European Journal of Medicinal Chemistry Reports 12 (2024) 100225

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry Reports

journal homepage: www.editorialmanager.com/ejmcr/default.aspx

A review on progress of thiazole derivatives as potential anti-inflammatory agents

Kereyagalahally H. Narasimhamurthy [a,1], Toreshettahally R. Swaroop [a,1], Kanchugarakoppal S. Rangappa [b,*]

[a] Department of Studies in Organic Chemistry, University of Mysore, Manasagangotri, Mysuru, 570 006, Karnataka, India
[b] Institution of Excellence, University of Mysore, Manasagangotri, Mysuru, 570 006, Karnataka, India

ARTICLE INFO

Keywords:
Inflammation
Thiazole
LOX
COX
MAPK
JNK
JAK-STAT

ABSTRACT

Inflammation is a body response against infection that activates other biological components that include various cytokines, chemokines and other biological compounds that trigger body response against pathological activities. The Arachidonic acid pathway is involved in the inflammation that is connected with lipoxygenase (LOX) and cyclooxygenase (COX) enzymes. The importance of the isoforms of LOX and COX in inflammation is well studied. At the cellular level, some of the thiazole derivatives showed potent anti-inflammatory activities especially to block LOX5 and COX2 in the inflammation. These factors include both acute and chronic inflammation in various tissues like the heart, kidney, pancreas, brain, intestine, lungs and other organs as well that lead to the damage of the organs or cells. Whether it's the infectious or non-infectious response it will further activate some of the downstream signaling pathways like lipoxygenase, cyclooxygenase, cytochrome 450, JAK-STAT, MAPK, JNK, TNF-α, Nfr2, and many more pathways that lead to activation of another chronic disease in the body. In this review, we will concentrate on thiazole molecules that serve as anti-inflammatory responses to both acute and chronic inflammation. Further, we discussed the evidence that correlates the possible connection with LOX and COX enzymes in the inflammatory pathways and their blocking ability especially through thiazole derivatives has been discussed in this present review. The current assessment is the best part of the present consequence of thiazole derivatives on anti-inflammatory studies, covering articles published from 1973 to 2023.

1. Introduction

The local and defensive response of living tissue triggered against damage caused by harmful chemicals, physical pain, bacterial and microbial agents are called inflammation [1]. During the occurrence of an injury or acute inflammation, the response is very much essential in fighting infections to heal and restore the normal functions as the first line of defence. In contrast, chronic inflammation can cause numerous diseases. Prolonged inflammation leads to cancer due to activation of cell injury or continuous tissue damage. Some disorders, such as Alzheimer's disease, arthritis, diabetes, atherosclerosis, autoimmune diseases, multiple sclerosis, psoriasis, and rheumatoid arthritis, exist in addition to these inflammatory diseases. Inflammation refers to a multifactorial network of chemical signals that regulates the release of many mediators as well as changes in local blood flow. Local impacts are accounted for by the mediators. The inflammation site includes increased vascular permeability, migration of leukocytes, redness, swelling due to vasodilatation, vascular systems such as renal apparatus and cardiovascular system [2]. The primary anti-inflammatory target includes phospholipase A2 (PLA2), lipoxygenase (LOX), and cyclooxygenases (COX 1 and 2). Inflammation also includes interleukins (IL-1β, IL-6), tumor necrosis factor (TNF-α) and transcription factor nuclear factor (NF-κB) [3]. During the inflammatory process, leukotrienes play a major role [2] which along with several cytokines and growth factors plays a significant role during the initiation and progression of cancer. Precursors of prostaglandins and other bio lipids which are inflammatory mediators also play significant roles during metastasis [4].

Arachidonic acid (AA), a major constituent of biomembranes, is an essential fatty acid. Phospholipase A2 releases AA which exerts many physiological actions after getting converted to numerous lipids mediates. AA and its metabolites play an important role in cancer biology and

* Corresponding author.
E-mail addresses: rangappaks@gmail.com, rangappaks@ioe.uni-mysore.ac.in (K.S. Rangappa).
[1] Both authors contributed equally.

https://doi.org/10.1016/j.ejmcr.2024.100225
Received 16 May 2024; Received in revised form 18 September 2024; Accepted 3 October 2024
Available online 4 October 2024

adenoma-carcinoma sequence. Cyclooxygenase (COX), cytochrome P450 (CYP), and lipoxygenase (LOX) are the three major pathways associated with AA cascade [5]. The Arachidonic Acid cascade is one of the most abundant polyunsaturated fatty acids with twenty-carbon fatty acids involved in inflammatory responses. This fatty acid is present in phospholipid bilayer cells. The release of AA into the cellular milieu is triggered by the activation of PLA2 which is cytoplasmic PLA2. Also, the stimuli are due to the various lipases which bring about the discharge of Arachidonic acid into the cellular environment. This ultimately gets metabolized by LOX, COX, and CYP – the three enzymatic pathways [5]. The prostanoids are mostly pro-inflammatory mediators, which are known as the COX pathway of AA metabolites [6]. The LOX pathway comprises eicosanoid metabolites which also consist of pro-inflammatory hydroxyl eicosatetraenoic acids, leukotriene, and lipoxins. The latter are the mediators of inflammation resolution [7]. The enzymes CYP epoxygenases and CYP hydroxylases generate anti-inflammatory epoxyeicosatrienoic acids and vasoconstrictor 20-HETE respectively. The epoxyeicosatrienoic acids get metabolized to their corresponding dihydroxyeicosatrienoic acids and diols using soluble epoxide hydrolase which have low biological activity [8].

We are actively engaged in organic synthesis [9–20] and as our continuing interest in bioorganic and medicinal chemistry [21–28], we herein present a review on anti-inflammatory activities of thiazole derivatives. To the best of our knowledge, a specific review on anti-inflammatory activities of thiazole compounds is not reported.

1.1. The cyclooxygenase pathway

The COX pathway has two isoforms in mammals, namely, COX, COX-1 and COX-2 [5]. Under physiological conditions; COX-1 in most mammalian cells is constitutively expressed. Proinflammatory stimuli; for instance, bacterial lipopolysaccharides, cytokines, tumor-promoting agents, and growth factors induce the COX-2 expression [29]. The latter is expressed in quite a few issues which include the brain, kidney, and spinal cord, although the essential roles of COX-2 expression are not completely understood. For therapeutic purposes, expression patterns pose challenges in selectively targeting COX-2 [5].

The dual-functional COX enzymes initially transform AA into two types of prostaglandin. First, unstable prostaglandin G2 and second, stable prostaglandin G2. The first transformation takes place *via* COX and the second *via* the peroxidase function. Stable prostaglandin G2 (PGH2) is then transformed into many bioactive prostanoid syntheses and cell and tissue-selective prostanoid syntheses. The former generates (PGE2 PGD2, PGF2α, and PGI2) and TXA2. Of late, PGE2 synthases, membrane PGE synthases-2 and cytosolic PGE synthases have attracted attention as promising targets in dealing with pain and inflammation treatment [2]. Unlike COX-mediated disruption of PGI2, the downstream enzymes of COX will not produce the same side effects. Of the two constitutively expressed enzymes, namely, mPGES-1 and cPGES, only the former primarily coupled with COX-2 is induced by inflammatory stimuli. These experimental outcomes infer that mPGES-1 is attractive for pain and inflammation targets [30].

1.2. Biological effect of prostanoid

Prostanoid widely distributed autocrine and paracrine lipid mediators' have a wide range of physiological responses. Characteristically these metabolites are G protein-coupled receptors which are high-affinity agonists that modulate second messenger levels. The second messenger levels are Ca^{2+}, inositol phosphates, and cAMP [31]. In 1936, Von Euler isolated nine human prostanoid receptors. He cloned two isoforms activated by PGD2, four by PGE2, PGF2α, PGI2, and TXA2. PGD2 contained DP1, DP2, PGE2 contained EP1, EP2, EP3, EP4, and TXA2 contained FP, IP, and TP respectively. The diversity of biological effects of prostanoids is well explained by the diverse functions of prostanoids receptors in the body [32]. Prostanoids with PGE2, PGF2α, and PGI2 have important roles in gastrointestinal function protecting the gastric mucosa blood flow, bicarbonate secretion, and stimulating mucus formation [33]. PGD2, PGE2, and PGI2 in the cardiovascular systems mediate vascular tone by triggering vasodilatation, while, PGE2 acts as a bronchodilator, and TXA2 is a potent vasoconstrictor. It is also a well-established fact that PGE2 has a role in inflammatory pain [5] which includes pain, redness and swelling. Thus, prostanoid receptors alert pain-specific neurons by binding with PGs. For instance, PGE2 acts on EP1 and EP2 receptors, and PGI2 act on IP receptors. EP1 and EP2 receptors are in the peripheral and central nociceptive systems, while IP receptors in the peripheral nociceptive systems respectively. PGE2 adds to the systemic responses to pain, hypersensitivity, fever, and fatigue by acting on neurons. In brief, prostanoids require an intricate balance to maintain homeostasis and to evade inflammatory responses by catering through diverse and differential roles.

1.3. The lipoxygenase pathway

Three lipoxygenases (LOX) isozyme 5, 12, and 15 convert AA into their corresponding pro-inflammatory hydroperoxy eicosatetraenoic acids (−5, −12 & −15) [5,34]. 15-LOX initiates the synthesis of lipoxins which are participating in the resolution phase of inflammation. 12-LOX and 15-LOX are associated with psoriasis and atherosclerosis which are commonly known as inflammatory diseases. However, 5-LOX is a unique isozyme that uses two cofactors, namely, adenosine triphosphate (ATP) and Ca^{2+} as catalysts for protein-protein interactions with LOX activating protein (FLAP) [5]. 5-LOX metabolizes AA to generate 5s hydroperoxy eicosatetraenoic acids (HPETE) as an intermediate which reduced to the resultant alcohol (5HETE) or epoxy leukotriene (LTA4) which has a short life [35]. LTA4 on hydrolysis undergoes a systematic metabolism resulting in epoxide by LTA4 hydrolase to the corresponding LTB4, diol, or cysteine - adduct LTC4. Further LTC3 gives rise to sequentially other cys-LTs, LTD4 and LTE4 [36].

1.4. Inflammation is a critical component of tumor progression

Cancer as a disease is also known as neoplasm or malignant tumor which is categorized by a decreased rate of apoptosis. The mutation prevents cancer cells from undergoing apoptosis while; damaged cells will undergo apoptosis under normal conditions. Cancer develops to the formation of tumors due to cell proliferation. Genetic alterations, for instance, a mutation in oncogenes or tumor suppressor genes are the causes of cancer [37]. The disease also causes alterations to the macromolecules, for example, carbohydrates, lipids, nucleic acids, and proteins. Many types of cancers are named after the location of the initial development of tumors which most of the time are the result of chronic inflammation. Inflammation caused due to human papillomavirus subtypes may result in cervical cancer. Hepatitis B and hepatitis C virus may lead to hepatocellular cancer due to hepatocellular cancer [38] and growth factors contribute to initiation and maintenance of cancer cells [39].

The progression of tumors also known as tumorigenesis is a diversiform consecutive process that generally takes many years. It has been comprehended that the metabolites of AA and phospholipid release one of the two enzymes by the action of PLA2 substrate which plays a significant role in tumor biology. The oxidation of AA by COX and LOX mediated products proceeds by a sequence of enzymatic reactions to produce regulatory molecules corresponding to PGs and LTs. Also, studies have revealed that tumors and inflammatory cells are responsible for the higher levels of PGE2 production [40,41]. Several mechanisms have revealed PGE2 supports tumor growth and supplies the required nutrients and oxygen by inducing the process of angiogenesis [42,43]. PGE2 boosts tumor development, arrests cancer cell apoptosis, and induces cancer-cell proliferation. The tumor development is realized by increasing cell motility and movement and by changing cell morphology [44,45]. Ding et al. have shown that in all activities of

human pancreatic cancer cell lines take place in the presence of 5-LOX and 12-LOX mRNA. This will not hold well in normal human pancreatic ductal cells. Though 5-HETE and 12-HETE, the metabolites of LOX initiate tumor growth, propagation of human pancreatic cancer cells is blocked by LOX inhibitors [46].

Inflammation signaling cascade influence the pathological effects on various human diseases, and involves regulatory as well common inflammatory response mediators. Inflammatory signals activate the downstream signaling cascade that will trigger the actual inflammatory mechanism inside the body. Preliminary inflammatory response includes microbial counteracts and cytokines such as 1Beta (IL-1beta), interleukins −6, and tumor necrosis factor-alpha and its specific receptors. Receptors activate the intercellular response like MAPK, NFkB, JAK-STAT, and other signaling pathways that will lead to the activation of chronic inflammation and ultimately leads to diseases in the human body.

Chemotherapy is a treatment procedure that uses the chemical substance as anti-cancer drugs which are cytotoxic. Consequently, the chemicals kill cancer cells by inhibiting growth or multiplication eventually during the life cycles. The management of chemotherapy is subjected to cycles of rest period and treatment. Radiation therapy as an alternative treatment involves killing cancer cells by impinging ionizing radiation on the targeted area which makes it difficult for the cancer cells to grow. The undesirable side effects of chemotherapy and radiation therapy have resulted in the development of alternative therapies. Recent studies have shown and many mechanisms are established to demonstrate that several natural products which act as potent antioxidants and free radical scavengers are capable of displaying potent anticancer activity [47,48]. This accelerates the need to discover new treatments and therapeutics which will become more challenging. In this context, the field of drug design assumes importance and heterocyclic compounds widely distributed in nature provide hopes for a future. Innumerable pharmacologically active chalcones are in clinical use [49]. Diclofenac, Indomethacin, Licofelone, and Piroxicam which are dual inhibitors of COX and LOX possess significant analgesic, anti-inflammatory, and anti-asthmatic effects. These drugs have lower gastrointestinal side effects. The approach of dual inhibition of the COX/LOX enzymatic pathways offers more advantages compared to selective inhibitors of COX in the designing of the new safe drugs with minimum side effects [50]. In brief, the discovery of novel anti-cancer and anti-inflammatory drugs assumes paramount importance.

1.5. Signaling pathways in inflammation

The activation of JAK-STAT pathways is usually connected with the activation of cytokines, growth factors, and interferon's that includes growth hormones and leptons that lead to the alteration in the downstream signaling cascade. The JAK-STAT signaling pathways are activated by the interaction of specific ligand and receptor interaction and downstream phosphorylation of STAT will dimers and ultimately leads to the activation or acts as transcriptional factors and it enters into the nucleus that will activate the genes that are responsible for the chronic inflammation. Tyrosine phosphorylation site is the important area where actual STAT gets dimerize and finally begins with JAK-STAT pathways to activate. In the IL-6 signaling pathway cell membrane activates the receptor and ligand interaction and finally, the downstream signaling pathway activated when the tyrosine site gets phosphorylated with the ATP, and inactivated STAT in the nucleus gets dimerizes inside the cytosol and recruits to the nucleus and it acts as a transcriptional factor. Dysregulation of one of these pathways leads to the overactivation of inflammatory response genes and ultimately leads to death.

Inflammation is also activated by the stress-inducing protein like JNK and p38 and it is activated by the IL-1β through the receptor and ligand interactions. These inflammatory proteins also can trigger the MAPK pathways so that inflammation and cancer could be the possible link between two different pathways and still these possible links are poorly understood. Once the activation or over expressions of these stress proteins will act as transcriptional factors where inflammatory genes are more accessible for the DNA replications and hence the inflammation-mediated pathways will proceed through stress-induced proteins *via* interleukins 1β.

2. Anti-inflammatory potency of thiazoles in *in-vivo* and *in-vitro* methods

2.1. 2-Aminothiazolyl sulfonamides

N-(2-(*N*-(thiazol-2-yl)sulfamoyl)ethyl)nicotinamide **1a** (Fig. 1) was found to have anti-inflammatory properties as reported by Naito and Shimizu [51]. Compound **1a** (ED_{50} = 43.5 mg/kg) has about eight times the efficacy of sodium salicylate (ED_{50} = 370 mg/kg) against serotonin-induced edema. Because of its strong absorbability, low toxicity, and potent anti-inflammatory action, it is an interesting compound for clinical trials. Besides, they have also studied anti-inflammatory activity against edema induced by carrageenan in which **1a** showed ED_{50} of 185 mg/kg. While, reference drug sodium salicylate was not active at doses lower than 500 mg/kg. Authors have studied anti-inflammatory activity for only one compound and they have not disclosed structure activity relationships.

Sondhi et al. used a carrageenan-induced paw edema assay to investigate the anti-inflammatory activity of methane sulfonamide and amidine derivatives of 3,4-diaryl-2-imino-4-thiazolines. Phenyl butazone was used as a positive control. The anti-inflammatory efficacy of (*Z*)-*N*-(4-(4-methoxy phenyl)-3-(2-nitrophenyl) thiazol-2(3*H*)-ylidene) methane sulfonamide **1b** (34.7 %) (Fig. 1) was equivalent to that of the standard medication Phenylbutazone (37.0 %). The excellent activity of this lead compound **1b** is due to the fact that this molecule meets stereochemical, lipophilicity and electronic requirements of the target in a better way than other molecules [52].

2.2. 2-Aminothiazole derivatives

Nagatami et al. [53] investigated the anti-inflammatory efficacy of a series of 4-aryl-2-aminothiazole acetic acid derivatives in rat carrageenin edema. There were several active compounds discovered that substantially reduced the formation of paw edema. Two compounds 4-(4-chlorophenyl)-2-phenylaminothiazole acetic acid **2a** and 4-(4-chlorophenyl)-2-diethylaminothiazole acetic acid **2b** (Fig. 2) were chosen for further analysis because they slightly hindered albumin denaturation during heat treatment.

The formalin-induced rat paw edema inhibition [54] system was used to assess triheterocyclic thiazoles [55] for anti-inflammatory action. Slow-acting anti-inflammatory agents were discovered in the compounds studied. However, the activity of the same compounds increased significantly from 4 to 8 h. 4-{[4-(6,8-Dibromo-2-oxo-2*H*-chromen-3-yl)-thiazol-2-ylamino]-methyl}

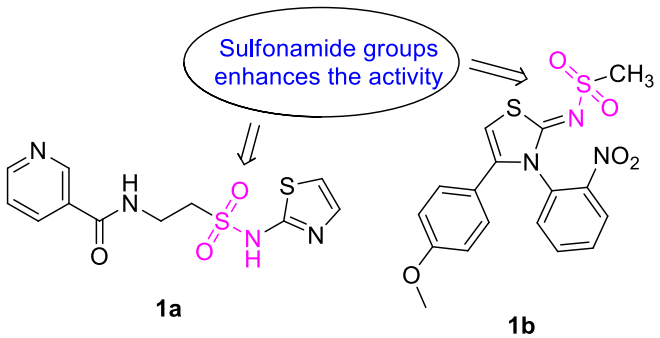

Fig. 1. Sulfonamides of 2-aminothiazole.

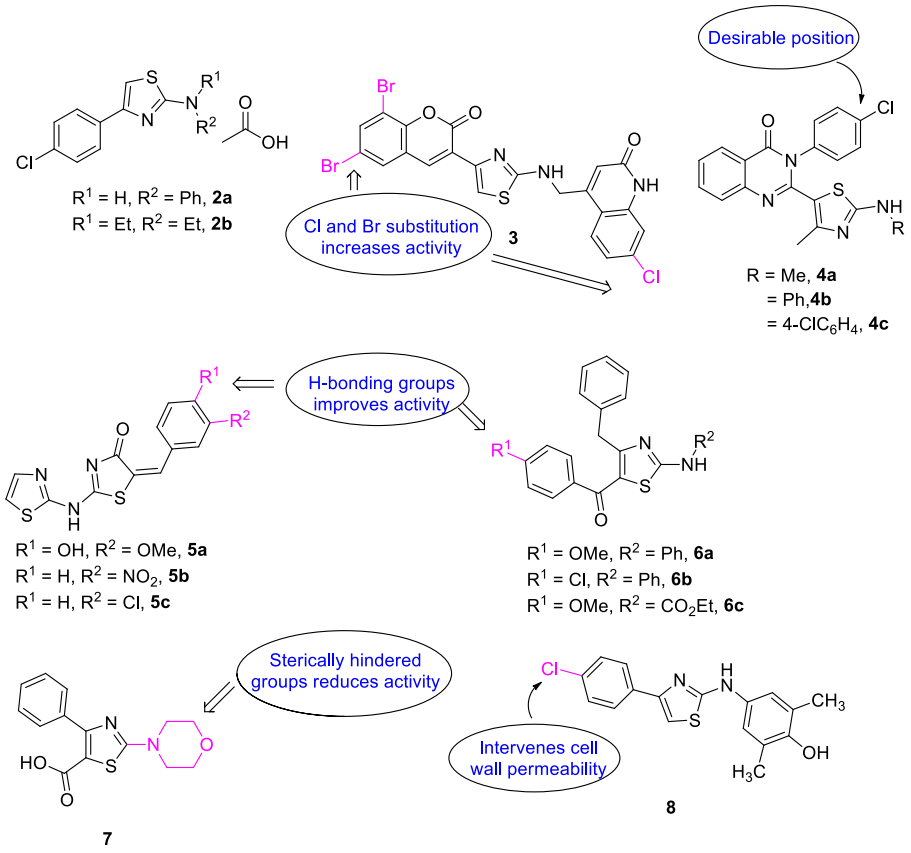

Fig. 2. 2-Aminothiazole derivatives.

t-7-chloro-1*H*-quinoline-2-one **3** (41.47 % after 8 h) (Fig. 2) inhibition was equivalent to that of Phenyl butazone (39.71 % after 8 h). The chloro group at C-7 in carbostyril and the 6,8-dibromo substitution in the coumarin ring improved anti-inflammatory function than other substituents, according to qualitative SAR research.

