Anticancer Agents

Antibiotics

Classification of Antibiotics:

- Anthracycline
- Mitomycin C
- Bleomycin
- Actinomycin D

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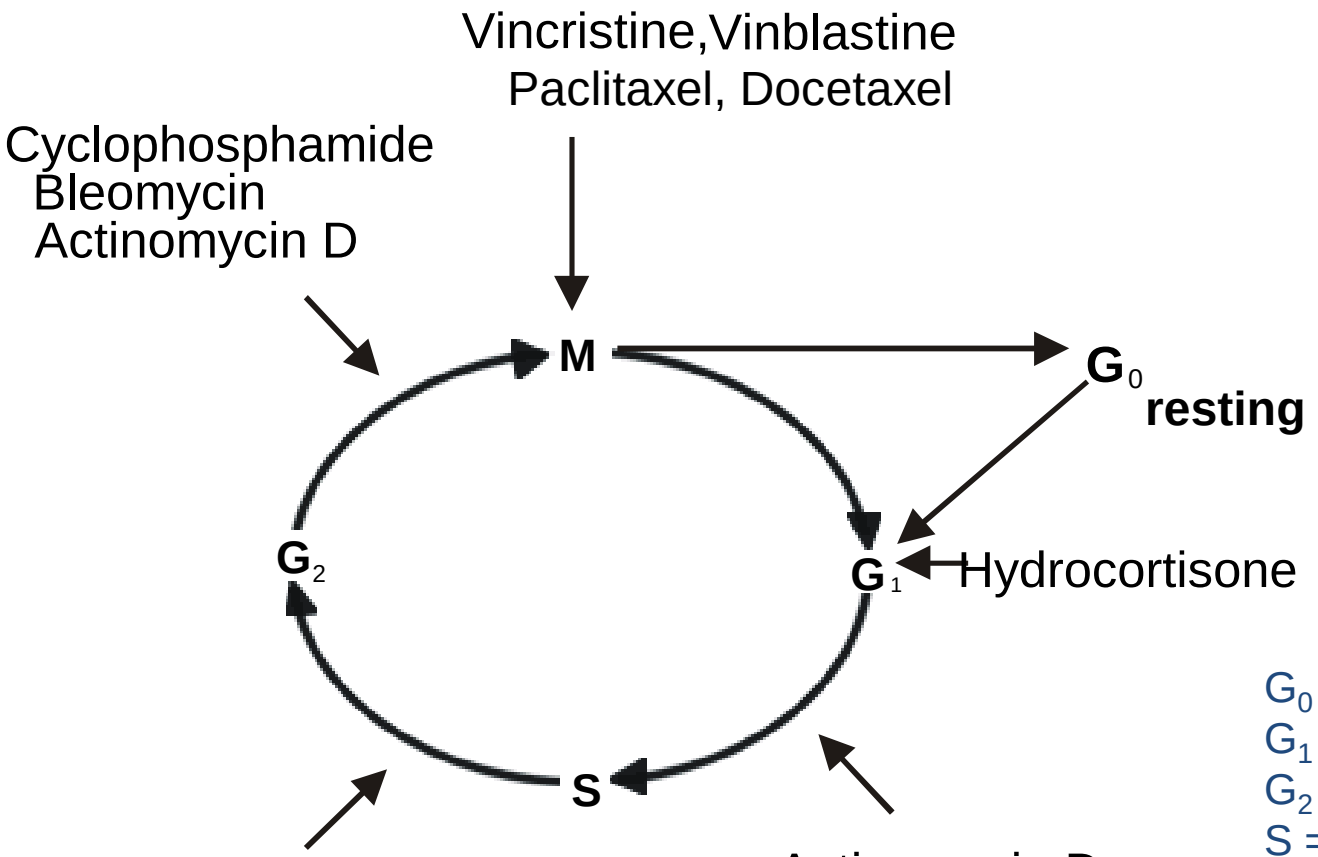
- 91) Which of the following statements is true regarding the cell cycle?
- **Feedback:** The four phases are G1, S, G2 and M. The G1 phase is where a cell is actively growing in size and preparing to copy its DNA in response to various growth factors or internal signals. The next phase is the S phase (Synthesis) where replication of DNA takes place. Once the cell's chromosomes are copied, there is another interval called the G2 phase during which the cell readies itself for cell division. Finally, there is the M phase (Mitosis) where cell division takes place to produce two daughter cells.
- **Page reference:** 491-493
- a. It is the life time of the cell
- *b. It is the various stages that the cell goes through leading up to and including cell division
- c. The cell cycle involves four stages labelled G1 S, G2 and D
- d. The cell cycle includes 3 growth stages
-

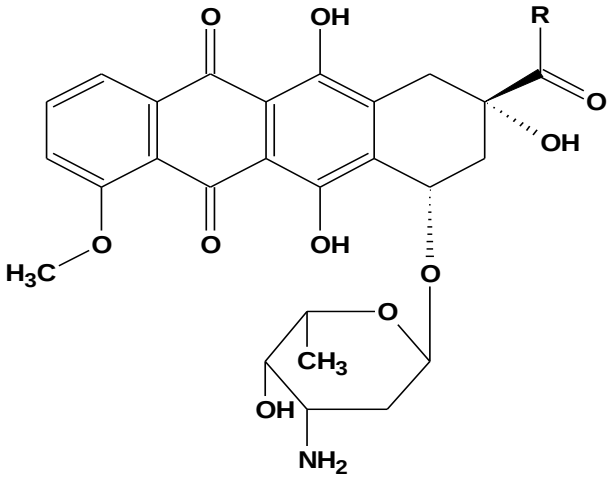
Cell cycle specificity of Anti-Neoplastic Agents



G_0 = resting phase
G_1 = pre-replicative phase
G_2 = post-replicative phase
S = DNA synthesis
M = mitosis or cell division

