REVIEW

Recent development on COX-2 inhibitors as promising anti-inflammatory agents: The past 10 years

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Abstract Cyclooxygenases play a vital role in inflammation and are responsible for the production of prostaglandins. Two cyclooxygenases are described, the constitutive cyclooxygenase-1 and the inducible cyclooxygenase-2, for which the target inhibitors are the non-steroidal anti-inflammatory drugs (NSAIDs). Prostaglandins are a class of lipid compounds that mediate acute and chronic inflammation. NSAIDs are the most frequent choices for treatment of inflammation. Nevertheless, currently used anti-inflammatory drugs have become associated with a variety of adverse effects which lead to diminished output even market withdrawal. Recently, more studies have been carried out on searching novel selective COX-2 inhibitors with safety profiles. In this review, we highlight the various structural classes of organic and natural scaffolds with efficient COX-2 inhibitory activity reported during 2011−2021. It will be valuable for pharmaceutical scientists to read up on the current chemicals to pave the way for subsequent research.

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1. Introduction

Inflammation is an important part of the immune system's response against hostile world and has been linked to a variety of immunological diseases[1]. Chemical agents, physical injuries, immunological reactions and Infection by pathogenic organisms usually cause acute or chronic inflammations[2]. Non-steroidal anti-inflammatory drugs (NSAIDs) have long been known to alleviate inflammation. They treat a variety of diseases caused by inflammation, such as rheumatoid arthritis, acute fever as well as relieving common daily pains[3]. In the history of medicine development, the first therapeutic NSAID was aspirin, which has been used for more than 100 years since 1898. For more than a century, more typical NSAIDs, such as celecoxib, indomethacin, ibuprofen, and diclofenac (Fig. 1), have been latterly developed, and approved by the U.S. Food and Drug Administration (FDA) for clinical treatment. NSAIDs competitively inhibits the activity of cyclooxygenases (COXs) and thereby interferes with the bioconversion of the downstream inflammatory mediators. In 1971, Vane et al.[4,5] first confirmed that the therapeutic target of NSAIDs is cyclooxygenase, further investigation found that the inhibition of cyclooxygenase directly resulted in termination of the biosynthesis of prostaglandins (PGs), which are crucial mediators of inflammation.

Four major bioactive PGs, prostaglandin E_2 (PGE_2), prostacyclin I_2 (PGI_2), prostaglandin D_2 (PGD_2), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), along with a thromboxane A_2 (TXA_2) are generated during inflammation[6]. The formation of PGs was shown in Fig. 2, initially, arachidonic acid (AA) is released from the phospholipid by the catalysis of the phospholipase A_2 (PLA_2), and then a prostaglandin H_2 (PGH_2) is subsequently formed by the actions of both COX-1 and COX-2. These four PGs and TXA_2 are eventually produced through the bioconversion of PGs and TXA_2 synthases in downstream mechanism. The level of prostaglandin production mainly depends on the expression of cyclooxygenases (COXs) in inflammatory tissues, especially cyclooxygenases-2[7]. PGs are hormone-like lipid compounds and are involved in many physiological reactions and play a key role in the generation of inflammatory responses[8]. In general, PGs exert their effects by mediating the body's responses to tissue injury or inflammation. Among them, PGE_2 is the dominated prostaglandin that induces typical symptoms of inflammation, such as pain, fever, tumor, and anaphylactic reaction[9].

Two functional COXs are identified and defined as COX-1 and COX-2 according to their different structures and functions. COX-1 belongs to constitutive isoenzyme and extensively existed in most cells. Prostaglandins catalyzed by COX-1 have protective effects on gastrointestinal tract. COX-2 is an inducible enzyme which acts as the most important source of prostaglandins, so it is always regarded as a pathologic enzyme chiefly responsible for inflammation[10–12]. NSAIDs exhibits anti-inflammatory effects by the non-selective/selective inhibition
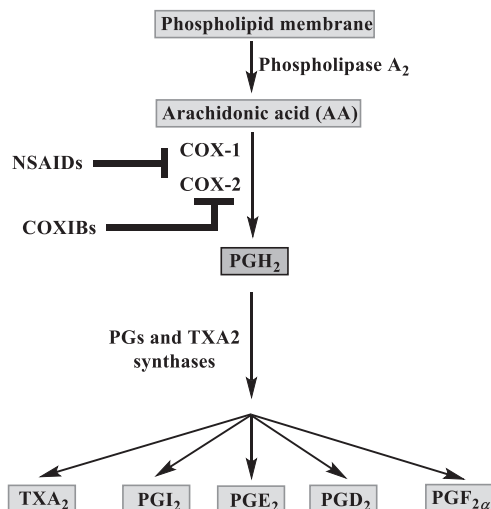

Figure 2 A diagram of the biochemistry of prostanoids.

of cyclooxygenase (COX) activity and subsequently blocks the biosynthesis of prostaglandins in lesion sites[13–15]. However, due to simultaneous inhibition of COX-1 and COX-2, non-selective NSAIDs not only achieve anti-inflammatory and analgesic purposes, but also cause serious adverse effects, such as digestive tract damage and platelet function disorder. While selective NSAIDs only inhibits COX-2 but does not affect the protective effect of prostaglandins catalyzed by COX-1 on gastrointestinal tract and platelet, thus greatly decreasing the risk of gastrointestinal side effects[16,17]. The traditional anti-inflammatory mechanism of COX-2 inhibitor has been confirmed by recent studies. As depicted in Fig. 3, COX-2 inhibitors exert pharmacological activity through inhibition of the NF-κB pathway. Since COX-2 is responsible for producing reactive oxygen species (ROS), COX-2 inhibition causes a sharp drop in the amount of reactive oxygen species (ROS) in the upstream mechanism and keep NF-κB in an inactive state of bondage to P-IκB in the downstream, and thereby prohibit the production of pro-inflammatory cytokines, including NO, PGE_2, IL-6, and TNF-α[18]. Although selective COX-2 inhibitors are the most common choice of treatment for inflammatory diseases, they are often found to be associated with potential adverse effects of cardiovascular disorder, and a possible increased risk of heart attack, blood clots and stroke. Therefore, discovering new selective COX-2 inhibitors that can reduce such side effects appear more popular[19,20].

To prevent undesirable outcomes, finding new NSAIDs with improved safety profiles remains the most effective approach to inflammation treatment. This paper reviews the classification and pharmacological action of new COX-2 inhibitors which have been
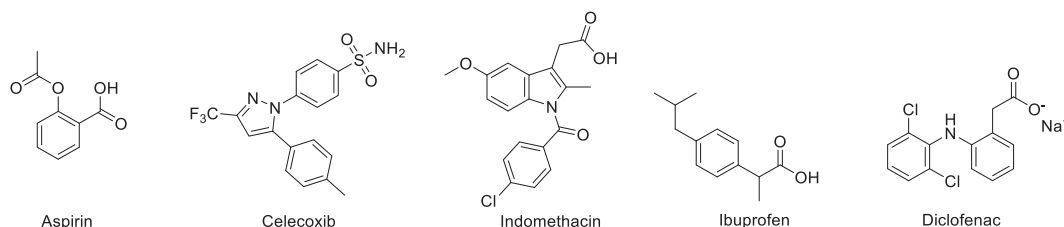

Figure 1 Structure formulas of clinically used COX-1 and COX-2 inhibitors.
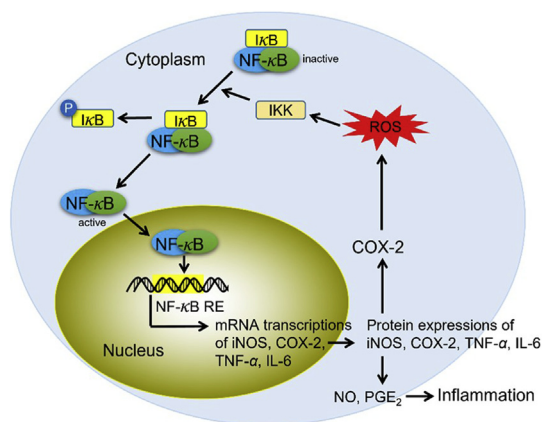
Figure 3 A diagram of the putative anti-inflammatory mechanism of the COX-2 inhibitor in RAW264.7 cells.

reported in organic synthesis in the last ten years. In addition, new compounds from natural origins with potent COX-2 inhibitory and anti-inflammatory activity are also included, which are the promising COX-2 inhibitor for drug design and clinical use.

2.   Chemistry and pharmacology of new synthetic COX-2 inhibitors

2.1.   *Compounds having a pyrazole ring*

Pyrazole is a π-excess aromatic heterocycle, which has been recognized as a pharmacologically important active scaffold for organic synthesis, especially for new COX-2 inhibitor development. Clinical agents containing pyrazole fragments are celecoxib, antipyrine, aminopyrine, and metamizole[21]. During the past ten years, a number of pyrazole derivatives were reported and screened for their COX-2 inhibition and anti-inflammatory activity (Fig. 4). In 2014, a new compound **1** containing pyrazole fragment was synthesized by Bansal et al.[22]. Compound **1** showed excellent

