Plant products: Vinca Alkaloids

The alkaloids are composed of a catharanthine moiety containing the indole subunit and the vindoline moiety containing the dihydroindole subunit joined by a carbon–carbon bond.

Vincristine and vinblastine differ only in the group attached to the dihydroindole nitrogen, which is a methyl group in vinblastine and a formyl group in vincristine.

Vinorelbine is a semisynthetic material resulting from loss of water across the 3`,4` bond and first prepared by the use of a modified Polonovski reaction of vinblastine followed by hydrolysis.

The vincas bind to tubulin disrupting formation and function of the mitotic spindle. (binding to tubulin to prevent polymerization or binding to the microtubules to prevent depolymerization).

The mitotic spindle is composed of the microtubules, which function as part of the cell's cytoskeleton and are important in maintaining cellular shape.

They are also involved in transport within the cell and cell signaling as well as playing a pivotal role in the movement of chromosomes during mitosis.

Vinca Alkaloids

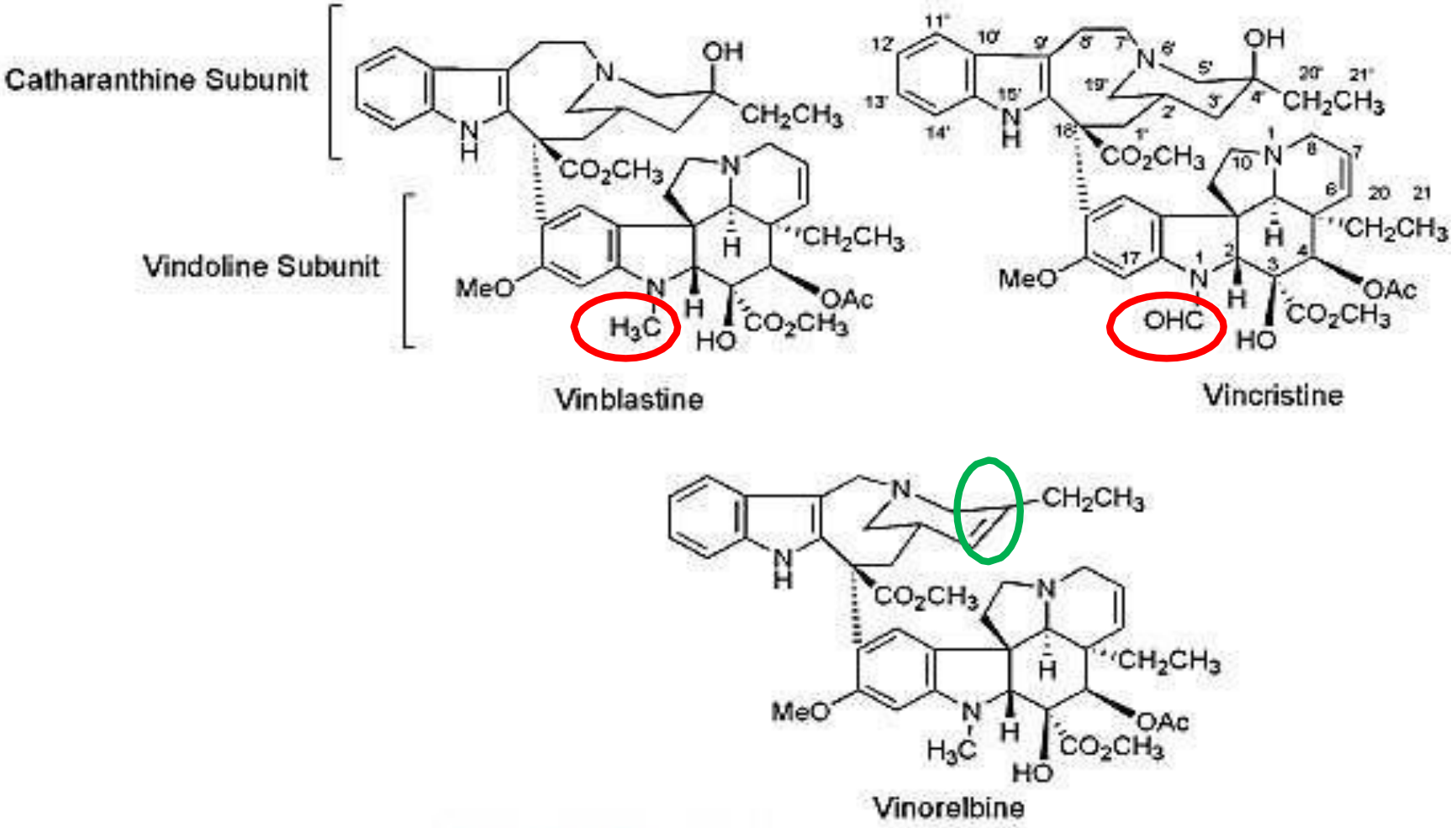


Figure 10.21 • Structures of vinca alkaloids.

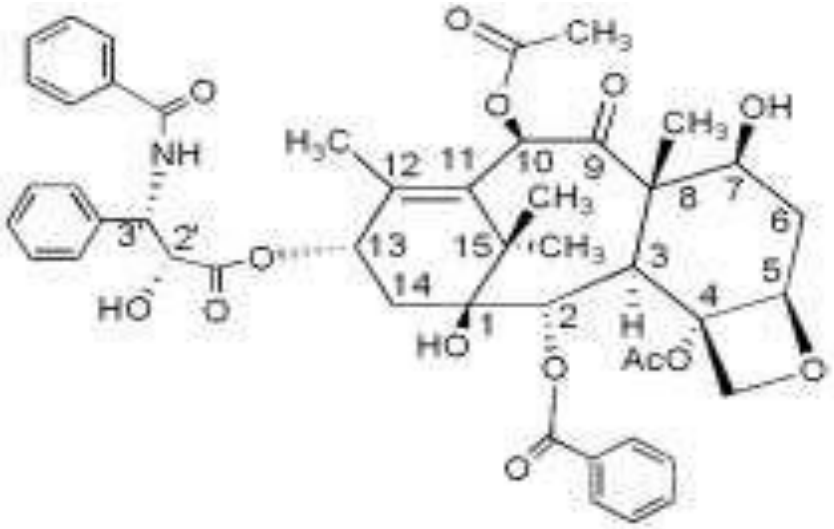
Taxanes

The taxanes, specifically, taxol (or paclitaxel) was isolated from the bark of the pacific yew tree, proved to be active against various cancer models; These drugs bind to beta-tubulin subunits of microtubules. Paclitaxel is one of several cytoskeletal drugs that target tubulin.

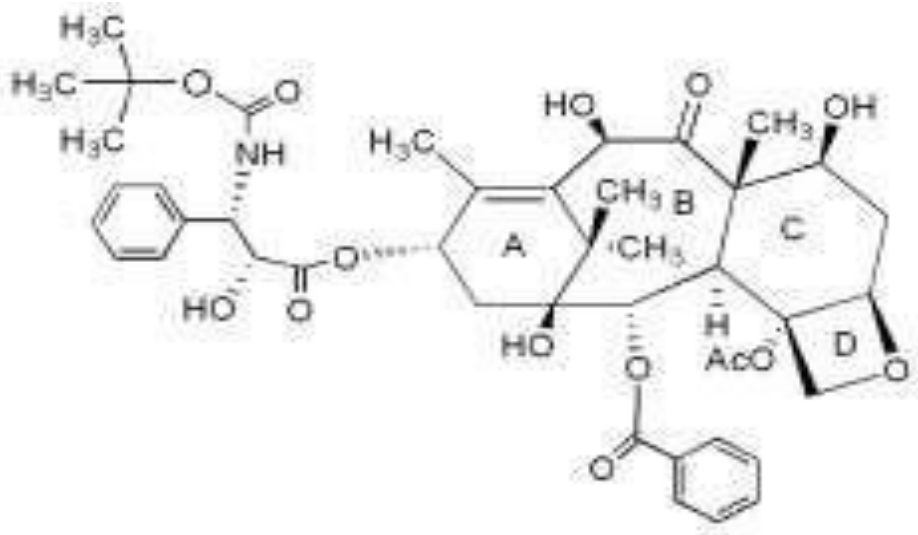
The major difference between Colchicine and Paclitaxel is that Colchicine inhibits the microtubule assembly whereas Paclitaxel stabilizes and protects microtubule against disassembly.

Paclitaxel or Taxol enhances the polymerization of tubulin to stable microtubules and also interacts directly with microtubules, stabilizing them against depolymerization.

Hence, it interferes with the spindle formation process. Chromosomes are unable to move to the opposite sides of the dividing cells. Cells division is inhibited and eventually, cell death is induced



Paclitaxel



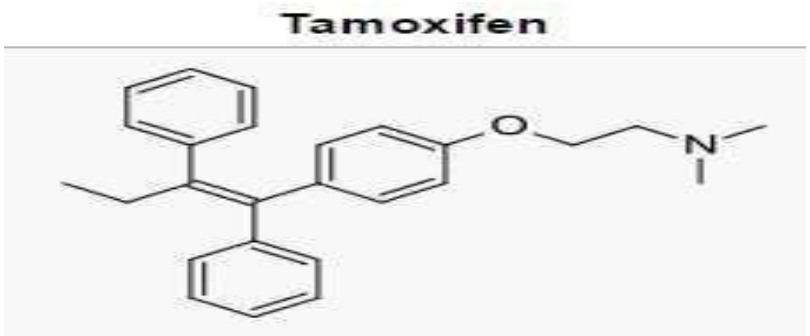
Docetaxel

Figure 10.22 • Structures of the taxanes.

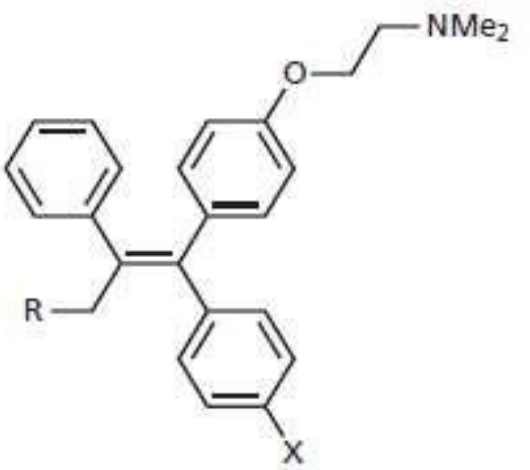
Hormones and their antagonists

Anti-estrogens

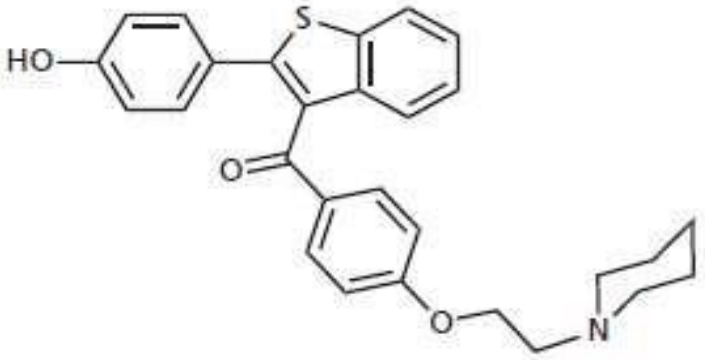
Tamoxifen is an antagonist of the estrogen receptor in breast tissue via its active metabolite, 4-hydroxytamoxifen which have 30-100 times more affinity with the estrogen receptor than tamoxifen itself. preventing estrogen from binding to its receptor, blocking cancer cell growth.



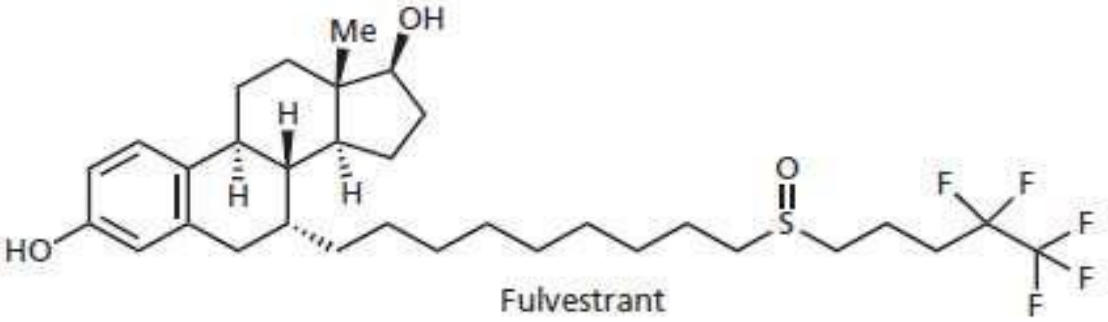
Anti-estrogens



Tamoxifen; X=H, R=Me
4-Hydroxytamoxifen; X=OH, R=Me
Toremifene ; X=H, R=CH_2Cl



Raloxifene



Fulvestrant

4-Hydroxytamoxifen binds to estrogen receptors competitively (with respect to the endogenous agonist estrogen) in tumor cells and other tissue targets, producing a nuclear complex that decreases DNA synthesis and inhibits estrogen effects.

It is a nonsteroidal agent with potent antiestrogenic properties which compete with estrogen for binding sites in breast and other tissues.

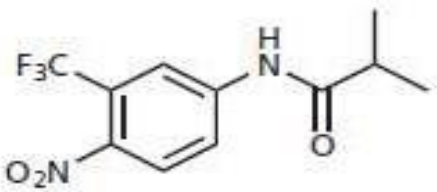
Anti-androgens

Flutamid is an oral, non steroidal antiandrogen drug primarily used to treat prostate cancer.

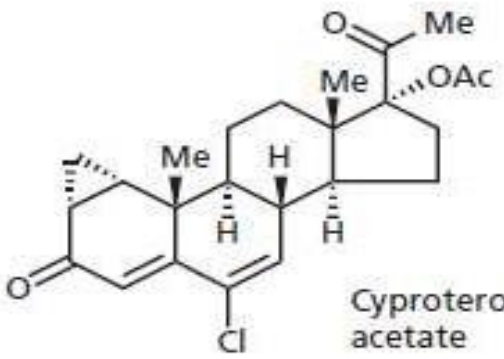
It acts as a silent antagonist of the androgen receptor (AR), competing with testosterone and its powerful metabolite,

dihydrotestosterone (DHT) for binding to ARs in the prostate gland.

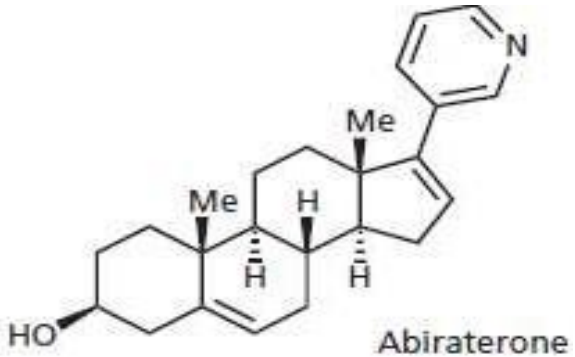
cyproterone acetate used to treat prostate cancer and work by blocking the action of androgens at their receptors.



Flutamide



Cyproterone acetate

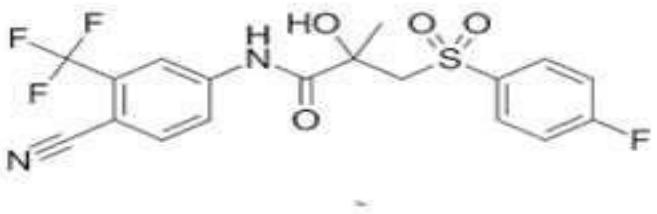


Abiraterone

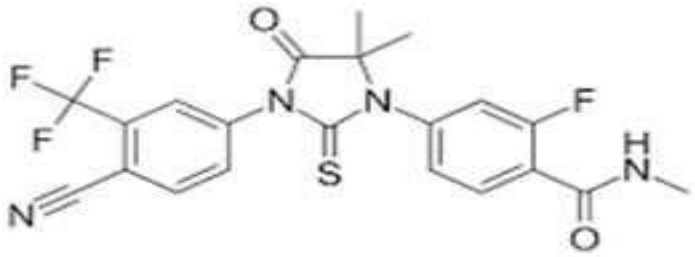
- A different approach which has recently proved successful is to inhibit a metabolic enzyme called 17α-hydroxylase-17(20)-lyase . This is a cytochrome P450 enzyme which is involved in the biosynthesis of androgens from cholesterol and so its inhibition results in lowered androgen levels.
- Abiraterone is a potent and selective inhibitor of this enzyme, and was approved in 2011 for the treatment of prostate cancer.

The pyridine ring plays a key role in its action by interacting with the iron of haem in the enzyme's active site.

The medication has largely been replaced by newer and improved NSAAs (nonsteroidal antiandrogen), namely bicalutamide and enzalutamide, due to their better efficacy, tolerability, safety, and dosing frequency (once per day), and is now relatively little-used.



Bicalutamide



Enzalutamide