## 7.4 SCREENING

### 7.4.1 General Concepts

In the most general sense, screening refers to the process of investigating sources of compounds that exhibit a particular type of property or biological activity. In this chapter we explore ways of using natural products for drug discovery, and therefore the "investigations" are typically linked to a biological assay. A positive response in the assay (a "hit") is determined by the intrinsic potency of a given compound and its concentration in the screening sample. The sources of natural products used in the screening process can be quite diverse, ranging from bacterial products to higher plants and animals; however, the processes involved are similar. Once a sample, which is typically an extract of an organism, or a part of an organism (e.g., fermentation broth, fruiting body of a mushroom, leaves or roots of plants, etc.) has shown a positive response in a given assay, the process of "bioassay-guided fractionation" begins. This process is shown as a loop diagram in Figure 7.6. Resolution of the active principle(s) in these materials is a highly experimental process. The ease of resolution is dependent upon such parameters as the concentration of the active compound in an extract, the overall constitution of the extract, in terms of interferences (e.g., tannins, fatty acids and other lipids, and complex carbohydrates), as well as the chemical properties of the compound of interest. Trial and error is the operational mode of these processes and is highly dependent on the preferences and experience of the individual investigator. As indicated in Figure 7.6, the original crude material is initially split into fractions by a rough process such as differential solubility in solvents with different polarities, or by liquid–liquid partitioning between immiscible phases, usually aqueous versus organic. Subsequent steps are generally of higher resolution often with different forms of chromatography, perhaps using a normal phase high-capacity technique like silica gel chromatography in organic mobile phases first, followed by a reversed phase system with a hydrophobic stationary phase eluted with an aqueous-organic mixture. It is usually the case that a suite of structurally related compounds is isolated in this process, each having some activity in the bioassay of interest. Subtle differences in the potency or selectivity shown by these congeners form the basis for the "natural structure–activity relationship" of the series that may be useful in designing improved compounds by synthetic or biosynthetic methods during subsequent optimization of the lead. Once a compound is shown to have the activity of interest and passes a criterion of purity, it can proceed for resolution of its chemical structure and further biological evaluation.

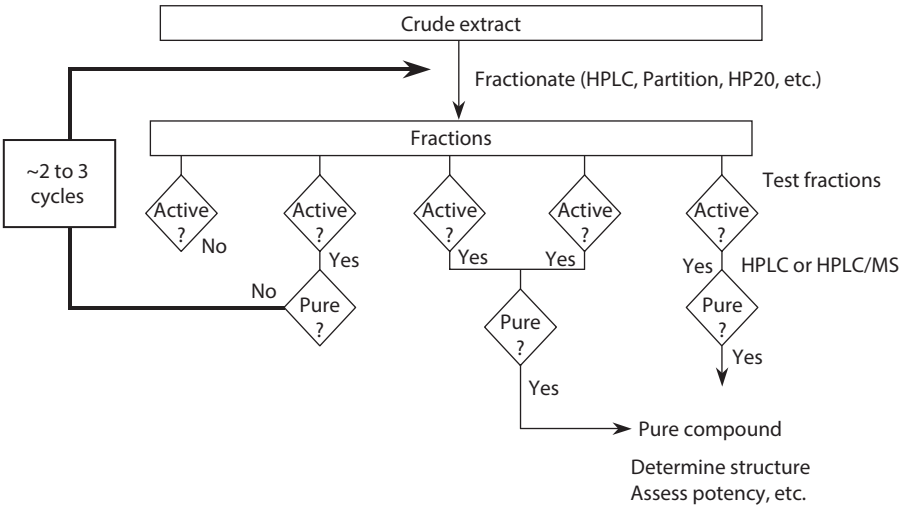


**FIGURE 7.6** Bioassay-guided fractionation of natural products.