selective inhibition of COX-2 [IC_{50} = 0.31 μmol/L, selectivity index (SI) > 222] and potential anti-inflammatory activity with ED_{50} of 74.3 mg/kg in a carrageenan-induced rat paw edema model. The COXs inhibition activity of compound **1** was obtained by using a COX fluorescent inhibitor screening assay kit consisting of ovine COX-1 and human recombinant COX-2 enzymes [an enzyme immunoassay (EIA)]. Further investigation indicated that compound **1** presented suppression of acetic acid-induced writhes, and it showed better gastro-spasm profile compare to that of aspirin. In a molecular docking study, compound **1** showed higher selective binding affinity towards COX-2 than to COX-1. An important hydrogen bond between the oxygen of the nitro group and the hydrogen of Arg[120] was observed, which is important for the interaction with COX-2. El-Sayed et al.[23] reported the synthesis of a series of potentially useful 1,5-diphenyl pyrazoles. Compounds **2** and **3** displayed a considerable COX-2 inhibitory activity and a good selectivity (EIA) (IC_{50} = 0.45 μmol/L, SI = 111.1). Compounds **2** and **3** also presented high anti-inflammatory activity (ED_{50} = 118 and 120 mg/kg) comparable with diclofenac (ED_{50} = 114 mg/kg) in carrageenan-induced rat raw paw oedema assay. Notably, replacement of cycloalkanone moiety can significantly influence their activity. Meanwhile, molecular docking analysis indicated that compounds **2** and **3** bind into the active site of COX-2 in a similar manner to SC-558, a selective COX-2 inhibitor. Xu's group[24] reported a novel class of molecules, adopting a new pyrazole *N*-aryl sulfonate synthetic approach. This inspiration came from the selective COX-2 inhibitor-celecoxib, which has a typical sulfonamide fragment. *In vitro* EIA experiments indicated that compounds **4**, **5**, **6**, and **8** have strong COX-2 inhibitory activity (Table 1). According to the selectivity index on COXs, compounds **4**−**8** displayed comparable selective COX-2 inhibition with that of celecoxib. Importantly, compounds **4**, **5**, **7**, and **8** showed excellent *in vivo* anti-inflammatory activity (**5**, **7**, and **8**: % inhibition of auricular edemas = 27.0, 27.0 and 25.7, respectively; **4** and **7**: % inhibition ratios of writhing = 50.7 and 48.5, separately, at the oral dose of 30 mg/kg, 8 mice/test group). El-Sayed et al.[25] continued to report some pyrazole derivatives
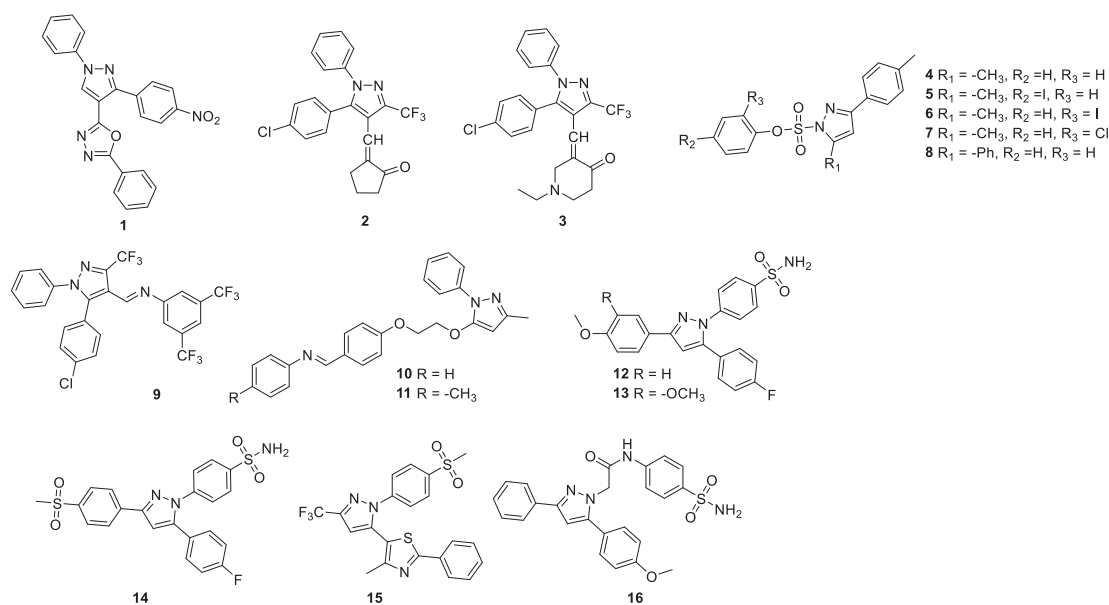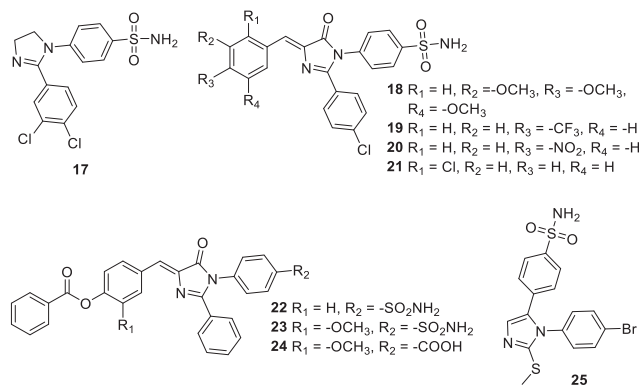

Figure 4   Chemical structures of compounds **1**−**16**.

Table 1 *In vitro* COX-1/COX-2 inhibition (IC_{50}, μmol/L) and selectivity index for compounds 4−8, and standard agent.

Compd.	COX-1[a]	COX-2[a]	COX-2 selectivity[b]
4	0.5	0.0011	455
5	96.57	0.0092	10,479
6	>100.00	0.092	>1087
7	>100.00	0.53	>189
8	>100.00	<0.01	–
Celecoxib	>100.00	0.056	295

[a]The result (IC_{50}, μmol/L) is the mean of three determinations acquired using a COX fluorescent inhibitor screening assay kit (Cayman Chemical, MI, USA).
[b]COX-2 selectivity index (COX-1 IC_{50}/COX-2 IC_{50}).

based on the skeleton of SC-558 and celecoxib in 2012. Some of the newly synthesized compounds showed increased COX-2 inhibitory and anti-inflammatory activity. Example as compound **9**, exhibiting excellent COX-2 inhibitory activity (EIA) with IC_{50} of 0.26 μmol/L and selectivity index (SI = 192.3). Furthermore, the carrageenan-induced rat paw edema assay showed that compound **9** exerted equivalent anti-inflammatory activity with ED_{50} of 0.170 mmol/kg in comparison to the reference drug (diclofenac: ED_{50} = 0.198 and celecoxib: 0.185 mmol/kg, respectively). Per the docking result, the trifluoromethyl moiety of compound **9** inserts deep inside the COX-2 pocket and forming hydrogen bond with Gln^{192} and Arg^{513}, this result was consistent with COX-2 inhibition. A novel series of pyrazole derivatives that have unusual flexible fragments were reported by Gopi's group[26], of these, compounds **10** and **11** exhibited moderate selective COX-2 inhibitory potency by using a chromogenic assay (IC_{50} = 16.8 and 14.3 μmol/L, SI = 0.5100 and 0.4400, respectively). In docking calculations, an interaction between the ligands and Arg^{513} was observed, which is required for the dependent inhibition of COX-2. In 2020, on the basis of the structure of celecoxib, several halogenated triarylpyrazoles were prepared by Abdellatif et al.[27]. *In vitro* COX-2 inhibition assay indicated that three fluorinated compounds **12−14** exerted excellent efficacies (IC_{50} = 0.049, 0.057, and 0.054 μmol/L, respectively) close to that of celecoxib (IC_{50} = 0.055 μmol/L) and showed better selective index (SI = 253.1, 201.8, and 214.8, respectively) than celecoxib (SI = 179.4). Moreover, compounds **12−14** exhibited close gastric profile (ulcer index (UI) = 1.25−2.5) to celecoxib (UI = 1.75). In this study, halogenated aryl ring was found to be crucial to affect activity and selectivity, and halogen atom fluoro derivatives showed better COX-2 selectivity than celecoxib.

Abdelall et al.[28] prepared a new series of 1,5-diaryl pyrazoles as both COX-2 and 15-lipoxygenase inhibitors. Compound **15** was more effective (ED_{50} = 0.98 μmol/L) on COX-2 inhibition than that of references celecoxib (ED_{50} = 1.54 μmol/L) and meclofenamate sodium (ED_{50} = 5.64 μmol/L) in an EIA assay. Meanwhile, compound **15** showed good anti-inflammatory activity and selectivity index (SI = 4.89) in *in vivo* assay, which was almost identical to that of celecoxib (SI = 4.93). Moreover, the *in vivo* ulcerliability activity assay was explored in this study, compound **15** presented good ulcerous profile (UI = 2.78) and it was as safe as the reference celecoxib (UI = 2.9). In addition, the results suggested that presence of a (CF3) moiety in pyrazoles had no effect on COX-2 selectivity. Aiming to directly inhibit the production of PGE_2 in serum samples of rats, some novel pyrazole derivatives were recently designed by Mohammed et al.[29]. Of these, compound **16**, which contains an acylamino linker, presented COX-2 inhibition with IC_{50} = 1.76 μmol/L and a good selectivity index value of 11.1. Moreover, compound **16** showed potential anti-inflammatory activity (% edema inhibition = 81) and was less ulcerogenic than indomethacin in the *in vivo* ulcer liability assay. Unfortunately, the potency and selectivity of compound **16** cannot be compared with that of celecoxib, further structural modification is required to improve the activity.

2.2. Compounds having imidazole and imidazoline rings

The imidazole and imidazoline groups, as structurally similar pharmacophores, have been widely explored in the development of NSAIDs[30]. From 2014 to 2021, several literatures have reported new COX-2 inhibitors containing imidazole and imidazoline moieties (Fig. 5). In 2014, Sarnpitak et al.[31] designed and synthesized an active imidazoline analog **17**. Compound **17** displayed prominent COX-2 inhibitory activity (IC_{50} = 0.3 μmol/L) comparable to clinically used celecoxib (IC_{50} = 0.091 μmol/L) upon *in vitro* evaluation. This study also proved that replacement of methylsulfonyl group by sulfonamide showed no pronounced suppressive effect on COX-2 inhibition. Four years later, Abdellatif et al.[32] reported a number of 4-substituted-imidazoline analogs. Compounds **18−20** were more active towards COX-2 compare to celecoxib. Compounds **18**, **20**, and **21** were less ulcerogenic than clinical drugs including ibuprofen and celecoxib (Table 2). Structure–activity relationship study (SAR) revealed that multiple −OCH₃ (**18**) substituent on benzene ring has more favorable effect on the COX-2 inhibition and selectivity than other analogs. Some new substituted imidazoline-5-one derivatives **22**, **23**, and **24** were prepared by Metwally et al.[33] Compounds **22−24** showed similar anti-inflammatory activity (% inhibition of edema = 43.1, 41.8, and 49.0) compared to celecoxib (% inhibition of edema = 43.1%), which suggested that keeping the same sulfonamide (SO_2NH_2) moiety in new structures is crucial to maintain or increase the anti-inflammatory activity. Further study indicated that compounds **22−24** exhibited a high efficacy towards COX-2 inhibition (EIA) with IC_{50} of 0.090, 0.087, and 0.092 μmol/L, respectively. In addition, several substituted 1,5-diarylimidazole derivatives having the thioalkyl group at position 2 were reported by Navidpour et al.[34] in 2014. Of these, compound **25** showed the moderate inhibition (EIA) (IC_{50} = 14.2 μmol/L) of COX-2 and displayed less selectivity (SI = 3.1) than celecoxib (IC_{50} = 0.544 μmol/L; SI = 19.4). The results suggested that compounds bearing thiomethyl group at position 2 have better activity as compared with thioethyl derivatives in this study.

18 R₁ = H, R₂ = -OCH₃, R₃ = -OCH₃, R₄ = -OCH₃
19 R₁ = H, R₂ = H, R₃ = -CF₃, R₄ = -H
20 R₁ = H, R₂ = H, R₃ = -NO₂, R₄ = -H
21 R₁ = Cl, R₂ = H, R₃ = H, R₄ = H

22 R₁ = H, R₂ = -SO₂NH₂
23 R₁ = -OCH₃, R₂ = -SO₂NH₂
24 R₁ = -OCH₃, R₂ = -COOH

Figure 5 Chemical structures of compounds 17−25.

Table 2 *In vitro* COX-1/COX-2 inhibition (IC$_{50}$, μmol/L), selectivity index, ulcerogenic evaluation for compounds **18–21**, and standard agents.

Compd.	COX-1[a]	COX-2[a]	COX-2 selectivity[b]	Ulcer index
18	4.52	0.42	10.76	1.22
19	6.74	0.62	10.87	3.02
20	4.52	0.52	8.69	2.60
21	7.86	0.86	9.14	2.61
Celecoxib	7.23	0.84	8.61	2.93
Ibuprofen	–	–	–	20.25

[a]The result (IC$_{50}$, μmol/L) is the mean of three determinations acquired using a COX fluorescent inhibitor screening assay kit (Cayman Chemical, MI, USA).

