

In-silico molecular docking of ezetimibe and malic acid into cyclooxygenase enzymes

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Abstract:

The study of interactions of malic acid and ezetimibe molecules with cyclooxygenase enzymes is facilitated by molecular docking, which provides information on probable binding modalities and affinities important in drug discovery and studying molecular mechanisms. Ezetimibe, with lipid-lowering action, and malic acid, with antioxidant and gastroprotective action, have shown individual therapeutic efficacy. However, their combined action on COX enzymes is poorly studied. Ligand and enzyme structures were obtained from PubChem and the Protein Data Bank (PDB). Molecular Operating Environment (MOE) 2015.10 was used for ligand preparation, protein optimisation, and docking. Biovia Discovery Studio 4.5 was used for 2D and 3D representation of protein-ligand interactions. Binding energy, RMSD values, hydrogen bonding, and hydrophobic interaction parameters were compared to establish affinity and stability.

Ezetimibe displayed potent binding affinity against both COX-1 (−8.364 kcal/mol) and COX-2 (−8.7288 kcal/mol), whereas malic acid showed weak interactions (−4.63 kcal/mol). The combination enhanced COX-2 affinity (−8.8037 kcal/mol) with a slight decrease in COX-1 affinity (−7.7017 kcal/mol), indicating increased COX-2 selectivity. The ezetimibe–malic acid combination exhibited the greatest COX-2 binding among individual ligands and reference NSAIDs with lower COX-1 affinity, indicating a diminished risk for gastrointestinal side effects. The results endorse the prospects of this combination as a dual-action therapeutic with anti-inflammatory and lipid-lowering properties.

Keywords: Molecular docking, In-silico, Cyclooxygenase enzymes, COX-1, COX-2, Ezetimibe, Malic Acid, Ibuprofen, Celecoxib, Anti-inflammatory

Introduction

Arachidonic acid is catalysed by cyclooxygenase (COX) to prostaglandins (PGs), which regulate a diversity of physiological and pathological conditions [1]. Constitutive COX-1 maintains gastric protection and gastric circulation. COX-2, meanwhile, is inducible and is primarily related to inflammatory reactions and conditions such as arthritis, cancer, and neurodegeneration [2]. Both the non-selective and selective NSAIDs (inhibitors) are used to act on the COX enzymes, although they are usually reported to be associated with gastrointestinal and cardiovascular complications [3].

Malic acid, a natural compound and an intermediate of the TCA cycle, has been found to have antioxidant, anti-inflammatory and gastroprotective effects. It also plays roles in drug absorption and drug metabolism regulation [4,5]. Ezetimibe, meanwhile, is a cholesterol-lowering drug that inhibits the NPC1L1 protein. In addition to having an effect on hypercholesterolemia, ezetimibe exhibits anti-inflammatory properties by altering oxidative stress and inhibiting macrophage activity [6,7].

Although ezetimibe and malic acid have therapeutic potential, very little is known regarding

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their interaction with COX enzymes. Their combination effect has not been evaluated, and both are believed to contribute to the reduction of inflammation. For example, malic acid reduced oxidative stress in animal models, and ezetimibe has shown an effect on inflammatory markers [8,9]. Molecular docking is the most widely used in-silico method for predicting the binding interactions of small molecules with enzymes.

In-silico procedures provide data on the affinity and selectivity of binding, with the more negative binding energy values representing a stronger interaction [10–12]. This article examines the docking of ezetimibe and malic acid, alone and in combination, to the COX-1 and COX-2 enzymes. In pursuit of this objective, it evaluates the feasibility of a novel, two-pronged therapeutic solution to the treatment of inflammation and the lowering of cholesterol, hence bridging the gap in the current anti-inflammatory treatment modalities.

Materials and Methods

The docking experiments based on a computer-aided method were carried out by using the structures of COX-1 (PDB ID: 6Y3C) and COX-2 (PDB ID: 3LN1), which were retrieved from the RCSB Protein Data Bank (<https://www.rcsb.org>) in legacy PDB format. A docking simulation study of ezetimibe and malic acid was performed with the COX-1 and COX-2 structures. The ligand structures were derived from the PubChem database. Ezetimibe (Compound CID: 150311), malic acid (Compound CID: 525), ibuprofen (Compound CID: 3672) (non-selective COX inhibitor), and celecoxib (Compound CID: 2662) (standard selective COX-2 inhibitor) were retrieved from the PubChem database (<https://pubchem.ncbi.nlm.nih.gov>) in the simplified molecular-input line-entry system (SMILES) format (Table 1). Ligands were further prepared, and a docking simulation was finally done by using MOE Dock 2015 software. The ligand, enzyme preparation, and molecular docking followed the protocol using MOE Dock 2015 software [13,14]. The workflow involved:

Table 1. Compounds/ligands with their PubChem IDs

S. no.	Compound/Ligands	PubChem ID
1.	Ibuprofen	3672
2.	Celecoxib	2662
3.	Ezetimibe	150311
4.	Malic Acid	525

Ligand and Protein Preparation

To prepare configurations of each ligand, the SMILES string of each ligand was added to the builder module, followed by geometry optimisation and partial charge assignment on the structures. In preparation for the structure of target proteins (COX-1 and COX-2), structures were prepared by removing unwanted molecules, like water molecules, ligands, and redundant chains. Additions in the protonation state were made with the help of Protonate 3D, and the missing residues were fixed in the Structure Preparation mode. Active sites of the proteins were determined with the help of the Site Finder option, and dummy atoms were inserted to establish a binding pocket to conduct docking.

Molecular Docking

The ligands were docked into the active sites of both COX isoforms by means of the MOE Dock module. Docking was performed using a rigid receptor and a flexible ligand; the placement method was Triangle Matcher and the refinement method was Forcefield. The poses with the highest scores were ranked according to their least binding energy (S score) and Root Mean Square Deviation (RMSD), and those with RMSD less than 2.0 Å were regarded as valid [15].

Combination Docking

The docking of combinations has been done by adopting the sequence docking method to observe the binding energy of a combination of ligands separately. First, ezetimibe was docked onto the protein and then malic acid. The ligands were docked together (in succession) and simultaneously to each other at the same site to check their potential synergistic binding interactions. The docking simulations were done at least three times to prove consistency in the results attained. Energy minimisation was performed on the lowest-energy conformation selected.

Interaction Analysis and Visualisation

Analysis of binding interactions was done in Discovery Studio to display 2D and 3D hydrogen bonds, hydrophobic interactions, pi-stacking, and halogen bonding. The dominant ligand-binding sites and the amino acid residues pivotal to binding were noted. Binding stability was determined by binding interaction distances. Referring to standard NSAIDs like ibuprofen (non-selective COX inhibitor) and celecoxib (selective COX-2 inhibitor), the docking method was validated, and the binding affinity, as well as selectivity profiles, were compared.

This research was limited to in-silico docking simulation, which is not representative of the in vivo conformation dynamics or pharmacokinetics. There was no molecular dynamics simulation, no experimental validation, e.g., in vitro assay and animal test, due to resource and time limitations.

