a while. However, it became apparent in HTS that the hit rate, when using these combinatorial libraries, was distinctly lower than with the historical libraries (Lahana 1999). 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 above. 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.

2.2 HTS

Compound collections used for high-throughput screening are typically based on chemically diverse molecules as well as on chemotypes from previous projects and can reach a size of 1–2 million substances. The compounds are screened in biological test systems, and hits, once validated by independent biochemical or biophysical methods, are further optimized to drug candidates. An example is the discovery of the anticoagulant rivaroxaban, a factor Xa inhibitor approved by the FDA in 2011. The HTS hit selected for further optimization was an oxazolidinone derivative (Perzborn et al. 2011), a compound class previously worked on for inhibition of the 50S ribosomal subunit A site in bacteria.

2.3 FBS

A specific variant of HTS is fragment-based screening. It is based on the idea that smaller molecules (usually with molecular weights below 250 Da) are better suited to sample the chemical space because it is much less complex for small molecules than it is for bigger ones. Hits are generally more frequent but may only bind 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 (Tsai et al. 2008). The 7-azaindole compound was subsequently optimized to the final inhibitor by conventional medicinal chemistry methods.