Computer aided drug design through molecular docking: Identification of selective COX-2 inhibitors as potential NSAIDs

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ABSTRACT
Background and Aim: From the ages, NSAIDs are having a prominent role in antiinflammatory action and pain management. But on other hand it is having numerous adverse effects like when NSAIDs are orally administered they can cause gastric mucosal and renal damage. Recently, introduced curcumin and its derivatives have shown improved activities with reducing adverse effect of the NSAIDs. Moreover, curcumin showed the effects on the cellular target sites in variety of diseases. To impede the adverse effects of NSAIDs particularly celecoxib a selective COX inhibitor has been combined with curcumin to design the new ligands in this study. Methods: The AutoDockVina (ADT) 1.5.6 software is used for molecular docking purposes. The molecular structures were drawn in ChemBiodraw ultra and by the help of ChemBiodraw 3D, all structures were energy minimized by MM2 method and converted to pdb, extension file which is readable at the ADT interface. Results: The newly designed ligands studied through molecular docking on COX-1 and COX-2 proteins through AutodockVina molecular modeling software. Sb1 to Sb7 derivatives come up with remarkable binding affinity and among them Sb3 found most potent and selective to COX-2 isoenzyme. Conclusion: Among the designed ligand Sb3 which found selective COX-2 inhibitor could serve as a potential alternate with better antiinflammatory properties and reduced adverse effects accompanied with NSAIDs.

KEY WORDS: Celecoxib, curcumin, molecular docking, COX inhibitor, NSAIDs

1. INTRODUCTION
NSAIDs are considered for antipyretic, analgesic and antiinflammatory activity, and a large number of these drugs are available currently in mono or combination therapy for the treatment of fever and pain as well as in rheumatoid arthritis (RA), osteoarthritis (OA), acute gouty arthritis, and dysmenorrhea (Fig. 1). All of these drugs show their effects by impeding the biosynthesis of prostaglandins, \(^{[1,2]}\) but inhibition of prostaglandins through NSAIDs leads to ulceration, mucosal damage in GIT as unwanted side effects. \(^{[2,3,4]}\)

Cyclooxygenase helps in cascade of biosynthesis of prostaglandins. There are two isoform of COX enzymes involved in COX cycle i.e cyclooxygenase1 (COX-1), cyclooxygenase-2 (COX-2). \(^{[5,6]}\) COX-1 constitutively expressed in GIT and play a protective role whereas, COX-2 plays prominent role in biosynthesis of prostaglandins through arachidonic acid and mainly involve in inflammation. \(^{[7]}\) In 1995, first generation selective COX-2 was introduced for pain and, inflammation, later on in 2004 rofecoxib (Vioxx) was withdrawn from the market due to cardiovascular concerns (increased risk of heart attack). \(^{[8,9]}\) Other COX-2 inhibitors also showed similar issues so advisory committee of FDA suggested that celecoxib would be marketed only with black box warning with it. Worldwide different groups of scientists are trying to decrease the adverse effects of NSAIDs particularly COX-2 inhibitors. \(^{[10]}\) Various natural products also possess the antiinflammatory properties and among them curcumin obtained from turmeric rhizome has good potential for antiinflammatory activity. \(^{[11]}\) It’s a traditional Chinese medicine. It’s a non-toxic chemical which shows various biological activities including antiinflammatory such as antioxidant, anticarcinogenic, antidiabetic, antibacterial, anti-fungal, antiviral, antilulcer etc. \(^{[11-14]}\)

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Fig. 1: Classical NSAIDs

Aspirin
Ibuprofen
Indomethacin
Celecoxib
2. MATERIAL AND METHODS
Molecular modeling is well explored tool for identification of potent compound without investing to much effort and money in research. Molecular docking study was done by AutodockVina a molecular docking software. The COX-1 and COX-2 proteins i.e. 3kk6 and 3ln1 respectively were downloaded from protein data bank. The molecular structures were drawn in ChemBiodraw ultra and by the help of ChemBiodraw 3D, all structures were energy minimized by MM2 method and converted to pdbextension file which is readable at the ADT interface.

3. RESULTS AND DISCUSSION
To impede the adverse effects of NSAIDs particularly celecoxib a selective COX-2 inhibitor, a curcumin is introduced with it (Fig. 2). The designed molecules will be screened through AutodockVina molecular modeling software.

