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PYRAZOLE DERIVATIVES IN DRUG DISCOVERY: BIOLOGICAL ACTIVITIES, STRUCTURE-ACTIVITY RELATIONSHIPS, AND COMPUTATIONAL PERSPECTIVES

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Abstract

Pyrazole and pyrazole derivatives have always constituted a privileged family of five-membered nitrogen-containing heterocycles, and the versatility of their structure, together with the wide spectrum of their biological activities, have made them of considerable interest in medicinal chemistry for many years. During the last twenty years, the pyrazole structure has been demonstrated through extensive studies to respond to rational modifications in order to afford potent agents for the treatment of inflammatory diseases, antimicrobial agents, anticancer agents, antivirals, antioxidants, antidiabetics, neuroprotectants, gastroprotectants, and drugs for the treatment of cardiovascular diseases, respectively. Some clinically used drugs, such as celecoxib, lonazolac, and deracoxib, aptly prove the translational value of pyrazole derivatives as an important heterocyclic system. Recent advances in the synthetic approaches, structure-activity research, and combination of the above with the power of the aid of the currently available tools of molecular docking simulation, molecular dynamic simulation, and in silico ADMET studies have further accelerated the process of the discovery of pyrazole-based leads for the treatment of the abovementioned diseases. This manuscript endeavours to present an in-depth discussion of the biologic activity of pyrazole derivatives, with special emphasis on biologic mechanism, structure-activity correlation, and the increasing use of the power of the aid of the above tools in the process of the discovery of the anticancer drugs.

1. Introduction

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Heterocyclic compounds form the foundation of contemporary medicinal chemistry, and among these, Nitrogen-containing heterocycles are of primary importance in drug discovery. Of these, pyrazole, which is a five-membered aromatic heterocyclic compound featuring two contiguous nitrogens, has been identified as one of the most versatile and biologically relevant templates [1]. The electronic and hydrogen-bonding as well as tautomeric features of the pyrazole core make it biologically adept at binding to a diverse set of targets, as a result of which it earns the label of being a privileged structure [1, 2]. Traditionally, pyrazole derivatives have been used as active ingredients of a number of commercially accepted medications, most notably nonsteroidal anti-inflammatory drugs (NSAIDs) like phenylbutazone and the selective COX-2 inhibitor celecoxib [3–5]. These medicinal successes encouraged researchers to investigate the pyrazole compounds in depth across various therapeutic areas to update their databases with considerable activity in the areas of infectious diseases, anticancer, CNS, metabolic diseases, and cardio-vascular diseases [6-9]. The broad spectrum of bioactivities confirms that the pyrazole cores exhibit well versatility towards modifications and combinations from other bioactive species.

In the area of anti-inflammatory drug design, the pyrazole derivatives have been well studied as selective inhibitors of the enzyme cyclooxygenase-2 (COX-2) to offer improved gastrointestinal profiles in contrast to traditional non-selective nonsteroidal anti-inflammatory drugs [4,6]. SAR studies have identified the structure modification of the pyrazole backbone, specifically the diarylpyrazoles, as crucial in the improved selectivity and affinity of COX-2 inhibition [6, 8, 10]. Conversely, the pyrazoles have demonstrated exceptional antimicrobial activities in multi-drug resistant bacteria and fungi by targeting different molecules, for example, DNA gyrase, topoisomerase IV, dihydrofolate reductases, and succinyl dehydrogenases [10, 12].

In cancer therapy, there has also been an increase in the importance of pyrazole compounds as specific inhibitors of crucial molecular targets involved in cancer development, such as cyclin-dependent kinases (CDKs), tubulin, epidermal growth factor receptor (EGFR), and vascular endothelial growth factor receptor-2 (VEGFR-2) [13-16]. The capacity of these compounds to affect the regulation of the cell cycle, angiogenesis, and apoptosis pathways suggests their effectiveness as multitarget antineoplastic compounds. Likewise, emerging evidence also suggests the potential of antiviral compounds against RNA viruses including dengue virus, influenza virus, HIV, and coronaviruses including SARS-CoV-2 [17-20].

Recently, the advent of computer-based methods in the field of pyrazoles has led to a major shift in the drug discovery process. Molecular docking, Molecular Dynamics simulation studies, Density Functional Theory (DFT), and ADMET modeling are commonly being used today even before the laboratory synthesis of compounds for the purpose of prioritization of compounds, understanding the binding orientation, and determining the pharmacokinetics/toxicity risks [21]. Nevertheless, there are still some issues in these compounds that must be solved, especially regarding target selectivity, off-target toxic effects, and accessibility in pyrazole derivative synthesis [22]. Overcoming these challenges has increased attention towards multitarget drugs and hybrid molecules in which the pyrazole ring acts as a core pharmacophore that can interact simultaneously with different pathways related to a disease [23]. The review will attempt to offer a full and current survey of the biological properties of pyrazole derivatives, with special focus on recent advances within the realm of medicinal chemistry and SAR studies. By incorporating both the theoretical and practical ways of addressing the topic, the review aims to educate and guide future research directions toward the development of more safe and more efficacious therapeutic agents from the pyrazole moiety.

2. Biological Activities of Pyrazole Derivatives

Pyrazole and its analogs have been found to be of utmost importance in medicinal molecular scaffolding, being a core for a plethora of drugs used in clinical settings. The numerous pharmacological properties of such molecules

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have resulted in the development of a plethora of drugs over the course of various decades, which target conditions such as inflammation, cancers, infectious diseases, and cardiovascular diseases. The timeline below depicts the continuous trend of drugs derived from pyrazole being used over the course of years until September 2023 (Fig 1).

