Fragment screening for a protein-protein interaction inhibitor to WDR5

WDR5 is a critical component of the mammalian SET/MLL histone methyltransferase (HMT) complex which regulates hematopoietic cells, and dysregulation of this complex in these cells can lead to leukemia. Deregulation of MLL accounts for about 70% of acute lymphoblastic leukemia (ALL) in infants (1). WDR5 is one of the three catalytically inactive core components of this regulatory complex (along with ASH2l and RBBP5). Others have described how WDR5 mediates MLL-dependent histone methylation, specifically on H3K4, by physically interacting with histone H3 (2). WDR5 uses the same binding site to interact with MLL and as WDR5 is a required component of this regulatory complex, we performed a fragment screen and medicinal chemistry campaign based on the fragment hits to develop an inhibitor to block the association of WDR5 with the SET/MLL complex. We obtained an extraordinarily ligand efficient fragment hit and show that this could be exploited to develop further chemical compounds that were used as probes for SAR studies. SPR studies showed that several compounds synthesized were low micromolar binders and over a dozen crystal structures at high resolution allowed a detailed assessment of the binding modes of these compounds. One outcome is a moiety that substitutes well for the guanidinium sidechain of arginine, which is one of the main components of binding in this protein-protein binding site. The fragment screening, SPR, crystallography and compounds generated will be described in detail.

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