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

M. Konstantinidou [1*], F. Sutanto[1], F. Magari [2], M.Y. Ünver [3], V.R. Jumde [3,4], A.K.H. Hirsch [3,4], G. Klebe [2], A. Dömling[1]

[1]Group of Drug Design, Groningen Research Institute of Pharmacy, University of Groningen, A. Deusinglaan 1, 9713 AV, Groningen, the Netherlands, [2] Department of Pharmaceutical Chemistry, Philipps University Marburg, Marbacher Weg 6, 35032 Marburg, Germany, [3] Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 7, 9747 AG Groningen, The Netherlands, [4] Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) - Helmholtz Centre for Infection Research (HZI), Department of Drug Design and Optimization, 66123, Saarbrücken, Germany

* Correspondence: M.Konstantinidou@rug.nl

Aspartic proteases represent a protein family with significant drug targets, including renin, HIV-protease, β-secretase (BACE-1) and plasmepsins. The common structural feature in these proteins, are the two aspartic acid residues in the active site, which form the catalytic dyad. Various warheads have been studied for interacting either directly with the catalytic dyad of aspartic acids or indirectly mimicking the tetrahedral intermediate.

Aims

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]. In order to target the catalytic dyad in the active site, we designed a novel multicomponent reaction (MCR) scaffold [d] with the potential to interact with both acidic residues.

Methods

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 enumerating and docking virtual libraries. A series of new derivatives was then synthesized.

Results / Conclusions

Results from an activity assay indicated that most of the derivatives were active and co-crystal structures with endothiapepsin supported the design of the scaffold.

References:

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