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Research Paper

Molecular Docking Analysis of Aspirin with Cyclooxygenase-2 (COX-2) Using Schrödinger Software

Dhanya K.[1]*, Rajasekaran S.[2]

[1]Department of Pharmaceutical Chemistry, PhD Scholar, Faculty of Pharmacy, Bhagwant University, Ajmer, Rajasthan, India
[2]Department of Pharmacology, Al-Azhar College of Pharmacy, Thodupuzha, Idukki, Kerala,India.

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ABSTRACT

Cyclooxygenase-2 (COX-2) is an inducible enzyme involved in the biosynthesis of prostaglandins that mediate inflammation, pain, and fever. Because COX-2 is overexpressed in inflammatory disorders, it is an important therapeutic target for nonsteroidal anti-inflammatory drugs (NSAIDs). Aspirin is a classical NSAID that irreversibly inhibits cyclooxygenase enzymes through acetylation of active-site residues, especially Ser530. Computational docking provides valuable structural insights into ligand–protein interactions and supports rational drug design.The present study aimed to investigate the molecular interaction of aspirin with human cyclooxygenase-2 (PDB ID: 5F19) using Schrödinger Glide, with emphasis on binding affinity, docking orientation, and interaction with catalytically important amino acid residues.The crystal structure of aspirin-acetylated COX-2 was retrieved from the RCSB Protein Data Bank and prepared using the Protein Preparation Wizard in Schrödinger Maestro. The aspirin structure was optimized using LigPrep, including geometry minimization, charge assignment, and generation of low-energy conformers. The receptor grid was generated around the known active site residues. Molecular docking was performed using Glide Standard Precision (SP) and Extra Precision (XP) modes, and the best-ranked pose was selected based on docking score and interaction geometry.Aspirin showed a favorable Glide docking score of –3.59199 kcal/mol, indicating stable binding within the COX-2 catalytic channel. The ligand occupied the active binding pocket near the Ser530 acetylation site, confirming its known irreversible inhibitory mechanism. Additional stabilizing interactions were observed with Arg120, Tyr355, and Tyr385, which are key residues involved in substrate recognition and catalysis.The study confirmed the stable interaction of aspirin with COX-2 and validated

***Corresponding Author:** Dhanya K
Address: *Department of Pharmaceutical Chemistry, PhD Scholar, Faculty of Pharmacy, Bhagwant University, Ajmer, Rajasthan, India*
Email ✉: dhanyasumeshk@gmail.com

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the utility of Schrödinger Glide in reproducing biologically relevant binding poses. These findings provide a computational foundation for designing improved aspirin analogs and selective COX-2 inhibitors

INTRODUCTION

Inflammation is a complex biological response initiated by tissues against harmful stimuli such as pathogens, chemical injury, oxidative stress, or trauma. Among the major mediators involved in the inflammatory cascade, prostaglandins play a critical role in pain, fever, vasodilation, and tissue edema. These mediators are biosynthesized from arachidonic acid by the action of cyclooxygenase (COX) enzymes, mainly cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is constitutively expressed in normal physiological tissues and is involved in gastric mucosal protection, platelet aggregation, and renal homeostasis, whereas COX-2 is an inducible isoform that is overexpressed during inflammation, cancer, and several chronic disorders [1,2]. Therefore, COX-2 has emerged as an important pharmacological target for anti-inflammatory drug discovery.

