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Diploma in Pharmacy 1st Year
Pharmaceutical Chemistry
Chapter 13 : Anti-Neoplastic Agents

Chapter 13

Anti-Neoplastic Agents

→ Cancer is a disease characterised by abnormal and uncontrolled cell division attacking the surrounding tissues and organs, and also the distant body parts by circulating with blood and lymph.

→ Cancer is classified into the following categories

- **Carcinoma :** This type of cancer starts in the skin or tissues lining the internal organs. There are many sub types of carcinoma, like adenocarcinoma, basal cell carcinoma, squamous cell carcinoma, and transitional cell carcinoma.
- **Sarcoma :** This type of cancer starts in the bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissues.
- **Leukaemia :** This type of cancer starts in the blood forming tissues (i.e., the bone marrow) and produces numerous abnormal blood cells.
- **Lymphoma and Myeloma :** This type of cancer starts in the cells of immune system.
- **Central Nervous System Cancers :** This type of cancer starts in the brain and spinal cord tissues.

→ Antineoplastic or anticancer drugs are used for treating malignancies or cancerous growths. Either these drugs are used alone (chemotherapy) or in combination with surgery or radiation therapy.)

Examples

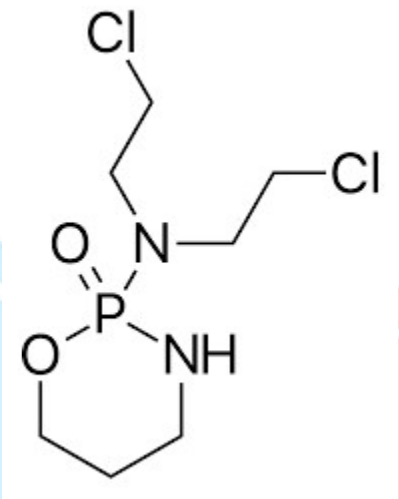
The following alkylating agents are discussed

- Cyclophosphamide,
- Busulfan,
- Mercaptopurine,
- Fluorouracil,
- Methotrexate,
- Dactinomycin,
- Doxorubicin hydrochloride,
- Vinblastine sulphate,
- Cisplatin, and
- Dromostanolone propionate.

Cyclophosphamide

→ Cyclophosphamide is a precursor of alkylating nitrogen mustard antineoplastic and immunosuppressive agent. It activates in the aldophosphamide.) liver to form the active

Chemical Structure



Mechanism of Action

➢ Aldophosphamide is cleaved to the active alkylating agent phosphoramide mustard and acrolein. The phosphoramide metabolite forms cross-linkages within and between adjacent DNA strands at the guanine N-7 position. These modifications are permanent and eventually lead to programmed cell death.

Uses

- It is used in the treatment of malignant lymphomas, multiple myeloma, leukaemia, mycosis fungoides, neuroblastoma, adenocarcinoma of the ovary, retinoblastoma, and carcinoma of breast.
- It is also used in biopsy-proven minimal change nephrotic syndrome in paediatrics.

Stability and Storage Conditions

▪ These preparations should be refrigerated in glass containers for up to 14 days before using.

Types of Formulations

1. Injection
2. Powder for solution

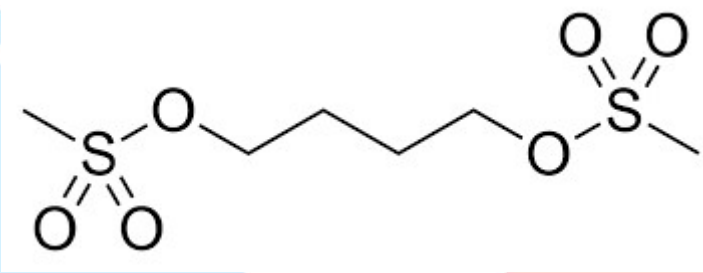
Popular Brand Name

♦ Procytox

Busulfan

→ Busulfan is a bifunctional alkylating agent. It exerts a selective immunosuppressive effect on bone marrow. It is not a structural analogue of nitrogen mustards. It is used in the treatment of chronic myeloid leukaemia; however, it provides only symptomatic relief and no permanent cure.

Chemical Structure



Mechanism of Action

➢ Busulfan is a bifunctional alkylating agent and cell cycle- non-specific. It interacts with the thiol groups of proteins and nucleic acids and forms DNA-protein and DNA-DNA cross-links. These cross-linkages prevent the synthesis and function of DNA.

Uses

- It is used with cyclophosphamide as a conditioning regimen before allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous (myeloid, myelocytic, and granulocytic) leukaemia.
- It is also a component of pre-transplant conditioning regimen in bone marrow transplantation for acute myeloid leukaemia and non-malignant diseases.

