Allosteric inhibitors, by definition exert their influence at sites other than the active site of the enzyme in question just as their name implies. The active site of the targeted enzyme remains unoccupied, but is made inaccessible to the natural substrate as a consequence of the presence of an allosteric inhibitor. When the allosteric inhibitor binds to an allosteric binding site (a binding site on the enzyme that is different from the active site), it induces changes in the enzyme's overall configuration such that the binding site is no longer capable of interacting with the natural ligand (Figure 3.17(d)). MEK1, a member of the kinase class of enzymes that plays an important role in the progression of cancer, for example, can be allosterically inhibited by compounds such as CI-1040. Although this compound is a potent inhibitor of MEK1 and MEK2, it does not bind to the ATP-binding domain, which is the active site of MEK1. Rather, it binds to an adjacent binding site and produce inhibition of MEK1 via conformational changes induced by its presence in the allosteric site (Figure 3.19).[26]

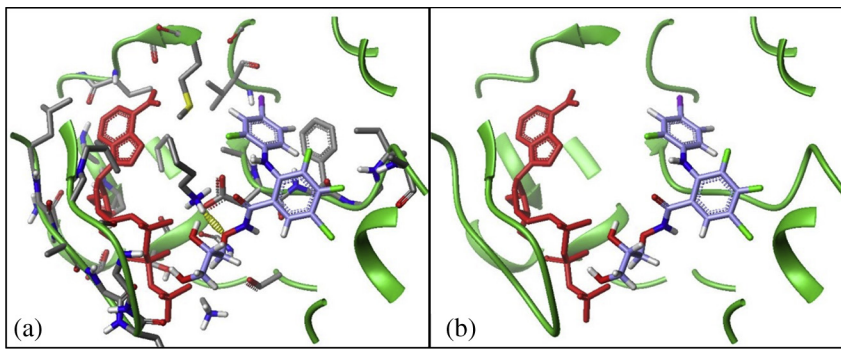

FIGURE 3.19 (a) CI-1040 bound adjacent to the active site of MEK1 occupies an allosteric binding site. ATP (red) and key side chain residues are displayed. (b) CI-1040 and ATP (red) bond to Mek1 with side chains hidden. *RCSB file 1S9J.*

Although the kinase family of enzymes shares a high degree of homology at the ATP-binding site, the same is not necessarily true of allosteric binding sites. This provides an opportunity to design compounds with a higher degree of selectivity within the kinase family.

Unlike competitive and allosteric inhibitors, irreversible inhibitors covalently attach to the active site of the target enzyme, blocking entry of the natural substrate and inactivating the enzyme. β-Lactams, such as benzylpenicillin (penicillin G), for example, react with a serine residue in the active site of penicillin-binding proteins (PBPs), deactivating the enzyme (Figure 3.20). PBPs are essential for the final stages of peptidoglycan synthesis, a major component of bacterial cell walls. Irreversible inhibition by β-lactams leads to decreased cell wall strength and cell death of the targeted microorganism.[27] Since there is no human counterpart to PBP,