Chemotherapeutic Agents

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Drugs to Treat Neoblastic Agents- Section 3- DNA Topoisomerase Poisons & DNA Intercalating Agents

SRAmini Mar2024

Foye's 2019

CHAPTER 33

Drugs Used to Treat Neoplastic Diseases

Victoria F. Roche

Foye's2019

PART III • Pharmacodynamic Agents

SECTION 7 DRUGS IMPACTING INFECTIOUS AND NEOPLASTIC DISEASE PROCESSES

Foye's 2019

CHAPTER 33

Drugs Used to Treat Neoplastic Diseases

Victoria F. Roche

TOPOISOMERASE POISONS

CAMPTOTHECINS

- Irinotecan
- Topotecan

EPIPODOPHYLLOTOXINS

- Etoposide
- Teniposide

ANTHRACYCLINES AND ANTHRACENEDIONES

- Aldoxorubicin
- Daunorubicin
- Doxorubicin
- Epirubicin
- Idarubicin
- Mitoxantrone
- Valrubicin

MISCELLANEOUS ANTICANCER AGENTS

- Arsenic trioxide
- Bexarotene
- Bleomycin
- Dactinomycin
- Gemtuzumab ozogamicin conjugate
- Inotuzumab ozogamicin conjugate
- Mitomycin
- Mitotane
- Trabectedin
- Tretinoin

Pharmacologic Classification of Chemotherapeutic Agents

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

II. Antimetabolites

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

IV. DNA interacting antibiotics: miscellaneous antibiotics:
IV.1. Phenoxazine; IV.2. Glycopeptide; IV.3. Mitomycin

III. DNA Topoisomerase Poisons & DNA Intercalating Agents

- Natural compounds:

✓III.1.Camptothecins: alkaloid

✓III.2.Epipodophyllotoxins

- Antibiotics:

✓III.3.Anthracyclines

✓III.4.Anthracenediones

Topoisomerase

- Topoisomerase IIα (TopII):

✓ cleaves double stranded DNA during replication phase via a transesterification reaction,

✓ involving a topoisomerase tyrosine residue & a terminal 5'-phosphate,

✓ but through a reverse transesterification,

✓ repairs its own damage after replication is complete.

- Topoisomerase I (TopI):

✓ functions in essentially the same way, but cuts and a religates a single DNA strand.

- Topoisomerase Poison:

✓ stimulate DNA cleavage reaction,

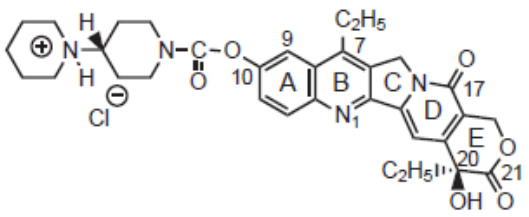
✓ but inhibit the DNA resealing activity of the enzymes,

✓ leaving the DNA irreversibly damaged and unable to replicate.

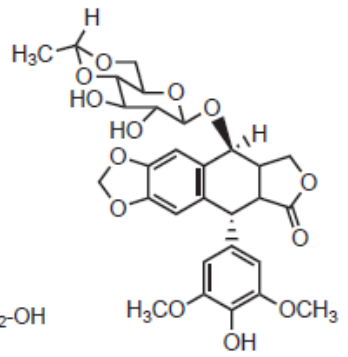
Chemical Classification for III. Topoisomerase Poisons & DNA Intercalating Agents & DNA Interacting Antibiotics

III.1. Camptothecins

Camptothecins

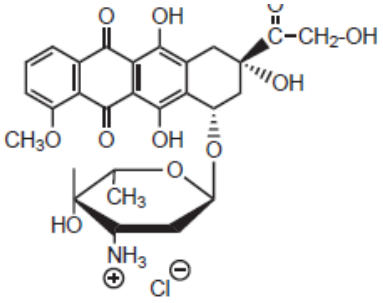


Epipodophyllotoxins



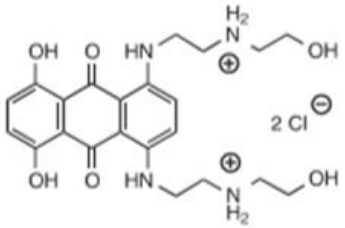
III.2. Epipodophyllotoxins

III.3. Antibiotics: anthracyclines



Doxorubicin hydrochloride
(Adriamycin)

III.4. Anthracenediones



Mitoxantrone hydrochloride
(Novantrone)

Chemical Classification for Topoisomerase Poisons & DNA Intercalating Agents

- Natural compounds:

III.1. Camptothecines: Topotecan; Irinotecan

III.2. Epipodophyllotoxins: Etoposide;Teniposide

- Antibiotics:

III.3. Anthracyclines:

✓Doxorubicin(Adriamycin); Daunorubicin;

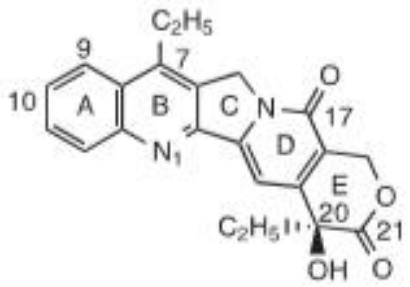
✓Epirubicin; Idarubicin; Valrubicin

III.4. Anthracendiones:

