ANTINEOPLASTIC AGENTS

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- Classification of antineoplastic agents
- Mechanism of action
- Resistance to antineoplastic agents
- Some treatment protocols

Classification of Antineoplastic agents

I. Cytotoxic drugs (directly act on cells)

   a) Alkylating agents

      i. Nitrogen mustards

      ii. Ethyleneimine

      iii. Alkyl sulfonate

      iv. Nitrosoureas

      v. Triazine

b) Antimetabolites (act on metabolic pathway involved in DNA synthesis)

i. Folate antagonist

ii. Purine antagonist

iii. Pyrimidine antagonist

c) Plant derivatives

i. Vinca alkaloids

ii. Taxanes

iii. Epipodophyllotoxin

d) Antibiotics

II. Hormones (mainly steroids which suppress hormone secretion or antagonize hormone action)

a) Glucocorticoids

b) Estrogen

c) Progestins

d) Antiandrogens

III. Miscellaneous (include Hydroxyurea, Cisplatin, Monoclonal antibodies and L.Asparginase)

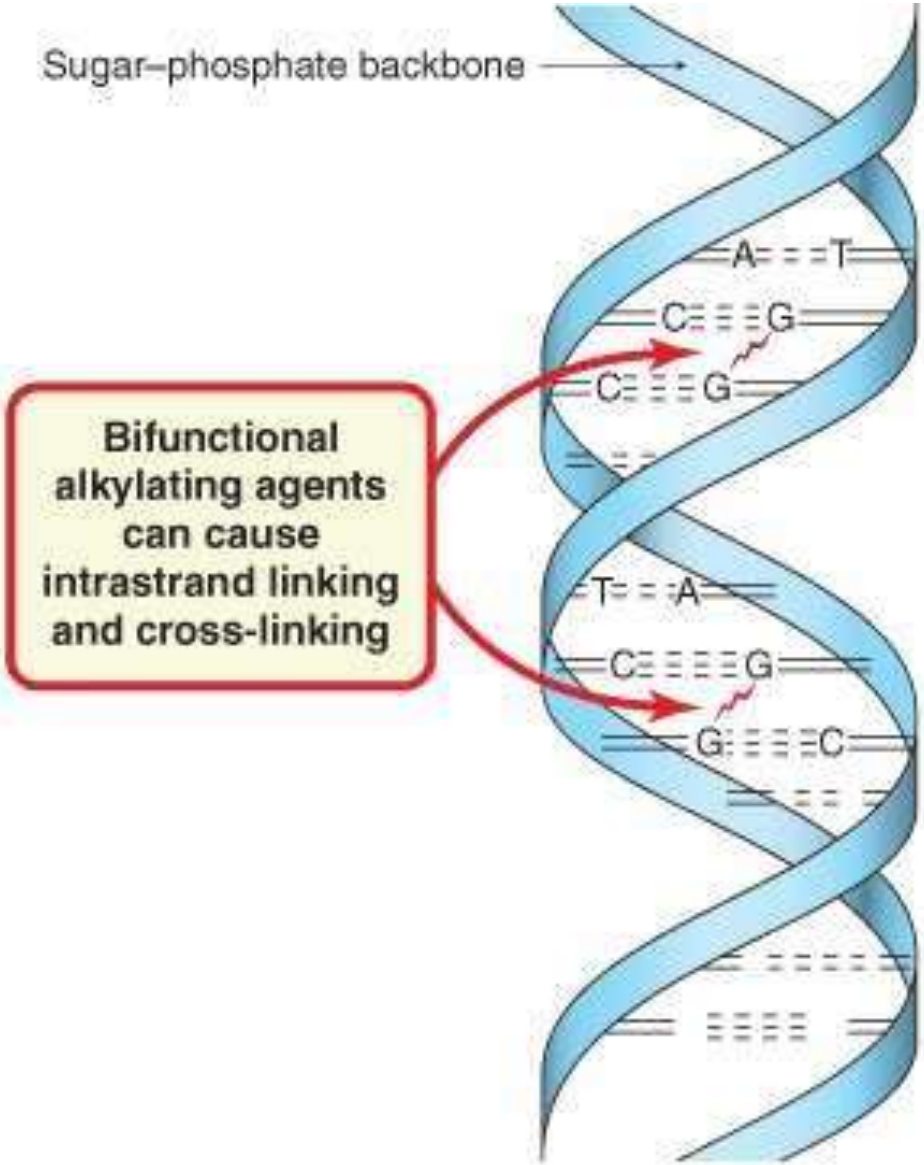
I. CYTOTOXIC DRUGS

a) Alkylating Agents

- Contain chemical groups that can form covalent bonds with particular nucleophilic substances in the cell.
- Produce highly reactive carbonium ion intermediates.
- Forms covalent bond with electron donors like amine, hydroxyl and sulfhydryl groups.
- Alkylating agents are *bifunctional*, i.e. they have two alkylating groups .