Results

Molecular Docking Analysis

Protein-ligand docking was performed with the software Molecular Operating Environment (MOE) 2015.10. Ezetimibe, malic acid, a combination of both, and two reference NSAIDs (ibuprofen and celecoxib) were docked separately into the prepared structures of COX-1 (PDB: 6Y3C) and COX-2 (PDB: 3LN1). The docking pose with the lowest binding energy score was considered the best docking pose, and the binding score represents the strength of affinity of the ligand to the active site of the enzyme. RMSD (Root Mean Square Deviation) values were obtained in Angstrom (Å) and only those poses with RMSD < 2.0 Å were regarded as valid and stable [15]. Docking results and binding energies, RMSD range, as well as essential amino acid interactions are summarised in Table 2, and common amino acid residue interactions among the ligand pairs are listed in Table 3. Further details for each ligand are given below.

Table 2. Docking results for various ligands with COX-1 and COX-2, including binding energy, RMSD values, and amino acid interactions for each compound.

Name of Ligand	Protein	Binding Energy	RMSD Value	H-bonding Conventional	Carbon hydrogens	Hydrophobic alkyl and pi-alkyl	Interaction others
Ibuprofen	COX-1	-6.3046	0.7748	HIS A:43	LYS A:468	ARG A:469 LEU A:152 CYS A:36 CYS A:47 CYS A:41 PRO A:40	-
	COX-2	-6.0871	1.4074	ARG A:29 GLN A:27 ASN A:28	LYS A:454	PRO A:139 CYS A:32 LEU A:138 ARG A:455	-
Celecoxib	COX-1	-7.2421	1.0696	ARG A:469	-	ILE A:46 LEU A:152 PRO A:153 CYS A:47 LYS A:468 TYR A:130	Pi-Sulfur (CYS A:36) Halogen(fluorine) (ILE A:151)
	COX-2	-7.3350	1.8046	ASN A:24, ARG A:29	ASN A:24	PRO A:139 LYS A:242 LEU A:138 ARG A:455 TYR A:116	Halogen (ASP A:111, GLU A:31)
Ezetimibe	COX-1	-8.364	2.000	ARG A:469, CYS A:47, CYS A:36, HIS A:43	ILE A:46	PRO A:153, PRO A:156	Pi-Sulfur (CYS A:36)

Name of Ligand	Protein	Binding Energy	RMSD Value	H-bonding Conventional	Carbon hydrogens	Hydrophobic alkyl and pi-alkyl	Interaction others
Malic Acid	COX-2	-8.7288	1.4095	ALA A:142, CYS A:32, ARG A:29	GLY A:30, ASN A:28, ARG A:29	ARG A:455, CYS A:21, PRO A:139, ARG A:29, LYS A:454	Pi-Donor Hydrogen Bond (ASN A:28, GLY A:30, ARG A:29)
	COX-1	-4.6356	1.8219	CYS A:41, GLN A:461	PRO A:40, TYR A:39	-	-
	COX-2	-4.6326	1.7023	GLY A:30, ARG A:29, GLN A:447, CYS A:26	PRO A:139, GLU A:31	-	-
Combination (Ezetimibe + Malic Acid)	COX-1	-7.7017	1.8692	CYS A:47, ARG A:469, HIS A:43, LYS A:468, GLU A:465, GLN A:461, GLY A:45, GLN A:44	ILE A:46, GLN A:42	PRO A:156, PRO A:153, LEU A:152	Pi-Sulfur (CYS A:36)
	COX-2	-8.8037	1.1717	ASN A:28, GLN A:447, ASP A:111, CYS A:21, CYS A:26, ARG A:29, LYS A:454	ARG A:29, GLY A:30, PRO A:140, ARG A:455, ARG A:29	LYS A:454, ARG A:455, PRO A:139, ARG A:29, CYS A:21	Pi-Pi T-shaped (TYR A:116), Halogen (Fluorine) (PRO A:140), Aromatic ring, Fluorine Atom

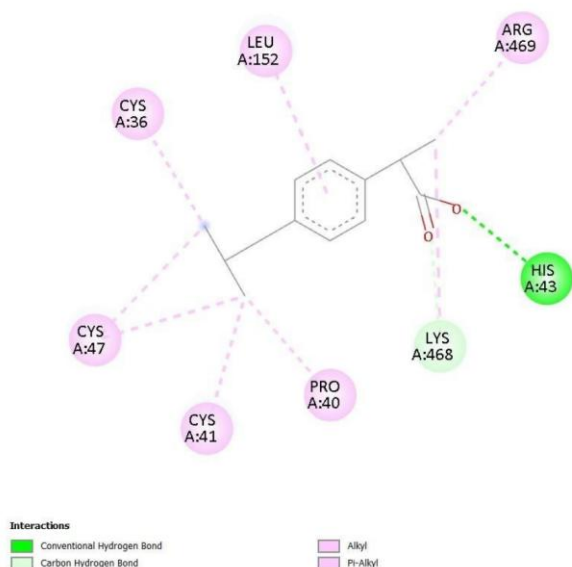
Table 3. Common Amino Acid Residue Interactions Among Ligand Pairs

Protein	Ligand pair	Common interaction
COX-1	Ibuprofen and Celecoxib	LEU A:152, CYS A:36, CYS A:47, ARG A:469, LYS A:468
	Ibuprofen and Ezetimibe	HIS A:43, ARG A:469, CYS A:36, CYS A:47
	Ibuprofen and Malic Acid	-
	Ibuprofen and Complex (Ezetimibe and Malic Acid)	HIS A:43, LYS A:468, ARG A:469, LEU A:152, CYS A:36, CYS A:47
	Celecoxib and Ezetimibe	ARG A:469, ILE A:46, PRO A:153, CYS A:47, CYS A:36
	Celecoxib and Malic Acid	-
	Celecoxib and Ezetimibe-Malic Acid complex	ARG A:469, ILE A:46, LEU A:152, PRO A:153, CYS A:36
	Ezetimibe and Malic Acid	-
	Ezetimibe and Ezetimibe-Malic Acid complex	ARG A:469, CYS A:47, HIS A:43, PRO A:153, PRO A:156, CYS A:36
COX-2	Ibuprofen and Celecoxib	ARG A:29
	Ibuprofen and Ezetimibe	ARG A:29, ASN A:28, LYS A:454, PRO A:139
	Ibuprofen and Malic Acid	ARG A:29, PRO A:139
	Ibuprofen and Complex (Ezetimibe and Malic Acid)	ARG A:29, ASN A:28, PRO A:139, ARG A:455
	Celecoxib and Ezetimibe	ARG A:29, PRO A:139
	Celecoxib and Malic Acid	ARG A:29, PRO A:139, GLU A:31
	Celecoxib and Ezetimibe-Malic Acid complex	ARG A:29, PRO A:139, ARG A:455, TYR A:116
	Ezetimibe and Malic Acid	GLY A:30, PRO A:139, ARG A:29
	Ezetimibe and Ezetimibe-Malic Acid complex	ARG A:29, GLY A:30, ARG A:455, CYS A:21, LYS A:454

