IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

# Molecular docking study of Novel Chalcone derivatives Towards PDB: 1CX2

**Jayshree B. Naik* ,Shubham A. Cheke, Vishal P. Kakde**
Raosaheb Patil Danve College of Pharmacy Badnapur
Dr. Babasaheb Ambedkar Marathwada University Aurangabad- M. S.

**Corresponding Author**
**Miss. Jayshree B. Naik**
Raosaheb Patil Danve College of Pharmacy Badnapur
Dr. Babasaheb Ambedkar Marathwada University Aurangabad- M. S.

## Abstract :-

Chalcones are the natural phytoconstituents recognized as secondary metabolites of plant, with marked biological significance such as Anti-inflammatory, Antioxidant, Anticancer, and Antimicrobial activity. On the basis of literature we were design Novel chalcone derivatives & were access for anti-inflammatory activity. This research deals with a molecular docking study of newly designed (1-(5- chloro-2-hydoxyphenyl)-3-(3-methylphenyl)propanr-1,3-dione) derivatives was performed by using Auto Dock Tool (V 1.5.7) with PDB Id: 1CX2 for drug protein interaction study. The main objective of molecular docking is to predict the biological activity of given ligand. In above research we done molecular docking study of JBN-1 to JBN-5 towards COX-2 Inhibitor. In this manuscript molecular docking study compound JBN-2 shows better docking score (-9.4) and compound JBN-3 shown moderate docking score (-6.6) compare to standard Celecoxib (-8.3) respectively.

**Keyword: Molecular docking ,Anti-inflammatory, Auto Dock Tool, COX-2.**

## ❖ INTEODUCTION :-

Molecular docking evaluation may be carried out to look at the interplay of those herbal compounds with numerous molecular objectives of anti inflammatory pastime. Further, the structure- pastime courting may be used to expand new spinoff herbal compounds with better antiinflammatory pastime. Inflammation is the body's first reaction to contamination or damage and is important for each innate and adaptive immunity. The look for herbal compounds and phytoconstituents which are capable of intrude with those mechanisms by stopping a extended infection may be beneficial for human health.

The complex series of preventive and reparative reactions to tissue injury brought on by either mechanical and autoimmune stressors or infection are known as the inflammatory cascade. It's possible for inflammation to be acute or persistent. Neutrophils, macrophages, and dendritic cells all contribute to the cytokine synthesis that spreads during the acute phase of inflammation.

Although inflammation has a beneficial function, many diseases, including atherosclerosis, arthritis, cancer, and ischemic heart disease, have their etiological roots in inflammatory processes. Proinflammatory mediators are produced and secreted by a variety of routes. This chapter examines various intracellular signalling pathways involved in inflammation. The two main classes of anti-inflammatory medications are steroidal anti-inflammatory drugs, which reduce inflammation by attaching to cortisol receptors, and nonsteroidal anti-inflammatory drugs.may prevent damage by cyclooxygenase enzyme inhibition. These anti-inflammatory medications carry a number of hazards, including hepatotoxicity, bleeding, and gastrointestinal ulcers.

