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Structure-Based Fragment Screening using High Throughput Crystallography. R.J. Rosenfeld, J. Badger, P. Collins, D. Bensen, L. Tari, R. Athay, D.E. McRee, ActiveSight, 4045 Sorrento Valley Blvd., San Diego CA 92121 USA.

Fragment-based screening is a method for developing novel lead compounds. The goal of fragment screening is to identify small fragments that bind efficiently in an active site and can be linked together to create new high affinity scaffolds for drug design. We present a complete home laboratory system for rapid structure based fragment screening. In our pilot project, we created a library of 450 small molecular weight fragments (mw. 100-300 Da). We soaked apo protein crystals in solutions containing four fragments and performed follow-up experiments with single soaks to verify fragment hits. We used the ACTOR automated robot crystal-mounting system and automated data collection on a high intensity FR-E home x-ray source with CCD detector. Integrated automated processing, refinement and fitting software developed by Molecular Images was used to quickly generate refined structures with electron density maps that were viewed in MiFit. Our pilot project resulted in a 4% hit rate for fragments in our library binding to a protein kinase. This validates our library and demonstrates that structure based fragment library screening can be achieved rapidly and successfully in a home laboratory.