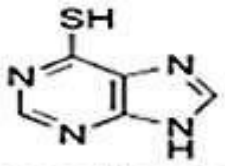
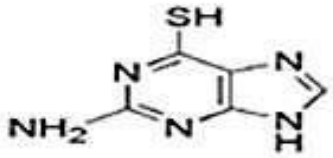
B. Purine Drugs

The design of antimetabolites based on purine structure began with isosteric thiol/sulfhydryl group to replace the 6-hydroxyl group of hypoxanthine and guanine.

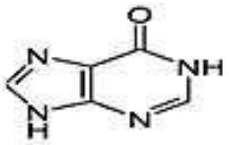
One of the early successes was 6-mercaptopurine (6-MP), the thiol analog of hypoxanthine.



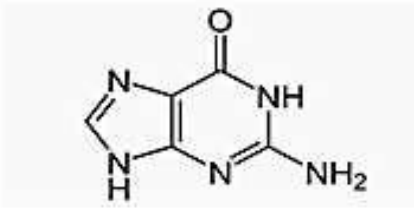
6-Mercaptopurine



Thioguanine



Hypoxanthine



guanine

- The mechanism of action of 6-mercaptopurine includes incorporation of 6-mercaptopurine into DNA and RNA via the triphosphate metabolite (inhibition of purine biosynthesis).
- This incorporation inhibits synthesis and function of the resulting modified DNA or RNA.
- The parent drug is inactive and requires phosphorylation for activity.

- Inhibition of the enzymes responsible for the catabolic breakdown of the purine drugs can potentiate the drug's antineoplastic activity.
- This purine requires bioactivation to its ribonucleotide, 6-thioinosinate (6-MPMP), by the enzyme HGPRT. (hypoxanthine-guanine phosphoribosyl transferase).
- The resulting nucleotide is a potent inhibitor of an early step in basic purine biosynthesis, the conversion of 5-phosphoribosylpyrophosphate into 5-phosphoribosyl amine.

- Allopurinol is a potent inhibitor of xanthine oxidase and is often used as an adjuvant in purine anticancer drug therapy.
- Allopurinol increases both the potency and the toxicity of 6-mercaptopurine.
- Its main importance is that it prevents the uric acid kidney toxicity caused by the release of purines from destroyed cancer cells.

- Heterocyclic derivatives of 6-mercaptopurine, such as azathioprine, were designed to protect it from catabolic reactions.

- Adenine arabinoside (Vidarabine) contains the sugar, D-arabinose, which is epimeric with D-ribose at the 2-position.

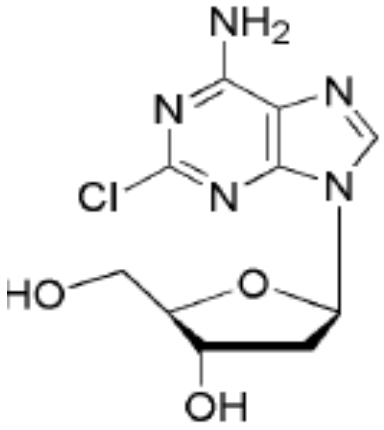
- This structural change makes it a competitive inhibitor of DNA polymerase, and this activity accounts for its antineoplastic activity as well as its antiviral action.

- Adenine arabinoside and some of its derivatives are limited in their antitumor effect by susceptibility to adenosine deaminase.

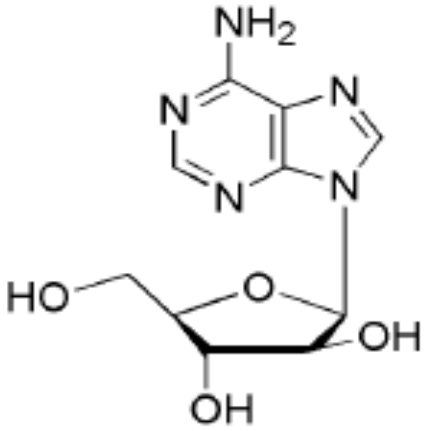
- The addition of fluorine to the sugar moiety(clofarabine) has produced some purine-based drugs with resistance to the catabolic activity of adenosine deaminase.

- 2-fluoro derivative, fludarabine, is also stable to this enzyme.