- The nitrogen at position 7 (N_7) of guanine, being strongly nucleophilic, is probably the main molecular target for alkylation in DNA.
- N_1 and N_3 of adenine and N_3 of cytosine may also be affected.
- Being bifunctional they can cause intra- or interchain cross-linking, abnormal base pairing or chain scission.
- Interferes not only with transcription but also with replication.

- Main impact is seen during replication (S phase) when some zones of the DNA are unpaired and more susceptible to alkylation.
- Results in a block at G_2 and subsequent apoptotic cell death.



Types of Alkylating agents

Category	Drugs
Nitrogen mustards	Cyclophosphamide , Meclorethamine, Chlorambucil
Ethyleneimine	Thiotepa
Alkyl sulfonate	Busulfan
Nitrosoureas	Carmustine, Lomustine
Triazine	Dacarbazine

Mechanism of activation: Cyclophosphamide

Inactive Cyclophosphamide

Metabolised in the liver by P450 mixed function oxidases

4-hydroxycyclophos-phamide

(Reversibly) forms aldophosphamide.

Aldophosphamide is conveyed to other tissues

Converted to phosphoramide mustard, the actual cytotoxic molecule

b. ANTIMETABOLITES

i. ***Folate Antagonist:*** Methotrexate

- Folates are essential for the synthesis of purine nucleotides and thymidylate which in turn are essential for DNA synthesis and cell division.
- The main action of the folate antagonists is to interfere with thymidylate synthesis.

