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Cytotoxic Drugs

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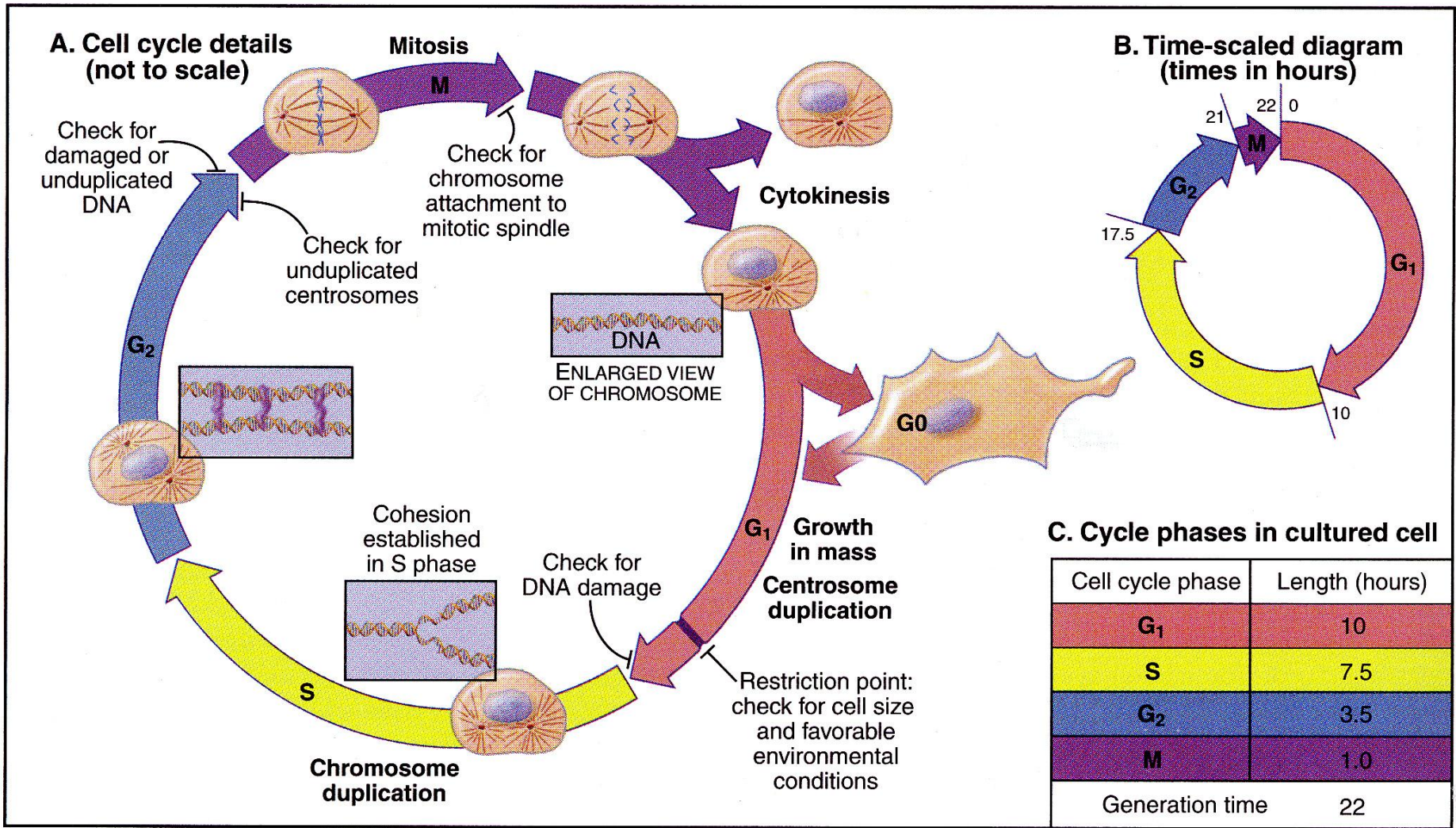
Objectives

- To be able to define the term 'Cancer.'
- To be able to describe the characteristics of cancer cells.
- To be familiar with the molecular basis of chemotherapy.
- To be able to discuss the potential targets for chemotherapy.
- To be able to identify the major classes of anticancer drugs and describe their mechanisms of action.

Cytotoxic drugs

- **Definition:** drugs that modify the growth of cells and tissues.
- **The uses:**
 - Anti-cancer agents
 - To eradicate disease
 - Induce a remission
 - Control symptoms
 - Control of immune responses in organ transplantation
 - Management of autoimmune disease

Cell cycle – The key to life, death and cancer



- Cycle checkpoints (growth arrest ensures genetic fidelity).

The Hallmarks of Cancer

The Cancer Cell Phenotype

- Disregard of signals to stop proliferating.
- Disregard of signals to differentiate.
- Capacity for sustained proliferation.
- Evasion of apoptosis.
- Ability to invade.
- Ability to promote angiogenesis.

Problems with anti-cancer therapy

- Difficult to find exploitable differences between cancer cells and normal cells.
- Need to produce a near total cell kill.
- Cancer is usually far advanced before diagnosis.
- Tumour cells can be:
 - Dividing (sensitive to anticancer treatment)
 - No longer able to divide (not a problem)
 - Resting in G0 phase (insensitive to anticancer treatment and could start dividing again after chemotherapy).

