Design of a multi-component reaction scaffold with inhibitory activity on aspartic proteases

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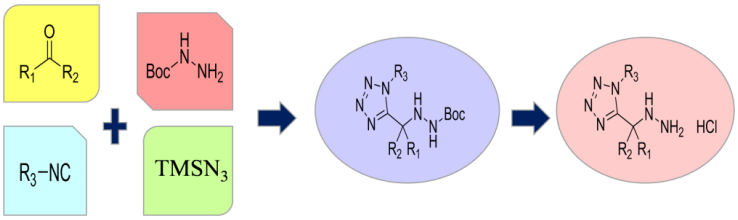
Aspartic proteases represent a protein family with significant drug targets, including renin, HIV-protease, β-secretase (BACE-1) and plasmepsins. Various warheads have been studied for interacting either directly with the catalytic dyad of aspartic acids or indirectly mimicking the tetrahedral intermediate. 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 and also in the clinical development of renin and β-secretase inhibitors. In this work, we designed a novel multi-component reaction (MCR) scaffold with the potential to interact with both acidic residues. The scaffold can be accessed via a two-step synthesis.



Preliminary screening results and crystallization studies supported the choice of the scaffold. Optimized derivatives were designed by docking virtual libraries and the selected hits were synthesized. Finally, novel crystal structures were obtained.

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