

# In Silico Design of New Selective Cyclooxygenase-2 (COX-2) Inhibitors

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Prostaglandin Hormone Synthases (COX-1 and COX-2) are enzymes that produce prostaglandins. Prostaglandins have several physiological functions, such as protecting the stomach from the acid-pepsin secretion and keeping the osmotic differences responsible for the urine concentration in the kidney. However, in inflammatory situations, prostaglandins are responsible for fever, pain, swelling, and other inflammatory signs. COX-1 is found mainly in the gastrointestinal lining, and COX-2 at sites of inflammation. Non-steroidal anti-inflammatory drugs (NSAIDs) are compounds that inhibit COX. Non-selective inhibitors decrease the activity of both isoforms. The present work aims to design new selective COX-2 inhibitors employing an in silico approach.

First, we developed the 3D-model structures of COX-1 and COX-2 using homology modeling method. To achieve this goal, the amino acid sequences of COXs taken from the NCBI website were submitted to the SWISS-MODEL server (Automated Comparative Protein Modeling Server). The crystal structures of (1Q4G and 3NT1) were obtained as suitable templates for COX-1 and COX-2 respectively with sequence identities of 93.85% and 88.2%.

Two separate 10 ns molecular dynamics simulations (performed using the GROMACS simulation package [1]) refined the homology modeled COX structures under physiological conditions. The GROMOS 96 force field was chosen for COX simulations, while the water molecules were simulated using SPC216 model. Equilibration was confirmed via analysis of RMSD plots and gyration radiuses.

In order to find suitable lead compounds for rational drug design, we took 35 previously introduced selective COX-2 inhibitors, drew them by GaussView and optimized by Gaussian 03. These drugs were docked then into COX-1 and COX-2 via AutoDock Vina. After performing nine docking iterations for each ligand, averaged free energy of bindings were calculated and used to estimate selectivity indexes (ratio of  $\Delta G_b$  for COX-2 to  $\Delta G_b$  for COX-1). On this basis, 6 compounds with higher selectivity indexes were chosen as lead compounds. Inspiring from the shape and structure of these compounds, we designed three groups of compounds (each having 24 members) with triazole, pyrazole and imidazole scaffolds. After structure optimization, these new compounds were docked to COX enzymes and again selectivity indexes were obtained. Finally, based on docking results, considering Lipinski's rule of five and ADME properties, some compounds were introduced as new candidates for COX-2 selective inhibitors.

## References

1. B. Hess *et. al* : *J. Chem. Theor. Comp.* (2008) 4, 435–447.
2. O. Trott *et. al* : *J. Comput. Chem.* (2010) 31, 455-461.