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PYRAZOLE AS A PRIVILEGED HETEROCYCLIC SCAFFOLD: SYNTHETIC INNOVATIONS, STRUCTURE ACTIVITY RELATIONSHIPS, AND TRANSLATIONAL CHALLENGES

Aleeha Afzal[1], Uzma Owais[2], Sohaib Iqbal[3], Mobeen Ghulam Ahmed[4], Waleed Maqbool[5], Maria Shafaqat[6], Iqra Zulfiqar[7], Syed Muzzammil Masaud[8], Muhammad Nouman Arif[9], Ahmed Hassan[10], Hafiz Aamir Ali Kharl[*11]

[1,5,6,10]*Department of Pharmacy, Faculty of Health and Pharmaceutical Sciences, University of Agriculture, Faisalabad*
[2]*Faculty of Pharmacy, Ibadat International University, Islamabad, Pakistan.*
[3]*College of Pharmacy, Lyallpur Institute of Advanced Studies, Faisalabad, Pakistan.*
[4]*Faculty of Pharmaceutical Sciences, Government College University, Faisalabad, Pakistan.*
[7, *11]*Riphah Institute of Pharmaceutical Sciences, Riphah International University Islamabad, Pakistan*
[8]*Department of Allied Health Sciences, The Saifee Burhani University, Karachi, Pakistan*
[9]*Department of Pharmacy, Iqra University H-9 Campus, Islamabad, Pakistan.*

[*11]aamirkharl43@gmail.com

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Corresponding Author: *
Hafiz Aamir Ali Kharl

Abstract

Pyrazole has been recognized as a privileged structure because of its versatility, desirable physicochemical characteristics, and universal applicability in medicinal chemistry, agricultural chemicals, and functional materials. In this article, the recent progress in pyrazole research has been critically surveyed, focusing on the relationships between molecular structure, synthetic method, and bioactivity or functionality. From a medicinal chemistry perspective, the structure-activity relationship studies have clearly demonstrated that substitution at the C-3, C-5, and N-1 atoms of pyrazole plays a key role in modulating affinity, selectivity, tautomerism, and ADME characteristics. Although pyrazole derivatives have been found to possess potential activity in cancer, inflammation, infectious diseases, and metabolism-related disorders, their translational potential has been hindered by inadequate ADMET characteristics. The review also analyses modern synthetic strategies, such as green, solvent-free reactions, reactions catalysed using microwaves, ultrasonic waves, mechano-chemical reactions, and flow chemistry, which have increased the molecular diversity and reaction efficacies. Although there are concerns related to scalability and reproducibility in laboratory reactions, pyrazole merged with different pharmaceutical scaffolds are stated to be an exciting strategy for developing multi-target drugs in which there exists a large gap between cellular and in vitro efficacies. Further, implications of the emergence of pyrazole-based materials, particularly pyrazole metal–organic frameworks, are also touched upon in this article. It also points out that the role of computing tools in pyrazole-based design is on the upsurge, but docking score predictions must be validated by experimental evidence. In conclusion, this review can be considered an important paper in providing a complete overview on the research on pyrazole, contributing to the field in highlighting many challenges for future developments.

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1. Introduction

Pyrazole is a five-membered heteroaromatic compound ($C_3H_3N_2H$) belonging to the 1,2-diazole family, characterized by two adjacent nitrogen atoms within its ring system. The N-1 atom behaves similarly to the NH group of pyrroles, serving as a hydrogen bond donor, whereas the N-2 atom resembles the pyridine nitrogen, acting as a hydrogen bond acceptor [1-3, 8]. Such varying chemical environments lead to discrepancies in the bond lengths of the rings. However, the most interesting part of the molecular structure of these molecules is the phenomenon of tautomerism, which occurs in these molecules. Such phenomena have various profound effects on the reactivity and synthesis of the molecules, along with influencing the biological properties of these molecules, because of the minute variation in the molecular structure of the molecules caused by such phenomena [10]. The name 'pyrazole' has been assigned after Ludwig Knorr discovered the pyrazolone 'antipyrine' in the year 1883. Later on, after the discovery of 'antipyrine,' Edward Buchner synthesized pyrazole molecules successfully for the first time in the year 1889 [4-6]. The pyrazole molecules have been discovered now to be one of the most thoroughly investigated 'azole' molecules and have been synthesized successfully and also serve as a lead molecule of many drugs [4, 7]. The versatility also led to its applications not only in medical fields but also in agrochemicals, polymer science, cosmetics, and the food industry [12-14].

