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REVIEW

Structural and Functional Insights of Thiazole Derivatives as Potential Anti-inflammatory Candidate: A New Contender on Chronic and Acute SARS-CoV-2 Inflammation and Inhibition of SARS-CoV-2 Proteins

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Thiazoles are notable five-membered heterocyclic rings and their moieties can be found in several biologically active compounds of natural origin, as well as synthetic molecules that possess a wide range of pharmacological activities. Inflammation is the common cause that is associated with different disorders and diseases such as psoriasis, arthritis, infections, asthma, cancer, *etc*. In this article, the synthesis pattern of these novel molecules are discussed and their anti-inflammatory activities against cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) were reviewed and documented. The potent 26 thiazole analogs were validated with molecular docking against main protease (6LU7) and spike binding domain ACE2 receptor (6M0J) to defeat from the COVID-19 infections. Among this, THI-9a showed excellent binding energy and affinity against deadly SAR CoV-2. The reviewed and theoretical study information strongly suggested that thiazole derivatives can be used for the development of futuristic target drugs against death-causing diseases like SAR-CoV-2.

Keywords: Anti-inflammatory, COX-1, COX-2, PLA2, Thiazole, SARS-CoV-2.

INTRODUCTION

Novel coronavirus-19 (SARS-CoV-2), epidemic responsible COVID-19 disease was first reported in Wuhan city, Hubei province, China in December-2019. Then onwards, many countries all over the world have been affected by this and making it pandemic disease across various continents. Based on the etiological data, human coronavirus epidemics severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), predominantly disturbs the respiratory system and causes acute inflammation [1,2].

Inflammation is the prominent responses of the body to tissue damage or microbial attack [3]. Inflammation is the sudden reaction of the tissues and cells against detrimental effects carried by pathogens or provocative effects of toxic chemical substances or physical injuries. The treatment of inflammation is overcome by the class of medicines named non-steroidal anti-inflammatory drugs [4]. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most often used anti-inflammatory drug and they show anti-inflammatory action by preventing the production of prostaglandin which is a powerful mediator of inflammation [5]. These inflammatory reactions are directly or indirectly related to the changes in the production of leukotrienes and prostaglandins in the arachidonic acid pathway [6]. At present NSAIDS are essential in the treatment of various inflammations and have serious side effects causing gastrointestinal destruction, hemorrhage, ulceration and their related sequelae [7]. The key cyclooxygenase enzyme exists in two isoforms, in particular, the constitutive structure COX-1 and the inducible form COX-2. The COX-1 is available in most tissues and COX-2 is expressed during inflammation. Traditionally, NSAIDs that hinder both cyclo-

oxygenase enzymes may cause gastrointestinal side effects and selective COX-2 inhibitors, for example, coxibs have been accounted to cause significant cardiovascular side effects. To overcome the above said problems, it is necessary to develop a novel compound with improved drug profiles [5].

There is significant progress in the research on heterocyclic ring systems and efforts are continuously done to identify their potential bioactivities. The five-membered heterocycles, for example, imidazole, oxazole, thiazole and thiadiazole possess biological activities and the thiazole containing compounds offers a wide scope of applications as pharmaceutical agents [8,9]. Thiazole and its related nucleus are the most significant potential entities in the chemical world of heterocyclic compounds and exhibit remarkable pharmacological activities and is essential structural motif present in a wide range of natural products like vitamin B_1 [10,11]. Thiazole ring also occurs in microbial and marine sources *viz*. alkaloids, epothilone, peptides and chlorophyll. According to the literature, the thiazoles have moderately low toxicity to vertebrates and are easily metabolized in our digestive system and are non-cancerous in nature [12]. In addition to this, the thiazole-containing compounds have shown various biological activities like antioxidant [13], analgesic [14], antibacterial [15], anticancer [16], antiallergic [17], anti-hypertensive [18], anti-inflammatory [19], antimalarial [20], antifungal [21] and anti-psychotic [22]. Thiazole subordinates also show a wide range of possible pharmacological activities and have wide clinical applications [23]. The advancements in the research pertaining to medical sciences over the past years has enabled rapid improvement in the detection, analysis and treatment of infectious diseases. This has resulted in the better health status of human beings with fewer side effects [24].

Antiviral drug research in the past primarily focused on the development of nucleoside analogues and in recent year's the nonnucleoside analogues have created interest as antiviral drugs. Among the nonnucleoside analogues, some novel thiazole compounds have been reported to have high antiviral activity [25]. The thiazole platform is present in more than 18 FDA-approved drugs like sulfathiazole, ritonavir, dasatinib, tiazofurin, cinalukast and others (Fig. 1) [9]. Viral diseases causes self-limiting to the more serious complications and the chances of life threatening complications are more in case of SARS, MERS-CoV, hepatitis infections (HAB and HAC) and AIDS [26-29]. Developing novel selective antiviral agents is a difficult and intransigent aspect for many researchers as the replicative cycle of viruses is in interwined with normal cell metabolism [30]. Antiviral drug medication has significantly reduced the spread of epidemics, but their continuous usage has led in the emergence of drug resistant mutants over a period of time [31-33]. Several antiviral drugs have low oral bioavailability, show adverse side effects and are too expensive [34-36]. Hence, there is important necessity to develop safe and effective nonnucleoside antiviral agents.

SARS CoV-2 acute pulmonary inflammation pathway: The SARS-CoV-2 invades through a key entry point *via* the respiratory tract epithelium into the human host (Fig. 2) [37,38]. The mucosal secretions of the epithelium act as first line barrier by producing mucosal secretions, which prevents the tissue damage by nasal mucociliary clearance (NMC). After the inhalation, SARS-CoV-2 particles infect various epithelial cell types on airway passage of distal lungs by attaching to the nasal mucosal line and binding the viral S (spike) protein to the ACE2 (angiotensin-converting enzyme-2) receptor. In the next step, the S protein is cleaved by TMPRSS2 (transmembrane serine protease 2). The type I trans membrane ACE2 protein consisting of metallocarboxypeptidase the angiotensin 2 to metabolites, most of these metabolites vasodilatory properties or restrict the renin-angiotensin-aldosterone arrangement.

After entering the host cell, the virus releases the pieces of nucleocapsid and the viral genome. Then the host ribosome translate the open reading frame (ORF) of the viral genome la/b into two subunits of polyproteins *viz.* ppla and pplab encoded

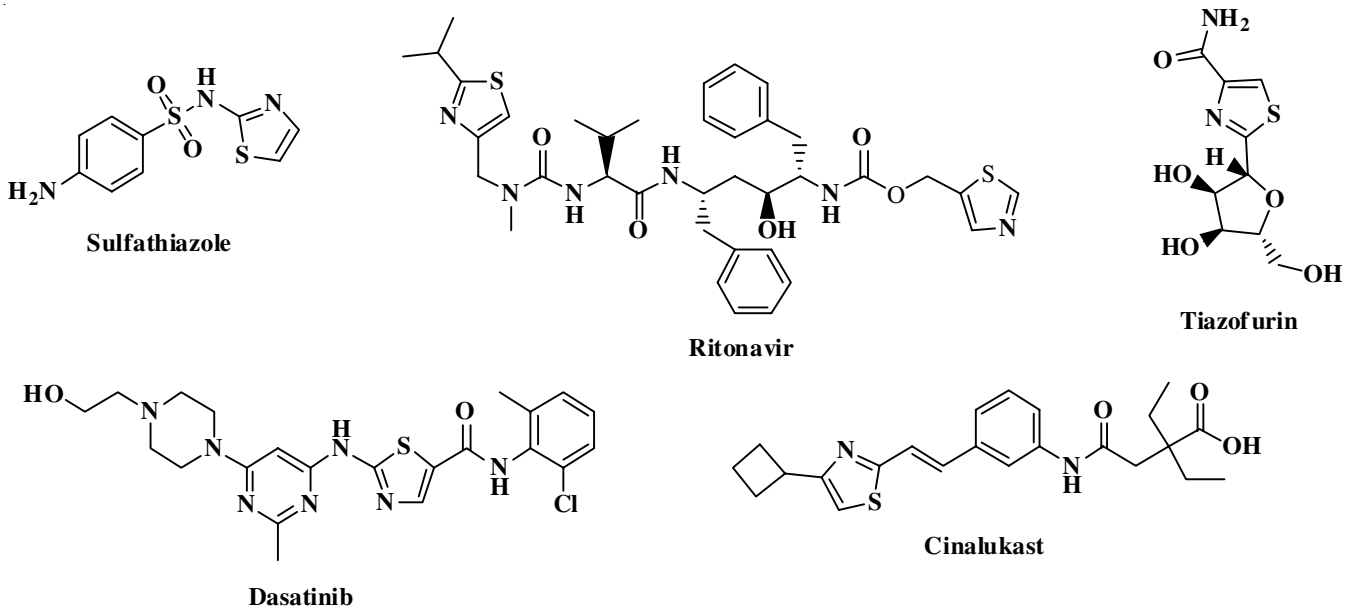


Fig. 1. Thiazole skeleton containing FDA-approved drugs

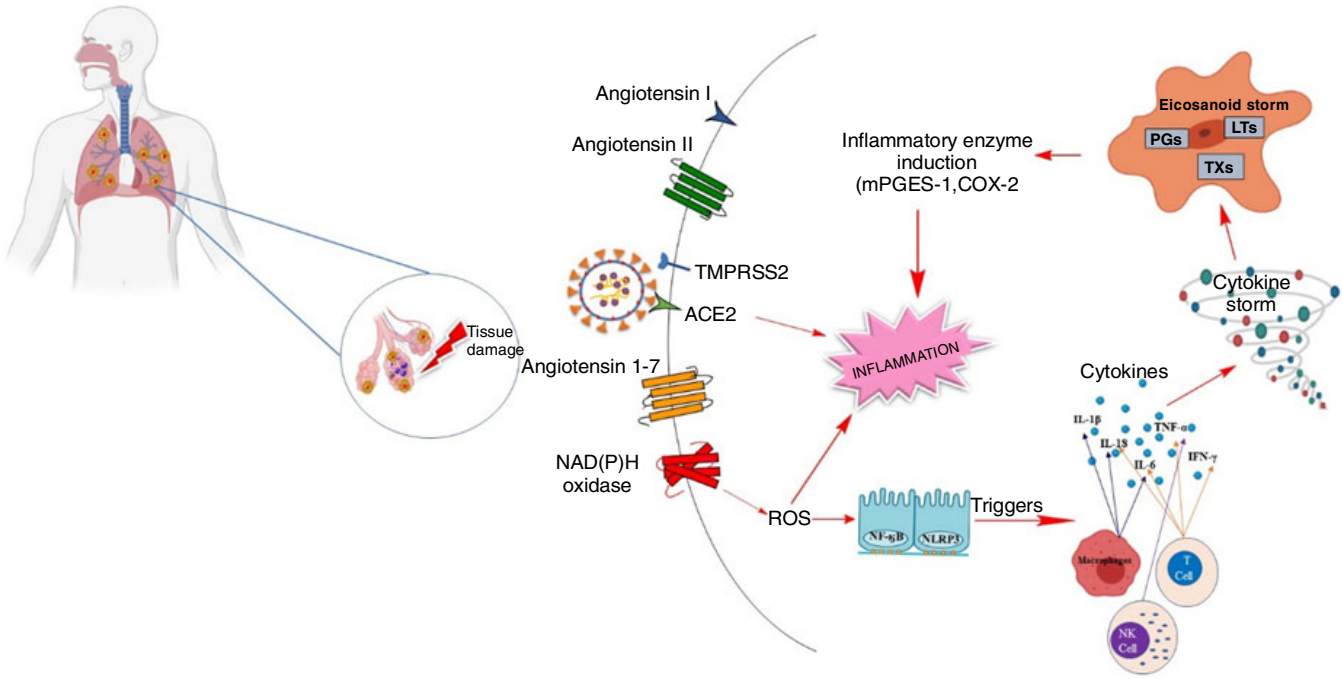


Fig. 2. SARS-CoV-2 acute inflammation pathway and cause severe lung infection

with 16 nsps. In addition to this, the ORFs encode structural and accessory proteins, (chymotrypsin-like protease) 3CLpro and nsp5 proteases involved in the cleavage of the polyproteins and the papain-like protease (PLpro, nsp3), involved in the replication-transcription complex (RTC). The complex transcribes an endogenous genome template of viral entry to negative sense genes of both the progeny genome and subs genomic RNA as intermediate products and is followed by transcription to positive-sense mRNAs that are mainly mediated by RNA-dependent RNA polymerase (RdRP). The subgenomic proteins become translated into structural and accessories proteins such as M, S and E proteins, which subsequently are insulated in the endoplasmic reticulum and then moved to the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). Meanwhile, the previously replicated genome program can directly join the N protein to the nucleocapsid to form and move into the ERGIC. In this compartment, nucleocapsid will meet with several other structural proteins and form small wallet vesicles to be exported out of the cell through exocytosis [39-42].

The changed structure in the ACE-2 results in the risk of acute respiratory distress syndrome (ARDS) or developing Covid-19. Recent *in vitro* study strongly indicates that the ciliated epithelium airway assisted the main site for viral infection. After invasion and replication SARS-CoV-2 triggers an immune and inflammatory response, showing clinical signs and symptoms of COVID-19 [43]. Epithelial cells may express inflammatory mediators *viz*. CXCL10 (C-X-C motif chemokine 10) and interferon's [44,45] and the current data indicates that small airway ACE2 expression is strongly linked in smokers and people suffering from the chronic obstructive pulmonary disease (COPD). On other hand, deficiency of ACE2 in aged people or people suffering from diabetes, or heart diseases are more vulnerable to over-reactive ACE-angiotensin 2-angiotensin 1 receptor and are noticeable in increased inflammation and thrombosis [46].

The normal antiviral immune response needs activation of inflammatory pathways in the immune system. The abnormal or embellished responses of the host's immune system cause server disease [47]. Cytokines play a key role in the inflammatory process and it is produced by numerous immune cells together with natural killer cells, macrophages, dendritic cells and the adaptive T and B lymphocytes. At the time of an innate immune response to an inflectional virus, the pattern recognition receptor (PRRs) recognizes various molecular structures of invading viruses. The molecular structure is also known as pathogen-associated molecular patterns (PAMPs). The PAMPs binds to PRRs and triggers the inflammatory process against invading virus. Following that signaling pathways and transcription factors that drive gene expression for the release of numerous factors involved in the host's immune system, particularly genes encoding pro-inflammatory cytokines are activated [48]. The most important transcription factors activated by PRRs include nuclear factors Kb, activation protein 1, interferon's response factors 3 and 7. These TFI induce the gene expression encoding inflammatory cytokines, chemokine's and molecule adhesion. In this scenario, leukocytes and plasma proteins are staffing to a specific site triggering infection. IL-1, TNF-α and IL-6 are the most important pro-inflammatory cytokines in an innate immune response. The macrophages tissue, endothelial and epithelial cells are responsible for cytokines released during inflammation. The cytokine storm is evidenced in an increased flow of different pro-inflammatory cytokines *viz*. IL-6, IL-1, TNF-α and interferons. The increase of cytokines causes an influx of different immune cells such as macrophages, T cells and neutrophils into the site of infection with negative effects on human tissue causing the destabilization of endothelium

cell to cell interaction, vascular barriers damage, diffuse alveolar, capillary, multi-organ failure and finally death. Pulmonary injury is one of the significances of the cytokine storm and progression lead to lung injury or severe acute respiratory distress syndrome (ARDS). The main cause of mortality in Covid-19 is ARDS, which causes a decrease in oxygen saturation [49-51].

The entry of SARS-CoV-2 *via* alveolar epithelium, mainly depends on the ACE2 enzyme expression (angiotensin converting enzyme-2) and TMPRSS2 (transmembrane serine protease 2). Initially, SARS-CoV-2 binds to ACE2 alveolar type II (AT2) cells by the use of 4 structural proteins and spike protein (glycoprotein S) and initiating the union of virus to host cell membranes. In next steps, ACE2 is cleaved by TMPRSS2 and stimulating clearance of cell surface and convert the viral glycoprotein S into S_1 and S_2 and release of viral genome to the cytoplasm. Both viral genome and other accessories of the SARS-CoV-2 are replicated and synthesized in endoplasmic reticulum (ER). The ER-Golgi intermediate assembles the viral components and is moved to the plasma membrane for exo-cytosis. SARS-CoV-2 initiates to cause induced alveolar type II (AT2) malfunction or sever injury to lung is due to, decline of surfactant release, failure in AT2 precursors for replacement of mismatched alveolar type 1(AT1) cell, down regulation of ACE2, Viral-induced cytokine release by AT1/AT2 cells results in capillary leak and alveolar interstitial immune cell infiltration.

COX-originates eicosanoids and its response to infection: Eicosanoids are lipid intermediates of arachidonic acid which play important fragments in the host reaction to infection. The cyclooxygenase (COX) compounds catalyze the initial phase in the biosynthesis of prostaglandins from arachidonic acid, have explicitly been involved as being significant in have a response to infections and the capacity of COX substances to modulate inflammation and immune reactions are very much archived. The effect of COX-1 and COX-2 in the host response to infections are discussed here with Influenza viral infection as example. The studies done with influenza virus have shown that the parts of COX-1 and COX-2 are there in influenza viral disease to the parts of COX-1 and COX-2 in influenza viral disease. The host reactions are important in deciding the morbidity and mortality following influenza infection and COX enzymes have significant impact on inflammation and host responses. It is attractive to have comprehensive analysis of the impact of COX compounds in the host reactions in viral diseases or Influenza disease. The modifying is possible immune responses in the COX pathway and is a major target of non-steroidal anti-inflammatory (NSAI) drugs. The research data indicates that the group of influenza A viruses causes more severe illness in mice which lacks COX-1 and less severe illness in mice which lacks of COX-1. It was also observed that mortality was considerably reduced in COX-2 deficient mice. COX-1 deficient mice had enhanced inflammation and an earlier appearance of pro-inflammatory cytokines, whereas the COX-2-deficient mice exhibited blunted inflammatory and cytokine responses along with increased viral titers. Thus, a deficiency of COX-1 and COX-2 leads to contrasting effects in the host response to influenza infection. COX-1 deficiency is detrimental, whereas COX-2 deficiency is beneficial to the host during influenza viral infection.

