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REVIEW ARTICLE

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Small molecule compounds with good anti-inflammatory activity reported in the literature from 01/2009 to 05/2021: a review

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ABSTRACT

Inflammation and disease are closely related. Inflammation can induce various diseases, and diseases can promote inflammatory response, and two possibly induces each other in a bidirectional loop. Inflammation is usually treated using synthetic anti-inflammatory drugs which are associated with several adverse effects hence are not safe for long-term use. Therefore, there is need for anti-inflammatory drugs which are not only effective but also safe. Several researchers have devoted to the research and development of effective anti-inflammatory drugs with little or no side effects. In this review, we studied some small molecules with reported anti-inflammatory activities and hence potential sources of anti-inflammatory agents. The information was retrieved from relevant studies published between January 2019 and May, 2021 for review. This review study was aimed to provide relevant information towards the design and development of effective and safe anti-inflammation agents.

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1. Introduction

Inflammation is a complex response to noxious signals that for the host survival, it has been implicated in the pathogenesis of many human diseases[1]. Pro-inflammatory mediators, such as cytokines that are secreted in excess from inflammatory cells leads to development of arteriosclerosis when they chronically affect blood vessels. They also cause tissue degeneration and/or dysfunction to various organs. Chronic inflammation is also involved in sarcopenia that brings hypofunction in the elderly, dementia, osteoporosis, or cancer, several chronic diseases, and negatively affects life expectancy[2]. It has been reported that patients with neuropsychiatric disorders have increased levels of inflammatory mediators. Depression facilitates inflammatory reactions whereas inflammation promotes depression and other neuropsychiatric disorders. Patients with neuropsychiatric disorders exhibit all cardinal features of inflammation, including increased circulation levels of inflammatory inducers, activated sensors, and inflammatory mediators targeting various tissues. Therefore, neuropsychiatric disorders and inflammation are closely intertwined, and they possibly induce each other in a bidirectional loop[3,4]. Inflammation also plays an important role in the development of several age-related diseases, such as frailty. It has been reported that low-grade chronic inflammation can also increase the risk of atherosclerosis and insulin resistance which are the leading mechanisms in the development of cardiovascular diseases[5]. Inflammation is usually associated with the development and progression of cancer[6]. The relationships between inflammation and cancer are varied and complex. However, an important connection between inflammation and cancer development is DNA damage. Reactive oxygen and nitrogen species are generated during inflammation to combat pathogens and to stimulate tissue repair as well as regeneration. However, these chemicals can also damage DNA, causing mutations that initiate and promote cancer[7]. Currently, there are several experimental and clinical evidence that atherosclerosis is a chronic inflammatory disease[8]. Further, inflammation is closely related to several other diseases and hence deserves our attention.

The anti-inflammatory drugs currently used are associated with several side effects at varying degrees including gastrointestinal toxicities, cardiovascular risks, renal injuries, and hepatotoxicity as well as hypertension, sudden cardiac death, and other minor disorders[9–13]. Most of the anti-inflammatory drugs in clinical practice are becoming superseded due to their potential adverse effects. These are found to be highly unsafe for long-term use[14]. Therefore, it is of urgently significance to develop anti-inflammatory drugs with low toxicity and good efficacy. At present, the design of anti-inflammatory compounds has great limitations due to undesirable side effects but this has not curtailed enthusiasm of researchers in exploring for potent anti-inflammatory drugs[15].

This review focuses on the latest developments in the design and synthesis of anti-inflammatory small molecules since 2019, as well as the corresponding structure–activity relationship (SAR) research. The compounds discussed in this report have shown significant anti-inflammatory activity in pharmacological experiments or potential candidates for anti-inflammatory drugs. It is hoped that this article will help in the identification of potent scaffolds, which can provide new ideas for the development of new effective anti-inflammatory drugs.

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2. Recent development in anti-inflammatory agents

2.1. Pyrazole derivatives as anti-inflammatory agents

According to Kim et al. compound **1** (Figure 1) was developed and screened for its anti-inflammatory mechanisms following lipopolysaccharide (LPS)-induced neuroinflammation *in vitro* and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity *in vivo*. It was found that prophylactic treatment with compoud **1** decreased pro-inflammatory molecules through NF-κB and p38 mitogen-activated protein kinase (MAPK) signalling. These results suggest that compound **1** is a promising neuroprotective agent for prevention and treatment of microglia-mediated neuroinflammatory conditions[16].

In another study, El-Shoukrofy et al. designed and developed a new thiophene and annulated thiophene-pyrazole hybrids. The hybrids were screened for their *in vitro* COX-1/COX-2 enzymatic inhibition and *in vivo* anti-inflammatory activities. The thiophene analogue 2a (Figure 1) and the thienopyrimidine derivative 2b (Figure 1) are promising anti-inflammatory candidates that exert moderate selective COX-2 inhibition with acceptable physicochemical properties. The SAR study has found that replacement of the 5-hydroxypyrazole-4-carboxylate moiety by dimethylpyrazole ring system or diarylpyrazole functionality decreased the *in vivo* anti-inflammatory activity especially in the acute mode. It was found that replacement of the hydroxyl group in compound **2b** with amino group decreases the *in vivo* anti-inflammatory activity[17].

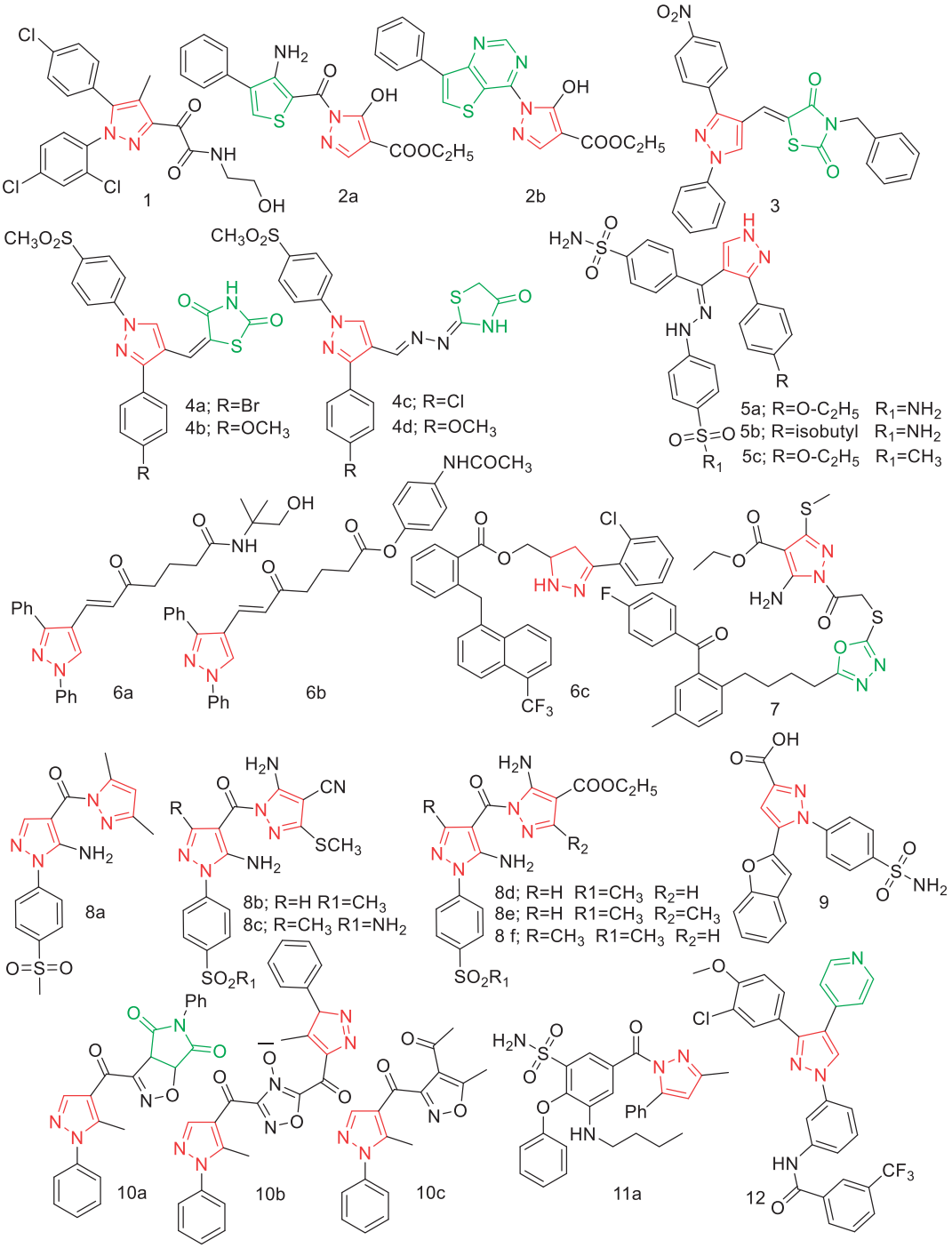

Figure 1. Pyrazole derivatives 1–12 reported as anti-inflammatory agents.

A total of 14 novel diaryl pyrazolyl thiazolidinediones were synthesised by Bansal et al. Compound **3** (Figure 1) was found to be potent anti-inflammatory agent in terms of reducing inflammatory markers (TNF-α, IL-β, and MDA)[18].

According to Abdellatif et al., two new series (thiazolidinedione series and thiazolidinone series) were synthesised containing pyrazole ring with vicinal diaryl rings as selective COX-2 moiety. Of these compounds, four compounds **4a**, **4b**, **4c**, and **4d** (Figure 1) had higher COX-2 selectivity index (SI) values (8.69–9.26) than the COX-2 selective drug celecoxib (COX-2 SI = 8.60) and showed the highest anti-inflammatory activities as well as the lowest ulcerogenicity than other derivatives[19].

Further, Abdellatif et al. also designed and synthesised three novel series of diarylpyrazole and triarylpyrazole derivatives. It was found that all the synthetic compounds were tested for both *in vitro* and *in vivo* inhibitory activity. All compounds were more selective for COX-2 isozyme than COX-1 isozyme and had excellent anti-inflammatory activity. All compounds showed significant COX-2 isozyme inhibitory activities (IC_{50} = 0.023–0.125 μM) and SI = 85.3–185.2 μM which was comparable to reference drug celecoxib (IC_{50} = 0.063 μM, SI = 142.2 μM). Compounds **5a**, **5b**, and **5c** (Figure 1) are more potent than celecoxib. The bisaminosulphonyl compounds showed higher anti-inflammatory activity compared with aminosulfonyl-methylsulfonyl compounds and were comparable to celecoxib[20].

Taher et al. reported novel pyrazole and pyrazoline derivatives. It was observed that compounds **6a**, **6b**, and **6c** (Figure 1) possessed significant anti-inflammatory activity (28.57–30.95%) in which **6a** gave comparable potency to that shown by reference drug, Indomethacin (30.95%). These results suggested that the length of carbon chain plays an important role in both anti-inflammatory activities. The lengthening of carbon chain in compounds **6a** and **6b** gave higher anti-inflammatory activities. Further, cyclisation of chalcones into pyrazolines gave compounds **6c** more potent anti-inflammatory effects[21].

According to Zabiulla et al. a series of benzophenones conjugated with oxadiazole sulphur bridge pyrazole pharmacophores were synthesised by incorporating fluoro, cholro, bromo, methoxy, and methyl groups at different positions of the benzoyl ring of benzophenone. After these were evaluated for anti-inflammatory activities, it was found that compound **7** (Figure 1) with electron withdrawing fluoro group at the para position of the benzoyl ring of benzophenone was characterised by the highest IC_{50} values (11.18, 0.10 μM) for both COX-1 and COX-2 inhibition[22].

In a separate study by Abdellatif et al. 13 pyrazole derivatives were synthesised and evaluated for their anti-inflammatory activity (*in vitro* and *in vivo*). All the compounds were found to be more potent against COX-2 than COX-1 isozyme and showed significant anti-inflammatory activity *in vivo*. Compounds **8a**–**8f** (Figure 1) showed good COX-2 SI (246.8–353.8) in comparison with the COX-2 selective drug: celecoxib (326.7). Furthermore, these compounds showed appreciable anti-inflammatory activity with oedema inhibition (51–86 and 83–96%) relative to celecoxib (60.6 and 82.8%) after 3 and 5 h, respectively [23].

Gedawy et al. designed new series of pyrazole sulphonamide derivatives. *In vitro* assessment of all the designed derivatives, COX-1, COX-2, and 5-LOX inhibitory activities were performed in the study. It was reported that compound **9** (Figure 1) showed the most potent analgesic and anti-inflammatory activities that surpassed the effectiveness of conventional drugs, celecoxib, and indomethacin. The compound **9** (Figure 1) showed potent COX-1, COX-2, and 5-LOX inhibitory activity with IC_{50} of 5.40, 0.01, and 1.78 μM, respectively. This indicated a SI of 344.56 that was more effective than the reference standards and its parent. In addition, it was confirmed that changing the carboxyl group in the structure of compound **9** with an ester derivative does not change activity of the compound **9**[24].

Abdelall et al. reported novel isoxazoles and the furoxan derivative as new safe anti-inflammatory agents. According to Abdelall et al., all these compounds were evaluated for COX-1/COX-2 and most of them were reported to show promising selectivity. The furoxan derivative 10b (Figure 1) gave 59% inhibitory activity using carrageenan-induced paw rat oedema model. Compounds **10a** and **10c** (Figure 1) were more found to be more selective than celecoxib and nearly with equal potency to celecoxib as anti-inflammatory agents *in vivo*. However, compounds **10a** and **10b** were found to be equally safe compared with celecoxib[25].