Figure 1: The timeline depicts the continuous trend of drugs derived from pyrazole being used over the course of years until September 2023 [1]

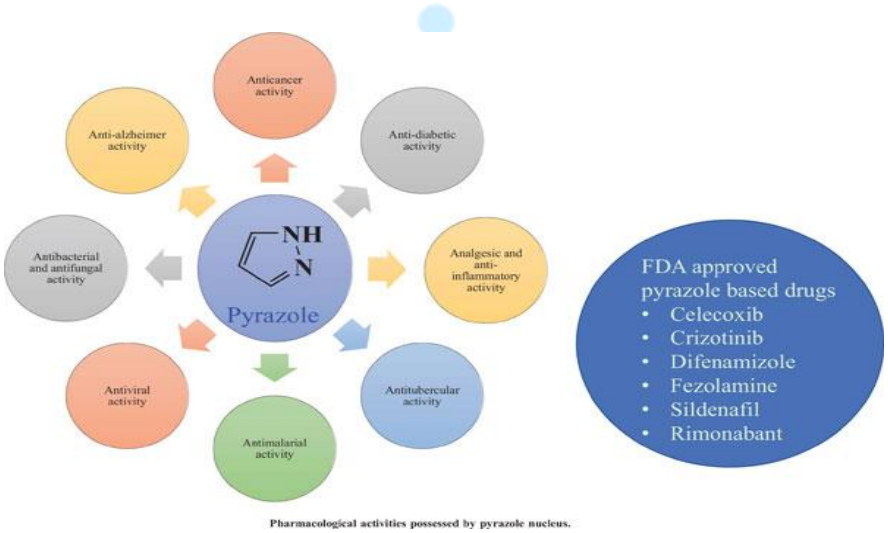

Figure 2: FDA Approved Pyrazole based drugs [1]

2.1Anti-inflammatory and Analgesic Properties

Pyrazole is a well-recognized privileged structure in medicinal chemistry and has been extensively investigated as an anti-inflammatory agent. The main mode of action is the selective inhibition of cyclooxygenase-2 (COX-2), resulting in the reduced formation of prostaglandin E2 (PGE2), a major endogenous pro-inflammatory and pain mediator. Notably, several reported commercial anti-inflammatory drugs, namely celecoxib, lonazolac, and deracoxib, have the pyrazole nucleus in their molecular architecture, establishing the relevance of the molecule. Nevertheless, all drugs possessing the pyrazole moiety are nonselective NSAIDs, except the following, which remain nonselective despite the presence of the pyrazole moiety in their molecular architecture: phenylbutazone [3-6]

SAR analysis carried out by different studies has identified the patterns of substitution of the pyrazole nucleus as critical for the selectivity and potency of COX-2 inhibitors. The replacement of the sulfone-aryl group at the pyrazole nucleus's para position was identified to considerably increase the selectivity of the compounds for COX-2 over COX-1 [24]. Other modifications have also been identified; these include

Frontier in Medical & Health Research

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halogenation and the replacement of the pyrazole nucleus with a bioisostere [24, 33].

With this aim in mind, a high affinity of several newly synthesized pyrazole derivatives has been found to be nanomolar to low micromolar IC_{50} values against COX-2, combined with large ratios of COX-2/COX-1 selectivity in vitro [25,26]. While the assignments to COX-2 remain as the major mechanism, a multi-target approach of pyrazole derivatives has been found to possess an anti-inflammatory effect. Certain derivatives target the reduction of PGE_2 through other pathways of enzymatic activity and suppressed the oxidative burst of leukocytes, which indicates a putative immunosuppressive activity [27]. This aspect can be attributed to overcome the shortcomings of COX-2 inhibitors alone. Certain pyrazole derivatives, such as 1,5-diarylpolyrazole-3-carboxamides, aim to selectively target COX-2 and also irreversible inhibitors of soluble epoxide hydrolase (sEH), to generate more analgesic and anti-inflammatory activity with fewer side effects [8].

2.2 Antimicrobial activity

Apart from their use as anti-inflammatory agents, pyrazole derivatives have been explored as a diverse class of antimicrobials against a large variety of pathogens, including multi-drug-resistant ones like MRSA and vancomycin-resistant *Enterococcus*. From the application perspective, their significance as drugs can be attributed to the use of cephalosporins cefoselis and ceftolozane. Ceftolozane, a Zerbaxa formulation with a pyrazolium structure, resists β-lactamase enzyme breakdown more effectively. Various studies based on Structure-Activity Relationship (SAR) suggest that the MIC of pyrazole derivatives against microbes relies heavily on hybridization. Hydrazone and hydrazides of the derivatives prove to be broad-spectrum agents, often more potent than gentamicin against *Neisseria gonorrhoeae*. Derivatives with difluorophenyl, dibenzoic acid, and naphthyl substitutes prove to be very selective against specific strains, with very low MICs of < 1 μg/ml. Other hybrid derivatives bearing a coumarinyl and trisubstituted pyrazole structure prove to be very effective against MRSA and infections from biofilms. Other derivatives, like pyrazole-thiazole and pyrazole-triazole conjugates, prove to be very efficient inhibitors of *S. aureus*, inhibiting the enzyme topoisomerase II/IV of the microbes (Fig 3).