[b]COX-2 selectivity index (COX-1 IC$_{50}$/COX-2 IC$_{50}$).

2.3. Compounds having an indole ring

The indole moiety belongs to an important pharmacophore core for the synthesis of novel selective COX-2 inhibitors[35]. To discover novel selective COX-2 inhibitors, Hayashi et al.[36] designed a new acid-type compound **26** in 2012 (Fig. 6). Compound **26** maintained the basis structure of indomethacin and exerted potent selective COX-2 inhibition with IC$_{50}$ of 0.009 and 0.155 μmol/L in human cells and HWB cells, respectively. Moreover, compound **26** had good oral anti-inflammation efficacy and potent *in vivo* anti-oedematous effect. Meanwhile, a new N-1 and C-3 substituted indole derivative **27** was synthesized by Kaur's group[37] that showed selective COX-2 inhibitory activity (EIA) with IC$_{50}$ of 0.32 μmol/L and SI of >312. According to the docking result, the phenyl CF$_3$ substituent attached to the C=N is located near the COX-2 active site and formed an important hydrogen bond to His^{90}, which is crucial for the COX-2 inhibition. Bhat's group[38] reported a new COX-2 inhibitor **28**, compound **28** not only inhibited COX-2 expression but also possessed desirable gastral safety profile. This work provided valuable information for exploring gastro-protective COX-2 inhibitors. Recently, Singh et al.[39] reported several new compounds containing tosyl and dipeptide groups at N-1 and C-3 position, respectively, which were developed for COX-2 inhibitors. Of all the compounds,

compounds **29–31** showed similar *in vivo* anti-inflammatory activities to diclofenac. Moreover, an *in vitro* COX-2 selectivity assay showed that compounds **29** and **30** displayed competitive inhibition and selectivity of COX-2 (IC$_{50}$ = 0.006 and 0.099 μmol/L; SI = 351 and 440, respectively). However, compound **31** showed excellent COX-2 inhibitory activity IC$_{50}$ of 0.54 μmol/L, but the selectivity (SI = 24) is poor. Additionally, Estevão et al.[40] synthesized a new indole derivative **32**. In comparison with indomethacin, the methoxy at C-5 was replaced by a sulfonamide, the C-2 and C-3 positions were substituted by two 4-fluro benzyls, respectively. Compound **32** showed selective COX-2 inhibitory activity with 67 ± 6% (50 μmol/L) which is close to indomethacin (78 ± 3%). More recently, Jung group[41] designed and synthesized a novel N-1, C-3 substituted indole analog **33** that merge the structural motifs of anti-inflammatory ascidian metabolites, herdmanines. To form two vital hydrogen bonds with Tyr^{355} and Arg^{120}, the acid in indomethacin was replaced by a hydrazone moiety based on bioisosteric replacement drug design strategy. Compound **33** showed a considerable COX-2 inhibitory activity (7.59 μmol/L) and selectivity (SI = 5.16) compared with diclofenac (IC$_{50}$ = 1.21 μmol/L, SI = 15.18). The indole-containing analogues were mostly designed based on the structure of indomethacin. Consequently, replacement of the C-3 acetic acid moiety in indomethacin by various substitutes is an effective strategy to improves their activity and selectivity. In addition, the modification at N-1 and C-2 is also a reasonable option.

2.4. Compounds having a thiazole ring

Thiazole is a privileged pharmacophore in medicinal chemistry and bear high potential for the anti-inflammatory therapeutic option. In the past 10 years, three groups have reported several thiazole derivatives which were developed as selective COX-2 inhibitors[42] (Fig. 7). Sağlık et al.[43] recently designed and synthesized novel derivatives bearing thiazolyl-hydrazine-methyl sulfonyl moiety as selective COX-2 inhibitors. Compound **34** demonstrated significant and selective COX-2 inhibition potency with an IC$_{50}$ value of 0.140 ± 0.006 μmol/L and selectivity index of >714.28 comparable to nimesulide (IC$_{50}$ = 1.684 ± 0.079 μmol/L) and celecoxib (IC$_{50}$ = 0.132 ± 0.005 μmol/L) in *in vitro* COX-2 inhibition assay (EIA). Per the molecular docking results, compound **34** bounded in
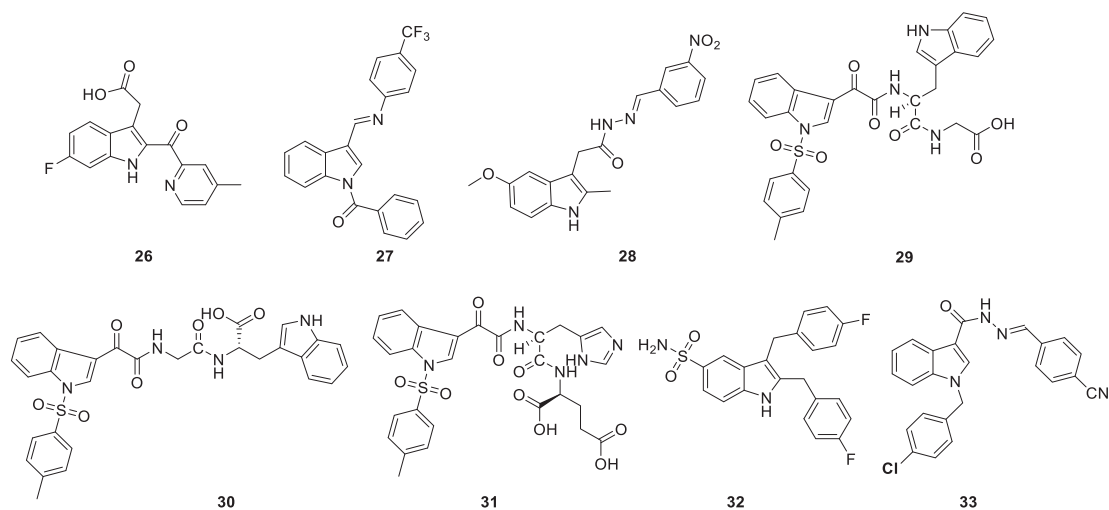

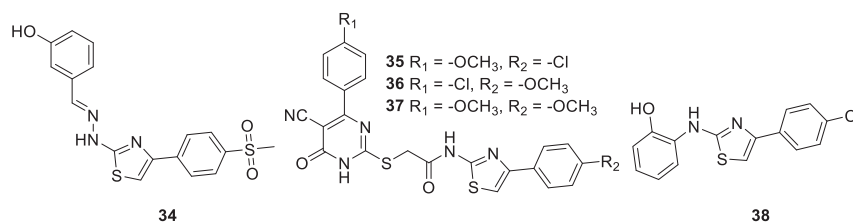**Figure 6** Chemical structures of compounds **26–33**.

Figure 7 Chemical structures of compounds 34−38.

a similar manner as celecoxib with COX-2 enzyme. Later, Abdel-Aziz et al.[44] synthesized a few novel anti-inflammatory EGFR inhibitors with cardiac and gastric safety profiles. Chemically, these compounds were formed with pyrimidine-5-carbonitrile hybrids with 2-amino-4-aryl-1,3-thiazole through an acetamide group linker. Compounds 35−37 displayed good and selective COX-2 inhibitions (EIA) (IC_{50} = 1.17, 1.13, and 1.03 μmol/L; SI = 5.78, 7.84, and 8.21, respectively) relative to celecoxib (IC_{50} = 0.88 μmol/L, SI = 8.31). Further study indicated that compounds 35−37 exhibited anti-inflammatory activity (the percentage of edema inhibition) up to 90%, 94%, and 86% of meloxicam after 4 h interval and higher gastric safety profiles than meloxicam. Compounds 36 and 37 had a superior safety profile with an ulcer index of 2.70 and 2.40, respectively, compared to meloxicam (UI = 18). In addition, Hofmann's group[45] designed a new thiazole analogue, with 4-chloro- and 2-hydroxy-substituted compound 38, which displayed good and selective COX-2 inhibition with activity of 9.1 ± 1.1% (COX-2 product formation) measured at a concentration of 10 μmol/L.

2.5. Compounds having a tetrazole ring

Since 2011, two groups have reported the synthesis and pharmacological studies of anti-inflammatory tetrazole derivatives (Fig. 8). Labib et al.[46] designed several tetrazole derivatives based on bio-isosteric replacement of SO_2NH_2 in celecoxib. Structurally, two classes of compounds were designed: isoxazoles (39, 40) and pyrazoles (41−44). Compounds 39−44 are active and displayed potential *in vitro* COX-2 inhibitory activity in an EIA assay (IC_{50} = 0.039−0.065 μmol/L). Notably, compounds 40, 42, and 44 attained significant COX-2 selectivity index values which were as selective as celecoxib. Moreover, compounds 40 and 44 showed

similar anti-inflammatory activity to celecoxib at different time intervals and were less ulcerogenic than celecoxib (Table 3). Downstream inflammatory factors were also detected, compounds 40 and 44 significantly decrease the production of PGE_2 (% inhibition = 81.042 and 82.724 in sequent) which is comparable to celecoxib (% inhibition = 79.666). The collected data indicated that the derivatives with methoxy are more active than those with hydrogen on the benzene ring. Al-Hourani et al.[47] reported a tetrazole-containing compound 45, which exhibited potent COX-2 inhibition with IC_{50} value of 2.0 μmol/L, but the SI value of compound 45 (SI = 210) was less than celecoxib (SI = 313). Five years later, this group[48] prepared more 1,5-diaryl-substituted tetrazoles by further modifications to the methylsulfonyl unit. The collected biological data showed that compounds 46 and 47 exhibited moderate COX-2 inhibitory activity (IC_{50} = 24 and 38 μmol/L, respectively) and selectivity (SI = 0.87 and 5.2, respectively); compound 48 displayed enhanced COX-2 inhibitory activity and selectivity towards COX-2 (EIA) (IC_{50} = 3 μmol/L, SI = > 67). The acquired results suggested that the presence of the methylsulfonyl unit, methylene spacer at C-1, and longer linker make the new derivatives more active towards COX-2 enzyme.