Ibrahim et al. designed and developed new benzenesulfonamide derivatives as selective COX-2 inhibitors based on bumetanide scaffold. Compounds **11a** (Figure 1), **11b,** and **11c** (Figure 13) were good inhibitors of COX-2 with IC_{50} values of 0.32, 0.28, and 0.17 μM, respectively. Further, compounds **11a**, **11b,** and **11c** were 12.6, 14.4, and 23.7-fold more potent than celecoxib, respectively. These compounds are selective on COX-2 with SI = 61.13 (**11a**), 71.93 (**11b**), and 115.82 (**11c**). Based on *in vitro* and *in vivo* experiment results, compounds **11b** and **11c** exhibited the highest anti-inflammatory activities and lowest incidence of pepticulcer[26].

It has been reported that the development of new triarylpyrazole derivatives and their biological activities at molecular, cellular, and *in vivo* levels. According to El-Gamal et al. compound **12** (Figure 1) was the most potent inhibitor of p38α/MAPK14 kinase (IC_{50} = 22 nM) among this series. It was reported that compound 12 inhibited p38α/MAPK14 kinase inside HEK293 cells in nanoBRET cellular kinase assay with EC_{50} value of 0.55 mM, which was comparable to the potency of dasatinib. Further, it was shown that compound **12** inhibits production of TNF-α in LPS-induced THP-1 cells with IC_{50} value of 58 nM. The *in vivo* anti-inflammatory effect of compound **12** was comparable to the effects of diclofenac with no ulcerogenic side effect on stomach[27].

New pyrazole derivatives were developed and evaluated for their COX-1 and COX-2 inhibitory activity *in vitro* by Hassan et al. It was reported that compounds **13a**, **13b**, **13c,** and **13d** (Figure 2) exhibited IC_{50} towards COX-2 enzyme of 39.43, 61.24, 38.73, and 39.14 nM, respectively. Furthermore, compounds **13a**, **13b**, **13c**, and **13d** exhibited SIs of 22.21, 14.35, 17.47, and 13.10, respectively. In the *in vivo* anti-inflammatory assay, it was reported that these compounds showed higher or comparable activity to positive control, celecoxib[28].

In separate studies, Abdelazeem et al. developed two 1, 5-diarylpyrazole series of urea- linked and amide-linked compounds. The two compounds were later evaluated as dual COX-2/sEH inhibitors using recombinant enzyme assays *in vitro*. Compounds **14a** and **14b** (Figure 2) showed the highest inhibitory activities against both COX-2 and sEH (IC_{50} of COX-2 = 1.85 and 1.24 μM; sEH = 0.55 and 0.40 nM, respectively). Further, the two compounds, **14a** and **14b** have a more favourable cardio-profile than celecoxib with much less cardiovascular risks associated with the common selective COX-2 inhibitors[29].

Mehta et al. developed a series of novel derivatives of N-(5–(1-methyl-indol-3-yl)-1, 3, 4-thiadiazol-2-yl)-2–(5-substitutedphenyl)-3-(phenylamino)-4 and 5-dihydropyrazol-1-yl) acetamide. They used carrageenan-induced inflammation in rat paw oedema model to screen for the anti-inflammatory activities of the derivatives. Compounds **15a**, **15b**, **15c**, and **15d** (Figure 2) were found to

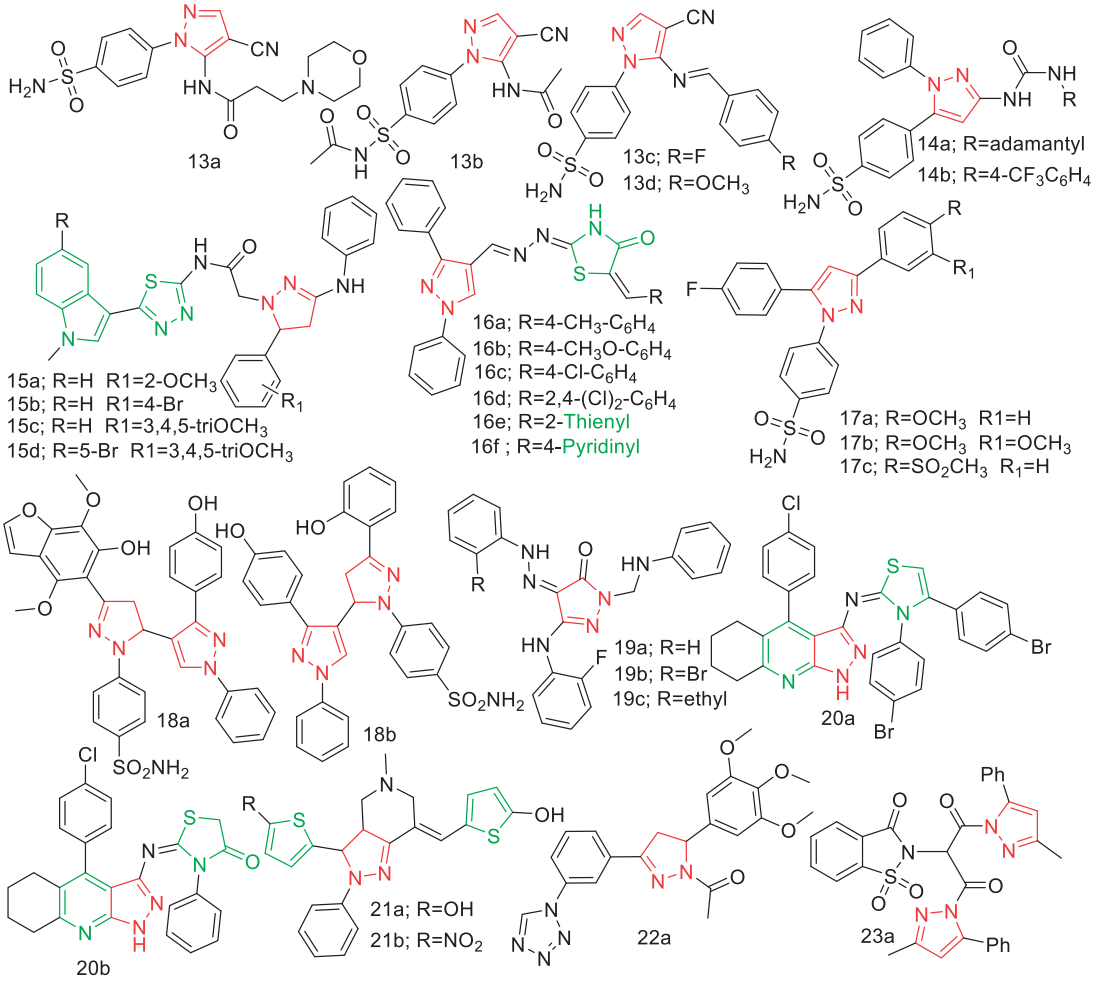

Figure 2. Pyrazole derivatives 13a–23a reported as anti-inflammatory agents.

possess good anti-inflammatory activity having percentage of inhibition to the extent of 46.8%, 48.1%, 49.4%, and 48.5%, respectively, whereas the effects of the standard drug, diclofenac were 50.0%[30].

In another study, Abd et al. designed and developed a new set of pyrazole-thiazolidinone conjugates. Experimental data showed that the compounds **16a**−**16f** (Figure 2) were the most promising anti-inflammatory candidates producing rapid onset of action. Further, the SAR study showed that the benzylidene scaffold without any substitution revealed no activity. In addition, the activity was improved *via* the insertion of electron-donating groups at *para*-position (4-methyl or methoxy groups) whereas alteration to *meta*-position caused a significant drop in the activity. Substitution of the benzylidene moiety with electron drawing groups (CN, F, or Br) weakened the anti-inflammatory activity whereas the reverse results were obtained by the Cl-substituted compounds afforded promising potency. However, it was reported that the heterocyclic rings can produce wide variations in the activity[31].

Another study by Abdellatif et al. designed and developed twelve halogenated triarylpyrazoles. All the target compounds in this study showed appreciable *in vitro* COX-2 inhibitory activity (IC_{50} = 0.043–0.17 μM) over COX-1 (IC_{50} = 7.8–15.4 μM) relative to celecoxib (COX-1/IC_{50} = 9.87 μM and COX-2/IC_{50} = 0.055 μM). Compounds **17a**, **17b**, and **17c** (Figure 2) displayed remarkable potency (IC_{50} = 0.049, 0.057, and 0.054 μM, respectively) which was marginally closer to the potency effect of positive control, celecoxib. The compounds (compounds **17a**, **17b,** and **17c**; Figure 2) displayed superior anti-inflammatory activity at all-time intervals (% oedema inhibition = 42.1–87.9) and showed lower ulcer index values (UI = 1.25–2.5) than indomethacin (UI = 14) and close to celecoxib (UI = 1.75). Through their research study, it was revealed that differences in size and electronegativity of the halo substituent have a remarkable effect on biological activity[32].

New hydroxybenzofuranyl-pyrazolyl chalcones, hydroxyphenyl-pyrazolyl chalcones and the corresponding pyrazolylpyrazolines were developed by Ragab et al. It was reported that there was no statistical deference in *in vivo* anti-inflammatory activities of compounds **18a** and **18b** (Figure 2) as compared with the effects of the standard drug, celecoxib. It was shown that derivatives 18a and 18b with obvious selectivity against COX-2 and still sustaining similar degree of COX-1 inhibition may have lower cardiovascular side effects than those with exclusive inhibition of COX-2[33].

According to Mohamed et al., the newly developed pyrazoles and pyrazolo [3, 4-b] pyridines were COX-2 inhibitors. It was found that compounds **19a**, **19b**, and **19c** (Figure 2) were the most active and selective as COX-2 inhibitors with IC_{50} values 0.071, 0.048, and 0.055 μM. Further, they were the most effective in protection from oedema and had the least ulcerogenic effect among all derivatives[34].

The synthesis of 13 chlorinated tetrahydro-1H-pyrazolo [3, 4-b] quinoline by Mroueh et al. was reported to serve as tacrine analogues with both lower hepatotoxicity and high COX-2 inhibitory activity. Compounds **20a** and **20b** (Figure 2) were able of

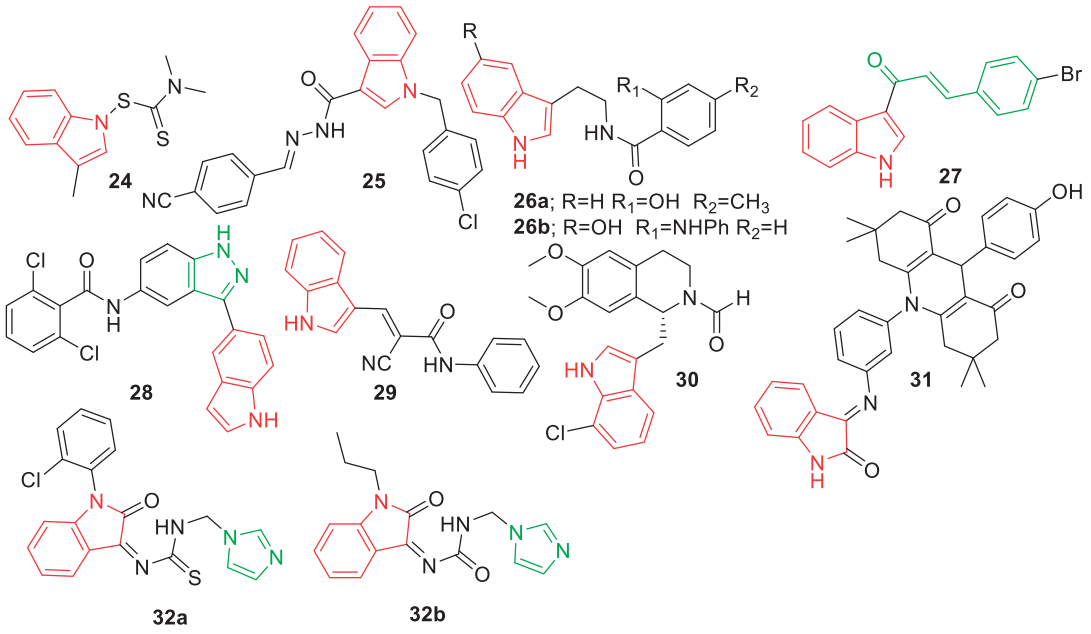

Figure 3. Indole derivatives 24–32b reported as anti-inflammatory agents.

inhibiting LPS-induced COX-2 protein expression at a concentration as low as of 10 μg/mL with COX-2 inhibitory IC_{50} of 0.76 and 0.84 μM, respectively, from levels analogous to non-stimulated control cells[35].

Elsewhere Dennis et al. developed pyrazolopyridines as anti-inflammatory agents. It was found that, in all *in vitro* and *in silico* studies, compounds **21a** and **21b** (Figure 2) showed the highest effects which were similar to the effect of the positive drug indomethacin, but higher than that the effects of indomethacin[36].

Elsewhere, Labib et al. reported the design and development of 4 novel sets of tetrazole derivatives as selective COX-2 inhibitors. Compounds **22a** (Figure 2) and **22b** (Figure 19) exhibited potent COX-2 inhibitory activity (IC_{50} = 0.039–0.065 μM) *in vitro*. For their *in vivo* anti-inflammatory activity applying carrageenan-induced paw oedema assay in rats at different time intervals, compounds 22 b (% oedema inhibition = 29.209–41.379) and 22a (% oedema inhibition =30.120–42.643) were more effective than reference celecoxib (% oedema inhibition = 28.694–40.114). Further, it was found that, trimethoxy derivatives were more potent inhibitors of COX-2, PGE2, TNF-α, and IL-6[37].

Taher et al. synthesised two new series of 1, 2-benzisothiazol-3(2H)-one-1, 1-dioxide derivatives and evaluated for their *in vitro* COX-1/COX-2 inhibitory activity. *In vivo* anti-inflammatory evaluation revealed that derivatives 23b (Figure 19), 23c (Figure 19), and its cyclised form **23a** (Figure 2) exhibited the highest anti-inflammatory activity with comparable potency to standard drug, celecoxib[38].

