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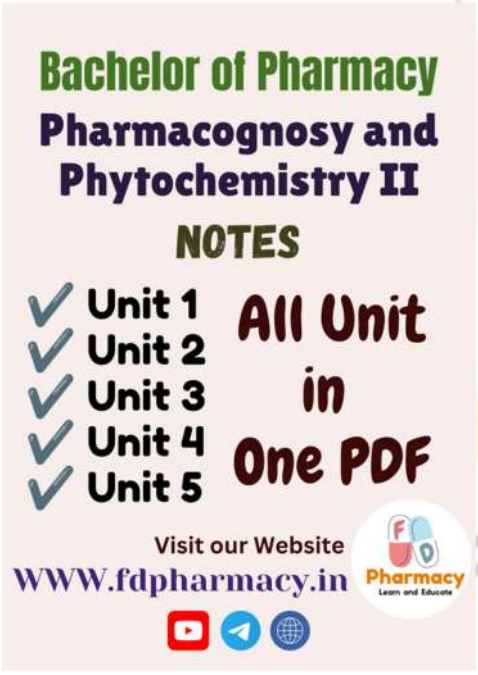
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MEDICINAL CHEMISTRY - II

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

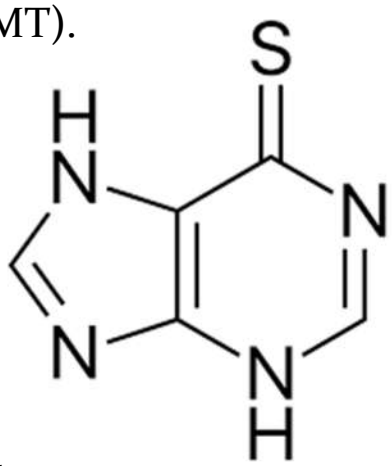
- Mercaptopurine*,
- Thioguanine,
- Fluorouracil,
- Floxuridine,
- Cytarabine,
- Methotrexate*,
- Azathioprine

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

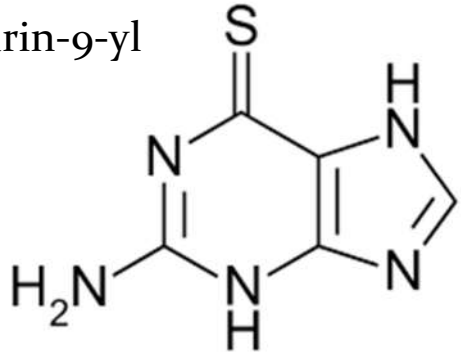
1. Acute lymphoblastic leukemia (ALL):
    - Mainstay therapy for maintenance chemotherapy.
2. Autoimmune disorders:
    - Off-label use in Crohn's disease, ulcerative colitis, and rheumatoid arthritis.
3. Other uses:
    - Occasionally combined with other chemotherapeutic agents for lymphoid malignancies.
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

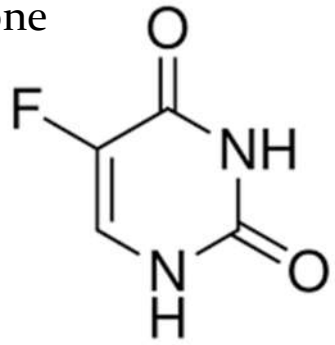
1. Acute Myeloid Leukemia (AML):
    - Commonly used in induction and maintenance therapy.
2. Other Hematologic Malignancies:
    - Occasionally used in combination chemotherapy for lymphoid leukemias.
3. Side Effects:
    - Myelosuppression, hepatotoxicity, nausea, vomiting, immunosuppression, and potential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

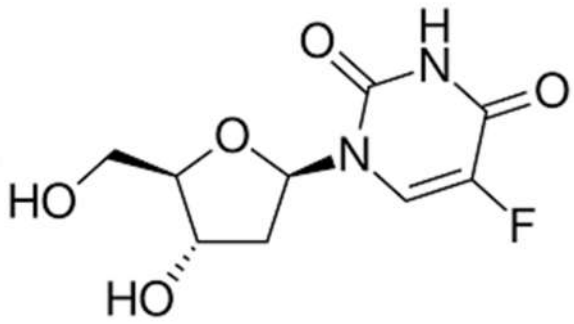
1. Colorectal cancer:
    - Most common use, often in combination with leucovorin.
2. Breast cancer and gastric cancer:
    - Used in combination chemotherapy regimens.
3. Topical therapy:
    - For actinic keratosis, basal cell carcinoma, and superficial skin cancers.
4. Side Effects:
    - Myelosuppression, 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

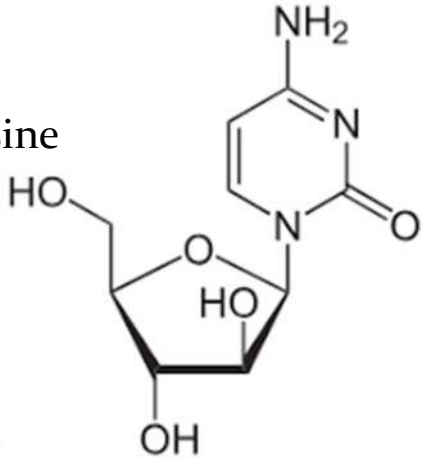
1. Liver metastases from colorectal cancer:
    - Most common application via hepatic artery infusion.
2. Other solid tumors:
    - Occasionally used in combination with systemic chemotherapy.
3. Mechanism-based selectivity:
    - Rapid hepatic extraction allows high local concentration in the liver 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

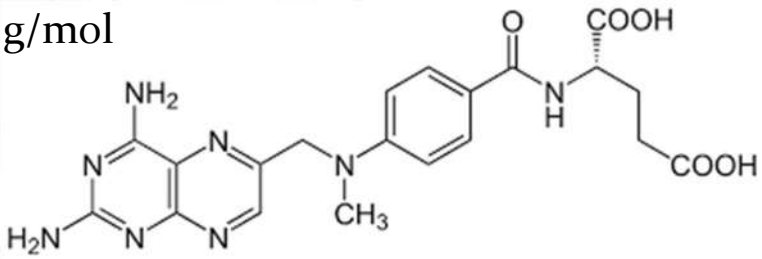
1. Acute myeloid leukemia (AML):
    - Mainstay therapy in induction and consolidation regimens.
2. Acute lymphoblastic leukemia (ALL) and Non-Hodgkin's lymphoma:
    - Used in combination chemotherapy protocols.
3. CNS leukemia:
    - Administered intrathecally to prevent or treat CNS involvement.
4. 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

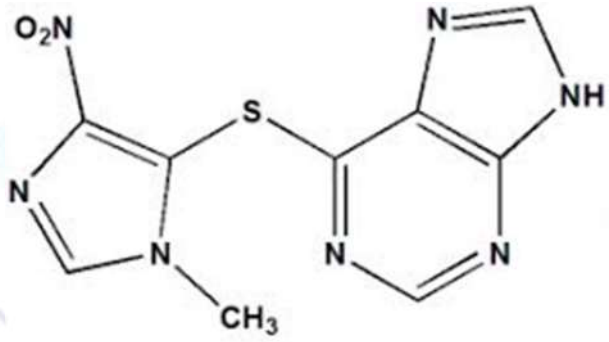
1. Cancer chemotherapy:
    - Acute lymphoblastic leukemia (ALL), breast cancer, head and neck cancer, osteosarcoma.
2. Immunosuppressive therapy:
    - Rheumatoid arthritis, psoriasis, and other autoimmune diseases.
3. Other uses:
    - Low-dose MTX for ectopic pregnancy and medical abortion in combination 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.