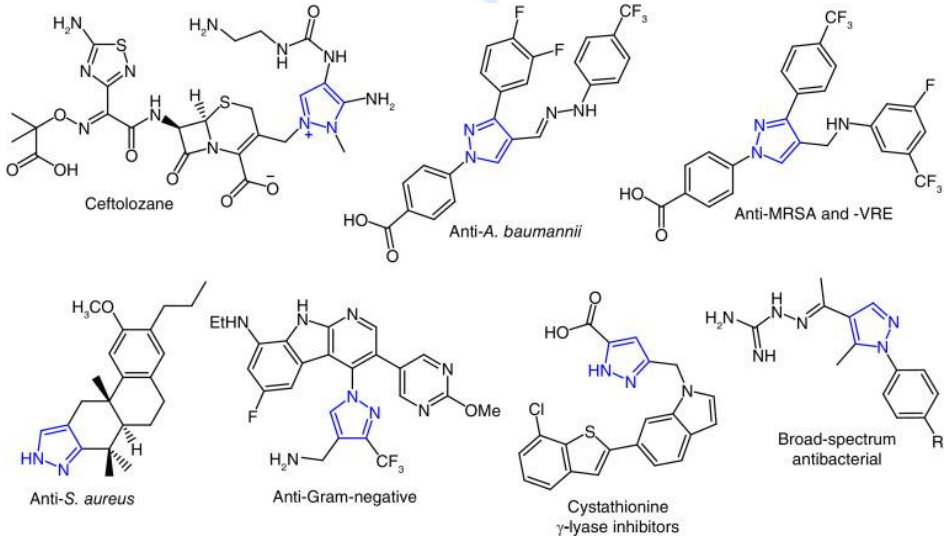

Figure 3: Pyrazole derivatives as a diverse class of antimicrobials against a large variety of pathogens, [10]

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However, SAR optimization has also led to the development of aminoguanidine pyrazoles that are comparable to or even more active than fluoroquinolones against resistant *S. aureus* and *Escherichia coli* strains. Of particular note are the oxazolidinone-pyrazole combination compounds, which are more effective than linezolid due to the compounds' enhanced capability to suppress the process of protein synthesis in bacteria. Apart from these, fused pyrazoles such as pyrazolopyridinones, triazines, and diterpenoid conjugate compounds of pyrazoles have also displayed improved antibacterial properties, with some of these compounds being more effective than Ciprofloxacin and tetracycline antibiotics [30, 31].

Mechanistically, antibacterial substances like pyrazoles target the bacterium along various pathways simultaneously. These compounds target the bacterium's DNA functions by inhibiting the action of DNA gyrase, topoiserase IV, and dihydrofolate reductases (DHFR) (Fig 4). Others target the process of protein synthesis or cell wall formation by inhibition of enzymes like MurB and UppS or by direct inhibition of beta-lactamases. Lastly, some of these compounds also target the bacterium's cell membrane by inducing membrane disruption, quorum sensing inhibition, and photodynamic-mediated killing by reactive oxygen species (ROS) [10].

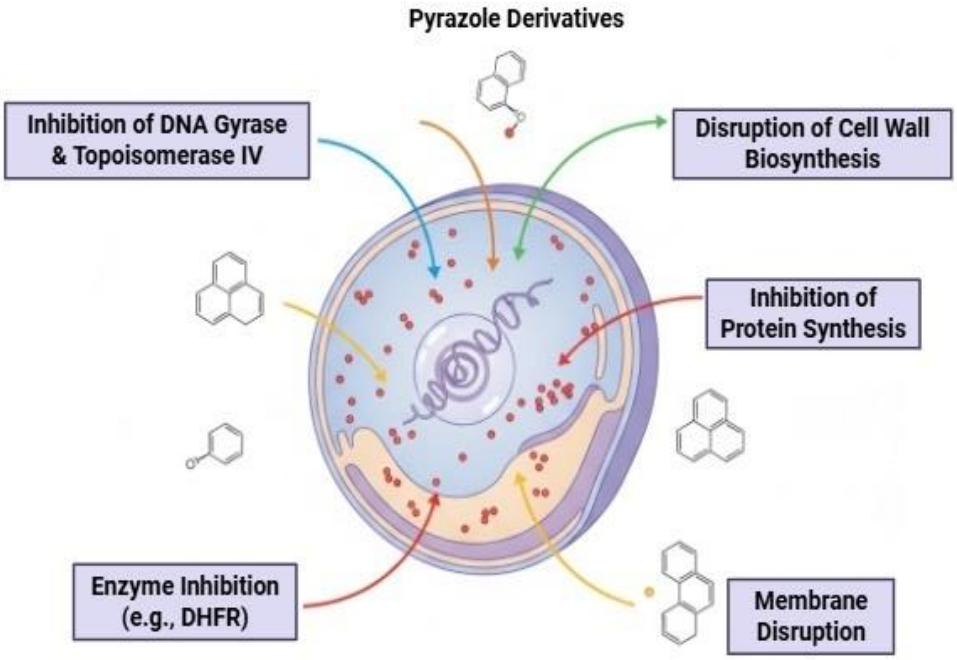

Figure 4: Multi-Target Antimicrobial Mechanisms of Pyrazole Derivatives

2.3 Anticancer Activity

Besides the anti-inflammatory and antimicrobial properties, the pyrazole derivatives have also been widely explored as potential anticancer agents due to their ability to bind to a variety of targets associated with the development of cancer. The flexibility in the structure of the pyrazole moiety allows for the design of effective inhibitors of the main enzymes involved in the regulation of cancer cell growth [32]. One of the well-studied mechanisms is inhibition of cyclin-dependent kinase 2 (CDK2), a key regulator of the cell cycle.

Frontier in Medical & Health Research

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Several substituted pyrazole derivatives (including fused or hybrid systems) have demonstrated CDK2 inhibitory activity (often in the low micromolar to submicromolar range). For example, some novel pyrazoles produce IC_{50} values against CDK2 in the micromolar range and suppress cancer cell proliferation and induce apoptosis [33, 34].