Cyclooxygenases (COX1 and COX2): Cyclooxygenase (COX) has been purified in 1976 and further developed as a clone in 1988 as the key enzyme in the synthesis of prostaglandins (PGs) in arachidonic acid cascade. Several scientists recognized the second gene with COX activity in 1991 and named as COX-2. The two isoforms of COX are practically indistinguishable and yet have significant contrasts in substrate and inhibitor selectivity and their intracellular areas. Protective PGs, which preserve the integrity of the stomach lining and maintain normal renal function in a compromised kidney, are synthesized by COX-1. The induction of COX-2 occurs in inflammatory lesions and is constitutively in the brain and spinal cord, where it may be involved in nerve transmission, particularly for pain and fever. COX-2 produce prostaglandins and are also important in ovulation and birth interaction. The discovery of COX-2 has revealed the way medication may be developed to reduce the pain without removing the prostaglandins produced by COX-1 in the stomach and kidney. These specific COX-2 inhibitors not only functions as anti-inflammatory substances and are dynamic against colon malignancy and Alzheimer's illness.

Mechanism of cyclooxygenase reaction: The first step in the conversion of arachidonic acid (AA) to the hydroperoxy endoperoxide (PGG2), is an abstraction of the pro-S hydrogen atom form carbon-13. The steps that follow (Fig. 3) are consistent with the mechanism of non-enzymatic lipid peroxidation, so the main contributions of COX to PGG2 formation are to restrict the options for hydrogen abstraction and dictate reaction stereochemistry. Cyclooxygenase catalysis requires that the enzyme first be activated, a process dependent on the peroxidase activity. Two-electron reduction of a peroxide substrate results in the oxidation of the ferric heme to an oxo-ferryl porphyrin radical cation. Transfer of an electron to heme from Tyr-385 of the protein generates a tyrosyl radical in the cyclooxygenase active site. This radical, as noted above, is positioned perfectly to abstract the pro-S hydrogen from carbon-13 of AA, initiating the cyclooxygenase reaction. The final step of the reaction, reduction of the peroxyl radical to the hydroperoxide to form PGG2, regenerates the tyrosyl radical. Thus, activated COX can carry out multiple turnovers without the need to repeat the activation step. After initiating the cyclooxygenase reaction, the primary function of the peroxidase is to reduce 15-hydroperoxy of PGG2 to the corresponding alcohol of PGH2 [52-55]. The enzyme lipoxygenase (5-LO or A LOX-5) transforms arachidonic acid to 5-hydroperoxyeicosatetraenoic acid (5-HPETE), which may be released and swiftly reduced to 5-hydroxyeicosatetraenoic acid (5-HETE) by ubiquitous cellular glutathione dependent peroxidases. Alternatively, A LOX-5 converts 5-HPETE to leukotriene A4 (LTA4) *via* its LTA synthase activity. LTA4 is then converted to LTB4 by Leukotriene A4 hydrolase or leukotriene C4 (LTC4) by LTC4 synthase or microsomal glutathione S-transferase 2 (MGST2). Either of the latter two enzymes act to attach the sulfur of cysteine's thio-(*i.e.* SH) group in the tripeptide glutamate-cysteine-glycine to carbon 6 of LTA4 thereby resulting LTC4. After release from its parent

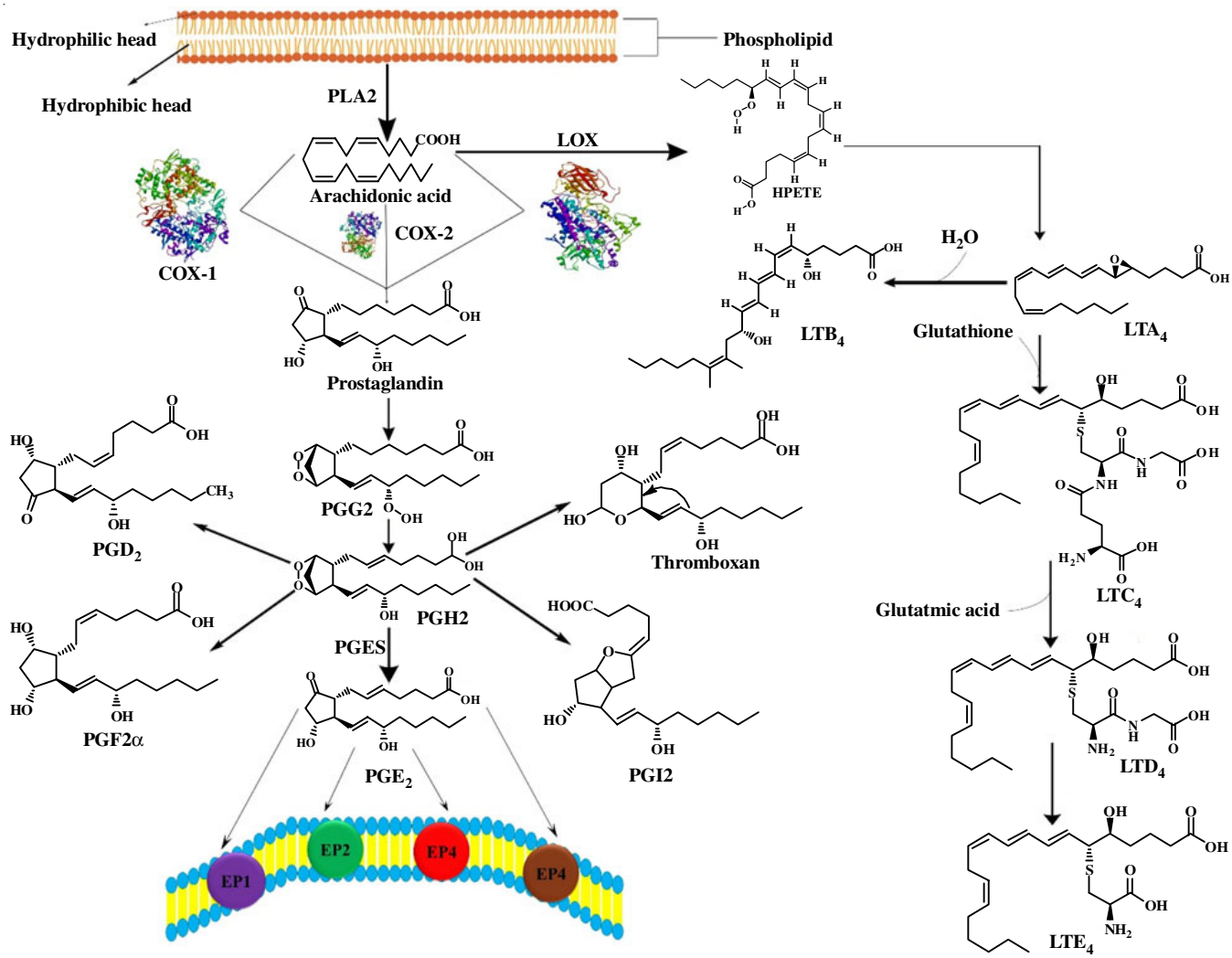


Fig. 3. Mode of prostanoid synthesis from arachidonic acid and the association of COX-2 in particular inflammation development. Arachidonic acid is released from membrane phospholipid by phospholipase A2. COX-1 or COX-2 modifies arachidonic acid to prostaglandin (PG) G2 followed by conversion to PGH2 into other PG isoforms or thromboxane (TX) A2. Among them, PGE2 is the major prostanoid and shows variability of biologic activities *via* its EP1-4 receptors coupled with G-protein-receptors

cell, the glutamate and glycine residues of LTC4 are eliminated stepwise by gamma-glutamyltransferase and a dipeptidase to form sequentially LTD4 and LTE4 [56].

Thiazole derivatives as potent anti-inflammatory agent: Thiazole is an important hetero-functional derivative used in most of the synthetic and medicinal compounds [9,19]. The thiazole derivatives act as core functional in many non-steroidal anti-inflammatory drugs like meloxicam and fanetinole, which are already in the market to treat inflammation. In this article, we discussed about thiazole derivatives, which acts as anti-inflammatory candidates and also to combat SARS-CoV-2 inflammation and inhibition of SARS-CoV-2 proteins.

Selective COX inhibitors: Initially, phenol (**1**) reacts with ester in presence of potassium carbonate and dry acetone to give ethyl 2-phenoxy acetate (**2**); compound **2** treated with NaOH in ethanol to give 2-phenoxy acetic acid (**3**); compound **3** reacts with amines substituted thiazole in presence of dichloromethane and TBTU as coupling specialist to give thiazole subsidiaries [THI-1]. One of the main biological activities of thiazole derivatives is their ability to act as anti-inflammatory agents. Several synthetic modifications with electron withdrawing/donating groups, biphenyl based or other substituents, have been reported to affect the anti-inflammation activities of thiazole derivatives. The *ortho*-difluoro group of THI-1a and methyl group of THI-1b at different positions of benzoyl ring increases the activity. The activity data revealed that the compounds THI-1a and THI-1b showed a significant COX-2 inhibitory activity [57]. Phenacyl bromide, thiosemicarbazide and ethyl acetoacetate (**4**) were taken in acetic acid, warmed at 60-80 ºC for around 2-3 h. The reaction mixture was cooled to room temperature, following which, sodium acetate and heteroaldehyde were added and warmed at 80-85 ºC for around 2 h. The obtained thiazole derivative [THI-2] was cooled, separated, washed with water and recrystallized from acetic acid. Thiazole-bearing pyrazole [THI-2a] as a potential pharmacophore was synthesized and assessed for its anti-inflammatory activity. The structure-activity relationship revealed that the introduction of electron-donating 4-OMe of phenyl substituent

on pyrazole nucleus might have increased the COX-2 inhibition potential, whereas introduction of electron-withdrawing Cl of phenyl substituent on thiazide nucleus might be the underlying cause in arresting COX-2 activity (Fig. 4) [58]. Thiobenzamide (**5**) reacts with bromo-pyruvate in ethanol resulting in ethyl-2-phenylthiozole-4-carboxylate (**6**). Compound **6** responds to hydrazine hydrate to provide 2-phenylthiazole-4-carboxy hydrazide (**7**). The acid hydrazide (**7**) formed when reacts with ethyl(ethoxymethylene)cyanoacetate in ethanol, to form the corresponding 5-amino-4-ethyl ester thiazole derivative [THI-3]. A series of substituted thiazide derivatives were synthesized to obtain a compound with potent anti-inflammatory activity. Pyrazole at 4th position of thiazide exhibited more prominent and consistent activity by inhibiting COX-2 enzyme with 60.31% inhibitory activity, than the standard drug diclofenac [59]. At first, 3-cyanopyridine (**8**) converted over to pyridine-3-carbothiamide (**9**) by treating with phosphorous pentasulphide (P_4S_{10}), compound **9** upon refluxing with ethyl-2-chloroaceto-acetate formed ethyl-5-methyl-2-(pyridine-3-yl)thiazole-4-carboxylate (**10**). The subsequent ester was treated with hydrazine hydrate to yield 5-methyl-2-(pyridine-3-yl)thiazole-4-carbohydrazide (**11**). Further, compound **11** was condensed with an aromatic aldehyde to synthesize the target compound [THI-4]. The synthesized compound is thiazole-based hydrazide having the highest inhibition. The structure-activity relationship study of the active compounds was deduced based on the IC_{50} value; it reveals that the presence of the hydroxy and methoxy group is responsible for the enhanced COX inhibition. The presence of hydroxyl substituent on the 4th position and the methoxy substituent on the 3rd position of [THI-4a] enhanced the anti-inflammatory activity (Fig. 5) [60].

4-Acetoxy benzoyl chloride (**12**) was dissolved in dry tetrahydrofuran and the obtained solution was poured to a stirred suspension of thiosemicarbazide in dry tetrahydrofuran. Then, the mixture was stirred at room temperature for 24 h to give 4-(2-carbamothioylhydrazine-1-carbonyl)phenyl acetate (**13**), the obtained compound **13** with an excess of phosphoryl chloride was evaporated under vacuum, the reaction mixture was stirred overnight, the solution was basified by conc. NH_4OH solution to give thiadiazol derivative (**14**). The obtained compound **14** was stirred in dry chloroacetyl chloride and phenyl to give hydroxyl phenyl (**15**) and the obtained compound **15** was recrystallized from dioxane/H_2O as white solid, compound **15** on stirring with ammonium thiocyanate in absolute ethanol resulted in thiazolidin-4-one (**16**) with brownish-yellow solid, which on treating with benzaldehyde gives thiazole derivatives (THI-5). A series of thiazole and thiazolidinone hybrids exhibit potent anti-inflammatory activity due to the arylidene ring substitution with 3,4-dichloro atoms, which leads to increase in enzyme inhibition. The synthesized (THI-5a) compound showed the highest inhibitory activity against the COX-2 enzyme [61]. 5,6-Diarylimidazo[2.1-*b*]thiazoles [THI-6] were prepared by the condensation of α-bromodiarylethanones (**17**) with appropriately substituted 2-aminothiazoles by refluxing in ethanol or isopentanol. The chlorinated analog **2** was obtained with treatment of sulfuryl chloride followed by DBU. An arrangement of 5,6-diarylimidazo[2,1-*b*]thiazole subsidiaries [THI-6a] was incorporated and their conceivable strong inhibitory activity against COX-1 and COX-2 enzymes. Accordingly, the compound was recognized as an intense, orally dynamic and particular inhibitor of COX-2 enzyme (Fig. 6) [62]. Accordingly, the reaction of 4-aminoacetophenone (**18**) with chloroacetyl chloride in chloroform under reflux conditions provided the corresponding chloroacetamide derivatives (**19**) in high yields (89-91%). Cyclization of chloroacetamide derivative with ammonium thiocyanate in ethanol gives thiazolidinone subordinates (**20**) in good yields (80-82%). Finally, the condensation of compound **20** with different aldehydes in acetic acid and sodium acetate gives the target compound 5-arylidenethiazolidin-4-one derivatives [THI-7] with (53-82%) yield. 4-Thiazolidinone is often frequently found scaffold in a wide variety of bioactive molecules including anti-inflammatory agents. A novel series of 2-arylimino-5-arylidenethiazolidin-4-ones derivatives [THI-7a] were synthesized. *In vivo* anti-inflammatory studies revealed that this compound showed the most potent and selective COX-2 hindrance and exhibited anti-inflammatory activity of ED_{50} = 38 µmol/kg very close to standard medication celecoxib (ED_{50} = 34 µmol/kg) [63]. Benzo[*d*]thiazole derivative [THI-8] was gotten through a two-step reaction, the halfway 2-(2-bromomethoxy) benzo[*d*]-thiazole (**22**) was synthesized which undergoes a nucleophilic substitution reaction with 1,2-dibromomethane and benzo[*d*]-thiazole-2-ol (**21**), then the obtained 2-(2-bromomethoxy)-benzo[*d*]thiazole in presence of substituted phenol gives [THI-8]. A series of benzo[*d*]thiazole analogs [THI-8a] were synthesized and evaluated for their anti-inflammatory effects. An excellent anti-inflammatory activity was observed when a halogen atom as electron-withdrawing groups was present. The compound exhibited the most effectiveness with Br at *p*-position. Therefore, the compound evaluated for their inhibitory effects against ovine COX-1 and COX-2, showed weak inhibition of COX-1 enzyme but showed moderate COX-2 enzyme inhibition activity (Fig. 7) [64]. The synthetic reaction pathway consists of the reaction of chalcone with a carbonyl compound (**23**) and gives (5-chloroistain thiozolidine-4-carboxylic acid or octahydro-1*H*-indole-4-carbolylic acid) (**24**), compound **24** reacts with amino acids, in this manner, wherein number of spiroxindole benzo-[*d*]furan thiazole scaffold [THI-9] was obtained. Some spiro-oxindole benzo[*d*]furan scaffolds were synthesized. Compound [THI-9a] with chlorine atom on the oxindole moiety and unsubstituted benzene on the benzyl nucleus shows the best and selective 57.83% inhibitory activity against COX-1 compared to the standard drug, celecoxib (IC_{50} = 29.19 ± 0.33µm and 8.7% inhibition) [65]. The equimolar volume of appropriate phenylhydrazine and benzaldehyde (**25**) were decomposed in methanol and then acetic acid was added to the corresponding medium as a catalytic reagent. The mixture was heated for 4 h, the solvent was evaporated to give phenylhydrazones (**26**). Mercaptoacetic acid on the treatment with phenyl hydrazones at 60-80 ºC, till the reaction get completed gives thiazolidine derivative [THI-10]. A novel series of 2-aryl-3-(4-sulfanoyl/methoyl-sulfonylphenylamino)-4-thiazolidinones [THI-10a] are appropriate scaffolds for the development of new COX-2 inhibitors. The synthesized compound [THI-10a] showed good

