



FIGURE 2.19

Mechanism of TS inhibition by 5-FdUMP, the 5-FU active metabolite.

false substrate of DNA polymerase and is misincorporated into DNA. As a consequence of the accumulation of dUMP after TS inhibition, dUTP can also be generated and incorporated into DNA. Ultimately, this change halts DNA synthesis and promotes DNA fragmentation by repair enzymes. Similarly, transformation of 5-FUDP, a metabolite of 5-fluorouracil, into the corresponding triphosphate allows the misincorporation of fluoronucleotides into RNA, leading to profound effects on cell metabolism and viability. Both TS inhibition and misincorporation of 5-FU metabolites in DNA result in the stabilization of p53, a tumor suppressor that maintains DNA integrity by activating genes that arrest cell cycle in response to DNA damage or trigger apoptosis (Figure 2.20). *In vitro* studies have proven that loss of p53 function is associated with a reduced sensitivity to 5-FU.<sup>33</sup>

The clinical efficacy of 5-FU may be decreased by several mechanisms, the first of which is diminished incorporation of 5-FUTP into RNA as a consequence of competition from high intracellular levels of UTP. On the other hand, the formation of the ternary TS–FdUMP–CH<sub>2</sub>-THF complex induces TS expression due to the inhibition of a negative feedback mechanism whereby TS binds to its own mRNA and inhibits the translation process. The ternary complex is not able to bind to this mRNA, leading to increased expression of TS and constituting a possible resistance mechanism. Finally, TS inhibition leads to an increase in intracellular dUMP pools, which eventually compete with 5-FdUMP for binding with TS.

### 4.3 5-FLUOROURACIL PRODRUGS

5-FU requires intravenous administration, and a number of oral prodrugs have been designed to circumvent this limitation.<sup>34</sup> One of them is tegafur (Ftorafur<sup>®</sup>), which is completely absorbed in the gastrointestinal tract and metabolized to 5-FU through two major pathways. The first involves microsomal