Antibiotics

a- Anthracyclines



Doxorubicin: R= CH_2OH

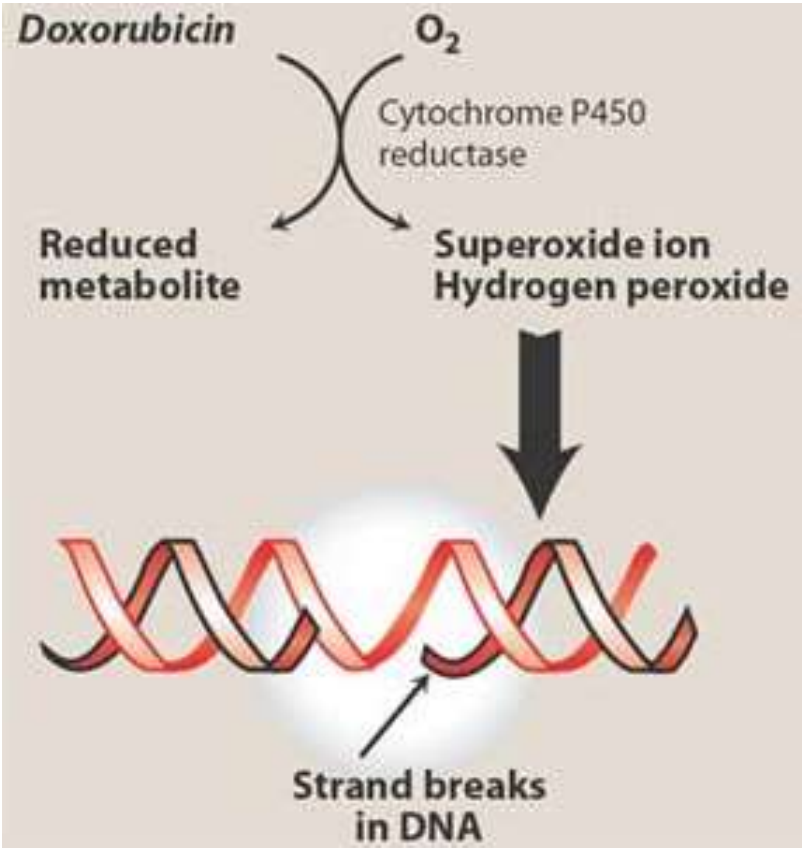
Daunorubicin: R=CH_3

Doxorubicin and Daunorubicin:

Properties:

- Anthracyclines are tetracycline rings with the sugar daunosamine. They are DNA intercalating agents that block the synthesis of DNA and RNA.
- These agents are primarily toxic during the S phase of cell cycle.
- Doxorubicin is probably the most important anticancer drug available because of its relatively broad spectrum of activity.

Doxorubicin & Daunorubicin



They:

- 1. intercalate between base pairs,
- 2. inhibit topoisomerase II
- 3. generate free radicals

- They block RNA and DNA synthesis and cause strand scission

Antibiotics

b. Mitomycin C:

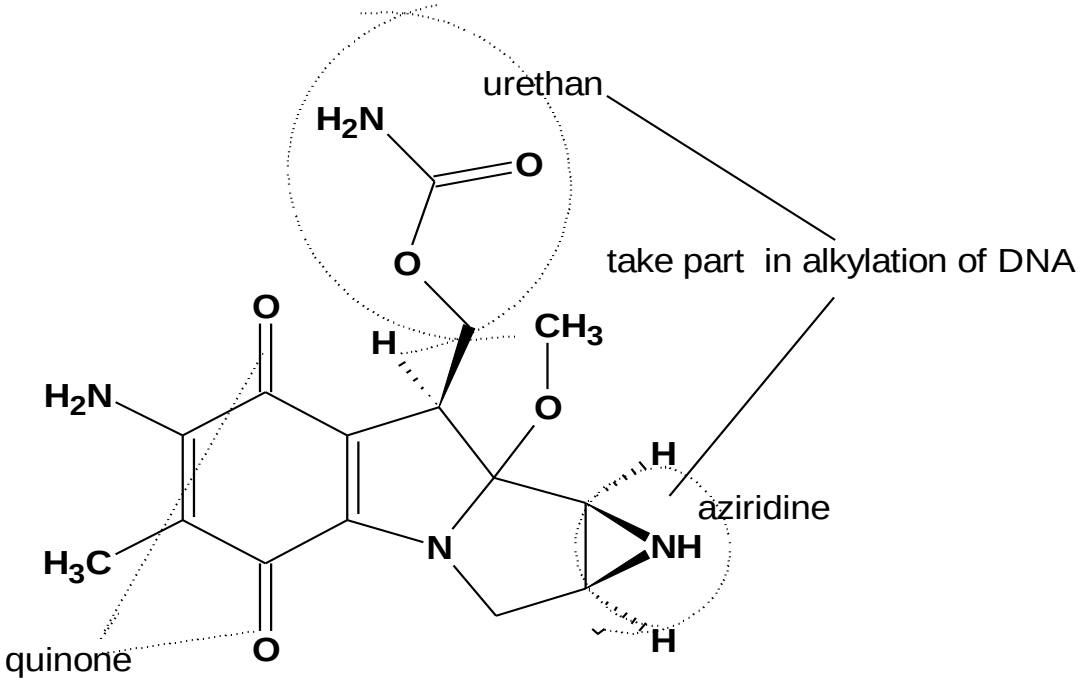
Mechanism:

- Mitomycin C is an antineoplastic antibiotic that alkylates DNA and thereby causes strand breakage and inhibition of DNA synthesis.

Adverse Effects:

- Mitomycin produces delays and prolonged myelosuppression that preferentially affects platelets and leukocytes.

b- Mitomycin C



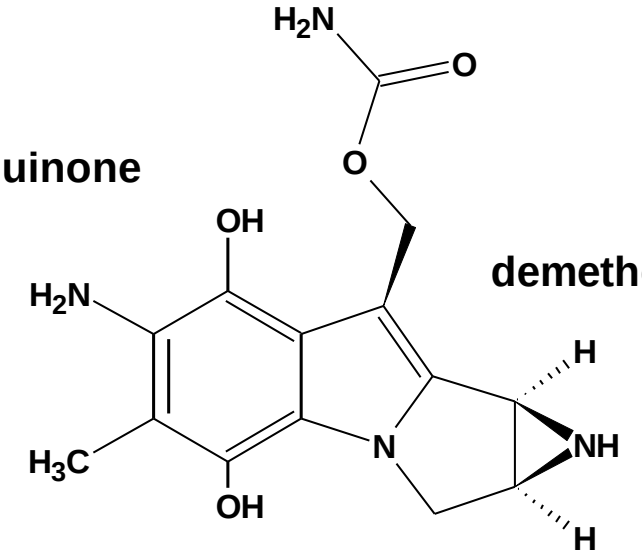
It is a natural product isolated from *Streptomyces verticillataus* as well as from other sources.

