Fluoroquinolone- metal complexes: A route to counteract bacterial resistance?

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Quinolones are amongst the most widely prescribed families of antibiotics, both in human and veterinary medicine, due to their broad spectrum of activity and safety profile [1]. Their mechanism of action relies on the inhibition of the enzymes responsible for DNA replication (DNA gyrase and topoisomerase IV) [2, 3]. Due to limited activity of the first quinolones (e.g. nalidixic acid), structural changes to the basic nucleus were introduced to broaden their antibacterial spectrum of activity namely, the introduction of a fluorine atom at position 6 of the basic quinolone ring, giving rise to fluoroquinolones [4] and a cyclic amino group at C-7. However, their overuse/misuse seems to be the basis of the emergence and dissemination of microbial resistance that results from the bacterial adaptations and compromises antimicrobial efficiency [5]. This increasing menace of bacterial resistance to quinolones, led to the need to improve existing antimicrobial drugs and/or develop new ones, pushing forwards the concept that metal complexes could be an alternative to conventional drugs, as novel derivatives of fluoroquinolones [6, 7]. Numerous studies regarding the interaction between various quinolones and metal cations have been reported and reviewed in the literature. In particular, the study of quinolones–copper–1,10-phenanthroline complexes has become an increasingly important field since they seem to exhibit high affinity towards DNA binding as well as nuclease activity towards plasmid, genomic and internucleosomal DNA [8, 9].

In this work we report the solution behaviour of some fluoroquinolones complexes with copper(II), nickel(II), cobalt(II) and zinc(II) in the presence and absence of 1,10-phenanthroline. The values obtained for the stability constants of the binary and ternary divalent metal ion complexes are very high and clearly show that the ternary complexes are more stable than the binary ones, suggesting stabilization due to an intra-molecular interaction between the ligands. Nevertheless, distribution diagrams indicate that only the copper(II) binary or ternary species are stable at physiological concentrations.

Binary copper(II)/fluoroquinolone and ternary copper(II)/fluoroquinolone/phenanthroline complexes were synthesised and characterized by elemental analysis, UV–visible spectroscopy and FTIR or X-Ray crystallographic. The antimicrobial activity of these complexes was tested against different Escherichia coli strains and compared to that of copper(II)/fluoroquinolone and copper(II)/fluoroquinolone/phenanthroline solutions, prepared by mixing of the individual components in the same stoichiometric proportion and concentration range used for the synthesised complexes.

The overall results are quite encouraging and suggest that the study of the ternary copper complexes as potential new antibacterial agents is worth pursuing since microorganisms resistant to free fluoroquinolones could be sensitive to their metal complex derivatives.

References:

Keywords Fluoroquinolones; Metalloantibiotics; Bacterial resistance; Solution equilibria