danger of getting lost. At the time when combinatorial chemistry became possible in the 1980s, eventually allowing the rapid synthesis of millions of compounds, it was thought that all possible compounds could be made when needed by starting from individual scaffolds, and the historical libraries were neglected for a while. However, it became apparent in HTS that the hit rate, when using these combinatorial libraries, was distinctly lower than that with the historical libraries. One reason for this was that combinatorial libraries were strongly dependent on chemical parameters, such as the possibility to do chemistry with molecules attached on beads rather than on potential biological activity alone. This insight led to a revalorization of the collection of historical compounds that had been made for pharmacological activity. It also led some companies to maintain and expand their natural-compound libraries, as these can be seen as compounds selected for biological activity for hundreds of millions of years. Medically useful compounds from natural substances are described previously. Today, the realization that even the millions of compounds available cover only a small part of the biologically active compound universe makes it important to continue the efforts to diversify our libraries, as repeatedly few or no ligands are found in the existing libraries for some newly discovered targets.

A specific variant of HTS is FBS. It is based on the idea that smaller molecules (usually with molecular weights less than 250 Da) are better suited to sample the chemical space, because it is much less complex for small molecules than it is for the bigger ones. Hits are generally more frequent but may bind only weakly to the biological target, which requires growing them or combining them to produce a lead with a high affinity. So far, the only successful example of this relatively new technology is the BRAF V600E mutant kinase inhibitor vemurafenib. The underlying chemotype was discovered by FBS, using a panel of recombinant kinases. The 7-azaindole compound was subsequently optimized to the final inhibitor by conventional medicinal chemistry methods.

1.1.8 Rational Drug Design

The renin inhibitor aliskiren has been approved for the treatment of hypertension in 2007. Renin is an aspartic protease that catalyzes the rate-limiting step in the renin–angiotensin system. Aliskiren is the product of rational drug design, utilizing the inhibitory principle of pepstatin, a naturally occurring hexa-peptide that contains the unusual γ-amino acid statin. The statin-based inhibitory principle was grafted onto small peptide-like compounds derived from the natural renin substrate, and these compounds were further optimized to the final drug by using structural information.

1.1.9 Target Family Knowledge

Leveraging target family knowledge is another way of generating chemical starting points for targets that are members of larger protein families such as kinases, proteases, E3 ligases, and G-protein-coupled receptors. The BCR-ABL kinase inhibitor imatinib, which revolutionized the treatment of chronic myelogenous leukemia (CML), was discovered based on an aminopyrimidine lead compound that was originally identified in a screen for the inhibitors of protein kinase C. Chemical optimization toward BCR-ABL selectivity and oral bioavailability led to the final molecule.