REVIEW
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Recent Advances in the Synthesis of Selective COX-2 Inhibitors: A Scaffold-Based Structure–Activity Relationship Review

ABSTRACT

Cyclooxygenase-2 (COX-2) is an inducible enzyme that plays a central role in inflammation and has long been recognized as a compelling target for anti-inflammatory therapy. The introduction of selective COX-2 inhibitors marked a major advance, offering improved gastrointestinal safety over traditional nonsteroidal anti-inflammatory drugs. However, concerns about increased cardiovascular risk with prolonged use, which is largely linked to the suppression of prostacyclin synthesis, have underscored the need for safer and more balanced therapeutic strategies. In response, substantial research efforts have focused on designing and synthesizing new COX-2 inhibitors with enhanced selectivity, optimized pharmacological profiles, and reduced adverse effects. This review provides a critical and up-to-date overview of recent advances in COX-2-targeted anti-inflammatory agents, emphasizing key chemical scaffolds, structure–activity relationship insights, and biological evaluation data. By bringing these findings together, this study aims to offer practical guidance and inspiration for medicinal and organic chemists working toward the development of next-generation anti-inflammatory therapies.

Keywords: Cyclooxygenase-2 structure, anti-inflammatory agents, selective inhibition, chemical scaffolds, activity relationship

INTRODUCTION

Inflammation is a tightly regulated defense mechanism that allows the body to respond to infection, chemical insults, and physical injury.[1] At the molecular level, this response is driven largely by cyclooxygenase (COX) enzymes, which convert arachidonic acid into prostaglandins, the key signaling molecules that orchestrate inflammatory processes.[2] In its acute and well-controlled form, inflammation is beneficial, facilitating pathogen clearance and tissue repair.[3] However, pathological consequences arise when this response becomes chronic or dysregulated. Persistent inflammation is now recognized as a major contributor to a wide spectrum of diseases, including asthma, arthritis, cancer, cardiovascular and cerebrovascular disorders, and neurodegenerative conditions.[4,5]

Nonsteroidal anti-inflammatory drugs (NSAIDs) remain a cornerstone in the management of inflammatory disorders because they inhibit cyclooxygenase (COX) enzymes, specifically COX-1 and COX-2.[6-8] The 2 isoforms, however, serve distinct physiological roles. Cyclooxygenase-2 is constitutively expressed and maintains homeostatic functions such as gastric mucosal protection, platelet aggregation, and renal blood flow. Consequently, inhibition of COX-1 is largely responsible for the gastrointestinal and renal adverse effects associated with conventional NSAIDs.[9] In contrast, COX-2 is an inducible isoenzyme, upregulated in response to inflammatory stimuli such as cytokines, mitogens, and endotoxins.[10] It drives the production of pro-inflammatory prostaglandins and has also been implicated in tumor progression, including breast, prostate, and lung cancers.[11-13] These differences provide a clear rationale for selectively targeting COX-2 to preserve anti-inflammatory efficacy while minimizing COX-1–related toxicity.[14,15]

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The clinical introduction of COX-2-selective inhibitors, most notably celecoxib and rofecoxib (Figure 1), was initially considered a major therapeutic milestone in anti-inflammatory therapy. Although these agents significantly reduced the incidence of gastrointestinal ulceration compared with traditional NSAIDs, their long-term safety soon came under scrutiny.[16] The suppression of prostacyclin (PGI_2), a cardioprotective and vasodilatory prostaglandin, without a concomitant effect on prothrombotic thromboxane A_2 (TXA_2), was linked to an increased risk of adverse cardiovascular events.[17,18] Ultimately, rofecoxib and valdecoxib were withdrawn from the market due to cardiovascular concerns.[19] These developments underscored a critical challenge in COX-2-targeted therapy: achieving optimal selectivity without compromising cardiovascular safety. Consequently, the development of next-generation COX-2 inhibitors requires not only improved anti-inflammatory potency and gastrointestinal tolerability, but also careful consideration of long-term cardiovascular safety and the clinical implications of excessive COX-2 selectivity.

Over the past decade, advances in medicinal chemistry, structural biology, and molecular modeling have reinvigorated efforts to develop COX-2 inhibitors with improved safety profiles. A broad array of novel chemical scaffolds has been explored with the aim of enhancing selectivity, optimizing pharmacokinetic properties, and reducing adverse effects. While most recently reported studies primarily focus on enzymatic potency and selectivity, several investigations have also incorporated preliminary safety and developability assessments, including cytotoxicity, ulcerogenicity, and gastrointestinal tolerability evaluations. Although several reviews have addressed specific classes of COX-2 inhibitors, comparative structure-oriented discussions focusing on recently developed heterocyclic scaffolds and their structure–activity relationships (SARs) remain relatively limited. In this context, the present review provides a focused overview of recently developed COX-2 inhibitors reported primarily from 2019 onward, emphasizing their chemical frameworks, biological performance, and SAR insights (Figure 2). The inclusion of studies was based on the availability of experimental COX-2 inhibitory activity together with supporting biological, mechanistic, or computational evaluation data. Consequently, the number of studies discussed for each scaffold reflects the current distribution of recently published COX-2 inhibitor research across different heterocyclic classes rather than an intentional emphasis on specific scaffold types. For clarity and consistency, compound numbering throughout this review follows a unified system defined by the authors and does not necessarily reflect the numbering used in the original publications.

PYRAZOLE-BASED INHIBITORS

The pyrazole ring is widely regarded as a privileged scaffold in the design of COX-2 inhibitors, owing to its favorable binding characteristics and structural adaptability. Its continued prominence is reflected in recent comprehensive reviews emphasizing the therapeutic relevance of pyrazole derivatives.[20,21] The clinical success of celecoxib, which incorporates a pyrazole core, further substantiates the value of this heterocycle in achieving selective COX-2 inhibition.[22] Building on this structural framework, recent efforts have focused on strategic modifications of the pyrazole nucleus to enhance anti-inflammatory efficacy while maintaining an acceptable safety profile. In this regard, Abdellatif et al[23] reported a series of thiohydantoin-linked 1,3,4-trisubstituted pyrazole derivatives (Figure 3) and evaluated their COX inhibitory and anti-inflammatory properties. In vitro assays showed a clear preference for COX-2 inhibition, with half-maximal inhibitory concentration (IC_{50}) values ranging from the submicromolar to low micromolar levels (0.56-1.72 μM), whereas COX-1 inhibition was comparatively weaker (4.22-9.87 μM). As a result, selectivity indices ranged from 5.34 to 10.72, with several derivatives demonstrating selectivity comparable to, or in some cases exceeding, that of celecoxib. Structure–activity relationship analysis suggested a positional effect of substituents on COX-2 selectivity. Chlorine substitution at position X (**1f**) was associated with enhanced selectivity, whereas methoxy substitution

