Is stereochemistry important in the antibacterial and antimalarial activity of 4-aminoalcohol quinoline derivatives?

C. Mullié¹, A. Jonet¹, A. Dassonville-Klimpt¹ and P. Sonnet¹

¹Laboratoires des Glucides FRE-CNRS 3517, Equipe THERA, Faculté de Pharmacie, 1 rue des Louvels, 80037 Amiens Cedex 1, France

Mefloquine (MQ) is a quinoline methanol derivative used in the preventive and curative treatment of malaria and is commercially available as a racemic mixture of its erythro enantiomers. Its antimicrobial activity has also previously been described on Gram positive bacteria (Staphylococcus aureus, Streptococcus pneumoniae and Enterococcus faecalis) [1] and on Mycobacterium avium complex [2]. However, adverse effects, such as neurotoxicity [3], as well as relatively high MICs limit its use as an antibiotic. Enantiomerism could play a part in the in vitro activity and toxicity of MQ derivatives. Indeed, IC₅₀ values for the antimalarial activity were found to be lower for the (S)-enantiomer (also termed (+)-enantioomer) of MQ than those of the (R)-enantiomer (also termed (-)-enantioomer) by a factor of 1.6 to 1.8 on some strains (D6 and W2) [4]. The (S)-erythro-MQ was also recently described as the more active enantiomer against M. avium [5]. Additionally, the (R)-enantiomer was found to block to central nervous system adenosine receptors, while the (S)-enantioomer did not, supposedly resulting in neuropsychiatric symptoms associated with MQ [6]. Previous reports indicate that the opening of the piperidine ring at the 4-position of the quinoline scaffold yields molecules with a better potency and a lesser neurotoxicity than that of MQ [7]. A way to reduce neurotoxicity and increase the antibacterial activity of MQ derivatives could therefore be the synthesis of enantiomerically pure 4-aminoalcohol quinolines. Accordingly, our team has recently proposed a new enantioselective pathway to synthesize pure enantiomers of MQ aminoanlogs, i.e. 4-aminoalcohol quinolines [8]. The (S)-enantiomers of this series of derivatives were found to be at least as effective as both chloroquine and MQ. The derivative with a 5-carbon side-chain length was the more efficient on W2 and 3D7 P. falciparum strains. (R)-enantiomers displayed an activity decreased by 2 to 15-fold as compared to their (S) counterparts, implying stereochemistry is important for these molecules to reach their maximal efficacy [9]. The same compounds were tested against reference strains of S. aureus, E. faecalis, Escherichia coli and Pseudomonas aeruginosa. While they were found to be only marginally active against E. coli (MICs ranging from 8 to 64 µg/ml) and inactive against P. aeruginosa, some of them displayed a 4 to 16-fold better activity than MQ on both S. aureus and E. faecalis, with a MIC of 1 µg/ml for the derivative with a 8-carbon side-chain length. This compound was the most active and further found to display a bactericidal activity within 2 hours of incubation. Interestingly, when tested against Meticillin-Resistant S. aureus, these compounds retained their activity. (R)- and (S)-4-aminoalcohol quinolines enantiomers displayed similar MICs against all strains. In conclusion, these new 4-aminoalcohol quinolines display significant antimalarial and antibacterial activities that warrant further investigations towards a clinical use (e.g. toxicity and pharmacokinetic studies). Their antimicrobial efficacy seems to depend on the length of the substituent’s side-chain whereas their antimalarial activity is more strongly affected by enantiomerism, maybe because this activity involves a stereoselective receptor or transport.

References

Keywords mefloquine, 4-aminoalcohol quinoline, antibacterial activity, stereochemistry