(RESEARCH ARTICLE)

In Silico study of 3-D structural interactions and quantitative structural drug likeness of marketed Cox-2 inhibitors

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Abstract

In the field of molecular modeling, docking may be a method which predicts the well-liked orientation of any molecule to a receptor to make a stable complex. Knowledge of the well-liked orientation successively could also be able to predict the strength of association or binding affinity between two molecules using, for instance, scoring functions.

Cyclooxygenase-2 (COX-2) inhibitors block cyclooxygenase-2 (COX-2), an enzyme that promotes inflammation. COX-2 enzyme converts to prostaglandin via arachidonic acid, causing pain and inflammatory responses. They are mainly present in places of inflammation and are responsible for formation of prostanoids (prostacyclins, prostaglandins and thromboxane) as part of the inflammatory response. COX-2 inhibitors are used to relieve pain raised from the inflammation.

In the present study, the marketed COX-II inhibitors are subjected for the docking study and the drug likeness study which validate that the drugs show the optimum binding energy and drug likeness score with optimum bioactive score.

Keywords: Cyclooxygenase-2 (COX-2) Inhibitors; Prostaglandin Synthase Kinase-2; Docking Study; Drug Likeness Study
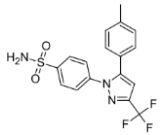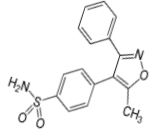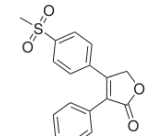
1. Introduction

Recent review reveals that pain and inflammation are the most common sign and symptom for almost all diseases so NSAIDs (Table 1) are found to be most commonly prescribed class of drug. Thus compare with all medications, NSAIDs approximately up to 5-10% part of prescription every year. In the general practice, patients over 65 years old treated with prevalence use as high as 96% of NSAID. Similarly 7.3% of elderly patients are prescribed by at least one NSAID in one year period. NSAIDs as like to their anti-inflammatory effect, also shows antipyretic and analgesic properties. Mostly all NSAIDs act by inhibiting Cyclooxygenase (COXs) enzymes, which are responsible for prostaglandins and other prostanoids synthesis, such as thromboxane, so termed as rate determining enzymes [1].

Selective cyclooxygenase (COX)-2 inhibitors are just as effective as NSAIDs in relieving arthritic pain and yet less gastrotoxic, they are being used in place of "conventional" nonsteroidal anti-inflammatory drugs (NSAIDs) [2].

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Table 1 COX-2 drugs studied for the said aim

Generic name	Structure
Celecoxib(Celebrex)	
Valdecoxib(Bextra)	
Rofecoxib(Vioxx) recalled in 2004	

However they selectively reduce prostacyclins production, the cardiovascular safety of selective COX-2 inhibitors has been questionedthose results in disruptions of the normal homeostatic balance and promoting a prothrombotic state.

2. Methods

2.1. Drug likeness study [3, 4, 5]

In 1997 Christopher A. Lipinski put a theory that describes relationship between the molecular properties and the drug likeness of the molecules. These molecular descriptors such as log P (partition coefficient), molecular weight (MW), topological polar surface area (TPSA), or hydrogen bond acceptors and donors counts in a molecule is termed as Lipinski's rule of five or Pfizer's rule of five (RO5). Molecular descriptor data is reviewed from the online software Molinspiration and Supercomputing Facility for Bioinformatics and Computational Biology, IIT, New Delhi. The data obtained is cited in table no 2.

2.2. Docking study [6, 7, 8]

2.2.1. Ligand preparation

In Marvinbeans-5.8.1 (Marvin Sketch) software the analogue that has to be synthesized is first edited by considering the Lipinski Rule of five. The proposed structure is then saved in pdb format [9, 10].

To attain the maximum stability with minimum energy, the pdb format structure is the clean for alignment of atom as per their hybridization so as the atom in molecule arrange in 3D confirmation. Following steps generate the 3D structure [11].

- File -> Open sdf file
- Edit -> Clean-> 2D
- Edit-> Clean-> 3D
- Save-> as ligand.pdb

2.2.2. Source Target Protein

After the formatting the ligand, the docking study was performed using Accelyrs Discovery Studio client version 2.5 software (Accelyrs Inc., http://www.accelrys.com) and AUTODOCK Tool 1.5.6. Target Protein (receptor) Prostaglandin Synthase-2(PDB Code: 1CX2) is downloaded from https://www.rcsb.org/. Selection of the Target Protein is based on the Ramchandran outliers and X-ray diffraction which should not more than 10^0A (Table No.2). Target Protein has to be prepared for the docking analysis should be opened in then DS Visualizer. Delete the water molecules, sulphate (SO_4) Phosphates, solvent, salts like Mg, Caetc can be removed as it is not needed in the docking. If the protein has two identical chains one chain can be removed [12].
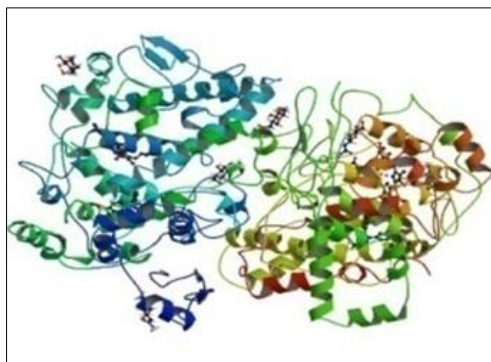
Figure 1 Cyclooxygenase-2 (Prostaglandin Synthase-2) Protein Receptor

