obtained using molecular dynamics simulations of XPLOR (Chakravarty, 1995). Ph.D. thesis, University of Bombay, India). Further simulations on nineteen other sulfonamide complexes whose crystal structures were not known, clearly revealed that the loop region comprising of L198, T199, H200, P201 and P202 were crucial for the design of HCAI - specific sulfonamide inhibitors. Several substituted aromatic and benzene sulfonamides were then docked into the active sites of the isozymes to optimise the interactions with these loop residues. Stereospecific substitution of methyl imidazole group in benzene sulfonamide resulted in strong interactions between the imidazole groups of the inhibitor and His 200 as observed from the energy minimised structure of the complex. Since His 200 is non - conserved between HCAI and HCAII, this indicated that the inhibitor would be more specific against HCAI. Energy minimisation of the resultant complex confirmed it. Further substitution of an alkyl chain resulted in additional stable non - bonded interactions with another non conserved active site residue Ala 712. The compound BARCZM1 has been synthesised (Ghosh et al.; To be published) and is being characterized for its inhibitory properties the details of which will be presented.


Thromboembolic diseases remain a leading cause of mortality and morbidity in developed societies. Thrombin, a trypsin-like serine protease, is a key mediator in such disease states, primarily through fibrin formation and platelet aggregation. In response to the well documented liabilities associated with warfarin, an industry wide search has been initiated to discover safe and effective, orally active thrombin inhibitors that can be used to treat thrombotic disorders. Over the past few years, a number of very potent and selective inhibitors of thrombin have been identified based on the NAPAP, Argatroban (MD-805), or a D-Phe-Pro-Arg structural motif. In general, however, the peptidal nature of these class of agents is prohibitive of high oral bioavailability.

In an effort to identify a non peptidal inhibitors of thrombin which might have a more favorable pharmacokinetic profile than their peptide-related counterparts, we have prepared LY 178550 as an initial lead for future structure-based drug design studies. Agent LY 178550 consists of two primary components: 1) 5-amidinoindole which has been previously employed as an arginine surrogate in the design of inhibitors of arginine endopeptidases, and 2) a hydrophobic 4-benzylpiperdine tail which has the potential to interact with the well characterized P3 pocket of the thrombin active site.

A crystal structure of human α-thrombin complexed with LY 178550 was determined by X-ray technique at 2.2 Å resolution. A final complex model has crystallographic R-factor of 14.4% with standard deviation from ideal for bond distances of 0.014 Å. A clear well defined electron density was observed for the inhibitor molecule in the active site. The inhibitor main chain has a L-shape and mimics conformation of arginal tryptepides. This post will describe the X-ray crystallographic study of the interaction of LY178550 with the active site of human α-thrombin.