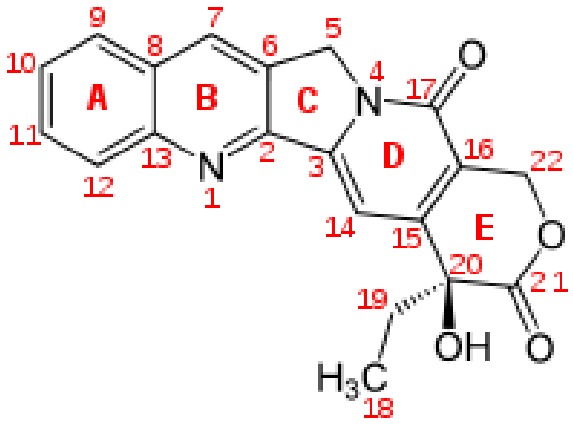
✓Mitoxantrone;

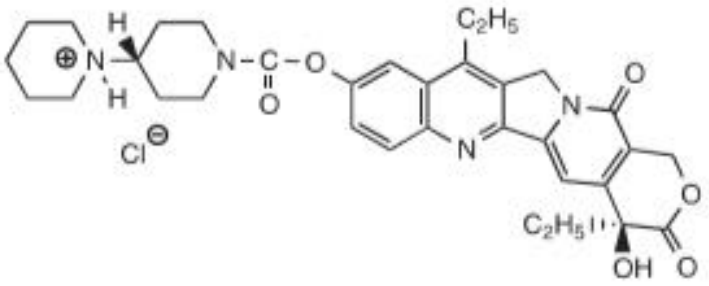
III.Topoisomerase Poisons:
III.1. Camptothecins

- Camptothecins: Irinotecan
  Topotecan

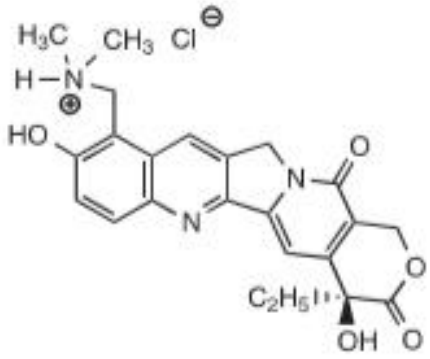


Camptothecin
(water-insoluble natural product)





Irinotecan hydrochloride
(Camptosar, Oinvyde)



Topotecan hydrochloride
(Hycamtin)

Figure 33.25 Camptothecin topoisomerase I (TopI) poisons.

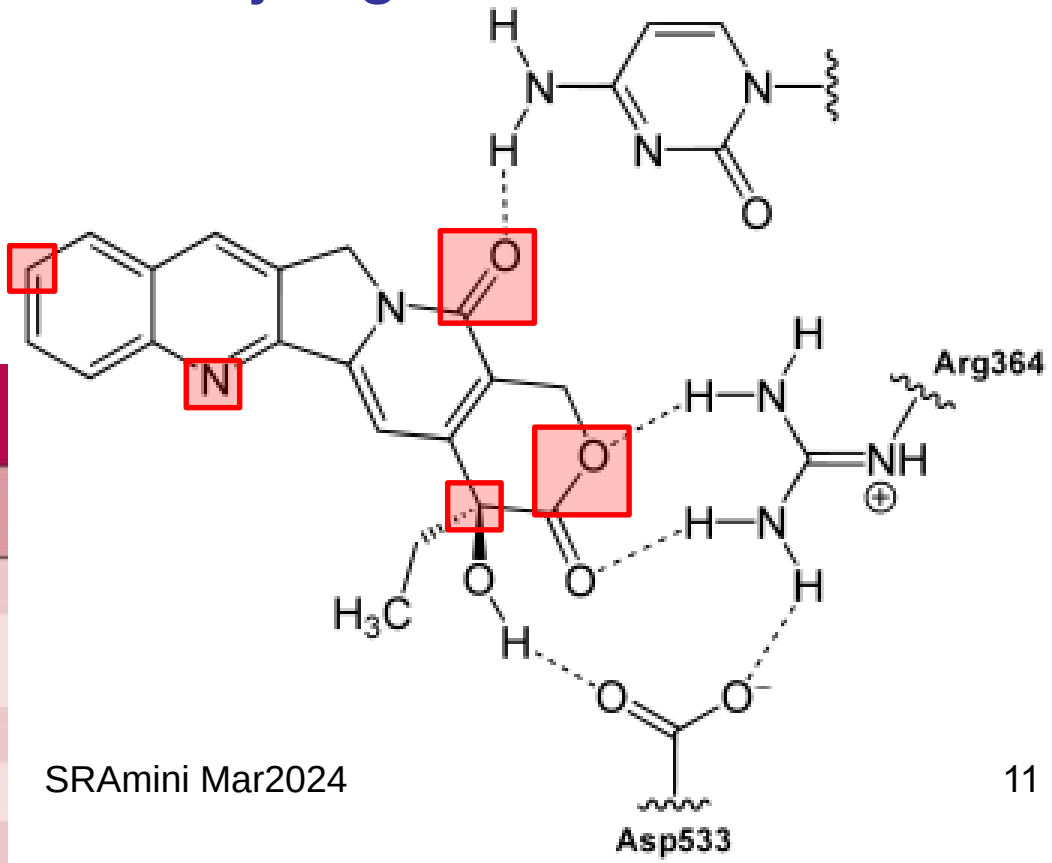
III.1. Camptothecins: Topo I Interactions Sites

