Successful generation of structural information for fragment-based drug discovery

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Fragment based drug discovery has evolved to a mature hit finding strategy and there are today numerous successful examples in the literature. For a fragment based campaign to be successful the ability to obtain a large number of structures of diverse chemical fragments is unquestionable, yet it is often challenging to generate structures with bound fragments. A summary of recent literature reveals that a wide repertoire of experimental procedures is employed to generate ligand-bound crystal structures[1], illustrating that each protein and project needs specific attention.

Here we share our experience from setting up and executing fragment crystallography in the Soluble Epoxide Hydrolase project that altogether resulted in 55 complex structures, where 38 are fragments. The size of this dataset has allowed us to make retrospective analysis of ligand properties such as potency, ligand solubility, clogP and ligand efficiency to identify success factors for structure generation and ask the question if any of these could be used to guide crystallization efforts. Our results reveals that potency, ligand efficiency and, to some degree, clogP influence the success of complex structure generation whereas the measured aqueous ligand solubility did not.

1. L. Öster, S. Tapani, Y. Xue, H. Käck, Drug Discov Today., 9, (2015), 1104