Demonstration of Interaction between Celecoxib and Sulindac Sulfide with COX-2 Using Docking Approach

Nikhilesh V. Alahari and Dr. Yaguang Xi

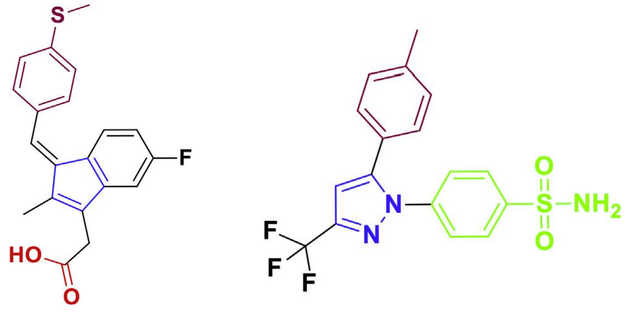
Department of Genetics, LSUHSC School of Medicine, New Orleans

Introduction

Cyclooxygenase-2 (COX-2) is a very important enzyme in the synthesis of prostaglandin. The enzyme promotes carcinogenesis and is linked to gastric cancer. COX-2 is the inducible form of cyclooxygenase and it promotes the conversions of arachidonic acid into prostaglandins. The enzyme is expressed by inflammatory cells. Not only is it responsible for the synthesis of prostaglandins, but it is also responsible for the synthesis of thromboxanes. Anti-inflammatory drugs can inhibit COX-2's processes. Sulindac Sulfide is a nonsteroidal anti-inflammatory drug (NSAID). It is most often used as treatment against inflammatory infections through the inhibition of the COX-2 enzyme. The inhibitory effect Sulindac Sulfide has on COX-2 can be very useful because an upregulation of COX-2 could potentially spark tumor growth. Another NSAID, Celecoxib, has a very similar effect and mechanism on the COX-2 enzyme and tumors. Celecoxib suppresses and inhibits prostaglandin. Molecular docking is the mechanism of observing how certain molecules bind to one another. Through molecular docking, it is clear to see the precise location on the molecules where they attach to one another. Molecular docking can show the overall efficiency and strength of certain molecular bonds. There are numerous docking softwares that are available online, but they all have different advantages and drawbacks. AutoDock Vina is one docking software that has provided some of the best results. Docking methods have been used to observe the interaction between Celecoxib and COX-2, and Sulindac Sulfide and COX-2. It is shown that COX-2 is linked to tumor growth, but both Celecoxib and Sulindac Sulfide act as inhibitors against it. The two drugs act very similarly on COX-2, inhibiting the synthesis of prostaglandins, which COX-2 is responsible for. Furthermore, Clinical trials with celecoxib have shown that it can also greatly reduce the effect of rheumatoid arthritis and osteoarthritis. My goal was that through AutoDock Vina, to observe and dock the binding of Celecoxib and Sulindac Sulfide with COX-2.

Methods

AutoDock Vina was chosen for this study. Along with the main AutoDock Vina software, a few other programs were downloaded. These were PyMOL, Raccoon, and AutoDockTools. PyMOL is a molecule viewing software that enables us to convert molecules into different formats. Raccoon is a virtual screening software. AutoDockTools is a program that we conduct the actual docking in. The pdb files for COX-2, Celecoxib, and Sulindac Sulfide were collected. Sulindac Sulfide did not have a readily available pdb file, so the existing Sulindac Sulfide file was converted into pdb format using PyMOL. Next, the pdb file of the first drug, Celecoxib, was uploaded into AutoDockTools. Then, in AutoDockTools, This pdb file was saved as a PDBQT file. After that, the COX-2 pdb file was uploaded into AutoDockTools. Next, a configuration file that defined the docking parameters and specifies the PDBQT files for the drug and protein was generated Then, the software was ran to dock the two molecules with one another. After that, visualization and illustration of the data for analysis were attempted. This method was repeated with Sulindac Sulfide instead of Celecoxib.



Chemical Structures of Sulindac Sulfide and Celecoxib

Celecoxib and COX-2

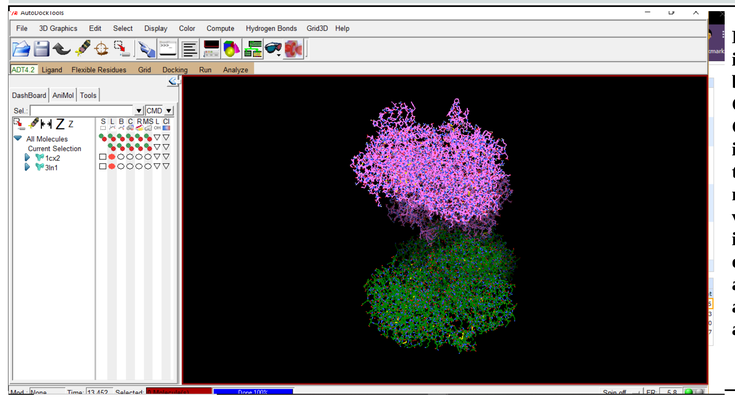


Figure 1 The interaction between Celecoxib and COX-2. it is evident that both molecules are very large and interact with one another at an adjacent angle.

