Design, Molecular Docking and ADME Studies of New Imidazolidine Derivatives

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Abstract

The protective reaction of an organism to potentially harmful stimuli is known as inflammation, and it can result from a variety of sources, including physical, chemical, or viral injuries. A large number of people in our society suffer from long-term inflammatory diseases, which makes it necessary to constantly develop new anti-inflammatory drugs. The development of powerful anti-inflammatory medications has advanced significantly in recent years. As a result, heterocyclic compounds made up a sizeable fraction of organic chemistry due to their pharmacological activity and distinct physical traits that distinguished them from other cyclic compounds. One of the most common N-based heterocyclic molecules is imidazolidine. Numerous scientists have become interested in it because of the variety of industrial and pharmacological uses. In the present study, the work dedicated to designed new imidazolidine derivatives. Molecular Docking Software (Schrodinger) was used to check the binding interaction between new derivatives (4N, 4M, 4D, 4In, 4Ib) and the cyclooxygenase active site of COX-2 in comparison with naproxen, mefenamic acid, diclofenac, indomethacin and ibuprofen as references drugs respectively. The results demonstrated that good binding affinity achieved by all new compounds with the exception of 4D derivative in comparison with diclofenac. Finally, the findings of the ADME study

demonstrated that all new derivatives met the Lipinski rule of five and expected to be highly absorbed from gastrointestinal tract.

Keywords: Imidazolidine, COX-2, Docking, ADME, Lipinski rule.

Introduction

The first-line medication for treating pain, inflammatory disorders, and arthritis is non-steroidal anti-inflammatory drug (NSAID)(1). By blocking the enzyme prostaglandin endoperoxidase, also referred to as cyclooxygenase (COX), NSAIDs suppress the production of prostaglandins from arachidonic acid (2). According to reports, there are two isoforms of COX: COX-1 and COX-2, which have distinct expression patterns and mechanisms of regulation. Despite sharing a similar structure, COX-1 and COX-2 exhibit subtle variations that impact drug binding and result in distinct actions(3). Arachidonic acid enters both enzymes' long, narrow channels and is transformed into prostaglandins (PGs); COX-2, on the other hand, has an extra side pocket. The chemical structure of selective COX-2 inhibitors has a stiff side extension that binds in this side pocket (4). In the gastrointestinal tract (GIT), COX-1 offers cytoprotection, while inducible COX-2 mediates inflammatory signals in a particular way (5). Because the majority of NSAIDs on the market today are more selective for COX-1 than COX-2, long-term NSAID use can cause noticeable GI discomfort, bleeding, and ulceration (6). The two main causes of gastrointestinal (GI) damage caused by nonsteroidal antidepressants (NSADs) such as mefenamic acid are: (1) local irritation caused by the topical effect of the carboxylic acid (–COOH) moiety of mefenamic acid on GI mucosal cells; and (2) decreased tissue prostaglandin production in tissues, which compromises the physiological role of cytoprotective prostaglandins in maintaining GI health and homoeostasis (7). Derivatization of the carboxylic acid group of NSADs to different five member heterocyclic compounds has been

reported to retain anti-inflammatory activity with reduced ulcerogenic potential, thereby mitigating the ulcerogenesis caused by the carboxylate group. The goal of the research was to reduce the possibility of adverse drug reactions and increase the potency of NSAID derivatives containing imidazolidine. When the imidazolidine moiety is introduced, the bulkiness may increase and the COX-2 enzyme is preferentially inhibited over the COX-1 enzyme.

