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Sequence based structure prediction of COX-2 (*Homo sapiens*)

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A B S T R A C T

The various NSAID's known to the scientists till date, reduces fever and inflammation when the body gets overzealous in its defenses against infection and damage but it may slows blood flow and blood clotting, reducing the chance of stroke and heart attack in susceptible individuals. Three-dimensional structures of pharmacologically important macromolecules offer a route to the discovery of new drugs. Understanding the macromolecule-ligand interactions and validation of method used for docking and virtual screening of chemical databases is crucial step in structure-based design. The complete computational analysis has revealed the best possible refined structure for COX-2. The structure determination was done through Geno 3D and visualization through VMD tool respectively, and the refinement was done through Kobamin.

Introduction

COX-2 is an enzyme responsible for the inflammation and causes pain. Cyclooxygenase (COX) is an enzyme responsible for the formation of prostanoids. Three groups of prostanoids like prostaglandin prostacyclins, and thromboxane are involved in the inflammatory responses.

Cyclooxygenase-2, an enzyme that acts to speed up the production of certain chemical messengers, called prostaglandins that play a key role in promoting inflammation. When COX-2 activity is blocked, inflammation is reduced. Unlike COX-1, COX-2 is active only at the site of inflammation, not in the stomach. Prostaglandins are fatty-acid derivatives located all over your body that are well known for their inflammation and immune response effects. However, they also have many different roles in the body. A scientific list would read as such: PG's are involved in as diverse normal processes as evolution, blood clotting, renal function, wound healing, vasomotor tone, platelet aggregation, differentiation of immune cells, nerve growth, bone metabolism, and initiation of labor

Induction of COX-2 expression and enzymatic activity promotes neuronal injury in a number of models of neurological

disease. COX -mediated neuronal injury is presumed due to downstream effects of one or more prostaglandin products including PGE_2, PGD_2, $PGF_{2\alpha}$, PGI_2 (prostacylin) and TXA_2 (thromboxane) that effect cellular changes through activation of specific prostaglandin receptor subtypes and second messenger systems. The effects of prostaglandin signaling on neuronal viability that is paradoxically protective, when taken in the context that COX-2 induces neuronal injury in the setting of excitotoxicity. Conversely, in the context of an inflammatory stimulus, the EP2 receptor enhances neuronal injury. These findings argue for an additional level of complexity in the prostaglandin response in neurological disease

Database and Tools

First, the query sequence was retrieved from NCBI (http://www.ncbi.nlm.nih.gov/) database and then the tool Geno 3d (http://geno3d-pbil.ibcp.fr) was used for determination of 3D structure. Then, the structure refinement was done by Kobamin (http://csb.stanford.edu/kobamin/) which brings native-like conformation means the best possible refined structure respective to the template. After refinement the structure was aligned for the best-selected template from VAST (http://www.ncbi.nlm.nih.gov/Structure/VAST/vast.shtml) that is used to identify similar protein 3D structure and from this, the ligand is discovered by using ligand explorer at PDB.

Result and Discussion

The conceptual framework and the properties of COX-2 have been developing effective NSAIDs in blocking the signs and symptoms of inflammation. Although this beneficial effect of specific COX-2 structure is evident, data suggest that in certain models. Prostaglandins may be unexpectedly beneficial in there solution of inflammation or tissue injury. This COX-2 structure prediction determines the designing of the new drug and as the more specialized structures are predicted, formation of new NSAID'S can be beneficial for the anti-inflammatory responses.

Structure prediction is formulated by sequence retrieval from NCBI and then structure predicted from Geno 3D (Fig.1) showing protein molecular modeling on the basis of identifying homologous proteins with known 3D structures and shows the alignment of the subject sequences also specifying the geometrical restraints (dihedral angles and distances) for corresponding atoms between the query and the template and the 3D construction of the protein having the combined study of various protein molecules and then determining simplified structure shown in Fig.2 which is showing the specific structure of the model obtained from the mixed complex.

The structure obtained from Kobamin (Fig. 3) was refined on the basis of energy minimization and stereochemistry correction and Kobamin bringing the best possible refined conformation and discovering of the active sites (Fig. 4) shown above.

The above mentioned table shows the detail list of the prone active sites (Fig. 4) and the catalytic triads as shown in Fig.5 shows the work scanning of a probe along all gridlines of a grid resolution surrounding the protein also specifying scans of cubic diagonals. Grid points are defined to be part of a site when the probe is within range of protein atoms followed by proteins atoms. Since, the protein is scanned in seven directions each

grid point can be defined to be part of a site up to seven times. Grid points are only retained if they are defined to be part of a site at least five times.