Sulindac Sulfide and COX-2

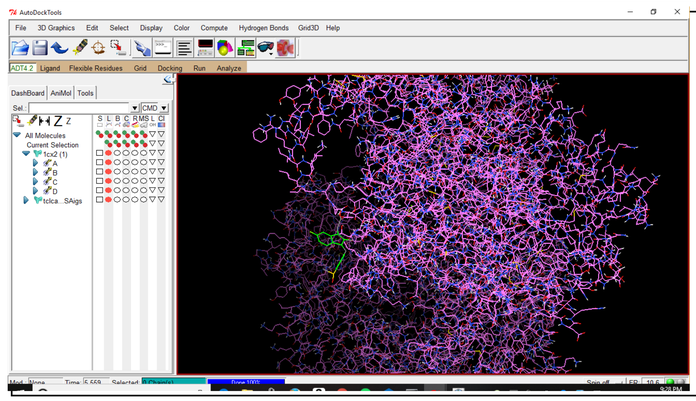


Figure 2. The interaction between Sulindac Sulfide and COX-2. It is evident that Sulindac Sulfide is a much smaller molecule than COX-2, and it binds to COX-2 at a single point.

Sulindac Sulfide COX-2 (cont.)

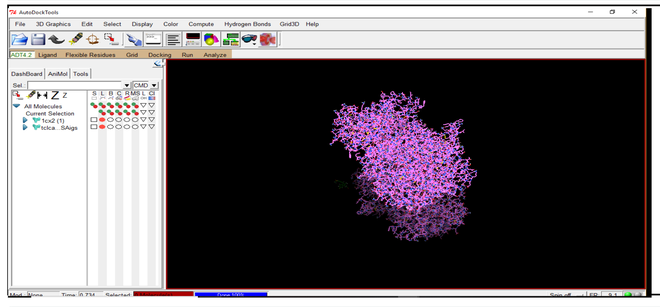


Figure 3. The interaction between Sulindac Sulfide and COX-2 from a different angle. It is evident that COX-2 in this situation has somewhat of an adjacent connection to Sulindac Sulfide.

References

1) Siah et al; Chemico-biological interactions, 234 (2015) 290-296
2) Maldonado-Rojas et al., J of Molecular Graphics and Modeling , 30 (2015) 157-166.

AutoDock Vina Homepage

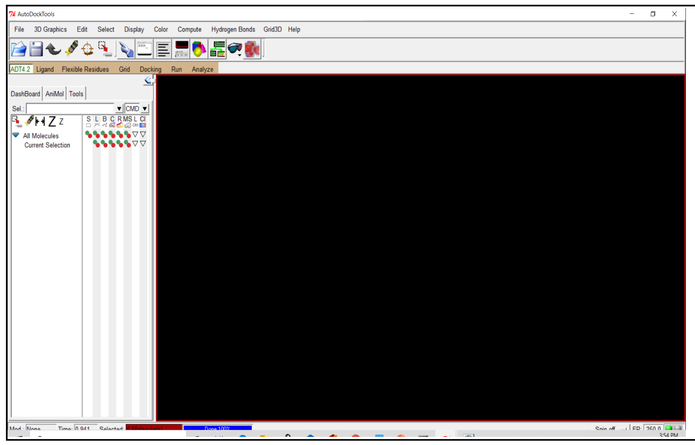


Figure 4. The homepage of the AutoDockTools program. The model and visualization of the molecular docking between two molecules is shown on a window like this one.

Celecoxib with COX-2 (Rojas et al, 2015)

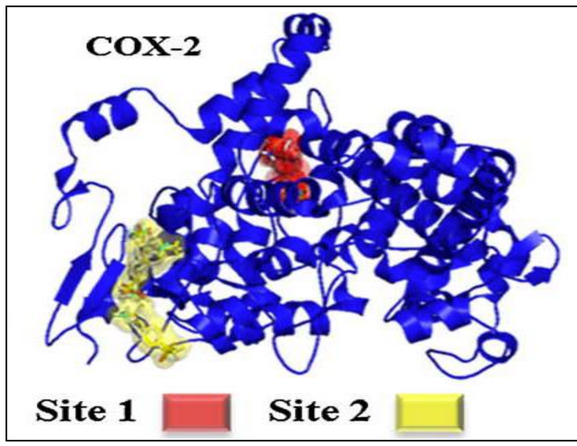


Figure 5. A clear and complete model of the docking between Celecoxib and COX-2. It is evident from the figure that Celecoxib binds to COX-2 at more than one point, unlike Sulindac Sulfide. This shows how Celecoxib can have a much larger effect on COX-2 as compared to Sulindac Sulfide due to its ability to bind at multiple locations. Celecoxib is also a large molecule, which gives it more opportunities to bind to COX-2. (Reference 2)

Conclusions

.

1) **Docking approaches predict the binding pattern of drugs with target proteins.**
2) **Newly discovered drugs function can be predicted based on the location of binding**
3) **The implications of these interactions can help inhibit and prevent tumor growth, finding a plausible treatment to cancer.**

This research project was supported through the LSU Health Sciences Center, School of Medicine.