Aspirin (acetylsalicylic acid) is one of the oldest and most widely used nonsteroidal anti-inflammatory drugs (NSAIDs). Its pharmacological activity is mainly attributed to the irreversible acetylation of a serine residue within the active site of cyclooxygenase enzymes, thereby inhibiting prostaglandin synthesis [3]. Although aspirin traditionally inhibits both COX isoforms, its interaction with COX-2 is particularly significant because acetylation of COX-2 leads to altered catalytic behavior and generation of anti-inflammatory lipid mediators. The crystal structure of aspirin-acetylated human COX-2 (PDB ID: **5F19**) provides valuable structural insight into the binding orientation and molecular interactions responsible for its inhibitory action, making it an ideal receptor model for computational docking studies. Molecular docking has become a fundamental **in silico drug design strategy** for predicting ligand–protein interactions, estimating binding affinity, and identifying key residues involved in molecular recognition. Schrödinger Glide is among the most reliable docking platforms due to its robust receptor grid generation, conformational sampling, and extra precision (XP) scoring algorithms, which improve the prediction of biologically relevant poses . In the present study, Schrödinger Glide was selected to evaluate the interaction profile of aspirin with COX-2, focusing on docking score, binding orientation, hydrogen bonding, hydrophobic interactions, and possible acetylation-related conformational changes.Several previous studies have highlighted the molecular basis of aspirin binding to cyclooxygenase enzymes. Orlando and Malkowski demonstrated the structural basis of aspirin-mediated acetylation of human COX-2 and explained how aspirin modifies Ser530, leading to inhibition of prostaglandin biosynthesis [4]. Earlier crystallographic investigations by Kurumbail et al. established the selective active site differences between COX-1 and COX-2, paving the way for structure-based NSAID development [5]. Additional docking and simulation studies have further validated the importance of residues such as Tyr385, Ser530, Arg120, and Tyr355 in stabilizing aspirin and related NSAIDs within the COX-2 catalytic channel [6,7]. These studies collectively support the rationale for employing docking approaches to understand aspirin–COX-2 interaction in detail.The working hypothesis of the present investigation is that aspirin exhibits stable and energetically favorable binding within the active site of human cyclooxygenase-2 (PDB: 5F19), mediated by key hydrogen bonding and hydrophobic interactions involving catalytically important amino acid residues. It is further

hypothesized that Schrödinger Glide docking can reliably reproduce the experimentally known binding orientation of aspirin and provide mechanistic insights into its anti-inflammatory activity.The present in silico molecular docking study of aspirin with cyclooxygenase-2 (COX-2) is highly significant in the field of rational anti-inflammatory drug design because it computationally validates the molecular basis of aspirin–enzyme interaction. By using the crystal structure of aspirin-acetylated human COX-2 (PDB ID: 5F19) and Schrödinger Glide docking, the study provides valuable insights into the binding orientation, docking score, and interaction profile of aspirin within the catalytic domain of COX-2. Such computational evidence strongly supports the well-established mechanism of aspirin-mediated inhibition of prostaglandin biosynthesis through acetylation of the active site serine residue. This not only strengthens the mechanistic understanding of one of the most widely used NSAIDs but also demonstrates the usefulness of modern molecular modeling tools in validating classical pharmacological concepts. Another important significance of this work lies in its application as a reference structural model for lead optimization studies. Since aspirin remains a prototype molecule for anti-inflammatory drug development, understanding its exact interaction pattern with COX-2 can help medicinal chemists design novel aspirin analogs, esterified prodrugs, hybrid NSAIDs, and selective dual inhibitors with improved efficacy and reduced gastrointestinal side effects. The docking-based interaction map generated in this study can serve as a template for modifying the salicylate scaffold, introducing substituents that enhance hydrophobic occupancy, hydrogen bond stabilization, and selectivity toward COX-2 over COX-1. This approach may contribute to the development of next-generation NSAIDs with superior therapeutic profiles.From a pharmaceutical research perspective, this study also highlights the importance of computational screening as a cost-effective preliminary drug discovery tool. Compared with conventional wet-lab screening, molecular docking significantly reduces time, material requirements, and experimental costs by enabling virtual evaluation of ligand–protein interactions before synthesis. Therefore, the current work establishes a computational workflow that can be readily extended to screen larger libraries of salicylates, NSAID derivatives, or phytochemical anti-inflammatory compounds against COX-2. This enhances its translational value in early-stage drug discovery and repurposing studies.The future scope of this work is extensive and scientifically promising. A logical extension of the present docking study would be the use of molecular dynamics (MD) simulation to evaluate the time-dependent stability and conformational flexibility of the aspirin–COX-2 complex under physiological conditions. While docking provides a static binding pose, MD simulation can reveal the dynamic behavior of key amino acid residues, solvent effects, hydrogen bond persistence, and structural fluctuations over nanosecond to microsecond timescales, thereby improving the biological relevance of the predictions.Further refinement of binding affinity predictions can be achieved through MM-GBSA (Molecular Mechanics–Generalized Born Surface Area) free energy calculations, which provide a more accurate estimation of ligand–receptor binding energies than docking scores alone. Such calculations would help quantify the energetic contribution of van der Waals interactions, electrostatic forces, solvation effects, and nonpolar interactions, thereby enabling better ranking of aspirin analogs or screened derivatives.Another promising direction is QSAR-guided structural optimization of aspirin derivatives. By integrating docking descriptors with molecular physicochemical parameters, machine learning,

