CALIFORNIA STATE SCIENCE FAIR
2006 PROJECT SUMMARY

Name(s)
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Project Number
S0511

Project Title
Identification of the Determinants of Antimalarial Drug Action

Abstract

Objectives/Goals
1) Identify which structural features of quinoline-based antimalarials prevent heme polymerization (therefore killing the malaria parasite Plasmodium with free heme inside the cell)
2) Find out whether such features can be systematically assembled in a molecule (and employed as possible antimalarials).

Methods/Materials
First, conditions were established that allowed heme polymerization studies in a non-enzymatic manner. The capacity to deter heme polymerization of several known antimalarials (like quinine and chloroquine) and chemicals with similar structures was assesed. Typically, ~50 mg of hemin was heated with ~10 mg of drug in 5M Na-acetate buffer (pH 7) at 70 degC for 60 min. The resulting product was filtered, washed, dried and identified by infrared spectroscopy (bands at ~1660 and 1210 cm-1 indicated presence of heme polymer: beta-hematin). Through these experiments, three structural features that appeared responsible for the prevention of heme polymerization were identified. Next, two analogues with and without these structural features were synthesized via standard peptide synthesis protocol. The analogues were identified by Nuclear Magnetic Resonance Spectroscopy and employed in heme polymerization reactions.

Results
The results clearly indicated that the specified structural features (a ring nitrogen, a long carbon chain with a positively charged terminus at the 4 position with respect to N) are indeed critical for the suppression of heme polymerization.

Conclusions/Discussion
The design of new antimalarials to combat Plasmodium resistant to commonly used drugs could use these features. This approach eliminates the need to search for novel natural products.

Summary Statement
My project identifies which chemical structures in common antimalarials are most essential for their drug action.

Help Received
Alegra Eroy-Reveles supervised me in the lab and helped me in data handling. Dr. Raman Afshar provided help in plotting the NMR spectra. Mike Rose superivised the synthesis of the 2 analogues. Finally, Dr. Pradip Mascharak helped in obtaining materials and in background research,