The Versatility of Pyrazole: Synthesis, Properties, and Applications

20

Khan Ayesha
Syed Ummul Khair Asema*
Anis Ahmed Sheikh

Abstract

Pyrazole, a prominent nitrogen-containing heterocycle, has emerged as a crucial scaffold in contemporary chemical research. Its five-membered aromatic ring, comprising two adjacent nitrogen atoms, imparts unique electronic characteristics that enable diverse substitution patterns and reactivity. Consequently, a wide array of synthetic methodologies—including classical cyclization reactions, one-pot strategies, and metal-catalyzed transformations—have been developed for the efficient synthesis of pyrazole derivatives.

Over the past decade, pyrazole-based compounds have attracted significant attention due to their extensive biological activities, including antibacterial, anticancer, anti-inflammatory, and enzyme inhibitory properties. In addition to pharmaceutical relevance, these compounds play an essential role in advanced materials, coordination chemistry, and agrochemical applications.

This chapter provides a comprehensive overview of recent advances in pyrazole synthesis, structure–activity relationships, and diverse applications, while also highlighting emerging trends and future perspectives in pyrazole chemistry.

Keywords: *Heterocyclic compounds, Pyrazole, Biological activity, Nitrogen heterocycles*

1. Introduction

Heterocyclic compounds constitute an important class of organic molecules

Khan Ayesha
Department of Chemistry, Maulana Azad College, Aurangabad, Maharashtra
Syed Ummul Khair Asema
Department of Chemistry, Maulana Azad College, Aurangabad, Maharashtra
Anis Ahmed Sheikh
Department of Chemistry, Maulana Azad College, Aurangabad, Maharashtra
Publisher: Anu Books
Book Name : Chemical Sciences at the Nexus of Sustainability: Bridging Disciplines

characterized by cyclic structures containing at least one heteroatom such as nitrogen, oxygen, or sulfur. These compounds are ubiquitous in nature and find widespread applications in pharmaceuticals, agrochemicals, dyes, and materials science. Unlike carbocyclic compounds, heterocycles exhibit distinct physicochemical properties due to the presence of heteroatoms within the ring system.

Pyrazole ($C_3H_4N_2$) is a five-membered aromatic heterocycle belonging to the diazole family, consisting of three carbon atoms and two adjacent nitrogen atoms [1]. Along with imidazole, it forms an important subclass of azoles. The unique arrangement of nitrogen atoms confers distinct electronic and chemical properties, making pyrazole a versatile scaffold in synthetic and medicinal chemistry.

The term *pyrazole* was introduced by Ludwig Knorr in 1883, while its first synthesis was reported by Edward Buchner in 1889. Since then, extensive research has been conducted to develop novel synthetic routes and explore the biological potential of pyrazole derivatives [2-3]. These compounds exhibit a wide range of pharmacological activities, including anti-inflammatory, anticancer, antimicrobial, antiviral, antiparasitic, and neuroprotective effects.

A notable example is celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, which represents a significant advancement over traditional nonsteroidal anti-inflammatory drugs (NSAIDs).

Recent research trends emphasize environmentally sustainable and green synthetic approaches, such as solvent-free reactions and the use of eco-friendly solvents. These methodologies offer advantages such as reduced reaction time, higher yields, simplified purification, and minimized environmental impact.

Beyond medicinal chemistry, pyrazoles have applications in supramolecular chemistry, polymer science, photophysics, and dye-sensitized solar cells (DSSCs) [4]. The electronic properties of substituted pyrazoles significantly influence their optical and electrochemical behavior, particularly in charge-transfer processes.

Thus, the pyrazole nucleus serves as a versatile and indispensable framework in modern chemistry, with applications spanning medicine, industry, and advanced technologies.

2. Structure and Aromaticity of Pyrazole

2.1 Aromaticity of Pyrazole

Pyrazole is a π-excess aromatic heterocycle containing a five-membered ring with two adjacent nitrogen atoms. One nitrogen atom is pyridine-like (sp^2-hybridized), while the other resembles pyrrole and possesses an acidic proton (-NH group) [5, 6].

The aromaticity of pyrazole arises from the presence of six π-electrons, satisfying Hückel's rule ($4n + 2$, where $n = 1$). The lone pair on the pyrrolic nitrogen

contributes to the aromatic sextet, whereas the pyridinic nitrogen retains a lone pair that does not participate in delocalization.