## AIM AND OBJECTIVE :-

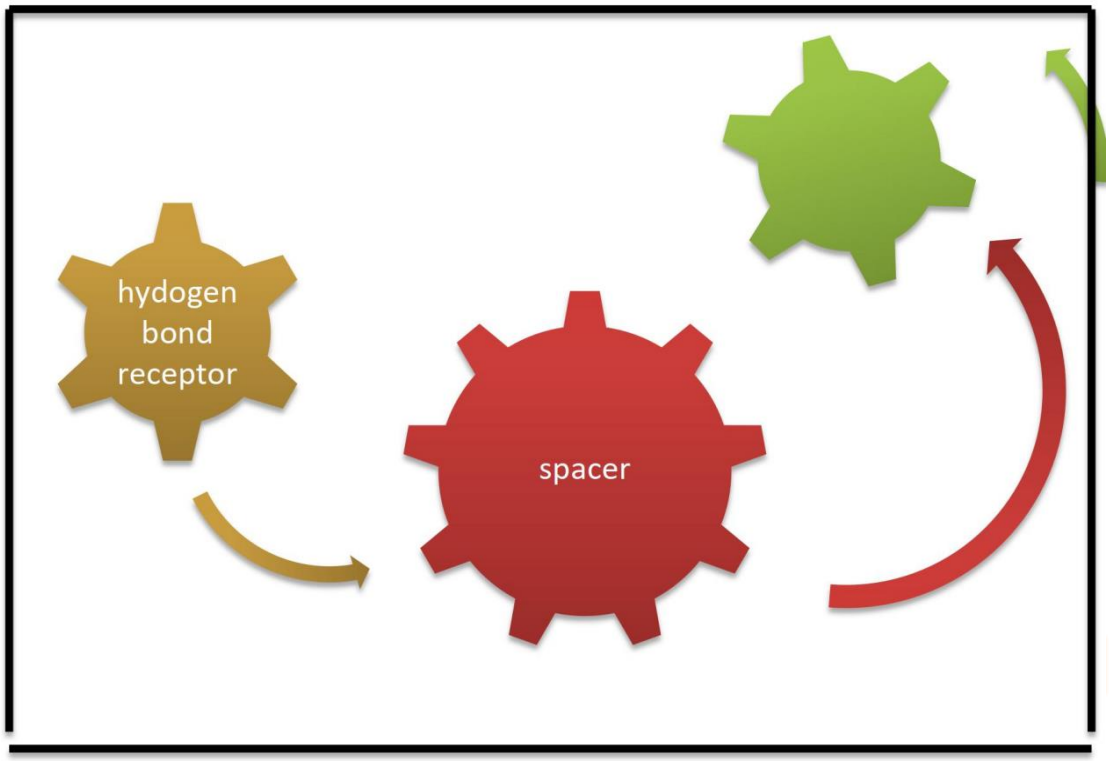



**Fig 1 : Pharmacophore Pattern of COX Inhibitors.**

### ❖ AIM :-

In order to precisely forecast a ligand's structure inside the confines of a receptor binding site and to accurately gauge the degree of binding, docking is used. The purpose of the current work is to conduct research on the design and assessment of medicinally significant chalcone derivatives, specifically (JBN-1, JBN-2, JBN-3, JBN-4, and JBN-5) for the anti-inflammation.

### ❖ Objective :-

Obtaining a ligand-receptor complex with an optimised shape and the idea of having less binding free energy is the main goal of molecular docking. Designing medicinally significant heterocyclic compounds towards aromatics is the specific goal of the objective. The following topics have been covered in discussion about the current research project:

1. The target compounds mentioned above are designed.
2. Chalcone derivatives were tested for their ability to fight inflammation.

The effort done to achieve the target molecules has been covered in the "Result and Discussion" section.

## SOFTWARE USE

AutoDock Tool :- Version 1.5.
A group of automated docking tools is called AutoDock. It is intended to forecast how tiny compounds, such as substrates or potential medications, would bind to a known receptor.

AutoDock vina:- Version 1.1.2
An open-source tool for molecular docking is called AutoDock Vina. Dr. Oleg Trott, of The Scripps Research Institute's Molecular Graphics Lab (now CCSB), was its original creator and implementer. AutoDock Vina is currently at version 1.2.0. One of the docking engines of AutoDock Vina
utilizing AutoDock Suite

Pymol :- version 4.6.0
One of the most popular pieces of bioinformatics software is PyMol. The majority of the time, it serves as a molecular viewer to display macro- and small-molecule structures. This article explores various applications and uses for PyMol.

## ❖ Experimental work :-

There are some different steps in the molecular docking
Molecular Docking Study of Chalcone derivatives (JBN-1, JBN-2, JBN-3, JBN-4 and JBN-5)with targeted proteins(1CX2)
For selective COX-2 inhibition anti-inflammatory activity PDB id: 1CX2 used.

