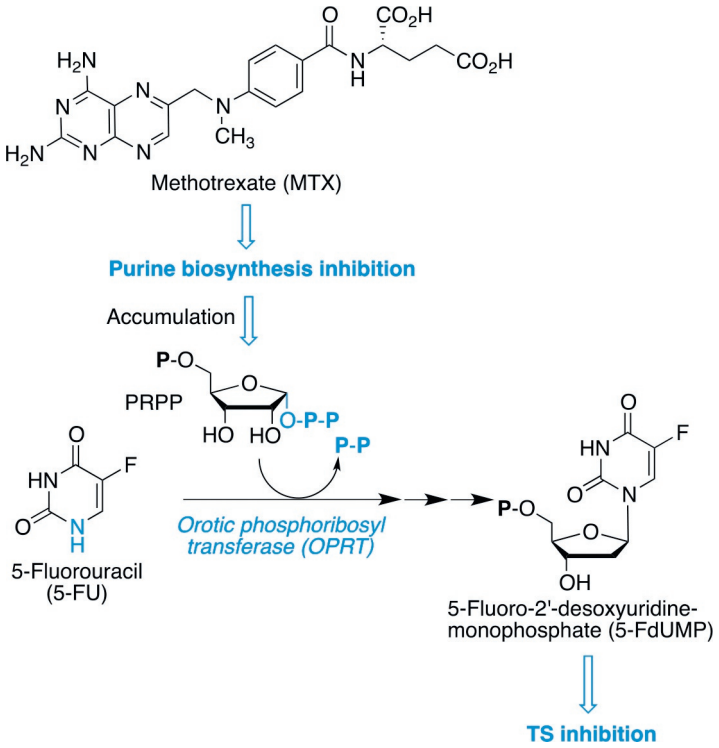

FIGURE 2.28

A strategy to enhance 5-FU activation.

Diarrhea is the most common dose-limiting toxicity associated with prolonged infusion of 5-FU. To prevent this gastrointestinal toxicity, some oral formulations have been proposed that contain the potassium salt of oxonic acid (oteracil potassium), a potent inhibitor of the phosphoriboxylation of 5-FU in the gastrointestinal mucosa. One of these formulations is S-1 (TS-1), which contains tegafur, oteracil potassium, and the previously mentioned gimestat (5-chlorodihydroxypyridine), an inhibitor of dihydropyrimidine dehydrogenase (see Section 4.4.1).[48] The combination of S-1 and cisplatin acts by the mechanisms summarized in Figure 2.29 and is approved for the treatment of gastric cancer in Japan.[49]

4.5 TRIFLURIDINE

Trifluridine (trifluorothymidine, TFT) is used as an anti-herpes drug, primarily for ocular treatments, and acting by incorporating into viral DNA. It is also an inhibitor of thymidylate synthase by the mechanism summarized in Figure 2.30. Thus, after phosphorylation to **2.28**, the initial nucleophilic attack of the Cys residue onto the substrate $C_5{=}C_6$ bond generates the enolate anion **2.29**, which evolves in this case by loss of a fluoride anion to furnish **2.30**. This intermediate bears a difluorinated α,β-unsaturated carbonyl fragment that undergoes attack by the Tyr-146 residue of the active site of thymidylate synthase, again with loss of HF, to give **2.31**. A final attack by a water, with concomitant loss of a third molecule of HF, yields the final product **2.32**.