Stability and Storage Conditions

- Refrigerate intact vials between 2°C and 8°C (36°F and 46°F).

Types of Formulations

1. Tablet
2. Solution

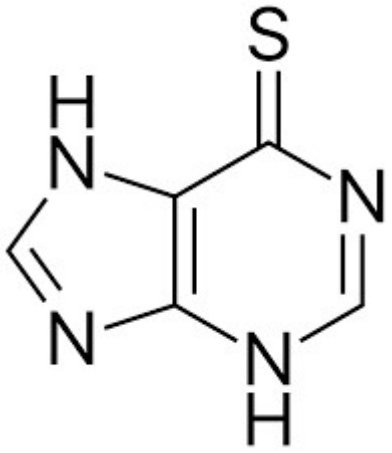
Popular Brand Names

- Busulfex
- Myleran

Mercaptopurine

→ Mercaptopurine is an antimetabolite antineoplastic drug having immunosuppressant properties. It prevents purine metabolism, thus inhibits nucleic acid synthesis. It is used with other drugs for the treatment of or in remission maintenance programs for leukaemia.

Chemical Structure



Mechanism of Action

➢ The anticancer drug 6-mercaptopurine (6-MP) inhibits de novo purine synthesis and acts as an antiproliferative agent by interfering with protein, DNA and RNA synthesis and promoting apoptosis.

Uses

- It is used for remission induction and maintenance therapy of acute lymphatic leukaemia.

Stability and Storage Conditions

▪ It should be kept at room temperature, free from heat and moisture (not in the bathroom). After the opening of the bottle, the mercaptopurine suspension can be kept at room temperature for up to 6 weeks)

Types of Formulations

1. Tablet
2. Suspension

Popular Brand Name

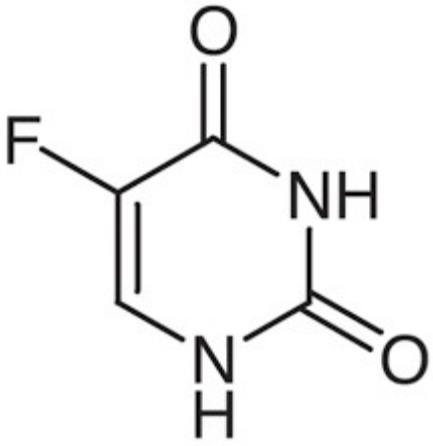
♦ Purixan

Fluorouracil

→ Fluorouracil is a pyrimidine analogue which is an antineoplastic antimetabolite. It inhibits DNA synthesis by preventing the conversion of thymidylate synthetase of deoxyuridylic acid into thymidylic acid.

Chemical Name and Structure

5-Fluoro-1H, 3H-pyrimidine-2,4-dione



Mechanism of Action

➢ Fluorouracil blocks an enzyme which converts the cytosine nucleotide into the deoxy derivative. In addition, DNA synthesis is further inhibited because Fluorouracil blocks the incorporation of the thymidine nucleotide into the DNA strand.

Uses

- It is used in acute lymphocytic leukaemia, Crohn's disease, and ulcerative colitis
- It is used for treating the slowly growing solid tumours (e.g., colorectal, breast, ovarian, pancreatic, and gastric carcinomas).
- It is used with levamisole (a veterinary anthelmintic agent) in patients having colon cancer.
- On topical application, it is effective in superficial basal cell carcinomas.

Stability and Storage Conditions

▪ 5-fluorouracil's stability has been evaluated in a variety of liquids and containers at temperatures ranging from 4°C to 35°C. When 5-fluorouracil was synthesised in NS and stored in polyolefin bags at 5°C 3°C for 28 days, it remained stable.

Types of Formulations

1. Injections
2. Solutions

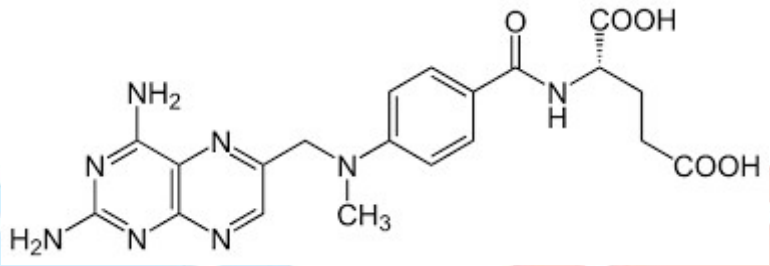
Popular Brand Names

♦ Actikeral
♦ Fluoroplex
♦ Carac
♦ Tolak

Methotrexate

→ Methotrexate (MTX) is an antineoplastic antimetabolite with immunosuppressant properties. It inhibits the formation of tetrahydrofolate dehydrogenase, which is required for the synthesis of thymidylate (an important DNA component

Chemical Structure



Mechanism of Action

➢ The mechanisms of action of methotrexate are complex. Developed as a folic acid analogue, methotrexate inhibits purine and pyrimidine synthesis, which accounts for its efficacy in the therapy of cancer as well as for some of its toxicities.