Pyrazole scaffolds, including certain 3,5-substituted and fused pyrazole derivatives, have shown efficacy in inhibiting tubulin polymerization via the colchicine binding site. For example, a 3-amino-5-phenylpyrazole derivative inhibited tubulin polymerization, induced G_2/M arrest, and triggered apoptosis in MCF-7 cancer cells [35]. Hybrid pyrazole systems further represent a versatile scaffold for anticancer drug design. For instance, trimethoxyphenyl-(trifluoromethyl)pyrazole derivatives have been shown to bind to the colchicine binding site of tubulin, disrupt microtubule dynamics, induce mitotic arrest, and trigger apoptosis in cancer cell lines (e.g., HeLa, MCF-7) [36]. Similarly, triazole-substituted quinazoline hybrids exhibit potent EGFR tyrosine kinase inhibition, suppress EGFR expression, and induce apoptosis in vitro, in some cases in non-small cell lung cancer (NSCLC) models [37, 38].

2.4 Antioxidant properties

Pyrazole derivatives have also been reported to exhibit significant antioxidant potential. Oxidative stress, resulting from the imbalance between reactive oxygen species (ROS) generation and endogenous antioxidant defenses, is closely linked to the onset of numerous pathological conditions, including neurodegenerative diseases, cancer, diabetes, and cardiovascular disorders. Therefore, the development of synthetic antioxidants remains an important therapeutic strategy [39-41]. Several pyrazole derivatives demonstrate potent free radical scavenging ability, particularly against the DPPH radical. Structural modifications, such as incorporation of electron-donating substituents (e.g., methoxy, methyl) or halogenated phenyl rings on the pyrazole scaffold, significantly enhance scavenging efficacy. For example, in a study of 3-(2-naphthyl)-1-phenyl-1H-pyrazole derivatives, some compounds had better DPPH radical scavenging activity than ascorbic acid, with IC_{50} values in the low-micromolar/μg-per-mL range, and the ones bearing methoxy or methyl groups on phenyl rings showed improved potency [42]. Purine-pyrazole hybrids also showed very strong DPPH scavenging (IC_{50}≈0.93 μg/mL), surpassing the reference ascorbic acid (IC_{50}≈15.34 μg/mL), and demonstrating that phenolic or hydroxyl-containing substituents contribute substantially [13].

2.5 Antiviral properties

Pyrazole derivatives have also been reported to display significant antiviral activity. Viral infections, particularly those caused by RNA viruses, remain a major global health burden, with limited therapeutic options and emerging resistance to existing drugs. Therefore, the development of novel small molecules with potent antiviral efficacy is of critical importance. Some pyrazole derivatives have proved to have a strong inhibitory effect on the replication of viruses in different ways. For example, diarylpyrazolyl-quinoline compounds have proved to inhibit the replication of dengue virus serotype-2 (DENV-2) strongly in terms of IC_{50} values ranging from 0.81 to 1.36μM, without much cytotoxicity (>200μM), and the mechanism of action illustrated the capacity of the compounds to strongly inhibit viral RNA synthesis/protein expression [14]. Repurposing pyrazole-triazine compounds were active against SARS-CoV-2 in Vero E6 cells with low micromolar IC_{50} values, and selectivity indices were favorable and were described within the same paper [15]. Hydroxyquinoline-pyrazoles were effective at inhibitory concentrations for the reduction of replication of SARS-CoV-2, MERS-CoV, and HCoV-229E viruses, and corresponding molecular docking studies were performed to reasonably interpret the interactions of compounds with the viral proteins [43]. In the case of Influenza A H1N1, pyrazoles were significantly effective inhibitors of the virus replication. In the context of HIV, a derivative of the compound 1H-pyrazole-5-carboxylate inhibited HIV-1 replication, and the ADME study suggested that the compound did not act through the well-known

Frontier in Medical & Health Research

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reverse transcriptase inhibitors, protease inhibitors, and integrase inhibitors but through an alternative antiviral [45].

2.6 Antifungal Activity

Pyrazole derivatives have also displayed potent antifungal activity, especially against phytopathogenic fungi. The mechanism of action mainly includes succinate dehydrogenase inhibition (SDH) along with damage to fungal cellular architecture. Pyrazole-4-carboxamide derivatives with N-phenyl-substituted amide moieties have displayed high potency against the fungal pathogen *Sclerotinia sclerotiorum*, comparable to that of existing antifungals like bixafen and fluxapyroxad. *In-vivo* tests have also proved high levels of preventative efficacy at preventive concentrations. Molecular docking studies supported these findings by demonstrating stable binding of pyrazole-4-carboxamides within the SDH active site, consistent with the binding mode of known SDH inhibitors [46].

Pyrazole-4-carboxamides incorporating ether substituents have been investigated for antifungal activity against a range of phytopathogens, including *Rhizoctonia solani*, *Sclerotinia sclerotiorum*, *Botrytis cinerea* and *Fusarium graminearum*. These derivatives displayed very high potency, in some cases surpassing commercial fungicides such as boscalid and fluxapyroxad. Strong protective and curative effects were further demonstrated in vivo, particularly in rice leaves infected with R. solani. Biochemical assays confirmed inhibition of SDH activity, with half-maximal inhibitory concentrations in the low micromolar range, in certain cases nearly twice as potent as boscalid [47].

2.7 Gastrointestinal / Anti-ulcer activity

Certain benzimidazole–pyrazole hybrid derivatives have demonstrated inhibition of ethanol-induced gastric ulcer formation in rats, producing ulcer inhibition ranging from 70 % to 83 % at 500 µg/kg. Notably, effectiveness is generally dose dependent, highlighting potency and pharmacological consistency [48]. Substitution on the pyrazole ring system is a decisive factor in determining ulcer protection. Evidently, derivatives with electron-withdrawing groups such as halogens or nitro substituents on adjacent aromatic rings tended to enhance mucosal defense [49].

