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Quinolones in Medicinal Chemistry: are Potential Applications Compromised by Limited Synthetic Approaches?

Pedro Horta[1], Alina Secrieru[1,2], Andy Coninckx[1,2] and Maria LS Cristiano*[1,2]

[1]*CCMar - Centro de Ciências do Mar do Algarve, Campus de Gambelas, Universidade do Algarve, Portugal*

[2]*Departamento de Química e Farmácia, FCT, Campus de Gambelas, Universidade do Algarve, Portugal*

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***Corresponding author:** Maria LS Cristiano, CCMar and Department of Chemistry and Pharmacy, FCT, University of Algarve, P-8005-039 Faro, Portugal, Email: mcristi@ualg.pt

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Introduction

Quinolones (oxoquinolines) belong to the broad family of quinolines, bearing a carbonyl group at any position of the quinoline core [1]. The versatility of the quinolone chemo type attracted the interest of researchers for several decades, leading to a wealth of information that unravelled the potential of quinolones for applications in major fields, namely in medicinal chemistry. Quinolones are nowadays associated to several pharmacological properties, with quinolone derivatives being either used as drugs or under development as drug candidates, to target a variety of human diseases and disorders. From these, it is possible to highlight the use of quinolones as antibacterial [2], Antiparasitic and antiviral agents, targeting a range of infectious diseases that include TB [3], malaria [4-8], hepatitis, HIV and herpes [9-11]. Additionally, quinolone derivatives are under investigation as antineoplastic agents [12], as immunosuppressant agents [13], and even as tools to control obesity, diabetes and neurodegenerative diseases [12,14].

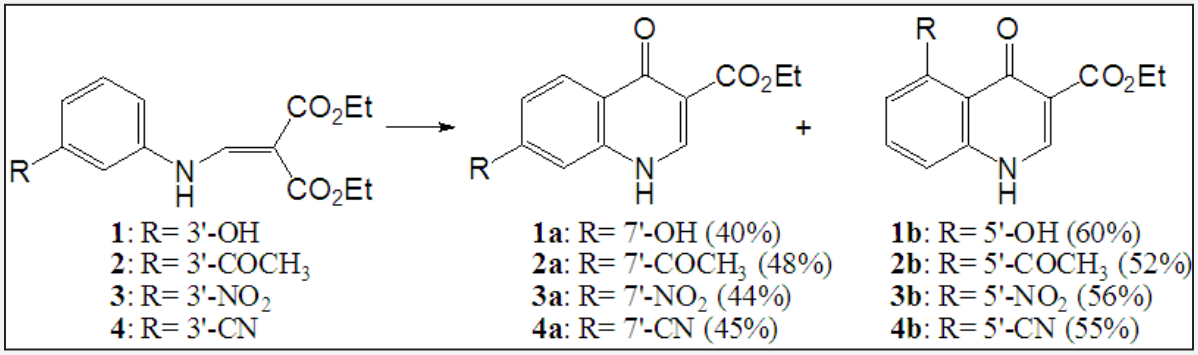
Discussion

In spite of the useful pharmacological properties, quinolone-based drugs present some clinical liabilities, especially related with side effects and toxicity [15,16], selectivity [17-20], development of resistance[7,21-23], and food-drug or drug-drug interactions [24-26], calling for optimization strategies that often require the rational design and synthesis of improved analogues to circumvent those weaknesses. Thus, the availability of easy-to-carry, affordable, selective and versatile synthetic routes to the preparation of quinolones is of upmost relevance. The first formal synthesis of the quinoline core was reported over a century ago and, since then, variations and new methods have been disclosed [27-32], enabling the preparation of libraries of chemically diverse derivatives bearing a wide range of substituent's and different substitution patterns at the quinoline core, often organised in subclasses within the quinoline family [5,33].

Quinolones are also challenging from a chemical viewpoint, stimulating the investigation of their properties (e.g. solubility) [34] synthesis and structure [8,35,36]. Recently, detailed structural studies have shown that the possibility of isomerism and/or tautomerism, characteristic of some quinolones, could explain some of the problems associated to the synthetic routes available that often lead to poor yields of the isolated products [8,35,36]. Within the frame of a project involving the preparation of a library of 7-substituted 4-oxoquinoline-3-esters (e.g. compounds 1a-4a; Scheme 1), designed to act as inhibitors of the cytochrome bc1 protein complex of *Plasmodium falciparum*, the causative agent of severe malaria, we have performed some studies directed to a better understanding of the steps involved in the synthetic route to quinolones, in view of its optimisation [8,36,37]. Following a strategy based on the Gould-Jacobs methodology, depicted in Scheme 1, the thermally driven intramolecular cyclisation requires nucleophilic attack of the phenyl ring on the electrophilic carbon of the ester carbonyl group [38].

We have demonstrated that the reaction often leads to formation of structural isomers. Cyclisation to both *ortho* carbons adjacent to the NH group of the malonate derivative may occur (unless one of the positions is hindered), leading to an isomeric mixture (7- or 5-substituted 4-oxoquinoline 3-esters Scheme 1). The two isomers bear different chemical structure

and properties, so they may bind differently to the enzyme active site, affecting pharmacodynamics, and may also show different pharmacokinetics. In addition, we have demonstrated that these compounds may exist in the 4-hydroxy- or 4-oxo- tautomeric forms, depending on the chemical environment [8]. Tautomerism may affect the synthesis, and its impact in pharmacologic properties deserves to be investigated.



Scheme 1: Summary of the synthetic approach followed to the preparation of 4-oxo-quinoline 3-esters. For compounds 1-4, the reaction afforded structural mixtures of 7- and 5-substituted compounds. Conditions: Dowtherm A, 250 ºC, 3 hours.

Conclusion

Given the interest in quinolones as drug leads, additional structural studies and deep efforts to develop reliable synthetic routes to this class are a major priority.

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