Ligand-induced global conformational changes in TBP-associated factor 1 (TAF1) tandem bromodomains – a novel strategy for targeting the TAF1.

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Targeting bromodomains by small molecule inhibitors is a novel therapeutic strategy to regulate various cellular functions of bromodomain-containing proteins. These inhibitors have been shown to regulate altered chromatin remodeling and aberrant gene transcription in several cancers and inflammatory diseases. However, small molecule inhibitor development targeting the bromodomains of TBP-associated factor 1 (TAF1) remained underexplored. TAF1 is overexpressed in several cancers and plays a pivotal role in the AML1-ETO fusion gene expressing acute myeloid leukemia (AML). Although two small molecule TAF1 bromodomain inhibitors (BAY299 and GNE-371) have been reported, their mechanism of action in the context of TAF1 tandem bromodomains (TAF1-T) is unknown. In this study, our objectives were to discover a novel TAF1-T bromodomain inhibitor and elucidate the binding modes of various TAF1 inhibitors in TAF1-T. We used diverse biochemical and biophysical assays to characterize inhibitor binding and applied X-ray crystallography and small-angle X-ray scattering (SAXS) for determining the structures of TAF1-inhibitor complexes. We identified AZD6738, an orally bioavailable Ataxia telangiectasia and Rad3-related (ATR) kinase inhibitor, as a TAF1 inhibitor that binds to the second bromodomain (BD2) of TAF1. Our studies with AZD6738 and its closely related analogs along with BAY299 and GNE-371 show that inhibitors stabilize different conformational states of TAF1-T through an open-closed transition. Our studies with TAF1-T/inhibitor complex solutions also show that BAY299 induces dimerization of TAF1-T. Overall, this study delineates a novel phenomenon of ligand-induced global conformational changes in TAF1 tandem bromodomains and provides a new structural framework to develop a dual TAF1-ATR inhibitor as potential cancer therapeutics.