This projecting the structure of COX-2 certifying the basic modulation done in the structure prediction of COX-2.

Table.1

Amino acid	$\hat{H}_i$
LYS	0.000
GLU	0.083
ASP	0.167
GLN	0.250
ARG	0.272
ASN	0.278
PRO	0.300
SER	0.422
THR	0.478
GLY	0.550
ALA	0.572
HIS	0.628
TYR	0.700
LEU	0.783
VAL	0.811
MET	0.828
TRP	0.856
ILE	0.883
PHE	0.906
CYS	1.000

Fig.1 Super bound structure of COX-2 obtained from Geno 3D

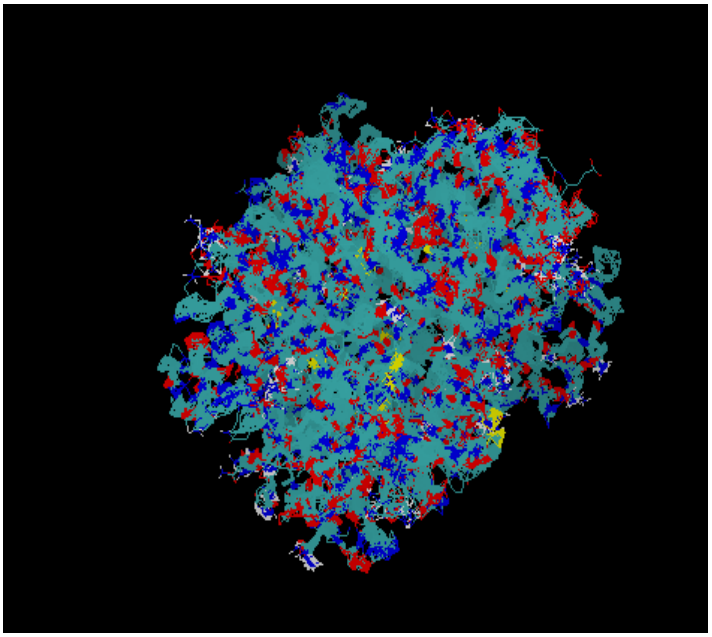