The gastroprotective action of pyrazole derivatives is multifactorial, i.e., enhancement of mucosal defense (mucin secretion, prostaglandin induction), antioxidant activity (scavenging free radicals generated by ethanol), and inhibition of acid secretion (possibly via proton pump or H^+/K^+ ATPase suppression) [50-52]. Given that NSAID-associated ulcers are closely related to COX-1 inhibition, pyrazole derivatives engineered for *COX-2 selectivity* may help reduce ulcerogenic risk, a strategy seen in other pyrazole-COX inhibitors [53-55].

2.7 CNS Activity

2.7.1 Antidepressant / Monoamine Oxidase (MAO) Modulation:

Several 2-pyrazoline (i.e., dihydropyrazole) derivatives were evaluated in the tail suspension test (TST) and forced swim test (FST). Without altering locomotor activity, compounds (e.g., "3d", "3e") reduced immobility time comparable to imipramine, suggesting antidepressant-like behavior with relatively low off-target CNS stimulation [56]. A more recent work on 4,5-dihydro-1H-pyrazole derivatives used computational docking to human MAO-A and in vivo FST/TST models. Superior antidepressant efficacy was shown by derivatives bearing para-chloro or para-fluoro substituents on phenyl rings, reducing immobility by over ~50% in mice [57]. In earlier work, Abdel-Aziz and colleagues synthesized substituted pyrazole derivatives and tested them in TST. They reported that compounds had antidepressant activities nearly twice that of imipramine at 10 mg/kg, while in anticonvulsant assays, some of the pyrazole derivatives showed significant protection in PTZ-induced seizure models, approaching phenobarbital potency [58]. Another study explores that pyrazole, pyrazoline, and related analogues have frequently appeared in the design of MAO inhibitors, because the N–N framework and adjacent substituents can interact favorably with the flavin cofactor in the enzyme's active site [59].

Frontier in Medical & Health Research

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The docking studies support the idea that electron-withdrawing substituents (Cl, F) may strengthen binding to MAO-A via favorable electrostatic or π–π interactions. However, most studies stop at docking; enzyme inhibition assays (IC_{50}, Ki for MAO-A/B) are often missing [60, 61]. It is crucial to distinguish whether the observed antidepressant-like behavior is mediated via MAO inhibition or via alternate mechanisms (e.g., serotonin/norepinephrine modulation, sigma receptors). Future work should pair behavioral assays with enzyme assays, neurotransmitter measurements, and selectivity toward MAO-A vs. MAO-B.

2.7.2 Anticonvulsant / Neuroprotective Activity

Promising anticonvulsant effects have been demonstrated by pyrazole derivatives in preclinical models, such as maximum electroshock and pentylenetetrazole-induced seizures. Fewer behavioral side effects and less CNS depression have been observed with some pyrazole substitutes, having efficiency almost similar to that of reference drugs. They can also lessen inflammation and oxidative damage in addition to controlling seizures, which supports their potential use in neuroprotection and epilepsy treatment [62]. Some studies also reported that these derivatives reduced biomarkers of oxidative stress and neuroinflammation (e.g. decreased lipid peroxidation, suppression of pro-inflammatory cytokines) in treated animals, suggesting a neuroprotective dimension beyond seizure suppression [63, 64].

The precise mechanisms for the anticonvulsant activity of pyrazole derivatives are still under investigation, but plausible pathways include enhancing GABAergic transmission by increasing GABA-A receptor activity, blocking voltage-gated sodium or calcium channels to stabilize excitable membranes, suppressing oxidative stress and neuroinflammation, and modulating glutamate excitotoxicity. Such varied mechanisms may reflect a complex role for pyrazoles in anticonvulsant activity.

AntiBy inhibiting the key enzymes involved in the breakdown of carbohydrates, such as α-glucosidase and α-amylase, pyrazole compounds have the potential to inhibit diabetes. The pyrazoles acting as substitutes for sulphonamide are more potent than Acarbose. The strong binding to the active sites of the enzymes was verified to have a molecular mechanism to explain the regulation of glucose levels. These findings suggest the potency of pyrazole derivatives as a medicinal option in the regulation of type 2 diabetes [67]. The molecular modeling done was in support of the drug having a sweet binding to the active pockets of the enzymes through hydrogen bonding, π-π interactions, and hydrophobic pockets. The second role of the pharmacological aspect in the study includes the exhibition of antidiabetic activities [68, 69].

Affinity based on docking is frequently proposed, but there is a lack of affinity information expressed as IC_{50} values or studies of competitive/noncompetitive inhibition as well as glucose uptake studies using cellular systems. The selectivity of pyrazole derivatives for α-glucosidase over α-amylase is important in diabetic treatments since dual inhibitors of both enzymes may retain a potential to inhibit the whole carbohydrate digestion pathway instead of delaying it. This might increase side effects such as gastrointestinal problems experienced with current α-glucosidase inhibitors. In addition to this, information regarding metabolic stability, absorption rates, as well as glucose tolerance studies in vivo is not provided in most studies conducted so far [70].

2.8 Cardiovascular applications

2.8.1 Cardioprotective Potential of Pyrazole Derivatives

Thiazole–pyrazolone and pyrazole–thiadiazole hybrids have demonstrated notable cardioprotective activity in experimental myocardial infarction models. Certain thiazole-pyrazolone compounds inhibited angiotensin-converting enzyme (ACE) with moderate to excellent potency and, in isoproterenol (ISO)-induced myocardial infarction in rats, improved cardiac function, reduced oxidative stress and inflammatory cytokines, and normalized histopathological alterations. Similarly, pyrazole-thiadiazole derivatives alleviated myocardial injury

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biomarkers (CK, CK-MB, LDH), reduced lipid peroxidation (MDA), restored antioxidant defenses (SOD, GPx), improved cardiac histology, lowered apoptosis through regulation of Bcl-2 family proteins, and modulated NF-κB/IκBα signaling pathways. Collectively, these findings indicate that pyrazole-based hybrids exert cardioprotection through complementary mechanisms involving ACE inhibition, oxidative stress reduction, anti-inflammatory effects, and apoptosis modulation [71, 72].

