Design and Synthesis of Bivalent Inhibitors for Bromodomain and Extra-Terminal (BET) family proteins

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Extra-Terminal (BET) family proteins (BRD2, BRD3, BRD4 and BRDT) are transcriptional coactivators that interact with acetylated lysine residues of histones. Each BET protein has two bromodomains. BET proteins are involved in multiple cell functions and processes. Among them, BRD4 was identified as a promising target for cancer therapy and BRDT emerged as a potential target for male contraception. Therefore, targeting BET family proteins is of interest, however high sequence homology between different BET family proteins is a significant challenge for the discovery of selective inhibitor for a specific family member.

Recent research revealed that bivalent inhibitors can either induce the dimerization of proteins intermolecularly or bind to both bromodomains intramolecularly. In light of the new mechanism of BET bivalent inhibitors, we prepared bivalent inhibitors based on a potent BET inhibitor SG3-179. Symmetric inhibitors with a PEG₁ linker maintained potency and selectivity similar to the parent compound with activity against all BET proteins. Through iterative optimization of attachment and linker chemistry, a series of symmetric bivalent inhibitor with PEG-linkers (PEGₙ, n=2–5) exhibited up to 70-fold higher selectivity for BRDT-1 over BRD4-1 in the AlphaScreen assay. Compared to the parent compound, these compounds also showed improvements in potency (~10 fold) for BRDT-1. The selectivity profile of one of the compounds, GXH-II-052, was validated in a BROMOscan assay, which confirmed selectivity for BRDT-1. This compound was about two-fold more selective for tandem BRDT compared to BRD4. Notably, GXH-II-052 was also active in a multiple myeloma (MM1.S) cell-based assay. Investigations into the possible mechanism for the observed selectivity profile of bivalent BET inhibitors is underway.

References: