Pyrazolone Derivatives: A Comprehensive Review of Pharmacological Evaluations as Potent Anti-Inflammatory Agents

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Abstract

Pyrazolone, a key pyrazole derivative, has attracted significant attention from medicinal chemists for decades owing to its strong anti-inflammatory properties, serving as a foundational scaffold for novel drug development. This review traces the progression of pyrazolone-based research, emphasizing its incorporation into bioactive hybrids aimed at enhancing therapeutic efficacy beyond that of traditional non-steroidal anti-inflammatory drugs (NSAIDs). Global studies underscore pyrazolone's effectiveness in managing inflammation associated with autoimmune diseases, arthritis, and pain, especially in cases where standard treatments are limited by adverse effects such as gastrointestinal toxicity and cardiovascular risks. Green synthetic methodologies, including microwave- and ultrasound-assisted techniques, have streamlined the production of pyrazolone derivatives, generating diverse compound libraries with improved pharmacokinetic profiles. Emerging research trends focus on pyrazolone hybrids combined with flavonoids, sulfonamides, and metal chelators, which hold promise for expanded clinical applications.

Keywords: *Pyrazolone, anti-inflammatory agents, pyrazole scaffold, green synthesis, drug hybrids.*

1. Introduction

An essential component of the body's defensive mechanism, inflammation promotes tissue regeneration and the immune system's ability to identify and eliminate undesirable or harmful substances. The body's defensive reaction to stimuli

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like infections or injuries is inflammation. Whether this process results in acute or chronic inflammation depends on the duration and type of immune response. Pharmacological treatments such as NSAIDs or specific pyrazolone derivatives may be required to break the cycle of destruction and repair that can lead to organ failure if inflammation is not addressed [1].

1.1. Inflammation: An Overview

The human body is continuously exposed to dangerous outside influences. In order to preserve homeostasis, a variety of systems have evolved to detect, respond to, and heal damage. An adaptive reaction to a variety of stressors, including infections, trauma, and surgery, burns, and ischemia or tissue damage, inflammation takes place. The phrase "para-inflammation" refers to a biological state that lies between normal tissue homeostasis and a fully initiated inflammatory response, and it is not an easy process to understand [2].

1.2. Types of Inflammation

Inflammation is defined as a biological response that facilitates tissue regeneration and the immune system's detection and elimination of unwanted stimuli. It is categorized into two primary types based on duration and physiological impact:

1.2.1. Acute Inflammation

Trauma, microbial infection, or the presence of toxic chemicals are some of the reasons that cause acute inflammation. It usually resolves in a short amount of time and grows and advances swiftly. Acute pneumonia and cellulitis are two instances of this process. Between acute and chronic types of inflammation, sub-acute inflammation is a transitional phase. It might last for two to seven weeks. It differs from both long-term chronic inflammation and quick acute reactions due to its intermediate length. Five main signs define acute inflammation. Pain, redness, loss of function, swelling, and heat are some of these symptoms. At the afflicted place, they together indicate the body's active inflammatory reaction [3].

1.2.2. Chronic Inflammation

Depending on the original damage and the body's capacity for healing, chronic inflammation is a slow-burning, protracted immunological response that can last for months or years and range in severity from moderate to severe. Tiredness (like in systemic lupus erythematosus), fever (like in TB), stiffness or discomfort in the joints (like in rheumatoid arthritis), mouth ulcers (like in HIV), and skin rashes (like in psoriasis) are common symptoms. Muscle discomfort, joint pain, sleeplessness, chronic fatigue, mental disorders like sadness or anxiety, changes in weight, and digestive problems like acid reflux, diarrhoea, or constipation are examples of common but frequently mild symptoms.

1.3. Etiology and Epidemiology of Inflammation

Numerous factors can cause inflammation, such as bacterial, viral, or other microbiological diseases; physical damage like burns, wounds, or foreign objects; and chemical irritants like pollution, alcohol, or poisons. Non-infectious causes, such as autoimmune diseases like lupus, occur when the immune system unintentionally targets healthy tissues. Chronic stress, poor nutrition, obesity, and unresolved acute inflammation from exposures or injuries are other contributors.

1.4. Epidemiology of Inflammation

A major contributor to the epidemiology of many diseases, chronic inflammation is linked to three out of five deaths worldwide. These include cardiovascular disease, cancer, type 2 diabetes mellitus (T2DM), chronic respiratory diseases like asthma and COPD, Alzheimer's dementia, rheumatoid arthritis (RA), and ankylosing spondylitis (AS). According to prevalence rates of up to 50% among Non-Hispanic Blacks and 35% for systemic inflammation generally, about 60% of individuals in the US have at least one chronic illness, many of which are caused by inflammation. Patients with RA are more likely to have concomitant conditions such as anaemia (up to 49%), hypertension (33%), and an increased risk of CVD, whereas AS is associated with a higher risk of dementia.

