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Design, Molecular Docking, Molecular Dynamic Simulations, MM-GBSA Study, and Pharmacokinetics Prediction of New Imidazolidinone Derivatives as Selective COX-2 Inhibitors

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ABSTRACT: Cyclooxygenase-2 (COX-2) is necessary for inflammation and pain, making it a prime target for anti-inflammatory drugs. Selective COX-2 inhibitors can reduce inflammation without the gastrointestinal side effects often seen with non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This study aimed to find new imidazolidinone derivatives as potential selective COX-2 inhibitors. Seven imidazolidinone derivatives were designed and tested using molecular docking with Glide software; the crystal structure's source of enzyme (protein data bank code: 5KIR) and removed solvent molecules during preparation to create a clean and suitable environment for docking simulations; the binding energies of these compounds were analyzed using the Prime-MMGBSA module, molecular dynamic simulations lasting 100 nanoseconds were performed using the Desmond program, Drug-likeness properties were predicted using Swiss-ADME. Molecular docking emphasized the importance of hydrophobic and hydrophilic amino acid residues for ligand stability. Compounds 3 and 5 showed strong affinities to COX-2, with docking scores of -11.569 and -11.240 kcal/mol, respectively, compared with reference ligand rofecoxib was -9.309 kcal/mol. Molecular dynamics simulations confirmed the stability of the COX-2-compound 3 complex, revealing consistent ligand-protein interactions. MM/GBSA calculations indicated that all compounds had favorable binding free energies. Additionally, all compounds demonstrated acceptable drug-likeness profiles and desirable pharmacokinetic properties. The study identified new imidazolidinone derivatives, particularly compound 3, as potential selective COX-2 inhibitors with strong binding affinities and stable interactions. These findings support further investigation and optimization of these compounds as therapeutic agents for inflammatory conditions. The recommendation of this work will focus on the in vivo evaluation of these compounds to confirm their therapeutic potential and further refine their pharmacological profiles.

Keywords: Molecular dynamic simulation, Molecular docking, Imidazolidinone, COX-2, MM-GBSA, Rofecoxib.

INTRODUCTION

The cyclooxygenase enzyme plays a key role in making prostaglandin arachidonic acid. This substance involves several important processes, including inflammation, pain-sensing, and fever [1]. In the scientific world, two isoforms of COX are well-known: COX-1 and COX-2. Interestingly, these enzymes share 67% of their amino acid chain structure. The big difference is that COX-1 has isoleucine (Ile523), while COX-2 has valine (Val523). This tiny change means COX-2 has a more extensive binding area than COX-1. This structural difference is essential for figuring out how selective COX-2 inhibitors work. The smaller Val523 in COX-2 leads to a broader binding pocket, letting the selective inhibitors fit correctly. Conversely, COX-1 is crucial for the proper function of many things in our body, like kidneys, platelets, and digestive organs [2–4]. COX-2 gets activated by various pro-inflammatory cytokines and other triggers. That's why using COX-2 selective inhibition can help manage inflammation better while keeping side effects down, especially gastrointestinal issues often seen with regular nonsteroidal anti-inflammatory drugs [5].

The clinical Data shows that excessive COX-2 enzyme could lead to problems like cancer growth and fast reproduction of cancer cells. In many inflammatory situations and tumors, such as inflammatory bowel disease (IBD) and colon cancer, the levels of COX-2 are much higher. Conversely, the presence of COX-2 enzymes is negligible or undetectable in normal colon cells. This is why researchers looking for new anti-inflammatory drugs focus on finding compounds that target only COX-2, especially since this enzyme can cause inflammation when tissues get hurt [6-7].

This study chose imidazolidinone derivatives because they have many different pharmacological actions, such as anti-inflammatory and analgesic effects [8], anticancer [9], antiviral [10], and antibacterial properties [11]. The imidazolidinone group has nitrogen and carbonyl groups that effectively assist its interactions with COX-2. Previous studies showed that imidazolidinone derivatives effectively reduced inflammation and pain, making them promising options for anti-inflammatory medicines [12-13].

Boronic acid (BA) also has a notable impact in medicinal chemistry due to its unique chemical features, like forming bonds with diols and interacting with various biological molecules [14]. It has significant characteristics that are advantageous in drug design, especially for making enzyme inhibitors and anti-inflammatory drugs. Research indicates that BA's presence can help manage inflammation by influencing cytokine levels. In studies involving ovariectomy models, BA led to significantly lower levels of pro-inflammatory cytokines like TNF-α and boosted anti-inflammatory ones like IL-11. This points to BA

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being quite helpful in handling menopause symptoms alongside related inflammation. Combining imidazolidinone derivatives with boronic acid functions opens up a potential new path for creating innovative anti-inflammatory medicines that are more selective and effective [15-16].

This work is significant because there's a strong need for safer, more effective anti-inflammatory medications. Traditional NSAIDs help but often lead to stomach issues since they don't selectively inhibit both COX-1 and COX-2 [17]. The goal is to develop new therapeutic molecules that provide the benefits of selective COX-2 inhibitors while lowering those unpleasant gastrointestinal risks. Using imidazolidinone derivatives and boronic acid functions brings ideas into drug design that might result in more effective medicines with better specificity.

Figure 1 shows the seven designed compounds containing an imidazolidinone moiety. This study utilizes computational molecular docking techniques to study the influence of recently developed imidazolidinone derivatives on their target proteins.

The binding energies of seven compounds (1, 2, 3, 4, 5, 6, and 7) were evaluated when interacting with the COX-2 receptor to assess the interaction between ligands and target receptors. The primary MM-GBSA (molecular mechanics with generalized born and surface area solvation) technique is employed to predict the relative ligand-receptor complex binding free energies, enabling a comprehensive evaluation of the thermodynamic aspects of binding. Analyze the individual energies of the ligand, COX-2 receptor, the complex formed between them, and the numerous energy components that contribute to the overall binding energies. The main parameters that drive the binding interactions can be identified through this analysis. An in silico ADME prediction analysis should be conducted. Obtain an estimate of the pharmacokinetic characteristics and drug-likeness of the designed compounds. MDS analysis was performed for 100 nanoseconds on the compound that exhibited the most favorable docking in a complex with COX-2 to confirm the interaction further.

