MINING FROM NP-LIKE FRAGMENTS IN 3D
DISCOVERY OF A POTENT CASPASE-1 INHIBITOR

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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 pharmacopeia. 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. 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.

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

Some illustrative replacement scaffolds are described (Sc-1 to Sc-6). We found a strong interest in Sc-6, a bridged 2-azacyclob[2.2.2]octane (2-ABO) scaffold belonging to Edelris Keymical Space™. This composite hit was further validated through docking experiments using FlexX® 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.

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 a strong and stable hydrogen bond with the protein’s Asp284. 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.

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 chemistry and was accomplished within a short timeframe. X-Ray structure confirmed the postulated binding mode, thus fully validating our approach.

References: