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MEDICINAL CHEMISTRY - II

UNIT 1

TOPIC :

- **Antimetabolites :** Mercaptopurine, Thioguanine, Fluorouracil, Floxuridine, Cytarabine, Methotrexate, Azathioprine

Antimetabolites

- Antimetabolites are a class of **anticancer agents** that are **structurally similar to natural metabolites** required for DNA and RNA synthesis, such as **purines, pyrimidines, and folic acid**.
- These drugs **interfere with normal cellular metabolism** and are particularly effective against **rapidly dividing cancer cells**.

Mechanism of Action

Antimetabolites work primarily by:

1. **Inhibiting synthesis of nucleotides** – Blocking the formation of purines or pyrimidines prevents DNA and RNA synthesis.
2. **Competing with natural metabolites** – They are incorporated into DNA or RNA in place of normal nucleotides, causing **faulty DNA/RNA and impaired cell function**.
3. **Cell cycle specificity** – Most antimetabolites **kill cells in the S-phase**, when DNA synthesis occurs.

Examples

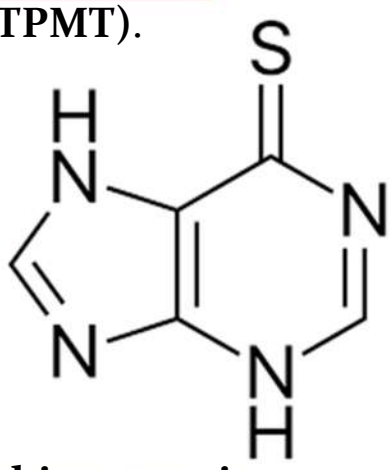
- Mercaptopurine*,
- Thioguanine,
- Fluorouracil,
- Floxuridine,
- Cytarabine,
- Methotrexate*,
- Azathioprine

Mercaptopurine (6-Mercaptopurine, 6-MP)

- Mercaptopurine (6-MP) is a **purine analog** and an **antimetabolite** used in **cancer chemotherapy**.
- It **inhibits nucleic acid synthesis** by interfering with **purine metabolism**, preventing DNA and RNA synthesis in rapidly dividing cells.
- Primarily used in **acute lymphoblastic leukemia (ALL)** and sometimes in **autoimmune diseases** like Crohn's disease.
- Administered **orally**; rapidly absorbed with hepatic metabolism primarily via **thiopurine methyltransferase (TPMT)**.

Chemical Structure

- **IUPAC Name:** 1,7-dihydro-6H-purine-6-thione
- **Molecular Formula:** $C_5H_4N_4S$
- **Molecular Weight:** 152.19 g/mol
- **Chemical Structure**



Mechanism of Action

- **Activation:**
  - Mercaptopurine is converted by **hypoxanthine-guanine phosphoribosyltransferase (HGPRT)** into **6-thioinosine monophosphate (TIMP)**, an active nucleotide analog.
- **Inhibition of Nucleotide Synthesis:**
  - TIMP inhibits:
    - **Amidophosphoribosyltransferase** → blocks de novo purine synthesis
    - **Conversion of IMP to AMP and GMP** → reduces purine nucleotide pool
  - Incorporated into DNA and RNA as **fraudulent bases**, causing **DNA damage and faulty RNA**.
- **Cell Cycle Effect:**
  - S-phase specific; affects **rapidly dividing cells**.
- **Cytotoxicity:**

- Leads to **apoptosis or growth arrest** in leukemia and other proliferating cells.

Synthesis of Mercaptopurine

1. **Starting Material:**
   - Purine derivatives such as **hypoxanthine**.
2. **Thiolation Reaction:**
   - Replace **C6 oxygen** with **sulfur** using **hydrogen sulfide or thiourea** in the presence of acid/base.
3. **Purification:**
   - The crude product is purified to yield **mercaptopurine** suitable for oral administration.

Uses

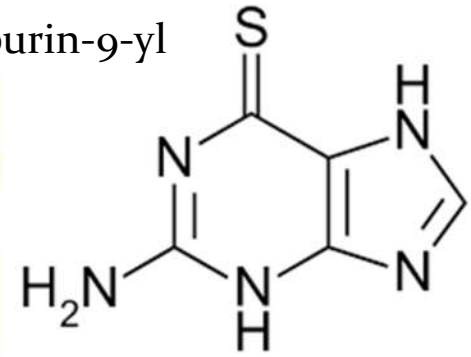
1. **Acute lymphoblastic leukemia (ALL):**
   - Mainstay therapy for **maintenance chemotherapy**.
2. **Autoimmune disorders:**
   - Off-label use in **Crohn's disease, ulcerative colitis, and rheumatoid arthritis**.
3. **Other uses:**
   - Occasionally combined with **other chemotherapeutic agents** for lymphoid malignancies.
4. **Side Effects:**
   - Myelosuppression, hepatotoxicity, nausea, vomiting, risk of infections, and potential for long-term malignancy.

