the choice of solid support material and linker chemistry is crucial. Many different solid supports have been developed over the past two decades, which vary according to their reactivity, solubility, stability, swelling, and surface chemistry. Even though polystyrene resins are commercially available and have found application in many research labs, the choice of solid support still relates to the synthetic route desired and may require case-by-case adjustment. The same is true for the choice of linker chemistry. In general, the linker should be chemically resistant but specifically cleavable to release the product from the resin. Moreover, the cleavage should not result in any artifacts left on the scaffold. Many UV-cleavable linkers have been developed that fulfill these requirements.

Secondly, a starting scaffold has to be attached to the linker on the solid support. This step determines the ability to optimize and scale up the generation of analogs, when lead structures are identified. In this, the choice of scaffold significantly establishes the diversity of the library. It is important to emphasize that the definition of diversity already varies from approach to approach at this particular stage of the synthesis. Diversity can result from similar scaffolds presenting diverse appendages or diverse scaffolds presenting similar functional groups in different spatial arrangements. This then determines how much investment into synthetic chemistry will be done at an early stage of the high-throughput synthesis pipeline. There is a great variability in current approaches in this point ranging from no diversity of the scaffold to high structural complexity of the starting skeletons. Finally, the third aspect of strategic planning of a high-throughput synthesis comprises the further diversification chemistries of the scaffold, again restricted by the ADMET, price, ease, and robustness of the chemistry in mind.

3 Combinatorial Peptide Synthesis

A powerful combinatorial approach arose with the availability of solid-phase peptide synthesis developed by Merrifield in 1963 (Merrifield 1963). Geysen and Houghten opened a new area with their pioneering work in combinatorial peptide synthesis (Geysen et al. 1984; Houghten 1985). Initially designed for the synthesis of very large libraries, using methods such as “divide, couple, and recombine” (DCR) (Houghten et al. 1991), many other studies followed exploring the newly developing field of combinatorial chemistry. Even though the diversity of these libraries was restricted to peptide chemistry, significant contributions in the field of lead discovery were already made in these early days (Houghten et al. 1991). Choosing mesh-packets as a solid support, so-called tea bags, or polyethylene rods (or pins), many important questions in combinatorial chemistry were addressed (Houghten et al. 1991; Weiner et al. 1992). The idea of systematic analysis of peptide binding targets using combinatorial libraries arose, and these studies directly contributed to biology and immunology (Pinilla et al. 1992).

In a seminal positional-scanning synthetic-peptide combinatorial library (PS-SPCL) approach, peptide mixtures of approximately 3×10^{11} components were screened for their ability to be recognized as T cell epitopes, adding up to a total of 6.4×10^{12} decapeptides analyzed (Hemmer et al. 1998). In another