



# Chemotherapeutic Agents

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## Drugs to Treat Neoplastic Diseases- Section 4- Mitosis Inhibitors

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## MITOSIS INHIBITORS

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

## *Drugs Used to Treat Neoplastic Diseases*

Victoria F. Roche

# Pharmacologic classification 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

# V. Mitosis Inhibitors: (Antimitotic Agents)

# V. Mitosis Inhibitors (Antimitotic Agents):

V.1. Taxan

V.2. Epothilone

V.3. Vinca Alkaloids

V.4. Stramustine

# Mitosis

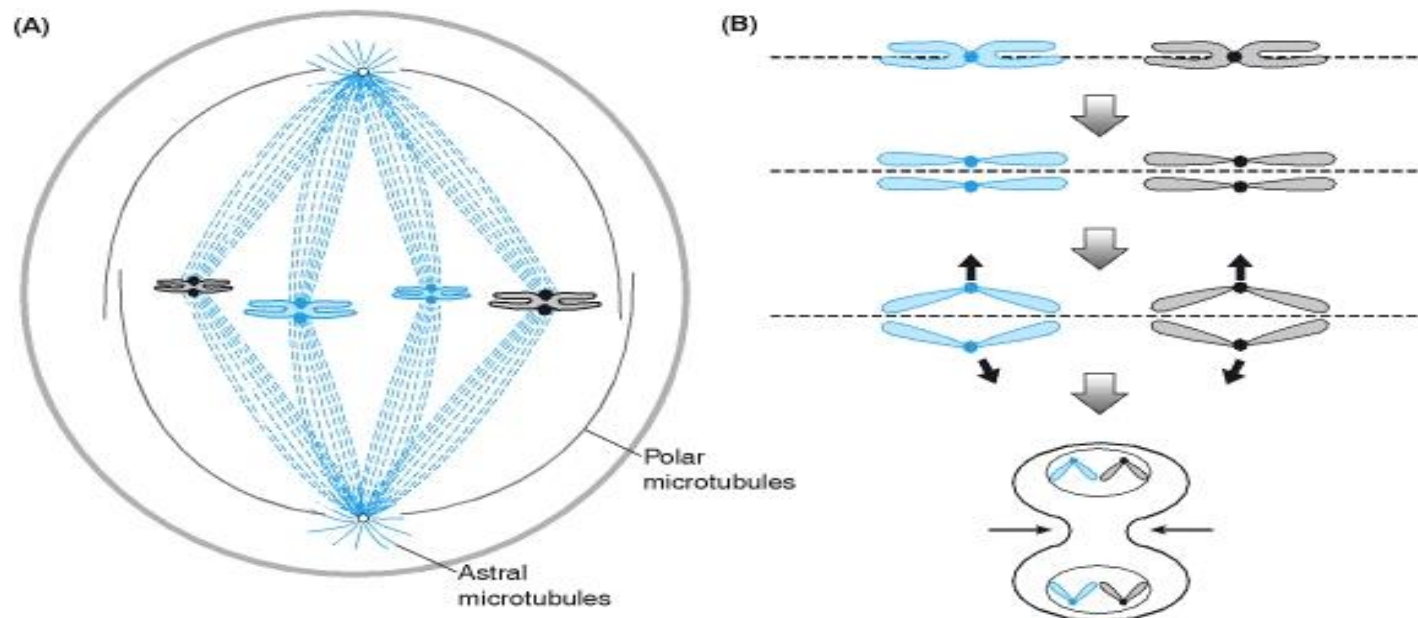
- Microtubules: consist of  $\alpha, \beta, \gamma$ - Tubulins
  - ✓ lie adjacent to one another
  - ✓ dynamic stability
  - ✓ polymerization (elongation)
  - ✓ and depolymerization (shortening):
  - ✓ through GTP, Ca dependent processes.
- Microtubule associated proteins: MAPs

# V. Antimitotic Agents

- 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: MOA by Image

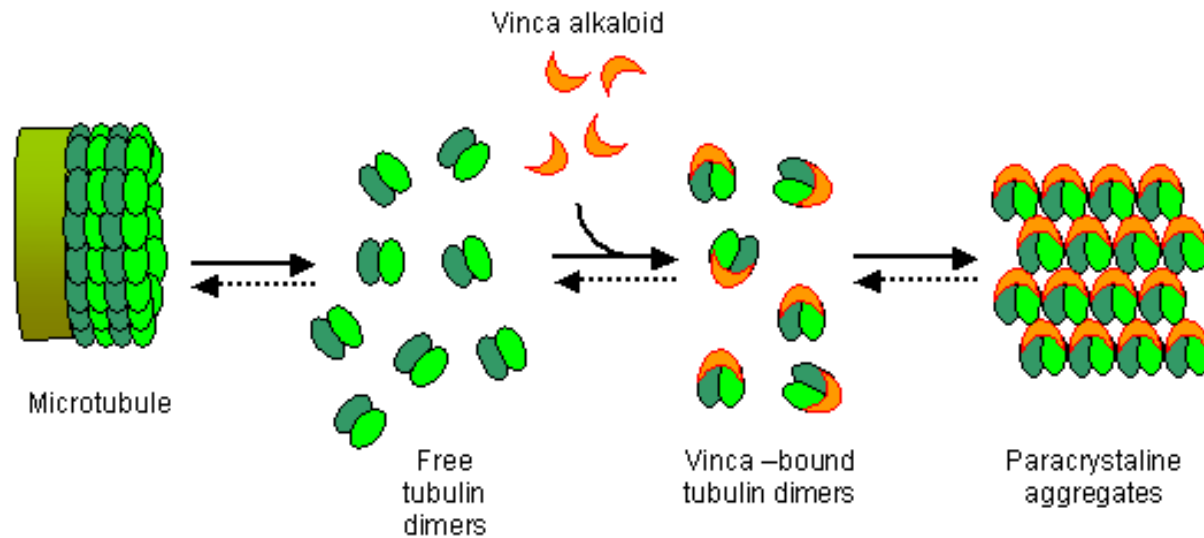
- MOA: interfere with the formation of mitotic spindle; hence prevents mitosis