The necessity for early management to prevent tissue damage and chronic progression is highlighted by the recognition of inflammation as a complex immunological response to injury or infection. Although NSAIDs provide symptomatic relief, their safe and effective use in the presence of certain comorbidities requires careful consideration [4].

2. Anti-Inflammatory Drugs

NSAIDs are a unique class of substances that can physiologically reduce or eliminate inflammation symptoms, such as fever, edema, redness, and pain brought on by various inflammatory triggers. NSAIDs are drugs that reduce inflammation and are effective in treating fever and pain (see analgesic). Many NSAIDs are available over the counter and are usually used for short periods of time to treat minor discomfort. NSAIDs work by preventing the production of prostaglandins, which are important mediators of pain and inflammation.

The blood vessel wall produces prostaglandins, which have local effects that relax blood vessels and improve blood flow. This mechanism causes inflammation following tissue damage or trauma [5].

2.1. NSAIDs

The pyrazolone scaffold is being used more and more in contemporary medicinal chemistry to create "multi-target ligands" that overcome the safety

concerns of conventional NSAIDs. Designed to fit the larger hydrophobic side pocket containing Valine 523 while being sterically excluded from the narrower, isoleucine-containing COX-1 channel, these novel derivatives are structurally modified with bulky aromatic or sulfonamide groups to achieve selective COX-2 inhibition. These substances frequently have dual COX/LOX inhibitory effects in addition to enzyme selectivity.

This inhibits the prostaglandin and leukotriene pathways, giving it a stronger anti-inflammatory impact. Additionally, by scavenging free radicals, certain pyrazolone derivatives, such as Edaravone, have strong antioxidant effects and lessen the oxidative stress linked to long-term tissue damage. Superior therapeutic effectiveness with a much lower risk of gastrointestinal and renal damage is the goal of this multifaceted pharmacological strategy [6].

2.2. Classification and Limitations of NSAIDs

Pyrazolone-based NSAIDs [Figure 1] are divided into groupings such as 4-aminophenazones (like dipyrone), 3, 5-pyrazolidinediones (like phenylbutazone), and contemporary 5-pyrazolone derivatives (like edaravone), depending mostly on nitrogen placement and substitutions in their five-membered ring. To reduce gastrointestinal and blood-related adverse effects, COX-2 selective modifications have replaced older drugs like propyrazones, which provided potent analgesia but came with hazards. Functionally, they range from non-selective COX inhibitors to advanced COX-2/LOX dual or multi-target ligands with ROS-scavenging, reducing issues like leukotriene shunts and respiratory effects. Beyond only relieving symptoms, this development supports a broader anti-inflammatory effect.

Despite their effectiveness in lowering pain and inflammation, conventional NSAIDs often result in prescription failure because of severe gastrointestinal (GI) toxicity, which includes irritation and the development of ulcers. Non-selective inhibition compromises mucosal integrity by interfering with protective prostaglandins in the stomach lining, which results in these negative consequences.

Because they can increase the risk of heart attack or stroke by altering prostaglandin balance and impairing vascular function, certain traditional NSAIDs also raise cardiovascular concerns that restrict their long-term usage. Systemic adverse effects occur from NSAIDs' blockage of prostaglandin production, which not only reduces inflammation but also compromises vital functions, including blood vessel wall maintenance and local blood flow.

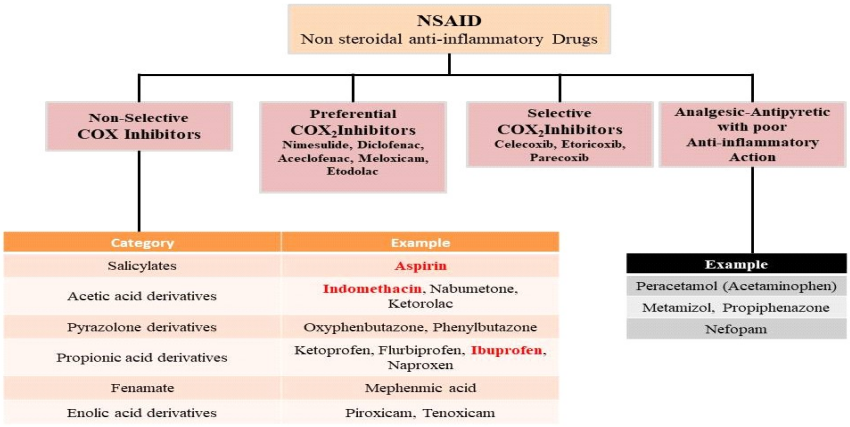


Figure 1: Classification of the NSAIDs

While newer drugs strive for improved discrimination, selectivity concerns make matters worse since classic non-selective inhibitors more easily reach the smaller COX-1 channel (containing isoleucine) than the wider COX-2 pocket, causing GI damage [7].

