PLAYING AGAINST THE ODDS
SCAFFOLD HOPPING FROM COMPLEX 3D FRAGMENTS

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Introduction

New small molecule entities originating from HTS or fragment-based paradigms are mostly composed of heterocyclic structures that hardly match the chemical diversity of natural products that have been for centuries the leading source of active drugs in the pharmacopeia.[1] Here we disclose our strategy to elaborate complex drug-like molecules using small 3D fragments as starting point in a rescaffolding approach.

Virtual screening of 3D fragments

There is a strong interest for the discovery of novel inhibitors of Caspase-1 (ICE), a protein involved in various inflammatory diseases such as rheumatoid arthritis, osteoarthritis, or psoriasis.[2] In order to develop new inhibitors, we used our **EDEN** platform (***Edelris Discovery ENgine***) to explore the possibility to design or rescaffold ligands from innovative, 3D-enriched fragments that offer multiple vectors for growing, merging, or linking operations.

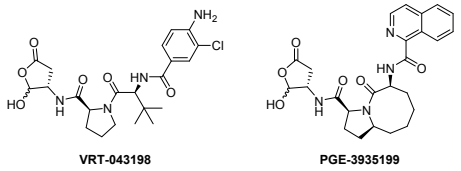


Figure 1: Structure of known Caspase-1 inhibitors VRT-043198 and PGE-3935199

ReCore software[3] was used as rescaffolding engine, using a Caspase-1/PGE-3935199 X-ray structure as reference.[4] The query was designed as follow :

- Disconnection between C10-C11 and C20-N23 (S2-S3 pockets)
- H-bond acceptor (HBA) required at the atom coordinates of the carbonyl O22
- Exclusion volume (*r*=0.7 Å) around binding site atoms to avoid steric clashes with the protein.

Data mining from our proprietary Edelris Keymical Space™ (153.000 fragments derived from a dataset of 12.000 natural product mimetic compounds) allowed us to scan for P2-P3 replacement solutions.

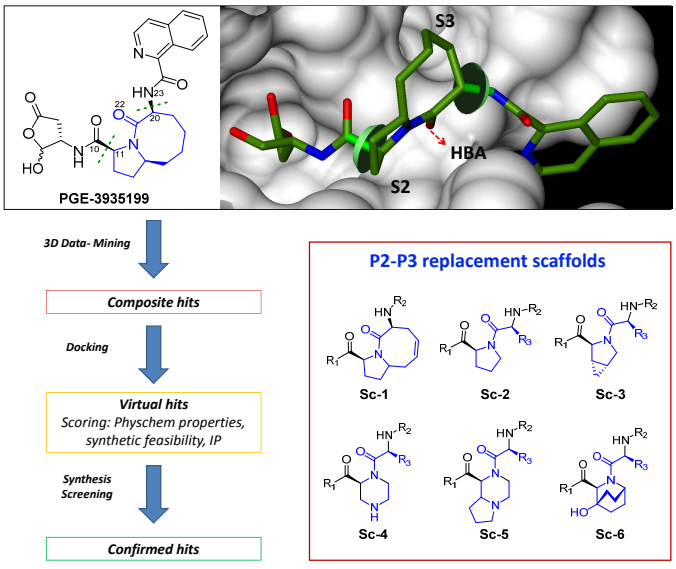
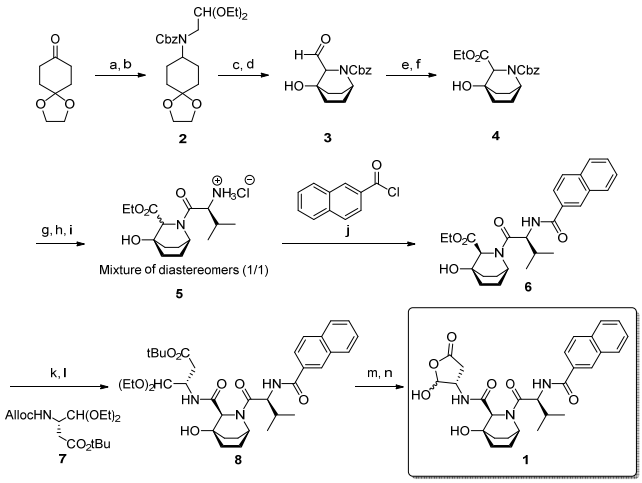


Figure 2: Scaffold hopping process implemented to identify new Caspase-1 inhibitors

Some illustrative replacement scaffolds are described (**Sc-1** to **Sc-6**). We found a strong interest in **Sc-6**, a bridged 2-azabicyclo[2.2.2]octane (2-ABO) scaffold belonging to Edelris Keymical Space™. This composite hit was further validated through docking experiments using FlexX,[3] and the promising results obtained prompted us to initiate a wet chemistry program.

