# In Silico Molecular Docking & ADME Studies Approach for Designing of New Schiff Base Derivatives of Indomethacin as Both Anti-Inflammatory and Anticancer Agents

**Jessica Shlimoon Hanna[1*], Kanar Muthanna Alawad[2]**

## Abstract

New Schiff base derivatives were designed, and the computational methods were used to predict their anti-inflammatory activity *in silico* against cyclooxygenase-2 (COX-2) and tubulin polymerization inhibition (TPI) protein to expect their anticancer activity. The developed compounds [S] & [S1-S6] were designed by incorporating thiadiazole moiety into indomethacin the well-known anti-inflammatory drug. Computational approaches, such as ADME studies, were done by using the SwissADME server used to predict the pharmacokinetics of the new compounds. The outcomes demonstrated that all compounds fulfilled the Lipinski rule of five (RO5), except for compound [S4]. Furthermore, using the GOLD suite program (*v.* 2021.3.0), to evaluate the selectivity of designed compounds towards the COX-2 and tubulin polymerization proteins. Docking studies for ligand interactions with COX-2 protein predict potential activity for compounds (S2, S4, S5) interacting with amino acids in the active pocket with higher PLP fitness values than the reference (Flurbiprofen and Indomethacin). Moreover, for tubulin inhibition, the compounds (S1, S4, S5) exceed the reference ligand colchicine in terms of PLP fitness values. As a result, compounds (S4 & S5) show good impacts on both proteins COX-2 and TPI. The findings highlight the compounds' relevance as promising lead choices for cancer therapy associated with inflammation, which might help researchers develop and synthesize more effective candidates in the future. The research also proposed that the identified substances be investigated in vivo and in vitro to confirm the computer findings.



**Key Words:** Inflammation, Indomethacin, ADME, GOLD, Thiadiazole.

**DOI Number: 10.14704/nq.2022.20.8.NQ44120** **NeuroQuantology 2022; 20(7): 1093-1103**

## Introduction

Inflammation is the body's first response to an infection or damage. It is a series of immunological responses that occur as a result of a disruption in tissue homeostasis and act to eliminate the source of infection or restore damaged tissue (1). A large and complicated series of events happen. Persistent immunosuppression and catabolism may follow, eventually leading to multiple organ failures (2). Inflammation is either acute or persistent. However, untreated acute inflammation can progress to chronic inflammation. This mechanism reaction is critical for good health. Typically, this occurs with acute inflammation (3). Acute Inflammation may lead to tissue damage brought on by trauma, microbial invasion, or toxic substances. It begins suddenly, worsens quickly, and the symptoms might continue for a few days. Subacute inflammation, which can persist from two to six weeks, falls between acute and chronic inflammation, while chronic inflammation can endure for years (4,5). Inflammation is one of the mechanisms that contribute to tumor growth.

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Although acute inflammation is one of the first reactions to tissue injury and aids in the defense against the invasion of foreign pathogens, persistent inflammation can promote tumor start and progression. Chronic inflammation in the tumor microenvironment also promotes tumor invasion and metastasis because pro-inflammatory mediators stimulate tumor cells to extravagate into the stroma (6,7).

The production of different pro-inflammatory and carcinogenic mediators such as nitric oxide (NO), cytokines, interleukin-6, tumor necrosis factor-α (TNF-α), and the growth factor is linked with an inflammatory microenvironment. These mediators increase the inflammatory microenvironment's susceptibility to cancer (8,9). However, in a chronic inflammatory state, particularly in the tumor microenvironment, the presence of inflammatory cells benefits cancer cells by promoting their survival and proliferation (4,10).

Anti-inflammatory medications have also been demonstrated to be effective in slowing tumor development and preventing cancer, combating chemo-resistance, reducing cancer morbidity, and enhancing cancer patient survival (11,12). Nonsteroidal anti-inflammatory drugs (NSAIDs) also reduce the risk of developing various types of solid tumors, including melanoma, prostate cancer, and breast cancer(13). The cyclooxygenase (COX) enzyme family is the molecular target of NSAIDs, which reduce the activity of cyclooxygenase isozymes (COX-1 and COX-2) (14).

Based on the previously mentioned chemopreventive properties of NSAIDs, as well as earlier results supporting the modification of NSAID scaffolds to get more effective and less systemically toxic anticancer drugs, we need to make some chemical changes in this research to one of the NSAIDs, indomethacin, using Molecular docking or drug design strategies.

In recent years, a new paradigm in cancer treatment has emerged, focusing on the transition from cytotoxic to targeted molecular medicines(15). Tubulin inhibitors were the primary choice in the development of targeted drug delivery systems due to their high effectiveness in killing cancer cells(16). Inhibiting microtubule synthesis by targeting tubulin protein triggers apoptosis. Taxanes, vinca alkaloids, colchicine, and other drugs bind at various locations of the tubulin protein within microtubule filaments, influencing the kinetics of microtubule assembly (16,17). Colchicine binding site inhibitors (CBSI) exhibit their biological effects by inhibiting the critical process of tubulin assembly, hence inhibiting microtubule formation (17).