3. The Pyrazolone Scaffold

The presence of two nearby nitrogen atoms and a keto group inside the ring structure defines pyrazolones, which are five-membered heterocyclic compounds. These substances, which are substantial oxo derivatives of pyrazoles, have historical significance since they served as the foundation for the first synthetic non-opioid painkillers and fever-reducing drugs. Ludwig Knorr, a German scientist, created phenazone (Antipyrine), the first synthetic antipyretic medication, in 1883. The most common of them in medication development and medical research is the 5-pyrazolone isomer. These compounds frequently display prototropic tautomerism, which influences their chemical reactivity by enabling them to exist as various tautomeric forms in solution. The pyrazolone scaffold is being used in pharmaceuticals to make popular medications like Metamizole, edaravone, a neuroprotective drug, and propyphenazone. They are still being studied for a variety of therapeutic actions, such as anticancer, anti-inflammatory, and antioxidant benefits, because of their various chemical characteristics. The pyrazolone ring is a "privileged scaffold" for the creation of multi-target ligands in drug development since it may be modified with different functional groups [8].

3.1. Structural Features and Isomeric Forms

The reactivity of pyrazolone, a five-membered heterocyclic molecule that is generated from pyrazole, is based on two neighbouring nitrogen atoms at positions 1 and 2.

The 3- or 5-position is usually occupied by a defining keto (C=O) group, which permits tautomerism between keto-enol forms that affects its solubility and binding affinity.

The versatile replacement sites at N1, N2, C3, and C4 enable precise chemical alterations to customize pharmacological effectiveness, such as improving ROS scavenging or COX inhibition [Figure 2]. From traditional NSAIDs like phenylbutazone to contemporary variants that target specific inflammatory pathways, these structural components support Pyrazolone's biological diversity.

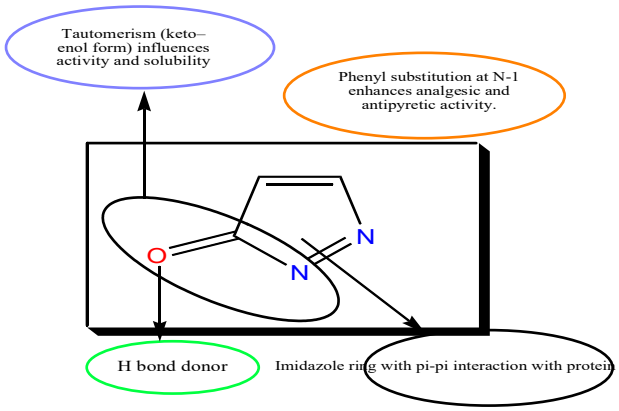


Figure 2: Structure of Pyrazolone and its Structural Activities Relationships

3.1.1 Isomeric Forms (Tautomerism)

Because of tautomerism, which entails the migration of a hydrogen atom and the shifting of double bonds, pyrazolones exist in several isomeric forms.

Three main tautomeric forms are highlighted in the review:

The CH-form (keto form) of pyrazolone is formed when oxygen forms a carbonyl (C=O) group and hydrogen binds to the carbon at position 4. The oxygen transforms into a hydroxyl group (-OH) in the OH-form (enol form), creating a double bond inside the ring; this tautomer is more common in polar protic solvents. The hydrogen atom is bound to one of the nitrogen atoms in the NH-form, changing its reactivity and electrical distribution.

3.1.2 Structure Activity Relationship (SAR)

Biological data indicate that substituents at the C4 position of pyrazolone critically determine potency, with electron-withdrawing groups (EWGs) like methyl sulfonyl (Deriv 1) and Trifluoro (Deriv 2) achieving the highest inhibition rates, exceeding 80% (Table 1). These EWGs enhance ring acidity, promoting stronger binding to protein NH_2 groups and preventing denaturation. Heterocyclic thiophene

in Deriv 3 delivers moderate-to-high activity via sulfur's lipophilicity, aiding membrane stabilization, while Deriv 5's phenolic hydroxy group exerts notable effects at elevated concentrations by neutralizing ROS to curb protein damage.

Table 1: Structure–Activity Relationship (SAR) of Substituents in Pyrazolone Derivatives and Their Impact on Anti-Inflammatory Activity

Substituent Type	Functional Groups	Effect on Activity
Electron-Donating Groups (EDGs)	-OH, $-OCH_3$, $-N(CH_3)_2$	Improved protection performance and anti-inflammatory activity.
Electron-Withdrawing Groups (EWGs)	Chlorine (-Cl), Nitro ($-NO_2$)	Diminished anti-inflammatory action in some models.
Sulfonic Groups	$-SO_2NH_2$ at the 4-position	Enhanced potency and improved selectivity for the COX-2 enzyme.