b- Mitomycin C

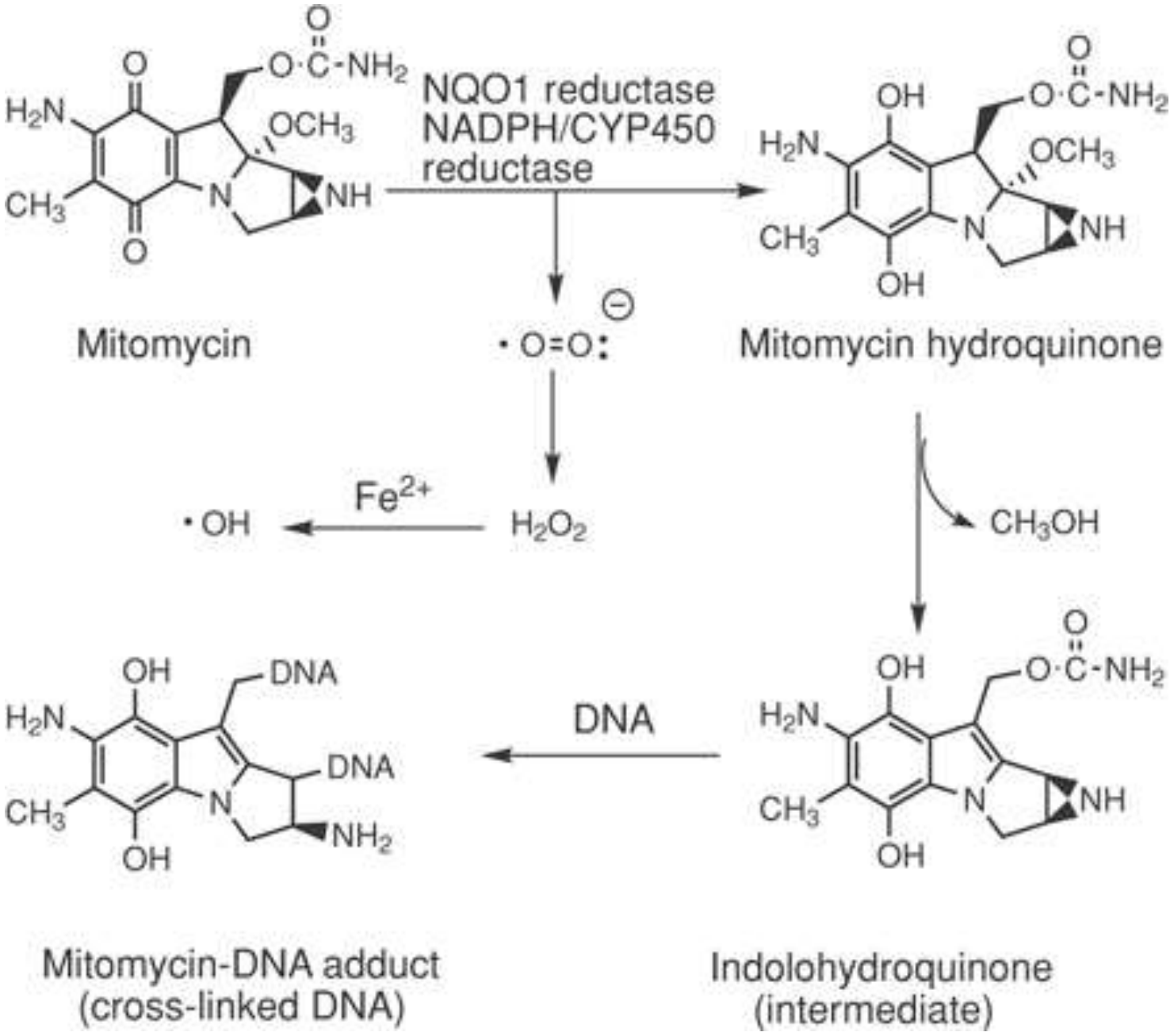
It is activated *in vivo* to bifunctional or trifunctional DNA alkylating agent, leading to cross-linking of DNA, thus inhibiting DNA synthesis and function.

reduction of quinone

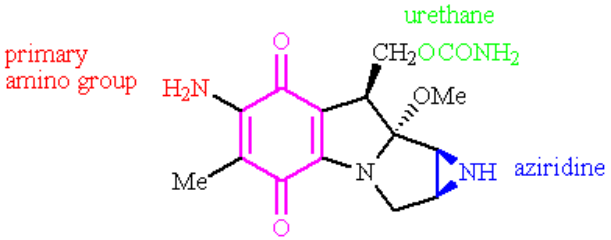
demethoxylation



Bioactive form of mitomycin C


NQO1 reductase
NADPH/CYP450
reductase
Mitomycin
Mitomycin hydroquinone
Fe^{2+}
H_2O_2
CH_3OH
DNA
Mitomycin-DNA adduct
(cross-linked DNA)
Indolohydroquinone
(intermediate)

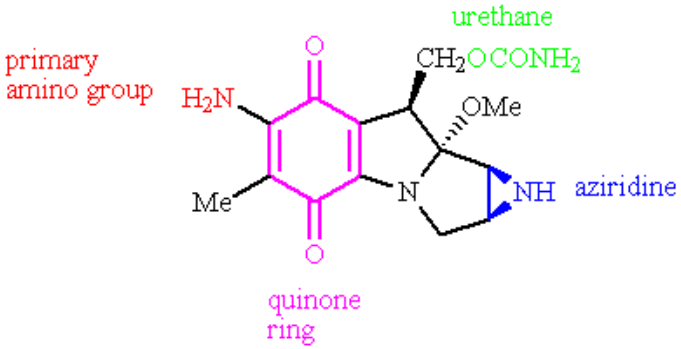
58) The following agent is called mitomycin C and is used as an anticancer drug against a variety of cancers.



The structure is a prodrug which is converted in the body to the active compound. What is the initial step in this activation process?
Feedback: Reduction of the quinone ring system generates a diphenol which then results in ring opening of the aziridine ring. Hydrolysis of the urethane group takes place subsequent to that. The primary amino group is not alkylated at all during the process. The drug is acting as an alkylating agent and so it an amino group on DNA that gets alkylated.
Page reference: 511-512
a. Ring opening of the aziridine ring
b. Hydrolysis of the urethane group
c. Alkylation of the primary amino group
*d. Reduction of the quinone ring system

Title: Chapter 18a Question 59

59) The following agent is called mitomycin C and is used as an anticancer drug against a variety of cancers:



Which of the following statements is true regarding the above drug?

Feedback: Mitomycin is one of the most toxic anticancer drugs in clinical use. Interstrand cross linking takes place and not intrastrand cross linking. Guanine units are alkylated by the agent and not adenine units.

Page reference: 511

a. It is one of the safest anticancer agents used in clinical practice.

b. It promotes intrastrand cross linking in DNA.

c. Adenine units are alkylated by the agent.

*d. It is possible that the drug may be more effective against tumours in oxygen starved environments.