Uses

- It is effectively used with other drugs in acute lymphocytic leukaemia, choriocarcinoma, Burkitt lymphoma in children, breast cancer, and head and neck carcinomas.
- It is alone effective in low doses against certaininflammatory diseases (e.g., severe psoriasis)

Stability and Storage Conditions

▪ Multidose vials of methotrexate injection USP (with benzyl alcohol as a preservative) should be stored at temperatures between 15°C and 25°C. The vials should be stored between 2°C and 8°C for a maximum of four weeks after being punctured (30 days). It should be protected from light and freezing.

Types of Formulations

1. Injectable solution
2. Powder for injection

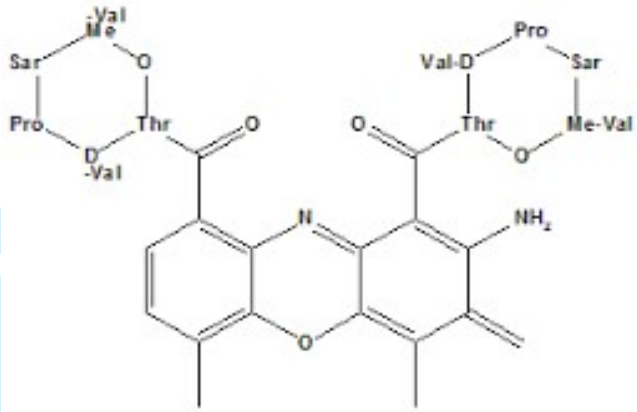
Popular Brand Names

♦ Trexall
♦ Xatmep

Dactinomycin

→ Dactinomycin is a high molecular weight antineoplastic antibiotic, which is isolated from Streptomyces parvulus.

Chemical Structure



Dactinomycin

Mechanism of Action

➢ Dactinomycin binds to DNA and blocks the RNA transcription with chain elongation more sensitive than initiation, termination, or release. This impaired mRNA production also declines the protein synthesis.

Uses

- It is used as a part of combination chemotherapy and/or multi-modality treatment regimen for treating Wilms' tumour, childhood rhabdomyosarcoma, Ewing's sarcoma and metastatic, non-seminomatous testicular cancer.

Stability and Storage Conditions

- Temperatures should be kept between 20° and 25° Celsius (68° and 77 °F) and away from light and humidity. It is caustic to the skin, irritating to the eyes and mucous membranes of the respiratory tract, and highly poisonous when taken orally, according to animal studies.

Type of Formulation

1. Powder for injection

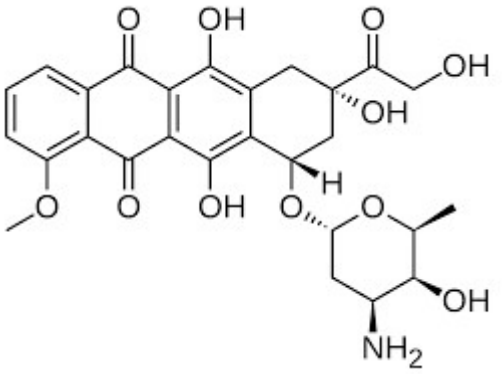
Popular Brand Name

♦ Cosmegen

Doxorubicin Hydrochloride

→ Doxorubicin is a cytotoxic anthracycline antibiotic. It is obtained from cultures of Streptomyces peucetius var. caesius. It binds to nucleic acids by intercalation of the planar anthracycline nucleus with the DNA double helix.

Chemical Structure



Mechanism of Action

➢ Doxorubicin exerts its antimitotic and cytotoxic activity by forming complexes with DNA through intercalation between base pairs. It blocks the activity of topoisomerase II by stabilising DNA-topoisomerase II complex, inhibiting the religation portion of the ligation-religation reaction catalysed by topoisomerase II.

Uses

- It is used for producing regression in disseminated neoplastic conditions such as acute lymphoblastic
- It is also used as a part of adjuvant therapy in women showing signs of axillary lymph node involvement after the resection of primary breast cancer.

Stability and Storage Conditions

▪ It should be stored at a temperature of 2° to 8°C.