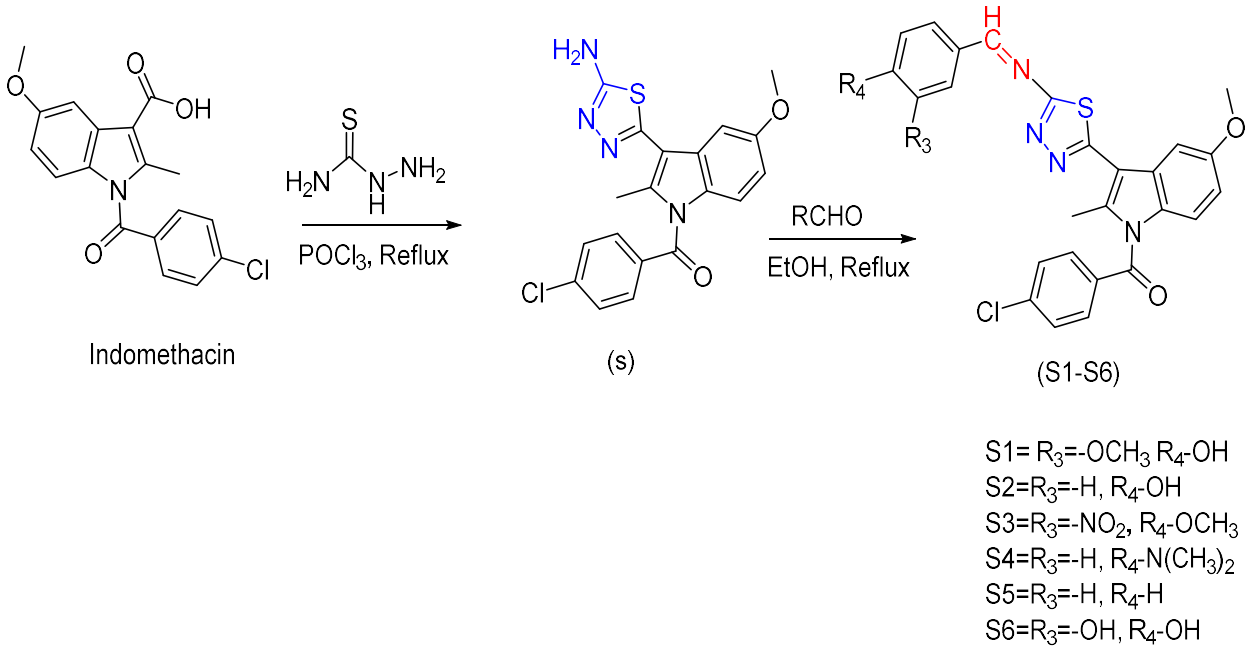
The goal of this research was to use a molecular docking approach to virtual screen new Schiff base derivative products with COX-2 and tubulin polymerization proteins as targets, and to identify a possible lead molecule as a template to design hypothetical molecules with improved binding affinities and molecular residual interactions with the receptor. In-silico absorption, distribution, metabolism, and excretion (ADME) and drug-likeness features of the compounds were also investigated. Other assessments included physicochemical properties of a molecule such as saturation, lipophilicity, polarity, size, solubility, and flexibility, which give vital information on whether the molecule may be used as a therapy at an early stage of development.

## Materials and Methods



### *Chemical Synthesis*

The assumed synthesis pathway for the intermediate chalcone derivative compound [S] and the final compounds [S1-S6] is derived from indomethacin, as the following scheme:




**Scheme 1.** Hypothesized synthetic pathway of compounds [S] and [S1-S6]

## Computational Methods

### *In-silico ADME/Pharmacokinetic Predictions*

The ADME (Absorption, Distribution, Metabolism, and Excretion) investigations and other physicochemical features of the newly designed compounds were accessed via the SwissADME service (18). ChemAxon's Marvin JS program was used to draw the chemical structures of the novel compounds [S], & [S1-S6]. To estimate their pharmacokinetic and physicochemical features, these structures were translated to the SMILE name using the Swiss ADME program. Finally, the BOILED EGG was utilized in these tests to examine passive gastrointestinal absorption and brain penetration, as well as the polarity and lipophilicity of small compounds (19).

### *Molecular Modelling*

Docking experiments for the modeled compounds were performed using the CCDC (Cambridge Crystallographic Data Center) (GOLD) (Genetic Optimization for Ligand Docking) program (v 5.7.1.).

Molecular docking studies are an essential technique for the detection of new drugs since they predict affinity, interaction with receptors, and, primarily the biological activity (20).

The CCDC GOLD Suite (v. 2021.3.0) includes Hermes visualizer software (v. 2021.3.0), which is used to help prepare input files for docking with GOLD. Additionally, visualize the receptors, ligands, interaction type (H-bond, hydrophobic...etc.), active site, bond length calculation, pose prediction, and obtain photos.



### *Ligands Preparation and Protein Receptor*

The chemical structure of our ligands was sketched using ChemDraw professional (v.16.0) software. Our molecules' energy was then minimized using Chem3D (v.16.0) and the MM2 force field.

The newly developed ligands were then docked utilizing the three-dimensional structures of two active targets: the crystal structure of COX-2 protein (PDB code: 4M11) complexed with flurbiprofen and the crystal structure of tubulin polymerization inhibitor enzyme (PDB code: 1SA0) complexed with colchicine as reference ligand. The receptors supplied into GOLD's Hermes module from the protein data bank (PDB). To validate the docking procedure, the co-crystalized ligands were re-docked. To obtain accurate ionization and tautomeric states of amino acid residues polar Hydrogen-atoms were also added. The crystalline structures of the two active targets were also cleaned up by removing all water molecules.

### *Molecular Docking Protocol*

The complete license version of Genetic Optimization for Ligand Docking (GOLD) was used to prepare the molecular docking (v.2021.3.0). The

docking procedure was provided by the Hermes visualizer application within GOLD. To conduct a docking examination, two proteins (4m11 and 1SA0) were downloaded from the protein data bank (PDB) Flurbiprofen is a protein reference ligand in 4m11 that is used to define the active site within a radius (10°A). By default, all variables utilized throughout the docking process are preserved, and all solutions are recorded using the Piecewise Linear Potential (CHEMPLP). The docking solution reveals the binding mode and optimal docking location and the free binding energy has been calculated to evaluate the interaction between amino acid residues in COX-2 and TPI proteins with our developed compounds.

## Results and Discussion

### *Chemical Synthesis*

The new derivatives were designed by incorporating thiadiazole pharmacophore into indomethacin to get the final compounds [S1-S6]. The intermediate derivative was compound [S]. The hypothesized synthetic pathway that might be used in the upcoming research is shown in scheme (1). The targeted Compounds were designed based on a research article (21).

### *ADME Results Interpretation*

SwissADME (18) was used to predict the physicochemical and ADME characteristics of developed compounds in silico. It is a helpful and low-cost method for detecting ADME properties prior to synthesis and biological testing, as well as excluding ligands with insufficient pharmacokinetics; these parameters include the topological polar surface area (TPSA), which is used to define the capacity of drugs to permeate cells; compounds with TPSA < 140Å, which indicate high permeability and bioavailability (19). Our findings revealed that all compounds had TPSA <140Å ranging from (97.61-152.49). However, all of the compounds met the traditional lipophilicity description (log Po/w). In the meantime, molar solubility in water (log S) shows that all of the substances have poor solubility. compound [S] with high intestinal absorption, all ligands are predicted to be passively and poorly absorbed from the GIT.
Lipinski's "rule of five" (RO5) indicates that substances should have a molecular mass < 500 Daltons, < 5 H-bond donors, <10 H-bond acceptors, and log p< 5 (octanol-water partition coefficient) to be taken orally, otherwise they would have low bioavailability and permeability (22). Except for compound [S4], all of the other designed compounds satisfied the RO5. Furthermore, the bioavailability score for all ligands was 0.55, except for compound [S4], which was 0.17, as shown in table (1) which also demonstrates that the compounds do not penetrate the BBB. Compounds in red dots are not exported from CNS cells by P-glycoprotein. The BOILED-EGG for designed compounds is represented in figure (1). Show that the compounds in the yellow ovule (yolk) are molecules that are predicted to pass across blood-brain barriers passively. White ovules (white): These are molecules that are predicted to be passively absorbed by the GIT. PGP-: Red dots indicate compounds that are not predicted to be effluted from the CNS by the P-glycoprotein (P-gp).



