CALIFORNIA STATE SCIENCE FAIR
2010 PROJECT SUMMARY

Name(s)
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Project Number
J0414

Project Title
Effects of 3-Membered Heterocycle-Derived dTTP Analogs on the Inhibition of Nucleic Acid Polymerases Using Docking

Abstract

Objectives/Goals
The objective was to determine the inhibitory effects of novel three-membered heterocyclic compound-derived analogs on several nucleic acid polymerases in silico using molecular docking.

Methods/Materials
Protein files of HIV Reverse Transcriptase, HCV NS5B Polymerase, and DNA Polymerase Kappa were imported from the Protein Data Bank and modified for the docking procedure with ArgusLab and Maestro. Ligands were created and prepared for the docking procedure using ArgusLab and LigPrep. Glide performed grid generation and the docking process and a total of 327 docking calculations in Extra Precision (XP) Mode were made. Inhibition was measured by the binding energy of the best ligand pose, determined by EModel, and measured in kcal/mol. The following materials were used: Protein Data Bank (RSCB); Calculation of Molecular Properties and Drug-likeness (Molinspiration); Online SMILES Translator and Structure File Generator (NCI/CADD Group); ArgusLab (Planaria Software); Symyx Draw 3.2 (Symyx); Maestro (Schrödinger); LigPrep (Schrödinger); Protein Preparation Wizard (Schrödinger); Prime (Schrödinger); Glide (Schrödinger)

Results
Several potential inhibitors have been identified through this experiment: for DNA polymerase kappa, Ligand 102 with a binding energy of -6.09 kcal/mol; for HCV NS5B polymerase, Ligand 35 with a binding energy of -5.67 kcal/mol; and for HIV reverse transcriptase, Ligands 15 and 96 with a binding energy of -6.03 kcal/mol. The majority of ligands had a greater binding affinity than the control ligand, dTTP. Analysis of data found that three-membered rings increased binding affinity through both hydrophobic interactions and through an extensive network of hydrogen bonds. The decreased steric repulsion of three-membered rings relative to the five-membered rings of dTTP also contributed to increased binding affinity.

Conclusions/Discussion
The majority of ligands that were docked to their protein targets had higher binding affinities than dTTP, which also served as the controlled variable for the experiment; approximately half of the ligands had binding affinities that were one standard deviation above the average binding affinities. The objective was attained, and this discovery may lead to a new class of drugs that use a different ring structure to combat diseases linked to the targeted enzymes or drug resistance.

Summary Statement
The aim of this project is to determine the inhibitory effects of a new dTTP analog on enzymes that are targets for treating cancer, HIV, and HCV.

Help Received
Mrs. O'Brien and Debra Innis edited my report, and Mrs. Driscoll was my advisor. Schrödinger, LLC provided a free license to use their software.