Chapter: I
L.1&2

2024

Org.Pharm.Chem.III

4th. Stage Pharmacy Students

Anti-neoplastic Agents

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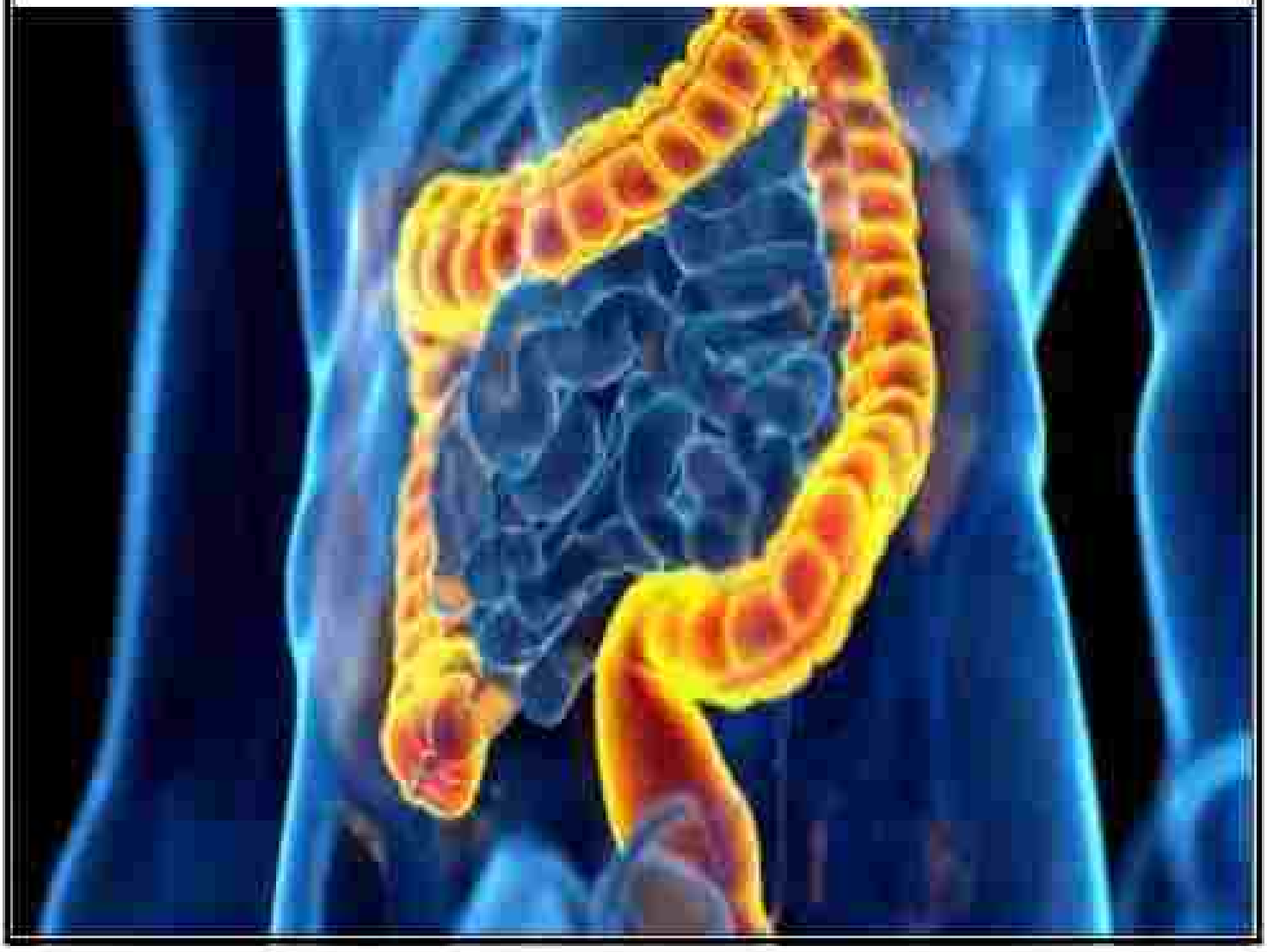


What is Cancer ?

Cancer is a term used for diseases in which abnormal cells divide without control and are able to invade other tissues. Cancer cells can spread to other parts of the body through the blood & lymph systems.