Chemical scheme

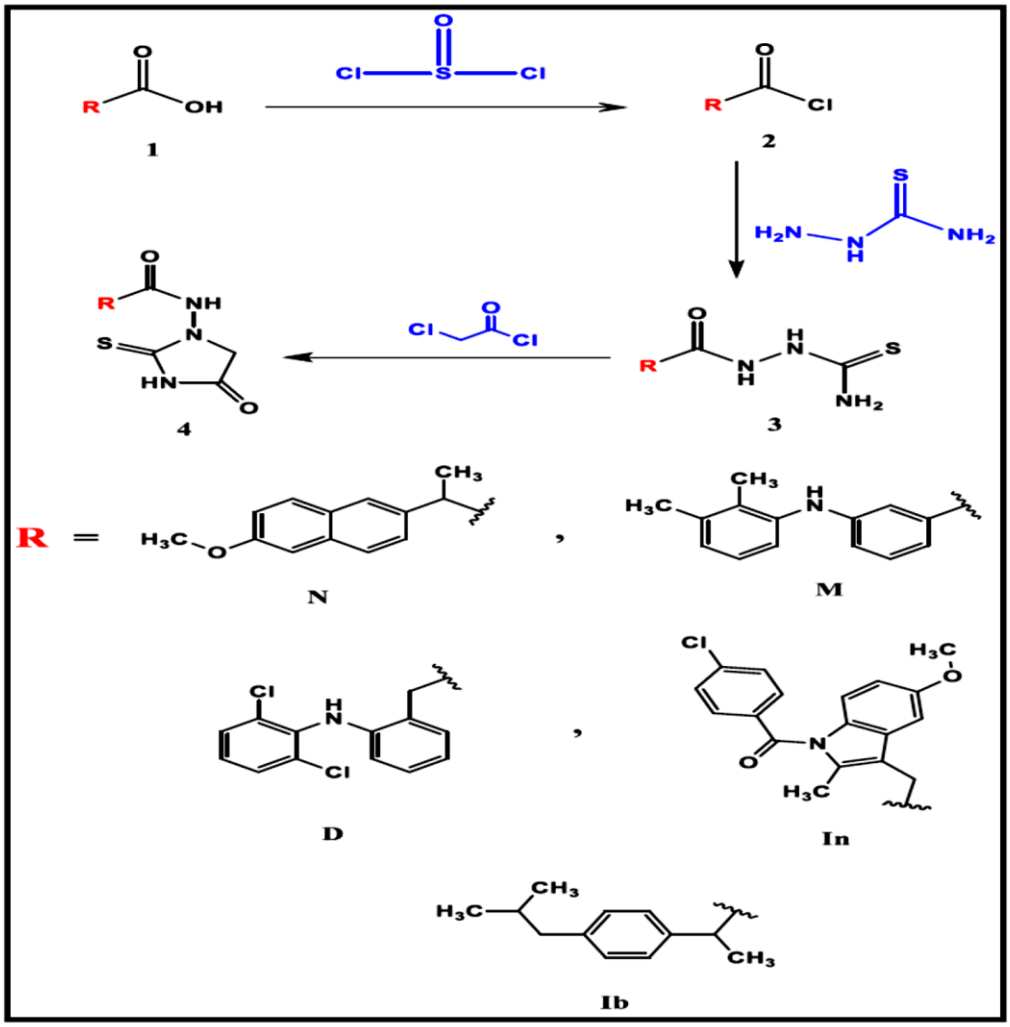

Figure1. The Scheme represented Synthesis of Imidazolidine derivatives.

Computational approaches

The molecular docking study to produce compounds (4N, 4M, 4D, 4In, 4Ib) as well as the prediction of pharmacokinetic ADME of these compounds is both included in the computational approaches.

Molecular docking study for the designed compounds

By utilizing Glide TM, (Schrödinger, version 5.7, New York, LLC, NY, 2011), the derivatives (4N,4M,4D,4In,4IB) were docked into the active site of cox-2 which obtained from the enzyme's crystal structures form which complexed with references drugs Naproxen, Mefenamic acid, Diclofenac, Indomethacin and Ibuprofen (PDB ID:3LNI). The metal ions and water molecules were eliminated from enzymes beyond 5Å radius of the trimethoprim (reference ligand). An application named Protein Preparation Wizard™ employed the OPLS-2005 force field to minimize structure of protein. Then, by using the OPLS-2005 force field, the Ligand Preparation™ program produces the lowest energy state by optimization of each ligand. The highest score and the best pose for each molecule was exhibited after simulations of docking produced 5 poses for each ligand.

ADME procedure for the designed compounds

At the early stages of development, *in silico* technologies like Swiss ADME, a free online application that converts a compound's structure to a SMILE name, can be used to anticipate ADME characteristics of the molecule (8).

Results and Discussion

Interpretation of ADME study results

The disposition and fate of pharmaceutical compounds inside an organism, particularly in the human body, are explained by their absorption, distribution,

metabolism, and elimination (ADME). Throughout the drug development process, poor pharmacokinetics (PK) rather than poor effectiveness of the proposed molecule is the main cause of failure (9). The Swiss ADME Web tool used in identifying crucial properties for one or more substances like physicochemical, drug-like, pharmacokinetic (10). One of the many features of Swiss ADME is topological polar surface area (TPSA), which gauges how well drugs penetrate cells. Compounds with TPSA values less than 140Å2 indicate high permeability and bioavailability (11). TPSA values for every compound were found to be less than 140 $^{0}A^{2}$ range from (93.53–124.76 $^{0}A^{2}$). The majority of these compounds were shown significant GIT absorption. Additionally, all compounds had a bioavailability score of 0.55, indicating that they all entered the systemic circulation. The "Rule-of-Five" by Lipinski states that a substance to be ingested should have < 500 Dalton molecular weight, hydrogen bond acceptors and donors < 10 and < 5 respectively, and an octanol-water partition coefficient (log P) less than 5, may have pioneered *in silico* prediction of oral bioavailability(12). The rule of five is supposed to be followed by all manufactured compounds, according to the findings from the ADME study. In table (1), the findings of the ADME research of freshly synthesized compounds are presented. The findings indicated that the majority of chemicals are highly absorbed from GIT.

