2016 Publication using an Affinity ITC LV Auto for Fast and Accurate Enthalpy Screening of Drug Candidates

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Enthalpy Screen of Drug Candidates
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PUBLISHED ABSTRACT:

The enthalpic and entropic contributions to the binding affinity of drug candidates have been acknowledged to be important determinants of the quality of a drug molecule. These quantities, usually summarized in the thermodynamic signature, provide a rapid assessment of the forces that drive the binding of a ligand. Having access to the thermodynamic signature in the early stages of the drug discovery process will provide critical information towards the selection of the best drug candidates for development. In this paper, the Enthalpy Screen technique is presented. The enthalpy screen allows fast and accurate determination of the binding enthalpy for hundreds of ligands. As such, it appears to be ideally suited to aid in the ranking of the hundreds of hits that are usually identified after standard high throughput screening.

SUMMARY:

Known inhibitory drugs with known activity against HIV-1 protease were evaluated with a modified Isothermal titration calorimetry (ITC) technique called an enthalpy screen. A limited number of injections (3) of the protease were made into each drug and enthalpy value calculated from the average of the three injections. The enthalpy values determined by this enthalpy screen correlated very well with previous values reported in other publications. This technique allows for accurate binding enthalpy measurements in an automated manner with the Affinity ITC LV Auto instrument using approximately 5 ug of protein per compound. The Affinity ITC Auto is the only automated ITC available with dedicated Enthalpy Screen experimental designs for programming the hardware and an Enthalpy Screen data fitting model in the data analysis software, NanoAnalyze. The binding enthalpy determined by the enthalpy screen is shown to be as accurate as the binding enthalpy determined by conventional ITC titrations. The authors show that by combining the enthalpy values with knowledge of the entropic contributions ($-T\Delta S$) which can be estimated from knowledge of K_d, K_i or IC_{50} is key to understanding the full thermodynamic signature of drug-protein interactions. The thermodynamic signatures of compounds such as those in this study can be a powerful tool in fully characterizing the quality of the compounds as potential drug candidates.

For more information on the Affinity ITC, go to http://www.tainstruments.com/