Imperial College London

Cytotoxic Drugs

Nigel Gooderham

BioMolecular Medicine, Faculty of Medicine
Imperial College London

Cytotoxic Drugs

Nigel Gooderham

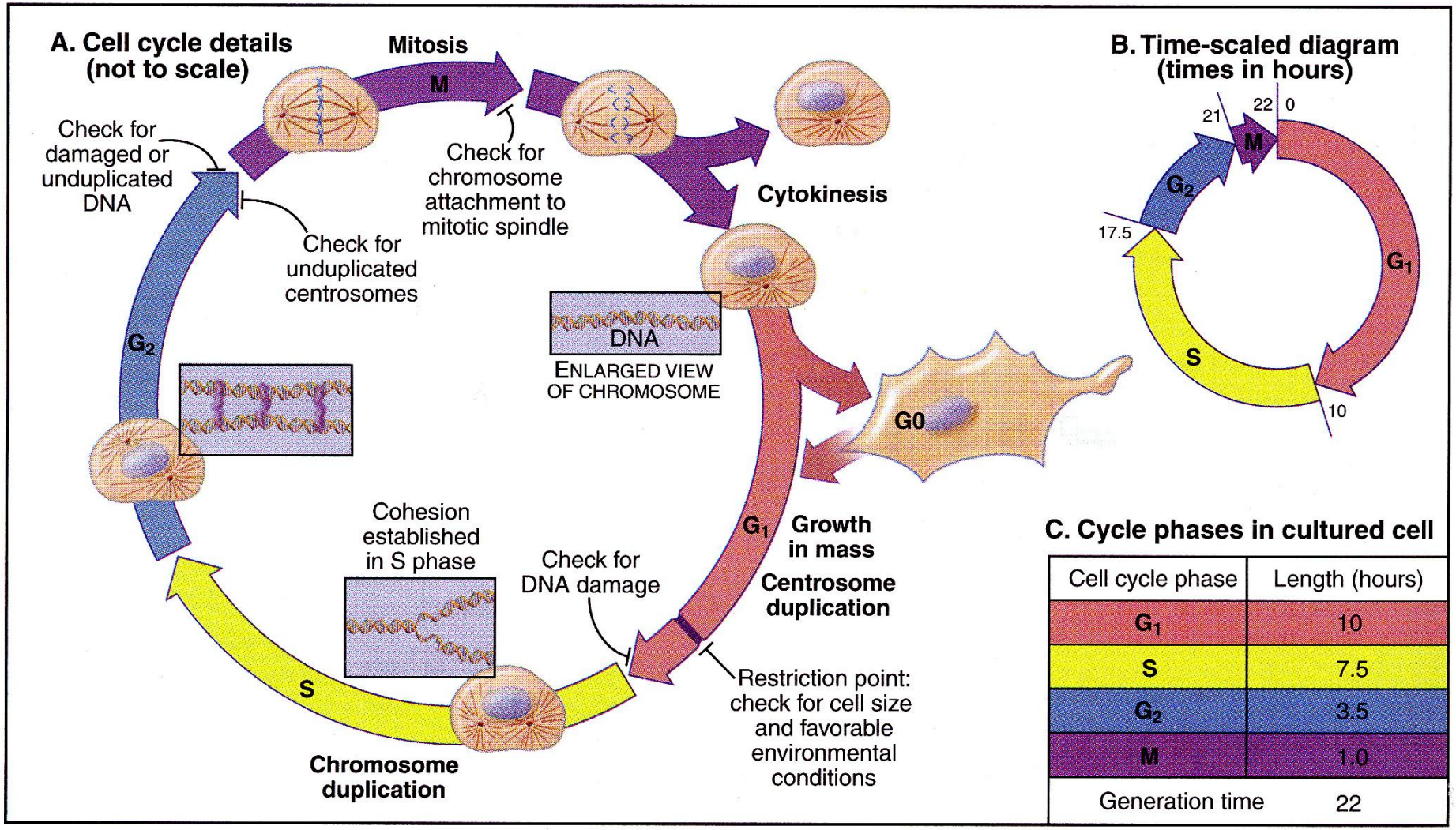
Objectives

- 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



Cell cycle phase	Length (hours)
G_1	10
S	7.5
G_2	3.5
M	1.0
Generation time	22

- 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.

Hanahan and Weinberg (2000)

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.

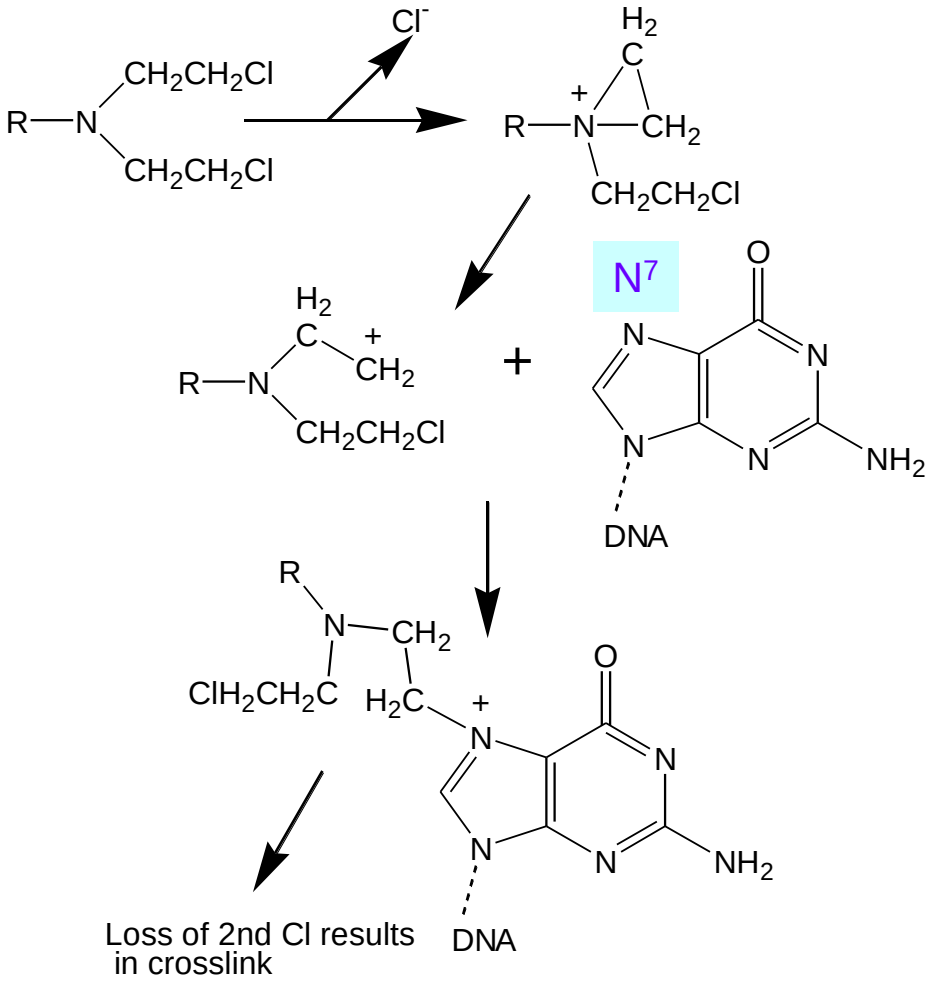
- **Alkylating agents and related compounds**.
- **Antimetabolites**
- **Cytotoxic antibiotics**
- **Mitotic inhibitors (Plant derivatives)**
- **Miscellaneous agents**

Alkylating agents

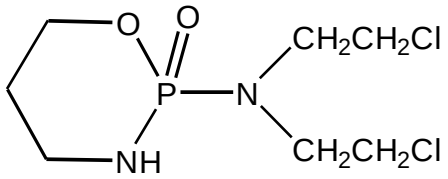
- Covalently bond with nucleophiles.
- Reactive group is a carbonium ion.
- Most are bifunctional.
- Guanine N7 is main target, also N1 and N3 of adenine and N3 of cytosine.
- Can cause intra- or interchain crosslinks.
- Interfere with transcription and replication.