The anti-inflammatory efficacy of a series of 2-(2,4-disubstituted-thiazole-5-yl)-3-aryl-3*H*-quinazoline-4-one derivatives [56] was tested in an *in vivo* model of acute inflammation. A carrageenan-induced rat paw edema model was used to test these compounds for anti-inflammatory action. Compounds 3-(4-chlorophenyl)-2-(4-methyl-2-(methylamino) thiazol-5-yl)quinazolin-4(3*H*)-one **4a** (71 % at 50 mg/kg), 3-(4-chlorophenyl)-2-(4-methyl-2-(phenylamino)thiazol-5-yl)quinazolin-4 (3*H*)-one **4b** (72 % at 50 mg/kg) and 3-(2-chlorophenyl)-2-(2-((4--chlorophenyl)amino)-4-phenylthiazol-5-yl)quinazolin-4(3*H*)-one **4c** (38 % at 50 mg/kg) (Fig. 2) as compared to the well-known medication Ibuprofen (52 % at 50 mg/kg), they showed substantial *in vivo* efficacy. At the second position of the thiazole ring, molecules with substituents like aryl amino and methyl amino have showed strong selectivity, while electron-withdrawing groups like -Cl are more desirable on the para and ortho positions of the phenyl ring at the third position of the quinazoline ring.

Athina et al. described the synthesis of nine 2-(thiazole-2-ylamino)-5-phenylidene-4-thiazolidinone derivatives that showed anti-inflammatory activity in *in vivo* and COX/LOX activity *in vitro*. Using a carrageenin-induced mouse paw edema protocol, compounds (*E*)-5-(4-hydroxy-3-methoxybenzylidene)-2-(thiazol-2-ylamino)thiazol-4(5*H*)-one **5a** (72.7 ± 6.8 % at 0.01 mmol/kg) and (*E*)-5-(3-nitrobenzylidene)-2-(thiazol-2-ylamino)thiazol-4(5*H*)-one **5b** (69.4 ± 2.3 % at 0.01 mmol/kg) (Fig. 2) have the best anti-inflammatory efficacy compared to the reference drug Indomethacin (47 % at 0.01 mmol/kg). The COX-1 and COX-2 inhibitory function of compound (*E*)-5-(3-chlorobenzylidene)-2-(thiazol-2-ylamino)thiazol-4(5*H*)-one **5c** (Fig. 2) was the maximum (90 % and 30.4 % respectively). They also tested compounds for inhibitory activity in a soybean lipoxygenase-based enzyme assay, with compound **5b** being the most active (76 %). The substantial activity of lead compounds is due to the fact that they form hydrogen bonding and electrostatic or π-π interactions at the active site of the enzymes. Steric factors and hydrophilicity are also important factors when we consider SAR. The docking studies are in agreement with experimentally found results [57].

An acute *in vivo* model was used to evaluate a series of novel 4-benzyl-1,3-thiazole derivatives [58]. The greater effectiveness of the para substituted phenyl carbonyl group could be because of the possibility of a lone pair of electrons on OCH_3 promoting hydrogen bonding with the receptor site. Ethyl (4-benzyl-5-(4-methoxybenzoyl)thiazol-2-yl)carbamate **6c** (60.8 ± 1.45 % after 3h) (Fig. 2) appeared as the strongest compound in the entire series. *In vivo* tests revealed that (4-benzyl-2-(phenylamino)thiazol-5-yl)(4-methoxyphenyl)methanone **6a** (55.8 ± 1.21 %) and (4-benzyl-2-(phenylamino)thiazol-5-yl) (4-chlorophenyl)methanone **6b** (44.2 ± 1.89 %) (Fig. 2) had better percent protection than preferential COX-1 inhibitor Ibuprofen (60.1 ± 1.75 %) and selective COX-2 inhibitor Rofecoxib (43.6 ± 1.23 %). The superimposition data substantiated the experimental results.

Using the carrageenan-induced rat paw edema procedure, Patel and co-workers documented the synthesis and anti-inflammatory evaluation of substituted 4-phenyl-1,3-thiazole derivatives. 2-Morpholino-4-phenyl thiazole-5-carboxylic acid **7** (88.88 % after 3 h) (Fig. 2) with the morpholine group as a substituent was found to be more active than the standard drug Diclofenac (80.55 % after 3 h) in the series. Notably, when morpholine is substituted by dimethylamine resulted in good activity. Other substituents like diethylamine, diphenyl amine and pyrrolidine reduced activity probably due to steric hindrance [59].

In vitro and *in vivo* assays were used to assess the biological activity of 1,3-thiazoles for anti-inflammatory effects [60]. The thiazole

compounds inhibited 5-lipoxygenase, a central enzyme in the synthesis of leukotrienes that is implicated in inflammatory disorders such as asthma and rheumatoid arthritis. Compound **8** (IC_{50} = 25 nM, 98 % at 1 μM) (Fig. 2) was the most potent of the 1,3-thiazole analogs. SAR indicated that introduction of halogen has intervened cell wall permeability and affect cellular metabolism. Pursuing arachidonic acid (AA) spreading into the ear, topical application of 4-((4-(4-chlorophenyl) thiazol-2-yl)amino)-2,6-dimethylphenol **8** to mice decreased inflammatory responses such as ear swelling and MPO operation. More interestingly, it not only had a stronger anti-inflammatory effect than Zileuton, but it also had a longer-lasting protective effect in the AA-inflamed ear model. More importantly, it inhibited 5-LOX preferentially to 12- or 15-LOX, with IC_{50} levels 10–100 times higher for 12- or 15-LOX than for 5-LOX, resulting in fewer side effects.

Using Mefenamic acid (62 % at 100 mg/kg) and Ibuprofen (75 % at 20 mg/kg) as standard drugs, Mansuri et al. established the synthesis of certain trisubstituted thiazoles and tested there *in vivo* anti-inflammatory role in carrageenin-induced rat hind paw edema. The anti-inflammatory activity of 3-(4-(3-chlorophenyl)-2-(piperidin-1-yl) thiazole-5-carbonyl)-2*H*-chromen-2-one **9** (57 % at 20 mg/kg) (Fig. 3) was the highest in *in-vivo*. The anti-inflammatory role of thiazoles is enhanced by the presence of piperidino moiety and chlorophenyl at the second and fourth positions, respectively. The other substituents have moderate activity [61].

El-Achkar and colleagues investigated the synthesis of thiazole derivatives and their effects on prostaglandin E2 (PGE2) production and COX activity in inflammatory settings *in vitro* and *in vivo*. The compounds *N*-[4-(4-hydroxy-3-methoxyphenyl)-1,3-thiazol-2-yl]acetamide **10a** (IC_{50} = 9.01 ± 0.01 μM) and 4-(2-amino-1,3-thiazol-4-yl)-2-methoxyphenol **10b** (IC_{50} = 11.65 ± 6.20 μM) (Fig. 3) both inhibit COX-2 dependent PGE2 development effectively. COX-1 behavior was also tested with these molecules, in which **10a** emerged as selective COX-1 inhibitor with IC_{50} of 5.56 × 10^{-8} ± 2.26 × 10^{-8} μM. Inhibition of PGE2 secretion shows that both compounds have an anti-inflammatory effect in the dorsal air pouch model of inflammation. The selective COX-1 inhibitory activity of **10a** is because of hydrogen bonding at the active site of enzyme, while **10b** has not formed any hydrogen bonding due to the presence of sterically hindering benzyl group. On the other hand, compound **10a** has formed only one hydrogen bond and **10b** has formed two hydrogen bonds at the active cite of COX-2 enzyme site. Notably, standard Celecoxib establishes many hydrogen bonds at the active site as evident from docking studies against PDBID:1EQG [62].

Priyanka and coworkers developed the synthesis and pharmacological examination of substituted 4-arylthiazole-2-amino acetanilides. The

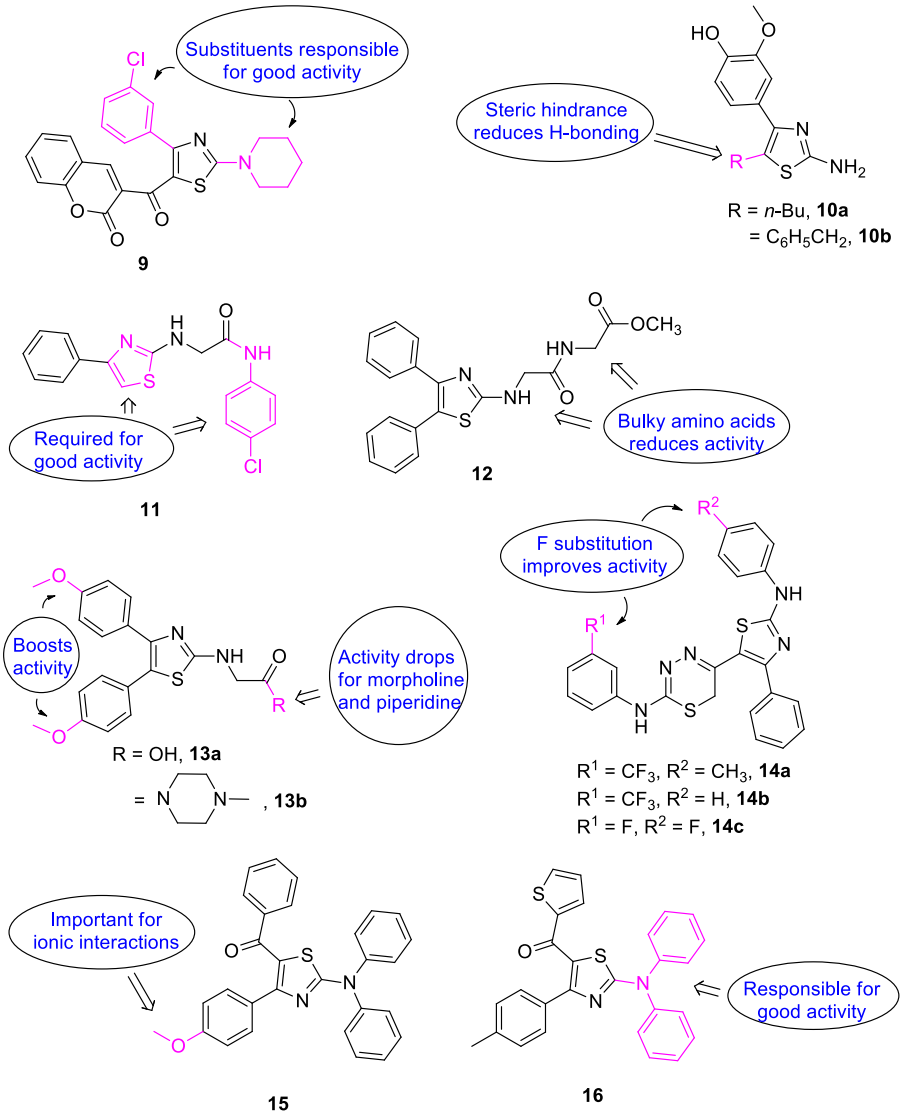

Fig. 3. 2-Aminothiazole derivatives (continued).

anti-inflammatory ability of the synthesized compounds was assessed using the carrageenan-induced hind paw edema procedure. The above derivatives had mild to strong anti-inflammatory efficacy, with compound *N*-(4-chlorophenyl)-2-((4-phenylthiazol-2-yl)amino)acetamide **11** (64.17 % after 3 h) (Fig. 3) providing a higher percentage inhibition of paw edema throughout the third hour. Its inhibitory effect was almost identical to that of the reference drug Diclofenac sodium (73.79 % after 3 h). Presence of thiazole linked with substituted acetanilide is an important pre-requisite for anti-inflammatory activity than other substituents [63].

Said and co-workers produced a series of diphenylthiazole-amino acid conjugates and tested their anti-inflammatory properties *in vivo*. The carrageenan-induced rat paw edema system was used to test the anti-inflammatory response. The reference standard was Indomethacin (86 % inhibition after 3 h). Methyl 2-(2-((4,5-diphenylthiazol-2-yl) amino)acetamido)acetate **12** (Fig. 3) has the best *in vivo* anti-inflammatory property (0.6 μM–4.0 μM, 80–84 % after 3 h) of all the compounds studied. In addition, when bulky amino acid groups were substituted for the compact methyl glycine one, activity dropped dramatically [64].

The synthesis of diarylthiazoles was developed by Abdelazeem and co-workers, and the anti-inflammatory action of the above compounds was tested *in vitro* and *in vivo*. Thus, Mofezolac and FR122047 analogs were designed and synthesized, while retaining the structural features that are essential for COX-1 selectivity. The structure-activity relationship was investigated using various linkers and cyclic amines in place of methylpiperazine. The findings revealed that COX-1 ligands with an acetic acid moiety were the most active and selective. Incorporation of two methoxy groups increased COX-1 activity, example: 2-(4,5-bis(4-methoxyphenyl)thiazol-2-yl)amino)acetic acid) **13a** (IC_{50} = 0.32 ± 1.12 μM) (Fig. 3). COX-1 activities were significantly reduced as they replaced methyl piperazine with morpholine or piperidine moieties. The *in vivo* anti-inflammatory efficacy was assessed using the carrageenan-induced rat paw edema assay, which used Diclofenac sodium as a positive control. When compared to the reference drug (84.52 % after 7 h), all the compounds studied had only minor anti-inflammatory activity. The most potent compound in the series was 2-((4,5-bis(4-methoxyphenyl)thiazol-2-yl)amino)-1-(4-methylpiperazin-1-yl)ethanone **13b** (61.91 % after 7 h) (Fig. 3), which had the methyl piperazine moiety and displayed greater average edema inhibition. The most effective COX-1 selective agent, compound **13a** (50.30 % after 7 h) (Fig. 3), had the least anti-inflammatory activity *in vivo*. These results are substantiated by docking studies as well against into COX-1 active site (PDB code: 1PGF) [65].

The synthesis and anti-inflammatory activity of thiazolyl-thiadiazines were stated by Sagar et al. [66] The *in vivo* acute inflammation trial in rats was done using the carrageenan-induced acute inflammation model. Compared to the reference drug Diclofenac, satisfactory results were got for thiazole compounds. Importantly, these newly formed molecules fit non-selectively into the catalytic pocket of COX-1 and COX-2 enzymes, eliciting anti-inflammatory action. As a result, they put the developed multitarget-directed ligands (MTDLs) to the test in a rat-based chronic inflammation model [67]. When compared to the standard (68 %) on the fifth day of the chronic model, the percent edema inhibition for compounds **14a-c** (47–58 %) (Fig. 3) was comparatively moderate. The thiazole and thiadiazine heterocyclic rings containing fluorine substituents are essential to exhibit anti-inflammatory activity. The high docking scores (against PDB ID: 3LN1) for lead compounds substantiate the anti-inflammatory activity [66].

Sinha et al. documented the synthesis and *in vitro* anti-inflammatory activity of 2-amino-4-aryl thiazole [68]. They conducted *in vitro* tests against the 5-LOX enzyme. Incorporating a benzoyl residue and a diphenylamine in the central thiazole ring resulted in (2-(diphenylamino)-4-(4-methoxyphenyl)thiazol-5-yl)(phenyl)methanone **15** (Fig. 3), an extremely potent drug. Incorporation of an electron-donating methoxy group in the 4′-position of the phenyl group helps to increase the hydrophobicity of the aromatic centroid connected at the 4th position of the thiazole ring, which could explain the strong enzyme inhibition. Docking experiments (against PDB ID 3O8Y) also show that the methoxy group could be involved in ionic interactions with amino acid carbonyl groups. Compound **15** (92.8 ± 0.7 %) has a higher inhibitory effect than the standard medication Zileuton (86.9 ± 2.2 %).

The green synthesis of thiazole derivatives as possible dual COX-2/5-LOX inhibitors was identified in a report. Anti-inflammatory efficacy of synthesized derivatives was tested *in vitro* and *in vivo*. *In vitro* tests revealed that the compound (2-(diphenylamino)-4-(*p*-tolyl) thiazol-5-yl) (thiophen-2-yl)methanone **16** (Fig. 3) as the COX-2 (0.09 ± 0.002 μM) and 5-LOX (0.38 ± 0.01 μM) dual inhibitor with a diphenylamino group and a *p*-tolyl group on the thiazole center are the most successful. Interestingly, compound **16** exhibited high selectivity for COX-2 (SI = 61.66) that was similar to Etoricoxib (0.07 ± 0.007 μM). *In vivo* anti-inflammatory assays were performed using the carrageenan-induced rat paw edema model with Indomethacin as a control drug (53.21 ± 0.76 % after 6 h), with compound **16** (60.82 ± 1.96 % after 6 h) showing a substantial reduction in edema among the series. Thiazole and diphenylamino group are important moieties for the exhibition of excellent activity. Other secondary amines at position-2 of thiazole reduced the activity. Molecular docking studies at COX-2 and 5-LOX active sites were in agreement with biological studies with significant protein-ligand interaction [69].

Ahmed et al. reported the synthesis of 2,3,5-tri-substituted thiazoles and then tested the synthesized compounds for *in vitro* anti-inflammatory activity using a human red blood cell membrane stabilization process. In addition, *in-vivo* methods for anti-inflammatory action were developed using Ibuprofen (76.34 % after 1 h) and Diclofenac sodium (77.87 % after 1 h) as standard drugs in a carrageenan-induced rat hind paw edema model. Compounds **17a** (68.71 % after 1 h) and **17b** (65.68 % after 2 h) (Fig. 4) had the strongest anti-inflammatory effects. The anti-inflammatory behavior of the phenyl ring with electron-withdrawing groups such as –Cl at position 4, is important. The other substituents reduced the activity at this position. The replacement of 2-methyl-4-nitro-1*H*-imidazole-1-yl for well-documented thiazole molecules at position 5 provides a basis for use as a monotherapy of anti-inflammatory activity and gastrointestinal selectivity [70].

