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(REVIEW ARTICLE)

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Review on Thiazolidinone possessing heterocyclic analogues, their potential binding sites with Cyclooxygenase and Lipoxygenase; Their SAR and Docking studies for Anti-inflammatory activity

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Abstract

This review summarizes the work done in the last few years to overcome the limitations and side effects of marketed drugs, including the structure, structure-activity relationship and molecular docking study of some thiazolidinone-based derivatives. Molecular docking analysis is useful in the prediction of binding affinity, the detection of fragments responsible for the interaction with enzyme binding sites, their modes of interactions with the active site, and the efficacy of compounds in inhibiting cyclooxygenase (COX), lipoxygenase (LOX), and tumor necrosis factor (TNF-α). Inhibition might be a promising for the treatment of multifactorial diseases such as inflammation. Some of these compounds exhibit COX and LOX dual inhibition actions. This study discloses some structural features for binding to 15-LOX, COX, and TNF-α, thus providing the way to design new anti-inflammatory agents with better inhibition of these enzymes.

Keywords: Thiazolidinone; Anti-inflammatory; COX; LOX; SAR; Molecular docking

1. Introduction

Drug discovery is a capital and time-intensive process which is aimed at developing new drug candidates. One way of achieving this has been through the aid of computational means in the pre-clinical phase of drug discovery. Computer-aided drug design (CADD) can be defined as computational approaches that are used to discover, develop, and analyse drug and active molecules with similar biochemical properties [1, 2].

Computer-aided drug design has come of age and it has greatly influenced the development of several therapeutically crucial small molecules (drug leads), many of which have led to the successful development of commercially available drugs [3]. Molecular docking has been widely used within virtual screening to assist in streamlining the search especially where a protein 3D structure is available [4]. There are essentially three categories of docking i.e., ensemble, induced work and lock and key docking. Docking methodologies include rigid ligand and rigid receptor docking; flexible ligand and rigid receptor docking; and flexible ligand and flexible receptor docking. Various docking and scoring software programs are available as in-house or opensource applications for use to that effect, employing different algorithms and functions [5, 6].

The anti-inflammatory activity of nonsteroidal anti-inflammatory drugs NSAIDs arises from their ability to inhibit the cyclooxygenase (COX) and Lipoxygenase (LOX) enzyme and TNF-α [7, 8]. COX catalyzes the production of pro-inflammatory prostaglandins (PGs) and thromboxanes. Pro-inflammatory prostaglandins play a key role in the generation of the inflammatory response [9]. Cyclooxygenase enzyme exists in at least two distinct isoforms, a

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constitutive form (COX-1) and an inducible form (COX-2). COX-1 maintains physiological functions such as protection of the gastric mucosa, vascular homeostasis, and platelet aggregation.COX-2 is upregulated during acute and chronic inflammation, pain, and oncogenesis [10].

Lipoxygenase belongs to the family of non-heme iron-containing enzymes that catalyze lipid peroxidation. They classified according to the peroxidation site of arachidonic acid into 5-LOX, 12-LOX and 15-LOX [11, 12]. 15-LOX is responsible for the production of 15(S)-hydroxy-eicosatetraenoic acid (15-HETE) and eoxins and is also associated with some inflammatory diseases such as osteoarthritis and asthma. Compounds that combine COX and LOX inhibition present multiple advantages because they act on two major arachidonic acid metabolic pathways and possess a wide range of anti-inflammatory activity [13]. Structure-activity studies demonstrated that a SO_2NH_2 or SO_2CH_3 substitution on the phenyl ring of the inhibitor provides COX-2 selectivity, but no other substitutions are tolerated [14, 15]. Some new target derivatives were evaluated for their in vivo anti-inflammatory activity along with their *in vitro* TNF-α inhibitory potency. Molecular docking study was also carried out for the most potent inhibitors to find out their modes of binding with the active site of TNF-α [16, 17].

1.1. Thiazolidinone derivatives with selective COX-2 inhibitory activity

In order to test for their COX inhibitory activity, O. Unsal-Tan *et al*. presented a series of thiazolidinone derivatives, 2-aryl-3-(4-sulfamoyl/methayl-sulfonylphenylamino)-4-thiazolidinones. From SAR studies it was found that switching the functional group SO_2NH_2 to SO_2CH_3 increased both activity and selectivity. It is therefore assumed that the presence of a bulky group is necessary for improving the hydrophobic interaction between the compound and COX-2 enzyme. Leading to the additional conclusion that Compound **1a** shows impressive inhibitory action with reasonable selectivity, while Compound **1b** was found to be the most potent and selective COX-2 inhibitor. Molecular docking studies of compound **1c** show that 4-sulphamoylphenylamino is positioned in the COX-2 (PDB ID-1CX2) secondary pocket surrounded by His90, Ser353, Tyr355, Arg513 and Val523. Therefore, it is considered that the secondary pocket is responsible for the selective COX-2 inhibitors. Phenyl ring is oriented in a hydrophobic cavity formed by Phe381, Leu384, Tyr385, Phe513, Ser530. Binding energy of Compound **1b** and **1c** are -8.18 and -7.77 kcal/mol, respectively [18].

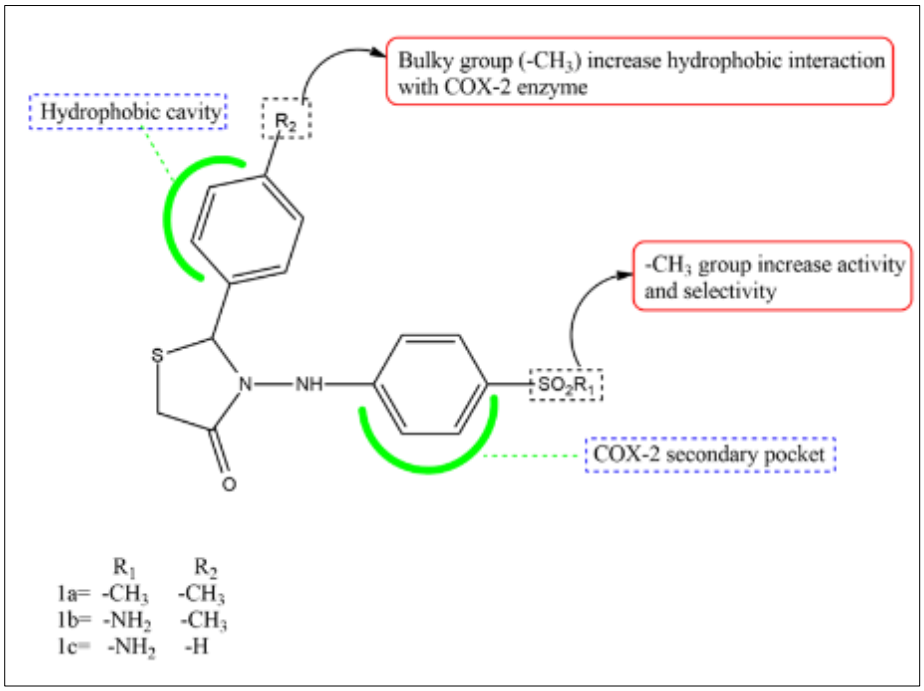

Figure 1 Structure and molecular docking of 2-phenyl-3-(4-aminosulfonylphenylamino)-4-thiazolidinone 1c

Another derivative of 4-thiazolidinone was synthesized and tested for inhibition activity against ovine COX-1 and human recombinant COX-2. It showed weak inhibitors of the COX-1 isoenzyme and exhibited moderate inhibition activity against COX-2. It is concluded that two bulky moieties attached to the central heterocyclic thiazole ring are not vicinal and show lower inhibitory activity against both COX-1 and COX-2. Thiazolidinone derivatives 2-(4-(4-nitrophenyl) thiazol-2-ylimino) thiazolidine-4-one (**2a)** and 2-(4-(4-isobutylphenyl) thiazol-2-ylimino) thiazolidine-4-

one **(2b)** showed moderate COX-2 inhibitory activity with a moderate selectivity index**.** Molecular docking studies show that compounds oriented in COX-2(PDB ID-3LN1) active site are closer manner to celecoxib (docking score -26.44) as a reference, with binding affinities of -13.30 and -6.05 kcal/mol, respectively. Iminothiazolidine-4-one is positioned in the primary hydrophobic pocket and the 4-nitro/isobutylphenyl moiety is oriented towards the secondary pocket, and does not form any hydrogen bond interaction with the amino acid, which reduces their inhibitory activity.

