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# Structure Based Design and In-Silico Molecular Docking Analysis of Some Novel Benzimidazoles

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**Abstract:** In the present investigation novel substituted benzimidazoles are designed and docked in to active site of Cyclooxygenase II. Ligands are designed based on the structure of receptor, COX-II and well known NSAID Celecoxib. Further In- Silico docking analysis of designed ligands are performed to predict binding mode, orientations and affinity. Ligands number 38, 39, 40, 41, 42, 43 and 44 are having less binding energy in kj/mole and said to possess more affinity for receptor than other molecules and celecoxib.

**Key words:** Structure based design, Benzimidazole, Molecular docking, COX-II

## 1. Introduction

Benzimidazole[1, 2] derivatives possessing anti-inflammatory and analgesic have been reported in some literature. Apart from the above-mentioned activities some interesting efficacy of antiallergic[3], antiproliferative, [4, 5] antitumour,[6] antiHIV,[7] and antibacterial[8] activities on benzimidazole derivatives has been reported. Due to broad spectrum of activities reported in the literature so far, structure based design for newer analgesic anti-inflammatory agents are described in the present investigation.

## 2. Design of benzimidazole based selective COX-II inhibitors

Cyclooxygenases (EC 1.14.99.1) are enzymes that take part in a complex biosynthetic cascade that results in the conversion of polyunsaturated fatty acids to prostaglandins and thromboxane(s)[9]. Their main role is to catalyze the transformation of arachidonic acid into the intermediate prostaglandin H2, which is the procursor of a variety of prostanoids with diverse and potent biological actions10. Cyclooxygenases have two main isoforms that are called COX-1 and COX-2. COX-1 is responsible for the synthesis of prostaglandin and thromboxane in many types of cells, including the gastro-intestinal tract and blood platelets. COX-2 plays a major role in prostaglandin biosynthesis in inflammatory cells and in the central nervous system. Prostaglandin synthesis in these sites is a key factor in the development of inflammation and hyperalgesia11. COX-2 inhibitors have analgesic and anti-inflammatory activity by blocking the transformation of arachidonic acid into prostaglandin H2 selectively[12]. One of the keys to developing COX-2 selective drugs is the larger active site of COX-2 which makes it possible to make molecules too large to fit into the COX-1 active site but still able to fit the COX-2. The larger active site of COX-2 is partly due

to a polar hydrophilic side pocket that forms because of substitution of Ile523, His513, and Ile434 in COX-1 by Val 523, Arg 513, and Val434 in COX-2. Val523 is less bulky than Ile523 which increases the volume of the active site. Substitution of Ile434 for Val434 allows the side chain of Phe518 to move back and make some extra space. This side pocket allows for interactions with Arg513 which is a replacement for His513 of COX-1. Arg513 is thought to be a key residue for diaryl heterocycle inhibitors such as the coxibs. The side chain of Leu384, at the top of the receptor channel, is oriented into the active site of COX-1 but in COX-2 it is oriented away from the active site and makes more space in the apex of the binding site. The bulky sulfonamide group in COX-2 inhibitors such as celecoxib and rofecoxib prevent the molecule from entering the COX-1 channel[13]. In the present investigation we reported design of some novel benzimidazoles which are same looking as that of sulphonamide NSAIDs. **Fig.1**

## 3.0. Materials and methods

### 3.1. Ligand structure preparation

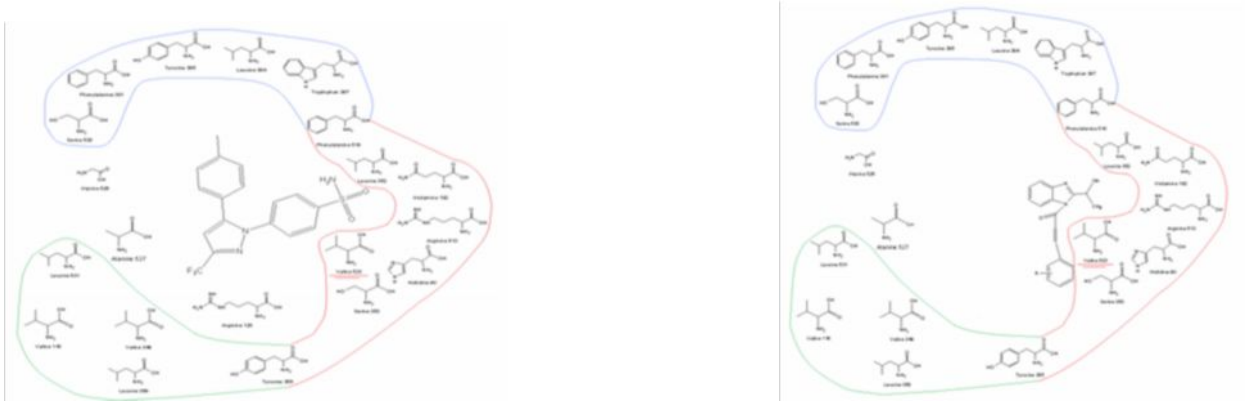
All the compounds were constructed using software Chem Draw Ultra, chemical structure drawing standard, Cambridge Soft Corporation, USA. Version-8.0 April 23, 2003. It is a Chem Tech tool used for the preparation or drawing of ligand molecules. It is used to apply correction to the structures, generate variations on structure and optimize the structure.