In addition, there is a pyrazole ring in the structure of compound **28** (Figure 3), compound **65e** (Figure 9), and compound **85** (Figure 15).

2.2. Indole derivatives as anti-inflammatory agents

A total of 29 novel indole-dithiocarbamate compounds were prepared and evaluated by Song et al. for their anti-inflammatory activity. Most of these compounds exhibited high potency on inhibiting the releasing of tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). It was also noted that compound **24** (Figure 3) exhibited a dose-dependent inhibition effect on both TNF-α and IL-6 production. Moreover, it was reported that compound **24** effectively suppressed the expression of TNF-α, IL-6, IL-1β, VCAM-1, and ICAM-1 at the mRNA level in lung tissues[39].

In different study, Ju et al. designed a series of substituted indole analogues and tested for their inhibitory activity against COX-1 and COX-2. Compound **25** (Figure 3) showed the most potent inhibition of the both enzymes with higher selectivity to COX-2, close to that of diclofenac. In addition, a possible anti-inflammatory mechanism of compound **25** was proposed based on the *in vitro* results. It was found that compound **25** can first inhibit COX-2, leading to a decrease in reactive oxygen species (ROS) production. Decreased ROS production culminates in to the suppression of NF-κB activation and endonuclear translocation, thereby attenuating the expression of pro-inflammatory mediators, such as iNOS, COX-2, TNF-α, and IL-6[40].

According to Fan et al. the newly synthesised 23 derivatives of N-salicyloyl tryptamine as multifunctional agents and revealed their new application for anti-neuroinflammation. Two of the compounds, **26a** and **26b** (Figure 3) displayed highly preferable COX-2 inhibition. On the other hand, compounds **26a** and **26b** reduced GFAP and Iba-1 levels in the hippocampus and displayed neuroprotection in Nissl staining *in vivo*. Besides, both compounds **26a** and **26b** had remarkable safety with LD_{50} > 1000 mg/kg[41].

The anti-inflammatory effect of indole-based chalcone derivative 27 (Figure 3) was evaluated on LPS activated murine macrophages RAW264.7 cells and carrageenan-induced acute in rats models. The IC-9 at a low dose (7.5 mg/kg bwt) showed more potent activity on carrageenan-induced inflammation in animal model. The study demonstrated that the compounds **27** responsive mechanism appeared to be dependent on NF-jB-sensitive transcriptional regulatory mechanism[42].

A new series of 3-(indol-5-yl)-indazoles was also designed, developed, and evaluated for their anti-inflammatory activities in macrophages. Among the compounds generated, compound **28** (Figure 3) inhibited LPS-induced expression of TNF-α and IL-6 in macrophages with IC_{50} values of 0.89 and 0.53 μM, respectively. The SAR analysis showed modification of electron-donating groups like 3-methyl, 3, 5-dimethoxy group or heterocycles, which led to a dramatic loss in inhibitory activity against both IL-6 and TNF-α. Halogen group substituted benzamide and this was found

to be crucial for the anti-inflammatory effect. However, the hydroxyethyl group may have not contributed to the anti-inflammatory benefits[43].

In the paw oedema assay, the compound **29** of newly designed and developed (E)-2-cyano-3-(1H-indol-3-yl)-N-phenylacrylamide by Silva et al. with 50 mg/kg (Figure 3) showed satisfactory anti-inflammatory activity. Moreover, in the peritonitis assay that assesses leukocyte migration, the compound **29** also exhibited promising results. Therefore, these preliminary studies demonstrated that compound **29** is a strong candidate for development of an anti-inflammatory drug with an improved gastrointestinal safety profile as compared to the conventional anti-inflammatory drugs[44]. Zhang et al. synthesised a series of novel tetrahydroisoquinoline derivatives based on the crystal structure of phosphodiesterase 4 (PDE4). *In vivo* studies demonstrated that a topical administration of 30 (Figure 3) achieved more significant efficacy than calcipotriol to improve the features of psoriasis-like skin inflammation[45].

Compound **31** (Figure 3) was developed by Periyasami et al. and was found to have excellent anti-inflammatory pharmacological efficiency in *in vivo* biological experiments. Anti-inflammatory activity of this compound was equivalent to that of the standard drug, indomethacin. The molecular mechanisms of target molecule might be related to the decline of NF-kB, TNF-α, IL-6, and IL-1β that may possibly result in inhibition of COX-2 and iNOS expression and its product (PGE2 and nitric oxide [NO])[46].

A wide range of substituted imidazoles was developed by Kumar et al. synthesised through a one-pot approach. The anti-inflammatory property of imidazoles was analysed by human red blood cell (HRBC) membrane stabilisation method. Imidazole moieties **32a** and **32b** (Figure 3) were adjudged to be the promising dual purpose drugs to treat both inflammation and breast cancer. These compounds also showed appreciable H_2O_2 scavenging activity[47].

In addition, there is an indole ring in the structure of compounds **15a**–**15d** (Figure 2).

2.3. Chalcone derivatives as anti-inflammatory agents

According to Fu et al. 38 chalcone derivatives bearing a chromen or benzo[*f*]chromen moiety were designed and synthesised. Six compounds bearing a chromen moiety were weak inhibitors of the COX-1 isozyme but showed moderate COX-2 isozyme inhibitory effects (IC_{50}s from 0.37 to 0.83 μM). The compounds bearing a benzo[*f*]chromen moiety were more selective towards COX-2 than those bearing a chromen moiety with IC_{50}s from 0.25 to 0.43 μM. Compounds **33a** and **33b** (Figure 4) were found to be the most active and selective COX-2 inhibitors with IC_{50} values of 0.39 and 0.43 μM. The order of activity for the compounds containing substitutions on the phenyl ring was *p*-F > *o*-F > *m*-F, *p*-Cl > *o*-Cl > *m*-Cl, and *p*-Br > *o*-Br > *m*-Br. Further, the order of activity for compounds containing the benzo [*f*] chromen moiety with substitutions on the phenyl ring was o-F > m-F > p-F and the order of activity for Br-substituted positions was *o*-Br > *m*-Br > *p*-Br. For compounds containing the electron-donating groups on the phenyl ring, the anti-inflammatory activities were in the order of *4*-CH_2CH_3 > *3*, *4*-$(OCH_3)_2$ > *4*-OCH_3 > *4*-N $(CH_3)_2$ > *4*-CH_3 > *4*-NH_2 > *3*, *4*-$(CH_3)_2$. Compounds containing the benzo[*f*]chromen moiety had activities in the order of *4*-CH_2CH_3 > *4*-OCH_3 > *4*-CH_3 > *4*-N $(CH_3)_2$ > *4*-NH_2 > *3*, *4*-$(OCH_3)_2$ > *3*, *4*-$(CH_3)_2$[48].

Ribeiro et al. synthesised a new series of cinnamic acid derivatives and evaluated in human blood for their inhibitory activity of COX-1 and COX-2 enzymes. The relationships between structure and activity showed that phenolic hydroxyl groups are essential for both COX-1 and COX-2 inhibition. In addition, the presence of bulky hydrophobic di-tert-butyl groups in the phenyl ring strongly contributes to selective COX-2 inhibition. This study revealed three effective selective inhibitors of COX-2, namely compound **34a** (Figure 4) with IC_{50}=3.0 ± 0.3 μM, compound **34b** (Figure 4) with IC_{50}=2.4 ± 0.6 μM and **34c** (Figure 4) with IC_{50}=1.09 ± 0.09 μM[49].

In another study, Tang et al. developed a series of novel chalcone derivatives bearing bispiperazine linker and screened *in vitro* anti-inflammatory. The IC_{50} values of compounds **35a** (Figure 4) and **35b** (Figure 4) were 0.42 and 0.82 μM, respectively. The preliminary SAR analysis indicated that the type of bispiperazinochalcone derivatives influences the anti-inflammatory activities as well as the linkers of bispiperazine. Further, it was found that the amide linker of the compounds had an obvious influence on anti-inflammatory activities[50].

In another study Boshra et al. designed and developed two novel series of 2′-hydroxychalconetriazole hybrid molecules. All the compounds were evaluated *in vitro* and *in vivo* for anti-inflammatory activity. Most of compounds were selective inhibitors of COX-2. Compounds **36a**–**36f** (Figure 4) demonstrated highly potent dual inhibition of COX-2 (IC_{50}=0.037–0.041 μM) and 15-LOX (IC_{50}=1.41–1.80 μM) [51].

A series of paeonol derivatives were also developed by Hu et al. Compound **37** (Figure 4) was found to have low toxicity, which showed 96.32% inhibitory activity at 20 μM and IC_{50}=6.96 μM against LPS-induced over expression of NO in RAW 264.7 macrophages. Preliminary mechanism indicated that compound **37** could significantly suppress LPS-induced expressions of iNOS, COX-2, and inhibit NO production through NF-κB/MAPK signalling pathway in a concentration-dependent manner. It was also found that the anti-inflammatory activity could be improved when the strong electron-withdrawing group was substituted by the aromatic ring, such as -CF_3, -OCH3, and -F[52].

Dozens of piperlongumine analogues were developed and tested on PC12 cells to examine neuroprotective effects against H_2O_2 and 6-OHDA induced damage Ji et al. designed and synthesised. Among them, compound **38** (Figure 4) was found to alleviate the accumulation of ROS, inhibit the production of NO, and down-regulate the level of IL-6. Preliminary mechanism confirmed that compound **38** exerted antioxidant and anti-inflammatory activities by activating Nrf2 signalling pathway[53].

Elsewhere, Yao et al. designed and developed a series of dissymmetric pyridyl-substituted 3, 5-bis (arylidene)-4-piperidones. It was reported that compound **39** (Figure 4) effectively promoted cell apoptosis through up-regulating cleaved caspase-3 and Bax expression and down-regulating Bcl-2 expression. Furthermore, compound **39** significantly inhibited NF-κB pathway activation by blocking the phosphorylation of IκBα and exhibited the strongest inhibitory effect against both TNF-α and IL-6 expression with inhibition rate of upto 15%. HE staining and immunohistochemistry results also proved that the antitumor and anti-inflammatory effect of compound **39** (10 mg/kg) is comparable to the positive drug[54].

In a separate study, Qian et al. prepared a novel series of dicarbonyl analogues of curcumin and evaluated for their anti-inflammatory properties. It was found that compounds **40a** and **40b** (Figure 4) showed the most potent anti-inflammatory activities. In addition, the two compounds had higher structural stability, orally bioavailability *in vitro* and markedly alleviated LPS-induced acute lung injury (ALI)[55]. Two chalcone derivatives as anti-inflammatory agents were developed by Emam et al. They reported that compound **41** (Figure 4) exhibited the highest

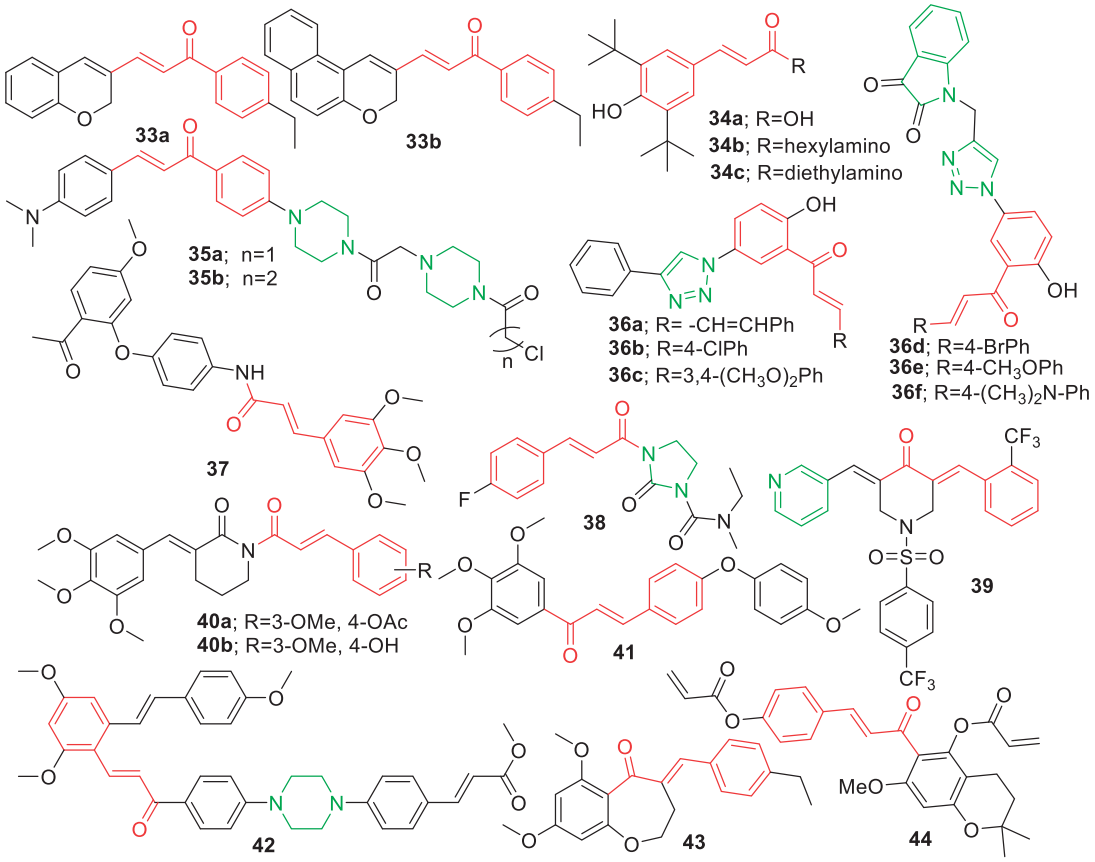

Figure 4. Chalcone derivatives 33–44 reported as anti-inflammatory agents.

anti-inflammatory activity by inhibition of NO concentration in LPS-induced RAW264.7 macrophages (IC_{50}=11.2 μM). Moreover, compound **41** decreased the expression of NF-κB and phosphorylated IκB in LPS-stimulated macrophages[56]. In a different study, Ma et al. synthesised a series of novel derivatives between resveratrol and chalcone possessing piperazine moiety. Derivative 42 (Figure 4) was found to be the most potent anti-inflammatory agent (IC_{50}=4.13 ± 0.07 μM) [57].

