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EXPLORING THE SYNTHETIC AND THERAPEUTIC APPLICATIONS OF PYRAZOLE DERIVATIVES: A COMPREHENSIVE REVIEW

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ABSTRACT
In this review, we explore recent advances in the chemical and pharmacological development of pyrazole derivatives, with a focus on their anticancer activity and multi-target therapeutic potential. Pyrazoles, as five-membered heterocycles, exhibit favorable chemical properties that support structural modification for diverse biological applications. Their ability to modulate key molecular targets, particularly kinases, renders them promising candidates for drug discovery. Special emphasis is placed on their role as inhibitors of the Epidermal Growth Factor Receptor (EGFR), a critical target in non-small cell lung cancer (NSCLC) therapy. The review outlines synthetic strategies for N-((5-phenyl-1H-pyrazol-3-yl) carbamothioyl) benzamide derivatives, evaluates their biological activity, and discusses structure–activity relationships (SAR). Molecular docking studies and mechanistic insights are also highlighted, offering a comprehensive foundation for future design and development of pyrazole-based anticancer agents.

KEYWORDS: Pyrazole, EGFR inhibitors, non-small cell lung cancer, kinase inhibition, heterocyclic compounds, biological activity, structure–activity relationship.

1. INTRODUCTION

Pyrazole derivatives have attracted increasing attention in recent years due to their diverse pharmacological properties and structural adaptability. These heterocyclic compounds, characterized by a five-membered aromatic ring containing two adjacent nitrogen atoms, offer a versatile platform for drug design and development (1). The pyrazole scaffold presents unique electronic features; the nitrogen at position one (N1) exhibits pyrrole-like behavior, contributing its lone pair of electrons to the aromatic system, while the nitrogen at position two (N2) resembles pyridine, retaining a non-bonded electron pair that is not involved in delocalization. This duality in electronic behavior allows for extensive functional modification and biological compatibility (2).

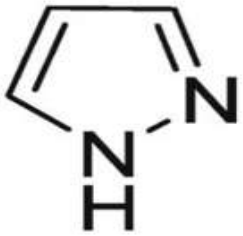


Figure (1) Structure of pyrazole (2)

From a medicinal chemistry perspective, the substitution pattern on the pyrazole ring greatly influences the compound's bioactivity, pharmacokinetics, and target specificity. Pyrazole derivatives have been studied across a broad therapeutic spectrum including anti-inflammatory, antimicrobial, antiviral, and especially anticancer applications (3). Among these, their role in oncology has become particularly significant due to their ability to inhibit various enzymes and signaling pathways implicated in cancer progression. This review provides a comprehensive overview of the therapeutic potential of pyrazole derivatives, emphasizing their anticancer properties and their emerging role as EGFR inhibitors in lung cancer. It further discusses their chemical synthesis, highlights structure–activity relationships critical to their efficacy, and explores broader pharmacological applications across multiple biological targets.

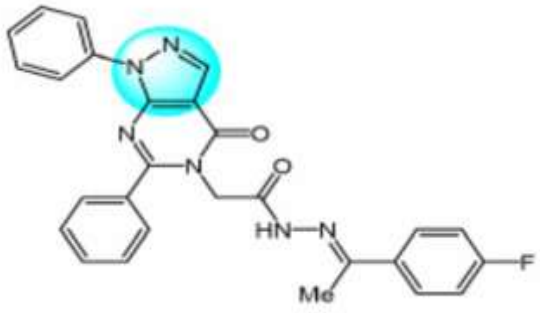
2. Chemical Synthesis of N-((5-phenyl-1H-pyrazol-3-yl) carbamothioyl) benzamide Derivatives