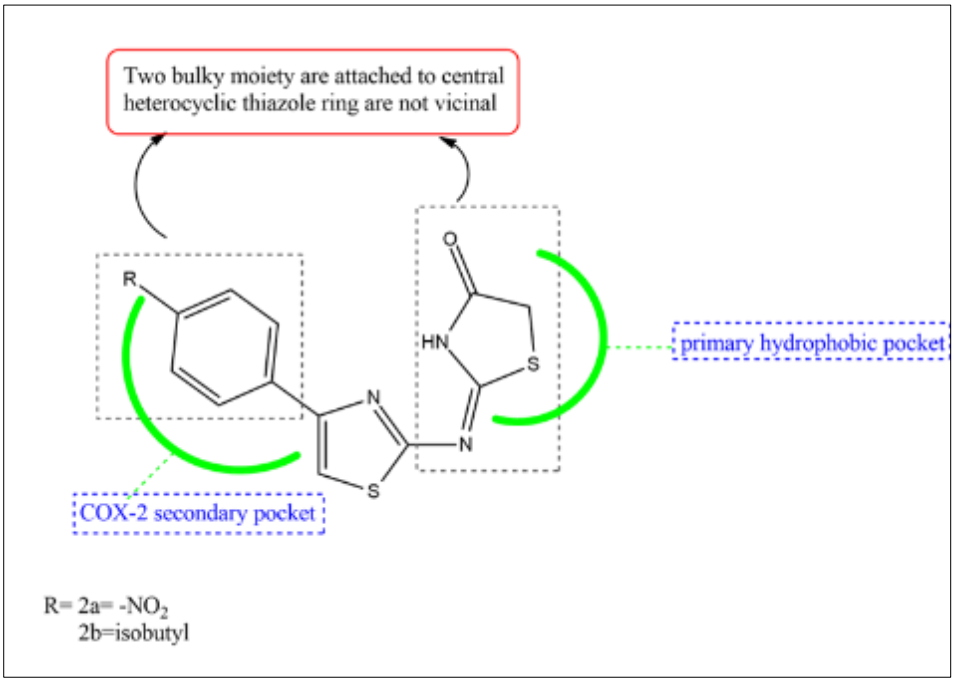

Figure 2 Structure and molecular docking studies of 2-(4-(4-nitrophenyl) thiazol-2-ylimino) thiazolidine-4-one 2a and 2-(4-(4-isobutylphenyl) thiazol-2-ylimino) thiazolidine-4-one 2b

Another, derivative was synthesized with two bulky moieties attached to the central heterocyclic 4-thiazolidinone moiety are vicinal, which shows comparable inhibitory activity against COX-1 and COX-2 with celecoxib reference. chloro and fluoro analogs 3-(4-aminosulfonylphenylamino)-2-(4-chlorophenyl)-5-methyl-4-thiazolidinone (**3a)** and 3-(4-aminosulfonylphenylamino)-2-(4-fluorophenyl)-5-methyl-4-thiazolidinone (**3b)** was more selective COX-2 inhibitors and the compounds with hydrophobic methyl or trifluoromethyl groups show good COX-2 inhibitory activity and exhibit moderate anti-inflammatory effects *in vivo*. Molecular docking studies show that compounds are positioned in the COX-2(PDB ID-3LN1) secondary pocket, surrounded by His75, Ser339, Arg499 and Gln178. Chlorophenyl derivative **3a** forms three hydrogen bonds with the amino acid present in the COX-2 secondary pocket, fluorophenyl derivative **3b** forms two hydrogen bonds and their binding affinities are -16.40 and -17.15 kcal/mol, respectively. π-π stack interaction of the phenyl ring with Tyr371 and Trp373 is due to the high electronegative nature of chlorine and fluorine atoms and it also increases the intermolecular interaction with active site [19].

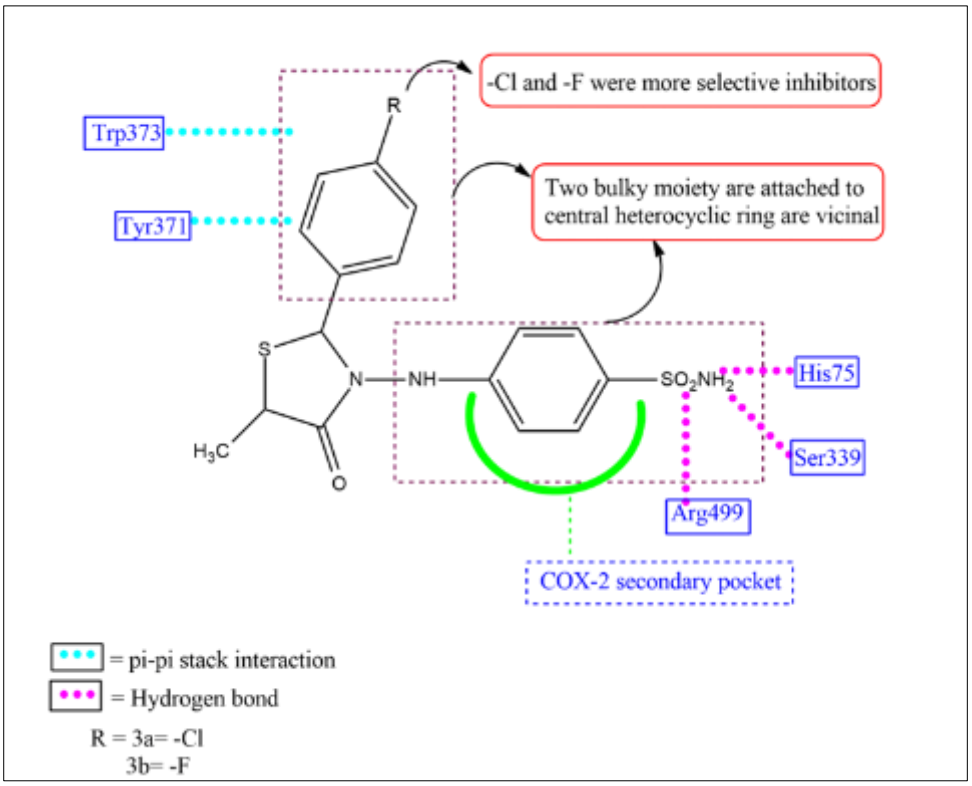

Figure 3 Structure and molecular docking studies of 3-(4-aminosulfonylphenylamino)-2-(4-chlorophenyl)-5-methyl-4-thiazolidinone 3a and 3-(4-aminosulfonylphenylamino)-2-(4-fluorophenyl)-5-methyl-4-thiazolidinone 3b

