Journal of Applied Pharmaceutical Science Vol. 3 (4 Suppl 1), pp. S13-S22, May, 2013
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2013.34.S3
ISSN 2231-3354

Molecular docking study of 3,6 bis(3'substituted propoxy) and 3,6 bis (5'substituted pentyloxy) xanthone derivatives as PGHS- 2 inhibitors

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ARTICLE INFO

Article history:
Received on: 02/04/2013
Revised on: 22/04/2013
Accepted on: 02/05/2013
Available online: 12/05/2013

Key words:
Xanthone derivatives, PGHS-2, Autodock 4.2, Exome Horizon™

ABSTRACT

The primary effect of the NSAIDs is to inhibit cyclooxygenase (COX or prostaglandin synthase), thereby impairing the ultimate transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes. Two related isoforms of the COX enzyme have been described, COX-1 and COX-2. Identification of this cyclooxygenase-2 (COX-2) isoform resulted in the development of selective COX-2 inhibitors, with the hope of producing a safer analgesic and anti-inflammatory agent**.** The principal benefit with the selective COX-2 inhibitors is the production of comparable analgesia and antiinflammatory effects to the nonselective NSAIDs, but with fewer symptomatic gastric and duodenal ulcers and a decrease in gastrointestinal symptoms. In the present work, twelve novel series of xanthone derivatives (A1-A6 and B1-B6) were allowed to dock against PGHS-2(prostaglandin endoperoxide synthase-2) protein (PDB ID: 3LN1) to evaluate their comparative efficacy in terms of docking performance. The results are discussed on the basis of binding energy value.

INTRODUCTION

COX-2 selective inhibitor is a form of non-steroidal anti-inflammatory drug (NSAID) that directly targets COX-2, an enzyme responsible for inflammation and pain. Targeting selectivity for COX-2 reduces the risk of peptic ulceration, and is the main feature of celecoxib, rofecoxib and other members of this drug class. The mouse COX-2 gene was cloned by UCLA scientist Dr. Harvey Herschman (Kujubu *et al*.,1991). The enzyme was discovered in 1988 by Daniel Simmons, a Brigham Young University researcher formerly of Harvard University (Xie *et al*.,1991). In the course of the search for a specific inhibitor of the negative effects of prostaglandins which spared the positive effects, it was discovered that prostaglandins could indeed be separated into two general classes which could loosely be regarded as "good prostaglandins" and "bad prostaglandins", according to the structure of a particular enzyme involved in their biosynthesis, cyclooxygenase. Prostaglandins whose synthesis involves the cyclooxygenase -I enzyme, or COX-1, are responsible for maintenance and protection of the gastrointestinal tract, while prostaglandins whose synthesis involves the cyclooxygenase-II enzyme, or COX-2, are responsible for inflammation and pain. In the brain, prostaglandin E2 (PGE2) levels are very low or undetectable in normal conditions, but can rise during inflammatory processes, multiple sclerosis, and AIDS-associated dementia (Fretland *et al*., 1992; Griffin *et al*.,1994). High levels of PGE2 can affect the activities of several cell types, including neurons, glial, and endothelial cells, and can regulate microglia/macrophage and lymphocyte functions during inflammatory and immune processes (Weissmann *et al*.,1993). Therefore, the interplay between PGE2 andother local factors, including pro- and anti-inflammatory cytokines, is likely to influence the outcome of inflammatory and immune responses in the central nervous system (CNS). Cyclooxygenase (COX) is the rate-limiting enzyme in PG synthesis and exists as two isoforms, constitutive(COX-1) and inducible (COX-2). These isoforms originate from distinct genes, but are structurally conserved (Smith *et al*.,1996; Williams *et al*.,1996).COX-1 is regarded as a constitutive enzyme whose expression is developmentally regulated.

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PGs produced by COX-1primarily function in fluid and electrolyte homeostasis, gastric acid secretion, and platelet aggregation. In contrast, COX-2 is expressed in response to inflammatory stimuli and is active in physiological responses to growth factors and glucocorticoids (DeWitt *et al*., 1993). Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used therapeutics, primarily for the treatment of pain and inflammation, especially arthritis. From a historical viewpoint, the first NSAID with therapeutic benefits was aspirin, which has now been used for more than 100 years as anNSAID. The overall worldwide production of about 50 000 tons a year reflects the importance of this substance even today (Kuhnert *et al*.,2000).