Molecular docking of proposed 5 chalcone derivatives were done with the help of Pymol 4.6.0software in order to choose the derivatives which shows good interactions with target protein. Chalcone derivatives taken into consideration are shown in following.

| **Compound Code** | **Chalcone Derivatives** |
|---|---|
| JBN-1 | 1,3-propanedione,1-[4-(1-methylethyl)phenyl]3-phenyl |
| JBN-2 | 1-(5- chloro-2-hydoxyphenyl)-3-(methylphenyl)propanr-1,3-dione |
| JBN-3 | 1-(5- chloro-2-hydoxyphenyl)-3-phenyl-1,3-propanedione |
| JBN-4 | 1-(3-methoxyphenyl)-3-phenyl-1,3-propandione |
| JBN-5 | 1,3-bis(4-methoxyphenyl)-1,3-propanedione |

Table:-1

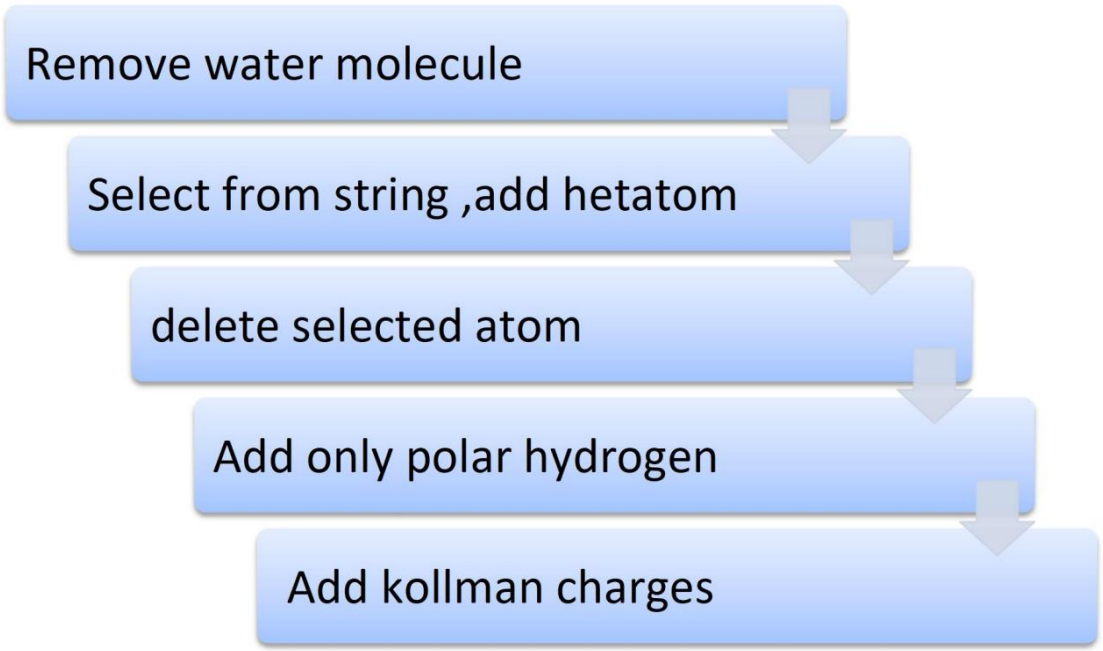
Following steps are taken in to consideration for molecular docking study:
1 Ligand preparation
2 Protein preparation and its refinement
3 Receptor grid generation
4 Protein ligand docking

## ❖ 1 Ligand preparation :-

The ligand preparation was done by using Pymol application which consists of series of steps that perform conversion of SDF file to PDB structure. Then PDB file into the PDBQT by the help of AutoDock Tool Software. Depending on the objective, different ligands will be used for docking. It can be accessed from a variety of databases, such as ZINC or/and PubChem, or it can be sketched using the Chemsketch tool. In the ligand preparation process, ligand are obtained from pubchem in SDF form. In order to use that file for docking, we must convert it to pdbqt because the auto dock vina tool will not take it in that format. Therefore, we use Pymol programme to convert the ligand into pdb form and save. Drag the ligand into the auto dock tool to create a pdbqt file and save it. We used 5 different lignds.

## ❖ 2 protein preparation

For molecular docking study protein is the essential component and it is necessary to minimize the energy of protein molecule prior to docking studies with ligands Protein for ligand docking study was prepared by using protein preparation wizard tool in which was used to import proteins for the protein data bank (PDB). Proteins obtained from the PDB, vendors and other sources frequently have missing hydrogen, partial charges, side chain and whole loops region. So, to overcome all these barriers in docking study the proteins to undergone through pre-processing
and it was done by selecting following parameters