The synthesis of N-((5-phenyl-1H-pyrazol-3-yl)carbamothioyl)benzamide and its analogs has been widely explored in medicinal chemistry due to their potential as anticancer and kinase-inhibiting agents. The general synthetic strategy involves two core steps: the formation of the 5-phenylpyrazole scaffold followed by the introduction of the carbamothioylbenzamide moiety. In a study by Gaber et al., the synthesis began with the cyclization of β-diketones or chalcone-like precursors with hydrazine hydrate, yielding the 5-phenyl-1H-pyrazole-3-amine intermediate. This compound was then reacted with phenyl isothiocyanate under reflux in ethanol to afford the corresponding thiourea derivative. The final condensation with benzoyl chlorides or substituted benzoic acid derivatives yielded N-((5-phenyl-1H-pyrazol-3-yl) carbamothioyl) benzamides in good yields (4). Mohamady et al. employed a similar strategy, using 1-phenyl-3-(hydrazinyl) prop-2-en-1-one for pyrazole formation, followed by reaction with various aryl isothiocyanates to introduce the thiourea group. Their method enabled rapid access to a library of N-arylcarbamothioyl-pyrazoles, which were further diversified via coupling with benzoic acid derivatives using standard peptide coupling reagents such as EDCI or DCC (5). Wang et al. reported an alternative method in which the pyrazole core was synthesized via condensation of phenylhydrazine with 1,3-diketones, followed by selective acylation at the 3-position using phenyl isothiocyanate. Benzoyl moieties were then introduced under basic conditions using potassium carbonate in DMF, promoting nucleophilic substitution to afford the final benzamide products (6). This pathway allowed for functionalization at multiple positions, enabling detailed SAR exploration. In another approach, Badr et al. utilized microwave-assisted synthesis to accelerate the formation of the thiourea linkage. Starting from preformed 5-phenylpyrazole-3-amines, the reaction with isothiocyanates and benzoyl derivatives under solvent-free microwave irradiation significantly reduced reaction times and increased yields, highlighting the potential for green and scalable synthesis (7). Additionally, El-Sayed et al. synthesized related scaffolds using thiocarbonyl diimidazole as a thiocarbamoylating agent, allowing for greater control over the introduction of the thioamide bond and minimizing side-product formation. Their method was particularly useful for generating thiourea intermediates with sensitive or electron-rich substituents on the phenyl rings (8). Overall, the literature demonstrates that the synthesis of N-((5-phenyl-1H-pyrazol-3-yl) carbamothioyl) benzamide is modular, reproducible, and amenable to a wide range of substituent variations. This synthetic flexibility makes it well-suited for medicinal chemistry campaigns aimed at optimizing biological activity and pharmacokinetic profiles.

3.Biological Significance of Pyrazole Derivatives

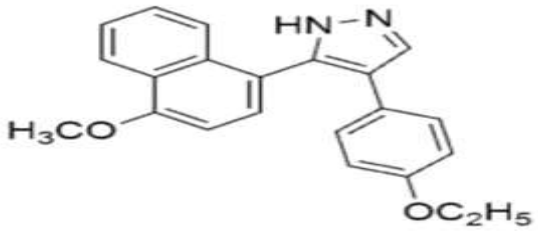
Pyrazole derivatives have demonstrated a wide range of biological effects, with anticancer activity being one of the most extensively investigated. Their chemical flexibility allows for the incorporation of diverse substituents, which can enhance target specificity and therapeutic potency (9). Numerous studies have validated their potential as cytotoxic agents, showing activity against various cancer cell lines through mechanisms such as kinase inhibition, apoptosis induction, and disruption of cell cycle progression (10).

For instance, Sivaramakarthikeyan et al. developed a series of pyrazole-benzimidazole hybrids that were evaluated for their antiproliferative effects on pancreatic cancer cells. Among the synthesized compounds, those bearing a para-fluorophenyl group exhibited the strongest cytotoxic activity, with IC_{50} values of 30.9 ± 0.77 and 32.8 ± 3.44 μM, outperforming the reference drug gemcitabine (11). Gaber et al. developed a series of pyrazolo[3,4-d]pyrimidine derivatives, strategically designed to align with the essential pharmacophoric features of known EGFR inhibitors. The compounds were evaluated for their cytotoxic effects on MCF7 breast cancer cells. Notably, compound [1] exhibited the most potent activity, with an IC_{50} value of 2.89 μM, demonstrating comparable efficacy to the reference drug toceranib (IC_{50} = 2.28 μM) and superior to doxorubicin (IC_{50} = 4.27 μM). (12)



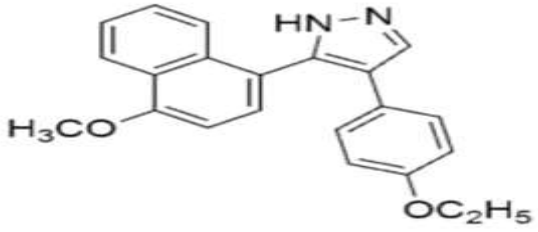
Compound [1]

Similarly, Mohamady et al. synthesized novel diarylpyrazoles and found that a thiophene-substituted analog displayed remarkable inhibitory activity against HepG2 liver cancer cells (IC_{50} = 0.083 μM). This compound [2] also caused cell cycle arrest at the G2 phase and triggered apoptosis by elevating caspase-3 levels nearly eightfold, in addition to significantly reducing key oncogenic proteins such as Akt, c-Met, c-Raf, and EGFR (13).