Maghraby and co-workers reported the synthesis of 2-methyl thiobenzimidazole conjugated to 2-aminothiazoles. The synthesized molecules were evaluated for cyclooxygenase (COX) and 15-lipoxygenase (15-LOX) enzymes inhibition and *in vivo* anti-inflammatory activity. In addition to the references, Celecoxib, Diclofenac sodium and Indomethacin, molecules studied had strong inhibitory action against the ovine COX-1 enzyme. Among the synthesized compounds, 4-(2-(methylthio)-1*H*-benzo[d]imidazole-1-yl)thiazol-2-amine **18** (4.17 ± 0.08 μM) (Fig. 4) was the most potent COX-1 inhibitor. In contrast to Celecoxib, which is superior to the action of Diclofenac sodium and Indomethacin, the synthesized molecules showed high inhibitory profiles against human recombinant COX-2 enzyme. The most potent COX-2 inhibitors were benzimidazole thiazole derivatives linked to acetyl moiety 1-((4-(2-(methylthio)-1*H*-benzo [d]imidazole-1-yl)thiazol-2-yl) amino)propan-2-one **19** (0.069 ± 0.001 μM), phenyl thiosemicarbazone (*E*)-2-(1-((4-(2-(methylthio)-1*H*-benzo [d]imidazole-1-yl)thiazol-2-yl)amino)propan-2-ylidene)-*N*-phenyl-hydrazinecarbothioamide **20** (0.075 ± 0.003 μM), 1,3-thiazolines **21a-c** (0.045 ± 0.002 to 0.058 ± 0.001 μM) (Fig. 4). To evaluate 15-LOX inhibitory activity of new benzimidazole-thiazole hybrids linked to 1,3-thiazoline substituted with *p*-chlorophenyl moiety **21b** (1.67 ± 0.06 μM) was the most potent 15-LOX inhibitor, as it displayed almost double 15-LOX inhibitory activity compared to the reference Quercetin (3.34 ± 0.06 μM). The newly synthesized hybrids' anti-inflammatory efficacy (71–83 %) *in vivo* was assessed using a carrageenan-induced paw edema bioassay with Indomethacin (69 %) as a control drug. On comparison among tested molecules, cyclization of thiosemicarbazone moiety in

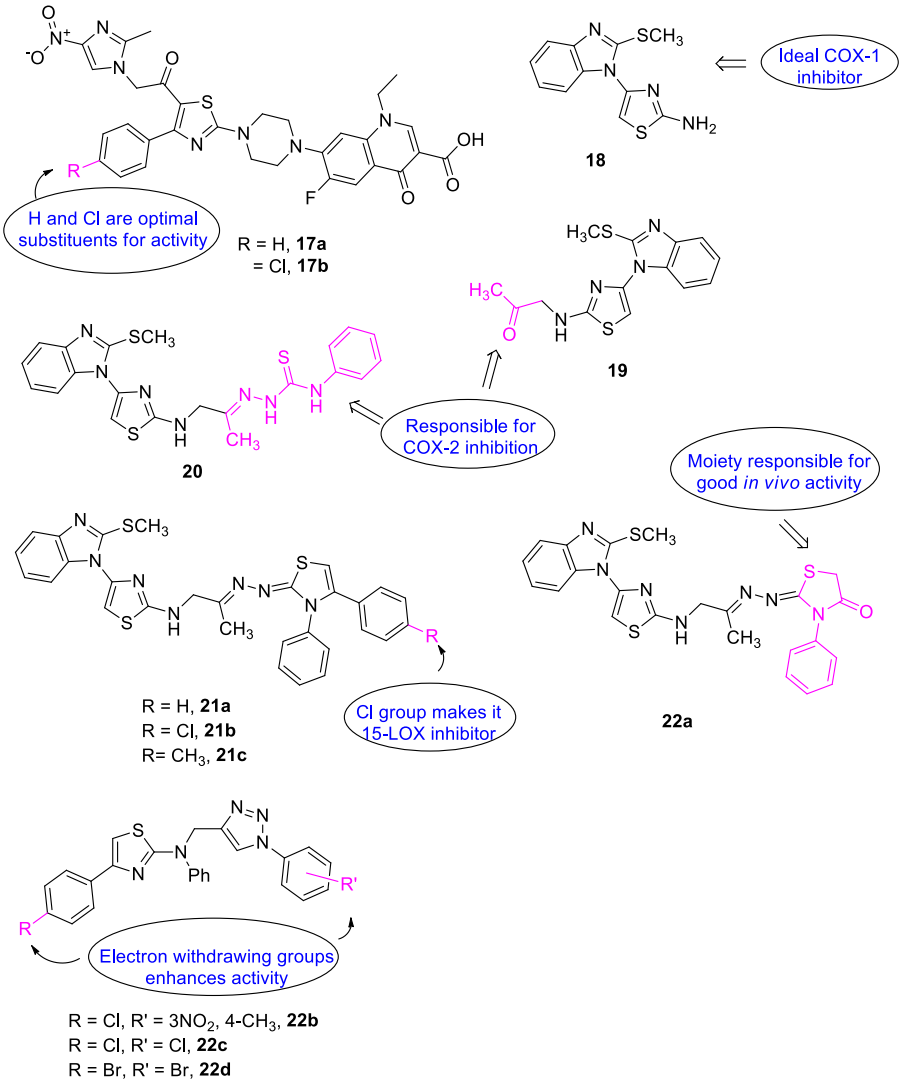

Fig. 4. 2-Aminothiazole derivatives (continued).

benzimidazole-thiazole **20** (70.97 after 3 h) to 1,3-thiazoline moiety in case of hybrid **21b** (75.67 % after 3 h) or 4-thiazolidinone ring as hybrid **22a** (82.83 % after 3 h) (Fig. 4) led to a marked improvement of the anti-inflammatory activity compared to the activity of un-cyclized one. At both 4 and 3 h intervals, compound (*Z*)-2-((*E*)-(1-((4-(2-(methylthio)-1*H*-benzo [d]imidazole-1-yl)thiazol-2-yl)amino)propan-2-ylidene) hydrazono)-3-phenylthiazolidin-4-one (**22a**) (Fig. 4) showed the most potent anti-inflammatory activity when compared to Indomethacin (78.83 % after 4 h). The enhancement effect of both 1,3-thiazoline and 4-thiazolidinone moieties on *in vivo* anti-inflammatory action of these hybrids was pronounced based on the above-mentioned observations. Docking of compounds at the active site of COX-2 receptor (PDB ID: 3LN1) substantiated the activity [71].

Ankali and co-workers developed new thiazole-triazole hybrids as anti-inflammatory agents. The anti-inflammatory potency was determined using carrageenan induced acute inflammation model. Among the tested compounds, 4-(4-chlorophenyl)-*N*-((1-(4-methyl-3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-*N*-phenylthiazol-2-amine **22b** (67.26 %) (Fig. 4) and 4-(4-chlorophenyl)-*N*-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-*N*-phenylthiazol-2-amine **22c** (78.91 %) and 4-(4-bromophenyl)-*N*-((1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl) methyl)-*N*-phenylthiazol-2-amine **22d** (86.54 %) emerged as lead compounds. The reference drug used was Diclofenac which exhibited 86.54 % edema inhibition after 0.5 h. Electron with drawing groups like nitro, chloro and bromo enhanced the activity. On the other hand, with donating groups like methyl and hydroxyl reduced the activity [72].

2.3. Amides of 2-aminothiazoles

A series of thiazolyl-N-substituted amides was developed by Hadjipavlou-Litina et al. Among the compounds in the series, 2-(4-methylpiperazin-1-yl)-*N*-(thiazol-2-yl)acetamide **23** (72.1 %) (Fig. 5) was the most potent. The longer the side chain, the more it inhibits carrageenan-induced mouse paw edema. A regression analysis was used to see whether there was a connection between anti-inflammatory behavior and a variety of physicochemical parameters. The anti-inflammatory effect was found to have weak correlations with the variables studied with low statistical significance [73].

The anti-inflammatory efficacy of trimethylsiloxyalkyl and trialkylsilylalkyl thiazole derivatives has been studied *in vivo* and *in vitro* [74]. Of all the compounds examined, *N*-(thiazol-2-yl)-3-(4-(-trimethylsilyl)oxy)piperidin-1-yl)propanamide **24** (57.2 % at 0.2 mmol/kg) and organosilicon salt **25** (55.0 % at 0.2 mmol/kg) (Fig. 5) were the most potent. Compound **24** exhibited similar Indomethacin inhibition but in a double dose. But compound **25** was potent as same as Indomethacin in lower dose in carrageenin-induced edema model. The UV absorbance-based enzyme assay [75] was used to evaluate the above trimethylsiloxyalkyl and trialkylsilylalkyl thiazole derivatives for

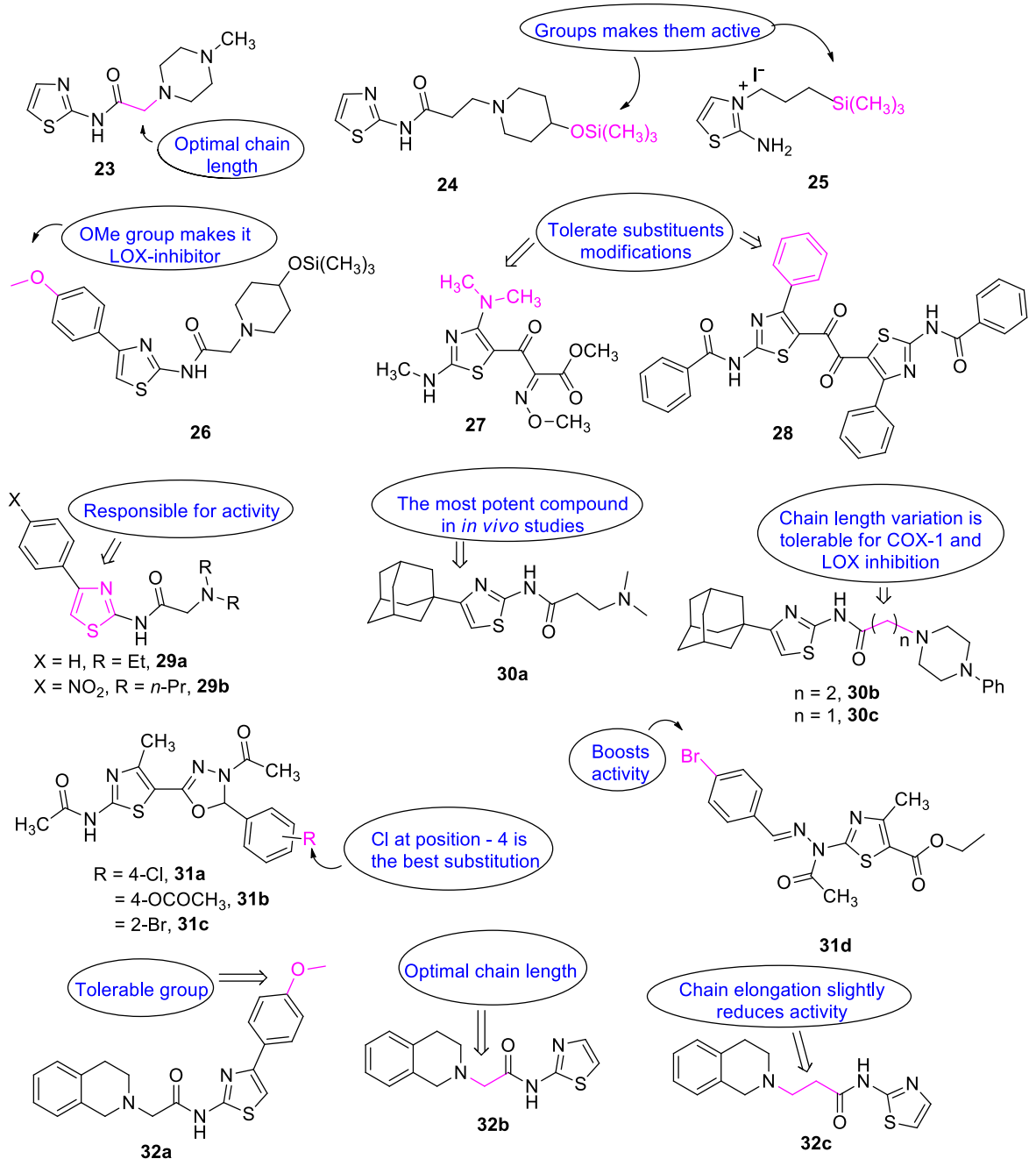

Fig. 5. Amides of 2-aminothiazole.

inhibition of soybean lipoxygenase (LOX). The most effective lipoxygenase inhibitor was *N*-(4-(4-methoxyphenyl)thiazol-2-yl)-2-(4-(trimethylsilyl)oxy)piperidin-1-yl)acetamide **26** (ID_{50} = 0.01 mmol) (Fig. 5). The structure of the C4-substituent also affects the degree of inhibition: 4-methoxyphenyl derivative **26** was found to be a stronger inhibitor than its 4-phenyl analogs.

The compounds (*Z*)-methyl 3-(4-(dimethylamino)-2-(methylamino) thiazol-5-yl)-2-(methoxyimino)-3-oxopropanoate **27** (83 %) and *N*,*N*′-(5,5′-oxalylbis (4-phenylthiazole-5,2-diyl))dibenzamide **28** (73 %) (Fig. 5) display promising anti-inflammatory properties in acute carrageenin induced rat paw edema model. Later, chronic formalin-induced rat paw edema models were employed to access anti-inflammatory activity. In chronic anti-inflammatory models, the activity of **27** (95 % on 3rd day) and **28** (92 % on 2nd day) was comparable to that of Ibuprofen (50 % on 5th day), Rofecoxib (39 % on 1st day) and Dexamethasone (96 % on 3rd day) [76]. The SAR revealed that position-4 on thiazole can tolerate diverse substituents like dialkylamino, alkyl and aryl moieties.

Pattan et al. documented the synthesis of many phenylthiazole derivatives and their anti-inflammatory assessment. The anti-inflammatory effect of these compounds was tested using the carrageenan induced rat hind paw model. Compound 2-(diethylamino)-*N*-(4-phenylthiazol-2-yl)acetamide **29a** (29.67 %) (Fig. 5) has shown significant anti-inflammatory activity. Here Nimesulide (31.86 %) was used as a standard drug. The promising anti-inflammatory activity of these series of compounds is due to the presence of thiazole ring [77]. Porwal and co-workers synthesized some novel thiazole molecules of similar kind and evaluated anti-inflammatory activity. Among the limited number of synthesized compounds, 2-(dipropylamino)-*N*-(4-(4-nitrophenyl)thiazol-2-yl)acetamide **29b** (Fig. 5) was the best (44 %) in carrageenan induced rat paw edema model. The activity of this lead

compound was poor when compared with standard Nimesulide (60 %). The same compound exhibited the highest inhibition (41 %) in formalin induced rat paw edema model. While, the standard Indomethacin showed 60 % inhibition. When nitro group on phenyl ring is replaced by amine functional group and when propyl group is replaced by phenyl, activities were diminished [78].

The anti-inflammatory efficacy of adamantane conjugated thiazolyl-N-substituted amides [79] was investigated *in vivo* using the carrageenin mouse paw edema model and Indomethacin as a control. Lipoxygenase and cycloxygenase inhibitory assays are used to measure *in vitro* activity. The activity of *N*-(4-((3r,5r,7r)-adamantan-1-yl)thiazol-2-yl)-3-(dimethylamino)propanamide **30a** (81.5 %) (Fig. 5), which has the adamantane group in position-4 of the thiazole ring, was significantly higher than that of other derivatives in *in vivo* studies. The lipoxygenase inhibitory activity of phenyl-piperazinyl derivatives showed that *N*-(4-((3r,5r,7r)-adamantan-1-yl)thiazol-2-yl)-3-(4-phenylpiperazin-1-yl)propanamide **30b** (39 %) and *N*-(4-((3r,5r,7r)-adamantan-1-yl)thiazol-2-yl)-2-(4-phenylpiperazin-1-yl)acetamide **30c** (33 %) (Fig. 5) exhibited the best inhibitory action. Human recombinant COX-1 and ovine COX-2 isoenzymes were used to assess cyclooxygenase inhibitory activity. COX-1 inhibitory activity was found to be the highest in phenyl-piperazinyl derivatives **30b** (28.6 %) and **30c** (43.6 %).

Using an acute model of inflammation, Oniga and co-workers assessed the anti-inflammatory efficacy of several new thiazolyl-1,3,4-oxadiazolines and 5-carboxyethyl-2-hydrazon-4-methyl-thiazoles. According to their protocol, if number of neutrophils and monocytes are reduced, number of lymphocytes increased and phagocytic capacity (PA) and concentration of nitrates/nitrites is decreased, anti-inflammatory potential is high. Thus, 4-*N*-acetyl- 2 [2'-(acetyl-amino)-4′-methyl-5′-thiazolyl]-5-aril-Δ_2-1,3,4-oxadiazoline **31a** (PA = 40 ± 2) (Fig. 5) contains a Cl substituent in the para position of the phenyl ring and has anti-inflammatory properties similar to Diclofenac. The anti-inflammatory activity is slightly reduced when the Cl substituent is replaced with an acetoxy moiety **31b** (PA = 60 ± 2) (Fig. 5). A Br substituent in the ortho position of the phenyl ring **31c** (PA = 90 ± 3) (Fig. 5) has a minor anti-inflammatory effect. Furthermore, 5-carboxyethyl-2-(*N*1-acetyl-hydrazone)-4-methyl-thiazole **31d** (PA = 70 ± 4) (Fig. 5) has a Br substituent in the para position of the phenyl ring and has a good anti-inflammatory effect [80].

N-[(Benzo)thiazol-2-yl]-2/3-[3,4-dihydroisoquinolin-2(1*H*)-yl]alkanamides were synthesized and shown to have anti-inflammatory action by Zablotskaya and co-workers [81]. The *in vivo* anti-inflammatory effects were evaluated using the reference drug Indomethacin (57.2 %) in a functional model of carrageenin-induced mouse paw edema. Among the tested compounds, 4-(*p*-methoxyphenyl)thiazolyl ethanamide **32a** (75.8 %) (Fig. 5) showed the highest inhibition, followed by 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-(thiazol-2-yl)acetamide **32b** (70.4 %) and 3-(3,4-dihydroisoquinolin-2(1*H*)-yl)-*N*-(thiazol-2-yl)prop **32c** (62.4 %) (Fig. 5). When comparing compounds **32a** and **32b** (n = 1) with compound **32c** (n = 2), it was fascinating to see how the gap elongation between the tetrahydroisoquinoline and thiazolyl moieties affected the biological response. To show good activity, the chain length between these two heterocyclic moieties is more important than bulky substituent at position-4 of thiazole ring.

Patil et al. developed some 3-substituted thiazolyl derivatives and studied their anti-inflammatory activity. The carrageenan-induced rat-paw edema model was used to test the compounds for anti-inflammatory action. The standard drug was Indomethacin. The most potent compound discovered to be (*E*)-*N*-(4-(1*H*-indol-3-yl) thiazol-2-yl)-3-(4-fluorophenyl)acrylamide **33** (40.39 %) (Fig. 6). It should be noted that indole and thiazole moieties are important to display anti-inflammatory activity [82].

The design and synthesis of N-substituted aminothiazole compounds as anti-inflammatory agents was stated by Fatima and colleagues. The anti-inflammatory activity of the synthesized compounds was tested using the carrageenan-induced rat paw edema procedure. Compared to unsubstituted compounds, compounds containing the 3-Cl group have mixed results. CF_3 substitution increased behavior in all trials. The compound *N*-(4-(3-fluorophenyl) thiazol-2-yl)-3-(trifluoromethyl) benzamide **34** (56 % after 3 h) (Fig. 6) with electron-withdrawing groups, which is the most potent in the series, can affect activity positively. While the standard drug Diclofenac sodium showed 50.6 % inhibition after 3 h [83].

Carrageenan-induced paw edema assay was used to test diphenylthiazole derivatives for their anti-inflammatory properties. The structural criteria for potent anti-inflammatory bioactivities of urea-

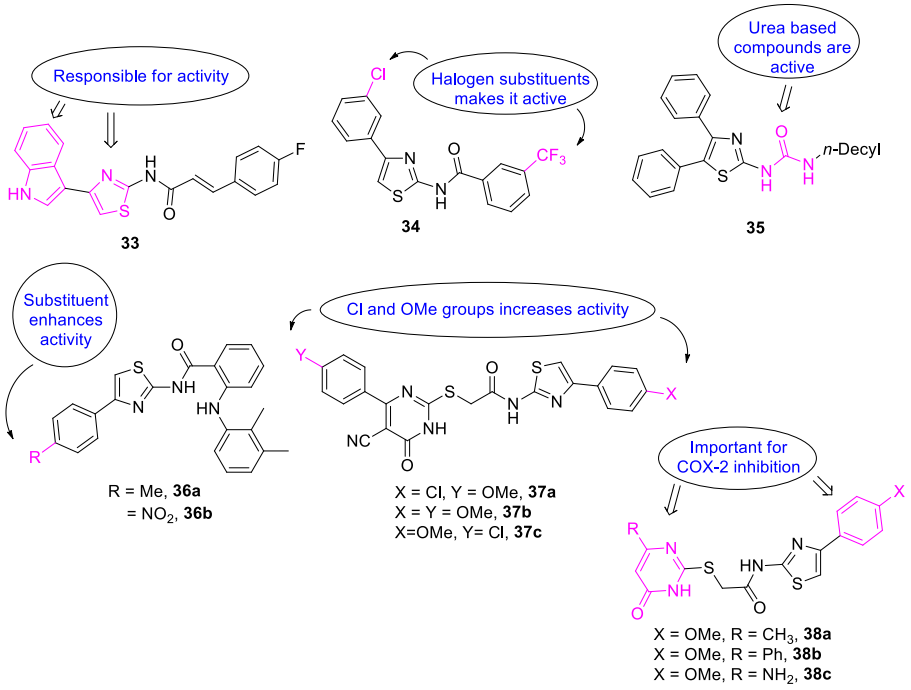

Fig. 6. Amides of 2-aminothiazole (continued).

based analogs vary from those found for amide-based analogs, according to a careful review of the structure-activity relationship. When compared to Diclofenac (11.3 % after 4 h), the urea derivative 1-decyl-3-(4,5-diphenylthiazol-2-yl)urea **35** (21.8 % after 2 h) (Fig. 6) showed superior anti-inflammatory properties after 1 h. Docking studies suggests that they primarily inhibit COX [84].