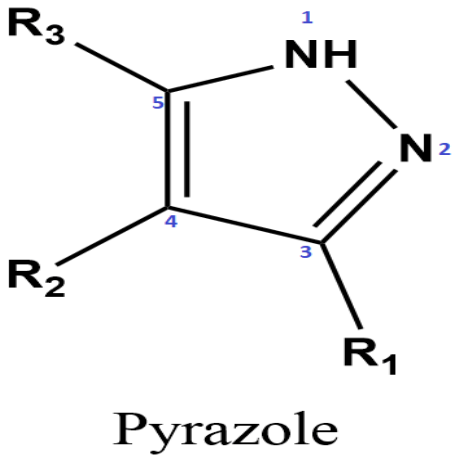

Figure 1. Structure of Pyrazole

More than fifty pyrazole-based drugs have been developed to date, out of which thirty were approved by the FDA since 2011. In fact, more than 60% of all FDA-approved therapeutics contain N-heterocycles in their molecular scaffold, and among those, pyrazoles represent one of the leading subcategories due to their broad molecular architecture and pharmacological diversity [3,8-10]. The pyrazole nucleus has been attributed to a wide range of biological activities, from antiviral [15], antibacterial [16], fungicidal [36, 37], and antimalarial [17] activities to anti-inflammatory [18], antidiabetic [19], antiglaucoma [20], and anticancer activities [21-23]. In addition, pyrazoles are present in naturally occurring biomolecules such as hormones, vitamins, antibiotics, and nucleic acids (DNA and RNA) [24, 25].

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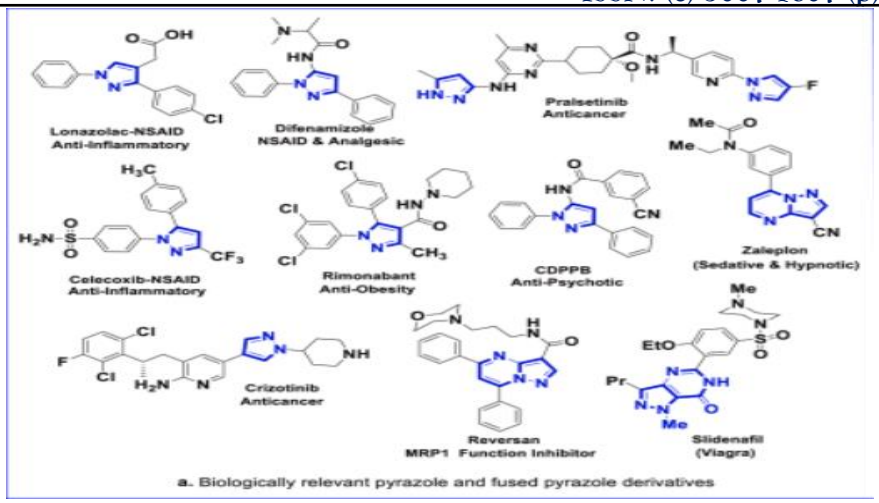

Figure. 2: Examples of biologically important pyrazoles and fused pyrazoles [11].

In agrochemistry, pyrazole derivatives have long served as key scaffolds for herbicides, insecticides, fungicides, and acaricides [30]. Their ring system forms the central unit of widely used agrochemicals, including furametpyr [26], cyantraniliprole [27], cyenopyrafen [28], tolfenpyrad [29], and fenpyroximate [26].