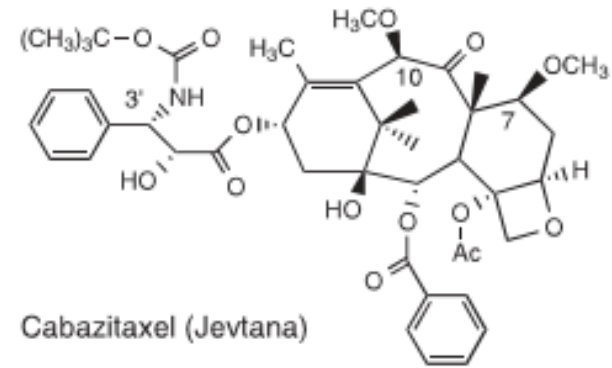
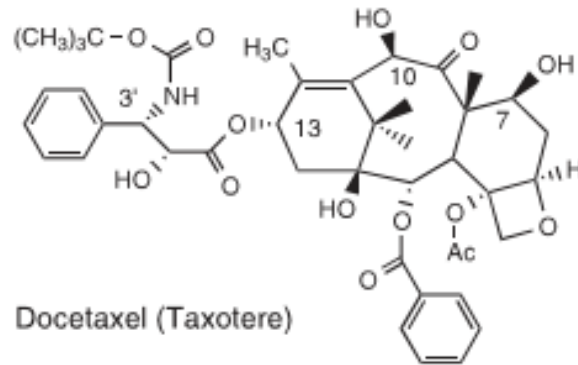
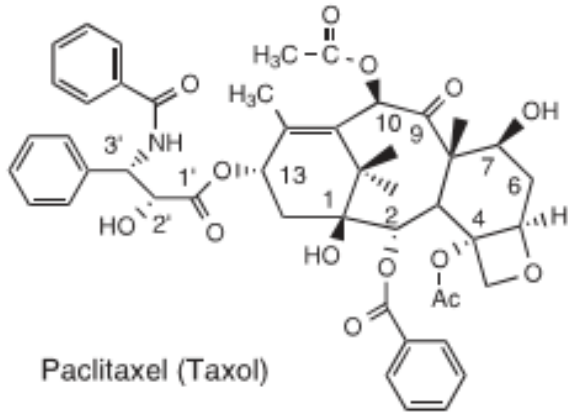
# Antimitotic Agents

- Vinca alkaloids
- Taxanes
- MOA: interfere with the formation of mitotic spindle; hence prevents mitosis

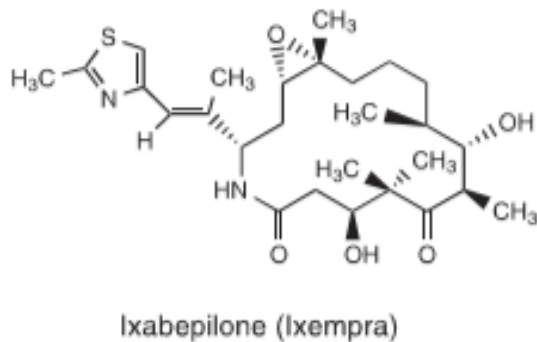


# Antimitotic Agent

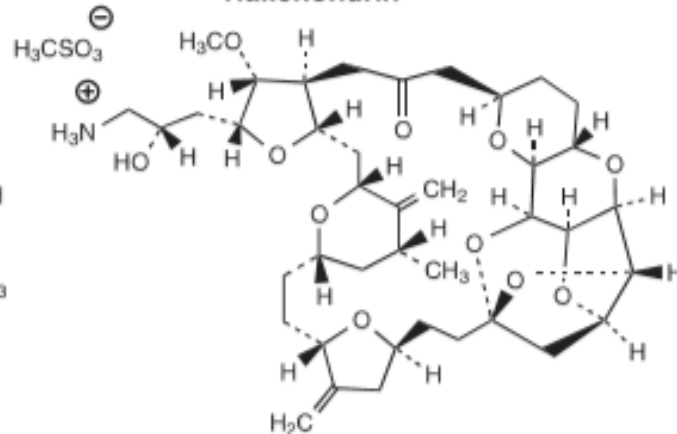
## Taxanes



## Epothilone



## Halichondrin



## Nitrogen mustard

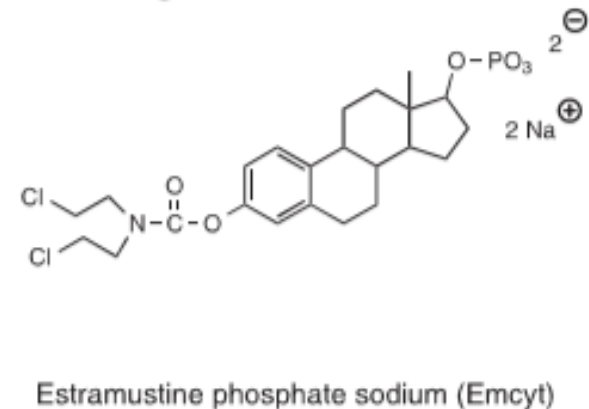
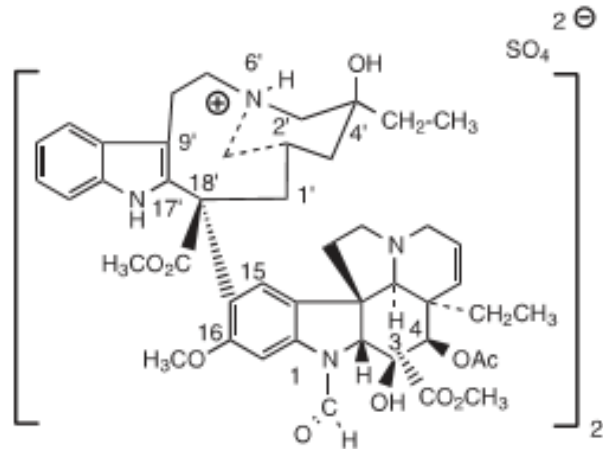


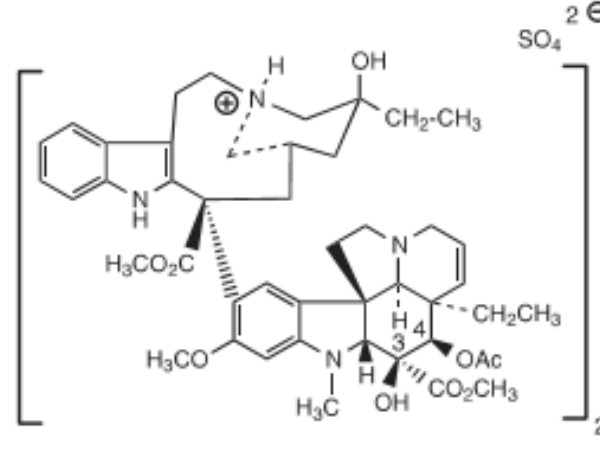
Figure 33.35 Mitosis inhibitors.