Cytotoxic Drugs

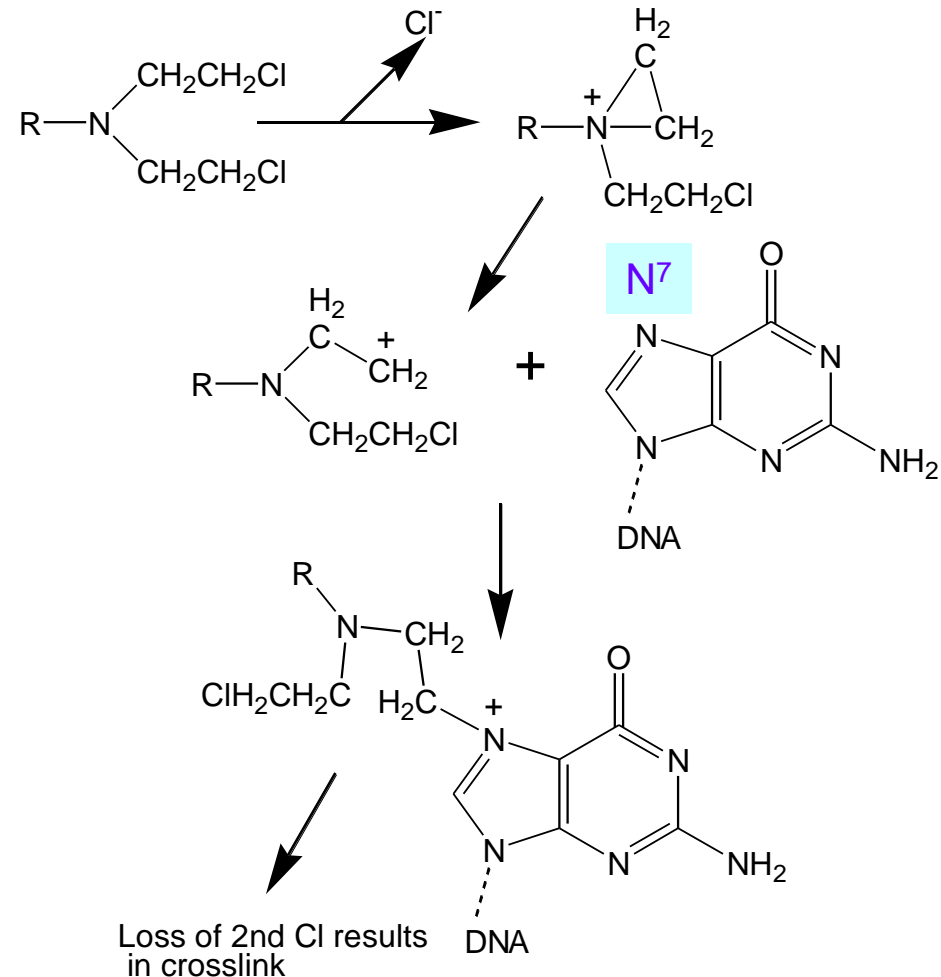
- Tend to be antiproliferative.
 - Do not affect invasiveness and tendency to metastasise.
 - Are commonly used as combinations to reduce chances of drug resistance.
 - Will affect all rapidly dividing normal tissues as well as tumour.
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- **Alkylating agents and related compounds.**
 - **Antimetabolites**
 - **Cytotoxic antibiotics**
 - **Mitotic inhibitors (Plant derivatives)**
 - **Miscellaneous agents**

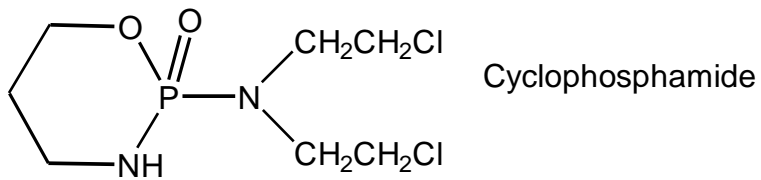
Alkylating agents

- Covalently bond with nucleophiles.
- Reactive group is a carbonium ion.
- Most are bifunctional.
- Guanine N7 is main target, also N1 and N3 of adenine and N3 of cytosine.
- Can cause intra- or interchain crosslinks.
- Interfere with transcription and replication.

Nitrogen mustards

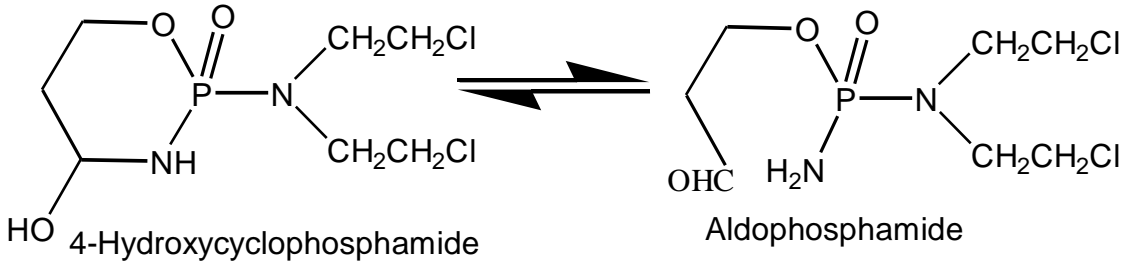
- Related to mustard gas.
- Highly reactive ethylene immonium derivative.
- E.g. cyclophosphamide, melphalan, chlorambucil.