Types of Cancer:

*Carcinoma: cancer that begins in the skin or in tissues that line or cover internal organs. There are a number of subtypes of carcinoma, including adenocarcinoma basal cell carcinoma, squamous cell carcinoma and transitional cell carcinoma.

* Sarcoma: cancer that begins in bone, cartilage ,fat, muscle, blood vessels. Or other connective or supportive tissue.

*Leukemia: cancer that starts in blood forming tissue such as the bone marrow and causes large numbers of abnormal blood cells to be produced and enter the blood.

*Lymphoma & myeloma cancer that begins in cells of the immune system.

Central nervous system cancers: cancers that begin in tissues of brain & spinal cord.

Classification of Anti-neoplastic agents:

1.Alkylating agents.

A) Nitrogen mustard: Cyclophosphamide, chlorambucil, Melphalan.

B) Alkyl Sulfonate: Busulfan.

C) Nitrosoureas: Carmustine,Lumustine, Semustine.

D) Ethylenimines: Thiotepa

E) Triazenes : Dacarbazine

2. Antimetabolites:

A) Folate antagonist: methotrexate and gemcitabine.

B) Purine analogues: thioguanine, mercaptopurine, pentostatin.

C) Pyrimidine analogues: 5-fluorouracil, cytarabine.

3.Plant –derived products:

Vinca alkaloids (vincristine ,vinblastine),epipodophyllotaxins(etoposide),taxanes(paclitaxel).

4.Antibiotics:

Doxorubicin, daunorubicin, bleomycin, mitomycin, dactinomycin.

5.Hormones and related drugs:

Tamoxifen, estramustine, flutamide ,progestins.

6.Miscellaneous agents:

Hydroxyurea,cisplatin,mitoxantrone, levamisole, interferon and aldesleukin.

7. Drugs that alters hormonal milieu.

-Glucocorticoids: prednisolone,prednisone

-Estrogens: Diethylstilbesterol

-Anti-estrogen: Tamoxifen

-Andeogens: Testosterone

-Progestins: Medroxy progesterone Acetate

8.Monoclonal Antibodies:

-Trantuzumab

-Rituximab

-Imatinib

Alkylating Agents

***Mode of action:**

they are capable of introducing an alkyl group into nucleophilic sites on DNA,RNA or any enzyme through covalent bond.

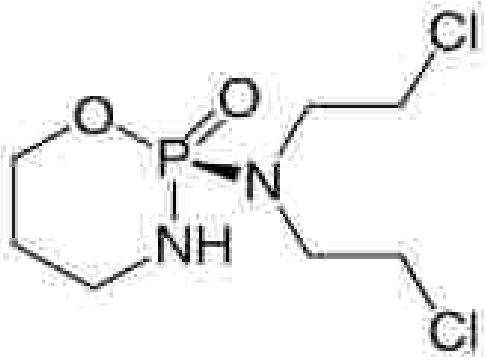
-these agents are thought to react with the 7-position of guanine (or any other nitrogen base) in each of the double strands of DNA, causing cross-linking that interferes with separation of the strands and prevents mitosis.

1. Cyclophosphamide

IUPAC name: N,N-Bis(2-chloroethyl)-1,3,2-oxazaphosphinan-2-amine-2-oxide

*The most widely used alkylating agent.

*Pro-drug: inactive in vitro but when administered it is metabolized by liver into phosphoramide mustard (active compound).

