New Inhibitors of Bacterial Type II Topoisomerases Derived from WRWYCRCK Octapeptide

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Introduction: DNA topoisomerases are highly exploited targets for antimicrobial chemotherapy. DNA gyrase and topoisomerase IV (topo IV) are examples of bacterial type II topoisomerases that control the topological state of DNA and consequently the cell growth. The increase of antibiotic resistance represents a significant threat to public health and emphasizes the urgent need for the development of new antibacterial drugs. **Objectives:** In the current study, we investigated the dimeric and cyclic forms of the synthetic peptide, WRWYCRCK, a recognized inhibitor of *vaccinia virus* type I topoisomerase. **Material and Methods:** The peptides were synthesized by SPPS methodology, purified and analyzed by HPLC and characterized by MS. Dimerization and cyclization reactions were monitored by LC-MS. Gel electrophoresis assays were employed to evaluate the ability of the peptides to inhibit the supercoiling reaction of gyrase and relaxation reaction of topoisomerase IV. **Results and Discussion:** The cyclic and dimeric peptides, showed best results of inhibition of both tested enzymes compared with linear and monomeric peptide. The dimeric peptide showed complete inhibition of DNA gyrase activity, with IC100 value of 50 $\mu mol.L^{-1}$. For topo IV, the IC100 was 10 $\mu mol.L^{-1}$. On the other hand, the cyclic form was less effective, with IC100 values of 100 $\mu mol.L^{-1}$ and 25 $\mu mol.L^{-1}$ for DNA gyrase and topo IV, respectively. The linear and monomeric peptide showed inhibitory activity only for topo IV, with an IC100 value of 50 $\mu mol.L^{-1}$. **Conclusions:** The structural changes implemented in the WRWYCRCK peptide was sufficient to turn it in a new DNA gyrase inhibitor with simultaneous inhibitory activity with topo IV. The peptides demonstrated a good potential for development of novel antimicrobial agents.

Key Words: peptide, topoisomerase IV, gyrase
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