High-throughput fragment docking into the BAZ2B bromodomain: Efficient in silico screening for X-ray crystallography

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Supplementary Figures

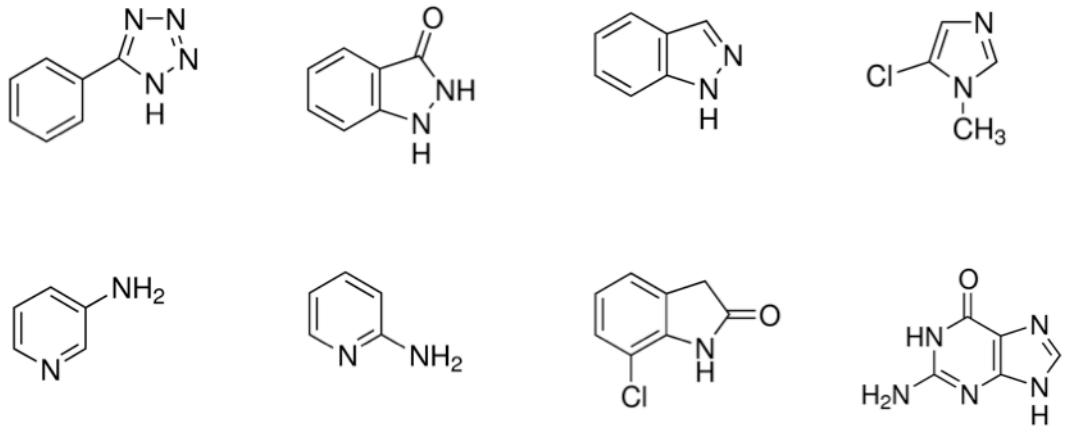

Figure S1. False positive generated by the fragment docking procedure into BAZ2B. These fragments were ranked among the top 12 by docking but no binding is observed by X-ray crystallography (soaking). Some of these false positives are due to incorrect protonation or tautomerization state, e.g., 5-phenyl-1*H*-tetrazole (top left) was erroneously considered protonated, i.e., neutral, while it is unprotonated at pH 7. Docking of the unprotonated version, i.e., with a negatively charged tetrazole, which was done a posteriori, resulted in a very unfavourable binding energy.

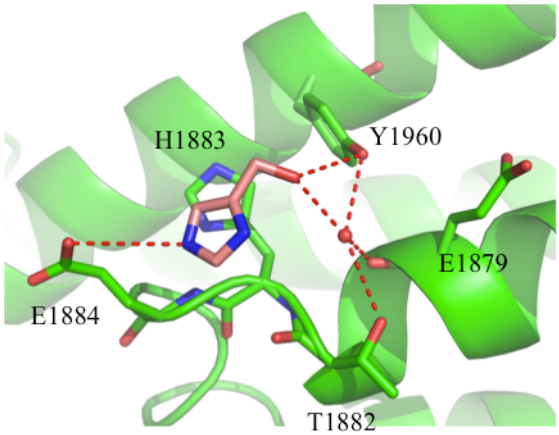

Figure S2. A second F39 molecule binds on the BAZ2B bromodomain surface. The F39 (pink) secondary binding site to BAZ2B (green, water molecule in red) involves the surface exposed residues Thr1882, His1883, Glu1884, Tyr1960 and Glu1879 (hydrogen bonds shown as red dashed lines).