PGs are produced by most cells and are also present in tissues, which explains their broad spectrum of biological responses. PGs mediate a number of characteristic features of the body's response to tissue injury or inflammation. The outstanding effects of the PGs include their cytoprotective properties in the gastrointestinal (GI) tract and control of renal functions in the kidney PGE2 is the most important PG which mediates the typical symptoms of inflammation: rubor, calor, tumor,dolor and functio laesa. Dilatation of small blood vessels initiates the development of redness and heat; the increase in vascular permeability causes the characteristic swelling of tissues. Moreover, PGs sensitize peripheral nerve endings and nociceptors to transmit pain signals to the brain and the spinal cord. In addition to the well-accepted proinflammatory role of PGs, there is also evidence of anti-inflammatory activity in certain COX-2-derived PGs in vivo, an experiment recently reported (Gilroy *et al*.,1999). Cyclooxygenase-1 (COX-1) is constitutively expressed in most tissues and is responsible for maintaining physiologic processes such as gastric and renal protection and platelet function. In contrast, cyclooxygenase-2(COX-2) is induced in response to growth factors (Perkins *et al*.,1997; Diaz *et al*.,1998) (ie,endothelial growth factor [EGF], vascular endothelial growth factor [VEGF], fibroblast growth factor [FGF-2]), cytokines (eg, tumor necrosis factor-α [TNF-α],interleukin-α [IL-α], and interleukin-1β [IL-1β]), and tumor promoters (eg, v-src, v-Ha-ras, HER-2/neu, and Wnt) (Howe *et al*.,1999; Vadlamudi *et al*.,1999). COX-2 is expressed in macrophages, synoviocytes, and endothelial cells in response to inflammation and cellular activation (Crofford *et al*.,1997; Koki *et al*.,1999; Williams *et al*.,1999). Conventional NSAIDs inhibit both COX-1 and COX-2, hence they also disrupt COX-1 dependent homeostatic functions. Therefore, molecular-based targeting strategies were employed to develop specific COX-2 inhibitors to circumvent thegastric and renal toxicities caused by mixed COX inhibitors (Lanza *et al*., 1998; Singh *et al*.,1997; Silverstein *et al*.,2000). Investigations of many naturally occurring xanthones as well as their synthetic derivatives, resulted in numerous publications described their broad spectrum of biological activities namely antiallergic (Pfister *et al*.,1972), anti-inflammatory (Chung *et al*.,2002; Lin *et al*.,1996; Marona *et al*.,1986; Shankaranarayan *et al*.,1979), anti-tumor (Ho CK *et al*.,2002; Pedro *et al*.,2002), antimycobacterial (Pickert *et al*.,1998), cardiovascular (Bisi *et al*.,1998; Chen *et al*.,1993; Chiarini *etal*.,1992; Valenti *et al*.,1990) and neuropharmacological effects (Da Re *et al*.,1968; Galt *et al*.,1989; Marona *et al*.,1998; Rampa *et al*.,1998). Some of natural and synthetic xanthones have shown anti-inflammatory and analgesic activity.

MATERIAL AND METHODS

Retrieval of 3D Structure

The 3D structure of the protein was downloaded from RCSB (Research Collaboratory for Structural Bioinformatics), Protein Databank (PDB, http://www.pdb.org). The PDB ID of the selected protein was found to be 3LN1. The Water molecules and ligands attached to the protein were removed by using Swiss PDB Viewer. The Protein was having 552 no. of groups, 8851 no. of atoms and 8987 no. of bonds.

Structural Assessment of the Protein

The protein was sent for structural assessment to Exome Horizon. The Ramchandran Plot, Ramachandran plots for all residue types was given in **Fig1**, Chi1-Chi2 plots, Main-chain parameters, Side-chain parameters, Residue properties, Main-chain bond length, Main-chain bond angles, RMS distances from planarity and distorted geometry were analyzed for input_atom_only (Ramachandran *et al*., 1963).

Ligand Preparation

The ligands were drawn using Moldraw tool of Exome^{TM} Horizon in 2D and were converted into 3D before submission for docking. The general structure was given in the **Fig2** and all the derived groups (X) and its chemical properties were provided in **Table 1**.