The boiled egg plot, which offers comforting assistance and a distinctive statistical plot to estimate passive gastrointestinal absorption and brain penetration, was used to examine the pharmacokinetic properties of the molecules. The area with white color indicates a significant possibility of passive gastrointestinal absorption, while the area with yellow color (yolk) indicates a significant possibility of brain penetration(13).Chemicals (4N, 4M, 4D, 4In, 4Ib) emerged as red dots, indicating that they are not substrates for p-glycoprotein (p-gp) as indicated in figure (1).

Table 1. ADME result of the final derivatives.

Compound	4N	4M	4D	4In	4Ib
Formula	$C_{17}H_{17}N_3O_3S$	$C_{18}H_{18}N_4O_2S$	$C_{17}H_{14}C_{l2}N_4O_2S$	$C_{22}H_{19}ClN_4O_4S$	$C_{16}H_{21}N_3O_2S$
MWT(g/mol)	343.40	354.43	409.29	470.93	319.42
H-bond acceptor	3	2	2	4	2
H-bond donor	2	3	3	2	2
Molar Refractivity (m^3/mol)	101.85	107.93	112.61	131.18	97.24
TPSA(A^2)	102.76	105.56	105.56	124.76	93.53
GIT absorption	High	High	High	High	High
BBB permeability	No	No	No	No	No
Lipiniski violation	0 violation	0 violation	0 violation	0 violation	0 violation
Bioavailability	0.55	0.55	0.55	0.55	0.55

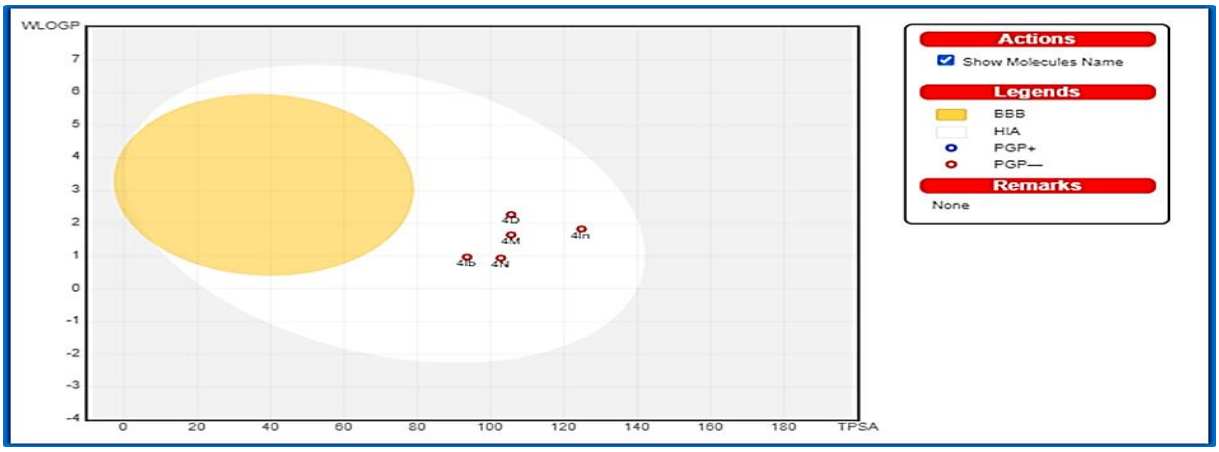

Figure 1. BOILED-EGG for the designed compounds.

Analysis of studies using molecular docking

The use of molecular docking in drug development is becoming increasingly importan(14). Estimating ligand-protein binding affinity and achieving a ligand-receptor complex with the ideal conformation and lowest binding free energy are its main objectives (15).According to a molecular docking research, the newly synthesized chemicals have an anti-inflammatory effect. Molecular Docking Software (Schrodinger) was used to check the binding interactions between new derivatives (4N, 4M, 4D, 4In, 4Ib) and the cyclooxygenase active site (COX-2**)** in comparison with naproxen, mefenamic acid, diclofenac, indomethacin and ibuprofen as references drugs respectively. The results demonstrated that good binding affinity achieved by all new compounds with the exception of 4D derivative in comparison with diclofenac as shown in table (2). Figures (2) to (11) display the positions and interactions of designed compounds and references drugs with the amino acid residues in the cyclooxygenase active site of COX-2. Hydrophobic interaction, pi-cation interaction, Pi-Pi stacking, and H-bond interaction are the crucial interactions apparent in these figures. These connections support and increase the chemicals' potent antibacterial activity.

Table 2. Docking binding scores in (kcal/Mol) of the newly discovered derivatives and their references drugs inside the active sites of cox-2.

