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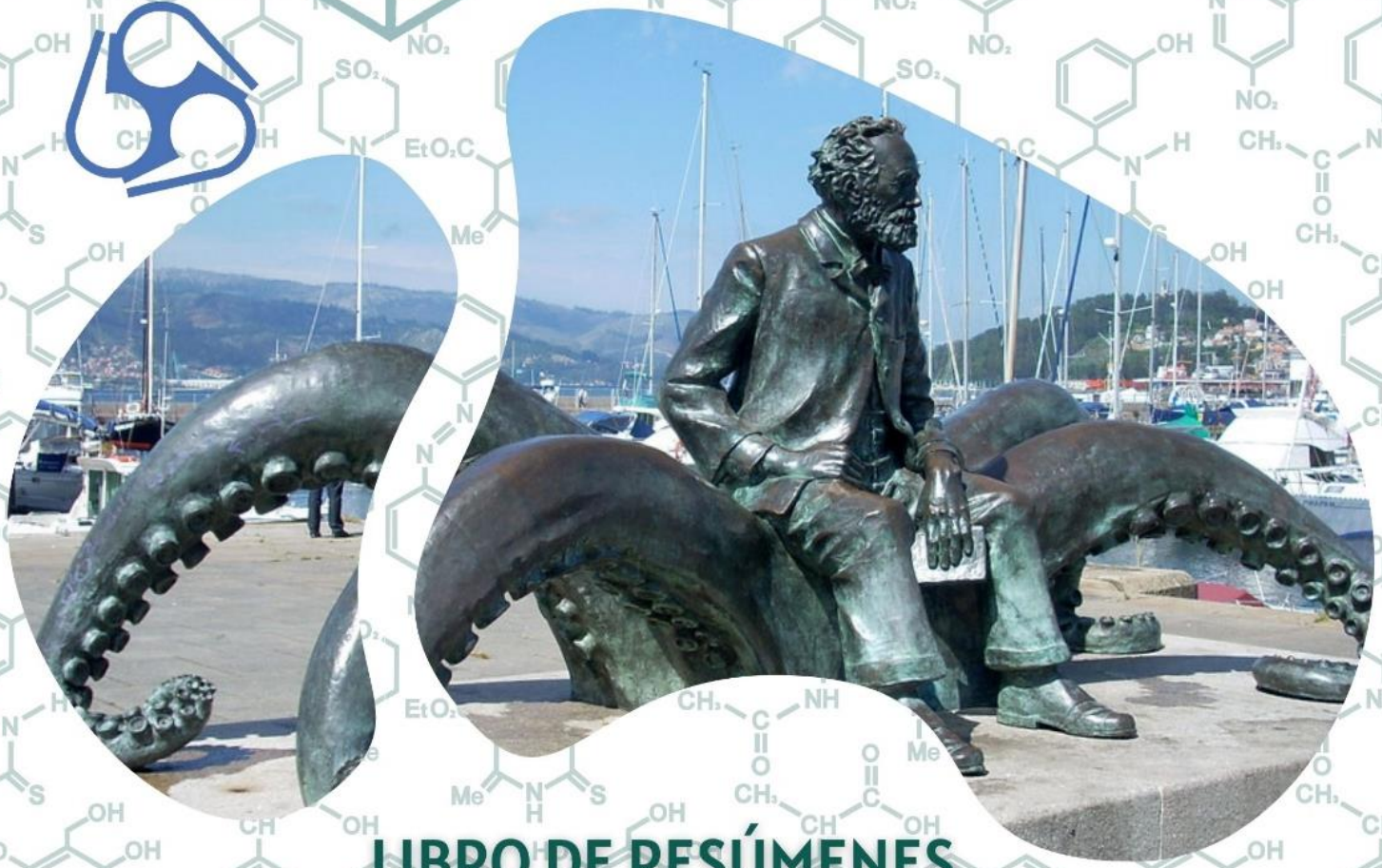

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Surface-Active Ionic Liquids derived from Antimalarial Drugs and Natural Lipids That Display Multi-Stage Antiplasmodial Activity

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The use of Ionic Liquids (ILs) in Medicinal and Pharmaceutical Chemistry has been greatly evolving since they were first used as alternative solvents for the chemical synthesis of active pharmaceutical ingredients (APIs). ILs are now used with other purposes in this area, such as adjuvants in drug formulation and delivery, or even as bioactive compounds *per se*. New ionic structures with biologically relevant properties can be easily obtained through straightforward reactions, as nearly all APIs are ionizable and can be paired with counter-ions that could be either inert or offer additional beneficial biological effects. This efficient, cost-effective strategy for the rescuing and repurposing of drugs is particularly appealing for finding new options to combat "diseases of poverty" like malaria.

We implemented this approach to “recycle” classical antimalarial aminoquinolines, namely, chloroquine (CQ) and primaquine (PQ), by pairing them with natural acidic lipids through acid-base reactions. Our goal was to create novel ILs capable of targeting multiple stages of the *Plasmodium* parasite’s life cycle. Additionally, we were interested in that such ILs could act as surface-active ionic liquids (SAILs), able to self-assemble into nanostructures displaying adequate bioavailability. For this purpose, we paired the antimalarial drugs with either fatty acids or bile acids, due to their biocompatibility and amphiphilic nature.

The antiplasmodial activity and self-aggregation properties of the new SAILs were determined. PQ fatty acid salts preserved the liver-stage antiplasmodial activity of the original drug, while exhibiting significantly enhanced activity against blood-stage parasites. In the case of bile salts, those derived from PQ retained the efficacy of the parent drug, whereas the CQ-derived salts proved to be novel triple-stage antiplasmodial agents. The SAILs obtained from bile acids showed a remarkable ability to self-aggregate, with a notably lower critical micelle concentration compared to their respective sodium salts.

Overall, these findings open a new strategy for drug repurposing, extending beyond antimalarials and other anti-infective therapies.

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