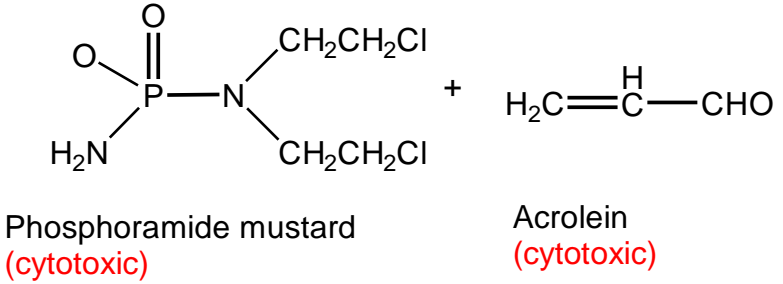
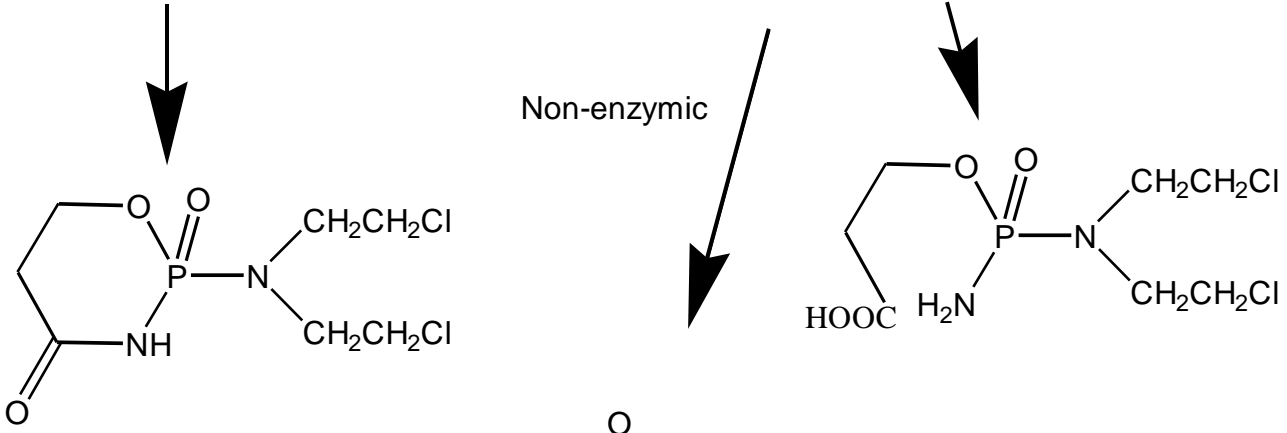


