Chemotherapeutic Agents

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Drugs to Treat Neoblastic Diseases- Section 4- Mitosis Inhibitors

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Pharmacologic Classification of Chemotherapeutic Agents

I. DNA (cross) linking agents; DNA alkylating agents

II. Antimetabolites

III. DNA topoisomerase poisons & DNA intercalating agents:
Natural alkaloids: III.1.Camptothecins;III.2.Epipodophyllotoxins;
Antibiotics: III.3.Anthracyclines; III.4.Anthracenediones

IV. DNA interacting miscellaneous antibiotics:
IV.1. phenoxazine; IV.2. glycopeptide; IV.3. mitomycin

Pharmacologic lassification of Chemotherapeutic Agents- Contd.

V. Mitosis inhibitors: natural compounds

VI. Tyrosine Kinase and related inhibitors

VII. Histone deacetylase inhibitors

VIII. Immunomodulators

IX. Miscellaneous: hormonal, and specific agents

Foye's 2019

CHAPTER 33

Drugs Used to Treat Neoplastic Diseases

Victoria F. Roche

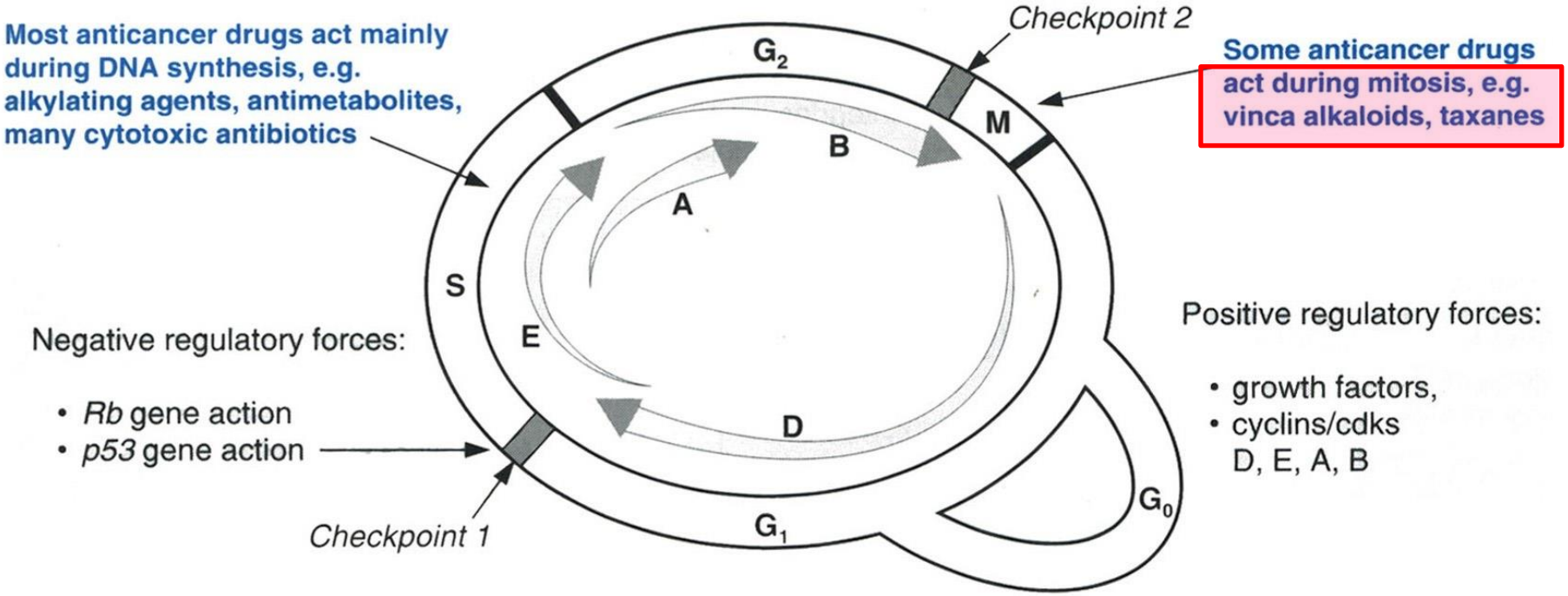
MITOSIS INHIBITORS

- Cabazitaxel
- Docetaxel
- Eribulin
- Ixabepilone
- Paclitaxel
- Vinblastine
- Vincristine
- Vinorelbine

V. Mitosis Inhibitors:

Antimitotic Agents

Established Possible Targets for Anticancer Agents in Cell Cycle



[1] Rang , Dale, Ritter *Pharmacology*. 4th ed.; 1999.p.664,665,666.

Mitosis

- Microtubules: consist of α,β and ɣ Tubulins

✓lie adjacent to one another

✓dynamic stability

✓ Polymerization: elongation

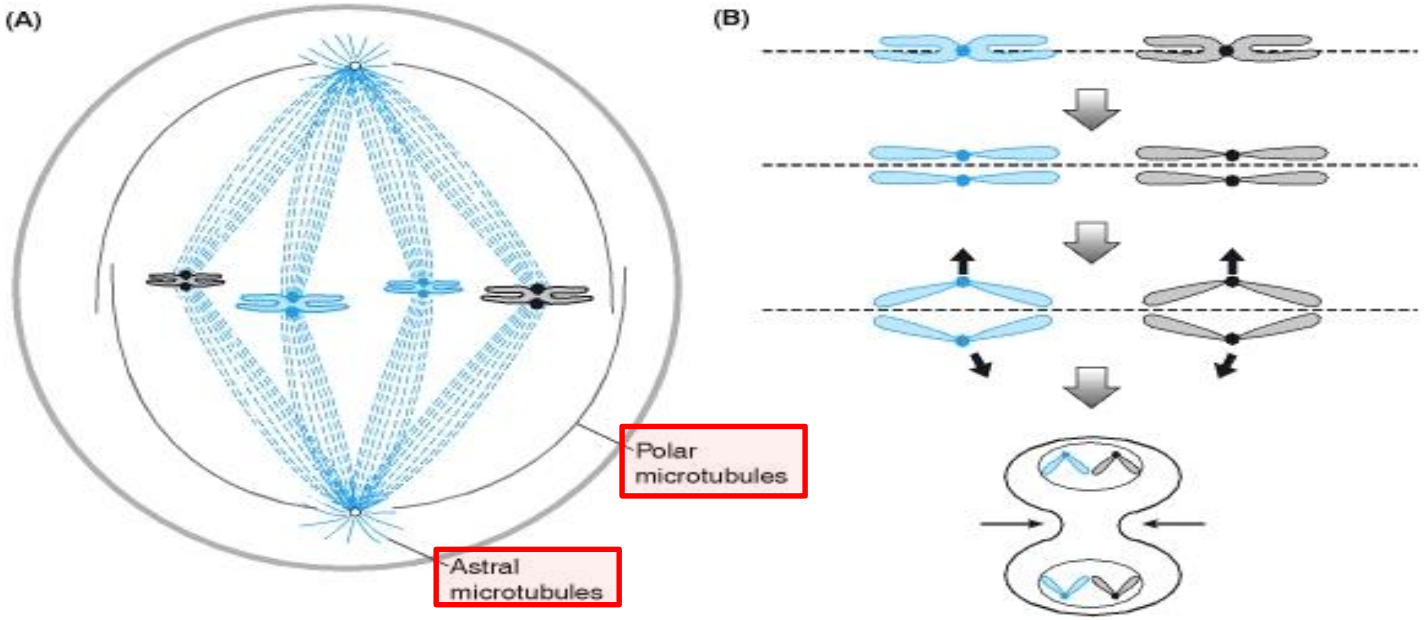
✓ & depolymerization: shortening:

✓ through GTP & Calcium dependent processes.

- Microtubule Associated Protein: MAP

Antimitotic Agents: MOA by Schematic Image

- MOA: interfere with the formation of mitotic spindle:
  hence prevents mitosis

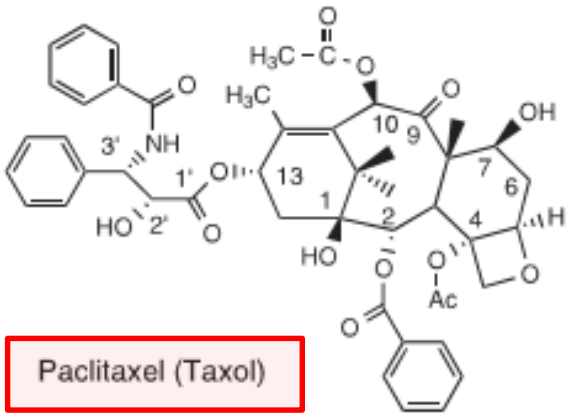


V. Antimitotic Agents: Chemical Classifications

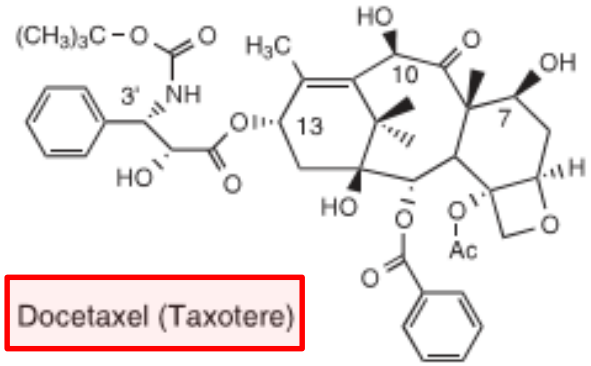
- V.1. Taxanes: Docetaxel; Paclitaxel; Cabazitaxel
- V.2. Epothilone: Epothilone A; Epothilone B; Ixabepilone
- V.3. Vinca Alkaloids: Vincristine; Vinblastine; Vinorelbine
- V.4. Stramustine: nitrogen mustard structure
- MOA: interfere with the formation of mitotic spindle: hence prevents mitosis

Antimitotic Agents

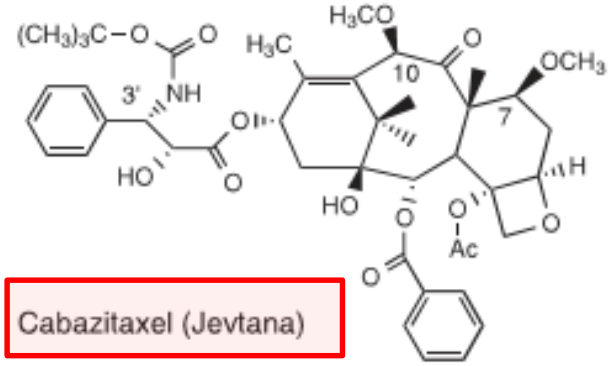
Taxanes



Paclitaxel (Taxol)

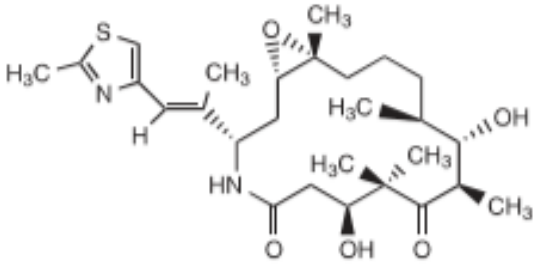


Docetaxel (Taxotere)



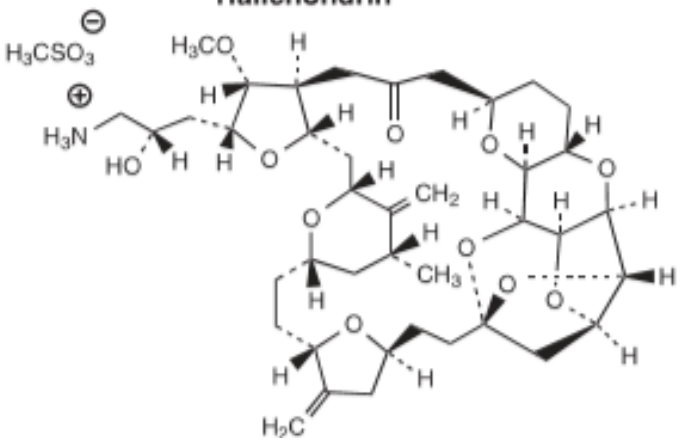
Cabazitaxel (Jevtana)

