5 INHIBITORS OF DIHYDROFOLATE REDUCTASE

Folic acid and its metabolites (collectively known as folates) are coenzymes of many essential biochemical transformations. Most important, they are involved in the previously mentioned transfer of one carbon unit in the *de novo* synthesis of thymidylic acid and purine nucleotides. Folate-dependent enzymes are obvious targets for cancer chemotherapy,[60,61] but until 1980, only DHFR was exploited in this regard; in fact, it was the first enzyme to be targeted for cancer chemotherapy.

In mammals, folic acid is taken with the diet and reduced to THF by dihydrofolic reductase in two stages, using NADPH as a cofactor. Further transformations of THF lead to 5,10-methylene-THF, 5,10-methenyl-THF, 5-formyl-THF, and 10-formyl-THF (Figure 2.33), which are known as folinic acids and are involved in the transfer of one-carbon units. DHFR inhibition leads to cell death due to the essential role of folinic acids in the synthesis of thymidylate and purine bases.

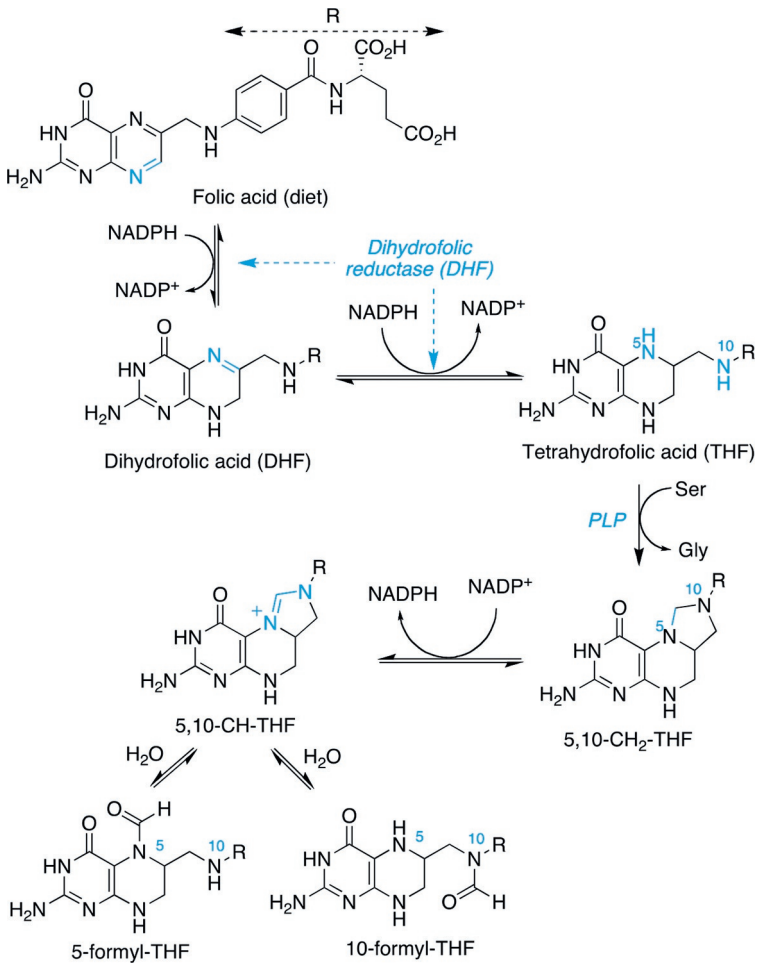

FIGURE 2.33

Biotransformation of folic acid into folinic acids.