

Recognition of 4-acyl pyrroles by acetyllysine epigenetic readers

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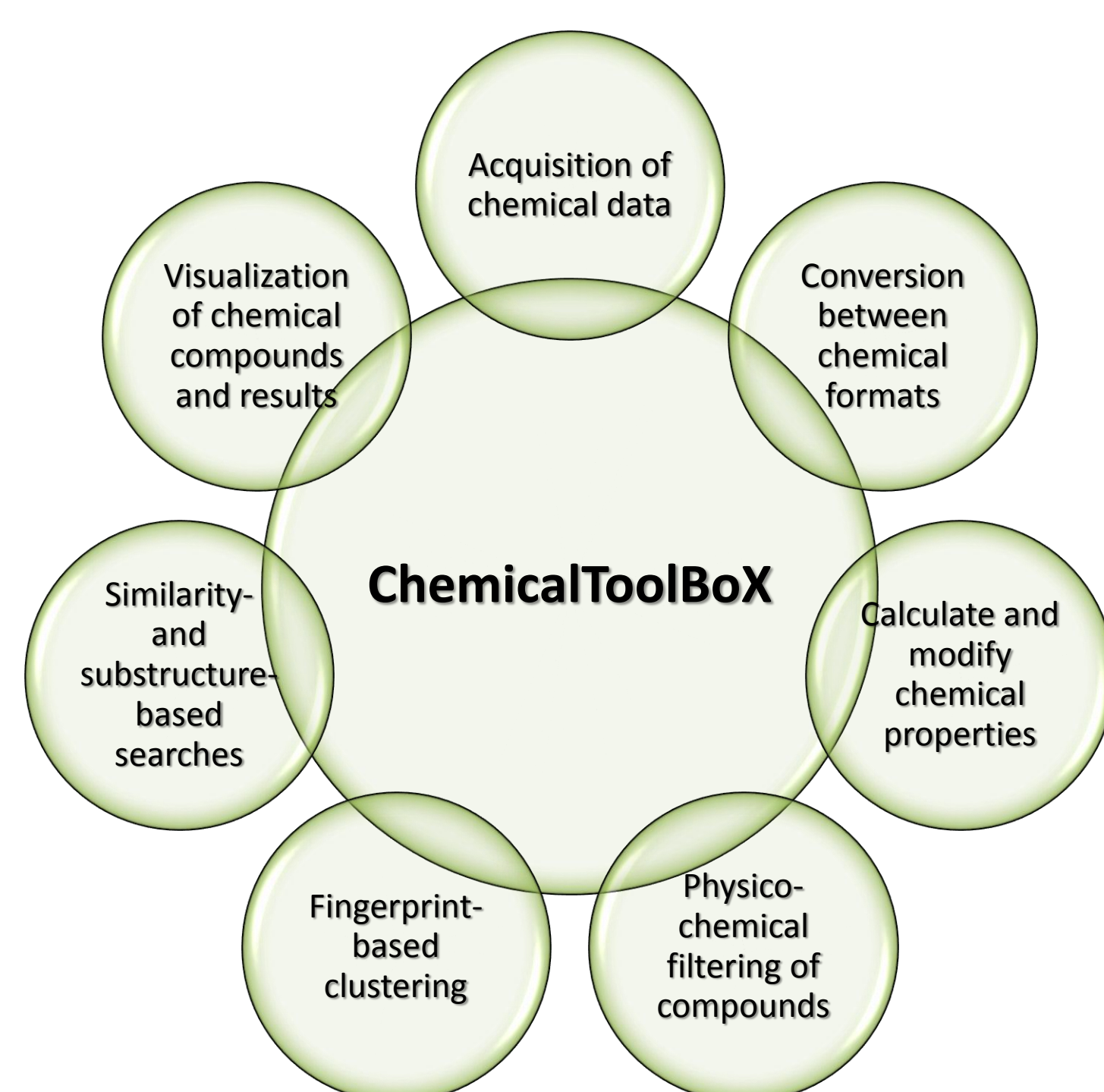
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Bromodomains are epigenetic mark 'readers' that specifically recognize ϵ -N-acetylated lysine residues. Their potential as therapeutic targets has attracted much attention due to their implication as regulators of disease-relevant gene expression. BET is the most studied bromodomain subfamily so far, and it has been characterized as a key determinant in several types of cancer, particularly leukemia [1,2]. We have performed a structure-based virtual screening and identified 4-acyl pyrroles as a novel class of bromodomain inhibitors [3].