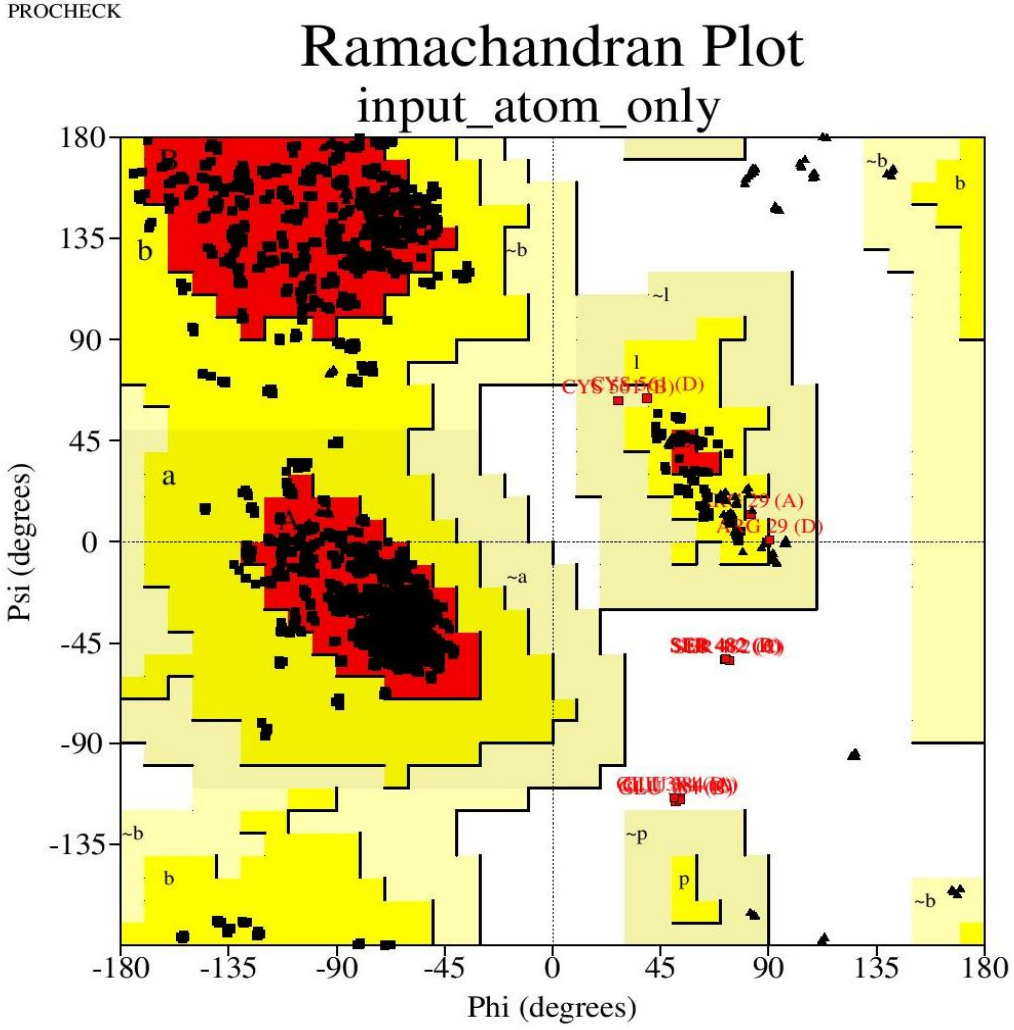
Protein-Ligand Docking Studies

Protein-ligand docking is used to check the structure, position and orientation of a protein when it interacts with small molecules like ligands. Protein-ligand docking aims to predict and rank the structures arising from the association between a given ligand and a target protein of known 3D structure. Protein-Ligand Docking module is further divided into different parts for user convenience like Receptor Preparation, Ligand Preparation, Binding Site Analysis, Dock and Analysis (Parida *et al*., 2012). The protein-ligand docking was performed using Lamarckian genetic algorithm with default parameter (Morris *et al*., 1996)**.**

Binding Site Analysis.

Binding Site analysis is a fast detection program for 'the identification and visualization of possible binding sites and 'the distribution of surrounding residues in the active sites'. The centre of active site was chosen as grid map values for preparation of the grids. The spacing of grid was set to 1.00 ^{0}A and the no. of grid point were taken as 60 x 60 x 60 ^{0}A and protein-ligand docking was performed using Lamarckian genetic algorithm using default parameter (Morris and Goodsell *et al*.,1998). The active sites were given in **Table 2.**

PROCHECK



Plot statistics

Residues in most favoured regions [A,B,L]	1683	88.2%
Residues in additional allowed regions [a,b,l,p]	213	11.2%
Residues in generously allowed regions [~a,~b,~l,~p]	4	0.2%
Residues in disallowed regions	8	0.4%
Number of non-glycine and non-proline residues	1908	100.0%
Number of end-residues (excl. Gly and Pro)	8	
Number of glycine residues (shown as triangles)	148	
Number of proline residues	144	
Total number of residues	2208	

Based on an analysis of 118 structures of resolution of at least 2.0 Angstroms and R-factor no greater than 20%, a good quality model would be expected to have over 90% in the most favoured regions.

Fig.1: Ramachandran plot analysis of 3LN1.

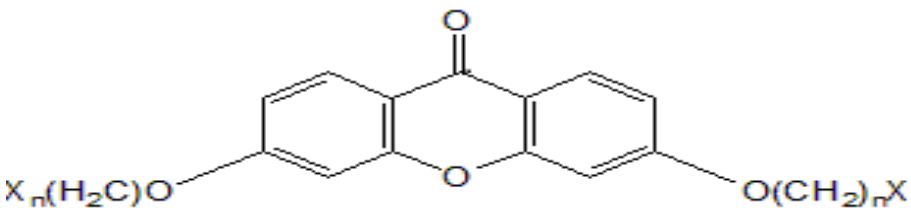


Fig. 2: General Structure of the proposed compounds.

Table . 1: Xanthone derivatives with their respective chemical properties.

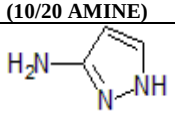
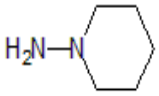
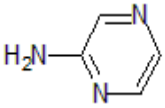
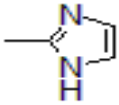
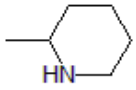
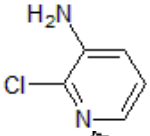
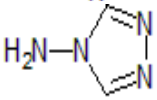
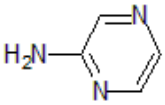
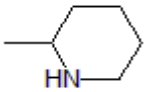
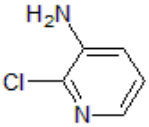
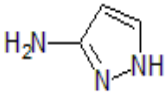
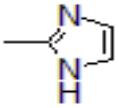
SL NO.	COMPOUND	N(NO. OF CH2 GROUP)	X (10/20 AMINE)	Mol. Wt.	IUPAC NAME
1.	A1	3		474.51	3,6-bis(3-(1h-pyrazol-3ylamino)propoxy)-9H-xanthen-9-one
2.	A2	3		508.65	3,6-bis(3-(piperidin-1-ylamino)propoxy)-9H-xanthen-9one
3.	A3	3		498.53	3,6-bis(3-(pyrazin-2-ylamino)propoxy)-9H-xanthen-9-one
4.	A4	3		472.54	3,6-bis(3-(2-methyl-1H-imidazol-1-yl)propoxy)-9H-xanthe-9-one
5.	A5	3		506.68	3,6-bis(3-(2-methylpiperidin-1-yl)propoxy)-9H-xanthen-9-one
6.	A6	3		565.45	3,6-bis(3-(2-chloropyridin-3-ylamino)propoxy)-9H-xanthe-9-one
7.	B1	5		532.59	3,6-bis(5-(4H-1,2,4-triazol-4ylamino)pentyloxy)-9H-xanthe-9-one
8.	B2	5		584.71	3,6-bis(5-(pyrazin-2-ylamino)pentyloxy)-9H-xanthen-9-one
9.	B3	5		592.85	3,6-bis(5-(2-methylpiperidin-1-yl)pentyloxy)-9H-xanthen-9-one
10.	B4	5		651.62	3,6-bis(5-(2-chloropyridin-3-ylamino)pentyloxy)-9H-xanthen-9-one
11.	B5	5		560.69	3,6-bis(5-(1H-pyrazol-3-ylamino)pentlxy)-9H-xanthen-9-one
12.	B6	5		528.64	3,6-bis(5-(2-methyl-11H-imidazol-1-yl)-9H-xanthen-9-one

