2.4 Rational Drug Design

The renin inhibitor aliskiren has been approved for treatment of hypertension in 2007. Renin is an aspartic protease which 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 which 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 using structural information (Maibaum and Feldman 2009).

2.5 Target Family Knowledge

Leveraging target family knowledge is another way of generating chemical starting points for targets which are members of larger protein families such as kinases, proteases, E3 ligases, or 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 inhibitors of protein kinase C (Capdeville et al. 2002). Chemical optimization toward BCR-ABL selectivity and oral bioavailability led to the final molecule.

2.6 In Silico Methods

The availability of three-dimensional structures and ever more sophisticated computer modeling programs also enables the in silico discovery of chemical starting points. An example is gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor for the treatment of lung and breast cancers. The proposed catalytic mechanism was used to define a query for structure-based searches which led to the discovery of anilinoquinazolines as potent inhibitors and suitable lead structure for this enzyme (Ward et al. 1994).

Today, in many cases, the X-ray crystal structure of a target is available early during a drug discovery project, and even the structures of membrane receptors can now be solved. With this structural information, it is often possible to combine the different lead-finding approaches into a broader, integrated lead-finding strategy. The structural information gained from each individual hit thereby adds to an overall understanding of how best to fill the binding pocket of a target and can be used to design new chemotypes based on a holistic understanding of the contributions of many diverse molecular substructures. Different to previous times, individual compound classes thereby no longer serve as separate and unconnected starting points for the medicinal chemist but contribute to an integrated strategy. Moreover, hit finding, in particular FBS, can be used to exhaustively map a target's binding site and provide the chemists and molecular modelers with