STRUCTURE BASED DESIGN OF CATHEPSIN S INHIBITORS

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Inhibitors of the cysteine protease cathepsin S, which is involved in antigen processing, have potential application for the treatment of autoimmune diseases. Additionally, the potent elastinolytic activity of cathepsin S may implicate this protease in atherosclerotic plaque destabilization and other tissue destructive diseases. Utilizing protein X-ray crystal structures and molecular modeling we have designed novel reversible inhibitors with picomolar potency and very high selectivity against the related cathepsins K, L, and B. Further optimization yielded orally bioavailable compounds with good pharmacokinetic profile.