Table. 2: Active sites and the centre of active sites of the protein 3LN1..

Sl No.	Name of Active Sites	Residues In Active Sites	Centre Of Active Sites
1	H1	RVLSYYMVEGAPS	31.536, -23.231, -14.984
2	H2	KPTPNYSRYFSE	34.072, -11.718, -16.103
3	H3	CNPCQNRGECYAPQER	38.626, -8.876, 2.854
4	H4	NRRTGFTKKYS	39.567, -4.296, -9.765
5	H5	AFAQHTHYHWHPL	28.380, -34.508, -6.960
6	H6	NCCNCMSYGYPPVACQ	40.892, -11.155, 10.315
7	H7	YHFKTHNHQ	33.716, -34.356, -0.221
8	H8	HTPQHLSGYHPDAI	22.389, -22.706, -23.035
9	H9	KYVLREHNRVDNN	42.151, -52.974, -22.661
10	H10	SYLIDSPQFQK	48.083, -14.729, -10.570
11	H11	NRYELGEKPRPFGET	20.717, -13.680, -12.095
12	H12	EDYQHTSFNQ	29.049, -32.562, -25.591
13	H13	KRGNGETRGQEV	43.328, -41.604, -0.476
14	H14	NRGEDCTRTDYK	45.048, -7.602, -2.914
15	H15	PDTFNEQIA	13.425, -39.380, -14.072

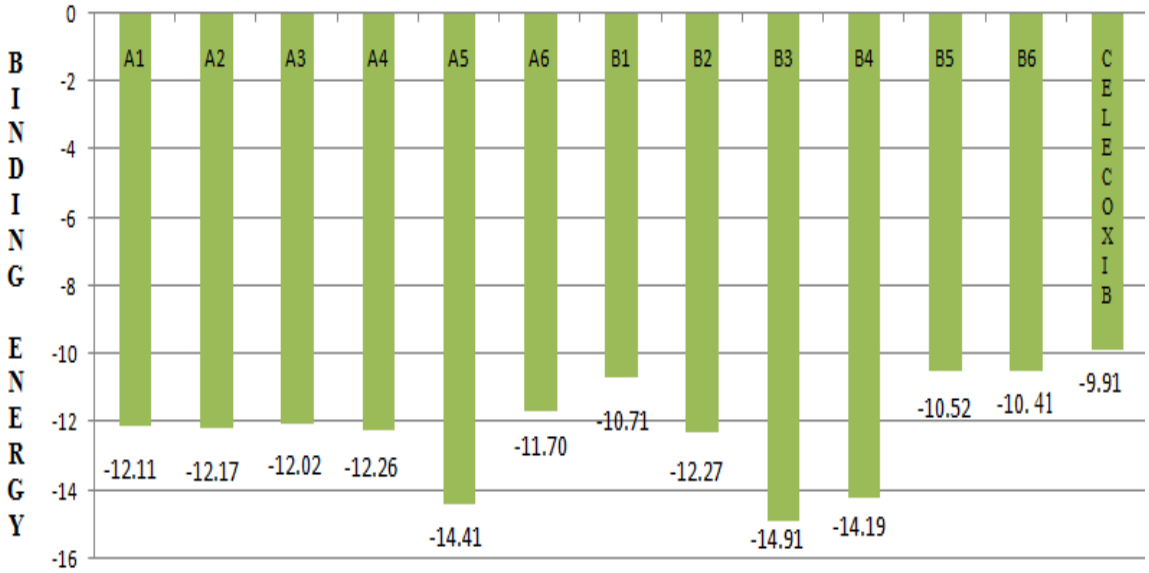
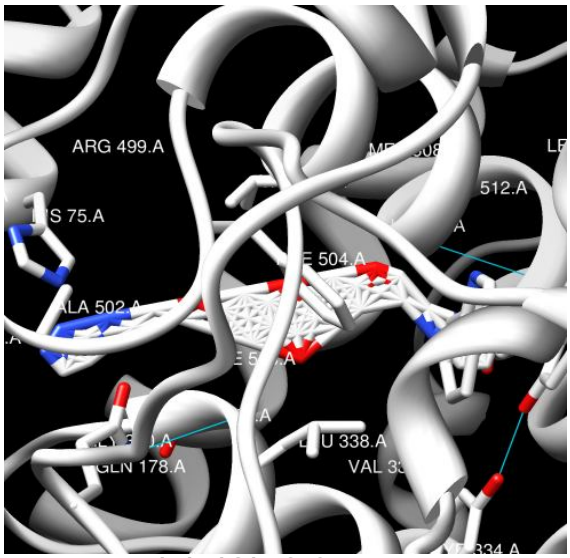
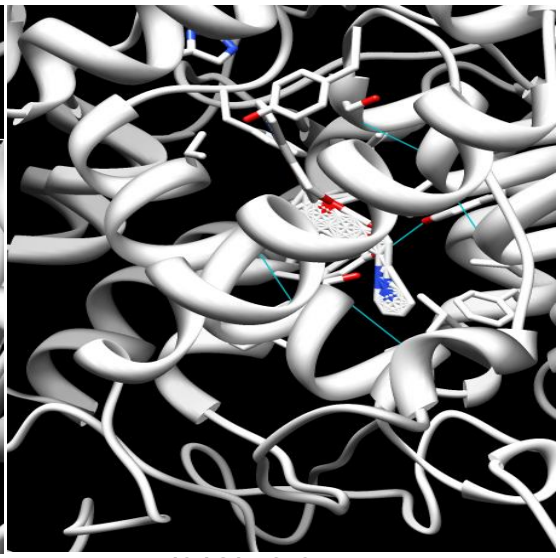