1.2. Thiazolidinone derivatives with dual inhibition of COX and LOX

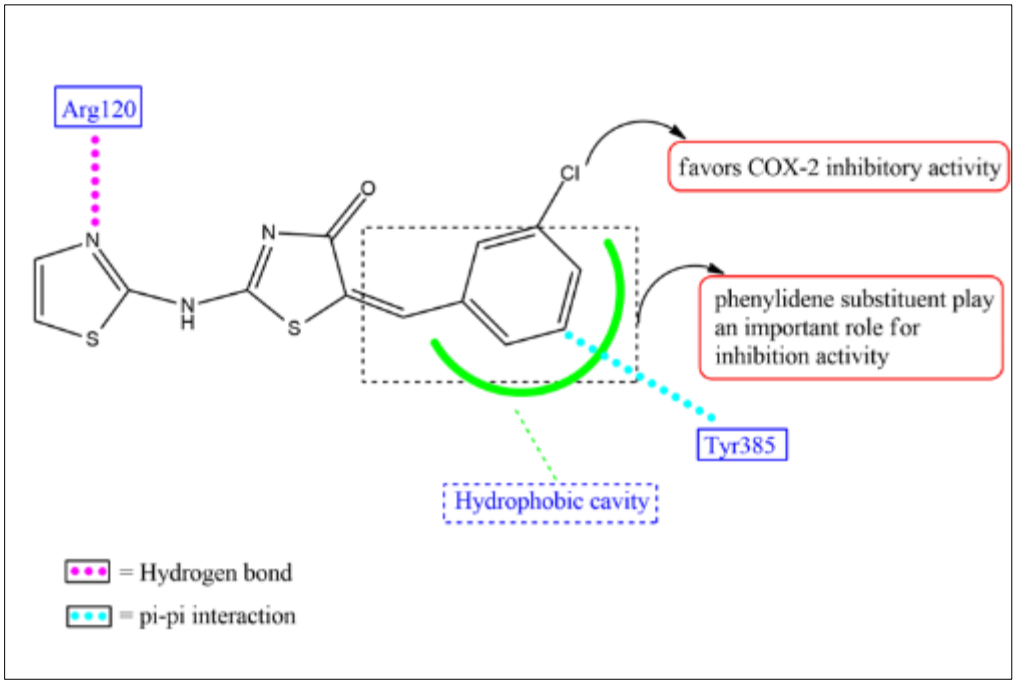

Figure 4 Structure and molecular docking studies of 2-(thiazole-2-ylimino)-5-(m-chlorophenylidene)-4-thiazolidinone 4a with COX-2 isoenzyme

A series of 2-thiazolylimino-5-arylidene-4-thiazolidinone synthesized and analyse their COX and LOX inhibitory activity. SAR study demonstrate that more lipophilic *m*-Cl **4a** substituents replaced by less lipophilic nitro group lead to a decrease in inhibitory activity to less than half. Additionally, it is also concluded that phenylidene substituents play an

important role in the inhibition of both COX isoenzymes. Analysis values suggest that compounds with a meta-nitro group **4b** demonstrate high inhibition activity for LOX compared to *m*-Cl substituted derivative. So, it is concluded that *m*-Cl substitution favours COX inhibitory activity, whereas *m*-NO_2 substitution fevers the best LOX inhibitory activity. Derivatives with the substituent *m*-OCH3, *p*-OH **4c** exhibit the strongest anti-inflammatory activity and are the most potent LOX inhibitors.

1.2.1. Docking study of compound 4a with COX-2

Docking study of compound **4a** in the COX-2 enzyme (PDB ID-1CX2) shows that compound docks in the active site surrounded by amino acids Phe518, Ser353, Gly354, Ile517, Arg513, His90, Tyr355, and Arg120, Nitrogen of the thiazole ring forms a hydrogen bond with Arg120 and the chlorophenyl ring settles in the hydrophobic cavity created by Tyr135, Phe381, Met522, Trp387 and Phe518. The chlorophenyl ring makes a π-π interaction with the phenyl ring of Tyr385.

1.2.2. Docking study of compound 4b with 15-LOX

Docking study of compound **4b** with 15-LOX (PDB ID-1LOX) shows favourable hydrogen bonding interactions with Asn406 and Arg403. The CO group of the compound makes hydrogen bond interaction with free NH_2 of Arg403. Amino nitrogen of the compound also contains a hydrogen bond interaction with Asn406 and nitro phenyl ring settles in the cavity created by Phe175, His366, Leu597 and Ile663. His366 present at the active site of LOX favours electrostatic interaction and the NO_2 group enables such interaction, so, it is also concluded that the high electro-static nature of the LOX active site favours the presence of NO_2 [20].

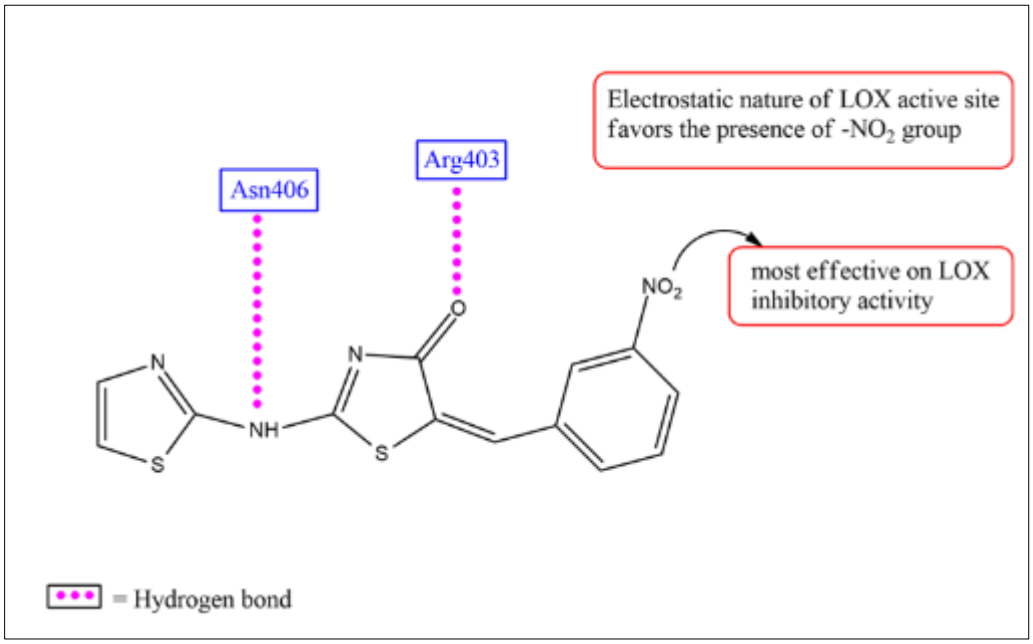

Figure 5 Structure and molecular docking studies of 2-(thiazole-2-ylimino)-5-(m-nitrophenylidene)-4-thiazolidinone 4b with 15-LOX enzyme

P. Eleftherious et al. synthesize benzothiazole containing thiazolidinone derivatives and from SAR study it was observed that the 2-Cl **5a** substitution exhibited the highest COX-2 inhibitory activity. Replacement of a more lipophilic chloro substituent by a less lipophilic nitro group lead to a decrease in inhibitory activity in the case of 2- and 4-substitutes while 3-NO_2 substitution exhibits the activity, and replacement with a 4-methoxy and 4-hydroxy group exhibits moderate activity. In the case of LOX, -OMe group favours the activity. *p*-OMe **5b** derivative is the most potent compound, while the compound bearing the -OH group at the p-position and two -OMe group at two *m*-position show the second most potent derivative on the other hand, *p*-OH derivative was even less active, and the m-OH derivative exhibits slightly higher activity than the *p*-OH analogue.

