CALIFORNIA STATE SCIENCE FAIR
2010 PROJECT SUMMARY

Name(s)
Tiffany Chien

Project Number
S0502

Project Title
Modifying TZD Drug to Improve Function in Body

Abstract

Objectives/Goals
This study investigates the particular interaction between the current TZD drugs and its protein active site to help propose more efficacious analogs of this drug. Computational experiments will primarily analyze the drug's stereocenter, which will further examine the importance of chirality in a drug's metabolism in the human body.

Methods/Materials
I first found the crystal structures of some known TZD drugs: trogliazone and rosigliatzone on the RCSB Protein Data Bank. I created the drug derivatives on Gaussview and docked those drugs with Fred Recepter with the known crystal structure. After determining the active site, I determined which drug should be the scaffold for building new drug analogs. I used this pharmacophore to construct confermers on Gauss View, which were also docked into the active site. The scores after the docking procedure proved which analogs were the more successful binding candidates.

Results
VIDA visualization aid helped identify which amino acids were interacting with the protein in the active site. I noticed potential hydrogen bonding or electron affinity interactions and began constructing conformers with stronger, more electronegative tails. I also tested how the new drug would interact if a functional group were to attach. I resolved that the oxygen replacement was the most promising modification. To further my research, I also looked into drug chirality, a prominent issue that pharmaceutical chemists have to face reguarly. I analyzed how each enantiomer of rosiglitazone would bind to the binding site, and as predicted, one of the enantiomers did not interact at all with the protein, which proved that enantiomers are distinct entities of the same drug.

Conclusions/Discussion
This drug design project focused on analyzing how certain components of a molecule interacted with its corresponding active site. I built the active site using the crystal structures given from the PDB website, and I docked my molecules into that structure. I created numerous analogs, and compared the docking scores of each one to propose the most successful modification. The oxygen I added to the aromatic ring proved to be the most useful in picking up another interaction with a neighboring amino acid, and thus it received the best score. The more negative the value, the better the docking.

Summary Statement
This study investigates the particular interaction between the current TZD drugs and its protein active site to help propose more efficacious analogs of this drug.

Help Received
Used Software and Computer at UC Davis under the guidance of Dr. Dean Tantillo and two of his graduate students.