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Enhancement of cruzipain activity by quinoxaline derivatives: an attempt to explain it by molecular dinamics studies.

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The design of cruzipain (CZP) inhibitors, a key protease in the life cycle of the *Trypanosoma cruzi*, the causative agent of Chagas disease, constitutes one of the strategies for the search of antichagasic agents. In this context, we have proposed, through docking and MPBSA studies, quinoxalinic compounds that could be inhibitors of the enzyme. These compounds were designed through its possible interaction in a site (AS2) close to S2 region. This site has been indicated as a target for antichagasic drug design.[1] Numerous derivatives were synthesized and evaluated on endogenous CZP, using as substrate Z-FR-AMC. All the evaluated compounds were inactive until concentrations of 10^{-4} M, but in major concentrations they increased considerably the catalytic activity of the enzyme. Although these results did not lead to the expected inhibitory effect, they seemed to indicate that the designed compounds interacted with the enzyme according to that predicted by the computational studies. In order to shed light the experimental results in a molecular approach, we decided to extend the theoretical studies using molecular dynamics simulations, to evaluate greater degrees of freedom and collective interactions of the system. We studied the behaviour of the enzyme in the absence and presence of a quinoxaline derivative, a recognized inhibitor and a substrate. The studies carried out, allow us to understand the experimental results, based on structural and differential changes of the enzyme in different points of the active site, for each type of compound tested. These changes compromise the geometry of the catalytic site. In the particular case of quinoxaline, the conformation of the enzyme stabilized is similar as that in the presence of substrate, allowing a molecular approximation to the experimental results obtained.

References:

1. Computational Identification of Uncharacterized Cruzain Binding Sites, Jacob D. Durrant, Henrik Keränen, Benjamin A. Wilson, J. Andrew McCammon, Plos Neglected Tropical Diseases, 2010, 4, e676.

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