Docking of Ibuprofen into COX-1 and COX-2

Ibuprofen had binding energies of -6.3046 kcal/mol (COX-1) and -6.0871 kcal/mol (COX-2), which means that it has non-selective, moderate-to-strong binding affinity. It made hydrogen bonds with ARG A:120 and TYR A:355 of COX-1 and ARG A:29, GLN A:27 and ASN A:28 of COX-2. Mostly, the interaction occurred through the carboxylic acid group that fixed the molecule in both isoforms. Hydrophobic contacts were also present (ILE A:46 and PRO A:153), though they did not involve deeper side-pocket contact. The 2D and 3D binding interactions are shown in Figures 1 and 2.

a)



b)

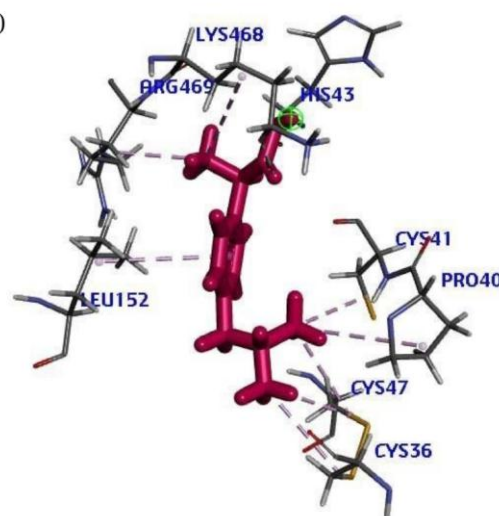
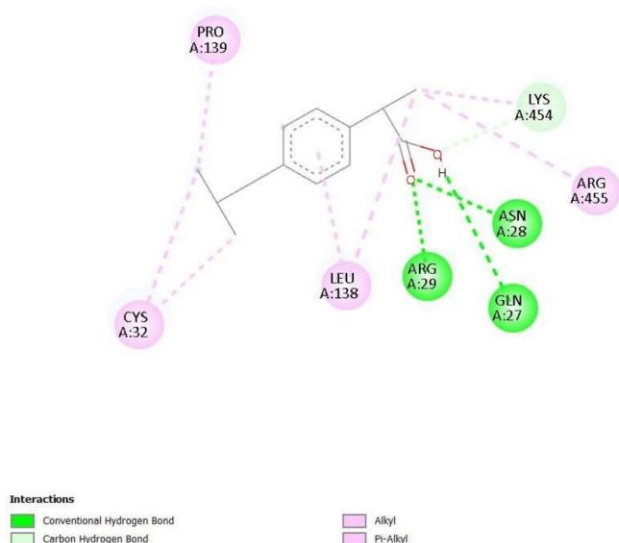


Figure 1. Binding of ibuprofen with COX-1: (a) 2D structure of the complex; (b) 3D structure of the complex.

a)



b)

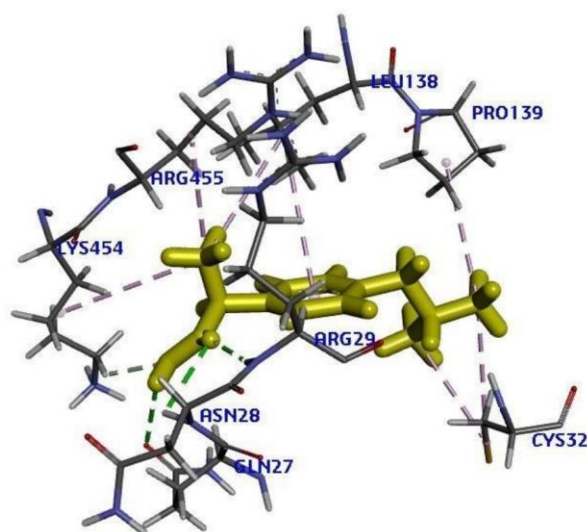


Figure 2. Binding of ibuprofen with COX-2: (a) 2D structure of the complex; (b) 3D structure of the complex.

Docking of Celecoxib into COX-1 and COX-2

Celecoxib produced binding energies of -7.2421 kcal/mol (COX-1) and -7.3350 kcal/mol (COX-2), which shows that it is selective for COX-2. In COX-1, the sulphonamide moiety was hydrogen-bonded to ARG A:469 and CYS A:47, while in COX-2, celecoxib occupied the Val523-lined side pocket, which forms stabilising interactions with ARG A:29, TYR A:116, and GLN A:27. Further pi-pi interactions and halogen-bonding interactions helped in the COX-2 specificity of celecoxib. The 2D and 3D binding interactions are shown in Figures 3 and 4.

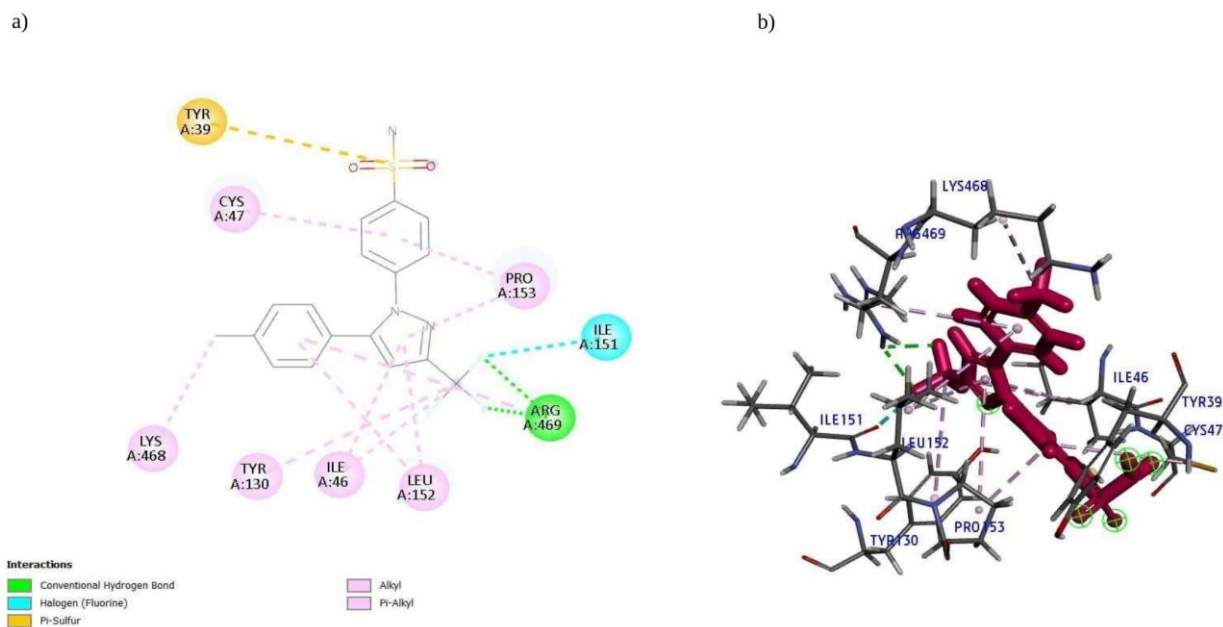


Figure 3. Binding of celecoxib with COX-1: (a) 2D structure of the complex; (b) 3D structure of the complex.