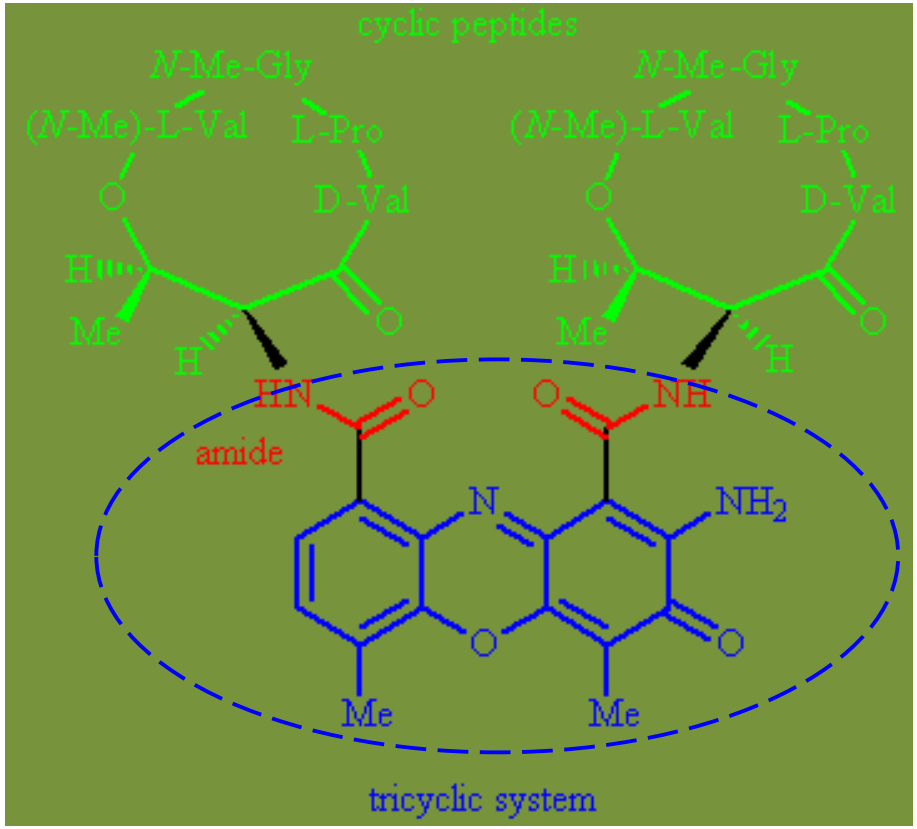
Antibiotics

c. Actinomycin D:

- Actinomycin D intercalates DNA and thereby prevents DNA transcription and messenger RNA synthesis.
- The drug is given intravenously, and its clinical use is limited to the treatment of trophoblastic (gestational) tumors and the treatment of pediatric tumors.

Actinomycin D

The actinomycins are a class of polypeptide antibiotics isolated from soil bacteria of the genus *Streptomyces*, of which the most significant is actinomycin D



Planar phenoxazinone ring system

Antibiotics

d. Bleomycin:

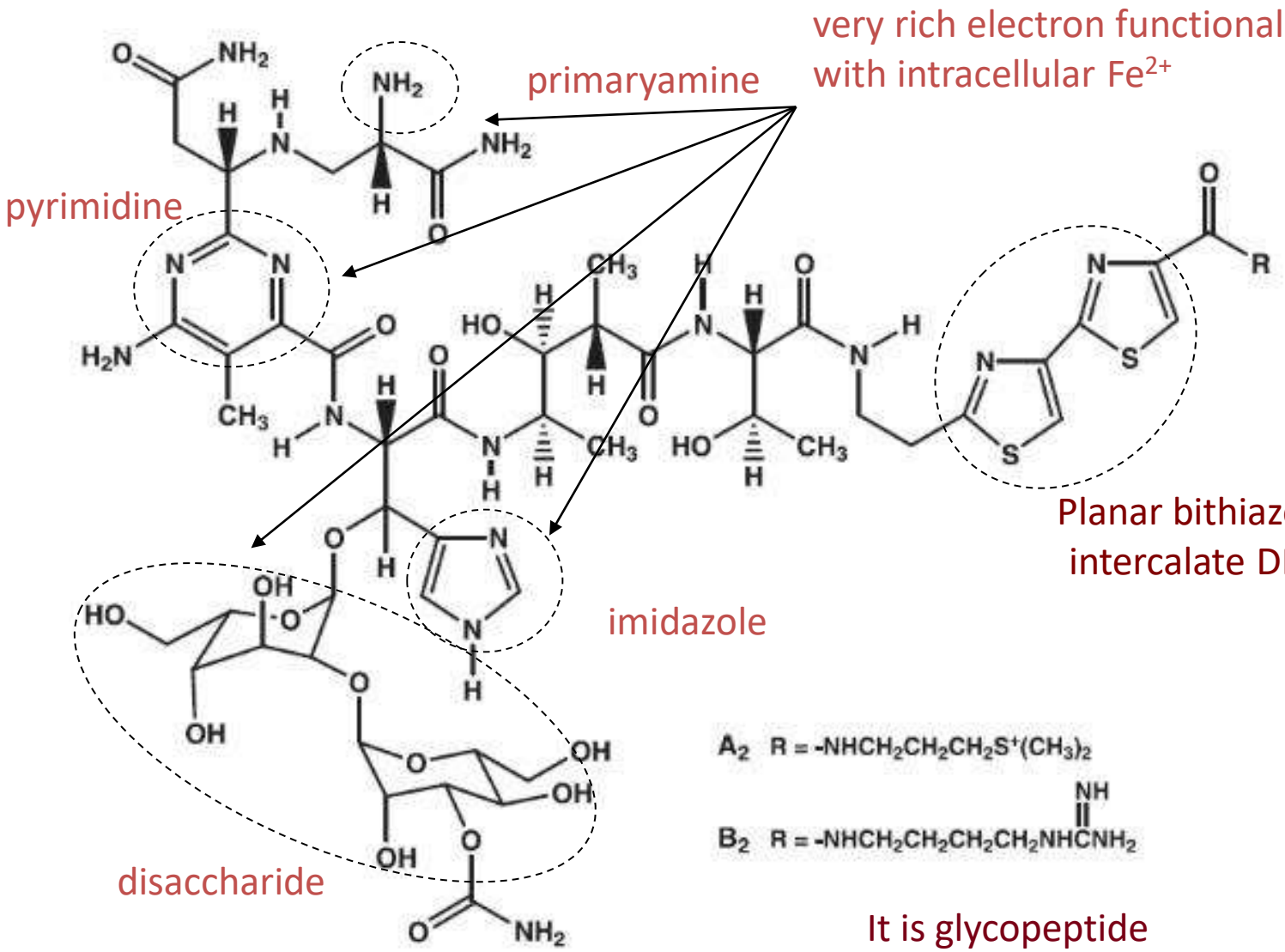
Mechanism:

- The drug has its greatest effect on neoplastic cell in the G2 phase of the cell replication cycle. Although bleomycin intercalates DNA, the major cytotoxicity is believed to result from ironcatalyzed free radical formation and DNA strand breakage.

