New Insights to Assist the Drug Design of IAP Antagonists: Structural and Calorimetry Approach

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The Inhibitor of Apoptosis Protein (IAP) antagonists have attracted a lot of attention in the recent past because of their potential therapeutic applications to induce apoptosis of cancer cells. This work aims a better understanding of the nature of XIAP-BIR3 inhibition by using eight different tetrapeptides antagonists. We characterized the binding parameters of these peptides, and verified their effects on the XIAP-BIR3 structure and stability. Circular dichroism, isothermal titration calorimetry (ITC) and differential scanning calorimetry (DSC) have been carried out in order to probe new details to be considered in drug design. Our ITC data showed that the binding of all tetrapeptides on XIAP-BIR3 is enthalpically and entropically favored. However, different combinations of enthalpy and entropy components can be observed. For example, the phenylalanine in the C-terminal increases the affinity by increasing the enthalpy, while the isoleucine increases the entropy. The tetrapeptide ARPF was considered the best model for drug design, since it presented higher affinity and higher enthalpy component, indicating more selectivity. DSC data showed that all peptides increased the BIR3 domain stability. Circular dichroism data showed that the different affinities and the changes on stability were strictly associated to the structural changes. The structural changes observed strongly contribute to the decrease in Gibbs free energy of the binding process. These data together with the available structural information for the XIAP-BIR3 complex provide important insights into the molecular forces that control the XIAP-BIR3 binding affinity and specificity leading to the conclusion that, the increase in the affinity is not associated only to local interactions, but is also a result of the contribution of the changes in overall structure.

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