The synthesis and anti-inflammatory action of 2,4-disubstituted thiazoles were developed by Gobala Krishnan and co-workers [85]. The Albumin denaturation procedure was used to evaluate the anti-inflammatory response [86]. Many of the synthesized substances had important anti-inflammatory properties, and some of them like 2-((2,3-dimethylphenyl)amino)-*N*-(4-(p-tolyl)thiazol-2-yl)benzamide **36a** (78.81 % at 1600 μg/mL) and 2-((2,3-dimethylphenyl)amino)--*N*-(4-(4-nitrophenyl)thiazol-2-yl)benzamide **36b** (79.93 % at 1600 μg/mL) (Fig. 6) had stronger anti-inflammatory properties than the standard medication Diclofenac sodium (77.27 % at 1600 μg/mL). When compared to other substituents, the expression of methyl, nitro, and hydroxyl substituents in 4-phenyl thiazole derivatives showed strong anti-inflammatory efficacy.

Abdel-Aziz and co-workers have reported the anti-inflammatory activities of a series of pyrimidine-5-carbonitrile derivatives bearing 1,3-thiazole moiety. They investigated the inhibitory activity of synthesized compounds against COX-1 and COX-2 subtypes. Notably, all compounds displayed potent COX-2 inhibition (IC_{50} = 1.03–3.98 μM) than COX-1 inhibition (IC_{50} = 8.46–13.90 μM) with high COX-2 selectivity indices (SI = 3.49–8.21). It should be noted that measured activities were relatively lower than standard Celecoxib (COX-2, IC_{50} = 0.88; SI = 8.31). The most potent compounds were **37b** (Fig. 6) (IC_{50} = 1.13 μM, SI = 8.21) and **37c** (IC_{50} = 1.13 μM, SI = 7.84) against COX-2. The unsubstituted compound (X = Y = H) was the least potent compound. Further, *in-vitro* lipoxygenase (LOX) inhibition assay indicated that compounds **37b** (5.29 μM) and **37c** (5.73 μM) (Fig. 6) were the most active 15-LOX inhibitors. These activities were comparable to that of Meclofenamate sodium (5.64 μM). Finally, authors have conducted *in vivo* anti-inflammatory activity using carrageenan induced rat paw edema method. The results indicated that compounds **37a-c** displayed gradual increase in edema inhibition. Meloxicam was used as standard, which was more potent than **37a-c**. Molecular docking studies revealed that these compounds have binding interactions as selective COX-2 inhibitors [87].

The same group of workers analyzed new pyrimidine/thiazole hybrids for *in vitro* COX-1/COX-2 inhibition by taking Celecoxib as a control. Interestingly, compounds **38a**, **38b** and **38c** (Fig. 6) displayed very good COX-2 inhibitory activities (IC_{50} = 1.02–1.43 μM) with high selectivity index (SI = 10–15) towards COX-2. These compounds are found to be 1.3–2.0 times more effective than Celecoxib. It should be noted that, phenyl group on thiazole moiety and pyrimidine moiety were critical for COX-2 inhibition with high SI. On the other hand, unsubstituted derivatives were less active than **38b** and **38c** [88].

2.4. Thiazoles containing imine moieties

Holla et al. developed a series of thiazoles, which were then tested for anti-inflammatory properties. They did the screening in two different models: acute inflammatory and chronic inflammatory. The carrageenan-induced rats paw edema method was employed in the acute inflammatory model. The cotton pellet granuloma method used in the chronic inflammatory model. Granuloma described the exudative and proliferative processes of inflammation. Thiazole derivative **39** (45.5 ± 0.5 %) (Fig. 7) has the highest chronic anti-inflammatory activity which was equivalent to that of Ibuprofen (45.10 %). Notably, compounds bearing 4-methylphenyl, 4-bromophenyl, 4-chlorobenzylideneamino, 3-chloro-4-fluorophenyl and 2-nitrophenylfurylideneamino active towards acute anti-inflammation. While, compounds bearing 3,4- methylenedioxybenzylidene amino and 4-bromophenyl are excellent inhibitors of chronic anti-inflammation [89].

The synthesis of amino thiazolyl chloro coumarin Schiff bases was described by Jayashree and colleagues. The carrageenan-induced rat hind paw edema model is employed to assess these compounds' anti-inflammatory function. Among the synthesized compounds, (*E*)-6-chloro-3-(2-((2-hydroxybenzylidene)amino)thiazol-4-yl)-2*H*-chromen-2-one **40a** (78.49 %) and (*E*)-6-chloro-3-(2-((2-hydroxybenzylidene) amino)thiazol-4-yl)-2*H*-chromen-2-one **40b** (78.49 %) (Fig. 7) demonstrated activity similar to Ibuprofen (89.24 %). Notably, compounds with chloro (at position-4) and hydroxyl (at position-2) are equally potent with standard Ibuprofen. Presence of electron withdrawing groups significantly reduced the anti-inflammatory activity [90].

The anti-inflammatory efficacy of thiazoles substituted indole derivatives against carrageenan-induced edema was tested in albino rats by Singh et al. When the (*E*)-4-(2-(4-chlorophenyl)-1*H*-indol-3-yl)-*N*-((2-methyl-1*H*-indol-3-yl)methylene)thiazol-2-amine **41** (68.2 %) (Fig. 7) was substituted with an indole comprising a methyl group at the second site of the thiazol moiety had greater anti-anti-inflammatory efficacy than the reference medication Phenyl butazone (65.4 %) [91]. Substituents other than methyl group such as ethyl and phenyl on indole moiety has reduced the activity.

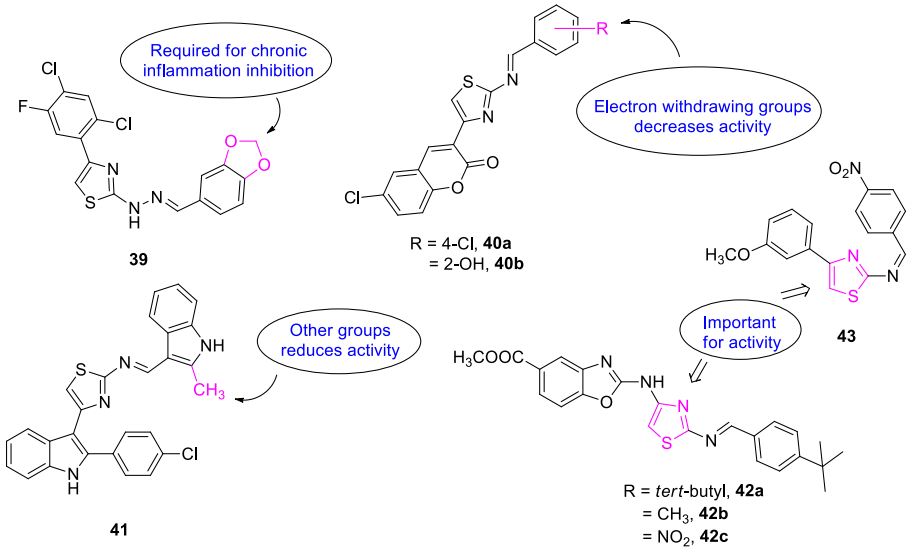

Fig. 7. Imines of aminothiazoles.

By condensation of methyl-2-(2-aminothiazol-5-ylamino)benzo [d] oxazole-5-carboxylate with various aromatic aldehydes, Ampati and co-workers reported the synthesis of a sequence of thiazole linked benzoxazole derivatives. The carrageenan-induced rat paw edema procedure was used to test these compounds for anti-inflammatory action. As a reference medication, Diclofenac sodium was used. Among the synthesized compounds, (*E*)-methyl 2-((2-((4-(tert-butyl)benzylidene)amino) thiazol-4-yl)amino)benzo [d]oxazole-5-carboxylate **42a** (86.62 % after 4 h), (*E*)-methyl 2-((2-((4-methylbenzylidene)amino)thiazol-4-yl) amino)benzo [d]oxazole-5-carboxylate **42b** (85.59 % after 4 h) and (*E*)-methyl 2-((2-((4-nitrobenzylidene)amino)thiazol-4-yl)amino)benzo [d] oxazole-5-carboxylate **42c** (88.68 % after 4 h) (Fig. 7) showed anti-inflammatory activity more than the standard (83.53 % after 4 h). The increased activity is due to the presence of a thiazole ring on the benzoxazole moiety at the second position [92].

The carrageenan-induced rat hind paw model was used to test for anti-inflammatory action of thiazole derivatives. Amongst, (*Z*)-4-(3-Methoxyphenyl)-*N*-(4-nitrobenzylidene) thiazol-2-amine **43** (29.67 % after 3 h) (Fig. 7) showed good anti-inflammatory effects as compared to the standard drug Nimesulide (31.86 % after 3 h) [93]. Thiazole is an important moiety for the existence of anti-inflammatory activity.

The synthesis and anti-inflammatory studies of some novel Schiff and Mannich bases of 5-substituted isatin derivatives were reported by Prakash and co-workers. A carrageenan-induced paw edema test in rats was used to assess anti-inflammatory effects. Among all tested compounds (3*Z*)-1-((dimethylamino)methyl)-5-fluoro-3-((4-(2-((4-methylbenzylidene)amino) thiazol-4-yl)phenyl) imino)indolin-2-one **44** (55 ± 1.14 % after 2 h) and (3*Z*)-3-((4-(2-((4-chlorobenzylidene)amino) thiazol-4-yl)phenyl)imino)-1-((dimethylamino)methyl)-5-fluoroindolin-2-one **45** (68 ± 0.15 % after 2 h) (Fig. 8) exhibited higher potency than Diclofenac (61 ± 0.44 % after 2 h) in terms of activity. The introduction of a methoxy, nitro or hydroxyl group resulted in a significant decrease in activity [94].

Haiba and coworkers reported the synthesis and anti-inflammatory activities of thiazolidinone and 1,2,3,4-tetrahydronaphthalen-6-yl-thiazoles. The anti-inflammatory efficacy of synthesized derivatives was tested in rats using a carrageenan-induced paw edema bioassay and Indomethacin as a reference standard. The compound (*E*)-3-((2-(5-(5,6,7,8-tetrahydronaphthalen-2-yl)thiazol-2-yl)hydrazono)methyl)-4*H*-chromen-4-one **46** (29.41 % after 4 h) (Fig. 8) hindered the edema volume greater than that provided by Indomethacin (25.49 % after 4 h). Chromone and thiazole are important moieties in exhibiting anti-inflammatory activity [95].

Chandak and group reported the synthesis of 2-amino-substituted 4-coumarinylthiazoles bearing the benzenesulfonamide moiety. The anti-inflammatory efficacy of all the synthesized compounds was tested *in vivo* using a carrageenan-induced paw edema assay. Anti-inflammatory activity was high in four compounds **47a** (90.96 % after 4 h), **47b** (91.52 % after 4 h), **47c** (93.22 % after 4 h) and **47d** (95.95 % after 4 h) (Fig. 8) than in Indomethacin (90.39 % after 4 h). Compounds with a methyl, methoxy, fluoro, or chloro substituent on pyrazole's position-3 were shown to have greater anti-inflammatory effect than unsubstituted pyrazole. However, compound **47c** and **47d**, which had a methoxy or chloro substituent on the pyrazole ring and a chloro substituent on the coumarin ring, had pronounced anti-inflammatory activity. The anti-inflammatory results were further confirmed by the docking studies at

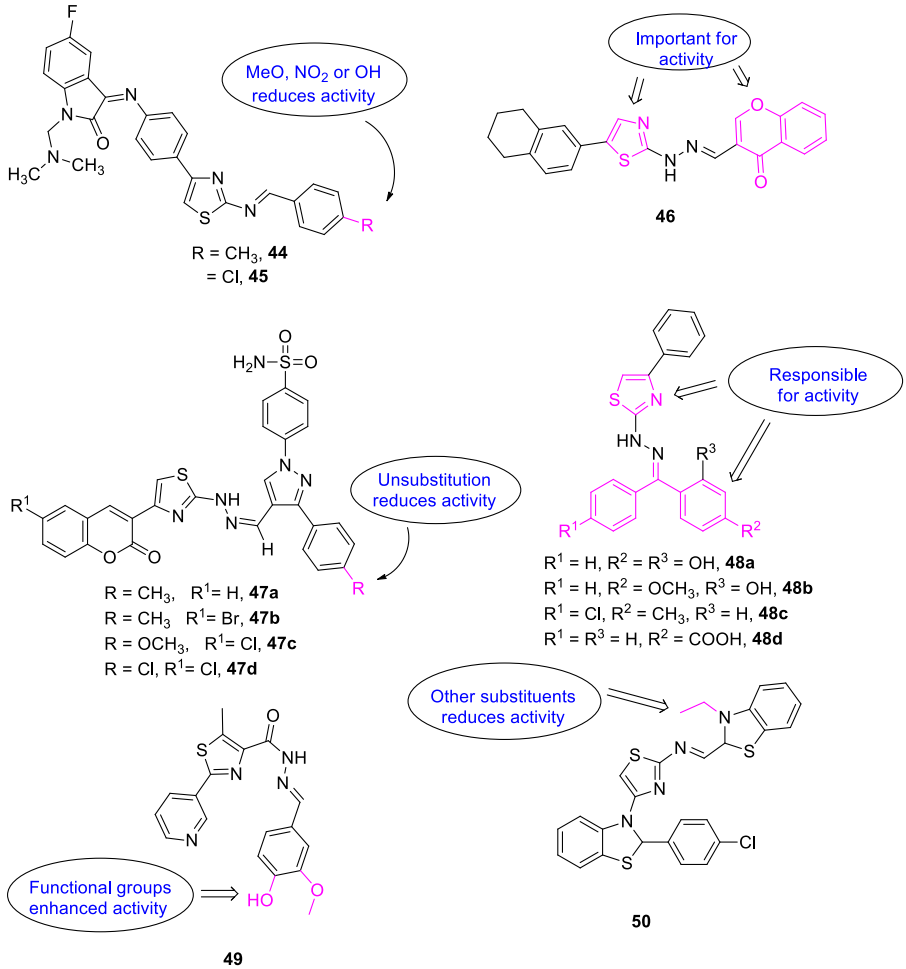

Fig. 8. Imines of aminothiazoles.

COX-1 and COX-2 active sites [96].

For the structural planning of these proposed drugs, the currently produced Ketoprofen [97] as a reference drug. The expected substances were first analyzed *in silico* for cyclooxygenase enzyme inhibition ability (COX-1 and COX-2) and positive results were considered. These benzophenone derivatives were synthesized [98], and they assessed their function using the ear edema test to see if they affected PG development and neutrophil recruitment. They also used multivariate regression analysis to assess the key structural features associated with anti-inflammatory activity. The anti-inflammatory activity of the above compounds was assessed *in vivo* using the croton oil-induced ear edema process, which assess both COX pathway inhibition and neutrophil recruitment in the same experiment [99] and the molecules inhibited edema in a way that was statistically comparable to the positive control Ketoprofen (68 %). Among them, **48a** (73 %), **48b** (74 %), **48c** (72 %) and **48d** (75 %) (Fig. 8) had a greater decrease in edema, which was similar to the positive controls' values. The amplified activity is due to the presence of thiazole and benzophenone moieties.

Kamat and co-workers reported the synthesis and anti-inflammatory activity of a series of thiazole-based hydrazides. The anti-inflammatory efficacy of these compounds in *in vitro* was assessed using the bovine serum albumin denaturation process. The compound (*E*)-*N*'-(4-hydroxy-3-methoxybenzylidene)-5-methyl-2-(pyridin-3-yl) thiazole-4-carbohydrazide **49** (87.97 ± 1.37 % at 100 μg/mL) (Fig. 8) has the highest IC_{50} value of all the compounds examined. The anti-inflammatory effect was increased by incorporation of the hydroxyl substituent in the fourth position and the methoxy substituent in the third position. The active compounds also had a higher docking score and behaved well with the target protein [100].

Gajendra Kumar and co-workers have reported the anti-inflammatory activity of a series of thiazole derivatives against carrageenin. The compounds showed anti-inflammation activity in the range between 29.7 % and 69.6 %. Amongst the tested compounds, 4-(2-(4-chlorophenyl)benzo [d]thiazol-3(2*H*)-yl)-*N*-((3-ethyl-2,3-dihydrobenzo [d]thiazol-2-yl)methylene)thiazol-2-amine **50** showed the best activity 38.5, 55.4 and 69.6 compared to positive control Phenylbutazone 22.2, 35.8 and 65.5 at doses 25, 50 and 100 mg/kg p. o. respectively. Compound **50** (Fig. 8) with ethyl group on position-3 of benzothiazole exhibited more activity (55.4 %) than other compounds. When ethyl group is substituted by phenyl group, the activity reduced to 25.8 % [101].

2.5. Thiazolylmethyl/aryl ethers

Bird et al. [102] developed methoxy alkyl thiazoles as potent orally active 5-lipoxygenase first-class inhibitors with high enantioselectivity. The technique of Aharony and Stein [103] has been used to assess inhibition of cell-free 5-LPO activity using the high-speed supernatant from either guinea pig PMNs or rat basophilic leukemia (RBL) cells as the enzyme source. Foster et al. identified a method for inhibiting LTC4 and PGE2 synthesis in plasma-free peritoneal macrophage cultures [104]. Foster et al. used heparinized rat or human blood to test the efficacy and selectivity of 5-LPO inhibitors. In the above series compound l-[3-(naphth-2-ylmethoxy) phenyl]-l-(thiazol-2-yl) propyl methyl ether **51** (ICI211965) ($IC_{50} = 0.4 \pm 0.1$ μM) (Fig. 9) proved better activity and it suppresses cell-free guinea pig 5-LPO activity, LTC4 synthesis in plasma-free mouse macrophages, and LTB4 synthesis in rat and human blood. In the human whole blood assay, shifting the point of attachment of the naphthalene ring from β to α resulted in a 10-fold loss of potency, according to SAR reports. Changing the central aromatic ring's substitution pattern from *meta* to *ortho* or *para* resulted in a 100-fold reduction in potency. Similarly, the thiazole's point of attachment was changed from 2 to 4 without a noticeable loss of potency. This study shows that high *in vitro* potency causes the existence of methoxy, thiazolyl and naphthyl groups and highly depends on the substitution pattern.

The anti-inflammatory effect of a series of newly developed 2-[4-(alkylthio)phenoxy] methyl-4-substituted-1,3-thiazoles was tested in rats using the carrageenan paw edema assay. Compounds like 2-((4-(methylthio)phenoxy)methyl)-4-phenylthiazole **52a** (1.12 %), 4-(4-chlorophenyl)-2-((4-(methylthio)phenoxy)methyl)thiazole **52b** (1.09 %), 2-((4-(methylthio)phenoxy)methyl)-4-(4-nitrophenyl)thiazole **52c** (1.21 %) and 2-((4-(ethylthio)phenoxy)methyl)-4-(pyridin-4-yl)thiazole **52d** (1.22 %) (Fig. 9) possess very good activity almost comparable with standard Diclofenac sodium (1.005 %) after 4 h. In the presence of groups including 4-methylthio, 4-ethylthio phenoxy groups at position 2 and 4-nitro phenyl, 4-chloro phenyl, and pyridine groups at position-4 of the thiazole moiety, the anti-inflammatory activity was improved [105].

