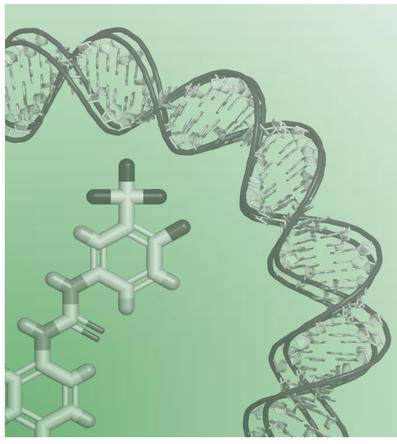

Discovery of novel binders of bromodomain BRD4

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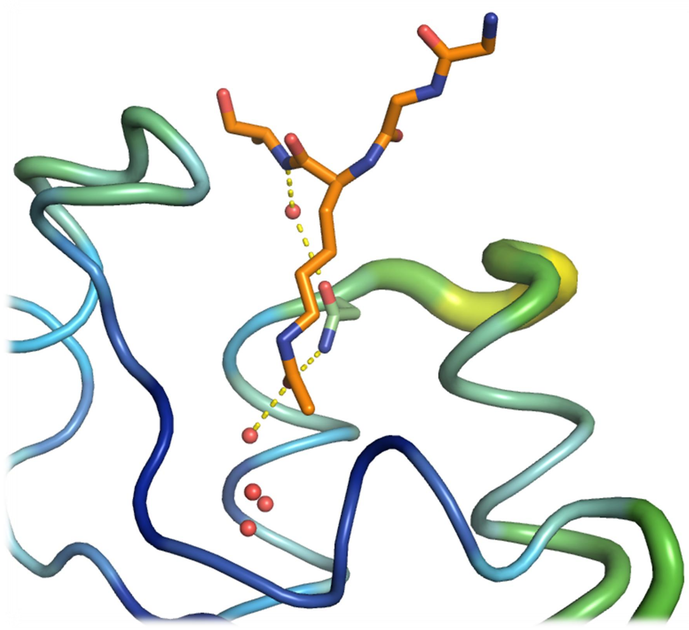
Introduction

Bromodomain-containing proteins are of biological interest as substantial components of transcription factor complexes and determinants of epigenetic control. They specifically recognize acetylated Lysines on histone tails, thus influencing the expression of genes. Not surprisingly, the therapeutic relevance of these protein-protein interactions has been shown recently[1,2]. For example, the BET bromodomain family member BRD4 has been proposed as a promising pharmacological target in AML and HIV[3,4].

To date, only a few binders and active compounds have been described for this protein[5,6]. Several crystallographic structures are available, allowing for the rational structure-based discovery of novel inhibitors of BRD4. Here, we present the results of a successful virtual screening experiment followed by *in vitro* validation performed on this protein.

Molecular model

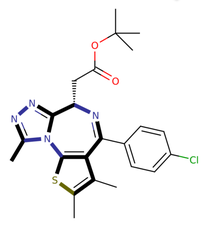
In the BET family of bromodomains (BRD4 depicted), recognition of acetylated Lysines in histone tails (in orange) is mediated by the universally conserved Asn140 (in lime). A water molecule interacts with the peptide's backbone. Additionally, 4 conserved waters assist in the interaction with known binders (water molecules represented as red spheres).