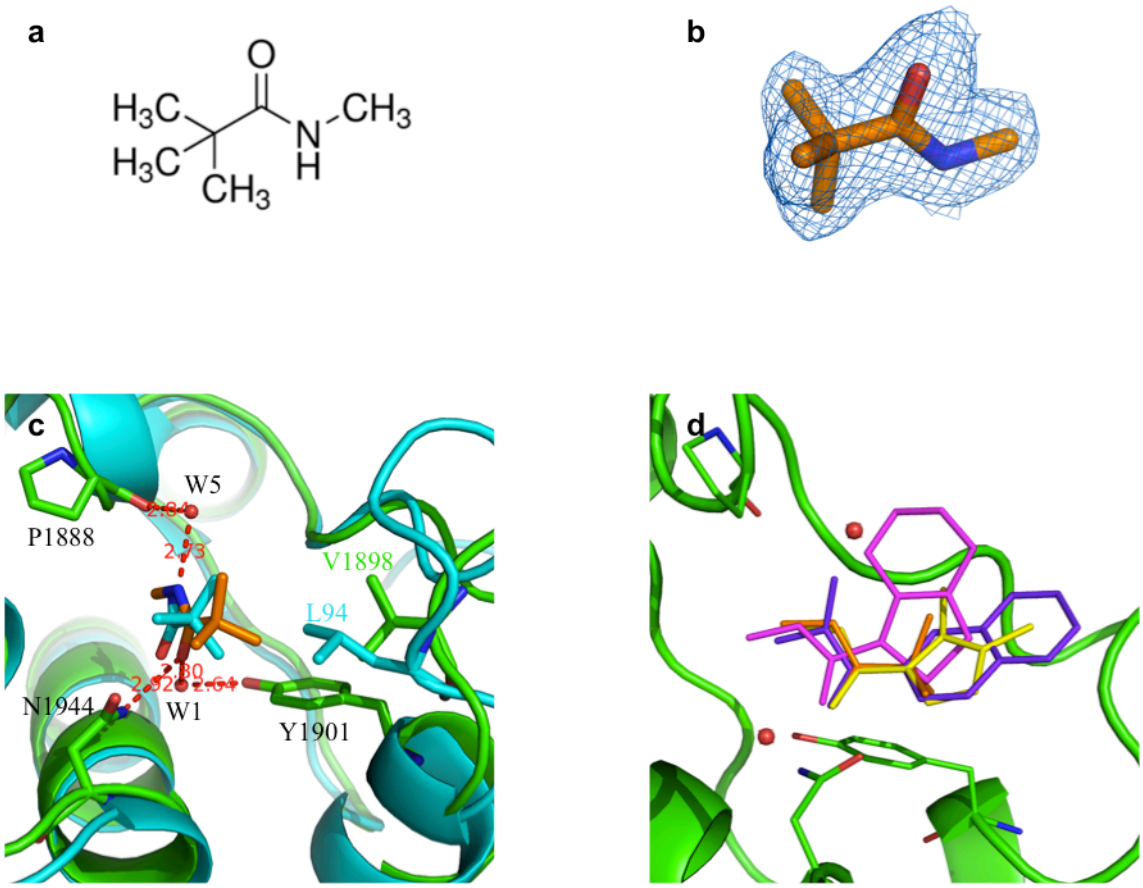

Figure S3. The Kac mimetic NMTA bound to BAZ2B bromodomain.

A. Chemical structural diagram of NMTA.

B. 2Fo-Fc electron density map contoured at 1σ.

C. Comparison of NMTA (orange) bound to the BAZ2B bromodomain (green, water molecules in red) and NMTA (cyan) bound to the N-terminal bromodomain of BRD4 (cyan). Hydrogen bonds are depicted by red dashed lines.

D. Binding poses similar to that of NMTA (orange) bound to BAZ2B (green, water molecules in red) are observed in PDB structures 5CUE (5-chloro-N,1-dimethyl-1H-pyrazole-4-carboxamide, yellow), 5CQ7 (N,N-dimethylquinoxaline-6-carboxamide, purple) and 5CQA (N-methyl-2,3-dihydrothieno[3,4-b][1,4]dioxine- 5-carboxamide, magenta) of N-methylacetamide containing molecules bound to BAZ2B.