Pyrazole exhibits amphoteric behavior:

- The NH group acts as a proton donor (acidic nature).
- The pyridine-like nitrogen acts as a proton acceptor (basic nature).

Substituents on the ring significantly influence its electronic distribution and reactivity.

2.2 Resonance Structure of Pyrazole

The stability of pyrazole is attributed to resonance delocalization of ð-electrons across the ring. Multiple resonance structures can be drawn, illustrating the movement of double bonds and electron pairs between nitrogen and carbon atoms[7].

Key features include:

- Delocalization of six π -electrons across the ring
- Contribution of the lone pair from the pyrrolic nitrogen
- Retention of a localized lone pair on the pyridinic nitrogen

This electronic distribution governs the molecule's chemical reactivity and biological interactions, particularly in drug design where binding affinity is influenced by electron density.

3. Reactivity of Pyrazole

Pyrazole exhibits distinctive reactivity patterns arising from its aromatic, ð-excess electronic structure and the presence of two adjacent nitrogen atoms [8,9]. The distribution of electron density within the ring plays a crucial role in determining the regioselectivity of substitution reactions. The combined influence of resonance, inductive effects, and the nature of substituents governs both electrophilic and nucleophilic transformations.

In general, the reactivity of pyrazole is characterized by:

- Preferential substitution at specific carbon positions (C-3, C-4, and C-5)
- Participation of nitrogen atoms in protonation and coordination
- Sensitivity to substituent effects, which modulate electron density

3.1 Electrophilic Substitution

Electrophilic substitution reactions are among the most important transformations of pyrazole and typically occur at the C-4 position, which is the most electron-rich and least sterically hindered site in the ring.

3.1.1 Regioselectivity and Mechanism

The preference for substitution at C-4 can be explained by resonance stabilization of the intermediate ó-complex [10, 11]. When an electrophile attacks the

C-4 position, the resulting carbocation intermediate is stabilized through delocalization of charge over the ring without significantly disrupting the aromatic sextet.

In contrast, substitution at C-3 or C-5 leads to less stable intermediates due to unfavorable charge distribution involving the electronegative nitrogen atoms [13].

Common Electrophilic Reactions

1. Nitration

Pyrazole undergoes nitration under controlled conditions (e.g., dilute nitric acid), yielding predominantly 4-nitropyrazole derivatives. Harsh conditions are generally avoided to prevent ring degradation or over-substitution.

2. Halogenation

Halogenation reactions (chlorination, bromination, iodination) readily occur at the C-4 position using halogens or halogenating agents. These reactions are valuable for introducing functional handles for further derivatization via cross-coupling reactions.

3. Sulfonation

Sulfonation leads to the formation of pyrazole sulfonic acids, typically at the C-4 position. These derivatives are important intermediates in medicinal and industrial chemistry due to their enhanced solubility and reactivity.

3.1.2 Influence of Substituents

The presence of substituents significantly affects electrophilic substitution:

- Electron-donating groups (EDGs) enhance reactivity and facilitate substitution.
- Electron-withdrawing groups (EWGs) decrease electron density and may reduce reaction rates or alter regioselectivity [14].

Thus, electrophilic substitution in pyrazole is highly controlled and predictable, making it a valuable strategy for functionalization.

3.2 Nucleophilic Substitution

Nucleophilic substitution reactions in pyrazole are relatively less common due to the stability of the aromatic ring and its electron-rich nature [15]. However, such reactions can occur under specific conditions, particularly when the ring is activated by electron-withdrawing substituents.

3.2.1 Activation of the Pyrazole Ring

Introduction of strong electron-withdrawing groups (such as nitro, cyano, or carbonyl substituents) reduces electron density in the ring, thereby facilitating nucleophilic attack. These groups stabilize the intermediate formed during nucleophilic substitution [16].

3.2.2. Mechanistic Considerations

Nucleophilic substitution may proceed via:

- Addition–elimination mechanisms (SNAr type), especially in halogenated pyrazoles
- Direct displacement reactions, when a suitable leaving group is present

Typical Reactions

1. Substitution in Halogenated Pyrazoles

Halogen atoms (e.g., Cl, Br) attached to the pyrazole ring can be displaced by nucleophiles such as amines, alkoxides, or thiols, leading to functionalized derivatives [17].