# Antimitotic Agent- Contd.

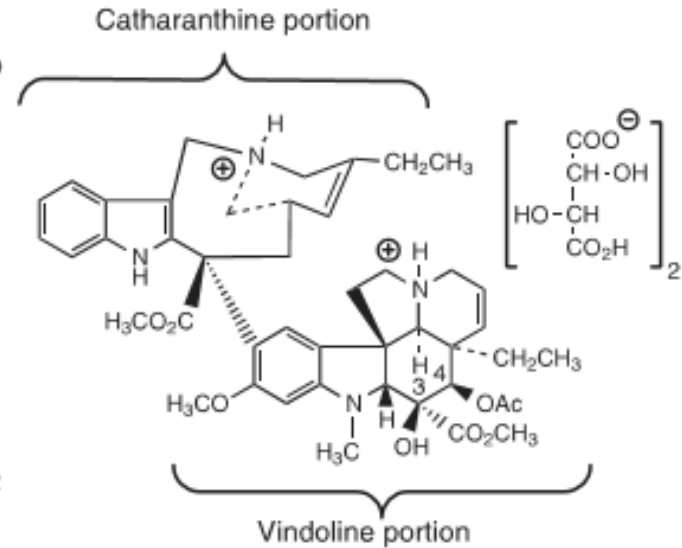
## Vinca alkaloids:



Vincristine sulfate (Vincasar PFS)



Vinblastine sulfate (Velban)



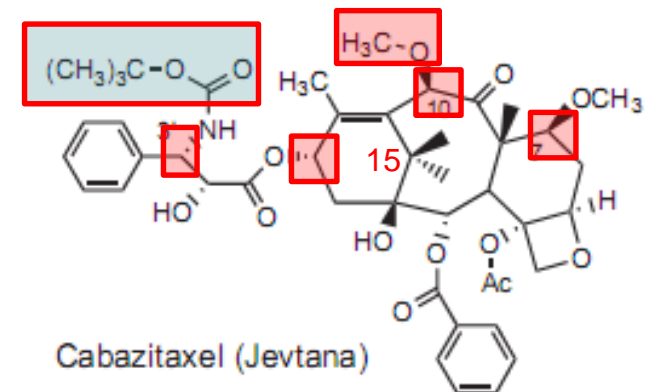
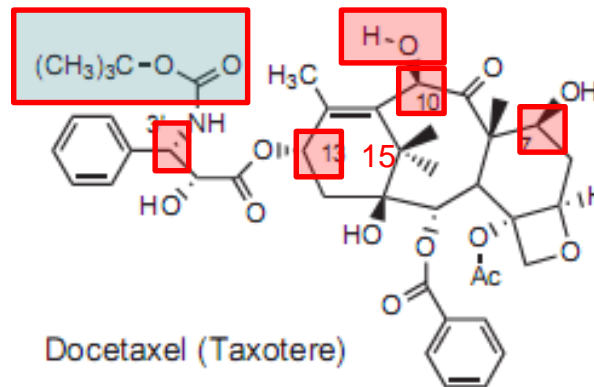
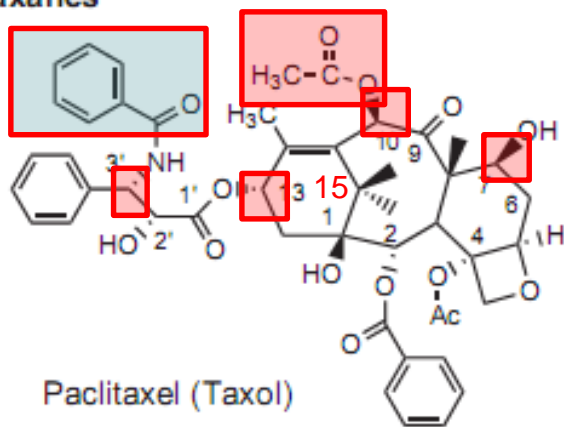
Vinorelbine tartrate (Navelbine)

# V. Antimitotic Agents: 1. Taxanes

- Taxanes: Paclitaxel (Taxol<sup>®</sup>)  
Docetaxel (Taxotere<sup>®</sup>)  
Cabazitaxel (Cabotax<sup>®</sup>)

• Chemistry:  
tricyclic-pentadecane (15-membered) fused to oxetane:

## Taxanes



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

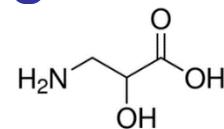
- Chemistry:

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

- SAR:

- ✓ butterfly conformation: “Northern & Southern” segments

- ✓ C13-β-phenyl-iso-serin: which is N-acylated

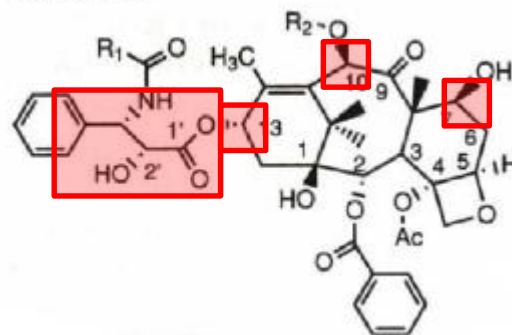


- ✓ differ in substitutes at C7, C10 & C13

- ✓ essential functional groups regarding interaction sites

(next slide)

Taxanes:



Paclitaxel: R<sub>1</sub> = C<sub>6</sub>H<sub>5</sub>; R<sub>2</sub> = Ac  
(Taxol, Onxol, Abraxane)

Docetaxel: R<sub>1</sub> = (CH<sub>3</sub>)<sub>3</sub>C-O; R<sub>2</sub> = H  
(Taxotere)

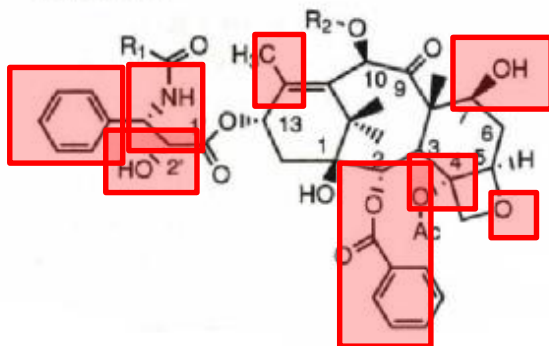
# Binding Interaction Points for Paclitaxel(Taxol®)

