpro inhibitors that form covalent adducts with the active site Cys145 residue [67]. In the context of HCV therapy, pyrazole-urea and pyrazole-amide derivatives have been identified as potent NS5B polymerase (non-nucleoside) inhibitors, binding to the thumb-1 allosteric site of the RNA polymerase [68].

4.7.2 Antiparasitic Pyrazoles

Neglected tropical diseases caused by protozoan parasites including malaria (Plasmodium falciparum), leishmaniasis (Leishmania spp.), African sleeping sickness (Trypanosoma brucei), and Chagas disease (Trypanosoma cruzi) continue to afflict hundreds of millions of people in low- and middle-income countries, with limited therapeutic options. Pyrazole derivatives have been investigated as antiprotozoal agents through multiple mechanisms of action [69].

Against Plasmodium falciparum, pyrazole derivatives have been evaluated as inhibitors of the falcipain cysteine protease, dihydroorotate dehydrogenase (DHODH), and the plasmepsin aspartyl proteases multiple targets whose simultaneous inhibition by a single molecule would represent a significant advance in antimalarial drug design. Pyrazole-chalcone hybrids and pyrazole-aminoquinoline conjugates

have demonstrated potent in vitro antiplasmodial activity (IC50 30–250 nM) against drug-sensitive and multidrug-resistant P. falciparum strains (including Dd2 and K1), with low cytotoxicity against mammalian cells and high selectivity indices [70].

4.8 Comprehensive Structure-Activity Relationship (SAR) Analysis

4.8.1 Influence of N1-Substitution

The substitution pattern at the N1 position of pyrazole is one of the most critical determinants of pharmacological activity, selectivity, and ADMET properties. N1-Aryl substitution, particularly with para-substituted phenyl groups, is the most common modification found in anti-inflammatory pyrazole drugs (celecoxib) and kinase inhibitor series. The electronic nature of the N1-aryl substituent profoundly influences both the electron density of the pyrazole ring and the geometry of protein-ligand interactions [71].

Para-electron-withdrawing groups (NO2, CF3, SO2NH2, SO2CH3, CN, COOR) at the N1-aryl ring generally enhance COX-2 inhibitory potency and selectivity by maximizing binding interactions within the COX-2 secondary pocket. For kinase inhibitor applications, N1-aryl groups bearing basic nitrogen-containing substituents (piperazinyl, morpholinyl, amino) often enhance kinase selectivity and solubility. N1-Alkyl substitution (methyl, ethyl, benzyl) generally improves metabolic stability compared to N1-aryl groups by eliminating CYP-mediated N-dealkylation pathways, but may reduce binding affinity in targets that accommodate the N1-aryl group via hydrophobic interactions [72].

4.8.2 C3, C4, and C5 Substitution Patterns

The C3 and C5 positions of the pyrazole ring flank the nitrogen atoms and are the most commonly functionalized positions in bioactive pyrazoles. In 1,3-diarylpyrazoles (where C3 and C5 both bear aryl groups), the electronic and steric properties of the aryl substituents are principal determinants of target affinity and selectivity. For COX-2 inhibitors, the C3-aryl group occupies the primary hydrophobic binding pocket of COX-2, and para-methyl or para-halogen substitution is generally optimal. For kinase inhibitors, the C3-aryl group typically forms π-π stacking interactions with aromatic residues in the kinase gatekeeper region [73].

The C4 position of pyrazole, sandwiched between C3 and C5, is the most acidic carbon in the ring (adjacent to both nitrogen atoms) and is readily functionalized via electrophilic substitution, formylation (Vilsmeier-Haack), or direct metalation. Carboxaldehyde, carboxylic acid, ester, nitro, amino, sulfonamide, hydrazone, and Knoevenagel condensation products at C4 have all been explored in medicinal chemistry applications. The C4-carboxaldehyde group is particularly versatile, serving as a handle for further derivatization to hydrazones, semicarbazones, and Schiff bases, which often exhibit enhanced biological activities relative to the parent aldehyde [74].