2. Reactions with Nitrogen Nucleophiles

Amines and hydrazines can react with activated pyrazoles to yield substituted products, which are important intermediates in pharmaceutical synthesis [18].

3. Ring Functionalization under Strong Conditions

In certain cases, nucleophilic attack can occur at carbon atoms adjacent to electron-withdrawing groups, resulting in substitution or rearrangement products [19].

Factors Affecting Reactivity

- Nature and position of substituents
- Strength of the nucleophile
- Reaction conditions (temperature, solvent, catalyst)

4. Biological Activities of Pyrazole

4.1 Anticancer Activity

Pyrazole derivatives have emerged as a highly promising class of compounds in anticancer drug discovery, owing to their structural versatility and ability to interact with diverse biological targets. Over the past decade, extensive research has demonstrated that functionalized pyrazole scaffolds exhibit potent cytotoxic effects against a wide range of cancer cell lines. Among these, pyrazole–oxindole hybrids have attracted particular attention due to their ability to interfere with microtubule dynamics [20]. These compounds inhibit tubulin polymerization, a critical process in cell division, thereby inducing cell cycle arrest and apoptosis in rapidly proliferating cancer cells.

In addition to targeting microtubules, several pyrazole derivatives function as enzyme modulators, further expanding their therapeutic potential. For instance, certain compounds act as activators of human pyruvate kinase M2 (hPKM2), an enzyme involved in cancer cell metabolism. Modulation of hPKM2 activity disrupts

metabolic pathways essential for tumor growth and survival [21]. These derivatives have shown significant antiproliferative activity against well-established cancer cell lines such as A549 (human lung carcinoma) and NCI-H1299 (non-small cell lung cancer), with inhibitory concentrations in the micromolar range. Such findings highlight the potential of pyrazole-based molecules as multitarget agents capable of interfering with both structural and metabolic pathways in cancer cells [22].

Structure–activity relationship (SAR) studies have played a crucial role in understanding and optimizing the anticancer potential of pyrazole derivatives. Variations in substitution patterns on the pyrazole ring, particularly at the 3-, 4-, and 5-positions, significantly influence biological activity. The incorporation of electron-donating or electron-withdrawing groups, as well as heteroaromatic moieties, has been shown to modulate lipophilicity, electronic distribution, and binding affinity to biological targets. For example, diaryl-substituted pyrazoles often exhibit enhanced cytotoxicity due to improved interaction with enzyme active sites or receptor binding pockets. Similarly, the presence of functional groups capable of hydrogen bonding can strengthen interactions with biomolecular targets, thereby increasing efficacy.

Moreover, many pyrazole derivatives demonstrate broad-spectrum anticancer activity, being effective against multiple cancer types including breast, lung, prostate, colon, and leukemia cell lines [23]. This wide-ranging activity suggests that these compounds may act through common cellular pathways such as apoptosis induction, inhibition of angiogenesis, or disruption of signal transduction mechanisms. Importantly, some derivatives have also shown selectivity toward cancer cells over normal cells, which is a desirable feature in reducing adverse side effects.

Overall, the combination of structural adaptability, diverse mechanisms of action, and promising biological profiles positions pyrazole derivatives as valuable lead compounds in anticancer drug development [24]. Continued research focusing on molecular optimization, mechanistic studies, and in vivo evaluations is expected to further advance their clinical potential and contribute to the development of more effective and targeted cancer therapies.

4.2 Anti-Alzheimer's Activity

Pyrazole-based compounds have gained considerable attention as promising therapeutic agents for the treatment of Alzheimer's disease (AD), a progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and neuronal degeneration. The structural versatility of the pyrazole scaffold enables the design of molecules capable of interacting with multiple biological targets

implicated in AD pathogenesis, making them attractive candidates for multitarget-directed ligand (MTDL) strategies [25].

One of the key mechanisms through which pyrazole derivatives exert their effects is the inhibition of monoamine oxidases (MAO-A and MAO-B). These enzymes are responsible for the oxidative deamination of neurotransmitters, and their overactivity leads to increased oxidative stress and neuronal damage [26]. Pyrazole-based MAO inhibitors help restore neurotransmitter balance and reduce the formation of reactive oxygen species, thereby offering neuroprotective benefits.

