FROM FRAGMENT HITS TO MCR SMALL MOLECULES: DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION

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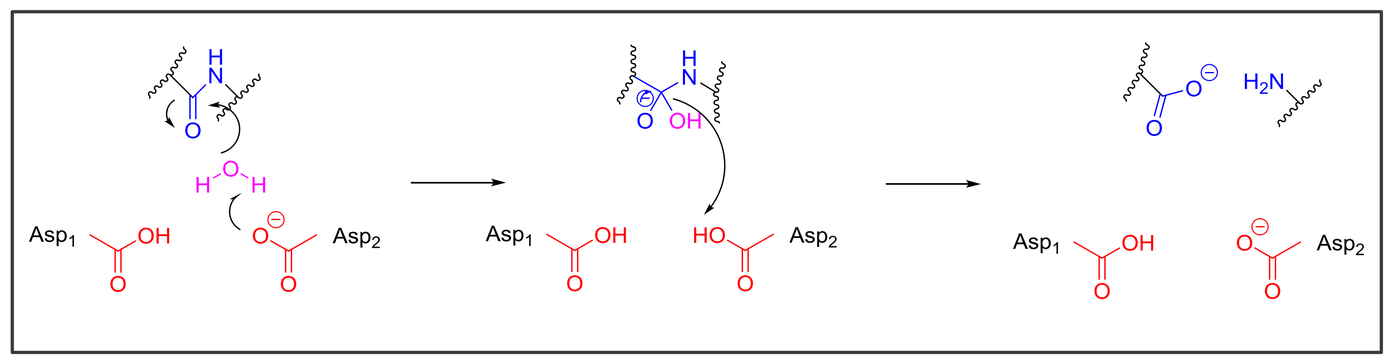
1 Introduction

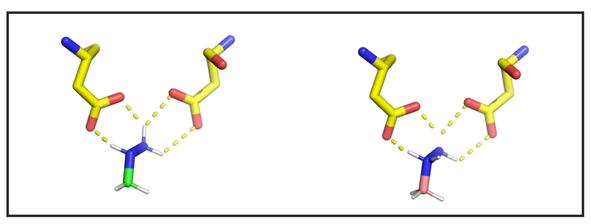
Fragment-based drug design is a well-established strategy for the identification of lead compounds. The initial fragment hits are typically grown, linked or merged, in order to become drug-like compounds with improved affinity.[1] Here we present how the fragments can be used as starting materials for multi-component reaction chemistry (MCR) to obtain drug-like scaffolds in one or two synthetic steps.

2 Design and synthesis

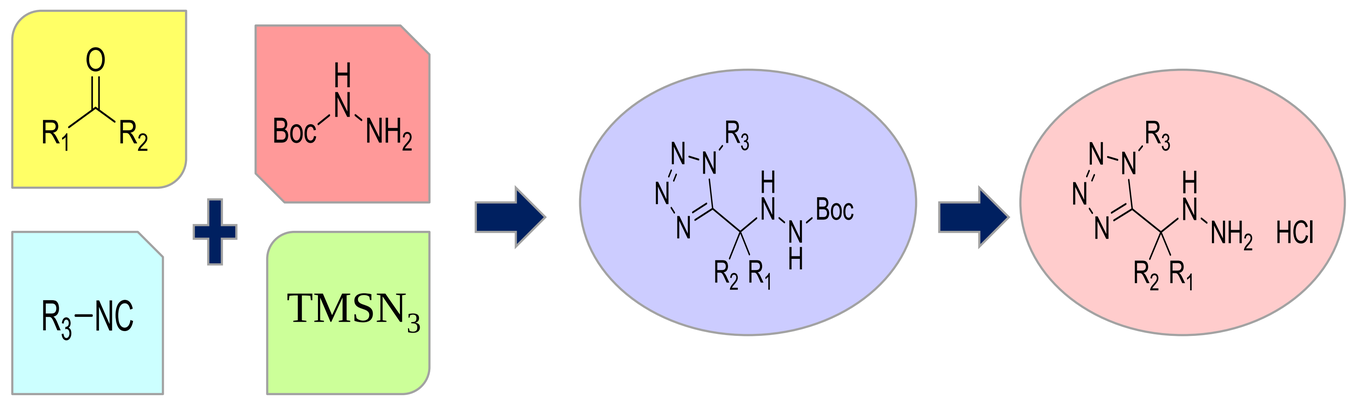
- Aspartic proteases contain two aspartic acid residues in the active site
- Direct inhibitors: targeting the catalytic dyad
- Indirect inhibitors: mimicking the tetrahedral intermediate
- The project focuses on endothiapepsin [2,3]
- Design of a warhead bearing two basic moieties (hydrazine)
- Hydrazine: amine-component in Ugi-tetrazole reaction [5]
- The Ugi-tetrazole reaction is chosen due to shape complementarity with the target protein.