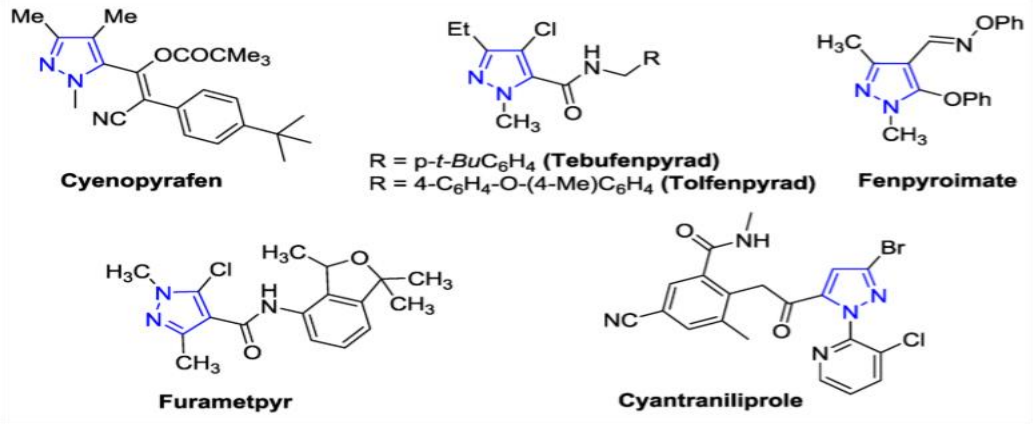

Figure. 3: Agrochemical molecules containing a pyrazole scaffold. [7]

Beyond biological and agricultural applications, pyrazole and pyrazolate frameworks are of increasing relevance in materials science. The metal-organic frameworks of pyrazolates are highly thermally and chemically stable, showing proven ability for selective adsorption of volatile organic compounds like formaldehyde even under humid conditions, thus making them promising candidates for indoor-air purification [31]. They also serve as robust catalysts for C-H activation and cross-coupling transformations [32]. Azo-pyrazole dyes, famed for their vivid and durable coloring, find applications in sustainable textiles and pigments. In addition, coordination frameworks containing pyrazoles exhibit tunable electronic and magnetic properties, opening new avenues in sensing and the development of multifunctional devices [33-35].

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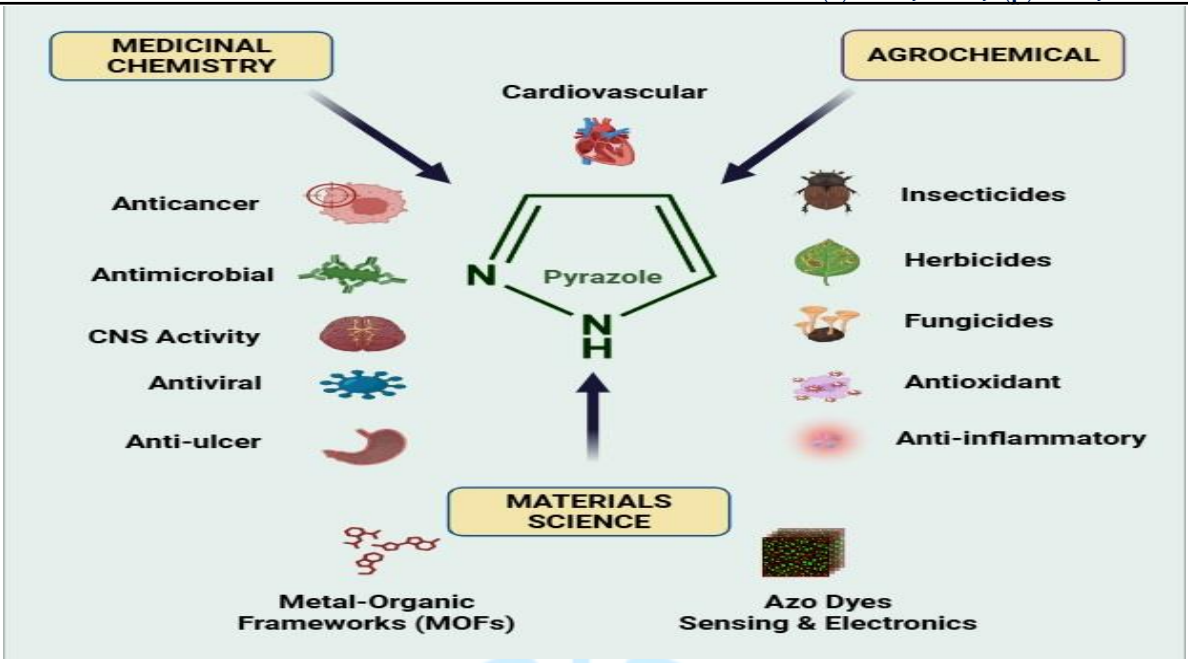

Figure 4: The Versatile Applications of the Pyrazole Scaffold

2. **General Chemistry of Pyrazole Derivatives**

a. **π-system constitution in pyrazole:** Pyrazole constitutes a heterocyclic five-membered ring compound ($C_3H_4N_2$) with two adjacent nitrogen atoms (N1 and N2) and three carbon atoms. Its parent ring possesses an aromatic (6π) system according to Hückel's rule. In pyrazole, one of the ring nitrogen (N1) atoms is pyrrolic (its electron pair is in the π-sextet), while another adjacent nitrogen atom (N2) is pyrid [37, 38]

b. **Planarity and bond characteristics:** The pyrazole ring is fairly planar. The C-N and C-C bonds are intermediate between single and double bonds. This is owing to delocalization. The C-N bond lengths for 1H-pyrazole compounds are usually about 1.33 to 1.36 Å at low temperatures. The five-membered ring is planar [39].

c. **Amphoteric character and intrinsic acid/base strengths:** Because N1 is pyrrolic and N2 is pyridinic, unsubstituted pyrazole is amphoteric: it is a weak base (pKa of the conjugate acid ≈2.5 at 25 °C) and a weak acid (N-H pKa ≈14 in water/related media; EWG substitution lowers this) [40,41].

d. **Hydrogen bonding & aggregation:** The N1–H can donate, and N2 can accept hydrogen bonds; solid-state structures frequently show N–H···N or N–H···O interactions, including dimer formation for hydroxy-pyrazolones/pyrazoles [10,42].

In crystal structures, these interactions often create aggregation motifs such as inversion dimers (via N–H···O or N–H···N), sheets, or chains key to both solid-state stability and tautomer populations [39, 43, 44].

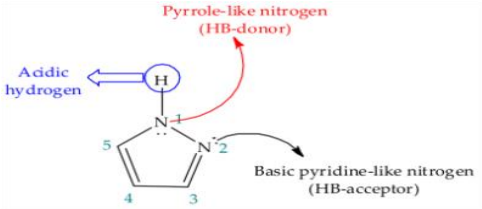

Figure. 5: Amphoteric nitrogen roles and H-bonding ability.

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e. **Resonance energy / "π-excessive" nature:** Experimental thermochemical estimates and comparative analyses describe 1H-pyrazole as slightly π-excessive with resonance energy between benzene and thiophene (≈˜100-130 kJ·mol^{-1} range in representative estimates), consistent with its high thermal/oxidative stability relative to non-aromatic analogues [41, 45].

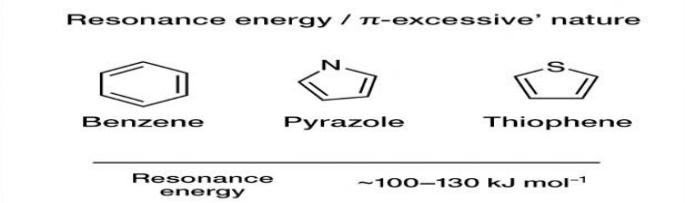

Figure. 6: Pyrazole showing resonance energy between benzene and thiophene.

3. **Tautomerism and Reactivity of Pyrazole Derivatives**

Different types of tautomerism can occur in pyrazoles. In heterocyclic systems, tautomerism is mainly influenced by two key factors. The first is the structural aspect, which describes how the shifting of atoms or groups occurs within the molecule. This can be further divided into annular tautomerism, side chain tautomerism, ring-chain tautomerism, and valence tautomerism. The second factor is the nature of the exchanged atom or group, which includes different types such as prototropy (exchange of protons), elementotropy (exchange of heteroatoms), metallotropy (exchange involving metals), as well as anionotropy and cationotropy (exchange involving negatively or positively charged species) [46-48]. NH-pyrazoles undergo rapid annular tautomerism, in which the protic hydrogen migrates between the two ring nitrogen atoms, interconverting 1H- and 2H/3H-tautomers. In unsubstituted pyrazoles, three tautomeric forms are possible, while mono-substituted pyrazoles can exhibit up to five. Among these, annular prototropic tautomerism in 3(5)-substituted pyrazoles is the most important [49, 54-56].

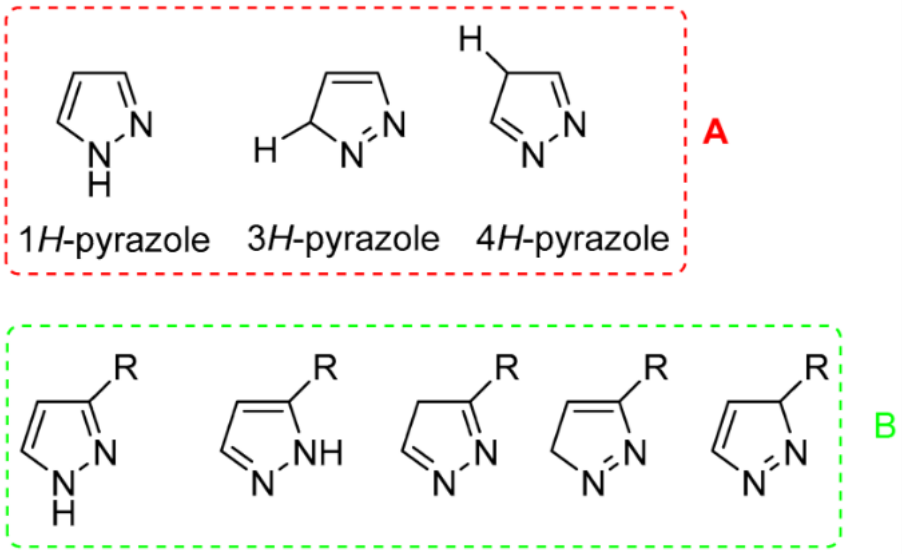

Figure. 7: tautomerism in unsubstituted (A) and monosubstituted(B) pyrazoles [49]

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The equilibrium between tautomers is influenced by:

a. Substituents: Electron-withdrawing groups (e.g., esters, amides, nitro) at C-3 or C-5 stabilize tautomers that localize negative charge near the EWG, often leading to single-tautomer dominance in solution or solid state. Electron-donating groups bias the opposite tautomer [50].

b. Solvent and H-bonding: In the vapor phase, tautomers behave as if in an inert medium; in solids, the most polar tautomer is typically stabilized. In solution, solvent polarity, hydrogen-bonding ability, and dipole moments dictate tautomer ratios. Hydrogen bonding can lock specific tautomers or assist proton transfer, as shown in NMR and CPMAS studies [51, 52]

c. Mechanism: Computational studies indicate water-assisted multistep proton-transfer pathways; for pyrazoles, the transition state can be cation-like in water, altering kinetics relative to other azoles [50]. Other tautomeric possibilities exist, such as sidechain tautomerism (e.g., 3(5)-aminopyrazoles theoretically yielding four forms, though experimentally only annular tautomerism is observed) and keto–enol tautomerism, seen in certain pyrazolones during crystallization. In 1-substituted pyrazol-5-ones, three tautomeric families -OH, CH, and NH forms are possible, with hydrogen bonding strongly influencing the predominant state [4].

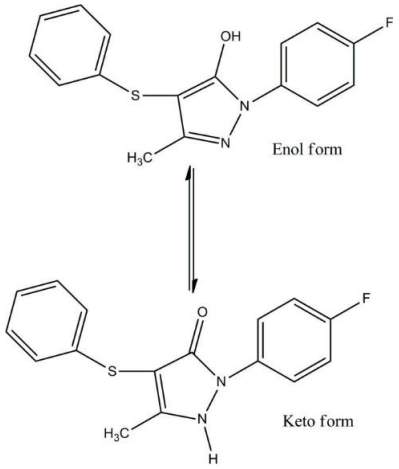

Figure. 8: Enol to keto tautomerism during the crystallization process [60].

3(5)-Aminopyrazoles are susceptible to sidechain tautomerism because the amine substituent is capable of proton exchange. This would theoretically give rise to four possible tautomeric forms. However, experimental findings reveal that the imino forms do not occur. Thus, only annular tautomerism between positions 1 and 2 is observed in 3(5)-aminopyrazoles (corresponding to structures (a) and (d)), like the behavior seen in pyrazole [10].