A series of new benzoxepane derivatives were designed and synthesised by Gao et al. According to the study, compound **43** (Figure 4) (inhibition of TNF-α release IC_{50} values of 5.2 μM) was the most effective compound *in vitro* with low toxicity. Further, compound **43** was shown to display anti-inflammatory effect *in vitro* and *in vivo via* inhibiting PKM2-mediated glycolysis and NLRP3 activation. The SAR analysis showed the position and number of methoxyl groups could affect the activity, OCH_3>*para*-OCH_3 >3, 4, 5-trimethoxyl. It was found that when replacing benzene ring to pyridine ring, the activity remained the same whereas the toxicity levels were aggravated. In addition, it was reported that insertion of a triple bond between double bond and benzene ring resulted in loss of the activity[58].

Ajiaikebaier et al. synthesised 25 derivatives of pyranochalcone and evaluated *in vitro* activities against TNF-α induced NF-κB inhibition in HEK293T cells. It was found that several displaying the same acrylate moiety on the B ring exhibited potent inhibition, with IC_{50} values ranging from 0.29 to 10.46 μM. It was reported that the most potent was compound **44** (Figure 4) with IC_{50} values of 0.29 μM. The study demonstrated that the inhibitory effect of compound **44** on LPS-stimulated inflammatory mediator production in the mouse macrophage cell line RAW 264.7 correlates with the suppression of the NF-κB and the MAPK signalling pathways[59].

2.4. Pyridine derivatives as anti-inflammatory agents

Jiang et al. synthesised a series of (hetero) arylethenesulfonyl fluorides and screened for their *in vitro* anti-inflammatory activities. Compounds **45a** (Figure 5) and **45b** (Figure 19) showed excellent anti-inflammatory activity with IC_{50} values of 18.77 ± 1.10 and 16.06 ± 1.09 μg/mL, respectively. Compounds containing electron-withdrawing (–Cl, $–NO_2$, –F, and –Br) groups on the phenyl ring were found to be the most potent anti-inflammatory agents. Notably, the presence of $-SO_2F$ group played a crucial role in increasing anti-inflammatory activities[60].

El-Kerdawy et al. synthesised a new series of benzimidazothiazole derivatives and conducted *in vitro* and *in vivo* anti-inflammatory screening of the compounds. Results revealed that the thiourea derivatives (46a and 46b (Figure 5)) had the most active compounds, with IC_{50} values of 4.52 and 16.02 nM, respectively. These values were equal to 1/10 and 1/2 values of celcoxib, respectively. In addition, the pharmacological data indicated the importance of the thiourea moiety for anti-inflammatory activity in contrast to the isocyanate ones[61].

Ali et al. synthesised a series of B-RAF^{V600E} imidazol-5-yl pyridine inhibitors to inhibit P38α kinase. According to the obtained results, compounds **47a** and **47b** (Figure 5) were the most potent inhibitors (IC_{50}=47 and 45 nM, respectively). In addition, compound **47b** effectively inhibited production of TNF-α, 1 L-6, and 1 L-1β proinflammatory cytokines in LPS-induced RAW 264.7 macrophages with IC_{50} values of 78.03, 17.6, and 82.15 nM, respectively. Compound **47b** exhibited significant inhibitory activity for the production of PGE2 and NO with IC_{50} values of 0.29 and 0.61 μM, respectively[62].

El-Dash et al. synthesised two novel series derived from nicotinic acid and evaluated their inhibitory activity against

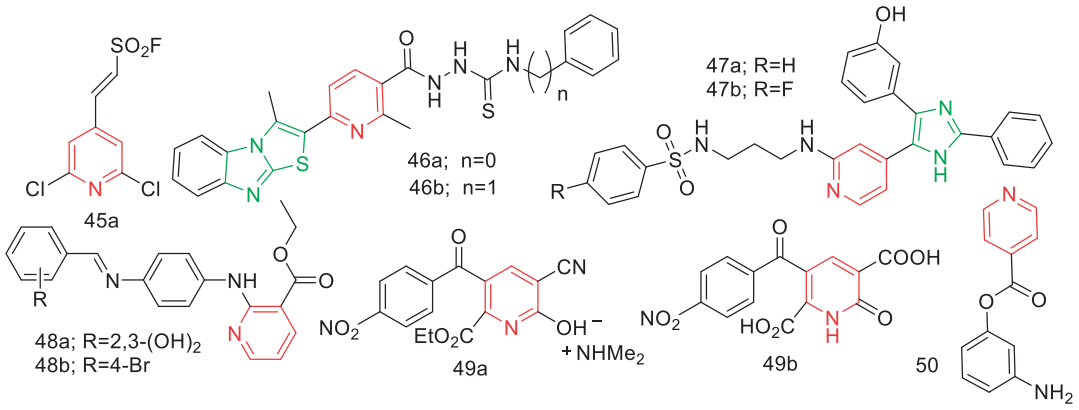

Figure 5. Pyridine derivatives 46a–50 reported as anti-inflammatory agents.

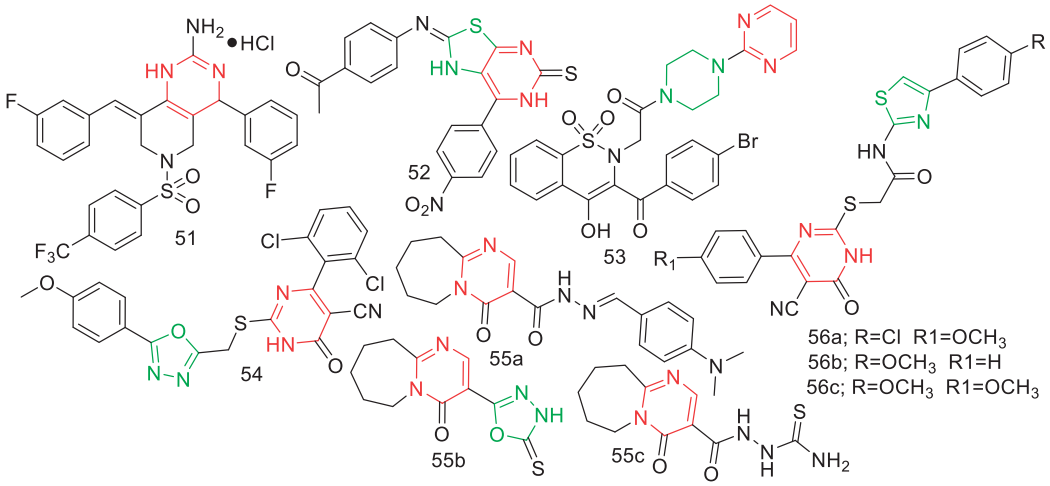

Figure 6. Pyrimidine derivatives 51–56c reported as anti-inflammatory agents.

cyclooxygenases (COX-1 and COX-2). All compounds showed highly potent COX-2 inhibitory activity and higher selectivity towards COX-2 inhibition compared to indomethacin. Moreover, compounds **48a** and **48b** (Figure 5) demonstrated SIs of 1.8–1.9 fold higher than celecoxib. Gastric toxicity and histopathological studies showed that compounds **48a** and **48b** had no gastric toxicity, which was consistent with their highly selective inhibitory effect of COX-2 enzyme *in vitro*[63].

Gonçalves et al. synthesised 35 novel 2-pyridone derivatives and 14 novel pyridinium salts. Among them, the pyridinium salt 49a (Figure 5) was the most active, and it selectively inhibited COX-2 enzyme activity at a concentration of 1.95 μM. Compound **49b** (Figure 5) was the most effective in reducing ear oedema, indicating that carboxylic acid plays a significant role in the anti-inflammation activity. The findings of the study suggest that 2-pyridone is an attractive scaffold for design of novel anti-inflammatory agents and its substitution pattern directly influences the anti-inflammatory activity profile. Furthermore, compound **49a** can be an interesting lead compound for developing novel selective inhibitors of COX-2[64].

Yaqoob et al.[65] synthesised novel scaffolds containing isonicotinoyl motif derivatives and screened for their *in vitro* anti-inflammatory activity. Results showed that compound **50** (Figure 5) exhibited an exceptional IC_{50} value (1.42 ± 0.1 μg/mL) with 95.9% inhibition at 25 μg/mL, which is eight folds better than the standard drug ibuprofen (11.2 ± 1.9 μg/mL)[65].

It should be noted that there is a pyridine ring in the structure of compound **12** (Figure 1) and compound **16f** (Figure 2).

2.5. Pyrimidine derivatives as anti-inflammatory agents

Sun et al. synthesised a series of fluoro-substituted hexahydropyrido[4,3-d]pyrimidines (PPMs) . Compound **51** (Figure 6), substituted by electron-withdrawing substitutes (*3*-F and *4*-CF_3) exhibited less toxicity and higher anti-inflammatory activity. Preliminary mechanistic studies revealed that compound **51** induced dose-dependent cell apoptosis at cell and protein levels. On the other hand, it inhibited NF-κB activation by suppressing LPS-induced phosphorylation levels of p65, IκBα, and Akt, and by indirectly suppressing MAPK signalling and inhibiting the nuclear translocation of NF-κB induced by TNF-α or LPS[66].

Bakr et al.[67] synthesised novel candidates of thiazolo[4,5-d]pyrimidines and screened for their anti-inflammatory activity. Compound **52** (Figure 6), with IC_{50}=0.87 μM, was the most active derivative with 57%, 88%, and 88% inhibition of inflammation after 1, 3, and 5 h, respectively. In comparison, celecoxib showed 43%, 43%, and 54% inhibition after 1, 3, and 5 h, respectively. In addition, the inhibitory effect of compound **52** on COX-2 was higher than that of celecoxib, a selective COX-2 inhibitor drug[67].

Szczęśniak-Sięga et al.[68] designed and synthesised novel arylpiperazine-1,2-benzothiazine derivatives as potential anti-inflammatory agents. Subsequent *in vitro* and molecular docking experiments showed that compound **53** (Figure 6) had the highest COX-2 selectivity compared to meloxicam (0.79 *vs.* 0.71)[68].

Alfayomy et al.[69] prepared two new series of 1,3,4-oxadiazole and coumarin derivatives based on pyrimidine-5-carbonitrile scaffold, and then assessed their COX-1/COX-2 inhibitory activity.

Compound **54** (Figure 6) was found to be the most potent and selective inhibitor of COX-2 (IC_{50}=0.081 μM, SI = 170.37). The *in vivo* anti-inflammatory activity study of COX-2 inhibitors indicated that the anti-inflammatory activity of compound **54** was higher than that of the reference drug celecoxib. In addition, it showed better safety compared to celecoxib in the ulcerogenic liability test[69].

Hassanein et al.[70] synthesised new hexahydropyrimido[1,2-a]azepine derivatives as anti-inflammatory agents with better safety profiles. Compounds **55a**, **55b**, and **55c** (Figure 6) were found to be the most selective COX-2 inhibitors *in vitro*. These derivatives showed *in vivo* anti-inflammatory activity that was comparable to celecoxib in the carrageenan-induced rat paw oedema method[70].

Abdel-Aziz et al.[71] synthesised a novel series of pyrimidine-5-carbonitrile derivatives and evaluated their anti-inflammatory activity against COX-1/COX-2 activity. Results indicated that compounds **56a**, **56b**, and **56c** were potent and selective COX-2 inhibitors (IC_{50}=1.03–1.71 μM) compared to celecoxib (IC_{50}=0.88 μM). Compounds **56a**, **56b**, and **56c** showed *in vivo* anti-inflammatory activity up to 90%, 94%, and 86% of meloxicam, respectively, after a 4 h interval. Moreover, the compounds showed higher gastric safety profiles than meloxicam[71].

Notably, there is a pyrimidine ring in the structure of compound **2b** (Figure 1).

2.6. Pyridazine derivatives as anti-inflammatory agents

Loksha et al. synthesised some novel derivatives of 2-alkyl 6-substituted pyridazin-3(2H) –ones and screened their cyclooxygenase (COX)-1/COX-2 inhibition activity and their abilities as analgesic and anti-inflammatory agents. Compounds **57a**, **57b**, and **57c** (Figure 7) showed anti-inflammatory activities with up to 65%, 62%, and 60% inhibition of oedema, respectively, which were higher than that of diclofenac (58%) at a dose of 10 mg/kg[72].

Ahmed et al. designed and synthesised a series of pyridazinone derivatives, which were then screened for preferential inhibition of COX-2 over COX-1 isoforms. Results showed that compounds **58a**, **58b**, **58c**, and **58d** (Figure 7) exhibited the most prominent COX-2 inhibitory activity, with IC_{50} values ranging between 15.56 and 19.77 nM. In addition, their sensitivity indices (SIs) were 24, 38, 35, and 24, respectively, which were 1.4–2.2 folds higher than celecoxib (SI 17). The results obtained after performing the carrageenan-induced rat paw oedema method and ulcerogenic liability test showed that compounds **58b**, **58c**, and **58d** demonstrated superior anti-inflammatory activity compared to both indomethacin and celecoxib, and none of these compounds showed gastric ulcerogenic effect[73].

