Antimalarials: Modeling the Next Generation Inhibitors

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Developing antimalarial drugs has always been an important objective for the pharmaceutical industry. However, in the past few decades, there has been an increase in malaria parasites that have developed resistance to common antimalarial agents. The problem of this project is by using molecular modeling, can I compare existing antimalarial drugs and generate ideas for analogs of the Walter Reed compound WR-965? I hypothesize that I will be able to design novel analogs of WR-965 by comparing existing antimalarial drugs. By using the molecular modeling program Maestro and supporting software Phase, LigPrep, and MacroModel, I built models of Chloroquine, Quinine, and Mefloquine. After generating approximately fifty low energy conformations of these molecules, I used Phase to generate superpositions comparing these molecules to WR-965. The hypotheses produced suggest ways to create analogs of the Walter Reed compound. For example, all of the compounds contain at least one fused aromatic ring but WR-965 does not. One series of designed analogs involves expanding one of the rings to mimic the alignments suggested by the modeled hypotheses. In conclusion, I successfully compared models of existing antimalarial drugs with WR-965 and designed several potential analogs to make, proving my hypothesis correct. Potential errors include calculation errors on the part of myself and the programs used. In the future, I hope to synthesize a few of these molecules and test them against both resistant and non-resistant malarial strains.