## 3 Receptor grid genereration:-

Grid generation must be performed prior to running a virtual screen with glide. The shape and properties of the receptor are represented in a grid by field that provides progressively more accurate scoring of the ligand poses. For receptors that adopt more than one conformation on binding, Glide prepares grids for each conformation, to ensure that possible actives are not missed
To open the Receptor Grid Generation panel, Receptor Grid Generation sub-menu of Glide was selected from the Application menu. The Receptor Grid Generation panel has three tabs, which are used to specify settings for the receptor grid generation job. These are □

1.Receptor □
2.Site
3.Constraints

## 1.Receptor

The structure obtained from PDB is a docked structure and it includes both a receptor and ligand. The ligand can be identified either as a molecule or as an entry in the workspace. When ligand was selected in workspace, it can be distinguished from the receptor (Fig. 4.3). The ligand molecule was highlighted with dark green markers

surround with a purple box. The purple bound box defines the region that the docked molecule can occupy to satisfy the initial stages of docking.

## 2.Site

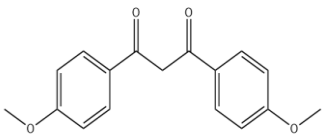
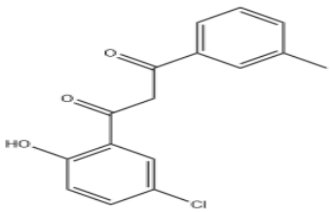
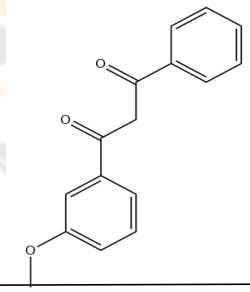
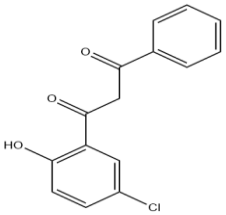
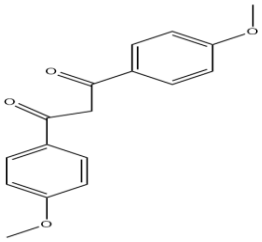
For the identification of the receptor site, a ligand molecule has to be excluded from the docked structure of a ligand with protein. For that, choose centroid of workspace ligand and click on 14 advance setting, a green inner bounding box appears which defines the region in which the centroid of the docked molecule must occupy to pass the initial stages docking (Fig. 4.4).

## 3. Constraints

Glide constraints are receptor-ligand interactions, which are important for the binding mode, based on structural or biochemical data. Setting constraints enable Glide to screen the ligands, their conformations, or poses that do not meet these criteria in their evaluation for docking suitability. There are four types of Glide constraints, positional constraints, H-bond constraints, metal constraints, and hydrophobic constraints. No constraints were defined for generating the grid box.

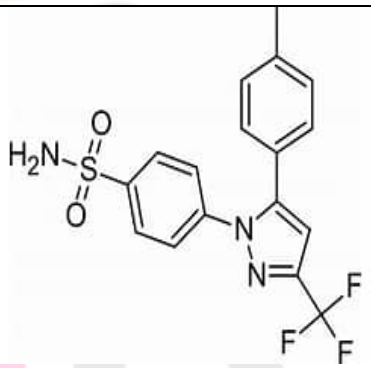
## ❖ 4 Protein ligand docking

For the docking five chalcone derivative were designed and docked on of cyclooxygenase-2 enzyme with (PDB: 1CX2). For the protein ligand docking we use the Autodock tools software and for command we use AutoDcok Vina (Command prompt). For the protein ligand docking we convert the PDB files into PDBQT files of Protein and Ligand The ligand docking process helps to predict ligand conformation and orientation (posing) within a targeted binding site and thus helps to interpret interactions of ligand atoms with amino acids of proteins, and to understand the binding affinity.

| Sr.no. | Code | IUPAC Name | Molecular formula | Molecular weight(g/mol) | Structure |
|---|---|---|---|---|---|
| 1 | JBN-1 | 1,3 propandion ,1 –(4-(1-methyl)phenyl)-3-phenyl | $C_{18}H_{18}O_2$ | 266.3 |  |
| 2 | JBN-2 | 1-(5-chloro-2-hydroyphenyl)-3-(3-methylphenyl)propane-1,3-dion) | $C_{16}H_{13}ClO_3$ | 288.72 |  |
| 3 | JBN-3 | 1-(5-chloro-2-hydroxyphenyl)-3-phenyl-1,3-propanedione | $C_{15}H_{11}ClO_3$ | 274.7 |  |
| 4 | JBN-4 | 1-(3-methoxyphenyl)-3-phenyl-1,3-propanedione | $C_{16}H_{14}O_3$ | 254.28 |  |
| 5 | JBN-5 | 1,3-bis(4-methoxyphenyl)-1,3-propanedione | $C_{16}H_{26}N_2O_2$ | 278.39 |  |

