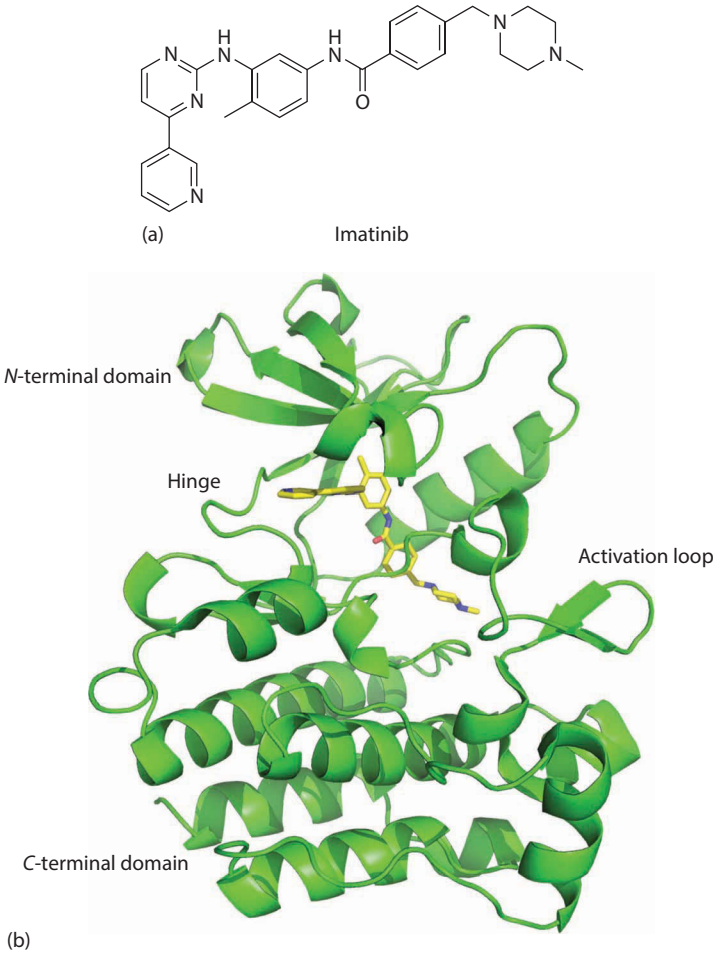

FIGURE 11.7 The structure of Imatinib (Gleevec; a) and the compound in complex with the catalytic domain of cAbl (PDB 1IEP; b).

tyrosine kinases. Thus, despite targeting the relatively well-conserved nucleotide-binding pocket of Abl, studies have shown that imatinib achieves its high specificity by recognizing the distinctive inactive conformation of the Abl activation loop. Biostructure-based methods have had a further impact on more recent efforts to design second-generation therapies targeting imatinib-resistant mutations in Bcr-Abl kinase that have been identified in CML patients. It is likely that these new inhibitors will have substantial clinical utility in the treatment of imatinib-resistant CML; continued exploration of the structural details of the interactions between these compounds and the mutant kinase are still necessary, as resistance remains an inevitable consequence of such drug treatment regimens.

The three catalytically active receptor tyrosine kinases (RTKs) of the ErbB family represent another attractive target group for the treatment of a variety of cancers: epidermal growth factor receptor (EGFR, also known as ErbB1), ErbB2 (also known as HER2/*neu*), and ErbB4. These RTKs are large, multi-domain proteins that contain an extracellular ligand binding domain, a trans-membrane domain, and a cytoplasmic domain responsible for the tyrosine kinase activity. Ligand binding to the extracellular domain induces the formation of receptor homo- and hetero-dimers which leads to the activation of the tyrosine kinase activity and subsequent phosphorylation of the cytoplasmic tail. A number of ErbB-targeted molecules have already reached the market, with a number of others