**Table 1.** ADME results of intermediates and target compounds

| Comp. | H-donor | H-acceptor | MR | TPSA (Å) | GI Abs. | BBB permeability | Bio-availability | Lipinski Violation |
|---|---|---|---|---|---|---|---|---|
| **S** | 1 | 4 | 107.88 | 111.27 | High | No | 0.55 | 0 |
| **S1** | 1 | 7 | 145.69 | 127.07 | Low | No | 0.55 | 1[Mwt.>500] |
| **S2** | 1 | 6 | 139.20 | 117.84 | Low | No | 0.55 | 1[Mwt.>500] |
| **S3** | 0 | 8 | 152.49 | 152.66 | Low | No | 0.55 | 1[Mwt.>500] |
| **S4** | 3 | 3 | 151.38 | 100.85 | Low | No | 0.17 | No, 2 violation |
| **S5** | 0 | 5 | 137.18 | 97.61 | Low | No | 0.55 | 1[MLOGP.>480] |
| **S6** | 2 | 7 | 141.22 | 138.07 | Low | No | 0.55 | 1[Mwt.>500] |

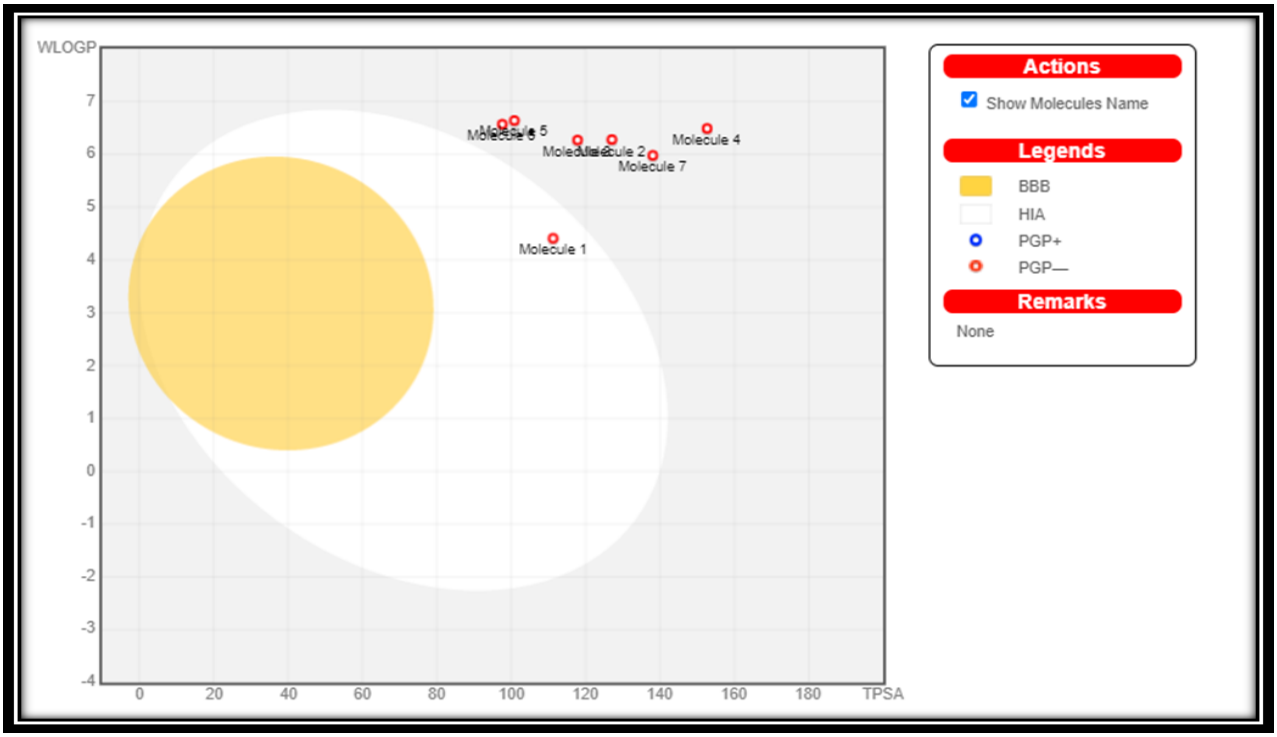



**Figure 1.** BOILED-EGG for the designed compounds

## *Interpretation the Results of Molecular Docking Studies*

GOLD stands for "Genetic Algorithm for Docking Flexible Ligands into Protein Binding." (23) In general, GOLD has the benefit of predicting the pose and providing outstanding results for virtual screening. It is given as part of the GOLD suite, which also includes Hermes, CSD python, mercury, ConQuest, mogul, and others. By modifying the geometry of the structure, energy optimization methods were employed to find a stable and low-energy conformation.

Docking studies indicate binding energies and selectivity of designed compounds to proteins (4M11, 1SA0) by analyzing the molecular interaction between the active binding sites of the proteins and designed compounds.

The inhibitory effects of the designed compounds, Indomethacin, and Colchicine, for [4M11 and 1SA0] proteins were rated based on their PLP fitness implicated in complex formation in the active sites. Tables (2) and (3) show the docked compounds' PLP fitness on 4M11 and 1SA0 proteins, respectively.

The GOLD software also provides the distance of hydrogen bonding between our designed ligands and a given protein, as well as the total length of all bonds, which was < 3A(20).

Docking studies demonstrate that all the designed compounds have good binding energies with the receptor active pocket and are likely to have promising activity with the 4M11 and 1SA0 proteins, because they attach to the amino acids (AAs) residue of the active site via H-bonds and other short contacts.

However, compounds [S2, S4, S5] with cox-2 protein have the greatest PLP fitness value (91.31,86.88,91.14 respectively) and H-bonding with AAs also are shown in table (2). The majority of other ligands have greater binding energies than the conventional medicines (Flurbiprofen and Indomethacin), which had PLP fitness values of 72.21 and 63.00, respectively.

Docking studies for the 1SA0 protein reveal that the most significant interaction inside the active region was with the amino acids ALA250, which were reported from standard colchicine. As shown in table (3), compounds [S1, S4, S6] with 1SA0 protein had the greatest PLP fitness value (74.21, 75.52, and 82.08).

Tables (2 and 3) and figures (2-11) depicted the best derivative and reference control.