Adverse Effects:

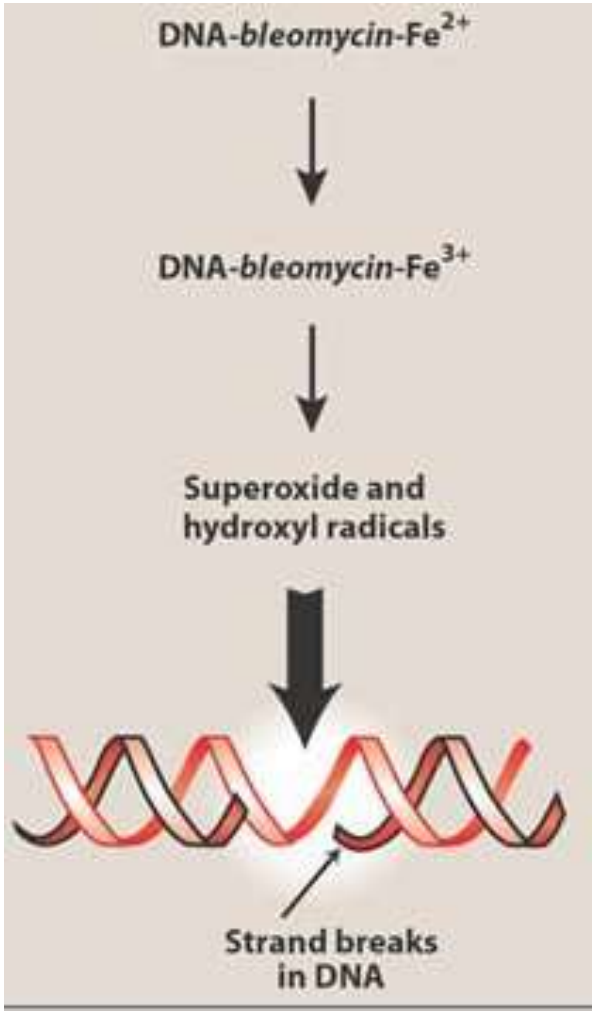
- Bleomycin produces very little myelosuppression. The most serious toxicities of Bleomycin are pulmonary and mucocutaneous reactions.

Bleomycin



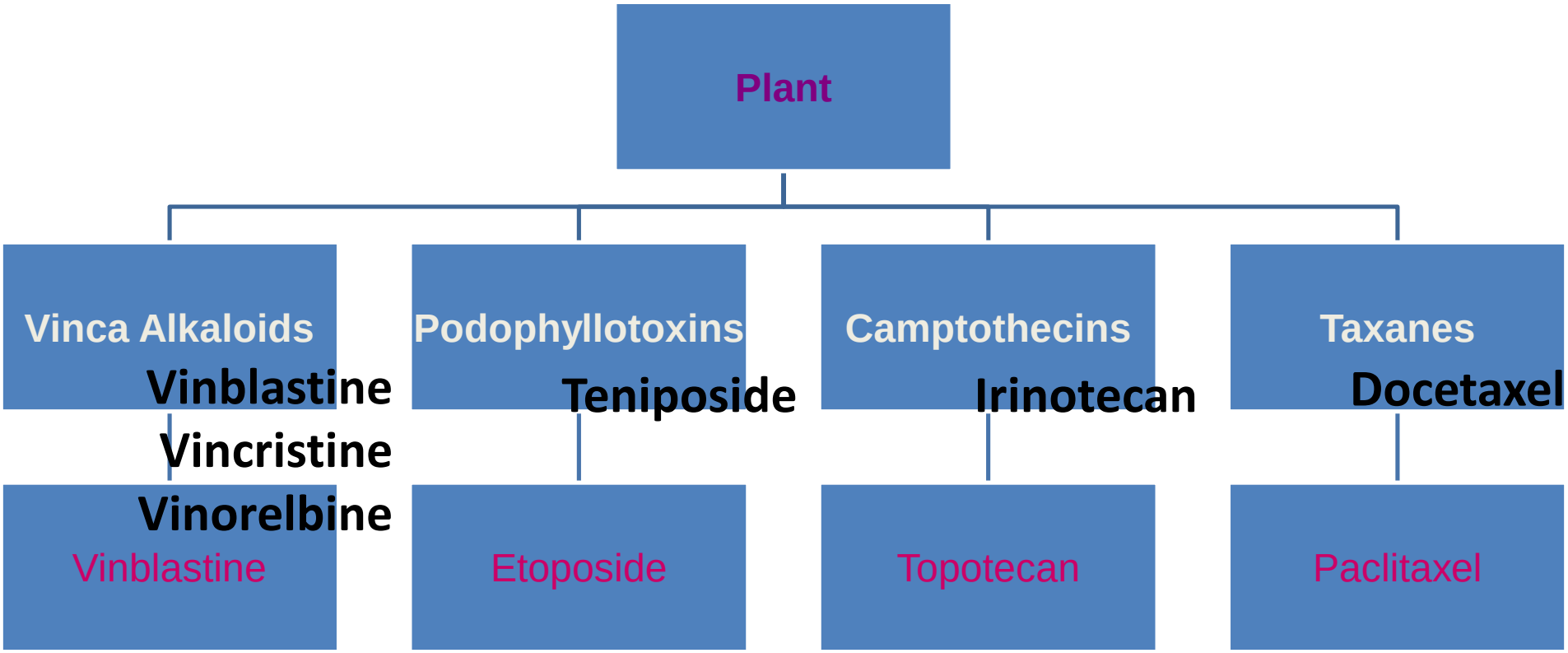
It is glycopeptide

Bleomycin



- Acts through binding to DNA, which results in single and double strand breaks following free radical formation and inhibition of DNA synthesis
- The DNA fragmentation is due to *oxidation of a DNA-bleomycin-Fe(II) complex and leads to chromosomal aberrations*