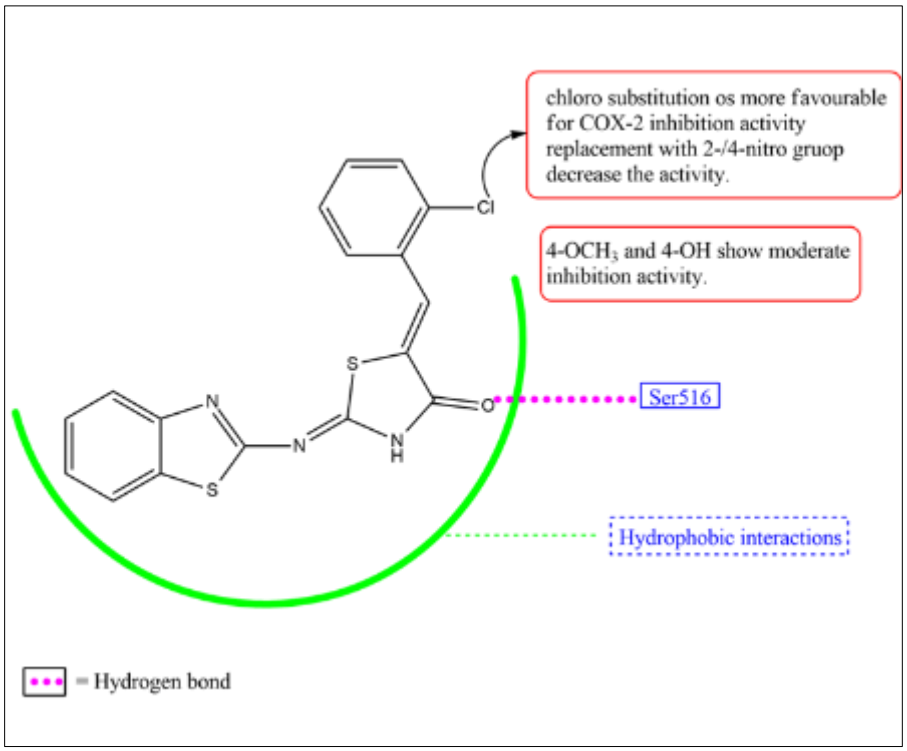

Figure 6 Structure and molecular docking studies of 5-(2-chloro-benzylidene)-2-(benzo[d]thiazol-2-ylimino) thiazolidine-4-one 5a with COX-2 isoenzyme

1.2.3. Docking study of compound 5a with COX-2

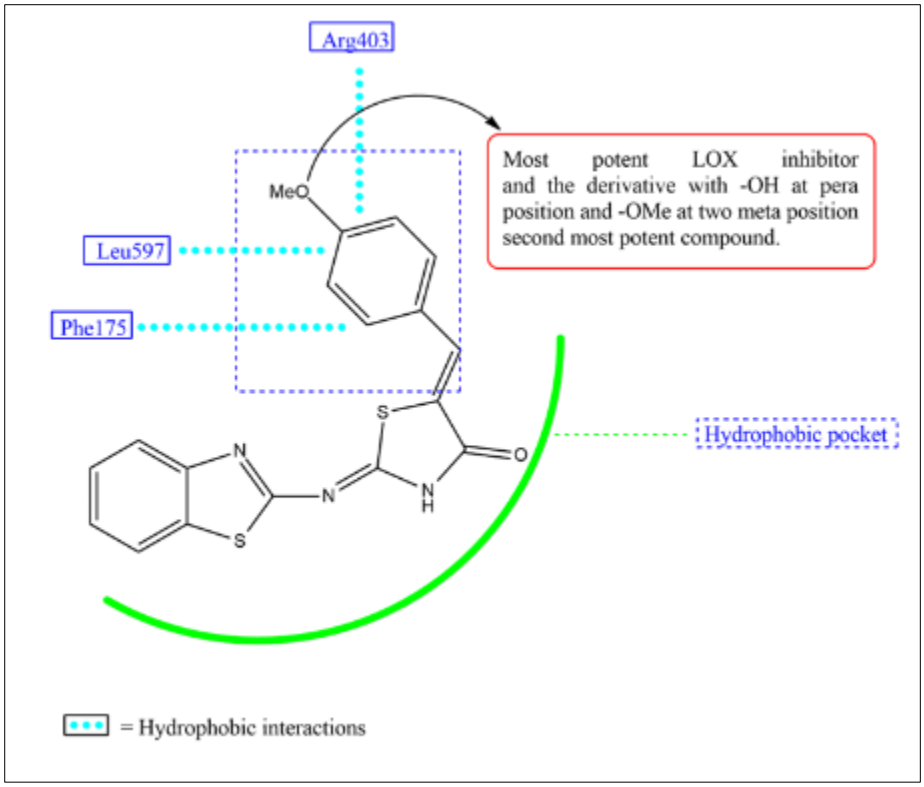

Figure 7 Structure and molecular docking studies 5-(4-methoxy-benzylidene)-2-(benzo[d]thiazol-2-ylimino) thiazolidine-4-one 5b with 15-LOX enzyme

Molecular docking study of compound **5a** with the COX-2 enzyme (PDB ID-3LN1) shows that the compound is oriented deep in the left of the binding site and has hydrophobic interaction with the surrounding residue Leu345, Met99, Val102, Ile331, Ala512 and Leu517 contribute strong stabilization and a hydrogen bond formed between the oxygen of the keto group of thiazolidinone ring and the hydrogen of the -OH group of Ser516. Presence of -NO_2 group partly prevents hydrophobic interaction which leads to lower activity.

1.2.4. Docking study of compound 5b with 15-LOX

Molecular docking study of compound **5b** with the LOX enzyme (PDB ID-1LOX) shows that the compound is oriented in a hydrophobic pocket formed by amino acid residues Phe353, Glu357, Leu358, Phe415, Ile418, Met419, Ile593, Val594 and Leu597, and the thiazolidinone ring is placed in parallel to His361 with the keto group projected towards the plane of His366.4-methoxybenzylidene group placed in pocket formed by Phe175, Leu597, Arg403 and Ile663 exhibit hydrophobic interaction.

Another series containing benzisothiazole was also synthesized and tested against the COX-2 iso enzyme. A derivative containing 4-Cl **6a** exhibited the best inhibitory activity. Derivative containing 4-OH group **6b** showed the most potent inhibitory activity. Therefore, it is concluded that the presence of the p-OH group is beneficial for the LOX inhibitory activity and the introduction of methoxy group in meta position decrease the activity.

1.2.5. Docking study of compound 6a with COX-2

A docking study of compound **6a** shows that the compound is placed in the deep pocket of COX-2 (PDB ID-3LN1) cavity created by the amino acids Met99, Val102, Ile331, Leu345, Ala512, and Leu517. Para substituted analogues show a particular role of lipophilic interaction within the COX-2 binding pocket as an essential factor for potential inhibition of the COX-2 enzyme.

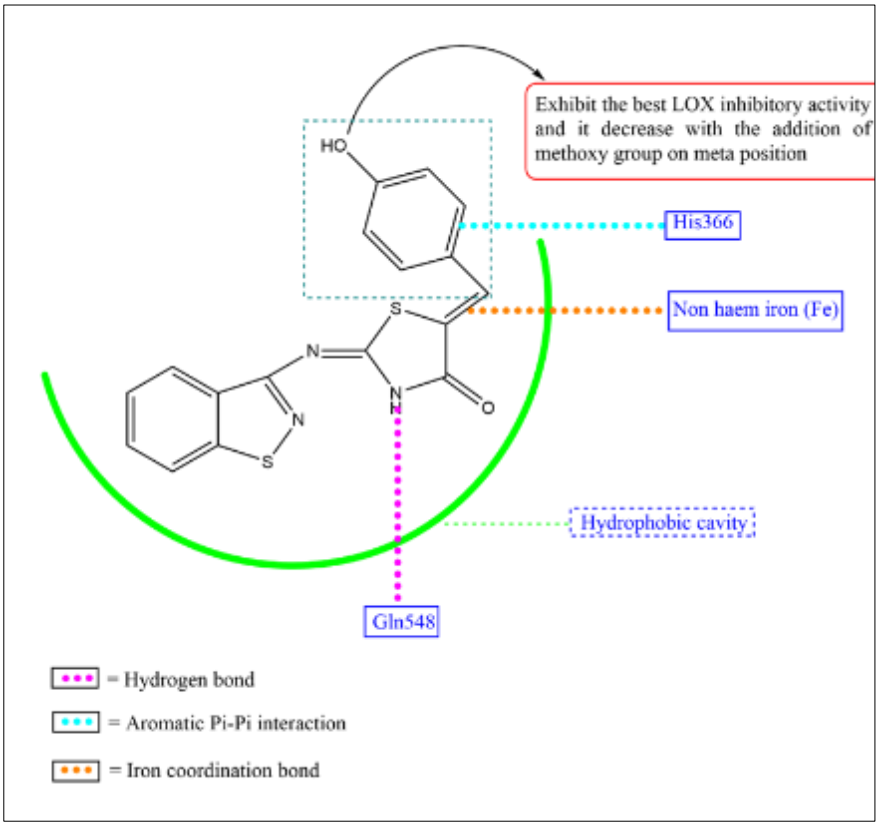

Figure 8 Structure and molecular docking studies 2-(Benzo[d]isothiazol-3-ylimino)-5-(4-hydroxybenzylidene) thiazolidine-4-one 6b with 15-LOX enzyme.