- Functional groups:N1,OatC10,C17(CO),C20(OH),C21(CO)-O
- Bulky substituents at C7, C9 & C10:

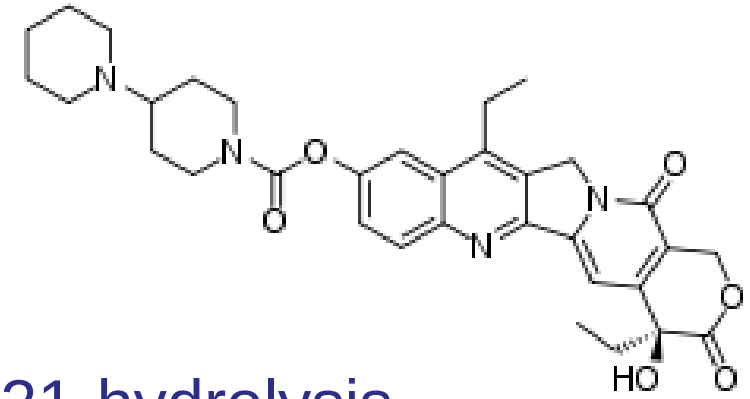
✓ project the structure into major groove of DNA, do not hinder binding.

Table 33.11 Topotecan Topisomerase I Interactions

Topotecan Functional Group	Topoisomerase I Residue
Pyridine N_1	Arg364
C_{10}-OH	Enzyme-associated water (H-bond)
C_{17}-pyridone carbonyl	Asn722
C_{20}-OH	Asp533 (H-bond)
C_{21}-lactone carbonyl	Tyr723-phosphate, Lys532



Metabolism of Irinotecan



- C21-hydrolysis
- C10:

✓ oxidation;

✓ O-dealkylation:

