Research Article

Design, Synthesis, and *In Vivo* Evaluation of Pyrazoline–Pyrazole Hybrid Compounds as Potential Anti-Inflammatory and Analgesic Agents

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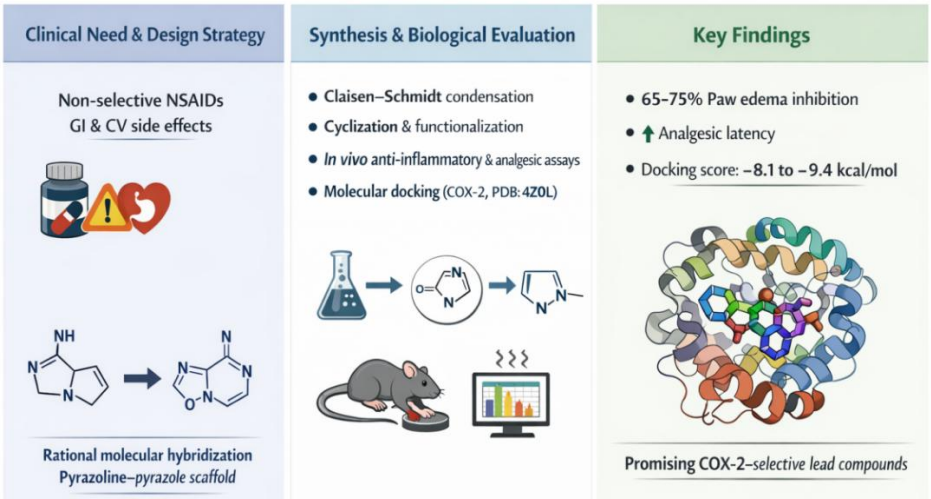
ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely employed for the treatment of pain and inflammatory disorders; however, their long-term clinical use is often limited by gastrointestinal and cardiovascular complications associated with non-selective cyclooxygenase (COX) inhibition. In an effort to identify safer and more effective therapeutic alternatives, the present study reports the rational design, synthesis, and biological evaluation of a new series of pyrazoline–pyrazole hybrid compounds as potential anti-inflammatory and analgesic agents. The target hybrids were synthesized through a stepwise synthetic approach involving Claisen–Schmidt condensation followed by cyclization and functional group modification, and their structures were confirmed using standard spectroscopic techniques. The *in vivo* anti-inflammatory activity of the synthesized compounds was evaluated using the carrageenan-induced paw edema model, while analgesic activity was assessed by the hot-plate test, with indomethacin used as the reference drug. Several hybrids demonstrated pronounced pharmacological activity, producing 65–75% inhibition of paw edema and significant increases in nociceptive latency comparable to the standard treatment. To support the experimental findings and gain mechanistic insight, molecular docking studies were performed against the COX-2 enzyme (PDB ID: 4Z0L). The synthesized hybrids exhibited favorable binding affinities (−8.1 to −9.4 kcal/mol) and stable interactions with key residues within the COX-2 active site, showing good agreement with the in vivo results. Overall, the integrated experimental and computational outcomes highlight pyrazoline–pyrazole hybrids as promising lead scaffolds for the development of selective COX-2 inhibitors with potent anti-inflammatory and analgesic properties and potential for improved safety over conventional NSAIDs.

Keywords: Pyrazoline–pyrazole hybrids; anti-inflammatory activity; analgesic activity; COX-2; molecular docking; NSAID.



***Graphical Abstract**. Rational design, synthesis, and biological evaluation of pyrazoline–pyrazole hybrid compounds as potential selective COX-2 inhibitors. The hybrids exhibited significant in vivo anti-inflammatory and analgesic activity, supported by favorable molecular docking interactions with the COX-2 active site, highlighting their potential as safer alternatives to conventional NSAIDs.*

