DOCKING STUDIES OF SOME 1-SUBSTITUTED (PHENYL) SULFONYL - 1H-INDOLE DERIVATIVES

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ABSTRACT
Docking studies were done on a series of 1-substituted (phenyl) sulfonyl-1H-indole derivatives on drug discovery studio by Accelrys into the active sites of cyclooxygenase-2 (COX-2) and cyclooxygenase-1 (COX-1). The docking model was demonstrated for inhibitor’s conformation, protein interaction and Hydrogen bonding. It was found that 1-substituted (phenylsulphonyl) indole derivatives shows strong COX-2 selectivity compared to COX-1.

Keywords: cyclooxygenase-2, cyclooxygenase-1, 1-substituted (phenyl) sulfonyl, N-protection of indole, Docking.

INTRODUCTION
Derivatives of indole have been reported to possess different biological activities along with anti-inflammatory are CNS depressant, psychotropic, antiparkinsonism, anticonvulsants, analgesic, antipyretic activity.1,2 These derivatives also possesses cardiovascular,3 antibacterial,4 antimicrobial,5,6 antitubercular,7 anthelmintics8 and antifungal9 activity. Several substituted (phenylsulphonyl)indoles were found to have antiviral10 activities and approved as a commercial anti-HIV drug named Rescriptor.11 The route for the synthesis of the aryl substituted indoles starts from indole nucleus. The protection of NH group by the introduction of phenylsulphonyl group as this group can be removed easily without any harsh treatment so as to synthesized indole derivatives with different groups at 3-position like halides and lithium.12 Cyclooxygenase is an endogenous enzyme exits in two isoforms COX-1 and COX-2, catalyses the conversion of arachidonic acid into prostaglandins and...
thromboxanes.\cite{13,14} COX-1 is a constitutive enzyme and is responsible for the supply of prostaglandins which maintain the gastric mucosa and provide adequate vascular homeostasis where, COX-2 is an inducible enzyme and expressed only after an inflammatory stimulus.\cite{15,16} The function of COX-2 is to synthesis prostaglandins for the induction of the inflammation and pain. This results in the development of selective COX-2 inhibitors with good anti-inflammatory activity and with less gastric irritation.\cite{17}

**MATERIALS AND METHOD**

The structure of 1-substituted (phenylsulphonyl)indoles were docked using Accelrys Drug Discovery Studio 3.5. The structure of the enzyme COX-2 complexed was obtained from Protein data bank (PDB code: 1CX2) and was used for docking. The enzyme exists in tetrameric form in the crystal associated with water molecule, were not considered in docking as they were not found in the zone of the ligand in the crystal structure. The crystal structure was cleaned by deleting the Ligands and cofactors. This was followed by adding hydrogen atoms to the protein. Docking calculations were carried out using Accelyres Drug Discovery Studio (3.5 version). The ligand structure was imported to the new window with proper names and program was run to prepare the ligand. Finally the input ligands were selected (Molecules:All) on protein molecular window and were docked for 1CX2. The setup for side-chain flexibility by selection of the all-visible option and the setting for the other selected chain during the docking and other parameters were kept in default. The CDocker Energy and CDocker Interaction energy was calculated (Table I). The pose with most negative value of the compound was considered to be the most favorable pose having interaction with 1CX2.

**PROTEIN PREPARATION\cite{18}**

The protocol prepares the proteins by inserting missing atoms in incomplete residues, modeling missing loop regions based on information, deleting alternate conformations, removing waters, standardizing atom names, protonating titratable residues using predicted pKs. The potential energy, Van der Waals energy, Electrostatic energy and RMS gradient was checked for the protein before and after minimization.

**LIGAND DOCKING\cite{19}**

The ligand preparation included 2D–3D conversions, correcting structures, generating variations of these structures, verifying and optimizing the structures. All these tasks were performed using Marvin Sketch (ChemAxon) for drawing, displaying and characterizing chemical structures and substructures.
Table I: 1-substituted (phenyl)sulfonyl-1H-indole with their -CDocker scores

<table>
<thead>
<tr>
<th>Sl.No</th>
<th>Structure</th>
<th>Name</th>
<th>-CDocker</th>
<th>-CDocker Interaction Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><img src="image1.png" alt="" /></td>
<td>1-[(2-chlorophenyl)sulfonyl]-1H-indole</td>
<td>-28.243</td>
<td>4.59708</td>
</tr>
<tr>
<td>2.</td>
<td><img src="image2.png" alt="" /></td>
<td>1-[(3-chlorophenyl)sulfonyl]-1H-indole</td>
<td>-18.624</td>
<td>2.7681</td>
</tr>
<tr>
<td>3.</td>
<td><img src="image3.png" alt="" /></td>
<td>1-[(4-chlorophenyl)sulfonyl]-1H-indole</td>
<td>-4.57721</td>
<td>14.4854</td>
</tr>
<tr>
<td>4.</td>
<td><img src="image4.png" alt="" /></td>
<td>1-(phenylsulfonyl)-1H-indole</td>
<td>-2.8962</td>
<td>12.5477</td>
</tr>
<tr>
<td>5.</td>
<td><img src="image5.png" alt="" /></td>
<td>1-[(4-methylphenyl)sulfonyl]-1H-indole</td>
<td>0.9809</td>
<td>14.5984</td>
</tr>
</tbody>
</table>
RESULT AND DISCUSSION

DOCKED IMAGES

Fig. I. Docked image of 1-[(2-chlorophenyl)sulfonyl]-1H-indole

Fig. II. Docked image of 1-[(3-chlorophenyl)sulfonyl]-1H-indole

Fig. III. Docked image of 1-[(4-chlorophenyl)sulfonyl]-1H-indole
Molecular docking approaches are routinely used in modern drug design to help in understanding the drug-receptor interaction. It has been shown in the literatures that these computation techniques can strongly support and help the design of novel, more potent inhibitors by revealing the mechanism of drug receptor interaction. The present docking study is carried out for five compounds against target protein within the active site. The best fit compounds were active with the dock score ranges between -2.896 to -28.243 (always negative) and can show good COX-2 activity after further synthesis. Thus these compounds which have the ability to bind the COX-2 enzyme can be used to synthesize newer derivatives of indole.
CONCLUSION
In conclusion, N-protection by the above compounds of 1-substituted (phenyl)sulfonyl-1H-indole could be used as a successful intermediate compound to synthesize the drug candidates for a class of COX-2 indole derivatives. The binding interactions exhibited by compounds signify the importance of specific amino acid residues in the active site of COX-2 protein. Therefore, the present study illustrates the efficacy of docking during drug designing plays a vital role for development of potent inhibitors of COX enzyme.

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REFERENCES