Discovery of XD14, a potent BET bromodomain inhibitor

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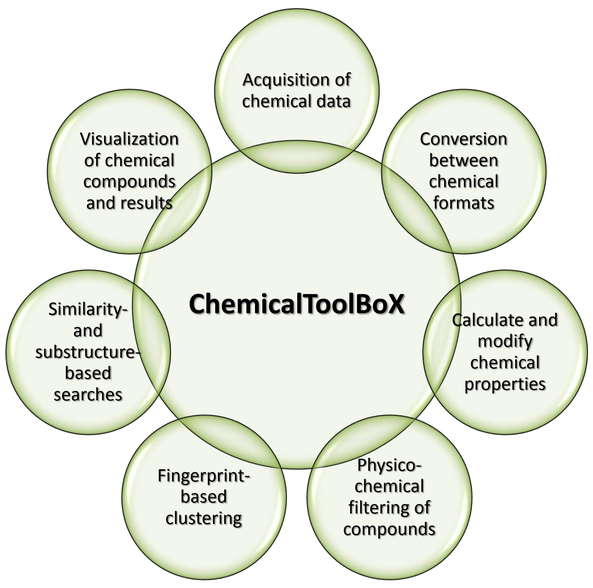
Bromodomains are epigenetic mark 'readers' that specifically recognize ε-*N*-acetylated lysine residues. Their potential as therapeutic targets has attracted much attention due to their implication as **regulators of disease-relevant gene expression**. BET is the most studied bromodomain subfamily so 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

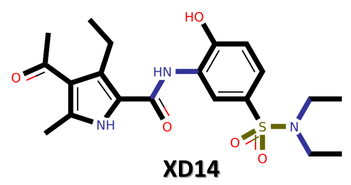
Millions of compounds for screening were collected and processed using the cheminformatics platform **ChemicalToolBoX** [4]. That in-house library is an appealing compilation of small molecules for structure- and ligand-based drug discovery:



- > 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

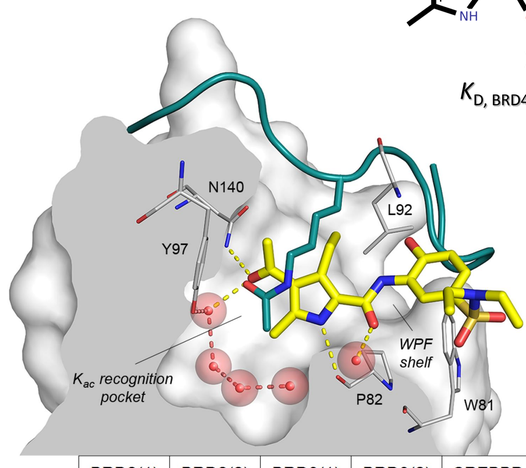
Discovery of XD14

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 and no acute toxicity [3]:



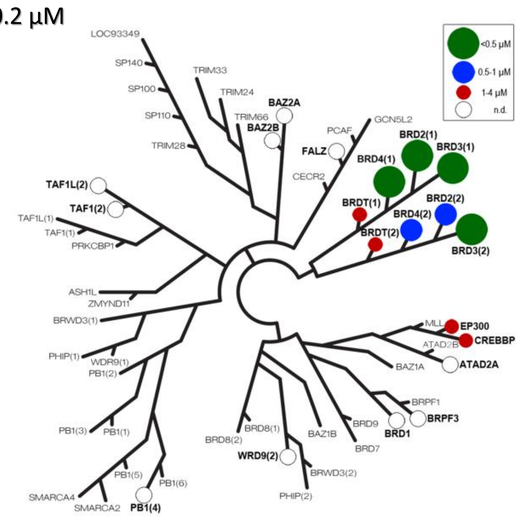
XD14

$K_{D,\ BRD4(1)}$ = 0.2 µM



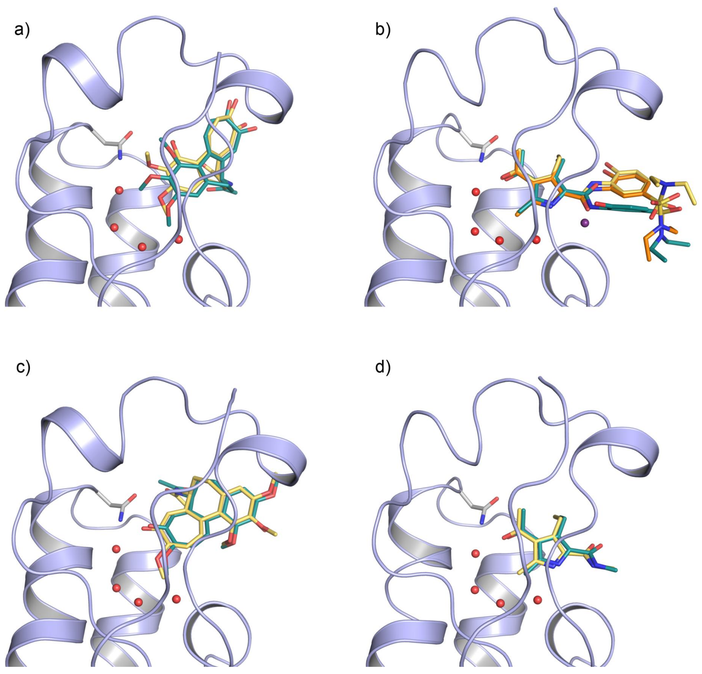
	BRD2(1)	BRD2(2)	BRD3(1)	BRD3(2)	CREBBP
K_D (nM)	170	830	380	490	1600

	BRD4(1)	BRD4(2)	BRDT(1)	BRDT(2)	EP300
K_D (nM)	160	850	1200	3700	2600



Robustness of the model

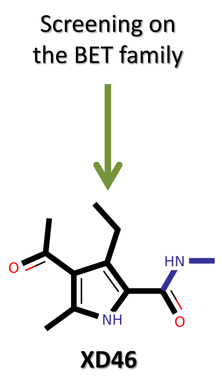
Molecular models (turquoise) **accurately** predicted the crystallographic binding mode (pale yellow) for some identified hits:



Shifting selectivity towards CREBBP and EP300

We have used the 4-acyl pyrrole scaffold to rationally design compounds with **improved affinity** towards CREBBP and EP300 compared to XD14:

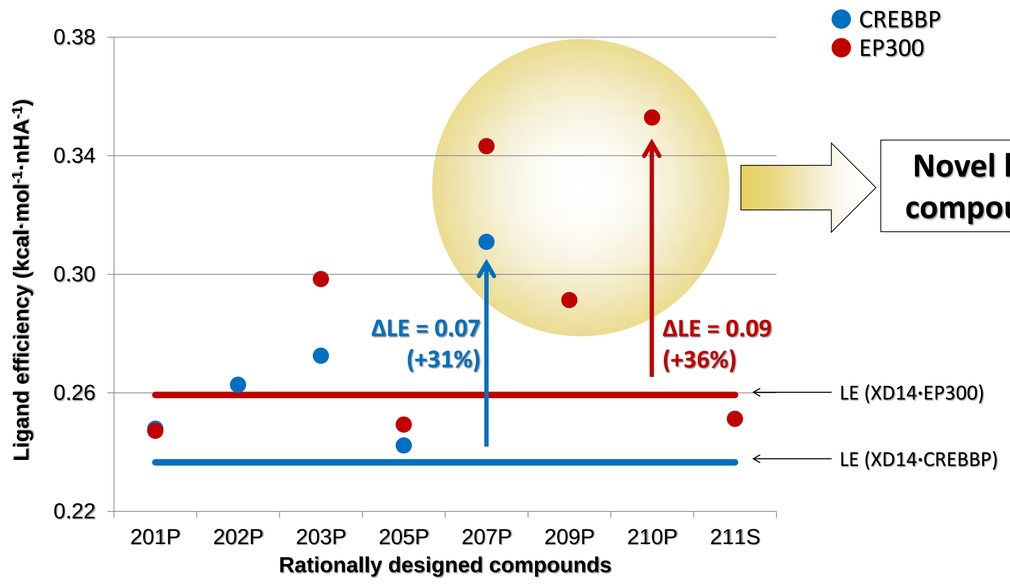
Screening on the BET family



XD46

$K_{D,\ BRD4(1)}$ = 16 µM

Starting point to **target other bromodomains!**



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, could be precisely predicted using *in silico* methods. Rational design allows for the modulation of XD46 to target other therapeutically relevant human bromodomains beyond the BET subfamily.

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[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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