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MOLECULAR DOCKING STUDIES OF OXAZEPINE DERIVATIVES AGAINST CYCLOOXYGENASE-2 ENZYME AS POTENTIAL ANTI-INFLAMMATORY AGENTS

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ABSTRACT

Non-steroidal anti-inflammatory drugs are widely used medications that reduce inflammation. It has been established that every inhibitor of the cyclooxygenase-2 enzyme exhibits anti-inflammatory activity. In this study, several oxazepine derivatives were designed and docked against the cyclooxygenase-2 enzyme to evaluate their anti-inflammatory potential. The ligands were compared with conventional cyclooxygenase-2 inhibitors, such as valdecoxib and celecoxib. To elucidate the potential interactions between the inhibitors and the designed ligands, molecular docking simulations were conducted.The ligands were drawn in mol format using ChemSketch software. Avogadro software was then used to convert the ligands to .pdb format. The results of the molecular docking studies, conducted using iGEMDOCK software, were visualized using Discovery Studio Visualizer. The majority of the compounds demonstrated a greater binding affinity to the cyclooxygenase-2 enzyme. All of the ligands exhibited binding energies comparable to standard cyclooxygenase-2 inhibitors, such as valdecoxib (-91.8 kcal/mol) and celecoxib (-102.1 kcal/mol). The top two compounds, 7d (-109.2 kcal/mol) and 8h (-102.6 kcal/mol) were selected for display. Oxazepine derivatives show promise as a new class of anti-inflammatory drugs due to their stronger binding affinity to the cyclooxygenase-2 enzyme compared to conventional inhibitors.

Keywords: Oxazepine Derivatives, Cyclooxygenase-2 Enzyme, Antagonists, Anti Inflammatory, Molecular Docking, iGemdock Software and Discovery Studio Visualizer.

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INTRODUCTION

Heterocycles are common in nature and essential to life, they have received a lot of attention in the development of sophisticated organic materials and physiologically active molecules.[1]The oxazepine unit is a readily accessible nucleus found in many natural and pharmacological substances and is one of many heterocycles that have been investigated for the development of pharmaceutically significant molecules. Furthermore, oxazepines exhibit a variety of organic reactivities and may be a useful tool for creating novel molecular scaffolds. A survey of the literature indicates that combining two biodynamic heterocyclic systems results in the generation of a molecule with higher biological activity. Because they have been found to have a better biological profile, medicinal chemistry has found great interest in the chemistry of these connected heterocycles.[2] It was believed that combining Schiff base compounds with different anhydrides in a single molecular framework to obtain new heterocyclic compounds might be of interest in light of these findings and as a follow-up effort to develop new heterocyclic compounds containing the oxazepine moiety. Oxazepine derivatives were first introduced in 1965 and it is used in the reliefofthepsychoneuroseswhichischaracterizedbyanxietyandtension.Oxazepines are seven-membered heterocyclic compounds with oxygen and nitrogen.[3]Oxazepines can be prepared by multistep reactions. In the first step,the Schiff basederivative is prepared from an amino group of primary amine compounds that reacts with an active carbonyl group of aldehydes or ketones. Within the second step condensation reaction takes place between imine or Schiff base(-N=CH-) compounds and various anhydrides such as phthalic, maleic and succinic anhydride to form oxazepine compounds according to pericyclic reaction.[4-9]Important biological and pharmacological actions of oxazepine and its derivatives include enzyme

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inhibitors,[10]anticancer,[11]psychoactive drugs, antidepressant,[12]anti-bacterial,anti-fungal,[13,14]anxiolytic,[15]antioxidant,[16]anti-epileptic[17]and anti-inflammatory activity.[18,19]

