Towards understanding the complexity of molecular interactions: A structure-based approach to develop high affinity leads

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The pharmaceutical industry and academic research laboratories are constantly facing challenging obstacles in their pursuit for novel and effective therapies. Over the past years, remarkable discoveries in the Chemical Biology field improved the design and synthesis of molecules that ultimately will lead to novel medicines. Structural characterization of ligand-protein complexes provides a powerful insight about crucial aspects such as mechanisms of action, intrinsic dynamics and function. This approach becomes highly important for our currently research, which aims to investigate the role of biologically relevant proteins and identify and characterize the binding mode of several inhibitors. In one remarkable example, we identified a water-mediated motif present in the protein tyrosine phosphatase from *Mycobacterium tuberculosis*, that modulates the accessibility to the catalytic pocket[1]. In another notable study, we assessed the binding activity of two new inhibitors of the bromodomain (BRD) family, the "epigenetic readers" that recognize acetylated lysine marks on histones and potential drug targets in cancer and inflammation[2]. In this study, we were able to disclose the complexity of the molecular interactions between BET proteins and the new molecules we have developed in our lab. To gain insight into the different binding modes of these potent inhibitors we determined the crystal structures of several inhibitors in complex with two different BRD-containing proteins (BDR2 and BDR4). The results clearly demonstrate new interactions that stabilize the protein-ligand complexes and the existence of structured water molecules between the ligands and the target proteins. Ultimately, we aim to optimize ligand affinity and develop novel chemotypes with increased potency and specificity.

References

[1] - J.B. Bertoldo, T. Rodrigues, L. Dunsmore, F.A. Aprile, M.C. Marques, L.A. Rosado, O. Boutureira, T.B. Steinbrecher, W. Sherman, F. Corzana, et al., *Chem* 2017, *3*, 665-677.
[2] - P. Filippakopoulos, S. Knapp, *Nat. Rev. Drug Discov.* 2014, *13*, 337-356.