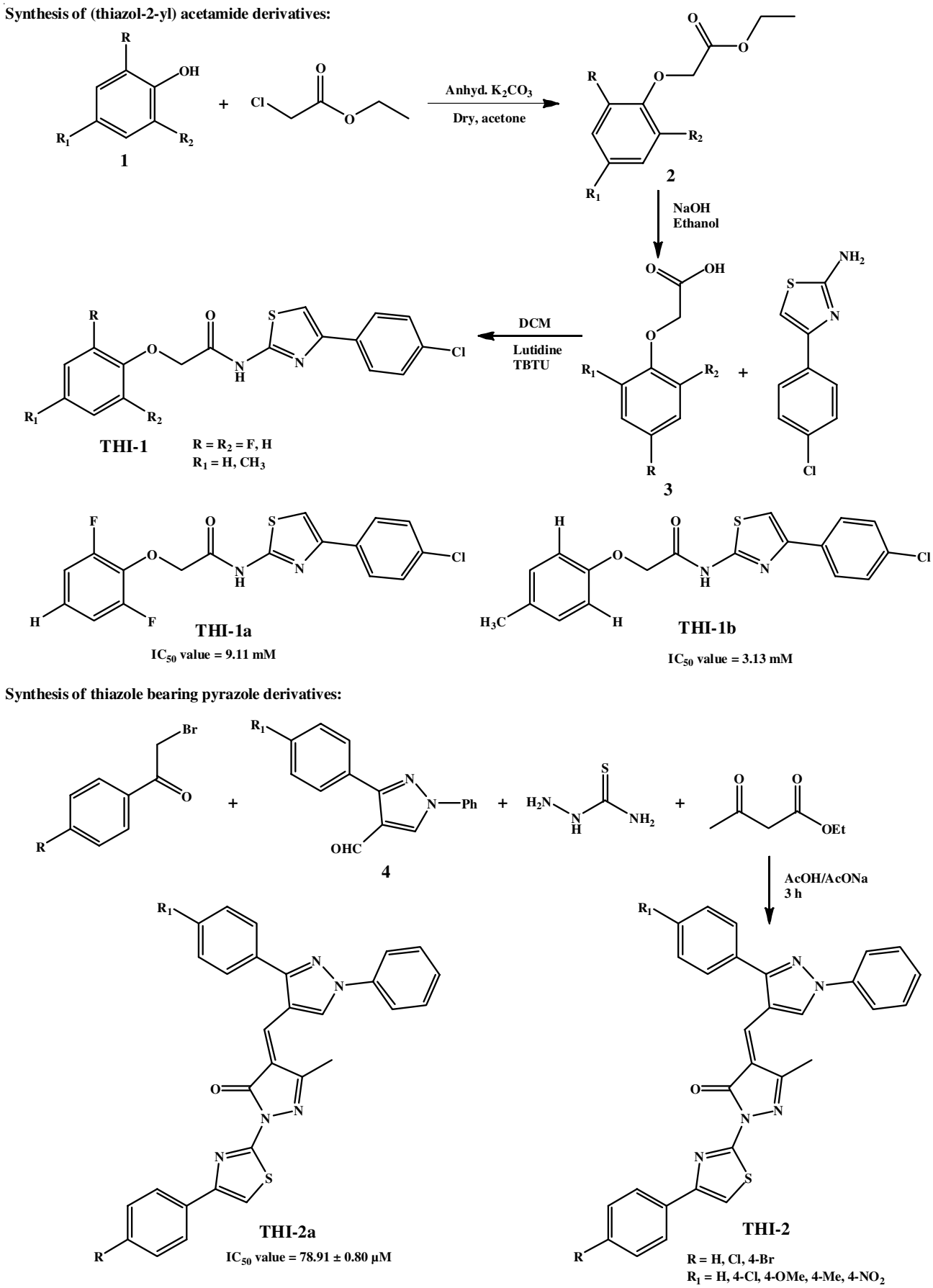


Fig. 4. Synthesis route of compound THI-1 and THI-2

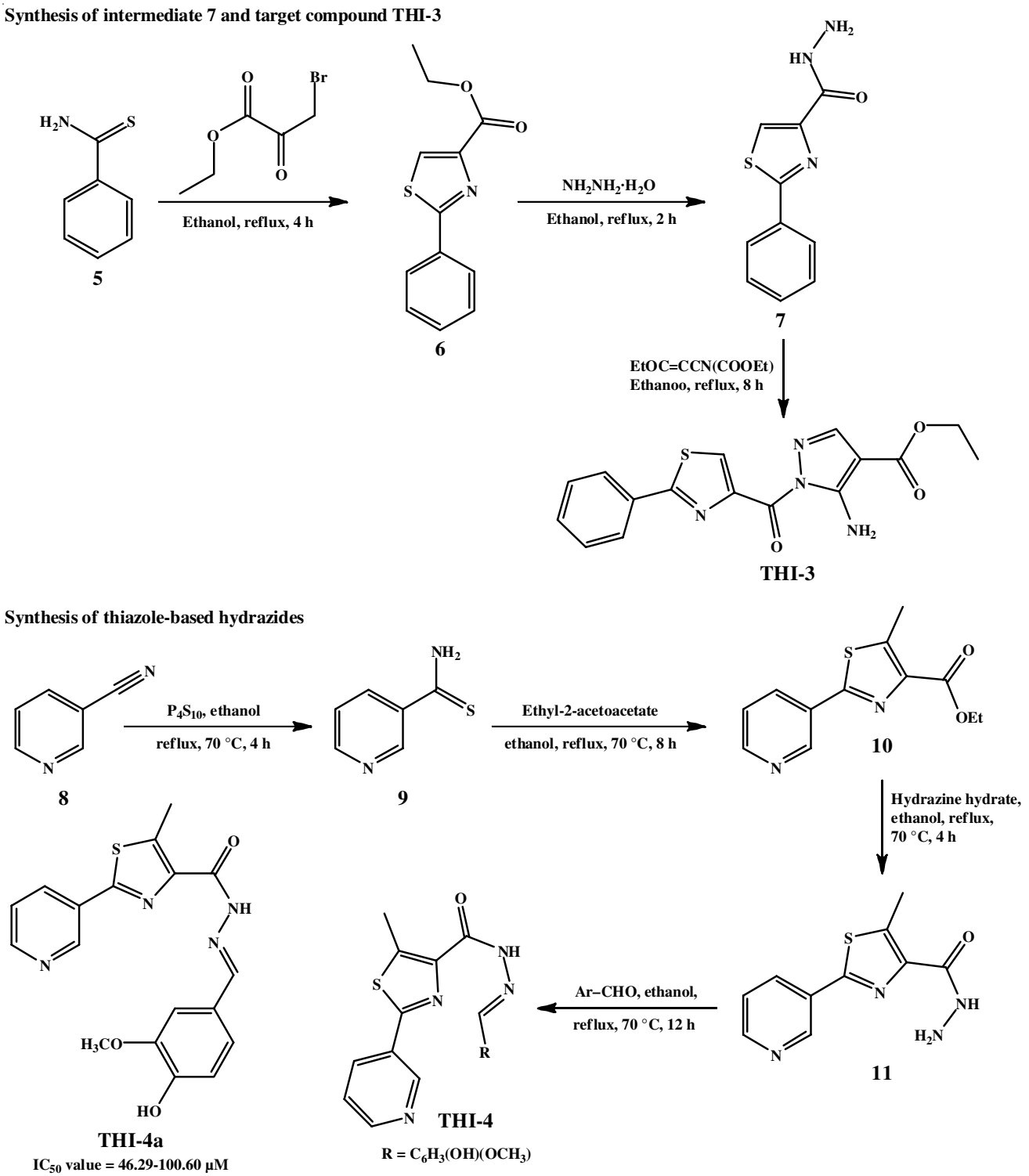


Fig. 5. Synthesis route of compound THI-3 and THI-4

COX-2 inhibitory activity, due to the presence of methyl group on the phenyl ring exhibited highly COX-2 inhibitory selectivity and potency (Fig. 8) [66].

A newly synthesized compound of 4-substituted thiazole analogs [THI-11a, 11b and 11c] of indomethacin, were tested as inhibitors of COX-1 and COX-2. It was found that compounds [THI-11a, 11b and 11c] exhibited activity due to the presence of aryl group carrying different substituents as the selective inhibitors of COX-2. Among these compounds, [THI-11a] shows good COX-2 inhibitory activity, while only moderate COX-1 inhibitory activity has been observed [67]. A novel series of 2,3-diaryl-1,3-thiazolidine-4-ones derivatives [THI-12] possessing a methane sulfonic acid pharmacophore at the *para*-position of the C-2 phenyl ring in conjugation with a substituent fluorine at *para*-position of the phenyl ring showed potent COX-2 inhibitory activity [68]. The incorporated (2-(diphenyl-

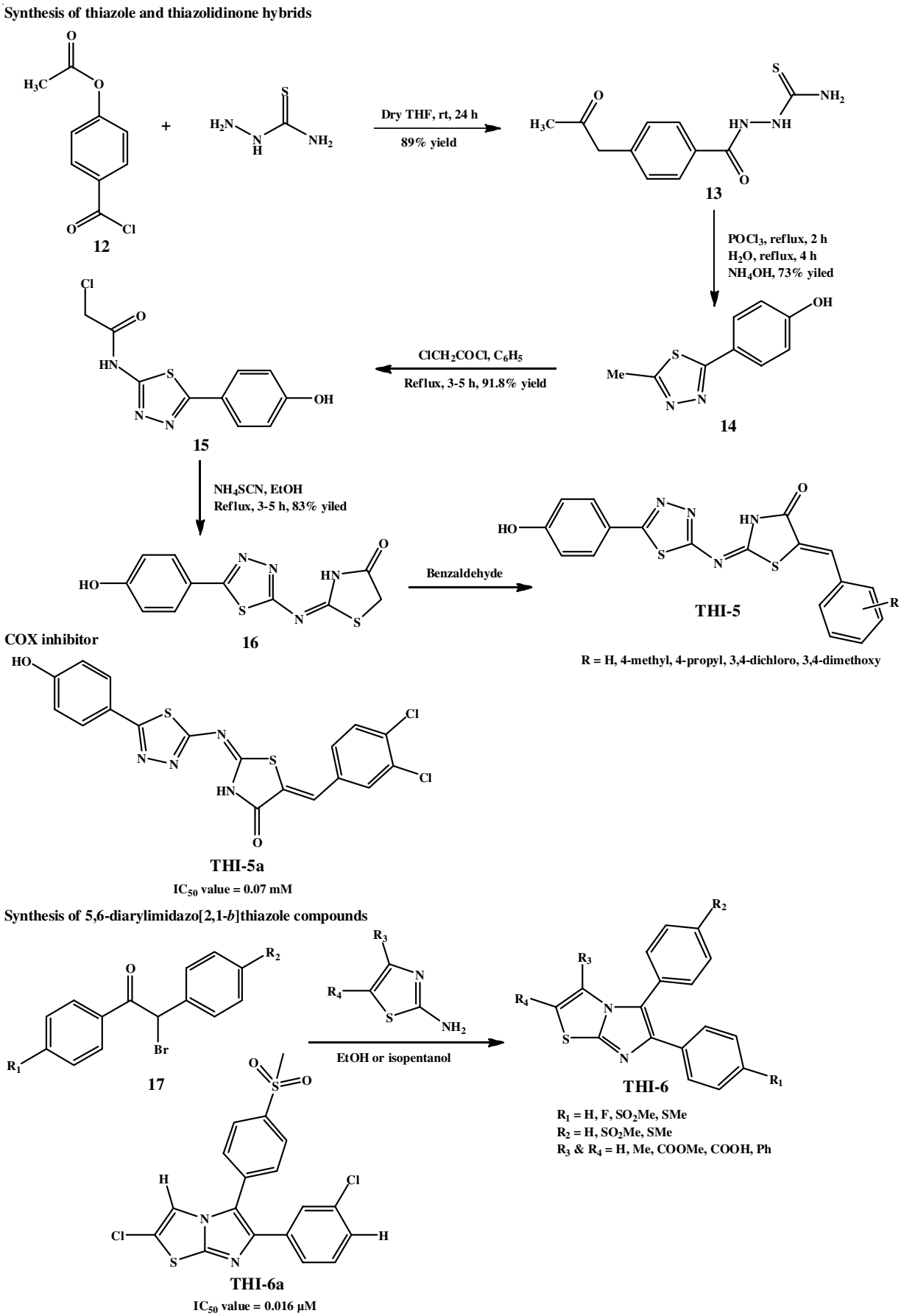
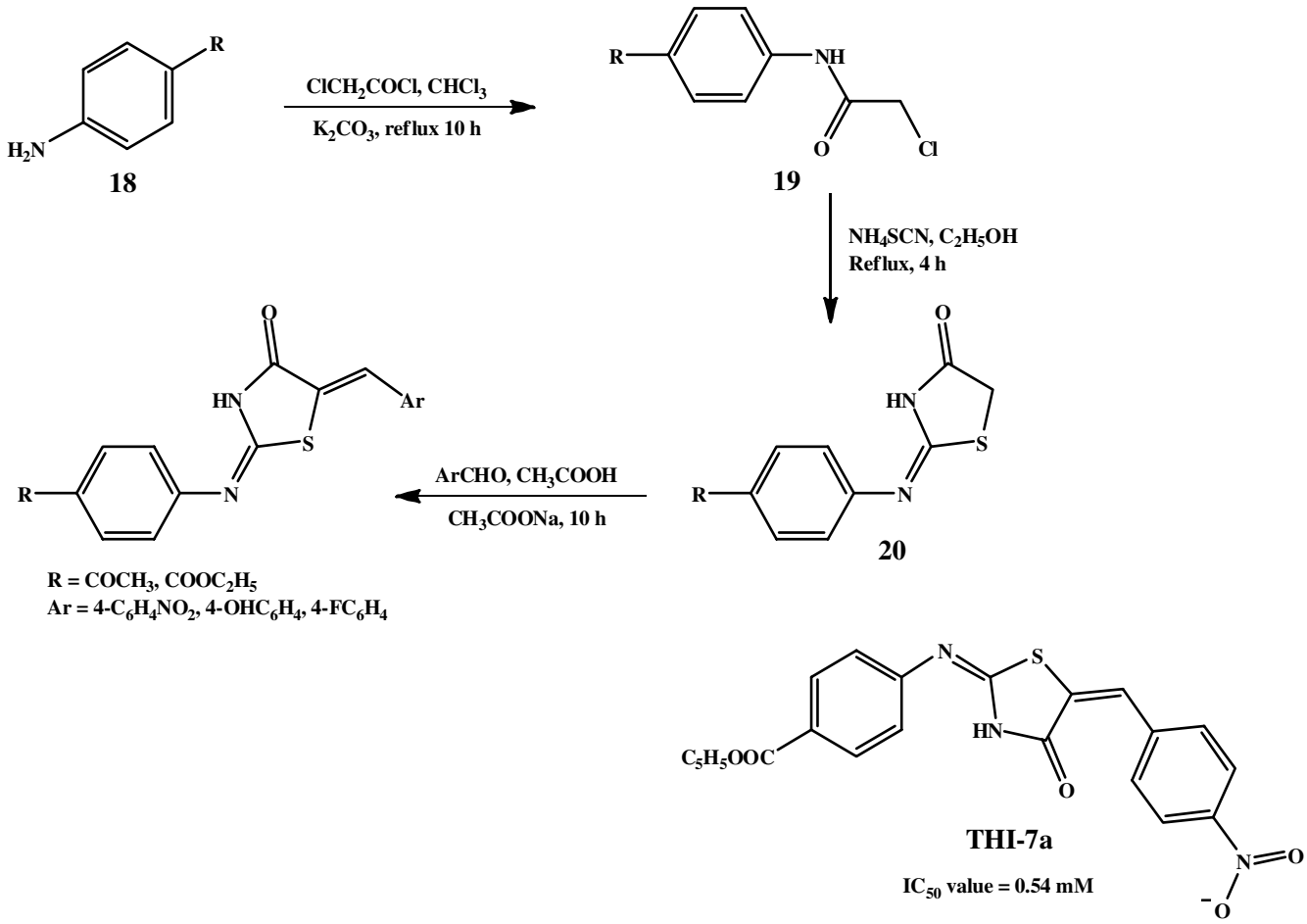


Fig. 6. Synthesis route of compound THI-5 and THI-6

Synthesis of 2-arylimino-5-arylidenethizolidin-4-ones derivatives



Synthesis of benzothiazole analogs

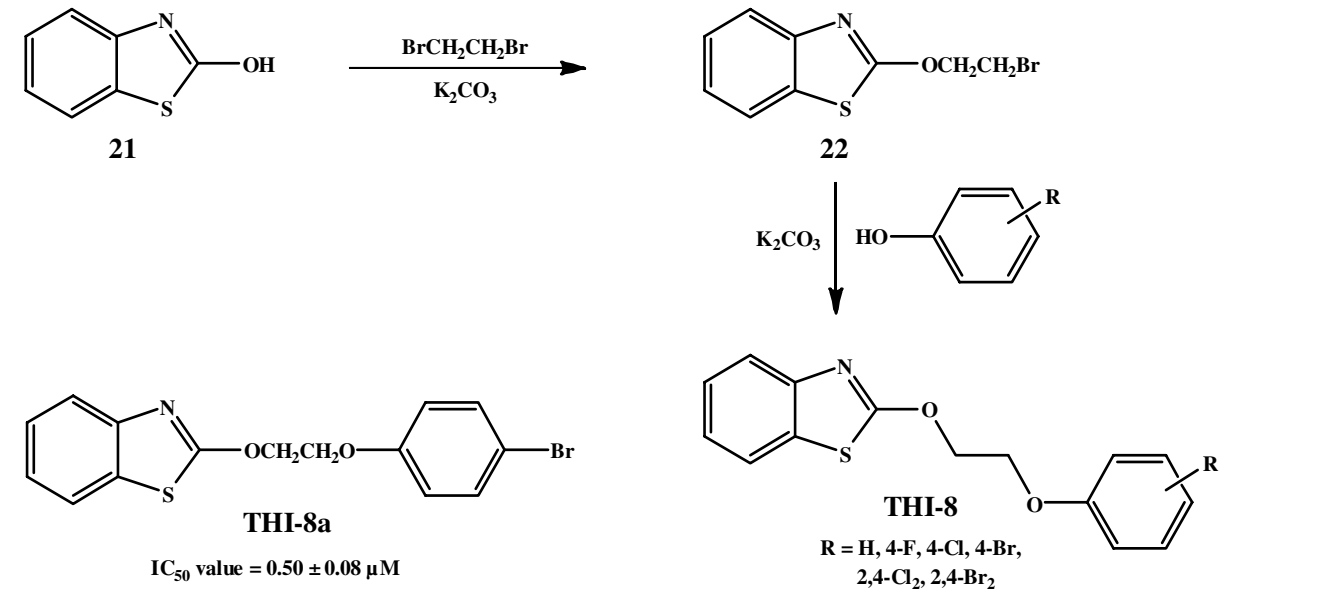


Fig. 7. Synthesis route of compound THI-7 and THI-8

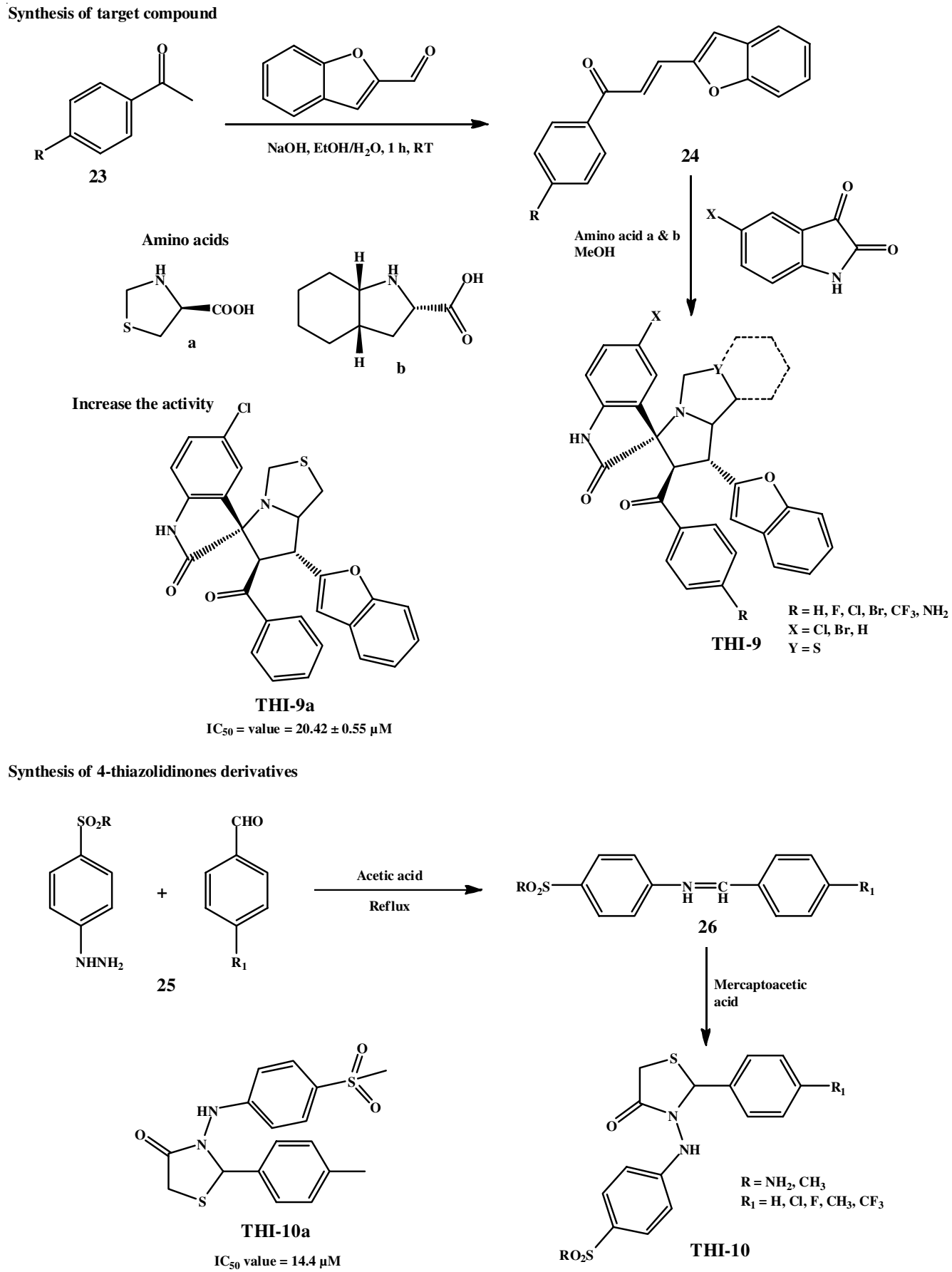


Fig. 8. Synthesis route of compound THI-9 and THI-10

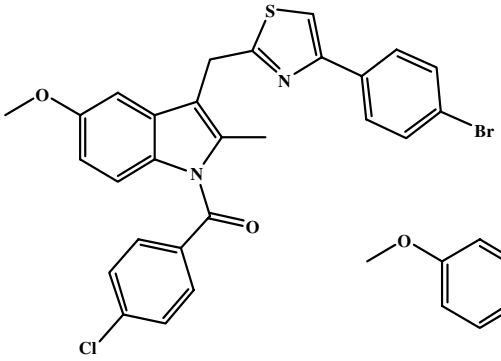
amino)-4-(4-nitrophenyl)thiazol-5-yl)(naphthalene-1-yl)-methanone [THI-13] shows an excellent COX-2 inhibitory activity, the presentation of *p*-phenyl substitutions tertiary amino group on the central thiazole core plays a key part in anti-inflammatory activity. In general, significant COX-2 inhibition was shown by compound [THI-13] with presence of an electron-giving group NO_2 at the *p*-position of phenyl ring [69]. A series of benzothiazoles [THI-14] showed the most significant COX-2 inhibitory activity. The acid and amide groups contributed promising COX-2 inhibitory action [70]. The synthesized (2-morpholino-4-(4-methyl phenyl)thiazol-5-yl)(naphthalene-1-yl)methanones [THI-15], indicated better inhibition of COX-2, because of the presence of compound [THI-15] substituted with *p*-CH_3 phenyl ring. For the most part, naphthoyl substitution at C_5 of thiazole ring improved COX-2 inhibition [69]. Two novel thiazole derivatives, namely compounds THI-16a and 16b were synthesized to analyze their effect on COX isoforms. Compound **16a** is a non-selective COX-1/COX-2 inhibitor, while **16b** is a selective COX-2 inhibitor [67]. A new series of imidazo [2,1-*b*]thiazole analogs [THI-17] were synthesized. The synthesized compound [THI-17] showed potency and the selectivity of COX-2 inhibitory activity was affected due to the presence of amine on C-5 of imidazo[2,1-*b*]-thiazole ring (Fig. 9) [71].

Selective LOX inhibitor: Benzoyl chloride (**27**) reacts with ammonium thiocyanate to give benzoyl isothiocyanate (**28**), compound **28** on treating with NH_4OH results in *N*-carbamothioyl substituted benzamide (**29**), compound **29** on treating with di-ketone derivative yields *N*-(5-acetyl-4-methyl thiazole-2-yl) substituted benzamide (**30**). Compound **30** treated with ethanol and NaOH results to form thiazole derivatives [THI-18]. The integrated chalcone-thiazole [THI-18a] half breed subordinates, the presence of electron giving substituents, methoxy in the region of both thiazole and chalcone of phenyl rings shows the exceptionally dynamic inhibitor of 5-LOX enzyme [72]. To a mixture of potassium thiocyanate and cetrimide, benzoyl chloride (**31**) in toluene is added followed by addition of 2º amine to the aromatic layer results in the formation of benzamide derivatives (**32**). Condensation of 2-bromoacetophenone (**33**) with the equivalent amount of benzamide derivative in the presence of catalyst, trimethylamine in acetonitrile at 70 ºC results in (2-(diphenylamino)-4-phenylthiazol-5-yl)phenyl methanone [THI-19]. The synthesized novel substituted 2-amino thiazide analogs [THI-19a], act as a competitive 5-LOX inhibitor by incorporating a benzyl group at the 5th and substituted 2º amine at the 2nd position, respectively, in the basic thiazide moiety provided by potent analog. This compound is found to be more potent than the drug, zileuton (Fig. 10) [6]. Chloro acetylation of 2-(methylthio)-1*H*-benzo[*d*]imidazole (**34**) in presence of NaH and DMF, gives pure product imidazole derivative (**35**), which undergoes cyclization with thiourea in presence of ethanol resulting in aminothiazole derivatives (**36**). Compound **36** on alkylation with the equivalent amount of chloroacetone in presence of acetone in anhydrous K_2CO_3 gives benzo[*d*]thiazole derivative (**37**). Compound **37** on treating with the equimolar volume of phenylthiosemicarbazide gives new benzimidazole thiazole (**38**) hybrid with thiosemicarbazone moiety. Heating **38** linked to thisemicarbazone hybrid **37** with an equivalent amount of appropriate *p*-(un)-substituted phenacylbromides in absolute ethanol, followed by neutralization with sodium acetate, afforded benzimidazole-thiazole hybrids [THI-20] linked to 1,3-thiazolines. Benzimidazol-thiazide hybrid linked to 1,3-thiazoline substituted with *p*-chlorophenyl moiety [THI-20a] was highest 15-LOX inhibitor, as it displayed almost double 15-LOX inhibitory activity compared to the reference quercetin [73]. Phenylthiazole derivative (**39**) treated with ester in presence of diethyl ether gives hydroxyphenyl thiazole derivative (**40**), compound **40** reacts with phenylhydrazine gives phenylthiazole imidazole derivatives [THI-21]. A new series of phenylthiazole derivatives [THI-21a] were prepared as 15-LOX inhibitors. Compound [THI-21a] showed good inhibitory activity due to the presence of methyl group having the highest relative potency in comparison with celecoxib, the compound **27** showed a promising safety profile to most of the synthesized compounds (Fig. 11) [74].

2-Aminothiazole (**41**) treated with acetyl chloride and DMF gives *N*-thiazole alkyl amide (**42**). Compound **42** reacts with NH_4SCN in ethanol to give amindithiazole derivative (**43**), compound **43** reacts with acetic acid and sodium acetate to provide thiazole derivatives [THI-22]. 2-(Thiazole-2-ylamino)-5-phenylidene-4-thiazolidinone derivatives were synthesized by differing the phenyl group substitution, which exhibits the anti-inflammatory activity. Compound [THI-22a] with *m*-OCH_3, *p*-OH derivative and compound [THI-22b] with *m*-NO_2, which exhibits the highest anti-inflammatory activity, also have the best LOX inhibition. This compound inhibits effectively inflammation, acting on enzymes involved in both arachidonic acid catabolic pathways and thus are promising anti-inflammatory agents with reduced undesired side effects [75]. The appropriate thiazole derivative (**44**) with chloro-acetyl chloride in presence of dry benzene gives an alkyl amide substitute (**45**). Compound **45** on refluxing with NH_4SCN in ethanol leads to the dithiazole derivative (**46**). The final thiazole derivatives [THI-23] were synthesized by refluxing the previous intermediate with aldehyde and anhydrous sodium acetate in acetic acid. As a part of ongoing studies in developing new thiazole derivatives as an anti-inflammatory agent, the synthesis of novel 5-arylidene-2-(1,3-thiazol-2-ylimino)-1,3-thiazolidin-4-ones [THI-23a] showed good LOX inhibitory activity due to the presence of -OCH_3 [76]. The benzothiazoyl moiety (**47**) reacts with acetyl chloride in DMF gives isothiazole derivative **48**, the compound **48** react with NH_4SCN in alcohol to form 2-(heteroarylimine) thiazolidine-4-ones (**49**). Compound **49** treated with aldehyde and carboxylic acids gives heterocyclic thiazole derivative [THI-24]. The benzo-thiazolyl moiety was proved to be of great significance for developing more potent inhibitors. Among the synthesized benzisothiazolythiazolidinone derivatives [THI-24a], the best LOX inhibitory activity was observed for compound THI-24a. It seems that the presence of *p*-OH group, in this case, is beneficial for LOX inhibitory activity (Fig. 12) [77].

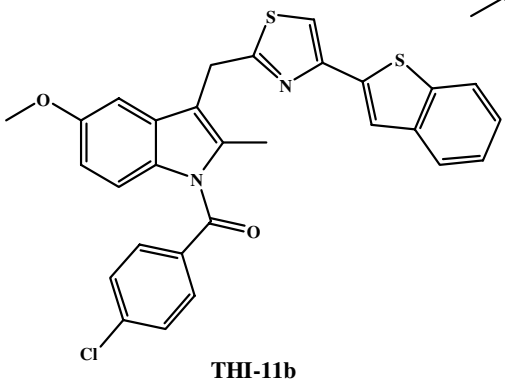
Pyrimidine (**50**) reacts with brominated alkyl ester in presence of thiobarbituric acid, TEA and dimethylformamide