Rai et al. developed a series of 2-[2-(aroyl-aroxy)-methyl]-4-phenyl-1,3-thiazoles and compared them to the standard drug Phenyl butazone for *in vivo* anti-inflammatory effect using the carrageenin mouse paw

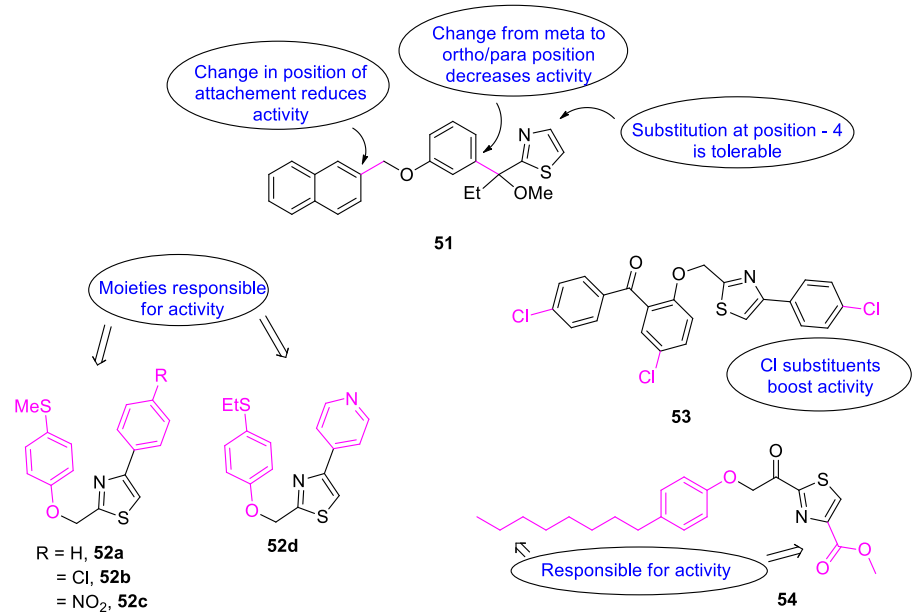

Fig. 9. Thiazolylmethyl/aryl ethers.

edema as a model. At all doses measured, (5-chloro-2-(4-(4-chlorophenyl)thiazol-2-yl)methoxy)phenyl)(4-chlorophenyl)methanone **53** (77.1 % at 80 mg/kg p.o.) (Fig. 9) with chloro substituents outperformed the standard drug (55.1 at 80 mg/kg p.o.). Then tested cyclooxygenase activity *in vitro*, compound **53** demonstrated strong COX activity, suggesting that compounds that inhibit PGs suppress inflammatory responses. The highest activity of compound **53** is due to the presence of three chloro groups in its structure [106].

Kokotos et al. developed the inhibition of group IVA cytosolic phospholipase A2 by thiazolyl ketones *in vitro*, *ex vivo*, and *in vivo*. However, by combining a para-*n*-octyl-phenoxy group with an ester group on the thiazole ring, the potent GIVA cPLA2 inhibitor methyl 2-(2-(4-octylphenoxy)acetyl)thiazole-4-carboxylate was developed **54** (Fig. 9). The CIA mouse model was used to test the inhibitor's *in vivo* activity. It had an anti-inflammatory activity similar to those of the reference drug Methotrexate in the prophylactic model, and it had effects comparable to those of the reference drug Enbrel in the therapeutic model. The 3-fold elevated PGE2 plasma levels were greatly decreased by around 40 % using inhibitor compound **54** in both the prophylactic and therapeutic models [107].

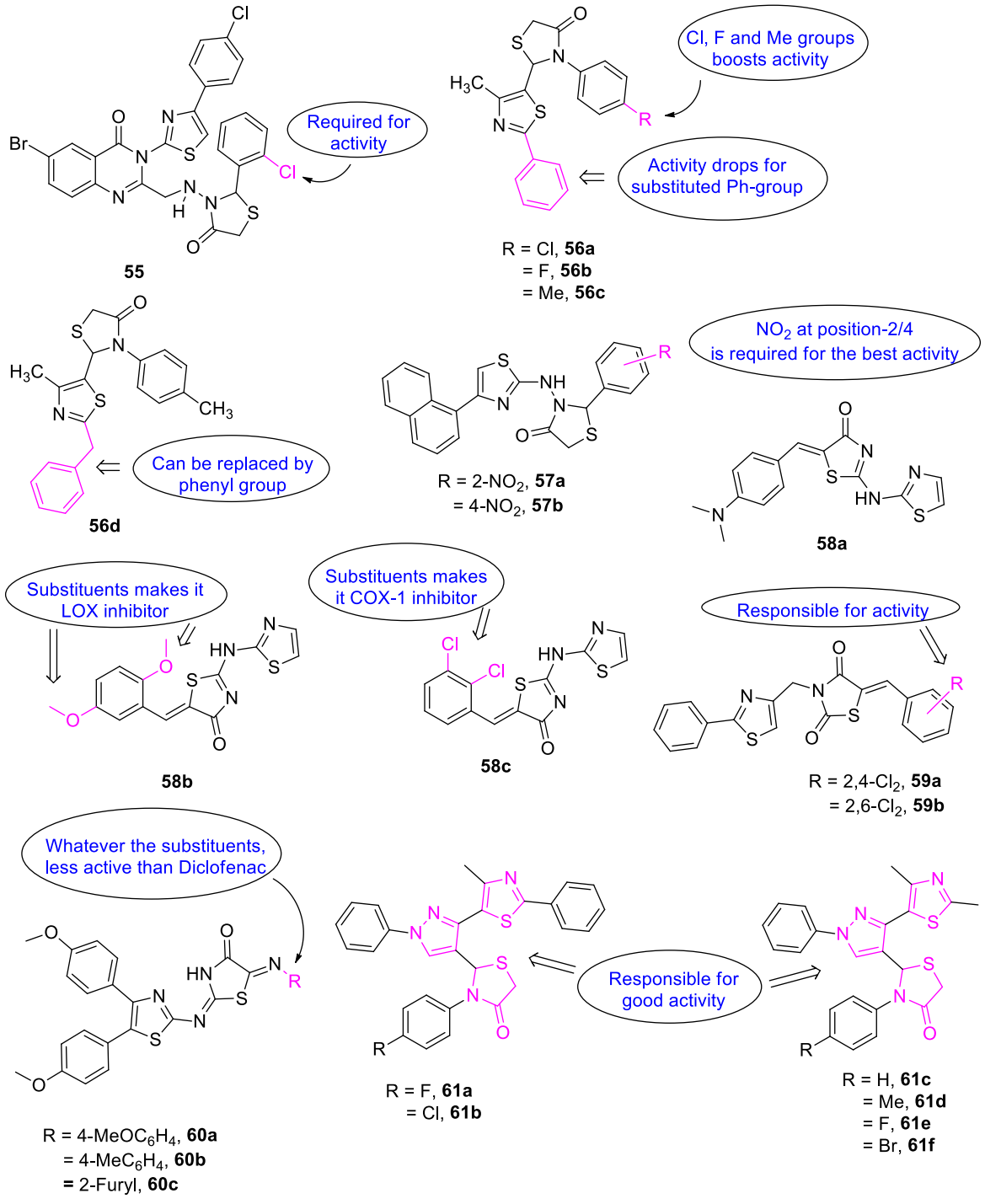

Fig. 10. Thiazole-thiazolidinone hybrids.

2.6. Thiazole-thiazolidinone hybrids

In the carrageenin-induced paw edema model, quinazolinone conjugated thiazole derivatives were assessed for anti-inflammatory activity. When compared to Phenylbutazone (38.90 at 50 mg/kg p.o.), 3-((6-bromo-3-(4-(4-chlorophenyl)thiazol-2-yl)-4-oxo-3,4-dihydroquinazolin-2-yl)methyl)amino)-2-(2-chlorophenyl) thiazolidine-4-one **55** (38.35 % at 50 mg/kg p.o.) (Fig. 10) exhibited better anti-inflammatory potency. The presence of chlorine as substituent at ortho-position is important to exhibit anti-inflammatory activity. The other substituents reduced the activity [108].

Shelke et al. documented the synthesis and anti-inflammatory activity of thiazole-thiazolidine hybrides. The carrageenan-induced paw edema method was used to test *in vivo* efficacy of 3-aryl-2-(2-substituted-4-methyl thiazole-5-yl) thiazolidin-4-ones. The maximum protection was showed by 3-(4-chlorophenyl)-2-(4-methyl-2-phenylthiazol-5-yl) thiazolidin-4-one **56a** (80.75 % after 4 h), 3-(4-fluorophenyl)-2-(4-methyl-2-phenylthiazol-5-yl)thiazolidin-4-one **56b** (85.33 % after 4 h) and 2-(4-methyl-2-phenylthiazol-5-yl)-3-(*p*-tolyl)thiazolidin-4-one **56c** (80.56 % after 4 h) (Fig. 10), having phenyl group at 2-position of thiazole. It was also seen that benzyl group containing compound 2-(2-benzyl-4-methylthiazol-5-yl)-3-(*p*-tolyl)thiazolidin-4-one **56d** (81.32 % after 4 h) (Fig. 10) also showed better anti-inflammatory activity. Notably, the standard drug Indomethacin (87.26 % after 4 h) is superior over these compounds. Compared to 2-(4-chlorophenyl)thiazole or 2-(4-chlorobenzyl) thiazole, 2-phenyl thiazole demonstrates stronger inhibition [109].

Gangwar and his group used the carrageenan induced paw edema method to screen for anti-inflammatory activity. As compared to the standard drug Diclofenac sodium, both the compound 3-((4-(naphthalen-1-yl)thiazol-2-yl)amino)-2-(2-nitrophenyl)thiazolidin-4-one **57a** (65.61 % after 2 h) and 3-((4-(naphthalen-1-yl)thiazol-2-yl)amino)-2-(4-nitrophenyl)thiazolidin-4-one **57b** (62.61 % after 2 h) (Fig. 10) showed excellent anti-inflammatory efficacy. But these compounds were not as much active as standard drug Diclofinac sodium (76.33 % after 2 h). The better activity of these compounds is attributed to the presence of nitro group at position-2/4 [110].

Using the carrageenan mouse paw edema bioassay, Apostolidis and colleagues established the synthesis and biological evaluation of 5-arylidene-2-(1,3-thiazolidin-4-ones as dual anti-inflammatory agents. Compared to the reference drug Indomethacin, the most active compound is (*Z*)-5-(4-(dimethylamino)benzylidene)-2-(thiazol-2-ylamino) thiazol-4(5*H*)-one **58a** (67.3 ± 4.5 %). Inhibitory actions against COX-1/LOX have also been published. Compound (*Z*)-5-(2,5-dimethoxybenzylidene)-2-(thiazol-2-ylamino)thiazol-4(5*H*)-one **58b** (IC_{50} = 52.0 μM) (Fig. 10) is the most potent LOX inhibitor. Compound (*Z*)-5-(2,3-dichlorobenzylidene)-2-(thiazol-2-ylamino)thiazol-4(5*H*)-one **58c** (IC_{50} = 10.0 μM) is the best effective COX-1 inhibitor. In addition to mono chloro substitution, having two chloro atoms in the molecule results in more potent COX-1 inhibition [111].

The synthesis of 5-arylidene-2,4-thiazolidinediones was recorded by Nastasa and co-workers, and they tested these molecules *in vivo* as anti-inflammatory agents in an acute phase bone marrow response and phagocyte activity. The reduction in absolute leukocyte count was linked to the reduction in total leukocyte count, with phagocytic activity (PA) for substance (*Z*)-5-(2,4-dichlorobenzylidene)-3-((2-phenylthiazol-4-yl)methyl)thiazolidine-2,4-dione **59a** and phagocytic index (PI) for substance (*Z*)-5-(2,6-dichlorobenzylidene)-3-((2-phenylthiazol-4-yl) methyl)thiazolidine-2,4-dione **59b** (Fig. 10). The derivatives **59a** and **59b** had a major impact on the decrease of the two parameters studied, PI and PA. As compared to Meloxicam, the presence of two chlorine atoms in a molecule resulted in a more strong activity [112].

Abdelazeem and colleagues published a sequence of novel diphenylthiazole-thiazolidin-4-one-based derivatives in 2015. The carrageenan-induced rat paw edema model and Diclofenac as a reference drug were used to test their anti-inflammatory properties. The anti-inflammatory efficacy was shown to be significantly improved when the 5-benzylidenemoiety was substituted with electron-donating groups as in (2*E*,5*Z*)-2-((4,5-bis(4-methoxyphenyl)thiazol-2-yl)imino)-5-((4-methoxyphenyl)imino)thiazolidin-4-one **60a** and (2*E*,5*Z*)-2-((4,5-bis(4-methoxyphenyl)thiazol-2-yl)imino)-5-(*p*-tolylimino)thiazolidin-4-one **60b** (Fig. 10). The anti-inflammatory efficacy of (2*E*,5*Z*)-2-((4,5-bis(4-methoxyphenyl)thiazol-2-yl)imino)-5-(furan-2-ylimino)thiazolidin-4-one **60c** (Fig. 9) was dramatically increased when the 5-benzylidene moiety was replaced with the less bulky furyl moiety. Notably, these molecules were less active than standard drug Diclofenac [113].

The synthesis of trisubstituted pyrazoles with thiazolyl and thiazolidinonyl moieties was stated by Khillare and colleagues. The carrageenan paw edema system was used to screen the new pyrazoles for *in vivo* anti-inflammatory activity. After 6 h, the series of compounds **61a-f** (12–25 % after 6 h) (Fig. 10) outperformed the reference drug Celecoxib (11 % after 6 h). The anti-inflammatory action is proved to be due to the presence of thiazolidinone, thiazole and pyrazole rings [114].

2.7. Thiazole-pyrazole/pyrazoline hydrids

Using a carrageenan-induced rat paw edema assay and Indomethacin (78 % after 3 h) as a standard drug, Abdel-Sattar and co-workers established the synthesis and biological evaluation of certain thiazoles for *in vivo* anti-inflammatory action. 2-(5-(Benzofuran-2-yl)-3-(4-(piperidin-1-yl)phenyl)-2,3-dihydro-1*H*-pyrazol-1-yl)-4-(4-chlorophenyl)thiazole **62** (≥70 % after 4 h) (Fig. 11), which has a chloro substituent at position-4 of the phenyl ring and is bound to the C-4 of the thiazole moiety, showed improved efficacy. Notably, compounds with halogen as substituent showed more anti-inflammatory activity than non-halogen-containing compounds [115].

The synthesis and anti-inflammatory efficacy of 2-(5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazol-1-yl)-4-(coumarin-3-yl)thiazole derivatives were developed by Ranjana et al. The anti-inflammatory activity of the synthesized derivatives was tested *in vivo* using the carrageenan-induced paw edema method. Many of the compounds studied had strong anti-inflammatory effects. (*R*)-3-(2-(5-Hydroxy-3,5-bis(trifluoromethyl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4-yl)-2*H*-chromen-2-one **63a** (83.10 % after 1 h) and (*R*)-6-chloro-3-(2-(5-hydroxy-3,5-bis(trifluoromethyl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4-yl)-2*H*-chromen-2-one **63b** (85.91 % after 1 h) (Fig. 11) demonstrated the highest anti-inflammatory activity, when related to standard drug Indomethacin (94.37 % after 1 h). The better anti-inflammatory action is due to the presence of coumarin, pyrazoline and thiazole moieties [116].

Thore et al. synthesized a series of substituted thiazole derivatives and tested them for anti-inflammatory activity. The carrageenan-induced paw edema test in rats was used to assess anti-inflammatory response. The ethyl 5-amino-1-(2-phenylthiazole-4-carbonyl)-1*H*-pyrazole-4-carboxylate **64** (62.96 % after 2 h) (Fig. 11) exhibited good activity than standard Diclofenac sodium (56.66 % after 2 h). Compounds with the pyrazole moiety had greater anti-inflammatory activity, according to the structural correlation [117].

A novel series of pyrazolylthiazole carboxylates and related acid derivatives was synthesized and biologically evaluated by Khloya's group. The carrageenan-induced rat paw edema procedure was used to assess these compounds' anti-inflammatory function *in vivo*. As per the biological study, most of the compounds showed strong anti-inflammatory activity 3 and 4 h after carrageenan injection. Out of all the compounds studied, three stood out, ethyl 4-(4-chlorophenyl)-2-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)thiazole-5-carboxylate **65a** (90.42 % after 4 h), 2-(1,3-diphenyl-1*H*-pyrazol-4-yl)-4-(4-fluorophenyl)thiazole-5-carboxylic acid **65b** (90.95 % after 4 h) and 2-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-4-(4-methoxyphenyl)thiazole-5-carboxylic acid **65c** (88.82 % after 4 h) (Fig. 11) anti-inflammatory efficacy was equivalent to that of the reference medication Indomethacin (91.48 % after 4 h). Ester derivatives are more potent than corresponding acids derivatives. The anti-inflammatory activity is

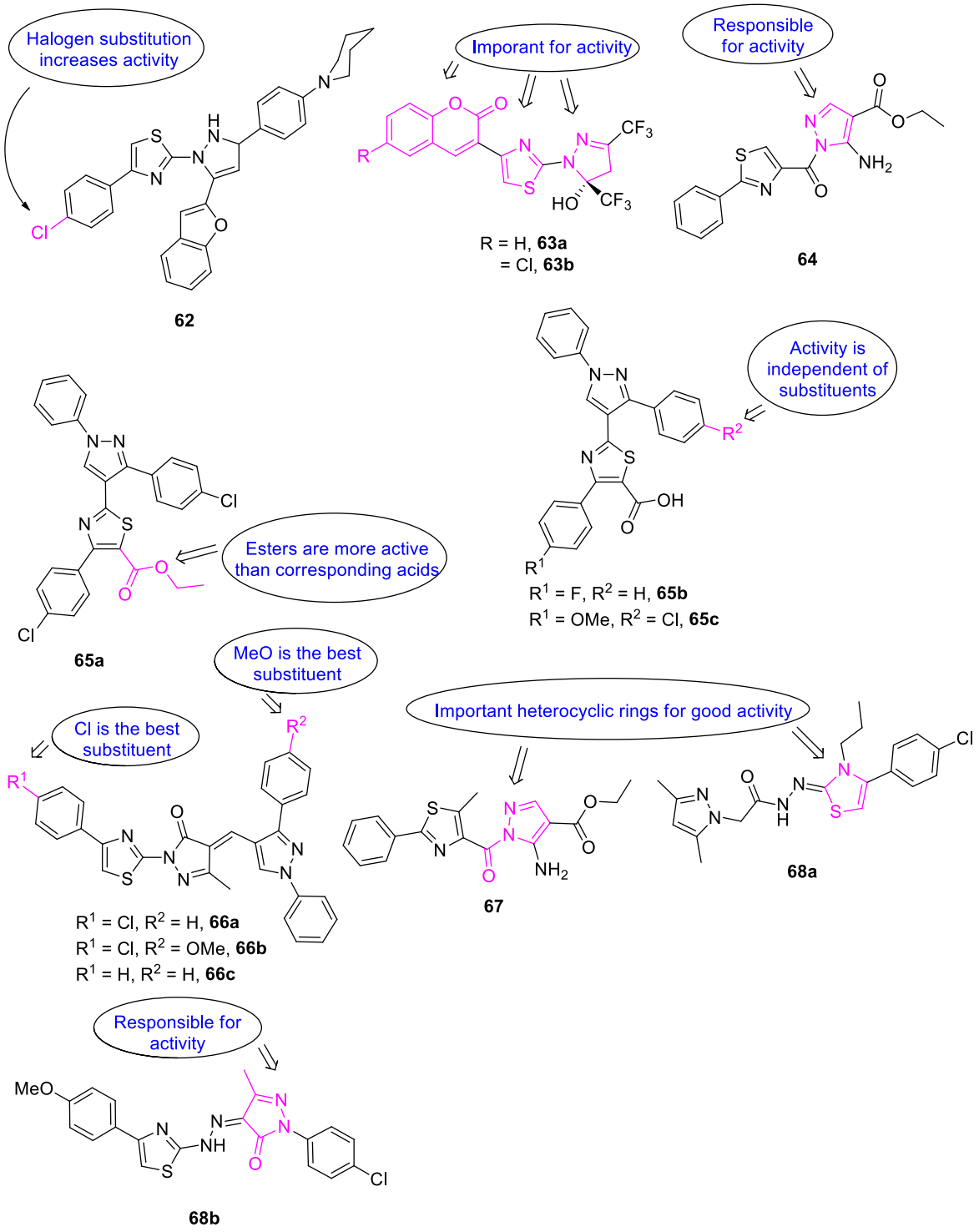

Fig. 11. Thiazole-pyrazole/pyrazoline hydrids.

independent of nature of substituents [118].

