Development of small molecule inhibitors that target protein-protein interactions in a transcription factor.

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Transcription factors are attractive targets for drug design, however, it has been difficult to develop small molecule inhibitors against this class of proteins. We describe our efforts at developing molecules that inhibit key protein-protein interactions in BCL6, a transcriptional repressor often misexpressed in B-cell lymphoma. BCL6 contains two folded domains: an N-terminal BTB protein-protein interaction domain that associates with corepressor complexes, and a series of C-terminal DNA-binding zinc-fingers that direct the protein to target transcriptional control sites. Structures of the BCL6 BTB domain in complex with peptides from the SMRT and BCOR corepressors were used to identify a critical binding site at the interface of the two chains of the BTB homodimer. We carried out an in-silico screen to identify compounds that would bind to the BTB peptide-binding groove, and validated a weakly binding compound by crystallography. Through a large number of structure-guided cycles, we reduced the binding constant of the initial ~300 micromolar hit to low nanomolar levels while maintaining favorable drug-like properties. We arrived at a series of potent, orally bioavailable compounds that target this key lymphoma protein.