**Table 2.** The Binding Energies of indomethacin Derivatives Docked with receptor COX-2 (PDB code: 4M11)

| Compound | binding energy (PLP fitness) | Amino acid included in H-bonding | Amino acid included in a short contacts |
|---|---|---|---|
| S | 60.91 | Arg120(2), TYR355, | VAL116(3), SER530, VAL349, GLY526, Arg120(2), TYR355(7), LEU352(3) |
| S1 | 75.64 | SER530, LEU531, | SER530, VAL116(5), TYR115, LEU93(6) |
| **S2** | **91.31** | Arg120(2), MET522, SER530, PHE357 | LEU93, VAL116(3), Arg120(3), TYR355, MET522(3), SER530 |
| S3 | 83.48 | Arg120(3), TYR355, | GLY526, LEU352(4), VAL349, TYR355(5), Arg120(4), PRO86, VAL89(4), SER119, VAL116 |
| **S4** | **86.88** | GLY526, Arg120(2), TYR355(2), LEU352 | PRO86(2), VAL116, Arg120(2), VAL349, TYR355(4), LEU352, GLY526 |
| **S5** | **91.14** | PHE357, LEU117, Arg120, SER530, | PHE357, LEU93(5), TYR355, VAL116, Arg120(4), ALA527, SER530, VAL523(5) |
| S6 | 78.06 | GLY526 | SER119, VAL116(6), LEU117, TYR355(4), MET522(6) |
| flurbiprofen | 72.21 | Arg120(2) | Arg120(2), SER530, TYR355 |
| indomethacin | 63.00 | Arg120, TYR355 | LEU352(2), TYR355(4), Arg120(4), VAL116, MET113(7) |

*Number in brackets refer to the number of bonds.

**Table 3.** The Binding Energies for indomethacin Derivatives Docked with TPI (PDB code: 1SA0)

| Compound | Binding energy (PLP fitness) | Amino acid included in H-bonding | Amino acid included in a short contacts |
|---|---|---|---|
| S | 61.31 | VAL238, ALA250 | LEU255, VAL238, ALA250(6), |
| **S1** | **74.21** | ASN349 | ASN349, ASN258, ALA250(2), CYS241 |
| S2 | 71.05 | - | CYS241, ASN350, MET259 |
| S3 | 67.72 | LYS352 | ALA250, LYS352(2), PRO348, LEU255 |
| **S4** | **75.52** | ALA250 | LYS352, ASN258, LEU248, LYS254, ALA250(4), LEU255(2), LYS352 |
| **S5** | **82.08** | ALA250 | ALA250(8), LYS352, LEU255, CYS241(3), |
| S6 | 71.13 | ASN349, LYS352 | ALA250(2), CYS241, ASN349, LYS352 |
| colchicine | 61.54 | ALA250 | LYS352, ALA250(6) |

*Number in brackets refer to the number of bonds.



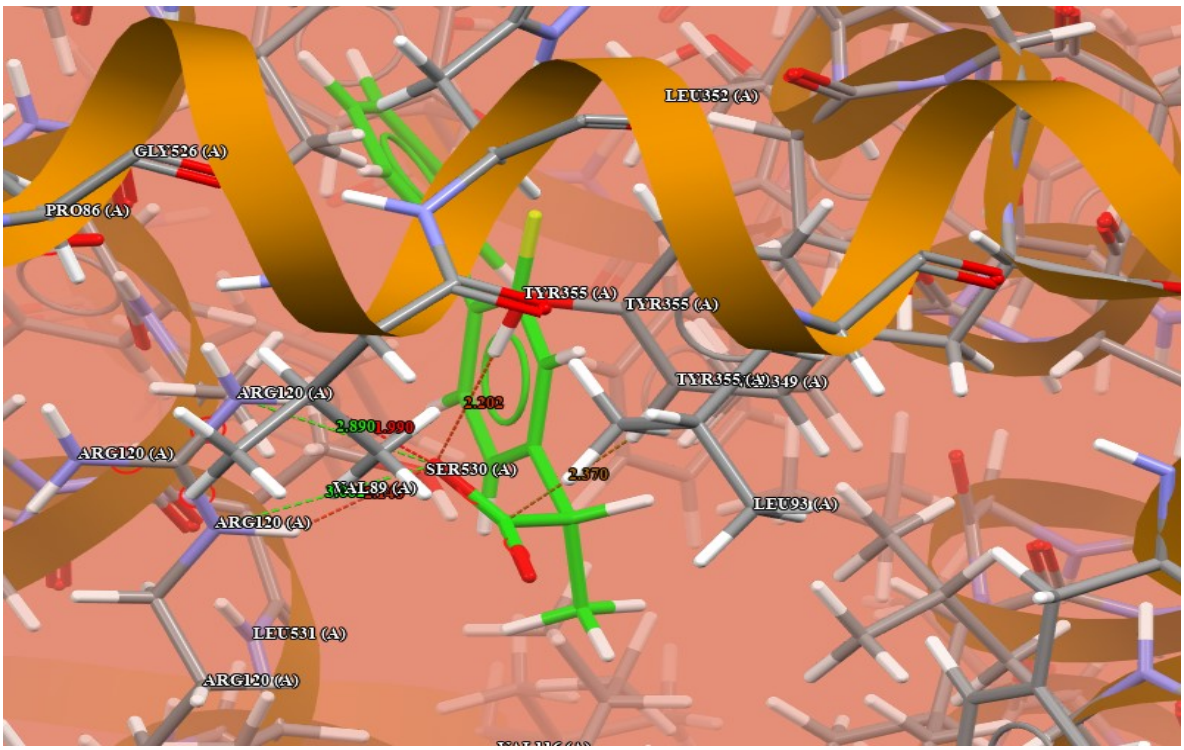



**Figure 2.** Flurbiprofen's H-bond and brief contact interaction profile with the COX2 receptor (PDB code: 4m11). Flurbiprofen's interaction with amino acid residues through H-bond [Arg120] is represented in green, whereas short contact is represented in red. [Flurbiprofen is shown in a ball and stick fashion, whereas amino acids are shown as capped sticks]

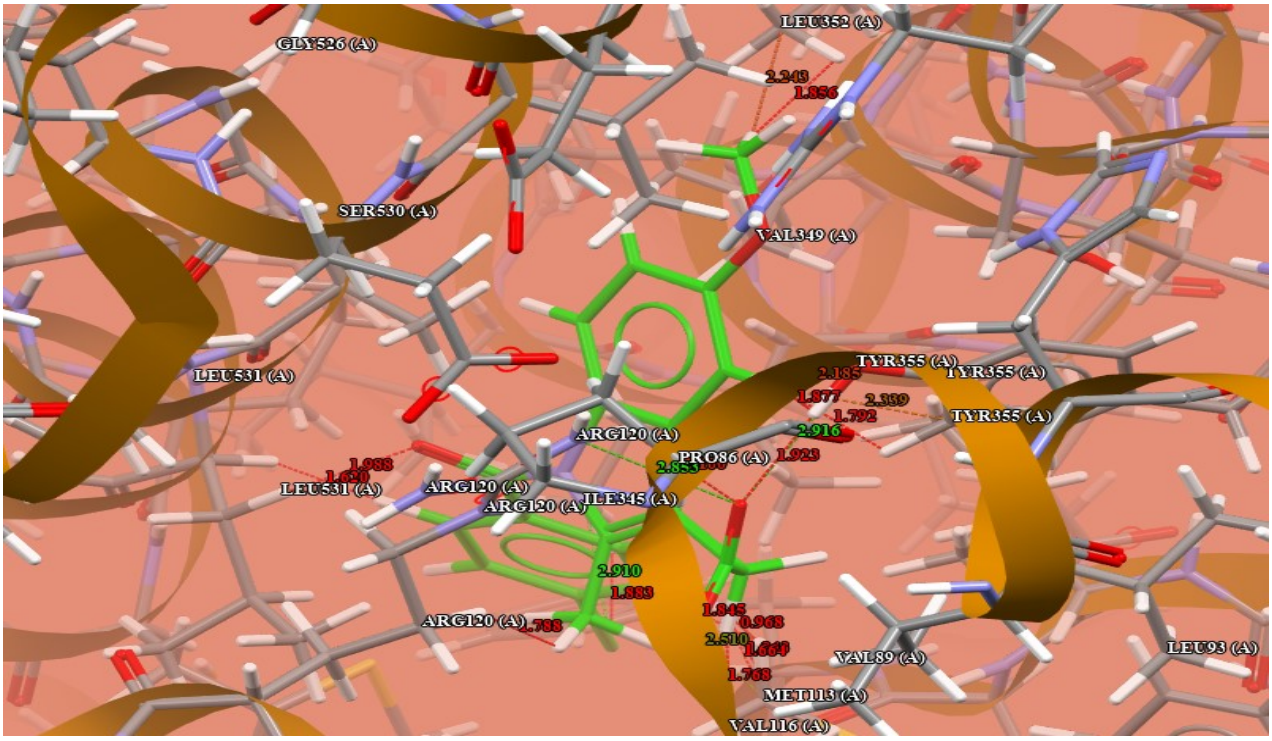



**Figure 3.** The standard drug Indomethacin's H-bond and short contact interaction profile with the COX2 receptor (PDB code: 4m11). The interaction of Indomethacin with amino acid residues through H-bond [Arg120, TYR355] is represented in green, whereas the short contact is represented in red. [Indomethacin is shown in a ball and stick fashion, whereas amino acids are shown as capped sticks.]



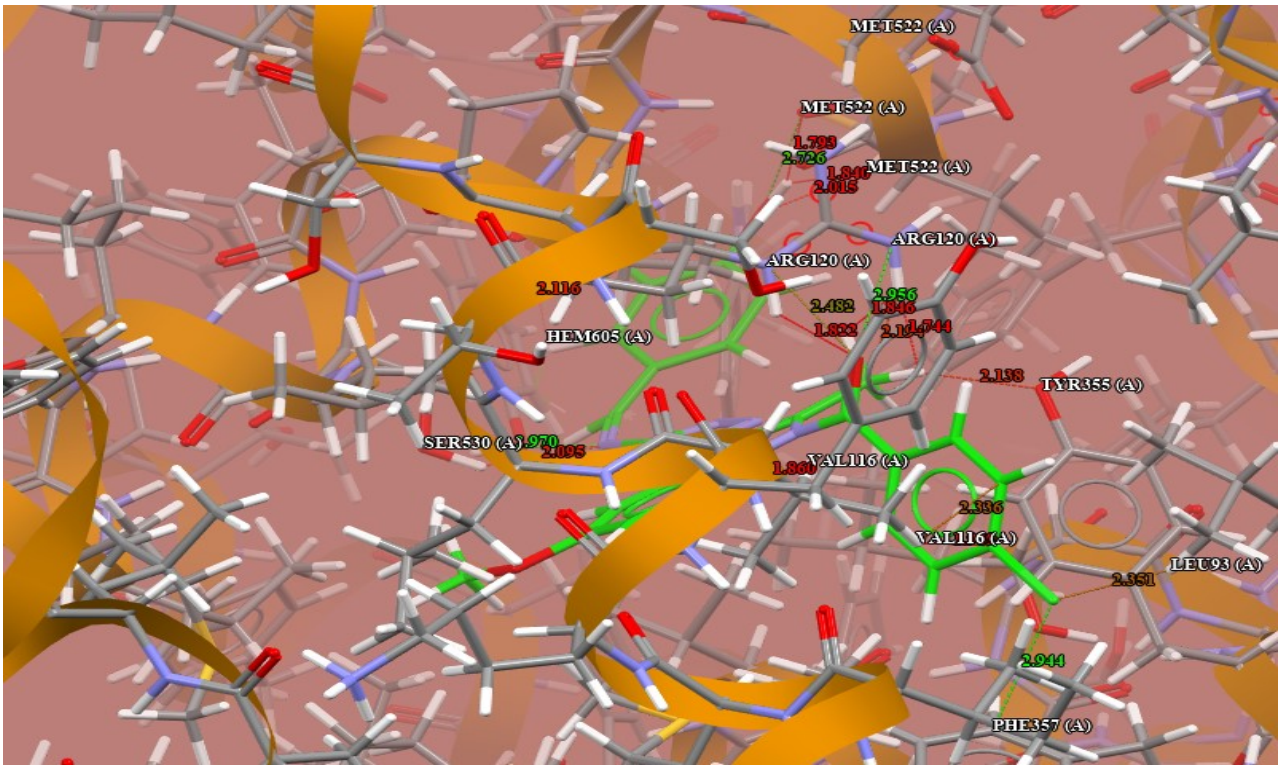



**Figure 4.** The interaction profile of compound [S2] with the COX2 receptor is characterized by H-bonds and short contacts (PDB code: 4m11). The interaction of substance [S4] with amino acid residues through H-bond [Arg120(2), MET522, SER530, PHE357] is represented in green, whereas short contact is represented in red. [S2: ball and stick, with amino acids in capped sticks]