Compound [2]

Another study by Wang et al. introduced a class of pyrazole-naphthalene derivatives evaluated against breast cancer (MCF-7) cell lines. The most active compound [3], characterized by an ethoxy substituent on the phenyl ring, demonstrated an IC_{50} of 2.78 ± 0.24 μM, which was five times more potent than cisplatin (14).



Compound [3]

Further exploration of hybrid molecules by Anwer et al. led to the synthesis of substituted pyrazole-carbonitrile derivatives, several of which showed strong cytotoxicity against MCF-7 and HCT-116 cells, with IC_{50} values ranging from 3.18 to 8.67 μM (15). Zhang et al. conducted the synthesis and biological assessment of pyrazole-4-carboxamide derivatives. Their lead compound, designated as demonstrated exceptional EGFR inhibitory activity, with an IC_{50} of 0.57 nM. Structure–activity relationship (SAR) analysis suggested that the presence of a hydrophilic linker and a substituted aryl moiety facilitated optimal binding to the EGFR active site. Furthermore, molecular modeling studies corroborated its high binding affinity and favorable docking conformation, consistent with known ATP-competitive inhibitors (16).

Beyond their anticancer applications, pyrazole derivatives have also been explored for anti-inflammatory, antimicrobial, and metabolic activities. El-Karim et al. reported that a series of compounds significantly reduced edema formation by over 96% and downregulated TNF-α levels, indicating a strong anti-inflammatory profile with a favorable gastrointestinal safety index (17). In the context of bacterial infections, Benezer et al. synthesized pyrazole-imidazo[1,2-α] pyridine hybrids that demonstrated broad-spectrum bactericidal activity, surpassing ciprofloxacin in efficacy against several resistant strains, including S. aureus and E. coli (18).

Pyrazole-based scaffolds have also shown promise in the development of antifungal agents. Dong et al. introduced a group of pyrazole-4-carboxamide derivatives, with compound 220 exhibiting superior in vitro and in vivo inhibition against A. solani, achieving complete fungal growth suppression at 10 μg/mL and demonstrating an EC_{50} of 3.06 μg/mL (19). Pyrazole derivatives have also been implicated in enzyme inhibition. Bizzarri et al. designed pyrazoles as selective monoamine oxidase B (MAO-B) inhibitors, as an effective modulator in the micromolar range, relevant for neurodegenerative disease management (20). In cardiovascular research, Bonesi et al. evaluated pyrazole analogs for angiotensin-converting enzyme (ACE) inhibition and reported compound 143 as a potent candidate with an IC_{50} of 0.123 mM (21).

These findings establish pyrazole scaffolds as valuable pharmacophores with versatile applications in drug development. Their ability to modulate multiple biological targets supports ongoing efforts to harness their potential across a wide spectrum of diseases, particularly in oncology.

4. Structure–Activity Relationship (SAR) of Pyrazole Derivatives Targeting EGFR

Understanding the structure–activity relationship (SAR) of pyrazole derivatives is essential for optimizing their affinity and selectivity toward the Epidermal Growth Factor Receptor (EGFR). The pyrazole core serves as a privileged scaffold due to its aromatic nature and ability to engage in multiple non-covalent interactions within the ATP-binding domain of kinases (9). Modifications at key positions on the pyrazole ring have been shown to significantly influence both potency and selectivity against EGFR, particularly in the context of drug-resistant non-small cell lung cancer (NSCLC) mutations (22). Substitution at the 1- and 3-positions of the pyrazole ring has been widely explored for enhancing kinase binding. Electron-donating groups, such as methoxy or methyl, when introduced at the para-position of the aryl ring linked to the pyrazole scaffold, have been associated with increased hydrophobic interactions and improved van der Waals contacts within the EGFR binding pocket (23). In contrast, electron-withdrawing substituents such as fluorine, trifluoromethyl, and

nitro groups enhance ligand binding through stronger electrostatic and dipole interactions, particularly in mutated EGFR variants like T790M (24,25).