2.6. Compounds having an oxadiazole ring

Oxadiazole moiety has precedent for use as a bioisosteric substitute in drug design and synthesis. In the past ten years, three groups had reported the synthesis of COX-2 inhibitors containing oxadiazole group. As summarized in Fig. 9, El-Sayed et al.[49] designed a novel heterocyclic oxadiazoles 49, which exhibited prominent COX-2 inhibitory activity (IC_{50} = 0.041 μmol/L) and selectivity (SI = 89.72) comparably to celecoxib

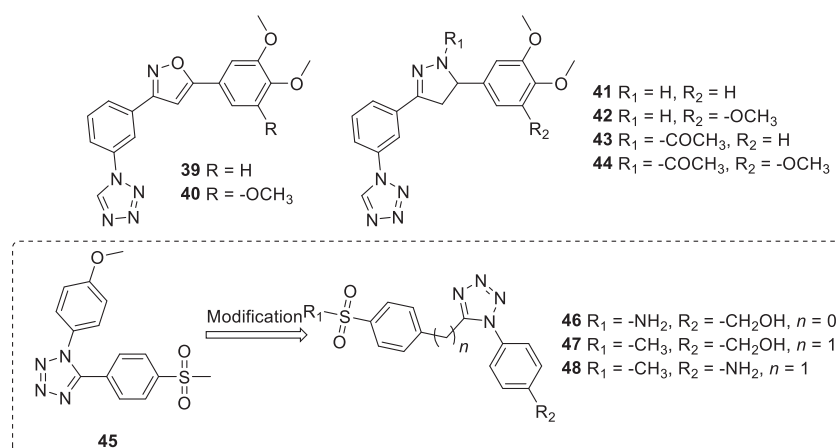**Figure 8** Chemical structures of compounds 39−48.

Table 3 *In vitro* COX-1/COX-2 inhibition (IC$_{50}$, μmol/L), selectivity index, ulcerogenic evaluation and *in vivo* anti-inflammation activity (dose = 50 mg/kg) for compounds **39–44**, and standard agents.

Compd.	COX-1[a]	COX-2[a]	COX-2 selectivity[b]	Ulcer index	Rat paw edema (mm) (% edema inhibition, 6 h)
39	11.3	0.045	251.11	0.21 ± 0.02	7.27 ± 0.14
40	12.4	0.041	302.44	0.123 ± 0.01	5.10 ± 0.36
41	10.5	0.064	164.06	0.26 ± 0.01	6.54 ± 0.0.14
42	12.8	0.043	297.67	0.21 ± 0.01	5.47 ± 0.23
43	10.9	0.065	167.69	0.55 ± 0.03	7.05 ± 0.35
44	12.4	0.039	317.95	0.11 ± 0.01	4.99 ± 0.19
Celecoxib	12.7	0.045	282.22	0.167 ± 0.01	5.21 ± 0.19
Indomethacin	0.10	0.080	1.25	0.88 ± 0.04	–

−Not applicable.

[a]The result (IC$_{50}$, μmol/L) is the mean of three determinations acquired using a COX fluorescent inhibitor screening assay kit (Cayman Chemical, MI, USA).

[b]COX-2 selectivity index (COX-1 IC$_{50}$/COX-2 IC$_{50}$).

(IC$_{50}$ = 0.049 μmol/L, SI = 308.16) by using an enzyme immunoassay. In 2020, Alfayomy et al.[50] reported two new selective COX-2 inhibitors **50** and **51**, which belong to pyrimidine-5-carbonitrile hybrids with 1,3,4-oxadiazole scaffold. Compounds **50** and **51** showed significant and selectivity on COX-2 inhibition. Further investigation indicated that compounds **50** and **51** displayed good *in vivo* anti-inflammatory activity up to 89.5% inhibition at 4 h in carrageenan-induced rat paw edema assay. Moreover, compound **50** displayed superior safety profile than celecoxib. The results revealed that the pyrimidinyl substituent markedly affected the activity against COX-2. Grover et al.[51] synthesized a new series of oxadiazole-comprising derivatives **52–55**. Compounds **52–55** exhibited good and selective inhibition of COX-2 (EIA), but the efficacy and selectivity were less than reference drug celecoxib. Besides, compounds **53** and **55** had better *in vivo* anti-inflammatory activity than celecoxib (Table 4). The results confirmed that *tert*-butyl is an indispensable moiety to enhance COX-2 inhibitory activity and selectivity. This approach provides an alternative inspiration for new COX-2 inhibitor development.

2.7. Derivatives having fused heterocyclic fragments

Recently, fused heterocyclic rings have been flexibly used as crucial core for COX-2 inhibitors (Figs. 10 and 11). Szczukowski et al.[52] produced a number of novel hybrid pyrrolo[3,4-*d*]pyridazinone derivatives bearing 4-aryl-1-(1-oxoethyl)piperazine pharmacophores. Compound **56** exerted no cytotoxicity and had significant selective COX-2 inhibition at lower concentrations. Structurally, the arylpiperazine pharmacophore is connected with 1,3,4-oxadiazole ring *via* sulfur. The results indicated that elongating the linker part is important to enhance the anti-inflammatory activity. Khatri et al.[53] prepared several benzothiophene derivatives, and compounds **57**, **58**, **59**, and **60** showed potent and selective COX-2 inhibition (EIA) (IC$_{50}$ = 0.33, 0.31, 0.67, and 1.40 μmol/L respectively, selectivity index: 48.8–183.8). Analysis of SAR indicated that various substitutions of benzyl were the major determinants for COX-2 inhibition, such as compounds **59** (4-SO$_2$NH$_2$) and **60** (−NHCOCH$_3$), which showed enhanced activity compared with **57** and **58**. Moreover, compounds **57–60** showed considerable anti-inflammatory activity *in vivo*. Sun et al.[54] reported a series of novel selective inhibitors of enzyme COX-2. Compound **61** had potential anti-inflammatory activity with no cytotoxicity. Moreover, compound **61** showed selective inhibition towards COX-2 (IC$_{50}$ = 0.2 μmol/L) and COX-1 (IC$_{50}$ = 8.35 μmol/L) in

an enzyme immuno assay (Bio-Swamp). Four bioactive benzoxazole analogs were prepared by Kaur et al.[55]. Compounds **62–65** showed significant COX-2 inhibitory activity and selectivity towards COX-2 over COX-1. Of all the compounds, compound **62** was the most active compound with excellent inhibition of COX-2 (EIA) (IC$_{50}$ = 0.04 μmol/L) and good selectivity (SI = 25.5). The *in vivo* assays results indicated that compounds **62–65** had significant anti-inflammatory activity (% inhibition = 84.09%, 68.18%, 79.54% and 72.72%, respectively), greater than reference drug ibuprofen (% inhibition = 65.90, dose = 60 mg/kg). More importantly, they demonstrated a more significant gastric tolerance than ibuprofen, the pharmacokinetic profile of compounds **62–65** showed their available druggability. Later, a group of benzoxazole-benzamide analogs **66** was reported by the same group[56]. Compound **66** exhibited potent and selective COX-2 inhibition (EIA) with IC$_{50}$ of 0.14 μmol/L as compared to celecoxib (IC$_{50}$ = 0.15 μmol/L). Compound **66** also exhibited *in vivo* anti-inflammatory activity (79.54%) superior to ibuprofen (65.90%) (dose = 20 mg/kg); The ulcerogenic activity results indicated that compound **66** had significant more gastric tolerance than ibuprofen. The collected data revealed that electron withdrawing substitutions at *ortho* and *para* positions to phenyl ring aide in improving activity. Molecular docking results suggested that the benzoxazole ring is a crucial moiety to interact with Tyr[355] and Arg[120] of the COX-2 enzyme. All the experimental date demonstrated that compound **66** is a potential COX-2 inhibitor and valuable for further clinical investigation. Chen's group[57] reported a novel dihydropyrazole sulfonamide derivative **67**, which exhibited remarkable and selective COX-2 inhibition (IC$_{50}$ = 0.33 μmol/L), the potency almost
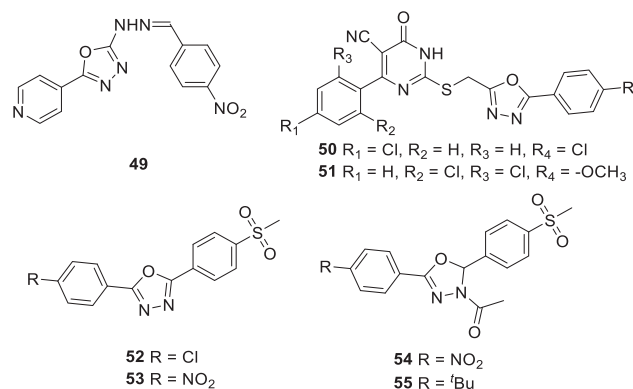

Figure 9 Chemical structures of compounds **49–55**.

Table 4 *In vitro* COX-1/COX-2 inhibition (IC$_{50}$, μmol/L), selectivity index and *in vivo* anti-inflammation activity (dose = 150 μmol/kg) for compounds **52−55**, and standard agents.

Compd.	COX-1[a]	COX-2[a]	COX-2 selectivity[b]	Rat paw edema (% edema inhibition, 5 h)
52	54.99	0.74	74.31	41.06 ± 2.64
53	63.76	0.48	132.83	58.04 ± 1.30
54	55.05	0.81	67.96	46.38 ± 2.47
55	60.61	0.89	68.10	59.33 ± 2.19
Celecoxib	37.98	0.10	379.80	49.81 ± 1.92
Indomethacin	98.23	50.99	−	−

[a]The result (IC$_{50}$, μmol/L) is the mean of three determinations acquired using a COX fluorescent inhibitor screening assay kit (Cayman Chemical, MI, USA).

[b]COX-2 selectivity index (COX-1 IC$_{50}$/COX-2 IC$_{50}$).
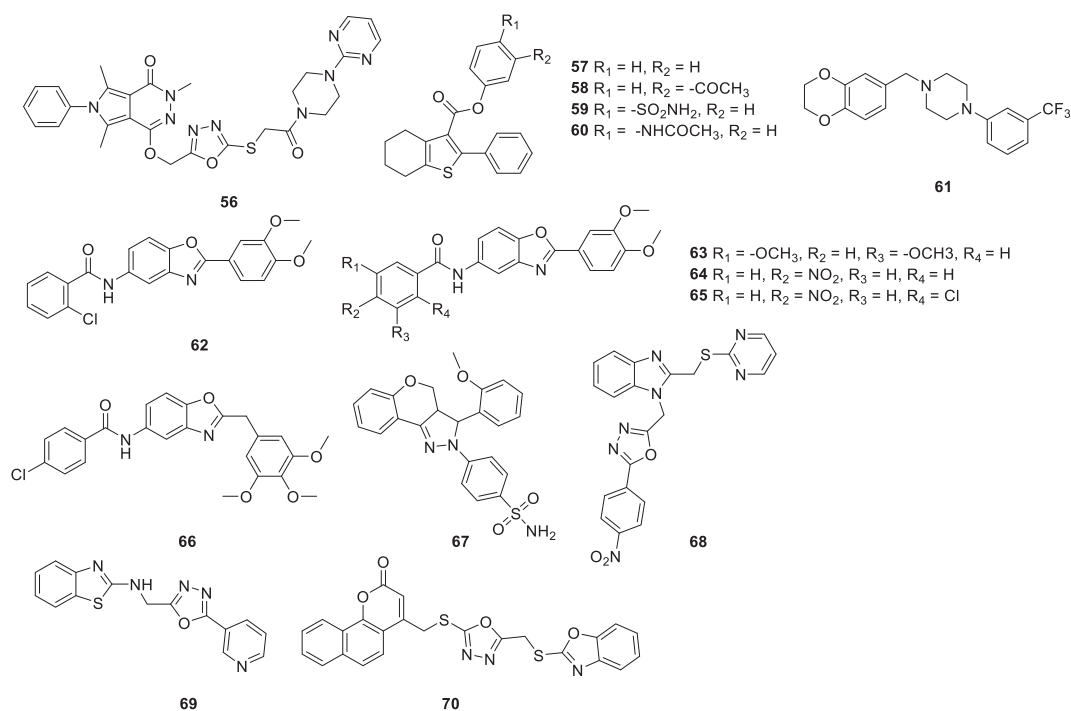
Figure 10 Chemical structures of compounds **56−70**.