EXPERIMENTAL

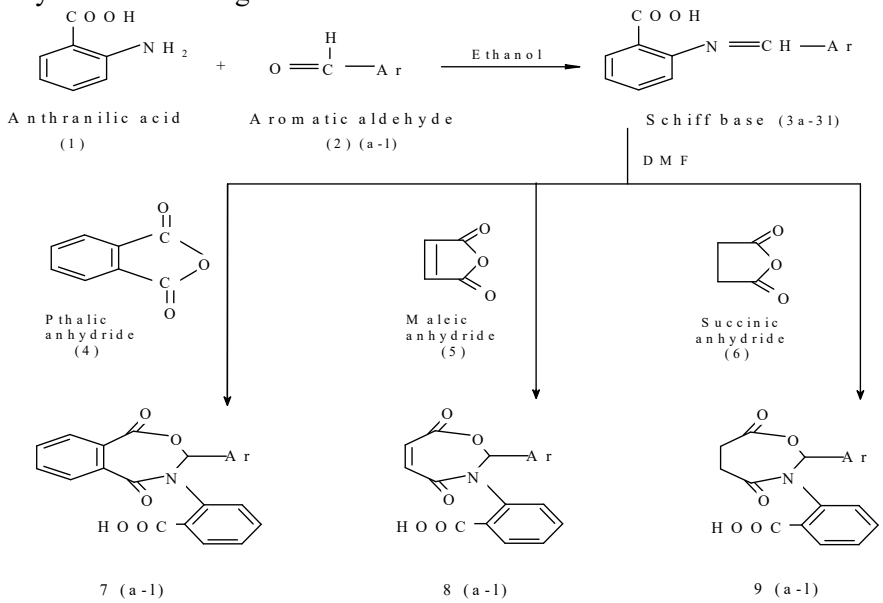
General Procedure for Synthesis of Oxazepine Derivative

Step-1: Preparation of Schiff Bases

Equimolar amounts of aldehyde derivatives (0.01 moles) and anthranilic acid (0.01 moles) were weighed and dissolved in 25 mL of ethyl alcohol. A small amount of glacial acetic acid and sodium lauryl sulfate was added to the mixture. The resulting mixture was refluxed for two to four hours. The solid product formed was vacuum-filtered, purified by recrystallization in ethanol and then dried.

Step-2:Preparation of Oxazepine Derivative

Equimolar amounts of Schiff base (0.01moles) from step-1 and various anhydrides (0.01moles) of phthalic anhydride (4), maleic (5) and succinic anhydrides (6) were taken and dissolved in 20 mL of dimethyl formamide (DMF) and add 2-3 drops of glacial acetic acid and reflex it for 6-8 hours. The reaction time was determined by thin layer chromatography with mobile phase n-hexane: ethyl acetate (6:4). The resultant synthesized oxazepines were collected after filtration of the reaction mixture and purified by recrystallization using absolute alcohol and then washed and dried.[20]



Scheme: Synthesis of Various Oxazepine Derivatives

The synthetic procedures for oxazepine derivatives were taken from the existing literature. Different aromatic aldehydes and aromatic amines were chosen from the synthesis method indicated above, and the finished products were created to comply with the system. Using SwissADME software,[22,27,28,29] a large chemical library was acquired and after an Insilico toxicity screening with TopKat,[21,27,28,29] their ADME features were predicted. Designed compounds with better ADME qualities and projected non-toxic and non-carcinogenic compounds were chosen for molecular docking studies.

Molecular Docking

The Swiss Target Prediction software[23,27,28,29]was used to choose the protein target from a library of compounds that were prepared by the previously outlined scheme. Swiss Target Prediction software predicted every possible combination for the target protein, including safe, non-toxic and non-carcinogenic ligands. Cyclooxygenase enzyme has been identified as a potential target for the majority of ligands.