### 3.2. Protein structure preparation

The available PDB protein complex structure is downloaded from internet. The PDB complex structure can be corrected using molecular modeling environment Molecular Design Suit. The protein is also optimized using Merck Molecular Force Field, embedded in Molecular Design Suite V 3.50, designed to ensure chemical correctness and optimize protein structure. The software is capable to simulating the receptor that is deleting the solvent molecules from the crystal structure of the receptor.

### 3.3. Molecular docking

To pre-asses the analgesic and anti-inflammatory behavior of designed ligands on a structural basis, automated docking studies were carried out and scoring functions, their binding affinities and orientation of these compounds at the active site of the COX- II enzyme were found out. The protein-ligand complex was constructed based on the X-ray structure COX-II. Each compound built using Chem Draw Ultra v.8.0 minimized using the Merck Molecular Force Field. Keeping program parameters to their default values, the docking was performed using Molecular Design Suite (MDS) into the 3D model of the catalytic site of COX-II enzyme. Genetic algorithm implemented in MDS has been successfully employed to dock inhibitors into the catalytic site of the COX-II and to well correlate the obtained binding score with inhibitory activities of compounds. We carried out comparative docking experiments of designed compounds with known non steroidal anti-inflammatory agent such as celecoxib. Obtained results were evaluated in terms of binding score in to the catalytic site of COX-II. (**Fig.1)** During the docking process the system search of conformational, orientational and positional space of the docked ligand and eliminating the unwanted conformations using the scoring, this is followed by energy optimization. For our studies, the structure available on PDB, using MMFF then is optimized. Batch docking in biopredicta tool embedded in MDS of designed ligands is performed with COX-II.



(A) (B)

**Fig. 1.** Design of novel COX- II inhibitor based on Sulphonamide Coxibs

A. Designed molecule in to active site
B. Sulphonamide coxib, celecoxib in active site

This software provides facility of batchdocking of the optimized ligand molecules with the simulated receptor. All the ligands are selectively docked against cavity#1 that is the active site cavity. Each molecule takes nearly half an hour for the completion of docking. Molecules which show minimum dock score are said by definition are having more affinity for COX-II receptor. Dock score are shown in Table.1 and Table.2.

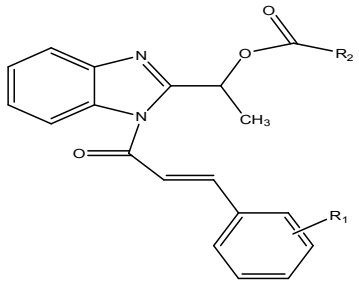



**Table.1.** In-Silico docking Analysis of 1-(1-(- (-3-Un/ Substituted -alipahatic/ aromatic acryloyl)-1H-benzoimidazol-2-yl)ethyl Un/Substituted benzoate/ metahnoate in to active site of COX-II