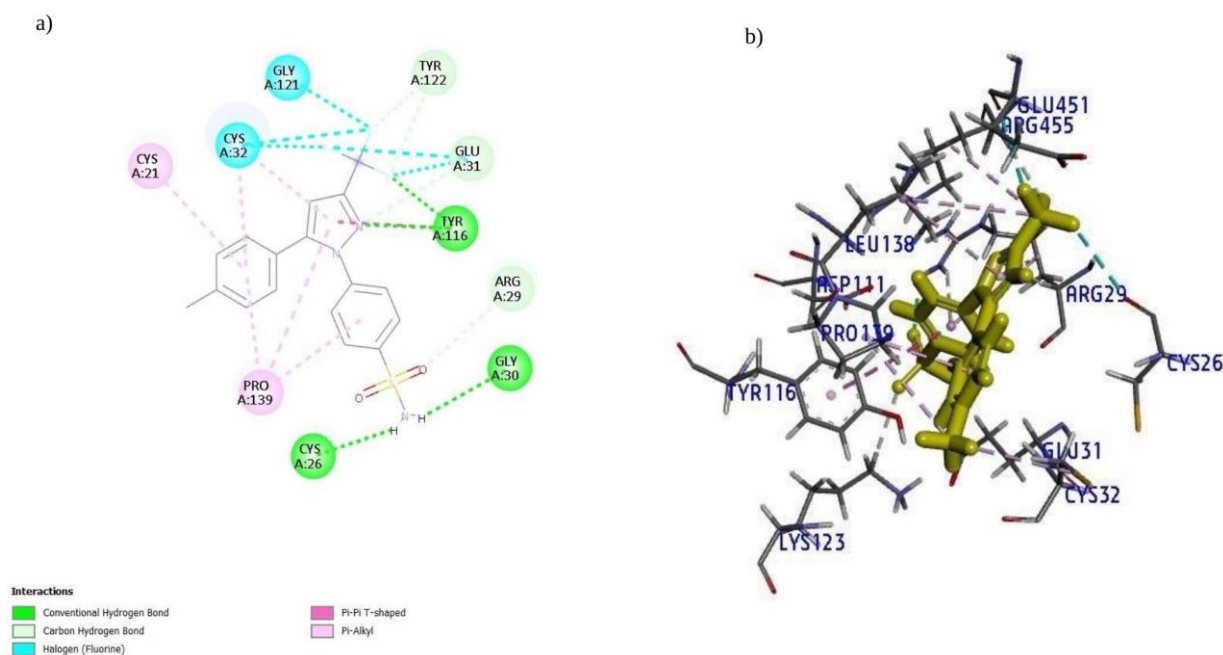


Figure 4. Binding of celecoxib with COX-2: (a) 2D structure of the complex; (b) 3D structure of the complex.

Docking of Ezetimibe into COX-1 and COX-2

Ezetimibe showed binding energies of -8.364 kcal/mol and -8.7288 kcal/mol to COX-1 and COX-2, respectively, showing high binding affinity to both isoforms. In COX-1, ezetimibe formed hydrogen bonds with amino acid residues ARG A:469, HIS A:43, GLU A:465, and CYS A:47 and a hydrophobic interaction with amino acid residue CYS A:458. The ligand was also pi-sulfur bound to CYS A:36, contributing to binding stability. In COX-2, ezetimibe bound favourably in the active-site cavity, forming hydrogen bonds with ARG A:29, GLN A:27, and ASN A:28, together with hydrophobic interactions with residues PRO A:153, ILE A:46 and CYS A:21. All these interactions were responsible for the high binding score of ezetimibe with COX-2. The 2D and 3D binding interactions are shown in Figures 5 and 6.

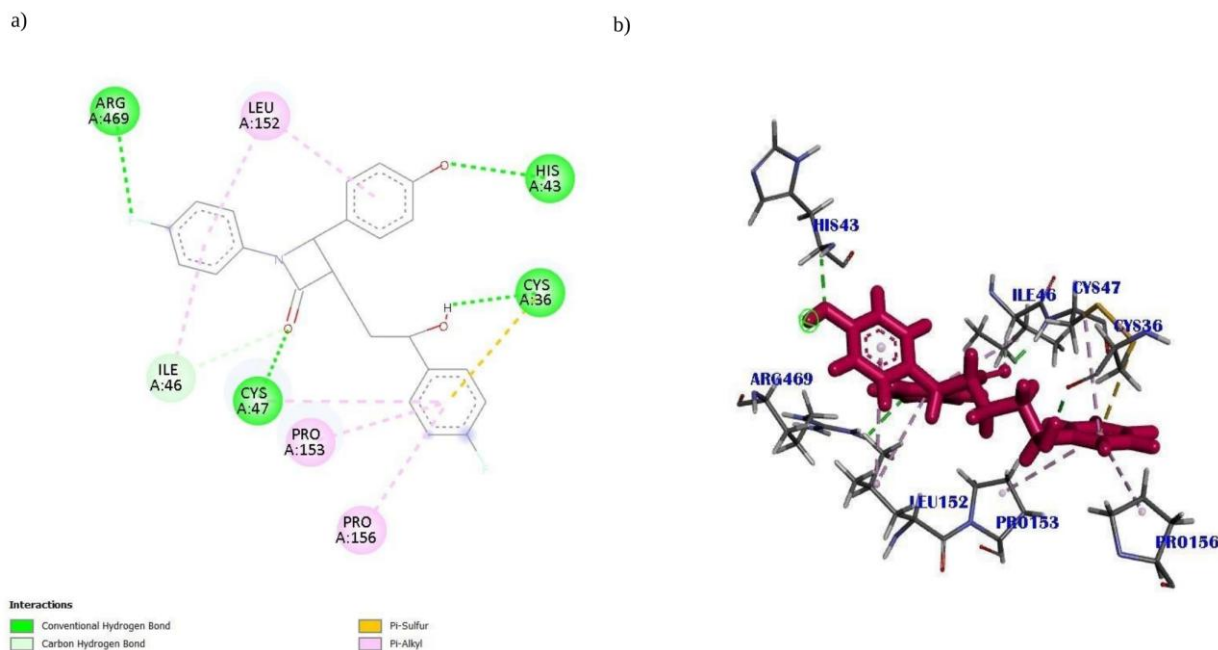


Figure 5. Binding of ezetimibe with COX-1: (a) 2D structure of the complex; (b) 3D structure of the complex.

