rapid and sensitive analytical instruments, have permitted the combinatorial synthesis of a substantial number of structurally distinct compounds using similar reaction conditions (6). The process is based on systematic molecular design either by linking separate building blocks or by adding substituents to a core structure. Many large international drug companies have established extensive molecular libraries. The most positive consequence of using combinatorial methods to synthesize NCE libraries is that several drug candidates can then be developed in parallel, in order to avoid the failure of a whole program if a single compound gives a negative result in its first application to humans. Combinatorial chemistry and the enormous capacity of high-throughput screening systems allow the synthesis and testing of thousands of compounds or mixtures per week. It has been estimated that combinatorial chemistry techniques have contributed to reducing the time required to discover drug candidates by 18–24 months. However, the obvious disadvantage to this approach is that the number of drug candidates entering the pipeline may soon overwhelm development resources. Although it is sometimes claimed that combinatorial libraries are valuable also for lead structure optimization, this claim needs to be questioned because of the lack of appropriate starting materials for their synthesis. In general, there continue to be questions as to whether this combinatorial approach will actually deliver new and better medicines more rapidly than in the past (7). The balance of this chapter contains a discussion of the major elements included in the pharmaceutical profiling of NCE and how each element contributes to the selection of lead medicinal compounds.

3. LEAD SELECTION AND OPTIMIZATION VIA PHARMACEUTICAL PROFILING

Pharmaceutical profiling (PP) has become a bridge between medicinal chemistry/pharmacology and pre-clinical studies. Most of the experimental procedures are conducted in vitro in order to maximize their capacity and minimize costs. This constraint has forced the modification of existing techniques and the development of new models and techniques, including the miniaturization of cell-based and cell-free assays.

3.1. Solution Properties

The behavior of NCE in biological solutions can markedly influence their success as orally administered medicines. The early determination of physicochemical (PC) behavior (aqueous solubility, partition coefficient, and serum protein binding) provides useful information concerning absorption, metabolism, and elimination; that is, their pharmacokinetic behavior. More importantly, these criteria may be useful in identifying compounds in drug