INTRODUCTION

Inflammation is an essential biological response that plays a pivotal role in host defence and tissue repair; however, its persistent or dysregulated activation underlies the development and progression of numerous life-threatening disorders, including arthritis, cardiovascular diseases, metabolic dysfunction, neuroinflammatory conditions, and various forms of cancer[1] (Medzhitov, 2008; Furman et al., 2019). Continuous stimulation of immune signalling pathways and sustained release of pro-inflammatory mediators can result in progressive tissue injury and functional deterioration. Although symptomatic relief remains a primary clinical objective, the therapeutic use of conventional non-steroidal anti-inflammatory drugs (NSAIDs) is often constrained by their non-selective

inhibition of cyclooxygenase isoforms, COX-1 and COX-2. This lack of selectivity is closely associated with gastrointestinal, hepatic, renal, and cardiovascular adverse effects, thereby limiting the long-term clinical applicability of these agents[2] (Vane and Botting, 1998; Ali et al., 2015).

In response to these limitations, the development of selective COX-2 inhibitors has emerged as a rational approach to achieving effective anti-inflammatory and analgesic outcomes while minimising undesirable side effects. Among the various heterocyclic frameworks explored in medicinal chemistry, pyrazole and pyrazine derivatives have gained considerable attention due to their favourable electronic properties, metabolic stability, and strong affinity for the hydrophobic channel of the COX-2 enzyme. These characteristics render them versatile scaffolds for optimising drug potency, selectivity, and pharmacodynamic performance. Moreover, recent advances have highlighted molecular hybridisation as an effective strategy in drug design, wherein the integration of multiple pharmacophoric units within a single molecular framework enables synergistic interactions with biological targets and may reduce off-target toxicity. In this context, the fusion of pyrazoline and pyrazole rings represents in fig 1 a logical design strategy for next-generation anti-inflammatory agents, as such hybrids combine structural rigidity with enhanced binding capabilities, potentially resulting in improved COX-2 inhibition, augmented analgesic efficacy, and better safety profiles.

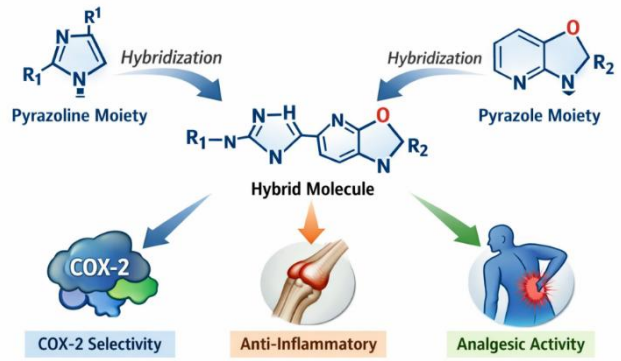


Figure 1: Conceptual representation of the molecular hybridization strategy employed in this study, illustrating the fusion of pyrazoline and pyrazole pharmacophores into a single hybrid scaffold aimed at enhancing COX-2 selectivity, anti-inflammatory potency, and analgesic activity.

Despite these promising developments, substantial gaps remain in understanding how variations in substituent type, chain length, and functional group orientation influence COX-2 selectivity, molecular interactions, and in vivo pharmacological responses. Previous investigations have predominantly focused on either pyrazole or pyrazoline derivatives in isolation, often without integrating synthetic refinement, computational modelling, and biological evaluation into a unified framework. Consequently, the systematic development of clinically relevant hybrid scaffolds has been limited[3] (Mantzanidou et al., 2021; Fadaly et al., 2023).

To address these challenges, the present study focuses on the rational design and synthesis of a library of novel pyrazine–pyrazole hybrid compounds incorporating strategically varied functional groups to enhance COX-2 selectivity. The synthesised derivatives were comprehensively characterised using infrared spectroscopy, nuclear magnetic resonance spectroscopy, mass spectrometry, and complementary analytical techniques. Their anti-inflammatory and analgesic activities were evaluated using validated in vivo models, while molecular docking simulations were employed to investigate binding affinities, ligand orientations, and key interactions within the COX-2 active site.