Thioguanine (6-Thioguanine, 6-TG)

- Thioguanine is a **purine analog** and an **antimetabolite** used in **cancer chemotherapy**.
- It is structurally similar to **guanine**, with a **sulfur atom at the C6 position**, which is critical for its cytotoxic activity.
- Primarily used in **acute myeloid leukemia (AML)** and sometimes in other **hematologic malignancies**.
- Administered **orally** and metabolized in the liver primarily by **thiopurine methyltransferase (TPMT)**.

Chemical Structure

- **IUPAC Name:** 2-amino-6-thioxo-1H-purin-9-yl
- **Molecular Formula:** $C_5H_4N_4S$
- **Molecular Weight:** 167.18 g/mol
- **Chemical Structure**



Mechanism of Action

- **Activation:**
  - Thioguanine is converted by **hypoxanthine-guanine phosphoribosyltransferase (HGPRT)** into **6-thioguanosine monophosphate (6-TGMP)**.
- **Inhibition of Nucleotide Synthesis:**
  - 6-TGMP inhibits **de novo purine synthesis** by blocking **amidophosphoribosyltransferase**.
  - Incorporated into DNA and RNA as **fraudulent bases**, causing **DNA damage, strand breaks, and faulty RNA**.
- **Cell Cycle Effect:**
  - S-phase specific; affects **rapidly dividing cells**, particularly leukemic cells.
- **Cytotoxicity:**
  - Leads to **apoptosis or growth arrest** in malignant cells due to disrupted nucleic acid synthesis.

Synthesis of Thioguanine

1. **Starting Material:**
   - Guanine or related purine derivatives.
2. **Thiolation Reaction:**
   - Replace **C6 oxygen** of guanine with **sulfur** using **hydrogen sulfide (H_2S)** or **thiourea** under acidic/basic conditions.
3. **Purification:**
   - Purified to yield **thioguanine** suitable for oral administration.

Uses

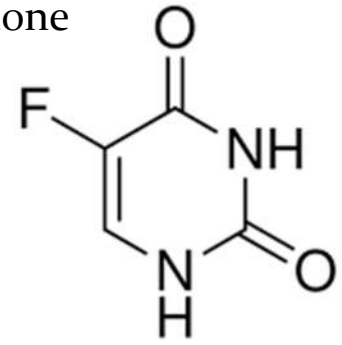
1. **Acute Myeloid Leukemia (AML):**
   - Commonly used in **induction and maintenance therapy**.
2. **Other Hematologic Malignancies:**
   - Occasionally used in **combination chemotherapy for lymphoid leukemias**.
3. **Side Effects:**
   - Myelosuppression, hepatotoxicity, nausea, vomiting, immunosuppression, and potential for long-term secondary malignancies.

Fluorouracil (5-FU)

- Fluorouracil (5-FU) is a **pyrimidine analog** and an **antimetabolite** used in **cancer chemotherapy**.
- It is a **fluorinated derivative of uracil** that inhibits **DNA synthesis** by acting as a **thymidylate synthase inhibitor**.
- Primarily used in **colorectal cancer, breast cancer, gastric cancer, pancreatic cancer**, and **skin cancers**.
- Administered **intravenously**, topically (cream), or in combination with other chemotherapeutic agents.

Chemical Structure

- **IUPAC Name:** 5-fluoro-1H-pyrimidine-2,4-dione
- **Molecular Formula:** $C_4H_3FN_2O_2$
- **Molecular Weight:** 130.08 g/mol
- **Chemical Structure**



Mechanism of Action

- **Metabolic Activation:**
  - 5-FU is converted intracellularly into active metabolites:
    - **Fluoro-2′-deoxyuridine-5′-monophosphate (FdUMP)**
    - **Fluorouridine triphosphate (FUTP)**
- **Inhibition of Thymidylate Synthase:**
  - FdUMP forms a stable **ternary complex with thymidylate synthase and 5,10-methylenetetrahydrofolate**, preventing **dTMP formation → DNA synthesis is blocked**
- **RNA Incorporation:**
  - FUTP is incorporated into RNA → **impaired RNA processing and function**
- **Cell Cycle Effect:**
  - **S-phase specific**; inhibits **DNA replication in rapidly dividing cells**
- **Cytotoxicity:**

- Leads to **apoptosis due to DNA damage** and faulty RNA function

Synthesis of Fluorouracil

1. **Starting Material:**
   - Uracil or its derivatives
2. **Fluorination:**
   - Introduce fluorine at **C5 position** using **fluorinating agents** like **silver(I) fluoride** or other selective fluorination reactions.
3. **Purification:**
   - The crude product is purified to yield **5-fluorouracil** suitable for clinical use.