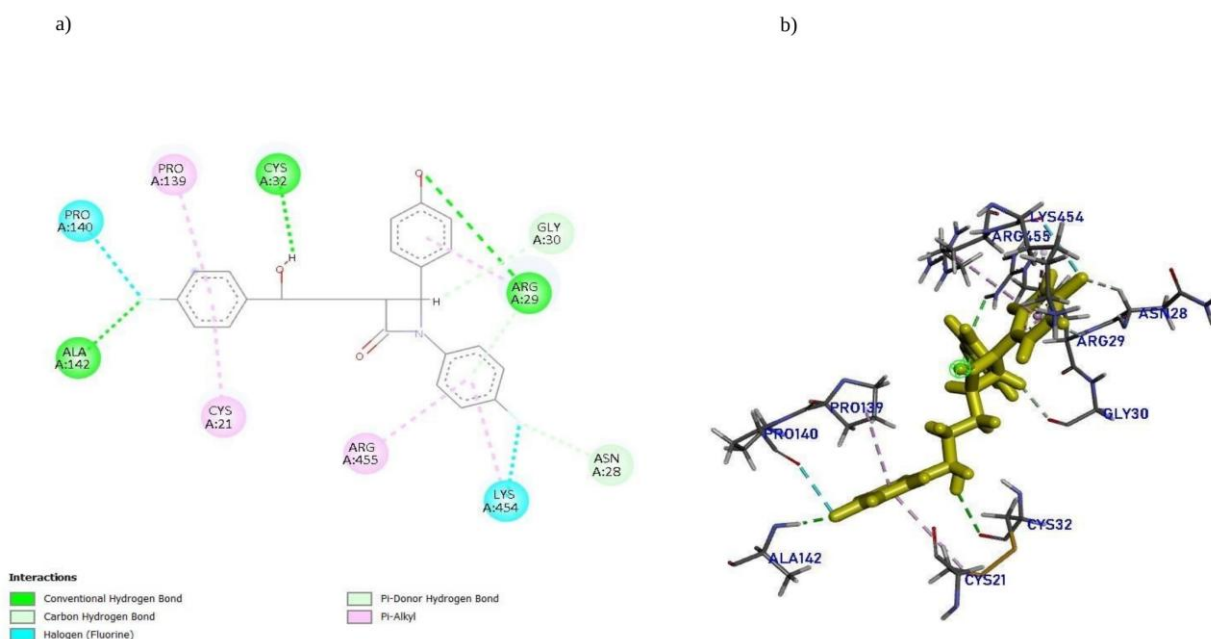


Figure 6. Binding of ezetimibe with COX-2: (a) 2D structure of the complex; (b) 3D structure of the complex.

Docking of Malic Acid into COX-1 and COX-2

Malic acid had weaker binding energies of -4.6356 kcal/mol and -4.6326 kcal/mol for COX-1 and COX-2, respectively. The compound was not able to enter deeply into the COX catalytic tunnel and formed only some peripheral hydrogen bonds with residues including THR A:212, GLN A:461, and CYS A:41. Malic acid, by virtue of its high polarity and small molecular size, could not form stabilising interactions with such catalytic residues as ARG120 or TYR355. Thus, it is unlikely to act as a potent COX inhibitor. The 2D and 3D binding interactions are shown in Figures 7 and 8.

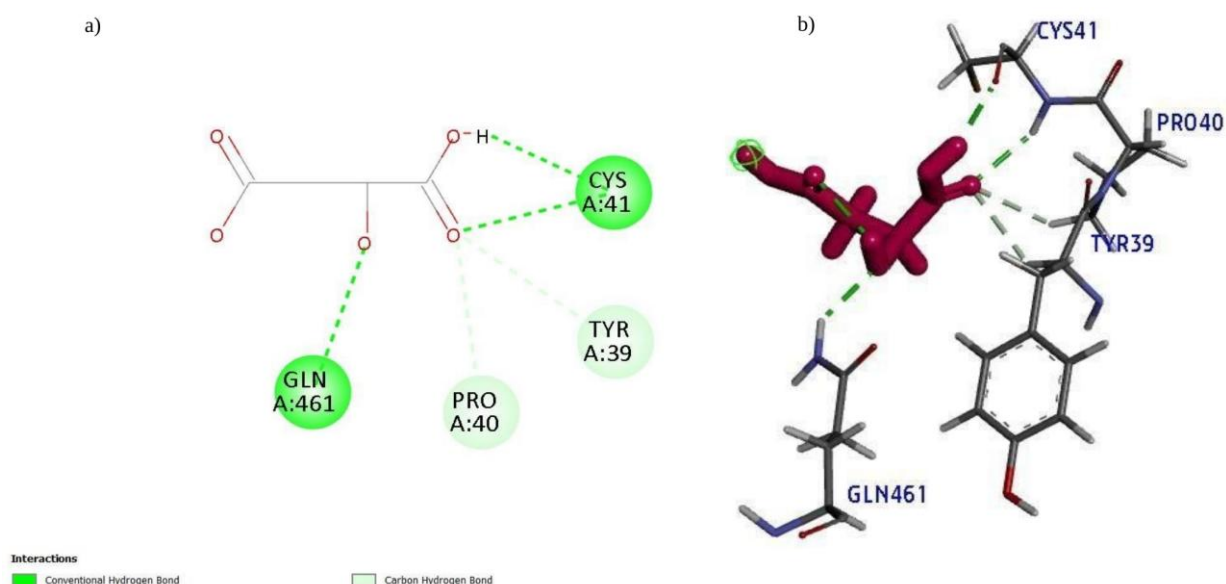


Figure 7. Binding of malic acid with COX-1: (a) 2D structure of the complex; (b) 3D structure of the complex.

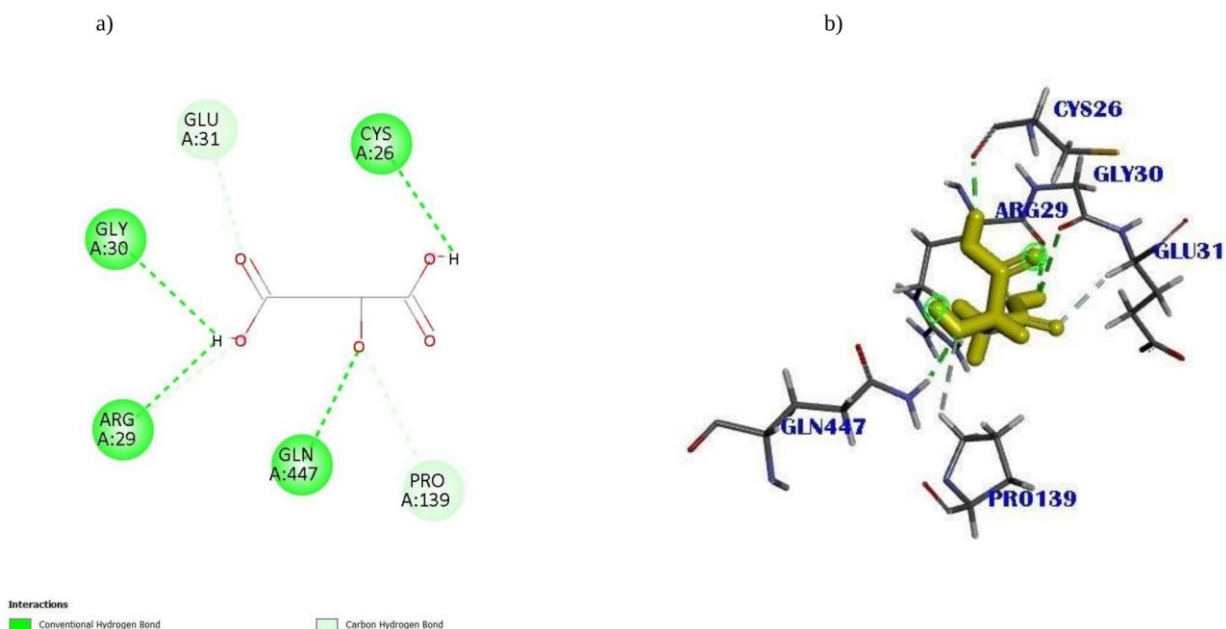


Figure 8. Binding of malic acid with COX-2: (a) 2D structure of the complex; (b) 3D structure of the complex.

