



FIGURE 2.41

Reaction catalyzed by GARFT.

concomitant replacement of the ring fused to the quinazolinone unit by an indole, leading to loss of stereochemical information at C-6. It employs the RFC for entering the cells, and its polyglutamation inhibits multiple targets in the folate pathway, including the previously mentioned TS and DHFR and two enzymes from the *de novo* synthesis of purines, namely GARFT and AICARFT. This complex mechanism of action has led to its designation as MTA (multitargeted antifolate). Pemetrexed was approved in 2004 for the treatment of malignant pleural mesothelioma in association with cisplatin and as second-line treatment of non-small cell lung cancer,⁷³ and two indication extensions were granted in 2008 and 2009. Replacement of the 4-oxo group by a methyl (AAG 113–161) led to a further increase in activity, which was explained by a hydrophobic interaction of the 4-methyl with Phe-31 and Leu-22.⁷⁴

A summary of the main targets for antifolate drugs and their relationships with nucleic acid biosynthesis is given in Figure 2.43.

6.3 INHIBITORS OF PHOSPHORIBOSYLFORMYLGLYCINAMIDINE SYNTHETASE

This enzyme catalyzes the reaction of formylglycinamide ribonucleotide with ammonia to give formylglycinamide ribonucleotide, with glutamine as cofactor (Figure 2.33). The enzyme activates the amide group adjacent to the ribose ring to nucleophilic attack by its transformation into iminoether **2.28**. On the other hand, another catalytic site of the enzyme hydrolyzes glutamine to glutamic acid and ammonia, which is then channeled to the first site and reacts with **2.28** by an addition–elimination mechanism, affording the amidine **2.29** (formylglycinamide ribonucleotide) (Figure 2.44).

Some analogs of glutamine bearing a diazomethyl moiety have antitumor activity because of their ability to inhibit several reactions in which glutamine is involved as a cofactor, specially the one catalyzed by formylglycinamide ribonucleotide synthetase. Azaserine (*O*-diazooacetyl-L-serine)