Lipophilic π-Delocalized Quaternary Ammoniums as Novel Antimalarial Candidates: Synthetic, Medicinal and Bioorganic Study

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Malaria remains a major health problem in many developing countries. Annually, it is estimated that there are 300-500 million cases of malaria leading in 1-3 million deaths. One of the major reasons for the morbidity and mortality is largely due to the widespread emergence of drug-resistant strains of the parasite. Therefore, new generation of antimalarial drugs, which possess a new class of molecular framework and display novel mechanism of action, will be welcome news to millions people.

We envisaged that DLCs (π-delocalized lipophilic cations) would display antimalarial activity by the selective accumulation into plasmodial mitochondria. Based on the hypothesis, it was found that synthetic rhodacyanines showed strong antimalarial activity in vitro against *Plasmodium falciparum* (drug-resistant strain) with high selective index. Structure-activity relationship study indicates that a DLC structure is important and essential for strong activity. Further investigation revealed the aza-analogs displayed good suppression effect against *P. berghei* in vivo (ip) without significant acute toxicity. In order to understand the action mechanism of rhodacyanines, their behavior in the malaria parasites was examined by microscopic-observation experiments. Fused-rhodacyanines showing strong fluorescence were newly designed and synthesized as bio-probes. As the results, it was proved that rhodacyanines specifically accumulate in plasmodial mitochondria and the uptake is closely related with parasitic survival. We also found phenoxazinium salts from in vivo screening test. In vivo evaluation reveals that they display good parasitemia suppression (ip). It is noteworthy that they show antimalarial potency even by oral administration (po) without remarkable acute toxicity.

The above results in this study suggest the lipophilic π-delocalized quaternary ammoniums would be applicable to the novel antimalarial drug design.