| Ligand | R1 | R2 | DOCK SCORE | Ligand | R1 | R2 | Energy |
|---|---|---|---|---|---|---|---|
| 1 | -H | -C6H5 | -3.02 | 20 | -3,Cl | -C6H5 | -5.04 |
| 2 | -H | -2,Cl C6H4 | -2.02 | 21 | -3,Cl | -2, C6H4 | -3.89 |
| 3 | -H | -3,Cl C6H4 | -3.43 | 22 | -3,Cl | -3, C6H4 | -5.21 |
| 4 | -H | -4, Cl C6H4 | -3.41 | 23 | -3,Cl | -4, C6H4 | -5.82 |
| 5 | -H | -2, NO2C6H4 | -3.69 | 24 | -3,Cl | -2, C6H4 | -4.10 |
| 6 | -H | -2,OH C6H4 | -4.03 | 25 | -3,Cl | -2, C6H4 | -4.85 |
| 8 | -H | -4,OH C6H4 | -3.00 | 26 | -3,Cl | -4,NH2 6H4 | -4.64 |
| 9 | -H | -CH3 | -6.82 | 27 | -3,Cl | -CH3 | -4.73 |
| 10 | -H | -H | -8.32 | 28 | -3,Cl | -H | -3.75 |
| 11 | -2,ClC6H4 | C3H7 | -4.33 | 29 | -4,Cl | -C6H5 | -6.32 |
| 12 | -2, ClC6H4 | -2, ClC6H4 | -5.76 | 30 | -4,Cl | -2,Cl C6H4 | -7.77 |
| 13 | -2, ClC6H4 | -3, ClC6H4 | -4.23 | 31 | -4,Cl | -3, Cl C6H4 | -7.49 |
| 14 | -2, ClC6H4 | -4, ClC6H4 | -3.31 | 32 | -4,Cl | -4,Cl C6H4 | -8.15 |
| 15 | -2, ClC6H4 | -2,NO2 C6H4 | -3.27 | 33 | -4,Cl | -2,NO2 C6H4 | -5.52 |
| 16 | -2, ClC6H4 | -2,OH C6H4 | -4.02 | 34 | -4,Cl | -2,OH C6H4 | -4.92 |
| 17 | -2, ClC6H4 | -2,NH2 C6H4 | -6.24 | 35 | -4,Cl | -CH3 | -3.97 |
| 18 | -2, ClC6H4 | -4,NH2 C6H4 | -4.83 | 36 | -4,Cl | -H | -4.08 |
| 19 | 2, ClC6H4 | -CH3 | -2.99 | 37 | -4,Cl | -2, NH2 C6H4 | -5.38 |

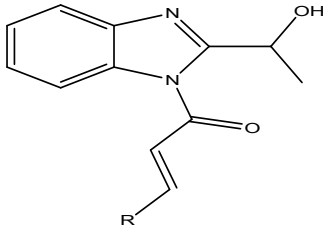



**Table.2.**1. In-Silico docking analysis of some-(2-(1-hydroxyethyl)-1H- (Un/Substituted aliphatic/ aromatic) benzimidazole -1-yl)-3-phenylprop-2-en-1-ones

| Ligand | R | *Dock Score |
|---|---|---|
| 38 | -C6H5 | -14.23 |
| 39 | -2,Cl,C6H4 | -12.34. |
| 40 | -3,Cl,C6H4 | -10.48 |
| 41 | -4,Cl,C6H4 | -10.9 |
| 42 | -2,OH,C6H4 | -12.58 |
| 43 | -4,OH,C6H4 | -10.84 |
| 44 | -2,NO2,C6H4 | -12.20 |
| 45 | -CH3 | -4.24 |
| 46 | -H | -4.32 |
| 47 | -C3H7 | -3.43 |
| Celecoxib | -- | -9.32 |

*** Dock Score represent binding energy in kj/moles**

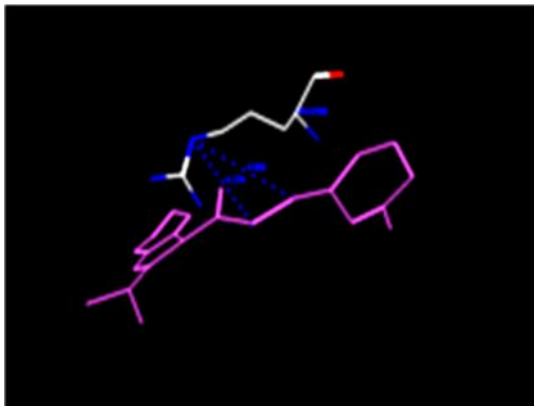


**Fig. 2.a** Molecule no. 39 in to the active site of COX-II showing charge interactions between double bond of ligand and ARG at 376B