Fig.2 Structure predicted from Geno 3D

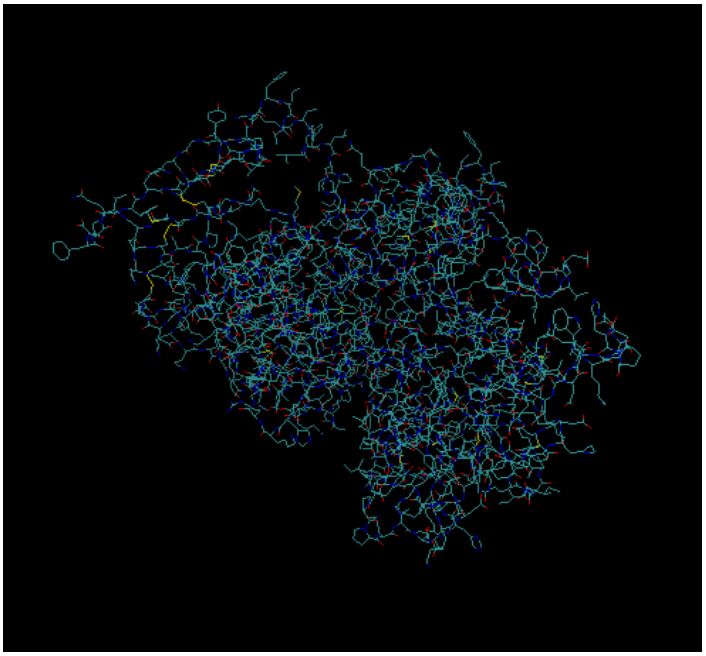


Fig.3 Refined structure of COX-2 obtained from Kobamin

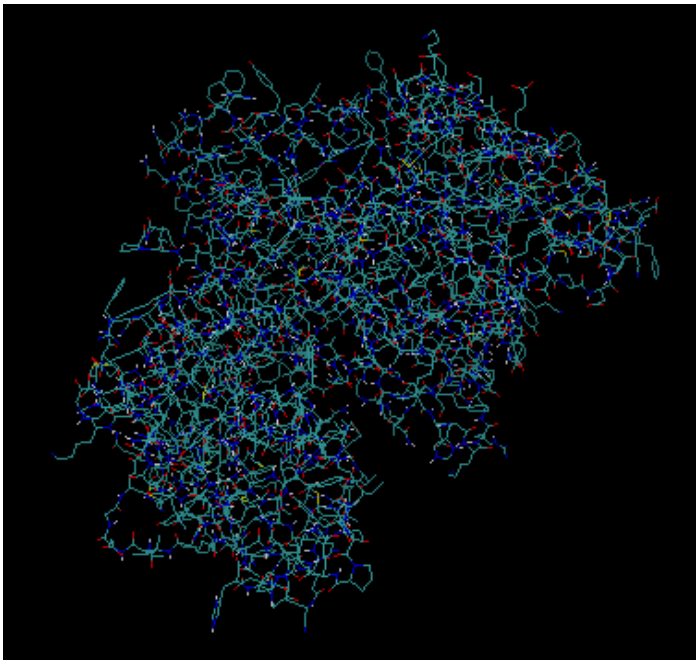


Fig.4 Predicted active site in COX-2

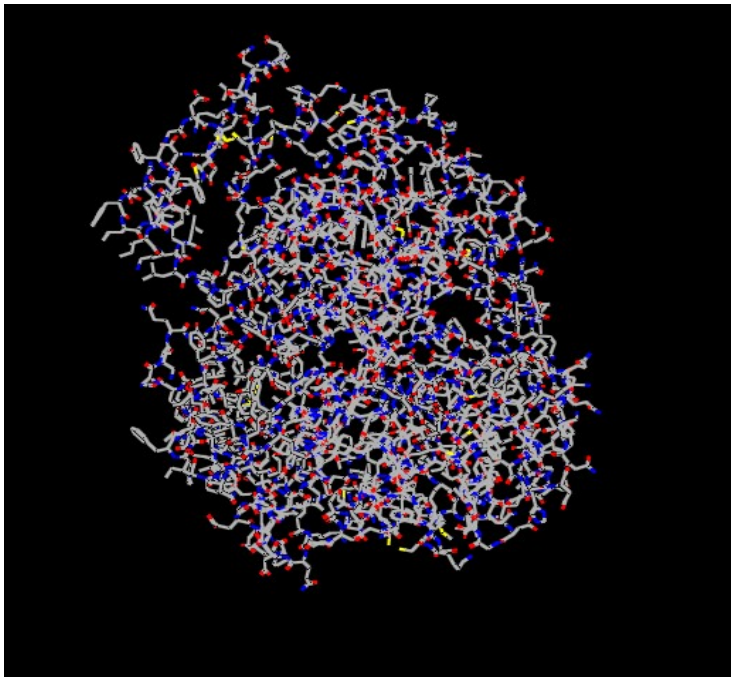
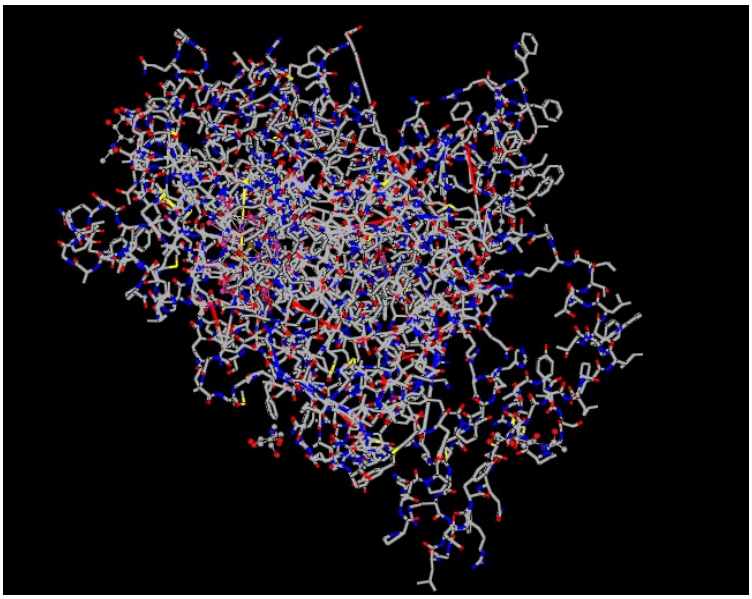


Fig.5 Catalytic triads of the predicted structure of Cox-2



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