phenolic SN38: active metabolite

✓ conjugation

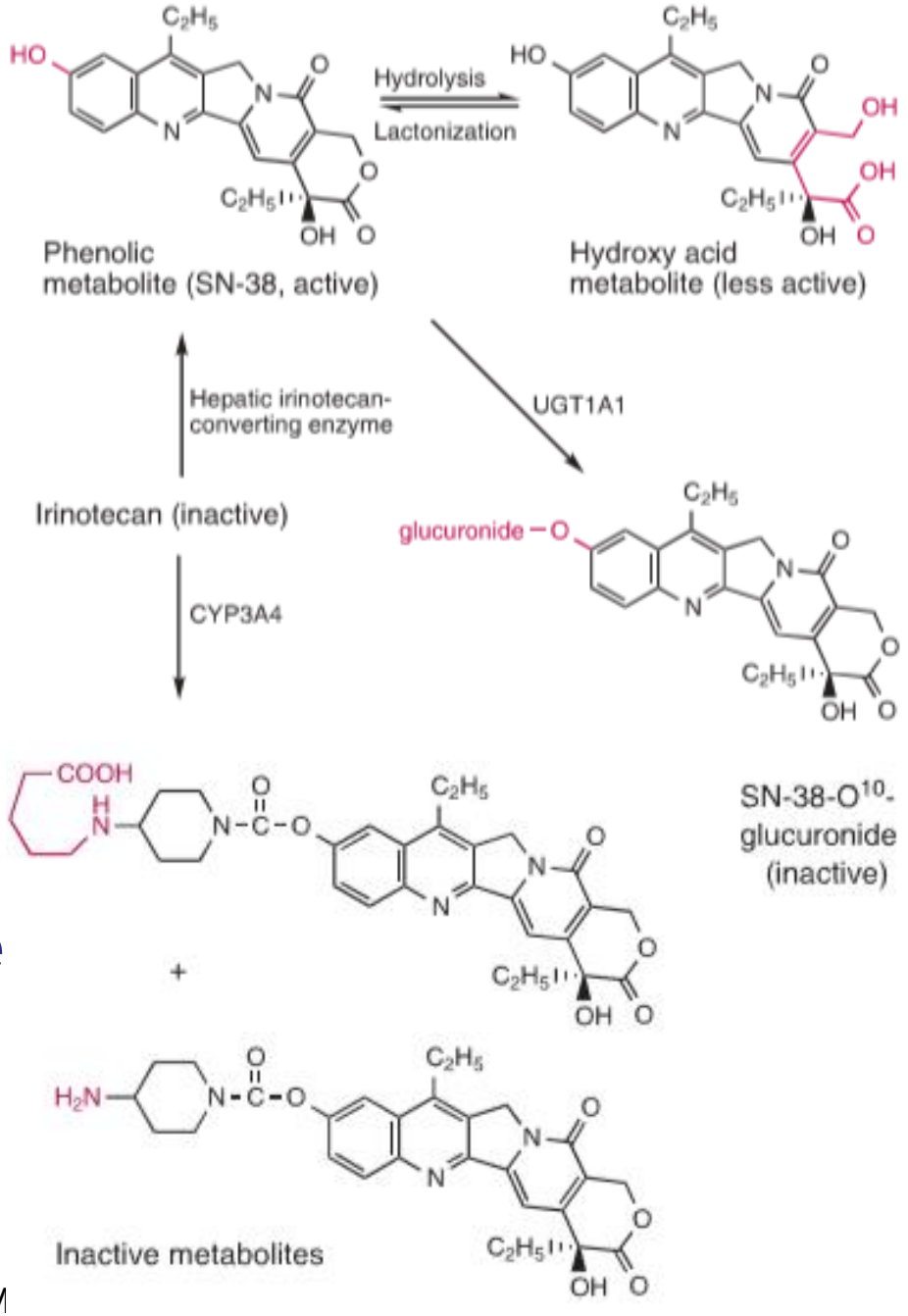
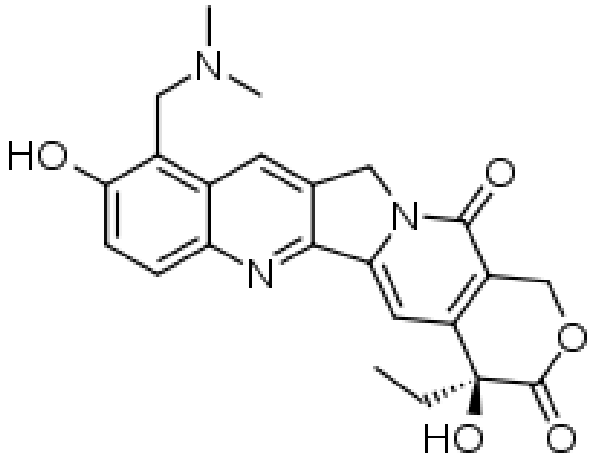
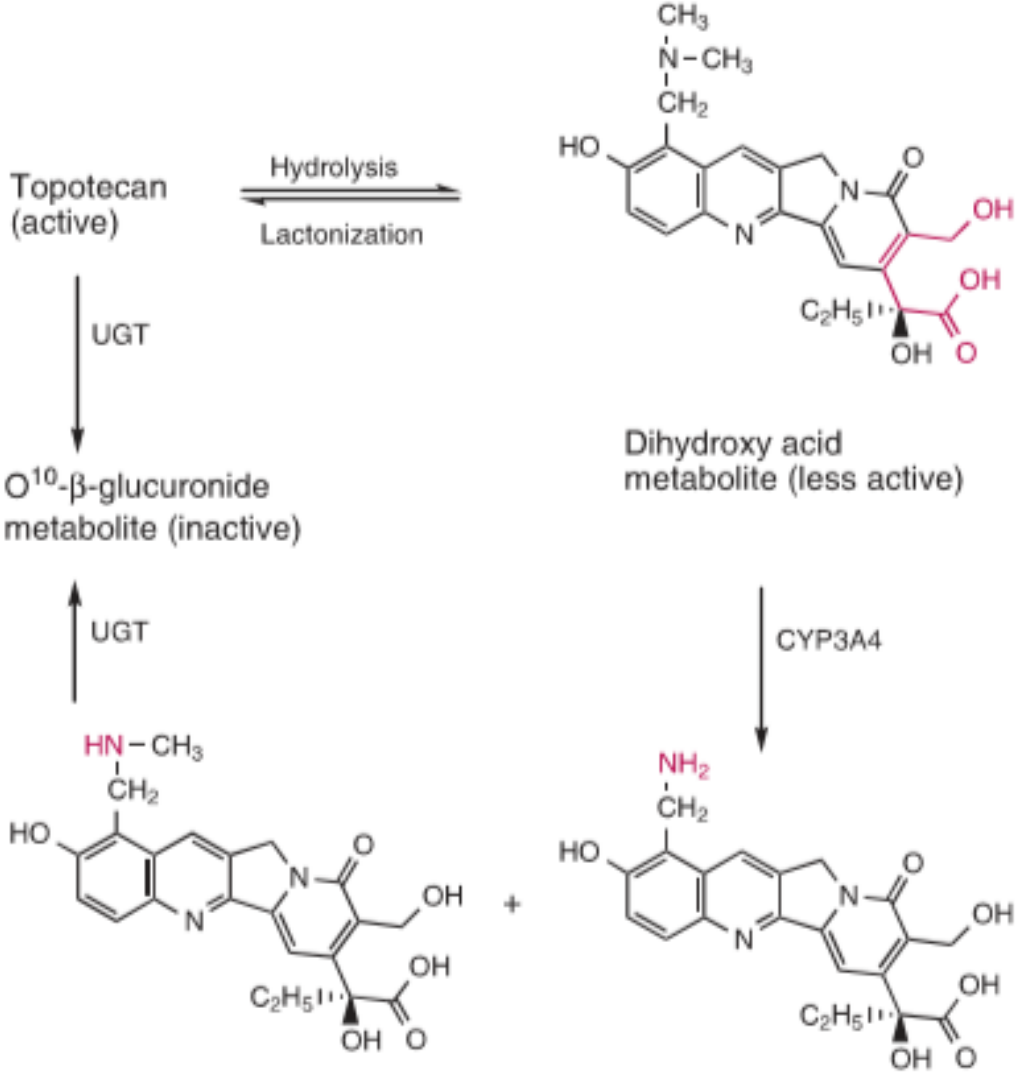


Figure 33.26 Irinotecan metabolism.