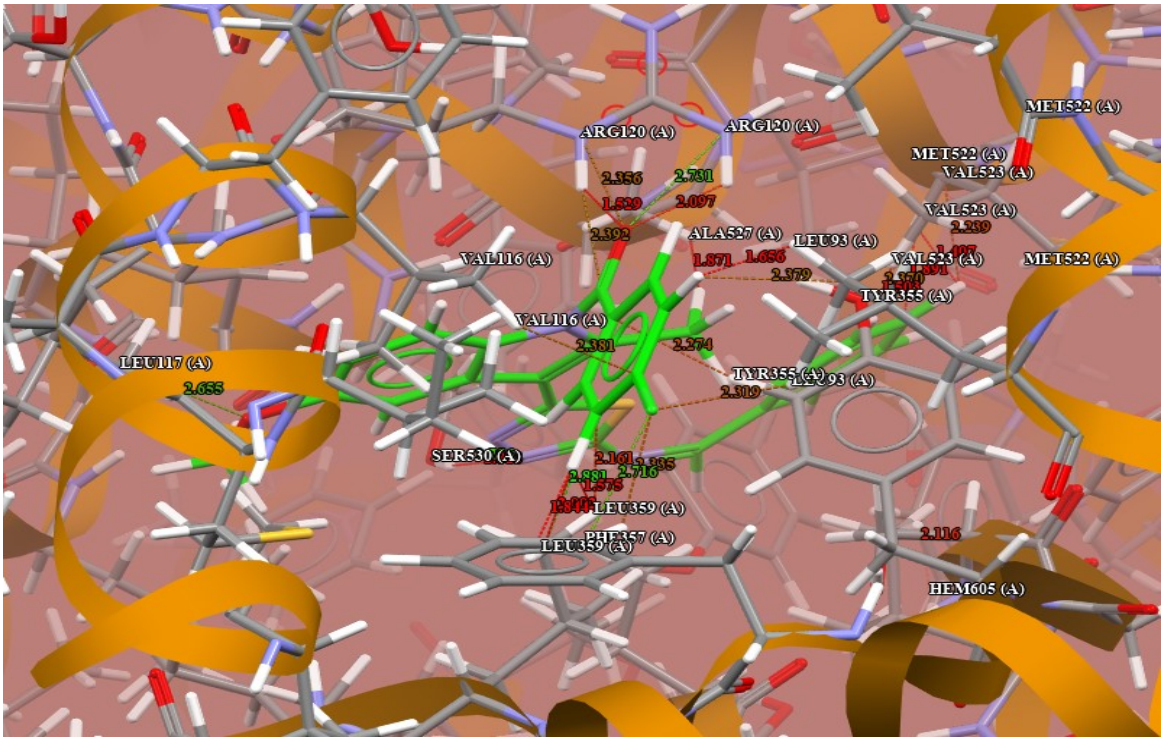



**Figure 5.** The interaction profile of compound [S4] with the COX2 receptor is characterized by H-bonds and short contacts (PDB code: 4M11). The interaction of compound [S4] with amino acid residues through H-bond [GLY526, Arg120(2), TYR355(2), LEU352] is represented in green, whereas short contact is represented in red. [S4: ball and stick, with amino acids in capped sticks]



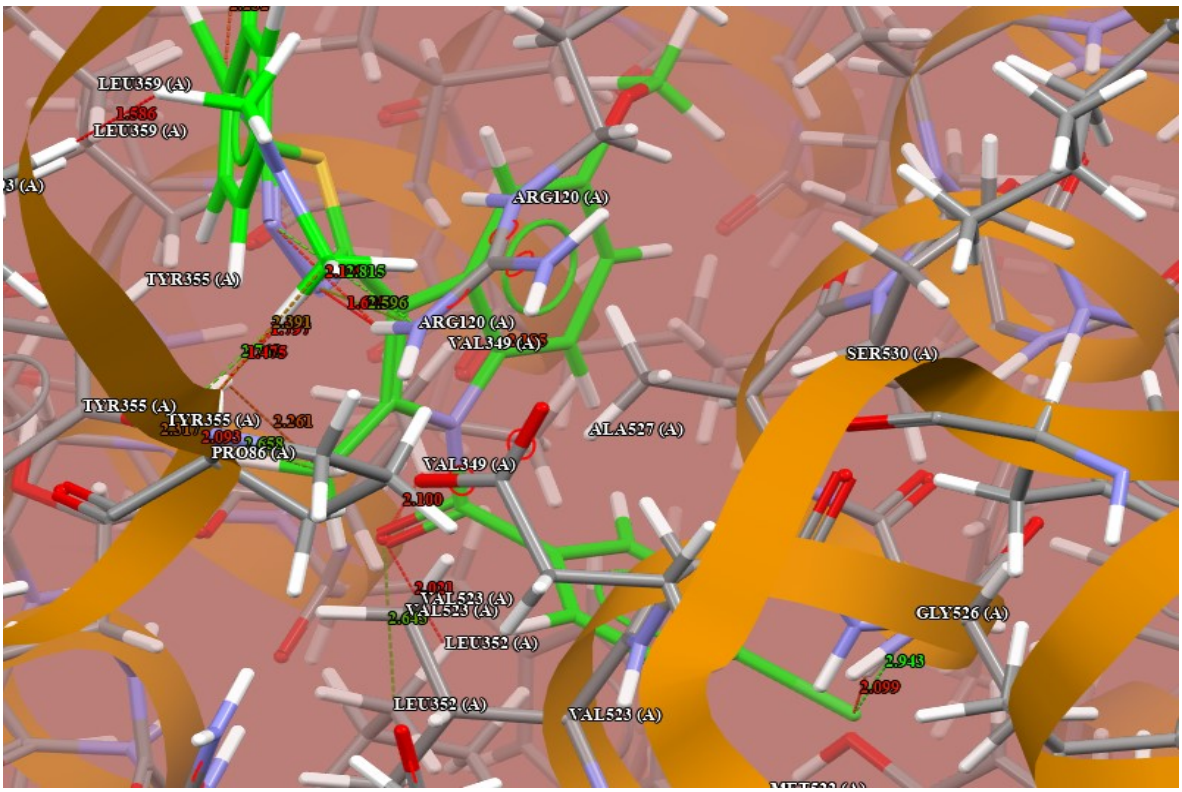



**Figure 6.** The interaction profile of compound [S6] with the COX2 receptor includes H-bonds and short contacts (PDB code: 4M11). The connection between compound [S6] and amino acid residues via H-bond [GLY526] is represented in green, whereas short contact is represented in red. [S6: ball and stick, with amino acids in capped sticks]