Uses

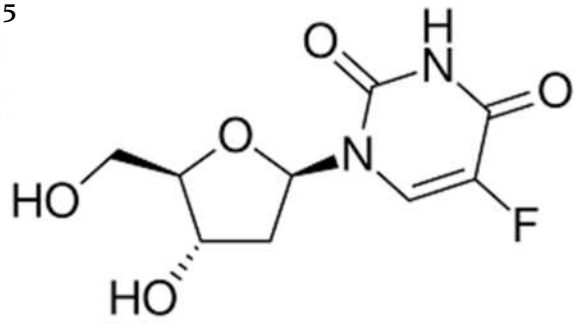
1. **Colorectal cancer:**
   - Most common use, often in combination with leucovorin.
2. **Breast cancer and gastric cancer:**
   - Used in combination chemotherapy regimens.
3. **Topical therapy:**
   - For **actinic keratosis, basal cell carcinoma**, and superficial skin cancers.
4. **Side Effects:**
   - Myelosuppression, mucositis, nausea, vomiting, diarrhea, hand-foot syndrome, and cardiotoxicity (rare).

Floxuridine (FUDR)

- Floxuridine is a **fluoropyrimidine antimetabolite**, structurally related to **5-fluorouracil (5-FU)**.
- It is a **deoxyribonucleoside analog** used in **cancer chemotherapy**, especially in **liver metastases from colorectal cancer**.
- Administered primarily via **intra-arterial infusion (hepatic artery)** due to **rapid hepatic extraction**.
- Floxuridine acts by **inhibiting DNA synthesis**, leading to cytotoxicity in rapidly dividing cancer cells.

Chemical Structure

- **IUPAC Name:** 1-[(2-deoxy-β-D-ribofuranosyl)-5-fluorouracil]
- **Molecular Formula:** $C_9H_{11}FN_2O_5$
- **Molecular Weight:** 246.19 g/mol
- **Chemical Structure**



Mechanism of Action

- **Metabolic Activation:**
  - Floxuridine is converted intracellularly into **fluoro-deoxyuridine monophosphate (FdUMP)**.
- **Inhibition of Thymidylate Synthase:**
  - FdUMP forms a stable **ternary complex with thymidylate synthase and 5,10-methylenetetrahydrofolate**, preventing **dTMP formation** → blocks DNA synthesis
- **DNA Incorporation:**
  - Fluoro-deoxyuridine triphosphate (FdUTP) is incorporated into DNA → causes **DNA strand breaks and faulty replication**
- **Cell Cycle Effect:**
  - **S-phase specific**, mainly affecting **rapidly dividing tumor cells**
- **Cytotoxicity:**
  - Leads to **apoptosis due to DNA damage and inhibition of cell proliferation**

Synthesis of Floxuridine

1. **Starting Material:**
   - 5-Fluorouracil and 2-deoxy-D-ribose
2. **Glycosylation Reaction:**
   - Condensation of **5-FU** with **2-deoxyribose** using **acid catalysis or silylated intermediates** to form **floxuridine**
3. **Purification:**
   - The crude product is purified to obtain **clinical-grade floxuridine** for intra-arterial infusion.

Uses

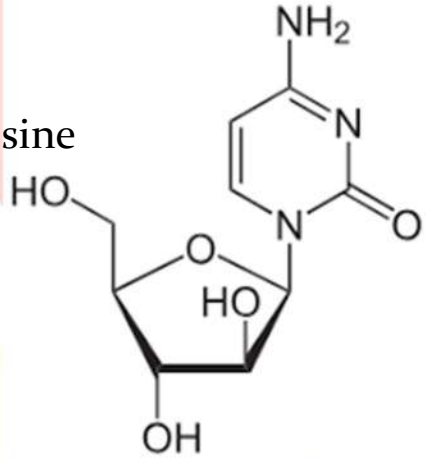
1. **Liver metastases from colorectal cancer:**
   - Most common application via **hepatic artery infusion**.
2. **Other solid tumors:**
   - Occasionally used in combination with **systemic chemotherapy**.
3. **Mechanism-based selectivity:**
   - Rapid hepatic extraction allows **high local concentration in the liver** with reduced systemic toxicity.
4. **Side Effects:**
   - Myelosuppression, mucositis, nausea, vomiting, hepatic toxicity, and gastrointestinal disturbances.

