Poster Presentation

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The inhibitory mechanism analysis of human chymase specific inhibitor TJK002

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Chymase is a mast cell specific serine protease that is stored within secretory granules and released together with heparin and histamine in response to allergen challenge or other stimuli. Recent study have shown that chymase possess processing activity for biological peptides and cytokines implicated in a variety of diseases. For example, the chymases of primateds and dogs have highly specific angiotensin II generating activity, and the results of animal studies suggest the chymase contributes to the pathogenesis of cardiovascular diseases via Ang II generation. Based on the results of these studies, inhibition of chymase is expected to provide therapeutic means for the treatment of these diseases. Recently, we have developed some novel benzimidazole derived in human chymase inhibitors and the crystal structure of human chymase complexed with a nobel benzimidazole inhibitor TJK002 was obtained at 2.8A. TJK002 showed potent inhibitory activity (Ki value 2.24nM) with respect to human chymase. X-ray crystallographic structure showed that THK002 forms an anon-covalent interaction with the catalytic domain of human chymase. 4-methylbenzothiophen-3-yl moiety of TJK002 occupies the S1 pocket. The carboxylic acid for hydrogen bonds with the imidazole N (e) atom of H57 and O (g) atoms of Ser195 at the catalytic site. The binding mode of TJK002 is very unique and attractive compared other cymase inhibitors. It depends on the binding mode of TJK002 and reflects to its biological function. Because by site-directed mutagenesis, human mast cell chymase are responsible for an acidic amino acid residue preference in the P2' position of substrates. Chymase inhibitors besides TJK002 have negatively charged p2' moiety. But TJK002 doesn't have such a moiety which binds to S2' site, but it still has a strong incisory activity. We clarify its strong inhibitory mechanism of TJK002 by Fragment molecular orbital (FMO) calculation. We discovered the stacking interaction between the benzimidazole ring and His57 is quite effective for the inhibitory activity of TJK002.

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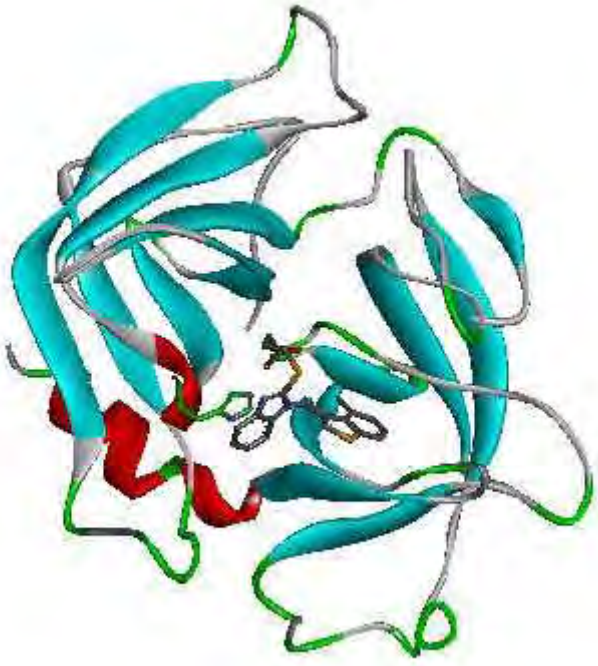

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