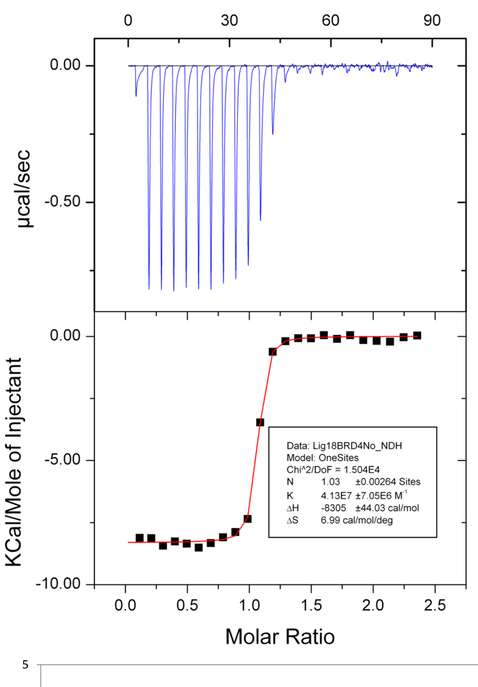


Experimental validation by ITC

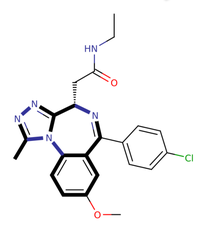
$$\Delta G = -RT \ln K_{eq} = \Delta H - T\Delta S$$

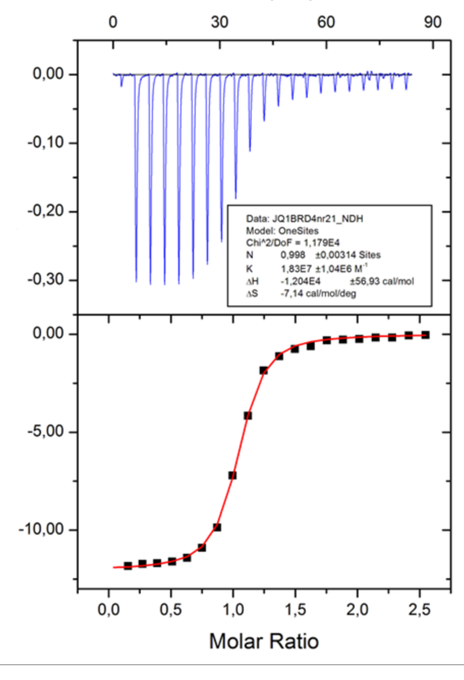
(+)-JQ1
K_d = 25 nM
ΔG_{298K} = -10.4 kcal/mol





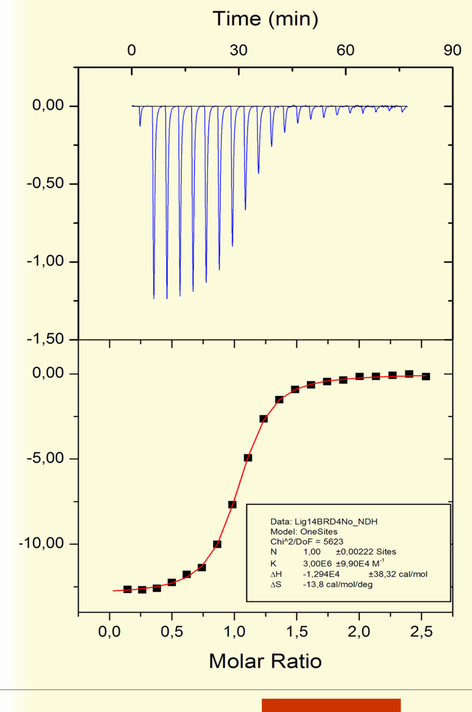
i-BET
K_d = 51 nM
ΔG_{298K} = -9.9 kcal/mol