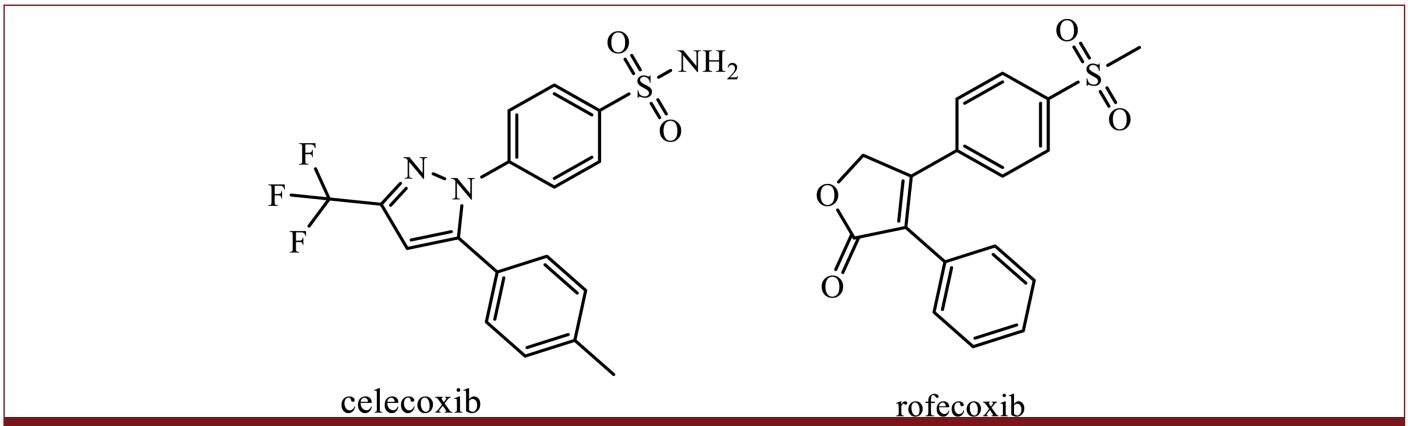


Figure 1. Chemical structures of celecoxib and rofecoxib, 2 early selective cyclooxygenase-2 inhibitors approved for clinical use.

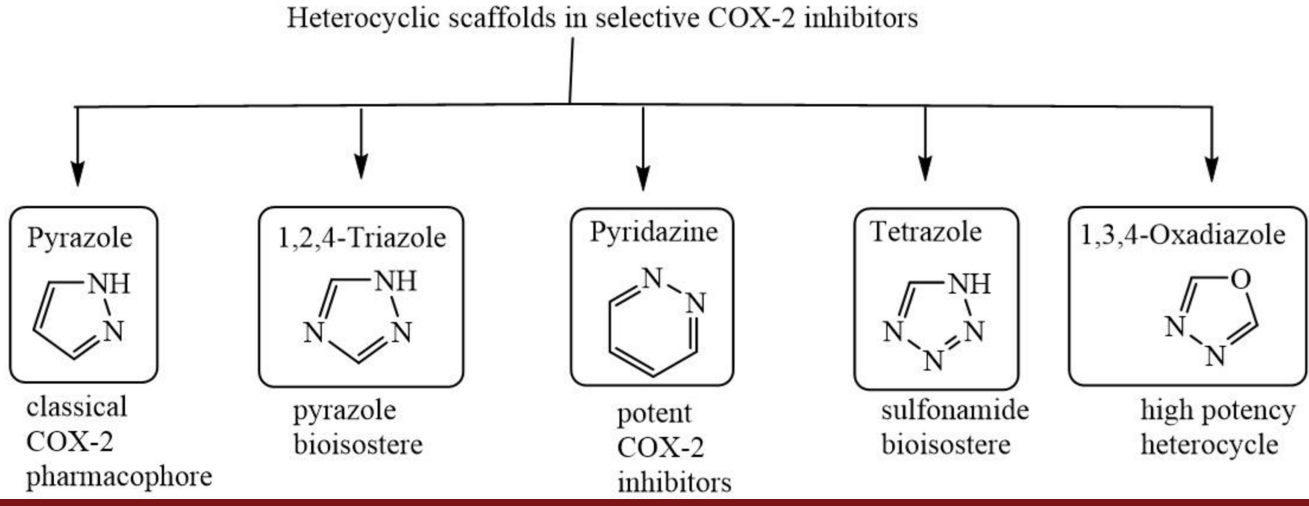
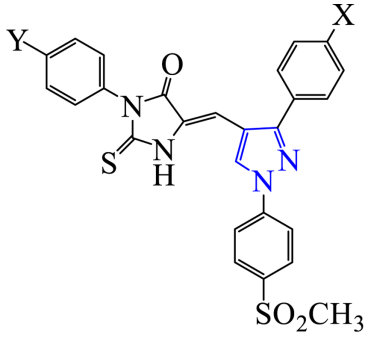


Figure 2. Representative heterocyclic scaffolds used in the design of selective cyclooxygenase-2 inhibitors.

at position Y alone (**1k**) resulted in comparatively reduced selectivity. Interestingly, the simultaneous presence of chlorine at position X and a methoxy group at position Y (**1e**) yielded a compound that maintained strong inhibitory activity together with pronounced COX-2 preference, indicating a cooperative substituent effect. The in vivo anti-inflammatory evaluation using a carrageenan-induced paw edema model further supported the therapeutic potential of these derivatives. Several compounds showed efficacy similar to celecoxib, particularly at early time points. Notably, methoxy-substituted analogs (**1a**, **1c**, **1e**, **1g**, **1i**, and **1k**) consistently exhibited enhanced anti-inflammatory responses relative to their unsubstituted counterparts, reinforcing the contribution of methoxy substitution to in vivo efficacy. Evaluation of ulcerogenic liability demonstrated improved gastric tolerability for the most active derivatives. All tested compounds (**1a**, **1b**, **1c**, **1i**, and **1k**) produced markedly lower ulcer indices (2.64-3.87) than ibuprofen (20.25) and showed ulcerogenicity comparable to celecoxib (2.99). Among them, compound **1i** displayed the lowest ulcer index (2.64), suggesting a gastrointestinal profile at least comparable to, and potentially slightly improved over, celecoxib. Collectively, these findings underscore the continued relevance of the pyrazole scaffold and highlight the importance of rational substituent positioning in balancing potency, selectivity, and safety.

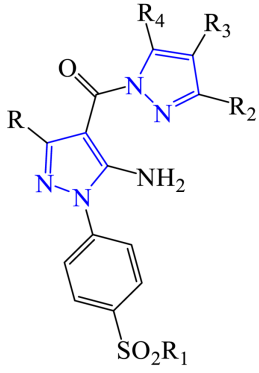
In a subsequent study, Abdellatif et al[24] designed and synthesized a new series of pyrazole derivatives incorporating an amino/methanesulfonyl pharmacophore to improve COX-2 preference (Figure 4). The synthesized compounds (**2a-2c**, **3a-3c**, and **4a-4f**) exhibited limited COX-1 inhibition while demonstrating moderate-to-strong COX-2 inhibitory activity. The calculated selectivity indices ranged from 56.6 to 417.6, reflecting substantial isozyme discrimination.



1a-1l

	X	Y
1a	NO_2	OCH_3
1b	NO_2	H
1c	Br	OCH_3
1d	Br	H
1e	Cl	OCH_3
1f	Cl	H
1g	$NHSO_2$	OCH_3
1h	$NHSO_2$	H
1i	OCH_3	OCH_3
1j	OCH_3	H
1k	H	OCH_3
1l	H	H

Figure 3. Chemical structures of thiohydantoin-linked 1,3,4-trisubstituted pyrazole derivatives reported by Abdellatif et al.[23]



	R	R_1	R_2	R_3	R_4
2a	H	CH_3	CH_3	H	CH_3
2b	CH_3	CH_3	CH_3	H	CH_3
2c	CH_3	NH_2	CH_3	H	CH_3
3a	H	CH_3	SCH_3	CN	NH_2
3b	CH_3	CH_3	SCH_3	CN	NH_2
3c	CH_3	NH_2	SCH_3	CN	NH_2
4a	H	CH_3	H	$COOC_2H_5$	NH_2
4b	H	CH_3	CH_3	$COOC_2H_5$	NH_2
4c	CH_3	CH_3	H	$COOC_2H_5$	NH_2
4d	CH_3	NH_2	H	$COOC_2H_5$	NH_2
4e	CH_3	CH_3	CH_3	H	NH_2
4f	CH_3	NH_2	CH_3	$COOC_2H_5$	NH_2

Figure 4. Chemical structures of pyrazole derivatives reported by Abdellatif et al.[24]

Notably, compounds **3a** and **4d** showed selectivity indices exceeding that of celecoxib.

In vivo anti-inflammatory activity was further evaluated using the carrageenan-induced rat paw edema model. Several derivatives demonstrated pronounced edema inhibition at 3 hours and 5 hours post-carrageenan administration. In particular, compounds **2a**, **2c**, **3a**, **3c**, and **4a-4e** showed superior anti-inflammatory effects, with edema inhibition percentages reaching 74%-88% at 3 hours and 78.9%-96% at 5 hours, compared to celecoxib (60.6% and 82.8%, respectively). Notably, the most potent in vitro COX-2 inhibitors generally maintained strong in vivo performance, suggesting a positive correlation between enzymatic selectivity and anti-inflammatory efficacy.

Evaluation of ulcerogenic liability following repeated oral administration (50 mg/kg for 3 consecutive days) indicated substantially reduced gastric injury for the most active derivatives. The tested compounds exhibited markedly lower ulcer indices (0.7-2.0) compared to indomethacin (21.3) and were also lower than celecoxib (2.7). Among them, compound **3a** displayed the lowest ulcer index (0.7), suggesting superior gastric tolerability, potentially associated with its pronounced COX-2 Selectivity Index (SI = 353.8), although further long-term cardiovascular safety evaluation remains necessary. Histopathological examination further substantiated these findings. Whereas indomethacin induced severe glandular and non-glandular gastric damage characterized by necrosis, ulceration, congestion, and leukocytic infiltration, compounds **3a** and **4a** were associated predominantly with mild degenerative changes and minimal inflammatory infiltration, with largely preserved mucosal architecture. In contrast, derivatives such as **3c** and **2a** produced moderate-to-severe histological alterations, consistent with their comparatively higher ulcer indices. Overall, the histological observations aligned well with the quantitative ulcer index data. To provide mechanistic insight into the observed selectivity and biological performance, molecular docking studies were conducted within the COX-2 active site (Protein Data Bank: 3LN1). All synthesized compounds displayed favorable binding energies (−12.52 to −15.00 kcal/mol), exceeding that of celecoxib (−12.96 kcal/mol). The sulfonyl moiety, present either as amino- or methyl-sulfonyl substitution, consistently engaged in hydrogen-bond interactions with key active-site residues such as Arg499, Gln178, Phe504, Tyr341, and Ser516. Notably, the top-performing compounds (**3a** and **4a-4e**) formed multiple hydrogen-bond interactions (1.94-3.23 Å) and exhibited the most favorable docking scores (−14.37 to −15.00 kcal/mol), supporting the critical role of the sulfonyl pharmacophore in stabilizing COX-2 binding and enhancing selectivity.

Hassan et al[25] reported the synthesis of several series of novel pyrazole derivatives bearing a benzenesulfonamide pharmacophore, which were designed as dual inhibitors of cyclooxygenase and prostaglandin E_2 biosynthesis pathways (Figure 5). In vitro evaluation yielded evidence that all synthesized compounds exhibited nanomolar inhibition of both COX isoforms, favoring COX-2 over COX-1. Notably, compounds **5a**, **6b**, **7a**, **8b**, and **8e** showed strong COX-2 inhibition together with selectivity indices comparable to or exceeding that of celecoxib.

The most active derivatives (**5a**, **6b**, **7a**, **8b**, and **8e**) were further evaluated in vivo using the carrageenan-induced

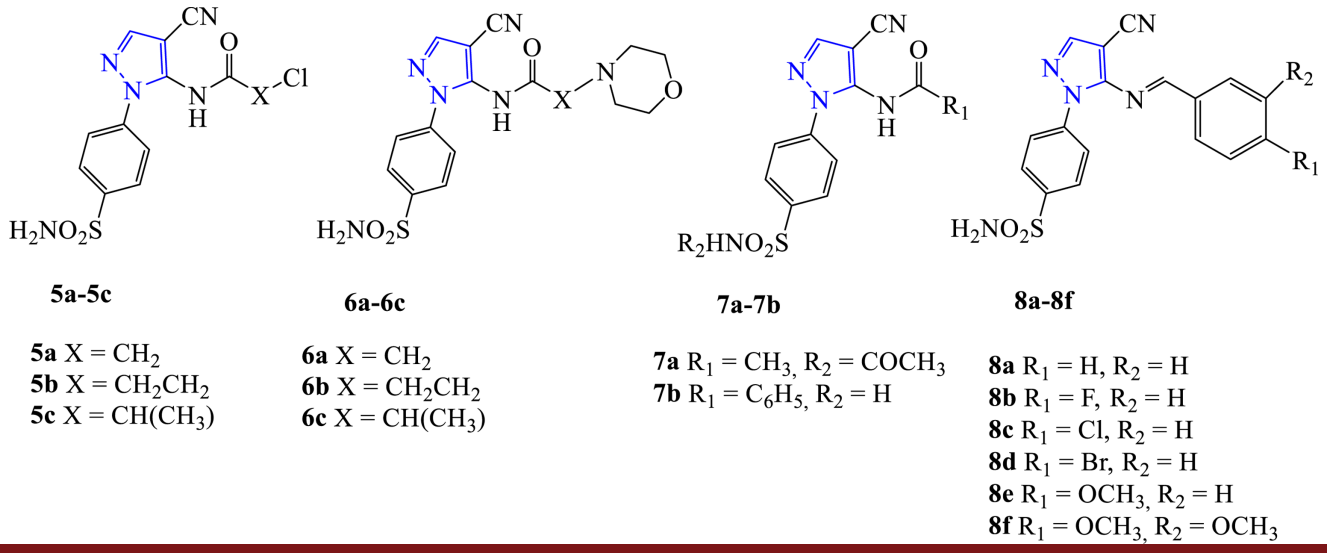


Figure 5. Representative chemical structures of pyrazole derivatives reported by Hassan et al[25] as dual cyclooxygenase-2 and mPGES-1 inhibitors.

rat paw edema model, where several compounds produced anti-inflammatory responses superior to celecoxib at specific time points. Beyond COX-2 inhibition, these compounds markedly decreased plasma prostaglandin E_2 (PGE_2) levels, confirming effective suppression of downstream prostaglandin-mediated inflammatory pathways. Notably, selected derivatives preferentially inhibited inducible microsomal prostaglandin E_2 synthase-1 (mPGES-1) over the cytosolic isoform. This indicates a dual mechanism of action that may confer improved safety profiles. Computational analyses rationalized the experimental SAR observations. The sulfonamide moiety of the active compounds occupied the COX-2 secondary binding pocket and formed key interactions with residues associated with COX-2 selectivity, including Arg513 and Ser530. Collectively, these findings support the concept that rational incorporation of sulfonamide functionalities into the pyrazole scaffold affords multifunctional anti-inflammatory agents targeting both COX-2 and PGE_2 biosynthesis.

Assali et al[26] reported diaryl-based pyrazole and triazole derivatives as COX-2 inhibitors, identifying sulfonamide and sulfone substitutions as key determinants of enzyme selectivity (Figure 6). Several compounds achieved nanomolar-level COX-2 inhibition, and triazole derivatives bearing an ethylene spacer linked to the phenyl moiety via an ester bond (–$COOCH_2CH_2$–) showed improved selectivity by accessing the COX-2 secondary pocket. Docking studies corroborated the experimental SAR trends, indicating well-oriented interactions with residues characteristic of COX-2 inhibition.

Overall, the pyrazole scaffold continues to represent a privileged structure for selective COX-2 inhibition. Across different substitution patterns, the presence of a sulfonamide or sulfone moiety consistently improves COX-2 preference by enabling access to the COX-2 secondary binding pocket. Electron-donating substituents such as methoxy groups frequently enhance anti-inflammatory activity, whereas appropriate spatial orientation of diaryl systems appears critical for optimal enzyme binding. These findings collectively reinforce the importance of maintaining a diaryl heterocyclic core combined with a para-sulfonamide pharmacophore for promoting strong isoform discrimination.