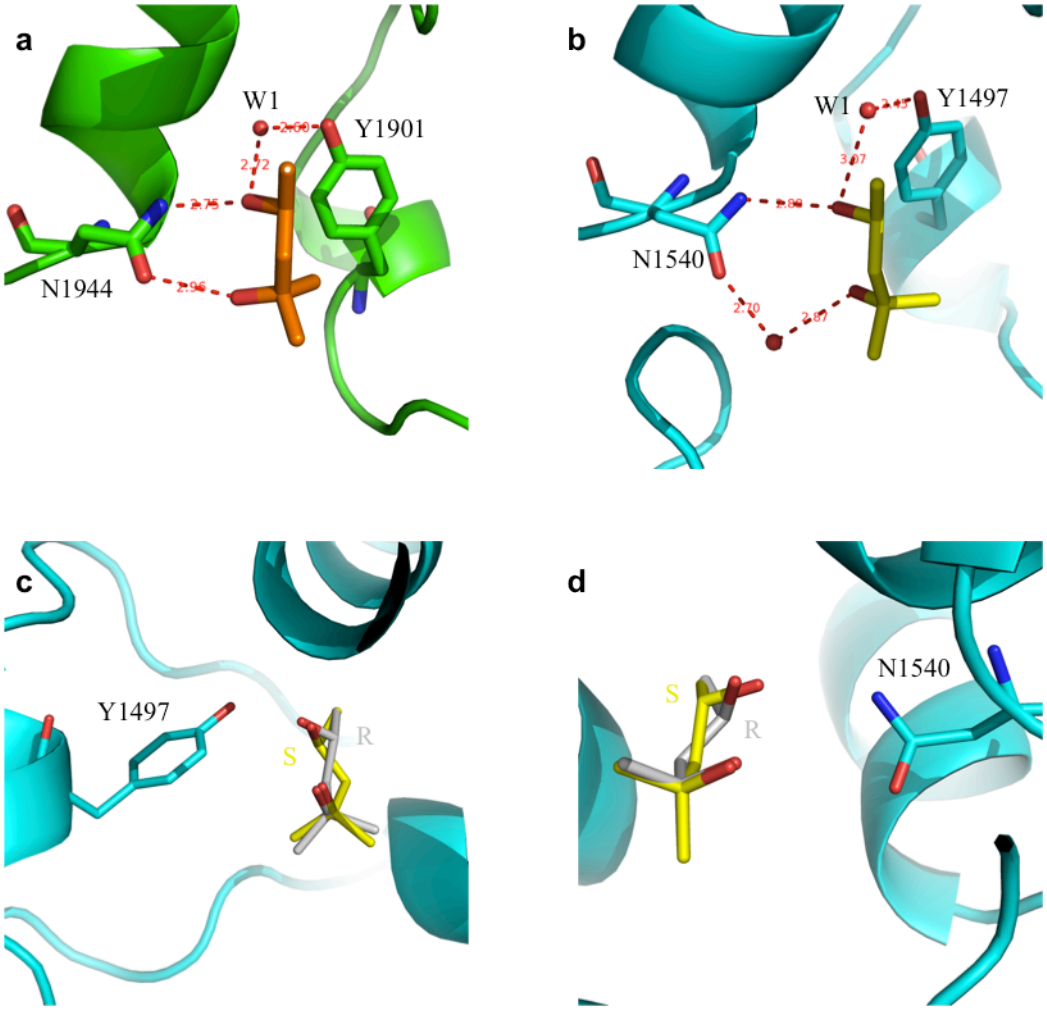

Figure S4. MPD binding in BAZ2B and SMARCA4 bromodomains is stereoselective.

A. Binding of MPD (orange) in BAZ2B bromodomain (green, water molecules in red) is specific for the S-(-) enantiomer. Hydrogen bonds to Asn1944 and Tyr1901 are shown as dashed lines.
B. 1-water binding mode of MPD (yellow, only S-(-) enantiomer is shown) in the SMARCA4 bromodomain (cyan, water molecules in red). Hydrogen bonds are depicted as red dashed lines.
C. MPD R-(+) enantiomer (grey) is largely favoured in the 0-water binding mode observed in chain B of the SMARCA4/MPD structure. MPD S-(-) enantiomer is shown in yellow.
D. MPD S-(-) enantiomer (yellow) is favoured in the 1-water binding mode observed in chain C of the SMARCA4/MPD structure. MPD R-(+) enantiomer is shown in grey.