Chemical structure of thiazoles and thiazolidinones derivatives



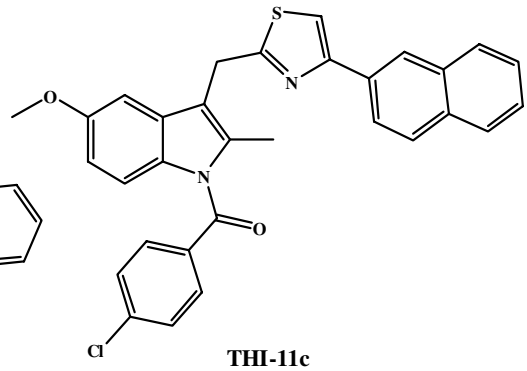
THI-11a

IC_{50} value = 0.3 ηM



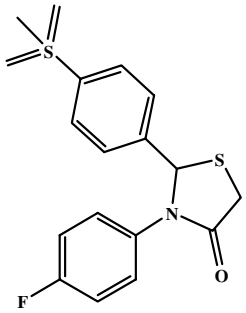
THI-11b

IC_{50} value = 1 ηM



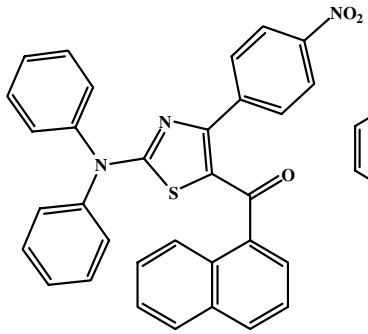
THI-11c

IC_{50} value = 7 ηM



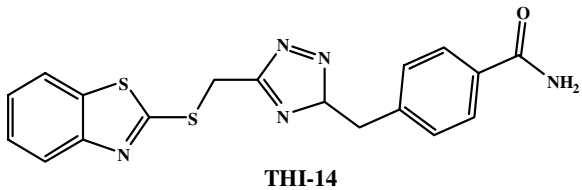
THI-12

IC_{50} value = 0.12 µM



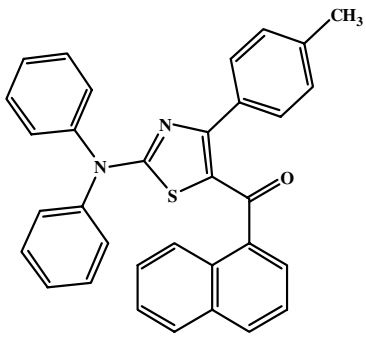
THI-13

IC_{50} value = 0.07 ± 0.02 µM



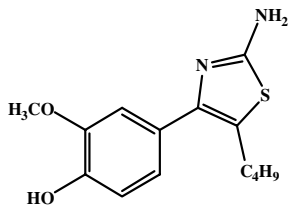
THI-14

IC_{50} value = 5.4 µM



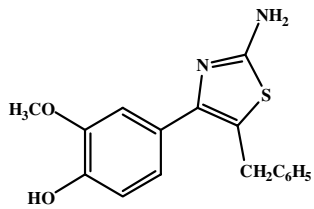
THI-15

IC_{50} value = 0.90 ± 0.064 µM



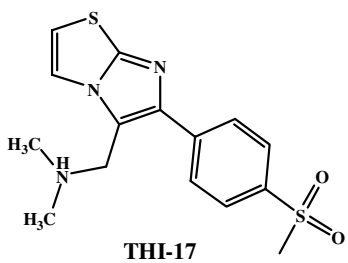
THI-16a

IC_{50} value = 9.01 ± 0.01 µM



THI-16a

IC_{50} value = 11.65 ± 620 µM



THI-17

IC_{50} value = 0.08 µM

Fig. 9. Synthesis route of compound THI-11 to THI-17

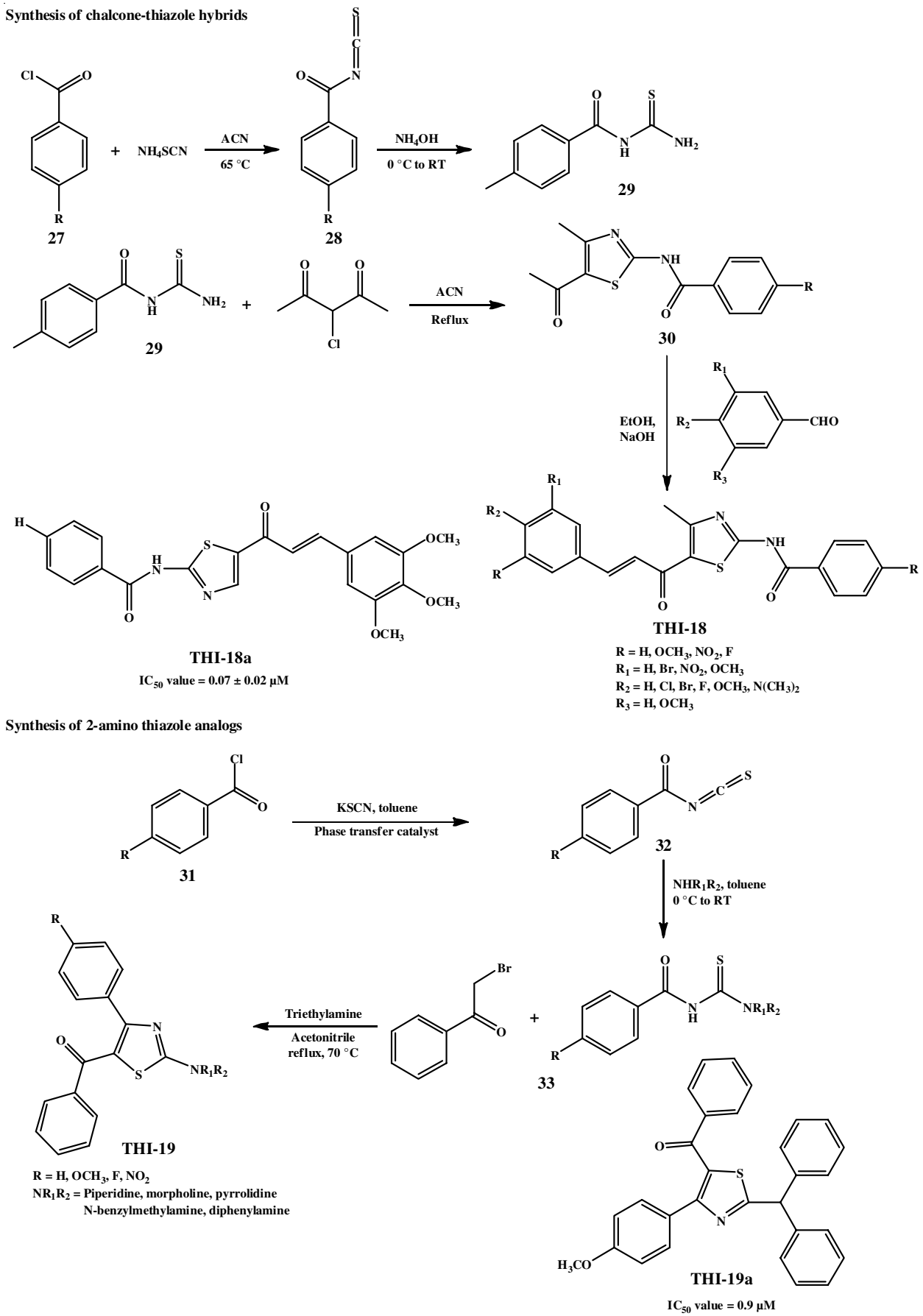


Fig. 10. Synthesis route of compound THI-18 and THI-19

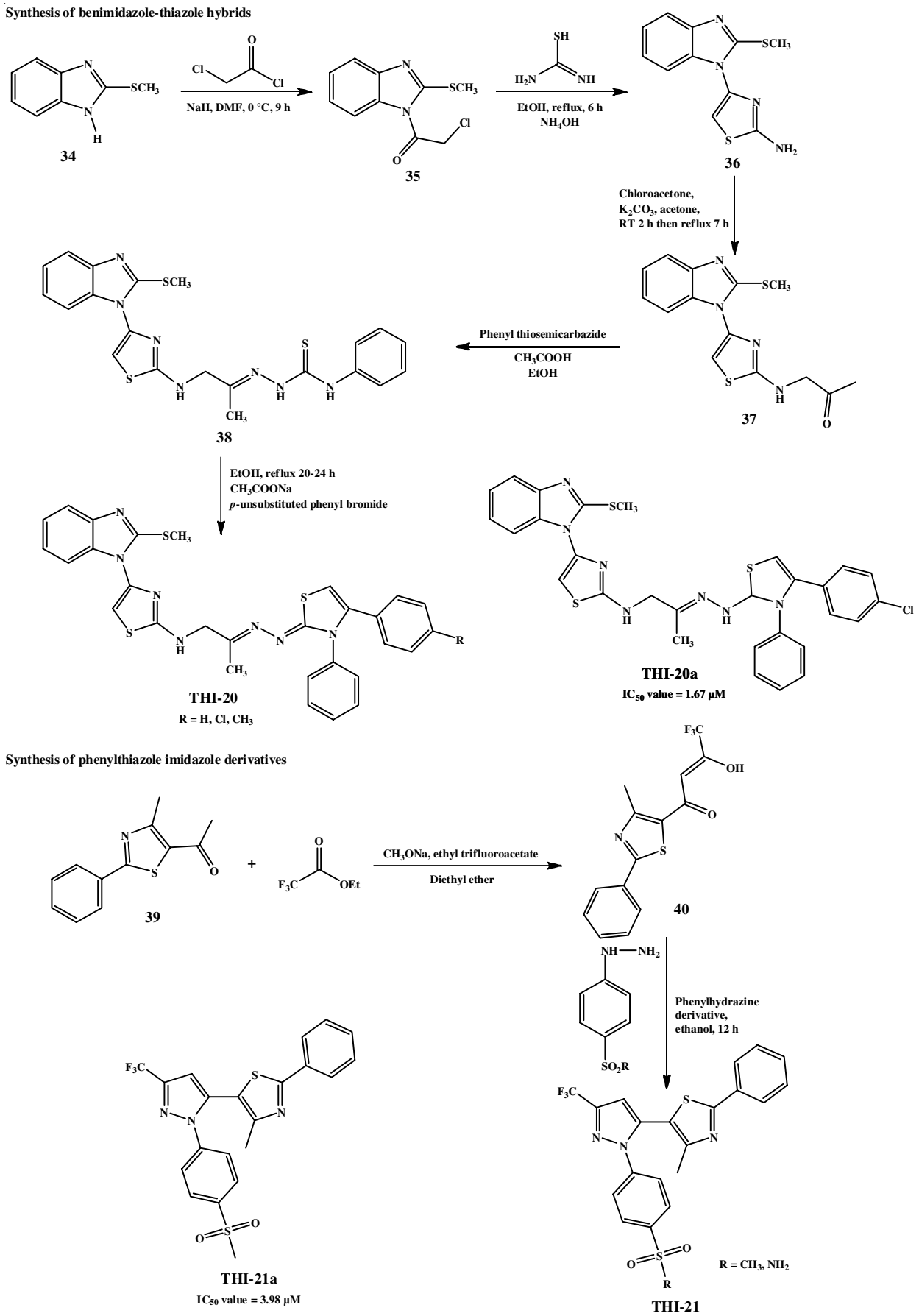


Fig. 11. Synthesis route of compound THI-20 and THI-21

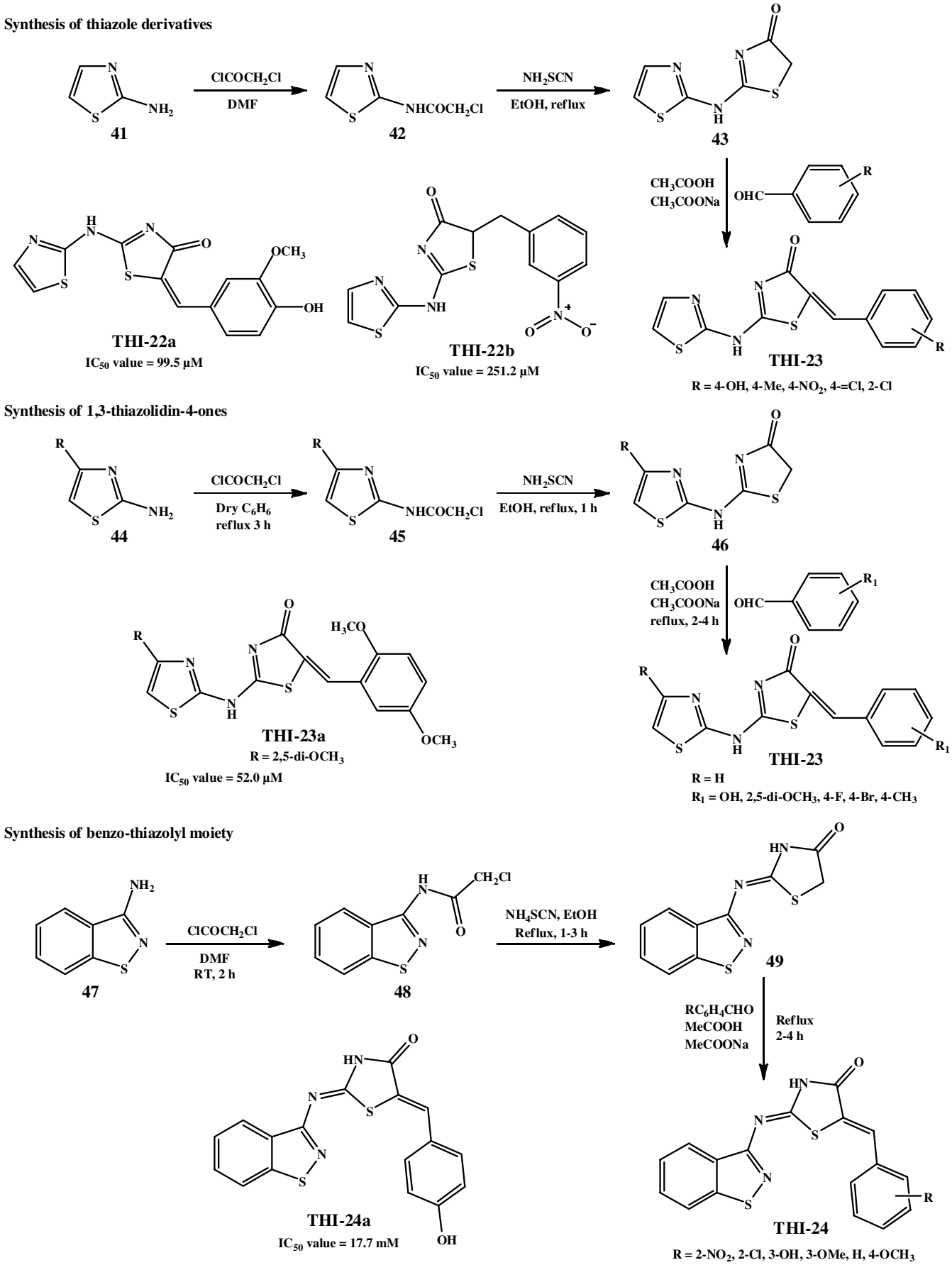


Fig. 12. Synthesis route of compound THI-22 to THI-24

to yield pyrimidine derivatives (**51**). Compound **51** chlorinated with $POCl_3$ in presence of diethylaniline to give dichloropyrimidine derivative (**52**), compound **52** react with Na_2CO_3 in presence of catalyst to give amine dihydrothiazole derivative (**53**), then compound **53** hydrated with LiOH in presence of tetrahydrofuran to give thiazole derivative [THI-25], pirinixic acid derivatives bearing 2-aminothiazole [THI-25a] moiety has potent inhibitory activity against 5-LOX. The presence of 2-napththyl moiety showed remarkable inhibition against 5-LOX [78]. Dione (**54**) derivative treated with benzyl ketone gives dione-imidazole derivative (**55**), compound **55** on cyclization with dimethylformamide provides dimidazole derivative (**56**), compound **3** treated with thiosemicarbazide gives carbazide derivatives (**57**), compound **57** reacts with phenacyl bromide gives thiazole derivative [THI-26]. Novel purine–pyrazole hybrids combining thiazoles, thiazolidines [THI-26a] were designed and tested as 15-LOX inhibitors. It was found that the compound exhibited the activity due to the presence of chlorine in the region of phenyl ring and C_6H_5 group in thiazole (Fig. 13) [79].

Molecular docking studies

Ligand preparation: The 3D chemical structure of thiazole derivatives was drawn by using Chemdraw software and those structure were converted into 3D structure by using Marvin JS software tool [80], later on all the ligand were converted into PDB format by using Marvin JS software tool. All the compounds were optimized and converted from PDB to PDBQT format by using AutoDock tools 4.2.6.

Protein preparation: To verify the effect of ligand with COVID-19 proteins, molecular docking technology was accepted. MGL tools 1.5.6 with Auto Dock Vina was used for the molecular docking analysis to detect the preferred binding sites [81]. The recently resolved X-ray crystal 3D structures of SARS-CoV-2 Spike binding domain with main protease (PDB code: 6LU7) in complex with the covalent peptide N3 and SARS-CoV-2 Spike binding domain with ACE2 receptor (PDB code: 6M0J) were downloaded from the Protein Data Bank (www.rcsb.org) in PDB format [82]. For molecular docking analysis the bound atoms were removed from selected proteins by using Biovia Discovery Studio 2019 visualizer and Autodock tool were used to add the non-polar hydrogen atoms to the receptors in a protein preparation. Finally, the structure of the receptor was saved in PDBQT format.

Grid box generation and virtual molecular docking: The binding affinity and nature of the interaction between selected ligands and the protein was analyzed by molecular docking. By using an Autodock vina software, binding energies were reported and determined in kcal/mol unit for ligand-protein. The grid box was generated by targeting the active site with a size of (x = 72.32, y = 68.31, z = 100.85) and centre of (x = -4.66, y = 16.07, z = -10.64) was set to cover the binding site for 6M0J protein and grid box with a size of (x = 51.01, y = 59.65, z = 52.382) and a centre of (x = -11.83, y = 12.45, z = 69.92) for main protease 6LU7 was adopted and the bioactive conformations were simulated [83]. Virtual molecular docking and analysis have been performed by using AutoDock Vina 1.5.6 tool. All the ligand molecules have been docked to active site of SARS-CoV-2 proteins 6LU7 and 6M0J. Finally, protein-ligand interactions were analyzed by using Biovia discovery studio visualizer [84].

***In silico* studies on SARS-COV-2 proteins**

Molecular docking: The docking analysis of all the 26 thiazole derivatives were docked successfully against the spike binding domain with ACE2 receptor (6M0J) and spike binding domain with main protease (6LU7) of SARS-CoV-2. The best dock score of compounds is thought to be a good candidate to inhibit the activity of the SARS-CoV-2. Based on their dock score all 26 compounds were ranked. By referring Table-1, it gives the list of active molecules after docking studies and the molecules having good dock score values were picked. Based on their interactions with the viral proteins of (PDB ID: 6M0J and 6LU7), the best 7 compounds were selected, among these 7 compounds THI-9a and THI-2a exhibited the best dock score with 6M0J and 6LU7 proteins and remaining compounds are also exhibited good interaction with the 6LU7 and 6M0J proteins. The docking results and interaction modes are obtained by discovery studio visualizer for evaluation of results. The best binding energy of protein-ligand interactions are listed in Table-1.

Interaction with spike binding domain with ACE2 receptor (PDB ID: 6M0J): The docking analysis of thiazole derivatives and FDA approved standard drugs containing thiazole moiety against SARS-CoV-2 spike binding domain with ACE2 receptor were analyzed and compared. All the compounds including standard drugs were found to exhibit a good interaction with SARS-CoV-2 protein (6M0J) and their interaction with the binding site of 6M0J are displayed in Fig. 14. Compound THI-9a shows a strong interaction towards receptor of 6M0J with a binding energy of -10.3 kcal/mol. It's docking mode showed its ability to form pi-alkyl bond with ARG393 amino acid residue through benzofuran ring and also conventional hydrogen bond with ASP350 *via* oxygen atom. Compound THI-26a formed the carbon hydrogen bond with TRP203 and TYR202 amino acid residues. Along with pi-alkyl, pi-donor and pi-pi-T-shaped bond with HIS195 residue through its bromine of the benzene ring and also *via* benzene ring. It also made conventional hydrogen bond with TRP203 residue through its oxygen of the benzene ring. Compound THI-11c forms a pi-alkyl and pi-sigma bond with LEU95, VAL209 and PRO565 *via* naphthalene ring and also form hydrogen bond with ALA99 and TRP203 residues *via* oxygen atom. Compound THI-2a made the carbon hydrogen bond with TRP203, ALA99 and GLU398 amino acid residues along with pi-sigma bond with ALA99 through its benzene ring. It also made alkyl bond with VAL209, PRO565 and LEU95 residues through its chlorine of the benzene ring and forms an unfavourable donor-donor bond with the TYR196 residue *via* nitrogen of the pyrazole ring. Compound THI-11b forms a 3 pi-pi-stacked interaction bond with TRP349 residue through indole ring and also form a 2 pi-cation bond *via* nitrogen of the indole ring. It also made pi-alkyl bond with ARG393 *via* thiophene rings. Compound THI-5a forms a conventional hydrogen bond with GLU564

