Fragment-Based Screening by X-ray Crystallography: An Alternative to High-throughput Screening

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Screening of libraries of small molecules (or drug fragments) by X-ray crystallography offers an alternative approach to discovering novel active site binders for enzymes, which may be used as a starting point in a drug discovery programme. This method can identify unique fragments with a potency in the millimolar range, and which are not found by most enzyme assay screening methods. Many of these compounds show efficient binding for their size. The use of crystallography as a screening tool gives access to precise structural data on identification of fragment binding, and this information can be used as a starting point for rational optimization of the fragment into a potent inhibitor. This may then be used as a potential lead compound for drug discovery. This method is illustrated with examples from two kinase projects [1].

[1] Hartshorn M.J., Murray C.W., Cleasby A., Frederickson M., Tickle I.J., JhotiH., *J. Med. Chem*., 2005, **48(2)**, 403-413.

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