TRIAZOLE-BASED INHIBITORS

Song et al[27] designed a series of celecoxib-inspired isosteric derivatives in which the pyrazole core was replaced by a 1,2,4-triazole scaffold bearing a carboxylic acid moiety, with the aim of improving isoform discrimination while minimizing gastric adverse effects. A series of 24 derivatives was synthesized (Figure 7) and subjected to comprehensive in vitro, in vivo, and in silico evaluation.

Initial cytotoxicity screening in RAW 264.7 macrophages revealed that most compounds were well tolerated, exhibiting negligible cytotoxicity even at high concentrations, thereby enabling subsequent anti-inflammatory assessment under non-toxic conditions. Given the central role of nitric oxide (NO) in inflammatory signaling, the compounds were evaluated for their ability to inhibit lipopolysaccharide (LPS)-induced NO production. Most derivatives demonstrated measurable NO suppression, and preliminary SAR analysis indicated that the electronic nature and positional arrangement of the substituents on the aromatic ring strongly influenced the activity. In general, electron-withdrawing substituents and para-substitution conferred enhanced activity. Among the series, compound **12l**, bearing a para-iodophenyl group, emerged as the most promising candidate, exhibiting NO inhibition approaching that of celecoxib. Further enzymatic studies revealed that compound **12l** displayed potent COX-2 inhibition with

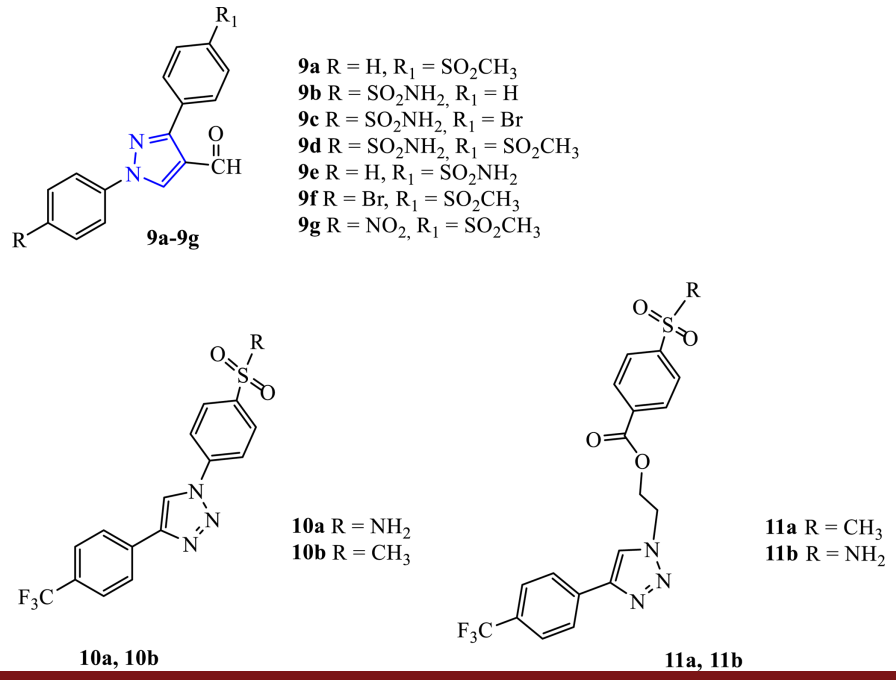
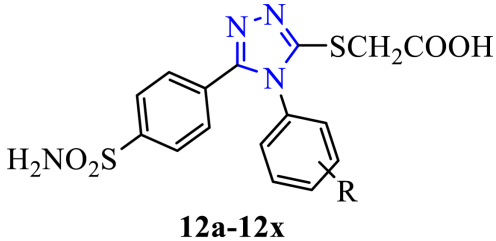


Figure 6. Diaryl-based pyrazole and triazole derivatives reported by Assali et al[26] as selective cyclooxygenase-2 inhibitors.

high selectivity over COX-1, surpassing celecoxib in terms of selectivity index. This enhanced selectivity profile was accompanied by effective suppression of COX-2 expression and downstream PGE_2 production in both LPS-stimulated macrophages and inflamed mouse ear tissue. Consistent with these findings, compound **12l** significantly attenuated inflammation in a 12-O-tetradecanoylphorbol-13-acetate–induced mouse ear edema model. Importantly, ulcerogenic liability studies demonstrated that compound **12l** induced minimal gastric damage, comparable to celecoxib and markedly lower than that of indomethacin, emphasizing its improved gastrointestinal safety profile. Molecular docking and molecular dynamics simulations were consistent with the experimental observations, showing stable binding of compound **12l** within the COX-2 active site through hydrogen-bond interactions involving the sulfonamide and triazole moieties, further stabilized by the arylacetic acid group. Collectively, this study shows that replacement of the pyrazole core with a 1,2,4-triazole scaffold, combined with strategic incorporation of a carboxylic acid functionality, represents an effective strategy for the development of COX-2–preferential inhibitors with improved anti-inflammatory efficacy and reduced gastrointestinal risk. Together with the negligible in vitro cytotoxicity observed for most derivatives, these findings support the favorable developability characteristics of this scaffold.



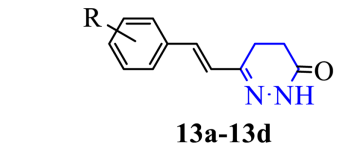
12a R = 2-F	**12g** R = 2-Br	**12m** R = 2-NO_2	**12s** R = 2-CH_3
12b R = 3-F	**12h** R = 3-Br	**12n** R = 3-NO_2	**12t** R = 3-CH_3
12c R = 4-F	**12i** R = 4-Br	**12o** R = 4-NO_2	**12u** R = 4-CH_3
12d R = 2-Cl	**12j** R = 2-I	**12p** R = 2-CF_3	**12v** R = 2-OCH_3
12e R = 3-Cl	**12k** R = 3-I	**12q** R = 3-CF_3	**12w** R = 3-OCH_3
12f R = 4-Cl	**12l** R = 4-I	**12r** R = 4-CF_3	**12x** R = 4-OCH_3

Figure 7. Chemical structures of 3,4,5-trisubstituted 1,2,4-triazoles reported by Song et al.[27]

From a structural and SAR perspective, the 1,2,4-triazole scaffold emerges as a promising bioisosteric alternative to the pyrazole core in selective COX-2 inhibitor design. The presence of a para-electron-withdrawing substituent enhances activity, while incorporation of a carboxylic acid functionality appears to improve both binding stability and gastrointestinal safety. Preservation of a diaryl heterocyclic framework and a sulfonamide pharmacophore remains essential for optimal interaction with the COX-2 secondary pocket. Although recent studies are limited, triazole-based derivatives represent a rational and underexplored direction for future COX-2 inhibitor development.

