

in the *de novo* synthesis of purines, through a retro-inhibition mechanism. Several other enzymes that are also inhibited, resulting in lower levels of adenosine monophosphate (AMP) and guanosine monophosphate (GMP), are the following:

1. HGPRT itself because of competition between MP and its natural substrate, hypoxanthine
2. Inosinic dehydrogenase, which transforms inosinic acid (IMP) into xanthylic acid (xanthosinic acid, xanthosine 5'- monophosphate), a precursor of guanylic acid (GMP)
3. Adenylosuccinate synthetase, which catalyzes the first step of the transformation of inosinic acid into adenylic acid (AMP)

In addition, thioinosinic acid is transformed into thioguanilyc acid, which is misincorporated into DNA and RNA. This leads to single strand DNA breaks and DNA–protein cross-links by alteration of DNA repair mechanisms (Figure 2.46). Thioguanine acts by a very similar mechanism, after its transformation into thioguanilyc acid by HGPRT.

The main degradative pathways of MP are its *S*-methylation by thiopurine methyltransferase (TPMT) and its oxidation by xanthine oxidase to an 8-oxo derivative, which is then further oxidized to give 6-thiouric acid (TUA). Allopurinol is a structural analog of hypoxanthine that is converted slowly to alloxanthine, which also inhibits the enzyme by trapping of an intermediate molybdenum(IV) species that participates in the catalytic cycle of the enzyme (Figure 2.47). Allopurinol interferes with the metabolism of MP (Figure 2.48), increasing its levels and leading to an interaction between both drugs; for this reason, patients taking allopurinol should have their MP dose reduced by up to 75%. However, the clinical benefit of this association in cancer patients taking MP is only slight, and renal damage may occur. *S*-methylation is another catabolic route of MP because the *S*-methyl derivative is not a substrate for the purine phosphoribosyl transferases.

Some heterocyclic derivatives of thiopurines have been designed to afford protection from the degradation processes described previously, two examples being the nitroimidazole derivatives azathioprine (Imuran[®]) and thiamiprine (Guaneran[®]). These compounds act as prodrugs and are presumably activated by an S_NAr mechanism involving nucleophilic attack from thiols onto the 5 position of the 4-nitroimidazole ring, followed by elimination of the thiopurine as a leaving group (Figure 2.49). None of these prodrugs are more effective as anticancer agents than the parent compounds, although azathioprine is an important immunosuppressant agent, widely used in autoimmune diseases.⁷⁶

Another prodrug that is activated by a related mechanism is *cis*-3-(9*H*-purin-6-ylthio)acrylic acid (PTA), which is activated by glutathione through a Michael addition to the acrylic acid moiety followed by elimination (Figure 2.50).⁷⁷

Considerable effort has been carried out to prepare other mercaptopurine and thioguanine analogs and their nucleosides in order to improve their antitumor efficacy.⁷⁸

7 INHIBITORS OF ADENOSINE DEAMINASE

Coformycin (CF) and pentostatin (2'-deoxycoformycin, dCF, Nipent[®]) are two natural products isolated from *Streptomyces* species that are analogs of inosine and 2'-deoxyinosine, respectively, in which the purine ring is modified and contains a seven-membered ring. These compounds behave as very potent inhibitors of adenosine deaminase, the enzyme that degrades deoxyadenosine by its