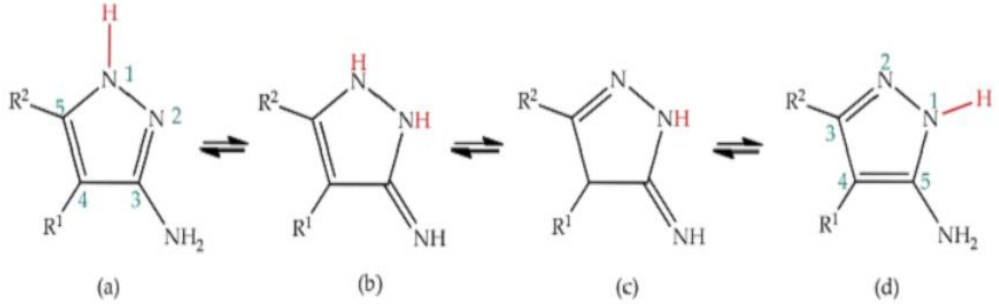

Figure.8: Tautomers of 3(5)-aminopyrazole [10]

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4. Electronic structure and reactivity

The heteroaromatic ring of pyrazole is electronically differentiated by its two vicinal nitrogen atoms: one pyrrole-like (proton donor) and one pyridine-like (proton acceptor). This dual character makes pyrazole valuable in coordination and supramolecular chemistry. The general regiochemical reactivity is given by the following equation,

a. Electrophilic aromatic substitution (EAS): Preferentially reacts with C-4 in unsubstituted pyrazoles, as evident from halogenation

b. Nucleophilic attack: Preferred at C-3 and C-5, due to electron deficiency at these points around the nitrogen atoms.

c. Directed metalation/halogen exchange: Halogenation at C-4 facilitates selective bromo/lithium or bromo/magnesium exchange reactions that have been extensively utilized for cross.

d. N-functionalization: N-alkylation/arylation of 1H-pyrazoles is typically N-1 selective under basic or thermodynamic control, often achieving >99:1 N1/N2 selectivity, supported by crystallographic and computational studies [53, 57]

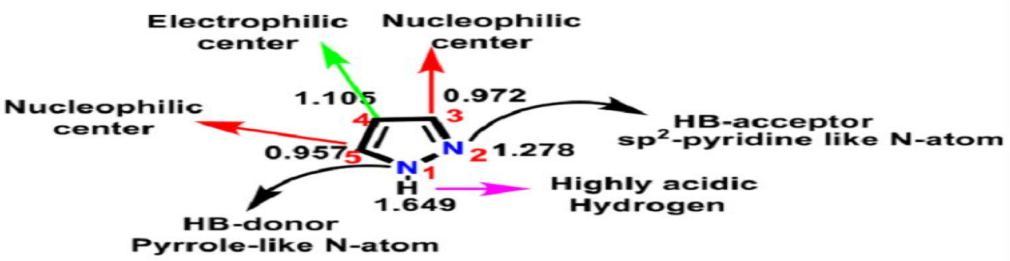

Figure. 9: The electronic structure of pyrazole, highlighting its electrophilic and nucleophilic centers, hydrogen-bonding characteristics, and the relative bond lengths [11].

e. Supramolecular and hydrogen-bonding motifs

The presence of the N-H group permits extensive hydrogen-bonding networks, forming dimers, trimers, tetramers, or catemers in the solid state. Substitution at C-3, C-4, or C-5 still allows N-H···N interactions, though the prediction of specific motifs remains limited due to insufficient crystallographic data [58].

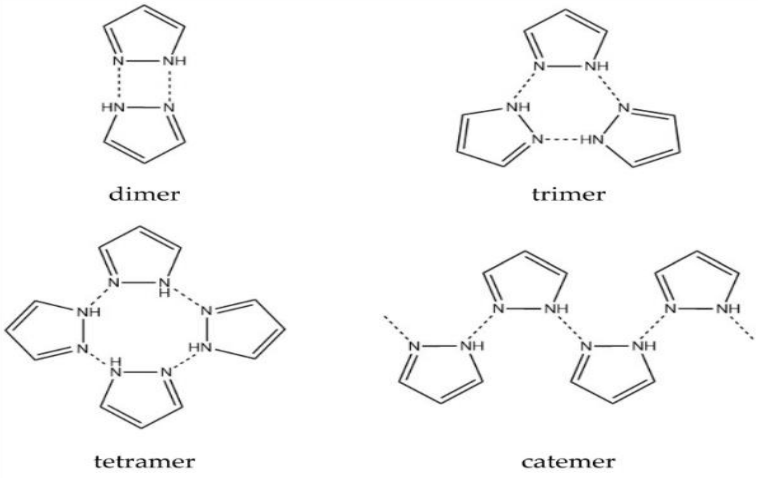

Figure. 10: Supramolecular motifs of 1H-pyrazoles, including dimer, trimer, tetramer, and catemer [59].

