consisting of the coordinates of atoms and/or bonds. All possible structures that contain any combination of a user-specified minimum number of matching atoms and/or bonds are retrieved. Combinations of hits can be generated automatically by a companion program (104), SPLICE, which trims molecules found from the database to fit within the active site and then logically combines them by overlapping bonds to maximize their interactions with the site (Fig. 3.21). The addition of bridging fragments to those recovered from the database allows generation of many novel ligands for further evaluation.

3.3.3 De Novo Design. Design of novel chemical structures that are capable of interacting with a receptor of known structure uses methodology that is much more robust, given that the geometric foundations of molecular sciences are much firmer than the thermodynamic ones. Techniques for the design of novel structures to interact with a known receptor site are becoming more available and show promise (227–229). It has become quite evident that much of a molecule acts simply as a scaffold to align the appropriate groups in the three-dimensional arrangement that is crucial for molecular recognition. By understanding the pattern for a particular receptor, one can transcend a given chemical series by replacing one scaffold with another of geometric equivalence. This offers a logical way to dramatically change the side-effect profile of the drug as well as its physical and metabolic attributes. Various software tools are already under development to assist the chemist in this design objective. Lewis and Dean described their approaches to molecular templates in a series of papers (230, 231). An alternative approach, BRIDGE (Dammkoehler et al., unpublished), is based on geometric generation of possible cyclic compounds as scaffolds, given constraints derived from the types of chemistry the chemist is willing to consider. Nishibata and Itai (232, 233) published a Monte Carlo approach to generating novel structures that fit a receptor cavity. Pearlman and Murko (234) combined a similar approach with molecular dynamics with illustrative applications to HIV protease and FK506 binding protein. CAVEAT is a program developed by Bartlett to find cyclic scaffolds (207) by searching the CSD (195) for the correct vectorial arrangement of appended groups.

All of these approaches attempt to help the chemist discover novel compounds that will be recognized at a given receptor. Van Drie et al. (207) described a program, ALADDIN, for the design or recognition of compounds that meet geometric, steric, or substructural criteria, and Bures et al. (235) described its successful application to the discovery of novel auxin transport inhibitors. As our knowledge base of receptors grows, such tools will prove increasingly useful. The ability to transcend the chemical structure of lead compounds, while retaining the desired activity, should dramatically improve the ability to design away undesirable side effects. Bohm developed the program LUDI (221,222) to construct ligands for active sites with an empirical scoring function to evaluate their construction.

3.3.4 Docking. The search for the global minimum, or the complete set of low energy minima, on the free energy surface when two molecules come in contact is commonly referred to as the "docking" problem [(236); see also Leach (21)]. Any useful molecular docking program must be computationally efficient in determining the most favorable binding mode, sufficiently sensitive in its scoring function to discriminate between alternate binding modes and the correct mode, and robust enough to allow various ligand-receptor systems to be studied.

3.3.4.1 ***Docking Methods.*** In the case of two proteins of known structure that can be approximated as rigid bodies, there are 6 degrees of freedom, the relative position (x, y, and z coordinates), and relative orientation (roll, pitch, and yaw to use the aeronautical expressions) to be explored. Several very intelligent approaches to this problem have been developed. The first and most well known approach is the DOCK program (http://www.cmpharm.ucsf.edu/kuntz/dock.html) (183) that was developed to solve the ligand-receptor problem. This program uses abstract representations (a set of spheres) of the convex shape on the receptor to be filled and the concave ligand and matches them to generate plausible binding modes with complementary