The anti-inflammatory efficacy of the thiazoles containing pyrazole was tested *in vitro* and *in vivo* by Kamble and co-workers. The standard drugs in this study were Celecoxib, Indomethacine and Aspirin. Among the compounds, (*E*)-1-(4-(4-chlorophenyl)thiazol-2-yl)-4-((3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-3-methyl-1H-pyrazol-5(4*H*)-one **66b** (78.91 ± 0.80 %) showed substantial COX-II inhibition. The pyrazole nucleus with an electron-donating phenyl substituent improved COX-II inhibition capacity, according to SAR research. Carrageenan-induced acute paw edema in albino rats was studied *in vivo* using Diclofenac (95.45 %) as a reference medication. Among tested six molecules, (*E*)-1-(4-(4-chlorophenyl)thiazol-2-yl)-4-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-3-methyl-1*H*-pyrazol-5(4*H*)-one **66a** (72.72 %), compound **66b** (92.85 %) and (*E*)-4-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-3-methyl-1-(4-phenylthiazol-2-yl)-1*H*-pyrazol-5(4*H*)-one **66c** (69.22 %) (Fig. 11) were more potent. Compound **66b** showed positive activity after 90 min, suggesting a promising response as opposed to the standard drug. The association of

strongly conserved residues affects thiazol-mediated COX-II inhibition, according to structural studies of docked complexes [119].

Thore et al. developed a series of 5-methyl-2-phenyl thiazole-4-substituted derivatives. The anti-inflammatory properties of these synthesized compounds were tested. The carrageenan-induced paw edema test in rats was used to determine anti-inflammatory function, with Diclofenac sodium serving as the reference standard. It was observed that the thiazole derivative ethyl 5-methyl-1-(5-methyl-2-phenyl-thiazole-4-carbonyl)-1*H*-pyrazole-4-carboxylate **67** (64.28 % after 3 h) (Fig. 11) has displayed improved activity than reference drug (57.14 % after 3 h). The structural comparison with anti-inflammatory behavior revealed that the pyrazole at position-4 of the thiazole had the most dominant and consistent anti-inflammatory activity compared to the standard sample [120].

Marzouk and co-workers have reported a series of thiazolo-pyrazole hybrids and evaluated their anti-inflammatory activity on rats by the acute formalin induced paw edema models. Many compounds showed good anti-inflammatory activity against Indomethacin (84.62 %) after 4 h. Among the series, compound **68a** (Fig. 11) showed the highest activity (97.30 %). The presence of thiazole and pyrazole moieties are important requirements to exhibit anti-inflammatory activity [121].

Yamsani et al. synthesized heterocyclic substituted thiazole derivatives and studied their anti-inflammatory activity using carrageenan-induced paw edema model. Among the tested compounds (*Z*)-1-(4-chlorophenyl)-4-(2-(4-(4-methoxyphenyl)thiazol-2-yl)hydrazono)-3-methyl-1*H*-pyrazol-5(4*H*)-one **68b** (Fig. 11) was found to be the best protector with 76 ± 0.35 % protection at 2nd hour. Notably, reference drug Diclofenac showed 74 ± 0.52 % protection. Thus, potency of **68b** is comparable to that standard drug. When pyrazole is replaced by pyrimidine or isoxazole, activity was slightly reduced. In pyrazole derivatives, aryl group is preferable over other groups (such as hydrogen, $CSNH_2$ and *p*-COC_5H_4N) at position-1. On aryl rings at position-1, para-substitution is better than meta-substitution. The anti-inflammatory potency is substantiated by docking studies [122].

2.8. Thiazolimines

The synthesis of acridinyl-thiazolino derivatives and their anti-inflammatory evaluation were reported by Sondhi et al. Among all the synthesized molecules, compounds (*Z*)-4-methoxy-*N*-(3-(2-methoxyphenyl)-4-phenylthiazol-2(3*H*)-ylidene)acridin-9-amine **69a** (29.1 %), (*Z*)-*N*-(3-(2-nitrophenyl)-4-phenylthiazol-2(3*H*)-ylidene)-4-methoxyacridin-9-amine **69b** (31.2 %)and (*Z*)-1-(3,4-diphenylthiazol-2(3*H*)-ylidene)-3-(4-methoxyacridin-9-yl)thiourea **69c** (32.5 %) (Fig. 12) have demonstrated strong anti-inflammatory efficacy in the carrageenin-induced paw edema model, using Ibuprofen (38.4 %) as a standard medication. Compounds with methoxy group on acridine ring and methoxy, nitro and hydrogen substituents respectively on the phenyl ring are favourable for anti-inflammatory action [123].

2.9. Thiazole-indole hybrids

Sunil et al. synthesized Bacillamide analogs, which were then screened for anti-inflammatory activity using the carrageenan-induced rat hind paw edema method. Many of the compounds examined had anti-inflammatory effects over a broad range. The anti-inflammatory activity of *N*-(2-(1*H*-indol-3-yl)ethyl)-2-(*p*-tolyl)thiazole-4-carboxamide **70a** (81 %), *N*-(2-(1*H*-indol-3-yl)ethyl)-2-(thiophen-2-yl)thiazole-4-carboxamide **70b** (82 %), *N*-(2-(1*H*-indol-3-yl)ethyl)-2-aminothiazole-4-carboxamide **70c** (86 %) and *N*-(2-(1*H*-indol-3-yl) ethyl)-2-((4-fluorophenyl)amino)thiazole-4-carboxamide **70d** (83 %) (Fig. 13) were discovered to be excellent. Bacillamide, on the other hand, does not seem to have any promising activity. In 1 h, the percentage inhibition of compounds **70a-d**, this is similar to the standard drug Indomethacin (94 %). The above results indicate that these compounds may be used as anti-inflammatory agents that function quickly. With percentage inhibition, compounds **70c** (82 %) is still active after 4 h. The promising activity is due to the presence of thiazole and tryptamide moieties [124].

2.10. Thiazole-pyrrole hydrids

Barghash and co-workers reported a synthesis of different thiazole motif linked with diethyl 2-amino-5-hydroxy-1*H*-pyrrol-3-ylphosphonates. The anti-inflammatory action of the above synthesized molecules was tested *in vivo* using a carrageenan-induced mouse paw edema model, with Indomethacin serving as a control (55.8 %). Most of the phosphonates were active from moderate to excellent. Amongst the tested compounds, ethyl 2-(2-(2-amino-3-(diethoxyphosphoryl)-5-hydroxy-1*H*-pyrrol-1-yl)thiazol-4-yl)acetate **71a** (77.4 %), diethyl (2-amino-5-hydroxy-1-(5-methylthiazol-2-yl)-1*H*-pyrrol-3-yl)phosphonate **71b** (73.2 %), and diethyl (2-amino-5-hydroxy-1-(5-methoxy-4-methylthiazol-2-yl)-1*H*-pyrrol-3-yl)phosphonate **71c** (70.6 %) (Fig. 14) were the most active phosphonates. The effect of the above compounds on

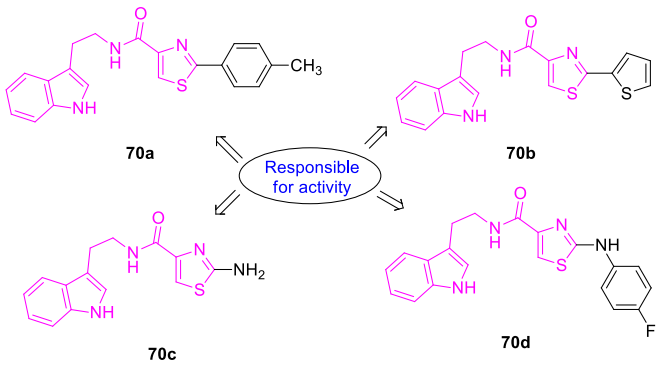

Fig. 13. Thiazole-indole hybrids.

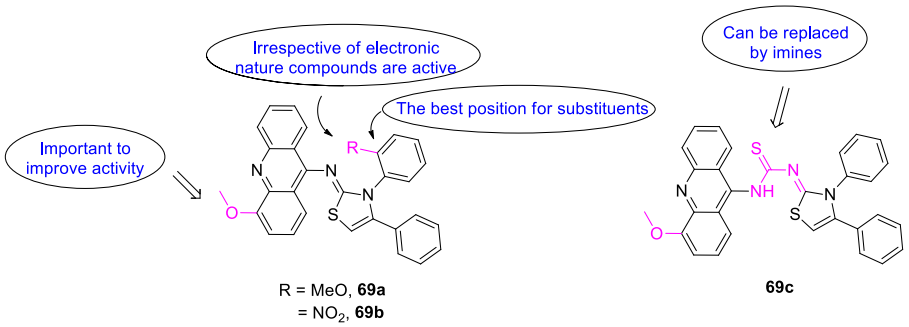

Fig. 12. Thiazolimines.

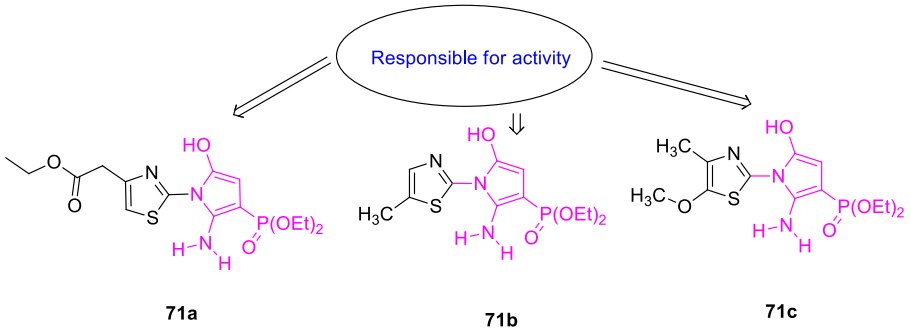

Fig. 14. Thiazole-pyrrole hydrids.

COX-2 behavior was investigated using docking experiments. It has been noted that the lead compounds **71a-c** showed significant docking scores than the reference drug. Notably, diethyl 2-amino-5-hydroxy-1*H*-pyrrol-3-ylphosphonate moiety is responsible for good activity [125].

2.11. Thiazolo-steroidal hybrids

Mohareb and colleagues developed thiazole, pyridine, and pyran derivatives derived from androstenedione and tested them for anti-inflammatory and anti-ulcer properties. The carrageenin-induced rat hind paw edema model was used to assess anti-inflammatory response. The standard drug is Indomethacin. Because of the inclusion of the cyano in the 2-phenylcrotenonitrile moiety, compound **72a** (73 %) showed high activity due to the 2-alkylated product. Compound 2,3-dihydrothiazole-5-carboxamide **72b** (82 %) outperformed compound **72a** in terms of activity. In the case of pyran derivatives, the activity of compound **72e** (89 %) with Cl and OH moieties is the highest. Furthermore, compound **72d** (86 %) with the OCH_3 and OH moieties outperformed compound **72c** (75 %) (Fig. 15) in terms of activity [126].

2.12. Thiazole-benzimidazole hybrids

Gullapelli and co-workers studied the *in vitro* anti-inflammatory activity of new thiazole-benzimidazole hybrids by choosing Diclofenac sodium as standard drug [127]. Among the tested compounds **72f** (85 % at 100 μg/mL) and **72g** (88 % at 100 μg/mL) (Fig. 16) showed remarkable inhibition in comparison with standard (90 %). Replacement of pyrazoline ring by isoxazoline slightly enhanced the activity.

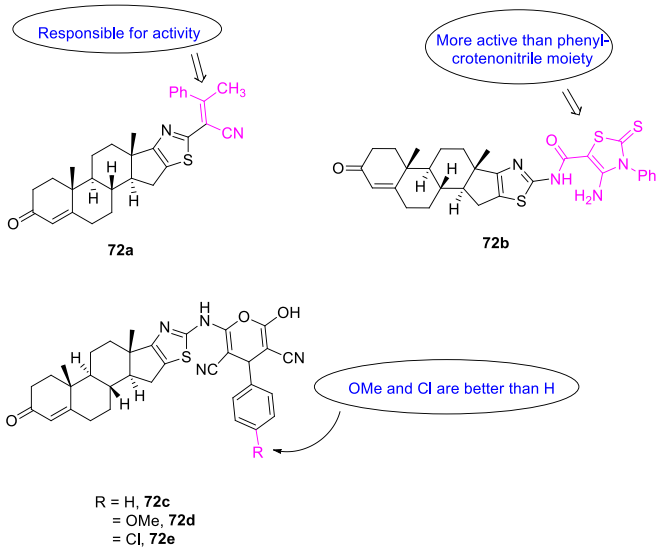

Fig. 15. Thiazolo-steroidal hybrids.

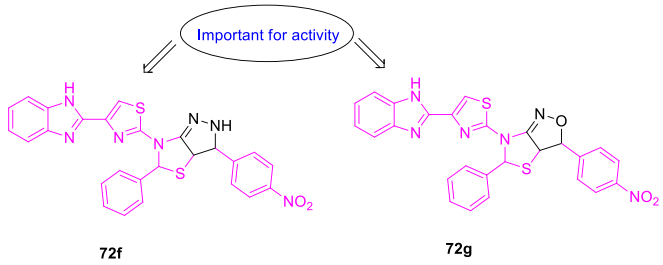

Fig. 16. Thiazole-benzimidazole hybrids.

When nitrophenyl group is replaced by other aromatic rings bearing substituents like methyl, methoxy and hydroxyl reduced the activity. The activity data is substantiated by docking studies with high docking scores for these compounds.

2.13. Thiazole-complex

Pontiki and colleagues produced a series of copper complexes containing dipropylenetriamine and 2-thiophene-carboxaldehyde, which were tested for anti-inflammatory properties. Using the carrageenin-induced paw edema experiment, both of the compounds examined outperformed the reference drug Indomethacin. However, Cu(dienOO)(2-amino-5-methylthiazole) **73** (Fig. 17) surpassed other copper complexes. Furthermore, the inclusion of halogens such as bromine in complexes increased the anti-inflammatory response considerably [128].

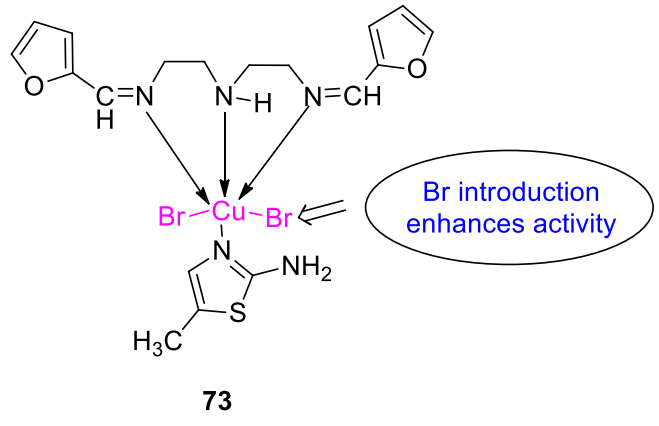

Fig. 17. Thiazole-complex.

2.14. Miscellaneous thiazole compounds

The anti-inflammatory activity of certain trimethoxy phenyl thiazoles was evaluated by Araniciu and co-workers. They tested the activity in rats *in vivo* using the acute phase bone marrow reaction during an experimental acute inflammation. 4-(4-Nitrophenyl)-2-(3,4,5-trimethoxyphenyl)thiazole **74a** and 4-(4-chlorophenyl)-2-(3,4,5-trimethoxyphenyl)thiazole **74b** on both overall leukocyte count (for **74a** 4255/mm^3 and for **74b** 4406/mm^3) (Fig. 18) and neutrophil percentage (53.88 % for **74a** and 60.6 for **74b**). They had a slightly higher inhibitory effect than Meloxicam (Leukocytes number = 4593/mm^3 and Neutrophiles percent = 65.6 %) [129].

Tratrat and co-workers have synthesized a series of thiazole-based chalcone derivatives and studied their anti-inflammatory activity on edema induced after carrageenan administration to muscles. Indomethacin was used as a positive control. The compounds **75a-h** (Fig. 18) were the most active, which showed better activity than reference drug. The authors emphasized that the activity of these compounds does not correlate with their lipophilicity. Thus, only other parameters could affect their action. When hydroxy group is at position-4, compounds are more active than when hydroxyl group is situated at position-3. Apparently, nature of alkyl substituent on amino group is immaterial and did not play any role [130].

Hawash and co-workers have synthesized a series of thiazole carboxamide derivatives and evaluated their anti-inflammatory activity using COX-1 and COX-2 inhibition assays. All derivatives exhibited good inhibitory activities on both COX enzymes. At 5 μM concentration, all thiazoles inhibited COX-2 higher than 53.9 %. While, COX-1 inhibition was observed in the range 32.2–74.8 %. The most potent molecule was **76a** which inhibited 81.5 % against COX-2 enzyme. On the other hand, reference drug Celecoxib exhibited 96.9 % inhibition. Compound **76b** (Fig. 18) was more selective inhibitor towards COX-2 enzyme. The reason for this selectivity can be attributed due to the fact that the phenyl ring contains three methoxy groups [131].

Our group has synthesized a series of 2,4-bis(aryl/heteroaryl)-5-acylthiazole derivatives and determined their lipoxygenase inhibition activity. Among the tested compounds, thiazoles **77a-c** (Fig. 18) showed good lipoxygenase inhibition (1.37–3.06 μM). Further, compounds **77a** and **77b** inhibited hemolysis of erythrocytes in PLA2 inhibition studies at 3.31 μM and 2.05 μM respectively. The standard, Aristolochic acid showed inhibition at 1.56 μM. Thus, activities of **77a** and **77b** were comparable to that of Aristolochic acid. Further, these lead compounds exhibited COX-2 inhibition at 4.36 μM and 2.10 μM respectively. While, standard Indometacin showed inhibition at 1.44 μM. Thus, COX-2 inhibitory activity of thiazole **77b** is comparable to that of standard drug. We attribute the good activities of the lead compounds is due to the presence of methoxy groups [23].

Hawash and co-workers studied the anti-inflammatory potency of thiazole carboxamide derivatives. Among the synthesized compounds, *N*-(4-(*tert*-butyl)phenyl)-2-(3-methoxyphenyl)-4-methylthiazole-5-carboxamide **78** (Fig. 18) behaved as a nonselective anti-inflammatory agent, which acted on both COX-1 (0.239 ± 0.18 μM) and COX-2 (0.191 ± 0.05 μM) with selectivity index 1.251. The highest activity of this compound is due to the hydrophobic interaction of *tert*-butyl group at the active cite of COX enzyme. When this group is replaced by other hydrophilic groups like methoxy and thiomethyl, the inhibition was reduced. This inhibitory action was further substantiated by docking studies in which the lead compound showed high docking score [132].

3. Conclusion

This review focused on thiazole molecules with potent anti-inflammatory activity that were published between 1973 and 2023 were the main subject of this review. To design compounds with superior anti-inflammatory activity through hybridisation of thiazole

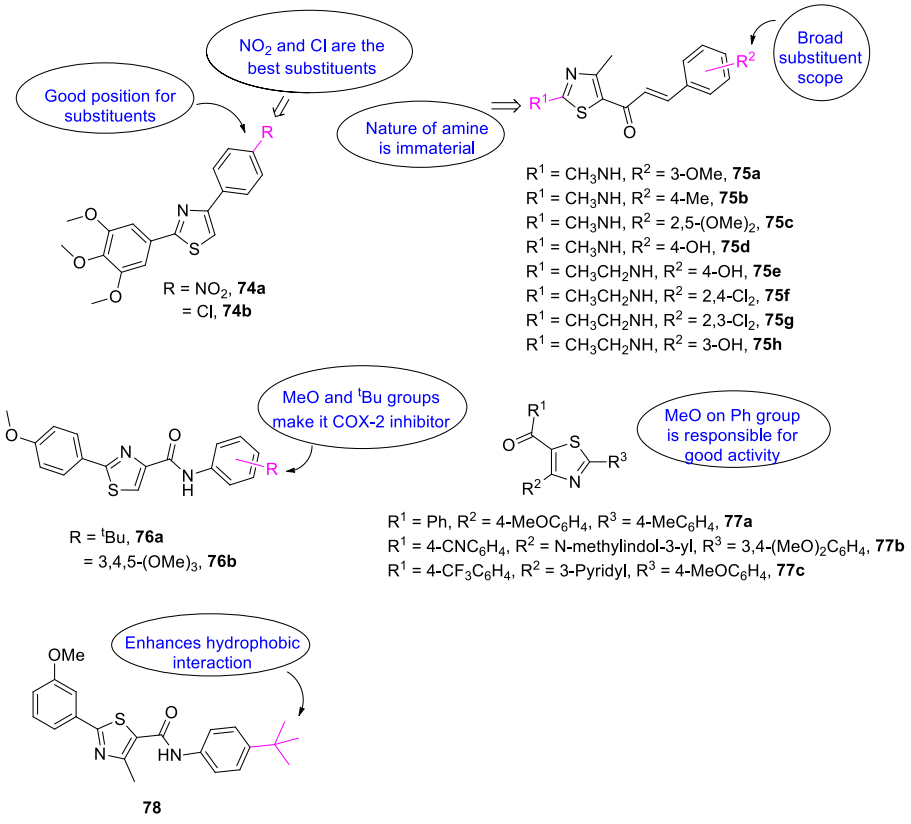

Fig. 18. Miscellaneous thiazole compounds.

heterocycles with some other basic functional groups/heterocycles, this review is required. Among thiazole derivatives, 2-aminothiazoles and their amides are very active. Furthermore, thiazoles containing sulphonamide groups have moderate activity. Further, thiazoles with an imine functional group and ether linkage are also active. Along with thiazole, other heterocyclic compounds such as thiazolidinone, pyrazole, pyrazoline, indole, and pyrrole boosted the activity. 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.