Library preparation

Millions of compounds for screening were collected and processed using the cheminformatics platform ChemicalToolBoX [4]. That in-house library is an appealing compilation of small molecules for structure- and ligand-based drug discovery.



> 35M drug-like compounds

> 1.4M fragments and building blocks

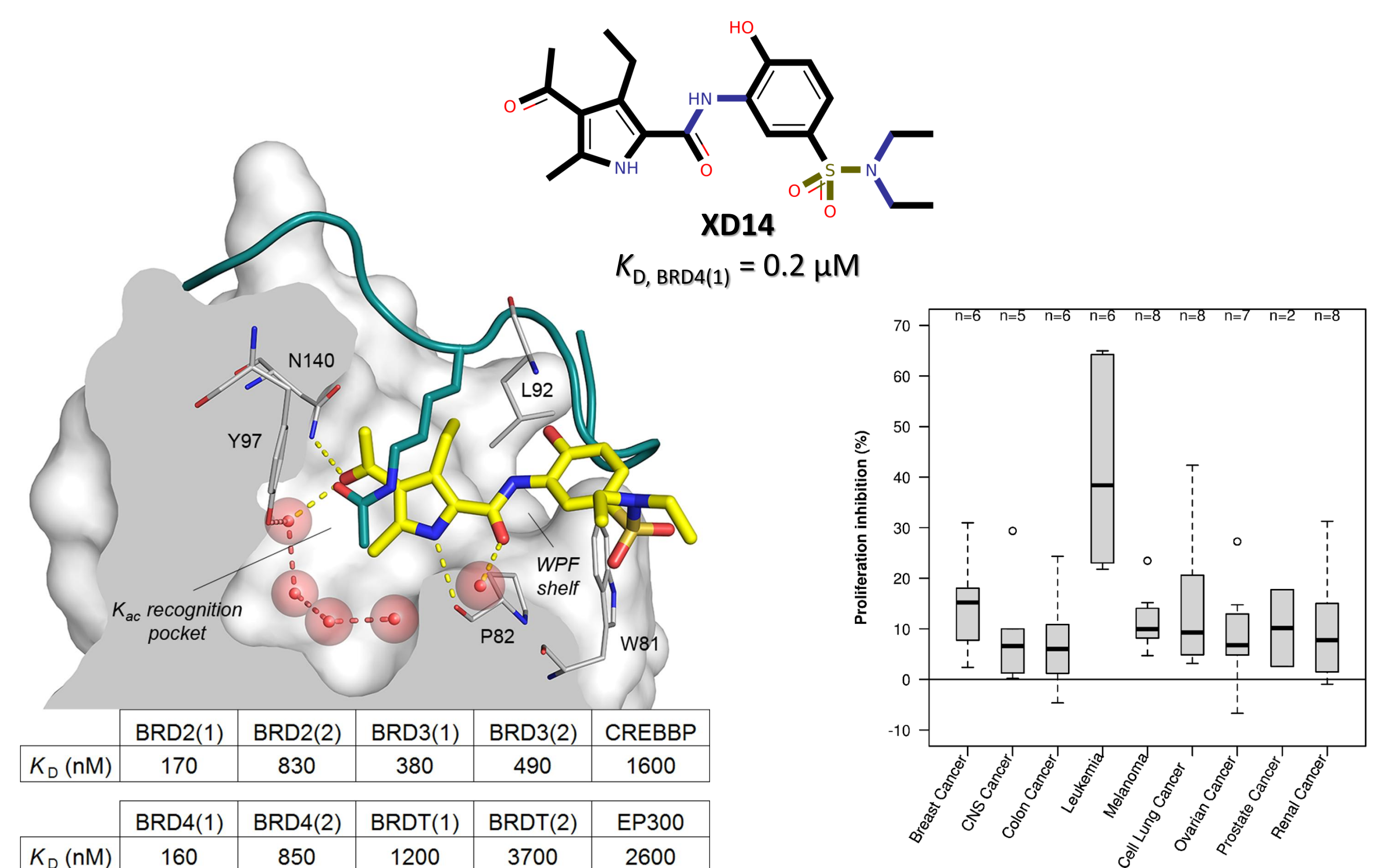
> 3.7M protein-protein interaction inhibitor-like compounds