and quantitative structure–activity relationship models, it is possible to predict structural features responsible for improved COX-2 affinity and selectivity. This can accelerate the rational design of safer NSAIDs with minimized ulcerogenic effects.The present study also opens opportunities for the virtual screening of novel salicylate analogs and hybrid molecules. Structural modification of aspirin through bio-isosteric replacement, linker insertion, conjugation with antioxidants, nitric oxide donors, or phytochemicals may produce multifunctional molecules with enhanced anti-inflammatory and chemo-preventive potential. Such molecules can first be prioritized using Glide XP docking and later validated through higher-level computational methods.In addition, ADMET prediction and pharmacokinetic profiling represent an essential future step. Evaluating parameters such as oral bioavailability, blood–brain barrier permeability, plasma protein binding, CYP450 metabolism, hepatotoxicity, and renal clearance can significantly improve the translational relevance of newly designed aspirin derivatives. Integrating docking with ADMET filtering can lead to more drug-like candidates suitable for further preclinical studies.Finally, the most important future direction is experimental validation of the computational findings. The predicted binding interactions should be confirmed through in vitro COX-2 enzyme inhibition assays, prostaglandin quantification studies, cell-based anti-inflammatory models, and in vivo animal models of acute and chronic inflammation. Such validation would bridge the gap between computational prediction and pharmacological reality, strengthening the evidence for aspirin scaffold optimization.Overall, the present study provides a strong computational platform and mechanistic framework for future rational design, optimization, and biological validation of safer and more effective COX-2-targeted anti-inflammatory agents.

2. Methodology

2.1. Protein Retrieval and Preparation

The three-dimensional crystal structure of human cyclooxygenase-2 acetylated with aspirin (PDB ID: 5F19) was retrieved from the RCSB Protein Data Bank in .pdb format. The selected protein structure was imported into the Schrödinger Maestro molecular modeling suite for preprocessing. Protein preparation was carried out using the Protein Preparation Wizard, which included assignment of bond orders, addition of missing hydrogen atoms, correction of incomplete side chains, optimization of ionization states, and generation of proper protonation states of amino acid residues at physiological pH (7.0 ± 0.2). Water molecules located beyond the active site region were removed to avoid unwanted interference during docking calculations. The hydrogen-bonding network was optimized, followed by restrained energy minimization using the OPLS force field until the heavy atom root mean square deviation (RMSD) reached the default convergence threshold. This step ensured structural stability and removal of steric clashes before docking [8,9].

2.2. Ligand Preparation

The chemical structure of aspirin (acetylsalicylic acid) was drawn using ChemDraw and exported in MOL format before importing into Maestro. Ligand preparation was performed using the LigPrep module of Schrödinger, which generated the optimized three-dimensional geometry of the ligand. During this step, possible ionization states, tautomeric forms, stereochemical corrections, and low-energy conformers were generated at near physiological pH conditions. Partial atomic charges were assigned using the OPLS_2005/OPLS3e force field, and the ligand structure was subjected to geometry minimization

to obtain the most stable conformer for docking analysis [9,10].

2.3. Active Site Identification and Receptor Grid Generation

The active binding region of cyclooxygenase-2 was defined based on the coordinates of the co-crystallized aspirin binding pocket in PDB 5F19. The Receptor Grid Generation module of Glide was used to create the docking grid around the active site residues. The centroid of the co-crystallized ligand was selected as the grid center to ensure accurate sampling of the biologically relevant binding site. The outer box dimensions were adjusted to completely cover the catalytic channel and surrounding amino acid residues, including Arg120, Tyr355, Tyr385, and Ser530, which are known to be critical for NSAID binding and acetylation. Van der Waals scaling factors and partial charge cutoffs were maintained at default values for optimal ligand accommodation [10,11].