3.1.3 Impact of Isomerism on Activity

The ability of pyrazolone to switch between these forms is crucial for its biological performance:

i. **Enol Form and Antioxidant Activity:** The OH-form (enol) is noted for its ability to facilitate radical scavenging through the donation of a hydrogen atom, which is essential for its antioxidant properties.

ii. **Binding Affinity:** The specific isomer present can influence how the molecule fits into the active sites of enzymes like COX-2.

iii. **Chemical Synthesis:** Tautomerism allows for diverse reactions, such as the formation of Schiff bases at the C4 position, which are used to create derivatives that better target inflammatory enzymes while reducing gastrointestinal side effects [9].

3.2. Pharmacological Significance

From early synthetic analgesics like Antipyrine and phenylbutazone, which addressed fever and pain, to contemporary multi-target medicines for chronic disorders, including rheumatoid arthritis and autoimmune diseases, the pyrazolone scaffold has advanced to the point where conventional NSAIDs are ineffective. While edaravone exhibits neuroprotective free radical scavenging in ischemia, modern derivatives function as dual COX/5-LOX inhibitors to prevent arachidonic acid shunting toward leukotrienes, decreasing respiratory and stomach side effects. The anti-inflammatory, antioxidant, and antibacterial properties of pyrazolones are enhanced by hybrid structures that contain sulfonamides or flavonoids (Table 2). Green synthesis techniques, including ultrasound and microwave, further improve pharmacokinetics, yield, and purity for increased medication efficacy [10].

Table 2: Major Pharmacological Activities of Pyrazolone Derivatives and Their Therapeutic Significance

Pharmacological Action	Significance
Analgesic	Reduction of pain in acute and sensitized models.
Antipyretic	Effective reduction of fever; foundational to synthetic drug history.
Anti-inflammatory	High inhibition rates in carrageenan-induced edema models.
Antioxidant	Scavenging free radicals to prevent tissue damage and ischemia.

4. Pharmacological Evaluations of Pyrazolone Derivatives

Ampyrone, phenazone, propyphenazone, and other pyrazolone moieties are known to have antibacterial and anti-inflammatory properties [Figure 3, 4, 5]. Another pyrazolone molecule, edaravone, is used to treat myocardial and cerebral ischemia. In recent years, the pyrazolone moiety has demonstrated anticonvulsant, antimycobacterial, anti-inflammatory, antipyretic, anticancer, stomach acid secretion-enhancing, antibacterial, and analgesic properties. Commercial aryl/heteroaryl pyrazolone dyes are also made using pyrazolone as a precursor. Furthermore, pyrazolones with halogen have been found to have fungicidal qualities and to be strong inhibitors of human telomerase. In addition, pyrazolones have immunosuppressive properties and have shown promise in the treatment of HIV, diabetes, and hyperlipidemia.

The pyrazolone chemical phenylbutazone may be used to treat inflammatory conditions such as acute gout and rheumatoid arthritis. Several pyrazolone moieties with heterocyclic rings, such as imidazole, benzimidazole, and benzotriazole groups, were evaluated for their anti-inflammatory qualities. The most promising pyrazolone analogues in terms of their anti-inflammatory properties were those that had benzimidazole groups [11].

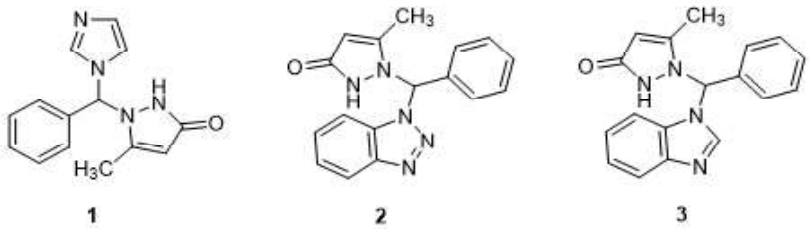
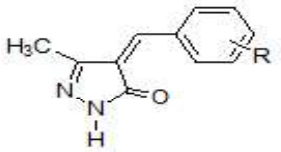


Figure 3: Pyrazole Derivatives (a)

The chemical's anti-inflammatory capabilities, namely the 3-methyl-4-substituted benzylidene-pyrazol-5-one moiety [12], were determined to be important throughout the examination. The analgesic properties of 3-methyl pyrazol-5-one derivatives, including drugs such as diclofenac, ibuprofen, and flurbiprofen, were examined, with most molecules showing significant analgesic effects. Analogues, such as 3-methyl-4-substituted benzylidene-pyrazol-5-one [13], were additionally assessed for their pain-relieving properties and showed significant results.



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R = -N(CH$_3$)$_2$, -OH

Figure 4: Pyrazole derivatives (b)

The anti-inflammatory effects of 4-trifluoroacetyl-1-phenyl-3-methyl pyrazolone [14] and 4-acetyl-1-phenyl-3-methyl pyrazolone (6, HAP) have been shown in rat models to be substantial. Selective inhibition of Phospholipase A_2 is a key strategy in developing effective anti-inflammatory drugs with reduced side effects.