PYRIDAZINE-BASED INHIBITORS

Ewieda et al[28] synthesized 5 different scaffolds of pyridazine derivatives as COX-2 inhibitors, including dihydropyridazinone (**13a**-**13d**), pyridazinone with substituted benzyl moiety at position-4 (**14a**-**14f**), *N*-substituted pyridazinone (**15a**-**15c**), 3-chloro pyridazine (**16a**-**16c**), and 3-arylamino pyridazine derivatives (**17a**-**17c**) (Figure 8). Most of the evaluated compounds exhibited high COX-2 inhibitory activity, with selectivity indices exceeding that of indomethacin. Notably, compounds **15c** (R = OCH_3) and **17b** (R = OCH_3, R_1 = CH_3) displayed IC_{50} values of 0.26 and 0.18 μM, respectively, and **17b** was identified as the most selective derivative. The anti-inflammatory potential of **17b** was further supported by in vivo studies, demonstrating efficacy comparable to indomethacin, without gastrointestinal toxicity. Molecular docking studies showed that **17b** fits well within the COX-2 active site and interacts favorably with His90 in the secondary pocket. These results support the pyridazine scaffold, particularly the **17b** derivative, as a

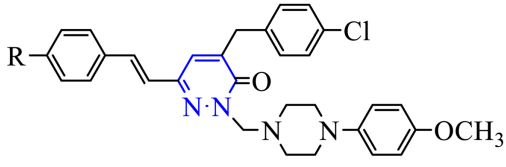


13a-13d

13a R = 4-Cl
13b R = 4-OH
13c R = 4-OCH_3
13d R = 3,4-$(OCH_3)_2$

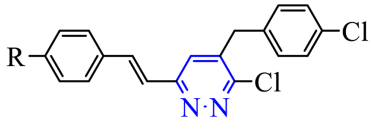
14a-14f

14a R= 4-Cl, R_1 = Cl
14b R = 4-OH, R_1 = Cl
14c R = 4-OH, R_1 = OCH_3
14d R = 4-OCH_3, R_1 = Cl
14e R = 4-OCH_3, R_1 = OCH_3
14f R = 3,4-$(OCH_3)_2$, R_1 = Cl

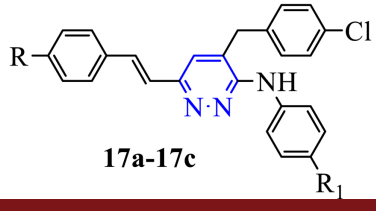


15a-15c

15a, **16a** R = Cl
15b, **16b** R= OH
15c, **16c** R = OCH_3



16a-16c



17a-17c

17a R = OH, R_1 = CH_3
17b R = OCH_3, R_1 = CH_3
17c R = OCH_3, R_1 = C_2H_5

Figure 8. Pyridazine-based cyclooxygenase-2 inhibitors synthesized by Ewieda et al.[28]

promising lead for the design of safe and effective selective COX-2 inhibitors.

Hassan et al[29] synthesized 3 sets of pyridazinone derivatives (**18a**-**18d**, **19a**, **19b**, and **20a**-**20f**) and evaluated their in vitro inhibitory activity against COX-1 and COX-2, with indomethacin and celecoxib as reference controls (Supplementary Figure 1). Among the tested derivatives, **20a** (R = Cl, R1 = Br) and **20f** (R = R1 = OCH_3) exhibited the most potent COX-2 inhibition, with IC_{50} values of 0.77 and 1.89 μM and selectivity indices of 16.70 and 13.38, respectively, whereas indomethacin and celecoxib showed IC_{50}/SI values of 0.42 μM/0.50 and 0.35 μM/37.03. Structure–activity relationship analysis of the pyridazinone derivatives indicated that the introduction of a $-OCH_2COOC_2H_5$ group at position-4 of the phenyl ring significantly enhanced COX-2 inhibition and selectivity. In contrast, substitution with 4-chloro-, 4-methoxy-, or 3,4-dimethoxyphenyl groups at the same position was unfavorable for COX-2 activity. Furthermore, conversion of ester moieties to hydrazide derivatives improved COX-2 inhibition, while selectivity remained largely unchanged. The promising in vitro profile of **20a** and **20f** was further corroborated in vivo using a carrageenan-induced paw edema model in rats, where both compounds significantly reduced inflammation and provided substantial gastroprotective effects, preserving gastric mucosa by 99.77% and 83.08%, respectively.

Ahmed et al[30] reported the design and synthesis of several series of pyridazine derivatives, including dihydropyridazinones (**21a-21g**), pyridazinthiones (**22a, 22b**, **23a,** and **23b**), and substituted pyridazinones (**24a-24f**), incorporating a phenylsulfonamide pharmacophore to enhance COX-2 selectivity (Figure 9). In vitro enzymatic assays revealed that all synthesized compounds exhibited substantial COX-2 inhibitory activity with IC_{50} values in the nanomolar range and selectivity indices superior to indomethacin. Among them, compounds **21d**, **21g**, and **23a** demonstrated greater potency than celecoxib, with compound **21g** emerging as the most selective derivative (SI ≈ 11). Structure–activity relationship analysis indicated that substitution at position-6 of the pyridazinone ring played a crucial role in modulating both potency and selectivity. In particular, incorporation of a 3,4-dimethoxyphenyl moiety significantly enhanced COX-2 inhibition, whereas mono-substitution or electron-donating groups at certain positions reduced activity. The presence of a phenylsulfonamide group was found to be essential for maintaining COX-2 selectivity, likely due to its ability to access the COX-2 secondary binding pocket. Conversely, replacement of the carbonyl group with a thione moiety was generally unfavorable for activity and selectivity.

The most promising compound, **21g**, was further evaluated in vivo using a carrageenan-induced rat paw edema model, where it demonstrated anti-inflammatory activity comparable to celecoxib and indomethacin. Importantly, gastric ulcerogenicity studies revealed significantly reduced ulcer formation compared to both reference drugs. Molecular docking studies supported these findings, showing that the sulfonamide moiety of compound **21g** engaged in key hydrogen-bonding interactions with

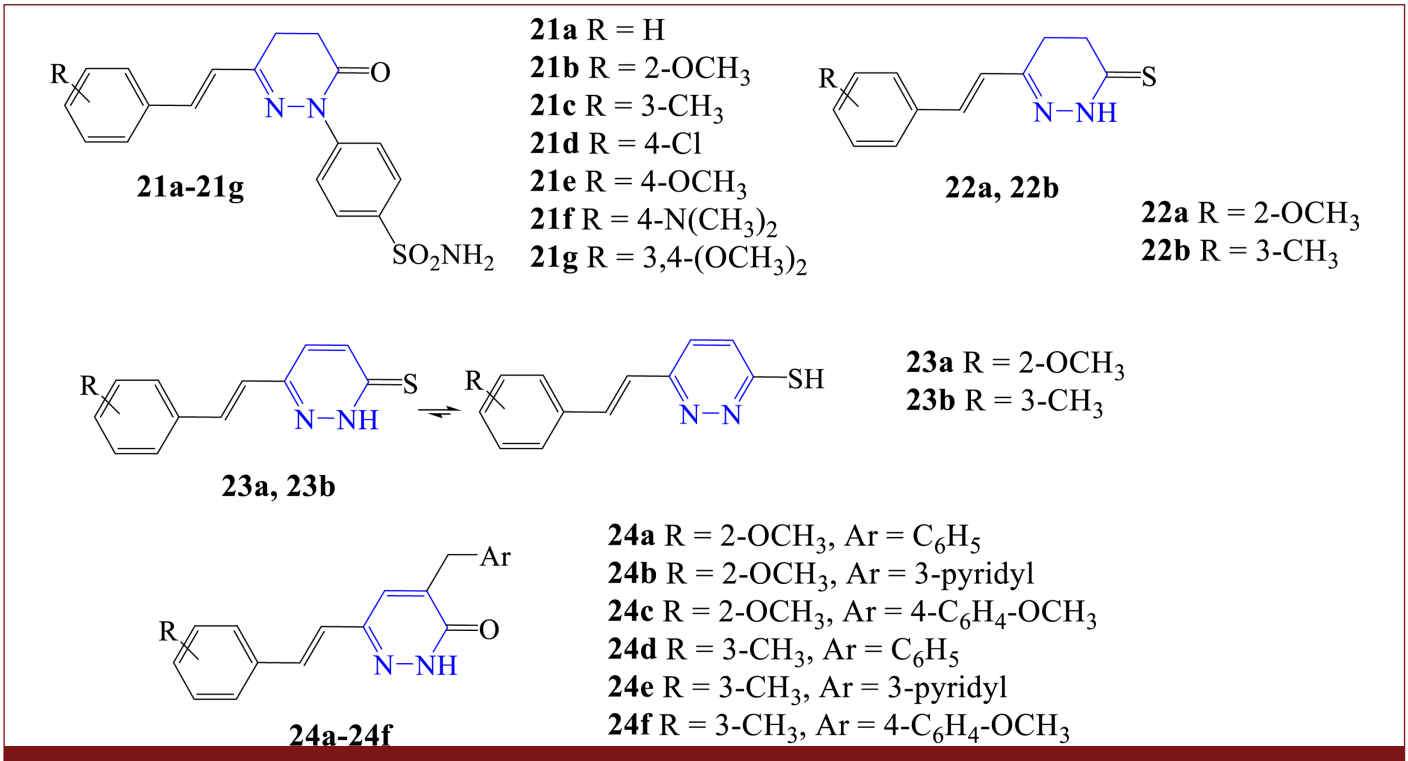


Figure 9. Pyridazine-based cyclooxygenase-2 inhibitors synthesized by Ahmed et al.[30]