1.2.6. Docking study of compound 6b with 15-LOX

Docking study of compound **6b** shows optimum binding mode into the active site of 15-LOX (PDB ID-1LOX). The compound is placed in the hydrophobic cavity formed by amino acid residues Phe353, Glu357, Leu358, Phe415, Ile418,

Met419, Ile593, Val594, and Leu597. The nitrogen of the thiazolidinone ring is involved in H-bond interaction with Gln548. The phenyl ring of the benzylidene moiety is in parallel with the His366 exhibiting aromatic π-π interaction, and the double bond C=C attached to the thiazolidinone core is placed above the non-haem iron (Fe), with Fe-CH and 4-OH substituents of the benzylidene moiety in close proximity to His366, Leu362, and Asn401 [21].

Another library of new hybrid compounds of 4-thiazolidinone and 1,3,4-thiadiazole was synthesized. (5Z) -5-benzylidene-2-{[5-(4-hyroxyphenyl)-1,3,4-thiadiazol-2-yl] imino} -1,3-thiazolidin-4-one (**7a)** shows better selectivity and potency against both COX-2 and 15-LOX enzymes. Replacement of the arylidene moiety with pyridine or cyclohexyl shows a significant change in selectivity and potency. Substitution of 3,4-dichloro **7b** on the arylidene ring led to an increase in inhibition activity with a marked effect on selectivity. Derivative with three methoxy **7c** groups is threefold more selective than the parent hybrid. The methyl group in the fourth position shows higher potency and selectivity, while the hydroxy group in the second position is more potent and selective than 4-hydroxy. Parent compound **7a** with an unsubstituted phenyl ring was the most potent derivative against the 15-LOX enzyme.

1.2.7. Docking study of compound 7b & 7c with COX-2

Most potent compounds **7b and 7c** explore good binding with the COX-2 enzyme (PDB ID-5KIR). compound **7b** (docking score -7.6 kcal/mol) forms three hydrogen bonds with Arg513, Phe518, and Ile517 and one hydrophobic interaction with Ala527; compound **7c** (docking score -7.9) forms two hydrogen bonds with Arg513 and Leu352 and one hydrophobic interaction with Ser353.

1.2.8. Docking study of compound 7a with 15-LOX

Compound 7a (docking score -5.03 kcal/mol) shows good binding affinity with human 15-LOX enzyme (PDB ID-4NRE) form hydrogen bond with Glu613 [22].

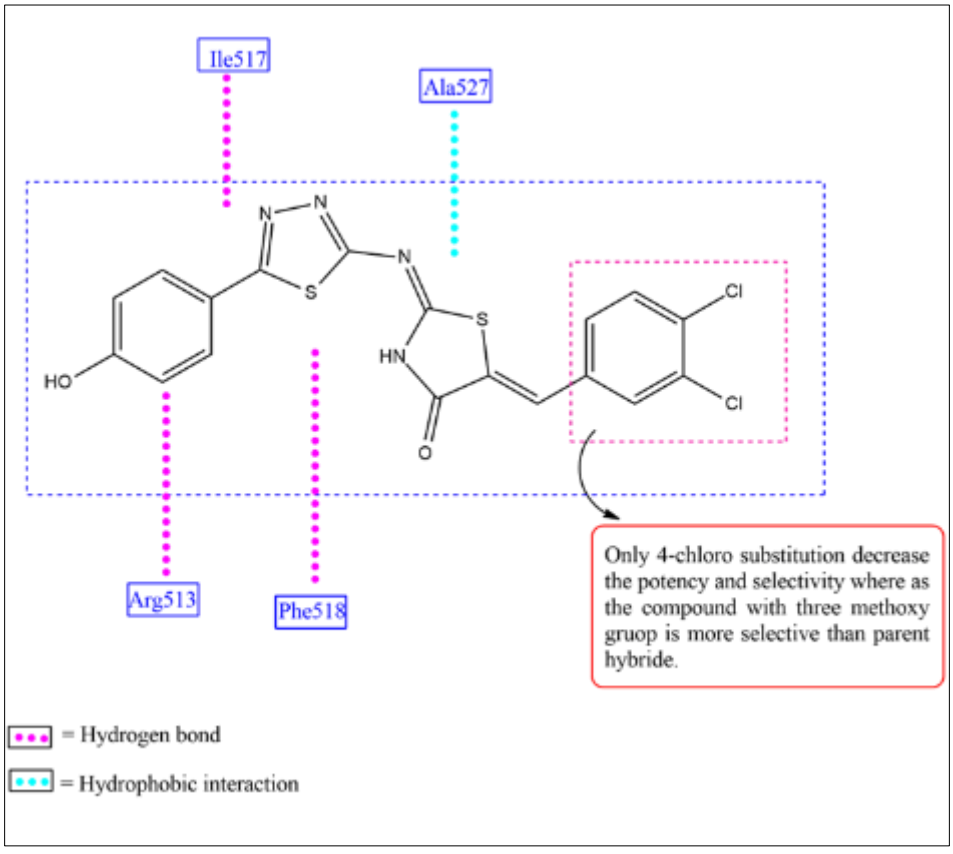

Figure 9 Structure and molecular docking studies of 7b with COX-2 isoenzyme

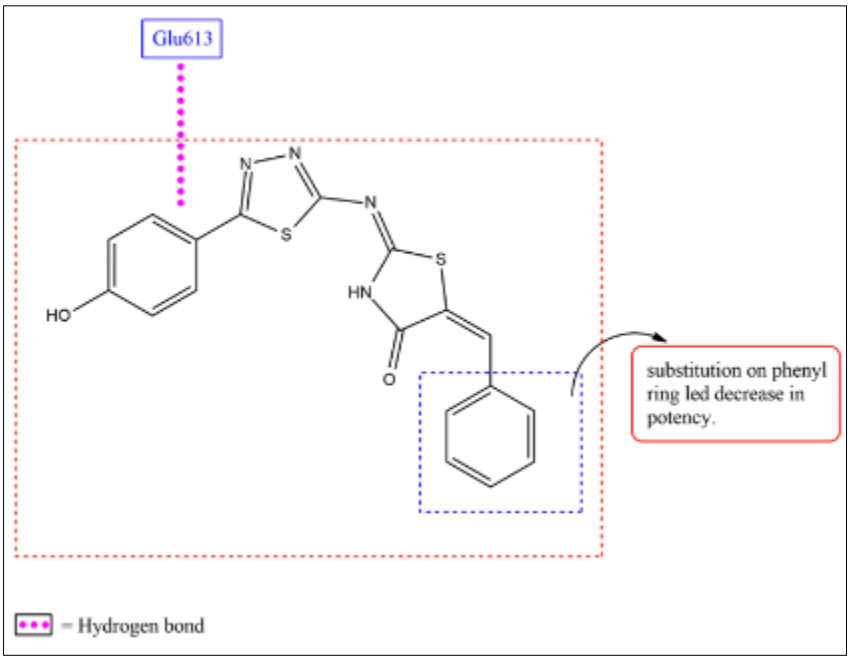

Figure 10 Structure and molecular docking studies of compounds 7a with 15-LOX enzyme