Dipyrone, a potent pyrazolone compound with anti-inflammatory properties, interacts strongly with Phospholipase A_2 (PLA_2) through 3 hydrogen bonds. On the other hand, 1-phenyl-3-methyl-5-pyrazolone (5) is unable to interact with PLA_2 to a significant extent because it creates an intramolecular hydrogen bond. Free radicals are involved in various aspects of inflammation and tissue damage. Edaravone, when administered intrathecal as a free radical scavenger, has demonstrated analgesic effects in models of inflammation-induced acute and sensitized pain [15].

5 **6**

Figure 5: Pyrazole derivatives (c)

4. Mechanism of Anti-Inflammatory Action

By blocking the cyclooxygenase (COX) enzymes, pyrazolone derivatives mainly modulate the arachidonic acid cascade and stop arachidonic acid from being

converted into the prostaglandins that cause inflammation. Inducible during injury or infection, COX-2 produces pro-inflammatory prostaglandins, while COX-1, a constitutive enzyme, maintains gastric mucosal protection and platelet aggregation. Pyrazole's selectivity for COX-2 over COX-1 reduces side effects like GI toxicity. In chronic illnesses, focused inhibition tackles larger inflammatory pathways in addition to reducing symptoms like pain and edema [16].

4.1. COX Inhibition

To prevent arachidonic acid from being converted to prostaglandins, which are responsible for pain, fever, and edema, pyrazolone-based NSAIDs mainly inhibit cyclooxygenase (COX) enzymes. In contrast to typical non-selective medicines, which fit the narrower COX-1 channel (with isoleucine) and cause GI toxicity, they demonstrate isoenzyme selectivity, which separates constitutive COX-1 (gastric protection) from inducible COX-2 (inflammation driver).

In order to reach the bigger COX-2 side pocket (containing valine), modern pyrazolone derivatives include bulky aromatic or sulfonamide (SO_2NH_2) groups, which increase their anti-inflammatory efficacy while reducing stomach injury. Significant COX-2 selectivity is demonstrated by compounds such as 17d and derivatives 10a–10e, which frequently outperform the reference medication Celecoxib [17].

4.2. Dual COX/LOX inhibition

Represents an advanced strategy in pyrazolone derivatives, targeting both cyclooxygenase (COX) and lipoxygenase (LOX) pathways for broader anti-inflammatory effects [Table 3]. Blocking only COX prompts arachidonic acid "shunting" to LOX, overproducing leukotrienes that drive bronchoconstriction and gastric damage. Compounds like 4a exhibit strong COX-2 selectivity and 5-LOX inhibition, yielding high potency, positive stomach safety, and reduced ulcerogenic risk by averting leukotriene-mediated injury [18].

Table 3: Molecular Targets of Pyrazolone Derivatives in the Arachidonic Acid Pathway and Associated Clinical Outcomes

Target	Effect of Inhibition	Clinical Outcome
COX-1	Reduced Prostaglandins (Gastric)	Potential for GI ulcers/toxicity.
COX-2	Reduced Prostaglandins (Inflammatory)	Relief from pain, swelling, and fever.
5-LOX	Reduced Leukotrienes	Prevention of gastric damage and respiratory side effects.
Dual COX/LOX	Combined reduction of mediators	Enhanced efficacy with superior safety.

4.3 Anti-Inflammatory Activity (In-vitro and In-vivo Studies)

Many compounds are examined for inhibiting COX-1, COX-2, and 5-LOX activities in in-vitro experiments for pyrazolone derivatives, which focus on enzyme inhibition and cellular protection. For example, compound 17d fared better than celecoxib in COX-2 inhibition. Along with assessments of protein denaturation and heat-induced hemolysis to gauge membrane stability, these investigations also measure decreases in the synthesis of prostaglandin E2 (PGE2) in blood, a crucial mediator of pain and inflammation. The wide anti-inflammatory potential of some conjugates, such as compound 37, is demonstrated by their efficient reduction of pro-inflammatory cytokines like TNF-á and IL-6 [19]

4.4 Antioxidant Activity

Evaluations like the DPPH assay are used to determine the radical scavenging potential of these derivatives, which helps mitigate tissue damage caused by free radicals during inflammation [Figure 6].

The in-vitro anti-inflammatory efficacy of a pyrazolone moiety chain was tested using celecoxib as a reference medication. Among the tested compounds, Compound demonstrated the highest potency, showing a significant 75% inhibition of inflammation. Pharmacological screening showed a range of anti-inflammatory effects for these compounds, with obstruction percentages varying from 16.67% to 76% after three hours. A comparison was made with the reference medicine celecoxib, which showed an inhibition of 83.34% during the same time period. Compound showed Anti-inflammatory action equivalent to celecoxib, while compounds displayed anti-inflammatory effects, although they were less potent than both Compound and celecoxib [20].