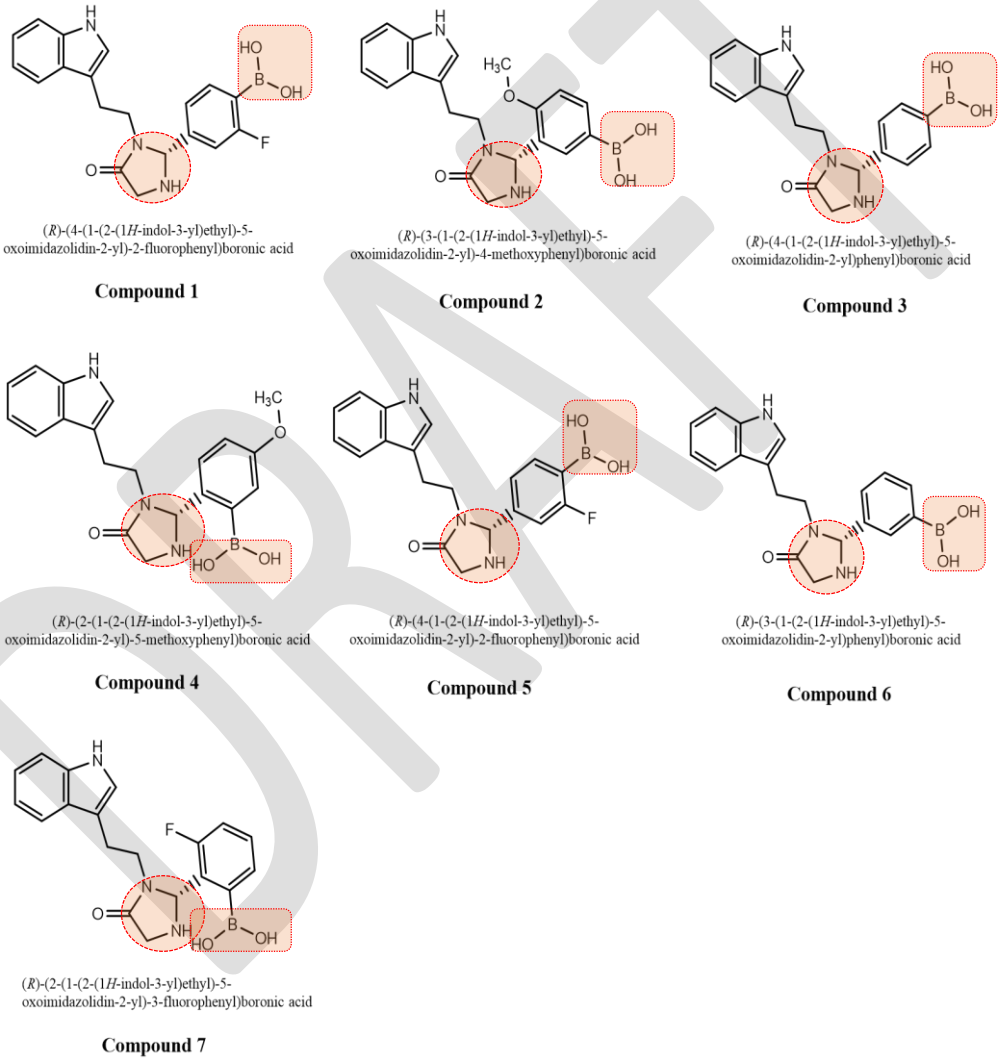

Figure (1): shows the chemical structures of compounds 1, 2, 3, 4, 5, 6, and 7 and their IUPAC names.

COMPUTATIONAL METHODS

Ligand Preparation

The LigPrep tool converts 2D structures into 3D models [18]. These 3D structures and their activity values are then used to refine and generate conformers for each minimized ligand using the OPLS (Optimized Potentials for Liquid Simulations) force field to prepare the ligands for the molecular docking study [19].

ADMET Prediction

To ensure the safety of candidate compounds in developing drugs, it is necessary to conduct preclinical research on safety and pharmacokinetics. The pharmacokinetic characteristics of seven imidazolidinone derivatives, including absorption, distribution, metabolism, and excretion (ADME), were evaluated using the freely available instrument Swiss-ADME (http://www.swissadme.ch). Determine the characteristics that may be comparable to the bioavailability and permeability of cells [20-21].

Molecular Docking

Glide software supplied by the Schrödinger suite was used for molecular docking experiments [22]. These experiments aimed to check the interactions between the COX-2 receptor (PDB code: 5KIR) and the newly designed imidazolidinone derivatives. It also examined how rofecoxib interacts with that same receptor. To study the protein interactions, we got the crystallographic structure of the receptor from the Protein Data Bank. Using the Protein Preparation Wizard, we prepared these structures for a closer look at their interactions. We added hydrogen atoms and removed solvent molecules during preparation to create a clean and suitable environment for docking simulations. We then reduced the protein-ligand complex to confirm that the ligands fit well in the protein binding site. A molecular docking was made by referencing the co-crystallized binding ligand. This grid helped identify possible binding sites in the target proteins' catalytic region, which was necessary for guiding the docking simulations [23].

Rofecoxib was also docked into the protein's active site to validate the docking protocol. We set up Glide extra-precision (XP) mode for these molecular docking simulations, which are known for their superior precision in expecting ligands' binding poses and affinities. Both rofecoxib and compounds 1-7 were included in this connection process. The docking simulations produced and saved three potential binding poses for each molecule using XP mode. This approach allowed us to explore different ligand orientations and conformations within the binding sites, making finding the best energetically favorable binding modes easier. This strategy has proven effective in predicting how these molecular inhibitors interact with their protein targets [24-25].

MM-GBSA Study

The Prime module in the Schrödinger molecular modeling package was used to calculate energy [26]. They relied on the MM-GBSA analysis to find the binding free energies of the suggested compounds and the co-crystallized ligand (Rofecoxib) when interacting with the COX-2 receptor (5KIR). The OPLS3 force field helped with these energy calculations [27]. This force field includes several mathematical equations that show how energy and molecular forces are arranged. It helps figure out binding strength and estimate binding affinity.

