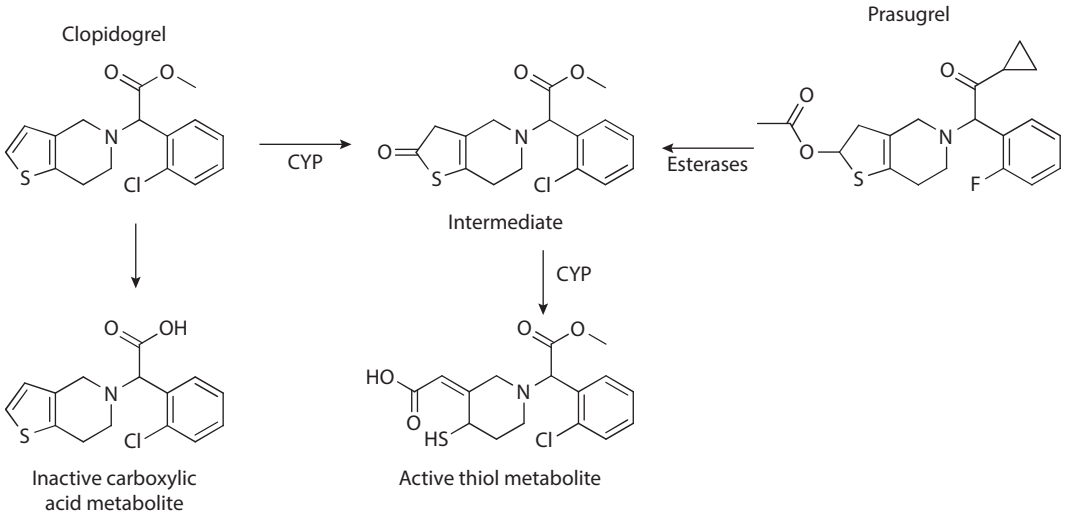

FIGURE 10.14 Bioconversion of clopidogrel and prasugrel to their active thiols.

P450-mediated oxidation. In 2010, clopidogrel has held the position of the second most prescribed drug in the world with over $9 billion in sales.

The increased knowledge about cytochrome P450-mediated bioconversion pathways has led to the design of the liver-specific cyclic phosphate or phosphonate prodrugs called HepDirect®-prodrugs. These prodrugs are cyclic 1,3-propanyl esters containing a ring substituent that render them sensitive to cytochrome P450-mediated oxidation. This oxidation results in ring opening and formation of transient negatively charged intermediate which cannot diffuse across cell membranes and is thus retained in hepatic cells. A consequent β-elimination reaction releases the phosphate or phosphonate drug, and aryl vinyl ketone as a by-product (Figure 10.15). Pradefovir is a HepDirect®-prodrug of adefovir which is currently under clinical development for the treatment of hepatitis B. In fact, pradefovir is developed to improve the therapeutical potential of adefovir dipivoxil which kidney toxicity limits its use. In contrast, pradefovir produces 12-fold liver/kidney and 84-fold liver/intestine targeting ratios compared to adefovir dipivoxil, and after its administration the systemic adefovir levels remain low. Pradefovir undergoes a cytochrome P450-mediated oxidation predominantly in the hepatocytes of liver (Figure 10.15).

Although the proton pump inhibitors, such as omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole and tenatoprazole, were not originally developed as prodrugs, they provide a good example of site-selective prodrugs. Due to the basic pyridine group (pK_a of omeprazole is 3.97), these drugs are protonated and accumulated in the acidic secretory parietal cells (Figure 10.16). In the acidic conditions of parietal cells (pH of 1–2), prazoles undergo spontaneous chemical reaction to their active sulfenamide metabolites followed by their irreversible binding to a cysteine group of H^+/K^+ ATPase. This irreversible binding inhibits the ability of parietal cells to secrete gastric acid. The fact that proton pump inhibitors are only effective on H^+/K^+ ATPases, which contain highly acidic compartments that nongastric H^+/K^+ ATPases lack, corresponds their excellent safety profiles. Therefore, proton pump inhibitors are converted to their active species only under highly acidic conditions at their site of action.

Examples of other site-selective prodrugs include ticlopidine, simvastatin, lovastatin, and hypoxia-activated prodrugs, such as AQ4N, PR104, and evofosfamide which are currently under clinical investigation.