Epothilone

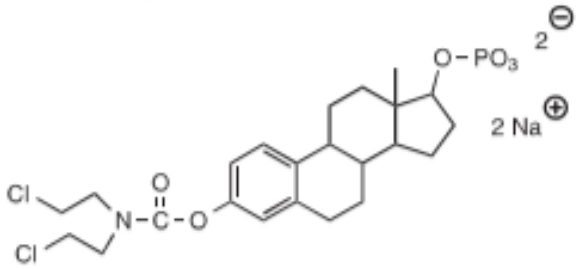


Ixabepilone (Ixempra)

Halichondrin



Nitrogen mustard

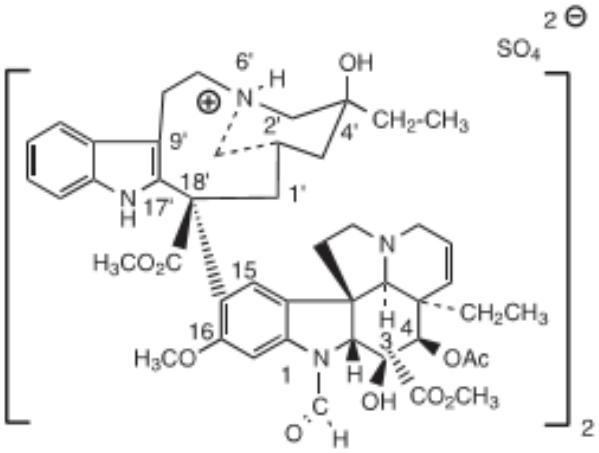


Estramustine phosphate sodium (Emcyt)

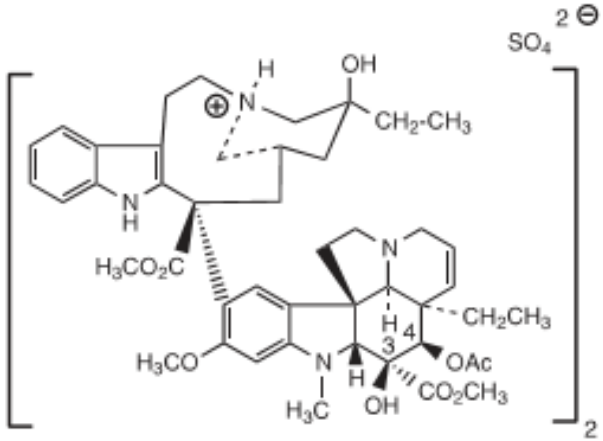
Figure 33.35 Mitosis inhibitors.

Antimitotic Agents- Contd.

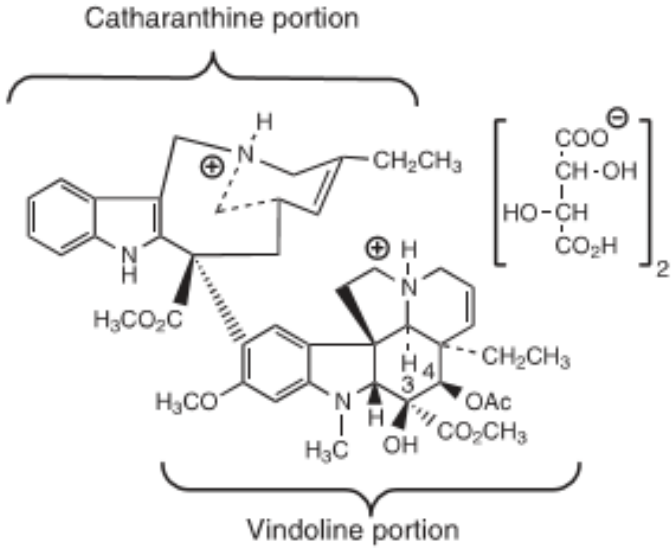
Vinca alkaloids:



Vincristine sulfate (Vincasar PFS)



Vinblastine sulfate (Velban)

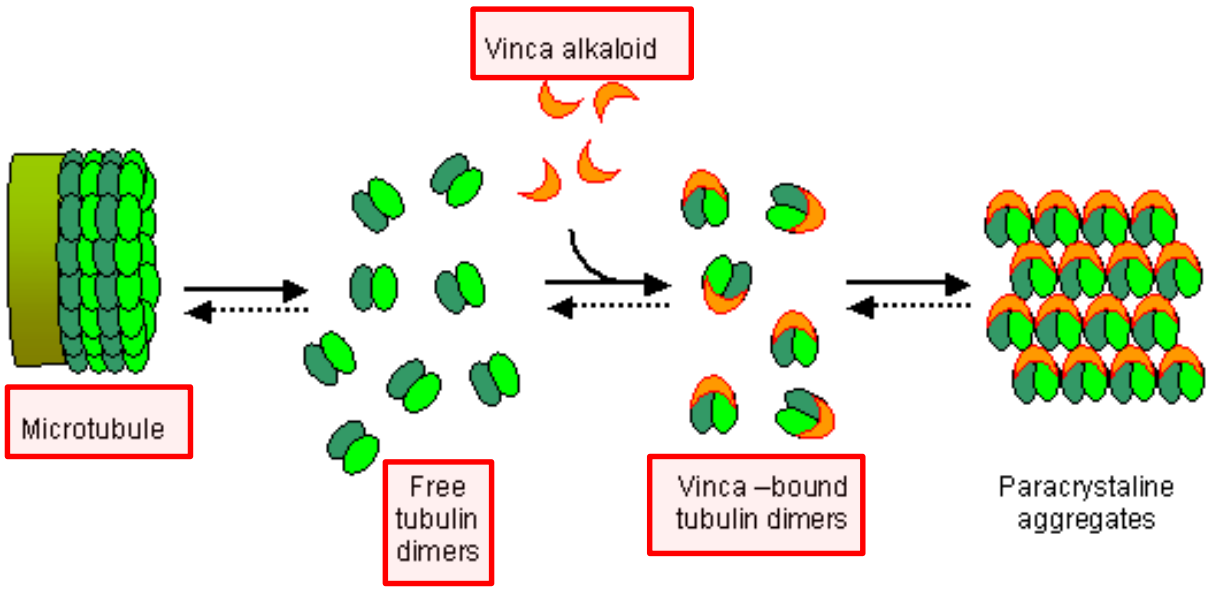


Vinorelbine tartrate (Navelbine)

Figure 33.35 Mitosis inhibitors.

MOA for Vincas in Schematic Image as Antimitotic Agents

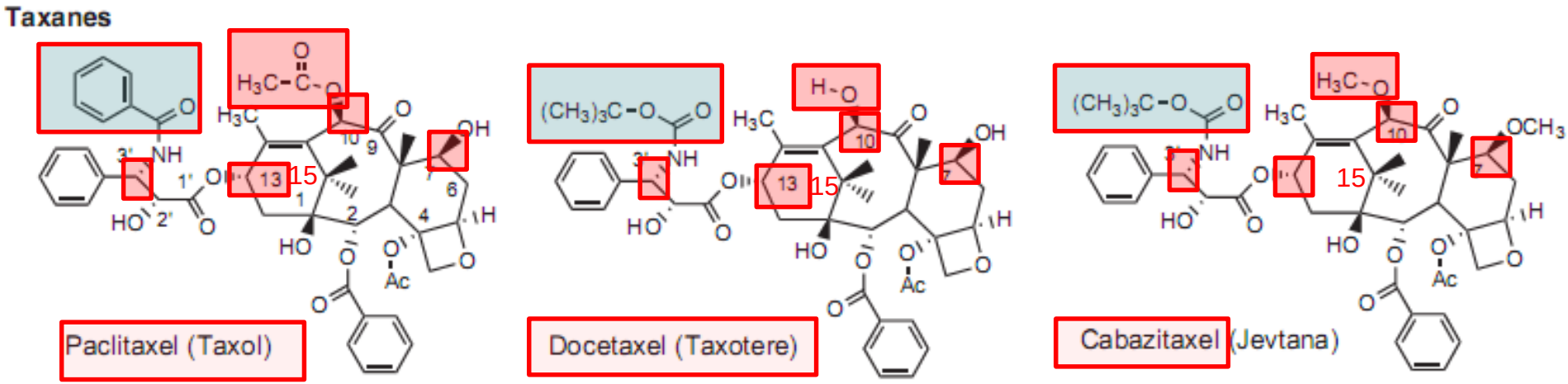
- MOA: interfere with the formation of mitotic spindle: hence prevents mitosis



V. Antimitotic Agents: 1.Taxanes

- Taxanes: Paclitaxel (Taxol®)
  Docetaxel (Taxotere®)
  Cabazitaxel (Cabotax®)
- Chemistry:

tricycle-pentadecane (15-membered) fused to oxetane:



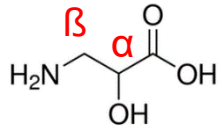
V. Antimitotic Agents:1.Taxanes: Chemistry & SAR

- Chemistry:

✓ tricycle-pentadecane (15-membered) fused to oxetane:

✓ butterfly conformation: “Northern & Southern” segments

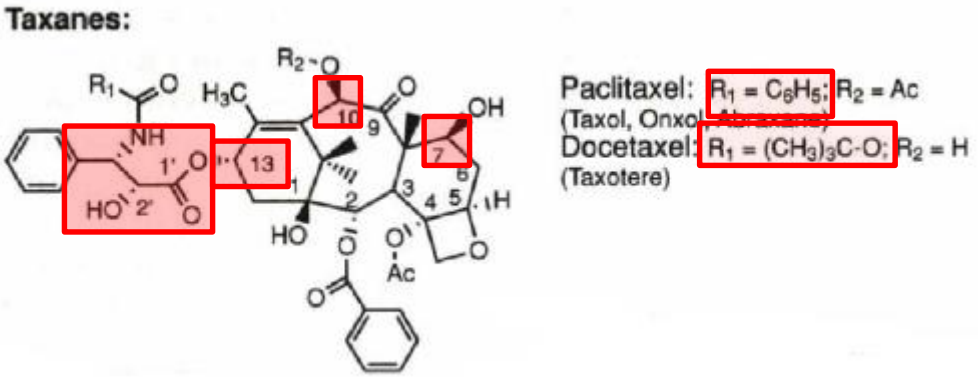
✓ C13-O-esterified by: ß-phenyl-iso-serin which is N-acylated



* find benzamide or carbamate portion.

✓ differ in substitutes at C7,C10 & C13

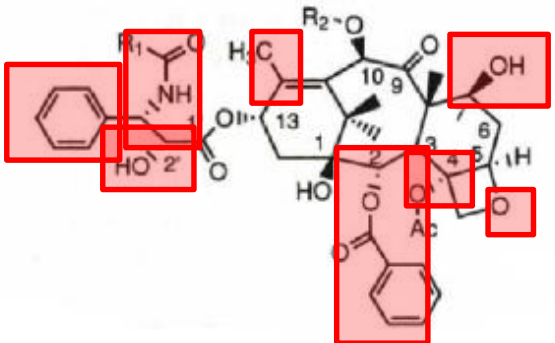
✓ essential functional groups regarding interaction sites: next slide



Receptor Interaction Points for Paclitaxel (Taxol®)

- C2-benozyloxy: -O-CO-phenyl
- C4-acetyloxy: -O-CO-CH_3
- C7-OH
- C11-C12: dehydro
- C12-CH_3
- Oxetane: oxygen
- C2'-OH & CO (carbonyl)
- C3'-benzamido-NH
- C3'-benzamido-CO (carbonyl)
- C3'-phenyl

Taxanes:



Paclitaxel: $R_1 = C_6H_5$; R_2 = Ac
(Taxol, Onxol, Abraxane)
Docetaxel: $R_1 = (CH_3)_3C\text{-}O$; $R_2 = H$
(Taxotere)

Table 33.12 Paclitaxel-β-Tubulin Binding Interactions

Paclitaxel Functional Group	β-Tubulin Binding Residues	Interaction
C_2-benzoyloxy phenyl	Leu217, Leu219, His229, Leu230	Hydrophobic
C_2-benzoyloxy carbonyl	Arg278	Hydrogen bond
C_3-benzamido NH	Asp26	Hydrogen bond
C_3-benzamido carbonyl	His229	Hydrogen bond
C_3-phenyl	Ala233, Ser236, Phe272	Hydrophobic
C_4-acetoxy	Leu217, Leu230, Phe272, Leu275	Hydrophobic
C_7-OH	Thr276 Ser277, Arg278	Hydrogen bond
C_{12}-CH_3	Leu217, Leu230, Phe272, Leu275	Hydrophobic
C_2-OH	Arg369, Gly370 (NH)	Hydrogen bond
C_3-carbonyl	Gly370 (NH)	Hydrogen bond
Oxetane oxygen	Thr276 (NH)	Hydrogen bond