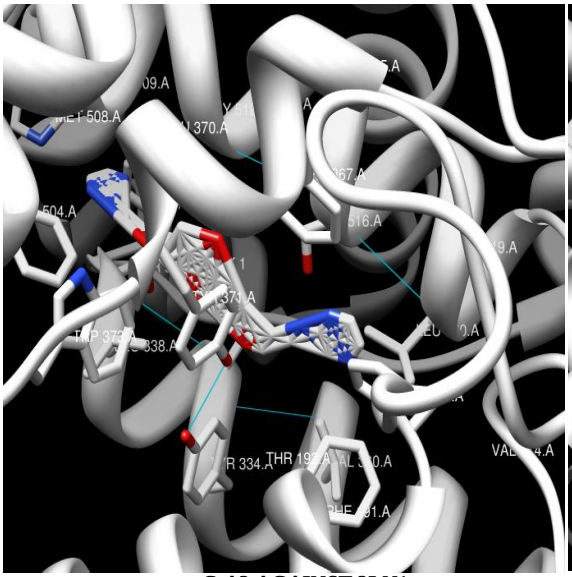
Fig. 3: Binding energies of the ligands against 3LN1.



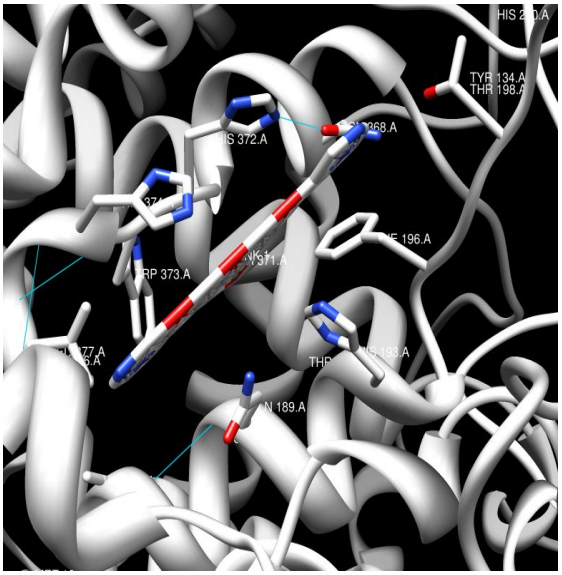
A- A1 AGAINST 3LN1



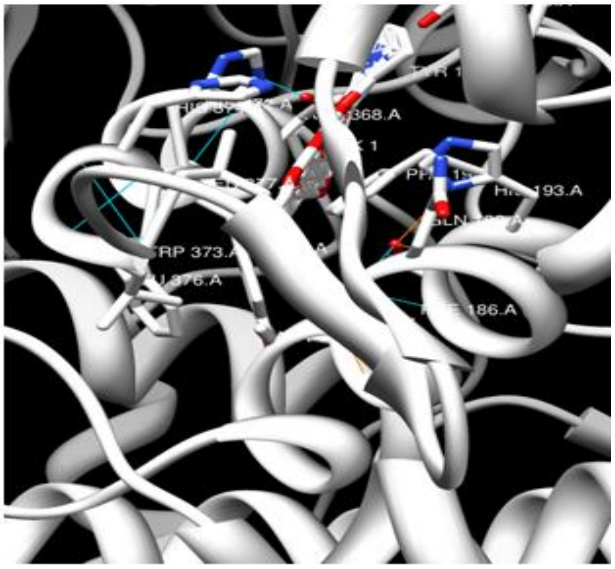
B-A2 AGAINST 3LN1



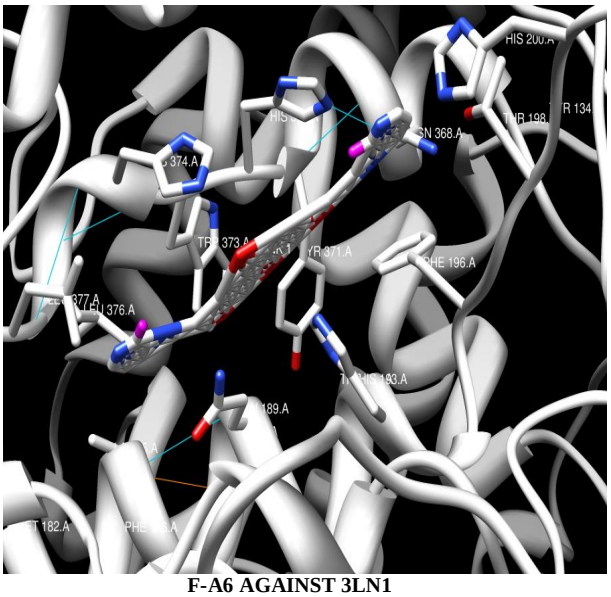
C-A3 AGAINST 3LN1



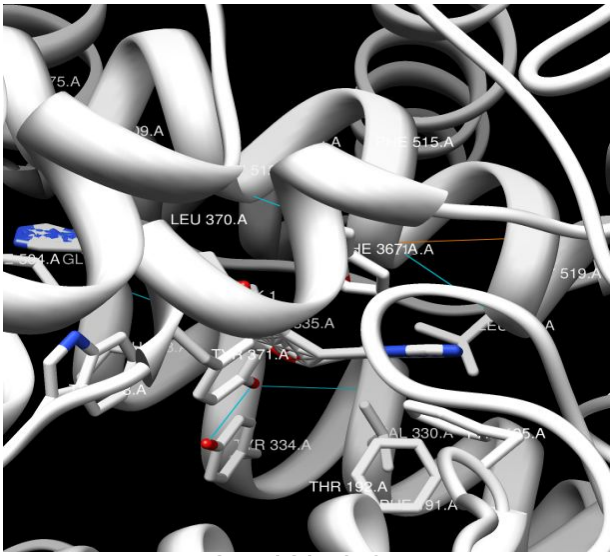
D-A4 AGAINST 3LN1



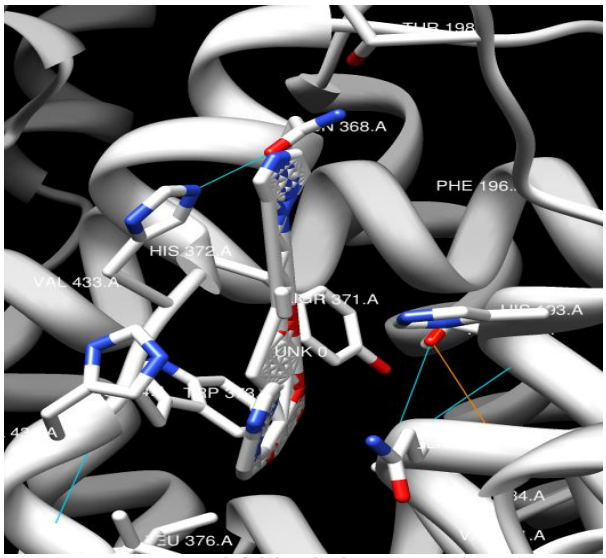
E- A5 AGAINST 3LN1



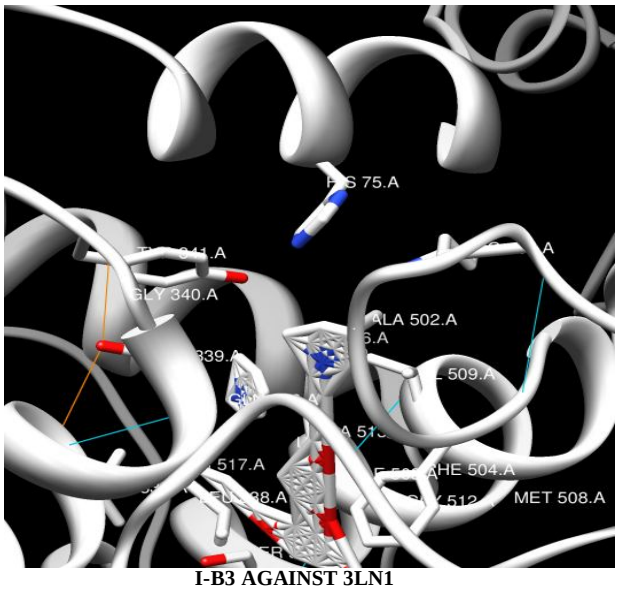
F-A6 AGAINST 3LN1



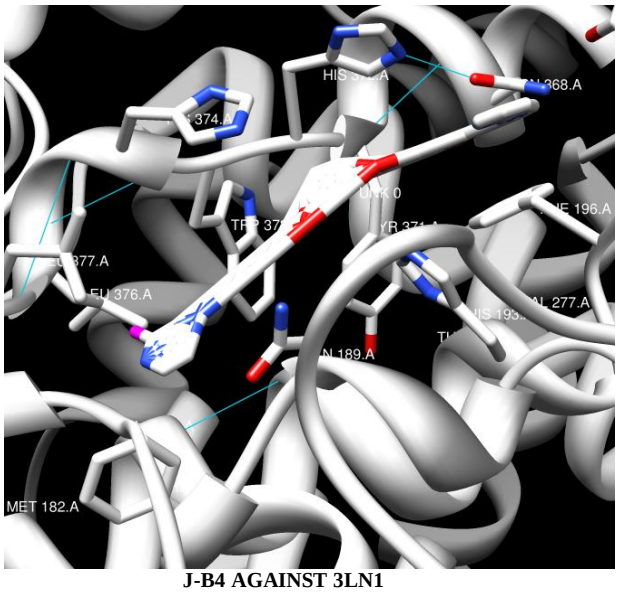
G- B1 AGAINST 3LN1



H-B2 AGAINST 3LN1



I-B3 AGAINST 3LN1



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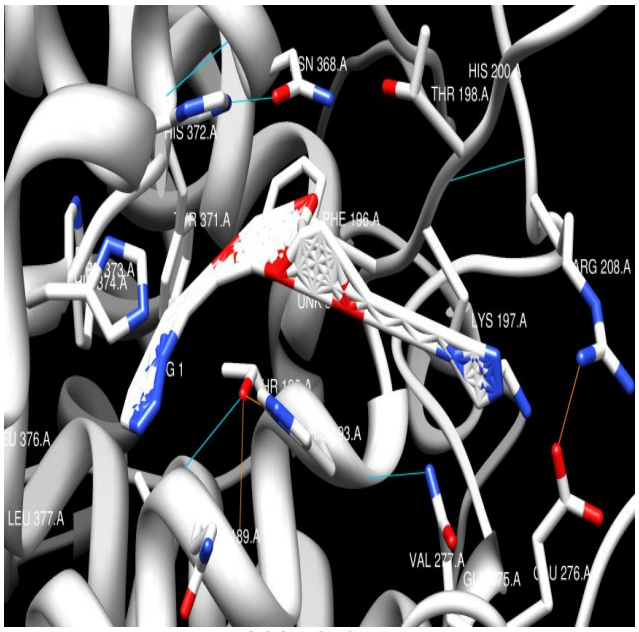
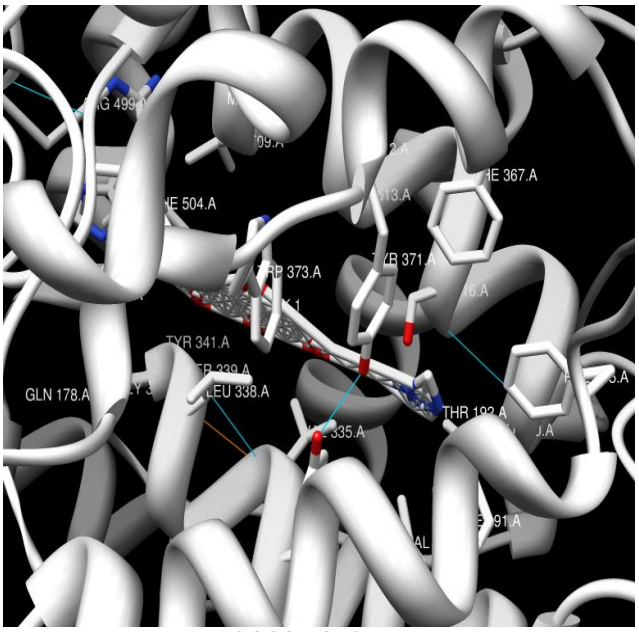
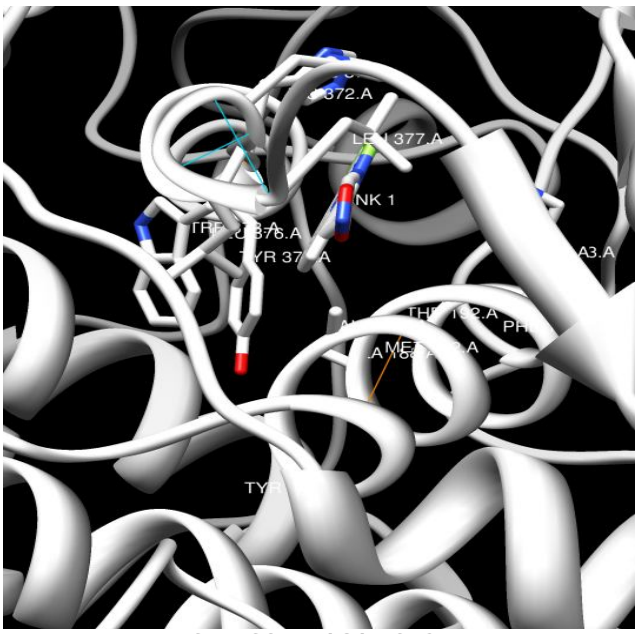