residues such as Arg513 and His90 within the COX-2 secondary pocket, while interactions involving the dimethoxyphenyl substituent provided additional stabilization. These results highlight the pyridazinone scaffold, particularly when functionalized with a phenylsulfonamide group and appropriately substituted aryl moieties, as a promising framework for the development of potent and selective COX-2 inhibitors.

TETRAZOLE-BASED INHIBITORS

Tetrazole derivatives have recently attracted attention as practical bioisosteric replacements in the design of selective COX-2 inhibitors.[31,32] In 1 notable study, the sulfonamide pharmacophore of celecoxib was strategically replaced with a tetrazole ring, giving rise to a structurally diverse series of derivatives (Figure 10).[33] The design strategy aimed to preserve the essential interactions within the COX-2 secondary binding pocket while fine-tuning inhibitory activity and isoform selectivity through systematic modifications of the scaffold and substituents. Enzymatic evaluation indicated a distinct pattern. All compounds exerted relatively weak inhibition against COX-1 (IC_{50} = 4.5-12.8 μM), yet displayed a marked preference for COX-2, with selectivity indices ranging from 14.52 to 317.95. Several derivatives matched or even exceeded the selectivity of celecoxib (SI = 282.22). The most compelling results were observed for compounds **26c**, **27c**, and **28c**, which displayed submicromolar COX-2 inhibition (IC_{50} = 0.039-0.043 μM), slightly outperforming celecoxib itself (IC_{50} = 0.045 μM). Their dimethoxy counterparts (**26b**, **27b**, **28b**) were also highly active, whereas the chalcone series (**25a-25f**), bearing an α,β-unsaturated carbonyl linker, showed noticeably lower potency against COX-2 (IC_{50} = 0.10-0.31 μM) compared with the heterocyclic analogs. This contrast underscores the importance of conformational constraint and heterocyclic rigidity in achieving optimal engagement within the COX-2 active site. The SAR proved to be clear and mechanistically meaningful. Incorporating a 5-membered heterocycle (particularly isoxazole or pyrazole) clearly enhanced both potency and selectivity relative to the more flexible chalcone framework. Equally important was the substitution pattern on the phenyl ring. A consistent activity gradient was observed: trimethoxy > dimethoxy > monomethoxy. The trimethoxy derivatives (**26c**, **27c**, and **28c**) were not only the most potent COX-2 inhibitors but also the most selective, suggesting that electron-donating methoxy groups strengthen favorable interactions within the COX-2 side pocket. Encouragingly, the in vitro results translated into meaningful in vivo activity. In the carrageenan-induced rat paw edema model, compounds **26c** and **28c** produced stronger and more sustained anti-inflammatory effects than celecoxib at 50 mg/kg. Importantly, their ulcerogenic liability was lower than that of celecoxib and substantially reduced compared with indomethacin, consistent with

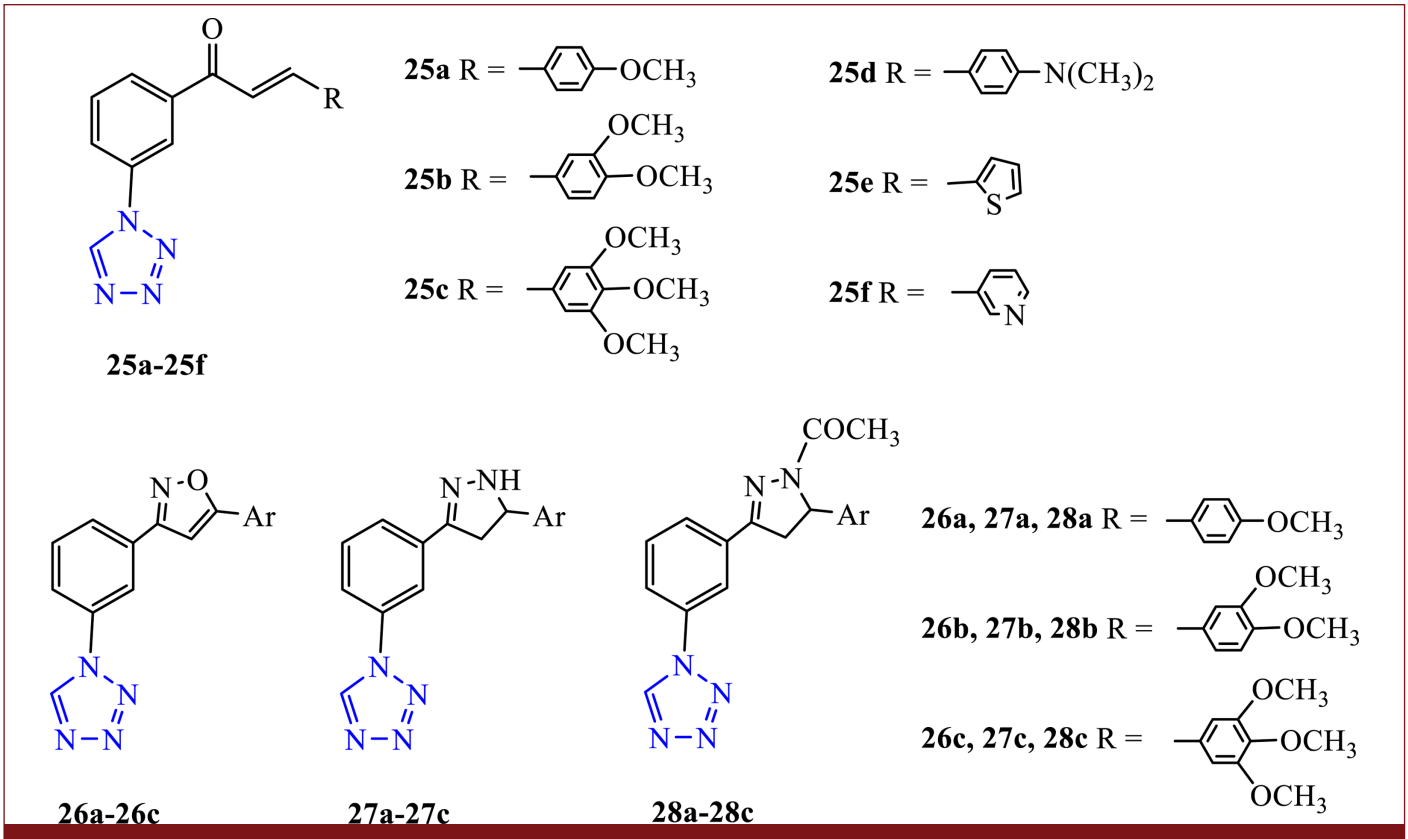


Figure 10. Tetrazole-based cyclooxygenase-2 inhibitors.

their high COX-2 selectivity and limited COX-1 inhibition. Molecular docking studies offered a mechanistic rationale for these observations. The tetrazole ring effectively mimicked the sulfonamide group of classical COX-2 inhibitors, forming key hydrogen bonds, particularly with His90, while the methoxy substituents engaged residues such as Ser530 and Tyr385. The favorable docking scores and coherent binding orientation support the idea that tetrazole is not merely a structural substitute but a functionally competent pharmacophoric replacement. This work convincingly demonstrates that replacing the sulfonamide group of celecoxib with a tetrazole ring is more than a theoretical exercise—it is a viable and productive design strategy. When combined with an appropriate heterocyclic core and electron-donating substitution, this approach can yield highly active, COX-2-preferring, and potentially safer anti-inflammatory agents.