2.8.2 Anti-hypertensive & Anti-fibrotic Hybrid Agents (ACE-1 / COX-2, etc.): Some novel hybrid pyrazole compounds were shown to inhibit both ACE-1 activity and COX-2, reduce systolic blood pressure in hypertensive animal models (e.g. ~18.6% drop with compound 17b), increase serum nitric oxide, upregulate eNOS, suppress markers of NF-κB and P38-MAPK pathway, and reverse histological changes induced by hypertensive insult (e.g. L-NAME) [73].

2.8.3 Cardiovascular Safety in Anti-inflammatory Pyrazoles: Given the cardiovascular risks associated with COX-2 selective NSAIDs, some pyrazole derivatives have been designed to retain COX-2 inhibition but with improved cardiovascular safety profiles. For example, compounds 6d and 11f in a diaryl-pyrazole / dual COX-2 / soluble epoxide hydrolase (sEH) inhibition series were shown to have favorable cardiac biomarker profiles (troponin I, CK, etc.) compared with celecoxib in animal studies [16].

3. Computational and Molecular Docking Studies

3.1 Role in target identification and binding-affinity prediction

Pyrazole moieties are five-membered ring-size heterocycles that contain nitrogen and are particularly helpful in synthesizing drugs. Because of their diverse range of pharmacological properties, pyrazoles are one of the most studied compounds within the entire azole family. Numerous synthesis methods and drug analogs have been well-validated [17]. More recently, the pyrazole compounds have been examined using in silico screening, computers using SwissADME and pkCSM, among other methods, to evaluate drug-likeness and Adler-Embeddedness. Subsequent structure-based modeling helps to determine potential targets, ranking these according to predicted binding affinity. The application of molecular dynamic studies helps to analyze complex binding conformation before synthesis is done. One study examined compounds from 2023-2025, screening candidates using pkCSM/ AutoDockVina, highlighting active site interactions as well as predicting MIC activity based on in vitro validation [18].

In cancer drug studies, docking methods have been used to direct the choice of targets, including VEGFR-2 and the PI3K/AKT pathway, as well as other kinases. In particular, anti-angiogenic pyrazoles have been docked into the VEGFR-2 receptor to develop hypotheses about the localization of the hinge area and the gatekeeper area prior to laboratory experiments. Furthermore, current "synergistic in silico" methods combine density functional theory (DFT), docking, and molecular dynamics simulation to reveal chemically stable and high-affinity ligands even before their laboratory preparation ([19, 74]. One such exemplary study involves the pyrazole-carboxamide compounds analyzed using docking and explicit solvent dynamic simulations, where the preferred poses of the dynamic simulations (H-bonding and hydrophobes buried within the active site) correlated with the best results of inhibiting the enzyme and cell-based activity, validating the role of dynamic simulations as a filter following docking experiments [75].

3.2 Recent docking studies that support biological evaluation

In recent research, the docking method has been successfully applied not only as a theoretical technique but also as a method to clarify the observed activities in the design of new assays.

The antimicrobial pyrazoles and pyrazolines were docked with the bacterial enzyme active site (PDB code 1FJ4). The drug likeliness filtering predicted the ability of the different analogs. The candidates predicted using computations were further tested

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

for antimicrobial activity, giving a distinct insight into the correlation between the outcomes of both docking and biological studies [76]. In the 2025 open-access publication "Curcuminoid-Pyrazole Hybrids," the investigators discussed their findings pertaining to the molecular interaction of the target protein and the design of compounds with optimal in vitro activity through the screening of molecules with the greatest binding affinity to DNA gyrase. Through this design and testing strategy of "design–predict–test," the selection of molecules of interest was achieved by plotting graphs of the interaction of different molecules and using the SwissADME prediction tool to select those with optimal permeability and solubility profiles. The docked molecules were well-correlated with those demonstrating optimal permeability and solubility profiles.

The following examples, replicated by recent umbrella reviews in synthetic/medicinal pyrazole chemistry, reflect a trend within the field from experimentation-translation via computational triage in lieu of docking studies relegated to supplemental material [78].

3.3 Integration with ADMET profiling

In most cases, every research paper dealing with docking of the pyrazole molecules from 2023 to 2025 considers the in-silico analysis of ADMET properties, including the risk of hERG, CYP inhibition, BBB permeability, and intestinal absorption, which is necessary to de-prioritize certain molecules. ADMET analysis includes verification of the following:

pkCSM-first for toxicity/PK, then Vina docking against target proteins (viral proteases, enzymes, kinases) for reducing synthesis lists [79]. Synthesis of green pyrazoles combined with the use of DFT+ ADMET+ Docking to illustrate the combined contribution of the electronic/geometry (DFT) and predictive PK to understanding observed assay data (Fig 5).

This integration goes beyond mere box-checking as in several studies, ADMET flags (e.g., predicted CYP inhibition or poor solubility) explained inactive or cytotoxic outliers even when docking scores were strong, reminding that binding affinity ≠ developability, and that ranking must balance potency, selectivity, and PK/Tox early [80].