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Table 1. Synthetic strategies for pyrazole Derivatives

Category	Method	Key features	Advantages	Limitations	References
Classical methods	Condensation of hydrazines with 1,3-dicarbonyl compounds (β-diketones, β-ketoesters)	Cyclocondensation forming a core pyrazole scaffold	Simple, well-established, good yields, easy workup procedure	Requires solvents, heating, and sometimes long reaction times	[53,60]
	Reaction with α,β-unsaturated carbonyl compounds	Hydrazine reacts with enones under acidic/basic conditions.	Versatile for substituted pyrazoles	Harsh conditions, limited functional group tolerance	[60,61]
	1,3-Dipolar [3+2] cycloaddition of diazo compounds with alkynes	Formation of the pyrazole ring via cycloaddition	Highly flexible, allows diverse substitutions	Handling of diazo compounds can be hazardous	[62,63]
Green & Sustainable Methods	Solvent-free synthesis	Thermal or mechanochemical condensation without solvents	Eco-friendly, reduces waste, cost-effective	Sometimes, limited scalability requires optimization	[64-67]
	Microwave-assisted synthesis	Rapid heating with microwaves accelerates condensation	Short reaction times, higher yields	Requires specialized equipment	[68-70]
	Ultrasound-assisted synthesis	Cavitation enhances reaction kinetics and mixing	Mild conditions, cleaner reactions, short reaction time	Limited industrial adoption	[71-74]
	Eco-friendly catalysts (clays, ionic liquids, natural catalysts)	Catalysis under mild, green conditions	Reusable catalysts, short reaction time, excellent yield	Catalyst preparation can be complex or expensive	[75-77]
Metal-Catalyzed & Multicomponent Reactions	Transition-metal catalysis (Pd, Cu, Ni, Fe)	Metal-mediated bond formation in pyrazole synthesis	Enables novel transformations, high selectivity	Cost, toxicity, and removal of metal residues	[78-82]
	Multicomponent reactions (MCRs)	One-pot synthesis from 3+ components	Atom- and step-economical, structural diversity	Reaction optimization can be challenging	[83-86]

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Recent Innovations	Click chemistry approaches	Modular, selective reactions (e.g., azide–alkyne click) adapted to pyrazoles	High yield, functional group tolerance, rapid synthesis	Requires specific substrates, sometimes metal catalysts	[87,88]
	Biocatalytic methods	Enzyme-mediated steps for pyrazole synthesis	Eco-friendly, stereoselective, sustainable	Limited enzyme availability, scalability issues	[89,90]
	Continuous-flow synthesis (advanced)	Real-time reaction control using flow reactors	Safe handling, reproducibility, and large-scale applicability	Expensive setup, specialized knowledge	[91-93]

5. Functionalization and Chemical Modification under Pyrazole-Based Hybrid Scaffolds

Functionalization of pyrazoles has been implemented by substitution of the N-H group, halogenation of the C-H moiety, and various cross-coupling reactions. Electrophilic halogenation of pyrazoles is an efficient way to install a functional group that can be further elaborated via palladium-catalyzed cross-coupling. Halogenation at the C-4 and C-5 positions is achieved using reagents such as N-bromosuccinimide (NBS), N-chlorosuccinimide (NCS), or N-iodosuccinimide (NIS) [60]. Zolazepam is a pyrazolodiazepinone derivative. Its chemical name is 4-(2-fluorophenyl)-1,3,8-trimethyl-6H-pyrazolo[3,4-e][1,4]diazepin-7-one.

It is used in combination with tiletamine as a veterinary anesthetic (Telazol, Zoletil). Zolazepam belongs to the benzodiazepine class but is structurally distinguished by a pyrazole ring fused to the diazepine nucleus, making it a pyrazolodiazepine [94].