Cyclophosphamide

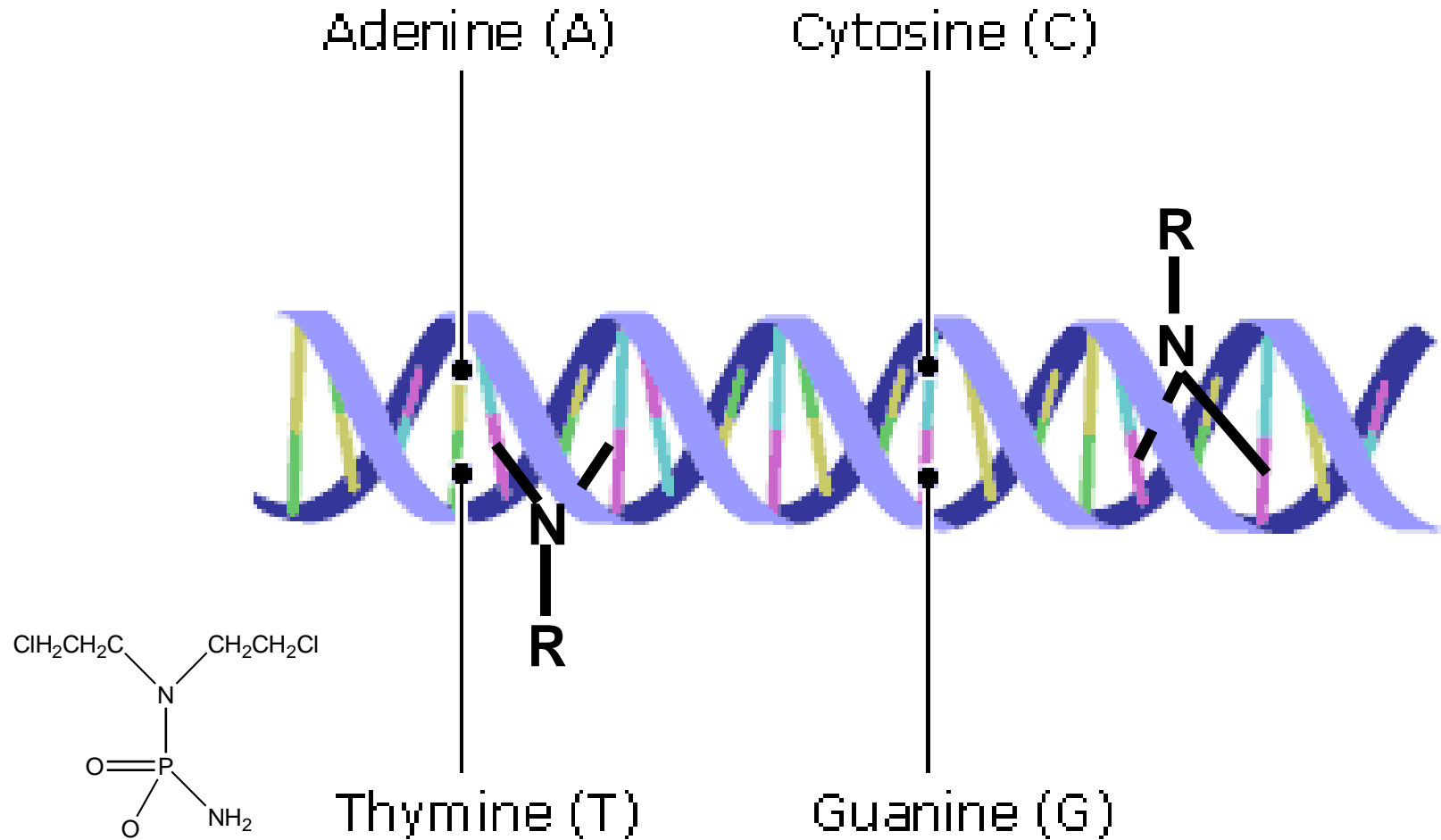
CYP450



Non-enzymic



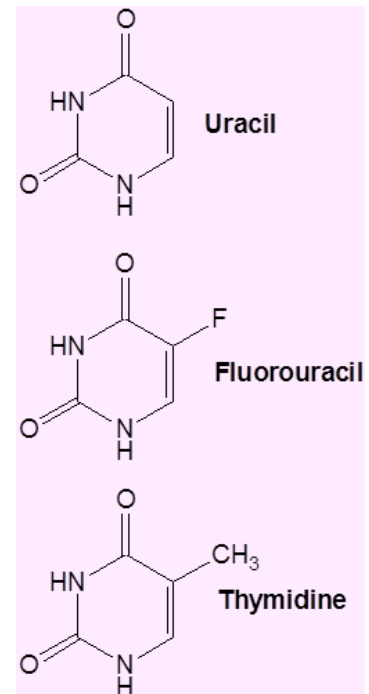
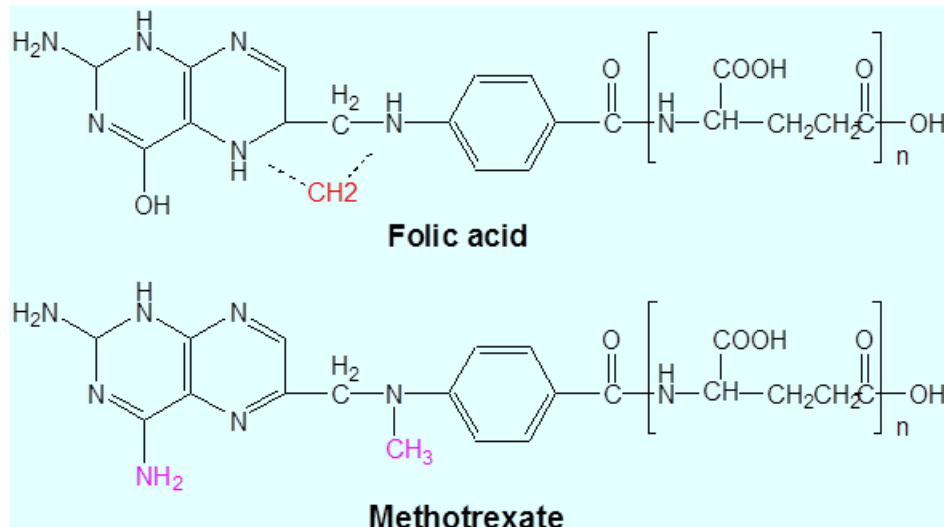
Bifunctional alkylating agents



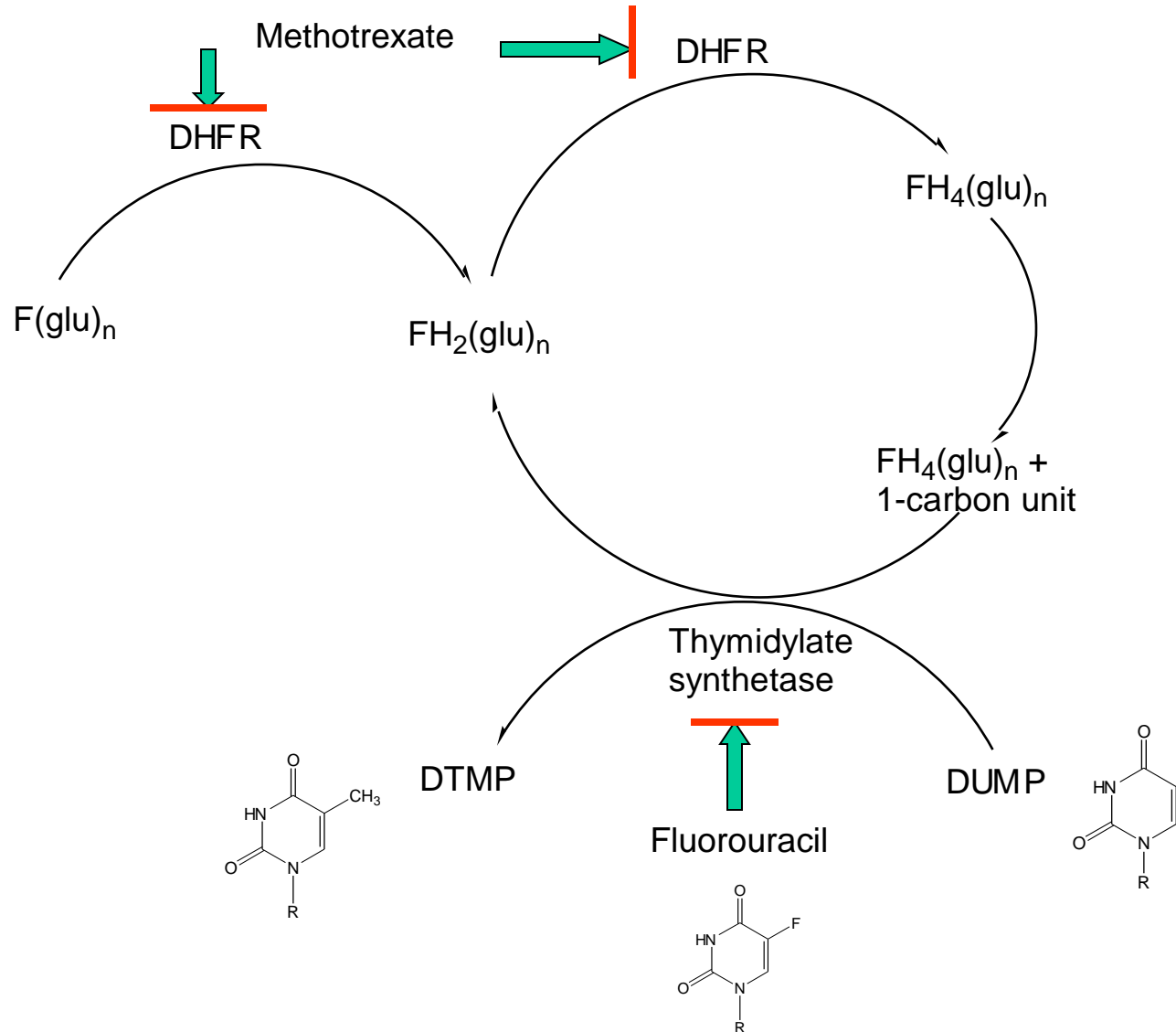
Phosphoramidate mustard
(cytotoxic)