The VSGB 2.0 solvation model simulated how ligands bind to receptors [28]. This model considers the role of solvent molecules in energetics and is pretty good at evaluating how solvation forces affect calculations. They used detailed constructs that showed how COX-2 receptor and ligand interact for chemical energy estimations. These computations aimed to understand the thermodynamics of ligand binding, focusing on the free energy associated with the binding process. This evaluation of the intensity of ligand-receptor bindings is contingent upon the free energies of binding [29].

Molecular Dynamics Simulation

A 100-nanosecond simulation was done to check how stable the complex molecular dynamic simulation is and how the ligand-receptor binding mode works [30]. The Desmond program in Schrodinger software was used on a Linux system for this experiment [31]. First, the receptor and ligand were mixed in a simple point charge (SPC) water model. They were put inside an orthorhombic box. To neutralize the system, sodium and chloride ions were added to a 50 mM solution. The simulation ran using the NPT ensemble, keeping the temperature steady at 300 K and pressure at 1.01325 bar. During this, an energy value of 1.2 was maintained, with results recorded every 100 picoseconds. The OPLS3e force field was applied all through the molecular dynamic simulation.

Following the dynamic simulation analysis, the Simulation Interaction Diagram generated trajectories. These trajectories, along with root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), and protein-ligand contacts, were analyzed to interpret the stability and interactions of the protein-ligand complex [29,32].

RESULTS AND DISCUSSIONS

Molecular Docking Analysis

We performed molecular docking simulations to analyze how potential ligands bind to COX-2 as inhibitors at a molecular level. The analysis of the docking findings helped us understand the expected COX-2 inhibition. All investigated compounds were effective inhibitors with binding solid affinities to the target protein COX-2, ranging from -11.569 to -9.349 Kcal/mol, compared with reference ligand rofecoxib, was -9.309 Kcal/mol, as shown in table 1. Studying the interaction of compounds 1-7 with COX-2 by determining the binding affinities of the designed compounds towards COX-2 enzyme. Compounds 3 and 5 had the highest docking scores of (-11.569 and -11.240 kcal/mol, respectively). Figure 2 (A and B) illustrates that compound 3 forms two hydrogen bonds with amino acid residue PHE518 with distance (1.81-1.91 Å) and Pi-Pi stacking with TRP387 and TYR385. Also, has a hydrophobic interaction with ALA516, TYR385, TRP387, ALA527, LEU531, ILE517, PHE518, MET522, VAL523, LEU534 and TYR355.

Table (1): Docking scores and interaction type for different imidazolidinone derivatives inside COX-2 active site.

compounds	Docking score Kcal/mol	Interaction type		
		H-bond with distance (Å)	Hydrophobic	Pi-Pi stacking
1	-10.388	MET522(2.62), GLN192 (2.12)	ALA516, ILE517, PHE518, TYR355, LEU352, VAL349, TYR348, LEU359, LEU531, ALA527, VAL523, MET522	
2	-9.579		ALA516, ILE517, PHE518, MET522, ALA527, VAL523, VAL525, PRO528, LEU531, LEU534, LEU93,	
3	-11.569	PHE518 (1.81), PHE518 (1.91)	ALA516, ILE517, PHE518, MET522, VAL523, TYR385, TRP387, ALA527, LEU531, LEU534, TYR355	TYR385, TRP387
4	-9.452		VAL116, MET113, MET522, VAL523, ALA527, LEU531, LEU534, VAL344, ILE345, TYR348, VAL349, LEU352, TYR355	TYR355
5	-11.240	TYR385(1.95), TYR355(2.06)	ALA516, ILE517, PHE518, VAL523, ALA527, LEU531, LEU534, TYR348, VAL349, LEU352, TYR355	
6	-9.349		ALA516, ILE517, PHE518, VAL523, ALA527, LEU531, LEU534, VAL344, ILE345, TYR348, VAL349, LEU352	
7	-10.620	TYR355(2.31), TYR385(1.67)	ALA516, ILE517, PHE518, VAL523, ALA527, VAL525, LEU531, LEU534	TYR355
Rofecoxib	-9.309	ARG513(2.36)	ALA516, ILE517, PHE518, MET522, VAL523, ALA527, LEU531, VAL116, TYR355, LEU531	

While rofecoxib forms a hydrogen bond with ARG513 and a hydrophobic interaction with ALA516, TYR355, MET522, VAL523, ALA527, LEU531, ILE517, PHE518VAL116, and LEU531when docked in the same COX-2 active site, as shown in figure 3 (A and B). The imidazolidinone ring of designed compounds contains nitrogen (NH) and carbonyl (C=O) groups, establishing crucial hydrogen bonds with polar residues essential for ligand stabilization. Also, the 2,4-difluorobenzyl group enhances hydrophobic interactions with residues such as VAL349 and LEU384, and the presence of fluorine atoms can form halogen bonds, increasing binding affinity. The phenyl ring attached to the imidazolidinone moiety participates in Pi-Pi stacking interactions with aromatic residues such as TRP387 and TYR385, further stabilizing the ligand within the binding site. Additionally, the boronic acid group forms two hydrogen bonds with PHE518, significantly enhancing the binding strength and specificity to COX-2. This distribution between hydrophobic and hydrophilic moieties makes optimal interaction with the enzyme, maximizing binding energy and stability and giving these compounds an excellent docking score [33–35].

Compound 3 interacts with the same amino acid as the reference drug. Its high docking score in the COX-2 active site suggests that this compound might prevent arachidonic acid from binding to COX-2, which helps with oxygenation. It also keeps the standard binding mode that the reference inhibitor usually uses. An investigation into molecular dynamics was conducted to evaluate the overall structural stability of the protein-ligand complex.