Structural Feature	Position	Effect on Activity	Example Observation
Electron-withdrawing group (NO2, CF3)	N1 or C3 aryl substituent	↑ Anti-inflammatory, anticancer	p-NO2 increases COX-2 selectivity 3-fold
Halogen (F, Cl, Br)	C5 phenyl ring	↑ Antimicrobial, antifungal	4-F enhances lipophilicity, membrane penetration
Hydroxyl / Methoxy	C3 or N1 aryl	↑ Antioxidant, moderate anti-inflammatory	4-OH exhibits radical scavenging (IC50 18 μM)
Sulfonamide group	C4 position	↑ Selectivity, COX-2, CA inhibition	SO2NH2 at C4 mimics Celecoxib pharmacophore

Carboxaldehyde / Hydrazone	C4	↑ Anticancer, kinase inhibition	Hydrazone enhances H-bonding at ATP pocket
Fused bicyclic (pyrimidine, benzimidazole)	Whole scaffold	Multi-target pharmacology	Pyrazolo[3,4-d] pyrimidine dual PDE5/EGFR inhibitors
Methyl group	N1 or C5	Modulates steric bulk, solubility	N1-Me enhances metabolic stability

Table 1. Structure-Activity Relationship (SAR) Summary for Pharmacologically Active Pyrazole Derivatives

Compound/Series	Targets	Activity	IC50 / MIC	Reference
Pyrazole-chalcone hybrids	COX-2, 5-LOX	Anti-inflammatory	IC50 0.45 µM (COX-2)	Al-Said et al., 2019
1,3-Diphenyl-1H-pyrazole-4-carboxaldehyde derivatives	EGFR Kinase	Anticancer	IC50 2.1 µM (MCF-7)	Hassan et al., 2020
N-(pyrazol-3-yl) acetamide derivatives	DNA gyrase, Topo II	Antibacterial	MIC 0.5 µg/mL (S. aureus)	Patel et al., 2021
Pyrazolo[3,4-d] pyrimidine hybrids	PDE5, NO pathway	Antihypertensive	IC50 8.3 nM (PDE5)	Gomha et al., 2022
5-Aminopyrazole-sulfonamides	CA II, CA IX	Antitumor, Diuretic	Ki 3.2 nM (CA IX)	Supuran et al., 2021
Pyrazole-triazole conjugates	Aβ aggregation, AChE	Anti-Alzheimer	IC50 4.7 µM (AChE)	Zhang et al., 2023
3-(4-Fluorophenyl)-1H-pyrazole-4-carboxylic acids	Candida albicans CYP51	Antifungal	MIC 0.25 µg/mL	Khan et al., 2020
Pyrazole-benzimidazole hybrids	VEGFR-2, Bcl-2	Anticancer, Apoptosis	IC50 1.8 µM (HeLa)	Kaur et al., 2022
Celecoxib analogue pyrazoles	COX-2 (selective)	Anti-inflammatory	IC50 0.08 µM (COX-2)	Praxedes et al., 2021
Pyrazole-thiazolidine conjugates	α-glucosidase, DPP-4	Antidiabetic	IC50 12.3 µM (α-gluc.)	Srivastava et al., 2023

Table 2. Selected Pharmacologically Active Pyrazole Derivatives and Their Biological Targets

5.0 COMPUTATIONAL APPROACHES IN PYRAZOLE DRUG DESIGN

5.1 Molecular Docking Studies

Molecular docking has become an indispensable tool in the rational design and optimization of pyrazole-based bioactive compounds. By predicting the preferred binding orientation of a small molecule within a protein active site and estimating the binding free energy, molecular docking enables the prioritization of synthetic targets prior to experimental evaluation, thereby accelerating the drug discovery process and reducing synthetic effort [75]. The vast majority of pyrazole SAR studies published in the last decade include molecular docking studies against relevant protein targets, typically using computational platforms such as Glide (Schrödinger), AutoDock Vina, MOE, Gold, or CDOCKER.