Docking of the Ezetimibe + Malic Acid Combination into COX-1 and COX-2

The combination of ezetimibe and malic acid gave a binding energy of -7.7017 kcal/mol in the case of COX-1 and a remarkably increased -8.8037 kcal/mol in the case of COX-2, indicating strong COX-2 selectivity. The complex also had hydrogen bonds in COX-1 with ARG A:469, GLY A:42, ILE A:44 and HIS A:43. Otherwise, a variety of stabilising interactions, such as hydrogen bonding of ASN A:26, GLN A:27, ARG A:29, CYS A:21 and pi-pi T-shaped interaction with TYR A:116, were associated with the COX-2 docked pose. There were also halogen bonding and pi-sulfur interactions with CYS A:36 that gave COX-2 a better docking score. Such forms of interaction could not be seen in individual ligands, and this could be used to support the hypothesis of a synergistic effect after the combination of the two compounds. The binding interactions of the combination are shown in Figures 9–12, and the binding energies of all ligands are compared in Figure 13.

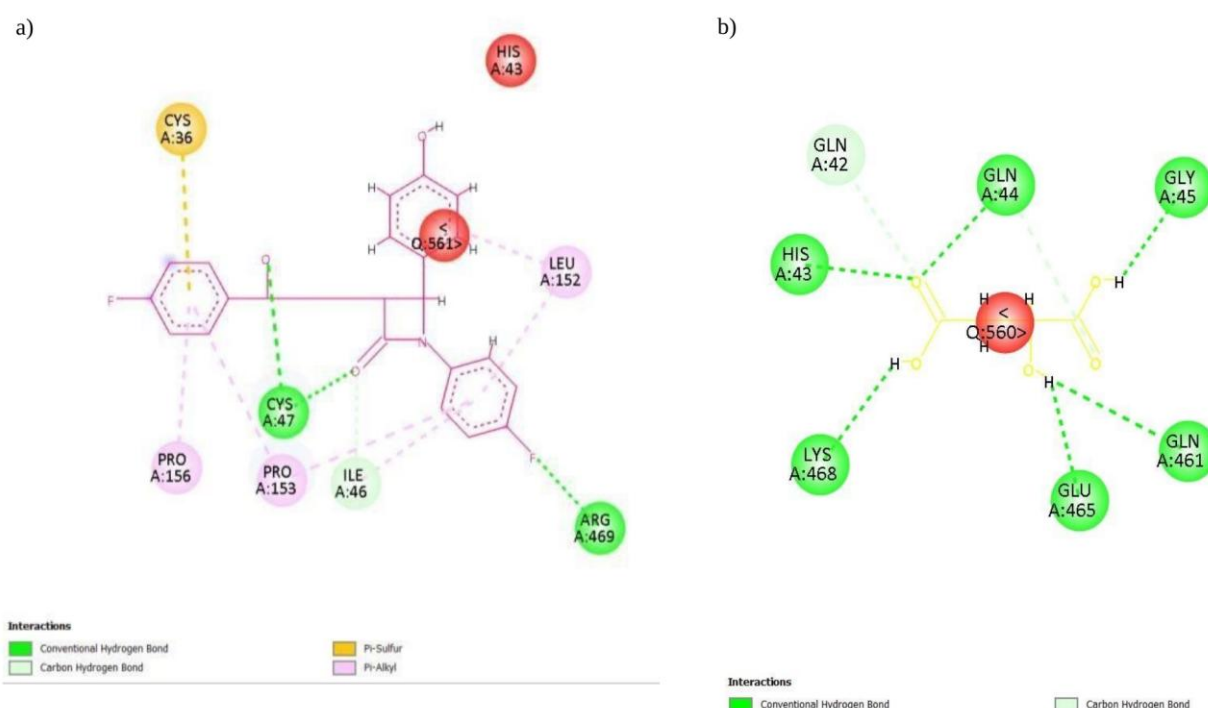


Figure 9. Docking interaction of the ezetimibe and malic acid combination with COX-1: (a) 2D structure of the ezetimibe-COX-1 complex; (b) 2D structure of the malic acid-COX-1 complex.

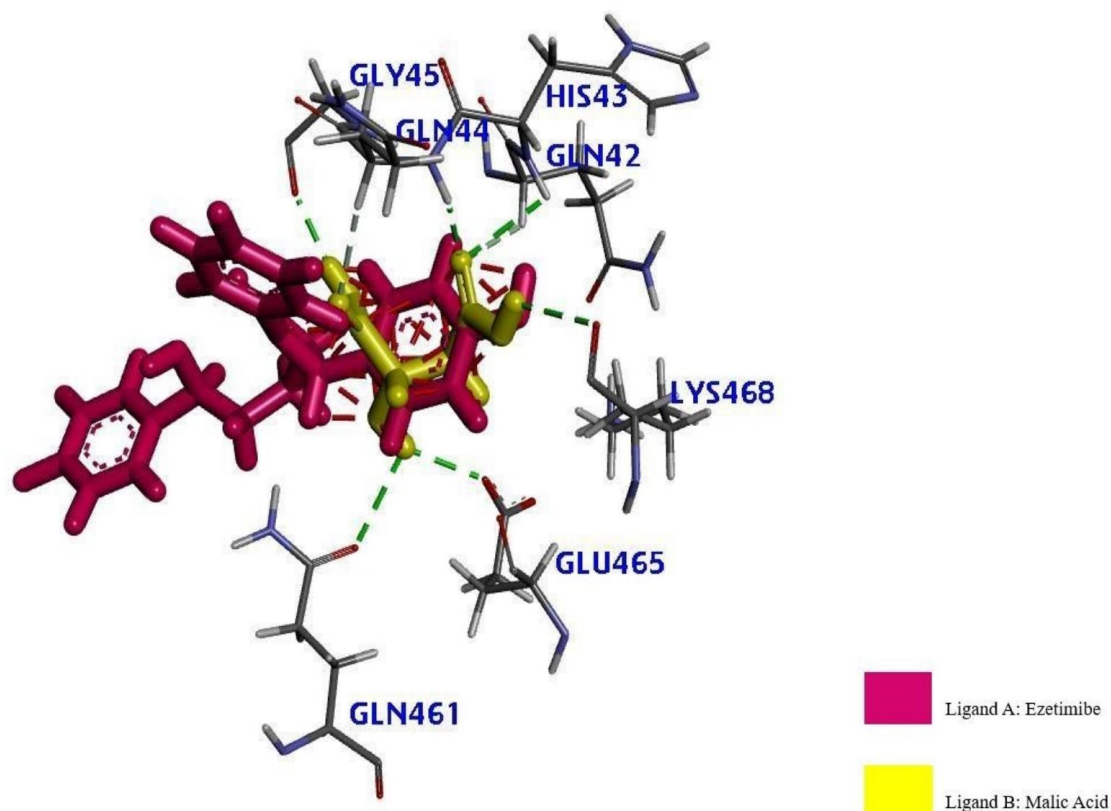
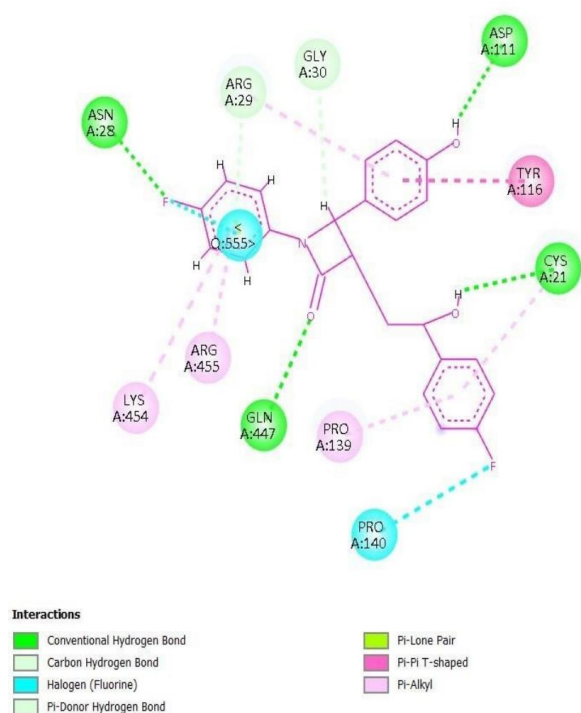