Compounds	Docking Score	Reference drugs	Docking Score
4N	-7.855	Naproxen	-8.252
4M	-8.983	Mefenamic acid	-8.128
4D	-5.9	Diclofenac	-7.491
4In	-10.9	Indomethacin	-9.64
4Ib	-7.931	Ibuprofen	-7.292

Ligend interaction view the compounds

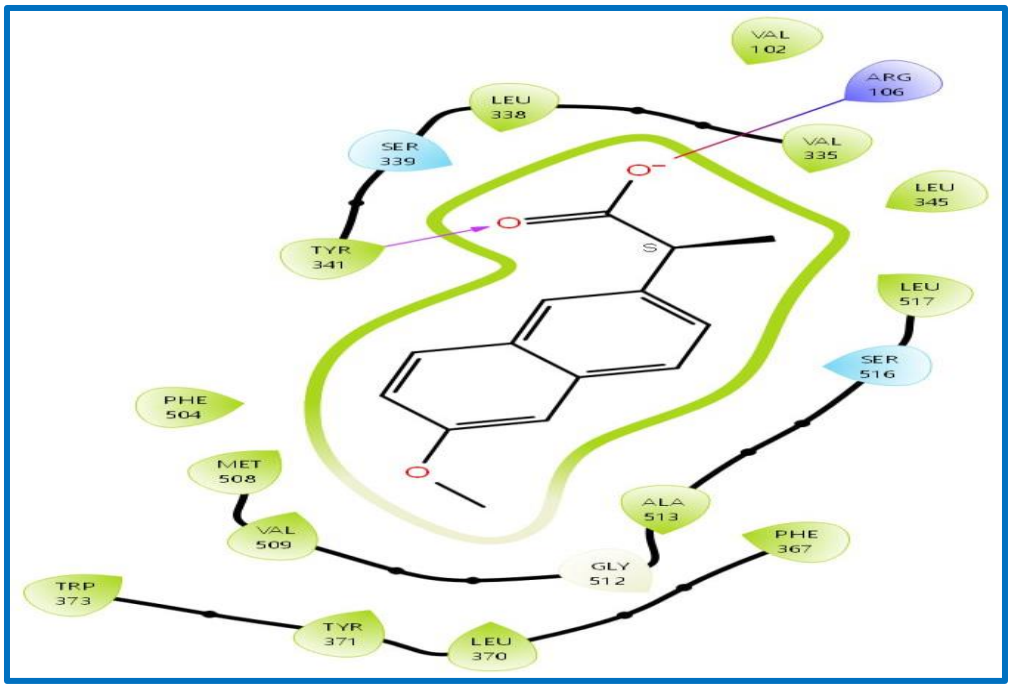

Figure 2. Reference drug (Naproxen) in the active site of Cox-2 (PDB ID: 3LN1), encircled by amino acids.

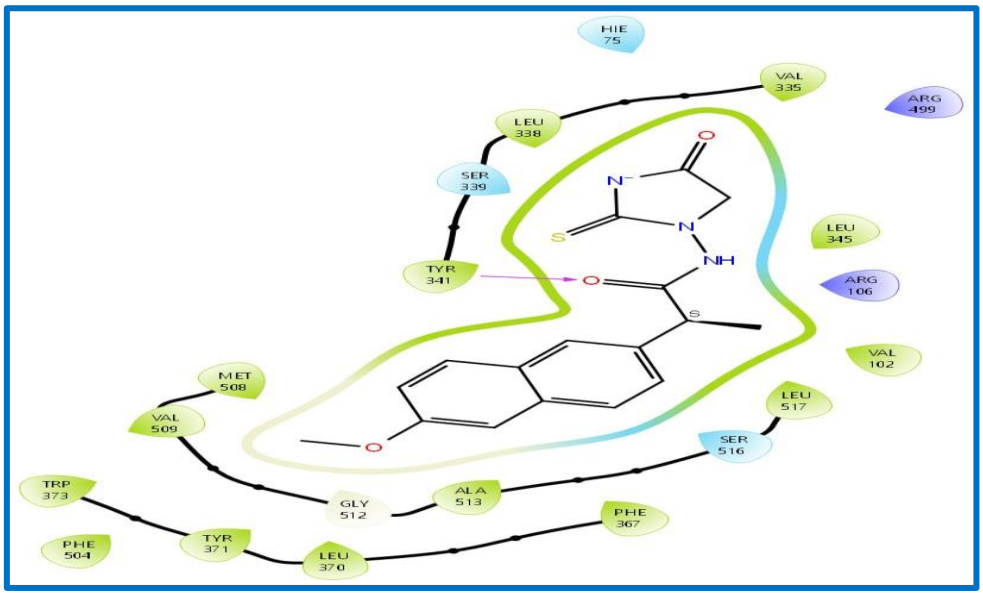

Figure 3. Derivative (4N) in the active site of Cox-2 (PDB ID: 3LN1), encircled by amino acids.