In addition, pyrazole derivatives have shown significant potential as â-site amyloid precursor protein cleaving enzyme 1 (BACE1) inhibitors. BACE1 plays a crucial role in the formation of amyloid-â (Aâ) peptides, which aggregate to form plaques—a hallmark of Alzheimer's disease. By inhibiting BACE1, pyrazole compounds can effectively reduce Aâ production and slow disease progression. Similarly, certain derivatives act as ã-secretase inhibitors, further contributing to the reduction of amyloid plaque formation by blocking another key step in Aâ generation [27].

Another important target is the receptor for advanced glycation end products (RAGE), which is involved in Aâ transport across the blood–brain barrier and mediates inflammatory responses. Pyrazole-based RAGE inhibitors can suppress neuroinflammation and limit the accumulation of toxic amyloid species in the brain. Notably, several pyrazole derivatives exhibit inhibitory activity in the nanomolar range, indicating high potency. Furthermore, these compounds often demonstrate favorable pharmacokinetic properties, such as enhanced solubility, good bioavailability, and the ability to cross the blood–brain barrier—critical factors for effective central nervous system drugs [28, 29].

Overall, the multifunctional nature of pyrazole scaffolds, combined with their strong biological activity and drug-like properties, underscores their significant potential in the development of novel therapeutics for Alzheimer's disease. Continued research in this area is likely to yield more selective and effective candidates for clinical application.

4.3 Anti-inflammatory Activity

Pyrazole derivatives constitute an important class of anti-inflammatory agents and have been extensively investigated due to their potent activity and improved safety profiles compared to conventional nonsteroidal anti-inflammatory drugs (NSAIDs) [30]. The anti-inflammatory potential of these compounds is primarily attributed to their ability to inhibit key enzymes involved in the biosynthesis of inflammatory mediators, particularly cyclooxygenase-2 (COX-2) and

lipoxygenase (LOX). By selectively targeting COX-2, pyrazole derivatives effectively reduce the production of prostaglandins responsible for pain and inflammation, while minimizing the gastrointestinal side effects commonly associated with non-selective COX inhibitors [31].

A significant advantage of pyrazole-based compounds lies in their enhanced efficacy when compared to standard drugs such as indomethacin and celecoxib. Several synthesized derivatives have demonstrated superior inhibition of inflammation in both in vitro and in vivo models, including carrageenan-induced rat paw edema assays. These studies highlight not only their potency but also their prolonged duration of action, which is beneficial for chronic inflammatory conditions.

In addition to enzyme inhibition, pyrazole derivatives also exhibit the ability to suppress key inflammatory mediators such as tumor necrosis factor-alpha (TNF-á), interleukins, and other cytokines [32]. This multifaceted mechanism contributes to their overall anti-inflammatory effect and supports their potential use in treating a variety of inflammatory disorders, including arthritis and autoimmune diseases.

Another important aspect of pyrazole derivatives is their improved gastrointestinal safety profile. Unlike traditional NSAIDs, which often cause gastric irritation and ulceration due to COX-1 inhibition, many pyrazole-based compounds show higher selectivity toward COX-2, thereby reducing adverse gastrointestinal effects. This makes them more suitable for long-term therapeutic use.

Molecular docking and computational studies have further provided insights into the interaction of pyrazole derivatives with enzyme active sites. These studies reveal strong binding affinities, primarily driven by hydrogen bonding, hydrophobic interactions, and ð–ð stacking. Functional groups such as sulfonamide and methanesulfonyl moieties play a critical role in enhancing binding efficiency and selectivity toward COX-2 and LOX enzymes [33].

Overall, the combination of high potency, selective enzyme inhibition, reduced side effects, and favorable binding characteristics positions pyrazole derivatives as promising candidates for the development of next-generation anti-inflammatory drugs.

4.4 Anti-Leishmanial Activity

Pyrazole derivatives have emerged as promising candidates in the search for new antileishmanial agents, targeting *Leishmania* species responsible for leishmaniasis—a neglected tropical disease with significant global health impact. The limitations of currently available therapies, including drug resistance, toxicity, prolonged treatment regimens, and high cost, necessitate the development of safer

and more effective alternatives [34]. In this regard, the structural flexibility and biological versatility of the pyrazole scaffold make it an attractive platform for drug design.

