Free and copper-complexed fluoroquinolones: a biological and biophysical study

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Fluoroquinolones are widely used antibiotics and cases of bacterial resistance to fluoroquinolones have been frequently reported. One important mechanism of resistance to these drugs is the decrease of permeability of the bacterial cell by mutation of OmpF porin. Fluoroquinolone modification by complexation with copper and a nitrogen-donor heterocyclic ligand is an approach that has been developed in the effort to counteract this mechanism of bacterial resistance [1]. In the present work, sparfloxacin, ciprofloxacin and their copper ternary complexes were studied. Biophysical studies in *E. coli* total extract liposomes, a mimetic system for bacterial outer membrane show that metalloantibiotics influx route can be strongly dependent on lipid interaction, proposing that their diffusion can be based in a hydrophobic mechanism. Biological studies showed that copper ternary complexes are as active as fluoroquinolones against *E. coli* strains and cell viability and cell proliferation assays attain for the safety of these new compounds. The combination of these biophysical and biological results show that the use of these metalloantibiotics may be a good choice to replace the pure fluoroquinolones and bypass, at least, one of the mechanisms of the bacterial resistance to fluoroquinolones. Moreover, the findings of this work provide insights that will be helpful to proceed with the study of metal-complexes as alternatives to free fluoroquinolones in resistant infections, avoiding the high-costing and time-consuming processes of discovering and synthetizing fully new antibiotics.

References

[1] P. Gameiro *et al.*, Journal of Inorganic Biochemistry **138,** 129–143 (2014).