Fragment-based virtual screening for unexplored bromodomains

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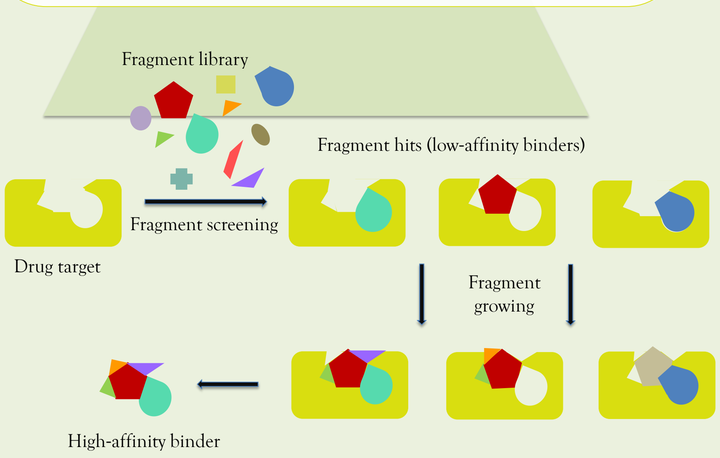
Fragment-based virtual screening

Fragment-based virtual screening (FBVS) utilizes low molecular weight (MW<300) compounds to target subpockets within a protein's binding site [1]. The identified fragments are generally weak binders which can be combined or optimized to produce high affinity binders. Compared to ligand-based virtual screening, FBVS allows for screening of a much larger chemical space by using a smaller library [2].



Bromodomains

Bromodomains are emerging epigenetic targets in various types of cancer [3]. They recognize ε-*N*-acetylated lysine residues (K_{ac}) on the unstructured histone tails. The K_{ac} binding site of most bromodomains features a conserved asparagine residue responsible for substrate recognition [4]. Conversely, some bromodomains such as BRWD1, PHIP, and BRWD3 have a threonine residue in the same position (Figures 1 & 2). This threonine could act both as a hydrogen-bond donor and acceptor and is a good starting point for the identification of selective inhibitors. In this project we target BRWD1(2) using the FBVS approach.

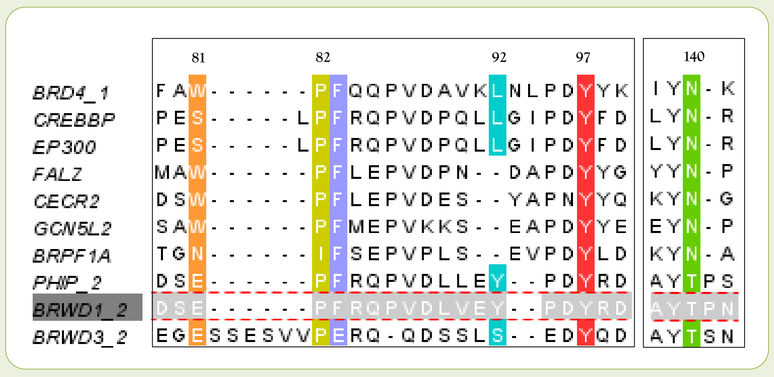


Figure 1. Multiple sequence alignment of selected bromodomains. The sequence of BRWD1(2) and residues involved in ligand recognition are highlighted.

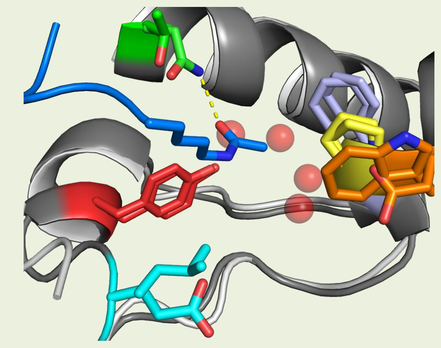
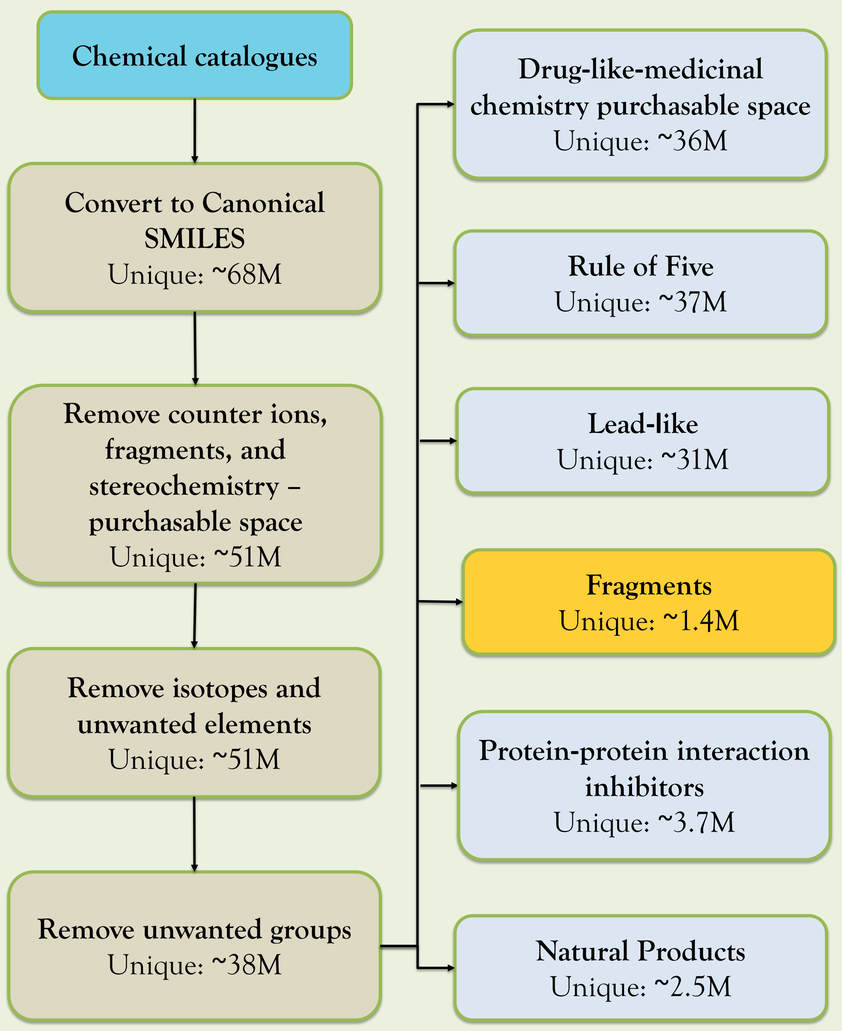