Detection Method

The 2D structures of the ligands were created using ChemSketch software and saved in. mol format. The

Avogadro tool[24,25,27,28,29]was then used to convert these structures from.mol to .pdb format. Docking studies were conducted on the developed compounds, which were non-carcinogenic and exhibited favorable ADME properties, to assess their binding poses and interactions.

iGEMDOCK version 2.1[26-29] Docking was performed using software known as iGemdock which represents the Genetic Evolutionary Method for Molecular Docking. A graphical and automated drug design system for docking, screening, and analysis is called iGEMDOCK. This program determines the shape and orientation of ligands about the active site of proteins. The chosen safe medications were examined using a co-crystallized ligand inhibitor that was acquired from the protein data repository to assess the molecular interactions with the cyclooxygenase-2 enzyme (PDB ID: 3LN1) (Fig.-1).

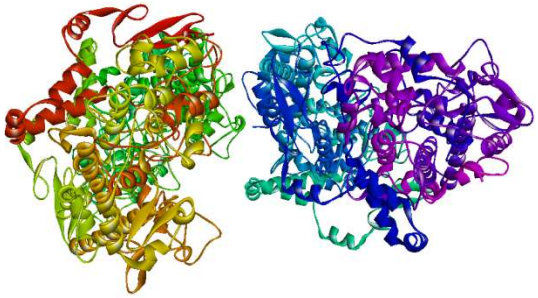


Fig.-1: Cleaned Cyclooxygenase-2 Enzyme –PDB ID: 3LN1

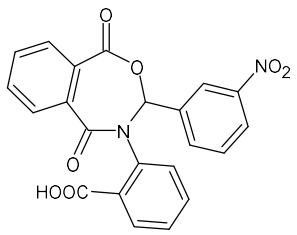
Discovery Studio Visualizer (Biovia)[27,28,29]

Was used to visualize and analyze the ligand interactions. An accurate docking technique was chosen, and the standard docking process was adhered to. The scoring function took Van der Waals forces, electrostatic energy, and hydrogen bonding into account while evaluating the optimal docking solutions. The post-docking interaction profiles of the optimal poses for the best compounds were examined to determine the interactions between the ligands and the target protein.In silico toxicity, prediction was employed to identify safe and non-carcinogenic compounds. Both these compounds and well-known COX-2 inhibitors, such as celecoxib and valdecoxib, were selected for molecular docking. Docking simulations were used to evaluate molecular interactions and binding affinities.

RESULTS AND DISCUSSION

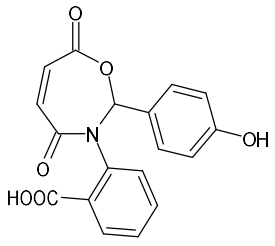
From the top 10 compounds, the two with the best binding energies were chosen for post-docking interaction analysis based on their molecular interaction profiles and binding energies.

7d



2-[3-(3-nitrophenyl)-1,5-dioxo-1,5-dihydro-2,4-benzoxazepin-4(3*H*)-yl]benzoic acid

8h



2-[2-(4-hydroxyphenyl)-4,7-dioxo-4,7-dihydro-1,3-oxazepin-3(2*H*)-yl]benzoic acid

Fig.-2: Structures of the top two ligands with better binding energies were selected for visualization

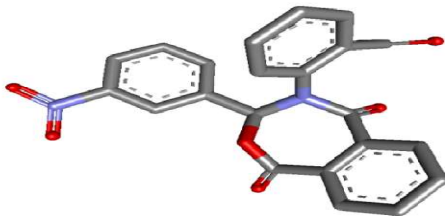
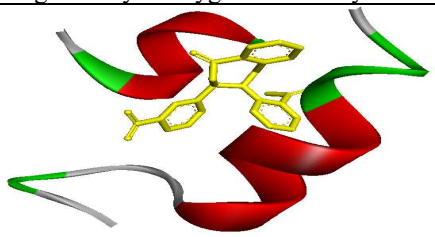
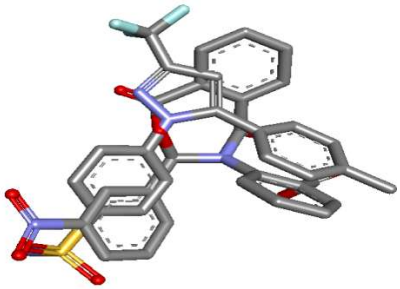
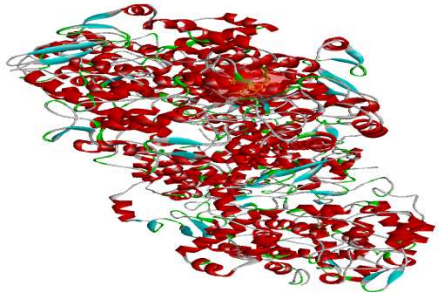
Table-1: Binding energies and interactions of the top ten compounds with cyclooxygenase-2 enzyme

