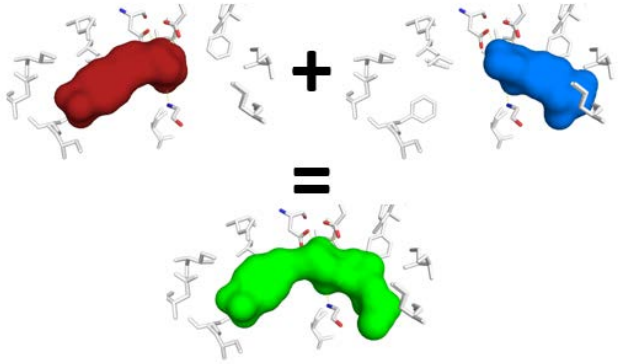
Fragment Evolution in the Endothiapepsin Bindingsite – A Fragment Merging Strategy

Lars Ole Haustedt[a*], Franziska Huschmann[b,c], Gerhard Klebe[b], Alexander Metz[b], Uwe Müller[c], Manfred Weiss[c], Serghei Glinca[d], Janis Müller[d], Nils Walter[e] and Christian B. W. Stark[e]

* l.haustedt@ac-discovery.com, www.ac-discovery.com
a) AnalytiCon Discovery GmbH, Hermannswerder Haus 17, 14473 Potsdam
b) Institut für Pharmazeutische Chemie, Universität Marburg, Marbacher Weg 6, 35032 Marburg
c) HZB-MX, Elektronenspeicherring BESSY 2, Albert-Einstein-Str. 15, 12489 Berlin
d) CrystalsFirst GmbH, Marbacher Weg 6, 35032 Marburg
e) Institut für Organische Chemie, Universität Hamburg, Martin -Luther-King-Platz 6, 20146 Hamburg

Fragments from Nature are rich in terms of pharmacophoric features and therefore deliver information dense data sets. Growing, merging and morphing opportunities for each fragment have been implemented making use of AnalytiCon's larger library of synthetic compounds based on natural product motifs and the corresponding virtual chemical space. The combination of high solubility by design (multiple polar functionalities and high FSP3) and tractable chemistry qualify the fragments as efficient starting points for fragment evolution. The characteristics of the fragment library are extraordinary favorable for a structure-based profiling using CrystalsFirsts SmartSoak® Screening after stabilization of the protein crystal system by SmartSoak® stabilization. High concentration soaking using SmartSoak® combined with *Fragments from Nature* enables acquisition of information rich datasets and bio-structural driven informed decisions in challenging drug discovery projects.



Endothiapepsin serves as an insightful model system for the large group of pepsin-like aspartic proteases. Many proteins out of this family are relevant in serious and life threatening diseases such as malaria (plasmepsins), fungal infections (secreted aspartic proteinases), Alzheimers's disease or hypertension (renin).[1]
After identification of two fragments both making essential polar interactions with the catalytic diad and a backbone glycine these fragments were progressed using a merging strategy. Elegant chemistry for merging the two fragments into one compound has been developed. This merged compound was soaked into stabilized crystals of endothiapepsin making advantage of CrystalsFirst SmartSoak® structural biology platform. High-resolution structural data was obtained featuring very similar binding modes for the merged compound in regard of the initial fragment binding. By ITC measurements, an improvement of K_I by one magnitude could be observed compared to the initial fragments. A merging strategy can be a valuable addition of fragment evolution modalities.

[1] Köster, H. et al. *J. Med. Chem.* **2011**, *54*, 7784.