Prodrug Approach for 4(1H)-Quinolones and Similar Compounds to Improve Oral Bioavailability

Researchers at the University of South Florida have invented prodrug approach for 4(1H)-Quinolones and similar compounds to improve their oral bioactivity for malaria treatment.

Malaria remains one of the most devastating parasitic diseases with approximately 200 million reported infections and over 0.6 million deaths annually. While malaria is an entirely preventable and treatable mosquito-borne illness, children under the age of five account for almost 80% of the documented deaths. Five species of the genus Plasmodium (P. falciparum, P. vivax, P. ovale, P. malariae, and P. knowlesi) are responsible for malaria in humans, of which P. falciparum and P. vivax are considered to be the most critical and prevalent ones.

Screening of a selected number of 4(1H)-quinolones identified several analogues as potent agents against erythrocytic stages of multidrug resistant P. falciparum. Unfortunately, the preclinical development of these analogues, particularly ELQ 300, failed due to limitations of aqueous solubility.

Our inventors have devised a novel prodrug approach which increases the aqueous solubility of ELQ-300 and other 4(1H)-quinolones.

These pH-triggered prodrugs are soluble, stable at low pH, and possess improved in vivo antimalarial efficacy. The pH-regulated strategy of releasing the parent compound is generally applicable to any other classes of 4(1H)-quinoline compounds and confers improved oral bioavailability on the compounds.

**ADVANTAGES:**

- Enhanced potency
- High aqueous solubility
- Improved oral bioavailability
- Applicable to multiple anti-malaria compounds

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