Poster Presentation

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Crystallographic fragment screening: challenges, opportunities, lessons learned

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Fragment-based approaches are now routinely applied for lead development in pharmaceutical drug research. Usually, a small but well selected library of low molecular weight compounds is pre-screened by biochemical or biophysical methods such as surface plasmon resonance (SPR), nuclear magnetic resonance (NMR) or thermal shift assay; often followed for promising hit candidates by X-ray crystallography. We designed a small fragment library consisting of 364 compounds that is not strictly compliant to the otherwise often followed Astex rule of three for fragment library composition.[1] Thereafter, our library was validated on the pepsin-like aspartyl protease endothiapepsin, which serves as a model system for proteins that are involved in serious diseases such as malaria (plasmepsins), hypertension (renin) and Alzheimer's disease (ß-secretase) and therefore, is a valid target for further drug development. Due to the small size of fragments, they frequently exhibit only low affinity to the applied target protein and thus are often hard to detect in any screening approach, reflected in little overlap between different screening methods. After initial screening, we decided to validate the entire library by X-ray crystallography, which requires a steady supply of crystals, reproducible soaking conditions and a reliable setup at a synchrotron source, such as HZB BESSY II BL14.1 [2], preferably with some automation in initial data processing and refinement. A total hit rate greater than 10% was obtained, which will be compared to results from other screening methods. The resulting crystal structures will be discussed and provide an ideal basis for further lead development.

[1] *H. Köster, T. Craan, S. Brass, C. Herhaus, M. Zentgraf, L. Neumann, A. Heine, G. Klebe, J. Med. Chem., 2011, 54, 7784-7796,* ***[2]*** *U. Mueller, N. Darowski, M.R. Fuchs, R. Forster, M. Hellmig, K.S. Paithankar, S. Puhringer, M. Steffien, G. Zocher, M.S. Weiss, J. Synchrotron Radiat., 2012, 19, 442-449*

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