Microbiological study on the translocation route of two fluoroquinolone-copper(II)-1,10-phenanthroline complexes through the outer membrane of *Escherichia coli*

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Microbial resistance to antibiotics is one of the major public health concerns that the world is facing nowadays [1], sadly there are many mechanisms that bacteria use to become resistant to the antimicrobial agents. Down-regulation or alteration of the outer membrane porins is a known mechanism of resistance. Fluoroquinolones (FQs) and β-lactams are frequently described as being dependent of the porins OmpF and OmpC to cross the outer membrane of Gram-negative bacteria [2]. Metal complexes as novel derivatives of FQs could be an alternative to conventional drugs and have been studied and analysed for that purpose. Accordingly, herein we have studied the antimicrobial activity of two FQ-copper(II)-1,10-phenanthroline complexes, where the FQ is ciprofloxacin (cpx) or sparfloxacin (spx), against the *E. coli* BL21(DE3) strain and a collection of mutant strains derived from the former strain that are devoid of one or more major porins (LamB, OmpA, OmpC and OmpF) [3]. The aim was to infer on the translocation route used by this two ternary copper complexes. To complement that aim, the MICs of the complexes were determined also in presence of spermine 1 mM, a polyamine that has been reported to modulate porin activity, by blocking OmpF and OmpC porins and thus decreasing outer membrane permeability. The two ternary complexes presented MICs values (0.004 μg/mL) against the *E. coli* BL21(DE3) strain that were not significantly different to the ones obtained for the free FQs (0.002 μg/mL). For the free FQs, cpx and spx, our data showed that cpx required the OmpF for the influx while spx seemed to prefer OmpC to enter the cell. Regarding the complexes, the Cu(II):cpx:phen complex seemed to use OmpF and OmpA for the translocation and the Cu(II):spx:phen complex, on the contrary, apparently uses OmpC and OmpA. The presence of spermine did not reveal in any of the cases (neither for free FQs or ternary complexes) to influence the values of the MICs, thus it may not block the porins OmpF and OmpC as initially thought. In conclusion, these two ternary complexes have an antimicrobial activity against *E. coli* comparable to the free FQs and they seem to use a similar translocation route as the free corresponding antibiotic. Therefore, these Cu(II):FQ:phen complexes are potentially interesting to be used in more advanced metalloantibiotic testing.

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