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Study of Structure Based Drug Design for 1,4 Dihydropyridine Derivatives as Cox-II Inhibitors

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Abstract: In this research, an attempt was made to develop the docking studies of series of 1,4 dihydropyridine derivatives with cyclo-oxygenase-2 (COX-2) inhibitor (PDB-code 1CX2) to identify potential candidates with minimum dock score for anti-inflammatory activity. Molecular docking analysis was carried out to better understand the interactions between 1CX2 target and inhibitors in this series. Hydrophobic, hydrogen bond and vanderwaal's interactions lead to the identification of active binding sites. A set of twenty-four novel 1,4 dihydropyridine derivatives with anti-inflammatory activity was subjected to the docking studies using Vlife MDS 4.0. drug designing module. The results of the docking studies were found to endorse the result of the experimental work in future. Therefore, it can be said that the strategy employed can serve as an important tool in future for the design and development of novel therapeutic agents with minimal side effects of various categories too.

Key words: Cyclo-oxygenase-2 (COX-2) inhibitor, 1, 4 dihydropyridine, inflammation, molecular docking

INTRODUCTION

In the past numerous advances have been taken place in the understanding of pathogenesis and as a result a significant progress have been made in the development of novel anti-inflammatory drugs (Bhandari *et al.*, 2009). Dihydropyridines (DHPs) represent a group of small organic compounds based on a pyridine core. Theoretically, five isomer DHPs can exist but actually, most of the recognized DHPs have either the 1,2-dihydro or the 1,4-dihydro structure (Eisner and Kuthan, 1972). 1,4 Dihydropyridines have broad range of pharmacological actions as agents in vasodilation, bronchodilation, hepatoprotection (Edraki *et al.*, 2009), antitumour, anticonvulsant (Safak and Simsek, 2006), calcium channel blocker (Young, 1984; Kotharkar and Shinde, 2006), antituberculour (Khoshneviszadeh *et al.*, 2009), antimutagenic, anti-microbial (Thore *et al.*, 1995) and anti-inflammatory (Winter *et al.*, 1962; Swamy *et al.*, 1998; Pattan *et al.*, 2008). Inflammation can be summarized as a complex process involving the release of several biochemical factors called inflammation mediators. Among these mediators, prostanoids, lipidic mediators deriving from fatty acids mediators have been identified as a key influencing mediators they can directly or synergistically in order to promote or maintain the inflammatory process

(Vane, 1971; Hoffman, 2000). Cyclo-oxygenases exist under two isoforms called COX-1 and COX-2. COX-1 is the constitutive form of the enzyme is present in the stomach, intestines, kidneys and platelets whereas COX-2 is also constitutively expressed in brain and spinal cord and kidneys is an inducible form and its expression is triggered under pathological condition such as inflammation (Cullen *et al.*, 1998; Renard *et al.*, 2009; Julemont *et al.*, 2004). COX-2 selective inhibitors are the safest way to reduce the inflammation (Antre *et al.*, 2011). Molecular docking is an important tool which predicts the proffered orientation by showing the interactions between ligand and the protein and the aim is to achieve an optimized conformation for both the protein and the ligand and the relative orientation obtained should be such that the free energy of the overall system should be decreased (Sawant *et al.*, 2012; Antre *et al.*, 2012; Halgren, 1996). Molecular docking studies have been carried out with series of 1,4 dihydropyridine derivatives which are potent and highly selective COX-2 inhibitors with PDB code 1CX2. We have carried out GA based docking using Vlife MDS 4.0 software to identify the binding modes of synthesized derivatives required for the potential anti-inflammatory activity. The crystal structure of was downloaded from RCSB protein data bank (PDB ID: 1CX2).

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MATERIALS AND METHODS

Docking studies

Data preparation: The database of molecular docking study consisted of 1CX2 with 24 ligand molecules. Docking studies of the title compounds was done on Vlife MDS 4.0 using grid-based docking method for anti-inflammatory activity. The final C-chain of 1CX2 complex of cyclo-oxygenase inhibitor is selected as a biological target for carrying out the docking study of title compounds. The crystal structure of 1CX2 (Kurumbail *et al.*, 1996) was obtained from protein data bank, opened in MDS sheet, saved by removing water molecule and used further for docking purpose. The 2D structures of the compounds were built and then converted into the 3D with the help of Vlife MDS 4.0 software. The 3D structures were then energetically minimized up to the rms gradient of 0.01 using Merck Molecular Force Field (MMFF) (More *et al.*, 2012). By using cavity determination option of software, cavities of enzyme were determined. The cavities in the receptor were mapped to assign an appropriate active site, the basic feature used to map the cavities was the surface mapping of the receptor and identifying the geometric voids as well as scaling the void for its hydrophobic characteristics. Hence, all the cavities that are present in receptor are identified and ranked based on their size and hydrophobic surface area. Cavity No. 1 is selected for docking. The active site for docking was defined as all atoms within 5 Å radius. Using Biopredicta tool of software, open docking and then batch grid docking. Batch docking shows browsing of receptor, ligand (molecule) and the result generated was saved in output file. Molecules saved in output file as a docked ligand format with proper conformation and further used to check binding interactions. Result generated was saved as log file in output folder. For checking binding interaction, first receptor structure was opened in MDS followed by compound which was saved as ligand dock file. From tool option clicked on merge molecule so that compound and receptor is merged together. From biopredicta tool edited this complex and selected ligand and receptor structure to check their interactions.