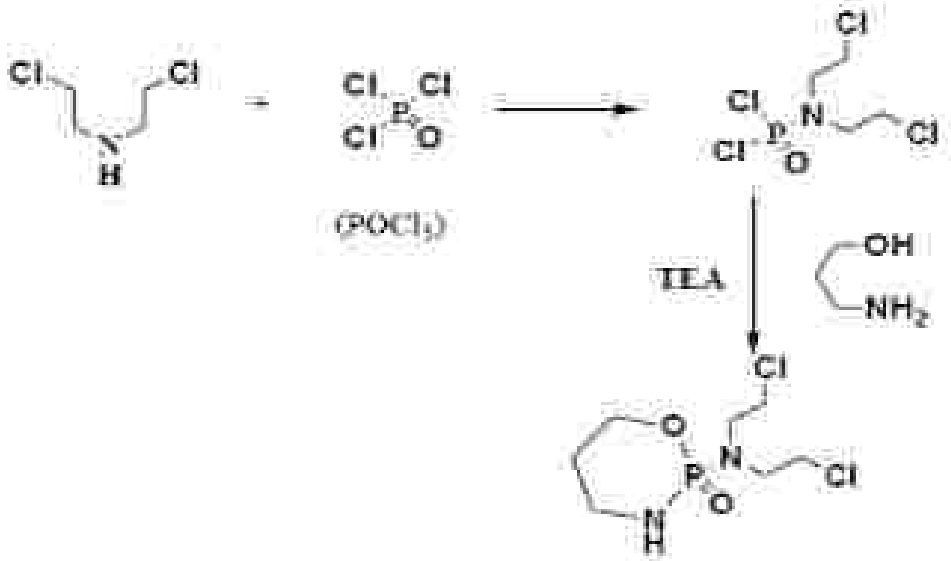


*Uses: Breast cancer, ovarian cancer, non-Hodgkin 's lymphoma, chronic lymphocytic leukemia (CLL), soft tissue sarcoma, neuroblastoma, Wilm 's tumor, rhabdomyosarcoma.

SAR:

-Bis-2-chloroethyl amino group is essential.
-Chloro atom provides maximum activity.
-Levo-isomer is inactive.
-Triethylene derivative is inactive.

Synthesis: Condensation of bis-(2-chloroethyl) amine and phosphorus oxy chloride followed by 3-aminopropanol in presence of triethyl amine (TEA)



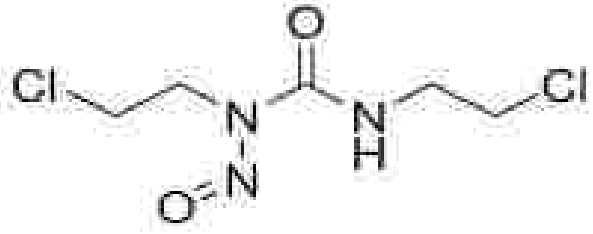
Nitroureas:

- Carmustine
- Lumustine
- Streptozocin

-They are compounds that have nitroso (R – NO) group and a urea, they have little cross resistance with other alkylating agents
-They cross blood brain barrier (lipophilic) so they used against brain cancer.

2.Carmustine

IUPAC name: N,N-Bis(2-chloroethyl)-N-nitroso urea



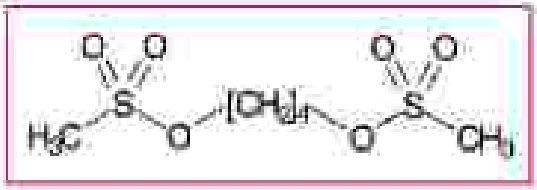
- It causes alkylation of DNA at o-6 position of DNA of guanine.
-It mainly used to treat brain cancer and lymphoma.
-It causes pulmonary toxicity and nephrotoxicity.

MOA: Nitrosoureas are unstable structures that decompose readily in the aqueous environment of the cell to generate cytotoxic electrophiles (vinyl carbocation, acetaldehyde, and 2-chloroethylamine) that are capable of alkylating DNA in the standard manner.

Alkyl sulphonates

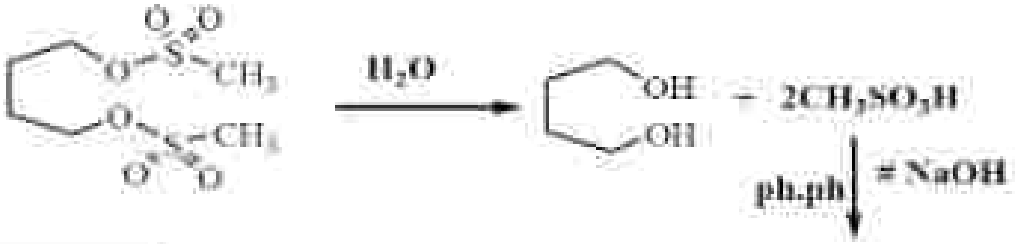
3.Busulfan

Butane-1,4-diyl dimethane sulfonate
-It is used for treatment of chronic myelogenous leukemia (CML) in bone marrow transplantation patients
-main side effects is seizure



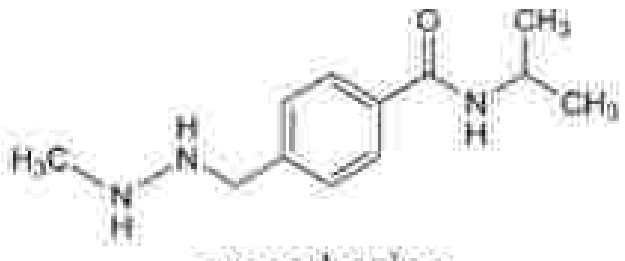
Synthesis:

Assay:



Methyl hydrazines:

4. Procarbazine



procarbazine

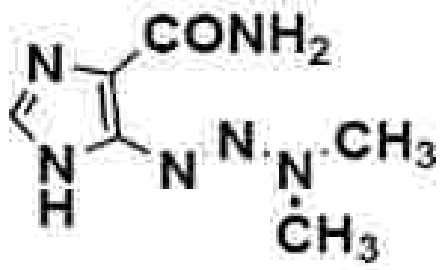
IUPAC name: N-isopropyl-4-[(2-methylhydrazino) methyl] benzamide.

-It must be converted into an azo derivative in vivo to become active against tumor cells.

Mode of action: alkylation of DNA or possible transmethylation.

Triazines:

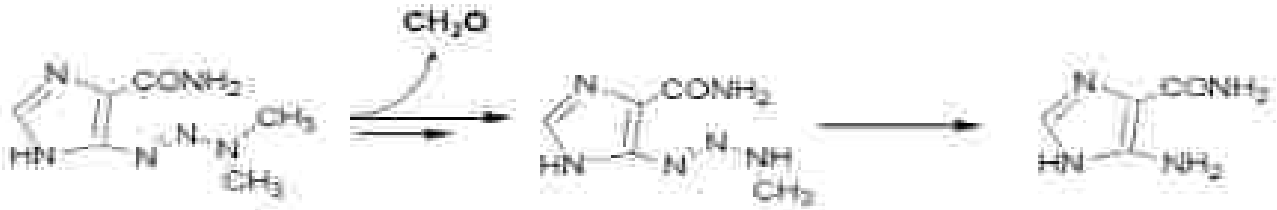
Dacarbazine:



5-(3,3-Dimethyl-1-triazino)-1H-imidazole-4-carboxamide

Synthesis

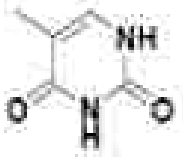
MOA:



Antimetabolites:

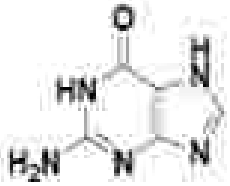
- The antimetabolites stop the de novo synthesis of DNA by inhibiting the formation of the nucleotides that make up these life-sustaining polymers. Antimetabolites, thus, can arrest chain elongation by promoting the incorporation of false nucleotides into the growing DNA strand. They serve as false substrates for critical nucleotide biosynthesis enzymes.
- They are nucleoside analogues
- The natural nucleotides are:

Uracil



Thymine

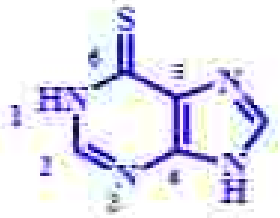
Cytosine



Guanine

A) Purine antagonists

6-Mercaptopurine

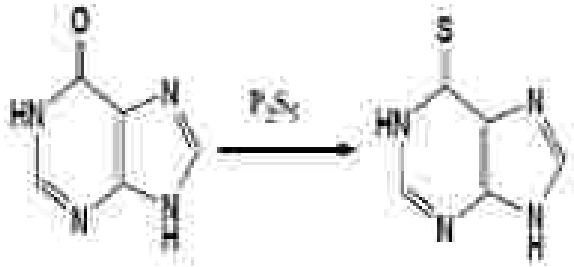


It is a hypoxanthine analogue.

It is activated into 6-thioinosine-5'-phosphate ,which inhibits adenine & guanine synthesis.

Uses: orally administered in combination with Ara-C (Cytarabine) for treatment of leukemia.

