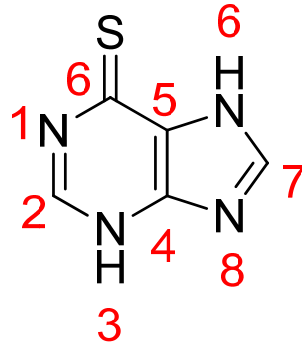
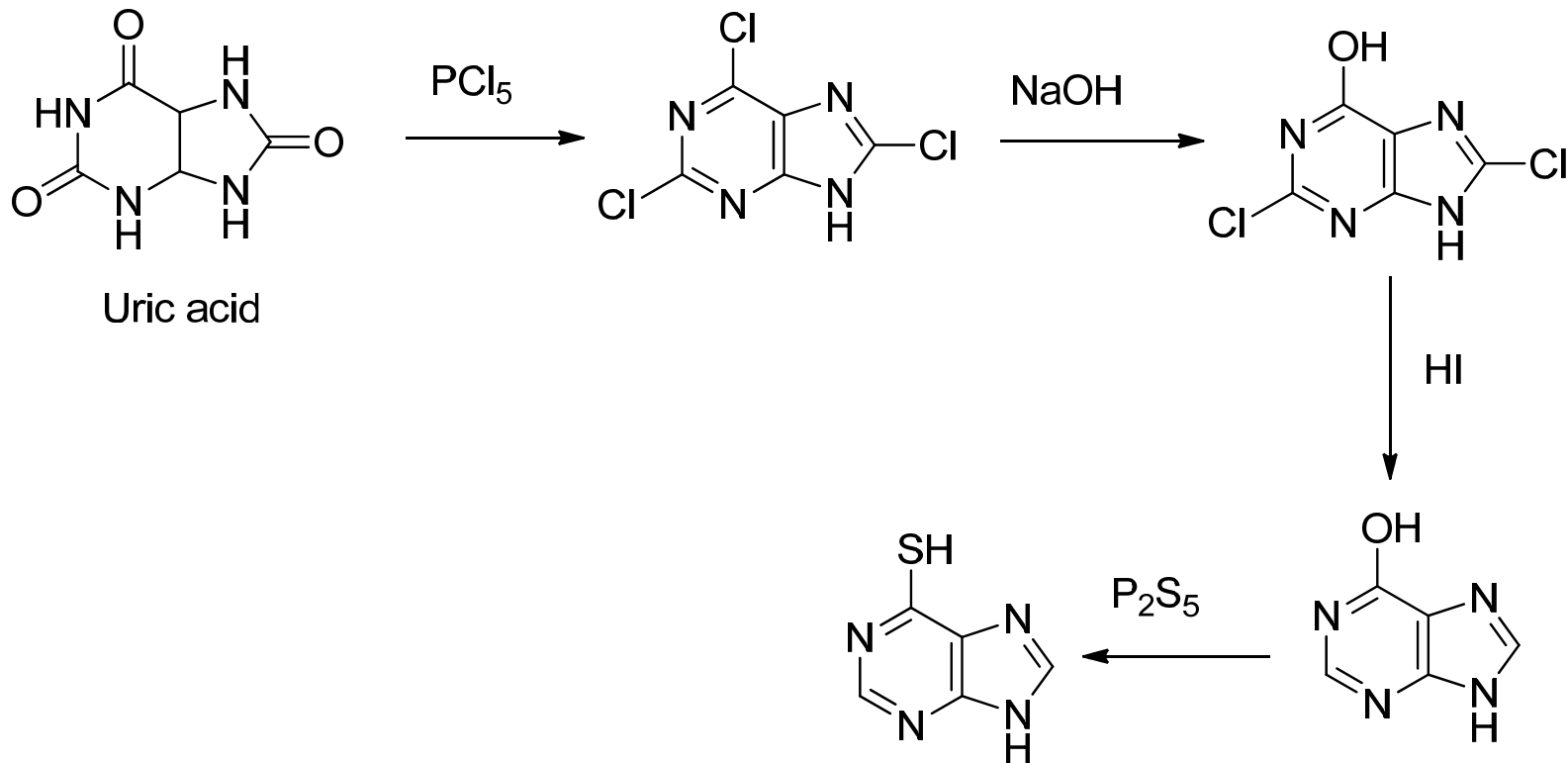


# Antimetabolites

## Mercaptopurine



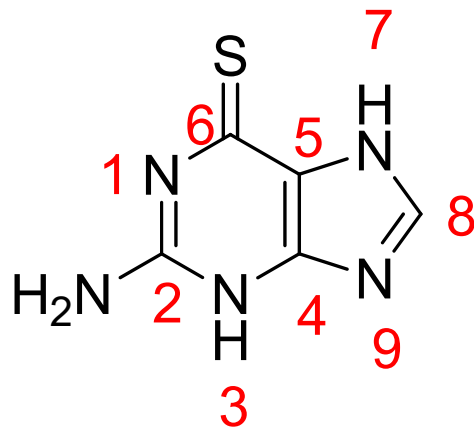
IUPAC: 6-Thioxopurine



MOA: Mercaptopurine is metabolised by hypoxanthine-guanine phosphoribosyltransferase (HGPRT) to 6-thioguanosine-5'-phosphate (6-thioGMP) and 6-thioinosine monophosphate (T-IMP). They inhibit nucleotide interconversions and de novo purine synthesis, thereby blocking the formation of purine nucleotides and inhibiting DNA synthesis. This agent is also incorporated into DNA in the form of deoxythioguanosine, which results in the disruption of DNA replication.

Uses: Used for maintenance therapy of acute lymphatic leukemia.

## Thioguanine

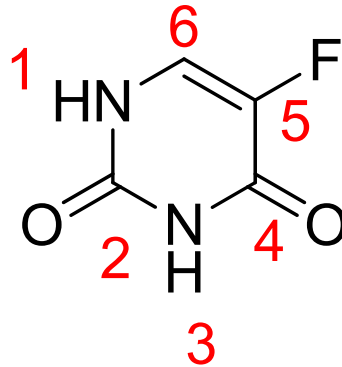


IUPAC: 2-Amino-1,7-dihydro-6H-purine-6-thione

**MOA:** Thioguanine is phosphorylated by hypoxanthine-guanine phosphoribosyltransferase to 6-thioguanilic acid (TGMP) and upon conversion to thioguanosine diphosphate (TGDP) and thioguanosine triphosphate (TGTP), this agent is incorporated into DNA and RNA, resulting in inhibition of DNA and RNA synthesis and cell death. This agent also inhibits glutamine-5-phosphoribosylpyrophosphate amidotransferase, thereby inhibiting purine ribonucleotide synthesis.

**Uses:** Used for the treatment of acute nonlymphocytic leukemias.

## Fluorouracil

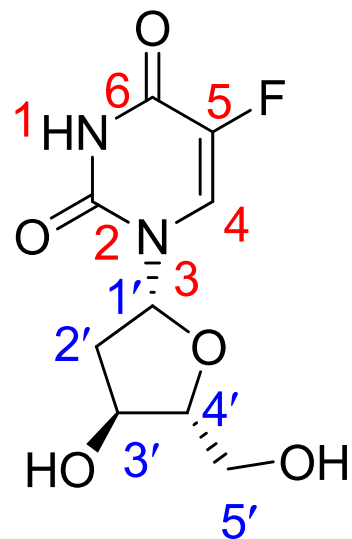


IUPAC: 5-Fluoropyrimidine-2,4-dione

MOA: 5-fluorouracil is a nucleobase analogue that is uracil in which the hydrogen at position 5 is replaced by fluorine. It is an antineoplastic agent which acts as an antimetabolite. fluorouracil is converted to the active metabolite 5-fluorouridylic acid. The active metabolite inhibits DNA synthesis (by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase) and so slows tumour growth.

Uses: Fluorouracil injection is indicated in the palliative management of some types of cancer, including colon, esophageal, gastric, rectum, breast, biliary tract, stomach, head and neck, cervical, pancreas, renal cell, and carcinoid.

## Floxuridine

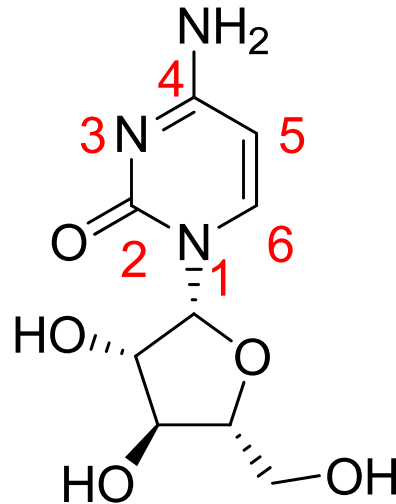


IUPAC: 1beta-D-2'-Deoxyribofuranosyl-5-fluorouracil

**MOA:** Floxuridine rapidly undergoes catabolism to form 5-fluorouracil, which is the active component of the drug. 5-Fluorouracil primarily works by interfering with DNA synthesis. It is also an inhibitor of riboside phosphorylase, preventing the utilization of pre-formed uracil in RNA synthesis. Floxuridine can also form 5-fluoro-2'-deoxyuridine-5'-phosphate (FUDR-MP), which is the monophosphate of floxuridine that inhibits thymidylate synthetase that plays a role in the methylation of deoxyuridylic acid to thymidylic acid during DNA synthesis. FUDR-MP thus interferes with DNA synthesis.

**Uses:** For palliative management of gastrointestinal adenocarcinoma metastatic to the liver. Also for the palliative management of liver cancer.

## Cytarabine

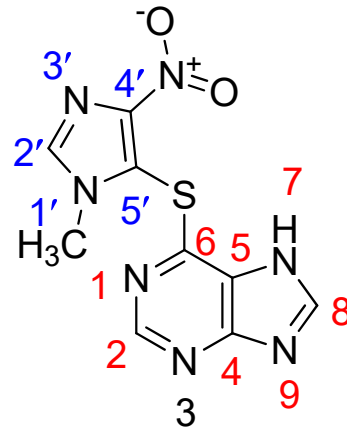


IUPAC: 4-Amino-1-beta-D-arabinofuranosyl-2(1H)-pyrimidinone

MOA: Cytarabine acts through direct DNA damage and incorporation into DNA. Cytarabine is cytotoxic to a wide variety of proliferating mammalian cells in culture. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G1 phase to the S-phase. Although the mechanism of action is not completely understood, it appears that cytarabine acts through the inhibition of DNA polymerase.

Uses: For the treatment of acute non-lymphocytic leukemia, acute lymphocytic leukemia and blast phase of chronic myelocytic leukemia.

# Azathioprine

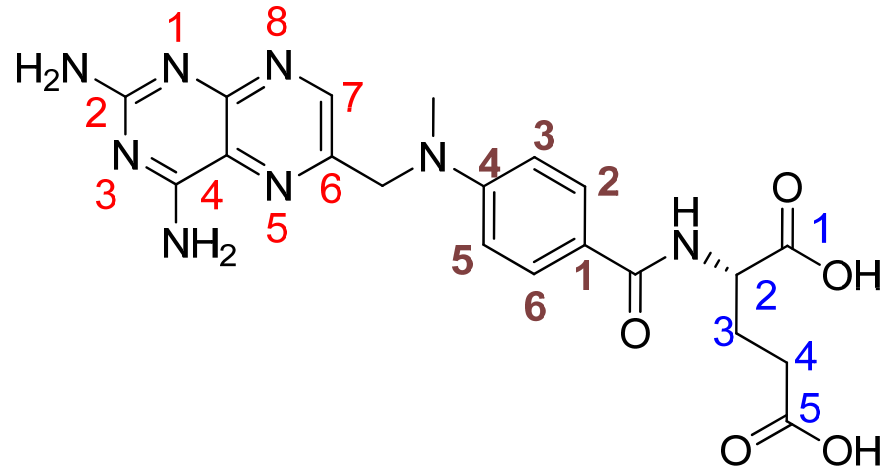


6-((1'-Methyl-4'-nitro-1H-imidazol-5'-yl)thio)-1H-purine

**MOA:** Azathioprine is converted within tissues to 6-mercaptopurine (6-MP). Some 6-MP is converted in turn to 6-thioguanine by the addition of an amino group. Both 6-MP and 6-thioguanine are conjugated with ribose, and then phosphorylated to form the nucleotides thioinosinic acid and thioguanilic acid respectively. The nucleotides are incorporated into newly synthesized (but non-functional) DNA, halting replication. The nucleotides act to inhibit glutamine-phosphoribosyl pyrophosphate amidotransferase (GPAT), one of the enzymes involved in purine biosynthesis, one of the earlier steps in the synthesis of DNA and RNA.

**Uses:** Azathioprine is indicated to treat rheumatoid arthritis and prevent renal transplant rejection.

## Methotrexate

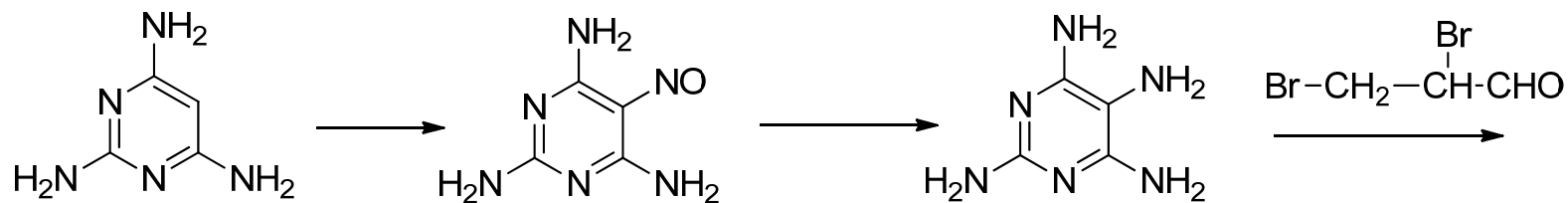


**MOA:** Methotrexate's mechanism of action is due to its inhibition of enzymes responsible for nucleotide synthesis including dihydrofolate reductase, thymidylate synthase, aminoimidazole carboxamide ribonucleotide transformylase (AICART), and amido phosphoribosyltransferase. Inhibition of nucleotide synthesis prevents cell division.

**Uses:** Methotrexate is indicated for pediatric acute lymphoblastic leukemia and pediatric polyarticular juvenile idiopathic arthritis. It is indicated to treat gestational choriocarcinoma, chorioadenoma destruens, hydatiform mole, breast cancer, epidermoid cancer of the head and neck, advanced mycosis fungoides, lung cancer, and advanced non-Hodgkin's lymphoma.



# Synthesis



pyrimidine-2,4,6-triamine