Nitrogen mustards

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

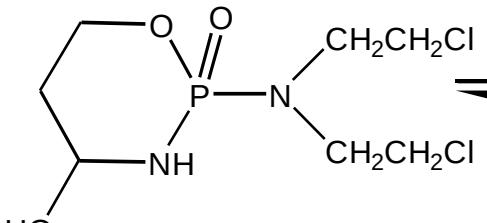


Cyclophosphamide

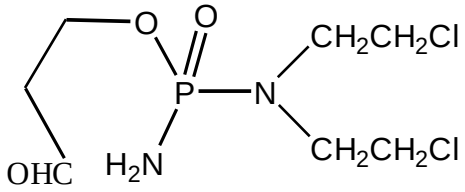


Cyclophosphamide

CYP450

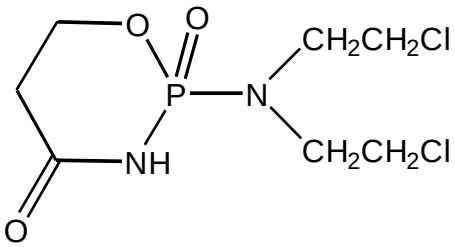


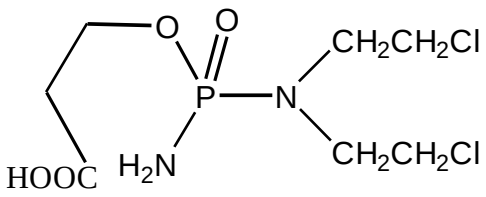
4-Hydroxycyclophosphamide

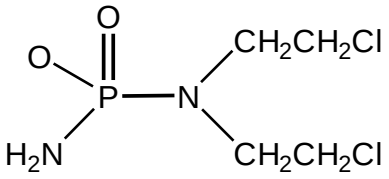


Aldophosphamide

Non-enzymic

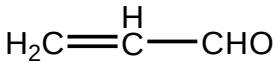






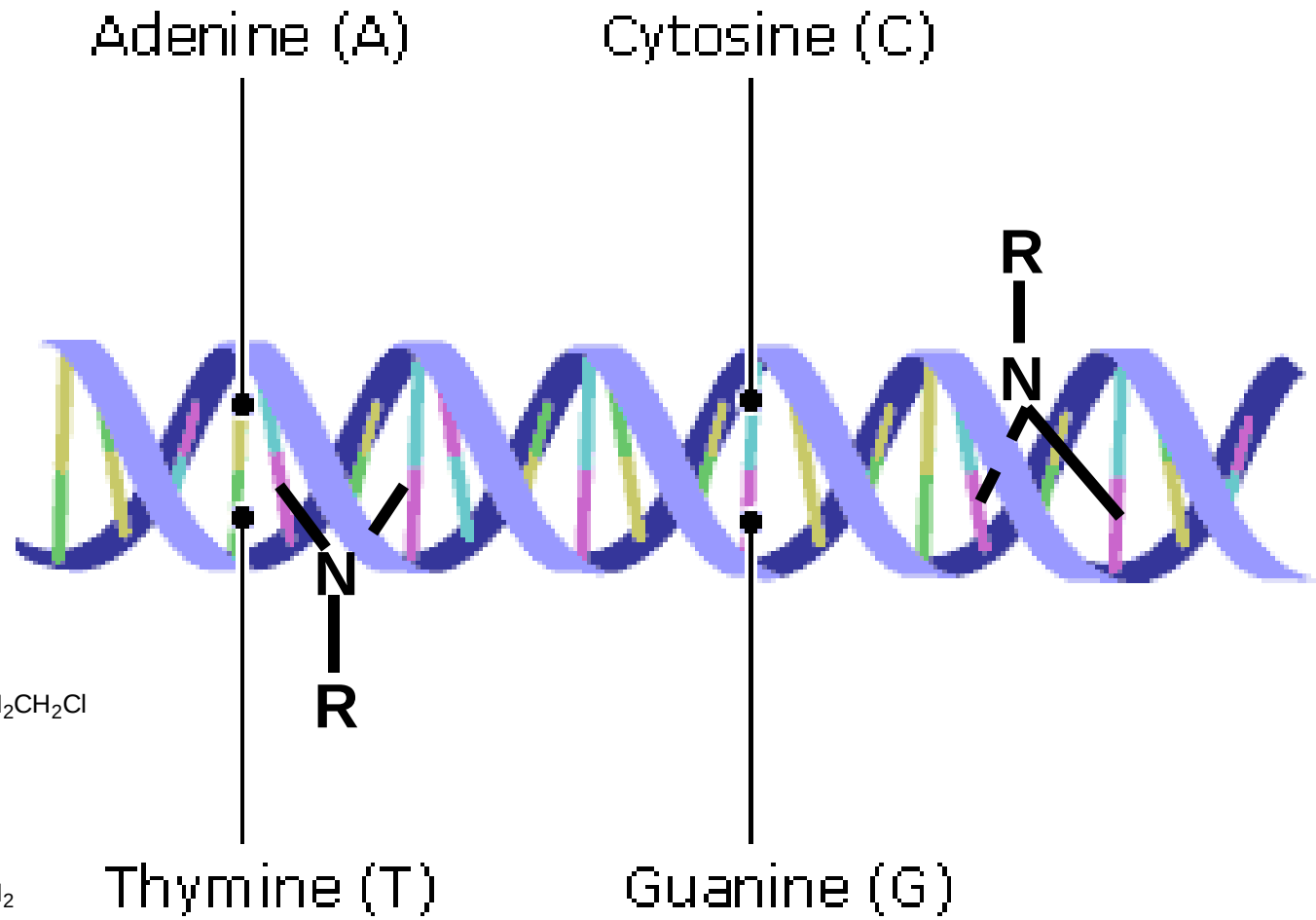
Phosphoramide mustard
(cytotoxic)