Further Kollman charges were added. Preparation of ligand was done by using Ligand tab to choose ligand, further polar hydrogens were added and it was saved in ligand.pdbqt file (Fig. 3). Validation of protein was done by docking the extracted ligand from the same protein by choosing grid center on ligand (Fig. 4).

To determine most potentially active ligand towards protein, we used Auto dock Vina molecular docking software. The COX-1 and COX-2 proteins i.e. 3kk6 and 3ln1 respectively were prepared.

3kk6 protein prepared by deleting chain B, water (HOH), ligand (CEL701) were deleted and thereafter missing atom were repaired.

The similar method was used for 3ln1 a COX-2 protein, after loading of 3ln1, the B, C, D chains were deleted and ligand CEL701 from chain A was extracted. By preparing ligand and protein the several designed ligand were docked. The molecular docking results of designed ligands are shown in table 1 for both COX-1 and COX-2 proteins. On examination of results and comparison with celecoxib the results
were found promising and come up with selective COX-2 inhibitor like Sb3 (Entry 3, table 1). Although the best binding affinity was shown by Sb7 but it is not a selective COX-2, hence Sb3 was selected as a selective COX-2 inhibitor. Further a detailed mechanistic study was done by examining the interaction with the COX-1 and COX-2 proteins.

Table 1.Celecoxib and curcumin derived ligand docking study

<table>
<thead>
<tr>
<th>S.No</th>
<th>Ligands</th>
<th>Structures</th>
<th>Binding affinity (Kcal/mol)</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>COX-1</td>
</tr>
<tr>
<td>1</td>
<td>Celecoxib</td>
<td><img src="image1" alt="Structure" /></td>
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</tr>
<tr>
<td>2</td>
<td>Sb1</td>
<td><img src="image2" alt="Structure" /></td>
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<td>8</td>
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<td><img src="image8" alt="Structure" /></td>
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</tr>
</tbody>
</table>

Sb3 is having hydrophobic interaction with the ARG97 and PHE356 amino acid residues of protein 3kk6 (COX-1). Hydrophilic reaction is observed for SO2NH2 and PRO514 amino acid residue. CF3 which is polar in nature undergoes hydrophilic interaction with ASN28 neighboring residue. Imidazole ring of molecule has showed interaction with nearby ARG29 amino acid residues of protein 3kk6 (COX-1) (Fig. 5a).

The molecule Sb3 has better interaction with 3ln1 (COX-2), which showed in Fig. 5b, SONH2 and CF3 of molecule showed hydrophilic interaction with the ARG97 residue of protein 3ln1. Sb3 also showed hydrophobic interaction with PHE356 of protein residue. Hydrophilic reaction is observed in SO2NH2 of ring C and PRO514 amino acid residue. There is one hydrogen bond is observed in NH of imidazole with GLY354 having carbonyl amino acid residue. Fig. 6 (a) and 6(b) represent the linkage between 3kk6 and 3ln1 protein in ribbon structure of COX-1 and COX-2 protein respectively were shown with Sb3.
Fig. 6: Representation of Sb3 (ball and stick model) and COX-1 (3kk6) (a); COX-2 (3ln1) in ribbon structure (b).

4. CONCLUSION

Hybrid molecules containing curcumin and celecoxib were evaluated as a selective COX-2 inhibitor. The newly designed ligands were studied through molecular docking on COX-1 and COX-2 proteins. Best binding affinity shown by Sb7 on both proteins but COX-2 selectivity was showed by Sb3. These derivatives came up with remarkable binding affinity. Binding affinity of Sb3 was -9.1 Kcal/mol on 3kk6 (for COX-1) and -9.3 Kcal/mol on 3ln1 (for COX-2). Sb3 showed hydrophilic interaction by CF3 group with the ARG97 residue with polar NH2NH group at the binding site of 3kk6 (COX-1). Similarly CF3 undergoes hydrophilic interaction with ASN28 neighboring amino acid residue of protein 3ln1 (COX-2). Imidazole ring of molecule has showed interaction with nearby ARG29 protein residues on 3ln1 (COX-2). The designed ligand could serve as potential alternate with better antiinflammatory properties and reduced adverse effects accompanied with NSAIDs. The designed ligand could serve as potential alternate with better antiinflammatory properties and reduced adverse effects accompanied with NSAIDs.

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REFERENCES


16. Energy minimizations were performed MM2 Interface program on ChemBio3D Ultra 12.0, and structures were drawn by ChemBioDraw Ultra 12.0 (CambridgeSoft).


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