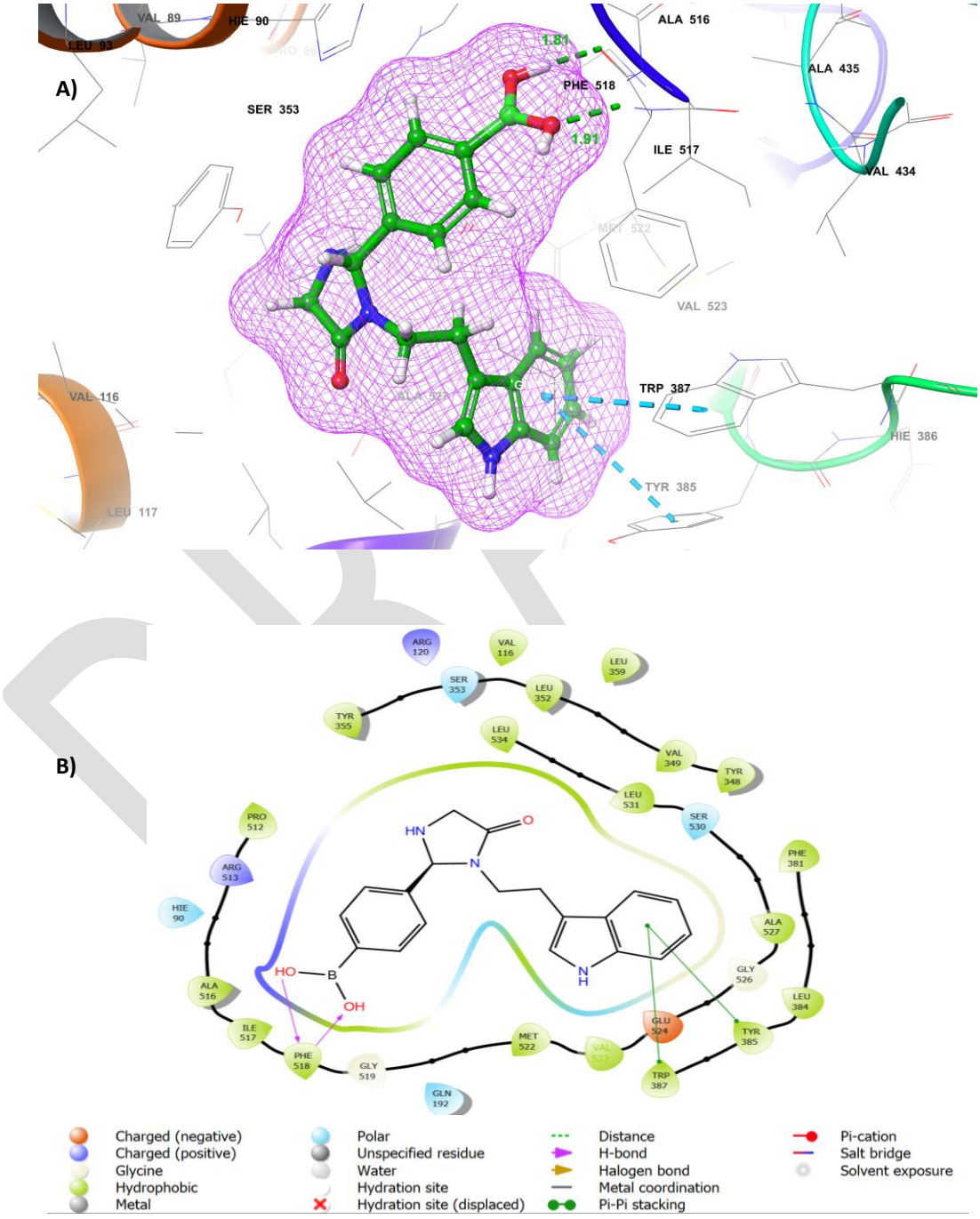

Figure (2): The interaction of compound 3 with the active binding site of COX-2 in 3D (A) and 2D (B) structures.

