Explaining Electrostatic Serine Protease Substrate Readout Similarity

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Serine proteases are key players in numerous fundamental cellular reactions and are amongst the most important targets in drug design [1]. Despite having the same fold, serine proteases often show different substrate specificities, depending on the biological processes they are part of. Here, we investigate the role of enthalpy in electrostatic serine protease substrate readout similarity. We used GRID [2] to calculate binding site interaction potentials for nine serine proteases with chymotrypsin fold probing for different types of binding site interactions. We then determined similarities in binding site interaction potentials of all nine proteins and compared them to electrostatic substrate readout similarities. We were able to explain electrostatic substrate readout similarities for all cases. The results give a detailed view of the enthalpic interactions in serine protease subpockets driving electrostatic substrate readout similarity and can be exploited in selective drug design.

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[2] Goodford, P. J., A Computational Procedure for Determining Energetically Favorable Binding Sites on Biologically Important Macromolecules. *J. Med. Chem.* **1985,** *28*, 849-857.