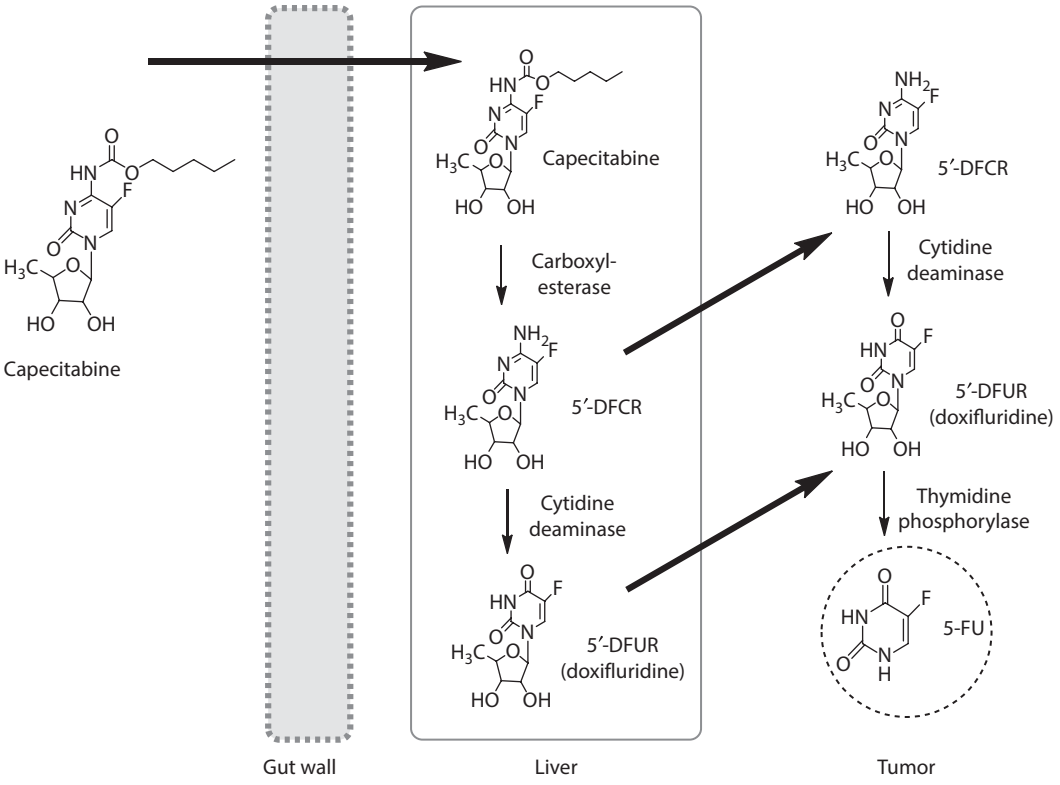

FIGURE 10.13 Tumor-selective activation pathway of capecitabine to cytotoxic 5-FU.

A need for more tumor selective delivery and reduced healthy tissue concentrations of the cytotoxic drug, 5-fluorouracil (5-FU), led to the rational design of capecitabine. Capecitabine is an orally administered chemotherapeutic prodrug, of which bioconversion to 5-FU requires three reaction steps that all are enzymatic (Figure 10.13). After its administration, capecitabine is first hydrolyzed to 5′-deoxy-5′-fluorocytidine (5′-DFCR) by carboxylesterase activity in the liver. Next, 5′-DFCR is converted into 5′-deoxy-5′-fluorouridine (5′-DFUR) by cytidine deaminase either in liver or in tumor tissue. Finally, the release of an active 5-FU occurs selectively at the tumor site by the catalytic activity of thymidine phosphorylase. The oral bioavailability of 5-FU after capecitabine administration is nearly 100% and the maximal concentrations of 5-FU are reached within 1.5–2 hours. In patients with advanced breast cancer, the 5-FU levels in tumor tissue were 2.5-fold higher compared to healthy tissue and 14-fold higher compared to plasma after capecitabine administration. Capecitabine enables more convenient and safer oral treatment for cancer patients with reduced adverse effects in healthy tissue.

The thienopyridine antiplatelet agents, clopidogrel and prasugrel, are excellent examples of liver-targeted prodrugs, which release their parent drugs at or close to their site of action (Figure 10.14). As a metabolizing organ, the liver possesses a wide variety of metabolizing enzymes that are capable of prodrug activation. Clopidogrel and prasugrel are both bioactivated through the hepatic cytochrome P450 enzymes to produce their active but unstable thiol-compounds which bind to the $P2Y_{12}$ class of platelet adenosine triphosphate receptors to inhibit platelet aggregation. The fact that about 85% of clopidogrel dose is hydrolyzed by esterases to yield an inactive carboxylic acid has led to the design of over 10-fold more potent prasugrel. Prasugrel undergoes bioconversion through a cascade of events which involve carboxylesterase 1-catalyzed hydrolysis and cytochrome