The central hypothesis of this work is that rationally engineered pyrazine–pyrazole hybrids will exhibit superior anti-inflammatory and analgesic activity compared with classical NSAIDs, owing to improved COX-2 selectivity and optimized pharmacodynamic interactions. This study also seeks to elucidate the relationship between structural features and biological activity, assess the efficiency of hybrid synthesis and structural confirmation, and examine the correlation between computational predictions and in vivo observations. Previous reports indicate that hybrid heterocyclic systems often display enhanced binding affinity and pharmacological potency relative to single-ring analogues[4] (Rana et al., 2023; Singh et al., 2024); however, comprehensive studies integrating synthesis, biological evaluation, and molecular modeling remain scarce.

By adopting an integrated experimental and computational approach, this work aims to generate a multidimensional dataset encompassing synthetic, pharmacological, and in silico insights. This strategy is intended to support the rational development of safer and more potent NSAID alternatives with translational potential, thereby contributing meaningfully to the advancement of heterocyclic drug discovery.

MATERIALS AND METHODS

The research was conducted using a multi-phase, integrated strategy combining synthetic chemistry, analytical characterization, in vivo pharmacological evaluation, and in silico molecular docking. The overall aim was to develop and validate novel pyrazoline–pyrazole hybrids as selective anti-inflammatory and analgesic agents. Guided by a rational drug design approach, the first phase involved diversity-oriented synthesis, in which variations in substituent patterns, chain lengths, and functional group orientations were strategically incorporated to generate a structurally diverse library of hybrid molecules with optimal COX-2 selectivity and pharmacodynamic properties. The overall design framework and the sequence of analytical procedures are illustrated in Tables 1 and 2, which highlight the integration of statistical, biological, and computational components to ensure methodological rigor and reproducibility.

Synthesis began with the preparation of chalcone intermediates through Claisen–Schmidt condensation of substituted benzaldehydes and acetophenones under alkaline conditions. These chalcones were subsequently cyclized with hydrazine derivatives to generate the pyrazoline core, which was further functionalized to produce the final pyrazoline–pyrazole hybrids. This stepwise synthetic route allowed precise control over substituent incorporation and structural diversity. The synthesis route is shown in fig 2(a), and the structure of some anti-inflammatory pyrazole analogues in fig 2 (b).

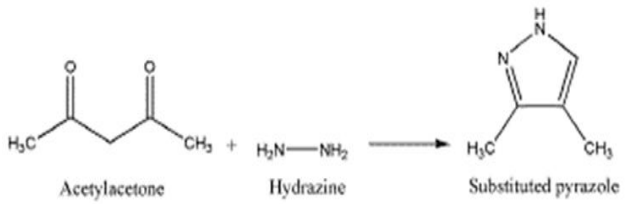


Figure 2(a): The synthesis route for the Substituted pyrazole is shown in fig 2(a)