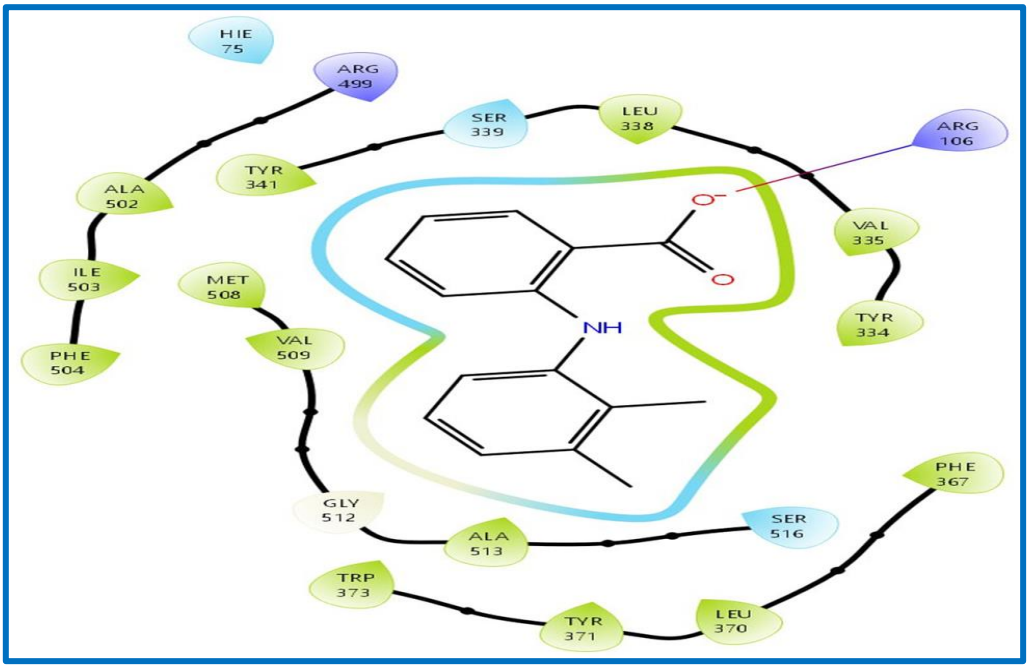

Figure 4. Reference drug (Mefenamic acid) in the active site of Cox-2 (PDB ID: 3LN1), encircled by amino acids.

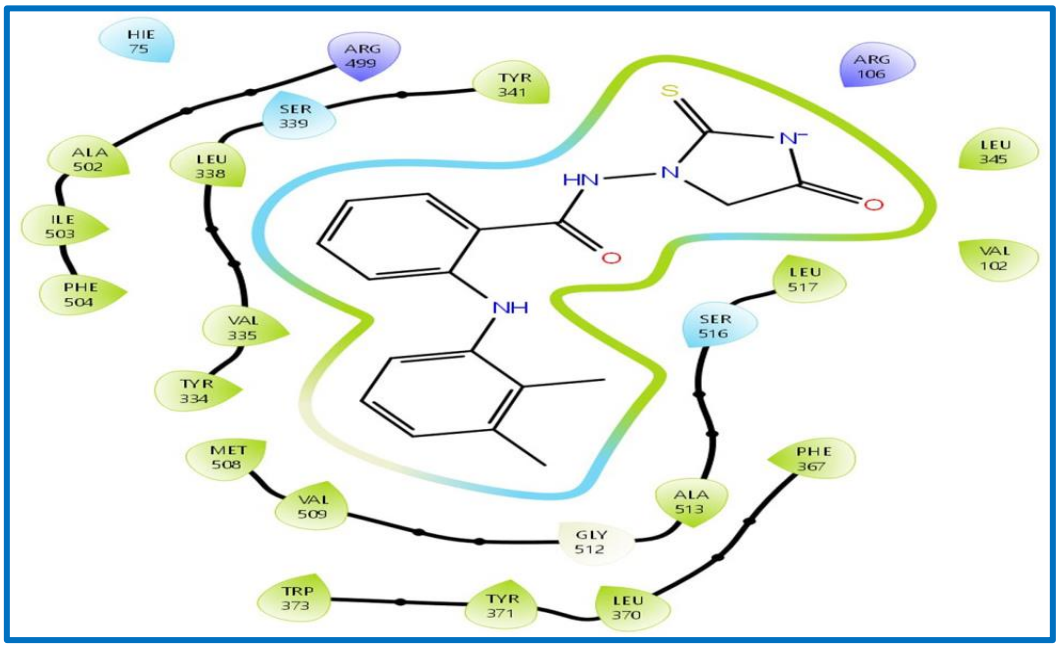

Figure 5. Derivative (4M) in the active site of Cox-2 (PDB ID: 3LN1), encircled by amino acids.

