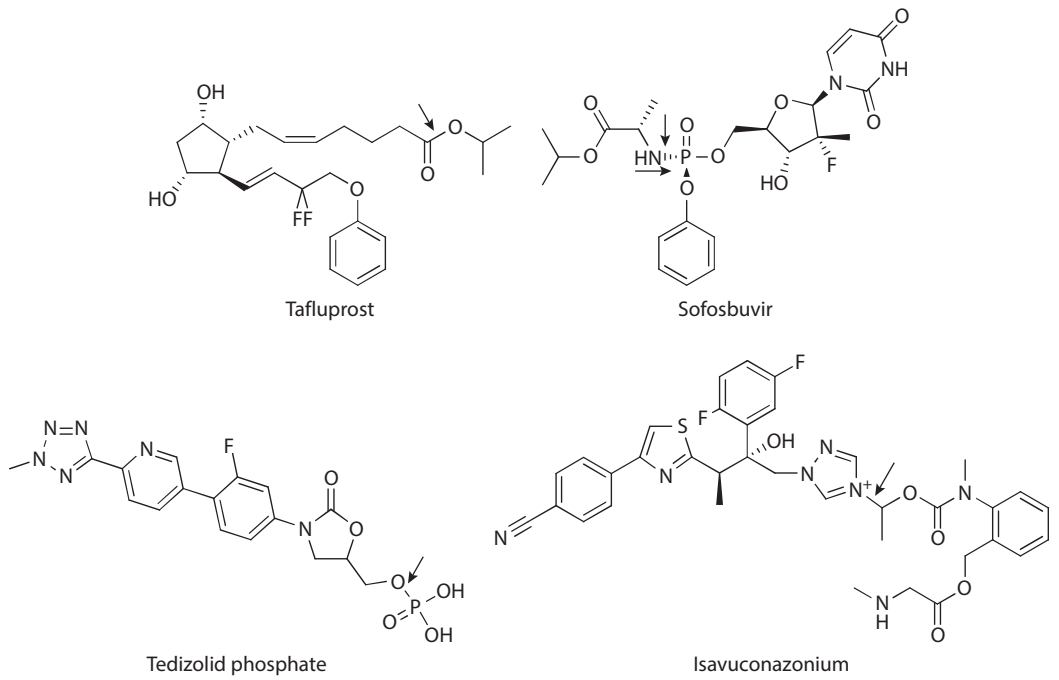

FIGURE 10.3 Recent prodrugs in clinical use. Bonds between an active drug and a promoiety are indicated by arrows.

reviews, and patents, as well as on the number of clinical studies and marketed prodrugs. From 2010 to 2014, 127 small molecular weight drugs were approved by the FDA. Of these, at least 12 drugs, or 9.4%, were prodrugs. Some of the recently approved prodrugs are tafluprost (in 2012), an ocular isopropyl ester for the treatment of glaucoma and ocular hypertension, an oral phosphoramidate prodrug sofosbuvir (2013) for the treatment of hepatitis C, as well as orally and/or intravenously given tedizolid phosphate (2014) and isavuconazonium (2015) for the treatment of skin and fungal infections, respectively (Figure 10.3). It is estimated that approximately 10% of all worldwide marketed drugs can be classified as prodrugs.

10.4 DESIGNING OF PRODRUGS

The design of a prodrug structure should always be considered at the early stages of preclinical development, keeping in mind that prodrugs may alter the tissue distribution, metabolism, efficacy, and even toxicity of the parent drug. For example, the intended hydrolysis of the inactive lactone form to the pharmacologically active hydroxyl acid of a HMGCoA reductase inhibitor simvastatin is relatively fast, but the more lipophilic lactone also predisposes the drug to unwanted metabolism by cytochrome P450 enzymes. Many times, the prodrug design can, however, represent a comparable smaller challenge and be more feasible than the alternative of searching for a new therapeutic agent that also inherently possesses the desired properties. The prodrug strategy can also enable the selection of a suitable drug candidate faster and with lesser costs. There are several factors that should be carefully considered when designing prodrug structures:

- What is the limitation of the parent drug that needs prodrug intervention?
- Which functional groups on the parent drug are suitable for chemical modification?
- Can the prodrug be readily synthesized?