

ANTIPARASITIC ACTIVITY OF CYCLOSPORIN A AND SOME DERIVATIVES ON *TRYPANOSOMA CRUZI*: MOLECULAR MODELLING OF *T. CRUZI* CYCLOPHILIN-CYCLOSPORIN COMPLEXES

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The immunosuppressive drug cyclosporin A (CsA) has shown antiparasitic activity against several protozoans and helminths, when complexed to proteins called cyclophilins. It has been reported the molecular characterisation of seven members of the cyclophilin family in *Trypanosoma cruzi*. Among others, the TcCyP19 gene was expressed in *Escherichia coli*. The TcCyP19 purified recombinant protein exhibited a prolyl peptidyl cis/trans isomerase activity that was inhibited by CsA (IC₅₀ = 18.4 ± 0.8 nM). The trypanocidal activity of CsA and some non-immunosuppressive analogs on epimastigotes and trypomastigotes was demonstrated. A tridimensional modelling of TcCyP19 and its complexes with CsA and CsA analogues was performed. In a first step, a sequence alignment (Fasta-SAS) allow us to select the NMR structure of cyclophilin A from human complexed with the CsA from *Tolypocladium inflatum* (Spitzfaden et al., 1994, J. Biomol. NMR, 4, 463) to make the molecular replacement of non conserved side chains (mdFrodo/TOM) and further structure refinement (REFI subprogram). With the resulting set of coordinates, a comparison of interactive contacts between cyclosporin A (and analogues) and *T. cruzi* and human cyclophilins was performed. This result jointly with an analysis of the quaternary structure of complexes were used to conjecture about the basis of specificity of cyclosporin-cyclophilin complexes.