A series of 1,3,4-thiadiazole-thiazolidinone hybrids were synthesized and screened for their dual COX-2 and 15-LOX inhibitory activity as anti-inflammatory agents. Compound with 4-methylphenyl **8a** exhibit the highest potency. It shows that increasing the length of the aliphatic substituent on the phenyl ring decreases the LOX inhibitory potency. Substitution of 2-hydroxyphenyl shows higher potency than the 4-hydroxyphenyl group. Increasing the number of hydroxyl groups also led to a decrease in inhibitory activity. A compound containing a 2-chlorophenyl group shows the highest potency among the halogenated phenyl series. The COX-2 inhibitor compound **8b** showed that decreasing the number of methoxy groups led to a decrease in potency and selectivity. Replacement of the bromine **(8c** atom by chlorine also results in a decrease in potency and selectivity. So, it is concluded that a bulky substituent is required at the 5th position of the thiazolidinone moiety for good activity and selectivity.

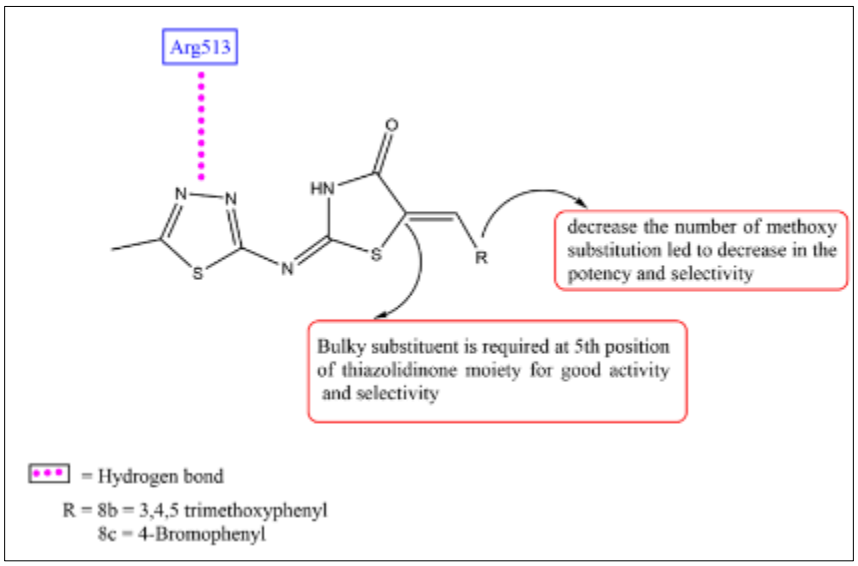

Figure 11 Structure and molecular docking studies of 8b with COX-2 isoenzyme

1.2.9. Docking study of compound 8b with COX-2

Molecular docking studies of synthesized compounds with the human COX-2 enzyme (PDB ID-5KIR) explore a hydrogen bonding between the 1,3,4 thiadiazole ring and amino acid Arg513; compound **8b** (docking score -7.46 kcal/mol) shows

additional bonding with Gln192; and compound **8c** (docking score -7.67 kcal/mol) shows a hydrogen bonding with Arg120 instead of Arg513 and a hydrogen interaction with Tyr355.

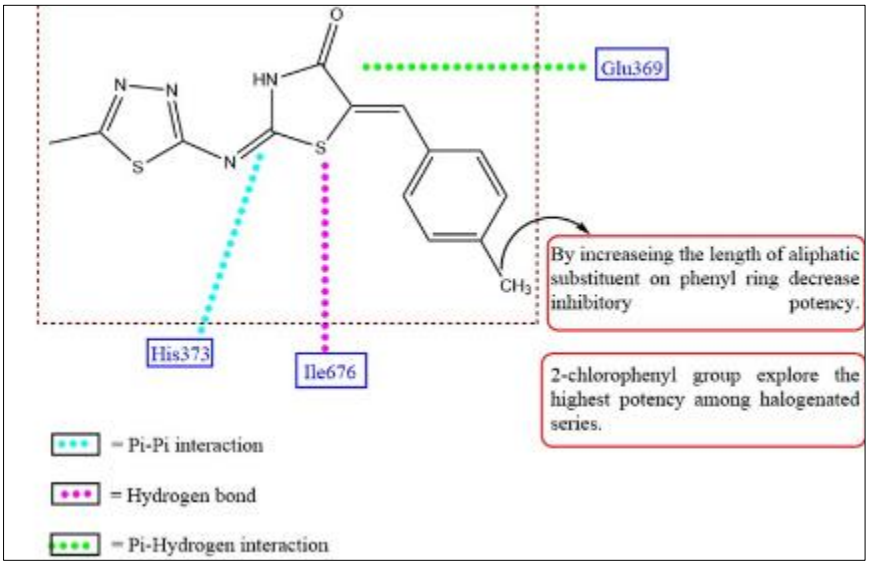

Figure 12 Structure and molecular docking studies of compounds 8a with 15-LOX enzyme

1.2.10. Docking study of compound 8a with 15-LOX

Molecular docking study of LOX (PDB ID-4NRE) with derivative **8a** (docking score -7.58 kcal/mol) showed π-π interaction between 1,3 thiazolidin-4-one ring and His373 and the sulfur atom of thiazolidinone ring form a hydrogen bond with amino acid Ile676 and also showed a π-hydrogen interaction with Glu369 which may explain its high potency [23]**.**

1.3. Thiazolidinone derivatives with TNF- α inhibitory activity

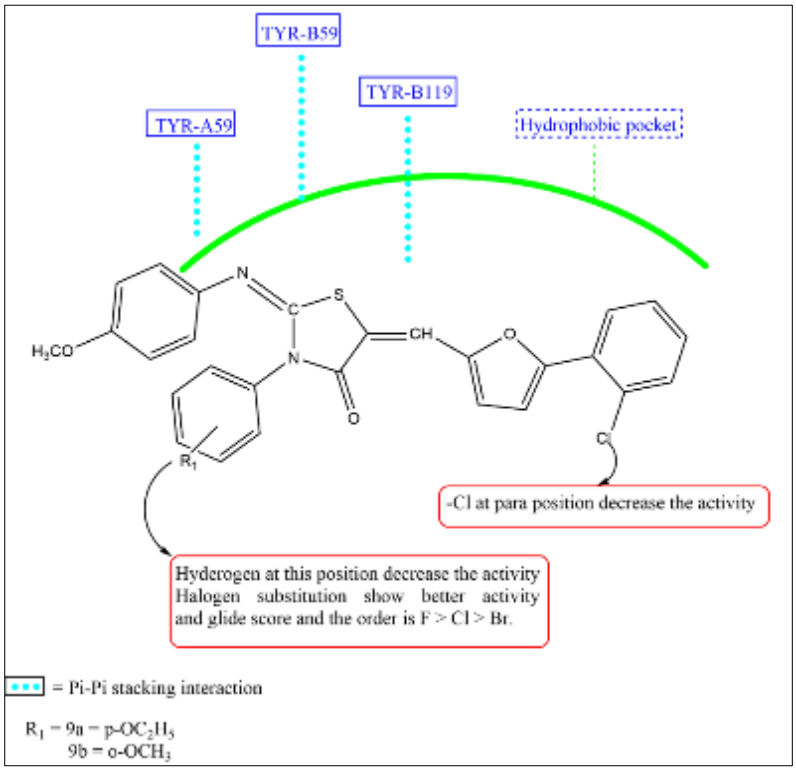

Figure 13 Structure and molecular docking studies of compounds 9b with TNF-α

Some new 2-imino-4-thiazolidinone derivatives were synthesized and tested against the TNF-α target. The structure-activity relationship shows that the presence of hydrogen in place of the R_1 position results in poor *in vitro* and *in vivo* activities. Halogen substitution at that position showed better *in vivo* and *in vitro* activity, and the activity order is F > Cl > Br. Molecular docking studies were performed using TNF-α protein (PDB ID-2AZ5). Compound **9b** (glid score -6.07) was found perfectly aligned in hydrophobic pocket and π-π stacking interactions with TYR-A59, TYR-B58, and TYR-B119, and compound **9a** (glid score -6.27) was found to form a hydrogen bond with GLY-B121 [24].

