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

Pedro Horta¹, Alina Secrieru¹,², Andy Coninckx¹,² and Maria LS Cristiano*¹,²

¹CCMar - Centro de Ciências do Mar do Algarve, Campus de Gambelas, Universidade do Algarve, Portugal
²Departamento de Química e Farmácia, FCT, Campus de Gambelas, Universidade do Algarve, Portugal

Submission: December 18, 2017; Published: December 22, 2017

*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

Keywords: Quinolones; Oxoquinolines; Drug Discovery; Quinolone 3-esters; 4-oxoquinoline/4-hydroxy-quinoline Tautomerism; Isomerism

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 chemotype 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 utmost 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.

### 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.

### Acknowledgements:

The authors acknowledge the Portuguese “Fundação para a Ciência e a Tecnologia” (FCT) and Centro de Ciências do Mar do Algarve - CCMAR, for financial assistance. CCMAR in funded by FCT, through the project UID/Multi/04326/2013.

### References

1. O’Donnell JA, Gelone SP (2000) Fluoroquinolones. Infect Dis Clin North Am 14(2): 489-513.
2. Sissi C, Palumbo M (2003) The quinolone family: from antibacterial to anticancer agents. Curr Med Chem Anticancer Agents 3(6): 439-450.
3. Kathrotiya HG, Patel MP (2013) Synthesis and identification of β-arylxyquinoline based diversely fluorine substituted N-aryl quinolone derivatives as a new class of antimicrobial, antituberculosis and antioxidant agents. Eur J Med Chem 63: 675-684.
4. Pidathala C, Amewu R, Pacorel B, Nixon GI, Gibbons P et al (2012) Identification, design and biological evaluation of bisaryl quinolones targeting Plasmodium falciparum type II NADH:quinone oxidoreductase (PINOH2). J Med Chem 55(5): 1831-1843.
5. Leung SC, Gibbons P, Amewu R, Nixon GI, Pidathala C, et al (2012) Identification and Validation of Novel Drug Targets for the Treatment of Plasmodium falciparum Malaria: New Insights. J Med Chem 55(5): 1044-1057.
6. Biagini GA, Fisher N, Shone AE, Mubarak MA, Srivastava A, et al. (2012) Generation of quinolone antimalarials targeting the Plasmodium falciparum mitochondrial respiratory chain for the treatment and prophylaxis of malaria. Proc Natl Acad Sci U S A 109(21): 8296-8303.
7. Cowley R, Leung S, Fisher N, Al-Helal M, Berry NG, et al. (2012) The development of quinolone esters as novel antimalarial agents targeting the Plasmodium falciparum bcl protein complex. Med chem commun 3(1): 39-44.
8. Horta P, Kuş N, Henriques MSC, Paixão JA, Coelho L, Nogueira, et al. (2015) The quinolone-hydroxyquinoline tautomeration in quinolone 3-esters: preserving the 4-oxoquinoline structure to retain antimalarial activity. J Org Chem 80(24): 12244-12257.
9. Kumar DV, Rai R, Bramedd KA, Somoza JR, Jagadoo R, et al. (2011) Quinolones as HCV NS5B polymerase inhibitors. J Bioorg Med Chem Lett 21(1): 82-87.
10. Serrao E, Debnath B, Otake H, Kuan Y, Christ F, et al. (2013) Fragment-based discovery of 8-hydroxyquinoline inhibitors of the HIV-1 integrase-lens epithelium-derived growth factor/p75 (IN-LEDGF/p75) interaction. J Med Chem 56(6): 2311-2322.
11. Dorow RL, Herrinton PM, Höhler RA, Maloney MT, Mauragis MA, et al. (2006) Development of an Efficient Synthesis of the Pyrroloquinolone PHA-529311. Org Process Res Dev 10(3): 495-499.
12. Nakamura S, Kozuka M, Bastow KE, Tokuda H, Nishino H, et al. (2005) Cancer preventive agents. Part 2: Synthesis and evaluation of 2-phenyl-4-quinolone and 9-oxo-9,10-dihydroacridine derivatives as novel antitumor promoters. Bioorg Med Chem 13(14): 4396-4401.
13. Sultana N, Naz A, Khan B, Arayne MS, Mesiak MA (2009) Synthesis, characterization, antibacterial, antifungal, and immunomodulating activities of gatifloxacin derivatives. Med Chem Res 19(9): 1210-1221.
14. Chatterjee A, Cutfer SJ, Doerksen RJ, Khan IA, Williamson JS, et al. (2014) Discovery of thienoquinoline derivatives as selective and ATP non-competitive CDK5/p25 inhibitors by structure-based virtual screening. Bioorg Med Chem 22(22): 6409-6421.
15. Jackson MA, Schutze GE (2016) The Use of Systemic and Topical Fluoroquinolones. Committee on Infectious Diseases-Pediatrics 138(5): e20162706.
16. Golomb BA, Koslik HJ, Redd A (2015) Fluoroquinolone-induced serious, persistent, multisymptom adverse effects. BMJ Case Rep pii: bcr2015209821.
17. Capper MJ, O’Neill PM, Fisher N, Strange RW, Moss D, et al. (2015) Antimalarial 4(1H)-pyridones bind to the Qi site of cytochrome bc1. J. Proc Natl Acad Sci 112(3): 755-760.
18. Barton V, Fisher N, Biagini GA, Ward SA, O’Neill PM (2010) Inhibiting Plasmodium cytochrome bc1: a complex issue. Curr Opin Chem Biol 14(4): 440-446.
19. Nixon GI, Pidathala C, Shone AE, Antoine T, Fisher N, et al. (2013) Targeting the mitochondrial electron transport chain of Plasmodium falciparum: new strategies towards the development of improved antimalarials for the elimination era. Future Med Chem 5(13): 1573-
1591.