Metabolism of Paclitaxel & Docetaxel

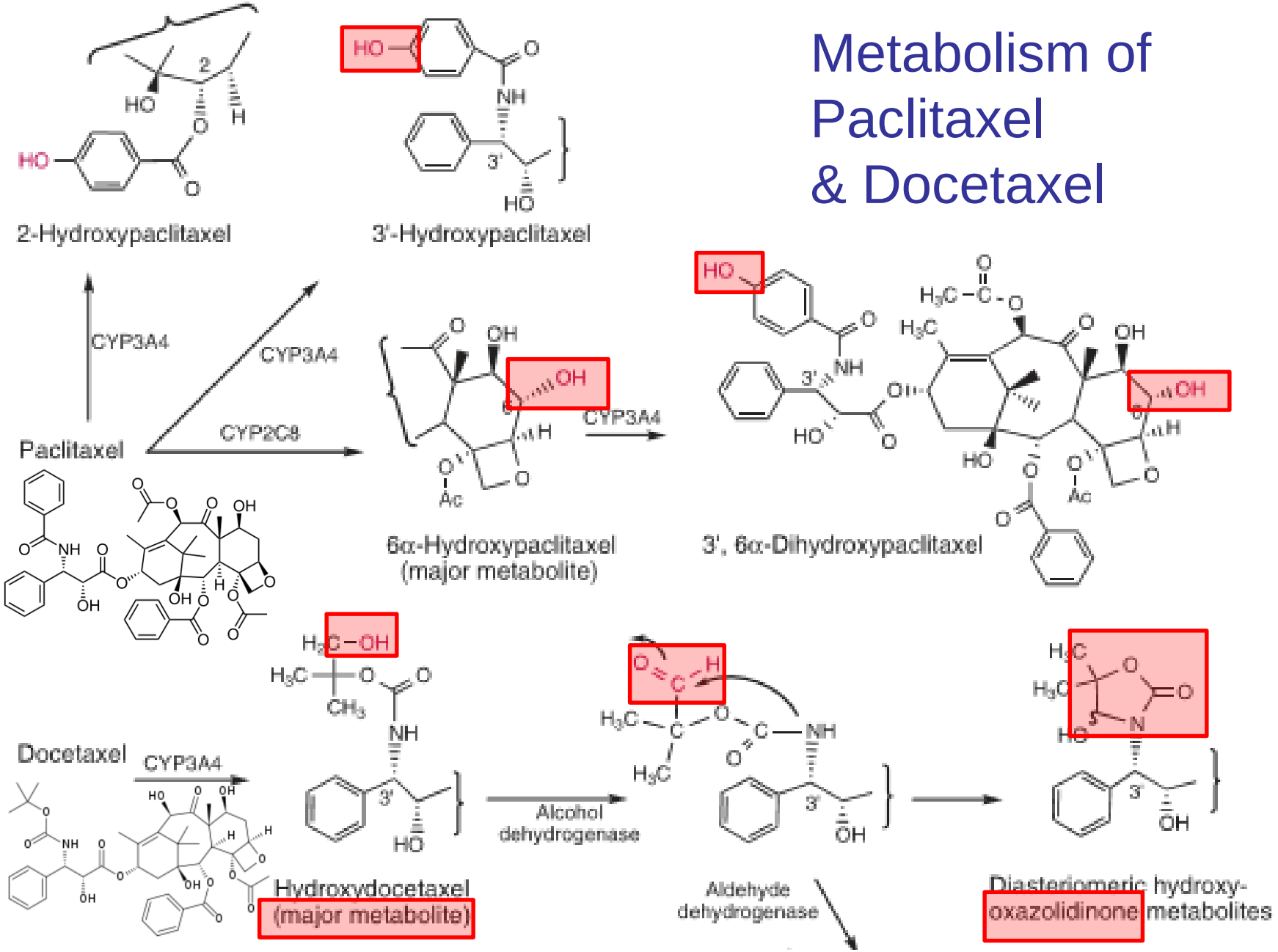


Figure 33.36 Taxane metabolism.