OXADIAZOLE-BASED INHIBITORS

El-Sayed et al[34] developed a series of 1,3,4-oxadiazole derivatives and evaluated their cyclooxygenase inhibitory properties. The authors prepared 3 closely related subseries: 2-substituted-5-(4-pyridyl)-, 2-substituted-5-(3-pyridyl)-, and 2-substituted-5-(phenyl or 4-chlorophenyl)-1,3,4-oxadiazoles, and assessed their activity against both COX isoforms to assess inhibitory strength and isoform preference (Supplementary Figure 2). Across the panel, the compounds displayed moderate inhibition of COX-1 (IC_{50} = 4.17-15.38 μM) but markedly higher activity toward COX-2 (IC_{50} = 0.038-0.56 μM), indicating a pronounced inclination for the inducible isoform. Several derivatives reached potency levels comparable to reference drugs such as indomethacin, diclofenac sodium, and celecoxib, reinforcing the value of the 1,3,4-oxadiazole nucleus as a platform for selective COX-2 inhibitor design. Two compounds, **29** and **30**, stood out as the most active members of the series, with COX-2 IC_{50} values of 0.041 and 0.038 μM, respectively. Their selectivity indices (89.7 and 118.68) confirmed a meaningful bias toward COX-2 over COX-1. Other analogs, most notably **31**, **32**, and **33**, also showed submicromolar COX-2 inhibition with respectable selectivity profiles. At the lower end of the spectrum, the cyanoacetamide derivative **34** exhibited the weakest activity (IC_{50} = 0.56 μM), though it still retained measurable COX-2 inhibition. The SAR trends are both coherent and instructive. Within the 5-(4-pyridyl)-1,3,4-oxadiazole subseries, para-nitro substitution on the phenyl ring clearly enhanced COX-2 potency compared with para-bromo, para-chloro, or unsubstituted counterparts. Notably, the 4-bromophenyl derivative (**31**) showed superior activity compared with its chloro and hydroxy analogs, indicating that subtle variations in aryl substitution significantly influence COX-2 inhibition. In contrast, COX-2 inhibition within the 5-(3-pyridyl) series was adversely affected by specific substitutions at the 2-position. Introduction of cyanoacetamide or ethylformimidate moieties (e.g., compounds **34** and **35**) led to diminished COX-2 inhibition. A comparable reduction in activity was observed in the phenyl and 4-chlorophenyl subseries upon introduction of cyanoacetamide or ethylformimidate groups. Interestingly, within the 5-phenyl series, the nitro derivative (**36**) surpassed its chloro analog (**37**), whereas in the 4-chlorophenyl series, the 4-chloro derivative (**33**) delivered the strongest inhibition relative to its unsubstituted and nitro analogs. Collectively, these results further support the utility of the 1,3,4-oxadiazole scaffold as a valuable template for the development of selective COX-2 inhibitors.

CONCLUSION

Recent advances in medicinal chemistry have led to the development of numerous structurally diverse COX-2 inhibitors with improved potency and selectivity. The studies discussed in this review highlight the importance of heterocyclic scaffolds and rational structural modifications in achieving selective inhibition of the COX-2 enzyme. Structure–activity relationship studies further demonstrate that subtle electronic and steric variations, together with appropriate pharmacophoric features enabling interactions with the COX-2 secondary pocket, can significantly influence enzyme binding, selectivity, and anti-inflammatory activity. Despite these promising advances, important challenges remain in the development of clinically safe COX-2 inhibitors. The cardiovascular complications previously associated with coxibs, including myocardial infarction and stroke, have been largely attributed to the suppression of vascular COX-2–derived PGI_2 biosynthesis without concomitant inhibition of platelet-derived TXA_2, thereby favoring a prothrombotic state. In addition to thrombosis, prolonged COX-2 inhibition has also been linked to endothelial dysfunction, hypertension, and accelerated atherogenesis, highlighting the complex physiological role of prostaglandin signaling in cardiovascular homeostasis. In this context, COX-2 selectivity alone should not be regarded as the sole criterion for the development of clinically successful inhibitors. Although many of the recently reported compounds demonstrated remarkable in vitro COX-2 inhibitory activity and favorable selectivity indices, comprehensive cardiovascular safety evaluations were generally limited or absent. Most studies primarily focused on enzyme inhibition assays, molecular docking analyses, and short-term anti-inflammatory models, whereas mechanistic investigations related to PGI_2/TXA_2 homeostasis, thrombogenic potential, vascular function, and long-term cardiovascular outcomes remain insufficiently explored. Therefore, the promising pharmacological profiles of these novel scaffolds should be interpreted cautiously until further in vivo and long-term safety studies clarify whether they provide a safer cardiovascular profile compared with classical coxibs such as rofecoxib and celecoxib. Future strategies in COX-2 inhibitor design should aim not only to maximize anti-inflammatory efficacy and gastrointestinal safety but also to achieve an improved balance between selectivity and cardiovascular tolerability. Integrating pharmacokinetic,

absorption, distribution, metabolism, excretion, and toxicity (ADMET), and cardiovascular safety assessments into the early stages of drug development may facilitate the identification of safer and more clinically viable COX-2-targeted therapeutics. In this regard, modern computational approaches, including structure-based drug design, molecular dynamics simulations, and integrated in silico ADMET prediction platforms, are expected to play an increasingly important role in guiding the rational optimization of novel inhibitors. In particular, artificial intelligence (AI)-assisted virtual screening, machine learning-guided Quantative Structure-Activity Relationship modeling, and de novo scaffold design have emerged as powerful strategies for accelerating the discovery of new COX-2 inhibitor candidates by enabling the early prediction of binding affinity, selectivity, pharmacokinetic behavior, and potential toxicity prior to synthesis. Artificial intelligence–driven molecular optimization platforms may also assist in prioritizing compounds with improved drug-like properties and reduced cardiovascular or systemic toxicity risks.

Beyond the development of highly selective COX-2 inhibitors, increasing attention has been directed toward multitarget anti-inflammatory strategies designed to improve both efficacy and safety profiles. Among these, dual COX-2/mPGES-1 inhibitors have attracted particular interest because they may reduce PGE_2 production while preserving physiologically protective prostanoids such as PGI_2 and TXA_2, thereby potentially minimizing the cardiovascular complications associated with selective COX-2 inhibition. Similarly, dual COX/5-lipoxygenase inhibitors represent another promising therapeutic approach capable of simultaneously suppressing prostaglandin- and leukotriene-mediated inflammatory pathways, which may contribute to enhanced anti-inflammatory efficacy together with improved gastrointestinal tolerability. Collectively, these emerging strategies suggest that future COX-2-oriented drug discovery efforts should move beyond selectivity alone and increasingly focus on achieving an optimal balance between efficacy, pharmacokinetic performance, and long-term systemic safety.

