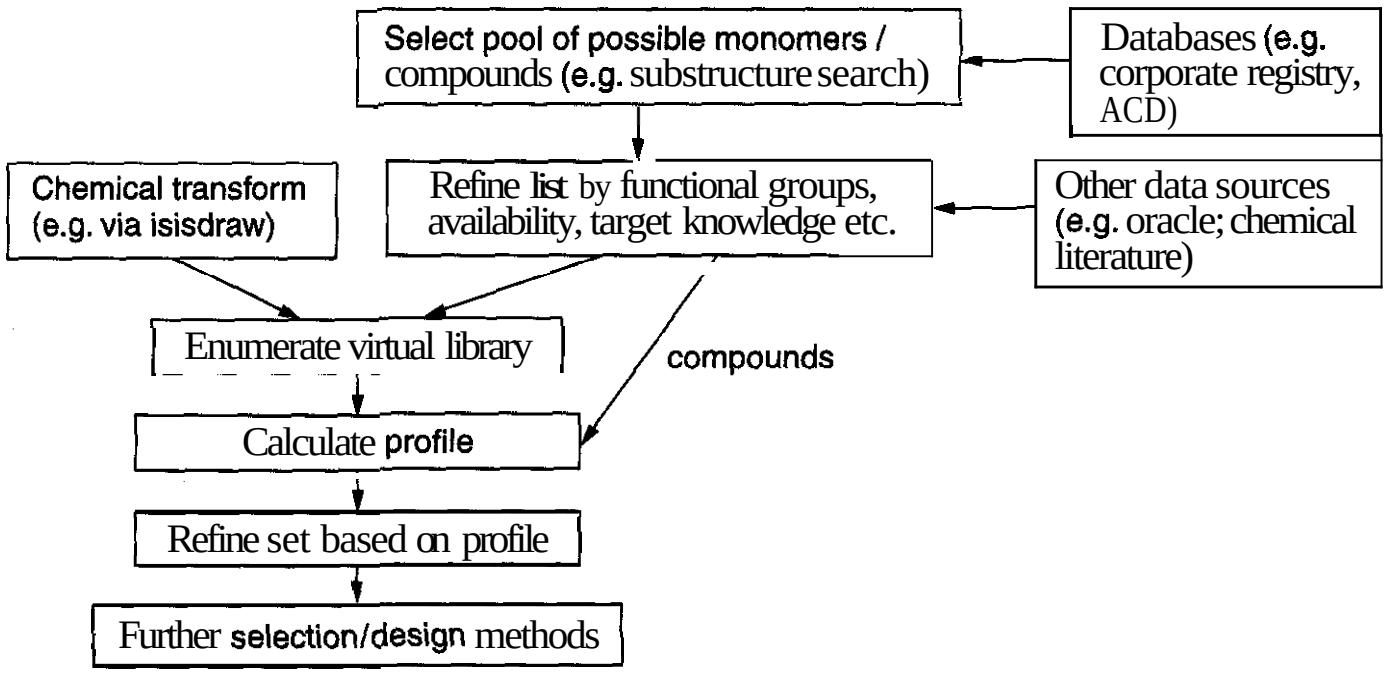

Figure 5.16. The workflow used within ADEPT (A Daylight Enumeration and Profiling Tool; GlaxoWellcome, UK) for compound selection and library design. [Reproduced from A. R. Leach and M. M. Hann, Drug Discovery *Today*, 5, 326–336 (2000), with permission of Elsevier Science.]

The ADEPT (A Daylight Enumeration and Profiling Tool) suite of programs developed at GlaxoWellcome (116) is a Web-based system providing access to a wide range of library design functionality, again based around the Daylight tool kit. Figure 5.16 provides an outline of the process workflow. Reactant lists are generated from searches in databases of in-house and commercially available monomers. A variety of filters can be applied to reduce the size of the lists. These include filters on molecular weight, rotatable bond count, and substructure filters to remove unwanted functionality. After library enumeration, various property histograms are calculated. This allows the user to further refine the reactant choice.

A product-based library design algorithm, PLUMS (117), has been developed to ensure that combinatorial constraints are satisfied in the design. The algorithm successively removes the monomer that adds least value to the library as governed by two terms, the effectiveness (number of molecules meeting user-defined criteria such as property ranges, fit to pharmacophore or dock to protein site) and efficiency (ratio of effectiveness to library size). The algorithm is sufficiently fast to work within the Web-based environment of ADEPT. Figure 5.17 shows screen shots from ADEPT, illustrating how a library can be specified and the resulting product histograms. A similar system has been implemented at Vertex (118a). A key component of this system is the REOS filtering tool (118b), which applies filters on molecular weight, lipophilicity, unwanted substructures, rotatable bond counts, and so forth to remove "obviously bad" compounds.

4.10 Structure-Based Library Design

Structure-based library design uses 3D structures of the biological targets to direct the design and selection of templates/scaffolds and of reactants that will produce compounds that can fit into the target and thus are likely to bind and have biological activity. The experimental structural information *can* be derived by a structural biology approach, using X-ray crystallography or NMR spectroscopy. Computational models can be built and used (e.g., homology modeling techniques for closely related proteins), but an experimental structure is always preferred. A structural biology approach can also be used to identify molecules or fragments thereof that bind to a target. For example, NMR screening (3) can be used to identify potential scaffolds or reactants for a combinatorial library that bind to a target site and is able to detect very low affinity binding (in the millimolar range, compared to the low micromolar range from biological screening); this *can* be done without the need to determine the 3D structure of the target.