effects were reversed by addition of compound **21**. Moreover, only fragments that did not display an STD effect in absence of BAZ2A were selected.

BROMOscan Assay.
BROMOscan is a competition-based technology using a ligand immobilized to a solid support and DNA-tagged bromodomains. Bromodomains are incubated with the ligand in the presence and absence of the putative inhibitors and eluted to be quantified by qPCR. Small molecules inhibiting the bromodomain binding to the immobilized ligand will reduce the amount of bromodomain captured and thus the qPCR signal.[11, 12] Dissociation constants (K_D) were calculated by fitting a 12-point dilution curve with starting concentration of 0.5 mM and dilution factor of 3.0. All dose-responses were measured in duplicates.

Crystallization, Data Collection and Structure Solution.
Crystallization and soaking for the BAZ2B bromodomain were performed as previously described.[18] For the BAZ2A bromodomain, showers of extremely thin needles were obtained at 4°C in Tris pH 8, $MgCl_2$ 0.2 M, PEG3350 26%. These were subsequently used for microseeding, obtaining more disperse and slightly larger needles in Tris pH 7.5, $MgCl_2$ 0.2 M, PEG3350 18–22%. Complexes with the compounds of interest (50 mM or saturating solutions for less soluble compounds) were obtained by co-crystallization. Compounds were dissolved in the crystallization solution devoid of DMSO, which does bind in the Kac pocket of bromodomains.[32] Co-crystals were cryoprotected with ethylene glycol and frozen in liquid nitrogen.

Diffraction data were collected at the Elettra Synchrotron Light Source (Trieste, Italy), XRD1 beamline. Data were processed with either XDS33 or MOSFLM,[34] and Aimless;[35] high resolution cutoff was selected according to Karplus and Diederichs.[36, 37] Structures were solved by molecular replacement with Phaser[38] using PDB 4IR5 as search model for BAZ2B and PDB 4LZ2 for BAZ2A. Initial models were refined alternating cycles of automatic refinement with either Phenix[39] or REFMAC[40] and manual model building with COOT.[41]

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information contains:
Biophysical evaluation of the seven compounds selected by the high-throughput docking, X-ray crystal structure refinement data, distribution of the chemical properties of the libraries, insights into the energetic contributions calculated *in silico*, and structural analyses of all reported crystal structures (PDF).
Molecular formula strings for ligands **1**–**20** (CSV).

Accession Codes.
PDB ID codes: 5MGJ (BAZ2A-1), 5MGK (BAZ2A-2), 5MGL (BAZ2A-3), 5MGM (BAZ2A-4), 5MGE (BAZ2B-1), 5MGF (BAZ2B-2), and 5MGG (BAZ2B-3).

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Notes
The authors declare no competing financial interest.

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ABBREVIATIONS

BAZ2A, bromodomain adjacent to zinc finger domain protein 2A; BAZ2B, bromodomain adjacent to zinc finger domain 2B; BET, bromodomain and extra terminal; CPMG, Carr-Purcell-Meiboom-Gill sequence; CREB, cAMP response element-binding protein; CSP, chemical shift perturbation; DMSO, dimethyl sulfoxide; DPFGSE, Double Pulsaed Field Gradient Spin Echo sequence; IMAC, immobilized metal affinity chromatography; IPTG, isopropyl β-D-1-thiogalactopyranoside; Kac, acetyllysine; LE, ligand efficiency; STD, saturation transfer difference; TSP, trimethylsilylpropanoic acid.

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