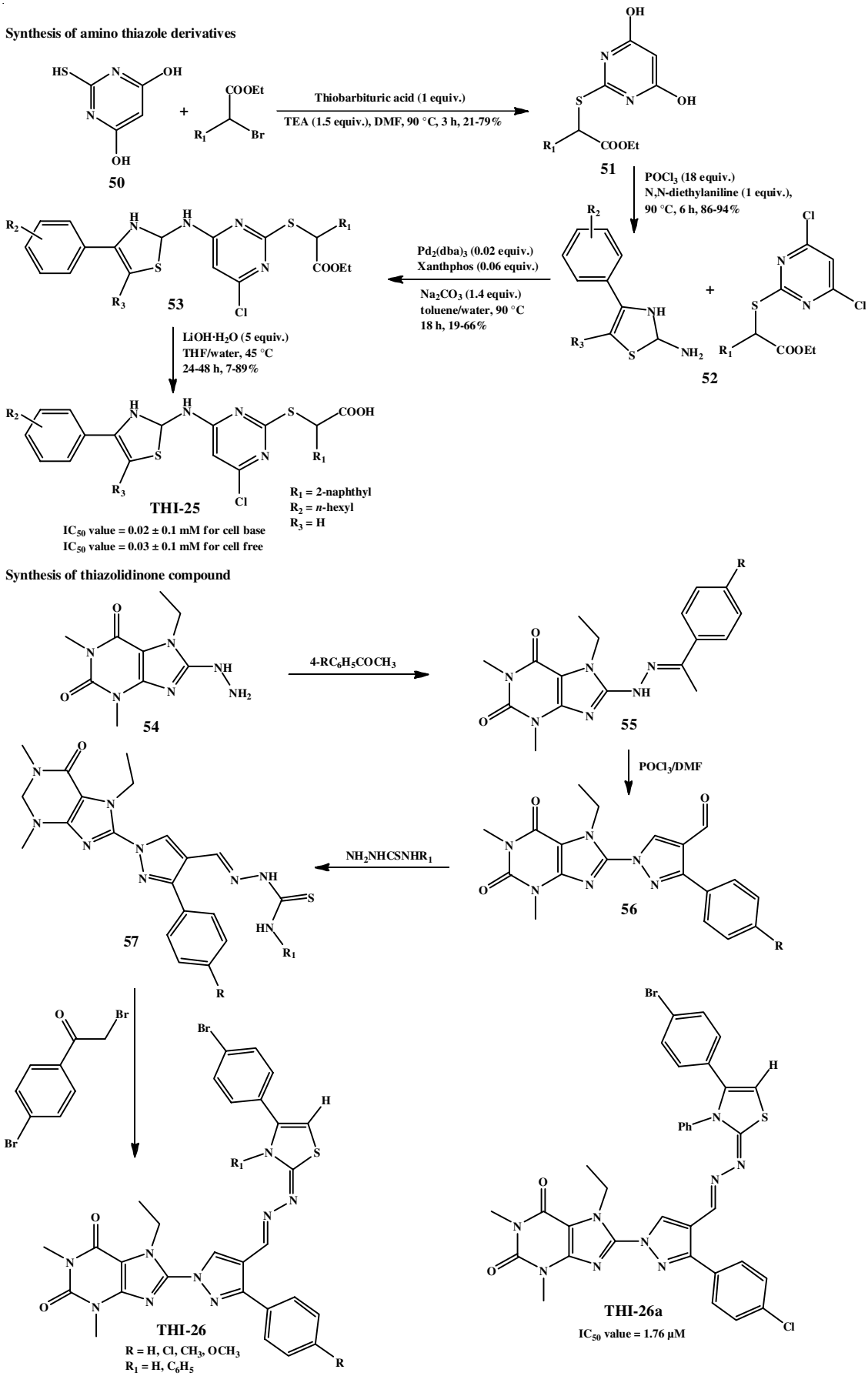
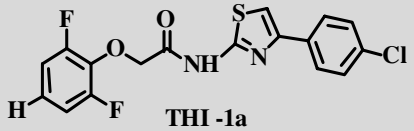
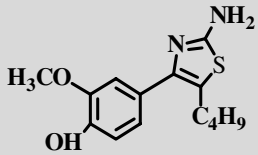
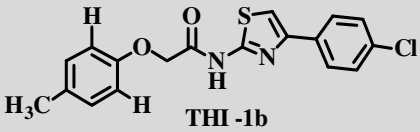
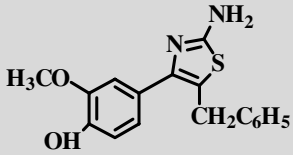
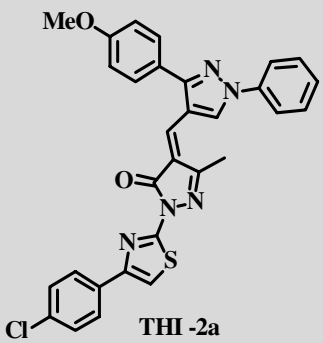
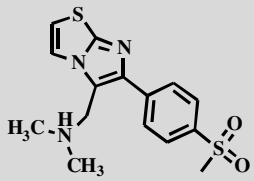
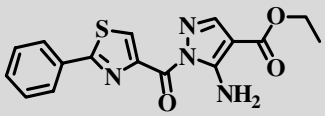
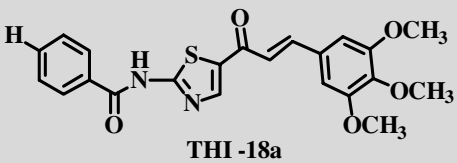
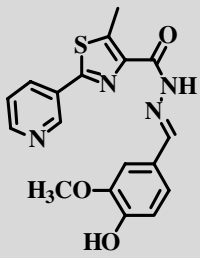
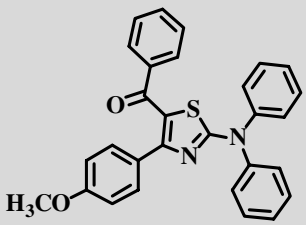
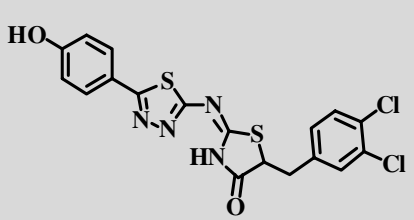
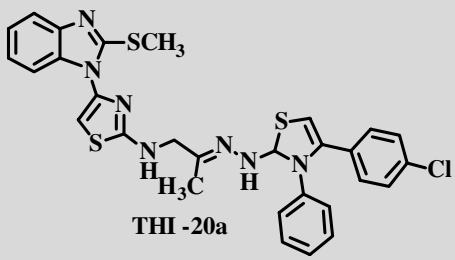
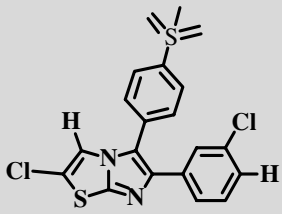
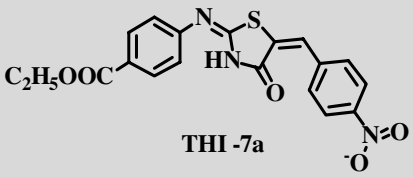
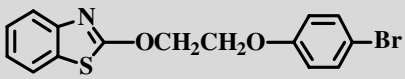
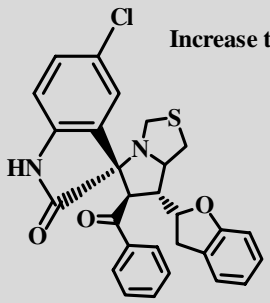
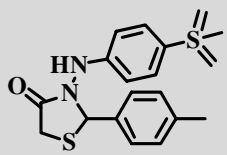
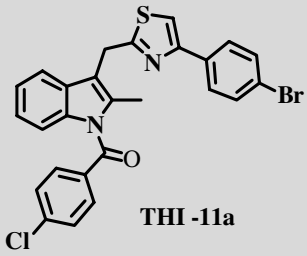
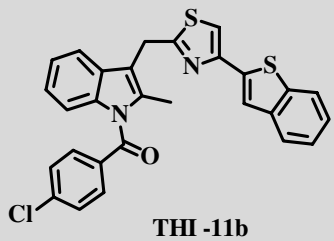
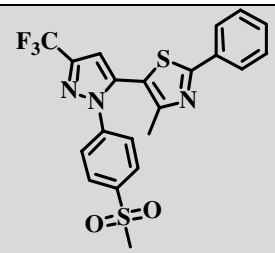
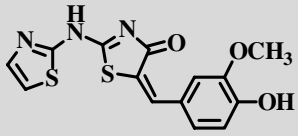
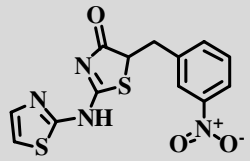
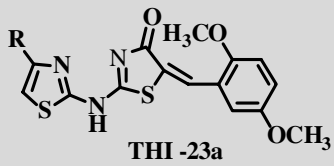
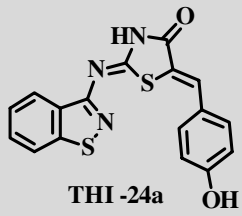
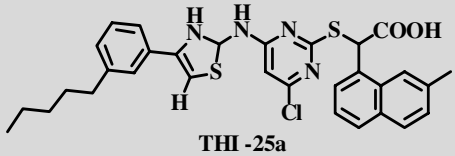
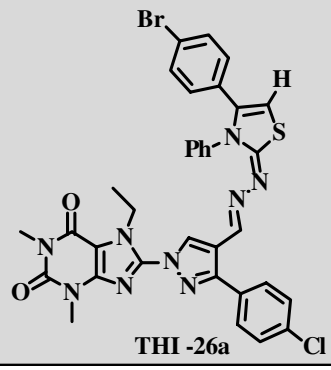


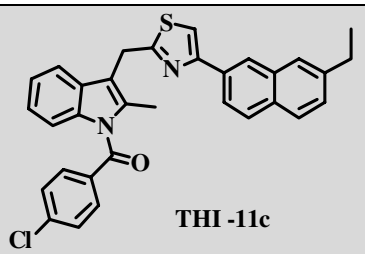
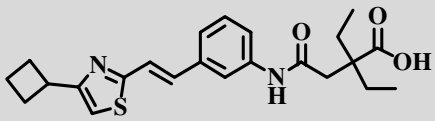
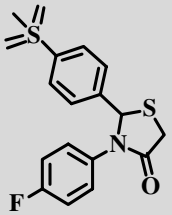
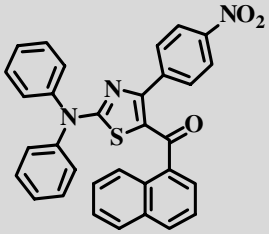
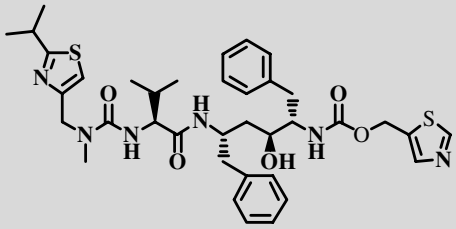
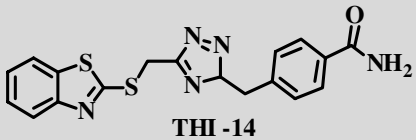
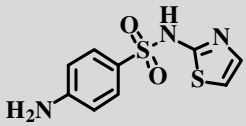
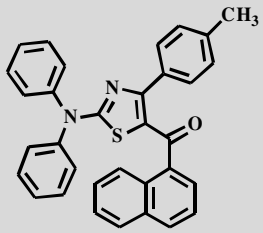
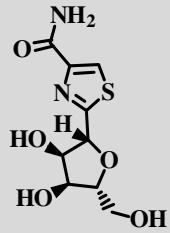
Fig. 13. Synthesis route of compound THI-25 and THI-26

TABLE-1
DOCKING SCORE OF PROTEIN-LIGAND INTERACTIONS

Compounds	Binding affinity (kcal/mol)		Compounds	Binding affinity (kcal/mol)	
	6M0J	6LU7		6M0J	6LU7
 **THI -1a**	-8.0	-7.2	 **16a**	-6.8	-6.6
 **THI -1b**	-8.0	-7.0	 **16b**	-6.8	-6.6
 **THI -2a**	-9.6	-9.2	 **THI -17** **IC_{50} value = 0.08 μM**	-1.8	-1.8
 **THI -3**	-7.6	-7.1	 **THI -18a**	-7.4	-6.5
 **THI -4a**	-7.9	-7.2	 **THI -19a**	-8.9	-8.4
 **THI -5a**	-9.1	-8.1	 **THI -20a**	-8.2	-7.4

 **THI -6a**	-8.0	-7.3
 **THI -7a**	-8.1	-6.7
 **THI -8a**	-6.5	-6.2
Increase the activity  **THI -9a**	-10.3	-8.1
 **THI -10a**	-6.9	-7.2
 **THI -11a**	-8.8	-7.4
 **THI -11b**	-9.2	-8.0

 **THI -21a**	-9.0	-7.5
 **THI -22a**	-7.8	-6.6
 **THI -22b**	-7.3	-6.7
 **THI -23a**	-6.7	-6.6
 **THI -24a**	-8.4	-7.2
 **THI -25a**	-9.1	-5.9
 **THI -26a**	-10.0	-9.9

 THI -11c	-9.7	-8.4	 Cinalukast	-7.7	-6.8
 THI -12	-7.8	-7.2	 Dasatinib	-9.5	-7.9
 THI -13	-9.1	-7.2	 Ritonavir	-8.0	-6.4
 THI -14	-8.8	-7.4	 Sulfathiazole	-6.3	-6.0
 THI -15 IC_{50} value 0.90 ± 0.064 µM	-9.3	-7.5	 Tiazofurin	-6.4	-5.9

and GLY205 residues. Compound THI-19a made the pi-alkyl bond with HIS378 residue *via* benzene ring and carbon hydrogen bond with HIS401 residue *via* oxygen atom. Standard drug molecule cinalukast made the conventional hydrogen bond with ASP350 and TYR385 amino acid residues *via* oxygen and hydrogen atom. along with pi-alkyl, pi-pi-stacked and pi-pi-T-shaped bond with ARG393, PHE390 and PHE40 residues through its benzene ring. It also made alkyl and pi-sigma bond with LEU73 and TRP69 residues through its cyclobutene and thiazole ring. Molecule dasatinid made conventional and carbon hydrogen bond with GLN98, ASN103 and TYR196 residues *via* oxygen and carbon atoms. It also forms alkyl bond VAL209 and PRO565 residues through its carbon atom along with pi-alkyl bond with LEU95 through benzene ring. Molecule ritonavir forms conventional hydrogen bond with ASP350 and ASP382 amino acids residues *via* oxygen and hydrogen atom and also pi-alkyl and pi-pi-stacked bond with ALA348 and PHE40 residues through its benzene ring. It also made pi-sulfur bond TRP69 residue *via* sulfur atom. Molecule sulfathiazole made conventional and carbon hydrogen bond with ASN210, GLU564 and GLN98 *via* oxygen, hydrogen and nitrogen atoms. It also made pi-sigma, pi-alkyl and pi-anion bond with LEU95, VAL209 and GLU208 residues *via* benzene and thiazole ring. Molecule thiazofurin made conventional and carbon hydrogen bond with LYS417, GLU23, ALA475 and ASP30 residues *via* oxygen, hydrogen and carbon atoms. It also made pi-donor bond with TYR473 residue *via* thiazole ring. Compounds THI-27a, THI-11c, THI-2a, THI-11b, THI-5a, THI-19a and standard drug molecules cinalukast, dasatinid, ritonavir, sulfathiazole and tiazofurin shows good binding with spike binding domain with ACE2 receptor of SARS-Cov-2 at the active site with the binding energies of -10.0 kcal/mol, -9.7 kcal/mol, -9.6 kcal/mol, -9.2

kcal/mol, -9.1 kcal/mol, -8.9 kcal/mol and -7.7 kcal/mol, -9.5 kcal/mol, -8.0 kcal/mol, -6.3 kcal/mol and -6.4 kcal/mol, respectively. The detailed interactions of all the 7 compounds and standard drugs are shown in Fig. 14, bond length and docking energies are depicted in Table-2. Thus, it clearly indicates that compound THI-9a interacted well and shows good inhibiting activity against spike binding domain with ACE2 receptor of SARS-CoV-2 over standard drug molecules.

Interaction with spike binding domain with main protease (PDB ID: 6LU7): The docking analysis of thiazole derivatives and FDA approved standard drugs containing thiazole moiety against SARS-CoV-2 spike binding domain with main protease were analyzed. All the compounds including standard drugs were found to be exhibit a good interaction with SARS-CoV-2 protein (6LU7) and their interaction with the binding site of 6LU7 are displayed in Fig. 15. Compound THI-2a exhibit a strong interaction towards receptor of 6LU7 with a binding energy of -9.2 kcal/mol. Herein, THI-2a has been surrounded with HIS163, MET165, PRO168, CYS145, GLU166 and HIS41 amino acid residues of the active site of the receptor 6LU7. It also forms a pi-alkyl bond with HIS163 and MET165 amino acid residues *via* benzene ring and also it forms an alkyl

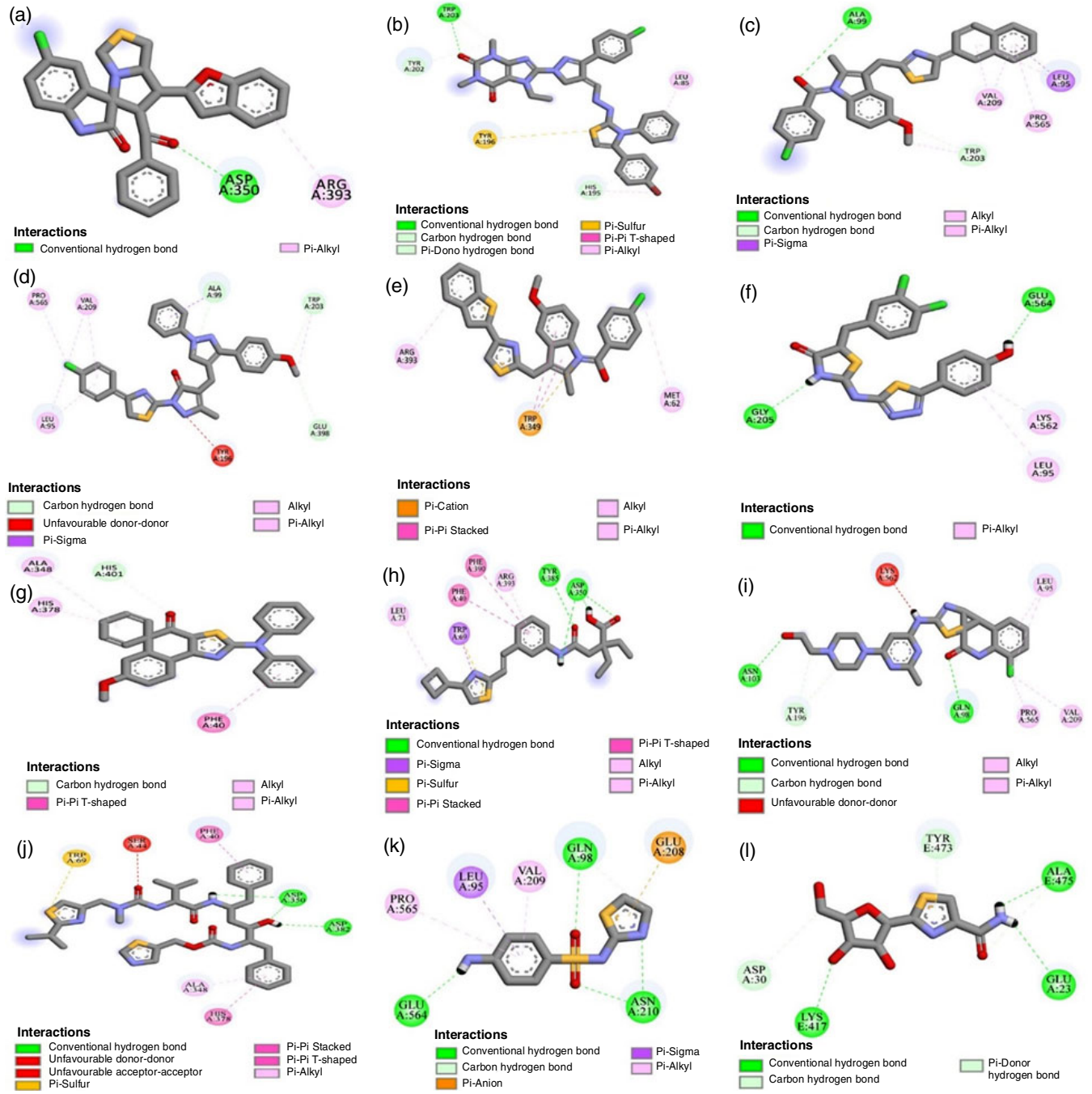


Fig. 14. 2-D protein-ligand interaction of 6M0J with (a) THI-9a, (b) THI-26a, (c) THI-11c, (d) THI-2a, (e) THI-11b, (f) THI-5a, (g) THI-19a, (h) cinalukast, (i) dasatinid, (j) ritonavir, (k) sulfathiazole, (l) tiazofurin