Figure 10. 3D structure of the ezetimibe and malic acid combination bound to COX-1.

a)



b)

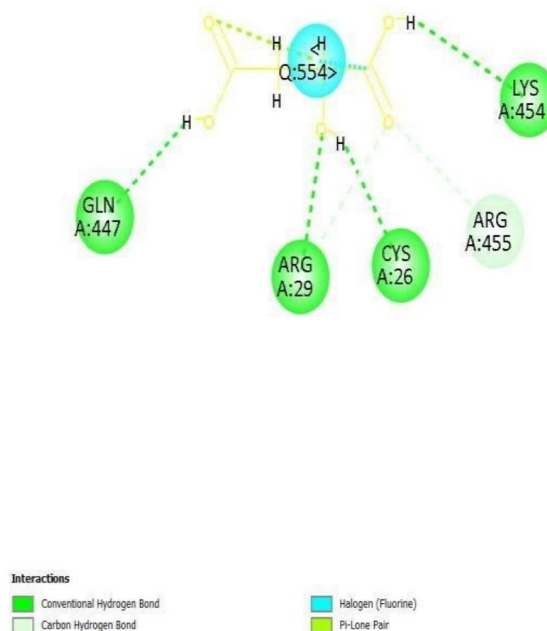


Figure 11. Docking interaction of the ezetimibe and malic acid combination with COX-2: (a) 2D structure of the ezetimibe–COX-2 complex; (b) 2D structure of the malic acid–COX-2 complex.

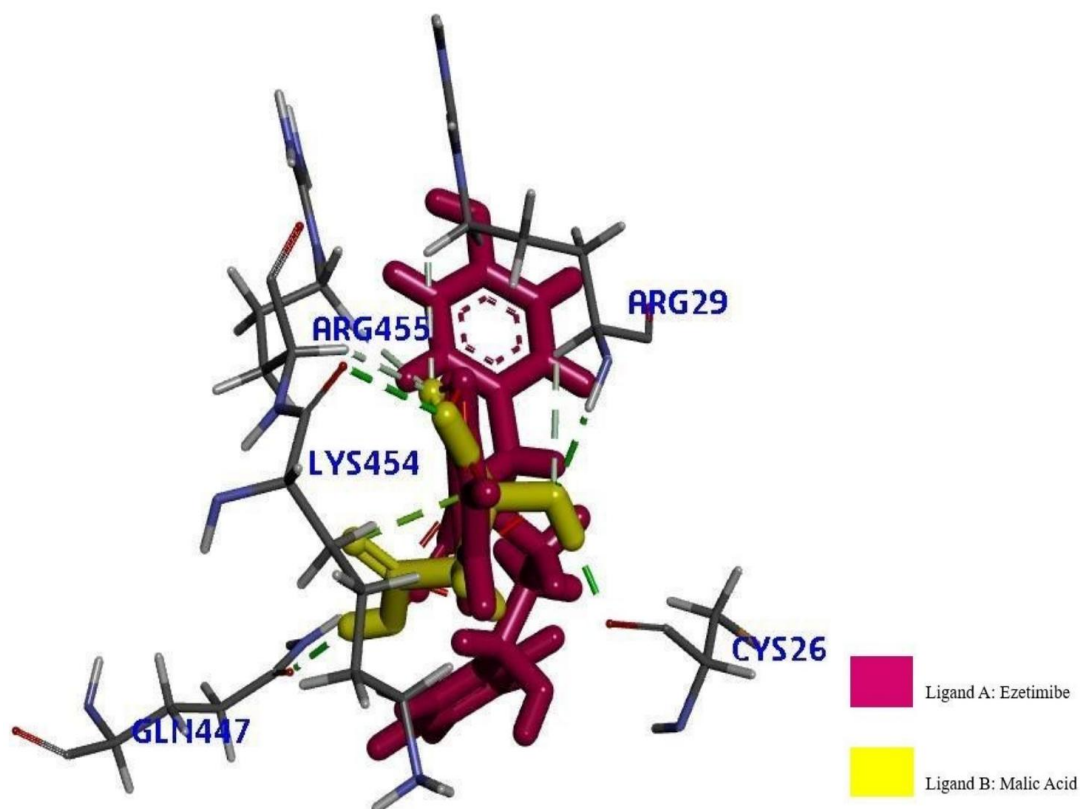


Figure 12. 3D structure of the ezetimibe and malic acid combination bound to COX-2.