1. •select ligand docking from glide in application menu.
2. •select grid then micromolecules then select the ligand molecule.
3. •select grid then choose protein.
4. •select the grid then click on grid box and cover chain by grid box.
5. •Generate the grid diamention file and save it.
6. • create the config file and save it.
7. •use the AutoDock vina (Command Prompt) and give docking command

**Table : 2**

| | | | | | |
|---|---|---|---|---|---|
| **6** | **Standard (Celecoxib)** | **4-[5-(4-methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide** | **$C_{17}H_{14}F_3N_3O_2S$** | **381.4** |  |

## ❖ RESULTS AND DISCUSSION :-

The section includes the finding of research project and data collected during project work. Result of the studies is discussed under three heads: 1 Molecular Docking Studies 1.1 Molecular docking study of chalcone derivatives on COX-2 enzyme 1.1.1 Docking score and Protein-Ligand intraction Molecular docking studies of all proposed Chalcone derivatives were carried using AutoDock tool software. Docking score is the function, designed to calculate the free energy of binding for a protein-ligand complex.Total 5 molecules of chalcone derivatives were designed and docked on COX-2 enzyme. Out of these, three molecules with good hydrogen bond interactions and glide score as compared to standard celecoxib are

| Sr.no. | Code | Docking score | | NO. of position |
|---|---|---|---|---|
| | | Highest | Lowest | |
| 1 | JBN-1 | -6.9 | -6.3 | 9 |

| | | | | |
|---|---|---|---|---|
| 2 | JBN-2 | -9.4 | -7.3 | 9 |
| 3 | JBN-3 | -6.6 | -6.2 | 9 |
| 4 | JBN-4 | - 6.4 | -5.7 | 9 |
| 5 | JBN-5 | -6.4 | -5.7 | 9 |
| 6 | Standard (Celecoxib) | -8.4 | -7.0 | 9 |

Tabel :3

In all the docked compounds almost all ligands have Nine Docking postion with 1CX2, so preferences is given according to Docking score while shortlisting the molecules. Compounds **(**JBN-1, JBN-2, JBN-3, JBN-4, JBN-5**)** possesses Nine Docking Postion with 1CX2 and having Docking score of **-6.9,-9.4,-6.6,-6.4,-6.4** respectively. Standard **Celecoxib has Nine Docking Postion and Docking score -8.4 .** Therefore from the docking result compound **(JBN-2)** are considered for the synthesis which may shows good cyclooxygenase-2 inhibitors activity as compare to Celecoxib. The ligand interaction diagram of some of the selected compounds and Celecoxib is given in **fig. (3,4,5,6,7,8).**