A library of 2-imino-4-thiazolidinone derivatives has been synthesized and evaluated for their anti-inflammatory activity and effect on TNF-α. The compound having a halogen atom on the phenyl ring showed better inflammatory activity as the size of the halogen atom increased, and the ethyl group in the para position showed better activity as compared to the methyl group at that position. The compound with benzyl substitution **10a** showed maximum in vivo anti-inflammatory activity, and the compound with cyclohexyl substitution **10b** showed significant activity as compared to any other substitution. Molecular docking studies were done using TNF-α (PDB ID-2AZ5) compounds **10a** and **10b,** which exhibit batter glid scores of -6.18 and -5.98, respectively, in comparison with indomethacin (glid score -5.02) reference and form hydrogen bonds with GLY121 residue and π-π stacking with Tyr119 and Tyr59, respectively [25].

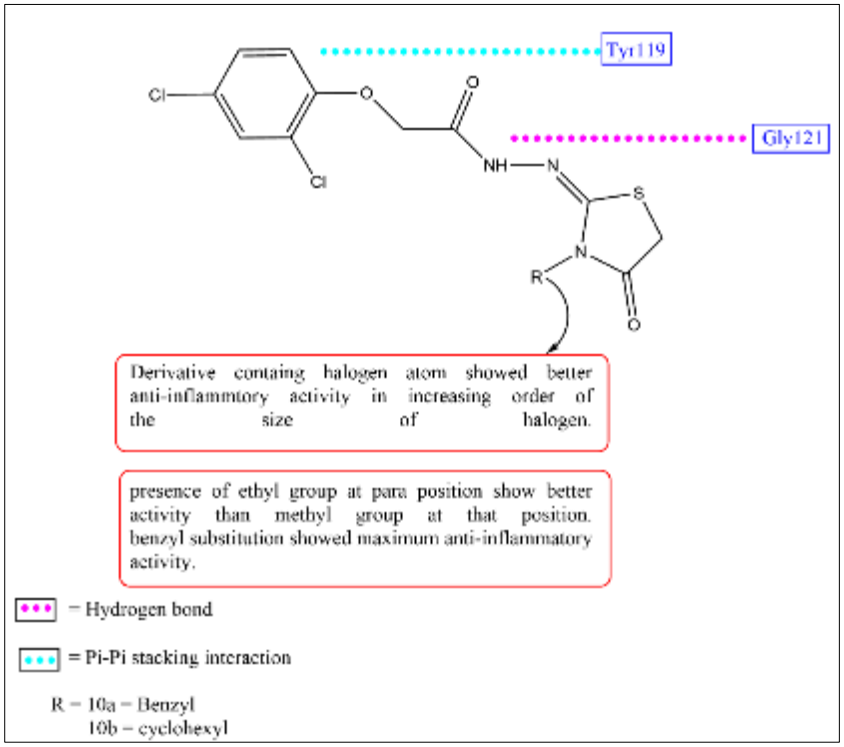

Figure14 Structure and molecular docking studies of compounds 10a with TNF-α

S.S. Abd El-Karim *et al*. synthesized a new series containing pyrazole-thiazolidinone derivatives and screened for their anti-inflammatory activity with TNF-α inhibition. Benzylidene scaffolds without any substitution exhibit no sound activity. The insertion of an electron-donating group at para position **11a** led to an improvement in inhibition. It is also concluded that the substitution of the electron-donating group at the ortho position of benzylidene ring **11b** exhibits excellent potency, which is decreased by changing the position to para. Heterocyclic ring pyridinyl **11d** revealed elevated activity. The molecular docking study shows strong binding affinity, and the compounds were fitted into the binding pocket via arene-arene interaction between the pyrazole moiety and the vital amino acid Tyr119. Compounds **11a** and **11c** shared a fixation through H-bond donors between their NH and side chains of Tyr151. Compound **11b** shares two H-bond acceptors with the backbone of Gly121 [26].

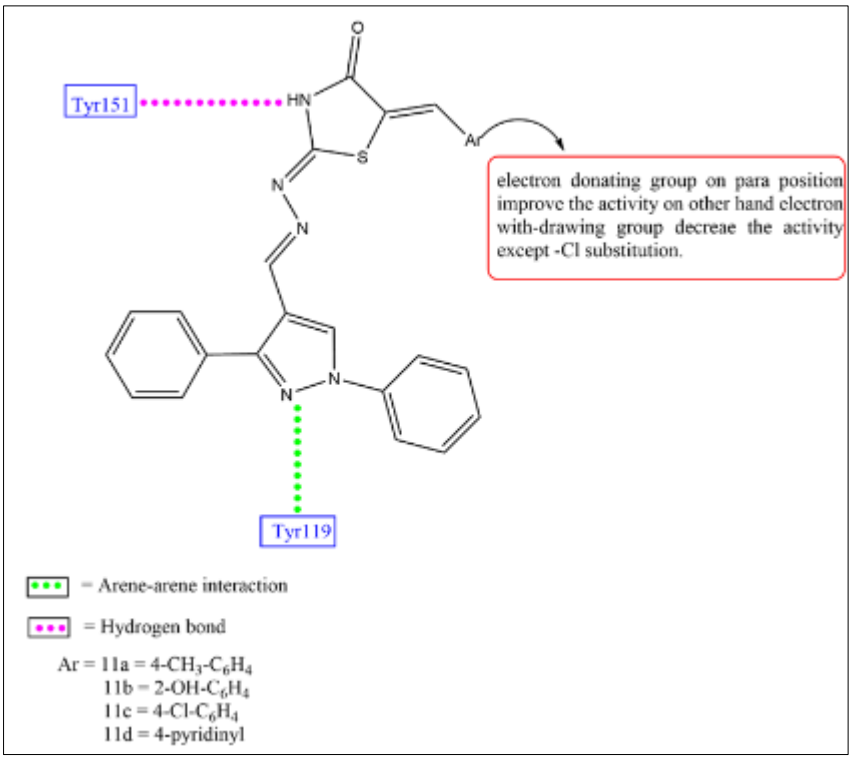

Figure 15 Structure and molecular docking studies of derivatives of compound 11

2. Conclusions

Thiazolidinone-based hybrids have a broad range of pharmacological and biological properties. The thiazolidinone scaffold has demonstrated significant COX/LOX inhibitory activity in vitro and anti-inflammatory activity in vivo. In this review, we have discussed thiazolidinone-based hybrids that were designed, synthesized, and evaluated for their anti-inflammatory activity. Several thiazolidinone compounds were reported to be comparable to or more potent than marketed drugs such as celecoxib, indomethacine, NS-398, etc. The SAR studies revealed that the anti-inflammatory activity of thiazolidinone derivatives depends on the nature of the peripheral substituent, the type of moiety, and the EWG and EDG substitutions on different moiety. In addition, the presence of an aminosulphonyl group in phenyl amino ring attach with thiazolidinone exhibits better COX-2 inhibition activity. -Cl substitution on the benzylidene ring attached to thiazolidinone also exhibits selective COX-2 inhibitory activity. -OH/-OMe present at the para position of the benzylidene ring show selectivity towards the LOX enzyme. It might be a fruitful resource for the development of new analogues with improved potencies and reduced toxicities.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Abdallah S. Abdelsattar, Alyaa D, Mohamed A. Helal. Interaction of nanoparticles with biological macromolecules: A review of molecular docking studies. Nanotoxicology. 2020 Dec;15(1):66-95.