> 2.5M natural products

Large amount of biomimetics

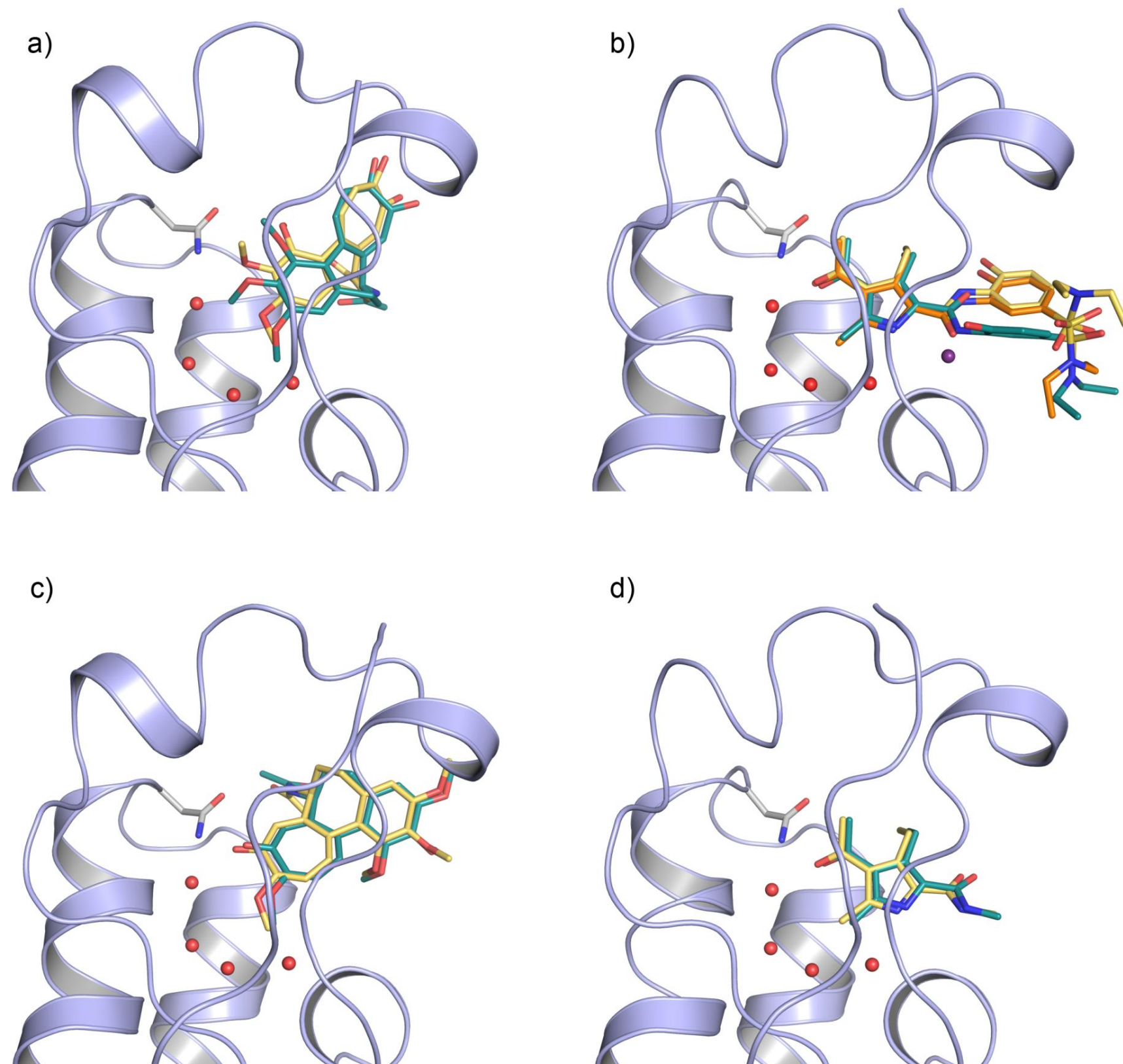
Discovery of XD14

We performed a structure-based drug discovery campaign and identified the potent BET bromodomain inhibitor XD14, which features a novel 4-acyl pyrrole core. The molecule shows potent and selective antiproliferative activity against leukemia cell lines in *in vitro* cellular studies [3].