Metabolism Of Docetaxel & Cabazitaxel

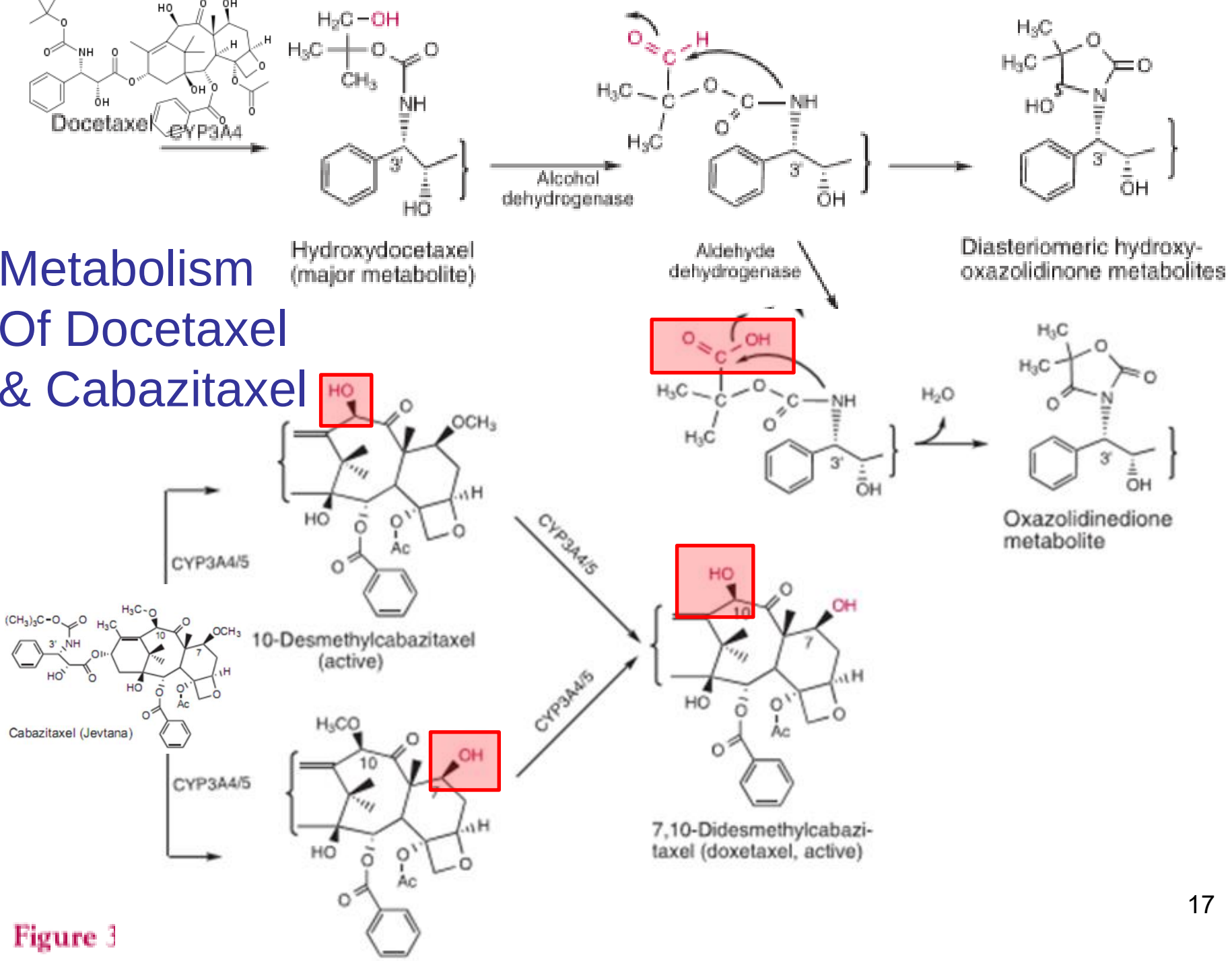
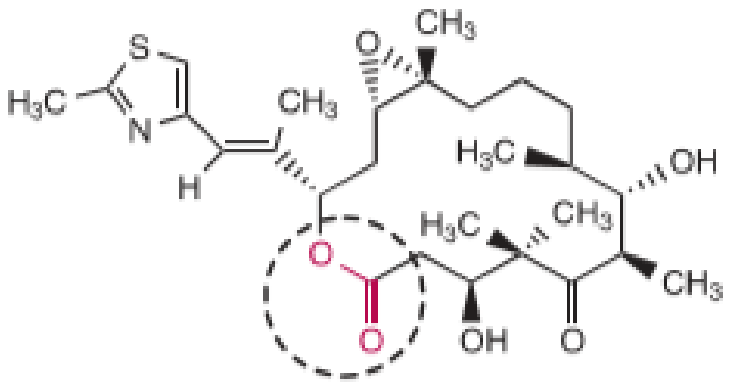


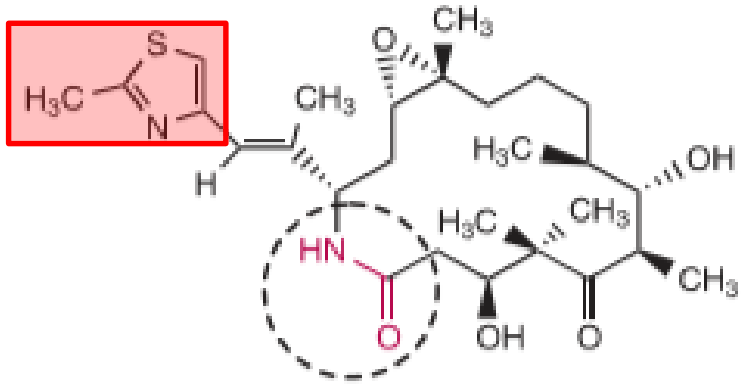
Figure 3

V. Antimitotic Agents: 2. Epothilones

16 membered
ß-hydroxy
lactone or lactam



Epothilone B



Ixabepilone (Ixempra)

Figure 33.38 Epothilones.

V. 2. Epothilones: Comparing Ixabepilone to Paclitaxel

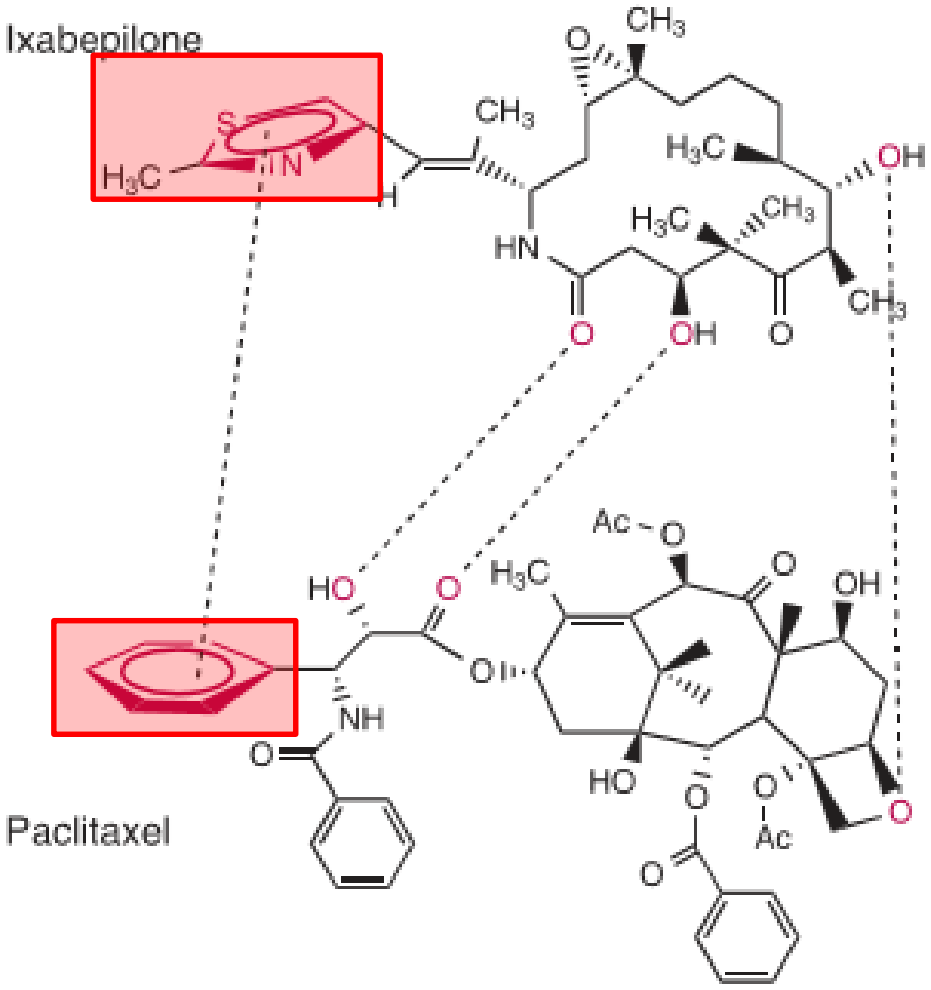
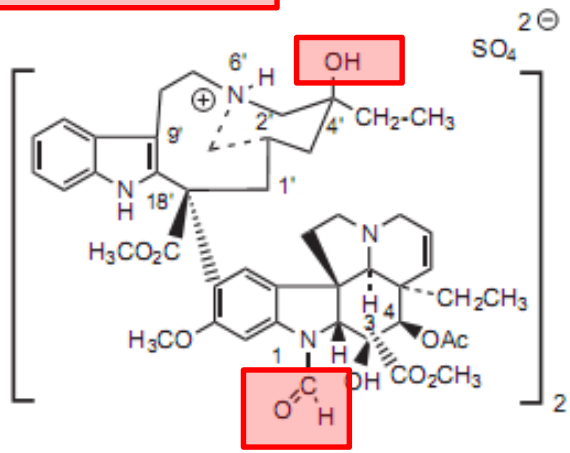