CRediT authorship contribution statement

Kereyagalahally H. Narasimhamurthy: Writing – original draft. **Toreshettahally R. Swaroop:** Writing – original draft. **Kanchugarakoppal S. Rangappa:** Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgements

KSR thank CSIR and ISCA for emeritus scientist fellowship and Asutosh Mookerjee fellowship respectively.

References

[1] N. Karajan, O. Röhrle, W. Ehlers, S. Schmitt, Linking continuous and discrete intervertebral disc models through homogenisation, Biomech. Model. Mechanobiol. 12 (2013) 453–466.
[2] J. Martel-Pelletier, J.P. Pelletier, H. Fahmi, Cyclooxygenase-2 and prostaglandins in articular tissues, Semin. Arthritis Rheum. 33 (2003) 155–167.
[3] J. Charles, L. Valenti, H. Britt, Australian family physician, Osteoarthritis 39 (2010) 621.
[4] J.C. Moore, E.A. Gross, Ann Commentary, Emerg, Méd. 55 (2010) 49–50.
[5] H. Hwang, A.T. Wecksler, K. Wagner, B.D. Hammock, Rationally designed multitarget agents against inflammation and pain, Curr. Med. Chem. 20 (2013) 1783–1799.
[6] M. Alhouayek, G.G. Muccioli, COX-2-derived endocannabinoid metabolites as novel inflammatory mediators, Trends Pharmacol. Sci. 35 (2014) 284–292.
[7] M. Bennett, D.W. Gilroy, Lipid mediators in inflammation, in: Myeloid Cells in Health and Disease, 2017, pp. 343–366.
[8] B.T. Larsen, H. Miura, O.A. Hatoum, W.B. Campbell, B.D. Hammock, D.C. Zeldin, J.R. Falck, D.D. Gutterman, Epoxyeicosatrienoic and dihydroxyeicosatrienoic acids dilate human coronary arterioles via BKCa channels: implications for soluble epoxide hydrolase inhibition, Am. J. Physiol. Heart Circ. Physiol. 290 (2006) H491–H499.
[9] N. Rajeev, T.R. Swaroop, S.M. Anil, Y.K. Bommegowda, K.S. Rangappa, M. P. Sadashiva, Base induced cyclization of active methylene isocyanides with xanthate esters: an efficient method for the synthesis of 5-alkoxy-4-(tosyl/ethoxycarbonyl)-1,3-thiazoles, Synlett 28 (2017) 2281–2284.
[10] A.C. Vinayaka, T.R. Swaroop, C. Prasanna Kumara, K.S. Rangappa, M. P. Sadashiva, Transition-metal-free solid phase synthesis of 1,2-disubstituted 4-quinolones via regiospecific synthesis of enaminones, RSC Adv. 6 (2016) 11528–11535.
[11] K.R. Kiran, T.R. Swaroop, K.P. Sukrutha, J.B. Shruthi, S.M. Anil, K.S. Rangappa, M. P Sadashiva, Acid catalyzed condensation of *o*-phenylenediammine and *o*-aminophenol with α-oxodithioesters: a divergent and regioselective synthesis of quinoxalines and benzoxazoles, Synthesis 51 (2019) 4205–4214.
[12] K.S. Vinay Kumar, T.R. Swaroop, N. Rajeev, A.C. Vinayaka, G.S. Lingaraju, K. S. Rangappa, M.P. Sadashiva, An one pot tandem approach for the synthesis of 5-(het)aryl oxazoles from substituted (het)aryl methyl alcohols and benzyl bromides, Synlett 27 (2016) 1363–1366.
[13] K.R. Kiran, T.R. Swaroop, C. Santhosh, K.S. Rangappa, M.P. Sadashiva, Cyclocondensation of *o*-phenylenediamines with 2-oxo-ethanimidothioates: a novel synthesis of 2-amino-3-(het)aryl-quinoxalines, ChemistrySelect 6 (2021) 7262–7265.
[14] N. Rajeev, T.R. Swaroop, S.M. Anil, K.R. Kiran, K.S. Rangappa, M.P. Sadashiva, A sequential one-pot tandem approach for the synthesis of 4-tosyl-5-aryloxazoles from carboxylic acids, J. Chem. Sci. 130 (150) (2018), 1-5.
[15] K. Ravi Singh, C. Santhosh, T.R. Swaroop, M.P. Sadashiva, Regioselective synthesis of 2,5- and 4,5-disubstituted thiazoles *via* cyclization of 2-oxo-2-(amino) ethanedithioates with isocyanides, Org. Biomol. Chem. 20 (2022) 5771–5778.
[16] T.R. Swaroop, K.S. Rangappa, L. Torun, Claisen type condensation of methyl ketones with carbimidothioates: a new gateway for the synthesis of β-enaminones, ChemistrySelect 6 (2021) 177–180.
[17] T.R. Swaroop, Z.-Q. Wang, Q.Y. Li, H.-S. Wang, Reductive coupling of aromatic aldehydes and ketones under electrochemical conditions, J. Electrochem. Soc. 167 (2020) 046504.
[18] N. Rajeev, T.R. Swaroop, S.M. Anil, K.R. Kiran, Chandra, P. E Georghiou, K. S. Rangappa, M.P. Sadashiva, Reaction of arylmethyl isocyanides/arylmethylamines with xanthate esters: a facile synthesis of carbamothioates, Beilstein J. Org. Chem. 16 (2020) 159–167.
[19] R.N. Suresh, T.R. Swaroop, V. Shalini, K. Mantelingu, K.S. Rangappa, Synthesis of 3,5-bis(acyl)-1,2,4-thiadiazoles *via* iodine mediated oxidative dimerization of α-oxothioamides, Tetrahedron Lett. 116 (2023) 154302.
[20] R.N. Suresh, T.R. Swaroop, Darshini Gowda, K. Mantelingu, K.S. Rangappa, A panoramic view on synthetic applications of α-oxothioamides: a highly regioselective synthesis of 2-acyl-4-(het)arylthiazoles and thioethers, RSC Adv. 13 (2023) 4910–4916.
[21] R. Roopashree, C.D. Mohan, T.R. Swaroop, S. Jagadish, K.S. Rangappa, Synthesis, characterization and in vivo biological evaluation of novel benzimidazoles as potential anticancer agents, Asian J. Pharmaceut. Clin. Res. 5 (2014) 309–313.
[22] K.S. Rakesh, S. Jagadish, A.C. Vinayaka, M. Hemshekar, M. Paul, R.M. Thushara, M. Shanmuga Sundaram, T.R. Swaroop, C.D. Mohan, S. Basappa, M.P. Sadashiva, K. Kemparaju, K.S. Girish, K.S. Rangappa, A new ibuprofen derivative inhibits platelet aggregation and ROS mediated platelet apoptosis, PLoS One 9 (2014) e107182.
[23] R.K. Sathya, S. Jagadish, T.R. Swaroop, N. Ashwini, H.K. Bhadraiah, K. S. Rangappa, Anti-oxidant and anti-inflammatory activities of synthetic 2, 4-bis (aryl/heteroaryl)-5-acylthiazole derivatives, Asian J. Biochem. Pharmaceut. Res. 4 (2014) 316–327.
[24] R. Roopashree, C.D. Mohan, T.R. Swaroop, S. Jagadish, Basappa, J. Shankar, K. S. Balaji, K.S. Rangappa, Novel synthetic bisbenzimidazole that targets angiogenesis in Ehrlich ascites carcinoma bearing mice, Bioorg. Med. Chem. Lett. 12 (2015) 2589–2593.
[25] K.S. Rakesh, S. Jagadish, T.R. Swaroop, C.D. Mohan, N. Ashwini, K.B. Harsha, Z. Farhan, K.S. Girish, K.S. Rangappa, Anticancer activity of 2,4-disubstituted thiophene derivatives: dual inhibitors of Lipoxygenase and Cyclooxygenase, Med. Chem. 11 (2015) 462–472.
[26] N. Ashwini, Manoj Garg, C.D. Mohan, J.E. Fuchs, R. Shobith, S. Anusha, T. R. Swaroop, K.S. Rakesh, K. Deepika, Vikas Madan, Andreas Bender, H. Phillip Koeffler, Basappa, K.S. Rangappa, Synthesis of 1,2-benzisoxazole tethered 1,2,3-triazoles that exhibit anticancer activity in acute myeloid leukemia cell lines by inhibiting histone deacetylases and inducing p21 and tubulin acetylation, Bioorg. Med. Chem. 18 (2015) 6157–6165.
[27] K.S. Rakesh, S. Jagadish, K.S. Balaji, F. Zameer, T.R. Swaroop, C.D. Mohan, S. Jayarama, K.S. Rangappa, 3,5-Disubstituted isoxazole derivatives: potential inhibitors of inflammation and cancer, Inflammation 39 (2016) 269–280.
[28] S.D. Preethi, K.S. Balaji, D.S. Prasanna, T.R. Swaroop, J. Shankar, K.S. Rangappa, S. Lokesh, Synthesis, characterization of 4-anilino-6,7-dimethoxyquinazoline derivatives as potential anti-angionic agents, Anti Cancer Agents Med. Chem. 17 (2017) 1931–1941.
[29] K. Hattar, R. Savai, F.S.B. Subtil, J. Wilhelm, A. Schmall, D.S. Lang, T. Goldmann, B. Eul, G. Dahlem, L. Fink, R.-T. Schermuly, G.-A. Banat, U. Sibelius, F. Grimminger, E. Vollmer, W. Seeger, U. Grandel, Endotoxin induces proliferation of NSCLC *in vitro* and *in vivo*: role of COX-2 and EGFR activation, Cancer Immunol. Immunother. 62 (2013) 309–320.
[30] R.W. Friesen, J.A. Mancini, Microsomal prostaglandin E2 synthase-1 (mPGES-1): a Novel anti-inflammatory therapeutic target, J. Med. Chem. 51 (2008) 4059–4067.
[31] E. Ricciotti, G.A. FitzGerald, Prostaglandins and inflammation, Arterioscler. Thromb. Vasc. Biol. 31 (2011) 986–1000.
[32] M. Oberg, M.S. Jaakkola, A. Woodward, A. Peruga, A. Prüss-Ustün, Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries, Lancet (London, England) 377 (2011) 139–146.
[33] C. Scarpignato, Nonsteroidal anti-Inflammatory drugs: how do they damage gastroduodenal mucosa? Dig. Dis. 13 (suppl 1) (1995) 9–39.
[34] H. Kuhn, B.J. Thiele, The diversity of the lipoxygenase family: many sequence data but little information on biological significance, FEBS Lett. 449 (1999) 7–11.
[35] I. Kologrivova, M. Shtatolkina, T. Suslova, V. Ryabov, Cells of the immune system in cardiac remodeling: main players in resolution of inflammation and repair after myocardial infarction, Front. Immunol. 12 (2021) 664457.
[36] N. Gualde, H. Harizi, Prostanoids and their receptors that modulate dendritic cell-mediated immunity, Immunol. Cell Biol. 82 (2004) 353–360.
[37] H. Osada, T. Takahashi, Genetic alterations of multiple tumor suppressors and oncogenes in the carcinogenesis and progression of lung cancer, Oncogene 21 (2002) 7421–7434.
[38] S.F. Moss, M.J. Blaser, Mechanisms of disease: inflammation and the origins of cancer, Nat. Clin. Pract. Oncol. 2 (2005) 90–97.

[39] Y. Zavros, Initiation and maintenance of gastric cancer: a focus on CD44 variant isoforms and cancer stem cells, Cell. Mol. Gastroenterol. Hepatol. 4 (2017) 55–63.
[40] J.L. Masferrer, P.C. Isakson, K. Seibert, Cyclooxygenase-2 inhibitors: a new class of anti-inflammatory agents that spare the gastrointestinal tract, Gastroenterol. Clin. N. Am. 25 (1996) 363–372.
[41] H.R. Herschman, Prostaglandin synthase 2, Biochim. Biophys. Acta Lipids Lipid. Metabol. 1299 (1996) 125–140.
[42] D.M. Form, R. Auerbach, PGE2 and angiogenesis, Proc. Soc. Exp. Biol. Med. 172 (1983) 214–218.
[43] D. Hanahan, J. Folkman, Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis, Cell 86 (1996) 353–364.
[44] S. Gately, The contributions of cyclooxygenase-2 to tumor angiogenesis, Cancer Metastasis Rev. 19 (2000) 19–27.
[45] K. Sumitani, R. Kamijo, T. Toyoshima, Y. Nakanishi, K. Takizawa, M. Hatori, M. Nagumo, Specific inhibition of cyclooxygenase-2 results in inhibition of proliferation of oral cancer cell lines via suppression of prostaglandin E2 production, J. Oral Pathol. Med. 30 (2001) 41–47.
[46] N.B. Janakiram, A. Mohammed, C.V. Rao, Role of lipoxins, resolvins, and other bioactive lipids in colon and pancreatic cancer, Cancer Metastasis Rev. 30 (2011) 507–523.
[47] M.K. Narasimhan, S.K. Pavithra, V. Krishnan, M. Chandrasekaran, *In vitro* Analysis of antioxidant, antimicrobial and antiproliferative activity of Enteromorpha antenna, Enteromorpha linza and Gracilaria corticata extracts, Jundishapur J. Nat. Pharm. Prod. 8 (2013) 151–159.
[48] G. Vilkickyte, L. Raudone, V. Petrikaite, Phenolic fractions from Vaccinium vitis-idaea L. and their antioxidant and anticancer activities Aassessment, Antioxidants 9 (2020) 1261.
[49] B. Salehi, C. Quispe, I. Chamkhi, N. El Omari, A. Balahbib, J. Sharifi-Rad, A. Bouyahya, M. Akram, M. Iqbal, A.O. Docea, C. Caruntu, G. Leyva-Gómez, A. Dey, M. Martorell, D. Calina, V. López, F. Les, Pharmacological properties of chalcones: a review of preclinical including molecular mechanisms and clinical evidence, Front. Pharmacol. 11 (2021) 592654, 592654.
[50] J. Jacob P, S.L. Manju, K.R. Ethiraj, G. Elias, Safer anti-inflammatory therapy through dual COX-2/5-LOX inhibitors: a structure-based approach, Eur. J. Pharmaceut. Sci. 121 (2018) 356–381.
[51] S.-I. Naito, S. Shimizu, 2-(Aminoethanesulfonylamino) thiazole and related compounds I: stability, absorption, excretion, and some pharmacological activities, J. Pharmaceut. Sci. 62 (1973) 82–87.
[52] S.M. Sondhi, R. Rani, P.P. Gupta, S.K. Agrawal, A.K. Saxena, Synthesis, anticancer, and anti-inflammatory activity evaluation of methanesulfonamide and amidine derivatives of 3,4-diaryl-2-imino-4-thiazolines, Mol. Divers. 13 (2009) 357–366.
[53] H. Nagatomi, K. Ando, Studies on the anti-inflammatory activity and ulcerogenic adverse effect of thiazole derivatives, especially 2-amino-thiazoleacetic acid derivatives, Arzneimittelforschung 34 (1984) 599–603.
[54] M. Ghate, D. Manohar, V. Kulkarni, R. Shobha, S.Y. Kattimani, Synthesis of vanillin ethers from 4-(bromomethyl) coumarins as anti-inflammatory agents, Eur. J. Med. Chem. 38 (2003) 297–302.
[55] R.G. Kalkhambkar, G.M. Kulkarni, H. Shivkumar, R.N. Rao, Synthesis of novel triheterocyclic thiazoles as anti-inflammatory and analgesic agents, Eur. J. Med. Chem. 42 (2007) 1272–1276.
[56] R.S. Giri, H.M. Thaker, T. Giordano, J. Williams, D. Rogers, V. Sudersanam, K. K. Vasu, Design, synthesis and characterization of novel 2-(2,4-disubstituted-thiazole-5-yl)-3-aryl-3H-quinazoline-4-one derivatives as inhibitors of NF-κB and AP-1 mediated transcription activation and as potential anti-inflammatory agents, Eur. J. Med. Chem. 44 (2009) 2184–2189.
[57] A.A. Geronikaki, A.A. Lagunin, D.I. Hadjipavlou-Litina, P.T. Eleftheriou, D. A. Filimonov, V.V. Poroikov, I. Alam, A.K. Saxena, Computer-aided discovery of anti-inflammatory thiazolidinones with dual cyclooxygenase/lipoxygenase inhibition, J. Med. Chem. 51 (2008) 1601–1609.
[58] R.N. Sharma, F.P. Xavier, K.K. Vasu, S.C. Chaturvedi, S.S. Pancholi, Synthesis of 4-benzyl-1,3-thiazole derivatives as potential anti-inflammatory agents: an analogue-based drug design approach, J. Enzym. Inhib. Med. Chem. 24 (2009) 890–897.
[59] A. D Patel, C.N. Patel, Synthesis and biological evaluation of substituted 4-phenyl-1,3-thiazole derivatives as potential anti-inflammatory agents, Int. J. Drug Dev. Res. 4 (2012) 106–111.
[60] J. Suh, E.K. Yum, H.G. Cheon, Y.S. Cho, Synthesis and biological evaluation of *N*-aryl-4-aryl-1,3-thiazole-2-amine derivatives as direct 5-lipoxygenase inhibitors, Chem. Biol. Drug Des. 80 (2012) 89–98.
[61] M. Mansuri, A. Ahmed, A. Shaikh, N. Haque, A. K Sheth, K.I. Molvi, Synthesis, antibacterial, anti-Inflammatory and antiplatelet activities of some trisubstituted thiazoles, Inventi Rapid, Med. Chem. 2012 (2012) 1–6.
[62] G.A. El-Achkar, M. Jouni, M.F. Mrad, T. Hirz, N. El Hachem, A. Khalaf, S. Hammoud, H. Fayyad-Kazan, A.A. Eid, B. Badran, R.A. Merhi, A. Hachem, E. Hamade, A. Habib, Thiazole derivatives as inhibitors of cyclooxygenases *in vitro* and *in vivo*, Eur. J. Pharmacol. 750 (2015) 66–73.
[63] Isha Priyanka, K.K. Jha, M. Vijayakumar, Synthesis, characterization and pharmacological evaluation of substituted 4-aryl thiazole-2-amino acetanilides, Indian J. Pharmaceut. Biol. Res. 4 (2016) 74–79.
[64] E.G. Said, M.T. El-Saadi, A.H. Abdelazeem, S.M. El-Moghazy, Exploring the anticancer and anti-inflammatory activities of novel diphenylthiazole-amino acid conjugates, J. Appl. Pharmaceut. Sci. 7 (2017) 212–217.
[65] A.H. Abdelazeem, M.T. El-Saadi, A.G. Safi El-Din, H.A. Omar, S.M. El-Moghazy, Design, synthesis and analgesic/anti-inflammatory evaluation of novel diarylthiazole and diarylimidazole derivatives towards selective COX-1 inhibitors with better gastric profile, Bioorg. Med. Chem. 25 (2017) 665–676.
[66] S.R. Sagar, D.P. Singh, N.B. Panchal, R.D. Das, D.H. Pandya, V. Sudarsanam, M. Nivsarkar, K.K. Vasu, Thiazolyl-thiadiazines as beta site amyloid precursor protein cleaving enzyme-1 (BACE-1) inhibitors and anti-inflammatory agents: multitarget-directed ligands for the efficient management of Alzheimer's disease, ACS Chem. Neurosci. 9 (2018) 1663–1679.
[67] A.D. Pillai, P.D. Rathod, P.X. Franklin, M. Patel, M. Nivsarkar, K.K. Vasu, H. Padh, V. Sudarsanam, Novel drug designing approach for dual inhibitors as anti-inflammatory agents: implication of pyridine template, Biochem. Biophys. Res. Commun. 301 (2003) 183–186.
[68] S. Sinha, M. Doble, S.L. Manju, Design, synthesis and identification of novel substituted 2-amino thiazole analogues as potential anti-inflammatory agents targeting 5-lipoxygenase, Eur. J. Med. Chem. 158 (2018) 34–50.
[69] J. Jacob P, S.L. Manju, Identification and development of thiazole leads as COX-2/5-LOX inhibitors through *in-vitro* and *in-vivo* biological evaluation for anti-inflammatory activity, Bioorg. Chem. 100 (2020) 103882.
[70] A. Ahmed, K.I. Molvi, H.M. Patel, R. Ullah, A. Bari, Synthesis of novel 2,3,5-tri-substituted thiazoles with anti-inflammatory and antibacterial effect causing clinical pathogens, J. Infect. Public Health 13 (2020) 472–479.
[71] M.T.E. Maghraby, O.M.F. Abou-Ghadir, S.G. Abdel-Moty, A.Y. Ali, O.I.A. Salem, Novel class of benzimidazole-thiazole hybrids: the privileged scaffolds of potent anti-inflammatory activity with dual inhibition of cyclooxygenase and 15-lipoxygenase enzymes, Bioorg. Med. Chem. 28 (2020) 115403.
[72] K.N. Ankali, J. Rangaswamy, M. Shalavadi, N. Naik, G.N. Krishnamurthy, Synthesis and molecular docking of novel 1,3-thiazole derived 1,2,3-triazoles and *in vivo* biological evaluation for their anti anxiety and anti inflammatory activity, J. Mol. Struct. 1236 (2021) 130357.
[73] D. Hadjipavlou-Litina, A. Geronikaki, R. Mgonzo, I. Doytchinova, Thiazolyl-*N*-substituted amides: a group of effective anti-inflammatory agents with potential for local anesthetic properties. Synthesis, biological evaluation, and a QSAR approach, Drug Dev. Res. 48 (1999) 53–60.
[74] A. Geronikaki, D. Hadjipavlou-Litina, A. Zablotskaya, I. Segal, Organosilicon-containing thiazole derivatives as potential lipoxygenase inhibitors and anti-inflammatory agents, Bioinorgan. Chem. Appl. 2007 (2007) 1–7.
[75] T. Kuroda, F. Suzuki, T. Tamura, K. Ohmori, H. Hosoe, A novel synthesis and potent antiinflammatory activity of 4-hydroxy-2(1H)-oxo-1-phenyl-1,8-naphthyridine-3-carboxamides, J. Med. Chem. 35 (1992) 1130–1136.
[76] P.X. Franklin, A.D. Pillai, P.D. Rathod, S. Yerande, M. Nivsarkar, H. Padh, K. K. Vasu, V. Sudarsanam, 2-Amino-5-thiazolyl motif: a novel scaffold for designing anti-inflammatory agents of diverse structures, Eur. J. Med. Chem. 43 (2008) 129–134.
[77] S.R. Pattan, R.L. Hullolikar, N.S. Dighe, B.N. Ingalagi, M.B. Hole, V.M. Gaware, P. A. Chavan, Synthesis and evaluation of some new phenyl thiazole derivatives for their inti-inflammatory activities, J. Pharmaceut. Sci. Res. 1 (2009) 96–102.
[78] P. Porwal, L. Tiwari, S. Paliwal, H. Sharma, H. Kushwah, K. Pal, Synthesis and anti-inflammatory activity of substituted phenylthiazole derivatives, World J. Pharm. Med. Res. 7 (2021) 152–155.
[79] O. Kouatly, A. Geronikaki, C. Kamoutsis, D. Hadjipavlou-Litina, P. Eleftheriou, Adamantane derivatives of thiazolyl-N-substituted amide, as possible non-steroidal anti-inflammatory agents, Eur. J. Med. Chem. 44 (2009) 1198–1204.
[80] S. Oniga, A.E. Parvu, B. Tiperciuc, M. Palage, O. Oniga, FARMACIA 59 (2011) 44–50.
[81] A. Zablotskaya, I. Segal, A. Geronikaki, T. Eremkina, S. Belyakov, M. Petrova, I. Shestakova, L. Zvejniece, V. Nikolajeva, Synthesis, physicochemical characterization, cytotoxicity, antimicrobial, anti-inflammatory and psychotropic activity of new *N*-[1,3-(benzo)thiazol-2-yl]-ω-[3,4-dihydroisoquinolin-2(1*H*)-yl] alkanamides, Eur. J. Med. Chem. 70 (2013) 846–856.
[82] V.C. Patil, K.P. Bhusari, P.B. Khedekar, Synthesis and anti-inflammatory activity of some 3-substituted thiazolyl and oxazolyl indole derivatives, World J. Pharm. Pharmaceut. Sci. 3 (2014) 1292–1306.
[83] A. Fatima, R. Kulkarni, B. Mantipragada, Design and synthesis of *N*-substituted aminothiazole compounds as antiinflammatory agents, Der Pharma Chem. 7 (2015) 212–220.
[84] A.H. Abdelazeem, M. Habash, I.A. Maghrabi, M.O. Taha, Synthesis and evaluation of novel diphenylthiazole derivatives as potential anti-inflammatory agents, Med. Chem. Res. 24 (2015) 3681–3695.
[85] P.G. Krishnan, K.G. Prakash, K.B. Chandra Sekhar, Synthesis, characterization and anti-inflammatory activity of certain novel 2, 4-disubstituted 1,3-thiazole derivatives, Rasayan J. Chem. 12 (2019) 366–371.
[86] N.I. Osman, N.J. Sidik, A. Awal, N.A.M. Adam, N.I. Rezali, *In vitro* xanthine oxidase and albumin denaturation inhibition assay of Barringtonia racemosa L. and total phenolic content analysis for potential anti-inflammatory use in gouty arthritis, J. Intercult. Ethnopharmacol 5 (2016) 343–349.
[87] S.A. Abdel-Aziz, E.S. Taher, P. Lan, G.F. Asaad, H.A.M. Gomaa, N.A. El-Koussi, B. G.M. Youssif, Design, synthesis, and biological evaluation of new pyrimidine-5-carbonitrile derivatives bearing 1,3-thiazole moiety as novel anti-inflammatory EGFR inhibitors with cardiac safety profile, Bioorg. Chem. 111 (2021) 104890.
[88] S.A. Abdel-Aziz, E.S. Taher, P. Lan, N.A. El-Koussi, O.I.A. Salem, H.A.M. Gomaa, B.G.M. Youssif, New pyrimidine/thiazole hybrids endowed with analgesic, anti-inflammatory, and lower cardiotoxic activities: design, synthesis, and COX-2/sEH dual inhibition, Arch. Pharm. 355 (2022) e2200024.
[89] B.S. Holla, K.V. Malini, B.S. Rao, B.K. Sarojini, N.S. Kumari, Synthesis of some new 2,4-disubstituted thiazoles as possible antibacterial and anti-inflammatory agents, Eur. J. Med. Chem. 38 (2003) 313–318.