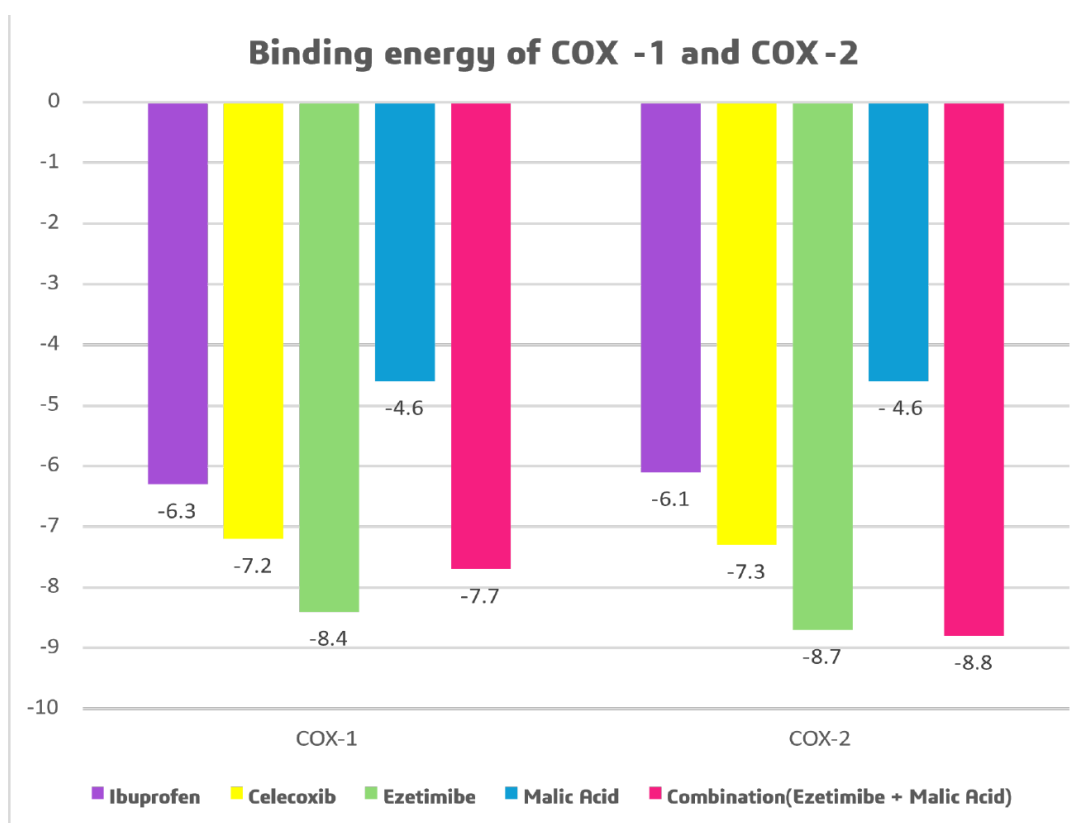


Figure 13. Bar chart of the binding energies of the ligands on COX-1 and COX-2.

Discussion

This study utilised molecular docking to determine the interaction of different ligands, namely ibuprofen, celecoxib, ezetimibe, malic acid and the ezetimibe–malic acid

combination, with the COX-1 and COX-2 enzymes. The binding patterns and affinity of these ligands provide a view of their selectivity and therapeutic interest. The docking scores of ibuprofen and celecoxib are consistent, as expected, with well-known pharmacological information. Ibuprofen had similar binding energies for COX-1 and COX-2, implying that the drug is not selective for either isoform. In contrast, celecoxib had lower binding energies and a higher affinity for COX-2.

The differential ΔE values +7.15 for celecoxib and -0.91 for ibuprofen support the established selectivity of celecoxib for COX-2 [16]. These docking figures are in line with the data regarding the ability of celecoxib to utilise the COX-2-specific side pocket and interact via the formation of pi-sulfur and halogen bonds that have been published earlier [17]. The increased binding ability of celecoxib can be attributed to the replacement of Ile523 by Val523 in COX-2 which enlarges the binding pocket, leading to favourable binding of bulkier ligands [18]. This selectivity is also promoted by hydrophobic interactions with residues such as ILE A:46 and PRO A:153.

Ezetimibe showed good binding capacity with the COX isoforms. The values are higher than those of celecoxib and ibuprofen and correspond to the reported docking range of successful drug-like ligands [19]. It has an enhanced binding affinity, complemented by contacts with important residues like ARG A:469 and CYS A:36, similar to the result in the case of other protein targets like interleukin-1 beta convertase [20,21]. HIS A:43 in COX-1 formed hydrogen bonds with ibuprofen and ezetimibe; histidine residues have been shown to stabilise ligand binding within hydrophobic cavities [22]. Ezetimibe has a greater affinity for COX-2 than for COX-1 because of structural differences, including the presence of Val523 in COX-2, which further explains its dual selectivity.

In contrast, malic acid showed the weakest binding of all the tested ligands, with docking scores of -4.64 kcal/mol against COX-1 and -4.63 kcal/mol against COX-2. This agrees with its small structure and strong polarity, which limit its ability to interact with the hydrophobic COX catalytic tunnel. It did not interact with important residues like Arg120 and Tyr385; thus, it was a low-potency binder [23,24]. Nevertheless, it has antioxidant and gastroprotective effects, which may be complementary when it is combined with other therapies [25].

The combination of ezetimibe and malic acid produced enhanced binding affinity for COX-2 compared to COX-1, showing improved selectivity for the inflammatory isoform. These results surpass the individual binding scores of ezetimibe and reference NSAIDs like celecoxib and ibuprofen [20]. The complex established multiple hydrogen bonds in both isoforms. In COX-1, it interacted with residues such as CYS A:47, ARG A:469, and HIS A:43, while in COX-2, interactions were noted with ASN A:26, GLN A:27, and ARG A:29. These amino acids are critical for COX enzyme function and contribute to ligand stabilisation [26,27].

Non-conventional interactions were also observed in the combination model. Pi-sulfur interactions with CYS A:36, pi-pi T-shaped interactions with TYR A:116 and halogen bonding with fluorine atoms were reported. Such advanced interactions increase binding affinities and have been linked with better selectivity to COX-2, as shown by work on doronine derivatives and other COX inhibitors [27,28].

Hydrophobic interactions also contributed to the stabilisation of the combination in the enzyme cavities. In COX-1, the ligands showed interaction with PRO A:156, PRO A:153 and LEU A:152, whereas in COX-2, they interacted with LYS A:454, ARG A:455 and CYS A:21. This

kind of interaction is necessary to maintain conformational fit [29]. The root mean square deviation (RMSD) values of 1.8692 Å for COX-1 and 1.1717 Å for COX-2 indicate stable computed poses. The smaller RMSD value for COX-2 suggests tighter binding and a more stable pose, which supports the selectivity for COX-2.

Greater performance was achieved with the combination as compared to individual ligands, suggesting a potential synergistic effect. This conclusion is supported by the presence of specialised interactions that were absent in single-agent docking. The weaker COX-1 binding energy suggests a reduced probability of side effects caused by COX-1 inhibition. Cytoprotective properties of malic acid could further provide an advantageous combination, and the pairing could be considered as a desirable therapeutic option [30].

These data provide a basis for co-administering a pharmacological agent (ezetimibe) and a nutraceutical (malic acid) to produce a dual-acting, selective COX-2 inhibitor with a minimised side-effect profile. This approach has the potential to become a new type of anti-inflammatory treatment, which would be effective and safe at the same time.

Conclusion

The molecular docking study carried out in this research showed that ezetimibe bound effectively to COX-1 and COX-2, with many stabilising interactions such as hydrogen bonds and hydrophobic interactions. When ezetimibe was combined with malic acid, a moderate-to-strong affinity for COX-1 was observed, while a strong affinity for COX-2 was retained. This implies that the combination strategy may minimise the gastrointestinal side effects commonly associated with COX-1 inhibition while maintaining the potential anti-inflammatory effects of COX-2 targeting. Furthermore, as malic acid has well-documented antioxidant and gastroprotective effects, it may add value by improving the mucosal protection of the stomach. To summarise, the findings show that ezetimibe not only has potential as an anti-inflammatory agent through selective COX-2 inhibition, but that its combination with malic acid may also offer a better therapeutic safety margin. These results suggest that the pharmacological versatility of ezetimibe extends beyond its classification as a lipid-lowering agent.

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Software

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Data Availability

All data generated or analysed during this study are included in this manuscript and are available from the corresponding author upon reasonable request.

Ethics Statement

This research did not involve human participants, animal subjects, or any biological material requiring ethical approval.

Informed Consent Statement

This study did not involve human participants; therefore, informed consent was not applicable.

Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this paper.

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