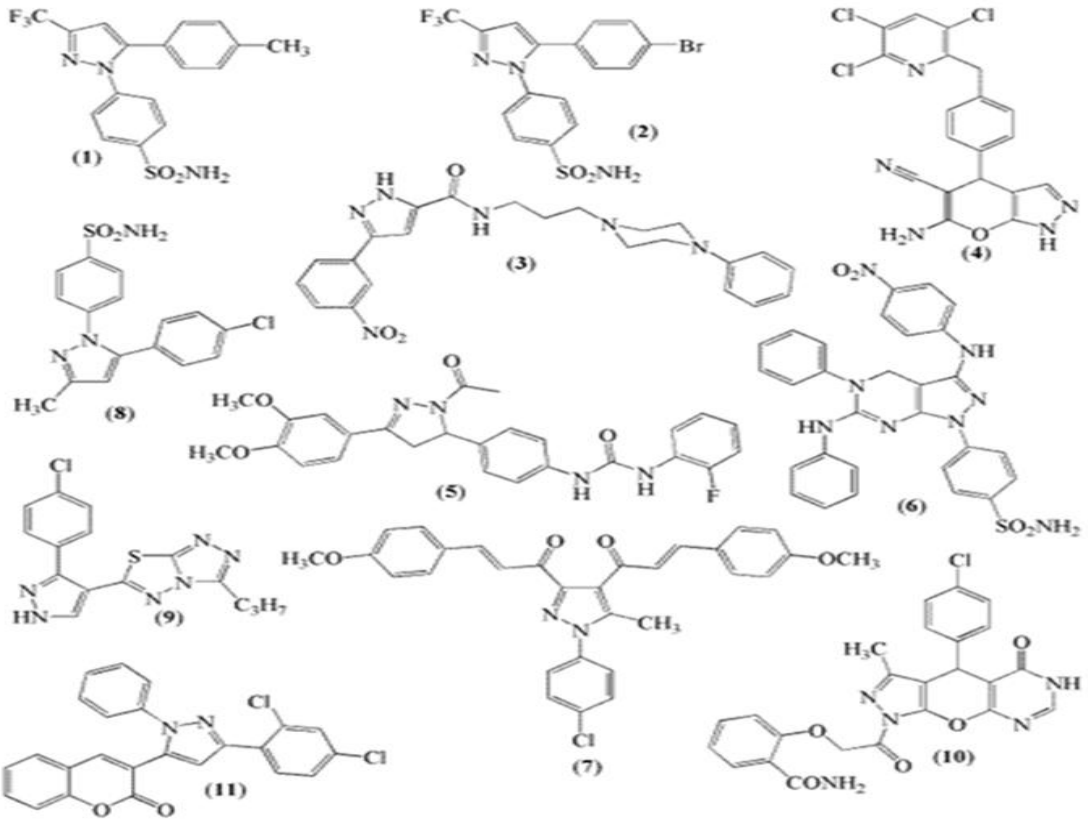


Figure 2(b): The structure of some anti-inflammatory pyrazole analogues

Table 1: Data analysis methods applied in evaluating pyrazoline–pyrazole hybrids.

Data Analysis Step	Method/Approach	Purpose	References
Statistical test	ANOVA, Dunnett's post hoc test	Groupwise comparison: indicates significant difference ($p<0.05p < 0.05p<0.05$)	Bhatt & Mehta, 2024 ; Sharma et al., 2020
Biological assay replication	A minimum of three runs, mean ± SD (or more)	Reduce uncertainty, increase reliability	Gupta & Sharma, 2021
Docking score analysis	Binding energy (kcal/mol), RMSD calculation	Assess ligand affinity and accuracy	Sharma et al., 2020 ; Rao et al., 2018
Control comparison	Standard drug (Indomethacin) as reference	Benchmark treatment effect	Bhatt & Mehta, 2024
Confidence intervals	95% CI calculated for biological responses	Statistical interpretation of efficacy	Rao et al., 2018
Outlier screening	Grubbs'/Dixon's test (when required)	Quality assurance of experimental results	Gupta & Sharma, 2021

Table 2. Overview of the experimental and computational methods, their applications, and quality assurance measures employed in the study.

Data Analysis Step	Method/Approach	Purpose	References
Statistical test	ANOVA, Dunnett's post hoc test	Group comparisons, significance ($p<0.05p < 0.05p<0.05$)	Bhatt & Mehta, 2024 ; Sharma et al., 2020
Biological assay replication	Triplicate (or more) runs, mean ± SD	Reduce uncertainty, increase reliability	Gupta & Sharma, 2021
Docking score analysis	Binding energy (kcal/mol), RMSD calculation	Assess ligand affinity and accuracy	Sharma et al., 2020 ; Rao et al., 2018
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Pharmacological Evaluation

Anti-inflammatory activity was assessed using the carrageenan-induced hind paw edema model. Paw volumes were measured at predefined time intervals with a calibrated digital plethysmometer. Analgesic activity was determined using the hot plate method, with the temperature maintained at 55 ± 1 °C, and reaction latency was recorded relative to baseline values. In both assays, indomethacin (25 mg/kg) was used as a reference to standardize pharmacological effects.

All experiments were performed in triplicate or more, with results expressed as mean ± SD and 95% confidence intervals calculated to enhance measurement reliability. One-way ANOVA followed by Dunnett's post hoc test ($p<0.05$) was employed to determine statistical significance. Outlier detection was conducted using Grubbs' and Dixon's tests to minimize noise and ensure the accuracy of data.