Compound Code	Binding Energy K.Cal/mol	Interacting active site amino acid residues
7d	-109.2	TYR:371[3.00], HIS:75, VAL:509, ALA:513, VAL:335, LEU:517, LEU:338.
8h	-102.6	HIS:75[3.08], LEU:338, VAL:335, GLY:512, SER:339, VAL:509.

7j	-96.7	ASN:18[3.88], ARG:576.23], TYR:100[7.33], ILE:94[4.87], LEU:54, LEU:28, MET;16, PHE:31, LYS:32, PRO:55, MET:20, GLU:17, SER:49, ILE:50, ILE:5, ALA:6, THR:46.
7g	-94.1	TYR:371, VAL:309, VAL:335, ALA:513, LEU:517, ALA:502, ARG:499, PHE:504, TYR:334, TRP:373, GLY:512, MET:508, LEU:370, ILE:503, GLN:178, LEU:345, TYR:341, SER:516, LEU:338.
7h	-92.2	ARG:106, TYR:341, VAL:509, ALA:513, LEU:345, LEU:517, VAL:335, SER:516, VAL:102, MET:99, ILE:331, LEU:520, TYR:371, LEU;370, TRP:373, PHE:504, LEU;338, MET:508, GLY:512, SER:339
8b	-92.1	TYR:341, SER:516, ALA:513, VAL:335, VAL:102, VAL:509, PHE:504, SER:339, LEU:338, TYR:371, TYR:334, PHE:367, TRP:373, LEU:370, MET:508, GLY:512, LEU:517, MET:99, LEU:345, ARG:106
8a	-89.8	TYR:371, ALA:513, VAL:335, LEU:517, ARG:106, MET:508, TYR:341, VAL:509, PHE:504, SER:339, LEU:338, TYR:334, SER:516, TRP:373, PHE:367, LEU:370, GLY:512
9i	-88.8	SER:516, TRP:373, ALA:513, LEU:517, MET:508, PHE:504, VAL:509, SER:339, LEU:398, TYR:371, LEU:520, PHE:367, GLY:512, LEU:370
9c	-88.8	ARG:106, SER:339, VAL:509, LEU:338, VAL:335, LEU:517, LEU:345, SER:516, GLY:512, TRP:373, PHE:504, MET508, ARG:499, HIS:75, TYR:341
8d	-88.5	ARG:499, LEU:338, VAL:335, GLY:512, VAL:509, LEU:370, SER:339, HIS:75, TYR:341, ALA:502, GLN:178, IE:503, PHE:504, TYR:334, SER:516, TYR:371, TRP:373, PHE:367, MET:508
Celecoxib	-102.1	PHE:504, ARG:499, ARG:106,HIS:75, GLN:178, LEU:338, SER:339, VAL:335, ALA:513, ALA:502, TRP:373, PHE:367, TYR:371,
Valdecoxib	-91.8	SER:516, TYR:341, TYR:334, TRP:373, LEU:338, ALA:513, VAL:335, VAL:509, SER:339
Co-Crystalized Ligand	-101.8	ARG:106, SER:339, GLN:178, LEU:338, ARG:499, LEU:517, TYR:371, TRP:373, LEU:370,ALA:513, VAL:335, VALL:509, HIS:75, ALA:502, ILE:503, PHE:504, PHE:367, SER:516, LEU:345, VAL:102, TYR:349

H-bond interacting residues are represented in green color. (Green color enzymes are missing)

Table-2: Docking and Visualization data of 7d against Cyclooxygenase-2 Enzyme

	
1. 7d LIGAND	2. 7d LIGAND + CYCLOOXYGENASE-2 ENZYME COMPLEX
	
3. 7d LIGAND + CO-CRYSTALLIZED LIGAND OVERLAP	4. 7d LIGAND+ CYCLOOXYGENASE-2 WHOLE ENZYME COMPLEX

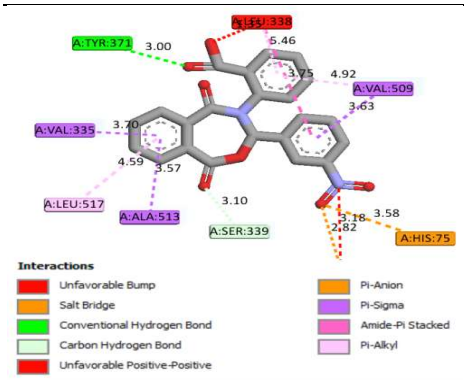
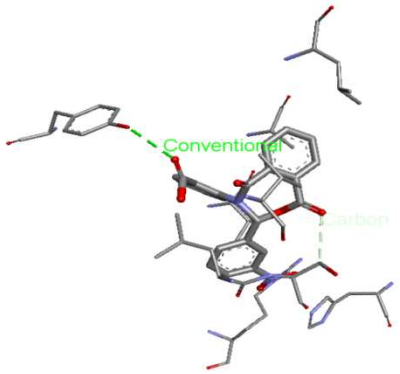
	
5. 7d LIGAND 2D INTERACTION WITH CYCLOOXYGENASE-2 ENZYME	6. 7d LIGAND 3D INTERACTION WITH CYCLOOXYGENASE-2 ENZYME

Table-3: Docking and Visualization data of 8h against Cyclooxygenase-2 enzyme

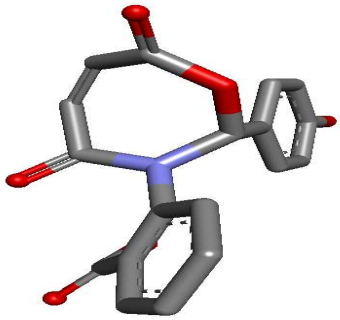
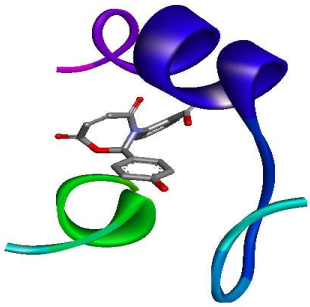
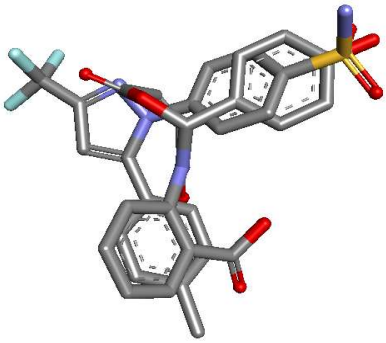
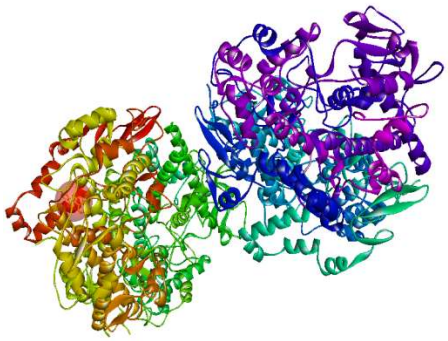
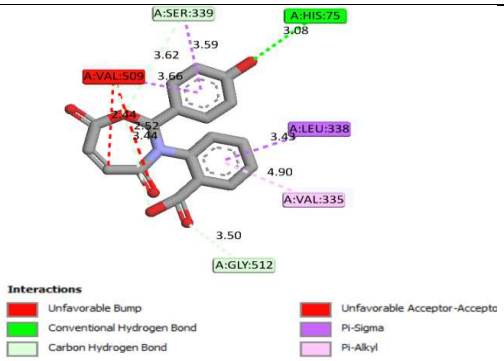
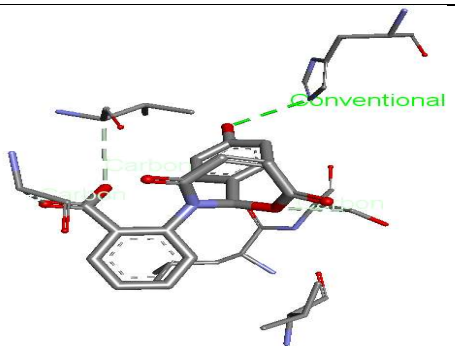
	