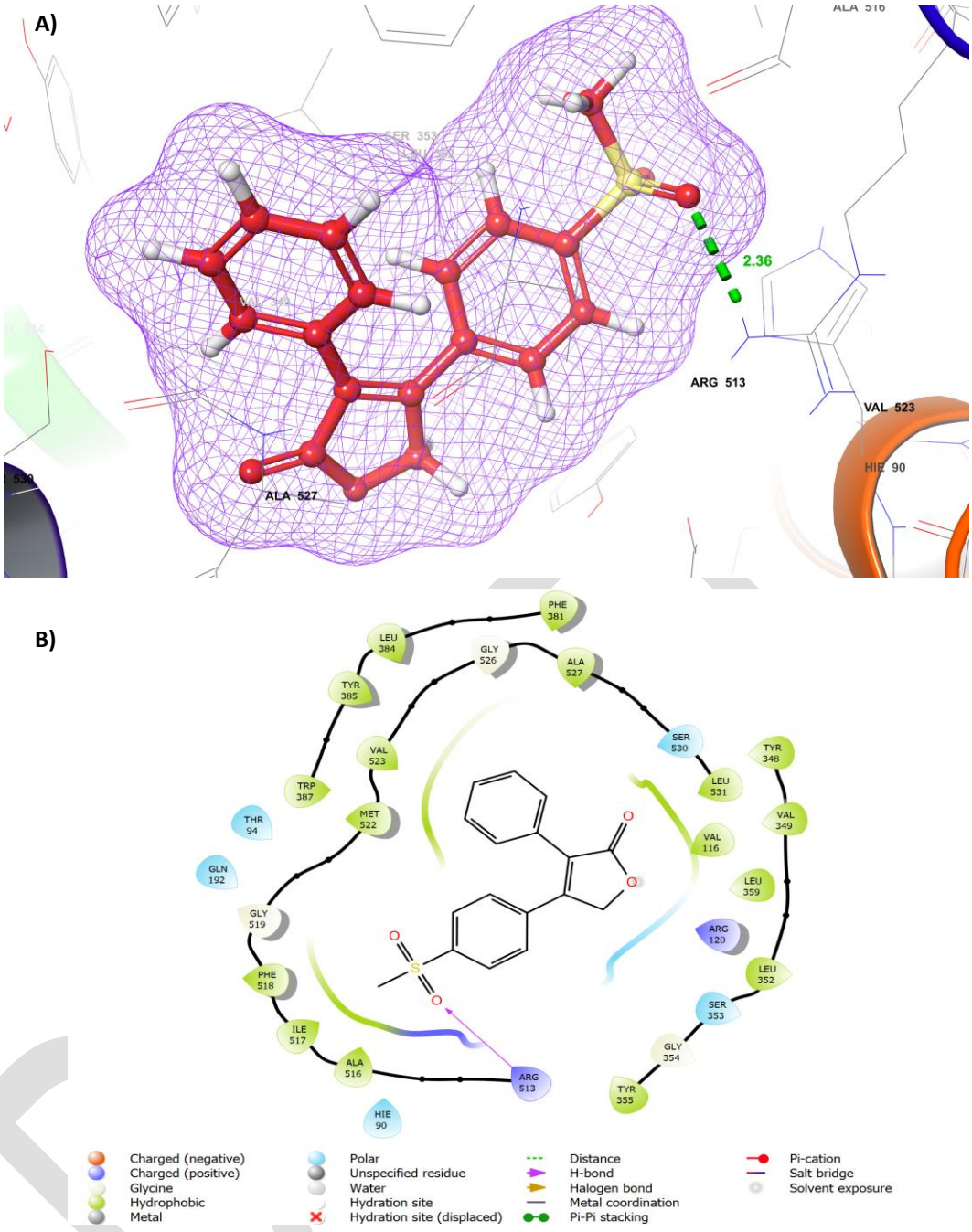

Figure (3): The interaction of standard drug (Rofecoxib) with the active binding site of COX-2 in 3D (A) and 2D (B) structures.

Our work aimed to examine the binding of imidazolidinone derivatives with rofecoxib instead of celecoxib. Rofecoxib is an accurate standard for assessing the selectivity of other COX-2 inhibitors due to its high selective for COX-2 over COX-1. Research shows rofecoxib binds to the COX-2 active site in a special way, and that's really important for making specific inhibitors. The structure and binding features of rofecoxib have been closely examined, giving us a solid standard to compare. Rofecoxib makes precise hydrogen bonds and hydrophobic contacts with key residues in the COX-2 binding pocket. These connections are super important when figuring out how well new inhibitors work. Also, rofecoxib has been used in many molecular docking and simulation studies as a reference compound owing to its extensively documented pharmacological characteristics. furthermore, its crystal structure data is available in the Protein Data Bank. This enhances the stability and dependability of comparisons, enabling us to understand better the potential of novel COX-2 inhibitors [36–38].

GBSA/MM Result

Using the MMGBSA free binding energy, an evaluation was conducted during molecular docking for the COX-2 enzyme (PDB code: 5KIR). This method aids in assessing the binding interactions and energetics between ligands and the COX-2 receptor. We found that Prime-MM/GBSA is the best method to look at stable ligand-receptor complexes. Various factors affect the overall stability of these complexes when we work out MM/GBSA. This detailed assessment gives us a clearer picture of those binding interactions' strengths. The solvent factor plays a major role in calculating the MM-GBSA for ligand-receptor interactions. In our experiments, we determined the MM/GBSA values for the COX-2 complex with rofecoxib and seven other designed ligands through molecular docking tests.

The strong potential of all the proposed analogs for incorporation effectively into the COX-2 receptor was indicated by their favorable free binding energies. The binding energies ΔG of Compounds 3 and 5 are the greatest for COX-2, with

values of nearly -58.41 kcal/mol and -54.05 kcal/mol, respectively (table 2). This value is significantly greater than the rofecoxib and has an ΔG of -51.54 kcal/mol. According to the MMGBSA results, The Van der Waals energy (ΔGvdW) and non-polar energy (ΔGLipo) are the energies that contribute the most substantially to ligand binding within the COX-2 binding pocket. This is evidenced by all compounds' extremely negative values for these energy components. These findings suggest that the compounds' robust binding to COX-2 depends upon favorable Van der Waals interactions and non-polar solvation effects. In contrast to (ΔGvdW) and (ΔGLipo), the other energy components, such as hydrogen bonding energy (ΔGHbond), are not significant in receptor binding.

Table (2): MM-GBSA values of rofecoxib and designed compounds in COX-2 receptor (PDB code: 5KIR).

Compounds	ΔG bind (Kcal/mol)	ΔG bind Vander	ΔG bind Lipophilic	ΔG bind H-Bond
1	-50.29	-41.50	-21.09	-2.01
2	-47.59	-27.46	-21.69	-1.58
3	-58.41	-43.45	-21.18	-1.82
4	-42.62	-23.30	-25.05	-0.02
5	-54.05	-37.87	-22.84	-0.40
6	-45.46	-43.96	-20.12	-0.34
7	-48.24	-30.44	-22.43	-1.15
Rofecoxib	-51.54	-35.02	-23.41	-0.80

This observation concludes that (ΔGvdW) and (ΔGLipo) primarily influence the interaction within the compounds and the COX-2 receptor. Nevertheless, hydrogen bonding plays a relatively minor function in this context.

Molecular Dynamics Simulations

Examining how ligands influence specific proteins through molecular dynamics (MD) simulations is valuable, given the importance of conformational stability in theoretical studies. This study investigates the conformational stability of COX-2 in the presence of compound 3 and rofecoxib over 100 nanoseconds. By analyzing the RMSD of the COX-2 backbone, we assessed the impact of compound 3 on the protein's structure over time, focusing on conformational changes and ligand interactions. The simulation data offer critical structural insights into the physical modifications occurring within the protein.

The RMSD plot for compound 3 showed a consistent connection with COX-2, with the ligand's RMSD fluctuations staying close to 1.4 Å and the protein within 0.9 Å, achieving stability after 10-ns during the MD simulation, as shown in figure (4-A). In contrast, rofecoxib's RMSD plot indicated that the system achieves stability with the ligand's RMSD values close to 1.1 Å and the protein RMSD stabilizing around 1.4 Å (figure 4-B). The RMSF for all binding residues for compound 3 and rofecoxib was below 1.5 Å, with low fluctuations, suggesting stable interactions within the binding pocket indicating a stable binding pocket throughout the MD simulation, as shown in figure (5-A and B).

During the molecular dynamic simulation, compound 3 strongly binds to COX-2 and interacts with most amino acids in its active site (figure 6). It shares interactions with rofecoxib (figure 7) with the following residues: SER530, ALA527, VAL523, PHE518, ARG513, TYR355, LEU352, VAL349, TYR384, and HIS90 through hydrogen bonds, hydrophobic interactions, and water bridges.