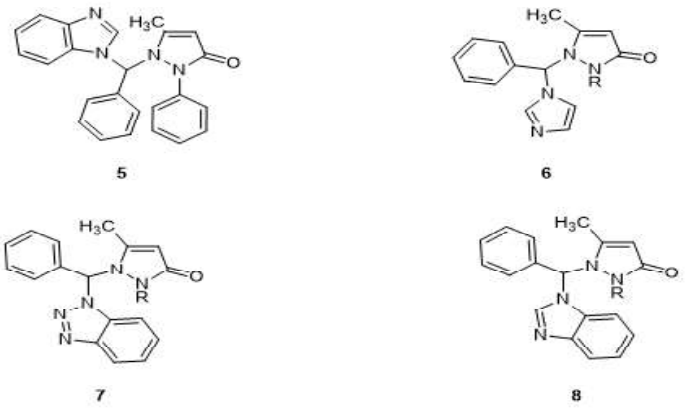

Figure 6: Pyrazole derivatives (d)

4.5. Additional Pharmacological Activities

The COX-2 enzyme is the target of the majority of new pyrazolone derivatives. They lessen pain and edema by preventing the creation of prostaglandins. N-substituted pyrazolones were synthesized by Maria et al. (2022) and were shown to be more GI safe than aspirin. Anti-Mycobacterial: By preventing the formation of cell walls, derivatives have demonstrated effectiveness against strains of Mycobacterium tuberculosis H37Rv. Anti-Cancer: By inhibiting Aurora kinase, pyrazolones stop the cell cycle in a variety of cancer cell types. Antiviral: Recently investigated as possible inhibitors of the major protease [21].

4.5.1. Analgesic Activity

Using models such as the Swiss Albino mice's acetic acid-induced writhing test to measure pain alleviation, pyrazolone derivatives have strong analgesic and anti-inflammatory properties. In models of acute and sensitive pain, these substances have a calming effect; they are frequently compared to industry standards like diclofenac, ibuprofen, and flurbiprofen.

Compound 23, which matched indomethacin's efficacy with superior GI tolerance; compound 38d, which is very effective for both pain and inflammation; compound 39b, which stands out for maximal analgesic and anti-inflammatory strength in its series; and 3-methyl-4-substituted benzylidene-pyrazol-5-one, which demonstrated significant pain-relieving potency, are notable analogues [22].

4.5.2. Antipyretic Activity

Building on the heritage of earlier synthetic medications like Antipyrine and amino phenazone, the antipyretic efficacy of pyrazolone derivatives continues to be a major pharmacological focus. Recent studies have shown that structural changes, including adding methyl groups to intracycle nitrogen atoms or fusing an amino pyrimidine core (compounds 43a–43j), greatly increase the molecules' ability to lower fever.

According to studies of the structure-activity relationship (SAR), these antipyretic qualities are further enhanced by adding electron-donating groups (EDGs), such as "OH or "OCH3, at the C-6 position of the amino pyrimidine ring. While some contemporary derivatives have a well-balanced profile of analgesic, antipyretic, and anti-inflammatory effects, well-known drugs like Metamizole (Dipyrone) are known for their strong ability to reduce temperature and relieve pain, but their anti-inflammatory properties are noticeably lacking. Because of this variation, distinct pyrazolone derivatives that are suited to particular therapeutic requirements where conventional "triple threat" NSAIDs may be less effective or inappropriate might be developed [22].

4.5.3. Antioxidant Activity

Furthermore, in addition to their anti-inflammatory properties, pyrazolone derivatives are an important new field of study. By neutralizing reactive oxygen species (ROS) before they worsen cellular damage, these derivatives serve as protective agents since oxidative stress and free radicals are major causes of tissue damage and chronic inflammation.

The DPPH (2, 2-diphenyl-1-picrylhydrazyl) test is frequently used to assess the radical scavenging mechanism, which is the main mechanism for this action. The molecule's tautomeric state has a major impact on this process; in particular, the OH-form (enol), which is common in polar protic solvents, makes it easier for unstable radicals to donate a hydrogen atom. This structural flexibility allows the pyrazolone scaffold to effectively "quench" oxidative triggers that would otherwise lead to protein and lipid degradation.

The most well-known clinical example of its effectiveness is Edaravone, a strong free radical scavenger that is used to lessen the devastation caused by myocardial and cerebral ischemia. After a heart attack or stroke, the oxidative damage cascade is avoided by eliminating free radicals during reperfusion. This emphasizes how pyrazolones can be used as neuroprotective and cardio-protective agents in addition to managing symptoms.

Pyrazolones are presently considered by modern medicinal chemistry to be multi-target ligands with a twofold therapeutic benefit: they simultaneously inhibit inflammatory enzymes and give systemic antioxidant protection. This dual effect is essential for lowering pain receptor sensitivity, which is frequently increased in the milieu of inflammatory tissues by oxidative stress.

