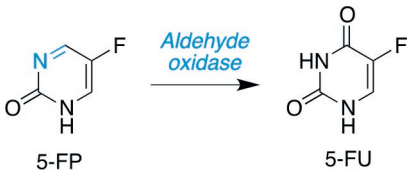

FIGURE 2.24

Bioactivation of 5-FP.

a TP deficiency due to a genetic defect, and tumors originated from the gene-modified cells could be selectively targeted by capecitabine.[37]

Another prodrug of 5-FU is 5-fluoro-2-pyrimidinone (5-FP), which is activated by hepatic aldehyde oxidase after oral or intravenous administration (Figure 2.24). A phase I clinical study proved that this compound is suitable for oral outpatient therapy.[38]

4.4 MODULATION OF 5-FLUOROURACIL ACTIVITY

Major efforts have been made to modulate the activity of 5-FU. These efforts have focused on the following aspects: (1) decreasing its degradation, (2) enhancing its potency as a thymidylate synthase inhibitor, and (3) increasing its activation.

4.4.1 Decreased Degradation of 5-FU

More than 80% of administered drug is degraded in the liver by dihydropyrimidine dehydrogenase (DPD), which reduces the pyrimidine double bond of 5-FU to give dihydrofluorouracil (DHFU).[39] This metabolite is inactive because it cannot give the initial Michael addition with the nucleophilic site of the active center in TS (Figure 2.25).

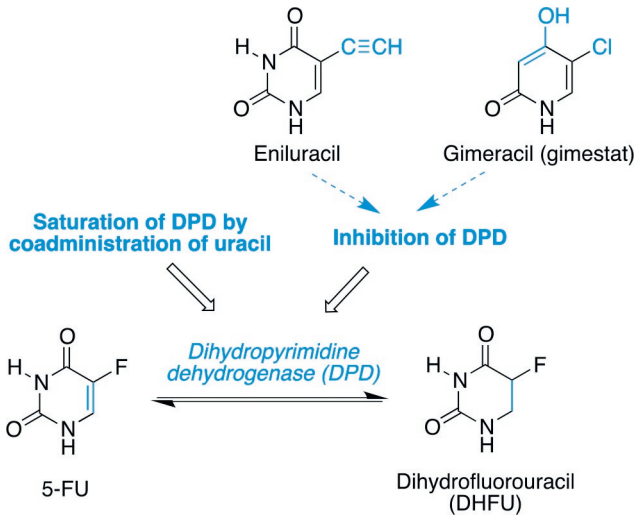

FIGURE 2.25

Drug combination approaches leading to a decreased degradation of 5-FU.