RESULTS AND DISCUSSION

Docking study: Life MDS 4.0 was used for docking studies of the title compounds to ascertain anti-inflammatory activity and using cyclo-oxygenase as target obtained from PDB with code 1CX2 (Fig. 1a). This

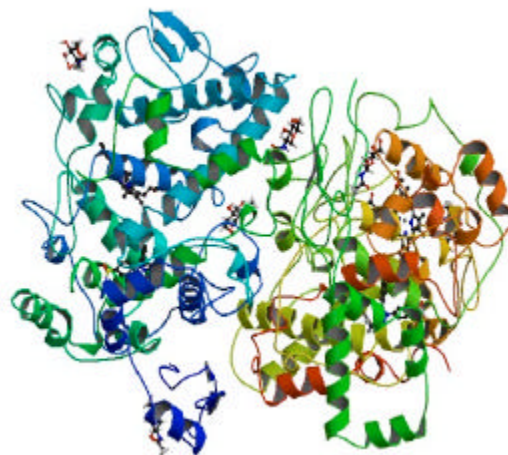


Fig. 1a: Cartoon representation of 1CX2

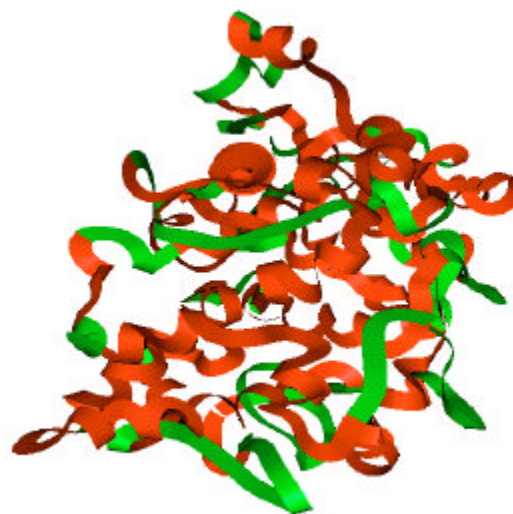


Fig. 1b: Ribbon representation of final C-chain of PDB code 1CX2

structure based drug design performed with cleaned PDB code that is final C-chain of 1CX2 (Fig. 1b). The docking of the title compounds yielded fitness scores ranging from -3.345192 to -4.569585 (Table 1). The docking study revealed that the title compounds have good interaction with final C-chain of 1CX2 and compounds 4C and 5C are potential candidates as a anti-inflammatory agent because of the highest negative dock score (-4.569585 of compounds 4E and -4.324429 of compound 5C). Compound 4A (Ball and Stick model) shows H-bond interaction in green colour with spacefill amino acid (LEU

Table 1: Docking score of compounds

Ligand	Substitution (Ar)	Dock score (Kcal mol ⁻¹)	Ligand	Substitution (Ar)	Dock score (Kcal mol ⁻¹)
3a	4-OH	-3.640003	3b	4-OCH ₃	-3.862023
3c	4-N(CH ₃) ₂	-3.602068	3d	4-NO ₂	-3.991639
3e	4-Cl	-4.279149	3f	4-F	-4.182506
3g	4-CH ₃	-3.646985	3h	3-OCH ₃ -4-OH	-4.321134
4a	4-OH	-3.625836	4b	4-OCH ₃	-3.759347
4c	4-N(CH ₃) ₂	-3.345192	4d	4-NO ₂	-3.700762
4e	4-Cl	-4.569585	4f	4-F	-3.628633
4g	4-CH ₃	-4.259096	4h	3-OCH ₃ -4-OH	-3.016540
5a	4-OH	-3.748603	5b	4-OCH ₃	-3.664001
5c	4-N(CH ₃) ₂	-4.324429	5d	4-NO ₂	-4.282435
5e	4-Cl	-3.929898	5f	4-F	-4.059721
5g	4-CH ₃	-3.812446	5h	3-OCH ₃ -4-OH	-3.963653
Std.	Diclofenac			-3.256343	