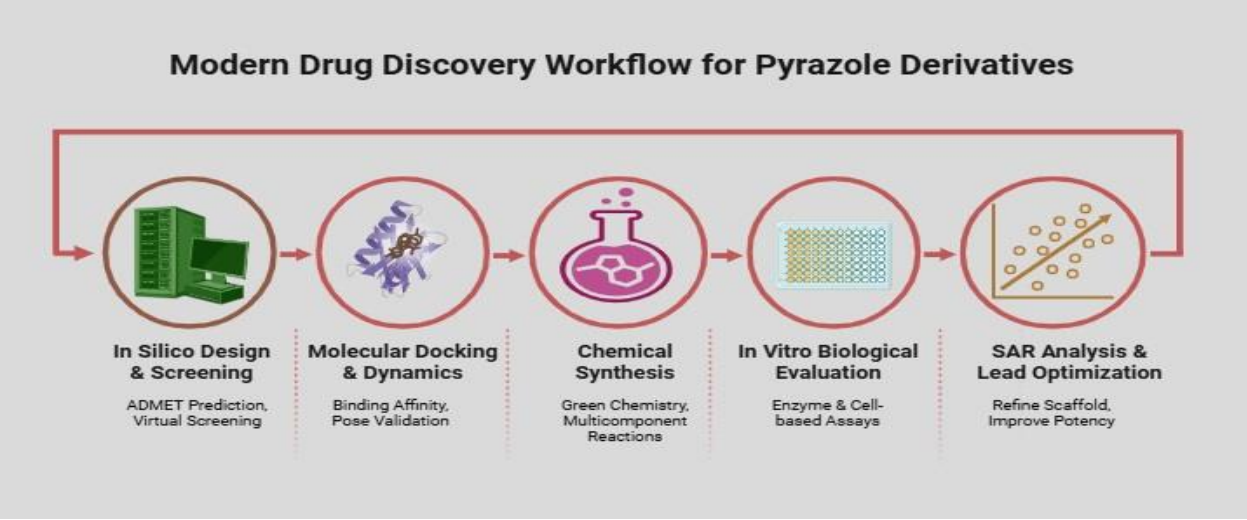

Figure 5: Modern Drug Discovery Workflow for Pyrazole Derivatives

4. SAR (Structure–Activity Relationship) Trends in Pyrazole Derivatives

4.1 Cross-series substituent effects (2020–2025)

Recent reviews aggregating 2014–2024/25 data highlight consistent SAR themes across antimicrobial, anti-inflammatory, and anticancer pyrazoles:

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(i) 1,3,4-trisubstitution is a privileged pattern for balancing potency and physicochemical properties.
(ii) Sulfonamide or sulfonyl-aryl groups often enhance potency via H-bonding/anchoring and improved polarity.
(iii) Diaryl-pyrazoles targeting COX-2/kinases benefit from para-substituted aryls that optimize π-stacking and fill hydrophobic channels; and
(iv) Carboxamide/heteroaryl fusions tune both affinity and permeability [81, 82].

4.2 Anti-inflammatory/COX-2

A 2024–2025 dataset on 1,5-diaryl-pyrazoles with benzene-sulfonamide substituents demonstrates a clear structure-activity relationship (SAR). Electron-withdrawing para-substituents enhance COX-2 docking scores and in vitro inhibition, while docking studies confirm interactions similar to celecoxib. This research links QSAR descriptors, docking rankings, and observed dual anti-inflammatory and anticancer activity [83].

4.3 Antimicrobial

Recent studies from 2016 to 2024 have found that halogenated aryls and basic side chains like morpholine and piperazine are often linked to better minimum inhibitory concentrations (MICs), likely due to improved membrane interactions and target engagement. ADMET screening helps identify hERG and CYP risks in more lipophilic analogs. Case studies combining molecular docking with MIC data from E. coli and fungal targets reinforce these findings [21, 85].

4.4 Antiprotozoal/antiparasitic

For antileishmanial pyrazoles (2024–2025), pyrano-fused or electron-rich aryl substitutions enhanced activity. Docking studies suggested improved occupancy of hydrophobic pockets and strengthened hydrogen bond networks unique to parasite enzymes [84].

4.5 Kinase/anti-angiogenic

Antiangiogenic pyrazoles benefited from heteroaryl N-linkers and donor–acceptor patterns positioned to form dual H-bonds with kinase hinge residues (e.g., VEGFR-2 Cys/Glutamate pairs), with para-EWG tuning increasing predicted affinity while maintaining drug-likeness in SwissADME/pkCSM screens [86].
Beyond hand-crafted analog series, SAR extraction increasingly leverages QSAR + docking. Recent works model descriptor–activity relationships (e.g., for diaryl-pyrazoles) and validate prioritized analogs by docking and ADMET prediction, shortening cycles between design and assay. Reviews from 2024–2025 synthesize these trends, reporting recurring pharmacophoric features (H-bond donor/acceptor at C-4 substituents; hydrophobic/aromatic bulk at N-1/C-5; polar handles to control logP) across therapeutic areas [86].

Table 1: Structure Activity Relationship of substituted Pyrazole Derivatives

Substituent	Typical Target	SAR Trend	Notes
1,5-Diaryl-pyrazole + sulfonamide	COX-2 / anti-inflammatory, anticancer synergy	Para-EWG (electron withdrawing group) or para-alkoxy on the distal aryl increases potency; sulfonamide improves H-bonding & selectivity	QSAR + docking reproduced celecoxib-like hinge contacts; ADMET screens were used to filter lipophilicity [99].
Carboxamide at C-3 or C-4	Enzymes (e.g., CA, bacterial targets)	Amide enables dual H-bonding; heteroaryl amides increase affinity; MD confirms pose stability	Docking + MD correlated with the best inhibitors in a pyrazole-carboxamide series [82].