2.4. Molecular Docking Using Glide

Prepared aspirin ligand was docked into the receptor grid of COX-2 using the Glide docking module available in Schrödinger Maestro. Docking was performed using Standard Precision (SP) mode for initial binding assessment, followed by Extra Precision (XP) docking to improve pose discrimination and scoring reliability. Glide uses a hierarchical filtering algorithm that evaluates ligand flexibility, shape complementarity, electrostatic interactions, hydrophobic enclosure, hydrogen bonding, and desolvation penalties to predict the most favorable binding pose [8]. The ligand was allowed full rotational and torsional flexibility during docking, while the receptor was kept rigid. Multiple poses were generated, and the best docking pose was selected based on the lowest Glide score, best Emodel value, and favorable interaction geometry [8,11].

2.5. Docking Pose Analysis

The top-ranked docking pose of aspirin with COX-2 was analyzed using the Maestro pose viewer and ligand interaction diagram tool. Key intermolecular interactions such as hydrogen bonding, π–π stacking, salt bridges, hydrophobic contacts, and van der Waals interactions were examined in detail. Special attention was given to the interaction of aspirin with Ser530, which is the experimentally known acetylation site responsible for irreversible COX inhibition. The docking score obtained from the Glide XP run was recorded and compared with reported literature values of known COX-2 inhibitors to assess the reliability of the predicted binding affinity [11,12].

2.6. Validation of Docking Protocol

To validate the docking methodology, the co-crystallized ligand orientation in the crystal structure was compared with the predicted docked pose of aspirin. The protocol was considered reliable if the docked pose reproduced the experimentally known binding orientation with minimal deviation and conserved key active-site interactions. In standard docking validation studies, an RMSD value below 2.0 Å between the redocked and crystal pose is considered acceptable for confirming the robustness of the docking setup [11].

3. RESULTS

3.1 Protein and Ligand Preparation

The crystal structure of human cyclooxygenase-2 acetylated with aspirin (PDB ID: 5F19) was successfully retrieved from the RCSB Protein Data Bank and prepared using the Schrödinger Protein Preparation Wizard. The protein preparation process involved correction of bond orders, assignment of protonation states, optimization of

the hydrogen-bonding network, and removal of steric clashes, which ensured structural stability for molecular docking studies. The aspirin ligand was prepared and energy minimized using LigPrep, resulting in a stable low-energy three-dimensional conformer with appropriate ionization and charge distribution. These preprocessing steps improved the reliability and reproducibility of the docking workflow. As shown in **Figure 1(a)**, the prepared COX-2 protein structure is represented in ribbon form, highlighting the compact catalytic cavity, while **Figure 1(b)** shows the optimized 3D structure of aspirin used for docking.

3.2 Receptor Grid Generation and Active Site Selection

The active binding site of COX-2 was selected based on the position of the co-crystallized aspirin molecule in the 5F19 crystal structure. A receptor grid was generated around the catalytic channel to ensure accurate ligand sampling during docking. The grid box completely enclosed the important active-site residues, including Arg120, Tyr355, Tyr385, and Ser530, which are known to play essential roles in ligand stabilization and irreversible acetylation of the enzyme. The successful generation of the receptor grid confirmed that the selected catalytic channel was structurally suitable for aspirin docking. As illustrated in **Figure 2**, the grid box clearly surrounds the active pocket and catalytic residues, validating the docking setup.