MOA: Methotrexate

Dihydrofolate reductase

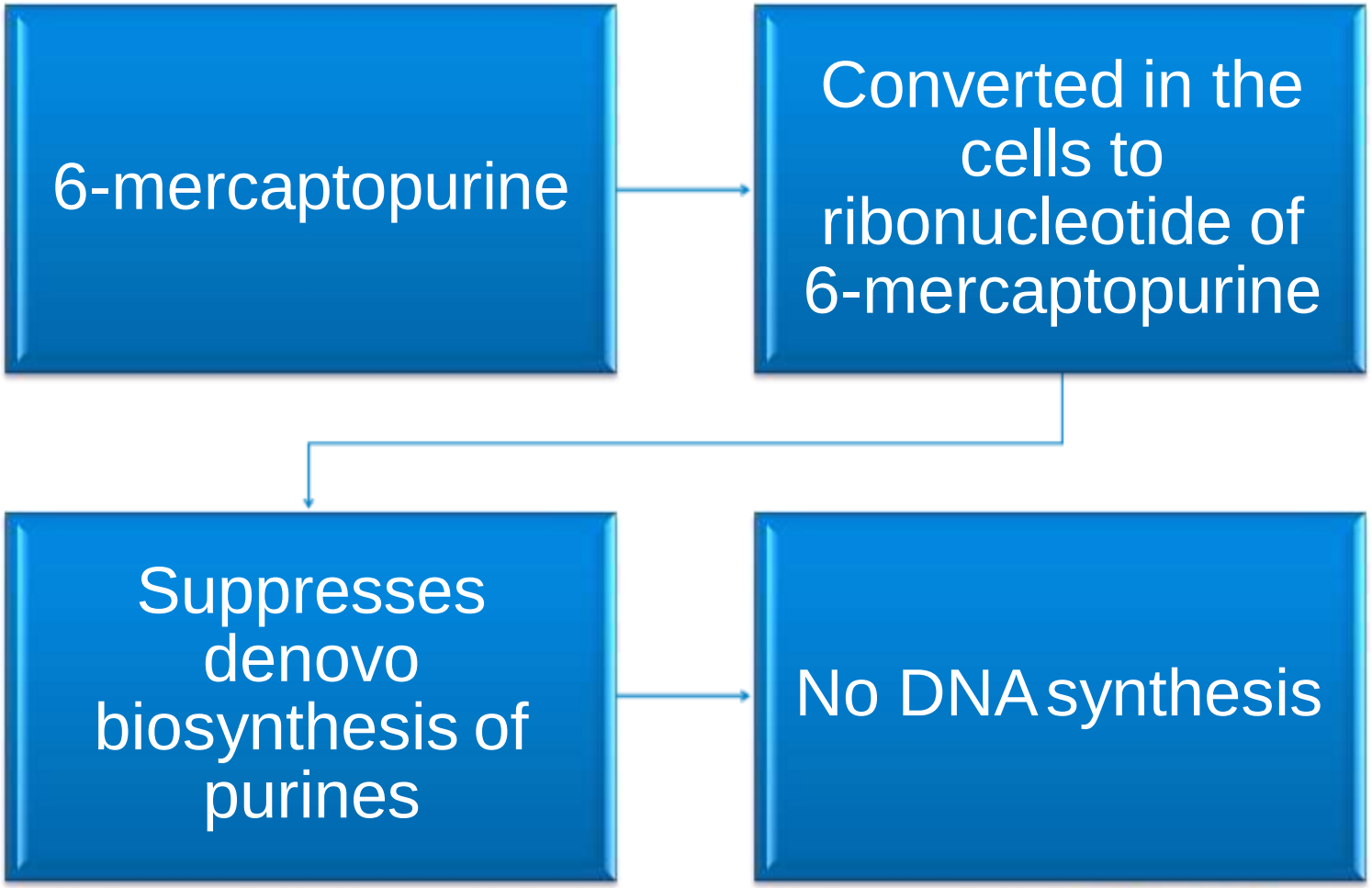
Folate

Dihydrofolate (FH_2)

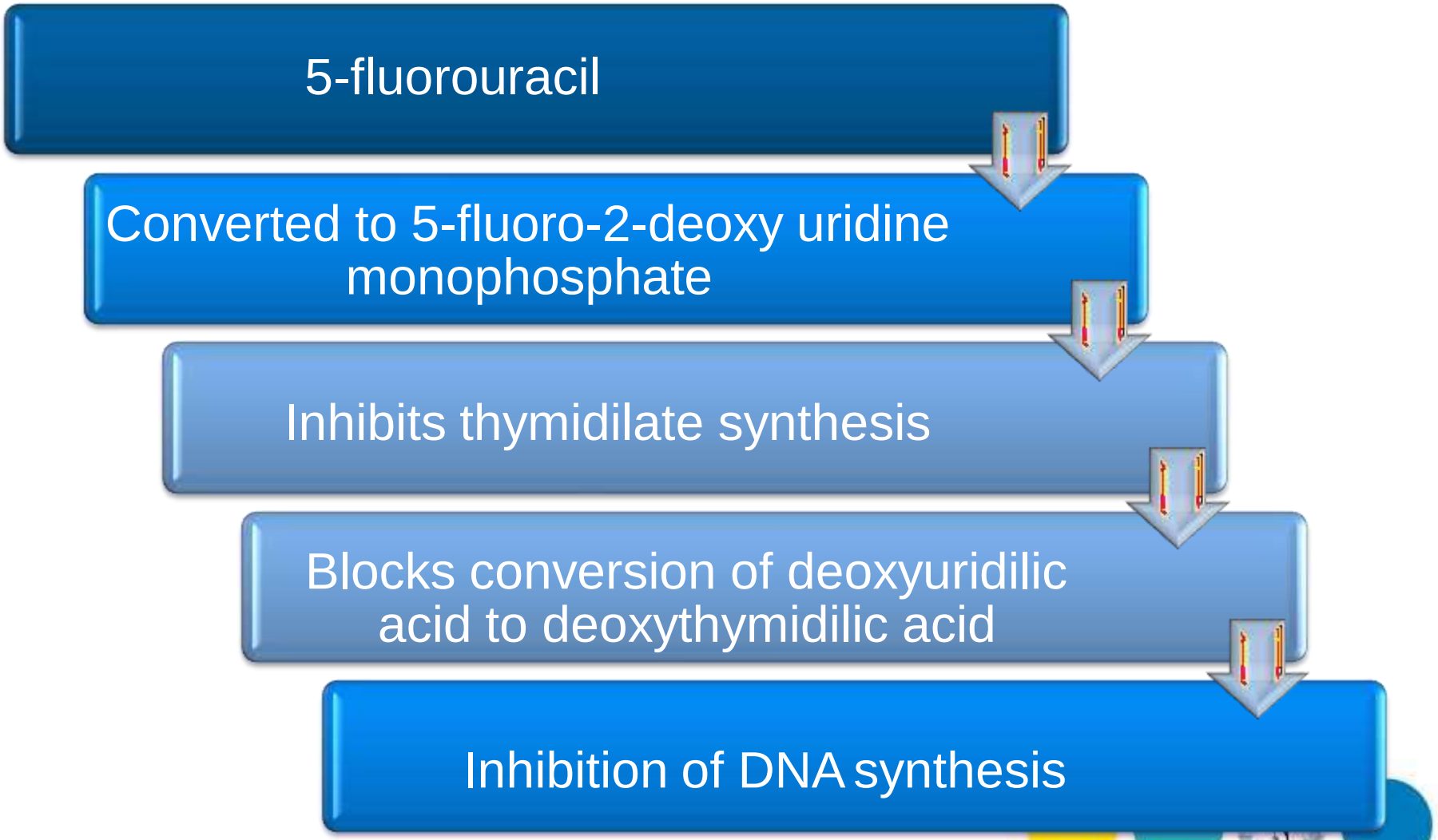
Tetrahydrofolate (FH_4)