Part III: Anti-Cancer from Plant

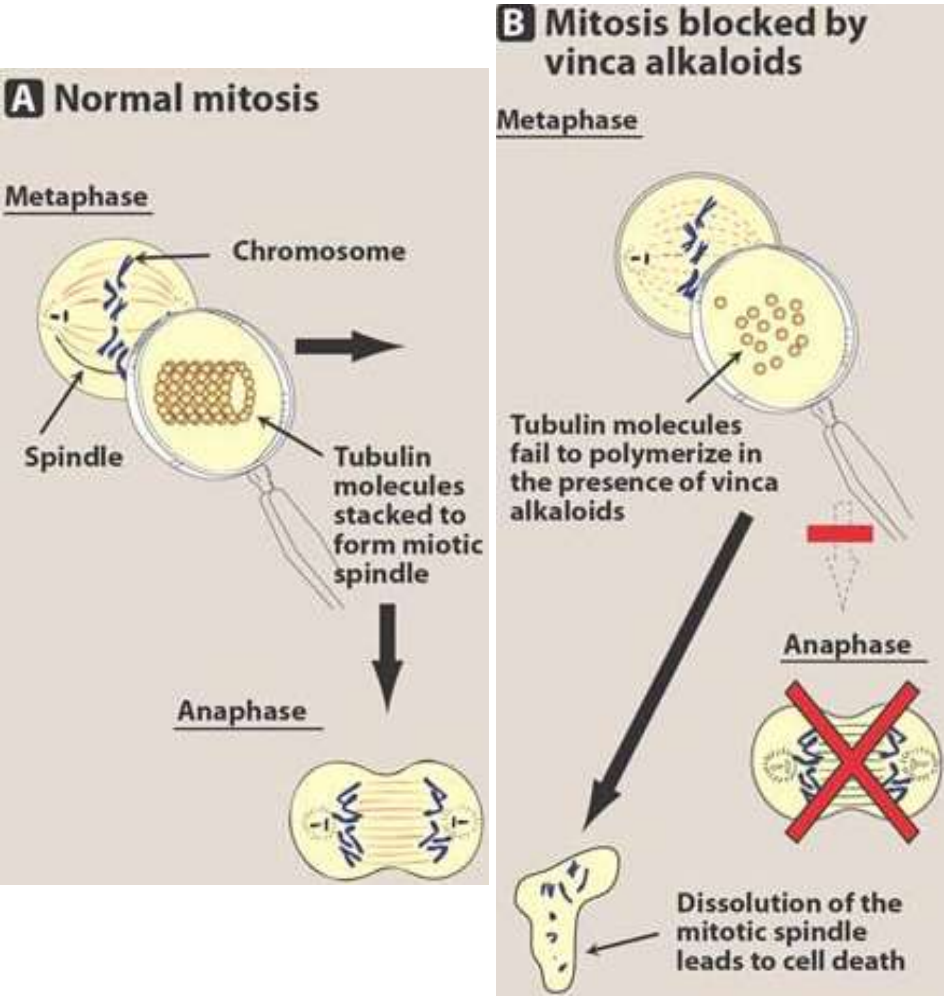


Part III: Anti-Cancer Plant Allaloids

- **Tubulin-Binding Agents**

  Vinca Alkaloids: The cellular mechanism of action of vinca alkaloids is the prevention of microtubule assembly, causing cells to arrest in the late G2 phase by preventing formation of mitotic filaments for nuclear and cell division.

Vinka alkaloids (Vinblastine, vincristine)



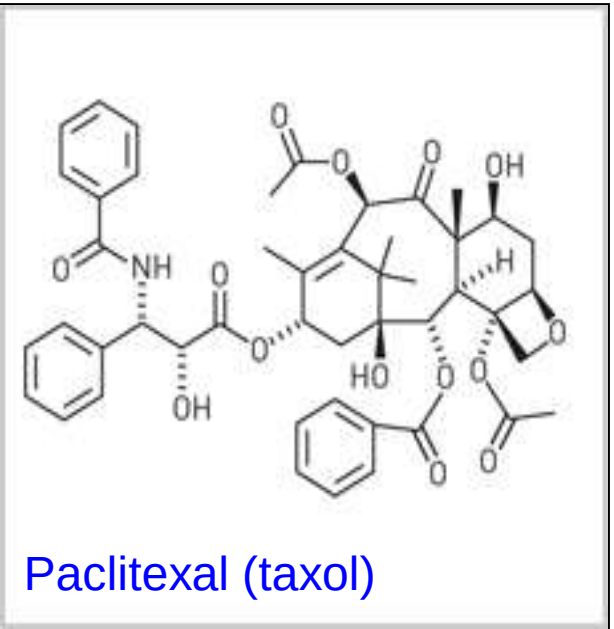
These drugs block the formation of mitotic spindle by preventing the assembly of tubulin dimers into microtubules

***They act primarily on the M phase of cancer cell cycle

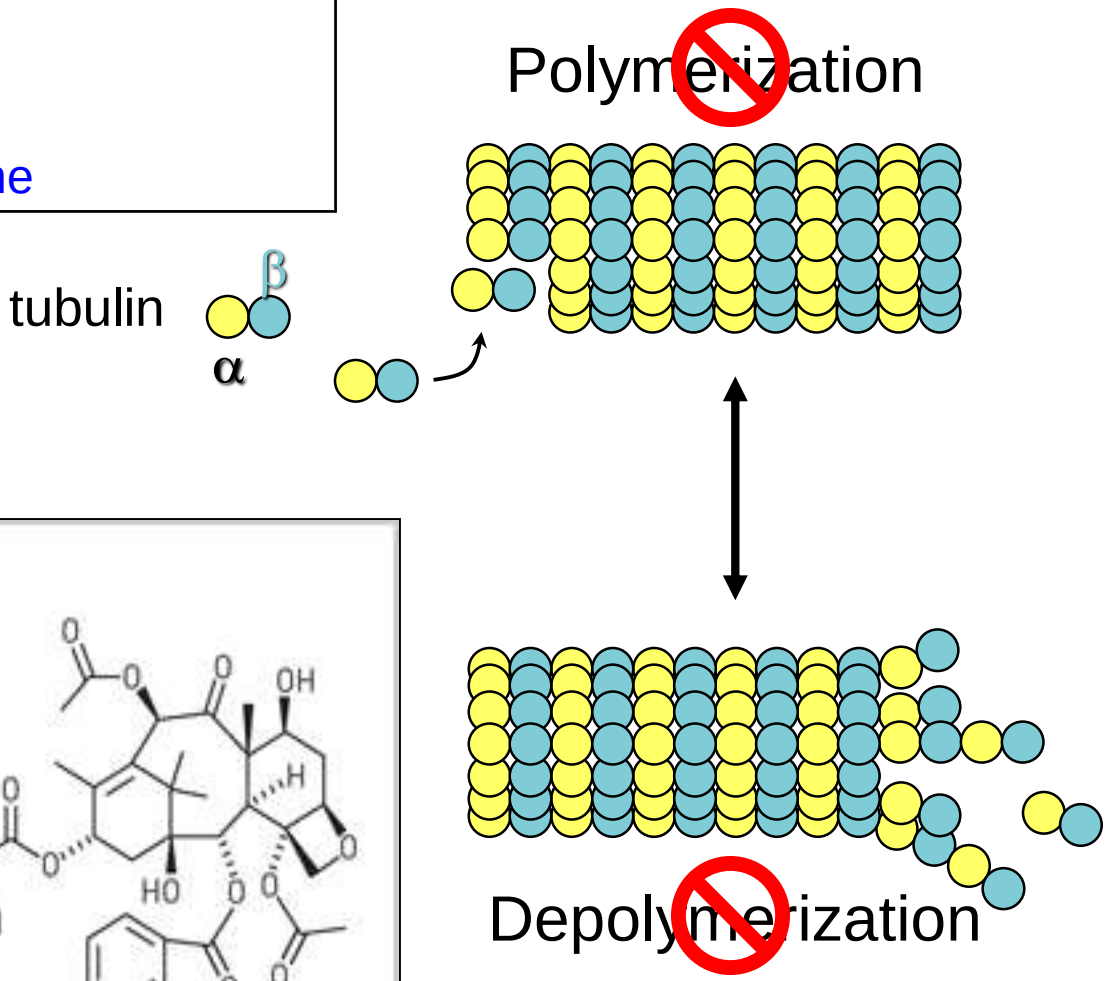
Resistance is due to ⇑d efflux of drugs from tumor cells