Ahmed et al. designed and synthesised new pyridazinone and pyridazinthione derivatives. All the synthesised derivatives were then evaluated for cyclooxygenase inhibitory activity and COX-2 selectivity using celecoxib and indomethacin as reference drugs. According to the results, compounds **59a**, **59b**, and **59c** (Figure 7) exhibited significantly increased potency towards COX-2 enzyme compared to celecoxib. Their IC_{50} values were 67.23, 43.84, and 53.01 nM, respectively, which were 1.1–1.7 folds more potent than celecoxib (IC_{50}=73.53 nM) and extremely much more potent than indomethacin (IC_{50}=739.2 nM). Compound **59b** was the most selective COX-2 inhibitor with a SI of 11, which was as high as that of celecoxib. Notably, the *in vivo* anti-inflammatory activity of compound **59b** was comparable to indomethacin and equipotent to celecoxib. Moreover, compound **59b** showed better gastric profile compared to both celecoxib and indomethacin[74].

2.7. Quinoline derivatives as anti-inflammatory agents

Zhang et al. synthesised 25 quinoline derivatives. Some compounds showed potential anti-inflammatory activity against the 12-*O*-tetradecanoylphorbol-13-acetate-induced mouse ear inflammation. The most potent compounds **60a** and **60b** (Figure 8), significantly inhibited the mRNA expression levels of cytokines and inflammatory mediators, including IL-17A, IL-22, IL-23, p65, TNF-α, and IFN-γ[75].

Zuo et al. synthesised a series of novel arylpropionic esters and evaluated their biological activity in LPS-stimulated RAW264.7 cells. Compound **61** (Figure 8) exhibited the most potent activity through dose-dependent inhibition of NO (IC_{50}=3.52 μM), TNF-α, and IL-6 (84.1% and 33.6%, respectively) production, as well as suppressing the expression of iNOS, COX-2, and TLR4 proteins[76].

Debnath et al. synthesised a series of aryl 7-chloroquinolinyl hydrazone derivatives and evaluated their anti-inflammatory activities based on their ability to inhibit secretion of pro-inflammatory cytokines from the macrophages after stimulation with LPS. It was found that compound **62** (Figure 8) was the most promising lead with IC_{50}=12.39 ± 0.97 μM[77].

Yang et al. synthesised 2-substituted 3-arylquinoline derivatives and evaluated their anti-inflammatory effects in LPS-activated murine J774A.1 macrophage cells. Among the compounds, **63a** and **63b** (Figure 8) were the most active and they could inhibit production of NO at non-cytotoxic concentrations. Moreover, the two compounds had significant anti-inflammatory activities on LPS-activated macrophages through inhibiting production of NO, TNF-α, and IL-6, attenuating the activity of NF-êB, repressing iNOS expression, and suppressing phosphorylation of MAPKs[78].

2.8. Pyrazolo[3,4-d]pyrimidine derivatives as anti-inflammatory agents

Somakala et al. synthesised nine new N-substituted-4-((1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)amino)benzamides compounds.

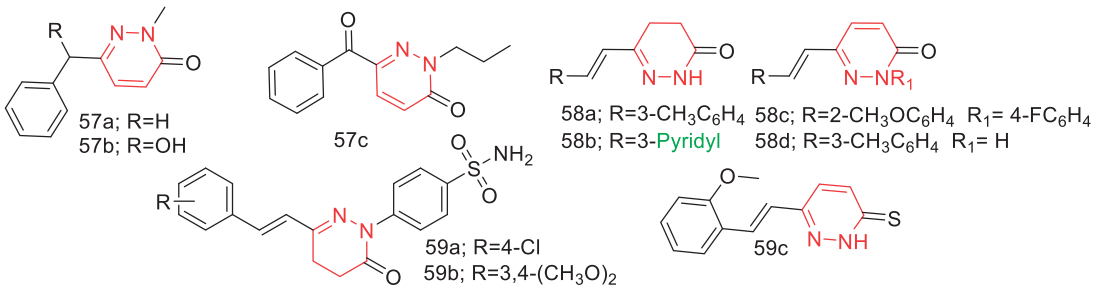

Figure 7. Pyridazine derivatives 57a–59c reported as anti-inflammatory agents.

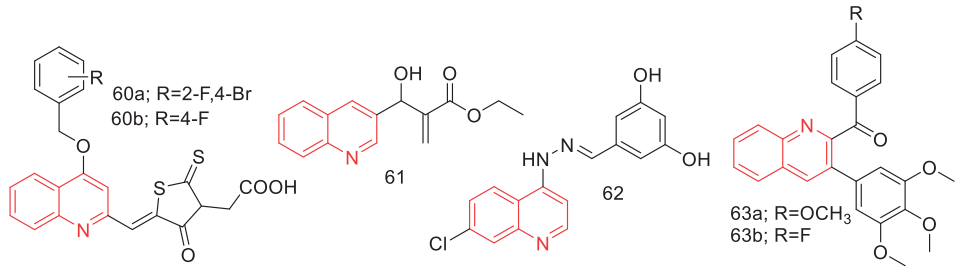

Figure 8. Quinoline derivatives 60a–63b reported as anti-inflammatory agents.

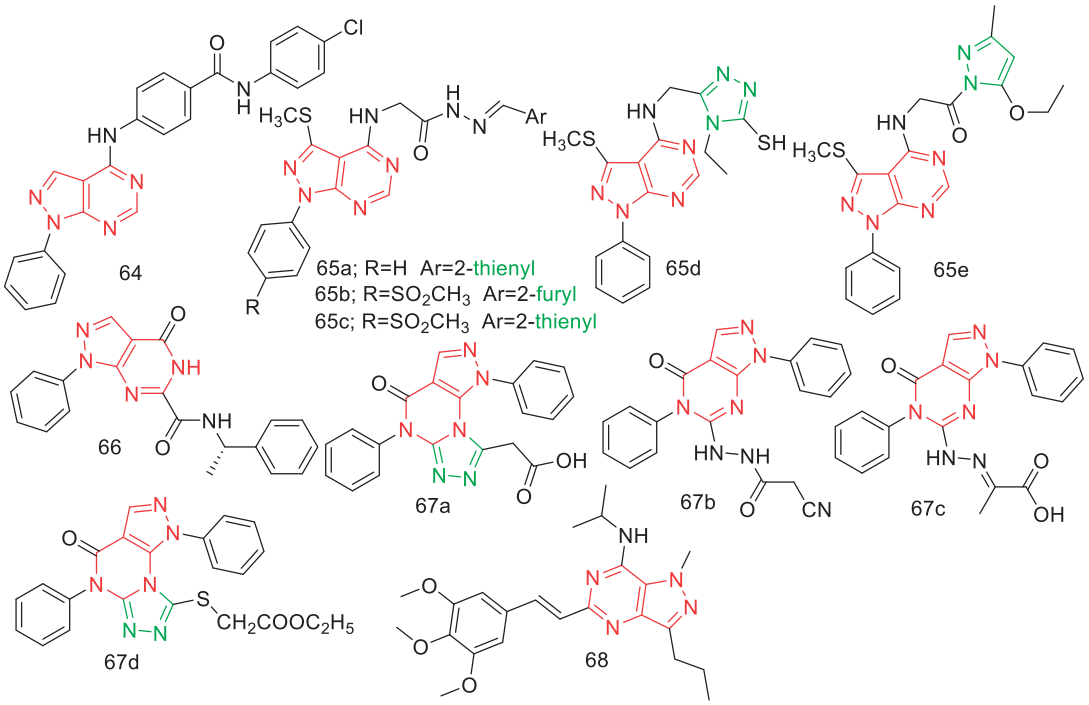

Figure 9. Pyrazolo[3,4-d]pyrimidine derivatives 64–68 reported as anti-inflammatory agents.

Compound **64** (Figure 9) bearing the 4-chlorophenyl group showed *in vitro* anti-inflammatory activity (82.35 ± 4.04) comparable to the standard drug diclofenac sodium (84.13 ± 1.63) and better p38α MAP kinase inhibitory activity (IC_{50}=0.032 ± 1.63 μM) than the prototypic inhibitor SB203580 (IC_{50} = 0.041 ± 1.75 μM). However, the activity was decreased when the *4*-chlorophenyl group was replaced by *4*-methoxyphenyl, *4*-methylphenyl, and *4*-fluorophenyl groups, respectively. It seems that the electron-donating properties of the methoxy group and the methyl group at the fourth position of the benzene ring are not as good as that of chlorophenyl group, which reduces the activity. When the 4-position of the benzene ring is substituted with a fluorine group, it may be due to its high electronegativity and small size, so the activity is not as good as compound **64**[79].

Abdelall et al. prepared four pyrazolopyrimidine series with the fourth position substituted with Schiff base, triazole, oxadiazole, and pyrazole moieties, respectively. With regard to the anti-inflammatory activity, compounds **65a**, **65c**, **65d**, and **65e** (Figure 9) showed higher activity compared to celecoxib. Compounds **65e**, **65b**, and **65c** (Figure 9) were closely selective to celecoxib. In addition, histopathological analysis indicated that compounds **65a** and **65b** were safer than indomethacin and similar to celecoxib. The long-lasting anti-inflammatory activity was observed in derivatives with the Schiff base, especially those bearing SO_2CH_3 pharmacophores. Moreover, the triazole derivative showed a good inhibitory activity compared to celecoxib[80].

Atatreh et al. synthesised novel pyrazolo[3,4-d]pyrimidine analogues. They then conducted enzymatic COX-1 and COX-2 inhibition assays to determine the *in vitro* ability of the compounds to inhibit COX-1 and COX-2. In addition, the *in vivo* anti-inflammatory activity of the compounds was evaluated using two different screening protocols, the carrageenan-induced paw oedema method and the turpentine oil-induced granuloma pouch bioassay. Compound **66** (Figure 9) showed promising experimental activity (COX-1 IC_{50} of 28 μM and COX-2 IC_{50} of 23 μM), but only slight selectivity towards COX-2. However, the selectivity can be further enhanced by optimising the pyrazolopyrimidine ring binding so that it reaches the selectivity region in the COX-2 active site[81].

Tageldin et al. reported synthesis of some new pyrazolo[3,4-d] pyrimidinone and pyrazolo[4,3-e][1,2,4]triazolo[4,3-a]pyrimidinone derivatives, and evaluation of their anti-inflammatory activities. Compounds **67a**, **67b**, **67c**, and **67d** (Figure 9) showed COX-2 inhibitory potency (IC_{50} =0.58, 0.38, 0.74, and 0.29 μM, respectively) and selectivity indices (SI = 7.46, 12.23, 7.93, and 9.82, respectively) higher than celecoxib (IC_{50}=0.78 μM and SI = 7.23). Results obtained after conducting *in vitro* formalin-induced paw oedema and cotton-pellet induced granuloma assays revealed

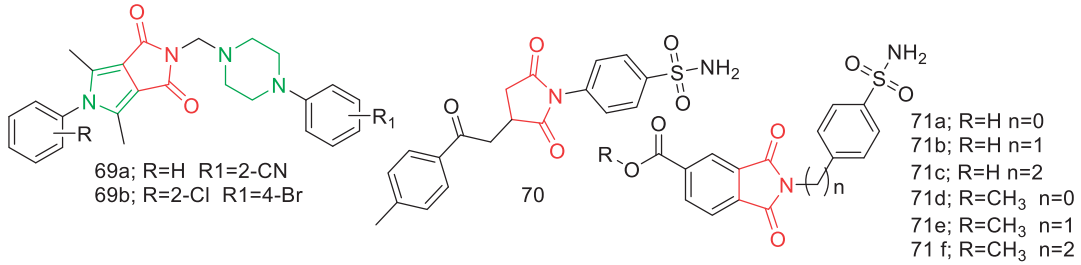

Figure 10. Pyrrolidinedione derivatives 69a–71f reported as anti-inflammatory agents.

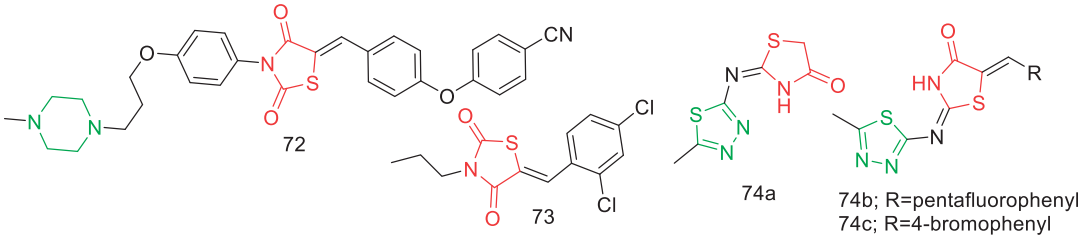

Figure 11. Thiazolidinone derivatives 72–74 reported as anti-inflammatory agents.

that compounds **67a**–**67d** displayed anti-inflammatory activity (AI = 64.3–78.6%) higher than celecoxib (AI = 46.4%) in the acute model, whereas compounds **67a** and **67b** possessed potent anti-inflammatory activity (AI = 43.4% and 46.9%) superior to both references (AI = 8.6% and 36.1% for celecoxib and diclofenac sodium, respectively) in the chronic model. All the tested compounds exhibited safe gastrointestinal profile, with the exception of compound **67a**[82].

Shi et al. designed and synthesised four series of total 90 new pyrazolo[4,3- d]pyrimidine compounds and evaluated their anti-inflammatory activities by inhibiting LPS-induced NO production. Results indicated that 3,4,5-trimethoxystyryl-1 H-pyrazolo[4,3-d]pyrimidine was the most active scaffold. Among them, compound **68** (Figure 9) was the most potent anti-inflammatory agent (IC_{50}=3.17 μM), with low toxicity and strong inhibition of NO release (IR = 90.4% at 10 μM). It also showed potent inhibition of iNOS with IC_{50} value of 1.12 μM. Furthermore, preliminary mechanism studies indicated that it could interfere with the stability and formation of active dimeric iNOS[83].