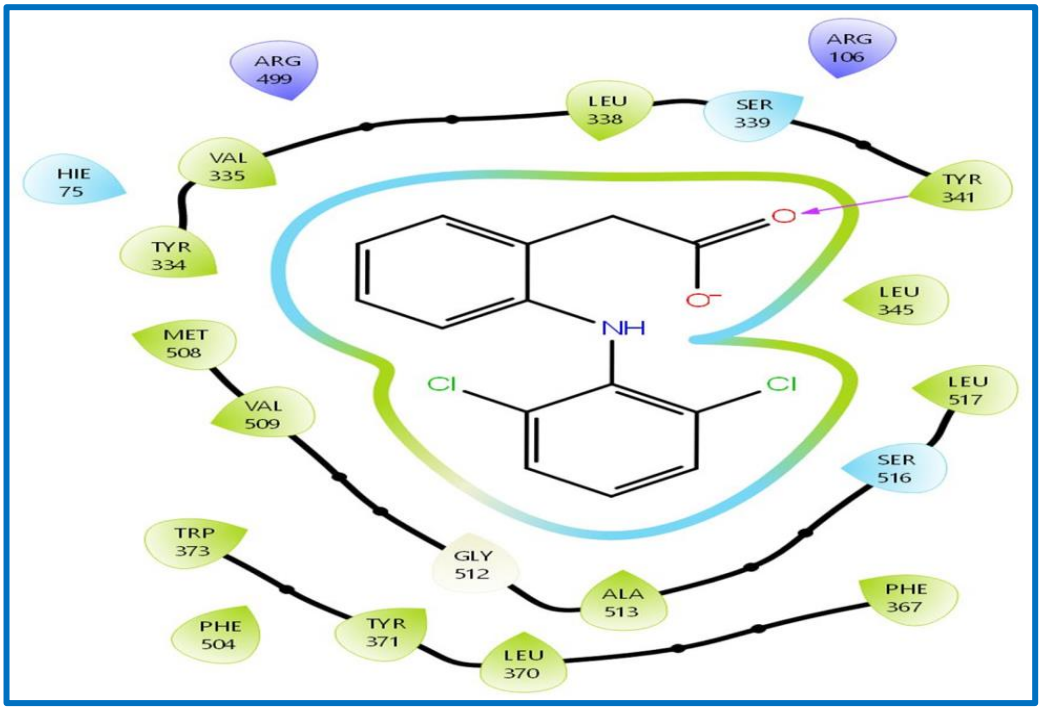

Figure 6. Reference drug (Diclofenac) in the active site of Cox-2 (PDB ID: 3LN1), encircled by amino acids.

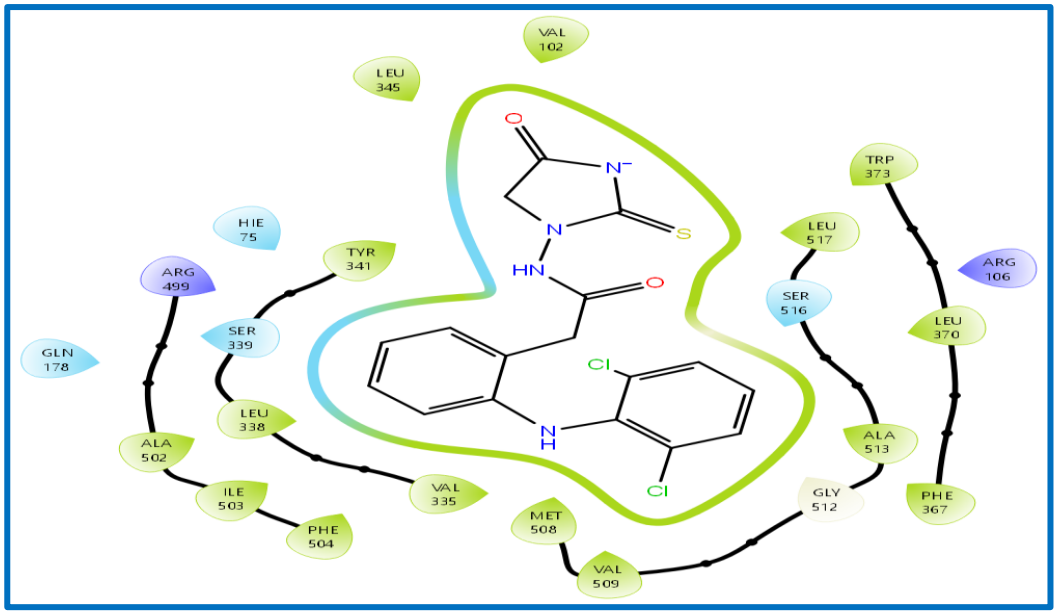

Figure 7. Derivative (4D) in the active site of Cox-2 (PDB ID: 3LN1), encircled by amino acids.