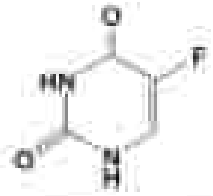
Synthesis:



Hypoxanthine

Direct inhibitors of thymidylate synthase
5-Fluorouracil (5FU)

1. **5-Fluorouracil (5-FU)**



5-Fluoro-2,4-(1H,3H)-pyrimidinedione

- 5-FU acts through inhibition of thymidylate synthetase.
- Uracil is the most incorporated nucleoside in tumor cells.
- F-atom has the same steric volume as H-atom
- Fluorine is much more electronegative than H resulting in enhanced binding to the enzyme
- The 5-position was selected since it is the mostly susceptible to enzymatic interaction
- 5-FU has a fluorine atom at the 5 position instead of a hydrogen. Further reaction is impossible since it would require fluorine to leave as a positive ion. Fluorine is too electronegative for this to occur since it prefers to ionize as the fluoride ion (F-).
- As a result, the fluorouracil skeleton remains covalently and irreversibly bound to the active site. The synthesis of thymidine is now terminated, which in turn stops the synthesis of DNA.

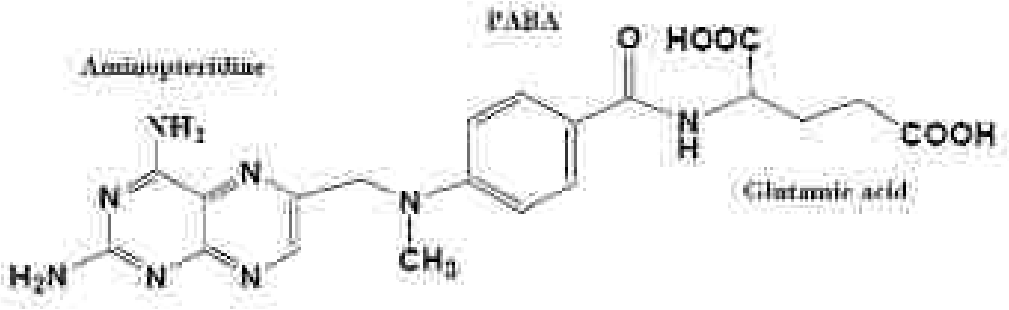
Uses:

- Single agent in adenocarcinoma
- Combination with methotrexate in breast cancer; carcinoma of ovary, stomach and pancreas.

Assay:

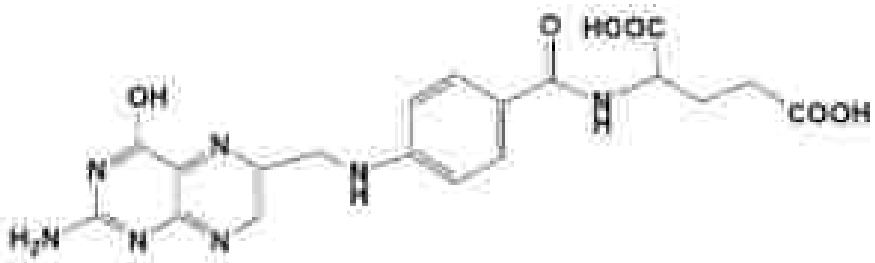
Non aq. titration in acid: solvent (DMF); titrant (t-Butyl ammonium hydroxide); indicator (Thymol blue)

Indirect inhibitors of thymidylate synthase
Methotrexate (Folinic acid)



N-[4-[[(2,4-Diamino-6-pteridinyl)methyl]methylamino] benzoyl]glutamic acid

Folic acid



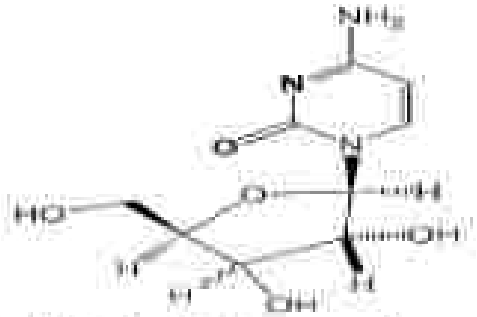
Mechanism of action:

- As analogue of folic acid, it binds strongly to DHF reductase resulting in depletion of THF. This leads to decrease in the 1-carbon transfer mechanism of purine synthesis.
- It forms **polyglutamyl-MTX** which traps MTX inside the cell and inhibits thymidylate synthase.

DNA polymerase / DNA chain elongation inhibitors:

Cytarabine:(Ara-C)

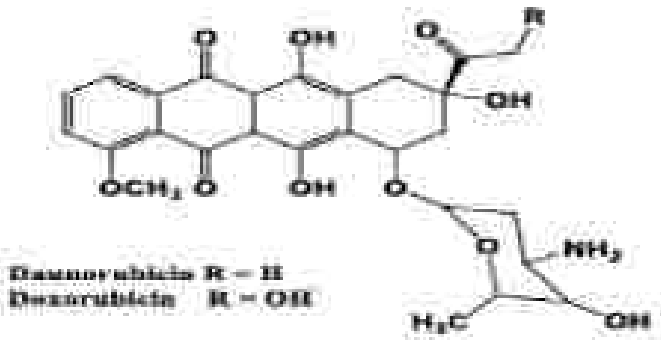
Must be converted to ***triphosphate*** nucleotides at first.