A variety of synthesized pyrazole derivatives have demonstrated potent inhibitory activity against both promastigote and amastigote forms of the parasite. The amastigote stage, which resides within host macrophages, is particularly important for therapeutic targeting. Several compounds have exhibited strong activity at low micromolar or nanomolar concentrations, with some derivatives showing greater efficacy than standard drugs such as miltefosine. These findings indicate that pyrazole-based molecules possess significant potential as lead compounds for antileishmanial drug development [35].

The mechanisms underlying the antileishmanial activity of pyrazole derivatives are multifaceted. These compounds are reported to interfere with critical biological processes within the parasite, including DNA replication, mitochondrial function, and redox balance. In particular, inhibition of key enzymes such as trypanothione reductase disrupts the parasite's defense against oxidative stress, leading to cell death. Additionally, certain derivatives may affect membrane integrity or inhibit essential metabolic pathways, further contributing to their antiparasitic effects.

Structure–activity relationship (SAR) studies have highlighted the importance of substituent effects in enhancing biological activity. The introduction of electron-withdrawing groups, aromatic rings, or heterocyclic moieties can improve lipophilicity, cellular uptake, and binding affinity to biological targets [36, 37]. These modifications often result in increased potency and selectivity toward the parasite.

Importantly, many pyrazole derivatives exhibit favorable selectivity indices, demonstrating lower cytotoxicity toward host cells while maintaining strong antiparasitic activity. This selectivity is crucial for minimizing side effects and improving therapeutic outcomes [38].

Overall, the promising biological activity, diverse mechanisms of action, and tunable chemical structure of pyrazole derivatives underscore their potential in addressing leishmaniasis. Continued research involving rational design, in vivo evaluation, and clinical studies is essential to fully realize their potential as effective treatments for this neglected tropical disease.

5. Conclusion

Pyrazole has established itself as one of the most versatile and significant heterocyclic scaffolds in modern chemical science. Its distinctive electronic configuration, arising from the presence of two adjacent nitrogen atoms within an aromatic five-

membered ring, imparts unique physicochemical and reactivity characteristics. These features enable extensive structural modifications, allowing the development of a wide range of functional derivatives with tailored properties [39].

The remarkable synthetic accessibility of pyrazole derivatives, through classical as well as modern methodologies such as one-pot reactions, multicomponent strategies, and metal-catalyzed processes, has further contributed to its prominence in organic and medicinal chemistry [40]. In particular, recent advancements in green and sustainable synthetic approaches—including solvent-free reactions and the use of eco-friendly catalysts—have significantly enhanced the environmental and industrial relevance of pyrazole chemistry.

From a biological perspective, pyrazole-based compounds exhibit a broad spectrum of pharmacological activities, including anticancer, anti-inflammatory, antimicrobial, neuroprotective, and antiparasitic effects. Their ability to interact with multiple biological targets highlights their importance in the development of novel therapeutic agents. In addition to pharmaceutical applications, pyrazole derivatives also play a vital role in agrochemicals, coordination chemistry, and advanced materials, further demonstrating their multidisciplinary significance.

Importantly, ongoing research into structure–activity relationships (SAR) continues to provide valuable insights into the optimization of biological activity and selectivity. The rational design of new derivatives, supported by computational tools and molecular modeling, is expected to accelerate the discovery of more potent and selective compounds.

In conclusion, the pyrazole nucleus represents a powerful and adaptable framework with immense potential across diverse scientific domains. Future research focusing on innovative synthetic strategies, sustainable practices, and targeted biological applications is likely to unlock new opportunities, reinforcing the central role of pyrazole chemistry in advancing science and technology.

References

1. Poudyal, B., & Bharghav, G. (2021). A review of pyrazole and its derivatives. National Journal of Pharmaceutical Sciences, 1(1), 34–41.
2. Rehman, M. U., He, F., Shu, X., Guo, J., Liu, Z., & Cao, S. (2024). Antibacterial and antifungal pyrazoles based on different construction strategies. European Journal of Medicinal Chemistry, 282, 117081.
3. Knorr, L. (1883). Einwirkung von Acetessigester auf Phenylhydrazin. Berichte der Deutschen Chemischen Gesellschaft, 16, 2597–2599.