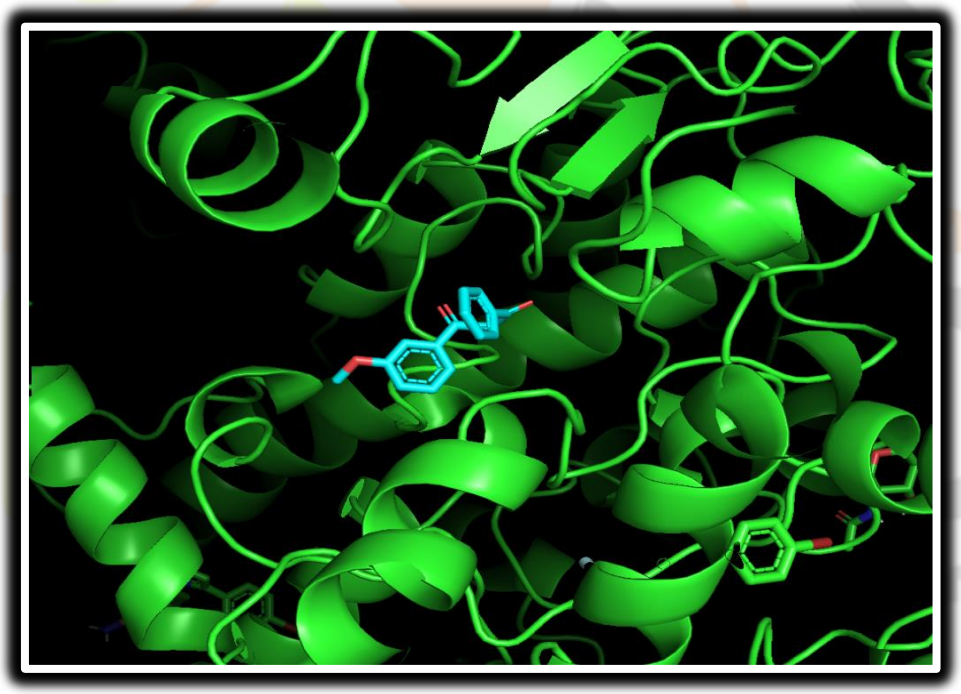


Fig. 3 Ribbon structure of COX-2 enzyme with JBN-1

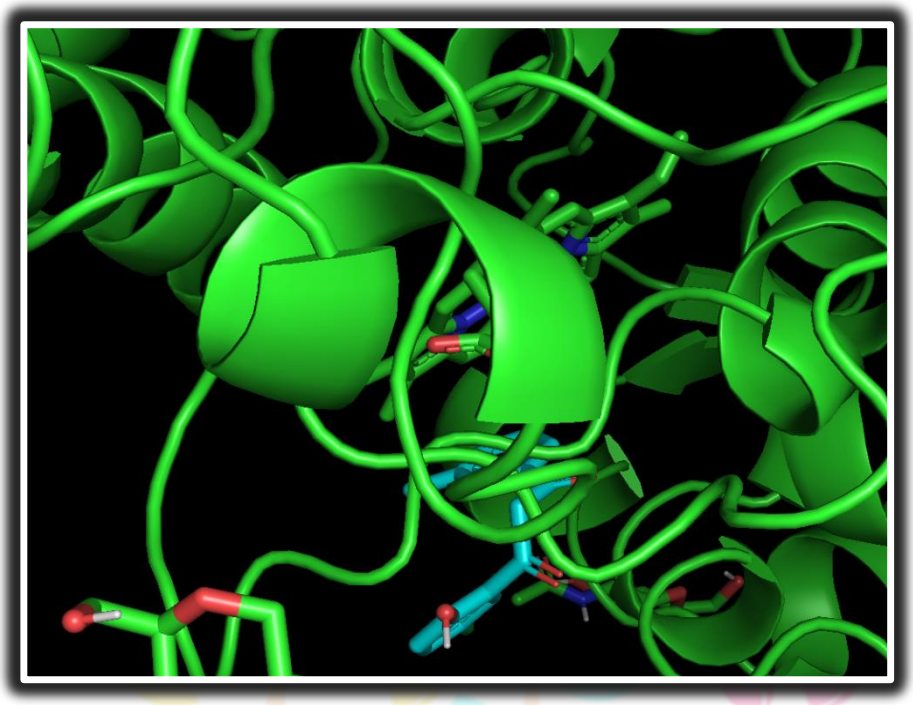


Fig. 4 Ribbon structure of COX-2 enzyme with JBN-2

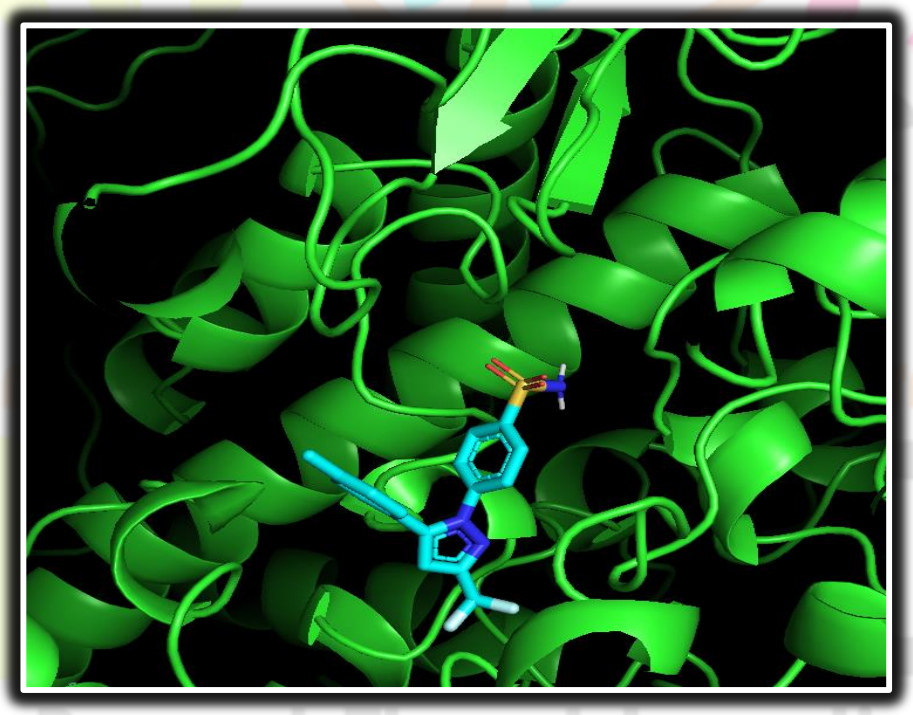


Fig. 8 Ribbon structure of 1CX2 enzyme with Celecoxib

## ❖ References :-


1. .Alvaewz-BJ, Barluenga J. Heterocyclic compounds: An introduction, Modern Heterocyclic Chemistry. First Edition, 2011.

2. Vidyalakshmi K, Viswanathan S, Pandurangan K, Ramaswamy S. Anti-inflammatory effect of certain dimethoxy flavones. Inflammopharmacology. 2015; 12-18.

3. Tran TD, Yeon SC, Jeong K, Hyun PK, Sanghee K, Haeil P. Synthesis and inhibitory activity against COX-2 catalyzed prostaglandin production of chrysin derivatives. Bioorg Med Chem Lett. 2004; 1165-1167.

4. Syahrul I, Muhammad T, Nor HI, Syed MK, Fazal R, Waqas J, Maywan H, Muhammad Y, Habibah W. Synthesis of novel flavone hydrazones: In-vitro of α-glucosidase inhibition, QSAR analysis and docking studies. Eur J Med Chem. 2015; 105: 156-170.

5. .B Mukesh, K Rakesh. Molecular docking: a review. IJRAP. 2011; 2: 1746-1751.

6. IA Guedes, CS de Magalhães, LE Dardenne. Receptor–ligand molecular docking, Biophysical Reviews. 2014; 6: 75-87.

7. Hendlich, M. (1998) Databases for protein-ligand complexes. *Acta Crystallogr D Biol Crystallogr*, **54**(Pt 6 Pt 1): 1178–1182.