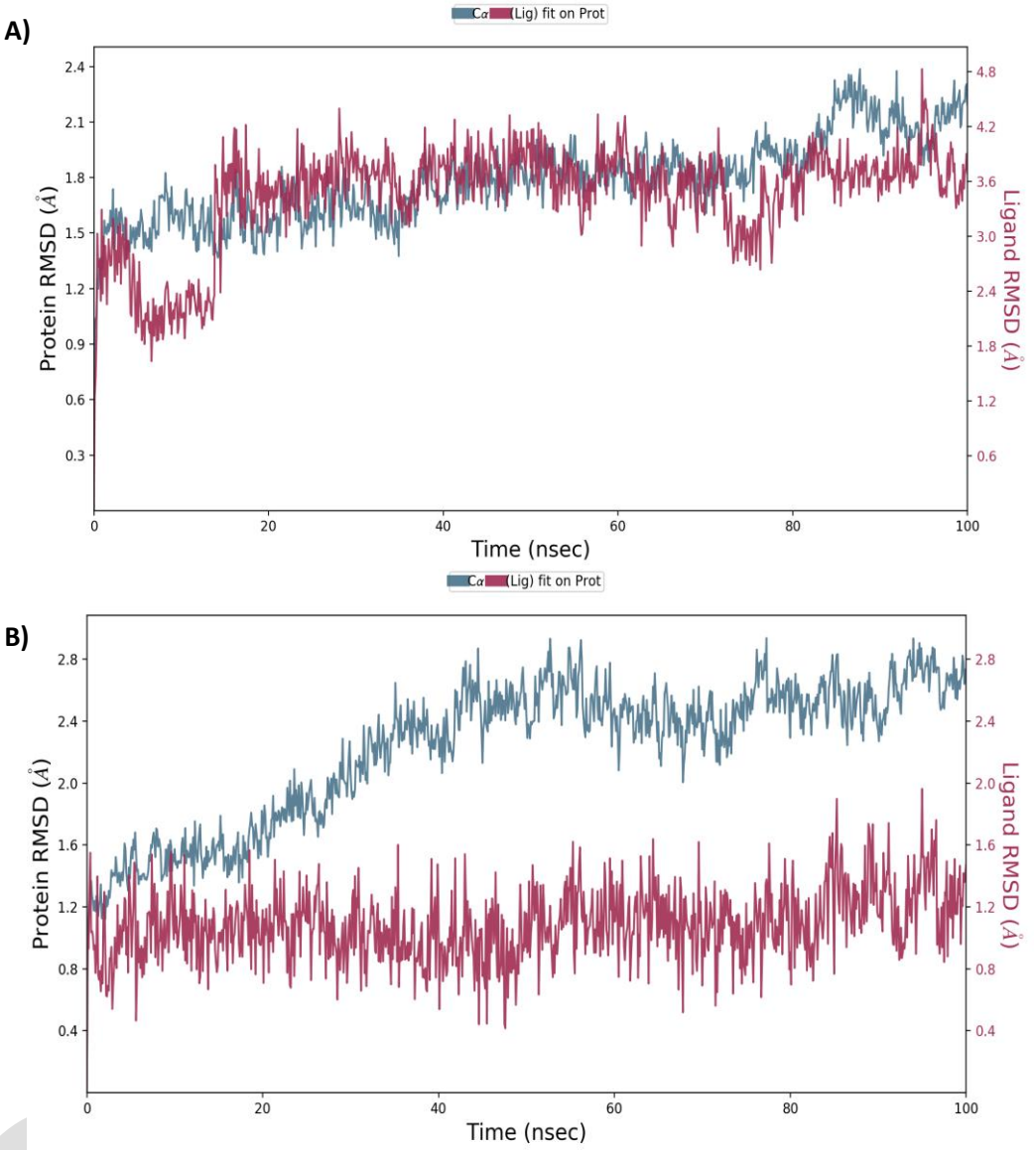

Figure (4): A) compound 3 RMSD plot, B) Rofecoxib RMSD plot.