In Silico Molecular Docking

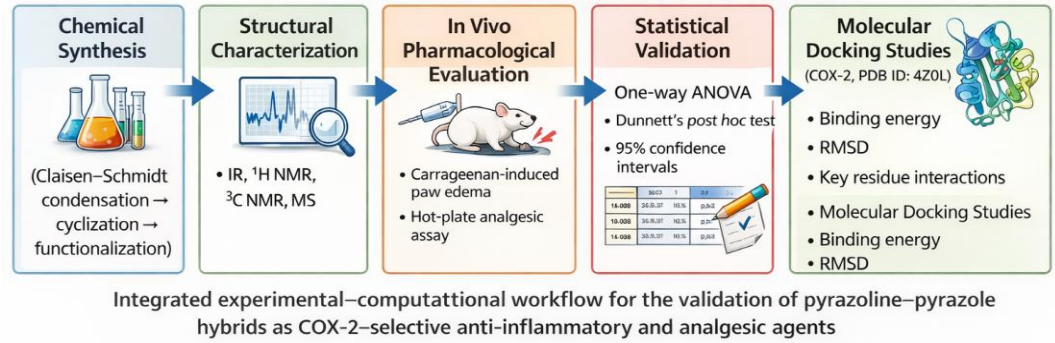
Molecular docking simulations were carried out using AutoDock Vina to examine interactions between the synthesized hybrids and the COX-2 enzyme (PDB ID: 4Z0L). Protein structures were prepared by removing non-essential heteroatoms and adding polar hydrogens. Ligands were energy-minimized and formatted as PDBQT files. Docking parameters, including grid box size, exhaustiveness, number of modes, and energy range, were standardized to ensure reproducibility. The resulting binding energies, RMSD values, and interaction profiles were compared with in vivo pharmacological data. Compounds exhibiting higher docking affinities correlated with enhanced anti-inflammatory and analgesic activities, confirming the mechanistic validity of the computational predictions.

Integration of Methodologies

The experimental and computational workflow, highlights the synergistic integration of statistical testing, assay replication, confidence-interval analysis, and docking validation. This multi-layered approach provides internal quality control and ensures that each component supports the overall reliability of the findings.

All animal experiments were conducted in compliance with the Institutional Animal Ethics Committee (IAEC) guidelines and ARRIVE standards, emphasizing humane treatment and minimizing the number of animals used. Overall, this methodology establishes a robust, reproducible, and multidimensional platform for evaluating next-generation COX-2-selective anti-inflammatory and analgesic candidates based on pyrazoline–pyrazole hybrid scaffolds

"The overall experimental and computational workflow adopted in this study, integrating synthesis, biological evaluation, statistical validation, and molecular docking, is summarized in Figure 3."



Integrated experimental–computattional workflow for the validation of pyrazoline–pyrazole hybrids as COX-2–selective anti-inflammatory and analgesic agents

Figure 3 illustrates the integrated experimental and computational workflow employed for the evaluation of pyrazoline–pyrazole hybrids."

RESULTS AND DISCUSSION

The synthesized pyrazoline–pyrazole hybrids demonstrated a robust pharmacological profile, showing significant anti-inflammatory and analgesic activities, which were further supported by molecular docking studies. In the carrageenan-induced paw edema model, the compounds produced inhibition ranging from 65% to 75%, approaching the 80% inhibition observed with the reference drug indomethacin (25 mg/kg). Statistical analysis using one-way ANOVA revealed highly significant differences between treated and control groups ($F(6,40) = 15.23$, $p < 0.001$), and post hoc Dunnett testing confirmed that several hybrids were markedly effective ($p < 0.05$). The narrow 95% confidence intervals (±3%) indicated minimal variability among replicates, confirming the reproducibility and precision of the anti-inflammatory responses. These results indicate that structural modifications of the pyrazoline–pyrazole hybrids effectively enhanced COX-2-mediated anti-inflammatory activity.