Figure 2. Superposition of K_{ac} binding sites of BRD4(1) (PDB: 3UVW) and BRWD1(2) (PDB: 3Q2E). The acetylated lysine residue (shown in blue) is engaged in a hydrogen-bond with the conserved asparagine of BRD4(1).

Purchasable space of fragments

Commercially available compounds were collected and filtered using an automated workflow designed within the ChemicalToolBoX [6, 7]. Fragments were selected using the Rule of Three [1].



Druggability and chirality analysis

We have recently shown that low-druggability binding sites can be addressed with chiral molecules [5]. To get insight into the chirality demands of BRDs, we have analyzed the druggability of their recognition site. The results suggest that BRWD1(2) binds preferably chiral molecules.

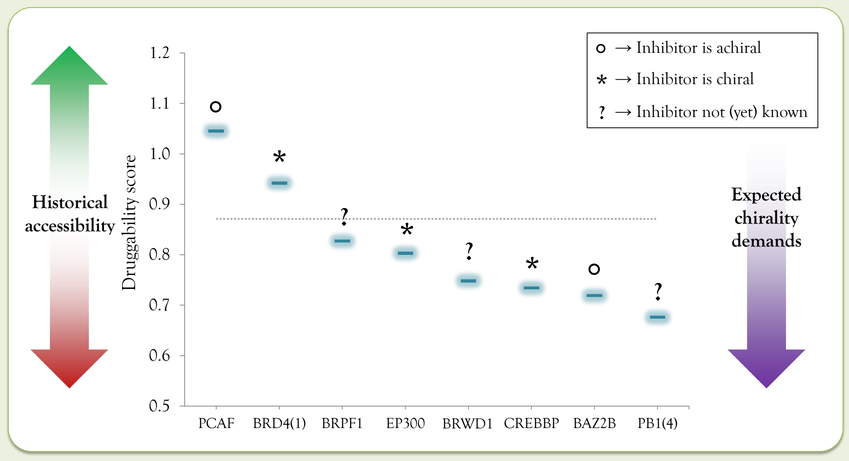


Figure 3. Druggability analysis of several BRDs. Historical accessibility of the targets and their expected chirality demands are indicated. The average druggability value for difficult targets (0.871) is indicated as a dashed line.

Future prospects

- Identification of putative binding fragments of BRWD1(2)
- Experimental validation of identified fragments
- Co-crystallization of fragments with the target
- Structure-based fragment growing and ligand optimization
- Preliminary cellular assays

Collaborations

Biochemistry (experimental validation, X-ray crystallography):
Martin Hügle

Dr. Daniel Wohlwend

Prof. Dr. Oliver Einsle

Chemistry (organic synthesis):
Dr. Dmytro Ostrovskyi

Prof. Dr. Bernhard Breit

Chemical epigenetics (cellular assays):
Prof. Dr. Manfred Jung

Acknowledgments and Funding

JUNIOR RESEARCH GROUP PROGRAMME

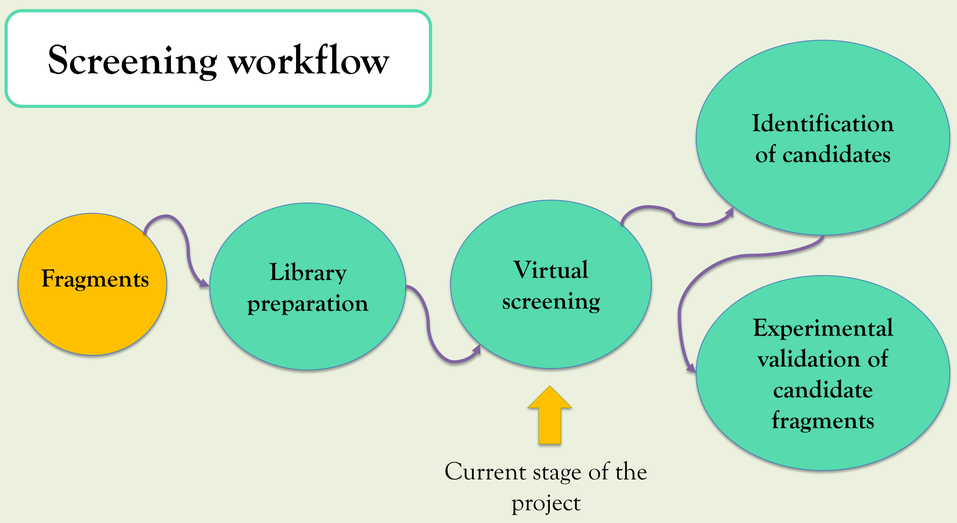
DFG Deutsche Forschungsgemeinschaft

Black Forest Grid

Ministerium für Wissenschaft, Forschung und Kunst Baden-Württemberg

bwGRiD

Screening workflow



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