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(Research article)

COMPUTER AIDED DOCKING STUDIES OF SOME NOVEL HETEROCYCLIC ANALOGUES OF NAPROXEN AS POTENT AND SAFER ANTI-INFLAMMATORY AGENTS.

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ABSTRACT

Naproxen sodium is being used for the treatment of pain and inflammation. But as all the NSAIDs are suffering from severe GI toxicities, Naproxen sodium is also not an exception to these toxicities due to its greater selectivity with COX-1 than COX-2. In the present work, the motto was to develop some novel 1, 3, 4-oxadiazole analogues of Naproxen, which have very good potency and greater selectivity with the COX-2 enzyme than the COX-1 enzyme with the help of fast flexible molecular docking studies in order to decrease the GI toxicity. For this purpose, we have designed ten new ligands. All the ligands showed greater COX-2 selectivity and very good potency than the standard Naproxen.

Key words: Naproxen, Molecular docking, COX-2, GI toxicities

INTRODUCTION

Drug design is a process which involves the identification of a compound that displays a biological profile and ends when the biological profile and chemical synthesis of the new chemical entity are optimized [1]. Drug designing is otherwise known as rational drug design, and it is a method of finding new medications based on the biological receptors and target molecules. It involves the designing of small molecules, which is complementary to the biological receptor to which they bind and interact to cause the pharmacological actions [2]. Rational Drug Design (RDD) also helps to facilitate and speedup the drug designing process, which involves the variety of methods to identify novel compounds. One such method is the docking of the drug molecule with the receptor (target) [3]. Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand-protein docking is to predict the predominant binding model(s) of a ligand with a protein of known three-dimensional structure [4].

In a simplified term, the inflammation process can be considered as an event of the immune response through which tissue damage occurs. The latter is accompanied by the release of several biochemical mediators such as histamine, bradykinin, platelet-activating factor, and a group of lipid materials known as leukotrienes (LTs) and prostaglandins (PGs) [5]. The pharmacological activity of NSAIDs is related to the suppression of prostaglandin biosynthesis from arachidonic acid by inhibiting the enzyme prostaglandin endoperoxidase, popularly known as cyclo-oxygenase (COX). It was discovered that COX exists in two isoforms, COX-1 and COX-2, which are regulated and expressed differently. COX-1 provides cytoprotection in the gastrointestinal tract (GIT), whereas inducible COX-2 selectively mediates inflammatory signals. Since most of the currently available NSAIDs in the market show greater selectivity for COX-1 than COX-2, chronic use of NSAIDs may elicit appreciable GI irritation, bleeding

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and ulceration. GI damage from NSAID is generally attributed to two factors [6].

- Local irritation by the direct contact of carboxylic acid (–COOH) moiety of NSAID with GI mucosal cells (topical effect).
- Decreased tissue prostaglandin production in tissues, which undermines the physiological role of cytoprotective prostaglandins in maintaining GI health and homoeostasis.

Naproxen sodium is one of the mostly used NSAID. But as all the NSAIDs are suffering from severe GI toxicities, Naproxen sodium is also not an exception to these toxicities due to its greater selectivity with COX-1 than COX-2 as mentioned above. In the present work, the motto was to develop some novel 1, 3, 4-oxadiazole analogues of Naproxen, which have greater selectivity with the COX-2 enzyme than the COX-1 enzyme with the help of fast flexible molecular docking studies.

MATERIALS AND METHODS

Retrieval of the target protein sequence

The structure homologues for COX-1 and COX-2 protein sequence query were retrieved from NCBI (National Center for Biotechnology Information). The sequences were converted into FASTA format. The FASTA format sequences were allowed into BLAST (Basic Local Alignment Search Tool) database to identify the PDB code of required protein. The protein structure files of *Cyclooxygenase-1* and Cyclooxygenase-*2* (PDB code: 1Q4G [7] and 6COX [8] respectively) were taken from Protein Data Bank (www.rcsb.org/pdb) and edited by removing the hetero atoms.

Prediction of binding site

CAST P (Computed Atlas of surface topography of Protein) server was used to cross check the active pockets on target protein molecules.

Three dimensional structures of inhibitors

The Chemical structures of inhibitors were designed, and the structure was analysed using Chem office 2004 software.

Molecular docking

Docking was done with the ARGUSLAB software (ArgusLab–www.arguslab.com/), in which the result is being obtained based on pose energy. Docking calculations attempt to place 'Ligands into Binding Sites.'. Before docking a molecule, first it is needed to define the atoms that make up the Ligand like drug, inhibitor, etc., and the Binding Site on the protein where the drug binds. The final results are based on the type of calculation we run such as Geometry optimization-search for 'Final Geometry' and Electronic spectra-search for 'Excited state properties.'

Structure visualization

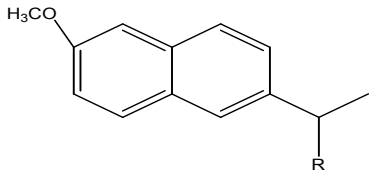
Pymol software was used to view the structure.

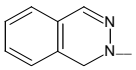
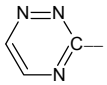
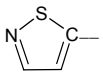
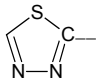
RESULTS AND DISCUSSION

Lead optimization

Various compounds were designed by replacing the carboxylic acid group present in the Naproxen with less acidic heterocyclics like phthalazine, triazine,

Table:1. Docking scores (kcal/mol) of newly designed lead compounds



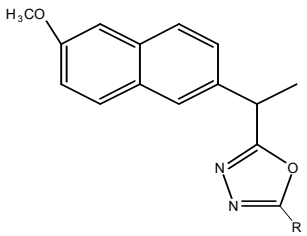
S.no	*R*	*Energy level (kcal/mol)*	*S.no*	*R*	*Energy level (kcal/mol)*
	*				
1.		-12.1416	6.		-11.309
2.		-10.9300	7.		-11.6623
3.		-11.4637	8.		-11.4655
4.		-11.2613	9.		-11.0074
5.		-11.2596	10.		-11.4964

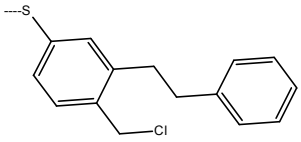
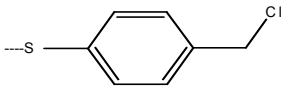
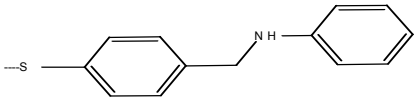
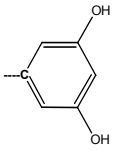
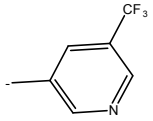
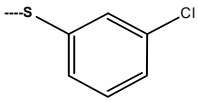
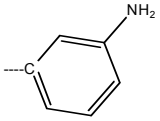
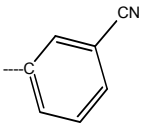
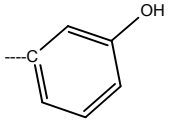
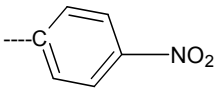
Where* ⟶ more potent compounds

1, 3, 4-oxadiazole, pyridazine, pyrole, pyrazole, imidazole, thiazole etc. using chemoffice2004 software and docking simulation was carried out to all the designed compounds against 6COX (COX-2 enzyme) With the help of arguslab program and the docking scores of each compound was analysed. Out of all the designed compunds, ten compounds showed very good interaction energies (tab.1.) even better than that of naproxen sodium which showed -10.5593 kcal/mol.

Among the above ten compounds, structure containing less acidic heterocycle like 1, 3, 4-oxadiazole nucleus showed highly negative interaction energy in molecular docking studies .The compound which showed highly negative energy was considered as potent compound. The most potent compound was selected as the lead on which we carried out structural modification in order to increase the binding ability. Structures of the newly designed ligands from the lead compounds were given in Tab.2.

Table.2.Structures of ligands designed from selected lead compound



S.No.	Ligand code	R
1.	Ligand 1	
2.	Ligand 2	
3.	Ligand 3	
4.	Ligand 4	
5.	Ligand 5	
6.	Ligand 6	
7.	Ligand 7	
8.	Ligand 8	
9.	Ligand 9	
10	Ligand 10	

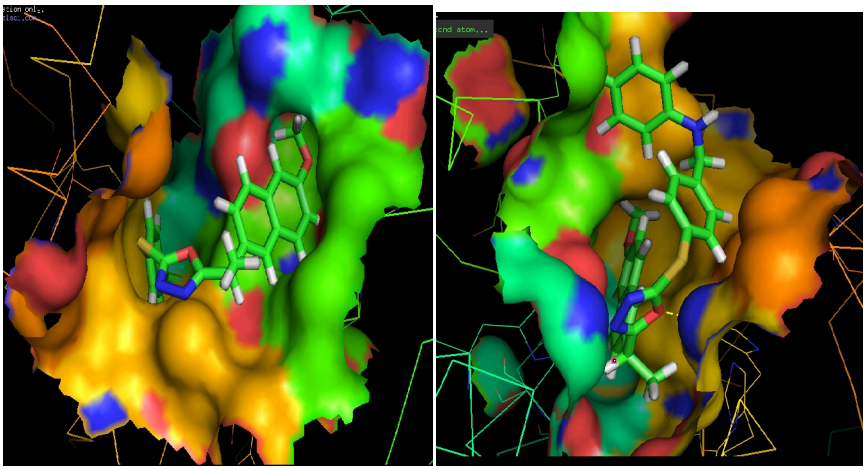
The binding ability of this newly designed ligands1-10 with COX-1 and COX-2 enzymes were determined with the help of molecular docking studies using arguslab program. The binding scores of designed ligands 1-10 with COX-1 and COX-2 enzymes ranging from -11.1201 to -14.6543 Kcal/mol, -16.519 to -12.2842 Kcal/mol and -12.1989 to -9.29692 Kcal/mol respectively (tab.3.). These data clearly indicate their potency as COX-2 inhibitors. All the designed ligands showed good interaction energy than the Naproxen which showed the following interaction energies -11.7146 Kcal/mol and -10.5593 Kcal/mol with COX-1 and COX-2 enzymes respectively. Especially ligands 2, 3, 5, 6 showed very good interaction energy with the COX-2 receptor.

Moreover, all the ligands showed very good ligand-receptor configuration. The binding modes of designed ligands were given in Fig.1. Naproxen (standard drug) shows the lot of void space in the active pocket region of COX-2 receptor. Due to that it showed only less negative interaction energy. But all the newly designed ligands properly fit into the active pocket of the COX-2 receptor. The docking images reveal that the 3D structures of the designed ligands have the ability to occupy properly into the active site. Hence they showed very good interaction energies with COX-2 receptor than the standard drug (naproxen).

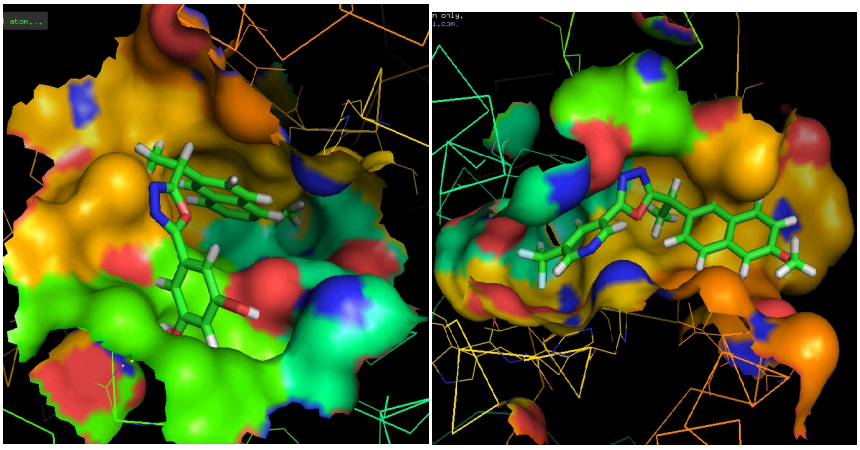
Table.3. Docking scores (kcal/mol) of various newly designed ligands (1-10) with COX-1(1Q4G) and COX-2 (6COX) enzymes.

S.No.	Ligand code	Dock score (kcal/mol) with COX-1 (1Q4G)	Dock score (kcal/mol) with COX-2 (6COX)
1	Naproxen(std)	-11.7146	-10.5593
2	Ligand 1	-11.6543	-12.4319
3	**Ligand 2**	**-14.581**	**-15.027**
4	**Ligand 3**	**-12.3255**	**-14.2553**
5	Ligand 4	-11.9954	-12.6156
6	**Ligand 5**	**-11.1201**	**-16.519**
7	**Ligand 6**	**-13.8367**	**-14.7816**
8	Ligand 7	-11.5404	-12.5047
9	Ligand 8	-11.8019	-13.0718
10	Ligand 9	-12.9293	-13.3909
11	Ligand 10	-11.9816	-12.3916

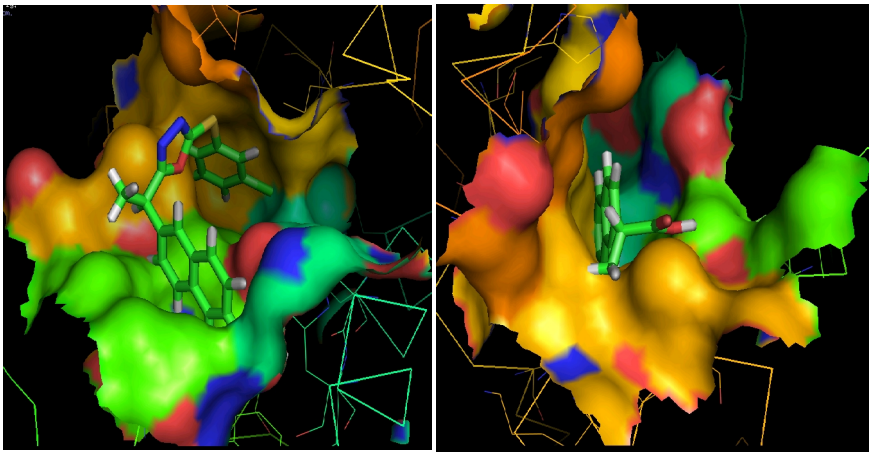
Fig. 1.Binding modes of newly designed ligands with COX-2 (6COX) enzymes.



Ligand 2 **Ligand 3**



Ligand 4 **Ligand 5**



Ligand 6 **Naproxen(std)**

CONCLUSION

The Protein-Ligand interaction plays a significant role in structural based drug designing. In the present work, we have taken COX-2 (6COX) which is an essential target for novel anti-inflammatory drug design than the COX-1(1Q4G). When the receptors (6COX and 1Q4G) were docked with Naproxen, the energy value obtained was -10.5593 and -11.7146 kcal/mol respectively. When the designed ligands 1-10 were docked against the same receptor, the energy values are negatively greater than the standard. So it can be concluded that the designed compounds can be a potent anti-inflammatory agent than the standard. Moreover, the standard naproxen showed greater COX-1 selectivity than the COX-2. But the designed ligands1-10 showed greater COX-2 selectivity than COX-1. Hence it can be said that all the newly designed ligands may be safer anti-inflammatory agents than the standard. In future research work the ADME/T (Absorption, Distribution, Metabolism, Excretion / Toxicity) properties of these compounds can be calculated using the commercial ADME/T tools available thus reducing the time and cost in the drug discovery process. Further we planned to synthesis these ligands1-10 and screen for their *in-vivo* anti-inflammatory activity.

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