Metabolism of Topotecan

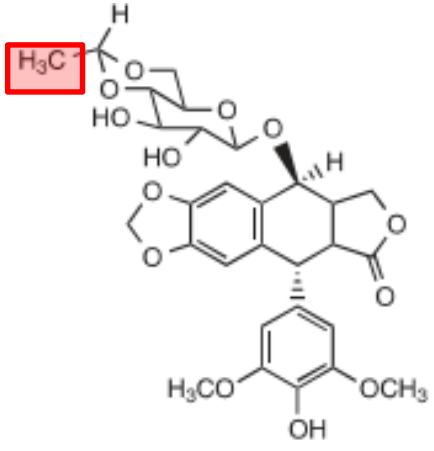


- C21-hydrolysis
- C9-N-dealkylation
- C10: conjugation

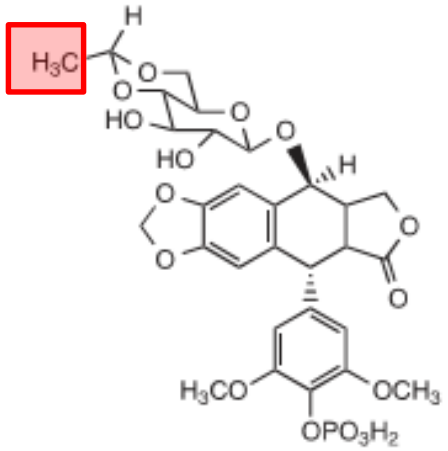


III. Topoisomerase Poisons: 2- Epipodophyllotoxins

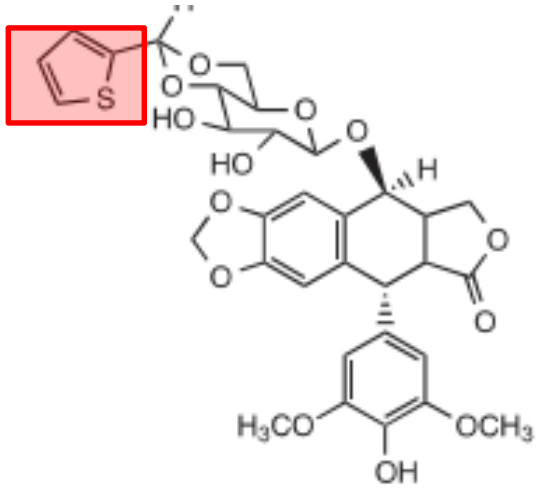
- Epipodophyllotoxin: Etoposide
  Teniposide



Etoposide
(VePesid)



Etoposide phosphate
(Etopophos)



Teniposide hydrochlorde
(Vumon)

Figure 33.28 Epipodophyllotoxin topoisomerase IIα (TopIIα) poisons.

III.2. Epipodophyllotoxins: Chemistry & SAR

- Chemistry: glycosidic derivative of podophyllotoxin:

✓ major component of resinous podophyllin isolated from root of mayapple

✓ semisynthetic glycosidic derivative of podophyllotoxin

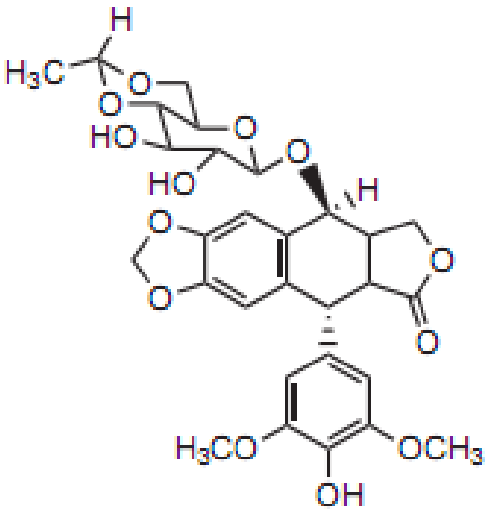
✓ difference in β-D-glucopyranosyl substituent (methyl/thienyl)

✓ solubility enhancers: polysorbate 80 (Tween)

or polyoxymethylated castor oil (cremophore)

- Possess various functional groups
- Critical SAR: ... phenol & …
- Binding site study in recent studies:

  to develop rational more potent agents



Etoposide (VePesid)