Figure 11 Chemical structures of compounds **71−79**.

Table 5 *In vitro* COX-1/COX-2 inhibition (IC$_{50}$, μmol/L), selectivity index, ulcerogenic evaluation for compounds **75–79**, and standard agent.

Compd.	COX-1[a]	COX-2[a]	COX-2 selectivity[b]	Ulcer index
75	276.44	4.320	63.99	0.603 ± 0.15
76	76.67	25.87	2.963	–
77	300.72	11.48	26.19	0.642 ± 0.25
78	33.58	7.750	4.332	–
79	225.68	21.87	10.31	1.991 ± 0.34
Celecoxib	>50	0.34	147.05	1.204 ± 0.06

[a]The result (IC$_{50}$, μmol/L) is the mean of three determinations acquired using a COX fluorescent inhibitor screening assay kit (Cayman Chemical, MI, USA).
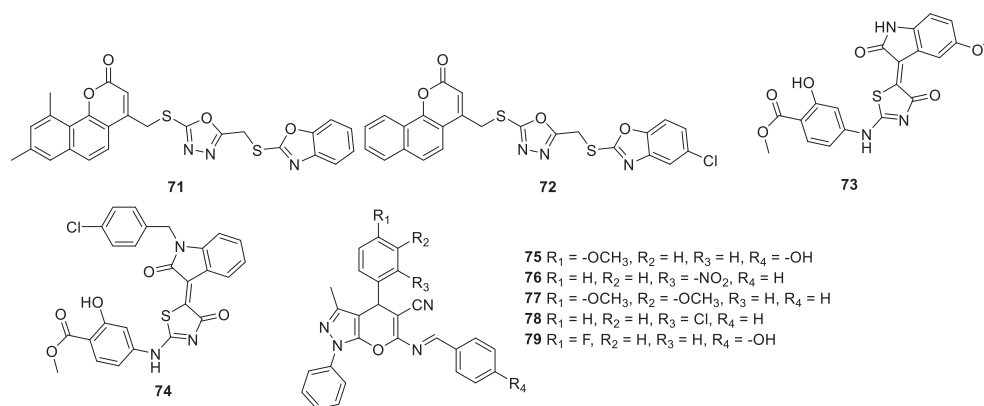[b]COX-2 selectivity index (COX-1 IC$_{50}$/COX-2 IC$_{50}$).

identical to that of celecoxib. Several new benzimidazole derivatives endowed with oxadiazole were described by Rathore et al.[58] in 2014. Compound **68** displayed reasonable COX-2 inhibition (EIA) (IC$_{50}$ = 8.2 μmol/L) and selectivity (SI > 12.1). Moreover, compound **68** was much safer in terms of gastric toxicity with a severity index of 0.48, lower than that of indomethacin. The SAR studies revealed that the electron-withdrawing compounds showed better COX-2 inhibitory activity than those of the electron-releasing ones. An oxadiazole analog **69** was reported by Iyer et al.[59] in 2016 and exerted good COX-2 inhibition but associated with moderate COX-1 inhibition *in vitro*. The undesirable COX-2 selectivity indicated that compound **69** need further modification. In the same year, Nesaragi's group[60] prepared some novel coumarinyl-1,3,4-oxadiazolyl-2-mercaptobenzoxazoles. Of these, compounds **70−72** displayed moderate and selective COX-2 inhibitions (IC$_{50}$ = 23.71, 33.47 and 23.95 μmol/L, respectively, SI = 33.95, 20.25 and 24.98, respectively). The results suggested that the activity is influenced by the bulkiness and lipophilicity of substituent on the benzene ring. Abdu-Allah et al.[61] synthesized two novel 4-aminosalicylate based thiazolinone derivatives **73** and **74**, both of which showed excellent COX-2 inhibitory efficacy (IC$_{50}$ = 44 and 39 nmol/L) and selectivity indexes (SI = 66.82 and 68.46). Unfortunately, the selectivity indices of tested compounds (**73** and **74**) were lower than celecoxib but still higher than diclofenac sodium and indomethacin. Additionally, compounds **73** and **74** showed improved safety profiles than indomethacin. Analysis of the biological data revealed that the bulkiness of the substituent at heterocyclic ring enhanced the COX-2 inhibition activity. Murahari et al.[62] introduced five active azomethine derivatives **75−79**. Compounds **75−79** showed potent and selective COX-2 inhibition revealing that substitution with electron donors such as methoxyl and hydroxyl has unfavorable effect on anti-inflammatory activity. Meanwhile, compounds **75−79** were subjected to an ulcerogenic activity assay, and showed safer profiles with low ulcer indices when compared to the clinically used drug celecoxib (Table 5).

3. Chemistry and pharmacology of structurally modified COX-2 inhibitors

3.1. Derivatives of existing market drugs

Structural modification of existing drugs is an effective approach for drug development. The structures of bumetanide, celecoxib, indomethacin, and nimesulide have also been altered to develop new

derivatives (Fig. 12). In 2020, Ibrahim et al.[63] have reported several novel benzenesulfonamide analogs which aim to developed as COX-2 inhibitors. Structurally, bumetanide was used as a precursor to synthesized new analogues. Of interest, the replacement of an acetic group by the bulky triazole moieties led to the potent COX-2 inhibitors, compounds **80** and **81**. Compounds **80** and **81** exhibited excellent inhibition (Cayman's COX (ovine) Colorimetric Inhibitor Screening Assay) of COX-2 with IC$_{50}$ values of 0.28 and 0.17 μmol/L, and a considerable selectivity index (SI = 71.93 and 115.82) in comparison to celecoxib (SI = 4.93). Further investigation indicated that compounds **80** and **81** showed good anti-inflammatory activity and lower ulcerogenicity when administered orally. On the basis of the structure of indomethacin, Ikeda's group[64] reported a fluorinated analog **82** of indomethacin, which bearing a lipophilic 3,3,3-trifluoroprop-1-enyl group at C-2 position. Compound **82** displayed greater COX-2 inhibitory activity and selectivity than indomethacin. Molecular docking results indicated that fluorine substituent of compound **82** contributed to a significant gain of the binding affinity for COX-2 by increasing van der Waals contacts. Aiming to discover novel selective COX-2 inhibitor. Chandna et al.[65] designed two series of celecoxib derivatives containing 1,5-diaryl fragments by bioisosteric replacement. The first series of celecoxib analogue were synthesized bearing a cyano group in place of sulfonamide moiety and then carbothioamide moiety was introduced and prepared the second series of analogues. Among these compounds, **83−86** exhibited potential selective COX-2 inhibitions (IC$_{50}$ = 7.07−19.22 μmol/L), but the activity of compounds **83−86** is weaker than that of celecoxib (Table 6). Nevertheless, compounds **83−86** showed potent *in vivo* anti-inflammatory activity which is comparable to indomethacin. Based on SAR study, the carbothioamide substituent compounds displayed better activity and selectivity than those of cyano substituent ones. In another study, Hassan et al.[66] reported a series of anti-inflammatory celecoxib analogs **87−91** by introducing a benzofuran moiety. It's worth noting that phenyl sulfonamide is an indispensable pharmacophore to maintain COX-2 selectivity. Accordingly, compounds **87−91** presented potent and selective COX-2 inhibitions with IC$_{50}$ values of 0.34−0.52 μmol/L. Meanwhile, changing the hydrogen in **87** into methyl in **89** led to minor decrease in COX-2 inhibition. The celecoxib analogue **91** with trifluoromethyl also had better COX-2 inhibition than fluoro analogue **90**. Compounds **87−91** also possess better gastric safety profile and less gastric ulceration effect compared to clinical drug celecoxib (Table 7). Renard et al.[67] prepared a series of nimesulide analogs **92−94** in accordance with its favorable gastric and cardiovascular safety profile. Chemically, these derivatives were designed in which the nitrobenzene ring was replaced by pyridine nucleus based on isosteric replacement. The oxygen atom also has been replaced with nitrogen to construct a new linker between two aromatic rings. As a consequence, compounds **92−94** exhibited remarkable inhibitory activity associated to a COX-2/COX-1 selectivity ratio (7.46, 15.35, and 7.67, respectively; IC$_{50}$ = 0.26, 0.09, and 0.30 μmol/L) similar or higher than that of celecoxib (ratio: 7.46, IC$_{50}$ = 0.35 μmol/L) in a human whole blood model. The SAR study indicated that the various substitutions on the benzene ring are the main factor affecting their activity towards COXs.

3.2. Derivatives having fragments of natural products

Pharmaceutical chemists continuously design new chemical scaffolds inspired by reported natural products from 2011 to 2021, including examples that were displayed in Fig. 13. Ribeiro et al.[68] designed a series of cinnamic acid derivatives, and found three
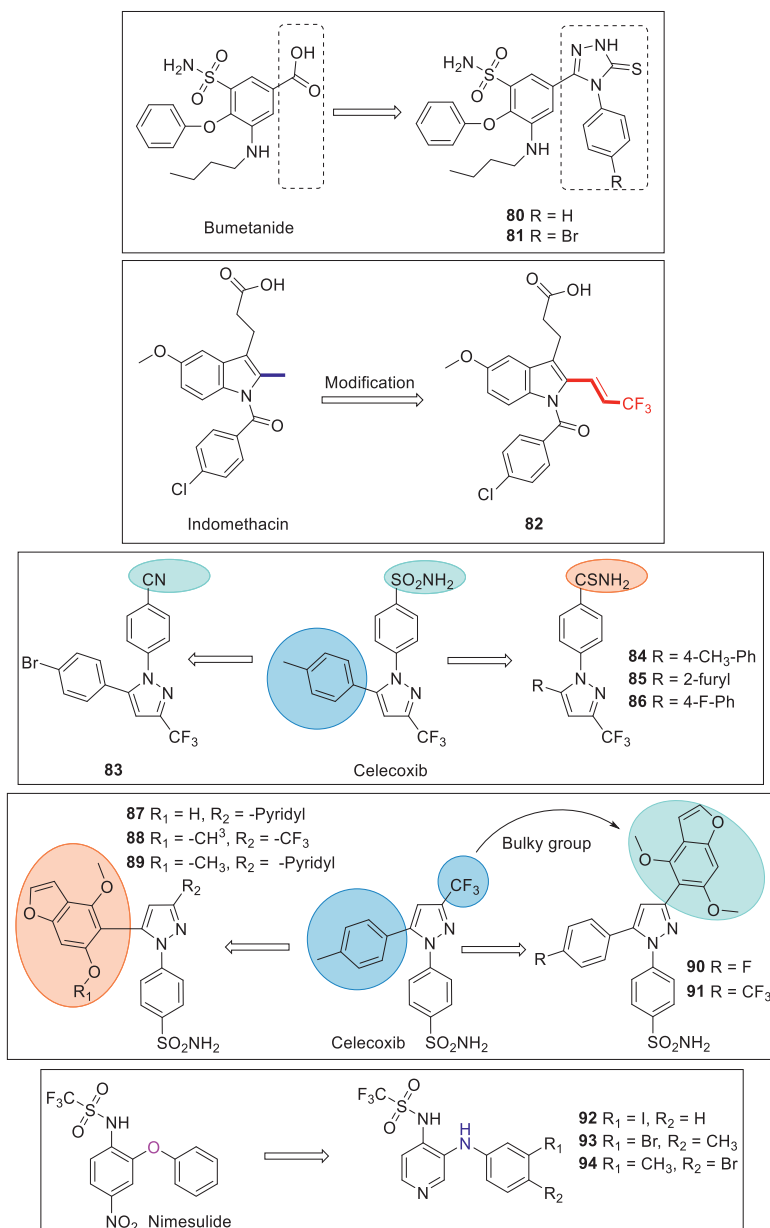
Figure 12 Chemical structures of compounds **80–94**.

