Hot Spot Analysis for Driving the Development of Hits into Leads in Fragment-Based Drug Discovery

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Mapping for fragment-based drug design

a. A binding site comprising three pockets

b. Mapping of the binding site to find molecular fragments that bind in particular pockets

c. Concatenation of molecular fragments into a possible lead using a core template. A number of good binding fragments can be used at each position resulting in a combinatorial library

d. Building lead compounds by extending the best binding molecular fragment.

*Nature Reviews Drug Discovery* 1; 45-54 (2002)
Multiple solvent crystal structures (D. Ringe, 1996)

C. Mattos and D. Ringe (1996)
Locating and characterizing binding sites on proteins, Nature Biotech. 14: 595-599
Part I: Finding hot spots by computational mapping

Find consensus sites: regions with several probes binding
ATTENTION!

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