Cytarabine (Ara-C)

- Cytarabine (Ara-C) is a **pyrimidine nucleoside analog** and an **antimetabolite** used in **cancer chemotherapy**.
- It is structurally similar to **deoxycytidine**, but the **ribose sugar is replaced with arabinose**, which is crucial for its cytotoxic activity.
- Primarily used in **acute myeloid leukemia (AML)**, **acute lymphoblastic leukemia (ALL)**, and **non-Hodgkin's lymphoma**.
- Administered **intravenously**, subcutaneously, or intrathecally (for CNS leukemia).

Chemical Structure

- **IUPAC Name:** 1-β-D-Arabinofuranosylcytosine
- **Molecular Formula:** $C_9H_{13}N_3O_5$
- **Molecular Weight:** 243.22 g/mol
- **Chemical Structure**



Mechanism of Action

- **Activation:**
  - Cytarabine is phosphorylated intracellularly to **cytarabine triphosphate (Ara-CTP)** by nucleoside kinases.
- **DNA Incorporation:**
  - Ara-CTP competes with **deoxycytidine triphosphate (dCTP)** for incorporation into DNA.
  - Incorporation into DNA → **inhibition of DNA polymerase → chain termination**
- **Cell Cycle Effect:**
  - **S-phase specific**, inhibiting DNA synthesis in rapidly dividing cells.
- **Cytotoxicity:**
  - Leads to **apoptosis** due to DNA synthesis inhibition and faulty replication.

Synthesis of Cytarabine

1. **Starting Material:**
   - Cytosine and arabinose sugar derivatives
2. **Glycosylation Reaction:**
   - Condensation of cytosine with **protected arabinose sugar** under **acidic or catalytic conditions** to form the nucleoside.
3. **Deprotection & Purification:**
   - Remove protective groups and purify to obtain **clinical-grade cytarabine**.

Uses

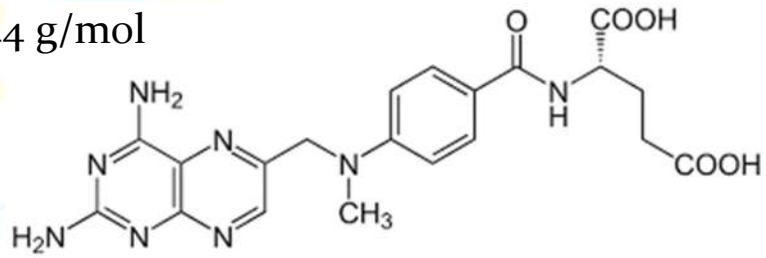
1. **Acute myeloid leukemia (AML):**
   - Mainstay therapy in induction and consolidation regimens.
2. **Acute lymphoblastic leukemia (ALL) and Non-Hodgkin's lymphoma:**
   - Used in combination chemotherapy protocols.
3. **CNS leukemia:**
   - Administered intrathecally to prevent or treat CNS involvement.
4. **Side Effects:**
   - Myelosuppression, nausea, vomiting, mucositis, neurotoxicity (with high-dose), and hepatotoxicity.

Methotrexate (MTX)

- Methotrexate (MTX) is a **folic acid analog** and an **antimetabolite** used in **cancer chemotherapy** and **immunosuppressive therapy**.
- It **inhibits dihydrofolate reductase (DHFR)**, preventing the formation of tetrahydrofolate, which is essential for **purine and thymidylate synthesis**.
- Used in **acute lymphoblastic leukemia (ALL), breast cancer, head and neck cancer, osteosarcoma**, and autoimmune diseases like **rheumatoid arthritis and psoriasis**.
- Administered **orally, intravenously, intrathecally, or subcutaneously**, depending on the condition.

Chemical Structure

- **IUPAC Name:** (2S)-2-[(4-{[(2,4-diaminopteridin-6-yl)methyl]methylamino}benzoyl)amino]pentanedioic acid
- **Molecular Formula:** $C_{20}H_{22}N_8O_5$
- **Molecular Weight:** 454.44 g/mol
- **Chemical Structure**



Mechanism of Action

- **DHFR Inhibition:**
  - Methotrexate competitively inhibits **dihydrofolate reductase**, preventing conversion of **dihydrofolate to tetrahydrofolate**.
- **Effect on Nucleotide Synthesis:**
  - Reduced tetrahydrofolate → decreased synthesis of **thymidylate, purines, and methionine** → impaired DNA, RNA, and protein synthesis.
- **Cell Cycle Effect:**
  - S-phase specific; affects **rapidly dividing cells** like cancer cells, bone marrow cells, and gastrointestinal epithelium.
- **Cytotoxicity:**
  - Leads to **apoptosis** due to inhibition of DNA replication and RNA transcription.