active compounds **95–97** as new COX-2 inhibitors. Compounds **95–97** exhibited moderate inhibition of COX-2 (human whole blood assay) (IC_{50} = 3.0, 2.4, and 1.09 μmol/L; SI ≥ 33, 10.0, and 3.9, respectively). The results confirmed that phenolic hydroxyl fragment is a potential pharmacological core for COXs inhibition. The data acquired also indicated that by introducing a couple of bulky hydrophobic groups may be a fruitful approach to increase the COX-2 selective inhibition. Takahash et al.[69] reported a new synthetic serotonin derivative: compound **98**. Compound **98** showed weak inhibition on COX-2 (IC_{50} = 42.5 μmol/L) and considerable selectivity in serotonin derivatives testing assay. In this study, it was confirmed that extending amide linkage of **98** is crucial to increase COX-2 inhibitory activity. Rayar et al.[70] prepared a cyclocoumarol analog **99**, which exhibited good inhibitory activity against PGE_2 production, and no inhibitory activity against the COX-1 was observed. Further study indicated that

compound **99** showed considerable anti-inflammatory activity in a concentration-dependent manner.

4. Chemistry and pharmacology of potential COX-2 inhibitors from nature origin

Naturally occurring compounds have been reported to inhibit COX-2 enzyme, thereby possessing beneficial effects against inflammation. In the past ten years, a large number of natural compounds were identified as COX-2 inhibitors or exerting COX-2 inhibitory activity, examples as natural phenols, flavonoids, terpenoids, alkaloids, and other hybrids. The characteristics of their structural core scaffolds, COX-2 inhibitory activity, anti-inflammatory effects, and structure–activity relationships are introduced as follows:

Table 6 *In vitro* COX-1/COX-2 inhibition (IC$_{50}$, μmol/L), selectivity index and *in vivo* anti-inflammation activity for compounds **83−86**, and standard agents.

Compd.	COX-1[a]	COX-2[a]	COX-2 selectivity[b]	Rat paw edema (% edema inhibition, 4 h)
83	>30	19.22	>1.56	0.24 ± 0.05
84	>30	7.07	>4.24	0.84 ± 0.01
85	>30	9.07	>3.31	0.7 ± 0.07
86	>30	17.43	>1.72	0.3 ± 0.01
Celecoxib	>30	0.15	>200	–
Indomethacin	0.18	>30	–	0.17 ± 0.03

[a]The result (IC$_{50}$, μmol/L) is the mean of three determinations acquired using a COX fluorescent inhibitor screening assay kit (Cayman Chemical, MI, USA).
[b]COX-2 selectivity index (COX-1 IC$_{50}$/COX-2 IC$_{50}$).

4.1. Phenols

Čulenová et al.[71] investigated a phenolic compound **100** from *Morus alba* root bark. Compound **100** showed significant more *in vitro* COX-2 inhibition with the IC$_{50}$ value of 15.85 μmol/L than indomethacin (IC$_{50}$ = 27.04 μmol/L, SI = 0.16), but the selectivity of COX-2 is low (SI = 0.47). Natu's group[72] isolated an anti-inflammatory compound **101** from *Alpinia officinarum* Hance. Biological investigation indicated that compound **101** exhibited potent anti-inflammatory ability by the inhibition of the release and/or action of histamine, serotonin and kinin, and by COX-2 inhibition. Liu et al.[73] recently discovered two novel anti-inflammatory compounds **102** and **103** from *Carissa spinarum*. Compounds **102** and **103** were identified and showed good COX-2 inhibition by the COX-2 inhibition screening method (EIA) and the activity of compound **102** (IC$_{50}$ value = 0.3 μmol/L) was comparable to indomethacin (IC$_{50}$ = 1.1 μmol/L). Nile et al.[74] investigated the anti-inflammatory potency of three natural acids: ferulic acid (**104**), caffeicacid (**105**), and gallic acid (**106**). Compounds **104−106** showed potent COX-2 inhibitory activity (EIA) (IC$_{50}$ = 68.5, 62.5, and 65.2 μg/mL, respectively). Further investigation suggested that compounds **104−106** exerted anti-inflammatory effect through suppressing the activity of xanthine oxidase and COX-2 enzyme. Paulino et al.[75] extracted and analyzed the phenols of propolis and grape pomace from Uruguayan species. Z-Fertaric acid **107** was identified and demonstrated good anti-inflammatory activity, and COX-2 inhibitory activity. The potential pharmacological activity of curcumin **108** was investigated[76]. Briefly, curcumin exhibited anti-inflammatory activity by significantly reducing the production of pro-inflammatory

mediators including COX-2 and PGE$_2$ through NF-κB pathway. A new homoegonol **109** was isolated from the extracts of Mamuyo (*Styrax ramirezii* Greenm)[77]. **109** displayed anti-inflammatory activity by nitric oxide reduction. In addition, **109** was able to decrease the LPS-induced transcription of inducible pro-inflammatory enzyme coding genes of COX-2. Cheng's group[78] reported the isolation and anti-inflammatory evaluation of two phenols, Periplanetol A (**110**) and Periplanetol B (**111**) (Fig. 14), from *Periplaneta americana*. **110** and **111** exhibited good COX-2 inhibition activity with IC$_{50}$ values of 0.768 and 0.617 μmol/L, but it is lower than that of celecoxib (IC$_{50}$ = 0.041 μmol/L).

4.2. Flavonoids

Honmore et al.[72] discovered a flavonoid derivative **112**, which exhibited selective COX-2 inhibition. The *in vivo* mice assay showed that **112** had potential anti-inflammatory activity in paw edema in comparison with diclofenac. Paulino et al.[75] extracted several flavonoids from propolis and grape pomace, flavonoid glycosylate (**113**), pinobanksin (**114**), and anthocyanin (**115**). **113−115** showed potent anti-inflammatory and selective COX-2 inhibitory activity (EIA) (SI = 1.82, 1.52, and 1.64, respectively). Hu et al.[79] identified a flavonoid, kaempferol-3-*O*-rutinoside **116**, which showed VEGF-C-mediated anti-inflammation by interfering with VEGF-C-related signal transduction and interfered with the NF-κB signaling pathway. Compound **116** exhibited high potency to trigger the receptor activation and inhibited the production of IL-6, TNF-α, and the expression of iNOS and COX-2. The anti-inflammatory effects of compound **116** was investigated in LPS-induced macrophages, and indicated that **116**, as a natural compound, could be developed as an anti-inflammatory agent with good drug likeness. Nobiletin **117** (NOB) is a potential anti-inflammatory candidate. Xiao's group[80] recently reported their work on the anti-inflammatory potency of **117**. **117** showed significant anti-inflammatory activity by inhibiting the expression of pro-inflammatory markers. Further investigation demonstrated that compound **117** sharply reduced the levels of iNOS and COX-2 protein in a concentration-dependent manner. Three new flavonoids **18−20** (Fig. 15) were found from the leaves of *Myrica rubra* sieb[81], which can inhibit the expression levels of iNOS and COX-2 protein in a dose-dependent manner, and they also showed significant anti-inflammatory activity by inhibiting LPS-stimulated pro-inflammatory cytokines. Hanáková et al.[82] isolated a new geranylated flavanone **121** from *Paulownia tomentosa* fruits. Compound **121** had moderate COX-2 inhibition activity (EIA) (IC$_{50}$ = 9.5 μmol/L, SI = 2.8) and was more selective than ibuprofen (IC$_{50}$ = 4.2 μmol/L, SI = 1.5). Hosek et al.[83] reported a new

Table 7 *In vitro* COX-1/COX-2 inhibition (IC$_{50}$, μmol/L), selectivity index, ulcerogenic evaluation (rat 50 mg/kg) and for compounds **87−91**, and standard agent.

Compd.	COX-1[a]	COX-2[a]	COX-2 selectivity[b]	Ulcer index
87	>50	0.40	>6.67	13.82 ± 0.62
88	>50	0.52	>96.15	11.56 ± 0.54
89	>50	0.36	>138.90	10.50 ± 0.63
90	>50	0.46	>108.70	11.75 ± 0.63
91	>50	0.34	>147.06	10.50 ± 0.59
Celecoxib	>50	0.28	>178.57	16.12 ± 0.86

[a]The result (IC$_{50}$, μmol/L) is the mean of three determinations acquired using a COX fluorescent inhibitor screening assay kit (Cayman Chemical, MI, USA).
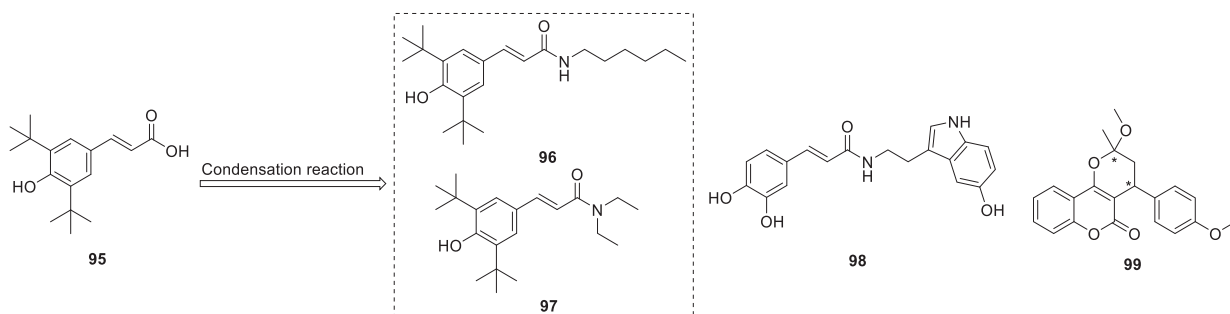[b]COX-2 selectivity index (COX-1 IC$_{50}$/COX-2 IC$_{50}$).