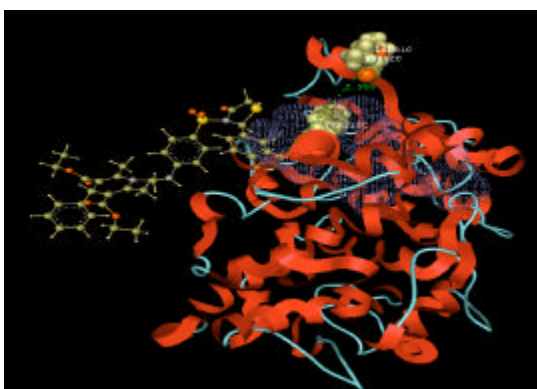


Fig. 2: H-bond interaction shown in green of 4A compound

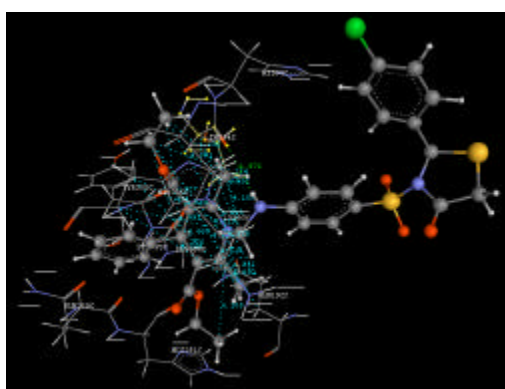


Fig. 4: H-bond interaction shown in green colour and hydrophobic interaction in cyan colour of 4E compound

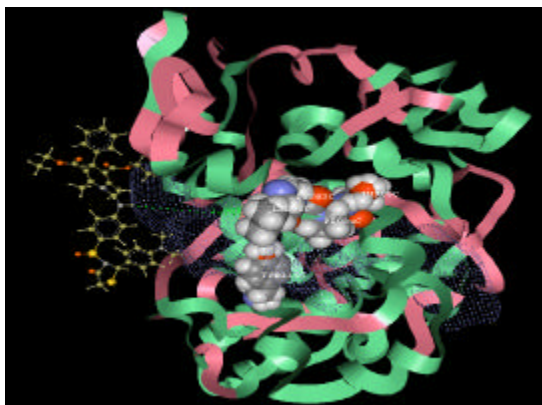


Fig. 3: H-bond interaction shown in green colour of 4C compound

81C) docked in dotted Surface cavity of 1CX2 with assorted representation of protein receptor (Fig. 2). Compound 4C (Ball and Stick model) shows H-bond interaction in green colour with space fill amino acid (LEU 82C) (Ball and Stick model) docked in dotted Surface cavity of 1CX2 with Ribbon representation of protein

receptor (Fig. 3). Compound 4E bind with final C-chain of 1CX2 by forming hydrogen bond interaction with amino acid residue shown in green colour with amino acid (TYR 94C) and hydrophobic interaction in cyan colour with amino acid (TYR 94C, LYS 97C, GLN 192C, SER 353C, GLY 354C, TYR 355C, HIS 356C) (Fig. 4). Compound 4F (Ball and Stick model) shows H-bond interaction in blue colour with space fill amino acid (THR 60C) and hydrophobic interaction in pink colour with space fill amino acids (THR 60C, ARG 61C, TYR 122C) docked in dotted Surface cavity of 1CX2 with Ribbon representation of protein receptor and stereo view of the same compound also generated (Fig. 5, 6). Compound 5C binds with final C-chain of 1CX2 by forming hydrogen bond interaction with amino acid (LEU 81C) in pink colour and hydrophobic interaction in cyan colour in hydrophobicity Surface cavity and assorted representation with amino acid (THR 85C, ASN 87C, THR 88C, TYR 91C, LYS 473C, LYS 511C) (Fig. 7, 8) and vanderwaal's interaction in green colour with amino acid (LEU 81C, TYR 115C, LEU 82C) (Fig. 9). The most active amino acids found to be TYR 94C and LEU 81C as they shows different types of interaction in the same