Proposed Interaction Sites for Etoposide

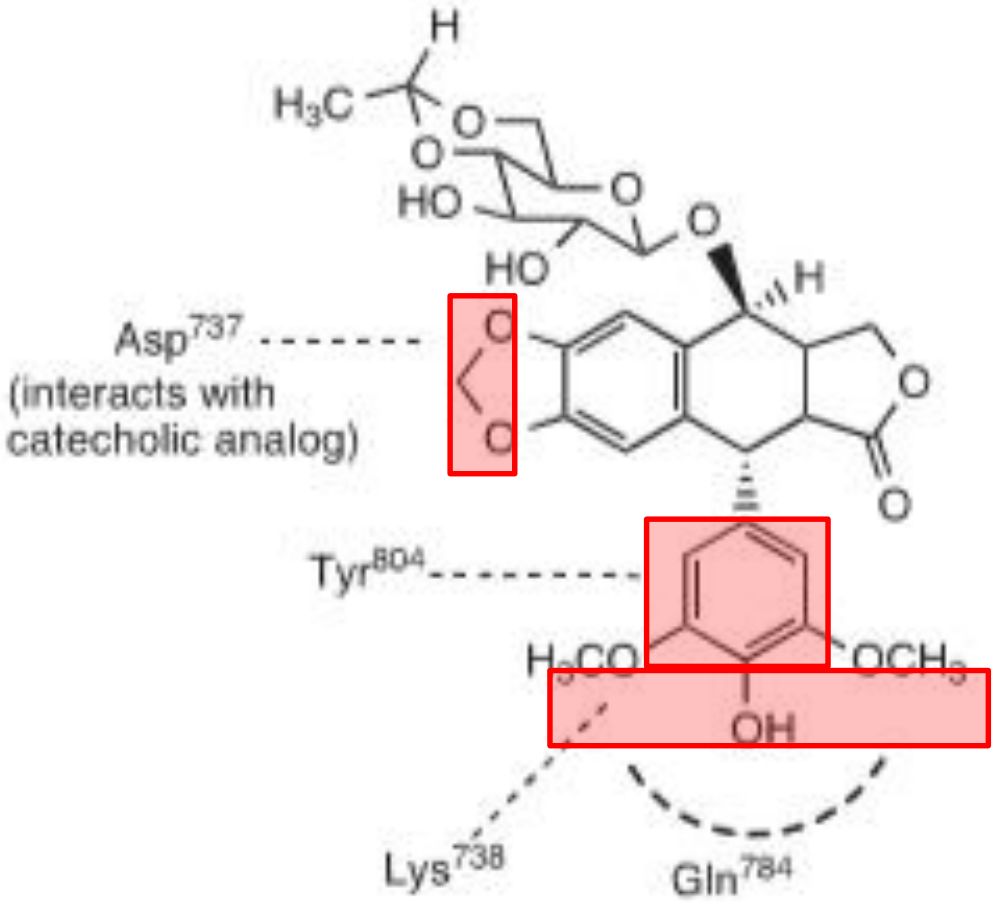


Figure 33.29 Proposed etoposide-TopIIα binding interactions.

Metabolism of Epipodophyllotoxin

- Lactone hydrolysis
- Phenolic OH conjugation
- O-de-alkylation: ortho-quinone

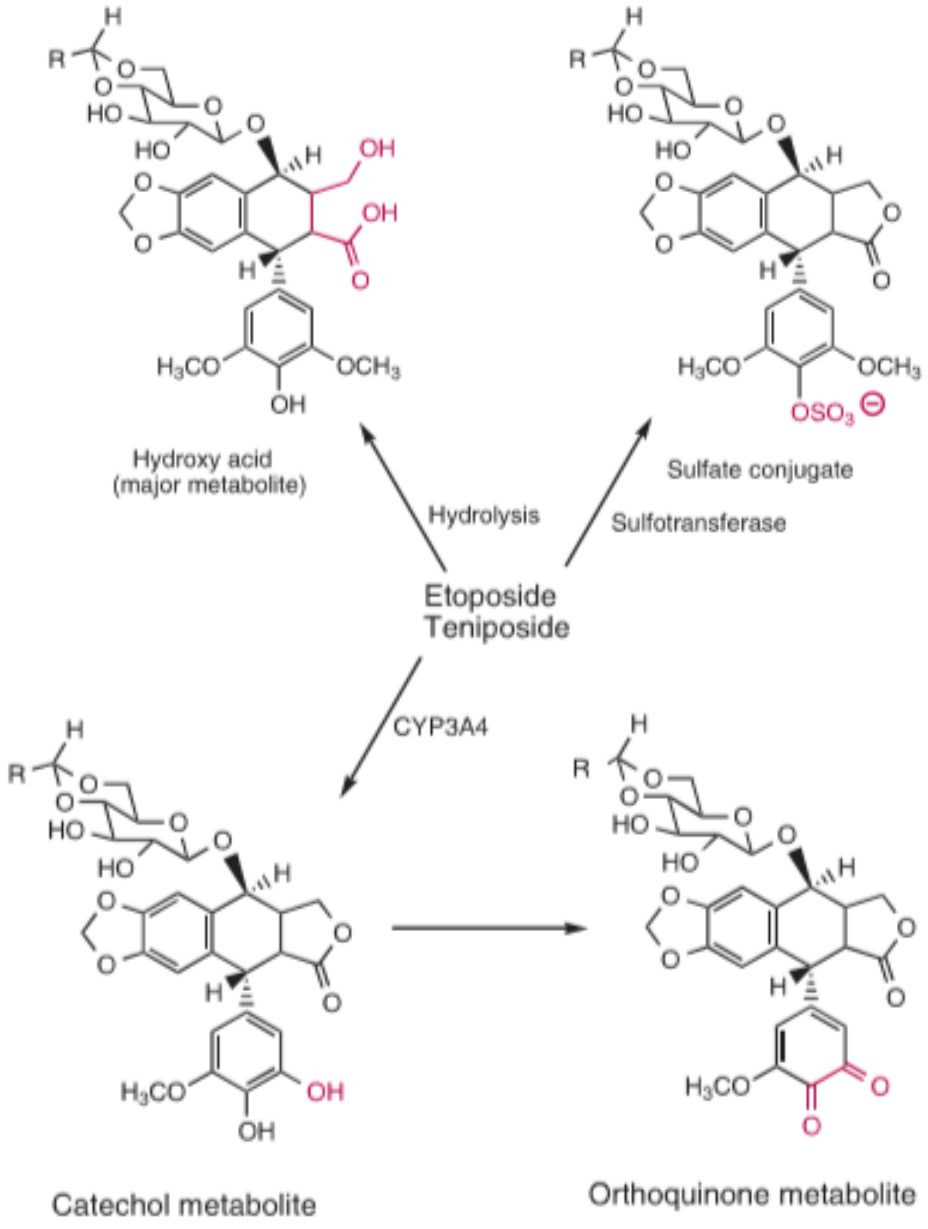
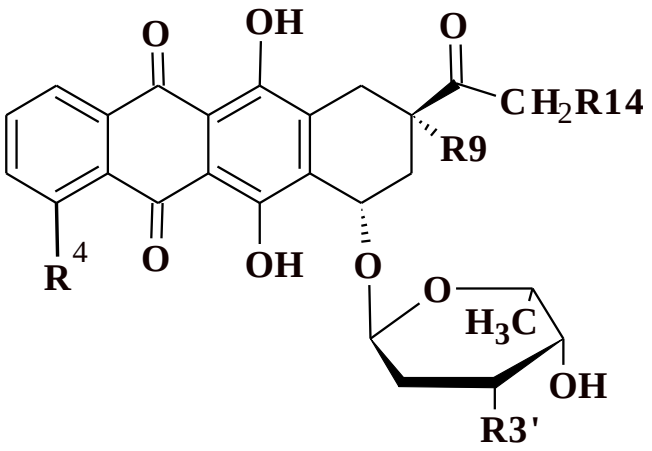