4. Buchner, E. (1889). Ein Isomeres des Glyxalins. Berichte der Deutschen Chemischen Gesellschaft, 22, 2165–2167.
5. Frampton, J. E., & Keating, G. M. (2007). Celecoxib: A review of its use in the management of arthritis and acute pain. Drugs, 67, 2433–2472.
6. Soltanzadeh, Z., Imanzadeh, G., & Noroozi-Pesyan, N. (2017). Green synthesis of pyrazole systems under solvent-free conditions. Green Chemistry Letters and Reviews, 10, 148–153.
7. Singh, R., Kaur, R., Ahlawat, P., Kaushik, P., & Singh, R. (2021). Green methods for the synthesis of pyrazoles: A review. Organic Preparations and Procedures International, 53, 317–351.
8. Fustero, S., Sánchez-Roselló, M., Barrio, P., & Simón-Fuentes, A. (2011). From 2000 to mid-2010: A fruitful decade for the synthesis of pyrazoles. Chemical Reviews, 111, 6984–7034.
9. Nitulescu, G. M., Stancov, G., Seremet, O. C., Nitulescu, G., Mihai, D. P., Duta-Bratu, C. G., Barbuceanu, S. F., & Olaru, O. T. (2023). The importance of the pyrazole scaffold in the design of protein kinase inhibitors. Molecules, 28, 5359.
10. Mori, T., Saomoto, H., Machitani, K., Inoue, K., Aoki, Y., Koshitani, T., Koumura, N., & Murakami, T. N. (2016). Photophysical properties of pyrazole derivatives. RSC Advances, 6, 13964–13970.
11. Gupta, R. R., Kumar, M., & Gupta, V. (1998). Heterocyclic chemistry (Vols. I–II). Springer.
12. Poletto, J., Ribeiro, G. M., Da Silva, M. J. V., Jacomini, A. P., Basso, E. A., Back, D. F., Moura, S., & Rosa, F. A. (2019). One-pot synthesis of N-arylpyrazoles. Organic Letters, 21, 6325–6328.
13. Meng, Y., Zhang, T., Gong, X., Zhang, M., & Zhu, C. (2019). Visible-light promoted synthesis of pyrazoles. Tetrahedron Letters, 60, 171–174.
14. Dang, T. T., Fischer, C., Görls, H., & Langer, P. (2008). Synthesis of pyrazole derivatives. Tetrahedron, 64, 2207–2215.
15. Ledovskaya, M. S., Voronin, V. V., Polynski, M. V., Lebedev, A. N., & Ananikov, V. P. (2020). Vinyl ethers as acetylene surrogates. European Journal of Organic Chemistry, 2020, 4571–4580.
16. Bishop, B. C., Brands, K. M., Gibb, A. D., & Kennedy, D. J. (2004). Regioselective synthesis of substituted pyrazoles. Synthesis, 2004, 43–52.
17. Wang, A., Quan, W., Zhang, H., & Li, H. (2021). ZnO catalysts for biodiesel production. RSC Advances, 11, 20465–20483.