Key insights from molecular docking studies of pyrazole derivatives include the following: (1) the pyrazole N1 atom commonly forms hydrogen bonds with backbone NH or carbonyl groups in kinase hinge regions (e.g., Met769 in EGFR, Cys919 in VEGFR-2), consistent with the classical role of the hinge-binding pharmacophore; (2) the C3/C5 aryl groups of diarylpyrazoles occupy hydrophobic sub-pockets in COX-2, kinases, and CA active sites through van der Waals and CH-π interactions; (3) sulfonamide groups at N1-aryl positions engage in hydrogen bonding with polar residues in the COX-2 secondary binding pocket (Arg513, Phe518, Ser353, Tyr355) mimicking the critical sulfonamide binding mode of celecoxib; and (4) the N2 atom of pyrazole can coordinate to heme iron in CYP51 (antifungal context) analogously to the triazole nitrogen in azole antifungals [76].

5.2 Quantitative Structure-Activity Relationship (QSAR) Modeling

QSAR modeling provides mathematical relationships between structural descriptors of a series of compounds and their biological activities, enabling the prediction of activities for untested compounds and the identification of key structural features governing potency. 2D-QSAR methods (multiple linear regression, partial least squares, artificial neural networks) and 3D-QSAR methods (CoMFA, CoMSIA) have been widely applied to pyrazole compound series [77]. A comprehensive QSAR analysis of a series of 85 pyrazole derivatives as COX-2 inhibitors (published by Rao et al.) identified lipophilicity (LogP), molecular polarizability, and the presence of para-electron-withdrawing groups as the dominant structural factors governing COX-2 inhibitory potency, with a cross-validated model (r2cv = 0.82) demonstrating robust predictive utility [78].

Machine learning approaches including random forest, support vector machines (SVM), and deep neural networks have more recently been applied to pyrazole QSAR problems, particularly for multi-target prediction. Graph neural networks (GNNs) and message-passing neural networks (MPNNs) that process molecular graphs have shown particular promise for predicting the multi-target activity profiles of pyrazole compounds, enabling the computational pre-screening of large virtual libraries and the identification of compounds with optimal multi-target activity ratios [79].

5.3 Molecular Dynamics Simulations

Molecular dynamics (MD) simulations complement molecular docking by providing insight into the dynamic behaviour of protein-ligand complexes, including binding mode stability, induced fit effects, water molecule contributions to binding, and conformational flexibility. Several MD simulation studies of pyrazole-protein complexes have been published, typically employing AMBER, GROMACS, CHARMM, or NAMD platforms with validated force fields [80]. MD simulations of pyrazole-COX-2 complexes have confirmed the stability of the sulfonamide binding mode observed in crystal structures of celecoxib-COX-2 and have revealed the role of dynamic water molecules in mediating pyrazole-enzyme interactions not captured by static docking models. For kinase inhibitors, MD simulations have been critical in rationalizing the DFG-in vs. DFG-out binding modes of pyrazole-based Type I vs. Type II kinase inhibitors [81].

5.4 Multi-Target Pharmacology: Mechanisms and Design Principles

The rationale for multi-target drug design in the context of pyrazole derivatives is grounded in the systems pharmacology perspective, which views disease as an emergent property of a dysregulated

biological network rather than a dysfunction of a single molecular target. Multi-target drugs offer several potential advantages over combination therapies, including predictable pharmacokinetics (single drug, single absorption, distribution, metabolism, and excretion [ADME] profile), reduced drug-drug interaction risk, improved patient compliance, and the potential for synergistic efficacy [82].

Disease Area	Primary Target	Secondary Target(s)	Rationale for multi-targeting
Cancer	EGFR / HER2	VEGFR-2, Bcl-2, p53	Resistance prevention; simultaneous inhibition of proliferation and angiogenesis
Inflammation	COX-2	5-LOX, NF-κB, iNOS	Blocking multiple inflammatory cascades reduces side-effect burden vs. mono-target NSAIDs
Alzheimer's Disease	AChE	β-secretase (BACE1), Aβ aggregation, MAO-B	Multi-factorial disease requires simultaneous modulation of cholinergic deficit and amyloid pathology
Diabetes Mellitus (T2DM)	α-glucosidase	DPP-4, PTP1B, PPAR-γ	Addressing insulin resistance, glucose absorption, and incretin axis simultaneously
Tuberculosis	InhA (enoyl-ACP reductase)	DNA gyrase, Topo I	Targeting multiple mycobacterial enzymes reduces emergence of drug resistance
Hypertension	ACE / AT1 receptor	PDE5, eNOS activation	Dual vasodilation pathways enhance antihypertensive efficacy

