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Inhibition of Protein-Protein Interactions and Signaling by Small Molecules[1]

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Protein-protein interactions are at the core of cell signaling pathways as well as many bacterial and viral infection processes. As such, they define critical targets for drug development against diseases such as cancer, arthritis, obesity, AIDS and many others. Until now, the clinical inhibition of protein-protein interactions and signaling has been accomplished with the use of antibodies or soluble versions of receptor molecules. Small molecule replacements of these therapeutic agents have been extremely difficult to develop; either the necessary potency has been hard to achieve or the expected biological effect has not been obtained. In this presentation, we show that a rigorous thermodynamic approach that combines differential scanning calorimetry (DSC) and isothermal titration calorimetry (ITC) provides a unique platform for the identification and optimization of small molecular weight inhibitors of protein-protein interactions. Recent advances in the development of cell entry inhibitors of HIV-1 using this approach will be discussed.

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