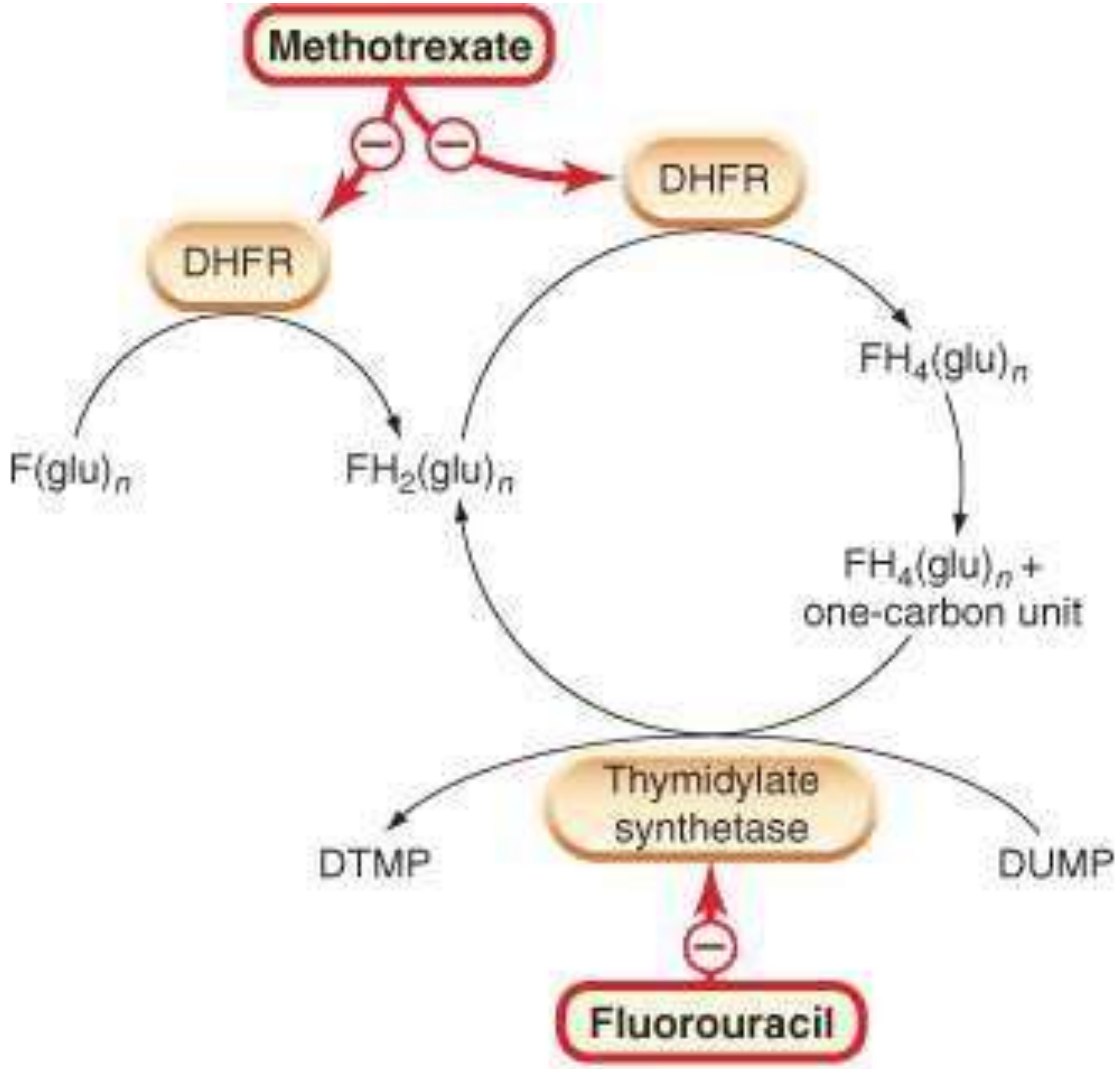
- FH_4 functions as an essential cofactor carrying the methyl groups necessary for the transformation of 2´-deoxyuridylate (DUMP) to the 2´-deoxythymidylate (DTMP) required for the synthesis of DNA and purines.
- During the formation of DTMP from DUMP, FH_4 is converted back to FH_2, enabling the cycle to repeat.
- Methotrexate has a higher affinity than FH_2 for dihydrofolate reductase.Thus inhibits the enzyme, depleting intracellular FH_4.

ii. ***Purine antagonist***: 6-mercaptopurine



iii. ***Pyrimidine Antagonist:*** 5-Fluorouracil (Analogue of uracil)





c) PLANT DERIVATIVES

i. Vinca Alkaloids

- ***Vincristine, vinblastine*** and ***vindesine***: Main vinca alkaloids used in cancer chemotherapy.
- Obtained from the plant Vinca rosea.
- Inhibit mitosis.
- Bind to tubulin and inhibit its polymerisation into microtubules, preventing spindle formation in dividing cells and causing arrest at metaphase.
- Cell cycle specific and phase specific.

ii. ***Taxanes*****:** Paclitaxel

- Obtained from western yew tree.
- Reversibly binds to tubulin and results in the formation of stable non-functioning microtubule by promoting polymerization and stabilization of the microtubules.
- Thus, interferes with mitosis causing cell death.

iii. ***Epipodophyllotoxins:*** Etoposide

- Semi-synthetic derivative of podophyllotoxin obtained from *Podophyllum peltatum*.
- Inhibits enzyme topoisomerase II, leading to DNA damage.
- Blocks the cell in S-G_2 phase of cell cycle.