1. 8h LIGAND	2. 8h LIGAND + CYCLOOXYGENASE-2 ENZYME COMPLEX
	
3. 8h LIGAND + COCRYSTALLIZED LIGAND OVERLAP	4. 8h LIGAND + CYCLOOXYGENASE- 2 WHOLE ENZYME COMPLEX
	
5. 8h LIGAND 2D INTERACTION WITH CYCLOOXYGENASE - 2 ENZYME	6. 8h LIGAND 3D INTERACTION WITH CYCLOOXYGENASE - 2 ENZYME

Table-4: Docking and Visualization Data of Celecoxib against Cyclooxygenase-2 Enzyme

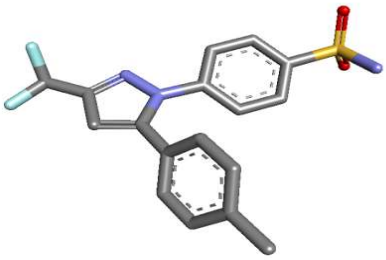
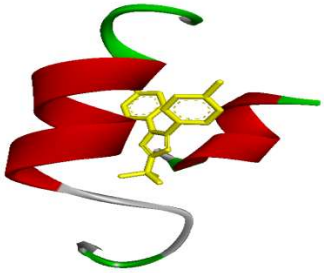
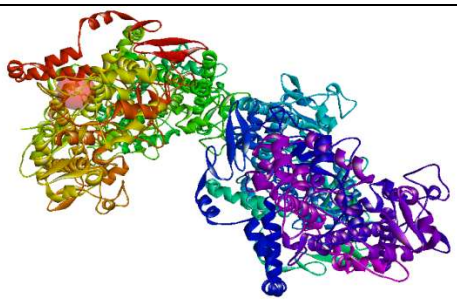
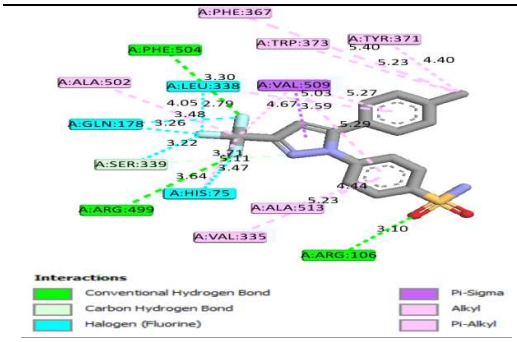
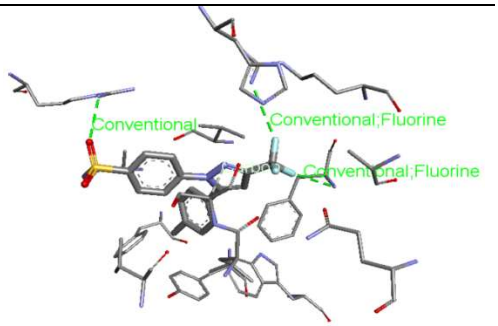
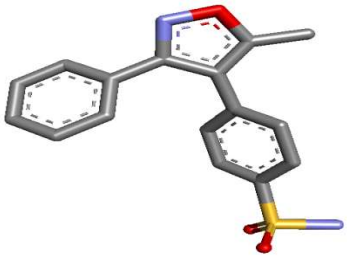
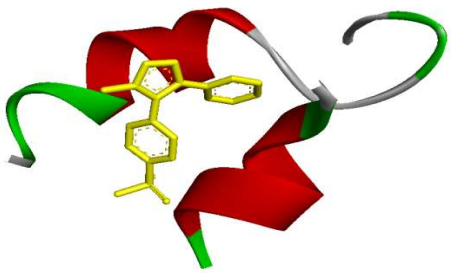
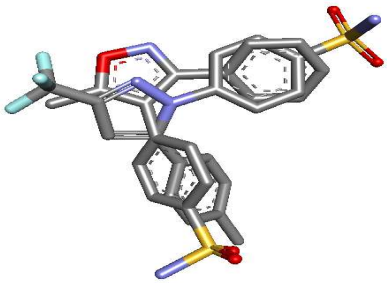
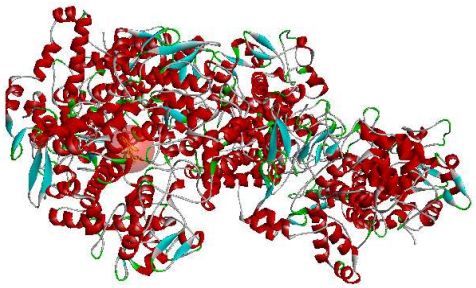
	