20. Xiang H, McSurdy-Freed J, Moorby GS, Hugger E, Bambal R, et al. (2006) Preclinical drug metabolism and pharmacokinetic evaluation of GW844520, a novel anti-malarial mitochondrial electron transport inhibitor. J Pharm Sci 95(12): 2657-2672.

21. Hooper DC, Jacoby GA, Ann NY (2015) Mechanisms of drug resistance: quinolone resistance. Ann NY Acad Sci 1354(1): 12-31.

22. Peters JM, Chen N, Gatton M, Korsinczyk M, Fowler E, et al. (2002) Mutations in cytochrome b resulting in atovaquone resistance are associated with loss of fitness in Plasmodium falciparum. Antimicrob Agents Chemother 46(8): 2435-2441.

23. Biagini GA, Viriyavejakul P, O’Neill PM, Bray PG, Ward SA (2006) Functional characterization and target validation of alternative complex I of Plasmodium falciparum mitochondria. Antimicrob Agents Chemother 50(5): 1841-1851.

24. Del Rosso JQ (2009) Oral Antibiotic Drug Interactions of Clinical Significance to Dermatologists. Dermatol Clin 27(1): 91-94.

25. Neuhoefel AL, Wilton JH, Victory JM, Hejmanowski LG, Amsden GW (2002) Lack of bioequivalence of ciprofloxacin when administered with calcium-fortified orange juice: a new twist on an old interaction. J Clin Pharmacol 42(4): 461-466.

26. Garrelts JC, Godley PJ, Peterie JD, Gerlach EH, Yakshe CC (1990) Sucralate significantly reduces ciprofloxacin concentrations in serum. Antimicrob Agents Chemother 34: 931-933.

27. Skrupa ZH (1880) Eine Synthese des Chinolins. Monatshefte für Chemie - Chem Mon 1(1): 316-318.

28. Edinger A (1896) Über die Einwirkung von Halogenschwefel auf aromatische Amine. Berichte der deutschen chemischen Gesellschaft 29(3): 2456-2460.

29. Friedländer P, Gohring CF (1883) Über eine Darstellungsmethode im Pyrindinkern substituierter Chinolinderivate. Berichte der Dtsch Chem Gesellschaft 16(2): 1833-1839.

30. Doehner O, Miller W (1881) Über eine dem Chinolin homologe Base. Berichte der Dtsch Chem Gesellschaft 14(2): 2812-2817.

31. Pfitzinger WJ (1886) Chinolinderivate aus Isatinsäure. Journal für Praktische Chemie 33(1): 100.

32. Povaros LS (1967) αβ-unsaturated ethers and their analogues in reactions of diene synthesis. Russ Chem Rev 36(9): 656-670.

33. Hong WD, Gibbons PD, Leung SC, Amezua R, Stocks PA, et al. (2017) Rational Design, Synthesis, and Biological Evaluation of Heterocyclic Quinolones Targeting the Respiratory Chain of Mycobacterium tuberculosis. J Med Chem 60(9): 3703-3726.

34. Ishikawa M, Hashimoto Y (2011) Improvement in Aqueous Solubility in Small Molecule Drug Discovery Programs by Disruption of Molecular Planarity and Symmetry. J Med Chem 54(6): 1539-1554.

35. Horta PC, Henriquez MSC, Kuş N, Paixão J, O’Neill PM, et al. (2015) Synthesis, structural and conformational analysis, and IR spectra of ethyl 4-chloro-7-iodoquinoline-3-carboxylate. Tetrahedron 71(40): 7583-7592.

36. Horta P, Henriquez MSC, Brás EM, Murtinheira F, Nogueira F, et al. (2017) On the ordeal of quinolone preparation via cyclisation of aryl-ynamines; synthesis and structure of ethyl 6-methyl-7-ido-4{3-ido-4-methylphenoxy)-quinoline-3-carboxylate. Pure Appl Chem 89(6): 765-780.

37. Gould RG, Jacobs WA (1939) The Synthesis of Certain Substituted Quinolines and 5,6-Benzoquinolines. J Am Chem Soc 61(10): 2890-2895.

Your next submission with Juniper Publishers will reach you the below assets

- Quality Editorial service
- Swift Peer Review
- Reprints availability
- E-prints Service
- Manuscript Podcast for convenient understanding
- Global attainment for your research
- Manuscript accessibility in different formats (Pdf, E-pub, Full Text, Audio)
- Unceasing customer service

Track the below URL for one-step submission
https://juniperpublishers.com/online-submission.php