Some clinically relevant deoxyadenosine derivatives acting primarily as inhibitors of DNA polymerases are also allosteric inhibitors of RNR after their conversion into the corresponding 5′-triphosphates, as discussed in Section 8. Therefore, these compounds have a dual action that has been described as "self-potentiation."

4 INHIBITORS OF THE BIOSYNTHESIS OF THYMIDILIC ACID

4.1 THYMIDYLATE SYNTHASE

Thymidylate synthase (TS) catalyzes the conversion of dUMP to thymidylate (TMP) in a reductive methylation that involves the transfer of a carbon atom from the cofactor 5,10-methylenetetrahydrofolate to the 5 position of the pyrimidine ring. Although methylation of uracil is apparently a small structural change, the extra lipophillicity and bulk associated with the methyl group is essential for the proper discrimination of thymine from the other three bases present in DNA chains by transcription factors, repressors, enhancers, and other DNA-binding proteins. This methylation process, which is the only *de novo* source of thymidilate, is part of the so-called thymidylate cycle (Figure 2.15), in which two other enzymes take part, namely serine hydroxymethyl transferase (SHMT) and dihydrofolate reductase (DHFR). SHMT catalyzes the formation of 5,10-methylenetetrahydrofolate from tetrahydrofolate (THF), coupled

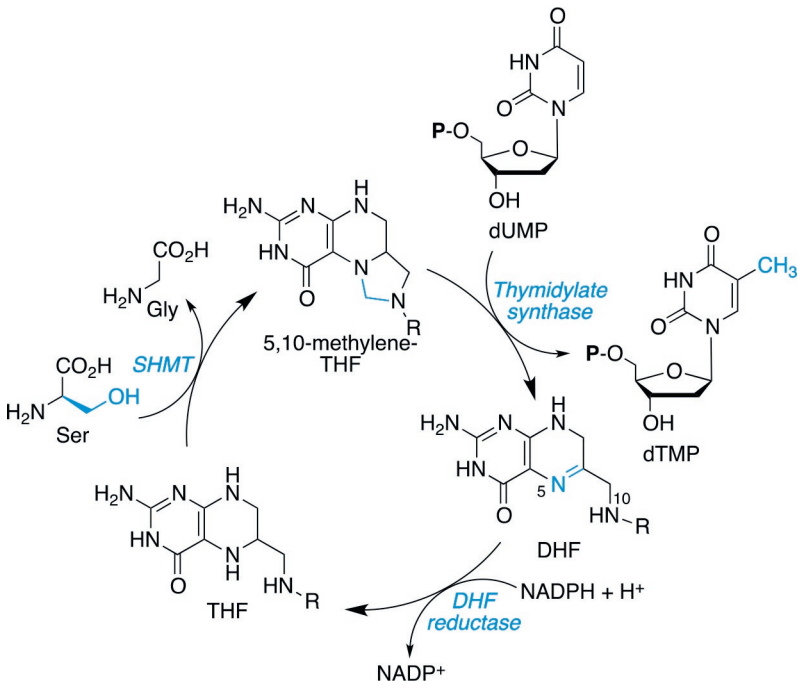

FIGURE 2.15

The thymidylate cycle.