d) ANTIBIOTICS

i. **MOA**: *Dactinomycin*

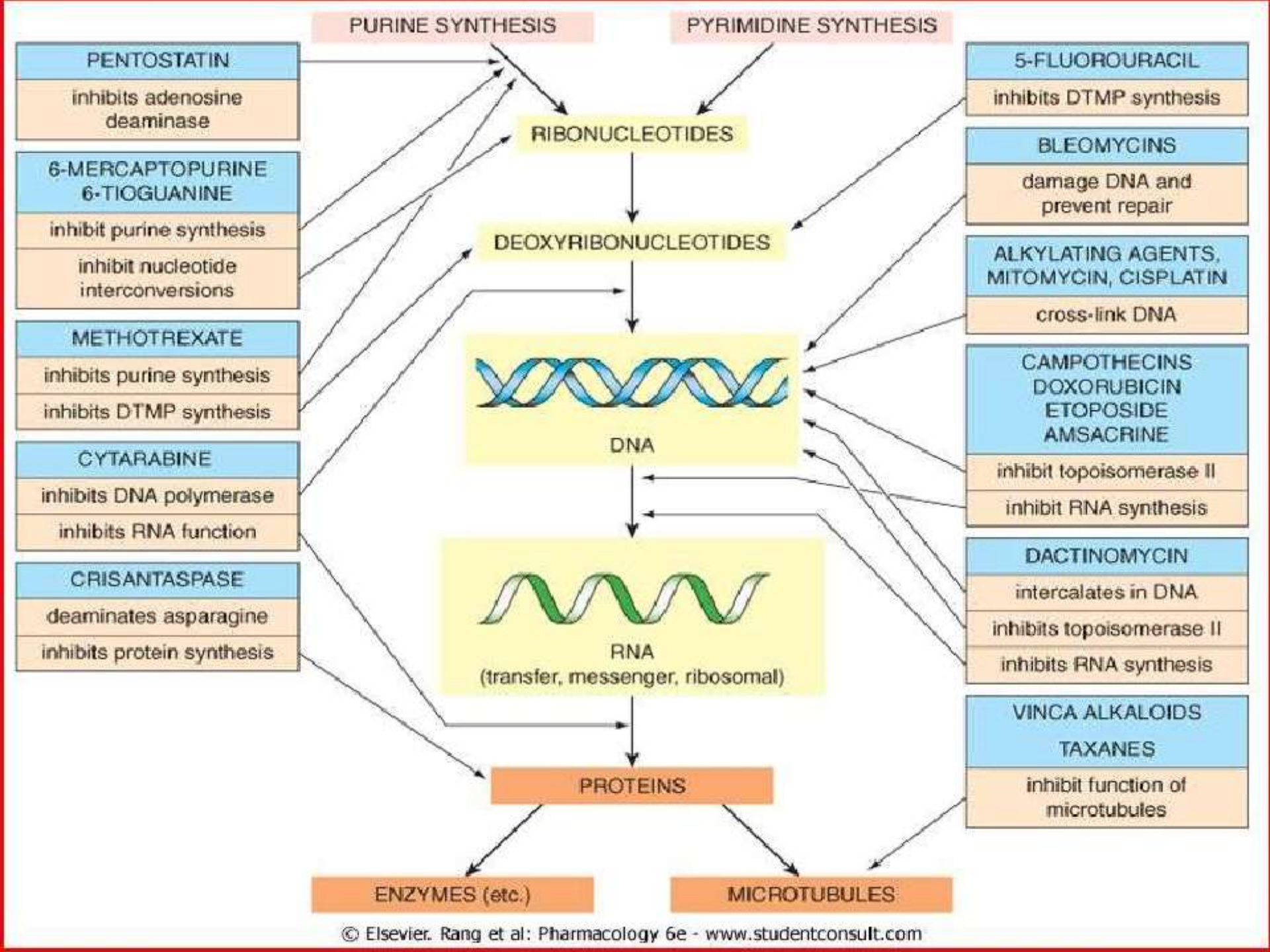
- Intercalates into the minor grooves of double helix between G-C base pairs of DNA ad interferes with the movement of RNA polymerase along the gene preventing transcription.
- May also cause strand breaks and stabilise DNA topoisomerase II complex.

