CS2-4 Defying Difficult Diseases: Design and Synthesis of Protease Inhibitors, Prodrug Forms and Click Peptides

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Based on the substrate transition state, we designed and synthesized novel classes of inhibitors of aspartic proteases such as renin, HIV protease, malarial plasmepsin II, containing the hydroxymethylcarbonyl (HMC) isostere. Among them, tripeptide KNI-272 was a highly selective and superpotent HIV protease inhibitor. Physicochemical studies suggested that the HMC isostere is an ideal transition-state mimic. We applied the substrate transition state concept to develop inhibitors against ß-secretase (BACE1) targeting Alzheimer's disease (AD), and designed a novel BACE1 inhibitor, KMI-429 that reduced amyloid ß peptide (Aß) production in transgenic and wild-type mice.

We developed the *O*-acyl isopeptide method for the synthesis of difficult peptide sequences including Aß. The native Aß1-42 tends to aggregate due to uncontrolled polymerization complicating AD research. On the basis of our study with the "*O*-acyl isopeptide method", we developed novel photo- and pH-triggered "click" peptides that readily convert to the native Aß1-42 upon activation. Click peptide Aß1-42 analogs migrated to generate Aß1-42 with a 'click' reaction via an *O-N* intramolecular acyl migration. The BACE1 inhibitors and amyloid ß 'click' peptide that we developed will pave the way to defy Alzheimer's disease.