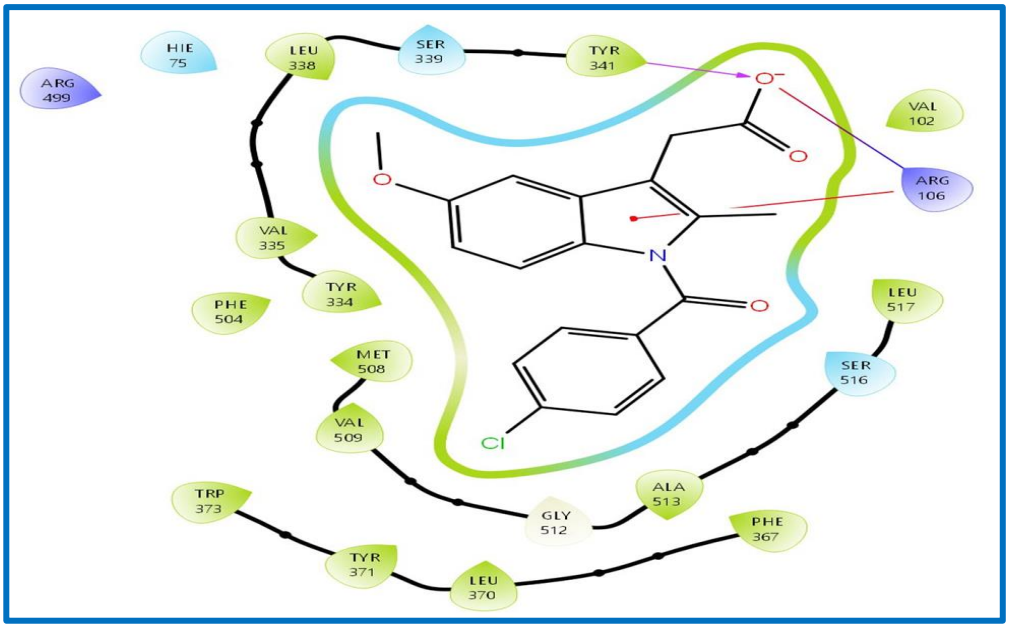

Figure 8. Reference drug (Indomethacin) in the active site of Cox-2 (PDB ID: 3LN1), encircled by amino acids.

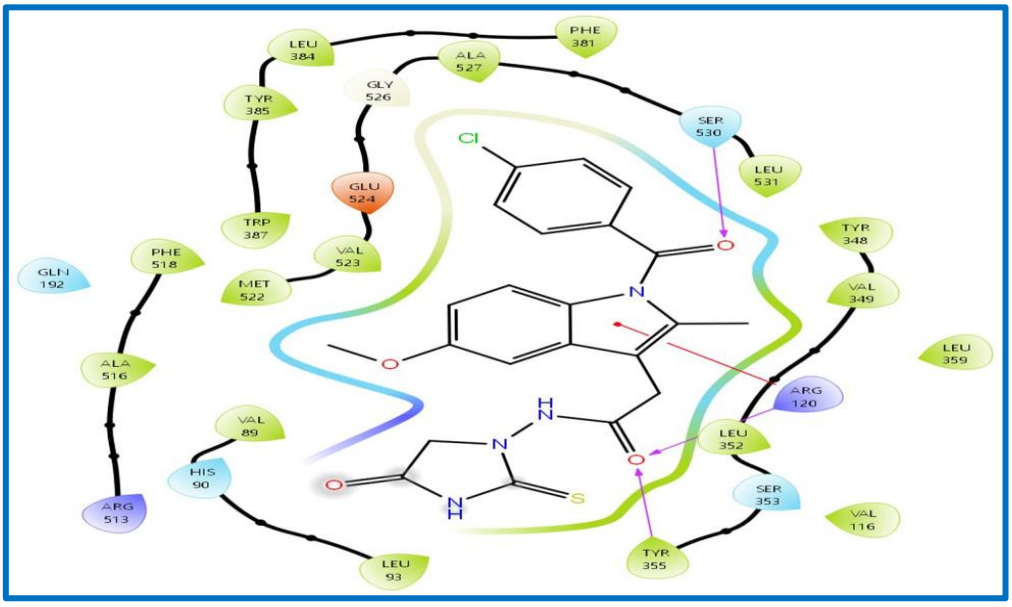

Figure 9. Derivative (4In in the active site of Cox-2 (PDB ID: 3LN1), encircled by amino acids.