Figure 13 Chemical structures of compounds **95**−**99**.

geranylated flavonoid, diplacone **122**, which can significantly down-regulated the expression of COX-2 in Western blot assay. Meanwhile, a new flavonoid **123** was purified from licorice residues[84], which displayed potent NO inhibitory effect (IC$_{50}$ = 9.89 μmol/L) compared with minocycline (IC$_{50}$ = 33.20 μmol/L). Compound **123** also notably exhibited IL-1β, IL-6, iNOS, and COX-2 inhibition. A new compound **124** was identified from *Daphne genkwa* Sieb and showed anti-inflammatory activity through NF-κB signaling pathway[85], decreased expression levels of iNOS and COX-2 mRNA were observed. A large family of flavonoids, comprising compounds **125–132** (Fig. 16), was isolated from lotus plumule[86]. Compounds **125–132** displayed significant anti-inflammatory activity by inhibiting the production of pro-inflammatory cytokines. Further study demonstrated that compounds **125–132** were considered as potential COX-2 ligands by computer modeling calculations. An et al.[87] analyzed the anti-inflammatory effect of Saxifragin (**133**) which is founded abundantly in plants, especially in *Saxifrage stolonifera*. Compound **133** showed outstanding anti-inflammatory activity and decreased the production of PGE$_2$ through suppressing the level of protein expression of COX-2. Puerarin (**134**) is a flavonoid derivative and possesses antipyretic and sedation activity. Pharmacological experiments indicated that puerarin exerted anti-inflammatory activity *via* the ERK/Nrf2/ARE pathway by inhibiting the production of pro-inflammatory markers including iNOS and COX-2[88], it has the

potential to be a COX-2 inhibitor. Toyama's group[89] reported their work on the anti-inflammatory activity of 8-*C*-rhamnosyl apigenin **135**, which demonstrated selective COX-2 inhibitory activity with an IC$_{50}$ value of 28.6 μmol/L and potent *in vivo* anti-inflammatory activity. Waller et al.[90] evaluated the COX-2 inhibitory activity of four flavonoids **136**−**139** from the bulbs of the Southern African *Ledebouria socialis*. Compounds **136**−**139** showed good activity towards COX-2. Notably, compounds **136** and **137** had reasonable and selective COX-2 inhibitory activity (EIA) (IC$_{50}$ = 1.12 and 2.87 μmol/L, respectively). Kim et al.[91] evaluated the anti-inflammatory activity of a new chalcone **140** from *Alpinia* species. Compound **140** demonstrated inhibition of COX-2 expression and NF-κB activation in a luciferase transcriptional assay. Recently, Zhou et al.[92] detected the anti-inflammatory therapeutic effects of a natural chalcone, iso-bavachalcone **141**, which showed strong iNOS, COX-2, and NF-κB p65 inhibitory activity and attenuated the production levels of pro-inflammatory cytokine PGE$_2$. This compound is also a potential lead for further modifications and pharmacological evaluation. In addition, the methanol extract of *Boerhaavia diffusa* roots was investigated and led to the discovery of two active rotenoids **142** and **143**[93], both of which showed moderate COX-2 inhibition with IC$_{50}$ value of 31.4 and 25.5 μmol/L, respectively. However, both compounds **142** and **143** exerted less COX-2 selectivity indices of 1.09 and 0.79.
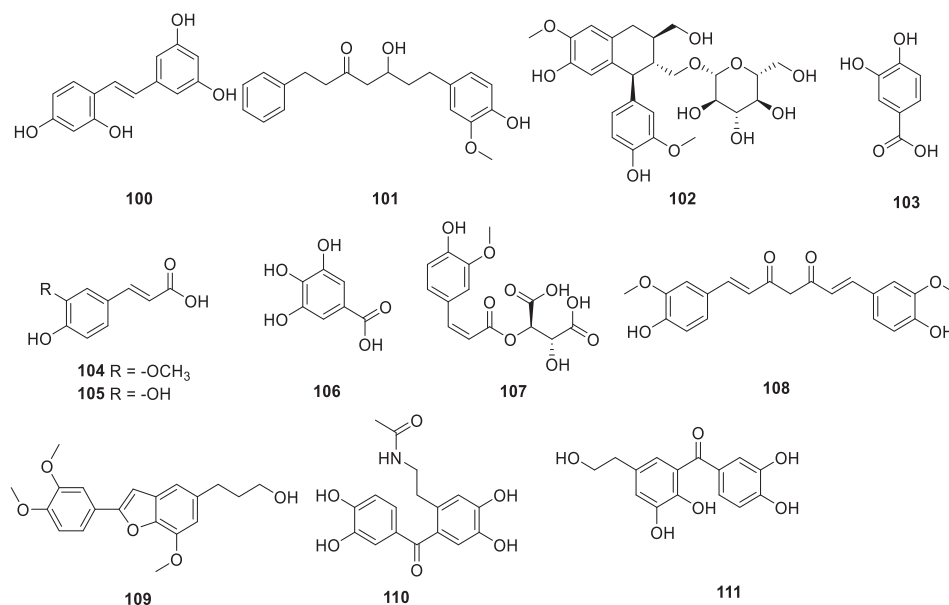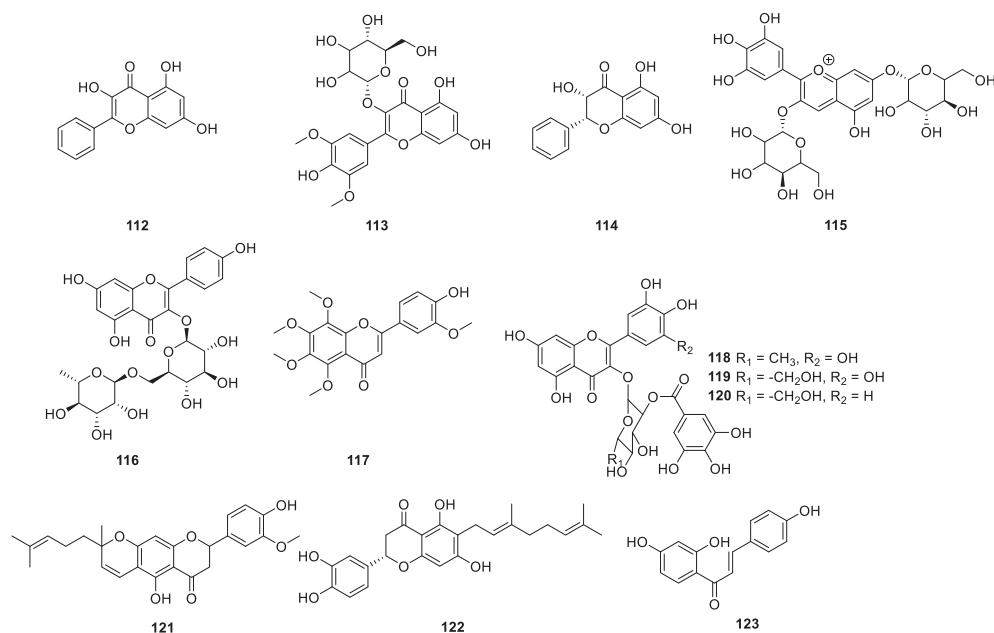

Figure 14 Chemical structures of compounds **100**−**111**.

Figure 15 Chemical structures of compounds **112**−**123**.

4.3. Terpenoids

Bauer's group[94] reported two new terpenoid derivatives: **144** and **145** from *Hypericum cistifolium*. Compounds **144** and **145** exhibited anti-inflammatory activity by inhibiting COXs activities (EIA). However, both of compounds **144** and **145** displayed relative low COX-1 and COX-2 inhibition. Zhang et al.[95] isolated and evaluated the ethyl acetate fraction of the ethanol extract from *Mallotus conspurcatus* croizat, and found two new terpenoids **146** and **147**, both of which demonstrated marked suppression of the secretion of PGE₂ and the expression of TNF-α, iNOS, NF-κB, and COX-2 proteins. Three new

sesquiterpenoids **148**, **149**, and **150** were isolated from the rhizomes and roots of *Nardostachys jatamansi* (Fig. 15)[96], which inhibit the expression of pro-inflammatory mediators COX-2 protein and cytokine PGE₂. An's group[97] reported a novel triterpenoid **151** from *Rosa rugosa* root, which potently inhibited the expression of COX-2 protein and also suppressed the production of PGE₂. Five new anti-inflammatory sesquiterpenes **152**−**156** (Fig. 17) were found from the leaves of *Artemisia lavandulaefolia*[98], the biological evaluation results showed that compounds **152**−**156** had weak COX-2 inhibitory activity with IC₅₀ values of 43.29−236.33 μmol/L. In 2020, Choo group[99] investigated the potential activity of a sesquiterpene
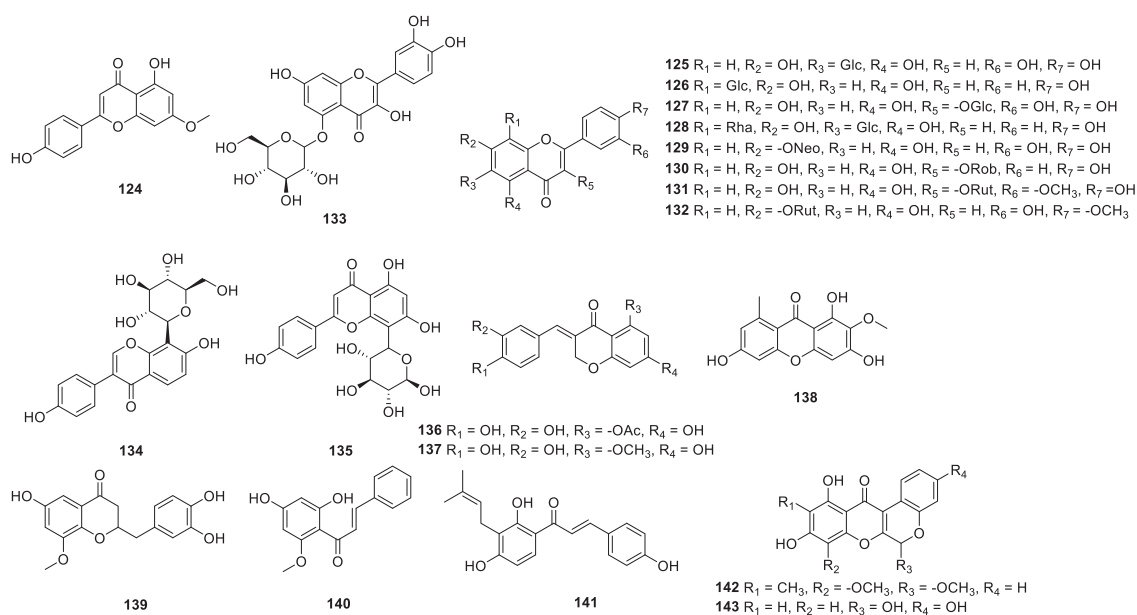

