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Practical Aspects of Crystallographic Fragment Screening

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Crystallographic fragment screening is an established method to initiate structure-based compound development and has become feasible for a wide scientific community. Our efforts within Frag2Xtal and Frag4Lead projects enable users to carry out these experiments in practicable time at the Helmholtz-Zentrum Berlin. Efficient soaking and handling of crystals is supported via our Frag2Xtal Screen (made available in collaboration with Jena Bioscience) and our Easy Access Frame tool (patent pending). Furthermore, robot-assisted beamlines with high sample changing rates, automated data processing and refinement of the protein-ligand structure models decrease manual labor. With our 12-compound pre-screen, users can get accustomed to the soaking optimization and crystal fishing procedure and are guided towards successful campaigns. Additionally, our collaboration partners from the drug design group in Marburg composed a 1270 fragment library based on advanced clustering to balance 3D-diversity versus pharmacophore representation. Currently, we establish handling of the library and providing ready-to-soak plates for users by utilizing an acoustic dispenser. Together, we are also advancing the follow-up methods for successfully identified fragment hits by employing our new Frag4Lead web service as well as molecular docking to choose purchasable, diversified compounds for downstream lead optimization. We present results of example campaigns and subsequent compound diversification.

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