[2] Bhatia P, Sharma V, Alam O, Manaithiya A, Alam P, Kaksha, Mohd I. Novel quinazoline-based EGFR kinase inhibitors: A review focussing on SAR and molecular docking studies (2015-2019). Eur. J. Med. Chem. 2020 Oct; 204:112640.

[3] Victor T. Sabe, Thandokuhle N, Lindiwe A. Jhamba, Glenn E. Maguire, Govender T, Naicker T, Hendrik G. Kruger. Current trends in computer aided drug design and a highlight of drugs discovered via computational techniques: A review. Eur. J. Med. Chem. 2021 july; 224:113705.

[4] Elizabeth Y, Paul A. Ramsland. Latest developments in molecular docking: 2010–2011 in review. Journal of Molecular Recognition. 2013 Jan; 26:215-239.

[5] Brian K Shoichet, Susan L McGovern, Binqing W, John J Irwin. Lead discovery using molecular docking. Current Opinion in Chemical Biology. 2002; 6:439-446.

[6] Xiaoqian L, Xiu L, Xubo L, A Review on Applications of Computational Methods in Drug Screening and Design. Molecules. 2020 Mar; 25:1375.

[7] Uddin J, Rao p,Knaus E, Design of acyclic triaryl olefins: a new class of potent and selective cyclooxygenase-2 (COX-2) inhibitors, Bioorg. Med. Chem. Lett. 2004; 27:1953-1956.

[8] Lafrance J, Miller D, Selective and non-selective non-steroidal anti-inflammatory drugs and the risk of acute kidney injury. Pharmacoepidemiol. Drug Saf. 2009 july;18(10):923–931.

[9] Fatma A. Ragab, Helmi I. Heiba, Marwa G. Gazzar, Sahar M. Abou-Seri, Walaa A. Sabbagh, Reham M. Hazek, Anti-inflammatory, analgesic and COX-2 inhibitory activity of novel thiadiazoles in irradiated rats, J. Photochem. Photobiol. 2017 Jan; 166:285–300.

[10] Sharma S, Kumar D, Singh G, Monga V, Kumar B, Recent advancements in the development of heterocyclic anti-inflammatory agents. Eur. J. Med. Chem. 2020 Aug; 200:112438.

[11] Omar Y, AbduAllah H, AbdelMoty S, Synthesis, biological evaluation and docking study of 1,3,4-thiadiazole-thiazolidinone hybrids as anti-inflammatory agents with dual inhibition of COX-2 and 15-LOX. Bioorg. Chem. 2018 Oct; 80:461–471.

[12] Jacob P, Manju S, Ethiraj K, Elias G. Safer anti-inflammatory therapy through dual COX-2/5-LOX inhibitors: A structure-based approach. Eur. J. Pharm. Sci. 2018 Aug; 121:356–381.

[13] Vlag R, Guo H, Hapko U, Eleftheriadis N, Monjas L, Dekker F, Hirsch A, A combinatorial approach for the discovery of drug-like inhibitors of 15-lipoxygenase-1. Eur. J. Med. Chem. 2019 Jul; 174:45–55.

[14] Abdelall E, Kamel G, Synthesis of new thiazolo-celecoxib analogues as dual cyclooxygenase-2/15-lipoxygenase inhibitors: Determination of regio-specific different pyrazole cyclization by 2D NMR. Eur. J. Med. Chem. 2016 Aug;118: 250–258.

[15] Afifi O, Shaaban O, Razik H, Shams E, Ashour F, Tombary A, AbuSerie M. Synthesis and biological evaluation of purine- pyrazole hybrids incorporating thiazole, thiazolidinone or rhodanine moiety as 15- LOX inhibitors endowed with anticancer and antioxidant potential. Bioorg. Chem. 2019 Jun; 87:821–837.

[16] He M, Smith A, Oslob J, Flanagan W, Braisted A, Whitty A, Cancilla M, Wang J, Lugovskoy A, Yoburn J, Fung A. Small-molecule inhibition of TNF α. Science. 2005 Nov;310(5750):1022–1025.

[17] Bradley J. TNF-mediated inflammatory disease. J. Pathol. 2008 Dec;214(2):149–160.

[18] Unsal-Tan O, Ozadali K, Piskin K, Balkan A. Molecular modeling, synthesis and screening of some new 4-thiazolidinone derivatives with promising selective COX-2 inhibitory activity. Eur. J. Med. Chem. 2012 Nov; 57:59-64.

[19] Khaled A. Abdellatif, Mohamed A. Abdelgawad, Heba H. Elshemy, Shahinda R. Alsayed. Design, synthesis and biological screening of new 4-thiazolidinone derivatives with promising COX-2 selectivity, anti-inflammatory activity and gastric safety profile. Bioorg. Chem. 2016 Nov; 64:1-12.

[20] Athina A. Geronikaki, Alexey A. Lagunin, Dimitra I. Hadjipavlou, Phaedra T. Eleftheriou, Dmitrii A. Filimonov, Vladimir V. Poroikov, Intekhab Alam, Anil K. Saxena. Computer-Aided Discovery of Anti-Inflammatory Thiazolidinones with Dual Cyclooxygenase/ Lipoxygenase Inhibition. J. Med. Chem. 2008 Jul; 51:1601-1609.

[21] Eleftheriou P, Geronikaki A, Hadjipavlou-Litina D, Vicini P, Filz O, Filimonov D, Poroikov V, Chaudhaery S, Saxena A. Fragment-based design, docking, synthesis, biological evaluation and structureeactivity relationships of 2-

benzo/benzisothiazolimino-5-aryliden-4 thiazolidinones as cycloxygenase/lipoxygenase inhibitors. Eur. J. Med. Chem. 2012 Oct; 47:111-124.

[22] Yasser M. Omar, Hajjaj H. Abdu-Allah, Samia G. Abdel-Moty. Synthesis, biological evaluation and docking study of 1,3,4-thiadiazole thiazolidinone hybrids as anti-inflammatory agents with dual inhibition of COX-2 and 15-LOX. Bioorg. Chem. 2018 May; 80:461-471.

[23] Yasser M. Omar, Samia G. Abdel-Moty, Hajjaj M. Abdu-Allah. Further insight into the dual COX-2 and 15-LOX anti-inflammatory activity of 1,3,4-thiadiazole-thiazolidinone hybrids: The contribution of the substituents at 5th positions is size dependent. Bioorg. Chem. 2020 Feb; 97:103657.

[24] Yakub A, Mohammad S, Hamid H, Husain A, Dhulap A, Hussain F, Kharbanda C. Molecular modeling and synthesis of some new 2-imino-4-thiazolidinone derivatives with promising TNF- α inhibitory activity. Royal Society of Chemistry. 2015 Nov;40(1):711-723.

[25] Ali Y, Mohammad A, Hamid H, Husain A, Dhulap A, Bano S, Kharbanda S. Novel 2,4-dichlorophenoxy acetic acid substituted thiazolidin-4-ones as anti-inflammatory agents: Design, synthesis and biological screening. Bioorg.Med.Chem.Lett. 2017 Feb;27(4):1017-1025.

[26] Somaia S. El-Karim, Hanaa S. Mohamed, Mohamed F. Abdelhameed, Abdulrahman A. Almehizia, Eman S. Nossier. Design, synthesis and molecular docking of new pyrazole-thiazolidinones as potent anti-inflammatory and analgesic agents with TNF α inhibitory activity. Bioorg. Chem. 2021 Mar; 111:104827