K-B5 AGAINST 3LN1



L-B6 AGAINST 3LN1



M- **CELECOXIB AGAINST 3LN1**

Fig. 4: Interaction of ligands against the protein 3LN1.

The thin lines with colours and represent interacting hydrogen bonds and electronic-interactions between the drugs and the protein respectively.

RESULTS AND DISCUSSION

The analogues were successfully docked into the binding pocket. The binding energy was observed in the range of -10.41 to -14.91 Kcal/mol. The key result in a docking log file (DLG) are the docked structure or conformation found at the end of each run, the energies of these docked structures and their similarities to each other. The DLG file provides docked conformations, orientations and the binding energies. The similarity of docked structures is measured by computing the root-mean-square deviation (RMSD) between the coordinates of selected molecular conformation with the molecular conformation having lowest interaction energy which is ranked on top. Clusters are created based on the comparison of conformations using RMSD values. The docking results consist of the PDBQT of the transformed 3D Cartesian coordinates of the ligand atoms as docked to the receptor molecule [13].The binding energy of the selected ligands were plotted in the graph and from the graph **(Fig. 3)** the binding energy of all the active sites were observed among which the best ligand which shows better activity in all the active site was found to be B3.The aminoacids and the drug interactions were given in the **Fig. 4 (a-m)**.