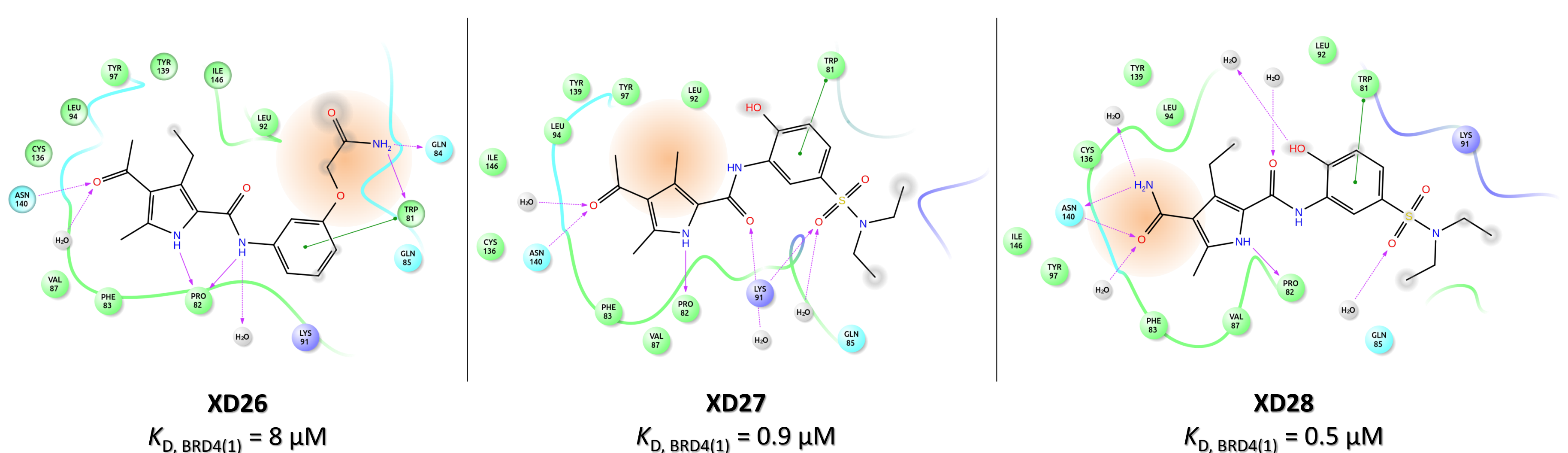
Robustness of the model

Docking models (turquoise) accurately predicted the crystallographic binding mode (pale yellow) for some identified hits.



Lead modification

We have explored the chemical space of 4-acyl pyrroles and identified several other BRD4 inhibitors containing this scaffold with average to promising binding affinity:



XD26: removing the sulfonamide moiety in XD14 carries a weakening of the CH- π interaction with W81 and a loss of affinity of 40-folds.

XD27: the 3-Me-pyrrol derivative of XD14 induces a loss of affinity of 4-folds.

XD28: adding a dual hydrogen-bond feature in position 4 of the pyrrol of XD14 retains low nM affinity.

Conclusions

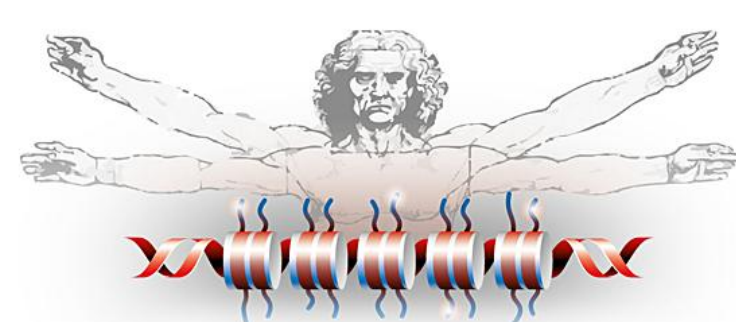
Structure-based virtual screening is presented as a valid approach in epigenetics. Here, a new class of potent BET bromodomain inhibitors based on 4-acyl pyrroles is described, that mimics the interaction with the natural substrate. The binding mode of XD14, as lead molecule of the new class ($K_D = 0.2 \mu M$), could be precisely predicted using *in silico* methods.

Rational modifications of this lead compound allowed for the structural and biological characterization of this new class.



Baden-Württemberg

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[1] Prinjha RK *et al.*, "Place your BETs: the therapeutic potential of bromodomains", *Trends Pharmacol. Sci.*, 2012, 33(3): 146-53.

[2] Lucas X and Günther S, "Targeting the BET family for the treatment of leukemia", *Epigenomics* (in press).

[3] Lucas X, Wohlwend D *et al.*, "4-acyl pyrroles: mimicking acetylated lysines in histone code reading", *Angew. Chem. Int. Ed. Engl.*, 2013, 52(52):14055-9.

[4] ChemicalToolBoX website: <http://132.230.56.143:8080>.

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