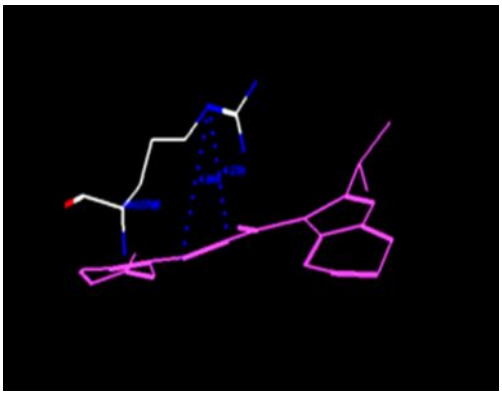


**Fig.2.b** Molecule 40 in active site it has dock score of -10.46, showing Charge interactions.

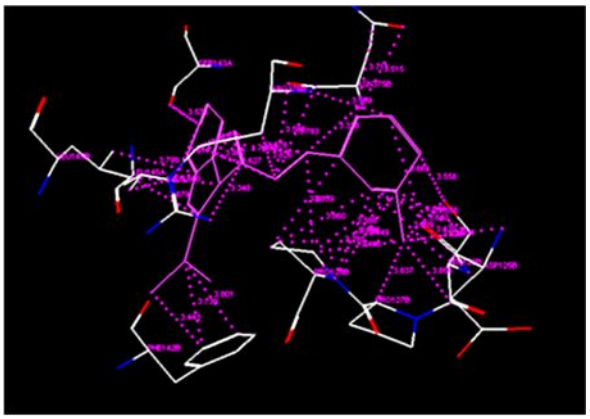


**Fig. 2.c** Molecule no.39 in the active site showing cavity vander-walls interactions.

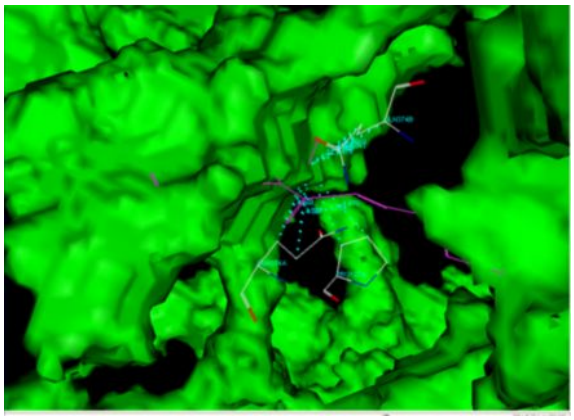


**Fig. 2.d.** Molecule no. 38 in active site of the It has score of -14.23

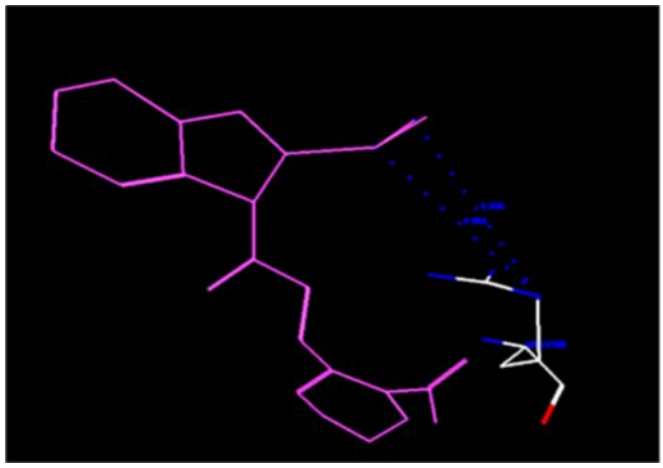


**Fig. 2.e** Molecule no. 44 in active site showing charge interactions between between hydroxyl group and ARG 376.

**Fig.2. Poses, orientation and interactions of some novel benzimidazoles in the active site of COX-II**

## 4. Result and Discussion

The intermolecular interactions in between the ligand and the protein (receptor) was investigated using the MDS, version-3.5., the 3-dimensional structure and the information about it was taken from PDB. It is processed by deleting the solvent molecule as well as correcting the structure with respect to bonds and the H- atoms. The benzimidazole derivatives were docked into active site of COX-2 receptor. A correlation was calculated by energy of binding calculated by MDS.

## 5. Validation of the docking protocol

The prediction of the potency or affinity of the ligand to the receptor done by considering some parameters such as dock score, the energy of binding of molecules with the COX-receptor, vander-walls interactions, hydrophobic interactions and rare charge interactions. The more the negative value of the energy of binding the better is affinity of the molecule to the receptor. The more the vander-walls interactions shows that the ligand structure is having more number of bulky groups due to which valder-walls interactions can be formed. If the hydrophobic interactions are more it shows that the ligand is having groups that can participate in the hydrophobic interactions. If the charge interactions are presents it helps finding more appropriate binding and so shows greater affinity to the receptor, contributing more potency.