Antimetabolites

- Block or subvert pathways in DNA synthesis.
- Folate antagonists e.g. methotrexate, interfere with thymidylate synthesis.
- Pyrimidine analogues e.g. fluorouracil interfere with 2'-deoxythymidylate synthesis.
- Purine analogues e.g. Azathioprine inhibits purine synthesis.

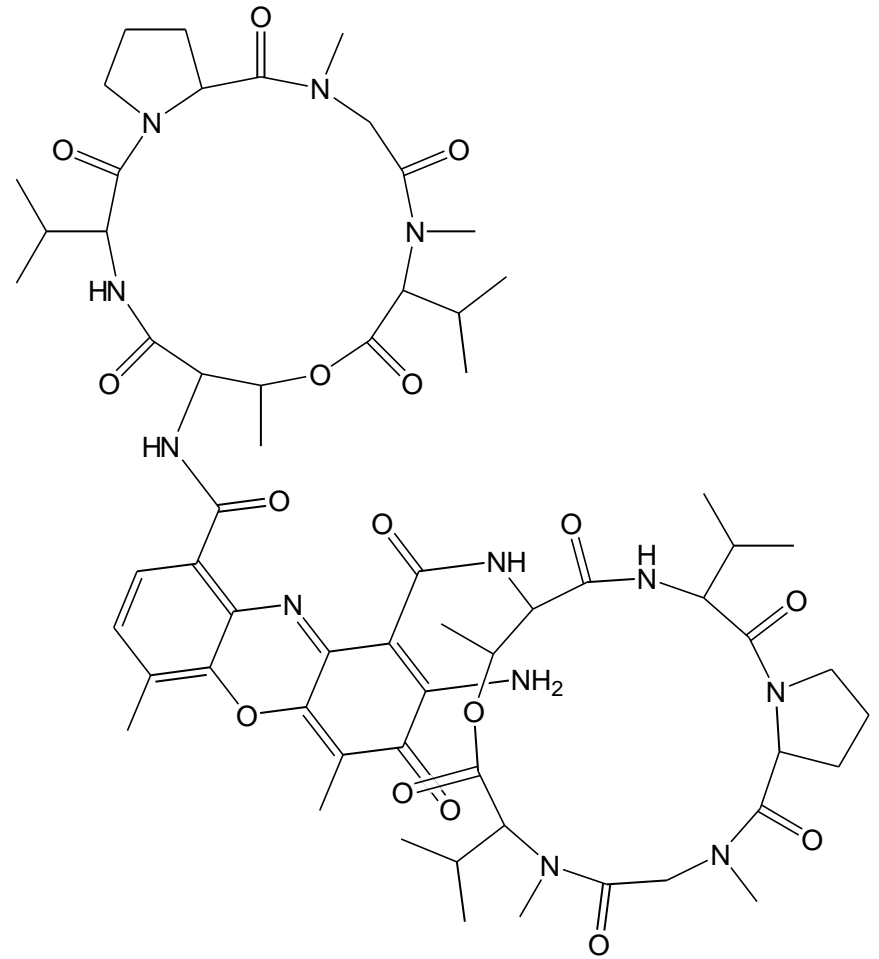


Methotrexate and Fluorouracil



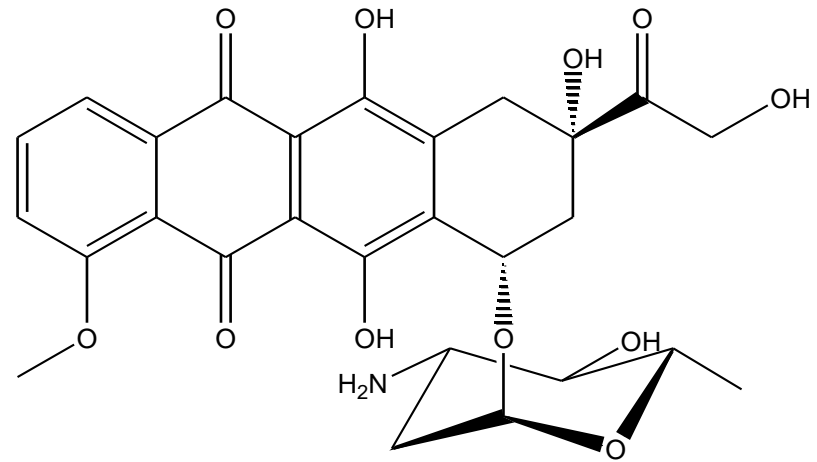
Cytotoxic antibiotics

- Direct interaction with DNA.
- E.g. Actinomycin D (Dactinomycin) intercalates DNA and interferes with topoisomerase II.