18. Govindaraju, S., Tabassum, S., & Pasha, M. A. (2018). Green synthesis of pyrazole derivatives. ChemistrySelect, 3, 3832–3838.
19. Dwivedi, K. D., Borah, B., & Chowhan, L. R. (2020). Green chemistry approach in pyrazole synthesis. Frontiers in Chemistry, 7, 944.
20. Kerru, N., Gummidi, L., Bhaskaruni, S. V. H. S., Maddila, S. N., & Jonnalagadda, S. B. (2020). Pyrazole derivatives as antimicrobial agents. Research on Chemical Intermediates, 46, 3067–3085.
21. Asad, M., Arshad, M. N., Oves, M., Khalid, M., Khan, S. A., Asiri, A. M., & Rehan, M. (2020). Pyrazoline derivatives: Synthesis and antimicrobial activity. Bioorganic Chemistry, 99, 103842.
22. Reddy, G. M., Garcia, J. R., Zyryanov, G. V., Sravya, G., & Reddy, N. B. (2019). Pyranopyrazoles as antimicrobial agents. Bioorganic Chemistry, 82, 324–331.
23. Kamal, A., Shaik, A. B., Jain, N., Kishor, C., Nagabhushana, A., Supriya, B., Kumar, G. B., Chourasiya, S. S., Suresh, Y., Mishra, R. K., & Addlagatta, A. (2015). Pyrazole–oxindole conjugates as anticancer agents. European Journal of Medicinal Chemistry, 92, 501–513.
24. Xu, Y., Liu, X. H., Saunders, M., Pearce, S., Foulks, J. M., Parnell, K. M., Clifford, A., Nix, R. N., Bullough, J., & Hendrickson, T. F. (2014). Pyrazole-based PKM2 activators. Bioorganic & Medicinal Chemistry Letters, 24, 515–519.
25. Viale, M., Anzaldi, M., Aiello, C., Fenoglio, C., Albicini, F., Emionite, L., & Gangemi, R. (2013). Antiproliferative activity of pyrazole compounds. Pharmacological Reports, 65, 717–723.
26. Tzanetou, E., Liekens, S., Kasiotis, K. M., Fokialakis, N., & Haroutounian, S. A. (2012). Pyrazole derivatives as anticancer agents. Archiv der Pharmazie, 345, 804–811.
27. Chimenti, F., Fioravanti, R., Bolasco, A., Manna, F., Chimenti, P., Secci, D., & Turini, P. (2007). MAO inhibitors based on pyrazole scaffold. Journal of Medicinal Chemistry, 50, 425–428.
28. Malamas, M. S., Erdei, J., Gunawan, I., Barnes, K., Hui, Y., Johnson, M., & Robichaud, A. (2011). BACE1 inhibitors based on pyrazole. Bioorganic & Medicinal Chemistry Letters, 21, 5164–5170.
29. Probst, G., Aubele, D. L., Bowers, S., Dressen, D., Garofalo, A. W., Hom, R. K., & Mattson, M. N. (2013). ã-Secretase inhibitors. Journal of Medicinal Chemistry, 56, 5261–5274.

30. Han, Y. T., Kim, K., Choi, G. I., An, H., Son, D., Kim, H., & Park, H. J. (2014). RAGE inhibitors for Alzheimer's disease. European Journal of Medicinal Chemistry, 79, 128–142.
31. Mantzanidou, M., Pontiki, E., & Hadjipavlou-Litina, D. (2021). Pyrazolines as anti-inflammatory agents. Molecules, 26, 3439.
32. El-Karim, S. S. A., Mohamed, H. S., & Abdelhameed, M. F. E. (2021). Pyrazole-thiazolidinones as anti-inflammatory agents. Bioorganic Chemistry, 111, 104827.
33. Abdellatif, K. R. A., Abdelall, E. K. A., & Lamie, P. F. (2020). COX-2 inhibitors based on pyrazole. Bioorganic Chemistry, 95, 103540.
34. Gedawy, E. M., Kassab, A. E., & El Kerdawy, A. M. (2020). Pyrazole sulfonamides as COX inhibitors. European Journal of Medicinal Chemistry, 189, 112066.
35. De Mello, H., Echevarria, A., Bernardino, A. M., Canto-Cavalheiro, M., & Leon, L. L. (2004). Antileishmanial pyrazolopyridine derivatives. Journal of Medicinal Chemistry, 47, 5427–5434.
36. Bernardino, A. M. R., Gomes, A. O., Charret, K. S., Freitas, A. C. C., Machado, G. M. C., & Leon, L. L. (2006). Pyrazole derivatives as antileishmanial agents. European Journal of Medicinal Chemistry, 41, 80–87.
37. Bekhit, A. A., Hassan, A. M. M., Abd El Razik, H. A., El-Miligy, M. M. M., & El-Agroudy, E. J. (2015). Pyrazole derivatives as antimalarial and antileishmanial agents. European Journal of Medicinal Chemistry, 94, 30–44.
38. Mowbray, C. E., Braillard, S., Speed, W., Glossop, P. A., Whitlock, G. A., Gibson, K. R., & Mills, J. E. J. (2015). Amino-pyrazole ureas as antileishmanial agents. Journal of Medicinal Chemistry, 58, 9615–9624.
39. Marra, R., Bernardino, A., Proux, T., Charret, K., Lira, M. L., Castro, H., & Rodrigues, C. (2012). Pyrazole sulfonamides for leishmaniasis. Molecules, 17, 12961–12973.
40. Reviriego, F., Olmo, F., Navarro, P., Marín, C., Ramírez-Macías, I., García-España, E., & Sánchez-Moreno, M. (2017). Pyrazole derivatives as antiparasitic agents. Parasitology, 144, 1133–1143.