- C2-benzyloxy: phenyl/carbonyl
- C4-acetoxy
- C7-OH
- C12-CH<sub>3</sub>
- Oxetane oxygen
- C2'-OH
- C3'-benzamido-NH
- C3'-benzamido-carbonyl
- C3'-phenyl

**Table 33.12 Paclitaxel-β-Tubulin Binding Interactions**

Paclitaxel Functional Group	β-Tubulin Binding Residues	Interaction
C <sub>2</sub> -benzyloxy phenyl	Leu217, Leu219, His229, Leu230	Hydrophobic
C <sub>2</sub> -benzyloxy carbonyl	Arg278	Hydrogen bond
C <sub>3</sub> -benzamido NH	Asp26	Hydrogen bond
C <sub>3</sub> -benzamido carbonyl	His229	Hydrogen bond
C <sub>3</sub> -phenyl	Ala233, Ser236, Phe272	Hydrophobic
C <sub>4</sub> -acetoxy	Leu217, Leu230, Phe272, Leu275	Hydrophobic
C <sub>7</sub> -OH	Thr276 Ser277, Arg278	Hydrogen bond
C <sub>12</sub> -CH <sub>3</sub>	Leu217, Leu230, Phe272, Leu275	Hydrophobic
C <sub>2</sub> -OH	Arg369, Gly370 (NH)	Hydrogen bond
C <sub>3</sub> -carbonyl	Gly370 (NH)	Hydrogen bond
Oxetane oxygen	Thr276 (NH)	Hydrogen bond

## Taxanes:



Paclitaxel: R<sub>1</sub> = C<sub>6</sub>H<sub>5</sub>; R<sub>2</sub> = Ac  
(Taxol, Onxol, Abraxane)  
Docetaxel: R<sub>1</sub> = (CH<sub>3</sub>)<sub>3</sub>C-O; R<sub>2</sub> = H  
(Taxotere)

# Metabolism of Paclitaxel & Docetaxel

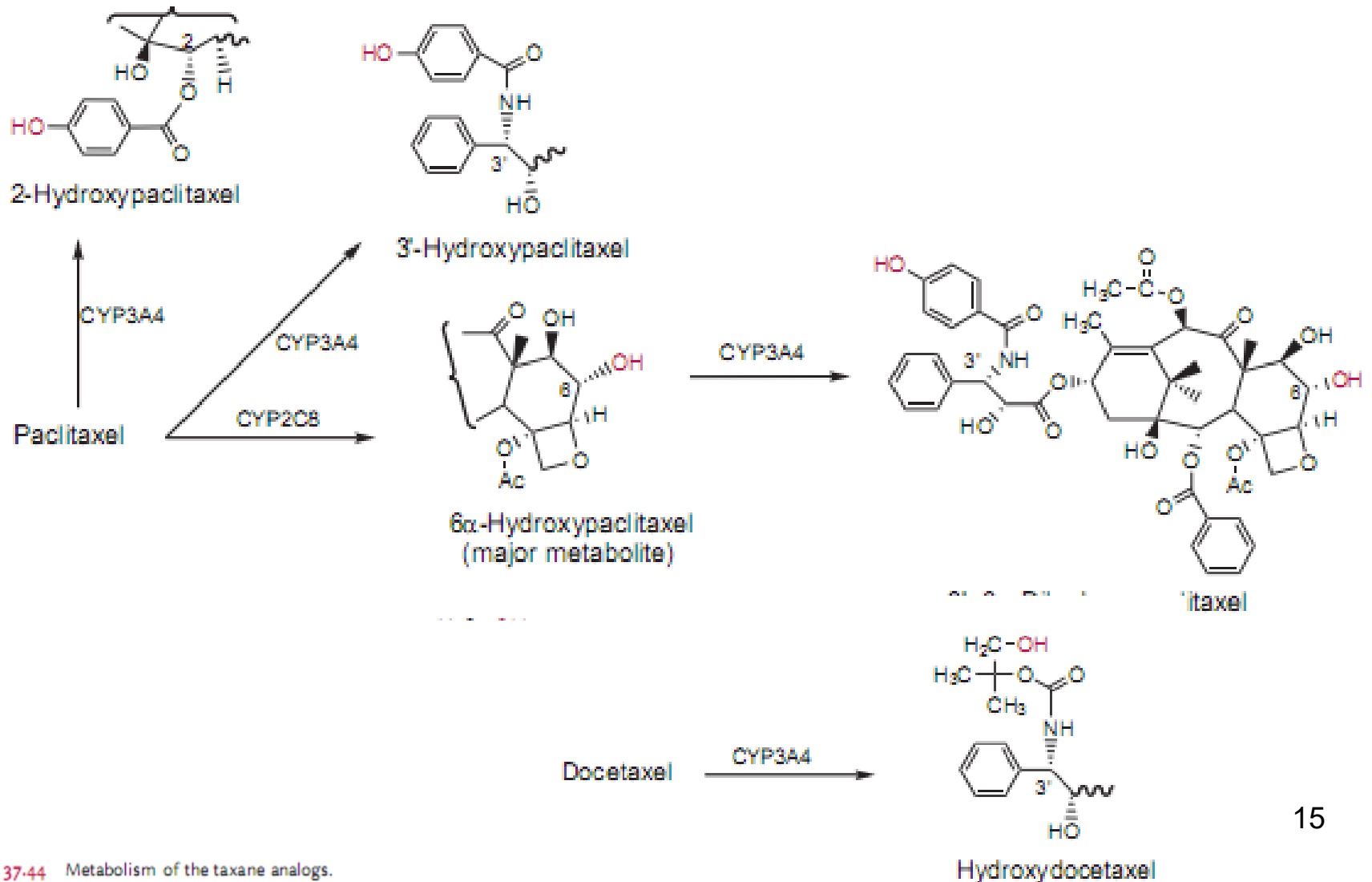
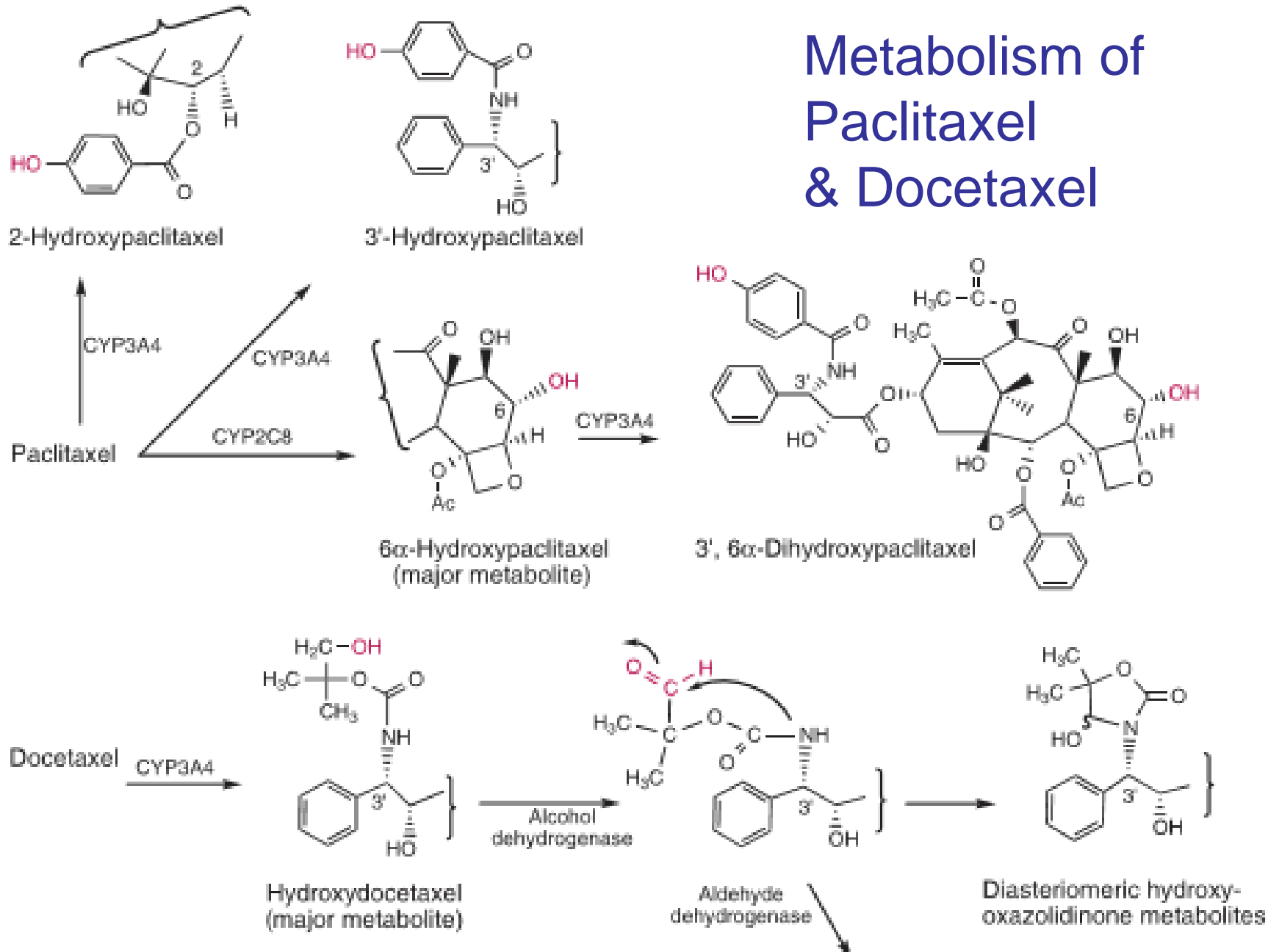