Table 2 Protein (Receptor) selection criteria

S.N.	PDB Code	Crystallographic Resolution (A⁰)	Ramchandran Criteria (%)		
			Favoured region	Allowed region	Outlier region
01	1CX2	3.00	82.10	14.20	3.70

3. Results and discussion

3.1. Drug-likeness Study report [13, 14]

Pharmacological activity of the molecule envisaged as ligand is mainly based on the physic-chemical properties. These physic-chemical properties or molecular descriptor decides the pharmaco-dynamics and pharmacokinetics of ligand that affects their absorption, distribution, metabolism, and excretion (ADME) in biological system. Table No.3 gives data about the drug likeness of the marketed drugs.

Table 3 Molecular descriptors of proposed compound

Compound	Mi Log P	TPSA	n. atom	Mole. weight	n. ON	N OHNH	n Violation	n rotb	Bioactive score
Celecoxib	3.61	77.99	26	381.38	5	2	0	4	0.17
Valdecoxib	2.73	86.20	22	314.37	5	2	0	3	0.21
Rofecoxib	0.71	60.45	22	314.36	4	0	0	3	0.61

3.2. Docking study of COX-2 Inhibitors (AUTODOCK TOOL 1.5.6)

Table 4 The dock scores on the basis of binding energy

Compound	Amino Acid	Bond	Binding Energy	Inhibitory constant	Inter molecular energy	Electrostatic energy
Celecoxib	-	-	-7.25	4.85	-8.44	0.06
Valdecoxib	LYS468	OH	-7.96	1.45	-8.86	-0.26
Rofecoxib	ASN43	OH	-7.98	1.42	-8.87	0.04

The main approach of *In Silico* method was to identify the magnitude interaction between target molecules and ligand in terms of binding energy (kcal/mol). This procedure identifies the most suitable confirmation with low energy that bind with the biological target to elicit the pharmacological action. In the Docking study, low energy confirmation ligand

was selected and docked with the grid generated from target molecule. The data represented in the following table no.4 revealed that the Coxibs show optimum binding energy which confirms to these COX-2 inhibitor drugs are potent enough to elicit analgesic-anti-inflammatory action.

Figures 2, 3 and 4 signify the interactions between receptor prostaglandin synthase kinase-2 (1CX2) with the Coxibs as illustrated
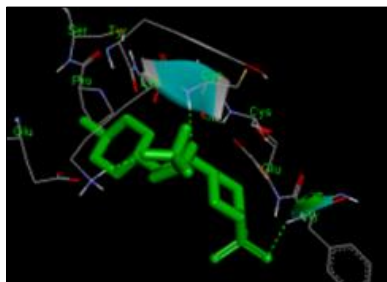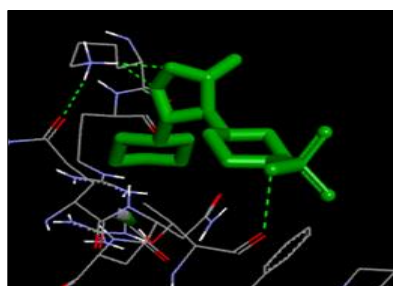

Figure 2 Interaction of 1CX2 with Celecoxib

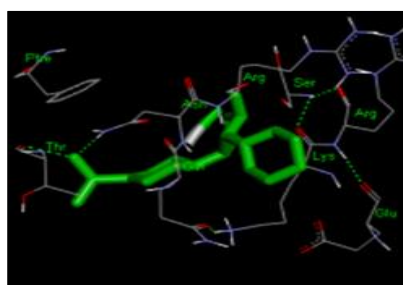**Figure 3** Interaction of 1CX2 with Valdecoxib

Figure 4 Interaction of 1CX2 with Rofecoxib

4. Conclusion

The marketed Coxibs studied for drug likeness and bioactivity using Molinspiration software. The results were predicted that all derivatives comply with the Lipinski rule and acceptable bioactivity score.

In Silico study was performed by using Molecular docking software AUTODOCK Tool 1.5.6 to identify the binding energy, inhibition constant and interaction modes between compounds and the target enzymes Cyclooxygenase-II (PDB code 1CX2). The dock scores on the basis of binding energy give an idea about agreement with the pharmacological results as reported in table no.4.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this article.

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