Discovery of unprecedented aspartic-protease inhibitors with applications in Alzheimer and other diseases

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Aspartic proteases represent a family of proteins that includes important drug targets. Here we focus on endothiapepsin, a pepsin-like aspartic protease that has been studied excessively as a model enzyme both for elucidating the catalytic mechanism [a] and also in the clinical development of renin [b] and β-secretase inhibitors [c]. The catalytic site of this enzyme, consists of two aspartic acid residues. We designed a novel multicomponent reaction (MCR) scaffold [d] with the potential to interact with both acidic residues. A small library of derivatives was synthesized with a straight-forward two-step synthesis and was biologically evaluated with two orthogonal methods. The initial hits were optimized by preparing and docking virtual libraries and a series of new derivatives was synthesized. A co-crystal structure of a small molecule in endothiapepsin was obtained, supporting the design of the scaffold.

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