Researchers are combining flavonoids and the pyrazolone ring to create new hybrids that will further increase these advantages. These hybrids create a synergistic impact that expands their therapeutic applicability by combining the natural antioxidant power of flavonoids with the synthetic potency of pyrazolones. These cutting-edge compounds are intended to be more successful in the treatment of complicated conditions where oxidative stress is a major clinical characteristic, such as rheumatoid arthritis and neurological illnesses [21].

5. Emerging Trends and Future Perspectives

Research on pyrazolones is evolving away from single-target compounds and toward complex hybrid structures, or "multi-target" treatment. Researchers are producing conjugates with great antioxidant capacity and precise COX-2 targeting by combining the pyrazolone scaffold with powerful moieties like flavonoids or

sulfonamide groups. Together with metal-chelating derivatives, these hybrids provide a potential avenue for the treatment of some malignancies and refractory inflammatory disorders that do not improve with conventional monotherapy.

The development of Dual COX/5-LOX inhibitors is a key objective for the upcoming generation of these medications. The goal of these potential treatments is to stop the "shunting" effect, which occurs when arachidonic acid is redirected to create toxic leukotrienes, by concurrently inhibiting the cyclooxygenase and lipoxygenase pathways. It is anticipated that this dual-pathway inhibition would offer a far better safety profile, successfully avoiding the stomach damage and asthma-like symptoms that commonly lead to the failure of traditional NSAID therapy in chronic patients [23].

Drug manufacture is moving toward Green Chemistry to enhance sustainability and purity in order to support these pharmacological breakthroughs. Higher yields of active isomers and quicker reaction times are made possible by methods like ultrasound-induced condensation and microwave-assisted synthesis. Instead of using hazardous organic alternatives, scientists are using water-based ethanol solvents to create more powerful derivatives, such as compound 21d, which have better pharmacokinetics and fewer chemical contaminants.

In the end, the new viewpoint sees pyrazolone derivatives as all-encompassing multi-target ligands. The four pillars of inflammatory care, reducing inflammation, decreasing pain, lowering fever, and scavenging free radicals to avoid long-term tissue damage, could be managed by a single medication based on this architecture. These potential derivatives have the potential to bypass the gastrointestinal and cardiovascular risks that now limit the use of conventional painkillers by designing compounds that precisely match the bigger side pocket of the COX-2 enzyme [23].

6. Conclusion

The exploration of the pyrazolone scaffold represents a significant advancement in medicinal chemistry, transitioning from its 19th-century use in antipyretics like Antipyrine to becoming a highly valued "privileged scaffold." With the global increase in chronic inflammatory diseases, the drawbacks of traditional NSAIDs, such as gastrointestinal toxicity and cardiovascular risks, have driven the development of more selective, multi-target therapies.

Contemporary research focuses on the structural differences between COX isoforms to improve drug safety. By designing compounds that specifically fit the larger Valine-containing pocket of COX-2, while avoiding the narrower Isoleucine channel of COX-1, scientists have created agents that better protect the gastric

mucosa. Additionally, the development of Dual COX/5-LOX inhibitors marks a noteworthy progression in drug design, offering enhanced therapeutic potential. These agents prevent the "shunting" of arachidonic acid toward leukotrienes, thereby reducing respiratory and gastric side effects that frequently contribute to clinical prescription failures. Beyond enzyme inhibition, pyrazolones serve as versatile multi-target ligands addressing the interplay between inflammation and oxidative stress. By incorporating flavonoid moieties or acting as radical scavengers (such as Edaravone), these compounds help mitigate oxidative damage that drives disease progression. This comprehensive profile combining analgesic, antipyretic, anti-inflammatory, and antioxidant properties provides a holistic therapeutic approach for complex conditions like rheumatoid arthritis.

The advancement of these compounds is strongly supported by Green Chemistry principles. Techniques like microwave-assisted synthesis and ultrasound-induced condensation in eco-friendly solvents have optimized purity, yield, and pharmacokinetic profiles. These methods enable faster onset of action and greater potency while upholding sustainability standards. Ultimately, the pyrazolone scaffold's distinctive tautomeric flexibility and chemical reactivity secure its ongoing prominence in pharmaceutical innovation, delivering robust treatments for chronic inflammatory diseases globally [26].

References

1. Serhan, C. N., et al. (2018). Resolving inflammation: Dual anti-inflammatory and pro-resolution lipid mediators. *Nature Reviews Immunology, 18*(12), 751–766.
2. Chen, M., & Xu, H. (2015). Para inflammation, chronic inflammation, and age-related macular degeneration. *Journal of Leukocyte Biology, 98*(5), 713–725.
3. Kumar, V., Abbas, A. K., & Aster, J. C. (2020). *Robbins & Cotran pathologic basis of disease* (10th ed.). Elsevier.
4. Alghamdi, M., Somaily, M. Y., Alemam, S., Majadah, S., Hassan, A. A. H., Meshary, A. A., Alasmri, S. A. A., Ali, M. S., Alsubaie, A. A., & Miskeen, E. (2024). Prevalence and comorbidities among individuals with rheumatoid arthritis in the Saudi Arabian context. *Cureus, 16*(2). https://doi.org/10.7759/cureus.53992
5. Amanullah, M. S., Shivamurthy, M. C., & Gupta, A. K. (2023). Nonsteroidal anti-inflammatory drugs (NSAIDs). *StatPearls*. https://www.ncbi.nlm.nih.gov/books/NBK547742/

