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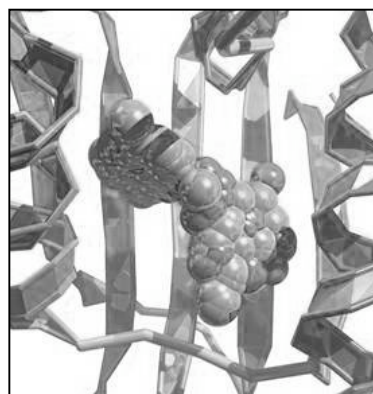
Structure-Based Fragment Screening: Finding Hits for Novel Lead Compound Design. Robin Rosenfeld, John Badger, Paul Collins, Vicki Nienabar, Duncan McRee, ActiveSight, 4045 Sorrento Valley Blvd, San Diego, CA, 92121 USA, www.active-sight.com.

Fragment-based screening is a method for developing novel lead compounds. The goal is to identify small, low molecular weight fragments that bind with high efficiency in an active site. Small fragments have "room to grow"- they can be linked together or built upon in order to generate novel high affinity compounds within the size constraints of a typical drug molecule.

Here, we present a complete home laboratory system for rapid structure-based fragment screening. We created a library containing 384 small molecular weight fragments organized into a kit of shape diverse mixtures of four. We screened our library against several proteins, including Hsp90.

For our pilot project, we soak apo Hsp90 protein crystals in solutions containing four fragments and used an automated data collection system to determine structures. Our pilot project with Hsp90 resulted in a 3.3% hit rate. In this work, we have identified general strategies for structure-based fragment screening. We streamlined the process by creating a fragment library kit generally suitable for screening against many protein targets.

Our fragment screening laboratory consists of the ActiveSight Fragment Library, the ACTOR robot crystal-mounting system, FR-E home X-ray source, and Saturn CCD detector. The Molecular Images software suite was used to go from diffraction data to refined structure files ready for viewing and analysis in MIFit. This work validates our fragment library and demonstrates that structure based fragment screening can be achieved rapidly and successfully in a home laboratory.



Superposition of HSP90 Hits