Bioactive Surface-Active Ionic Liquids: combining antimalarial drugs with natural amphiphilic lipids

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Ionic Liquids (ILs) have gained importance in Medicinal Chemistry, not only as alternative solvents for production of active pharmaceutical ingredients (APIs), but also for various other applications, such as adjuvants in drug formulation and delivery, or even as bioactive agents themselves. Through straightforward reactions, new ionic structures with significant biological properties can be developed, as most APIs are ionizable and can be paired with counter-ions that are either inert or offer additional beneficial biological effects. This efficient and cost-effective strategy holds great promise for combating diseases as malaria.

We employed the ion pairing strategy to repurpose the basic antimalarial aminoquinolines, chloroquine and primaquine, by acid-base reactions with natural amphiphilic lipids, namely, fatty acids and bile acids. This approach aimed at producing novel ionic liquids (ILs) capable of targeting multiple stages of the *Plasmodium* parasite's life cycle. The combination of the drugs with the selected natural lipids was based on the biocompatibility and amphiphilic properties of the latter, which we hypothesized would originate Surface-Active Ionic Liquids (SAILs) with enhanced pharmacokinetics as compared to the parent drugs.

The antiplasmodial activity and self-aggregation properties of the newly synthesized SAILs were studied. Primaquine fatty acid salts preserved the liver-stage antiplasmodial activity of the parent drug while demonstrating significantly enhanced efficacy against blood-stage parasites. In the case of bile salts, primaquine derivatives retained the original activity of the drug, whereas chloroquine-derived bile salts emerged as groundbreaking triple-stage antiplasmodial agents. Notably, the bile acid-based SAILs exhibited a strong self-aggregation capability, with a markedly lower critical micelle concentration compared to traditional sodium salts.

These results open new avenues for drug repurposing, extending beyond antimalarials to encompass a broader range of anti-infective therapies.