that actions of pharmaceutical drugs are governed by the law of mass action. This concept was further elaborated by Clark (1920). The receptor existed only as an abstract model, but its interactions with pharmacological drugs could be measured by constructing logarithmic dose-response curves as well as the interactions of agonists and antagonists at a particular receptor (Kenakin 1987; Arunlakshna and Schild 1959). The availability of radioactive selective receptor ligands and the development of receptor binding studies by Robert Lefkowitz et al. (1970) have greatly helped to localize receptors in different organs and tissues in particular in the brain (Cortes et al. 1987) as one example of many.

Meanwhile, due to advances in molecular biology, genetics, protein sequencing, and computing, many receptors and other drug targets are cloned, purified, and described atom by atom in spatial models allowing true target-based drug discovery, i.e., studying the interactions of targets with drug molecules in isolation and visualizing and calculating their interactions at atomic scale (Falchi et al. 2014; Chen et al. 2012).

2 Where Do Chemical Lead Structures Come from Today?

Target-based drug discovery has enabled a great expansion of chemotypes and pharmacophores available for the medicinal chemist during the past three decades. New techniques like high-throughput screening (HTS), fragment-based screening (FBS), crystallography in combination with molecular modeling, and combinatorial and parallel chemistry have created a considerable diversity of chemical lead structures well beyond the known natural products and ligands used as chemical starting points for drug discovery in the past. Moreover, this wealth of chemotypes can now be used as a source for tool compounds to study unexplored biological space and find new drug targets or for phenotypic screening using systems-based approaches to identify drug candidates in a target-agnostic manner (see below). Figure 3 shows examples of successful target-based drug discovery projects using the different methods available for identification of lead structures. These include high-throughput screening of diverse chemical libraries, fragment-based screening, rational drug design, the use of target family knowledge, and in silico drug discovery methods.

2.1 Origin of Libraries

Typically, the libraries are composed of the compounds synthesized over time by individual companies and influenced by a company's history, e.g., Novartis has a large number of ergot compounds in its library, and Roche would have many benzodiazepines. But as many companies work on similar targets or scaffolds, there must also be some overlap between the libraries. Nevertheless these libraries are a key component of the success of pharmaceutical companies, although they have once been in danger of getting lost. At the time combinatorial chemistry