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Halogenated aryl (para-Cl/-F) at N-1/C-4	Antibacterial/antifungal	High number of hydrophobic contacts and π-stacking may raise logP, watch ADMET flags	Summarized across 2016–2024 antibacterial/antifungal reviews; validated in recent MIC + docking sets [89].
Basic side chain (morpholine/piperazine)	Antimicrobial / CNS-oriented series	Increased solubility and potential target salt-bridge formation; risk of hERG/CYP interactions	Use pkCSM/SwissADME to balance potency vs. liabilities [38].
Heteroaryl fusion (pyrano-pyrazoles)	Antiparasitic (Leishmania)	Fused rings increase shape complementarity; E-rich aryls favored	Docking explains improved occupancy in parasite enzymes [71].
Hinge-directed donors/ acceptors (kinases)	Anti-angiogenic (VEGFR-2)	Properly spaced donor/acceptor pairs favour predicted binding; para-EWG helps	Docking guided selection before bioevaluation [61].

5. Challenges and Future Perspectives

5.1 Limitations in selectivity, toxicity, or synthetic accessibility

Despite the diverse pharmacological potential of pyrazole derivatives, several ongoing challenges impede their progression from lead compounds to clinically successful drugs.

Selectivity

Many active pyrazole analogues have exhibited off-targeting due to the flexibility of the pyrazole structure to accommodate different binding sites of enzymes, especially in the case of kinases that possess an ATP-binding pocket. For example, diaryl pyrazoles as COX-2 inhibitors have exhibited cross-reaction with other oxidoreductases and kinases, leading to an unpleasant pharmacological response [38].

Toxicity & ADMET properties

Some of the pyrazole molecules, which show high scoring in the in silico docking analysis, may present several unfavorable pharmacokinetic properties. For example, molecules that tend to be lipophilic (log P > 4) or the presence of electron-withdrawing groups may present properties like inhibition of CYP450, hERG, and hepatotoxicity, thus causing the early de-prioritization of those molecules despite the high binding affinity to the target [86].

Accessibility

Though newer methodologies such as microwave-assisted synthesis, solventless synthesis, and multicomponent green chemistry synthesis have enhanced the synthesis of pyrazoles, the synthesis of many complex or fused systems remains multi-step with particular requirements or catalysts, thereby impeding the diversification of libraries and SAR analysis [22, 86].

5.2 Opportunities in Dual-Acting or Multitarget-Directed Ligands

Pyrazoles are easy to diversify and are great candidates for the design of multi-target drugs, which is an attractive strategy for the treatment of complex diseases.

Dual InhA-VEGFR inhibitors

Recently, a new class of compounds has been developed that are hybrids of pyrazoles, demonstrating both anti-angiogenic activity against VEGFR-2 and the ability to inhibit the enzyme InhA, which targets tuberculosis, simultaneously in the same molecule with excellent multitarget activity [23].

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Multi-target agents with Schiff-base and hybrid frameworks

Schiff bases derived from pyrazole have been demonstrated to act as antibacterial, antioxidant, anti-diabetic, and AChE (anti-Alzheimer) agents altogether, indicating multi-targeting capabilities within one compound [22].

Insect Growth Regulator (IGR) candidates

A hexacyclic pyrazolamide derivative exhibited dual-target action against both EcR and IGR modes of action, emphasizing the importance of pyrazoles as multitarget insecticides [23].

5.3 Emerging Targets for Pyrazole Derivatives

In addition to the classic targets (COX, Kinases), other novel biological targets for pyrazole compounds have been explored in more recent research:

Coronaviral proteins (SARS-CoV-2)

Hydroxyquinolines-pyrazole reported strong binding affinity to essential proteins of the coronavirus, significant in vitro anti-plaque activity, and favorable ADMET properties, assessing their antiviral potential successfully [56].

Antimicrobial targets

The fused pyrazoles and Schiff base hybrids have shown appreciable activity against the major bacterial enzyme, the DNA gyrase, which reaffirms their potent ability to fight bacterial resistance.

Various biological activities

The biological structures offered by the fused pyrazole rings (pyrazolopyridine or pyrazolopyrimidine) include very broad bioactivities such as antimicrobials, anticancer, antioxidant, and enzyme inhibitors, among others, signifying their immense

6. Conclusion

The contemporary finding of pyrazole derivatives occurs through a closed-loop approach that is quite efficient. It involves screening compounds based on drug likeness and ADMET characteristics. Next is molecular docking/pose analysis for evaluating binding to target proteins. Verification through molecular dynamics MD is optional for evaluating stability. Biologically active compounds are synthesized for re-refining through computation. This approach has become a normative approach according to contemporary reviews.

In conclusion, the pyrazole core has ensured its relevance as a building block molecule in modern chemical and biological sciences. Through the review, the evolution of the pyrazole core has been discussed from its basic structural features and tautomerism to its synthetic approaches, which have currently adopted green, multi-component, and flow syntheses for more efficient and sustainable approaches to the wide range of pyrazoles. The wide scope of its biomedical applications as anti-inflammatory, antimicrobials, anticancer, neuroprotectants, and others is an indication of its ability to be adapted for various purposes. The integration of computational chemistry has, more importantly, revolutionized the discovery pipeline through rational design, target identification, and early prediction of pharmacokinetic and toxicity profiles. While there are still challenges associated with target selectivity and off-target toxicity, the future of pyrazole chemistry looks bright. Emerging opportunities lie in the design of multitarget-directed ligands in order to tackle complex diseases, and their utility in agrochemicals and advanced materials is being expanded. Continued innovation in both synthesis and computational modeling will undoubtedly unlock the full potential of this exceptional heterocyclic system.

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