Tautomerism in Quinolone 3-esters Targeting the *bc1* Complex of *P. falciparum*: Implications in Product Selectivity and Activity

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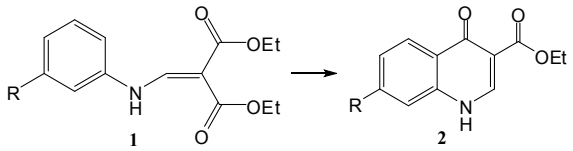
Considering the growing spread of resistance, development of new antimalarial drugs directed to new therapeutic targets remains a priority.[1] The approval of Malarone® for the treatment and prevention of multidrug resistant malaria validated the *P. falciparum bc1* protein complex as target for developing antimalarials. Inhibition of the *bc1* complex leads to a drop of mitochondrial function, resulting in collapse of the trans-membrane electrochemical potential and, ultimately, in parasite death.

Selected quinolone 3-esters (**2**) were proposed as inhibitors targeting the Qo site of the *bc1* complex and expressed activity at low concentrations. However, due to chemical and pharmacological liabilities, this chemotype requires optimization.[2,3]



Quinolones **2** may be prepared from an α,β-unsaturated derivative of aniline **1** by the Gould-Jacobs thermal cyclization. Alternatively, the cyclization may be mediated by phosphoryl chloride.[4] However, the possibility of quinolone/hydroxyquinoline tautomerism was found to limit the scope and selectivity and may also impact in antimalarial activity. Unexpected new products arose from the cyclization step,[3] raising structural and mechanistic issues. Results or our studies will be discussed.

References

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