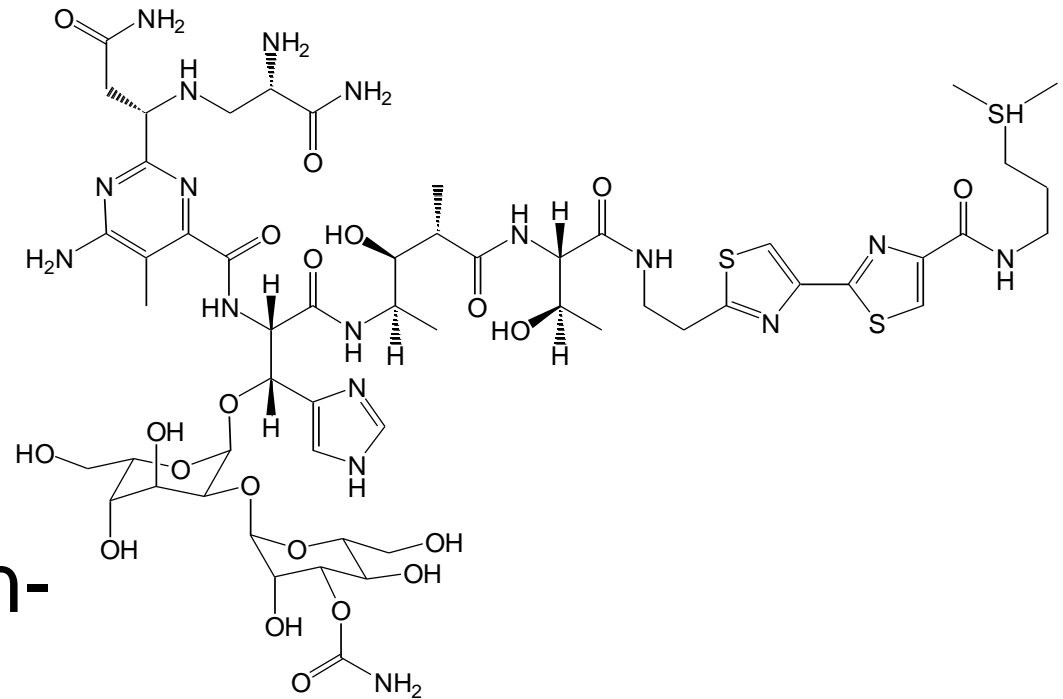
Cytotoxic antibiotics

- Doxorubicin inhibits DNA and RNA synthesis.



Cytotoxic antibiotics

- Bleomycins are metal-chelating glycopeptide antibiotics that degrade DNA.
- Bleomycins are active against non-dividing cells. Administered iv.

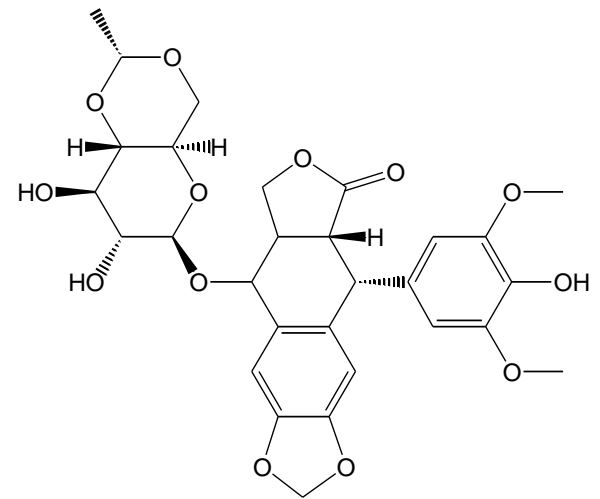


Plant alkaloids

- The podophyllotoxins e.g. etoposide, inhibit DNA synthesis.
- Causes cell cycle block at G2.



Podophyllum peltatum
May Apple, American Mandrake

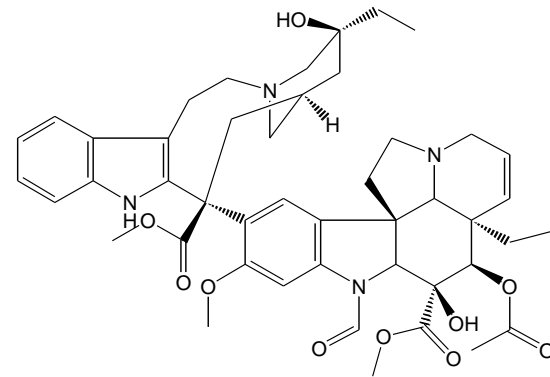


Plant alkaloids

- The vinca alkaloids e.g. vincristine, act by binding to tubulin and inhibiting polymerisation into microtubules.
- This prevents spindle formation.

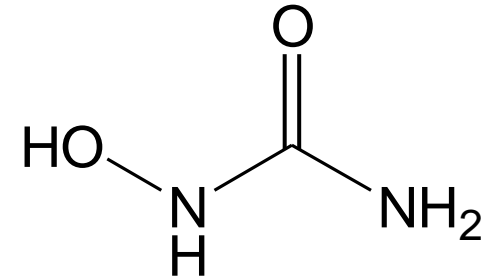


Vinca minor
Periwinkle

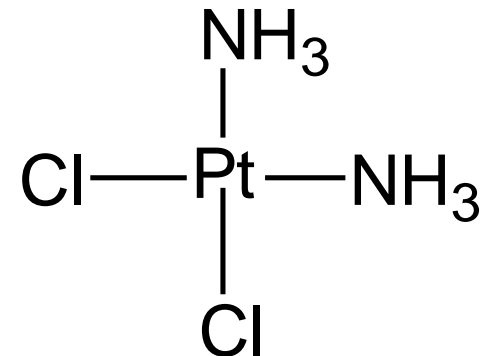


Miscellaneous agents

- Hydroxyurea inhibits ribonucleotide reductase.