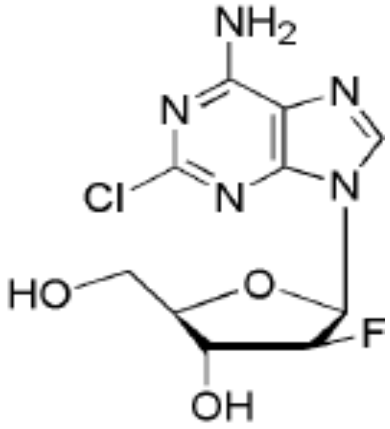
Anticancer drugs based on purines and related compounds.



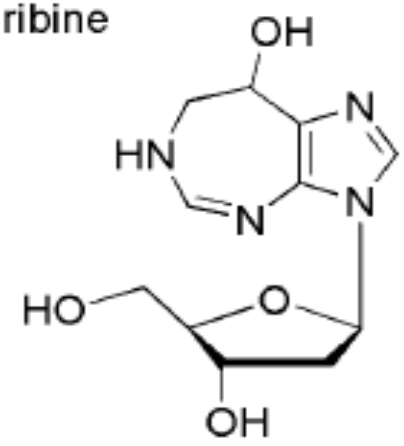
Cladribine



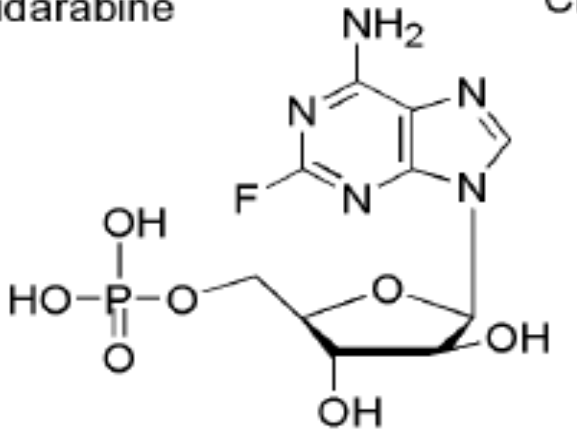
Vidarabine



Clofarabine

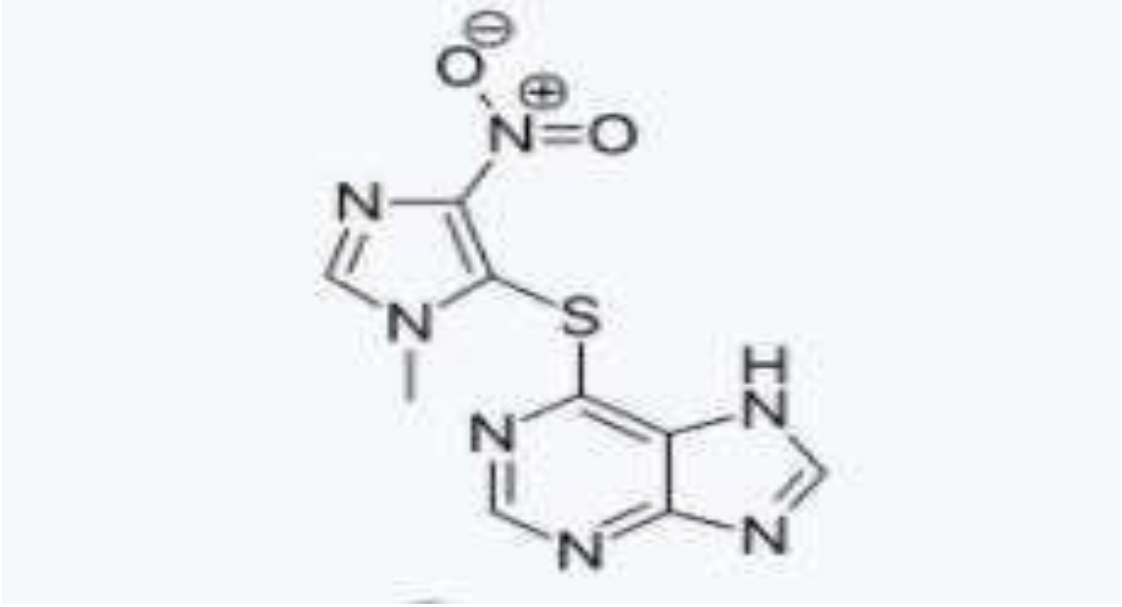


Pentostatin



Fludarabine

Azathioprine



Pathways of inactivation

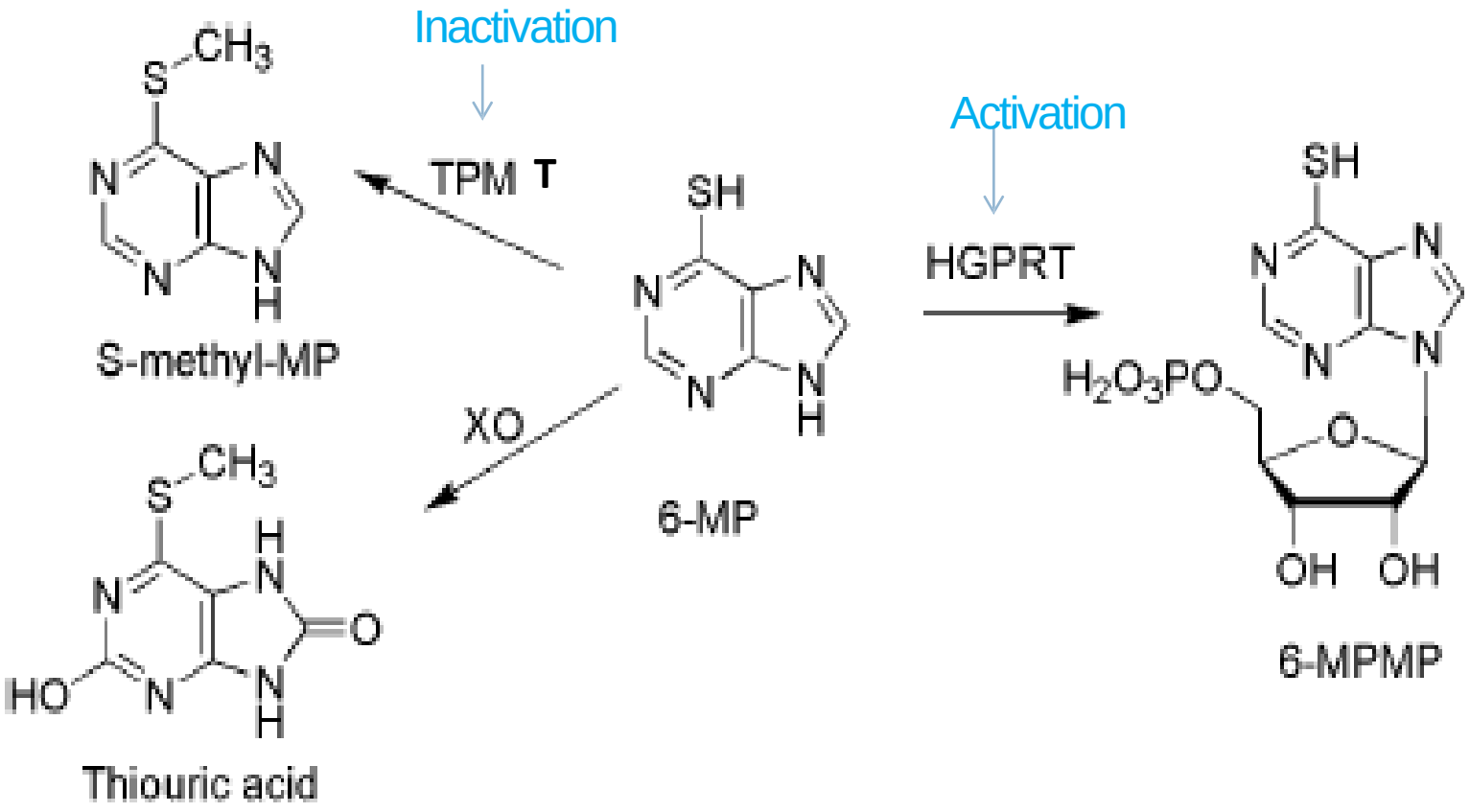
- purine antimetabolites 6-MP major pathways of inactivation include:

1. S-methylation via thiopurine-S methyl- transferase (TPMT).

2. oxidation by the enzyme xanthine oxidase (XO).

- Xanthine oxidase converts the drugs to the inactive thiouric acid.

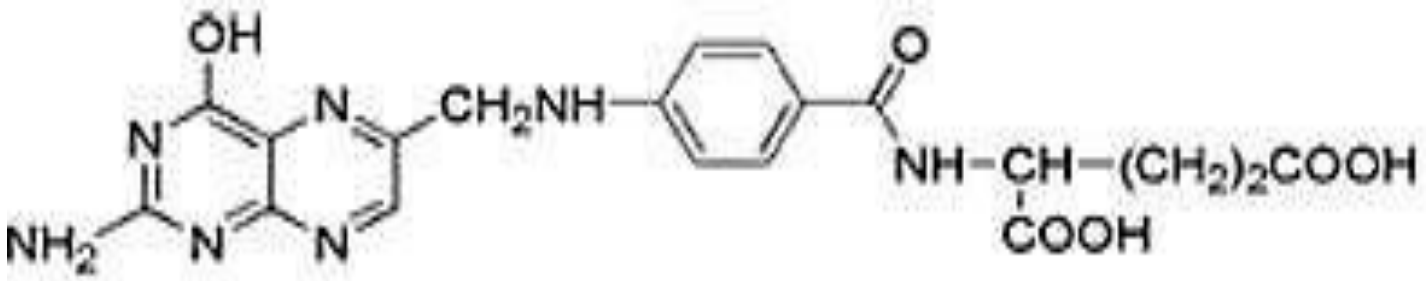
Conversion of 6-MP to active 6-thioinosine-5-monophosphate (6-MPMP) by HPGRT and inactivation by xanthine oxidase and thiopurine methyl transferase.



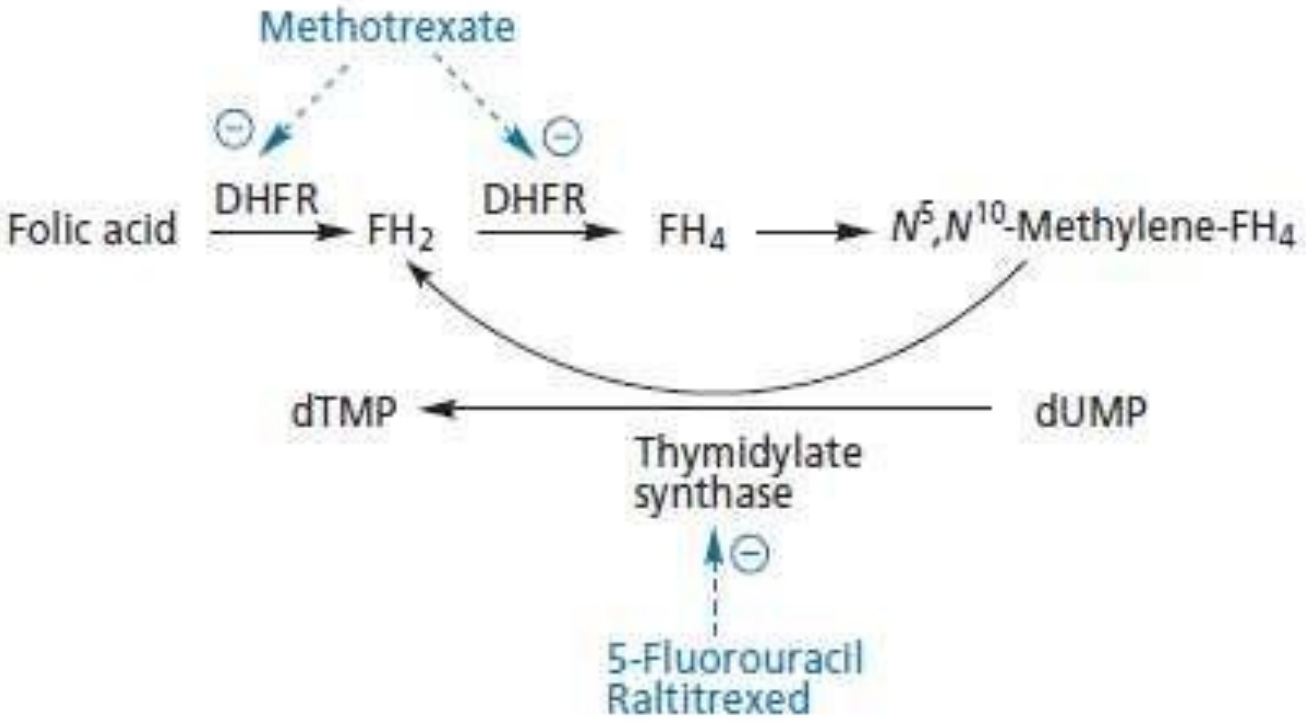
C.Folates

- Folic acid is substrate of the enzyme DHFR (dihydrofolate reductase).

- The reduced folates are necessary for biosynthesis of several purines and pyrimidines.



Folic Acid



Reactions catalysed by dihydrofolate reductase and thymidylate synthase.

