Molecular dynamics studies of potential inhibitors of dihydrofolate reductase from *Yersinia pestis* as new antiplague agents

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Keywords: *Molecular Dynamics, Yersinia pestis, Dihydrofolate reductase.*

Introduction

Plague is a disease, caused by the bacterium *Yersinia pestis,* which affects humans and other mammals. . Humans usually contract plague after being bitten by a rodent's flea carrying the plague bacterium or by handling an infected animal[1]. Considering the menace represented by the eventual use of *Y. pestis* in terrorist attacks, the search for new and effective drugs against plague is mandatory[1]. A known molecular target for the treatment of bacterial infections is the enzyme dihydrofolate reductase (DHFR), essential to the cellular metabolism by catalyzing the reduction of dihydrofolate to tetrahydrofolate, intermediated by the cofactor NADPH. In the present work we performed molecular dynamics studies, using the software GROMACS[2,3], of compounds previously selected by virtual screening and docking studies[4] (Figure 1), inside the active site of *Y pestis* DHFR (*Yp*DHFR).

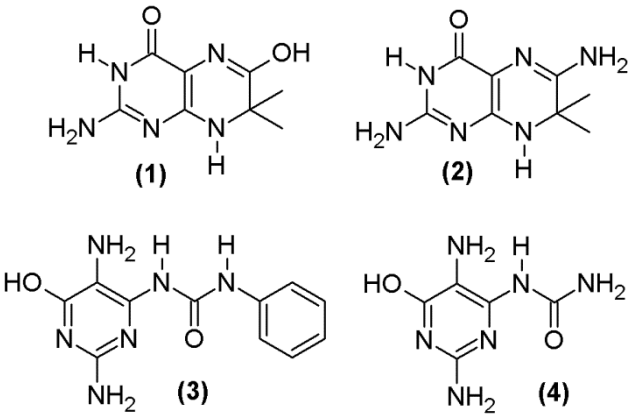

Figure 1. Structures of the compounds studied.

Results and Discussion

Our results suggest that all compounds studied could be potential inhibitors of *Yp*DHFR, considering former docking results and interactions observed with the same residues related to the stabilization of the natural substrate of DHFR (dihydrofolic acid), competing for binding site. Compound **(2)** was the most stable inside *Yp*DHFR with the larger number of H-bonds formed during the simulation time (Figure 2).

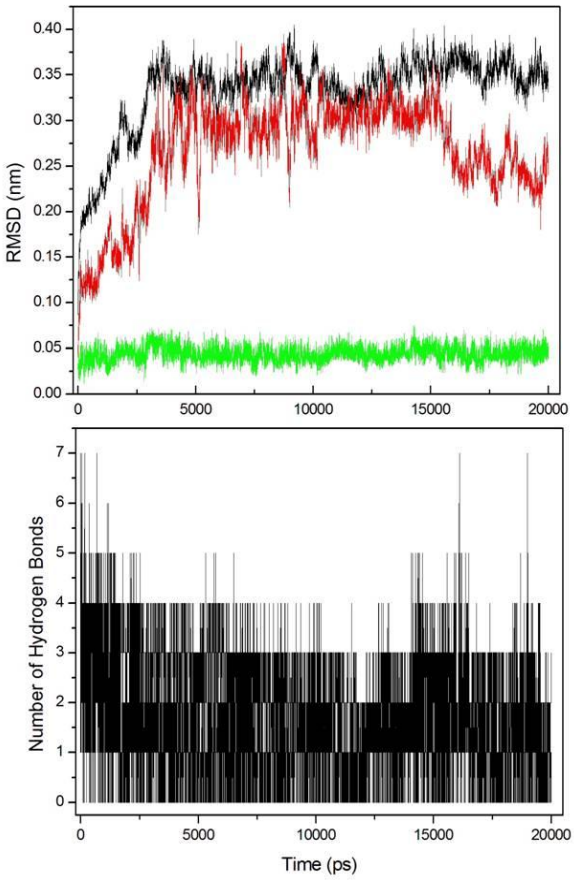

Figure 2. Top: RMSD of **(2)** (green line) and NADPH (red line) inside *Yp*DHFR (black line) during the simulation. Bottom: H-bonds formed by **(2)** during the simulation.

Conclusion

Our results suggest that the compounds studied, can be potential inhibitors of *Yp*DHFR, competing for the dihydrofolic acid binding site, especially **(2)**. These compounds should now be submitted to molecular dynamics inside human DHFR (*Hss*DHFR) in order to check a potential selectivity pointed in dockings studies.

Acknowledgements

FAPERJ, CAPES/PRODEFESA, CNPq, IME

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