The pyrazole nucleus has gained considerable attention as a privileged scaffold in medicinal chemistry because of its occurrence in a variety of drugs such as celecoxib, rimonabant, and sildenafil. Its structural flexibility allows diverse substitutions at the N-1 and C-3/C-4/C-5 positions, which is critical for optimizing interactions with biological targets. Functionalization methods, including halogenation, nitration, acylation, sulfonylation, and cross-coupling reactions, are routinely applied to derivatize the pyrazole ring.

6. Discussion

The weight of the literature unequivocally indicates that the pyrazole core is a privileged structure that exhibits remarkable flexibility in both the pharmacological and agrochemical and materials science domains [95-97]. Yet an appraisal of the most recent literature indicates that mere flexibility cannot guarantee biological efficacy and that the outcome is actually a rather subtle balance between the effects of substitution patterns and the role of tautomeric and electronic structures in biological recognition events [98, 99]. Of more direct relevance to medicinal chemistry, C-3 and C-5 substitution has repeatedly cropped up as an important determinant in terms of the potency and selectivity of kinase inhibitors and anti-inflammatory compounds in particular [100-102]. Electronegative substitutions can markedly raise affinity by favoring the stability of particular tautomers and increasing the strength of acceptor hydrogen bonding, but when overdone, lipophilicity can negatively impact solubility and metabolic stability [103,104]. It is significant that N-1 substitution can improve pharmacokinetics, although it can also interfere with hydrogen bonding if improperly further optimized [105,106].

Green and sustainable synthetic routes have greatly enhanced the availability of pyrazoles; however, scalability and reproducibility are underrepresented in literature [107, 108]. Reactions using microwave or ultrasonic irradiation are found to have premier laboratory-

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scale yields; however, they are yet to be tested on an industrial scale [109, 110]. Metal-catalyzed routes provide enhanced regioselectivity; however, contamination of metals, associated costs, and environmental factors are mechanisms that are mostly neglected in scientific publications [111–113]. Hybridization approaches are among the most promising domains in pyrazole science. Pyrazoles have been used to generate hybrids that feature higher multitarget properties and synergistic action of complementary pharmacophores in one molecule [114-116]. Although very promising in vitro data have been reported, very limited hybrid compounds proceed from in vitro studies to in vivo assays, thereby disclosing an existing translational gap [117,118]. The translational gap can be ascribed to compromised ADMET properties, thereby underlining the importance of integration at the early stages of hybridization [119,120].

Various computational tools have become indispensable in the design of pyrazoles as drugs; however, over-reliance on docking scores without validation by experimental work has been a significant drawback. Recent work has shown that the use of molecular dynamic simulations and free energy calculation methods can offer more realistic estimates of binding stability, especially when dealing with systems that exhibit the phenomenon of tautomerization, as seen in pyrazoles [123-125]. Binding mode correlation to biological responses will be valuable in future research.

Apart from medicinal chemistry, the other area in which pyrazole materials demonstrate very high potential includes catalyzing reactions, detecting substances, and water purification. In fact, pyrazolate metal-organic framework materials demonstrate enhanced properties compared to the regular framework materials in terms of chemical stability and the ability to be designed based on specific applications or requirements [127-129]. However, different experts in various fields need to collaborate in investigating more applications for the development of such materials ranging from the laboratory to practical applications [130-132].

7. Conclusion

Derivatives of pyrazole have continued to lead in the field of heterocyclic compounds because of their characteristic electronic structure, tautomerism, and unmatched ability to be functionalized. The current review seeks to highlight the massive developments that have been noted in terms of the pyrazole class of compounds, whether in terms of chemistry, synthesis, and applications. Nevertheless, several challenges still exist despite the massive developments. These include imbalance in innovation in terms of synthesis and biological application, lack of in vivo validation, and concentration on pharmacokinetics and toxicity studies. Green chemistry in synthesis has started to make synthesis friendlier, but synthesis relevance to industry still requires examination. Additionally, the approach of the computational methods in assisting technology needs to concentrate on predictive technology through integral incorporation with laboratory information. Future studies will focus on multitarget drugs, hybrid skeletons, and structure-activity in terms of optimization, evident by strong ADMET profiles, and simulations. There are, in addition, interdisciplinary applications in the area of catalysis, sensors, and environmental domains in pyrazoles.

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