1. CELECOXIB LIGAND	2. CELECOXIB AND CYCLOOXYGENASE-2 ENZYME
	
3. CELECOXIB LIGAND + COCRYSTAL LIGAND OVERLAP	4. CELECOXIB LIGAND AND WHOLE PROTEIN
	
5. CELECOXIB LIGAND 2D INTERACTION WITH COX-2 ENZYME	6. CELECOXIB LIGAND 3D INTERACTIONS WITH COX-2 ENZYME

Table-5: Docking and Visualization Data of Valdecoxib against Cyclooxygenase -2 Enzyme

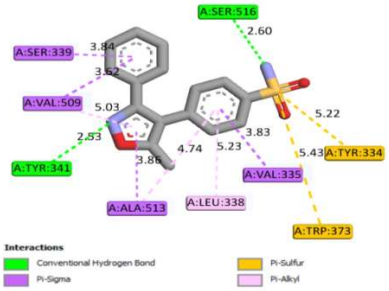
	
1. VALDECOXIB LIGAND	2. VALDECOXIB AND CYCLOOXYGENASE-2 ENZYME



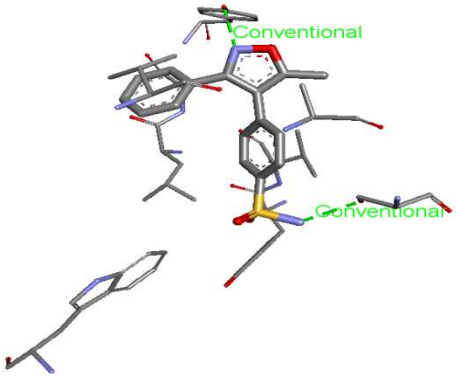
3. VALDECOXIB LIGAND AND COCRYSTAL



4. VALDECOXIB LIGAND AND WHOLE PROTEIN

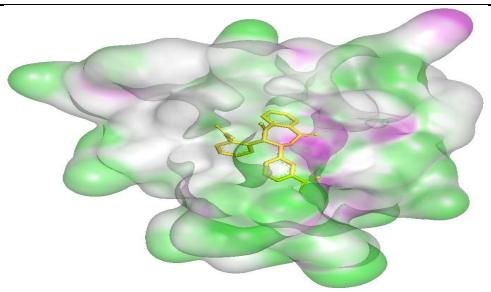


5. VALDECOXIB LIGAND 2D INTERACTION WITH COX-2 ENZYME

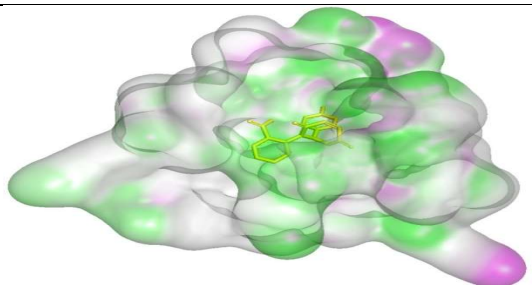


6. VALDECOXIB LIGAND 3D INTERACTIONS WITH COX-2 ENZYME

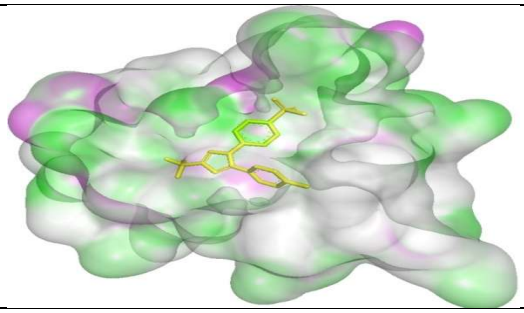
Table-6: Active Site Pocket Surface and Binding Modes 7d Ligand, 8h Ligand, Celecoxib and Valdecoxib



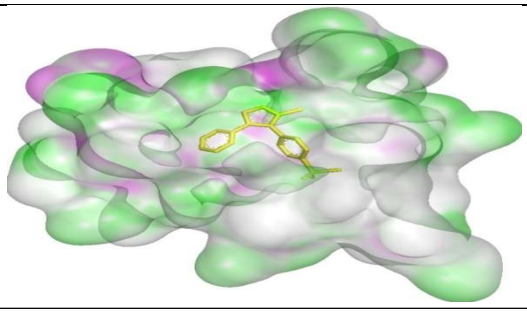
7d



8h



CELECOXIB



VALDECOXIB

CONCLUSION

The binding energies of nearly all of the top 10 compounds are close to those of standard cyclooxygenase-2 inhibitors. Due to their similarity to the binding energies of standard inhibitors, compounds 7d and 8h, which ranked highest, were chosen for visualization. Compared to standard

