The term “rational drug design” is often used to describe the application of structure-guided drug discovery approaches. Over the past three decades, several drugs have been made available to patients as a result of advances in protein crystallography and other structural methods. In 2007, at least 10 compounds whose discovery was reliant upon a structure-based approach had been approved by regulatory agencies. As improvements have been made to the technologies and methodologies needed for structure-based efforts, the impact of these approaches on drug development has increased. A review of the literature revealed that 9 of the 27 drugs approved by the FDA in 2013 had information on the structure of the protein target or the protein–inhibitor complex available, and at least 4 of these compounds utilized structure-based approaches during early development (Wasserman 2014). In this section, we exemplify how a detailed understanding of the topography of a ligand–enzyme complex can provide a basis for the design of better inhibitors and can complement enzymologic studies to rationalize their biochemical mode of action.

11.5.1 Structure-Based Design of Protein Kinase Inhibitors

Owing to their central roles in mediating cellular signaling pathways, protein kinases are increasingly important targets for treating a number of diseases. In particular, many of the over 500 kinases encoded by the human genome function to regulate tumor cell proliferation, migration, and survival, rendering them attractive targets for chemotherapeutic intervention in the treatment of cancer. Despite their diversity, all protein kinases catalyze the identical chemical reaction, the transfer of the γ-phosphate of ATP to the hydroxyl group of serine, threonine, or tyrosine residues on specific proteins. Their catalytic domains reflect this singular function in that they share a common feature called the protein kinase fold; this includes a highly conserved ATP-binding pocket, formed between the interface of the *N*-terminal and *C*-terminal domains. The ATP-binding site has been the major focus of inhibitor design; owing to its high degree of conservation, however, selectivity has been a major challenge for inhibitors that target this binding site of protein kinases. The use of biostructure-based approaches has therefore been of great importance in the optimization of kinase-targeted anticancer therapies.

X-ray crystallographic studies have indicated that the catalytic activity in most kinases is controlled by an “activation loop” which adopts different conformations depending upon the phosphorylation state of serine, threonine, or tyrosine residues within the loop. In kinases that are fully active, the loop is thought to be stabilized in an open conformation as a result of phosphorylation, allowing a β-strand within the loop to serve as a platform for substrate binding. While the “active” conformation of the loop is very similar in all known structures of activated kinases, there is great variability in the loop conformation in the inactive state of kinases. In this inactive-like conformation, the loop places steric constraints which preclude substrate binding.

One of the first protein kinase inhibitors developed as a targeted cancer therapy is imatinib (Gleevec®; Novartis Pharmaceuticals, Basel, Switzerland, see also Chapters 22 and 23). Imatinib has been used with remarkable success to treat patients with chronic myelogenous leukemia (CML), a malignancy resulting from the deregulated activity of the kinase Abl due to a chromosomal translocation which gives rise to the breakpoint cluster region-abelson tyrosine kinase oncogene (Bcr-Abl). Imatinib inhibits the tyrosine kinase activity of Bcr-Abl and it is considered as a frontline treatment for CML by virtue of its high degree of efficacy and kinase selectivity. Together with biochemical analyses, crystallographic studies of the interaction of imatinib with the Abl kinase domain have revealed that imatinib binds to the Bcr-Abl ATP-binding site preferentially when the centrally located activation loop is not phosphorylated, thus stabilizing the protein in an inactive conformation (Figure 11.7). In addition, imatinib’s interactions with the *N*-terminal lobe of the kinase appear to involve an induced-fit mechanism, further adding to the unique structural requirements for optimal inhibition. One of the most interesting aspects of this interaction is that the specificity of inhibition is achieved despite the fact that residues that contact imatinib in Abl kinase are either identical or very highly conserved in other Src-family