2.9. Pyrrolidinedione derivatives as anti-inflammatory agents

Redzicka et al.[84] designed and synthesised a series of N-substituted 3,4-pyrroledicarboximides. All compounds exhibited stronger inhibition of COX-2 than the reference drug (meloxicam) and compounds **69a** and **69b** (Figure 10) were proven to be the most effective against COX-2 enzyme. Replacement of aryl substituent in a series of piperazine derivatives with heteroaryl or cycloalkyl substitutes led to a significant reduction in COX-1 inhibition. Moreover, introduction of hydrophilic hydroxyethyl substitutes led to a decrease in the inhibitory activity in relation to both enzymes, while introduction of an OH group in a series of arylpiperidine derivatives significantly reduced COX-1 inhibition[84].

Jan et al.[85] synthesised N-substituted pyrrolidine-2,5-dione derivatives and determined their *in-vitro*, *in-vivo,* and acute toxicity as multitarget anti-inflammatory agents. It was found that compound **70** (Figure 10), with IC_{50} value 0.98 mM and SI of 31.5, was the most potent inhibitor of COX-2[85].

Abdel-Aziz et al.[86] prepared trimellitimides and evaluated their *in vivo* anti-inflammatory and ulcerogenic effects, and *in vitro* cytotoxicity. Results showed that compounds **71a**–**71f** (Figure 10) were the most potent COX-2 inhibitors (IC_{50}=0.14, 0.13, 0.10, 0.25, 0.25, and 0.20 μM, respectively) and were comparable to celecoxib (IC_{50}=0.12 μM)[86].

It is worth noting that there is a pyrrolidinedione ring in the structure of compound **10a** (Figure 1).

2.10. Thiazolidinone derivatives as anti-inflammatory agents

Elkamhawy et al. synthesised a series of thiazolidine-2,4-dione derivatives as irreversible allosteric covalent inhibitors of IKK-b with potential *in vivo* anti-inflammatory activity. Almost all derivatives elicited submicromolar IC_{50} values, with the most potent IKK-b inhibitor (IC_{50}=0.20 μM) being compound **72** (Figure 11). Most derivatives with a linker attached to the meta position were less effective, but the activity would increase when the 4-substituent on the phenoxy ring was the electron-withdrawing group nitro or cyano[87].

Ranjan et al. synthesised a series of 13 novel 2,4-thiazolidinedione derivatives. Compound **73** (Figure 11) showed great potential because it not only had maximum antidiabetic activity, but also possessed excellent anti-inflammatory and antioxidant potential. The anti-inflammatory activity of compound **73** was closer to the standard compound. Results obtained after performing the *in vivo* anti-inflammatory activity test indicated that the group at the fourth position of arylidene substituent attached to thiazolidnedione is vital for good anti-inflammatory activity[88].

Omar et al. designed and synthesised new 15-LOX/COX dual inhibitors based on 1,3-thiazolidin-4-one (15-lipoxygenase pharmacophore) and 1,3,4-thiadiazole (COX pharmacophore) scaffolds. Compounds **74a**, **74b**, and **74c** (Figure 11) were capable of inhibiting 15-LOX at 2.74, 13.11, and 10.21 μM, respectively, and COX-2 at 0.32, 0.1, and 0.1 μM, respectively. The compounds showed *in vivo* anti-inflammatory activity comparable to the reference drug (celecoxib)[89].

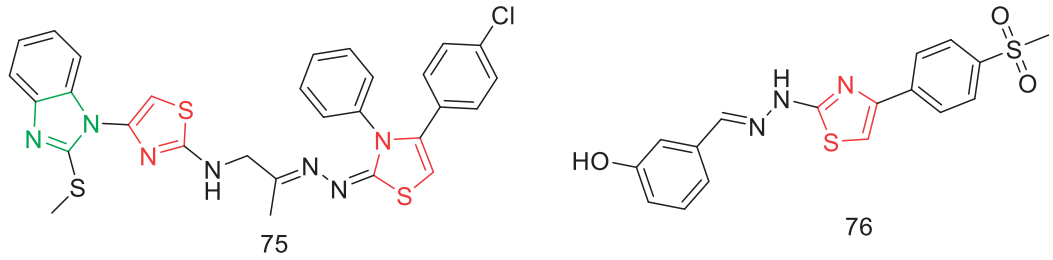

Figure 12. Thiazole derivatives 75–76 reported as anti-inflammatory agents.

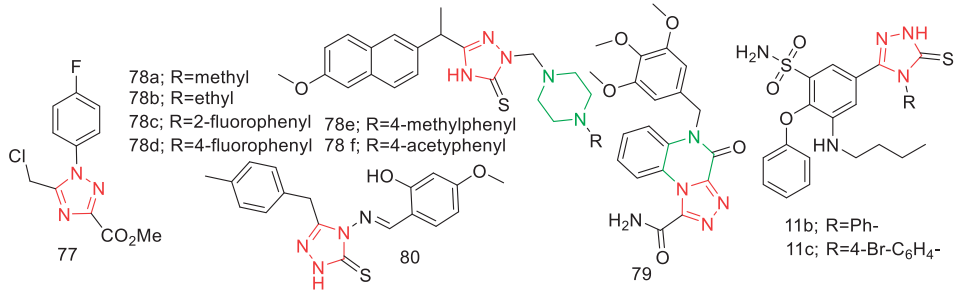

Figure 13. Triazol derivatives 77–80, 11b, 11c reported as anti-inflammatory agents.

Notably, there is a thiazolidinone ring in the structure of compound **3** (Figure 1), compounds **4a**–**4d** (Figure 1), compounds **16a**–**16f** (Figure 2), and compound **20b** (Figure 2).

2.11. Thiazole derivatives as anti-inflammatory agents

Maghraby et al. prepared new molecular hybrids of 2-methylthiobenzimidazole linked to various anti-inflammatory pharmacophores using a 2-aminothiazole linker. All hybrids revealed potent 15-LOX inhibitory activity (IC_{50}=1.67–6.56 μM). From the results, it was evident that compound **75** (Figure 12) was the most potent dual COX-2 (IC_{50}=0.045 μM, SI = 294) inhibitor compared to celecoxib (COX-2; IC_{50}=0.045 μM, SI = 327), with double inhibitory activity *versus* 15-LOX enzyme (IC_{50}=1.67 μM) relative to quercetin (IC_{50}=3.34 μM)[90].

Sağlık et al. synthesised a diverse series of thiazolylhydrazine-methyl sulphonyl derivatives and used an *in vitro* fluorometric method to evaluate their ability to inhibit COX enzymes. Results showed that compound **76** (Figure 12) had the highest COX-2 inhibitory activity (IC_{50}=0.140 ± 0.006 mM). Besides, it had a more potent inhibition profile, at least 12-fold, than nimesulide (IC_{50} =1.684 ± 0.079 mM). However, its inhibitory activity was similar to that of celecoxib (IC_{50}=0.132 ± 0.005 mM)[91].

In addition, there is a thiazole ring in the structure of compound **20a** (Figure 2), compounds **46a**–**46b** (Figure 5), compound **52** (Figure 6), and compounds **56a**–**56c** (Figure 6).

2.12. Triazol derivatives as anti-inflammatory agents

Li et al. developed a new method for synthesis of 1,2,4-triazole-3-carboxylates. Compound **77** (Figure 13) showed extraordinary COX-2 inhibition (IC_{50}=17.9 nM) and the best selectivity (COX-1/COX-2 = 1080). Furthermore, 5 mg/kg of compound **77** exhibited better *in vivo* anti-inflammation and gastric protection results compared to 10 mg/kg Indomethacin. SAR suggested that $-CH_2Cl$ moiety is the essential moiety, substitution of benzene ring with *p*-F possesses the best IC_{50} inhibition, and $-CO_2Me$ is an assisting group[92].

Avci et al. designed and synthesised a new series of 1,2,4-triazole-5-thione Mannich derivatives containing a naproxen moiety. Results obtained after performing acetic acid induced-writhing and carrageenan-induced paw oedema tests revealed that all compounds induced peripherally-mediated antinociceptive activities, as well as notable anti-inflammatory effects. The results of hotplate and tail-clip tests indicated that compounds **78a**–**78f** (Figure 13) centrally mediated anti-nociceptive activities in addition to their peripherally-mediated effects[93].

Shen et al. synthesised a series of 5-alkyl-4-oxo-4,5-dihydro-[1, 2, 4]triazolo[4, 3-a] quinoxaline-1-carboxamide derivatives and evaluated their anti-inflammatory effects using RAW264.7 cells. Results revealed that compound **79** (Figure 13) had the highest anti-inflammatory activity. Further studies showed that compound **79** reduced the levels of NO, TNF-α, and IL-6, and that its anti-inflammatory activity involves inhibition of COX-2 and iNOS, and downregulation of the MAPK signal pathway. Moreover, it displayed more prominent anti-inflammatory activity than the positive control (ibuprofen) in the *in vivo* acute inflammatory model[94].

Munir et al. synthesised 1,3,4-oxadiazole, 1,2,4-triazole, Schiff base, and 3,5-disubstituted pyrazole derivatives starting from salicylic acid and acyl acid hydrazides and tested their inhibitory activity against COX-1 and COX-2. Based on the results, compound **80** (Figure 13) showed excellent COX-2 inhibition, with IC_{50} value of 1.76 μM[95].

In addition, there is a triazol ring in the structure of compounds **11b**–**11c** (Figure 13), compounds **36a**–**36f** (Figure 4), compound **65d** (Figure 9), compound **67a** (Figure 9), and compound **67d** (Figure 9).

2.13. Oxazolidinone derivatives as anti-inflammatory agents

Phillips et al. synthesised oxazolidinone hydroxamic acid derivatives and evaluated their inhibitory activity against leukotriene (LT) biosynthesis in three *in vitro* cell-based test systems and on direct inhibition of recombinant human 5-lipoxygenase (5-LO). Compounds **81a** and **81b** (Figure 14) had outstanding potencies (IC_{50}<1 mM) comparable to that of zileuton, the prototype 5-LO

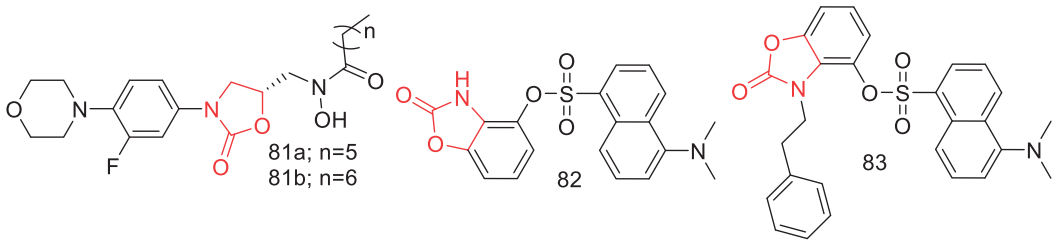

Figure 14. Oxazolidinone derivatives 81a–83 reported as anti-inflammatory agents.

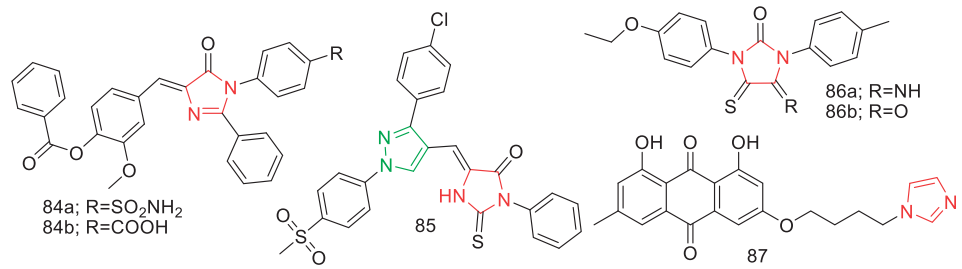

Figure 15. Imidazole derivatives 8ā4a–87 reported as anti-inflammatory agents.

inhibitor. Pronounced *in vivo* activity of compounds **81a** and **81b** was demonstrated in zymosan-induced peritonitis mice model[96].

Tang et al. synthesised 22 new 4-sulfonyloxy/alkoxy benzoxazolone derivatives. The most active compound **82** (Figure 14), exhibited the strongest inhibitory activity against NO, IL-1β, and IL-6 production, with IC_{50} values of 17.67, 20.07, and 8.61 μM, respectively. After 2 h, the induced effects were comparable or stronger than those of the positive control (celecoxib). Compound **82** also displayed higher activity *in vivo* than celecoxib in a mouse model of xylene-induced ear oedema. Further molecular analysis revealed that compound **82** could inhibit activation of the MAPK-NF-κB/iNOS pathway, thereby reducing excessive release of NO, IL-1β, and IL-6[97].

Tang et al. synthesised eighteen new disubstituted benzoxazolone derivatives and evaluated their activity against NO production in an LPS-induced RAW264.7 cells. According to obtained results, compound **83** (Figure 14) showed NO inhibitory activity (IC_{50} value = 14.72 μM) and iNOS inhibitory activity (IC_{50} value = 3.342 μM). Furthermore, it could significantly protect against the LPS-induced ALI. All results demonstrated that compound **83** could be a promising lead structure for iNOS inhibitors, with anti-inflammatory activity, to treat LPS-induced ALI[98].

2.14. Imidazole derivatives as anti-inflammatory agents

Metwally et al. synthesised new imidazol-5-one derivatives and screened for their *in vivo* anti-inflammatory activity using a standard acute carrageenan-induced rat paw oedema method. Compound **84b** (Figure 15) produced the maximum effect (49.0%) compared to celecoxib (43.1%). After studying the interaction of the derivatives with COX-2 enzyme compared to celecoxib, it was found that the inhibitory effect of compound **84a** (Figure 15) exhibited a high selectivity towards COX-2 inhibition (IC_{50} =0.087 μM)[99].

Abdellatif et al. synthesised a new series of hybrid structures containing thiohydantoin and evaluated their COX inhibition ability. Results revealed that all compounds were more potent against COX-2 than COX-1, and compound **85** (Figure 15) had higher COX-2 inhibitory activity (IC_{50} =0.76 μM) than celecoxib (IC_{50} =0.84 μM). In addition, all derivatives were significantly less ulcerogenic (ulcer indexes = 2.64–3.87) than ibuprofen (ulcer index = 20.25). Among all the compounds, compound **85** showed the highest COX-2 SI = 10.72, while the SI value for celecoxib was 8.60. In this series of compounds, the methoxy substituted analogues showed higher cytotoxic activities than the respective unsubstituted derivatives[100].

El-Sharief et al. synthesised new series of imidazolidineiminothione and imidazolidin-2,5-dione derivatives and evaluated for their anti-inflammatory activity. All the tested compounds exhibited high activity compared to the reference drug. Results showed that compound **86b** (Figure 15) was the most potent active agent (IC_{50}=0.0003 μM) compared to celecoxib (IC_{50}=2.8 μM). In addition, the IC_{50} value of compound **86a** (Figure 15) was 0.0021 μM. The study also determined the IC_{50} of all compounds against COX-2, with results showing that all of the synthesised products exhibited very low values reflecting their high potency[101].

Zhu et al.[102] synthesised 12 azole derivatives of emodin and assessed their anti-inflammatory activity. Among them, compound **87** (Figure 15) was the most potent anti-inflammatory agent, which showed the best inhibition of NO production. The IC_{50} of compound **87** in NO production was 1.35 μM, which was lower than that of indomethacin. Therefore, it can be deduced that compound **87** inhibited LPS-induced expression of inflammatory mediators in RAW 264.7 cells through blocking NF-κB pathways[102].

In addition, there is an imidazole ring in the structure of compounds **32a**–**32b** (Figure 3), compound **38** (Figure 4), compounds **46a**–**46b** (Figure 5), compounds **47a**–**47b** (Figure 5), and compound **75** (Figure 12).

2.15. Pyrrol derivatives as anti-inflammatory agents

Reale et al. synthesised and characterised a novel series of 1,5-diarylpyrrol-3-sulphur derivatives as COX-2 selective inhibitors endowed with anti-inflammatory/antinociceptive profile. Compound **88** (Figure 16), with IC_{50} =0.011 μM, showed a significant anti-inflammatory and antinociceptive activity *in vivo,* thereby providing insights into the development of a novel anti-inflammatory and antinociceptive agent[103].

Shawky et al. synthesised two new series of pyrrolizine-5-carboxamides and evaluated their anticancer and anti-inflammatory

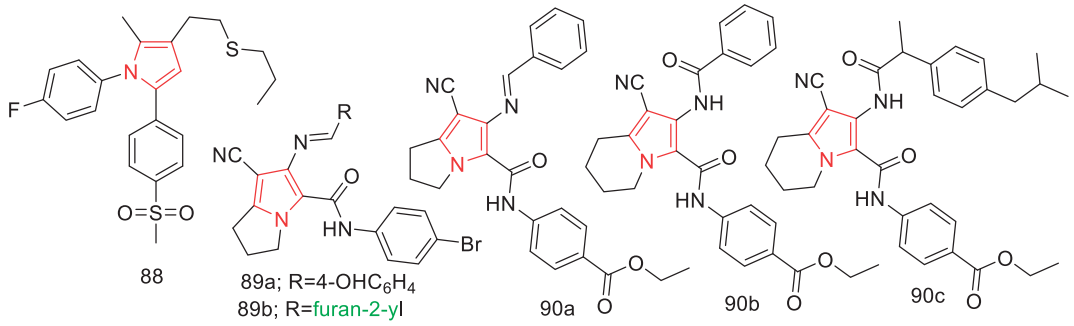

Figure 16. Pyrrol derivatives 88–90c reported as anti-inflammatory agents.

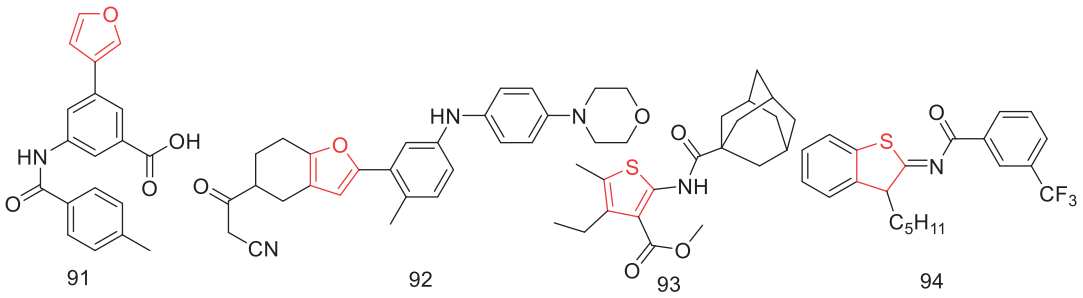

Figure 17. Furan derivatives 91–92 and Thiophene derivative 93–94 reported as anti-inflammatory agents.

activities. Results showed that compound **89a** (Figure 16) was the most potent COX-2 inhibitor (IC_{50}=0.64 ± 0.02 nM), while compound **89b** (Figure 16) was the most active COX-1 inhibitor (IC_{50}=13.16 ± 0.64 nM)[104].

Attalah et al. designed and synthesised two new series of ethyl benzoate bearing pyrrolizine and indolizine moieties. According to the obtained results, compounds **90a**, **90b**, and **90c** (Figure 16) displayed *in vivo* anti-inflammatory and analgesic activity nearly equal to or slightly higher than that of ibuprofen. Further mechanistic study of these compounds revealed inhibitory activity against COX-1/2 with preferential inhibition of COX-2[105].

In addition, there is a pyrrol ring in the structure of compounds **15a**–**15d** (Figure 2) and compounds **69a**–**69b** (Figure 10).

2.16. Furan derivatives as anti-inflammatory agents

Lu et al. designed a series of 5-aryl-3-amide benzoic acid derivatives as novel P2Y14 antagonists with improved pharmacokinetic properties. Among them, compound **91** (Figure 17) showed the most potent P2Y14 antagonising activity, with an IC_{50} value of 2.18 nM. Moreover, it exerted promising *in vivo* efficacy in alleviating paw swelling and inflammatory infiltration in monosodium urate-induced acute gouty arthritis mice model. Elucidation of the preliminary mechanism of compound **91** indicated that it blocked pyroptosis of macrophages through inhibiting activation of NLRP3 inflammasome[106].

Wang et al. designed and synthesised 4–(4,5,6,7-tetrahydrofuro[3,2-c]pyridin-2-yl) pyrimidin-2-amino derivatives as JAK inhibitors. The *in vivo* investigation revealed that compound **92** (Figure 17) possessed favourable pharmacokinetic properties and displayed slightly better anti-inflammatory efficacy than tofacitinib at the same dosage[107].

In addition, there is a furan ring in the structure of compound **65b** (Figure 9) and compound **88b** (Figure 16).

2.17. Thiophene derivatives as anti-inflammatory agents

Mugnaini et al. synthesised a set of selective cannabinoid type 2 receptor (CB2R) ligands based on the thiophene scaffold. Results revealed that compound **93** (Figure 17) was able to completely abolish release of the human monocyte chemotactic protein-2 in HaCaT cells at 10 mM concentration, which suggested that it has potential to treat skin inflammatory disease. The SAR showed that 3-carboxylate and 2-carboxamido moieties are not decisive for receptor binding. On the other hand, insertion of substituents at the fifth position seems to be more effective since it led to a progressive increase of CB2R affinity, often accompanied by higher selectivity, and can be noticed in compounds bearing an increasingly larger substituent. However, polar groups, such as the sulphone group, or isosteric replacement of thiophene with more polar heterocycles led to far less active compounds[108].

Ghonim et al. designed and synthesised novel thiazole and benzothiazole derivatives and screened for their binding affinity and functional activity on two G-protein coupled receptors (CB1 and CB2). Among them, compound **94** (Figure 17) exhibited remarkable protection against dextran sulphate sodium-induced acute colitis in mice model[109].

In addition, there is a thiophene ring in the structure of compounds **2a**–**2b** (Figure 1), compound **16e** (Figure 2), compounds **21a**–**21b** (Figure 2), compound **65a** (Figure 9), and compound **65c** (Figure 9).

2.18. Piperazine derivatives as anti-inflammatory agents

Liu et al. synthesised 20 novel talmapimod analogues and evaluated the *in vivo* anti-inflammatory activities. Results indicated that compound **95** (Figure 18) was the most potent. The *in vitro* enzymatic experiment identified compound **95** as a potent inhibitor against both p38a MAPK (IC_{50} =1.95 μM) and COX-2 (IC_{50} =0.036 μM). Furthermore, it had the ability to downregulate NF-κB and MAPK signalling pathways[110].

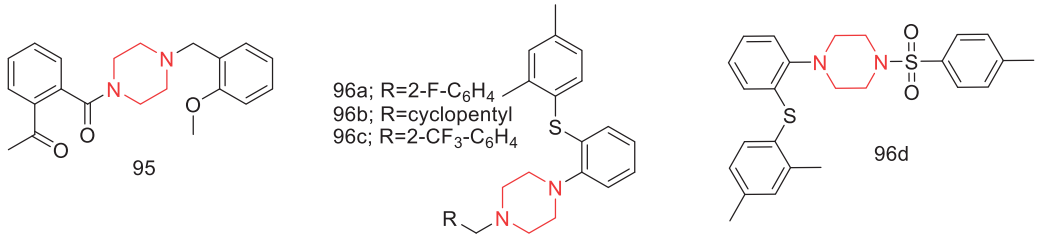

Figure 18. Piperazine derivatives 95–96d reported as anti-inflammatory agents.

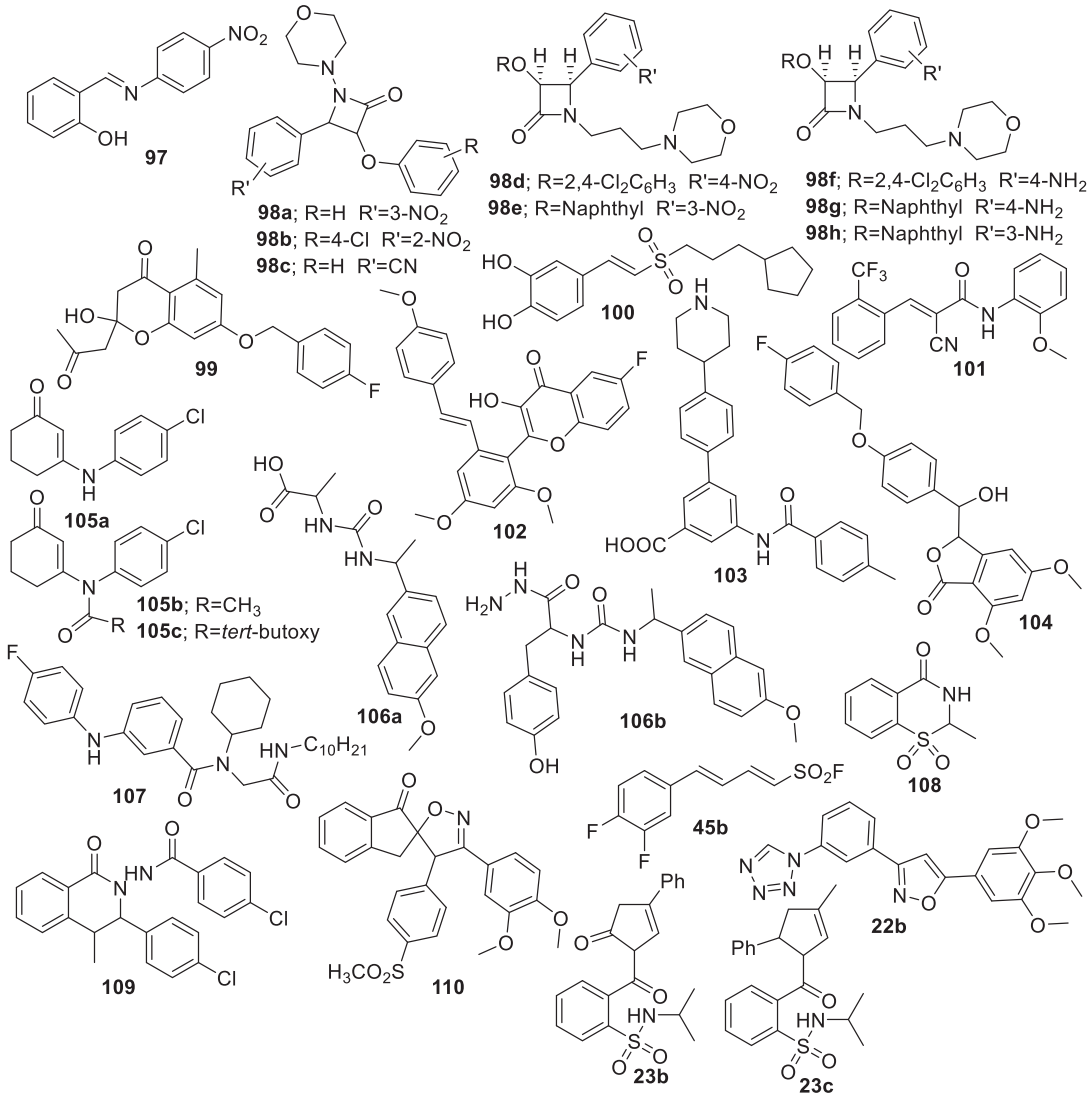

Figure 19. Other derivatives 97–110, 22b, 23b, 23c, and 45b reported as anti-inflammatory agents.