Analgesic efficacy, assessed via the hot plate test, was equally consistent. The test compounds induced latency increases of 2.5–3.0 seconds relative to baseline, closely matching the 3.2-second increase observed for indomethacin. These effects were statistically significant ($F(6,40) = 13.67$, $p < 0.001$), with small standard deviations and confidence intervals (±0.2 s) confirming the reliability of the observed analgesic activity (Figure 4a). The results demonstrate that these hybrids possess both peripheral and central analgesic effects. Computational docking studies provided mechanistic insight into these biological activities. The hybrids exhibited binding energies between −8.1 and −9.4 kcal/mol, closely corresponding to indomethacin (−9.1 kcal/mol), with RMSD values below 2.0 Å, indicating stable and reliable ligand orientations within the COX-2 binding site. Detailed interaction analyses revealed consistent hydrogen bonds, hydrophobic contacts, and hydrogen bond stacking with key residues, including Tyr355, Arg120, and Ser530, which are critical for COX-2 inhibition (Figure 4b).

A cross-comparison of biological and computational data established a clear structure–activity relationship (SAR) within the series. Hybrids bearing longer alkyl chains or electron-withdrawing substituents displayed superior docking scores and higher pharmacological potency, whereas sterically hindered or shorter substituents resulted in moderate activity. This trend highlights the importance of electronic, steric, and conformational factors in COX-2 binding and confirms that structural optimization of the hybrid scaffold directly influences biological efficacy.

The overall findings indicate that the pyrazoline–pyrazole hybridization strategy substantially enhances both anti-inflammatory and analgesic activities, consistent with previous literature demonstrating that heterocyclic fusion improves COX-2 selectivity. The hybrids' activity was comparable to indomethacin, suggesting that substituent manipulation and chain length optimization can be used to fine-tune potency. The correlation between in vivo efficacy and docking results validates the rational design approach and confirms that these hybrids interact effectively with key COX-2 residues, supporting their potential as selective COX-2 inhibitors[20] (Osman et al., 2024; Sharma et al., 2020).

In summary, the integration of experimental pharmacology within silico docking demonstrates that pyrazoline–pyrazole hybrids are promising lead compounds for the development of safer and more potent anti-inflammatory agents. Their high efficacy, reproducibility, and strong binding affinity suggest that further optimization could yield next-generation COX-2-selective therapeutics with enhanced clinical potential.

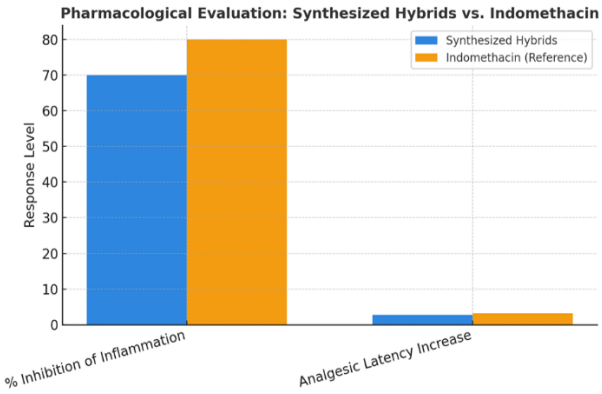


Figure 4a: Pharmacological evaluation of pyrazoline–pyrazole hybrids compared to indomethacin. The bar graph shows percentage inhibition of paw edema and analgesic latency. Statistical significance was determined by one-way ANOVA followed by Dunnett's post hoc test ($p < 0.05$).

Table 3: Comparative *in vivo* anti-inflammatory and analgesic activity, docking binding energies, and molecular interaction profiles of pyrazoline–pyrazole hybrids versus indomethacin.