[90] B.S. Jayashree, D. Anuradha, K.N. Venugopala, Synthesis and characterization of schiff bases of 2'-amino-4-(6-chloro-3-coumarinyl)thiazole as potential NSAIDs, Asian J. Chem. 17 (2005) 2093–2097.
[91] N. Singh, S.K. Bhati, A. Kumar, Thiazolyl/oxazolyl formazanyl indoles as potent anti-inflammatory agents, Eur. J. Med. Chem. 43 (2008) 2597–2609.
[92] S. Ampati, R. Jukanti, V. Sagar, R. Ganta, S. Manda, Synthesis and *in vivo* anti-inflammatory activity of a novel series of benzoxazole derivatives, Chem. Sin. 1 (2010) 157–168.
[93] F.A. Hassan, Synthesis, characterization, anti-inflammatory, and antioxidant activities of some new thiazole derivatives, Int. J. Appl. Sci. Technol. 2 (2012) 180–187.
[94] C.R. Prakasha, S. Raja, G. Saravanan, Synthesis, analgesic, anti-inflammatory and *in vitro* antimicrobial studies of some novel schiff and mannich base of 5-substituted isatin derivatives, Int. J. Pharm. Pharmaceut. Sci. 6 (2014) 160–166.
[95] M.E. Haiba, S.S. Abd El-Karim, R.S. Gouhar, M.I. El-Zahar, S.A. El-Awdan, Synthesis and evaluation of anti-inflammatory and analgesic activity of some substituted thiazolyl and thaizolidinonyl tetrahydronapthalene derivatives, Med. Chem. Res. 23 (2014) 3418–3435.
[96] N. Chandak, P. Kumar, P. Kaushik, P. Varshney, C. Sharma, D. Kaushik, S. Jain, K. R. Aneja, P.K. Sharma, Dual evaluation of some novel 2-amino-substituted coumarinylthiazoles as anti-inflammatory–antimicrobial agents and their docking studies with COX-1/COX-2 active sites, J. Enzym. Inhib. Med. Chem. 29 (2014) 476–484.
[97] Y.-S. Rhee, J.-G. Choi, E.-S. Park, S.-C. Chi, Transdermal delivery of ketoprofen using microemulsions, Int. J. Pharm. 228 (2001) 161–170.
[98] J.P. Januario, T.B. De Souza, S.N. Lavorato, T.C.S. Maiolini, O.S. Domingos, J. L. Baldim, L.R.S. Folquitto, M.G. Soares, D.A. Chagas-Paula, D.F. Dias, M.H. Dos Santos, Design and synthesis of new benzophenone derivatives with *in vivo* anti-inflammatory activity through dual inhibition of edema and neutrophil recruitment, Molecules 23 (2018) 1859.
[99] A. Tubaro, P. Dri, G. Delbello, C. Zilli, R. Della Loggia, The croton oil ear test revisited, Agents Actions 17 (1986) 347–349.
[100] V. Kamat, R. Santosh, B. Poojary, S.P. Nayak, B.K. Kumar, M. Sankaranarayanan, Faheem, S. Khanapure, D.A. Barretto, S.K. Vootla, Pyridine- and thiazole-based hydrazides with promising anti-inflammatory and antimicrobial activities along with their in silico studies, ACS Omega 5 (2020) 25228–25239.
[101] G. Kumar, N.P. Singh, Synthesis, anti-inflammatory and analgesic evaluation of thiazole/oxazole substituted benzothiazole derivatives, Bioorg. Chem. 107 (2021) 104608.
[102] P. Bruneau Bird, G.C. Crawley, M.P. Edwards, S.J. Foster, J.M. Girodeau, J. F. Kingston, R.M. McMillan, (Methoxyalkyl)thiazoles: a new series of potent, selective, and orally active 5-lipoxygenase inhibitors displaying high enantioselectivity, J. Med. Chem. 34 (1991) 2176–2186.
[103] D. Aharony, R.L. Stein, Kinetic mechanism of Guinea pig neutrophil 5-lipoxygenase, J. Biol. Chem. 261 (1986) 11512–11519.
[104] S.J. Foster, P. Bruneau, E.R.H. Walker, R.M. McMillan, 2-Substituted indazolinones: orally active and selective 5-lipoxygenase inhibitors with anti-inflammatory activity, Br. J. Pharmacol. 99 (1990) 113–118.
[105] T. Karabasanagouda, A.V. Adhikari, R. Dhanwad, G. Parameshwarappa, Synthesis of some new 2-(4-alkylthiophenoxy)-4-substituted-1,3-thiazoles as possible anti-inflammatory and antimicrobial agents, Indian J. Chem. 47B (2008) 144–152.
[106] N.P. Rai, T.D. Venu, B.K. Manuprasad, S. Shashikanth, P.N. Arunachalam, A. Firdouse, Synthesis of some novel 2-[2-(aroyl-aroxy)-methyl]-4-phenyl-1,3-thiazoles as potent anti-inflammatory agents, Chem. Biol. Drug Des. 75 (2010) 400–406.
[107] G. Kokotos, A.J. Feuerherm, E. Barbayianni, I. Shah, M. Sæther, V. Magrioti, T. Nguyen, V. Constantinou-Kokotou, E.A. Dennis, B. Johansen, Inhibition of group IVA cytosolic phospholipase A2 by thiazolyl ketones *in vitro, ex vivo*, and *in vivo*, J. Med. Chem. 57 (2014) 7523–7535.
[108] A. Kumar, C.S. Rajput, S.K. Bhati, Synthesis of 3-[4′-(p-chlorophenyl)-thiazol-2′-yl]-2-[(substituted azetidinone/thiazolidinone)-aminomethyl]-6-bromoquinazolin-4-ones as anti-inflammatory agent, Bioorg. Med. Chem. 15 (2007) 3089–3096.
[109] S.H. Shelke, P.C. Mhaske, M. Nandave, S. Narkhade, N.M. Walhekar, V.D. Bobade, Synthesis and pharmacological evaluation of a novel series of 3-aryl-2-(2-substituted-4-methylthiazole-5-yl)thiazolidin-4-one as possible anti-inflammatory and antimicrobial agents, Bioorg. Med. Chem. Lett. 22 (2012) 6373–6376.
[110] P. Gangwar, P. Sharma, B. Shrivastava, J. Sharma, S. Sharma, Synthesis and characterization of new thiazolidinone derivatives and screening for their anti-inflamatory activity, IJCTPR 1 (2013) 181–184.
[111] I. Apostolidis, K. Liaras, A. Geronikaki, D. Hadjipavlou-Litina, A. Gavalas, M. Soković, J. Glamočlija, A. Ćirić, Synthesis and biological evaluation of some 5-arylidene-2-(1,3-thiazol-2-ylimino)-1,3-thiazolidin-4-ones as dual anti-inflammatory/antimicrobial agents, Bioorg. Med. Chem. 21 (2013) 532–539.
[112] C. Nastasa, B. Tiperciuc, A. Parvu, M. Duma, I. Ionut, O. Oniga, Arch. Pharm. Chem. Life Sci. 346 (2013) 481–490.
[113] A.H. Abdelazeem, M.T. El-Saadi, A.G. Safi El-Din, S.M. El-Moghazy, Design, synthesis and biological evaluation of novel diphenylthiazole-thiazolidin-4-one-based derivatives as anti-inflammatory/analgesic agents, J. Chem. Pharmaceut. Res. 7 (2015) 1073–1079.
[114] L.D. Khillare, M.R. Bhosle, A.R. Deshmukh, R.A. Mane, Synthesis and anti-inflammatory evaluation of new pyrazoles bearing biodynamic thiazole and thiazolidinone scaffolds, Med. Chem. Res. 24 (2015) 1380–1386.
[115] E.N. Abdel-Sattar, S.H. Elgazwy, M.Y. Zaki, Synthesis, biological evaluation of some 2,3-dihydropyrazoles and thiazoles as anti-inflammatory and antibacterial agents, Organic Chem, Curr. Res. 1 (2012) 1–112.
[116] R. Aggarwal, S. Kumar, P. Kaushik, D. Kaushik, G.K. Gupta, Synthesis and pharmacological evaluation of some novel 2-(5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazol-1-yl)-4-(coumarin-3-yl)thiazoles, Eur. J. Med. Chem. 62 (2013) 508–514.
[117] S.N. Thore, S.V. Gupta, K.G. Baheti, Docking, synthesis, and pharmacological investigation of novel substituted thiazole derivatives as non-carboxylic, anti-inflammatory, and analgesic agents, Med. Chem. Res. 22 (2013) 3802–3811.
[118] P. Khloya, S. Kumar, P. Kaushik, P. Surain, D. Kaushik, P.K. Sharma, Synthesis and biological evaluation of pyrazolylthiazole carboxylic acids as potent anti-inflammatory–antimicrobial agents, Bioorg. Med. Chem. Lett. 25 (2015) 1177–1181.
[119] R.D. Kamble, R.J. Meshram, S.V. Hese, R.A. More, S.S. Kamble, R.N. Gacche, B. S. Dawane, Synthesis and in silico investigation of thiazoles bearing pyrazoles derivatives as anti-inflammatory agents, Comput. Biol. Chem. 61 (2016) 86–96.
[120] S.N. Thore, S.V. Gupta, K.G. Baheti, Synthesis and pharmacological evaluation of 5-methyl-2-phenylthiazole-4-substituted heteroazoles as a potential anti-inflammatory and analgesic agents, J. Saudi Chem. Soc. 20 (2016) S46–S52.
[121] A.A. Marzouk, E.S. Taher, M.S.A. Shaykoon, P. Lan, W.H. Abd-Allah, A. M. Aboregela, M.F. El-Behairy, Design, synthesis, biological evaluation, and computational studies of novel thiazolo-pyrazole hybrids as promising selective COX-2 inhibitors: implementation of apoptotic genes expression for ulcerogenic liability assessment, Bioorg. Chem. 111 (2021) 104883.
[122] N. Yamsani, R. Sundararajan, Analgesic and anti-inflammatory activities of novel heterocyclic substituted thiazole derivatives, Rasayan J. Chem. 15 (2022) 461–474.
[123] S.M. Sondhi, N. Singh, A.M. Lahoti, K. Bajaj, A. Kumar, O. Lozach, L. Meijer, Synthesis of acridinyl-thiazolino derivatives and their evaluation for anti-inflammatory, analgesic and kinase inhibition activities, Bioorg. Med. Chem. 13 (2005) 4291–4299.
[124] S. Kumar, R. Aggarwal, V. Kumar, R. Sadana, B. Patel, P. Kaushik, D. Kaushik, Solvent-free synthesis of bacillamide analogues as novel cytotoxic and anti-inflammatory agents, Eur. J. Med. Chem. 123 (2016) 718–726.
[125] R.F. Barghash, A. Geronikaki, W.M. Abdou, Synthesis of a series of substituted thiazole derivatives: new COX-2 enzyme inhibitors for colon cancer and inflammation treatment, ChemistrySelect 3 (2018) 13329–13337.
[126] R.M. Mohareb, M.Y. Zaki, N.S. Abbas, Synthesis, anti-inflammatory and anti-ulcer evaluations of thiazole, thiophene, pyridine and pyran derivatives derived from androstenedione, Steroids 98 (2015) 80–91.
[127] K. Gullapelli, R. Maroju, R. Merugu, Synthesis, in-vitro and in-silico anti-inflammatory activity of new thiazole derivatives, Res. J. Pharm. Technol. 14 (2021) 4253–4260.
[128] E. Pontiki, D. Hadjipavlou-Litina, A.T. Chaviara, Evaluation of anti-inflammatory and antioxidant activities of Copper (II) Schiff mono-base and Copper(II) Schiff base coordination compounds of dien with heterocyclic aldehydes and 2-amino-5-methyl-thiazole, J. Enzym. Inhib. Med. Chem. 23 (2008) 1011–1017.
[129] C. Araniciu, A.E. Pârvu, B. Tiperciuc, M. Palage, S. Oniga, P. Verité, O. Oniga, Synthesis and evaluation of the anti-inflammatory activity of some 2-(trimethoxyphenyl)-4-r1-5-r2-thiazoles, Dig, J. Nanomater. Biostructures 8 (2013) 699–709.
[130] C. Tratrat, M. Haroun, E. Tsolaki, A. Petrou, A. Gavalas, A. Geronikaki, Thiazole-based chalcone derivatives as potential anti-inflammatory agents: biological evaluation and molecular modelling, Curr. Top. Med. Chem. 21 (2021) 257–268.
[131] M. Hawash, N. Jaradat, M. Abualhasan, M.K. Şüküroğlu, M.T. Qaoud, D. C. Kahraman, H. Daraghmeh, L. Maslamani, M. Sawafta, A. Ratrout, L. Issa, Design, synthesis, molecular docking studies and biological evaluation of thiazole carboxamide derivatives as COX inhibitors, BMC Chemistry 17 (2023) 11.
[132] M. Hawash, N. Jaradat, R. Sabobeh, M. Abualhasan, M.T. Qaoud, New thiazole carboxamide derivatives as COX inhibitors: design, synthesis, anticancer screening, in silico molecular docking, and ADME profile studies, ACS Omega 8 (2023) 29512–29526.