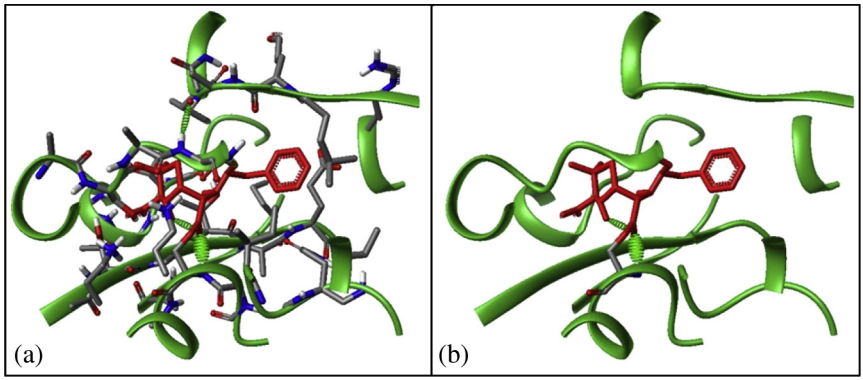

FIGURE 3.20 (a) Benzylpenicillin (Penicillin G, red) covalently bound to the active site of penicillin-binding protein A from *M. tuberculosis* with key side chains displayed. (b) Benzylpenicillin (Penicillin G, gray) covalently bound to the active site of penicillin-binding protein A from *M. tuberculosis* with key side chains hidden. *RCSB file 3UPO.*

the prospect of undesired side effect mediated by β-lactam antibiotics is generally low. The application of irreversible inhibitors for the treatment of conditions in which there is a human variant of the target enzyme can be an issue, however, as restoring enzymatic activity generally requires the synthesis of additional quantities of the target enzyme. Suppose, for example, an irreversible kinase inhibitor were developed targeting the ATP-binding site of MEK1. The irreversible inhibitor would bind to MEK1, suppressing its activity, but given the high degree of homology of the ATP-binding site within the kinase family, it is likely that many other kinases would also be irreversibly inhibited. Irreversible inhibition of enzymes that are involved in drug metabolism can also lead to significant negative consequences by altering the rate at which drugs are cleared from the body. This will be discussed in greater detail in Chapter 6. In general, the pharmaceutical industry favors the development of competitive and allosteric inhibitors over that of irreversible inhibitors.

G-PROTEIN-COUPLED RECEPTORS (GPCRs)

The flow of information across plasma membranes is absolutely essential to proper cellular function and coordination of bodily functions. Human cells must be in routine communication with neighboring cells, aware of their environment, and, in many cases, provide information to cells in distal locations of the body. Rapid responses are often required. The sensation of pain felt upon touching a hot surface, for example, must be relayed nearly instantaneously to the brain upon contact with the hot surface. Cellular