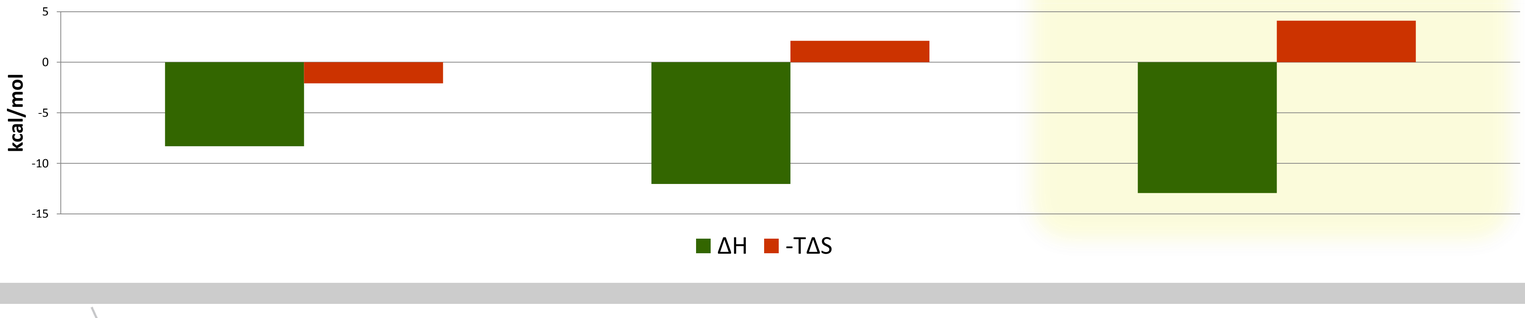




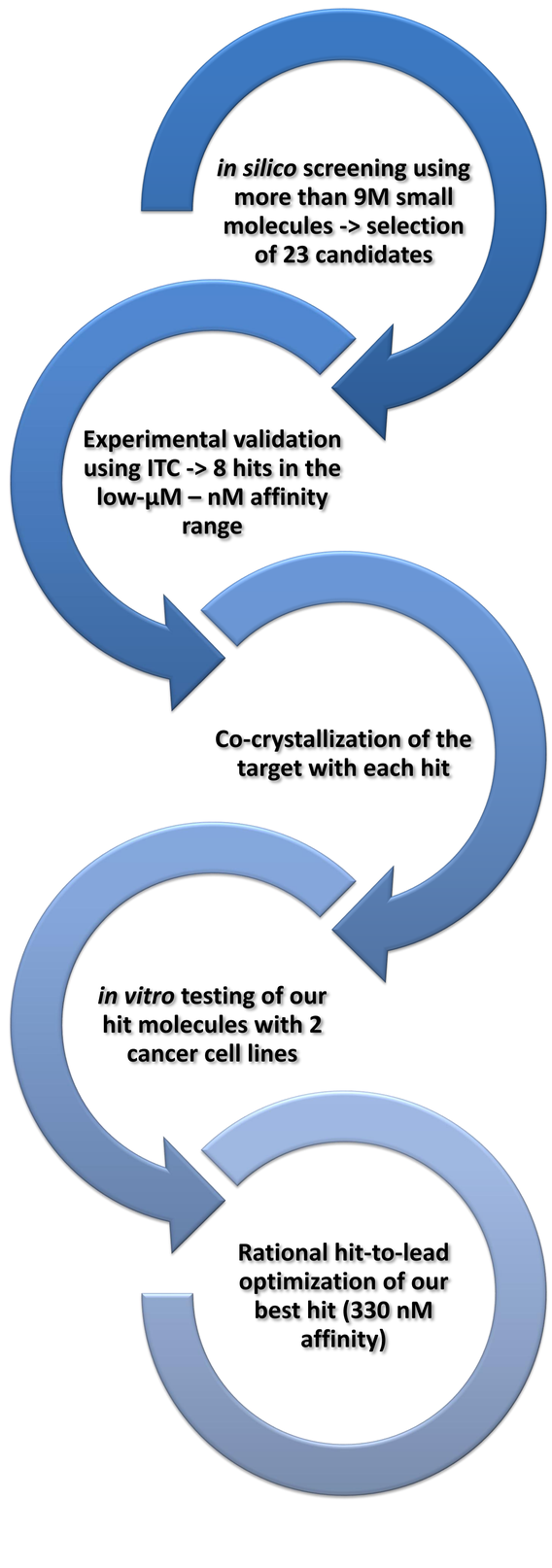
Ligand #14
K_d = 333 nM
ΔG_{298K} = -8.8 kcal/mol

Tanimoto similarity < 0.25





Screening workflow



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