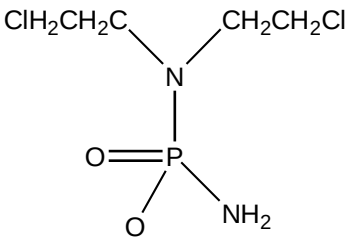
+



Acrolein
(cytotoxic)

Bifunctional alkylating agents

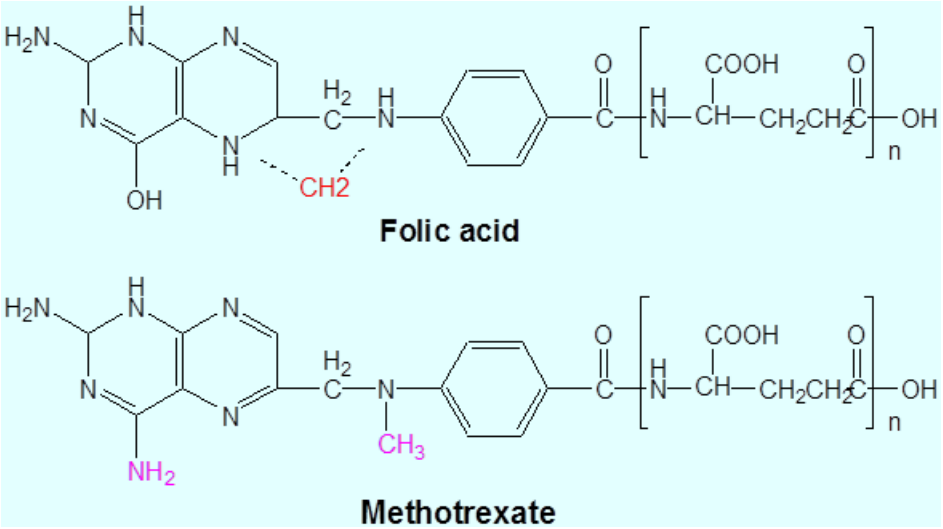


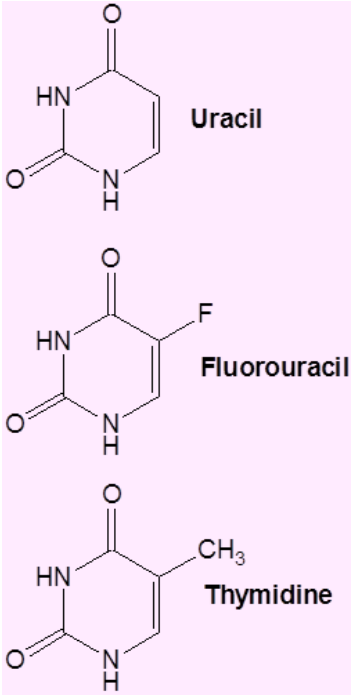


Phosphoramide mustard
(cytotoxic)