FIGURE 37.44 Metabolism of the taxane analogs.

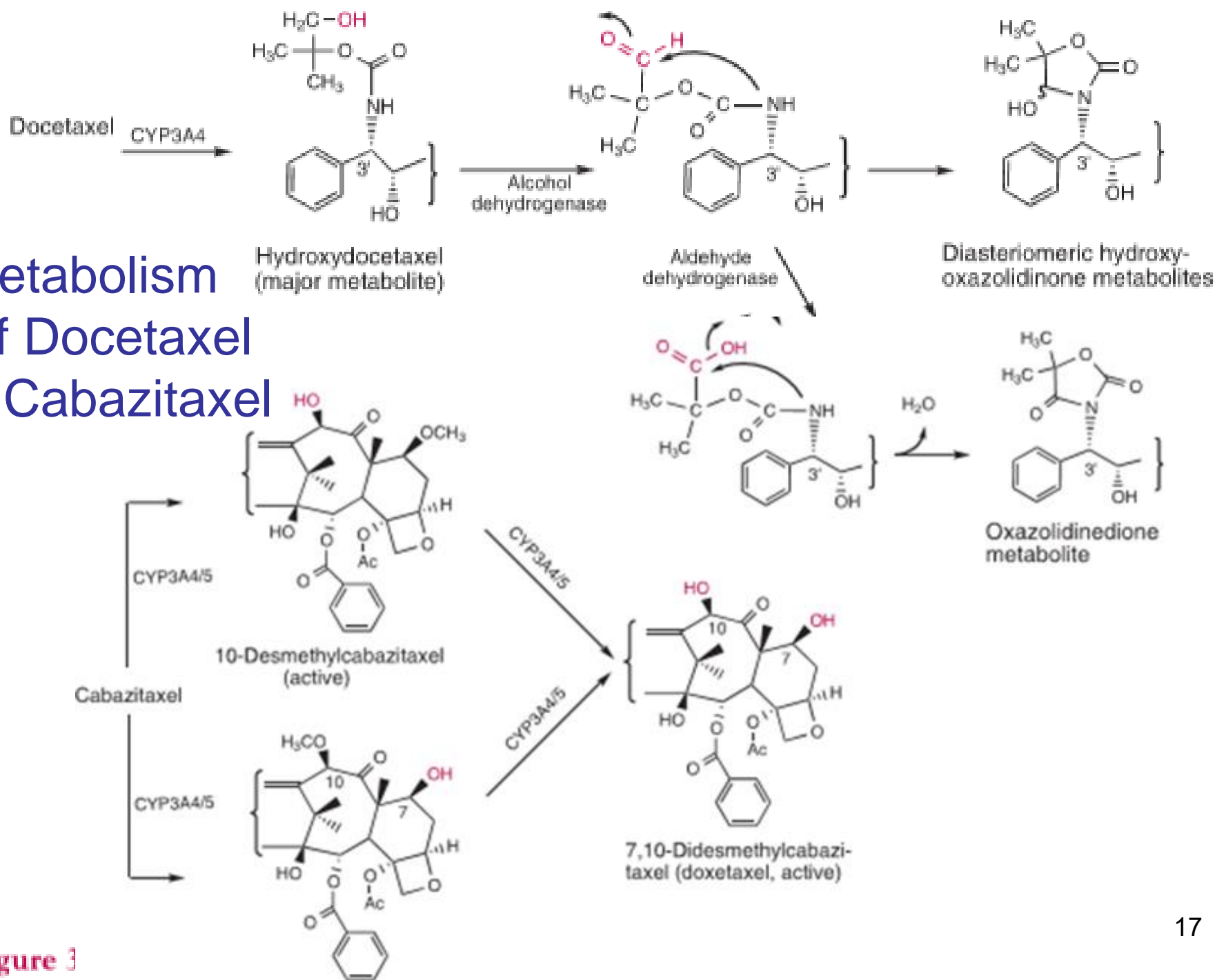
# Metabolism of Paclitaxel & Docetaxel



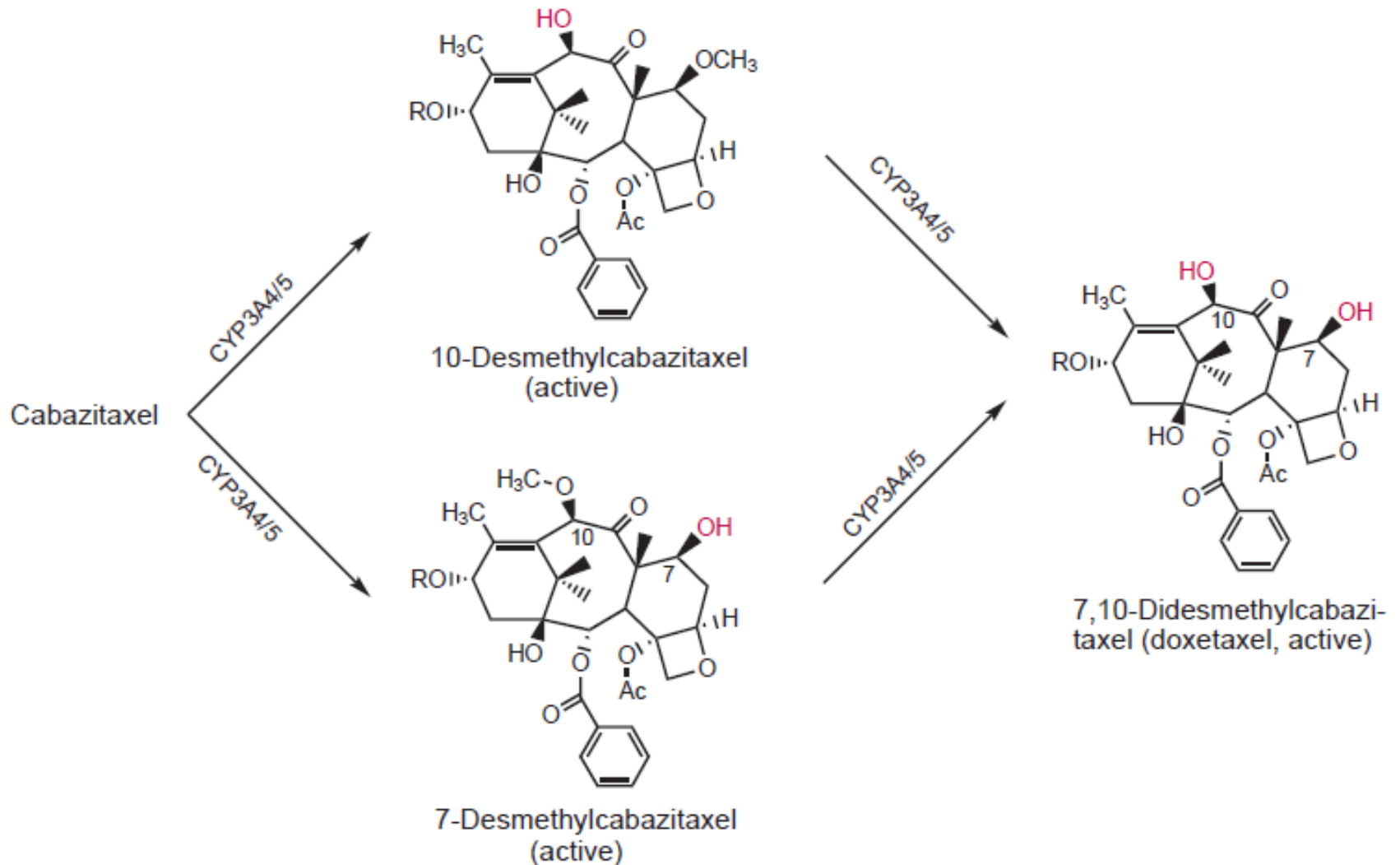
**Figure 33.36** Taxane metabolism.



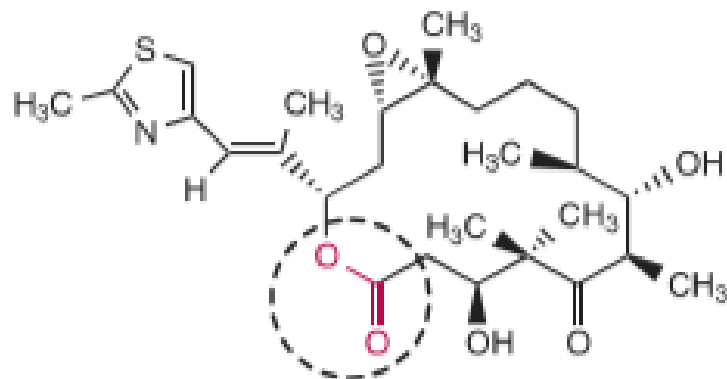
# Metabolism Of Docetaxel & Cabazitaxel



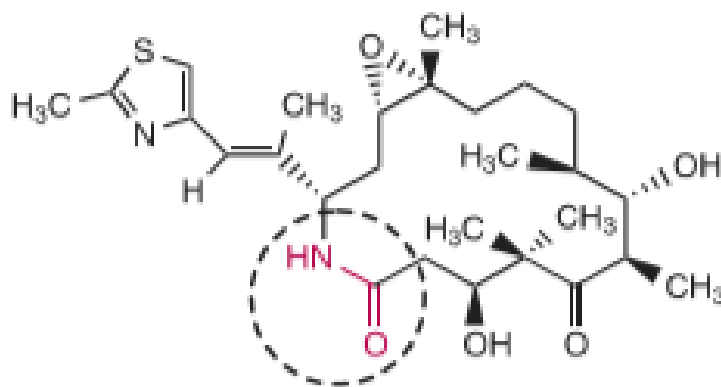
# Metabolism of Cabazitaxel



# V. Antimitotic Agents: 2. Epothilones



Epothilone B



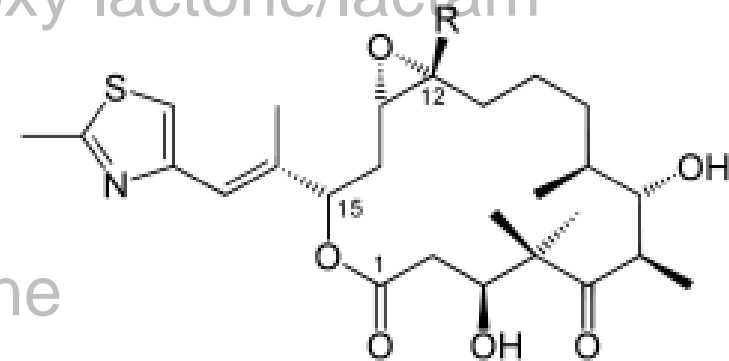
Ixabepilone (Ixempra)

**Figure 33.38** Epothilones.



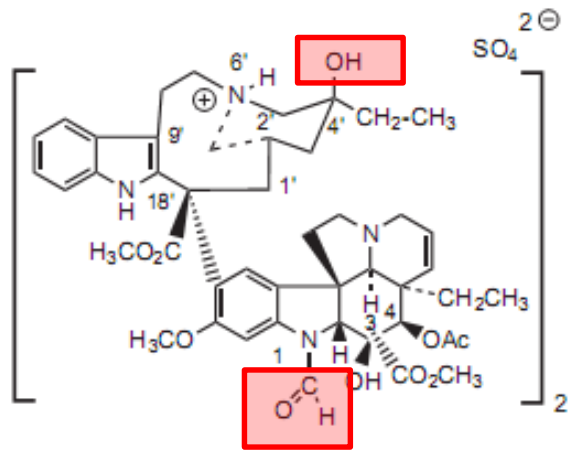
# V. Antimitotic Agents: 2. Epothilones: Chemistry & MOA

- Chemistry:
  - ✓ macrolide: 15-membered beta-hydroxy lactone/lactam
  - Epothilone A: lactone (R=H)
  - Epothilone B: lactone (R=CH<sub>3</sub>)
  - Ixabepilone: lactam instead of lactone
  - Superior efficiency to taxanes: simpler structure;
  - ✓ better water solubility: without side effects of cremophor
  - ✓ lower p-gp efflux
- MOA: inhibition of microtubule function;
- ✓ stops cell from proper dividing

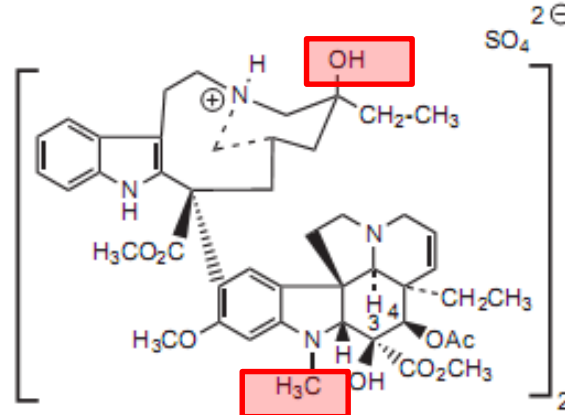


# V. Antimitotic Agents: 3. Vincas

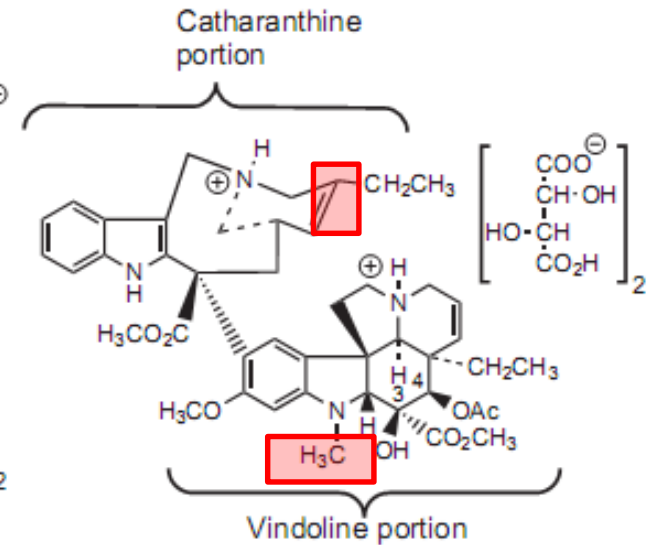
Vinca alkaloids:



Vincristine sulfate (Vincasar PFS)



Vinblastine sulfate (Velban)

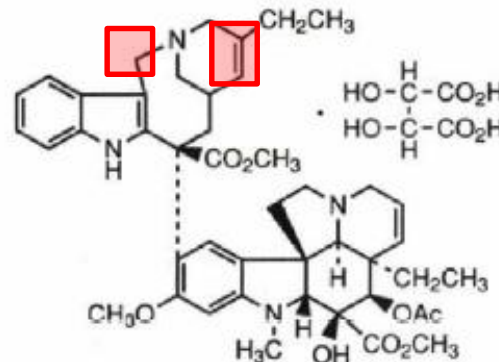


Vinorelbine tartrate (Navelbine)