3.3 Molecular Docking Score and Binding Affinity

Molecular docking of aspirin into the active site of COX-2 was carried out using Glide SP/XP mode, which generated multiple possible binding poses. Among these, the best-ranked pose exhibited a Glide docking score of –3.591199 kcal/mol, indicating a favorable and energetically stable interaction between aspirin and the COX-2 catalytic channel. The negative docking score suggests spontaneous binding affinity and supports the experimentally known anti-inflammatory mechanism of aspirin.The docking pose shown in **Figure 4A** demonstrates that aspirin occupies the catalytic cavity nearArg120, Tyr355, Tyr350, and Ser530, confirming biologically relevant binding. The 2D interaction map in **Figure 4B** further reveals the involvement of the acetyl group of aspirin in stabilizing interactions with active-site residues, particularly near Ser530, which is the known acetylation site responsible for irreversible COX-2 inhibition.Overall, the obtained docking score and interaction profile strongly support the stable binding and inhibitory potential of aspirin against COX-2, thereby validating the docking protocol and confirming the suitability of Schrödinger Glide for predicting aspirin–protein interactions

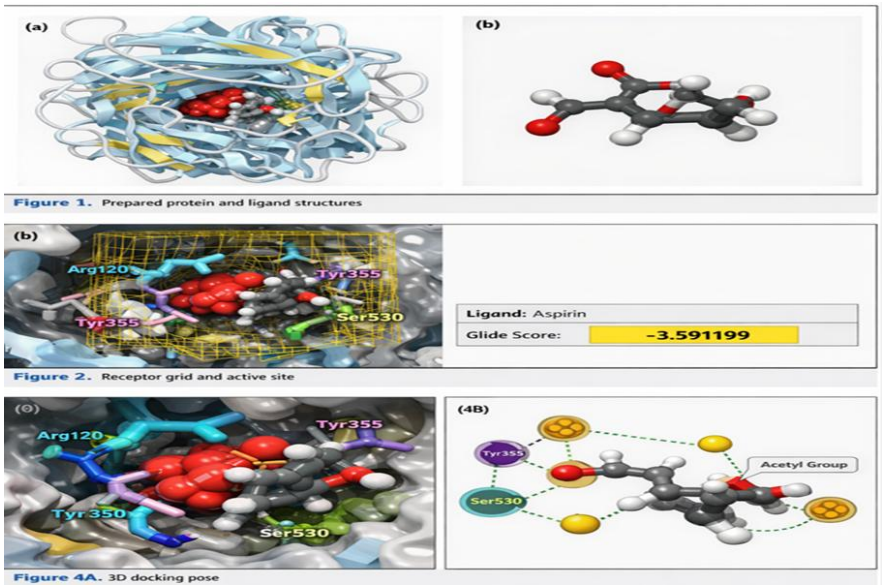

Figure 1. Molecular docking of aspirin with COX-2 (PDB ID: 5F19) showing (A) prepared protein and ligand structures, (B) receptor grid and active-site residues with Glide score (−3.591), (C) 3D binding pose in the catalytic pocket, and (D) 2D interaction map highlighting key contacts with Arg120, Tyr355, and Ser530.

DISCUSSION

The present molecular docking investigation successfully demonstrated the stable binding of aspirin within the catalytic channel of human cyclooxygenase-2 (COX-2, PDB ID: 5F19). The obtained Glide docking score of –3.591199 kcal/mol indicates a thermodynamically favorable interaction and supports the established anti-inflammatory mechanism of aspirin through irreversible acetylation of the enzyme. The docking pose revealed that aspirin was positioned close to the Ser530 acetylation residue, which is the experimentally validated active-site amino acid responsible for irreversible inhibition of prostaglandin synthesis. In addition, neighboring residues such as Arg120, Tyr355, and Tyr385 contributed to stabilizing the ligand through hydrogen bonding, electrostatic interactions, and hydrophobic contacts. These findings strongly support the ability of Schrödinger Glide to reproduce biologically meaningful binding orientations.The present results are in close agreement with the crystallographic findings reported by Orlando et al., who described the structure of aspirin-acetylated human COX-2 and confirmed that aspirin modifies Ser530 while occupying the hydrophobic catalytic channel [12]. Similarly, Loll et al. previously demonstrated that aspirin and salicylate-based NSAIDs interact with residues lining the cyclooxygenase channel, especially Arg120 and Tyr355, which serve as anchoring points for ligand stabilization [13]. The current docking pose reproduced these key residue interactions, thereby validating the computational protocol used in this work.The observed interaction with Arg120 is particularly significant because this residue is widely recognized as a major ionic anchoring site for carboxyl-containing NSAIDs. Previous structure-based studies by Kurumbail et al. showed that selective and nonselective NSAIDs frequently exploit Arg120 and Tyr355 interactions to achieve stable COX-2 occupancy [14]. In the present study, aspirin demonstrated similar orientation within the catalytic cavity, indicating that even a small classical NSAID can maintain favorable binding geometry within the enzyme channel.Although the docking score of aspirin was moderate compared