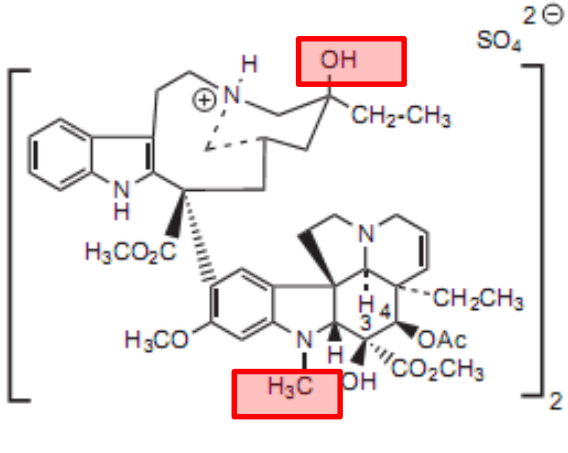
Figure 33.37 Complementary ixabepilone and paclitaxel functional groups.

V. Antimitotic Agents: 3.Vincas

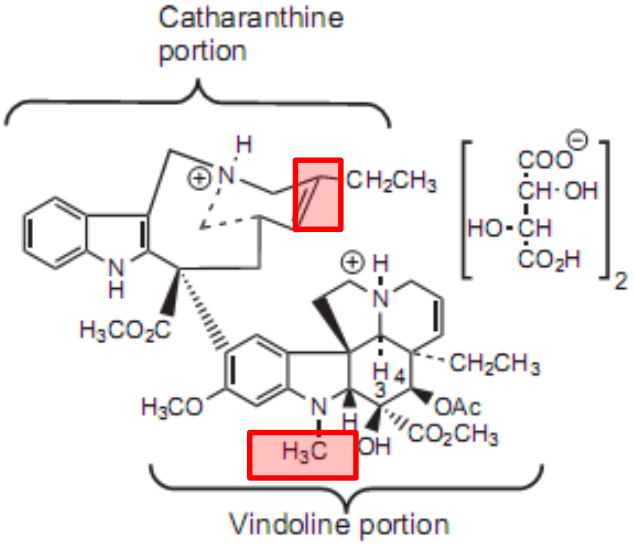
Vinca alkaloids:



Vincristine sulfate (Vincasar PFS)



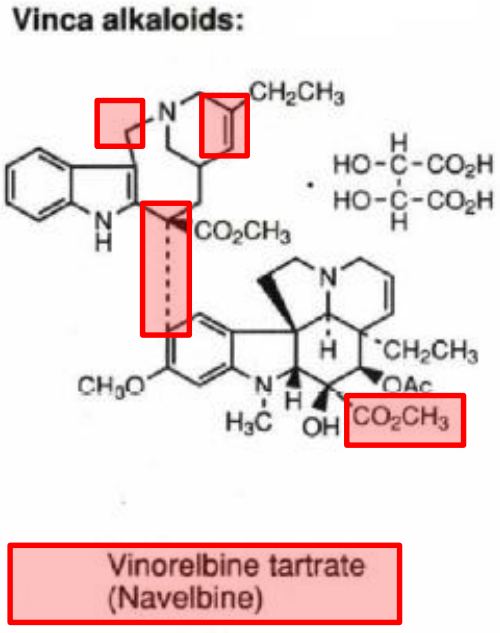
Vinblastine sulfate (Velban)

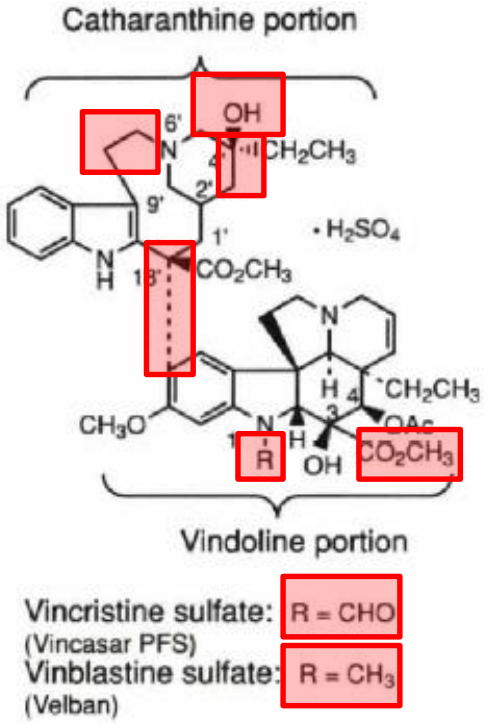


Vinorelbine tartrate (Navelbine)