Synthesis and binding assay

The desired target **1** has been prepared as described in Scheme 1. The key step to build the 2-ABO system rely on an acid catalyzed intramolecular selective aldol reaction to produce aldehyde **3**.[5]



Reagents and conditions :(a) $NH_2CH_2CH(OEt)_2$, $NaBH(OAc)_3$, DCE; (b) CBzCl, $NaHCO_3$, DCM, 74% (2 steps)
(c) HCl 5%, THF, r.t. (d) K_2CO_3, THF, 60 °C, 59% (2 steps) (e) $NaClO_2$, 2-Me-2-butene, *t*BuOH / THF / H_2O, r.t.
(f) H_2SO_4, EtOH, reflux, 66% (2 steps) (g) H_2 (1 atm), HCl, Pd/C, EtOH, r.t.
(h) Boc-L-valine, HATU, DIPEA, DCM/DMF, r.t., 92% (2 steps)
(i) HCl, dioxane, r.t. 98% (j) DIPEA, DCM, r.t. diastereomer separation (HPLC), 22%
(k) LiOH (2 eq.), H_2O / THF / EtOH 68% (l) i. DMBA, $Pd(PPh_3)_4$, DCM ii. EDCI, HOBt, DCM, 55%
(m) TFA, DCM, r.t. (n) HCl, MeCN, H_2O, r.t., 35%(2 steps)

Scheme 1 : Inhibitor **1** synthesis.

Compound **1** was then evaluated in a human recombinant Caspase-1 *in vitro* assay, showing a very high potency, close to the references.

Inhibitor	PGE-3935199	VRT-043198	1
IC_{50} (nM)	11	5	17

X-Ray co-crystal structure

X-Ray co-crystal structure of **1** and Caspase-1 protein revealed a binding mode consistent with the docking model (Figure 3). The aspartic residue P1 forms key interactions with Arg341, Arg179 and Gln283 in the S1 pocket. Cys285 is covalently bound to form a reversible thio-hemiacetal. Notably, the S2 pocket is nicely occupied with the bridged 2-ABO ring (hydrophobic contact with Trp340). Superimposition of **1** and PGE-3935199 X-Ray structures revealed a nice overlap.

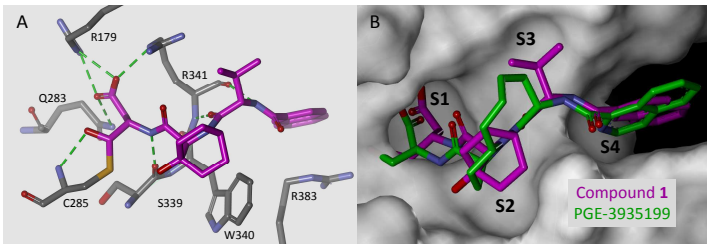


Figure 3: (A) X-Ray structure of compound **1** covalently bond to the Caspase-1 protein (B) Superimposition of X-Ray structures of **1** and PGE-3935199

Conclusion

3D fragments offering multiple anchors for expansion have proved to be a valuable source to design new inhibitors in a rescaffolding approach. The relevance of solutions identified using Recore were confirmed by docking and translated into a nanomolar inhibitor of Caspase-1. The high predictivity of the model allowed minimal efforts in terms of chemistry resources and was accomplished within a short timeframe. X-Ray structure confirmed the postulated binding mode, thus fully validating our approach.

References : 1) Hann, M. M., Leach, A.R., Harper, G. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 856–864. 2) Franchi, L; Eigenbrod, T.; Muñoz-Planillo, R.; Nuñez, G. *Nat. Immunol.* **2009**, *10*, 241–256. 3) Recore and FlexX in LeadIT v.2.1.8, BioSolveIT GmbH, St. Augustin, Germany, biosolveit.de/LeadIT, 2016; 4) Unpublished results. 5) Diaba , F., Bonjoch, J. *Org. Biomol. Chem.* **2009**, *7*, 2517-2519.