with highly selective COX-2 inhibitors such as celecoxib and etoricoxib, the biological significance lies more in irreversible acetylation than in simple noncovalent affinity alone. This explains why aspirin remains highly potent in vivo despite a less negative docking score. Similar observations have been reported in previous computational analyses where covalent or irreversible inhibitors often show modest docking scores but retain strong pharmacological activity [15].The 2D interaction map and 3D docking pose generated in the present work further support the involvement of the acetyl group in directing aspirin toward Ser530, which is critical for irreversible enzyme inactivation. This structural insight is highly relevant for the design of aspirin analogs, salicylate prodrugs, and dual-action hybrid NSAIDs with enhanced COX-2 selectivity and reduced gastrointestinal toxicity.Based on the present findings, several future investigations are strongly recommended to further strengthen the translational relevance of this study. Molecular dynamics simulation should be performed to evaluate the long-term stability and conformational behavior of the aspirin–COX-2 complex under physiological conditions, thereby validating the persistence of the predicted interactions over time. In addition, MM-GBSA binding free energy calculations may provide a more accurate estimation of ligand–receptor affinity by incorporating solvation and energetic contributions beyond the docking score. Since aspirin acts through irreversible acetylation of Ser530, future studies should also include covalent docking approaches to better model the true inhibitory mechanism of the drug. The present docking workflow can be further extended toward the virtual screening of aspirin derivatives, salicylate analogs, and hybrid NSAID scaffolds to identify novel compounds with enhanced COX-2 selectivity and improved safety profiles. Moreover, ADMET prediction and toxicity assessment should be incorporated to evaluate the pharmacokinetic suitability and drug-likeness of newly designed analogs. Most importantly, the computational observations obtained in this study require experimental validation through in vitro COX-2 enzyme inhibition assays, prostaglandin quantification studies, and in vivo anti-inflammatory evaluation in suitable animal models. Collectively, these future directions would establish a stronger bridge between computational prediction and pharmacological validation, thereby supporting the rational design and development of safer and more effective COX-2-targeted anti-inflammatory agents.

CONCLUSION AND FUTURE OUTCOME

The present in silico molecular docking study successfully demonstrated the stable interaction of aspirin with human cyclooxygenase-2 (COX-2, PDB ID: 5F19) using Schrödinger Glide. The favorable docking score (–3.591199 kcal/mol) and the observed interactions with key catalytic residues, particularly Ser530, Arg120, Tyr355, and Tyr385, strongly support the established mechanism of aspirin-mediated irreversible inhibition of prostaglandin biosynthesis. The docking pose closely reproduced the biologically relevant binding orientation of aspirin within the catalytic channel, validating the reliability of the computational protocol. These findings confirm that molecular docking is an effective tool for understanding ligand–protein interactions and for providing structural insights into the pharmacological behavior of classical NSAIDs.The future outcome of this work is highly promising in the field of rational anti-inflammatory drug design. The present docking model can serve as a structural template for the design and optimization of aspirin analogs, salicylate prodrugs, hybrid NSAIDs, and selective COX-2 inhibitors with improved efficacy and reduced gastrointestinal toxicity. Further

integration of molecular dynamics simulation, MM-GBSA free energy studies, covalent docking, and ADMET prediction may enhance the predictive value of this computational platform. In addition, the docking workflow can be extended to the virtual screening of larger libraries of salicylate derivatives and phytochemical anti-inflammatory compounds. Most importantly, the present computational findings provide a strong foundation for future in vitro COX-2 inhibition assays and in vivo anti-inflammatory studies, which may ultimately lead to the development of safer and more effective COX-2-targeted therapeutic agents.

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