8. Ewing, T.J.A. and Kuntz, I.D. (1997) Critical evaluation of search algorithms for automated molecular docking and database screening. *J Comput Chem*, **18**(9): 1175 1189.
9. Kuntz, I.D., Blaney, J.M., Oatley, S.J., Langridge, R., and Ferrin, T.E. (1982) A geometric approach to macromolecule-ligand interactions. *J Mol Biol*, **161**(2): 269–288.

10. Sousa, S.F., Fernandes, P.A., and Ramos, M.J. (2006) Protein-ligand docking: Current status and future challenges. *Proteins*, **65**(1): 15–26.

11. Friesner, R.A., Banks, J.L., Murphy, R.B., Halgren, T.A., Klicic, J.J., Mainz, D.T., Repasky, M.P., Knoll, E.H., Shelley, M., Perry, J.K., Shaw, D.E., Francis, P., and Shenkin, P.S. (2004) Glide: a new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. *J Med Chem*, **47**(7): 1739–1749.

12. M. El-Sayed et al. Synthesis, biological evaluation and molecular modeling study of pyrazole and pyrazoline derivatives as selective COX-2 inhibitors and anti-inflammatory agents. Part 2 Bioorg. Med. Chem. Lett. (2012)

## ❖ Acknowledgment :-

I Would like to express my gratitude to Professor Mr.Awinash Chavhan Sir ,my research supervisors, for their patient guidance, enthusiastic encouragement and useful critiques of this research work. I would also like to thank the staff of the Raosaheb Patil Danve College of Pharmacy, Badnapur for the supporting me in this Research Work