the number and nature of the "hits" identified. If 500,000 compounds are screened and only 0.1% of the compounds in the library provide interesting biological results, this still leaves 500 compounds to be evaluated. Ideally, the initial "hits" will belong to a relatively small number of structural classes, and then each structural class can be independently analyzed to determine if further effort in the class is warranted. Small groups of related compounds demonstrating the desired biological activity can provide a significant advantage in further efforts, as structure–activity relationship data may become apparent at an early stage. (The concept of structure–activity relationships will be covered in more detail in Chapter 5.) Also, the preparation of additional analogs may be simplified, as synthetic methods may already be available. On the other hand, the presence of set of related compounds within a library suggests that they may have been prepared for a project with a different biological target. Intellectual property issues may also exist, as patent rights and ownership could become a serious question, especially if the compounds were part of a set that has been previously patented, previously published, or purchased from a commercial vendor. Intellectual property consideration will be explored in more detail in Chapter 12.

In some instances, "hit" compounds may be singletons. Isolated compounds can be more difficult to follow up on, as the original HTS data set will not provide any additional guidance on how to proceed. It is, however, still possible to generate more data on related compounds that may be available from outside of the original compound library through either commercial sources or additional synthetic efforts.

Once the initial "hit" compounds have been identified, confirmed, and a compound class (or perhaps more than one compound class, depending on the available resources) has been selected for further study, an iterative process of compound acquisition/synthesis, biological screening, and data evaluation begins with the goal of improving the potency of the compounds (Figure 1.16). In each cycle of the "lead optimization" process,

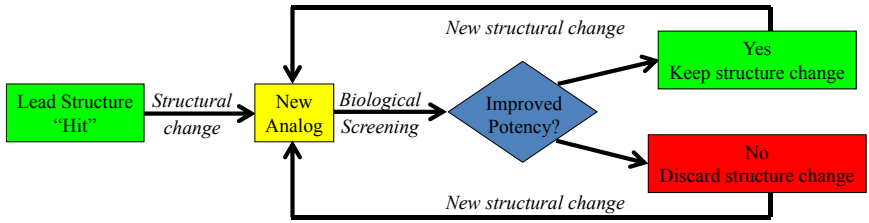

FIGURE 1.16 The lead optimization cycle begins with the identification of a lead structure ("hit") in a relevant biological assay. New analogs with structural modifications are prepared and screened in the biological assay. If the assay results improve, then the changes are kept and the cycle is repeated. If the changes are detrimental, then the changes are discarded and the cycle is repeated. This process continues until a candidate compound with the desired properties is identified.