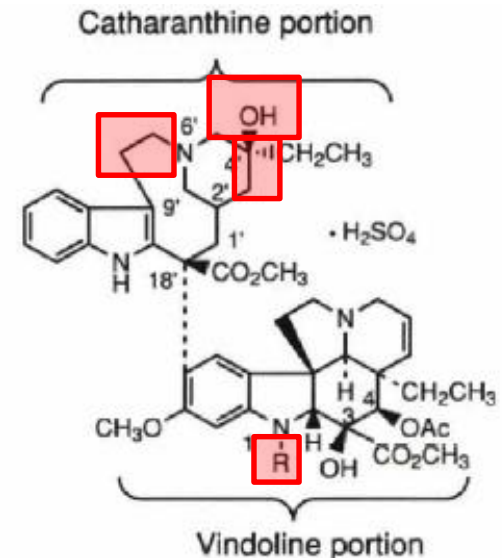
# V. Antimitotic Agents: 3.Vincas: Chemistry & SAR

- Chemistry: alkaloid: vindoline+ catharanthine(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

Vinca alkaloids:



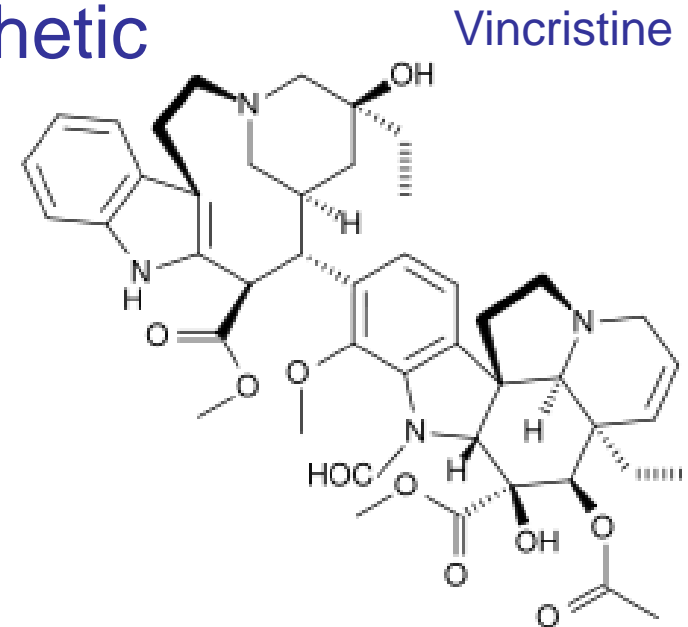
Vinorelbine tartrate  
(Navelbine)



Vincristine sulfate: R = CHO  
(Vincasar PFS)  
Vinblastine sulfate: R = CH<sub>3</sub>  
(Velban)

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

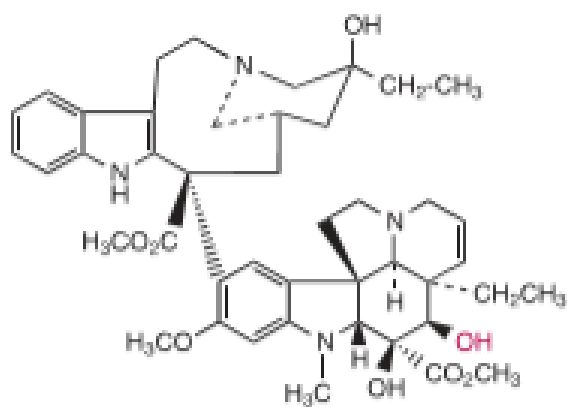
- Vinca alkaloids: vindoline + catharanthine
- ✓ Vinblastine (Velban<sup>®</sup>): lowest affinity
- ✓ Vincristine (Oncovin<sup>®</sup>): **highest** affinity
- ✓ Vinorelbine (Navelbin<sup>®</sup>): semisynthetic



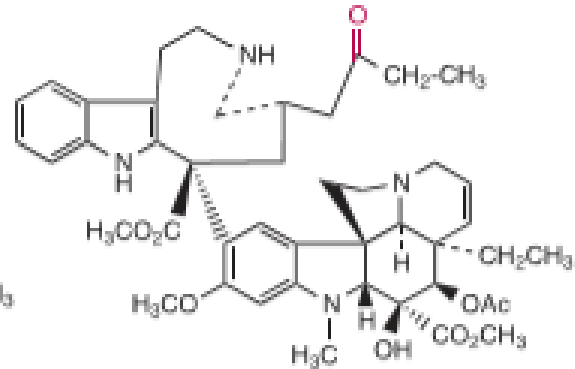
- MOA: interfere with the formation of the mitotic spindle



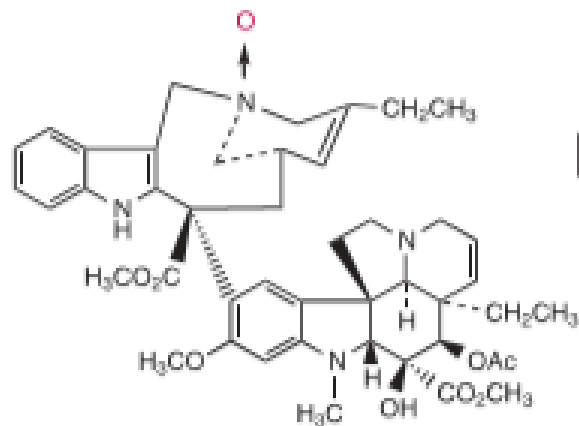
# Metabolism of Vincas



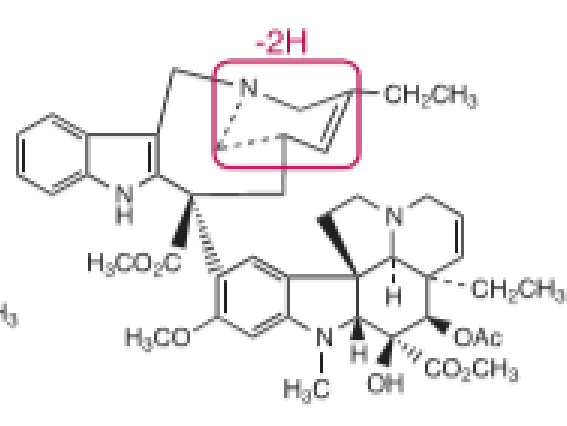
Desacetylvinblastine (active)



Vincristine M1 metabolite (inactive)



Vinorelbine N-oxide metabolite (inactive)



Vinorelbine didehydro metabolite (inactive)

**Figure 33.40** Major metabolites of vinca alkaloids.