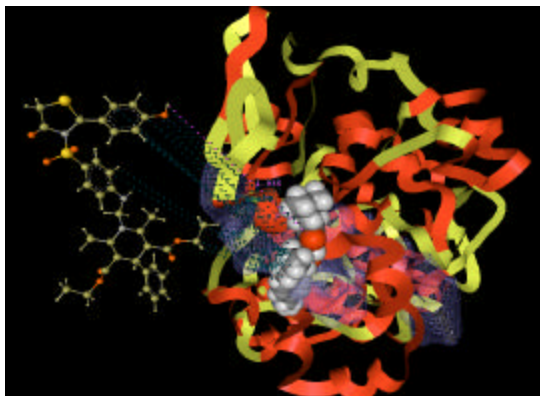


Fig. 5: H-bond interaction shown in blue colour and hydrophobic interaction in pink colour of 4F compound

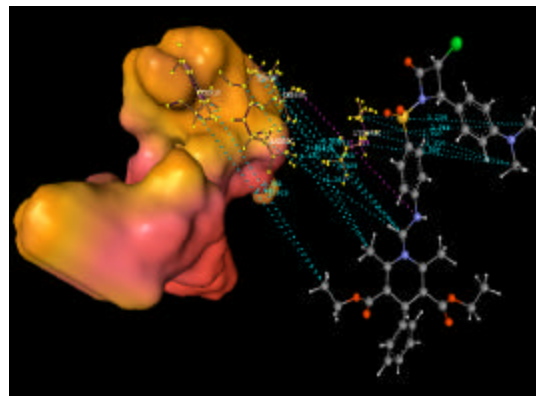


Fig. 8: H-bond interaction shown in pink colour and hydrophobic interaction in cyan colour of 5C compound

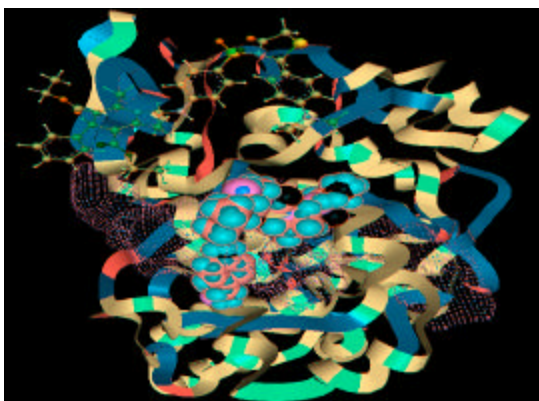


Fig. 6: Stereo view of 4F compound

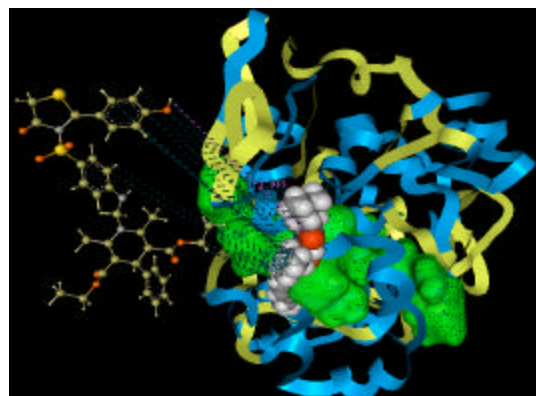


Fig. 9: H-bond interaction shown in pink colour and vanderwaal's interaction in green colour of 5C compound with Ribbon representation of protein receptor

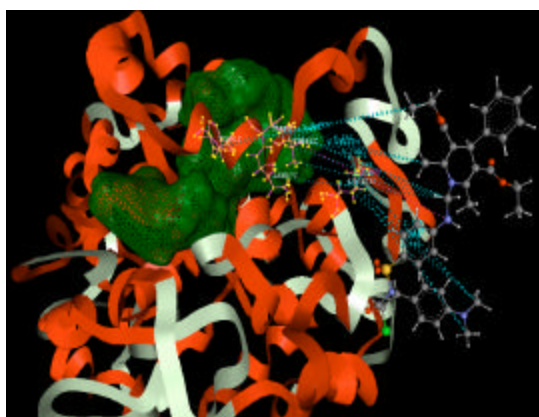


Fig. 7: H-bond interaction shown in pink colour and hydrophobic interaction in cyan colour of 5C compound

compound. Further these molecular docking studies will help us to proceed for the synthesis process of different derivatives as an anti-inflammatory agents mentioned in the docking studies and its 2D and 3D QSAR studies can also be performed.

CONCLUSION

The docking of novel series 1,4-dihydropyridine derivatives with final C-chain of 1CX2 and subsequent generation of good dock score of compounds reveals that anti-inflammatory activity is because of inhibition of final C-chain of 1CX2 which suggests that it will be helpful for designing of more potent anti-inflammatory agents. The

amino acid residues from COX-2 inhibitor like TYR 94C and LEU 81C has been actively participated in docking. Consequently this study may prove to be helpful in development and optimization of existing anti-inflammatory of this class of compounds.

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