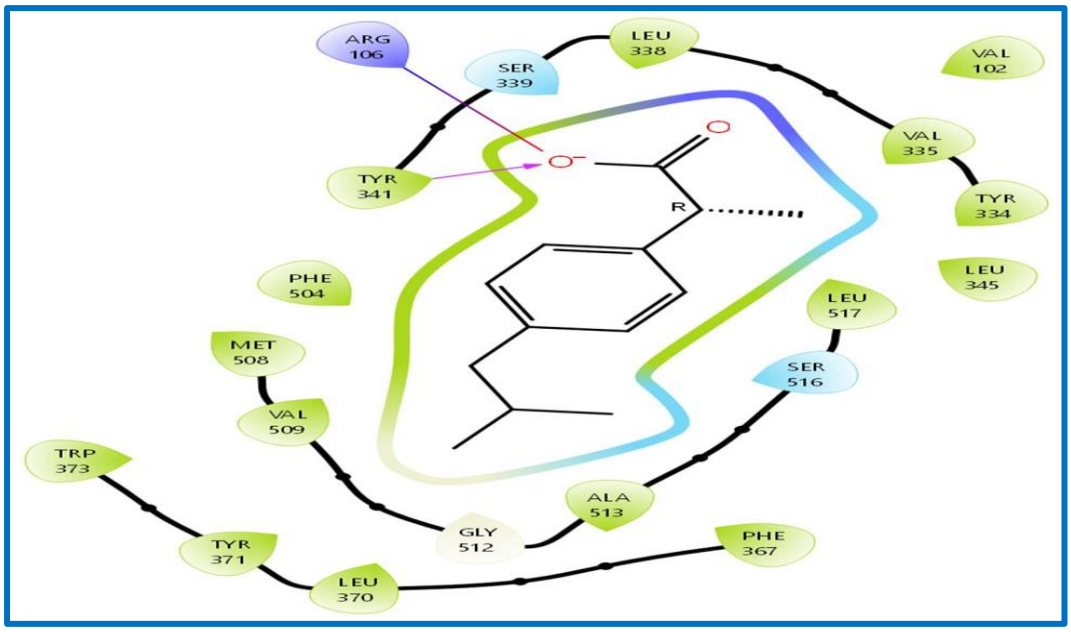

Figure 10. Reference drug (Ibuprofen) in the active site of Cox-2 (PDB ID: 3LN1), encircled by amino acids.

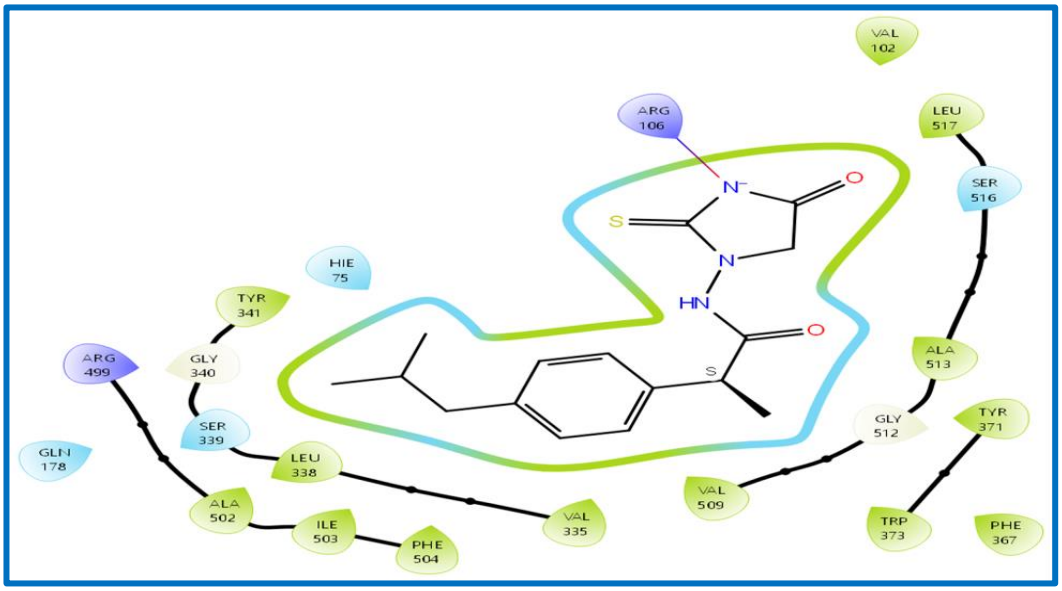

Figure 11. Derivative (4Ib) in the active site of Cox-2 (PDB ID: 3LN1), encircled by amino acids.

Conclusion

In Silico studies including ADME study showed that all designed compounds expected to be highly absorbed from the GIT and met the Lipinski rule of five. The results of molecular docking study showed that all newly designed compounds(4N, 4M, 4D, 4In, and 4Ib), with the exception of the 4D derivative when compared with the reference drugs, had good binding affinities to the cyclooxygenase active site of COX-2.

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