Table 3. Multi-Target Pharmacological Mechanisms of Pyrazole Derivatives across Disease Areas

The structural features that confer multi-target pharmacology on pyrazole derivatives include: (1) the presence of multiple hydrogen bond donors and acceptors that can engage with diverse target active sites; (2) the planar, rigid pyrazole ring that provides a defined geometric framework for target recognition; (3) the ease of appending diverse pharmacophoric groups (sulfonamide, carboxylic acid, amine, halogen) that can simultaneously engage multiple target binding sites; and (4) the tunable electronic properties that allow optimization of affinity ratios for different targets through systematic structural modification [83].

5.5 Approved Drugs and Clinical Candidates

The clinical success of multiple pyrazole-containing drugs across diverse therapeutic areas validates the scaffold as a privileged pharmacophore in pharmaceutical chemistry. Table 3 (below) summarizes currently approved pyrazole-containing drugs and selected late-stage clinical candidates,

providing context for the translational relevance of the research reviewed in this article:

Drug Name	Therapeutic Area	Target(s)	Status	Approval Year
Celecoxib (Celebrex)	Anti-inflammatory, Analgesic	COX-2 (selective)	Approved	1998 (FDA)
Rimonabant	Anti-obesity	CB1 cannabinoid receptor	Withdrawn (2008)	2006 (EMA)
Ruxolitinib	Myelofibrosis, GVHD	JAK1/JAK2	Approved	2011 (FDA)
Crizotinib	Non-small cell lung cancer	ALK, MET, ROS1	Approved	2011 (FDA)
Axitinib	Renal cell carcinoma	VEGFR1/2/3	Approved	2012 (FDA)
Lonafarnib	Progeria, HDV infection	Farnesyltransferase	Approved	2020 (FDA)
Compound A (Pyrazolo-EGFR)	Breast, lung cancer	EGFR T790M mutant	Phase II Clinical Trial	Ongoing (2023)
BMS-986142	Rheumatoid arthritis	BTK	Phase II Clinical Trial	Ongoing (2022)

Table 4. Approved Pyrazole-Containing Drugs and Selected Clinical Candidates

Celecoxib (Celebrex®; Pfizer/Searle) represents the landmark pyrazole pharmaceutical, with annual global sales exceeding $3 billion at peak. Its clinical success has been achieved not only in rheumatoid arthritis and osteoarthritis but also in familial adenomatous polyposis (FDA-approved indication) and multiple investigational oncology applications. The crystal structure of celecoxib-COX-2 (PDB: 3LN1) has served as a structural template for the design of thousands of synthetic derivatives [84].

Ruxolitinib (Jakafi®/Jakavi®; Incyte/Novartis) a JAK1/JAK2 inhibitor containing a cyclopentyl-pyrazole core has transformed the treatment of intermediate- and high-risk myelofibrosis and polycythemia vera, and has received additional approvals for steroid-refractory acute and chronic graft-versus-host disease (GVHD). Its clinical success demonstrated that pyrazole-based kinase inhibitors can achieve deep clinical responses in myeloproliferative neoplasms [85]. Crizotinib (Xalkori®; Pfizer) and axitinib (Inlyta®; Pfizer) further established the pyrazole scaffold as a productive kinase inhibitor pharmacophore in oncology, with crizotinib revolutionizing the treatment of ALK-rearranged NSCLC as the first selective ALK inhibitor and axitinib extending the survival of renal cell carcinoma patients [86,87].

5.6 ADMET Properties and Metabolic Considerations

The development of pyrazole derivatives into clinical drugs requires careful optimization of absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties alongside pharmacodynamic activity. While the pyrazole ring itself is metabolically stable and does not contain common structural alerts for toxicity (unlike furans, thiophenes, or anilides), substituents appended to the ring may introduce metabolic liabilities or toxicophores [88].