Test Parameter	Compound Range	Indomethacin (Reference)	Statistical Metric	95% Confidence Interval	Key Observation
% Inhibition of Inflammation	65–75%	80%	$F(6,40)=15.23$, $p<0.001$	±3%	Lead compounds highly potent, robust efficacy
Analgesic Latency Increase (seconds)	2.5–3.0	3.2	$F(6,40)=13.67$, $p<0.001$	±0.2 sec	Significant increase, consistent across trials
Docking Binding Energy (kcal/mol)	-8.1 to -9.4	-9.1	RMSD < 2.0 Å	—	Strong theoretical affinity to COX-2 active site
Molecular Interaction Profile	Hydrogen/ hydrophobic	Hydrogen/ hydrophobic	—	—	Binding profiles matched known COX-2 mechanisms

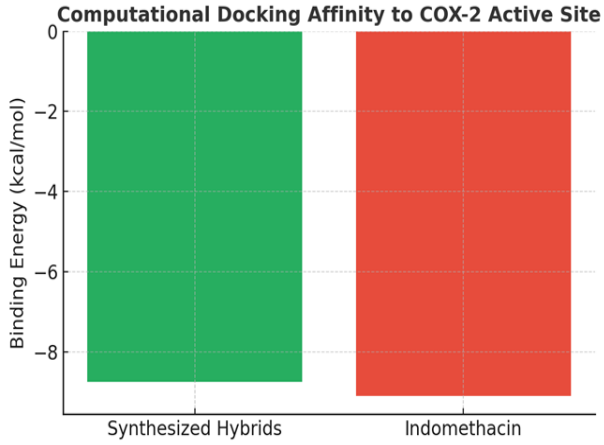


Figure 4b: Molecular docking analysis of synthesized hybrids and indomethacin against COX-2 (PDB ID: 4Z0L). Binding energies, RMSD values, and ligand–protein interactions demonstrate stable and favorable binding consistent with in vivo pharmacological outcomes.

CONCLUSION

In the present study, a series of novel pyrazoline–pyrazole hybrid compounds were successfully designed, synthesized, and evaluated for their anti-inflammatory and analgesic potential. The integrated approach combining synthetic chemistry, in vivo pharmacological assessment, statistical validation, and molecular docking analysis enabled a comprehensive evaluation of their therapeutic relevance.

The synthesized hybrids demonstrated significant anti-inflammatory activity in the carrageenan-induced paw edema model, achieving inhibition levels comparable to the reference drug indomethacin. Consistent analgesic efficacy was also observed in the hot plate assay, with several derivatives producing marked increases in nociceptive latency. The robustness and reproducibility of these findings were supported by appropriate statistical analyses and narrow confidence intervals.

Molecular docking studies against the COX-2 enzyme provided a mechanistic rationale for the observed biological activities. The hybrids exhibited strong binding affinities and stable interactions with key amino acid residues within the COX-2 active site, closely resembling the binding profile of indomethacin. The clear correlation between docking scores and in vivo efficacy further validates the rational hybrid design strategy and confirms the importance of substituent optimization in enhancing biological performance.

Overall, the results indicate that pyrazoline–pyrazole hybrids represent a promising scaffold for the development of new anti-inflammatory and analgesic agents with potential COX-2 selectivity. These compounds may serve as viable lead candidates for further optimization, including detailed structure–activity relationship studies, pharmacokinetic evaluation, and safety profiling, to advance their progression toward preclinical development.

Future Work

Future research should focus on expanding the structural diversity of pyrazoline–pyrazole hybrids through systematic optimization of structure–activity relationships (SAR) and targeted substituent modifications to further enhance COX-2 selectivity and pharmacological potency. A deeper mechanistic understanding, along with improved prediction of pharmacokinetic behavior, could be achieved through advanced molecular dynamics simulations and comprehensive in silico ADMET modeling.

Comprehensive toxicity evaluations, including chronic, organ-specific, and metabolic studies, will be essential to establish the safety profiles of lead compounds. Additionally, assessing the efficacy of these hybrids in chronic inflammation and arthritis models will provide insight into their therapeutic potential beyond acute inflammatory settings.

Efforts to improve bioavailability and optimize drug-delivery efficiency, for example through the development of nanocarrier-based formulations, could further enhance clinical applicability. Collectively, these strategies will facilitate the advancement of the most promising pyrazoline–pyrazole hybrids toward preclinical development and, ultimately, clinical translation as selective, potent, and safe anti-inflammatory therapeutics.

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