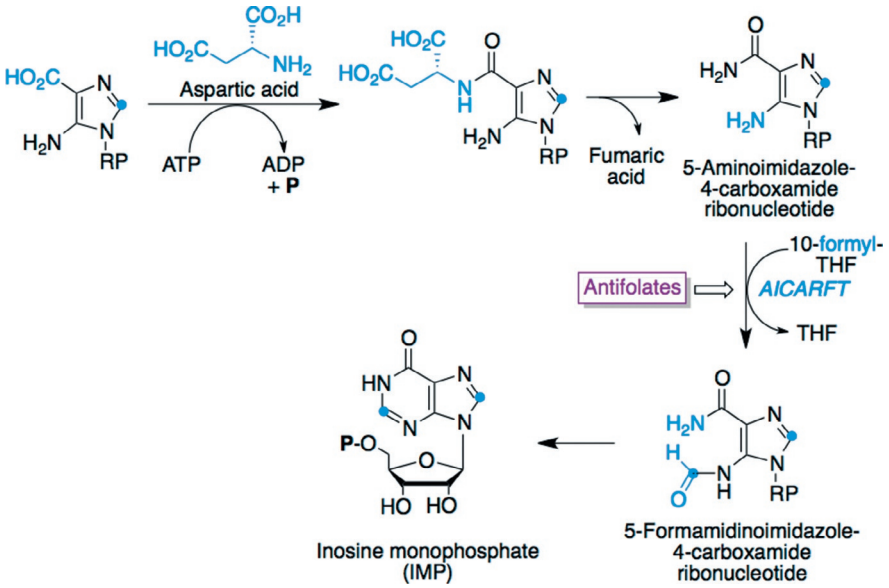

FIGURE 2.40

Final stages of the biosynthesis of purine nucleotides.

6.2 INHIBITORS OF GLYCINAMIDE RIBONUCLEOTIDE FORMYLTRANSFERASE

The third reaction in the *de novo* purine biosynthesis is the transformation of glycinamide ribonucleotide (GAR) into its formyl derivative (FGAR) using 10-formyltetrahydrofolate as the formyl donor (Figure 2.41). The enzyme that catalyzes this step is known as GARFT. In mammals, this enzyme is multifunctional, and it also catalyzes the second and fifth steps of the pathway.

The first selective and sufficiently potent GARFT inhibitor was lometrexol, designed as a folate analog lacking the 5 and 10 nitrogen atoms and therefore unable to participate in the transfer of single carbon units.[69] On the other hand, lometrexol has a 2-aminopyrimidin-4-one subunit identical to that found in the THF cofactor and, therefore, different from the 2,4-diaminopyrimidine pattern commonly present in DHFR inhibitors. Its glutamate side chain allows its ready transport into cells by means of the RFC and MFR as transport systems, and also its polyglutamation by FPGS. Lometrexol was investigated clinically, but unexpected observations of delayed cumulative toxicity[70] prompted a search for second-generation antimetabolites with a more favorable profile (Figure 2.42). Some of these compounds are LY-309887, an analog of lometrexol designed by benzene–tiophene bioisosteric replacement with a ninefold greater potency as a GARFT inhibitor; AG-2034, with an additional CH-S isosteric change and that underwent phase I studies[71]; and pelitrexol (AG-2037), an analog with the opposite configuration at C-6. In addition to being well tolerated, the latter compound shows an interesting synergism with 5-FU and has been studied in phase II trials in patients with metastatic adenocarcinoma of the colon or rectum when prior fluorouracil and leucovorin calcium therapy had failed.[72]

Pemetrexed (Alimta®, MTA), previously mentioned as an inhibitor of both TS and DHFR, was discovered during structure–activity studies of lometrexol, by removal of the C-5 carbon atom and