Cytochrome P450 (CYP) metabolism of pyrazole derivatives has been extensively studied. N1-Aryl pyrazoles are susceptible to CYP3A4-mediated aromatic hydroxylation, and the resulting hydroxylated metabolites may exhibit altered pharmacological profiles or increased toxicity risk. N1-Methyl or N1-ethyl substitution generally confers improved CYP metabolic stability compared to N1-aryl analogs. The C4-carboxaldehyde group in pyrazoles is metabolically labile (susceptible to aldehyde oxidase-mediated oxidation to the carboxylic acid) and must be protected or modified in lead optimization. Pyrazole sulfonamides generally display excellent metabolic stability, consistent with their successful incorporation into approved drugs such as celecoxib [89].

Blood-brain barrier (BBB) permeability is a critical consideration for pyrazole derivatives intended for CNS applications (Alzheimer's disease, antidepressant, antiepileptic). The optimal physicochemical properties for CNS penetration LogP 1–3, MW < 450 Da, TPSA < 90 Å2, H-bond donors ≤ 3, rotatable bonds ≤ 8 can generally be achieved with appropriately designed pyrazole structures. In vitro BBB assessment using PAMPA-BBB (parallel artificial membrane permeability assay) and MDCK-MDR1 cell monolayers has been incorporated into the ADMET characterization of pyrazole CNS candidates in recent publications [90].

Hepatotoxicity risk assessment is particularly important for pyrazole-based anti-inflammatory agents intended for long-term use. In vitro cytotoxicity assays (MTT, SRB) against HepG2 (human hepatocarcinoma) cells, CYP inhibition profiling (CYP1A2, 2C9, 2C19, 2D6, 3A4), and reactive metabolite trapping assays with glutathione or potassium cyanide are now routinely incorporated into the ADMET characterization of promising pyrazole leads. The sulfonamide group in celecoxib analogues has been associated with sulfonamide hypersensitivity reactions in a small subset of patients, and attention to this potential liability is warranted in pyrazole sulfonamide development [91].

6.0 CHALLENGES, LIMITATIONS, AND FUTURE PERSPECTIVES

6.1 Current Challenges

Despite the remarkable pharmacological diversity and the clinical validation of pyrazole derivatives, significant challenges remain in translating pyrazole research findings into clinical drugs. The primary challenges include: (1) selectivity achieving adequate selectivity for the intended therapeutic target(s) while avoiding off-target interactions that cause adverse effects; (2) multi-target ratio optimization — for multi-target drugs, achieving the optimal ratio of inhibitory activities at different targets is a complex optimization problem that is difficult to address with classical medicinal chemistry approaches alone; (3) metabolic stability and bioavailability improving the oral bioavailability of pyrazole leads that suffer from poor water solubility, rapid metabolism, or P-glycoprotein-mediated efflux; and (4) in vivo to in vitro translation many pyrazole derivatives that show potent activity in cell-based assays fail to replicate this efficacy in animal models due to pharmacokinetic limitations [92].

The synthetic accessibility and scalability of pyrazole derivatives also present challenges. While many pyrazole derivatives can be synthesized in research quantities, scale-up synthesis often reveals issues with yield, regiochemical control, environmental impact of solvent and reagent usage, and purification efficiency. The development of green chemistry approaches including aqueous-phase synthesis, flow chemistry, and catalytic processes is an important frontier for making pyrazole synthesis more sustainable and scalable [93].

6.2 Future Directions

Several emerging research directions promise to substantially advance the field of pyrazole multi-target therapeutics. First, the application of artificial intelligence (AI) and machine learning (ML) to pyrazole drug design including generative molecular design using variational autoencoders and reinforcement learning, and multi-objective optimization algorithms for simultaneous optimization of potency, selectivity, and ADMET properties represents a transformative opportunity [94]. Platforms such as RDKit, DeepChem, ChemProp, and commercial tools from Schrödinger, OpenEye, and Biovia are increasingly being applied to pyrazole library design and optimization.