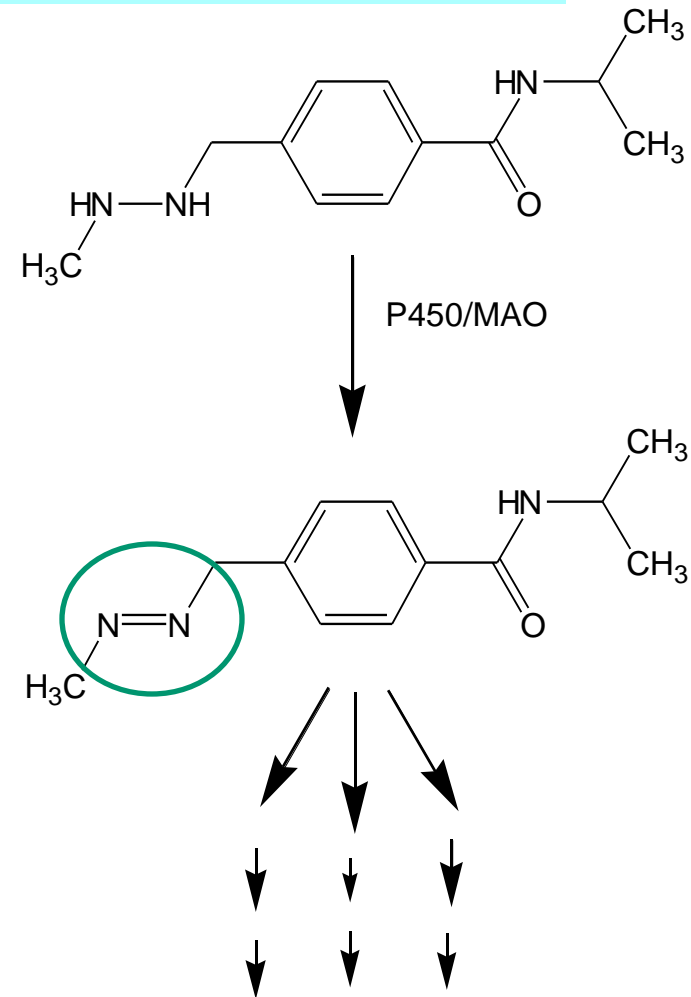


- Cisplatin interacts with DNA causing guanine intrastrand cross-links.



Miscellaneous agents

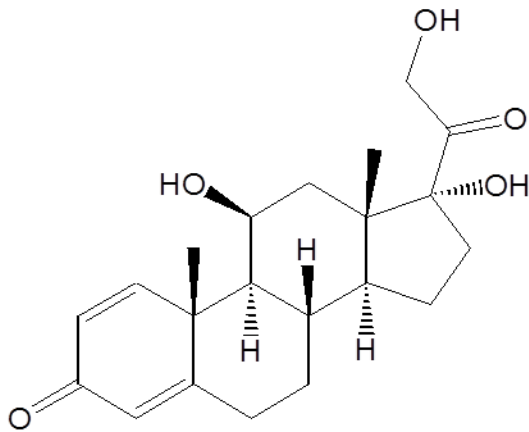
- Procarbazine inhibits DNA and RNA synthesis and interferes with mitosis at interphase.
- Metabolically activated by cytochrome P450 and monoamine oxidase to alkylate DNA (N7 and O6 of guanine).



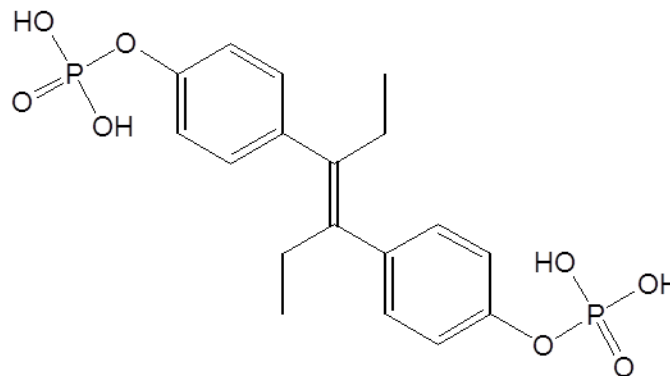
Multiple metabolites including alkylating agents, probably carbonium ions

Hormones

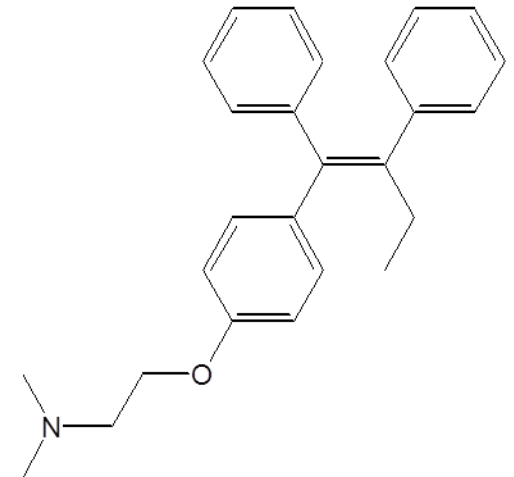
- Used for chemotherapy but are **not technically cytotoxic**.
- Can inhibit tumours in hormone-sensitive tissues.
- Gonadotrophin-releasing hormone analogues
 - e.g. Goserelin



prednisolone



fosfestrol



tamoxifen

General toxic effects

- Myelotoxicity.
- Impaired wound healing.
- Depression of growth (children)
- Sterility.
- Teratogenicity.
- Loss of hair.
- Nausea and vomiting