TABLE-2
INTERACTION BETWEEN LIGANDS AND 6M0J VIRAL PROTEIN

Compound	Protein (amino acids)	Ligand	Interaction type	Distance (Å)
9a	ASP350	Oxygen	Conventional	1.84
	ARG393	π of Benzofuran	π-Alkyl	4.63
26a	HIS195	π of Benzene	π-Donor	2.81
	TRP203	Oxygen	Conventional	3.02
	TRP203	Carbon	Carbon	3.37
	TYR202	Carbon	Carbon	3.80
	HIS195	π of Benzene	π-π-T-Shaped	4.67
	HIS195	π of Bromine	π-Alkyl	4.67
11c	ALA99	Oxygen	Conventional	3.20
	LEU95	π of Naphthalene	π-Sigma	3.45
	TRP203	Oxygen	Carbon	3.46
	VAL209	π of Naphthalene	π-Alkyl	4.07
	TRP203	π of Carbon	π-Alkyl	4.87
	PRO565	π of Naphthalene	π-Alkyl	4.93
2a	TYR196	Nitrogen	Donor-Donor	2.54
	ALA99	π of Benzene	π-Sigma	3.46
	TRP203	Carbon	Carbon	3.46
	ALA99	Carbon	Carbon	3.64
	TRP203	Carbon	Carbon	3.67
	GLU398	Carbon	Carbon	3.72
	VAL209	Chlorine	Alkyl	3.98
	PRO565	Chlorine	Alkyl	4.29
	LEU95	Chlorine	Alkyl	4.58
		π of Hydrogen	π-Alkyl	4.74
11b	TRP349	π of Indole	π-π-Stacked	3.85
	TRP349	π of Nitrogen	π-Cation	3.98
	TRP349	π of Indole	π-π-Stacked	4.35
	TRP349	π of Indole	π-π-Stacked	4.37
	TRP349	π of Nitrogen	π-Cation	4.50
	ARG393	π of Benzo-thiophene	π-Alkyl	4.80
5a	GLU564	Hydrogen	Conventional	2.05
	GLY205	Hydrogen	Conventional	2.21
19a	HIS401	Oxygen	Carbon	3.38
	HIS378	π of Benzene	π-Alkyl	3.78
Cinalukast	ASP350	Oxygen	Conventional	1.89
	TYR385	Oxygen	Conventional	2.19
	ASP350	Hydrogen	Conventional	2.40
	ASP350	Hydrogen	Conventional	2.60
	TRP69	π of Thiazole	π-Sigma	3.76
	ARG393	π of Benzene	π-Alkyl	4.56
	LEU73	π of cyclobutane	Alkyl	4.77
	PHE40	π of Benzene	π-π-T-Shaped	4.93
	PHE390	π of Benzene	π-π-Stacked	4.97
Dasatinid	ASN103	Oxygen	Conventional	2.59
	GLN98	Oxygen	Conventional	2.74
	VAL209	Carbon	Alkyl	3.46
	TYR196	Carbon	Carbon	3.51
	TYR196	Carbon	Carbon	3.65
	PRO565	Carbon	Alkyl	3.99
	LEU95	π of Benzene	π-Alkyl	4.92
Ritonavir	ASP350	Oxygen	Conventional	2.34
	ASP382	Hydrogen	Conventional	2.60
	ASP350	Oxygen	Conventional	2.68
	PHE40	π of Benzene	π-π-Stacked	4.45
	ALA348	π of Benzene	π-Alkyl	4.73
	TRP69	π of Sulfur	π-Sulfur	4.87

Sulfathiazole	ASN210	Oxygen	Conventional	1.89
	GLU564	Hydrogen	Conventional	2.07
	ASN210	Nitrogen	Conventional	2.11
	GLN98	Oxygen	Conventional	2.24
	GLN98	Carbon	Carbon	3.17
	GLU208	π of Thiazole	π-Anion	3.54
	LEU95	π of Benzene	π-Sigma	3.68
	VAL209	π of Benzene	π-Alkyl	4.48
Tiazofurin	ALA475	Hydrogen	Conventional	2.14
	LYS417	Oxygen	Conventional	2.25
	TYR473	π of Thiazole	π-Donor	2.76
	GLU23	Hydrogen	Conventional	2.78
	ASP30	Carbon	Carbon	3.32
	ALA475	Oxygen	Carbon	3.44

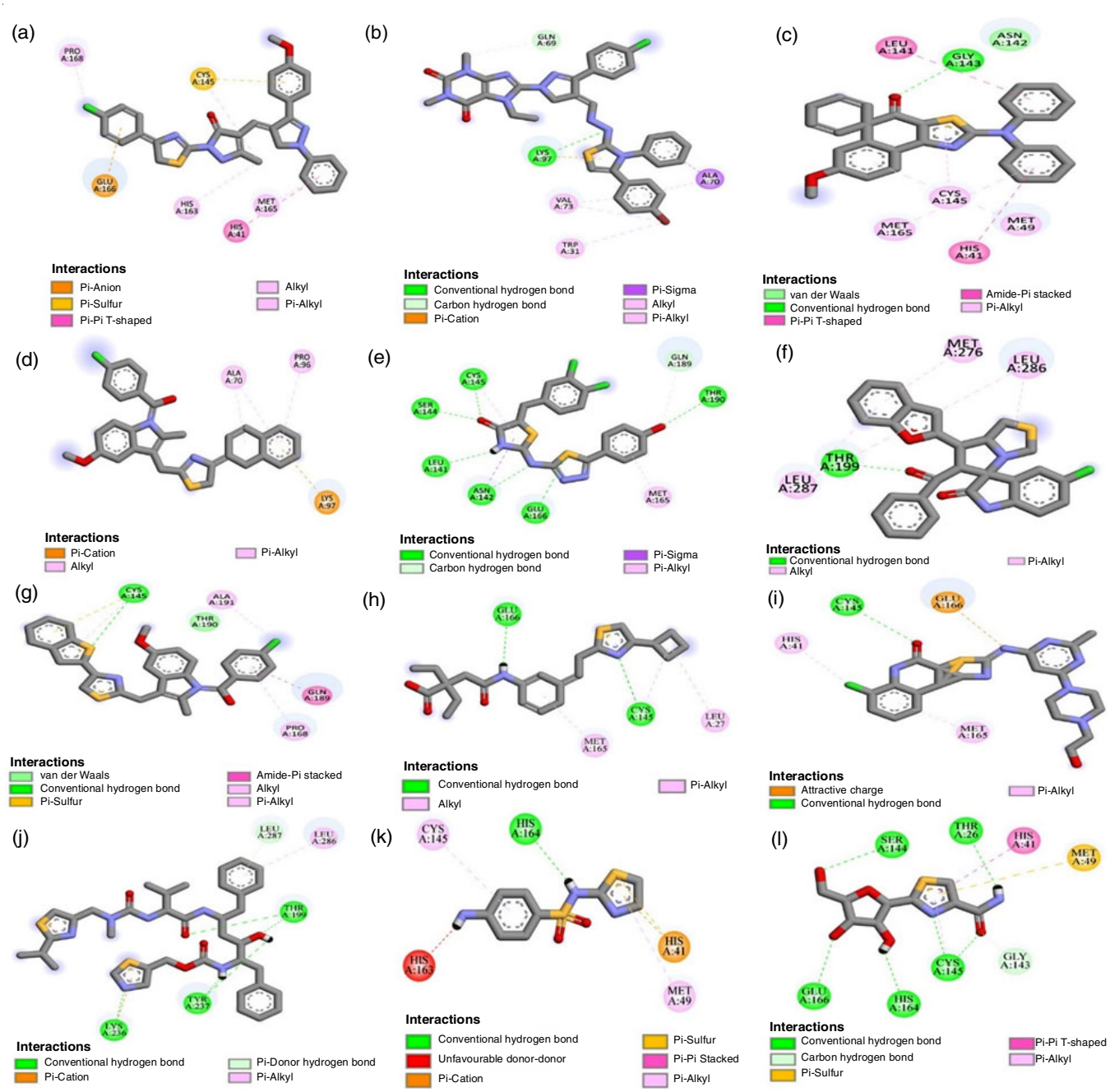


Fig. 15. 2-D protein-ligand interaction of 6LU7 with (a) THI-2a, (b) THI-26a, (c) THI-11c, (d) THI-19a, (e) THI-5a, (f) THI-9a, (g) THI-11b, (h) cinalukast, (i) dasatinid, (j) ritonavir, (k) sulfathiazole, (l) tiazofurin

bond with PRO168 and CYS145 through its chlorine of the benzene ring and carbon atom along with pi-anion and pi-pi-T-shaped bond with GLU166 and HIS41 *via* benzene ring. Compound THI-26a forms a pi-alkyl and alkyl bond with VAL73 residue through its bromine of the benzene ring and also along *via* benzene ring. Compound THI-11c forms a alkyl bond with ALA70 through naphthalene ring and pi-cation bond with LYS97 amino acid residue *via* benzene ring. Compound THI-19a forms conventional hydrogen bond with GLY143 residue *via* oxygen atom and amide-pi-stacked bond with LEU141 residue through benzene ring. Compound THI-5a exhibit a conventional hydrogen bond with CYS145, SER144 and THR-190 amino acid residues *via* oxygen atom along conventional hydrogen bond with GLU166 residue through its sulfur of its thiazole ring. Along with pi-sigma and conventional hydrogen bond with ASN142 residue through its thiazole ring and nitrogen atom. Compound THI-9a forms an alkyl bond with LEU286 residue *via* thiazole ring as well as conventional hydrogen bond with THR199 residue *via* oxygen atom. Compound THI-11b forms a pi-alkyl bond with LYS145 residue through thiazole ring and amide-pi-stacked bond with GLN189 residue *via* benzene ring and also conventional hydrogen bond with ARG40 amino acid residue *via* oxygen atom. Standard drug molecule cinalukast made the conventional hydrogen bond with CYS145 and GLU166 residues *via* nitrogen and oxygen atoms. It also made alkyl and pi-alkyl bond with LEU27, MET165 and CYS145 residues through its cyclobutane, benzene and thiazole rings. The molecule dasatinid made conventional hydrogen bond with CYS145 residue *via* oxygen atom along with pi-sigma and pi-alkyl bond with HIS41 and MET165 through its carbon and benzene ring. The molecule ritonavir forms conventional hydrogen bond with THR199, LYS236 and TYR237 residues *via* oxygen, nitrogen and hydrogen atoms. It also made pi-cation, pi-donor and pi-alkyl bond with LYS236, LEU287 and LEU286 through its thiazole and benzene rings. The molecule sulfathiazole made conventional hydrogen bond with HIS164 residue *via* hydrogen atom and also made pi-cation and pi-pi-stacked bond with HIS41 and MET49 residues *via* thiazole ring. It also made pi-alkyl and pi-sulfur bond with CYS145 and HIS41 residues through its benzene ring and sulfur atom and also forms an unfavourable donor-donor bond with the HIS163 residue *via* hydrogen atom. The molecule tiazofurin made a conventional hydrogen bond with SER144, THR26, GLU166, HIS164 and CYS145 amino acids residue *via* oxygen, hydrogen and nitrogen atoms and also forms an carbon hydrogen bond and pi-alkyl bond with GLY143 and CYS145 residues *via* carbon atom and benzene ring. Compounds THI-27a, THI-11c, THI-20a, THI-5a, THI-9a, THI-11b and standard drug molecules cinalukast, dasatinid, ritonavir, sulfathiazole and tiazofurin shows good binding with spike binding domain with main protease of SARS-CoV-2 at the active site with the binding energies of -9.1 kcal/mol, -8.4 kcal/mol, -8.4 kcal/mol, -8.1 kcal/mol, -8.1 kcal/mol, -8 kcal/mol and -6.8 kcal/mol, -7.9 kcal/mol, -6.4 kcal/mol, -6.0 kcal/mol, -5.9 kcal/mol, respectively. The detailed interactions of all the 7 compounds and standard drugs are shown in Fig. 15, bond length and docking energies are depicted in Table-3. Thus, it clearly indicates that compound THI-2a interacted well and shows good inhibiting activity against spike binding domain with main protease of SARS-CoV-2 over standard drug molecules.

TABLE-3
INTERACTION BETWEEN LIGANDS AND 6LU7 VIRAL PROTEIN

Compound	Protein (amino acids)	Ligand	Interaction type	Distance (Å)
2a	PRO168	Chlorine	Alkyl	3.94
	GLU166	π of Benzene	π-Anion	4.12
	CYS145	Carbon	Alkyl	4.14
	HIS163	π of Carbon	π-Alkyl	4.50
	MET165	π of Benzene	π-Alkyl	4.66
	HIS41	π of Benzene	π-π-T-Shaped	4.85
26a	LYS97	Nitrogen	Conventional	2.24
	LYS97	π of Thiazole	π-Cation, π-Donor	3.30
	GLN69	Carbon	Carbon	3.38
	VAL73	π of Benzene	π-Alkyl	4.21
	VAL73	Bromine	Alkyl	4.46
11c	ALA70	Naphthalene	Alkyl	4.15
	LYS97	π of Benzene	π-Cation	4.38
19a	GLY143	Oxygen	Conventional	2.70
	LEU141	π of Benzene	Amide-π-Stacked	4.83
5a	CYS145	Oxygen	Conventional	2.31
	SER144	Oxygen	Conventional	2.38
	LEU141	Hydrogen	Conventional	2.50
	GLU166	Sulfur	Conventional	2.68
	THR190	Oxygen	Conventional	2.85
	GLN189	Oxygen	Carbon	3.18
	ASN142	Nitrogen	Conventional	3.30
	ASN142	π of Thiazole	π-Sigma	4.00

9a	THR199	Oxygen	Conventional	1.87
	LEU286	Thiazole	Alkyl	4.98
	CYS145	π of Thiazole	π-Alkyl	4.68
	ARG40	Oxygen	Conventional	1.99
	GLN189	π of Benzene	Amide-π-Stacked	4.50
Cinalukast	GLU166	Hydrogen	Conventional	2.62
	CYS145	Nitrogen	Conventional	3.67
	MET165	Benzene	Alkyl	4.29
	CYS145	Thiazole	Alkyl	4.72
	CYS145	π of Thiazole	π-Alkyl	4.79
	LEU27	Cyclobutane	Alkyl	4.92
Dasatinid	HIS41	π of Carbon	π-Sigma	3.54
	CYS145	Oxygen	Conventional	3.69
	MET165	π of Benzene	π-Alkyl	4.33
Ritonavir	TYR237	Hydrogen	Conventional	1.82
	TYR237	Hydrogen	Conventional	2.56
	LYS236	Nitrogen	Conventional	2.73
	THR199	Oxygen	Conventional	2.68
	THR199	Oxygen	Conventional	2.86
	LEU287	π of Benzene	π-Donor	3.13
	LYS236	π of Thiazole	π-Cation	3.74
	LEU286	π of Benzene	π-Alkyl	4.91
Sulfathiazole	HIS163	Hydrogen	Donor-Donor	1.74
	HIS164	Hydrogen	Conventional	2.43
	MET49	π of Thiazole	π-π-Stacked	3.68
	HIS41	π of Sulfur	π-Sulfur	4.03
	HIS41	π of Thiazole	π-Cation	4.0
	CYS145	π of Benzene	π-Alkyl	4.91
Tiazofurin	THR26	Hydrogen	Conventional	2.24
	SER144	Oxygen	Conventional	2.33
	HIS164	Hydrogen	Conventional	2.38
	GLU166	Oxygen	Conventional	2.71
	CYS145	Oxygen	Conventional	2.90
	GLY143	Oxygen	Carbon	3.34
	CYS145	Nitrogen	Conventional	3.64
	CYS145	π of Thiazole	π-Alkyl	4.47

Conclusion

In this review, the study was carried to identify potential anti-inflammatory agents against SARS-CoV-2 of compounds containing thiazole rings. The core thiazole heterocyclic system could utilize a promising scaffold for the development of an effective anti-inflammatory drug candidate. Additionally, *in silico* studies like molecular docking analysis were carried out to investigate potentially inhibitory compounds against covid-19 proteins. The potent 26 thiazole derivatives exhibit good interactions with covid-19 proteins. Molecular docking studies predict that 7 active compounds showed a good binding affinity with SARS-CoV-2 proteins (6M0J and 6LU7). Among these, compound THI-9a gives excellent binding affinity with binding energies of -10.3 and -8.1 kcal/mol for 6M0J and 6LU7 proteins. Based on the comparison with thiazole containing FDA-approved drugs like sulfathiazole, ritonavir, dasatinib, tiazofurin and cinalukast. Compound THI-9a showed good interaction with target proteins. From the revealed information, it is clear that thiazole derivatives can be potential targets for future research in the field of COX/LOX inhibitors to discover novel, more effective and safer anti-inflammatory drugs.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. M. Pal, G. Berhanu, C. Desalegn and V. Kandi, *Cureus*, **12**, e7423 (2020); https://doi.org/10.7759/cureus.7423
2. A.A.T. Naqvi, K. Fatima, T. Mohammad, U. Fatima, I.K. Singh, A. Singh, S.M. Atif, G. Hariprasad, G.M. Hasan and M.I. Hassan, *Biochim. Biophys. Acta-Mol. basis Dis.*, **1866**, 165878 (2020); https://doi.org/10.1016/j.bbadis.2020.165878
3. L. Pang, C.Y. Liu, G.H. Gong and Z.S. Quan, *Acta Pharm. Sin. B*, **10**, 628 (2020); https://doi.org/10.1016/j.apsb.2019.09.002
4. P. Pathak, P.K. Shukla, V. Naumovich, M. Grishina, V. Potemkin and A. Verma, *Synth. Commun.*, **49**, 2725 (2019); https://doi.org/10.1080/00397911.2019.1643485

