Computational methods for fragment linking

Regine S. Bohacek, Boston De Novo Design

A common motif in bioactive molecules is a central cyclic scaffold to which a number of side chains are attached. Examples range from penicillin to drugs which inhibit HIV protease to inhibitors of kinases.

The time line for discovery of these drugs varies but can be long. Often the starting point is a natural product. Sections of the lead are removed, retaining those features believed to be most important for activity. Then the fragments are reconnected with linkers designed to improve affinity and to acquire better pharmacokinetic properties.

The *de novo* program, AlleGrow, has been developed to hasten the discovery of cyclic scaffolds which connect and incorporate fragments already positioned in the target binding site.

To test AlleGrow, it has been applied to some past drug discovery projects including the discovery of ACE inhibitors, inhibitors of the SH2 domain of Src kinase, and inhibitors of HIV protease.

(1) AlleGrow is a second-generation program based on GrowMol (R.S. Bohacek, C. McMartin, JACS (1994) 116,5560-5571.)