1-β-D- Arabinfuranosyl cytosine

MOA: In active triphosphate form, they can be mistakenly incorporated into the growing DNA chain, thus arresting further elongation, and inhibiting DNA-dependent polymerase leading to miscoding.

Antibiotics
Anthracyclines



- They are very closely related to tetracycline antibacterials.
- They are Anthraquinone glycoside derivative, attached to an aminosugar

MOA

1. This flat ring system slides between the two DNA strands, leading to intercalation of the DNA, which results in inhibition of synthesis and distortion of the formed strands. The protonated amino group on the sugar stabilizes the intercalated complex through interaction with an anionic DNA phosphate. Loss of the amino moiety decreases DNA binding.
2. Inhibition of topoisomerase II.
3. Chelation with some important cations e.g.; Ca & Fe resulting in cell death.

Hormone based theraby:

Hormone-based therapies are used against cancers which are ***hormone dependent***. If the cancer cell requires a specific hormone, then a hormone can be administered which has an opposing effect. Alternatively, hormone antagonists can be used to block the action of the required hormone.

Advantages:

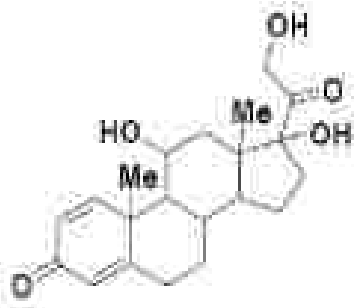
- Least toxic of anticancer drugs
- Highly selective

Uses: Breast, endometrial, prostate cancers.

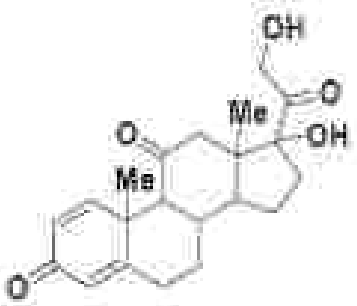
Types of hormones used in anticancer therapy:

1. Glucocorticoids
2. Estrogens
3. Progestins
4. Androgens
5. Analogues of LHRH (luteinizing hormone releasing hormone).
6. Antiestrogens
7. Antiandrogens
8. Aromatase inhibitors

Glucocorticoids:



Prednisolone



Prednisone

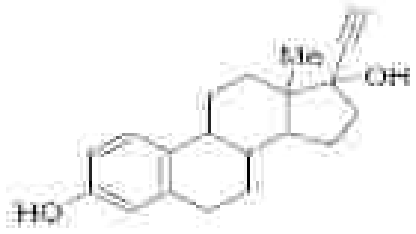
Prednisone is a prodrug and is enzymatically converted to prednisolone

Uses: Treatment of leukemias and lymphomas.

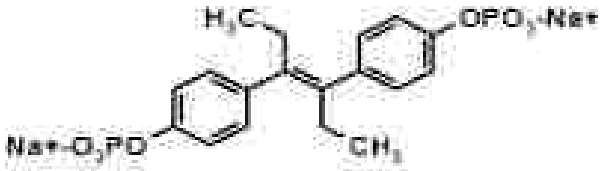
Estrogens:

Uses: Treatment of prostate cancer

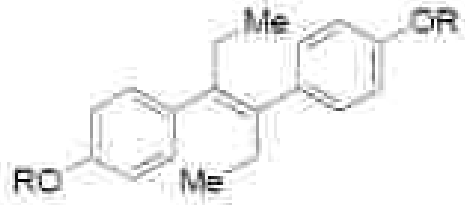
MOA: inhibit the production of LH and thus, decrease the synthesis of testosterone.



Ethinylestradiol



diphosphate - Stilphostrol®



R= Phosphate

Foxfestrol

It is the diphosphate prodrug of diethylstilbestrol. It is only activated in target cells where it can reach higher concentrations than if the drug itself was administered (**SELECTIVITY**).

This eagle is running to success