V. Antimitotic Agents: 3.Vincas:
Chemistry & SAR

- Chemistry: alkaloid: vindoline+ catharantine(velbanamine)
- ✓ steric position of connection of two polycyclic portions
- ✓ Vinblastine
- ✓ Vincristine
- ✓ Vinorelbine
- Structural difference:
- ✓ C6'-C9'bridge length
- ✓ C3'-C4' bond: de/hydro
- ✓ C4'-substitution: OH & Et
- ✓ N1-substitution





V. Antimitotic Agents: 3. Vincas: Structural & Potency Comparison

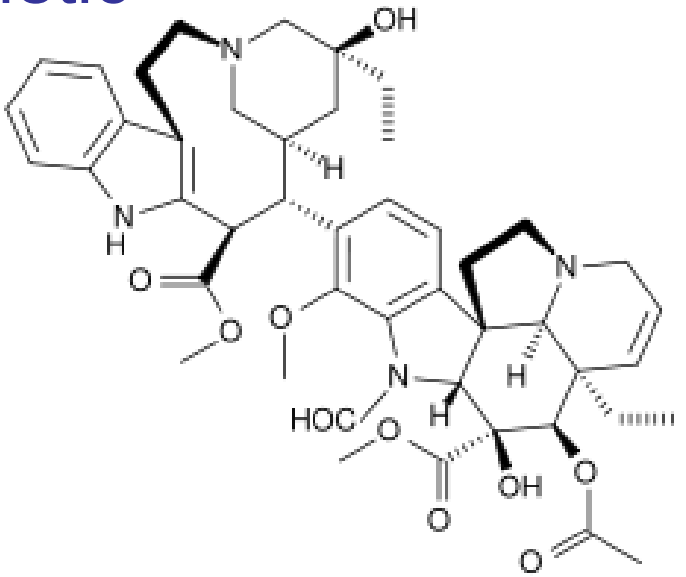
- Vinca alkaloids: vindoline + catharantine

✓ Vinblastine (Velban®): lowest affinity

✓ Vincristine (Oncovin®): highest affinity

✓ Vinorelbine (Navelbin®): semisynthetic

Vincristine



- MOA: interfere with the formation of the mitotic spindle

Metabolism of Vincas

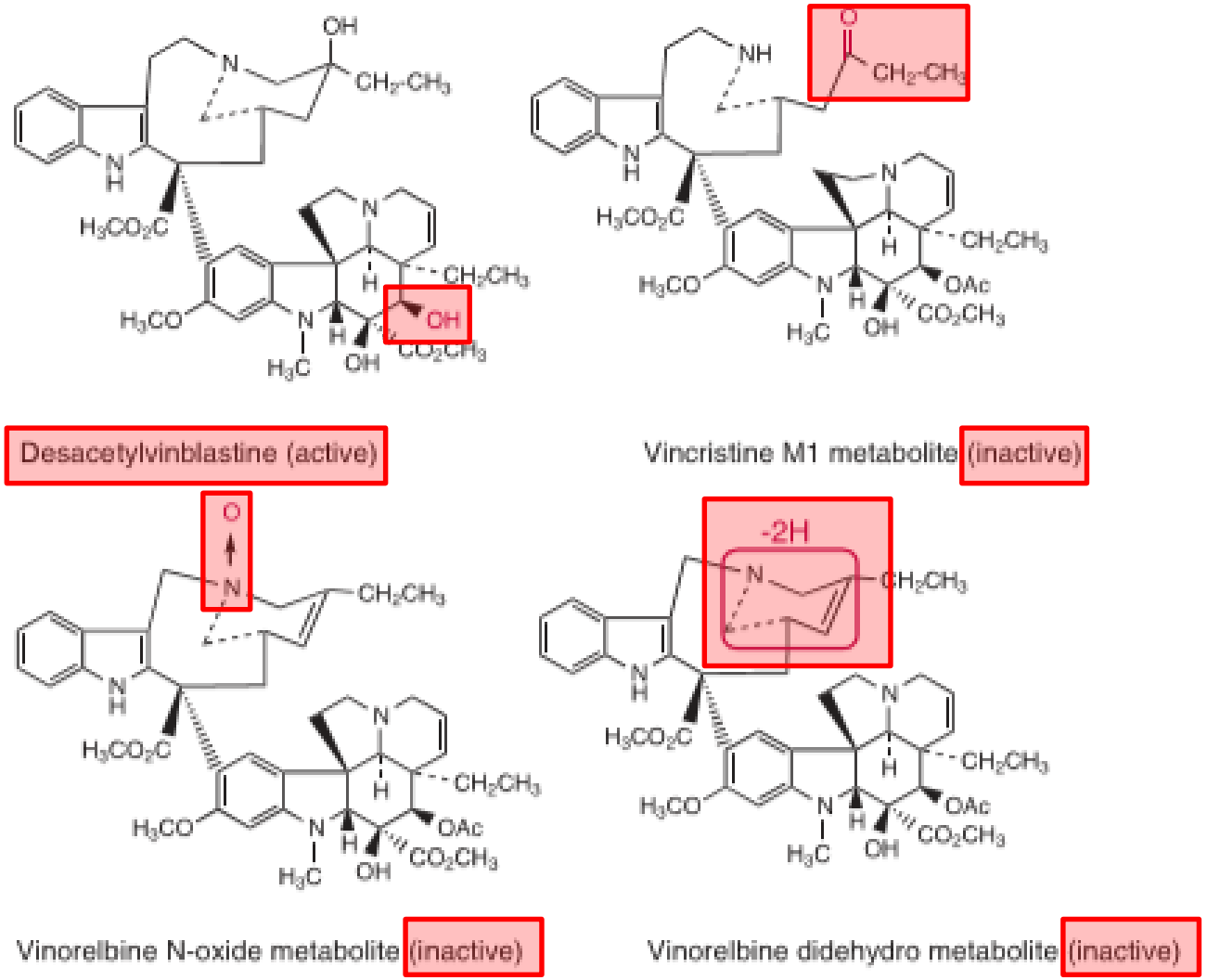


Figure 33.40 Major metabolites of vinca alkaloids.