Catalytic mechanism of aspartic proteases. [4]



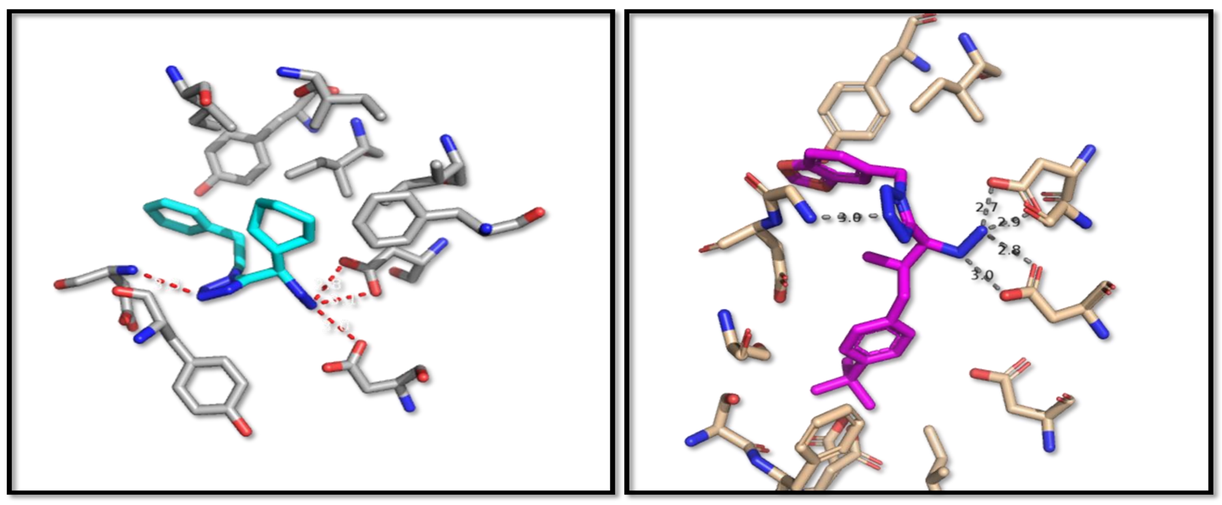
Hydrazine warhead: protonated in the exo- or endo-nitrogen



2-Step synthesis for the hydrazine-tetrazole scaffold

3 Results

- Initial screening with STD-NMR and a fluorescence-based assay
- 5 out of 17 derivatives showed inhibitory activity
- Development of in-house docking protocol for tailored-made MCR libraries
- Further computational optimization
- Docking hits selection
- Synthesis of optimized derivatives
- Fluorescence-based assay for biological evaluation
- Co-crystal structures were solved



Left: inhibitor from the 1st screening (IC_{50} 53μM), right: optimized inhibitor (IC_{50} 21.9μM)

4 Conclusion

- Design of new warhead with the potential to interact with both aspartic acids
- Biological results and crystal structures support the choice of the MCR scaffold

Acknowledgement

This project has received funding from the European Union's Framework Programme for Research and Innovation Horizon 2020 (2014-2020) under the Marie Skłodowska-Curie Grant Agreement No. 675555, Accelerated Early staGe drug discovery (AEGIS).

References

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