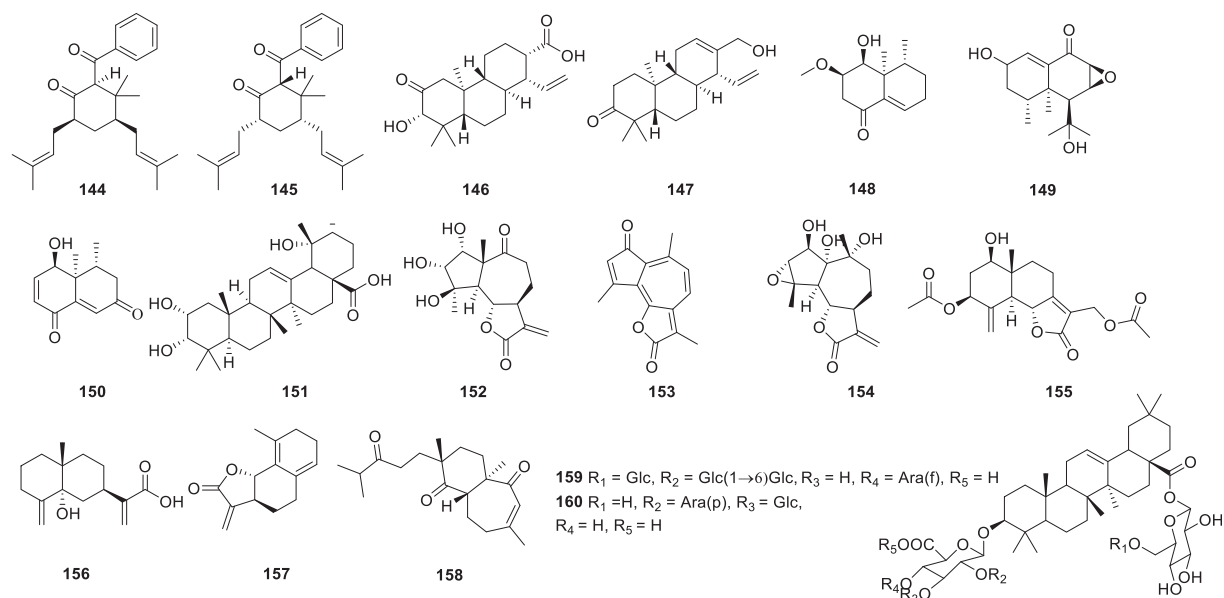**Figure 16** Chemical structures of compounds **124**−**143**.

Figure 17   Chemical structures of compounds **144**-**160**.

lactone, costunolide **157**. Compound **157** decreased the expression level of COX-2 protein and have good anti-inflammatory activity through NF-κB signaling pathway. Gao's group[100] recently isolated several new cyathane diterpenoids from the bird's nest fungus *Cyathus africanus*. Of the new compounds, compound **158** exhibited the most active COX-2 and iNOS inhibitory effects. Kim's group[101] reported two anti-inflammatory compounds, elatoside (**159**) and kalopanax-saponin F (**160**), which were first isolated from *Aralia elata*. Compounds **159** and **160** suppressed the NF-κB activation induced by TNF-α with IC$_{50}$ values of 4.1 and 9.5 μmol/L, respectively. Compounds **159** and **160** also showed inhibitory activity towards COX-2 in a dose-dependent manner.

4.4.   Alkaloids

More recently, a large family of quinolizidine alkaloids were purified from the seeds of *Sophora alopecuroides* (Fig. 18)[102]. Among them, a new anti-inflammatory alkaloid **161** exhibited higher NO inhibition with IC$_{50}$ values of 29.19 μmol/L than matrine (IC$_{50}$ = 38.90 μmol/L). Compound **161** also showed anti-inflammatory activity through decreasing the protein levels of COX-2. Feng et al.[103] had investigated the COX-2 inhibitory activity of berberine hydrochloride **162**, which showed inhibitory activity of the overexpressed COX-2 through PPAR-γ pathway.
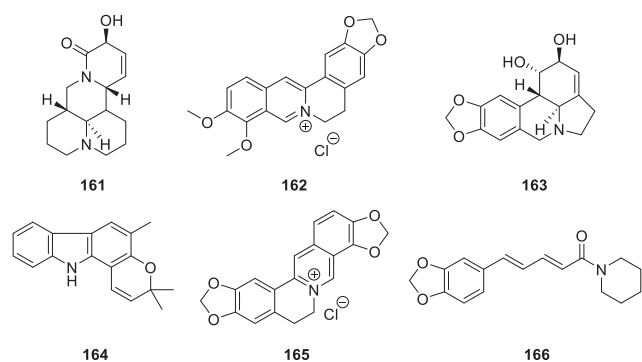

Figure 18   Chemical structures of compounds **161**−**166**.

Kang et al.[104] reported a new alkaloid **163** extracted from *Amaryllidaceae*, which exhibited anti-inflammatory activity *via* the P38 and STATs signal pathways. The expression levels of iNOS and COX-2 protein inhibited by **163** were observed, but didn't suppress the transcription of the COX-2 gene, suggesting that **163** may serve as a COX-2 inhibitor. Mohan et al.[105] investigated and assessed a major carbazole alkaloid girinimbine **164** presents in curry leaves, which exhibited potential anti-inflammatory activity. Compound **164** demonstrated suppressing effect on COX-2 enzyme, but no effect on COX-1 in an EIA assay. The result indicated that girinimbine **164** significantly inhibited COX-2 enzyme (% inhibition = 52.5; Dose = 25 μg/mL). Rui's group[106] reported an isoquinoline alkaloid (coptisine, **165**) from *Coptidis rhizome*. Similarly, compound **165** showed anti-inflammatory activity *via* the inhibition of NF-κB pathway. In particular, compound **165** effectively blocked the production of PGE$_2$ through COX-2 inhibition. Lee's group[107] evaluated and assessed the anti-platelet activity of a major alkaloid of black pepper and long pepper: piperine **166**, which showed anti-inflammatory activity by regulating the AA-metabolizing enzymes. In the downstream mechanism, compound **166** decreased the production of PGE$_2$ and PGD$_2$ *via* COX-2 inhibition.

4.5.   Others

In addition to the typical classes of natural products as introduced above, hybrid natural compounds (Fig. 19) were also discovered and showed COX-2 inhibitory and anti-inflammatory activity. Lin et al.[108] isolated and identified a novel quinone **167** from soft coral *Sinularia flexibilis*. The expression of COX-2 protein was significantly inhibited by compound **167** at 20 μmol/L with no cytotoxicity. Choi et al.[109] examined the anti-inflammatory activity of several naturally occurring anthraquinone derivatives, which were isolated from the Rhubarb Rhizome. The results indicated that compound **168** was the most potent of the compounds in inhibiting the protein expression of COX-2. Liu's group[110] reported a new phenyl compound **169**, which was identified from a mangrove plant derived fungus *Botryosphaeria* sp. Compound **169** exhibited remarkable COX-2 inhibitory activity (IC$_{50}$ = 1.12 μmol/L). A few
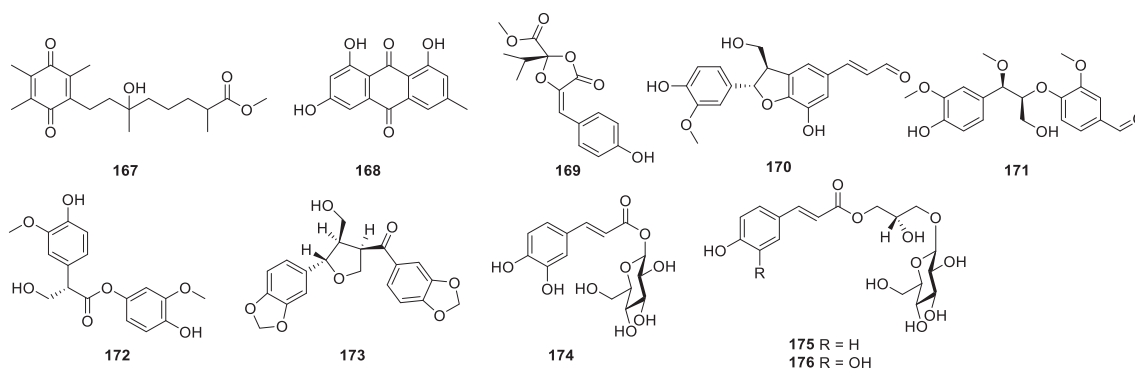
Figure 19   Chemical structures of compounds **167−176**.

phenylpropanoid derivatives **170−172** were purified from Chinese Olive by He's group[111]. Western blot analyses were performed in this study and found that they significantly and dose-dependently reduced the expression level of COX-2 protein. Shen's group[112] isolated a new phenylpropanoid (+)-episesaminone **173** from *Cinnamomum camphora,* which prominently suppressed the expression levels of COX-2 protein. Additionally, three phenylpropanoids **174−176** were isolated from *Lilium* Asiatic hybrids flowers by Baek's group[113]. At a concentration of 50 µg/mL, compounds **174−176** can effectively decreased COX-2 expressions.

5.   Conclusions and future perspectives

COX-2 is a bio-functional enzyme that catalyzes the biosynthesis of PGs during inflammation, and has become a significant therapeutic target when searching for anti-inflammatory drugs. Since 2011, more efforts have been focused on mining new chemical scaffolds as COX-2 inhibitors. The main emphasis of this review was on the potent COX-2 inhibitory and anti-inflammatory activity of various structural families of compounds, which have been reported within the last decade. With respect to the SAR, pyrazole analogs showed the most potent and selective inhibition of COX-2. Derivatives having fragments of natural products only showed moderate COX-2 inhibition and thereby demand more structural modification to improve their activity. Moreover, derivatives having indole, oxadiazole, thiazole, and tetrazole pharmacological cores also displayed acceptable COX-2 inhibitory activity. His[90], Arg[120] and Arg[513] were found to be most important amino acids for the inhibition and selectivity of COX-2. Meanwhile, extensive *in vitro* and *in vivo* pharmacological tests were performed and aim to discover new selective COX-2 inhibitors with safety profiles. In addition, a lot of natural compounds with good COX-2 inhibitory and anti-inflammatory activity were included herein. Natural products described in this review may provide inspiration for pharmaceutical chemists and also could serve as a foundation for novel COX-2 inhibitor design to avoid undesirable adverse effects.

Selective inhibition of COX-2 is a major feature of the new generation of NSAIDs, there are several prospects need to be considered for the development of next-generation of NSAIDs.

1) The new COX-2 inhibitors must be able to reduce stomach irritation and the risk of peptic ulcers.
2) In some respects, COX-1/COX-2 balanced inhibitors maybe a new direction for the development of NSAIDs, when the serious adverse effects of either non-selective or selective inhibitors are considered.

3) Majority of derivatives require the presence of aryl group as the basic scaffold for COX-2 inhibitors and thereby the solubility of the new compounds need to be further considered in clinical use. Introducing hydrophilic groups into the structures may be helpful to address this problem.

The above discussion will undoubtedly attract more interest in the coming years. Regarding the future research on COX-2 inhibitor, we strongly feel that utilizing the traditional medicinal chemistry approach seems to be insufficient for current clinical needs, combing genetic engineering, enzyme engineering, and computer science may be a fruitful way to confront future challenges.

Author contributions

Zhiran Ju and Fen-Er Chen generated the manuscript draft. Menglan Li, Junde Xu, Daniel C. Howell, and Zhiyun Li edited and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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