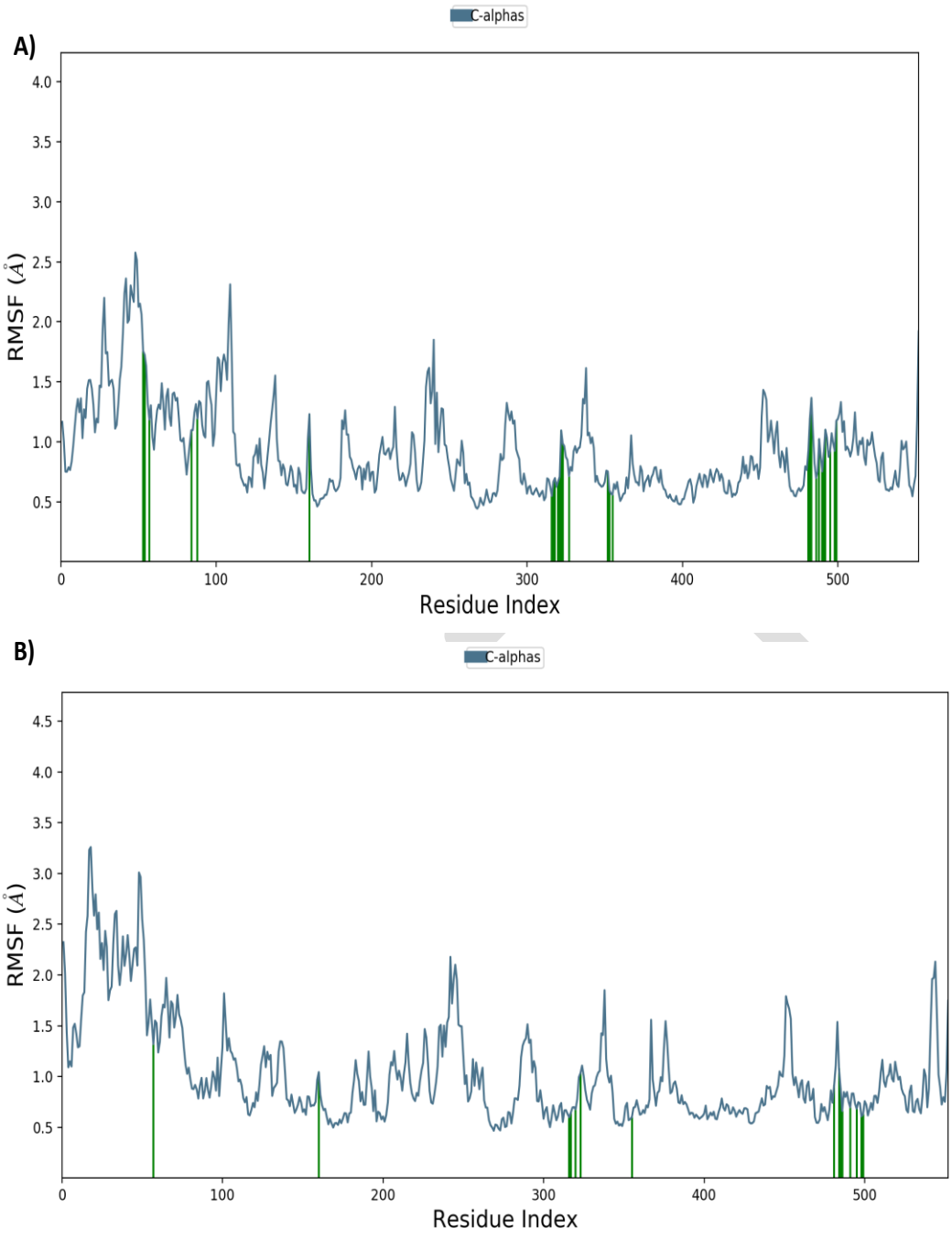

Figure (5): A) compound 3 RMSF, B) Rofecoxib RMSF.

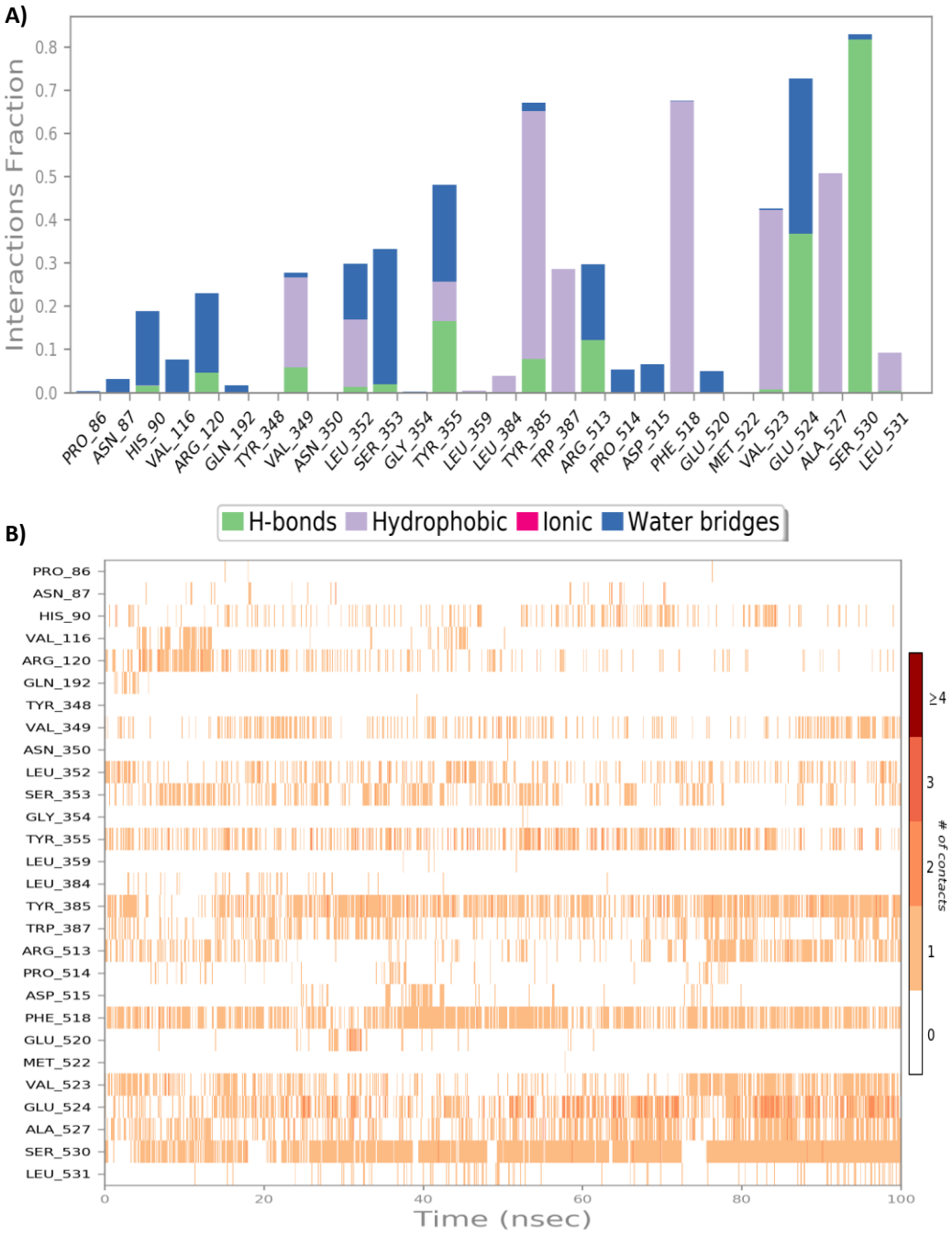

Figure (6): COX-2-compound 3 contacts (A, B) explain the proportion of binding interactions through 100 ns of MDS.