ii. **MOA:** *Doxorubicin*

- Bind to DNA and inhibit both DNA and RNA synthesis.
- Produces breaks in DNA strands by activating topoisomerase II and produces semiquinone free radicals.
- Semiquinone radicals reduce molecular oxygen to superoxide ions and H_2O_2 that mediates single strand scission of DNA.

iii. **MOA:** *Bleomycins*

- Group of metal-chelating glycopeptide antibiotics obtained from *Streptomyces verticullus.*
- Produces chelation of copper or iron ions which produces superoxide ions that interacts with DNA.
- Degrade preformed DNA, causing chain fragmentation and release of free bases.



II. HORMONES

a) Glucocorticoids

- Glucocorticoids such as **prednisolone** and **dexamethasone** have marked inhibitory effects on lymphocyte proliferation
- Used in the treatment of leukaemias and lymphomas.
- Their ability to lower raised intracranial pressure, and to mitigate some of the side effects of anticancer drugs, makes them useful as supportive therapy .

b) Oestrogens

- Diethylstilbestrol and ethinyloestradiol are two oestrogens used clinically in the palliative treatment of androgen-dependent prostatic tumours.
- The latter compound has fewer side effects. These tumours are also treated with gonadotrophin-releasing hormone analogues
- Oestrogens can be used to recruit resting mammary cancer cells into the proliferating pool of cells, thus facilitating killing by other cytotoxic drugs.

b) Progestins

- Progestins such as **megestrol** and **medroxyprogesterone** have been useful in endometrial neoplasms and in renal tumours to bring temporary remission.

c) Anti-Androgen

- Flutamide: androgen antagonist used in prostate tumors since they increase androgen levels.

III. MISCELLANEOUS DRUGS

a) Hydroxyureas

- Acts by blocking the conversion of ribonucleotide to deoxyribonucleotide by inhibing the enzyme ribonucleoside diphoshate reductase.

b) Cisplatin

Cisplatin enters the cell

Cl^- dissociates leaving a reactive complex that reacts with water

Interacts with DNA

Causes intrastrand cross-linking probably between N_7 and O_6 of adjacent guanine molecules

Results in local denaturation of DNA

c) L-Asparaginase

- Enzyme prepared from *E.coli.*
- Deaminates asparagine to aspartic acid and ammonia, and is active against tumour cells, such as those of acute lymphoblastic leukaemia.

d) Monoclonal Antibodies

- Ex: Rituximab
- Activate the host immune mechanism and kills the cancer cells.
- Used for β-cell lymphoma.

RESISTANCE TO ANTICANCER DRUGS

- *Decreased accumulation of cytotoxic drugs* in cells as a result of the increased expression of cell surface, energy-dependent drug transport proteins.
- *A decrease in the amount of drug taken up by the cell* (e.g. in the case of methotrexate).
- *Insufficient activation of the drug* (e.g. Mercaptopurine, fluorouracil and cytarabine).

- *Increase in inactivation* (e.g. mercaptopurine).
- *Increased concentration of target enzyme* (methotrexate).
- *Decreased requirement for substrate* (L-Asparaginase).
- *Increased utilisation of alternative metabolic pathways* (antimetabolites).
- *Rapid repair of drug-induced lesions* (alkylating agents).

- *Altered activity of target*, for example modified topoisomerase II (doxorubicin).
- *Mutations* in various genes, giving rise to resistant target molecules. (several cytotoxic drugs).

Treatment Protocols

- Combination is more effective than monotherapy without increasing toxicity.
- Also decreases possibility of development of resistance.
- Higher responsive rates due to both additive cytotoxic effects and non-overlapping host toxicities.

Some combination regimens:

- **POPM:** Methotrexate + Oncovin (vincristine) + Prednisone + Purinethol (mercaptopurine) in lymphocytic leukaemia
- **VAMP:** Vincristine + Amethopterine (methotrexate) + 6-mercaptopurine + Prednisolone in acute leukaemia