Future studies may benefit from the rational design of hybrid heterocyclic scaffolds integrating the most favorable structural characteristics identified across different compound series. In particular, pyrazole–tetrazole hybrid systems incorporating diaryl architectures together with sulfonamide or methanesulfonyl pharmacophores may represent a promising strategy for achieving strong COX-2 selectivity and favorable interactions within the COX-2 secondary binding pocket. In addition, tetrazole–pyridazinone hybrid derivatives bearing dimethoxyphenyl or other methoxy-substituted aromatic moieties warrant further investigation, as methoxy-containing substituents consistently enhanced COX-2 inhibitory potency and selectivity across several scaffold classes discussed in this review. Such hybrid approaches may provide a useful framework for the development of next-generation COX-2 inhibitors with improved efficacy and safety profiles.

In addition to enzymatic potency and COX-2 selectivity, pharmacokinetic and ADMET-related properties are important determinants of the translational potential of newly developed COX-2 inhibitors. However, detailed pharmacokinetic characterization and experimental ADMET evaluations were generally absent from the reported studies. Parameters such as metabolic stability, oral bioavailability, cytochrome P450 interactions, plasma protein binding, lipophilicity, and long-term toxicity were not systematically evaluated despite their critical importance for clinical development. These limitations highlight the need for more comprehensive pharmacokinetic and safety profiling during the preclinical evaluation of future COX-2 inhibitor candidates.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Artificial Intelligence Usage Statement: The authors declared that no artificial intelligence tool was used in the preparation of the manuscript.

Ethics Committee Approval: Ethical committee approval was not required this study as neither human nor animal participants were used in the present review.

Informed Consent: Informed consent was not obtained for this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – G.D., Z.K.; Design – G.D.; Supervision – G.D., Z.K.; Resources – G.D., Z.K.; Materials – G.D., Z.K.; Data Collection and/or Processing – G.D., Z.K.; Analysis and/or Interpretation – Z.K., G.D.; Literature Search – G.D., Z.K.; Writing – G.D.; Critical Review – G.D., Z.K.

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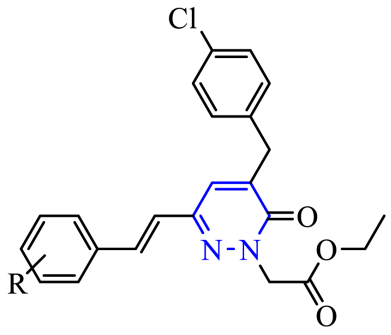
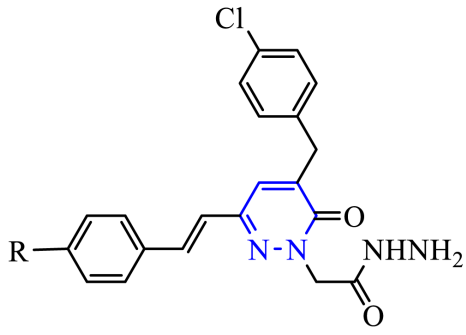


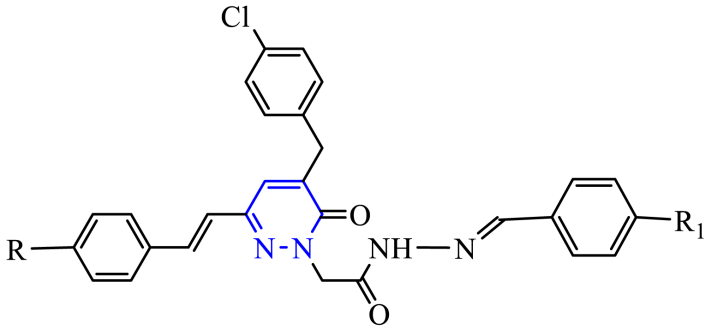
18a-18d



19a, 19b

18a R = 4-Cl
18b R = 4-OH
18c R = 4-OCH_3
18d R = 3,4-$(OCH_3)_2$

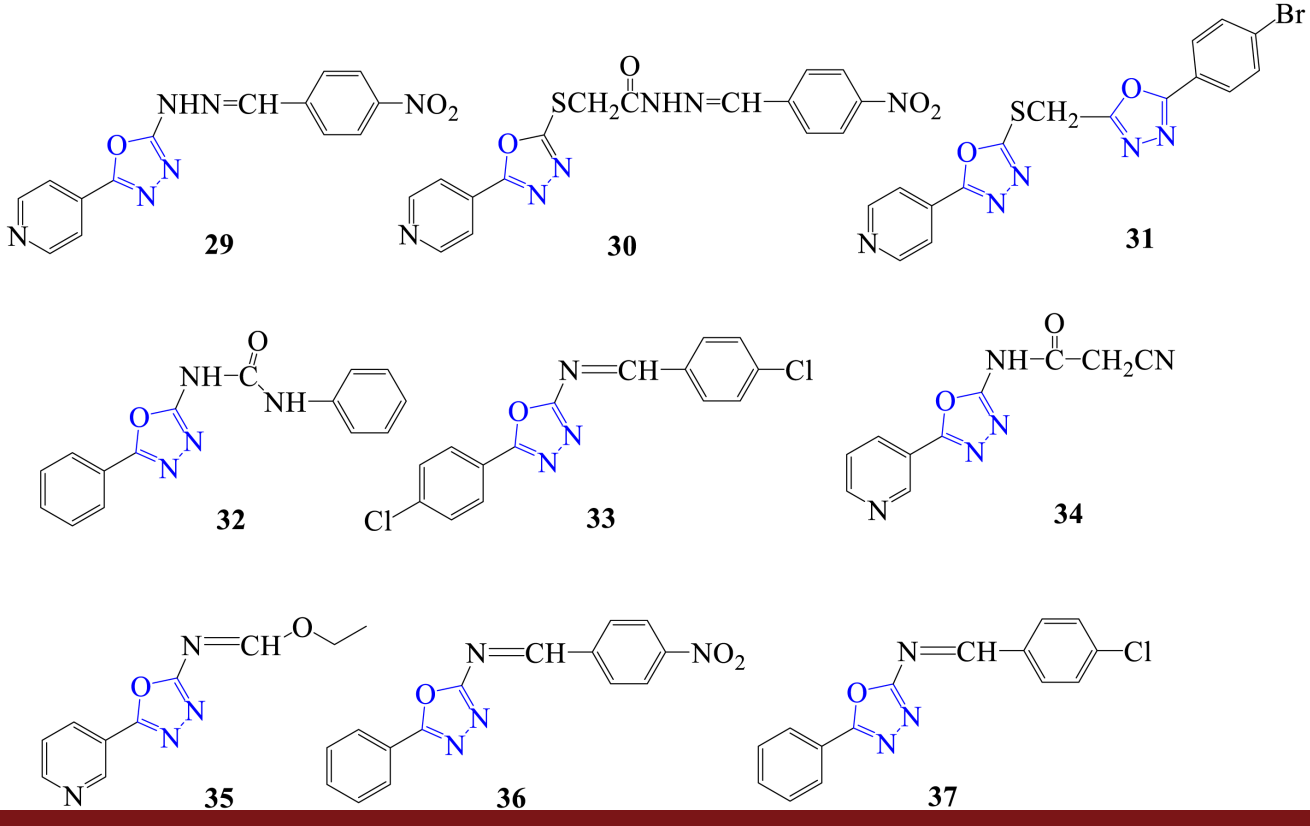
19a R = Cl
19b R = OCH3



20a-20f

20a R = Cl, R_1 = Br
20b R = Cl, R_1 = Cl
20c R = Cl, R_1 = OCH_3
20d R = OCH_3, R_1 = Br
20e R = OCH_3, R_1 = Cl
20f R = OCH_3, R_1 = OCH_3

Supplementary Figure 1. Pyridazine-based COX-2 inhibitors reported by Hassan et al.



Supplementary Figure 2. Oxadiazole-based COX-2 inhibitors reported by El-Sayed et al.