In a study by Zhang et al., incorporation of a hydrophilic linker between the pyrazole core and an aryl terminal group significantly improved water solubility and cellular permeability, without compromising binding affinity. This modification also allowed for favorable hydrogen bonding with key residues in the hinge region of the EGFR active site, such as MET793 and GLU762 (26). Moreover, substituents at the 4-position of the pyrazole ring often influence the compound's geometry and interaction depth in the allosteric pocket. Bulky groups, such as substituted phenyl rings, have been reported to enhance selectivity by restricting conformational flexibility, thereby improving binding orientation toward mutant EGFR forms (27).

Carboxamide and urea functionalities attached to the pyrazole nucleus have demonstrated high polar surface area, facilitating both hydrogen bonding and dipole-dipole interactions. Compounds featuring these motifs frequently show increased inhibition of EGFR phosphorylation, particularly when optimized with side chains that mimic the binding mode of known tyrosine kinase inhibitors (28). SAR studies have further shown that hybrid molecules combining the pyrazole ring with other heterocycles, such as pyrimidines or benzimidazoles, may result in synergistic effects, enhancing both target engagement and antiproliferative activity (29).

Collectively, these SAR insights underscore the importance of strategic substitution patterns, linker design, and hybridization approaches in optimizing pyrazole-based EGFR inhibitors. These findings offer valuable guidance for the rational design of next-generation compounds aimed at overcoming resistance in NSCLC therapy.

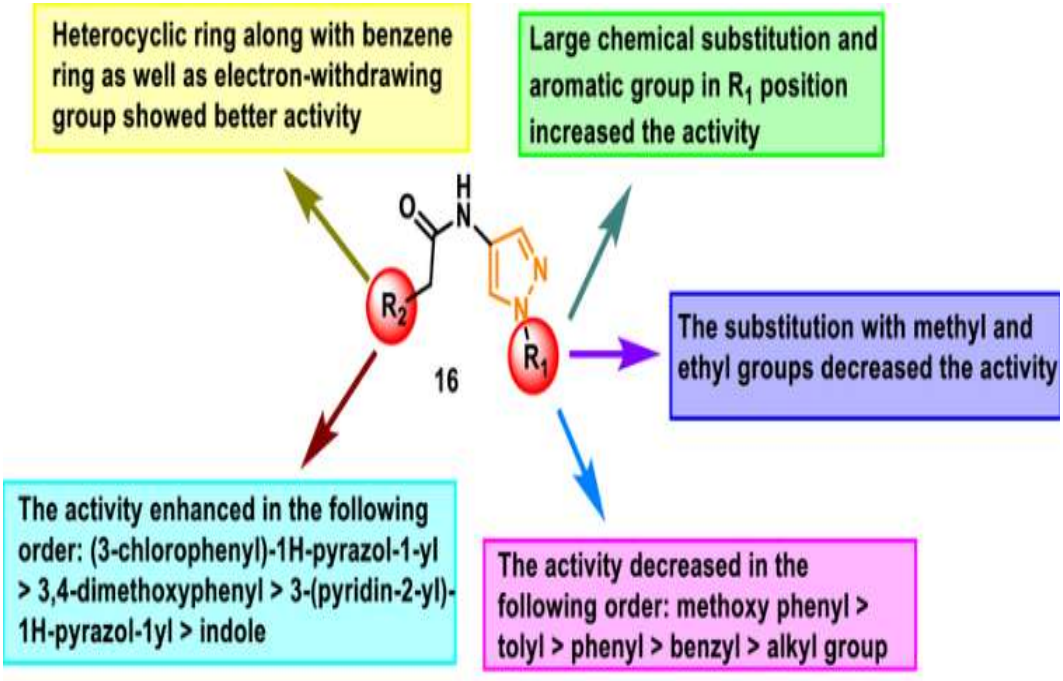


Figure (2) Chemical structure and SAR of pyrazole derivatives (30)

5. CONCLUSION

In summary, this review highlighted the crucial therapeutic relevance of pyrazole derivatives, with emphasis on their chemical synthesis, structure–activity relationships, and biological potential as EGFR inhibitors in non-small cell lung cancer. These compounds offer a structurally adaptable scaffold for rational drug design and optimization. Their synthetic accessibility and favorable interaction profiles position them as promising candidates for future anticancer drug development, particularly in overcoming EGFR-mediated resistance.

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