Second, the development of pyrazole-based proteolysis targeting chimeras (PROTACs) represents an exciting frontier. PROTACs are bifunctional molecules that recruit an E3 ubiquitin ligase to a target protein, promoting its ubiquitination and proteasomal degradation. Pyrazole-containing PROTAC molecules targeting oncogenic kinases (EGFR, BTK, CDK4/6) and nuclear receptors (AR, ER) have begun to appear in the literature, offering a wholly new modality for pyrazole-based drug action that extends beyond classical occupancy-driven pharmacology [95].

Third, targeted drug delivery of pyrazole derivatives using nanocarrier systems (liposomes, polymeric nanoparticles, metal-organic frameworks, dendrimers) represents a strategy to overcome pharmacokinetic limitations and achieve tissue- or tumor-selective drug delivery. pH-Responsive, redox-responsive, and light-responsive nanocarriers loaded with pyrazole anticancer or anti-inflammatory agents have been reported to substantially improve in vivo efficacy and reduce systemic toxicity compared to free drug administration [96].

Fourth, the exploration of pyrazole derivatives in the context of covalent drug discovery including electrophilic warheads for targeted covalent inhibitors (TCIs) of specific cysteine or serine residues in disease-relevant proteins is an area of growing interest. Covalent pyrazole derivatives targeting EGFR C797 (overcoming osimertinib resistance), BTK C481 (overcoming ibrutinib resistance), and SARS-CoV-2 Mpro C145 have been reported and represent compelling drug candidates [97].

Finally, the systematic exploration of pyrazole stereochemistry in multi-target drug design remains an underexplored area. Many pyrazoline (partially saturated pyrazole) derivatives contain stereocenters, and the individual enantiomers may exhibit significantly different pharmacological profiles, selectivity, and ADMET properties. Enantioselective synthesis of pyrazoline derivatives using asymmetric organocatalysis or chiral transition metal catalysis, combined with stereospecific pharmacological evaluation, represents a productive frontier for pyrazoline medicinal chemistry [98].

CONCLUSION

The pyrazole scaffold occupies a unique position in contemporary medicinal chemistry, combining synthetic accessibility, structural versatility, metabolic stability, and a remarkable breadth of pharmacological activities. This comprehensive review has systematically documented the contributions of pyrazole derivatives to multi-target therapeutic discovery across anti-inflammatory, anticancer, antimicrobial, antidiabetic, antifungal, antiviral, antiparasitic, neurological, and cardiovascular pharmacology. The structure-activity relationships governing pyrazole bioactivity have been critically analyzed, with emphasis on how systematic modification of the N1, C3, C4, and C5 positions — in conjunction with molecular hybridization strategies enables the rational engineering of compounds with defined multi-target pharmacological profiles.

The clinical success of pyrazole-containing drugs, including celecoxib (COX-2 inhibitor), ruxolitinib (JAK1/2 inhibitor), crizotinib (ALK/MET/ROS1 inhibitor), and axitinib (VEGFR inhibitor), validates the scaffold as a privileged pharmacophore and provides strong justification for continued investment in pyrazole-based drug discovery. The multi-target drug design paradigm, which leverages the structural flexibility of pyrazole to simultaneously modulate multiple disease-relevant targets, represents a particularly promising strategy for addressing the polypharmacology demands of complex, multifactorial diseases.

The integration of advanced computational approaches including structure-based drug design, QSAR modeling, machine learning-based multi-target prediction, and molecular dynamics simulations with modern synthetic methodologies and comprehensive ADMET profiling is progressively narrowing the gap between pyrazole research and clinical translation. Emerging modalities including PROTACs, covalent drugs, and nanoparticle-mediated delivery of pyrazole agents promise to further expand the therapeutic reach of this remarkable scaffold.

We anticipate that the convergence of these advances like rational design, computational prediction, green synthesis, AI-assisted optimization, and innovative

delivery strategies, will yield a new generation of pyrazole-based multi-target therapeutics with superior efficacy, improved safety profiles, and broader clinical applicability than existing agents. This review is intended to serve as a comprehensive and current reference that will guide and inspire future research at the forefront of pyrazole pharmaceutical chemistry.

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