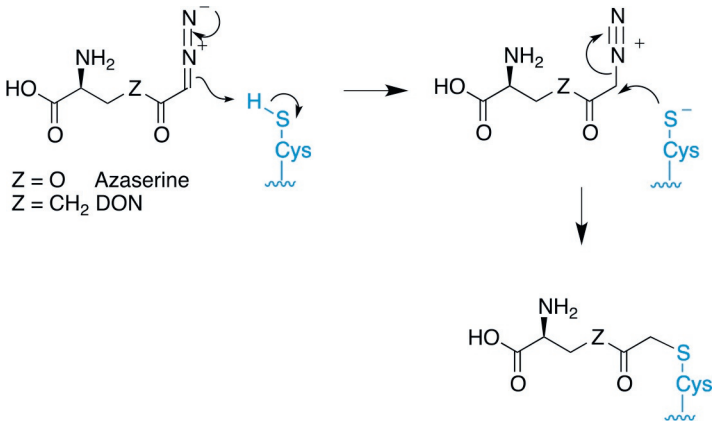


FIGURE 2.45

Covalent inactivation of phosphoribosylformylglycinamidine synthase by azaserine and DON.

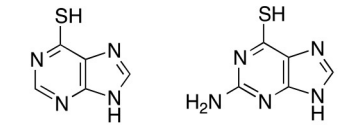
therapeutic use. Nevertheless, a phase IIa study evaluated the safety and clinical activity of the glutamine-depleting enzyme PEG-PGA (PEGylated glutaminase) in combination with DON.[75]

6.4 INHIBITORS OF 5-AMINOIMIDAZOLE-4-CARBOXAMIDE RIBONUCLEOTIDE FORMYLTRANSFERASE

Some antifolate drugs (e.g., methotrexate and pemetrexed) inhibit this enzyme, although it is not their primary target.

6.5 THIOPURINES AND RELATED COMPOUNDS

Among non-natural purine derivatives assayed as antitumor agents, 6-mercaptopurine (MP, Purinethol®) and 6-thioguanine (TG, tioguanine) are the most active. These compounds are among the oldest cancer chemotherapeutic drugs in clinical use. MP is used for lymphoblastic and myeloblastic leukemias, and the more toxic TG is employed for the treatment of acute nonlymphocytic leukemia.



MP requires intracellular metabolism by hypoxantine guanine phosphoribosyl transferase (HGPRT) to be transformed into thioinosinic acid, which shows cell cycle S-phase-specific cytotoxicity. Intracellular activation results in the inhibition of several enzymes belonging to the *de novo* purine synthesis pathway and misincorporation into DNA and RNA. Thus, thioinosinic acid, formed by incorporation of a ribose phosphate unit to MP catalyzed by HGPRT, inhibits PRPP amidotransferase, the first enzyme