5. S.M. Wang, G.F. Zha, K.P. Rakesh, N. Darshini, T. Shubhavathi, H.K. Vivek, N. Mallesha and H.L. Qin, *MedChemComm*, **8**, 1173 (2017); https://doi.org/10.1039/C7MD00111H
6. S. Sinha, M. Doble and S.L. Manju, *Eur. J. Med. Chem.*, **158**, 34 (2018); https://doi.org/10.1016/j.ejmech.2018.08.098
7. Z. Chulovska, T. Chaban, I. Drapak, V. Matiychuk, I. Chaban and I. Nektegaev, *Biointerface Res. Appl. Chem.*, **11**, 8009 (2021); https://doi.org/10.33263/BRIAC111.80098017
8. Y. Li, J. Geng, Y. Liu, S. Yu and G. Zhao, *ChemMedChem*, **8**, 27 (2013); https://doi.org/10.1002/cmdc.201200355
9. I.P. Singh, S. Gupta and S. Kumar, *Med. Chem.*, **16**, 4 (2020); https://doi.org/10.2174/1573406415666190614101253
10. R. Mishra, P.K. Sharma, P.K. Verma, I. Tomer, G. Mathur and P.K. Dhakad, *J. Heterocycl. Chem.*, **54**, 2103 (2017); https://doi.org/10.1002/jhet.2827
11. A. Chowdhury, S. Patel, A. Sharma, A. Das, P. Meshram and A. Shard, *Chem. Heterocycl. Compd.*, **56**, 455 (2020); https://doi.org/10.1007/s10593-020-02680-x
12. A. Chawla, H. Kaur, P. Chawla and U.S. Baghel, *J. Glob. Trends Pharm. Sci.*, **5**, 1641 (2014).
13. S. Jubie, B. Gowramma, K.M. Nitin, N. Jawahar, R. Kalirajan, S. Gomathy, S. Sankar and K. Elango, *Int. J. Pharm. Sci.*, **1**, 32 (2009).
14. M. Gopal, B. Padmashali, Y.N. Manohara and B.M. Gurupadayya, *Indian J. Pharm. Sci.*, **70**, 572 (2008); https://doi.org/10.4103/0250-474X.45393
15. K. Z. Laczkowski, A. Biernasiuk, A. Baranowska-Laczkowska, K. Misiura, A. Malm, T. Plech and A. Paneth, *Med. Chem.*, **12**, 553 (2016); https://doi.org/10.2174/1573406412666160201121310
16. A. Bishayee, R. Karmakar, A. Mandal, S.N. Kundu and M. Chatterjee, *Eur. J. Cancer Prev.*, **6**, 58 (1997); https://doi.org/10.1097/00008469-199702000-00010
17. K.D. Hargrave, F.K. Hess and J.T. Oliver, *J. Med. Chem.*, **26**, 1158 (1983); https://doi.org/10.1021/jm00362a014
18. W.C. Patt, H.W. Hamilton, M.D. Taylor, M.J. Ryan, J.R. Taylor Jr., C.J.C. Connolly, A.M. Doherty, S.R. Klutchko and I. Sircar, *J. Med. Chem.*, **35**, 2562 (1992); https://doi.org/10.1021/jm00092a006
19. Z. A. Muhammad, G. S. Masaret, M. M. Amin, M. A. Abdallah and T. A. Farghaly, *Med. Chem.*, **13**, 226 (2017); https://doi.org/10.2174/1573406412666160920091146
20. H.N. Karade, B.N. Acharya, M. Sathe and M.P. Kaushik, *Med. Chem. Res.*, **17**, 19 (2008); https://doi.org/10.1007/s00044-008-9089-0
21. S. Vengurlekar, S. Prachand, S. Jain and R. Gupta, *Int. J. Pharm. Life Sci.*, **5**, 3526 (2014).
22. S.R. Pattan, N.S. Dighe, S.A. Nirmal, A.N. Merekar, R.B. Laware and H.V. Shinde, *Asian J. Res. Chem.*, **2**, 196 (2009).
23. A. Leoni, A. Locatelli, R. Morigi and M. Rambaldi, *Expert Opin. Ther. Pat.*, **24**, 759 (2014); https://doi.org/10.1517/13543776.2014.910196
24. A.A. Nadaf, D.A. Barretto, M.S. Najare, S. Mantur, M. Garbhagudi, S. Gaonkar, S. Joshi and I.A.M. Khazi, *Med. Chem. Res.*, **29**, 442 (2020); https://doi.org/10.1007/s00044-019-02495-2
25. O.I. El-Sabbagh, M.M. Baraka, S.M. Ibrahim, C. Pannecouque, G. Andrei, R. Snoeck, J. Balzarini and A.A. Rashad, *Eur. J. Med. Chem.*, **44**, 3746 (2009); https://doi.org/10.1016/j.ejmech.2009.03.038
26. K.M. Dawood, T.M. Eldebss, H.S. El-Zahabi and M.H. Yousef, *Eur. J. Med. Chem.*, **102**, 266 (2015); https://doi.org/10.1016/j.ejmech.2015.08.005
27. J.V.J Silva Júnior T.R.R Lopes, P.S.B de Oliveira, R. Weiblen and E.F. Flores, *Viral Immunol.*, **34**, 358 (2020); https://doi.org/10.1089/vim.2020.0059
28. D.S. Hui, E.I. Azhar, Y.J. Kim, Z.A. Memish, M.D. Oh and A. Zumla, *Lancet Infect. Dis.*, **18**, e217 (2018); https://doi.org/10.1016/S1473-3099(18)30127-0
29. S. Anuradha, *J. Int. Med. Sci. Acad.*, **27**, 191 (2014).
30. E. De Clercq, *J. Pharmacol. Exp. Ther.*, **297**, 1 (2001).
31. F. Baldanti, M.R. Underwood, S.C. Stanat, K.K. Biron, S. Chou, A. Sarasini, E. Silini and G. Gerna, *J. Virol.*, **70**, 1390 (1996); https://doi.org/10.1128/jvi.70.3.1390-1395.1996
32. M.G. Ghany and E.C. Doo, *Hepatology*, **49(S5)**, S174 (2009); https://doi.org/10.1002/hep.22900
33. C. Marzolini, A. Telenti, L.A. Decosterd, G. Greub, J. Biollaz and T. Buclin, *AIDS*, **15**, 71 (2001); https://doi.org/10.1097/00002030-200101050-00011
34. A. Ammassari, R. Murri, P. Pezzotti, M.P. Trotta, L. Ravasio, P. De Longis, L. Caputo, P. Narciso, S. Pauluzzi, G. Carosi, S. Nappa, P. Piano, C.M. Izzo, M. Lichtner, G. Rezza, A.A. Monforte, G. Ippolito, M. Moroni, A.W. Wu and A. Antinori, *J. Acquir. Immune Defic. Syndr.*, **28**, 445 (2001); https://doi.org/10.1097/00042560-200112150-00006
35. E. Ewers, S. Anisowicz, M. Washington, W. Agee, B. Swierczewski, T. Ferguson, M. Burnett, S. Seronello, M. Nahid, O. Serichantalergs, W. Lurchachaiwong, J. Barnhill and V. Ngauy, *Open Forum Infect. Dis.*, **3(suppl_1)**, 1201 (2016); https://doi.org/10.1093/ofid/ofw172.904
36. K.E. Hanson and S. Swaminathan, *Future Microbiol.*, **10**, 1545 (2015); https://doi.org/10.2217/fmb.15.82
37. I. Astuti and Ysrafil, *Diabetes Metab. Syndr.*, **14**, 407 (2020); https://doi.org/10.1016/j.dsx.2020.04.020
38. M.A. Shereen, S. Khan, A. Kazmi, N. Bashir and R. Siddique, *J. Adv. Res.*, **24**, 91 (2020); https://doi.org/10.1016/j.jare.2020.03.005
39. M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, T.S. Schiergens, G. Herrler, N.-H. Wu, A. Nitsche, M.A. Müller, C. Drosten and S. Pöhlmann, *Cell*, **181**, 271 (2020); https://doi.org/10.1016/j.cell.2020.02.052
40. Y. Wan, J. Shang and R. Graham, *J. Virol.*, **94**, e00127 (2020); https://doi.org/10.1128/JVI.00127-20
41. W. Sungnak, N. Huang, C. Bécavin, M. Berg, M. Litvinukova, R. Queen, C. Talavera-López, H. Maatz, D. Reichart, F. Sampaziotis, K.B. Worlock, M. Yoshida and J.L. Barnes, *Nat. Med.*, **26**, 681 (2020); https://doi.org/10.1038/s41591-020-0868-6
42. A. Reyfman, J.M. Walter, N. Joshi, K.R. Anekalla, A.C. McQuattie-Pimentel, S. Chiu, R. Fernandez, M. Akbarpour, C.-I. Chen, Z. Ren, R. Verma, H. Abdala-Valencia, K. Nam, M. Chi, S.H. Han, F.J. Gonzalez-Gonzalez, S. Soberanes, S. Watanabe, K.J.N. Williams, A.S. Flozak, T.T. Nicholson, V.K. Morgan, D.R. Winter, M. Hinchcliff, C.L. Hrusch, R.D. Guzy, C.A. Bonham, A.I. Sperling, R. Bag, R.B. Hamanaka, G.M. Mutlu, A.V. Yeldandi, S.A. Marshall, A. Shilatifard, L.A.N. Amaral, H. Perlman, J.I. Sznajder, A.C. Argento, C.T. Gillespie, J. Dematte, M. Jain, B.D. Singer, K.M. Ridge, A.P. Lam, A. Bharat, S.M. Bhorade, C.J. Gottardi, G.R.S. Budinger and A.V. Misharin, *Am. J. Respir. Crit. Care Med.*, **199**, 1517 (2019); https://doi.org/10.1164/rccm.201712-2410OC
43. R.J. Mason, *Eur. Respir. J.*, **55**, 2000607 (2020); https://doi.org/10.1183/13993003.00607-2020
44. A.S. Hancock, C.J. Stairiker, A.C. Boesteanu, E. Monzón-Casanova, S. Lukasiak, Y.M. Mueller, A.P. Stubbs, A. Garcia-Sastre, M. Turner and P.D. Katsikis, *J. Virol.*, **92**, e01325 (2018); https://doi.org/10.1128/JVI.01325-18
45. N.L.-S. Tang, P.K.-S. Chan, C.-K. Wong, K.-F. To, A.K.-L. Wu, Y.-M. Sung, D.S.-C. Hui, J.J.-Y. Sung and C.W.-K. Lam, *Clin. Chem.*, **51**, 2333 (2005); https://doi.org/10.1373/clinchem.2005.054460
46. M. Fagyas, A. Kertész, I.M. Siket, V. Bánhegyi, B. Kracskó, A. Szegedi, M. Szokol, G. Vajda, I. Rácz, H. Gulyás, N. Szkibák, V. Rácz, Z. Csanádi, Z. Papp, A. Tóth and S. Sipka, *Geroscience*, **43**, 19 (2021); https://doi.org/10.1007/s11357-020-00300-2
47. J. Braciale and Y.S. Hahn, *Immunol. Rev.*, **255**, 5 (2013); https://doi.org/10.1111/imr.12109
48. M.R. Thompson, J.J. Kaminski, E.A. Kurt-Jones and K.A. Fitzgerald, *Viruses*, **3**, 920 (2011); https://doi.org/10.3390/v3060920
49. N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, J. Xia, T. Yu, X. Zhang and L. Zhang, *Lancet*, **395**, 507 (2020); https://doi.org/10.1016/S0140-6736(20)30211-7
50. C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang and B. Cao, *Lancet*, **395**, 497 (2020); https://doi.org/10.1016/S0140-6736(20)30183-5

51. C.C. Lai, T.P. Shih, W.C. Ko, H.J. Tang and P.R. Hsueh, *Int. J. Antimicrob. Agents*, **55**, 105924 (2020); https://doi.org/10.1016/j.ijantimicag.2020.105924
52. R.C. Langenbach, C. Loftin, C. Lee and H. Tiano, *Biochem. Pharmacol.*, **58**, 1237 (1999); https://doi.org/10.1016/S0006-2952(99)00158-6
53. K. Gudis and C. Sakamoto, *Dig. Dis. Sci.*, **50(Suppl. 1)**, S16 (2005); https://doi.org/10.1007/s10620-005-2802-7
54. W.L. Smith, D.L. DeWitt and R.M. Garavito, *Annu. Rev. Biochem.*, **69**, 145 (2000); https://doi.org/10.1146/annurev.biochem.69.1.145
55. W.A. van der Donk, A.L. Tsai and R.J. Kulmacz, *Biochemistry*, **41**, 15451 (2002); https://doi.org/10.1021/bi026938h
56. L.H. Heckmann, R.M. Sibly, M.J. Timmermans and A. Callaghan, *Front. Zool.*, **5**, 11 (2008); https://doi.org/10.1186/1742-9994-5-11
57. H.A. Khamees, Y.H.E. Mohammed, S. Ananda, F.H. Al-Ostoot, Y. Sangappa, S. Alghamdi, S.A. Khanum and M. Madegowda, *J. Mol. Struct.*, **1199**, 127024 (2020); https://doi.org/10.1016/j.molstruc.2019.127024
58. R.D. Kamble, R.J. Meshram, S.V. Hese, R.A. More, S.S. Kamble, R.N. Gacche and B.S. Dawane, *Comput. Biol. Chem.*, **61**, 86 (2016); https://doi.org/10.1016/j.compbiolchem.2016.01.007
59. S.N. Thore, S.V. Gupta and K.G. Baheti, *Med. Chem. Res.*, **22**, 3802 (2013); https://doi.org/10.1007/s00044-012-0382-6
60. V. Kamat, R. Santosh, B. Poojary, S.P. Nayak, M. Sankaranarayanan, S. Faheem, S. Khanapure, D.A. Barretto, B.K. Kumar and S.K. Vootla, *ACS Omega*, **5**, 25228 (2020); https://doi.org/10.1021/acsomega.0c03386
61. Y.M. Omar, H.H. Abdu-Allah and S.G. Abdel-Moty, *Bioorg. Chem.*, **80**, 461 (2018); https://doi.org/10.1016/j.bioorg.2018.06.036
62. M. Thérien, C. Brideau, C.C. Chan, W.A. Cromlish, J.Y. Gauthier, R. Gordon, G. Greig, S. Kargman, C.K. Lau, Y. Leblanc, C.-S. Li, G.P. O'Neill, D. Riendeau, P. Roy, Z. Wang, L. Xu and P. Prasit, *Bioorg. Med. Chem. Lett.*, **7**, 47 (1997); https://doi.org/10.1016/S0960-894X(96)00580-X
63. M.A. Abdelgawad, R.B. Bakr, A. El-Gendy, G.M. Kamel, A.A. Azouz and S.N.A. Bukhari, *Future Med. Chem.*, **9**, 1899 (2017); https://doi.org/10.4155/fmc-2017-0115
64. L.Y. He, S.S. Zhang, D.X. Peng, L.P. Guan and S.H. Wang, *Bioorg. Med. Chem. Lett.*, **30**, 127376 (2020); https://doi.org/10.1016/j.bmcl.2020.127376
65. M.S. Altowyan, A. Barakat, A.M. Al-Majid and H.A. Al-Ghulikah, *Saudi J. Biol. Sci.*, **27**, 1208 (2020); https://doi.org/10.1016/j.sjbs.2020.02.010
66. O. Unsal-Tan, K. Ozadali, K. Piskin and A. Balkan, *Eur. J. Med. Chem.*, **57**, 59 (2012); https://doi.org/10.1016/j.ejmech.2012.08.046
67. K. Liaras, M. Fesatidou and A. Geronikaki, *Molecules*, **23**, 685 (2018); https://doi.org/10.3390/molecules23030685
68. A. Zarghi and S. Arfaei, *Iran. J. Pharm.. Res.*, **10**, 665 (2011).
69. P. J. Jacob and S.L. Manju, *Med. Chem. Res.*, **30**, 236 (2020); https://doi.org/10.1007/s00044-020-02655-9
70. S. Yatam, S.S. Jadav, K.P. Gundla, K. Paidikondala, A.R. Ankireddy, B.N. Babu, M.J. Ahsan and R. Gundla, *ChemistrySelect*, **4**, 11081 (2019); https://doi.org/10.1002/slct.201902972
71. M. Shahrasbi, M.A. Movahed, O.G. Dadras, B. Daraei and A. Zarghi, *Iran. J. Pharm. Res.*, **17**, 1288 (2018).
72. S. Sinha, S.L. Manju and M. Doble, *ACS Med. Chem. Lett.*, **10**, 1415 (2019); https://doi.org/10.1021/acsmedchemlett.9b00193
73. M.T.E. Maghraby, O.M. Abou-Ghadir, S.G. Abdel-Moty, A.Y. Ali and O.I. Salem, *Bioorg. Med. Chem.*, **28**, 115403 (2020); https://doi.org/10.1016/j.bmc.2020.115403
74. E.K. Abdelall and G.M. Kamel, *Eur. J. Med. Chem.*, **118**, 250 (2016); https://doi.org/10.1016/j.ejmech.2016.04.049
75. A.A. Geronikaki, A.A. Lagunin, D.I. Hadjipavlou-Litina, P.T. Eleftheriou, D.A. Filimonov, V.V. Poroikov, I. Alam and A.K. Saxena, *J. Med. Chem.*, **51**, 1601 (2008); https://doi.org/10.1021/jm701496h
76. I. Apostolidis, K. Liaras, A. Geronikaki, D. Hadjipavlou-Litina, A. Gavalas, M. Sokovic, J. Glamoèlija and A. Ciric, *Bioorg. Med. Chem.*, **21**, 532 (2013); https://doi.org/10.1016/j.bmc.2012.10.046
77. P. Eleftheriou, A. Geronikaki, D. Hadjipavlou-Litina, P. Vicini, O. Filz, D. Filimonov, V. Poroikov, S.S. Chaudhaery, K.K. Roy and A.K. Saxena, *Eur. J. Med. Chem.*, **47**, 111 (2012); https://doi.org/10.1016/j.ejmech.2011.10.029
78. T. Hanke, C. Lamers, R.C. Gomez, G. Schneider, O. Werz and M. Schubert-Zsilavecz, *Bioorg. Med. Chem. Lett.*, **24**, 3757 (2014); https://doi.org/10.1016/j.bmcl.2014.06.077
79. O.S. Afifi, O.G. Shaaban, H.A. Abd El Razik, S.E.-D.A. Shams El-Dine, F.A. Ashour, A.A. El-Tombary and M.M. Abu-Serie, *Bioorg. Chem.*, **87**, 821 (2019); https://doi.org/10.1016/j.bioorg.2019.03.076
80. S.K. Sinha, S.K. Prasad, M.A. Islam, S.S. Gurav, R.B. Patil, N.A. AlFaris, T.S. Aldayel, N.M. AlKehayez, S.M. Wabaidur and A. Shakya, *J. Biomol. Struct. Dyn.*, **39**, 4686 (2020); https://doi.org/10.1080/07391102.2020.1779132
81. Mahesha, H.M. Krishnegowda, C.S. Karthik, P.J. Kudigana, P. Mallu and L.K. Neratur, *Polyhedron*, **185**, 114571 (2020); https://doi.org/10.1016/j.poly.2020.114571
82. S. Mahanta, P. Chowdhury, N. Gogoi, N. Goswami, D. Borah, R. Kumar, D. Chetia, P. Borah, A.K. Buragohain and B. Gogoi, *J. Biomol. Struct. Dyn.*, **39**, 3802 (2020); https://doi.org/10.1080/07391102.2020.1768902
83. R. Islam, M.R. Parves, A.S. Paul, N. Uddin, M.S. Rahman, A.A. Mamun, M.N. Hossain, M.A. Ali and M.A. Halim, *J. Biomol. Struct. Dyn.*, **39**, 3213 (2020); https://doi.org/10.1080/07391102.2020.1761883
84. N.A. Al-Shar'i, E.K. Al-Rousan, L.I. Fakhouri, Q.A. Al-Balas and M.A. Hassan, *Med. Chem. Res.*, **29**, 356 (2020); https://doi.org/10.1007/s00044-019-02486-3