Types of Formulations

1. Powder for injection
2. Solution

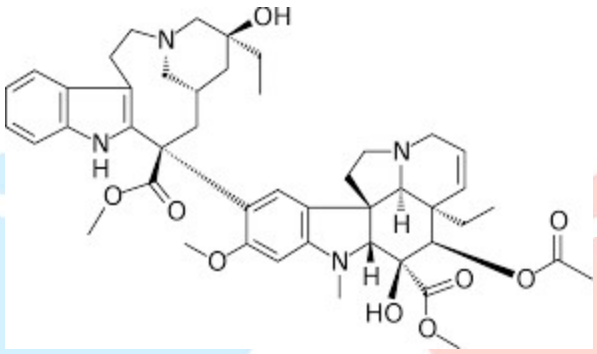
Popular Brand Names

♦ Adriamycin
♦ Rubex
♦ Adriamyc
♦ Adriamyc

Vinblastine Sulphate

→ Vinblastine sulphate is the sulphate salt of vinblastine, which is a natural alkaloid, obtained from Catharanthus roseus (Madagascar periwinkle). This plant possesses antineoplastic properties.

Chemical Structure



Mechanism of Action

➢ Vinblastine sulphate exerts its antitumour activity by interacting with tubulin and inhibiting mitosis at metaphase. Vinblastine binds to the microtubular proteins of the mitotic spindle and causes crystallisation of the microtubule and mitotic arrest or cell death.

Uses

- It is used in the treatment of breast cancer, testicular cancer, lymphomas, neuroblastoma, Hodgkin's and non- Hodgkin's lymphomas, mycosis fungoides, histiocytosis, and Kaposi's sarcoma.

Stability and Storage Conditions

▪ It is should be refrigerated between 20 and 8 °C. The vial should be kept in the outer carton to ensure safety from light

Types of Formulations

1. Injection solution
2. Powder

Popular Brand Name

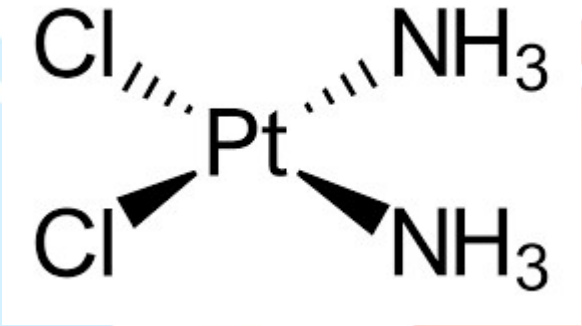
♦ Velban

Cisplatin

→ Cisplatin, cisplatinum or cis-diamminedichloroplatinum (II) (CDDP) is a platinum based chemotherapy drug. It isused for treating many types of cancers, such as sarcomas, some carcinomas (e.g., small cell lung cancer and ovarian cancer), lymphomas, and germ cell tumours.

Chemical Name and Structure

(SP-4-2)-diamminedichloroplatinum(II)



Mechanism of Action

➢ cisplatin mechanism of action is that the drug induces its cytotoxic properties through binding to nuclear DNA and subsequent interference with normal transcription, and/or DNA replication mechanisms.

Uses

- It is used for treating metastatic testicular tumours, metastatic ovarian tumours, and advanced bladder cancer.

Stability and Storage Conditions

- It is physically and chemically stable, when stored in glass containers or diluted with 0.9 % sodium chloride in PE bags at a concentration of 10 mg/ml at room temperature (15-25°C) for at least 30 days.

Types of Formulations

1. Injection
2. Solution

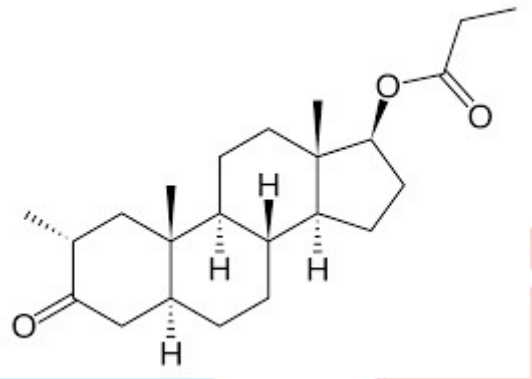
Popular Brand Names

♦ Platinol

Dromostanolone Propionate

→ Dromostanolone, like testosterone, is a synthetic androgen, or male hormone. Dromostanolone acts by binding to androgen receptors, which allows it to interact with cell components involved in protein synthesis.

Chemical Structure



Mechanism of Action

➢ Like testosterone and other androgenic hormones, dromostanolone binds to the androgen receptor. This causes downstream genetic transcriptional changes. This ultimately causes retention of nitrogen, potassium, and phosphorus; increases protein anabolism; and decreases amino acid catabolism.

Uses

- It is prescribed for the treatment of breast cancer in women, but it has been withdrawn from the market. It can also be used as to administer injection in the muscle.

Stability and Storage Conditions

- It should be stored at 0°- 4°C for short-term (days toweeks) or at -20°C for long-term (months to years) in dry and dark places.

Types of Formulations

1. Injection
2. Solutions

Popular Brand Names

- Drolban
- Masteril

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