antagonists like celecoxib (-102.1 kcal/mol) and valdecoxib (-91.8 kcal/mol), compounds 7d and 8h exhibit superior binding energies of -109.2 kcal/mol and -102.6 kcal/mol, respectively as depicted in Table-1, Fig.-2. During the visualization process, the co-crystallized ligand (celecoxib) and the top two ligands were analyzed for structural similarity. The ligand-binding site of the entire protein was also shown. The number of conventional hydrogen bonds was displayed in a 3D interaction view. The 2D interaction view clearly shows the interacting amino acid residues and their distances from the ligand at the active site (Table-2,3,4,5). CELECOXIB and 7d have five similar amino acid residues in common=TYR:371, HIS:75, ALA:513, VAL:335, LEU:338.

CELECOXIB and 8h have three similar amino acids in common LEU:338, VAL:335 and SER:339.

VALDECOXIB and 7d have four amino acid residues in common VAL:509, ALA:513, VAL:335, LEU:338.

VALDECOXIB and 8h have four common amino acid residues that are similar to LEU:338, VAL:335, SER:339, and VAL:509.

Binding Pocket Analysis

The top ligands, along with the conventional antagonists valdecoxib and celecoxib, were docked into the center of the binding pocket. This positioning may have contributed to the improved binding energies observed. Consequently, compounds 7d and 8h, which exhibit better binding affinities and energies similar to standard cyclooxygenase-2 inhibitors which are shown in Table-6, could be utilized for in vivo activities and further synthesis.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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