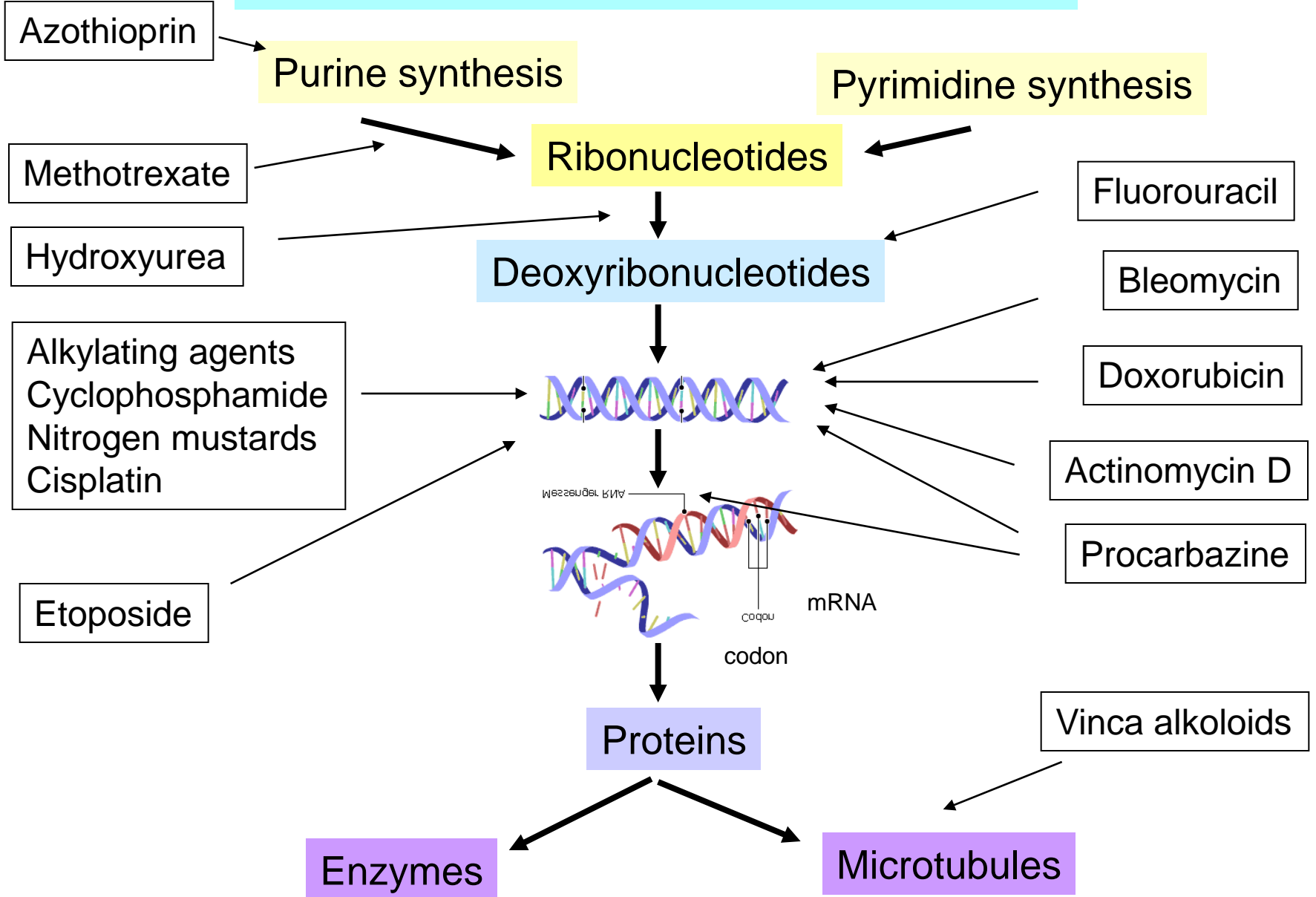
Side effects

- Fast growing cells
 - Inhibit cell division
 - Cell cycle specific drugs
 - Bone marrow, GI tract epithelium,
Hair & nails, Spermatogonia
- Slow growing cells
 - Introduce DNA mutations
 - Cell cycle independent (alkylating agents)
 - Secondary tumours

Immunopharmacology of cytotoxic drugs

- Immune system protects the host from invasion.
- Can cause autoimmune disease and reject allogenic tissue grafts after transplantation.
- Cytotoxic drugs can be used as immunosuppressants, **but at much lower doses than used to treat cancer.**
- At lower dose, the drugs selectively affect lymphocytes, which drive the immune response.
- Azathioprine, methotrexate and cyclophosphamide are the principle agents used for immunosuppression.

Cytotoxic agents



Summary

- Chemotherapy eliminates/ blocks proliferation of neoplastic cells and inhibits invasion and metastatic potential.
- **Elimination of cells** is achieved using very toxic chemicals that target rapidly proliferating cells.
- **Blocking the proliferation of cells** is aimed at stalling tumour growth and encouraging apoptosis and immunosurveillance (removal of abnormal cells by the immune system).

Suggested reading

- Pharmacology, 5th Ed, Rang, Dale, Ritter, Moore, Pub Churchill Livingstone, 2003.
- Pharmacology Condensed, Dale and Haylett, Pub Churchill Livingstone, 2004.
- Medical Pharmacology at a Glance, 3rd Ed, Neal, Pub Blackwell Science, 1997.