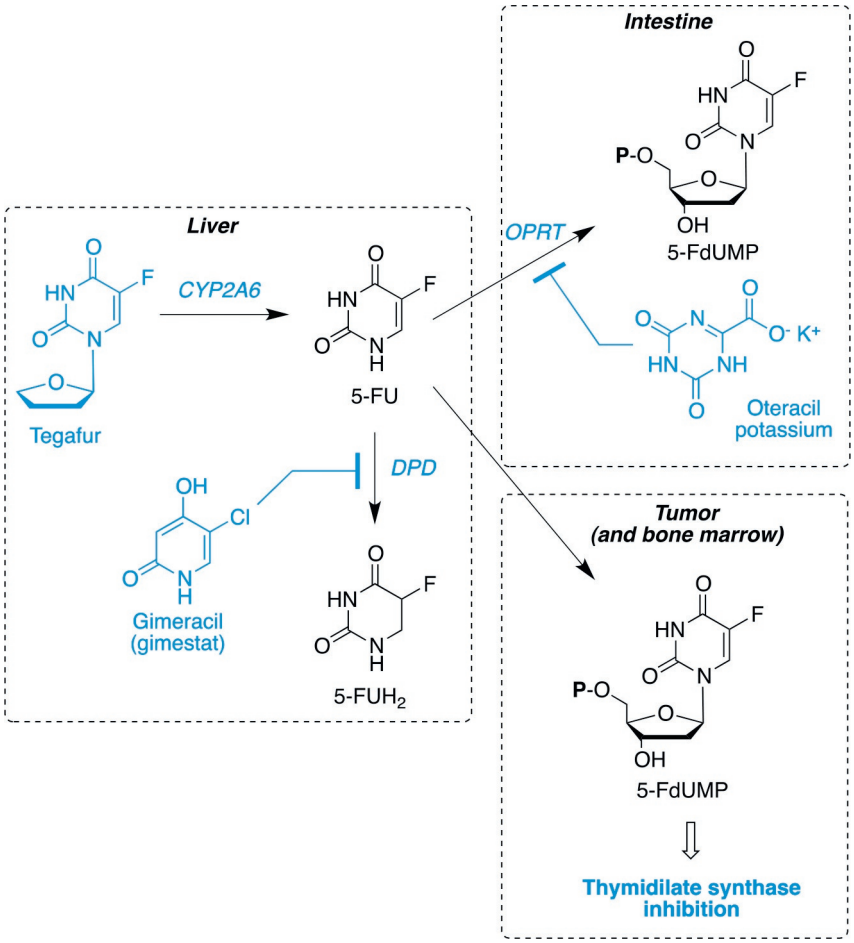

FIGURE 2.29

Mechanism of action of the S-1 combination (tegafur, oteracil potassium, and gimestat).

When taken orally, trifluridine undergoes extensive first pass hepatic metabolism by thymidine phosphorylase, which transforms it into inactive metabolite 5-trifluoromethyluracil. This observation led to the idea of associating trifluridine with tipiracil hydrochloride, a thymidine phosphorylase inhibitor (Figure 2.31). This association, known as TAS-102, is under phase II clinical trials in patients with metastatic colorectal cancer.

4.6 FOLATE-BASED THYMIDYLATE SYNTHASE INHIBITORS

As previously mentioned, TS inhibition by the fluoropyrimidines is not specific because of the effect of fluorinated nucleotides on other pathways, especially related to RNA. Also, the accumulated dUMP may compete with the antitumor drug for TS. For this reason, there has been much interest in the design