6. Bansal, R., & Sharma, P. K. (2021). Pyrazolone derivatives as a versatile scaffold for various biological activities: A review. *Journal of Molecular Structure, 1245*, 131065. https://doi.org/10.1016/j.molstruc.2021.131065
7. Zhao, Z., et al. (2020). Review of antipyrine analogs and biological activity enhancement.
8. Chauhan, P., Mahajan, S., & Enders, D. (2015). Asymmetric synthesis of pyrazoles and pyrazolones employing the reactivity of pyrazolin-5-one derivatives. *Chemical Communications, 51*(65), 12890–12907. https://doi.org/10.1039/c5cc04930j
9. Gurupadaiah, B. M., et al. (2023). Synthesis and biological evaluation of pyrazolone derivatives as selective COX-2 inhibitors and antioxidants. *Medicinal Chemistry Research, 32*, 442–456. https://doi.org/10.1007/s00044-023-03012-4
10. Abbady, M., & Youssef, M. (2014). Synthesis and biological activity of some new pyridines, pyrans, and indazoles containing pyrazolone moiety. *Medicinal Chemistry Research, 23*(7), 3558–3568.
11. Abd-Ella, A., Metwally, S., Abd Ul-Malik, M., El-Ossaily, Y., Abd Elrazek, F., & Aref, S. (2022). A review on recent advances for the synthesis of bioactive pyrazolinone and pyrazolidinedione derivatives. *Current Chemistry Letters, 11*(2), 157–172.
12. Abdelgawad, M., Labib, M., & Abdel-Latif, M. (2017). Pyrazole-hydrazone derivatives as anti-inflammatory agents: Design, synthesis, biological evaluation, COX-1,2/5-LOX inhibition and docking study. *Bioorganic Chemistry, 74*, 212–220.
13. Abdelgawad, M., Labib, M., Ali, W., Kamel, G., Azouz, A., & El-Nahass, E. (2018). Design, synthesis, analgesic, and anti-inflammatory activity of novel pyrazolones possessing aminosulfonyl pharmacophore as inhibitors of COX-2/5-LOX enzymes: Histopathological and docking studies. *Bioorganic Chemistry, 78*, 103–114.
14. Adhikari, S., Singh, M., Sharma, P., & Arora, S. (2021). Pyrazolones as a potential anticancer scaffold: Recent trends and future perspectives. *Journal of Applied Pharmaceutical Science, 11*(1), 26–37.
15. Abd-Ella, A., et al. (2022). Synthesis and anti-inflammatory evaluation of 4-prenyl-1,2-diphenyl-3,5-pyrazolidinedione.

16. Ricciotti, E., & FitzGerald, G. A. (2011). Prostaglandins and inflammation. *Arteriosclerosis, Thrombosis, and Vascular Biology, 31*(5), 986–1000. https://doi.org/10.1161/ATVBAHA.110.207449
17. Zhao, Z., et al. (2020). Pyrazolone structural motif in medicinal chemistry: Retrospect and prospect. *European Journal of Medicinal Chemistry, 186*, 111893. https://doi.org/10.1016/j.ejmech.2019.111893
18. Antre, R. V., et al. (2011). Antipyretic and analgesic effects of amino pyrimidine-pyrazolone skeletal structures.
19. Mehlotra, R. K. (2023). Aurora kinase inhibitors as anticancer agents: Recent advances in the pyrazolone series. *Expert Opinion on Therapeutic Patents, 33*(4), 281–295.
20. Siddiqui, Z. N., & Farooq, F. (2020). Synthesis and biological screening of some new benzylidene-pyrazol-5-one derivatives. *Medicinal Chemistry Research, 29*(4), 621–634.
21. Chowdhury, M. A., et al. (2020). Current status of pyrazolone derivatives in medicinal chemistry: A review. *European Journal of Medicinal Chemistry, 186*, 111917. https://doi.org/10.1016/j.ejmech.2019.111917
22. Maria, K. H., et al. (2022). Design, synthesis, and biological evaluation of some new N-substituted pyrazolones as potent anti-inflammatory agents with improved GI safety. *Bioorganic Chemistry, 120*, 105615. https://doi.org/10.1016/j.bioorg.2022.105615
23. Watanabe, K., et al. (2018). Edaravone as a free radical scavenger: Therapeutic potential and molecular mechanism in neuroprotection. *Free Radical Research, 52*(11–12), 1215–1230. https://doi.org/10.1080/10715762.2018.1505105