Tubulin Binding Agents

Vincristine



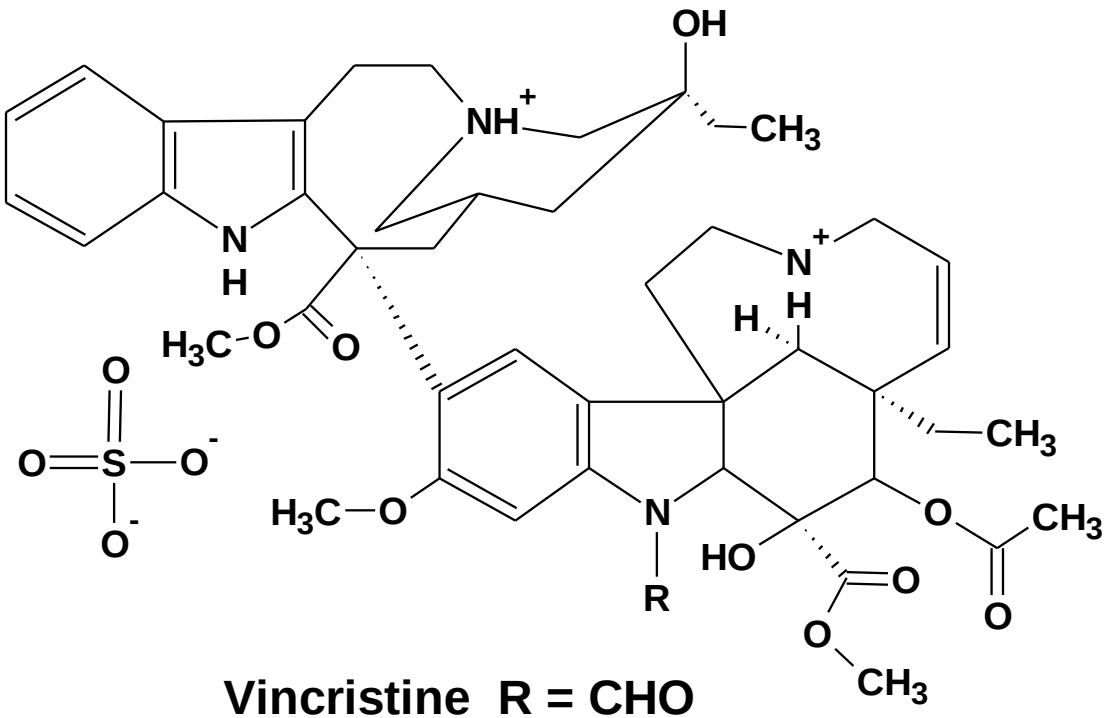
Paclitexal (taxol)



e.g., Vincristine, Vinblastine, Vindesine Vinorelbine: Inhibition of mitotic spindle formation by binding to tubulin.
M-phase of the cell cycle.

e.g., Paclitexal: binds to tubulin, promotes microtubule formation and retards disassembly; results in mitotic arrest.

The alkaloids of the periwinkle plant (*Vinca rosea*)



Vincristine R = CHO

Vinblastine R = CH_3

They are dimeric indole-dihydroindole derivatives

Vincristine sulfate (Oncovin®)

Uses

leukemias, lymphomas, sarcomas, and some carcinomas

Vinblastine sulfate (Velban®)

Vinblastine, the more active compound, has had much wide clinical application, including solid tumors, especially in combination with such drugs as cisplatin and BLM (bleomycin)

testicular tumor
advanced Hodgkin's disease
breast carcinoma

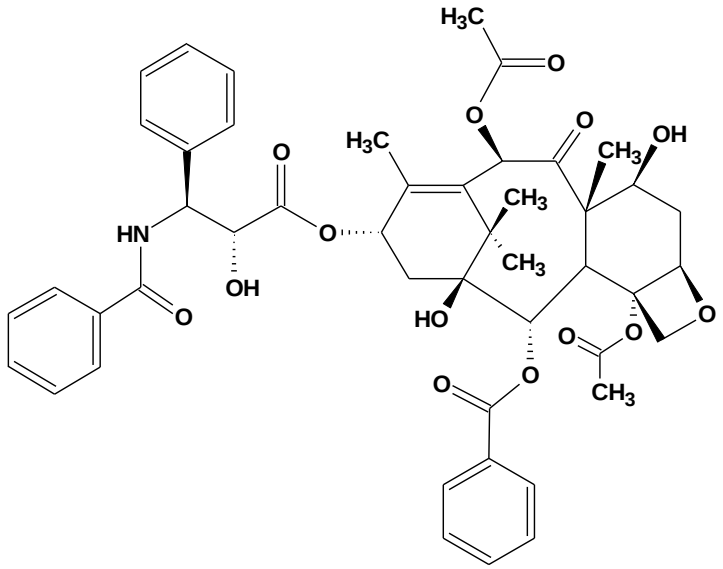
Anti-Cancer Plant Allaloids

- Tubulin-Binding Agents
- Paclitaxel:

Taxanes enhance all aspects of tubulin polymerization, an action that is the opposite to that of vinca alkaloids, but they are also cytotoxic, emphasizing the dynamic importance of tubulin polymerization as a target for cytotoxic drugs.