Talmon et al. synthesised a series of novel vortioxetine derivatives. Among them, compound **96a** (Figure 18) had significant antioxidant and anti-COX-1 activity, while compound **96b** (Figure 18) exhibited good antioxidant and mild anti-COX-1/2 inhibitor activities, while compound **96c** (Figure 18) was a good anti-COX-1/2 inhibitor and compound **96d** (Figure 18) was more specific *versus* COX-2[111].

In addition, there is a piperazine ring in the structure of compounds **35a**–**35b** (Figure 4), compound **42** (Figure 4), compound **53** (Figure 6), compounds **69a**–**69b** (Figure 10), compound **72** (Figure 11), compounds **78a**–**78f** (Figure 13), and compound **79** (Figure 13).

2.19. Other derivatives as anti-inflammatory agents

Roriz et al. synthesised a nitro-Schiff base derivative and examined its anti-inflammatory effects using *in vivo* models of inflammation such as neutrophil migration, paw oedema, and exudation assays. The production of NO was also estimated *in vivo* and *in vitro*. Results showed that the compound **97** (Figure 19) efficiently inhibited inflammation and might be a good candidate for the treatment of inflammatory-associated conditions[112].

Heiran et al. synthesised and characterised **29** monocyclic β-lactam derivatives bearing a morpholine ring substituent on the nitrogen. Compounds **98a**–**98h** (Figure 19) showed higher activity with anti-inflammatory ratio values of 38, 62, 51, 72, 51, 35, 55,

and 99, respectively, compared to the reference compound (dexamethasone) which had an anti-inflammatory ratio value of 32. This suggests that these compounds can be considered as potent iNOS inhibitors. The compounds also exhibited IC_{50} values of 0.48 ± 0.04, 0.51 ± 0.01, 0.22 ± 0.02, 0.12 ± 0.00, 0.25 ± 0.05, 0.82 ± 0.07, 0.44 ± 0.04, and 0.60 ± 0.04 mM, respectively, against HepG2 cells, and biocompatibility and non-toxic behaviour comparable to doxorubicin ($IC_{50} < 0.01$ mM)[113].

Liu et al. reported a concise total synthesis of an exceedingly potent anti-inflammatory agent (violacin A) and screened its anti-inflammatory activity against NO production using LPS-induced Raw264.7 cells. The derivative, compound **99** (Figure 19), showed stronger inhibition of NO, IL-1β, IL-6, and TNF-α production *via* inhibiting the NF-κB signalling pathway in Raw 264.7 cells[114].

Chen et al. designed and synthesised (E)-3,4-dihydroxystyryl alkyl sulphones, as new analogues of neurodegenerative agents. The results showed that compound **100** (Figure 19) displayed better anti-inflammatory activity (IC_{50}=1.6 μM). Further activity studies indicated that the length of the linker and the conformation of cycloalkyl play critical roles in anti-inflammatory activities[115].

Gu et al. synthesised a series of phenylacrylamide derivatives as novel anti-oxidant and anti-inflammatory agents. Compound **101** (Figure 19) could inhibit NO production and the activity of NF-kB in LPS-stimulated HBZY-1 mesangial cells, indicating its potential anti-inflammatory activity. Notably, compound 101 is associated with activation of the Nrf2 signalling pathway[116].

Chen et al. designed and synthesised thirty-seven new resveratrol-based flavonol derivatives. The preliminary experiment revealed that compound **102** (Figure 19) suppressed LPS-induced expressions of iNOS and COX-2, and production of IL-6, TNF-a, and NO through the NF-kB/MAPK signalling pathway in a concentration-dependent manner. According to SARs, the introduction of a hydroxyl group intoflavonoid is beneficial to the anti-inflammatory activity[117].

Zhang et al. synthesised a series of 3-amide benzoic acid derivatives as novel and potent P2Y14 receptor antagonists. The most promising antagonist, compound **103** (Figure 19), showed potent anti-inflammation in monosodium urate-treated THP-1 cells, which was comparable to PPTN (IC_{50}=1.77 nM). Compound **103** can be further optimised towards the development of novel anti-inflammatory agents[118].

Chen et al. designed and synthesised a total of 31 novel phthalide derivatives and screened their anti-inflammatory activities both *in vitro* and *in vivo*. Compound **104** (Figure 19) was found to be the most active one with low toxicity and it showed 95.23% inhibitory rate at 10 μM with a IC_{50} value of 0.76 mM against LPS-induced NO overexpression. Preliminary mechanism studies indicated that compound 104 activated the Nrf2/HO-1 signalling pathway *via* accumulation of ROS and blocking the NF-κB/MAPK signalling pathway. Moreover, the *in vivo* anti-inflammatory activity showed that compound **104** had obvious therapeutic effects against the adjuvant-induced rat arthritis model[119].

Kumar et al. synthesised new cyclic enaminone derivatives and evaluated their inhibitory activities against cyclooxygenase (COX-1 and COX-2). Results demonstrated that three compounds (**105a**, **105b**, and **105c** (Figure 19)) predominantly inhibited COX-2, with SIs of 74.09, 108.68, and 19.45, respectively. The anti-inflammatory potency of compound **105a** was comparable to that of celecoxib at a dose of 12.5 mg/kg, and compounds **105b** and **105c** were more/equally effective compared to celecoxib at 12.5 and 25 mg/kg doses[120].

Elhenawy et al. designed and synthesised a safe nonsteroidal anti-inflammatory drug agent based on the Naproxen scaffold. According to the obtained results, compounds 106a and 106b (Figure 19) showed a higher anti-inflammatory potency than Naproxen[121].

Chávez-Riveros et al. synthesised 16 diphenylamine derivatives and evaluated the *in vivo* anti-inflammatory activity through an ear oedema model using 12-*O*-tetradecanoylpholbol-13-acetate. Results revealed that compound **107** (Figure 19) analogue was more active than the commercial drug indomethacin in the *in vivo* study (92% and 89% inhibition of oedema, respectively). In addition to its remarkable anti-inflammatory capability, compound **107** was innocuous against RAW 264.7 cell line, with a comparable lethality in *Artemia salina* relative to diclofenac[122].

Li et al. synthesised a series of 1,3-benzothiazinone derivatives. All the compounds had no obvious cytotoxicity in the *in vitro* assay. Compound 108 (Figure 19) displayed lower gastrointestinal toxicity than meloxicam. Besides, compound **108** decreased the swelling in carrageenan-induced paw oedema inflammation models and significantly reduced the PGE2 level. Importantly, the study found that 1,3-benzothiazinone derivatives are unique scaffolds with anti-inflammatory activity and low toxicity[123].

Sakr et al. reported a new series of 1,4-dihydroquinazolin-3(2H)-yl benzamide derivatives as anti-inflammatory and analgesic agents, and COX-1/2 inhibitors. Compound **109** (Figure 19) showed the best *in vitro* COX-2 inhibitory activity (IC_{50} =0.05 μM). In addition, it showed the best results in most aspects where its oedema inhibition percentage (48%) was better than that of diclofenac sodium (37.8%), and the analgesic effect (3.4 writhes) was better than that of both indomethacin (12.6 writhes) and diclofenac sodium (17.4 writhes). The SAR study showed substitution of both phenyl rings was favourable because compounds with an unsubstituted phenyl ring showed lower activities in all the tests compared to their substituted analogues. Compounds carrying two nitro groups showed good *in vitro* COX inhibitory activity but with lower *in vivo* anti-inflammatory activity, which can be attributed to the high polarity of the two nitro groups that decreases the lipophilicity of the compound and hence decreases its bioavailability. To have good anti-inflammatory activity, at least one of the substituents should be halogen. This may be due to the lipophilicity of halogens which improves the bioavailability[124].

Abolhasani et al. synthesised new indanone compounds containing spiroisoxazoline derivatives and evaluated their inhibitory activities for COX enzymes. Compound **110** (Figure 19) showed superior selectivity with higher potency of inhibiting COX-2 enzyme. Furthermore, compound **110** exhibited the highest COX-2 inhibitory activity, and displayed the most potent cytotoxicity on MCF-7 cells, with an IC_{50} value of 0.03 ± 0.01 μM which was comparable to that of doxorubicin (IC_{50} of 0.062 ± 0.012 μM). Moreover, it can lead to apoptosis of MCF-7 cells, which may be mediated by upregulating the expression of Bax/Bcl-2 and activating the caspase-3 pathway[125].

3. Discussion and conclusion

This article screened and reviewed 110 articles of small molecules with good anti-inflammatory activity published from the literature since 2019. The figures in the article list 218 active compound structures. The statistical results from the elemental composition of these compounds are as follows: (1) Only the structures of compounds **20a** (Figure 2), **24** (Figure 3), **65d** (Figure 9), **75** (Figure 12), and **96a**–**96c** (Figure 18) do not contain an O element, notably these structures contain S element; (2) only the structures of compounds **33a**–**33b** (Figure 4), **34a** (Figure 4), **41** (Figure 4), **43** (Figure 4), and **100** (Figure 19) do not contain N element, almost

all of them are chalcone derivatives; (3) the S element appears in 105 active structures described in 52 articles; (4) the F element appears in 37 active structures described in 31 articles; (5) the Cl element appears published in 31 active structures in 28 articles; (6) the Br element appears discussed in 13 active structures in 13 articles. The statistical results from the functional group of these compounds are as follows: 60 pyrazole derivatives in 36 articles, 15 indole derivatives in 10 articles, 22 chalcone derivatives in 12 articles, 12 pyridine derivatives in eight articles, 11 pyrimidine derivatives in seven articles, 10 pyridazine derivatives in three articles, six quinoline derivatives in four articles, 12 pyrazolo[3,4-d]pyrimidine derivatives in five articles, 10 pyrrolidinedione derivatives in four articles, 16 thiazolidinone derivatives in seven articles, nine thiazole derivatives in six articles, 20 triazol derivatives in nine articles, four oxazolidinone derivatives in three articles, 14 imidazole derivatives in nine articles, 12 pyrrol derivatives in five articles, four furan derivatives in four articles, nine thiophene derivatives in seven articles, 19 piperazine derivatives in nine articles, and 12 morpholine derivatives 13a (Figure 2), 81a–81b (Figure 14), 92 (Figure 17), and 98a–98h (Figure 2) in four articles. From these results, it is evident that the structure containing the pyrazole ring as the selective COX-2 agent is now a research hot spot, and many pyrazole derivatives with good anti-inflammatory activity have been synthesised. Interestingly, there are two active compounds (**14a** (Figure 2) and **93** (Figure 17)) having adamantyl in the structure in two of the reviewed articles. All compounds, except 45a (Figure 5), 55b–55c (Figure 6), 58b (Figure 7), and 74a (Figure 11), contain a benzene ring structure. It is well known that the type and position of the substituents on the benzene ring have a significant impact on the biological activity of the structure. Therefore, we counted the substitutions of all benzene rings. Results indicated that there were many derivatives with a mono-substituted benzene ring: 54 unsubstituted derivatives of benzene ring in 30 articles, five derivatives with *p*-NO_2-phenyl in four articles, two derivatives with *o*-F- phenyl in two articles, two derivatives with *m*-F-phenyl in two articles, 20 derivatives with *p*-F-phenyl in 17 articles, one derivative with *o*-Br-phenyl in one article, 11 derivatives with *p*-Br-phenyl in 11 articles, three derivatives with *o*-Cl-phenyl in three articles, 14 derivatives with *p*-Cl-phenyl in 12 articles, three derivatives with *o*-CF_3-phenyl in three articles, one derivative with *m*-CF_3-phenyl in one article, three derivatives with *p*-CF_3-phenyl in three articles, one derivative with *o*-CH_3-phenyl in one article, three derivatives with *m*-CH_3 in two articles, eight derivatives with *p*-CH_3 in eight articles, three derivatives with *o*-OCH_3-phenyl in three articles, and 13 derivatives with *p*-OCH_3-phenyl in 11 articles. Importantly, it was found that there are no *m*-Br, *m*-Cl, and *m*-OCH_3 substituted compounds among all the compounds with benzene ring. In addition, we found some derivatives with a multi-substituted benzene ring: five derivatives with 2,4-$(Cl)_2$-phenyl in four articles, two derivatives with 2,6-$(Cl)_2$-phenyl in two articles, three derivatives with 3,4-$(OCH_3)_2$-phenyl in three articles, and 11 derivatives with 3,4,5-$(OCH_3)_3$-phenyl in eight articles. Moreover, the applications of some basic functional groups of all compounds were counted and the obtained results were as follows: six derivatives with -$SO_2NR_1R_2$ ($R_1 \neq H$, $R_2 \neq H$) in six articles, 16 derivatives with -SO_2CH_3 in eight articles, 32 derivatives with –SO_2NH_2 in 13 articles, 113 derivatives with amide in 68 articles (among them are 66 cyclic lactams derivatives in 30 articles), 12 derivatives with –NH_2 (–SO_2NH_2 not counted) in six articles, 14 derivatives with –COOH in 10 articles, 34 derivatives with –OH in 26 articles, and 24 derivatives with –CN in 14 articles. It was also found that the –C=N– bond is often used in the design and synthesis of anti-inflammatory compounds for molecular hybridisation or splicing of different structures (25 derivatives in 17 articles). Based on the above statistics, it is speculated that the above basic functional groups can be applied to the design of future anti-inflammatory drugs. Therefore, it is easier and direct to design compounds with good anti-inflammatory activity through hybridisation of many heterocycles with good anti-inflammatory activity (such as pyrazole) and some basic functional group molecules that perform well in anti-inflammatory compounds. However, researchers should not be limited to this because we have shown that there are many compounds with a simple structure but have good anti-inflammatory effects.

In summary, this review has discussed the active compound structures, biological activities, and SARs of newly reported derivatives with good anti-inflammatory activity. We hope that this article will provide more insights into the design of anti-inflammatory compounds, which will aid in the development of numerous anti-inflammatory compounds with good efficacy and low toxicity by researchers.

Disclosure statement

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