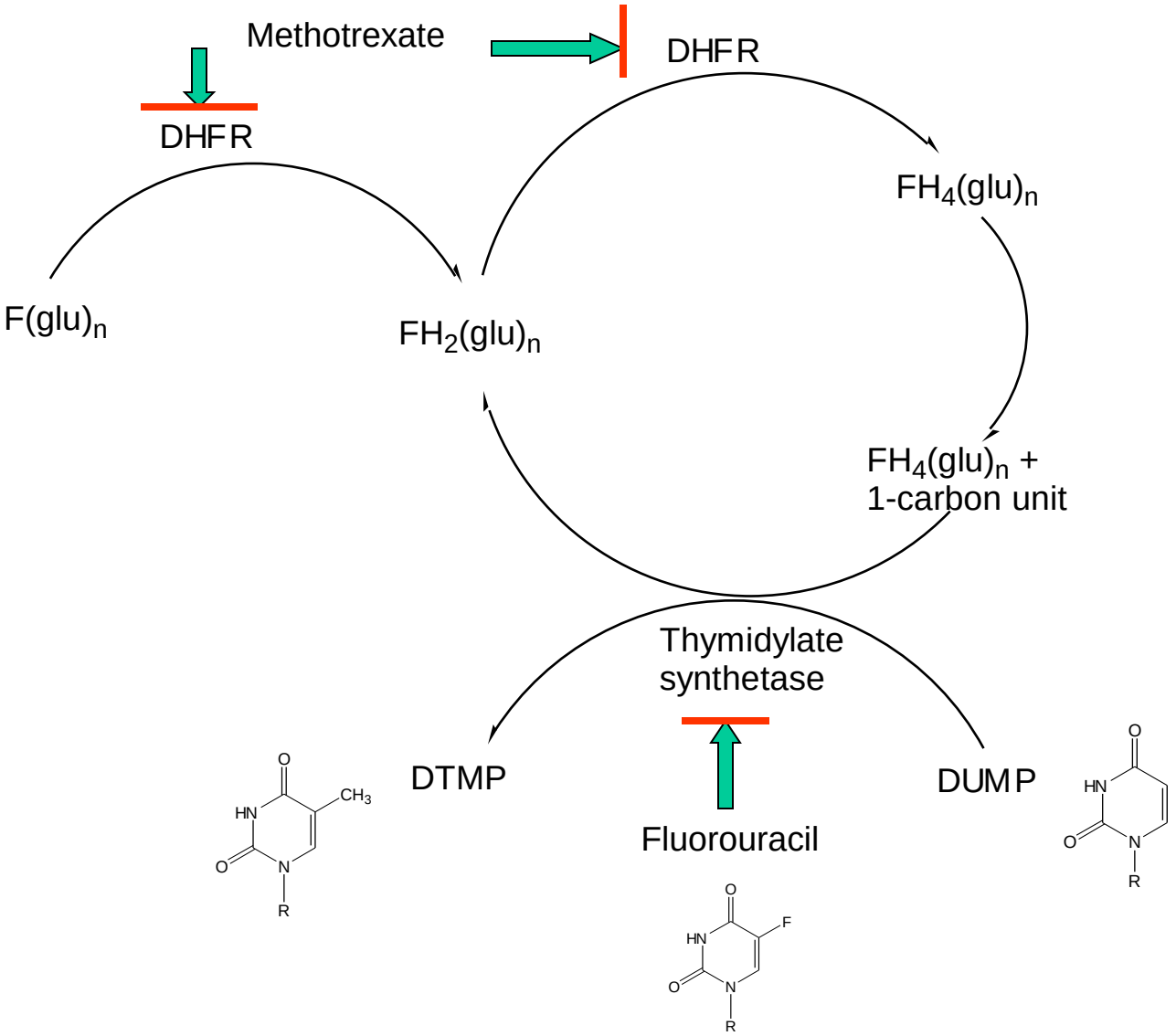
Antimetabolites

- 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.