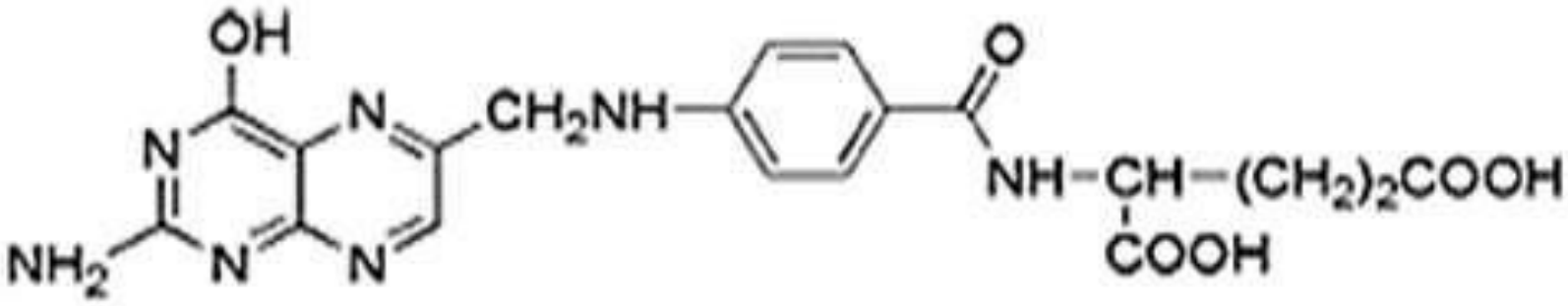
Methotrexate

- Methotrexate is the classic antimetabolite of folic acid structurally derived by N-methylation of the para-amino benzoic acid residue (PABA) and replacement of a pteridine hydroxyl by the bioisosteric amino group.

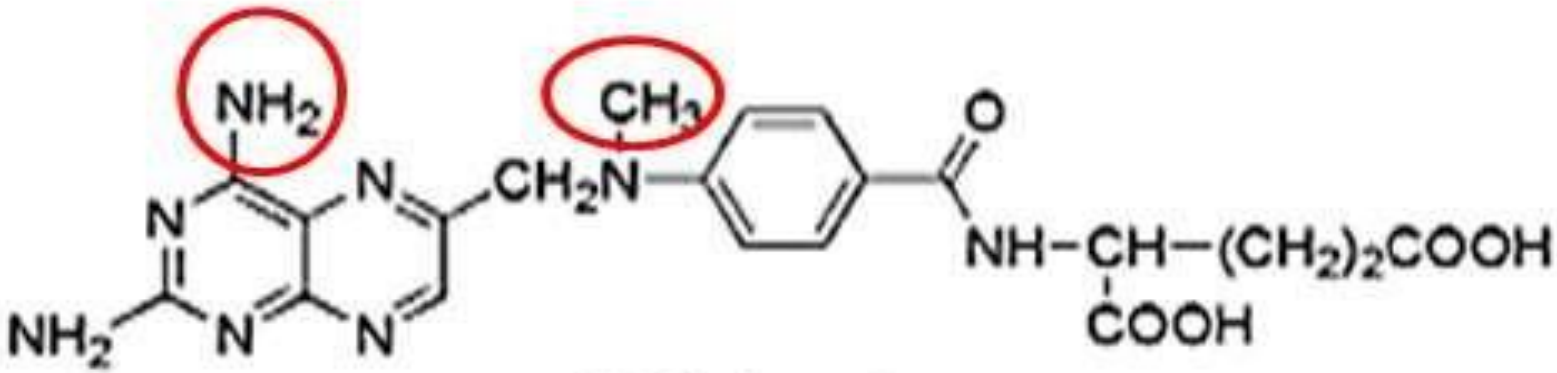
- The conversion of -OH to -NH2 increases the basicity of N-3 and yields greater enzyme affinity.

Methotrexate cont.….

This drug competitively inhibits the binding of the substrate folic acid to the enzyme DHFR, resulting in reductions in the synthesis of nucleic acid bases, perhaps most importantly, the conversion of uridylate to thymidylate as catalyzed by thymidylate synthetase.



Folic Acid



Methotrexate

Methotrexate cont.….

- In addition, purine synthesis is inhibited because the N-10-formyl tetrahydrofolic acid is a formyl donor involved in purine synthesis.
- Methotrexate is a broad-spectrum antineoplastic agent commonly used in the treatment of acute lymphoblastic and myeloblastic leukemia and other lymphomas and sarcomas.
- The major side effects seen are bone marrow suppression, pulmonary fibrosis, and GI ulceration.