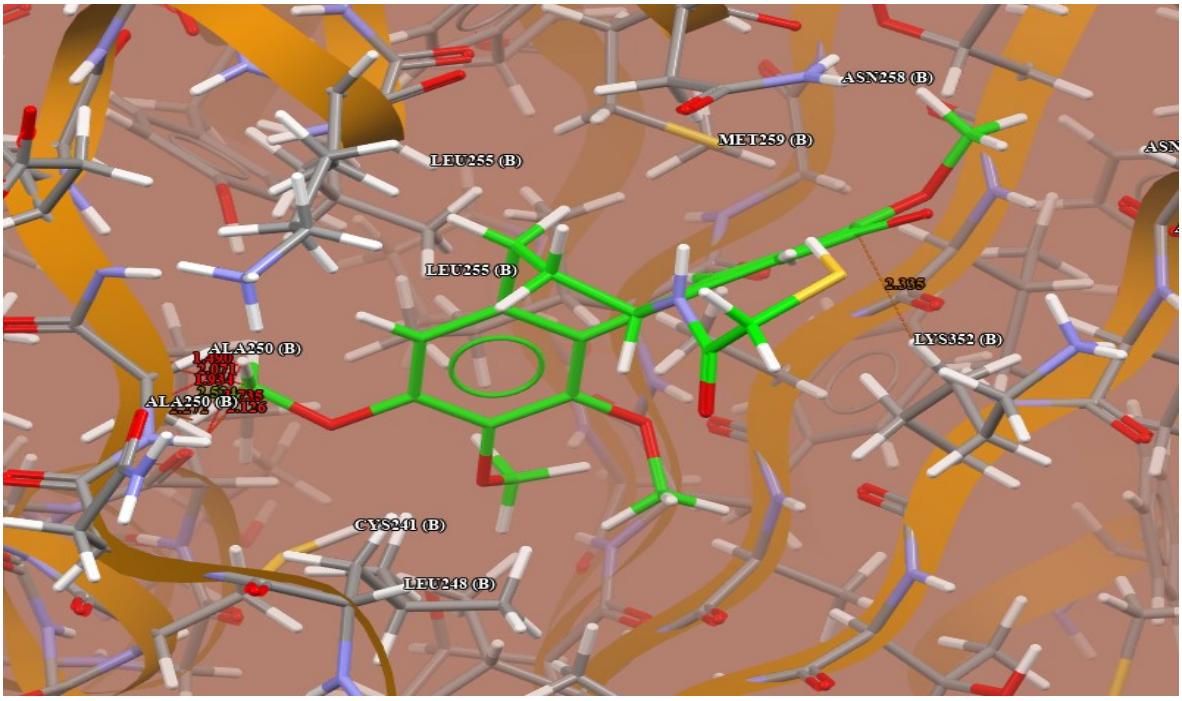



**Figure 7.** The standard medication Colchicine's H-bond and short contact interaction profile with the TPI receptor (PDB code: 1SA0). The connection between Colchicine and amino acid residues via H-bond [ALA250] is represented in green, whereas short contact is represented in red. [Colchicine is shown in a ball-and-stick fashion, whereas amino acids are shown in capped sticks]



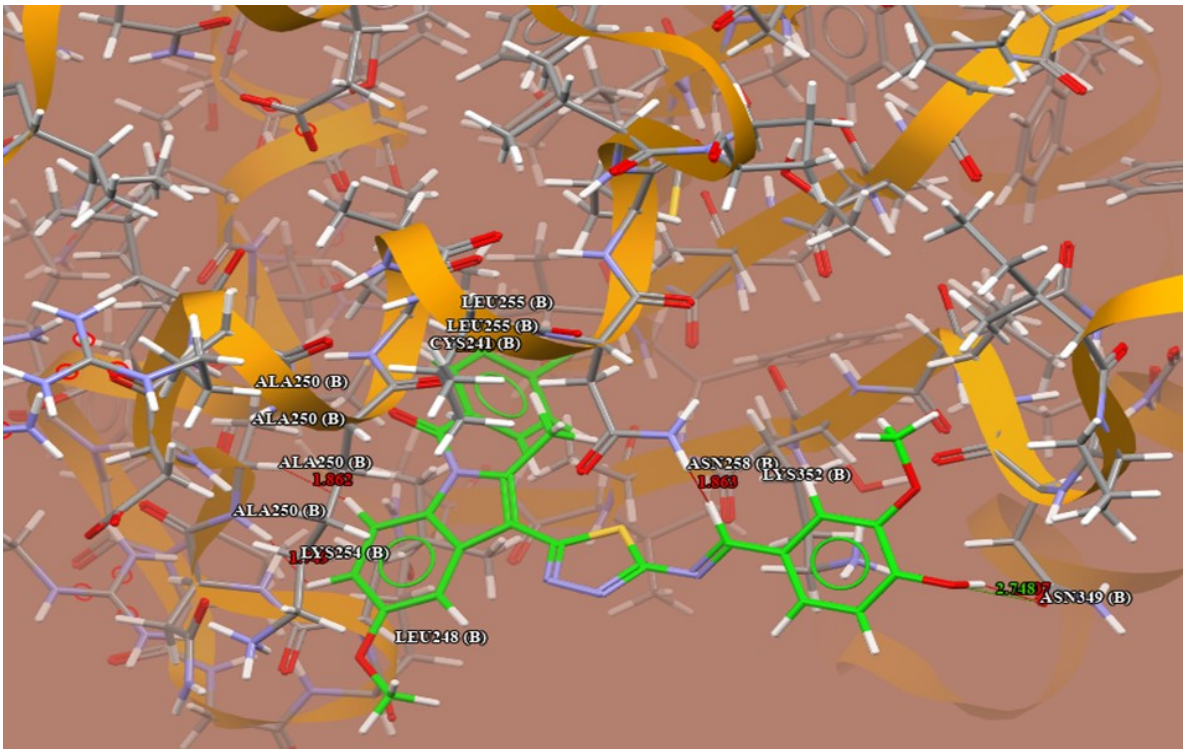



**Figure 8.** Compound [S1] H-bond and short contact interaction profile with TPI receptor (PDB code: 1SA0). The connection between compound [S1] and amino acid residues via H-bond [ASN349] is represented in green, whereas short contact is represented in red. [S1: ball and stick, with amino acids in capped sticks]