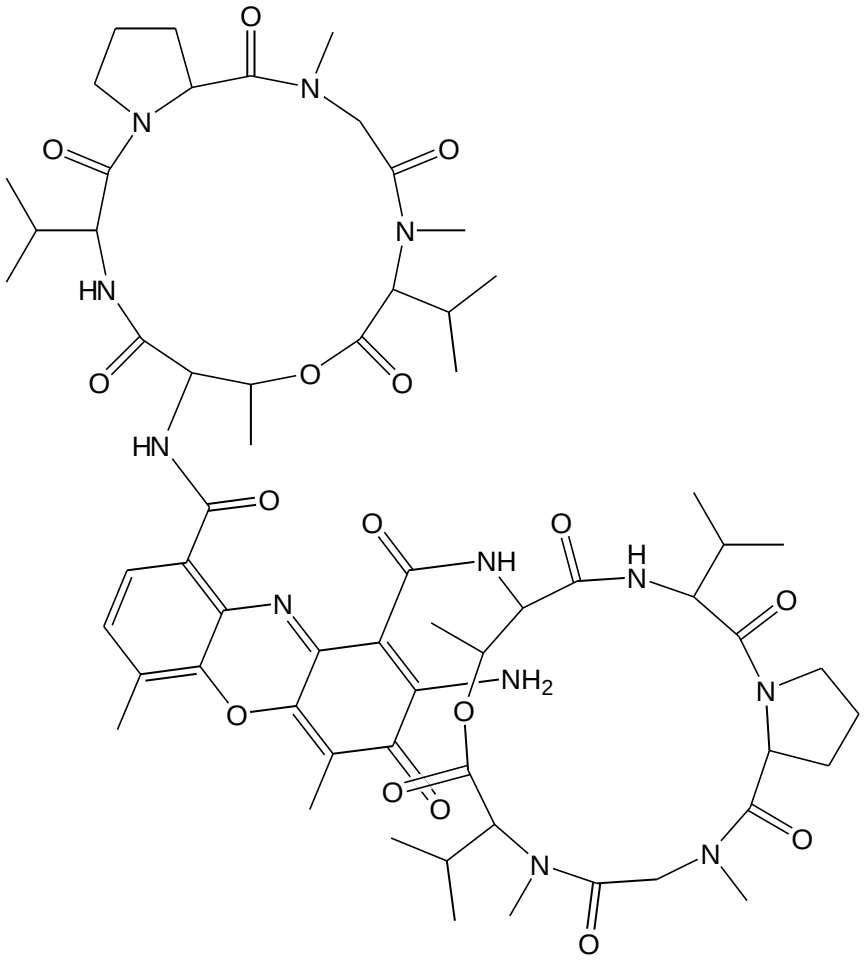


Methotrexate and Fluorouracil



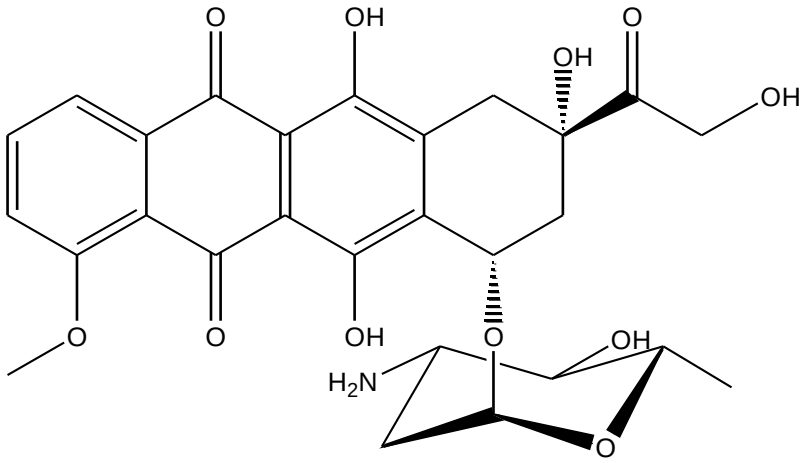
Cytotoxic antibiotics

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



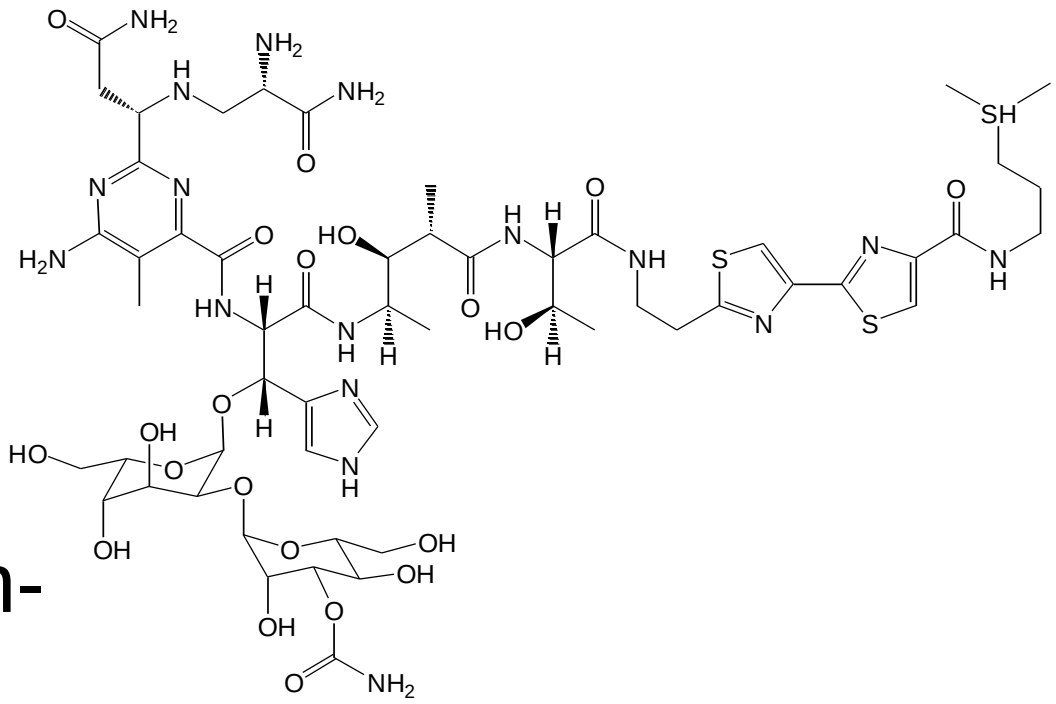
Cytotoxic antibiotics

- Doxorubicin inhibits DNA and RNA synthesis.