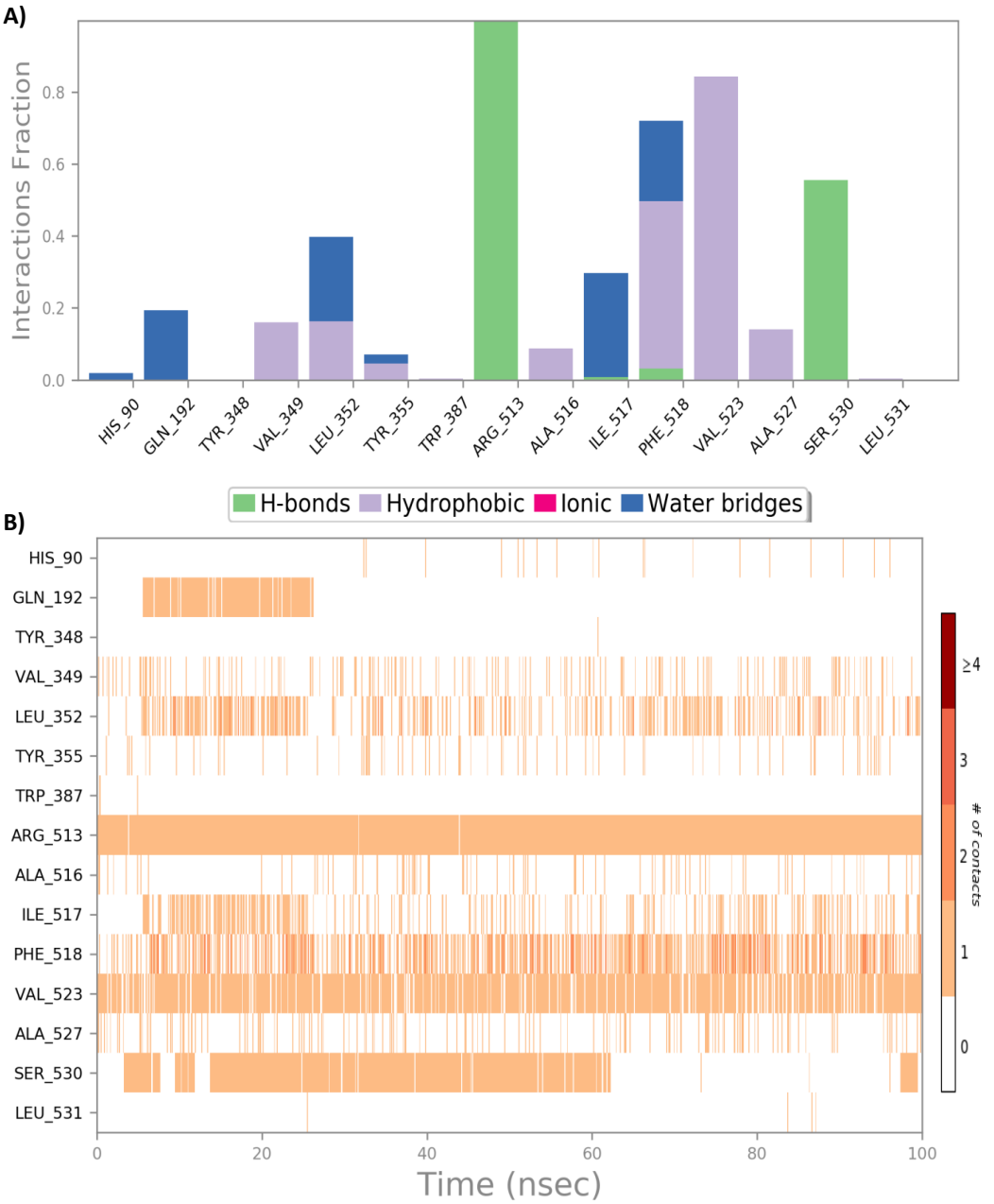

Figure (7): COX-2-Rofecoxib contacts (A, B) explain the proportion of binding interactions through 100 ns of MDS.

Drug-Likeness Evaluation

Lipinski's rule of 5 recommends that orally administered drugs have specific properties to be effective. Specifically, these drugs should have less than ten hydrogen bond acceptors, less than five hydrogen bond donors, a molecular weight of less than 500, and a LogP value of less than 5. Adhering to these guidelines can help ensure that orally administered drugs are more likely to be successful [39]. In addition, it is essential that the polar surface area of the drugs, a crucial characteristic linked to bioavailability, should be less than 140 Å. There is an inverse relationship between the topological polar surface area (TPSA) and the oral bioavailability of a drug, in which an increase in TPSA leads to a decrease in oral bioavailability. All designated compounds exhibit passive absorption with (TPSA) <140 Å to enhance their oral bioavailability [40]. Table 3 shows the compounds' chemical, pharmacokinetic, and physicochemical properties under examination.

Table (3): Computational estimations of pharmacokinetic characteristics of designed compounds.

C	TPSA(Å)	Water solubility	GI	BBB	P-gp substrate	Lipinski	Veber	BS
1	88.59	Soluble	High	No	Yes	Yes	Yes	0.55
2	97.82	Soluble	High	No	Yes	Yes	Yes	0.55
3	88.59	Soluble	High	No	Yes	Yes	Yes	0.55
4	97.82	Soluble	High	No	Yes	Yes	Yes	0.55
5	88.59	Soluble	High	No	Yes	Yes	Yes	0.55
6	88.59	Soluble	High	No	Yes	Yes	Yes	0.55
7	88.59	Soluble	High	No	Yes	Yes	Yes	0.55

C: Compounds number, BBB: blood-brain barrier permeation, GI: gastrointestinal absorption, TPSA: topological polar surface area, P-gp: P- glycoprotein, BS: Bioavailability Score.

CONCLUSIONS

This study identified novel imidazolidinone derivatives as promising selective COX-2 inhibitors. Compounds 3 and 5 showed binding solid affinities to COX-2. Molecular dynamics simulations confirmed the stability of these complexes, and MM/GBSA calculations indicated favorable binding energies. All compounds also demonstrated acceptable drug-likeness profiles and desirable pharmacokinetic properties. These results suggest that designed imidazolidinone derivatives, especially compound 3, have significant potential as selective COX-2 inhibitors. Their strong binding affinities, stable interactions, and favorable pharmacokinetic profiles warrant further investigation and optimization as therapeutic agents for inflammatory conditions. Future studies should focus on in vivo evaluations to confirm their efficacy and safety.

Conflict of interest

The authors declare no conflict of interest.

Ethics Approval

None to declare

Author Contribution

All Authors contributed equally to this work

Funding source

None

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