Synthesis of Methotrexate

1. **Starting Material:**
   - 2,4-diaminopteridine derivatives
2. **Formation of Side Chain:**
   - Attach **p-aminobenzoylglutamate** via **amide linkage** to the pteridine ring.
3. **Purification:**
   - Crystallization and purification yield **methotrexate** suitable for clinical use.

Uses

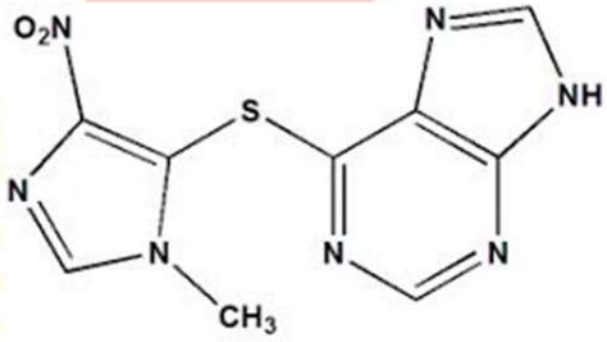
1. **Cancer chemotherapy:**
   - Acute lymphoblastic leukemia (ALL), breast cancer, head and neck cancer, osteosarcoma.
2. **Immunosuppressive therapy:**
   - Rheumatoid arthritis, psoriasis, and other autoimmune diseases.
3. **Other uses:**
   - Low-dose MTX for ectopic pregnancy and medical abortion in combination therapy.
4. **Side Effects:**
   - Myelosuppression, mucositis, hepatotoxicity, nephrotoxicity, pulmonary toxicity, and gastrointestinal disturbances.

Azathioprine

- Azathioprine is an **immunosuppressive antimetabolite** and a **prodrug** of **6-mercaptopurine (6-MP)**.
- It is primarily used to **prevent organ transplant rejection**, manage **autoimmune disorders** like **rheumatoid arthritis, Crohn's disease, and ulcerative colitis**.
- Administered **orally** and metabolized in the liver to **6-MP**, which then exerts cytotoxic effects on **rapidly proliferating immune cells**.

Chemical Structure

- **IUPAC Name:** 6-[(1-methyl-4-nitro-5-imidazolyl)thio]-7H-purine
- **Molecular Formula:** $C_9H_7N_7O_2S$
- **Molecular Weight:** 277.25 g/mol
- **Chemical Structure**



Azathioprine

Mechanism of Action

- **Prodrug Activation:**
  - Azathioprine is converted in vivo to **6-mercaptopurine (6-MP)** by **glutathione-dependent enzymes**.
- **Purine Synthesis Inhibition:**
  - 6-MP is metabolized to **6-thioinosine monophosphate (TIMP)** → inhibits:
    - **De novo purine synthesis** → blocks DNA and RNA synthesis
    - **Incorporation into DNA/RNA as fraudulent bases** → causes DNA damage
- **Immunosuppressive Effect:**
  - Preferentially affects **rapidly dividing T and B lymphocytes** → suppresses immune response.
- **Cell Cycle Effect:**

- S-phase specific; inhibits **lymphocyte proliferation**.

Synthesis of Azathioprine

1. **Starting Material:**
   - 6-Mercaptopurine (6-MP)
2. **Reaction with Imidazole Derivative:**
   - 6-MP is reacted with **1-methyl-4-nitroimidazole** under **alkylation conditions** to form azathioprine.
3. **Purification:**
   - Crystallization yields **clinical-grade azathioprine** suitable for oral use.

Uses

1. **Organ Transplantation:**
   - Prevention of **rejection in kidney, liver, and heart transplants**.
2. **Autoimmune Diseases:**
   - Rheumatoid arthritis, Crohn's disease, ulcerative colitis, systemic lupus erythematosus (SLE).
3. **Other Uses:**
   - Occasionally in combination therapy for **vasculitis or other immune-mediated disorders**.
4. **Side Effects:**
   - Myelosuppression, hepatotoxicity, gastrointestinal disturbances, increased risk of infections, and potential for long-term malignancy.