Cytotoxic antibiotics

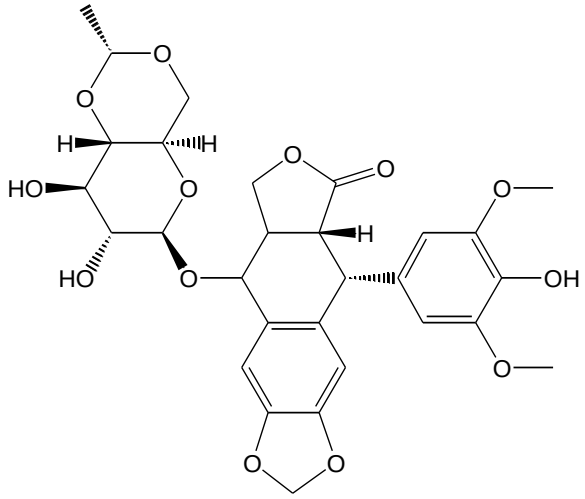
- Bleomycins are metal-chelating glycopeptide antibiotics that degrade DNA.
- Bleomycins are active against non-dividing cells. Administed iv.



Plant alkaloids

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

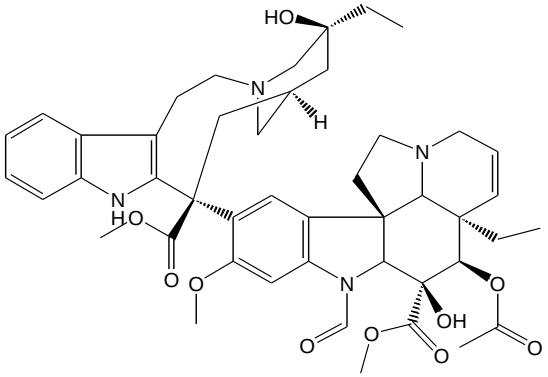
Podophyllum peltatum
May Apple, American Mandrake



Plant alkaloids

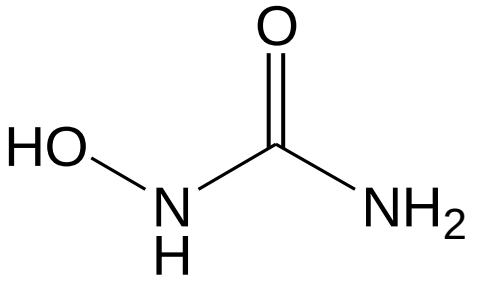
- The vinca alkaloids e.g. vincristine, act by binding to tubulin and inhibiting polymerisation into microtubules.
- This prevents spindle formation.

Vinca minor
Periwinkle

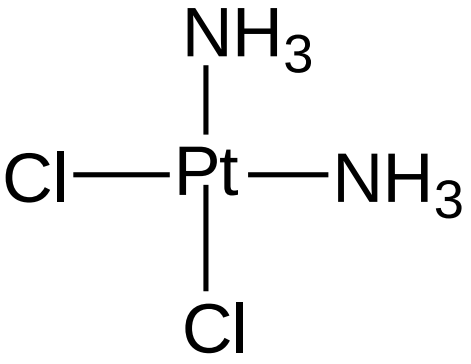


Miscellaneous agents

- Hydroxyurea inhibits ribonucleotide reductase.

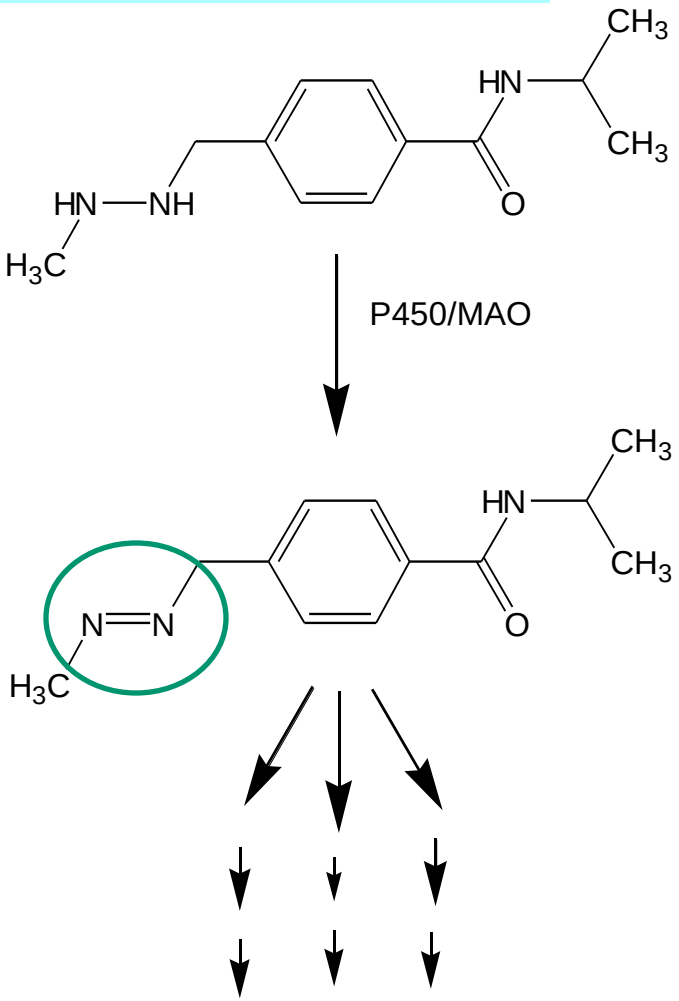


- Cisplatin interacts with DNA causing guanine intrastrand cross-links.