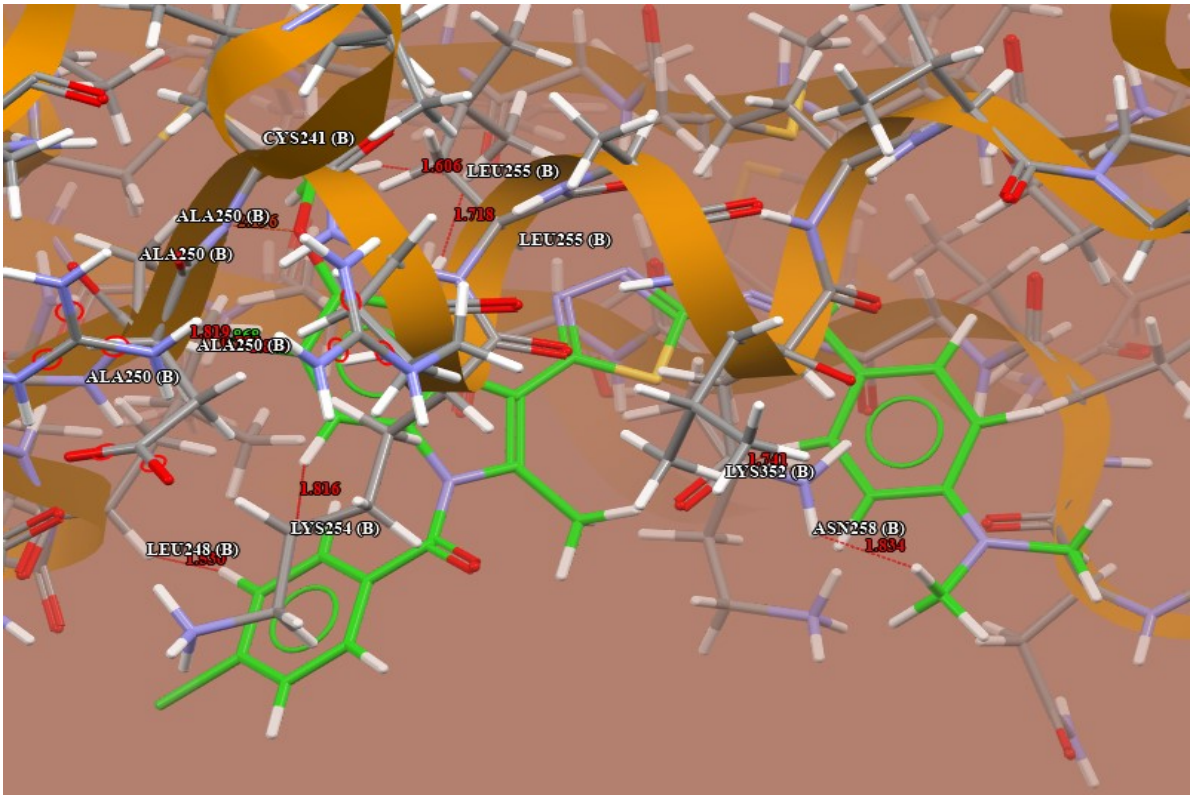



**Figure 9.** The interaction profile of compound [S4] with the TPI receptor includes H-bonds and short contacts (PDB code: 1SA0). The connection between compound [S4] and amino acid residues via H-bond [ALA250] is represented in green, whereas short contact is represented in red. [S4: ball and stick, with amino acids in capped sticks]



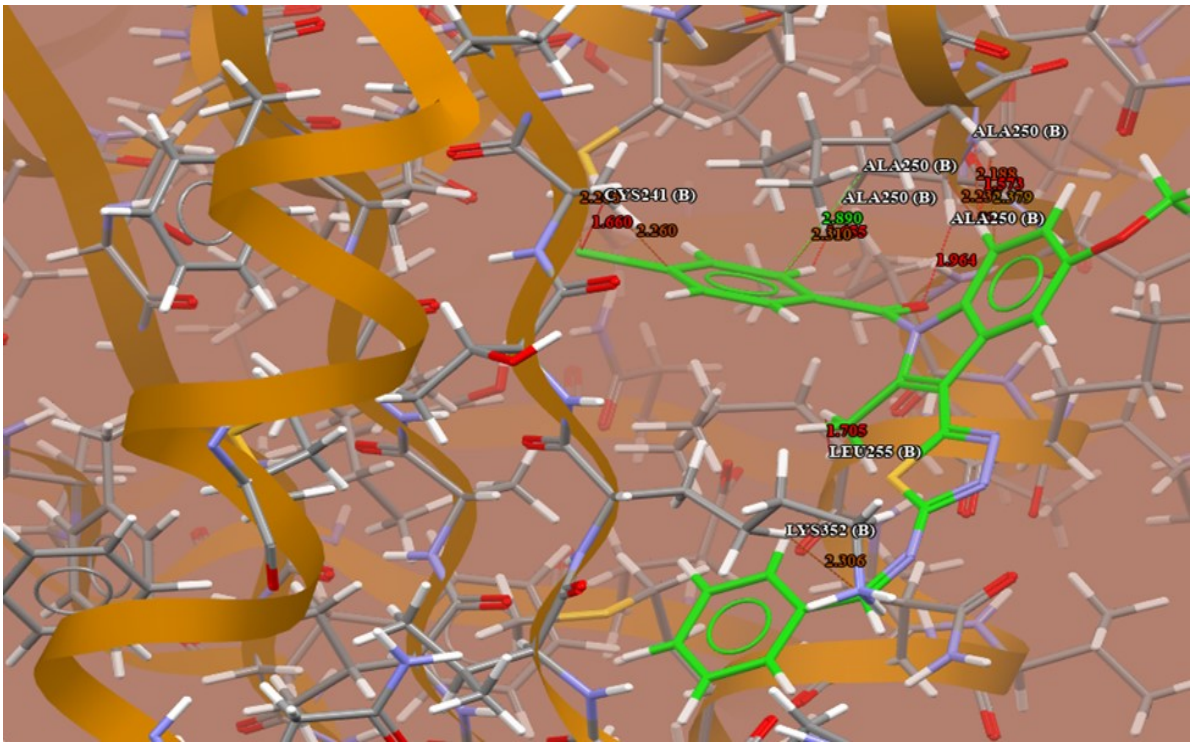



**Figure 10.** The interaction profile of compound [S5] with the TPI receptor includes H-bonds and short contacts (PDB code: 1SA0). The connection between compound [S5] and amino acid residues via H-bond [ALA250] is represented in green, whereas short contact is represented in red. [S5: ball and stick, with amino acids in capped sticks]

## Conclusion

- In conclusion, a new series of Schiff base derivatives [S, S1-S6] were designed from indomethacin. *In Silico* experiments including ADME studies predicted that all designed, all the compounds fulfilled the RO5 except compound [S4] & expected with low absorption from the GIT. The docking studies for ligands interaction with COX-2 protein showed promising activity for compounds (S2, S4, S5) by binding with AAs in the active pocket with more PLP fitness values than the reference drugs Flurbiprofen & Indomethacin. Meanwhile for tubulin inhibition protein the designed compounds (S1, S4, S5) show PLP fitness values more than the reference ligand colchicine. Compounds (S4 & S5) give favorable results for both proteins [COX-2, and TPI].

## Conflict of Interest

The authors declared no conflict of interest.

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