All the classic NSAIDs inhibit both COX-1 and COX-2 at standard anti-inflammatory doses. The beneficial anti-inflammatory and analgesic effects are based on the inhibition of COX-2, but the gastrointestinal toxicity and the mild bleeding diathesis are a result of the concurrent inhibition of COX-1(Dannhardt *et al*., 2001). It is now known that under basal conditions the constitutive enzyme COX-1 is expressed in nearly all tissues including the colon, kidney, spleen, stomach, liver, lung, heart and brain. In both the kidney and the stomach, for example, prostanoids synthesized by COX-1 act as vasodilatators. In the kidney these prostanoids help to maintain renal plasma flow and glomerular filtration during periods of systemic vasoconstriction. Similarly, in the gastric antrum, local vasodilatation appears to be critical in maintaining mucosal defenses. COX-1 in platelets on the other hand generates thromboxane which plays a key role in mediating platelet aggregation (Crofford *et al*., 1997). In contrast, COX-2 expression is largely undetectable unless induced by inflammatory stimuli in cells such as synoviocytes, macrophages and endothelial cells. Such stimuli are proinflammatory cytokines (IL-1b, TNFa), lipopolysaccharides such as LPS, mitogenes and oncogenes (phorbolic esters), growth factors (fibroblast growth factor, FGF; platelet derived growth factor, PDGF; epidermal growth factor, EGF), hormones (luteinizing hormone, LH) and disorders of water-electrolyte hemostasis (Needleman *et al*., 1997; Bakhle *et al*., 1996; Ristima *et al*., 1994). Commonly used NSAIDs play an enormous role in the therapy of inflammatory diseases. Over the years the pool of therapeutic substances has grown rapidly. Depending on their chemical structure, NSAIDs inhibit both COX-1 and COX-2 to different extents. This accounts for their anti-inflammatory and analgesic activities and also their unwanted GI side-effects (Carabaza *et al*., 1996). All currently marketed NSAIDs are inhibitors of both COX-1 and COX-2. The aspect of enzyme selectivity of NSAIDs becomes important particularly under the point of view of low risk NSAIDs with reduced side-effects. Therefore, the classic NSAIDs are being pushed increasingly into the background, whereas selective COX-2 inhibitors with an attractive pharmacological profile and reduced side-effects are being favoured (Dannhardt *et al*., 2001). The clinical results for selective COX-2 inhibitors such as celecoxib and rofecoxib are promising. However, the tendency to search for more specific inhibitors has also provoked critical reactions. Certainly selective COX-2 inhibitors reduce the risk of GI side-effects, but COX-2 is not only a proinflammatory inducible enzyme, it also has a number of physiological functions which means that it is constitutively expressed to a high extent in the human body (Katori *et al*., 2000). COX-2 seems to be involved into the regulation of the renin–angiotensin system (Morham *et al*., 1995; Harris *et al*., 1994), and to possess vasoactive and anti-atherogenic properties (Mitchel *et al*., 1998). Moreover, the hormonal induction is important for ovulation and, at the end of pregnancy, high uterine levels of COX-2 are necessary for the onset of labor (Morham *et al*., 1995; Chakraborty *et al*., 1996). The role of elevated COX-2 enzyme levels in ulcerative tissues for wound healing has already been mentioned.

Therefore, the following side-effects have been taken into account under therapy with selective COX-2inhibitors: Influence on the renin–angiotensin-system in the kidneys induces hypertension and renal failure; deleterious effects on ovulation and parturition as well as delayed wound healing. However, at the recommended therapeutic doses these drugs retain selectivity and do not affect platelet aggregation or bleeding time (Pairet *et al*., 1999). Hence drug safety should be discussed at the same time as the benefits of selective COX-2 inhibitors.

As an alternative, balanced COX-1: COX-2 inhibitors should be further investigated. Furthermore additional compounds being developed as GI-sparing anti-inflammatory drugs might be of interest: nitric oxide-releasing NSAIDs (NONSAIDs) which show markedly reduced renal toxicity and dual inhibitors of both cyclooxygenase and 5- lipoxygenase, a further enzyme of the AA metabolism responsible for leukotriene biosynthesis such as ML 3000. This compound is presently undergoing clinical testing and shows a promising pharmacological profile with low GI risks (Laufer *et al*., 1999; Augustin *et al*., 1994). The docking studies performed in our research work clearly indicates the better binding efficacy of xanthone derivatives in comparison to the standard drug celecoxib. Whereas celecoxib showed a docking score of -9.94 Kcal/mol, 12 ligands we took for study showed a docking score greater than celecoxib.

CONCLUSIONS

Some ligands like A5, B3 and B4 showed binding score greater than -14 Kcal/mol. Hence selective xanthone derivatives can prove to have better ligand binding efficacy and hence better invivo activity than available NSAIDS. Synthesis of novel Xanthone derivatives and study of their inflammatory activity

might be of profound importance in the view point of good ligand receptor interaction and may produce greater in vivo activity in relatively smaller doses thus reducing the chance of side-effects.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Bioinformatics Infrastructure Facility (BIF) funded by Department of Biotechnology, Govt. of India, at Centre for Studies in Biotechnology, Dibrugarh University.

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How to cite this article:

Aparoop Das, Pratap Parida, Neha Agarwal, Jaya shree, Brajesh Shankar, Dipankar Chakraborty., Molecular docking study of 3,6 bis(3'substituted propoxy) and 3,6 bis(5'substituted pentyloxy) xanthone derivatives as PGHS- 2 inhibitors. J App Pharm Sci, 2013; 3 (4 Suppl 1): S13-S22.