Miscellaneous agents

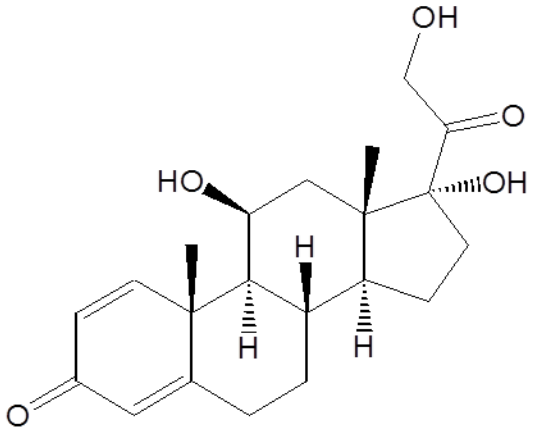
- Procarbazine inhibits DNA and RNA synthesis and interferes with mitosis at interphase.
- Metabolically activated by cytochrome P450 and monoamine oxidase to alkylate DNA (N7 and O6 of guanine).



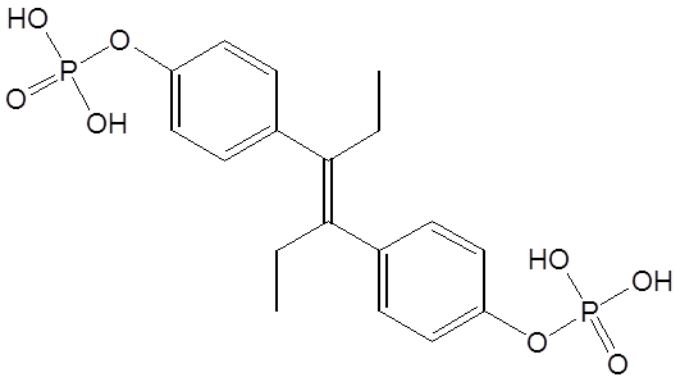
Multiple metabolites including alkylating agents, probably carbonium ions

Hormones

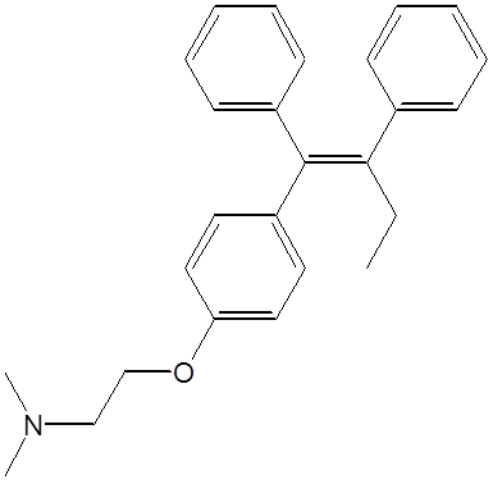
- Used for chemotherapy but are not technically cytotoxic.
- Can inhibit tumours in hormone-sensitive tissues.
- Gonadotrophin-releasing hormone analogues
  - e.g. Goserelin



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 selectivly affect lymphocytes, which drive the immune response.
- Azathioprine, methotrexate and cyclophosphamide are the principle agents used for immunosuppression.

Cytotoxic agents

Azothioprin

Purine synthesis

Pyrimidine synthesis

Methotrexate

Ribonucleotides

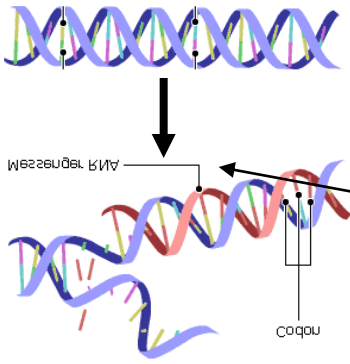
Fluorouracil

Hydroxyurea

Deoxyribonucleotides

Bleomycin

Alkylating agents
Cyclophosphamide
Nitrogen mustards
Cisplatin



Doxorubicin

Actinomycin D

Procarbazine

Etoposide

Proteins

Vinca alkoloids

Enzymes

Microtubules

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.