Paclitaxel, Taxotere

Taxol

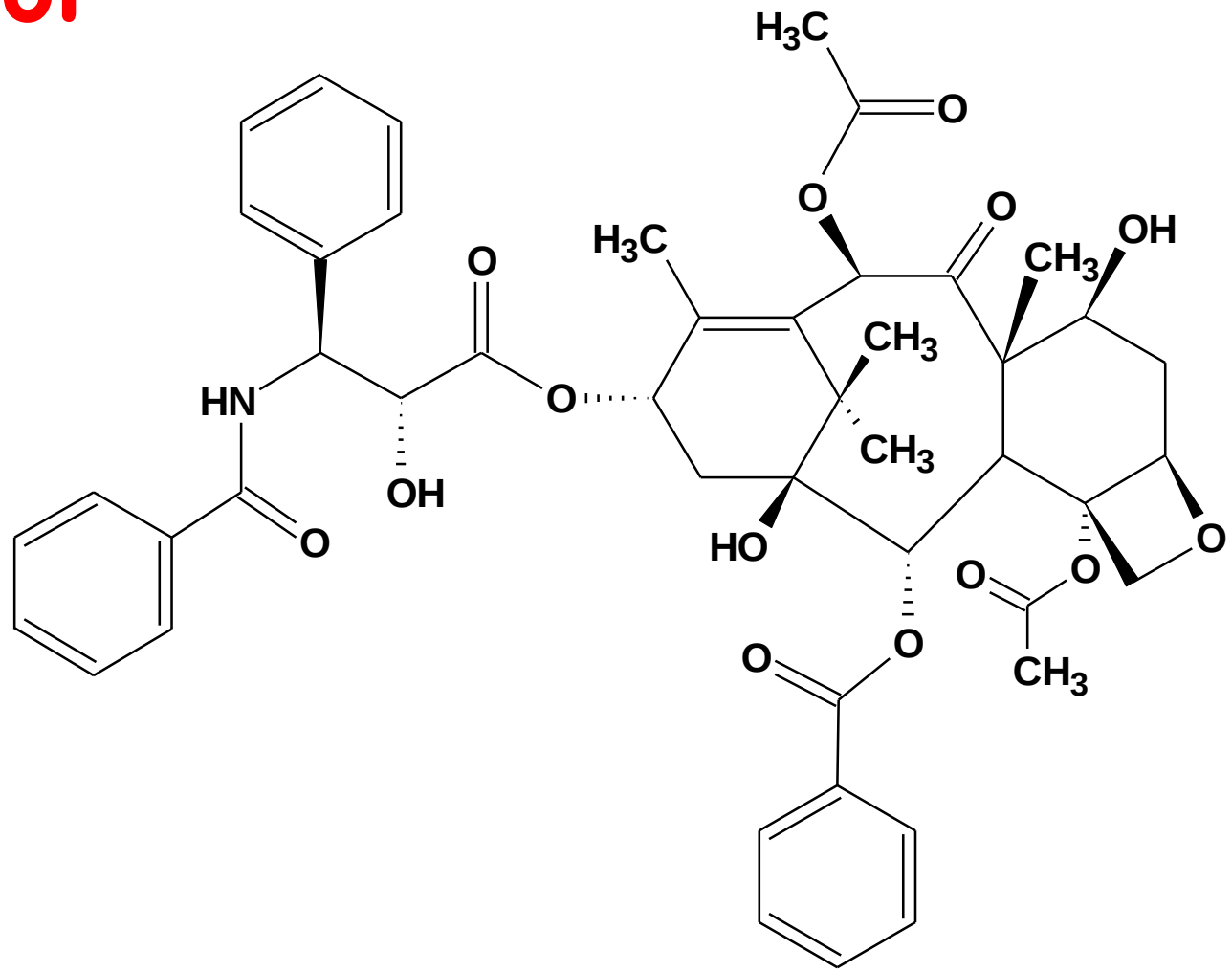


The newest antimitotic agent to be approved (1993) for clinical use is the diterpenoid taxol.
It is obtained from the bark of the pacific yew tree, *Taxus brevifola*.

Uses

leukemias, sarcomas, and lung cancer
ovarian and breast carcinoma

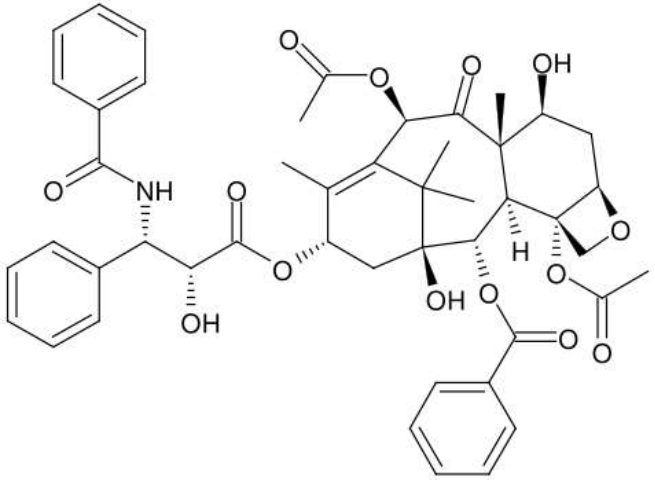
Taxol



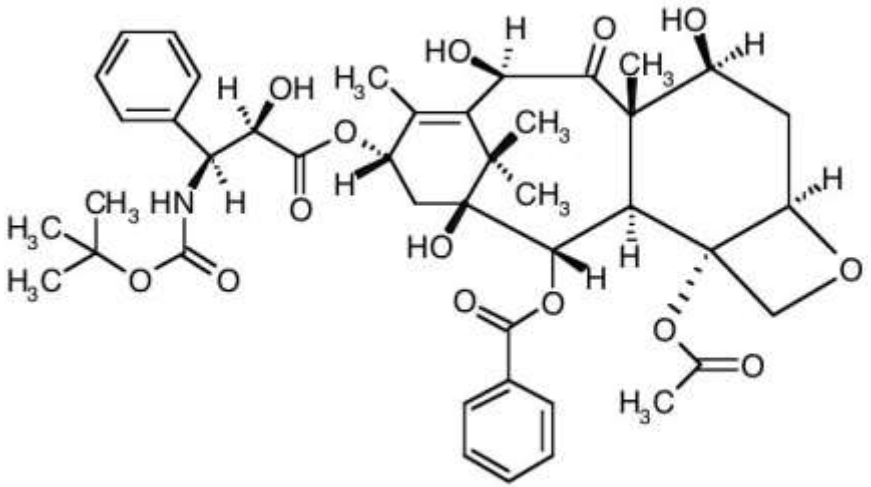
Docetaxel

A semi-synthetic derivative of compound extracted from the renewable and readily available European yew tree.

Used mainly for the treatment of breast, ovarian, and non-small cell lung cancer.

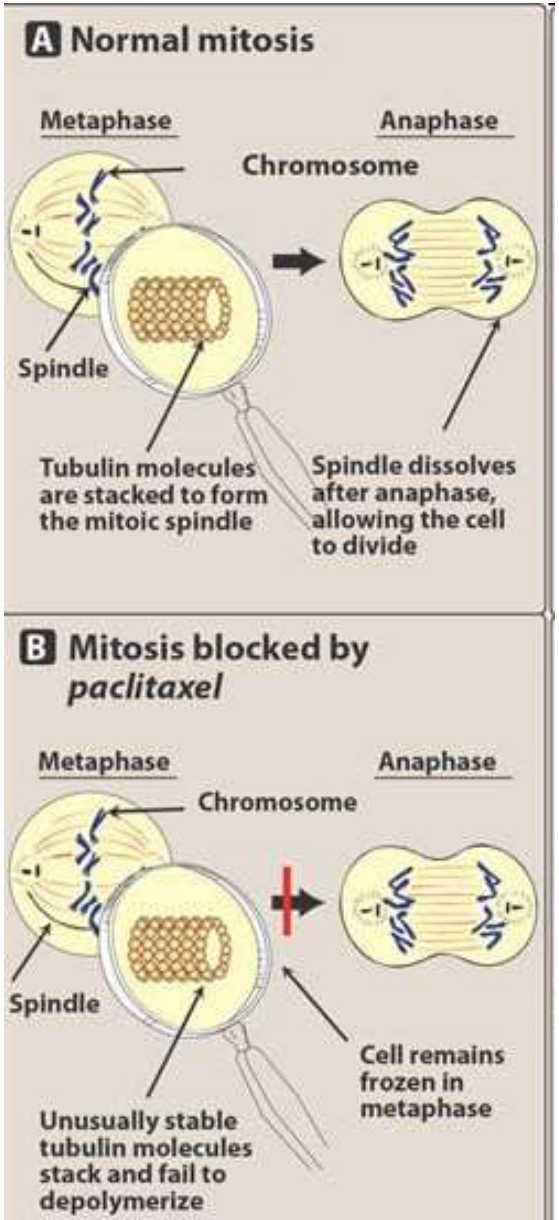


Paclitaxel



Docetaxel

Paclitaxel & Docetaxel



- These drugs act by interfering with mitotic spindle
- They prevent micotubule disassembly into tubulin monomers

ADR

- Neutropenia
- Peripheral neuropathy