XD46 – a potent fragment against novel anticancer targets

Targeting Bromodomains for the treatment of cancer

Technology

Bromodomains are promising new epigenetic targets for fighting various cancer types. Currently, two 1,4-diazepine derivatives, namely (+)-JQ1 and I-BET, are in preclinical development in cancer and inflammation, respectively, as potent antagonists of the BET bromodomains BRD2, BRD3, and BRD4. Furthermore, the BET BRD inhibitor RVX-208 increases transcription of the apolipoprotein A1 gene and is in clinical trials for atherosclerosis and diabetes, and OTX015 is in clinical trials for acute myeloid leukemia (AML) and other hematologic malignancies.
We have recently presented XD46, a novel fragment molecule with significant inhibitory activity against the BET bromodomain BRD4 as well as some other bromodomains. **XD14, an optimized derivative of XD46 selectively and potently inhibits BET BRDs**. In vitro and in vivo experiments indicate, respectively, that **XD14 selectively inhibits the growth of leukemia cell lines and that it is not acute toxic in mice.** Since there is an obvious pharmaceutical and marketing interest in epigenetics drug discovery, there is a huge potential for finely tuning XD46 and design selective inhibitors within and beyond the currently explored bromodomain proteins. For some derivatives of XD46 with high affinity to non-BET bromodomains it could be already shown that the **BRD-inhibition induces apoptosis in chronic lymphocytic leukemia (CLL) cells selectively**.

Developmental Status

- In silico drug discovery protocol established
- X-ray crystallographic structure of XD14, XD46, and many analogs determined
- Synthesis established (preliminary small-scale non-GMP protocol)
- Positive in vitro binding studies (ITC, ThermoFluor) to several human bromodomains
- In vitro growth inhibition against cancer cell lines determined
- Induction of apoptosis in primary tumor CLL cells determined
- Acute toxicity not detected in in vivo models
- XD46 is being used as starting template for the development of potent inhibitors of other bromodomain families

Market Potential

- Novel compound family with promising potential for selective inhibition of different bromodomain families
- Enhancement of activity in many chemotherapeutic classes such as anthracyclines such as doxorubicin, platin metal complexes such as oxaliplatin, cisplatin, carboplatin, topoisomerase inhibitors such as etoposide, purine analoga such as fludarabine

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Privileged pyrroles: beyond the BET family

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Introduction

Post-translational modification (PTM) readers include the **bromodomains** (BRDs), which specifically recognize acetyl-lysine (KAc) residues mainly in histones and transcription factors. BRDs of the BET subfamily have attracted increasing interest due to their association with many **diseases**, including leukemia [1,2]. We previously described **4-acyl pyrroles**, identified by *in silico* screening, as privileged scaffolds to inhibit BET BRDs [3].

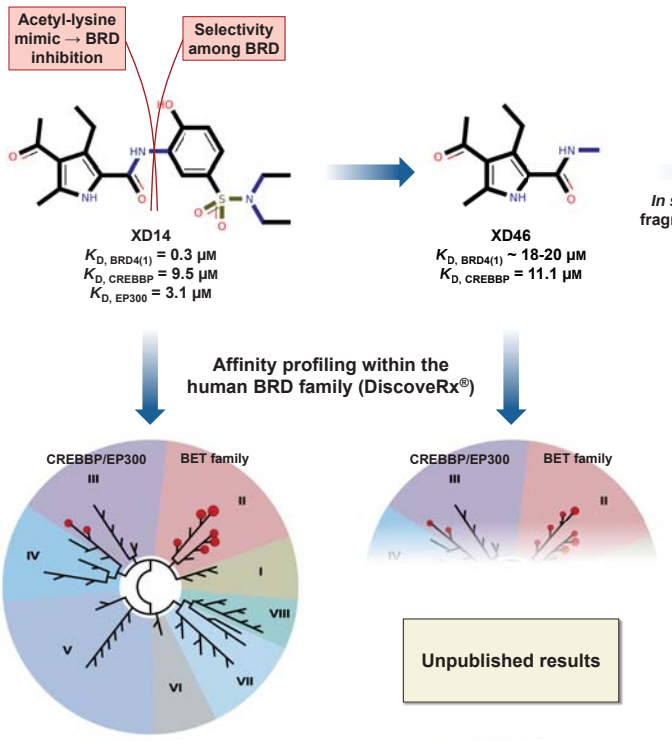
Conclusions

Using a rationally-driven **fragment growing approach**, we show that 4-acyl pyrrole derivatives can be exploited to modulate bromodomains **beyond the BET** subfamily. Antiproliferation experiments showed that a novel inhibitor of both CREBBP and EP300 is a very promising **anticancer** agent.

Our epigenetics drug discovery platform is an **efficient academic resource** for the development of inhibitors.

Characterization of 4-acyl pyrroles

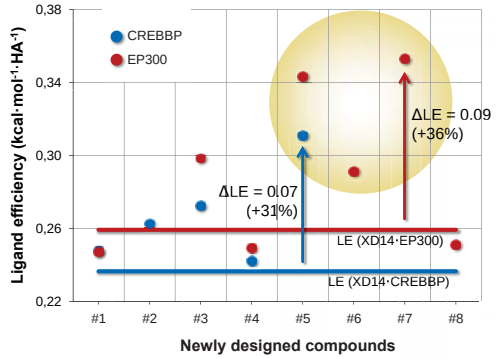
The lead compound **XD14** inhibits BET BRDs potent and selectively. The fragment **XD46**, comprising only its acetyl-lysine mimic moiety, inhibits BRDs within and beyond the BET subfamily, and opens the possibility to target understudied BRDs:



Inhibition of CREBBP and EP300

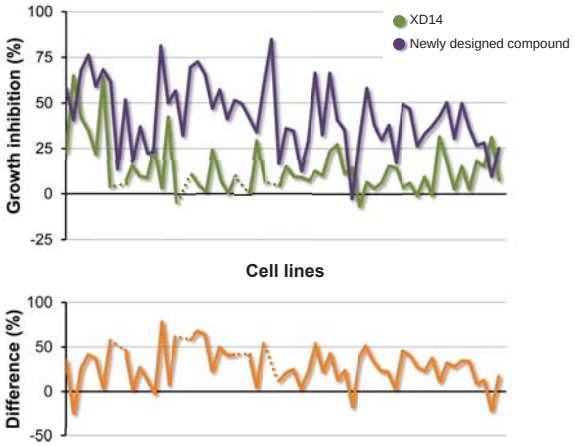
Based on XD46 and the crystal structures of CREBBP and EP300, superstructural analogs were selected using molecular docking aiming at improving ligand efficiency:

$$\text{Ligand efficiency (LE)} = \frac{\text{Gibbs free energy}}{\text{number of heavy atoms}}$$



Anticancer profiling of a hit compound

The **antiproliferation activity** of a newly designed compound inhibiting CREBBP and EP300 was assessed using the NCI60 panel, consisting of **60 cell lines corresponding to 9 cancer types**. The results are compared to those of XD14:



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