MS09-1-4 Identification of BAZ2A bromodomain hit compounds

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Abstract
BAZ2A is an epigenetic regulator affecting nucleolar transcription of ribosomal RNA. It is overexpressed in aggressive and recurrent prostate cancer where, in concert with EZH2, promotes cellular migration. Its bromodomain is characterized by a shallow and difficult-to-drug pocket. Here, we describe the identification of two hit compounds, based on different scaffolds, of the BAZ2A bromodomain. In a first approach (fragment-joining), a benzimidazole-triazole fragment was identified by a molecular docking campaign and validated by competitive binding assays and X-ray crystallography. Another ligand was observed in close proximity by soaking experiments using the BAZ2A bromodomain pre-incubated with the benzimidazole-triazole fragment. The crystal structure of BAZ2A with the two ligands was employed to design a few benzimidazole-triazole derivatives with increased affinity. In a second approach, a structure-based fragment-growing campaign was followed. By combining docking, competition binding assays and protein crystallography, we have extensively explored the interactions of the ligands with the rim of the binding pocket, and in particular ionic interactions with the side chain of Glu1820, which is unique to BAZ2A. We determined twenty-three high-resolution crystal structures of the holo BAZ2A bromodomain and analyzed common bromodomain/ligand motifs and favorable intra-ligand interactions. Binding of some of the compounds to the BAZ2A bromodomain is enantiospecific as also confirmed by isothermal titration calorimetry.

References
Dalle Vedove A., Cazzanelli G., Corsi J., Sedykh M., D'Agostino V.G., Caflisch A. and Lolli G. (2021) Identification of a BAZ2A bromodomain hit compound by fragment joining. ACS Bio & Med Chem Au 1, 5-10.