## 6. Conclusion

The docking model for the substituted benzimidazole derivatives with the COX-2 receptor has been developed in the paper. To the best of literature survey, this is the 1st report of the molecular modeling studies of these molecules with the COX-2 receptor. MDS, version 3.5, an automated docking program, successfully reproduce the binding mode of the crystal structure of the COX-2 inhibitors. The docking

simulation suggested that the modifications in the series that results in better binding potential. The vander-walls, hydrophobic and charge interactions are responsible for forming the stable compound of the ligands with ligands with receptor.

From the **Table.1** and **Table.2.** Ligands 12, 13, 14, 38-44 are do possess minimum dock score i.e. minimum binding energy in kilo joules per mole i.e these molecule have more affinity for active site of COX-II enzymes. Clearly, molecules with ester of bulky acids function at 2 position of benzimidazoles are having less affinity for the receptor. Whereas molecules which possesses alcoholic with less bulky function 38-44 are said to have more affinity for COX-II and can be used as analgesic and anti-inflammatory agents after synthesis.

## References


1. Labanauuskas, L.; Brukstus, A .; Udrenaite, E.; Gaidelis, P.; Bucinskaite, V. Chemija 2003, 14, 49;
   Labanauuskas, L.; Brukstus, A.; Udrenaite, E.; Gaidelis, P.; Bucinskaite,V. Chem. Abstr. 2003, 139, 180016.
2. Kataev, V. A.; Khaliullin, A. N., Nasyrov, Kh. M.; Gailyunas, I. A. Russ. Patent RU 2215002, Chem. Abstr. 2004, 141, 7110.
3. Nakano, H.; Inoue, T.; Kawasaki, N.; Miyataka, H.; Matsumoto, H.; Taguchi, T.; Inagaki, N.; Nagai, H.;Satoh, T. Bioorg. Med. Chem. 2000, 8, 373.
4. Hong, S.-Y.; Chung, K.-H.; You, H.-J.; Choi, I. H.; Chae, M. J.; Han, J.-Y.; Jung, O.-K.; Kang, S.-J.; Ryu, C.-K. Bioorg. Med. Chem. Lett. 2004, 14, 3563.
5. Garuti, L.; Roberti, M.; Pizzirani, D.; Pession, A.; Leoncini, E.; Cenci, V.; Hrelia, S. IL Farmaco 2004, 59, 663.
6. White, A. W.; Curtin, N. J.; Eastman, B. W.; Golding, B. T.; Hostomsky, Z.; Kyle, S.; Li, J.; Maegley, K. A.; Skalitzky, D. J.; Webber, S. E.; Yu, X.-H.; Griffin, R. J. Bioorg. Med. Chem. Lett. 2004, 14, 2433.
7. Novelli, F.; Tasso, B.; Sparatore, F.; Sparatore, A. Farmaco 1997, 52, 499; Novelli, F.; Tasso, B.; Sparatore, F.; Sparatore, A. Chem. Abstr. 1998, 128, 238983j.
8. Kazimierczuk, Z.; Andrzejewska, M.; Kaustova, J.; Klimesova, V. Eur. J. Med. Chem. 2005, 40, 203.
9. Marnett, L. J. and A. S. Kalgutkar (1999). "Cyclooxygenase 2 inhibitors: discovery, selectivity and the future." **Trends in Pharmacological Sciences** 20(11): 465-469. doi:10.1016/S0165-6147(99)01385-1
10. Mardini, I. A. and G. A. FitzGerald (2001). "Selective Inhibitors of Cyclooxygenase-2: A Growing Class of Anti-Inflammatory Drugs." Mol. Interv. 1(1): 30-38.
11. Marnett, L. J. and A. S. Kalgutkar (1998). "Design of selective inhibitors of cyclooxygenase-2 as nonulcerogenic anti-inflammatory agents." Current Opinion in Chemical Biology 2(4): 482-490. doi:10.1016/S1367-5931(98)80124-5
12. King, F. D., Ed. (2002). **Medicinal chemistry Principles and practice**. Cambridge, The royal Society of Chemistry.
13. Llorens, O., J. J. Perez, et al. (1999). "Structural basis of the dynamic mechanism of ligand binding to cyclooxygenase." **Bio. & Med. Chem. Let.** 9(19): 2779-2784. doi:10.1016/S0960- 894X(99)00481-3.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