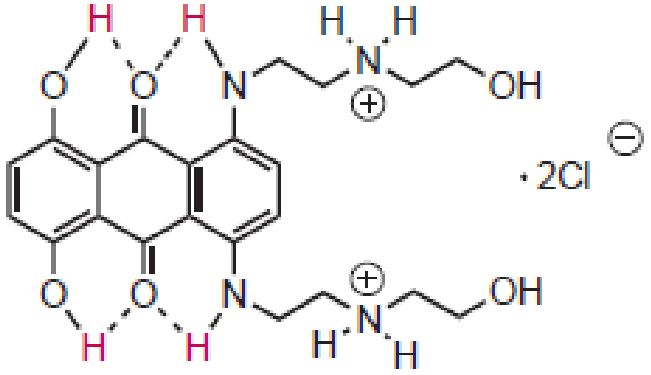
Figure 33.30 Epipodophyllotoxin metabolism.

III. DNA Topoisomerase Poisons&DNA Intercalating Agents: III. 3. Anthracyclines; III. 4. Anthracenediones

III. 3. Anthracyclines:



III. 4. Anthracenediones:



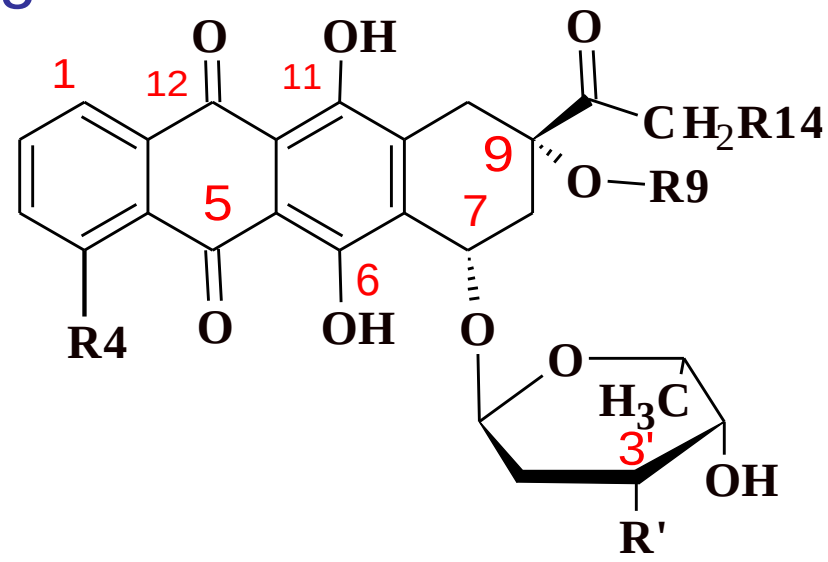
III. 3. Anthracyclines: Source & Structure

- From Streptomyces --- semi-synthetic derivatives
- Chemistry:

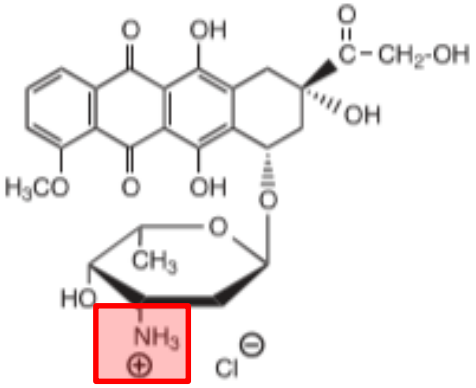
✓ aglycon region: tetracyclic quinone: anthraquinone

✓ glycon region: C7: glycosidic bond:

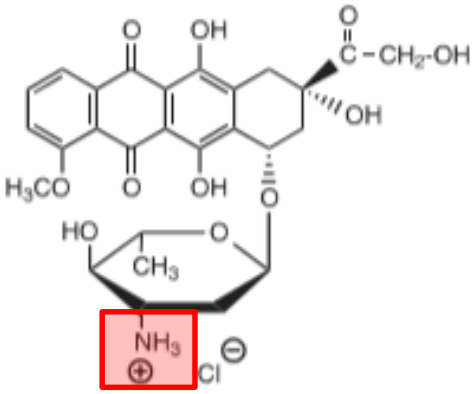
daunosamine: amino(3'-NHR)-sugar



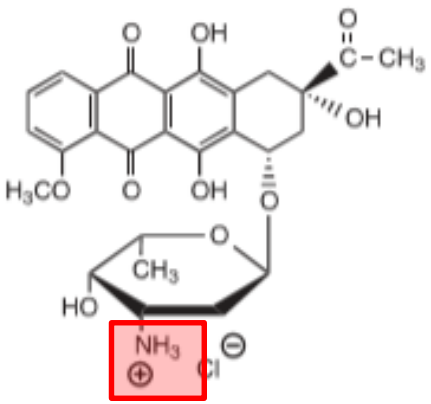
III. DNA Topoisomerase Poisons & DNA Intercalating Agents:
III. 3. Anthracyclines:1st, 2nd & 3rd Generations



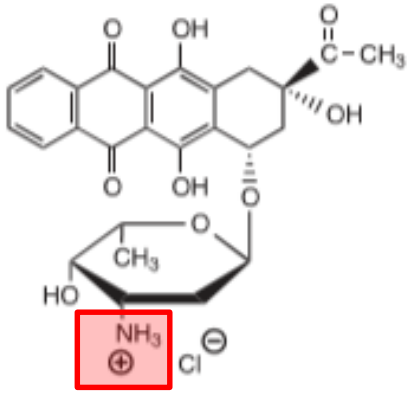
Doxorubicin hydrochloride
(Adriamycin)



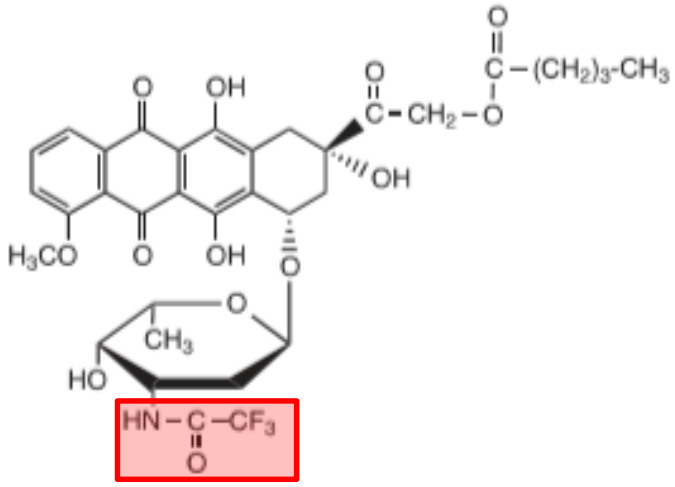
Epirubicin hydrochloride
(Ellence)



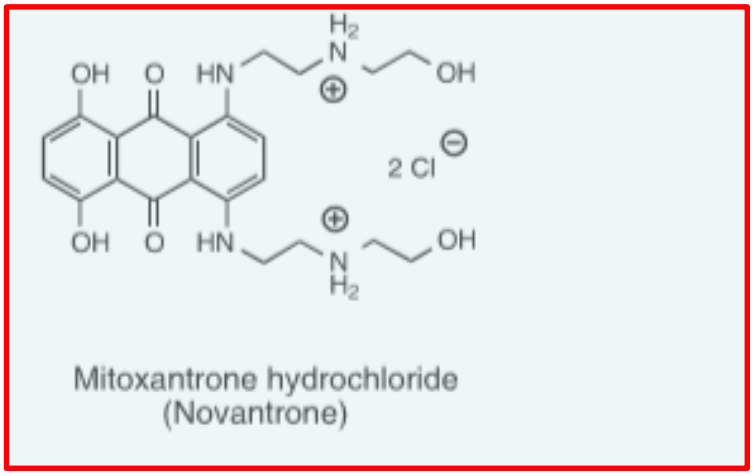
Daunorubicin hydrochloride
(Cerubidine)



Idarubicin hydrochloride
(Idamycin PFS)



Valrubicin
(Valstar)



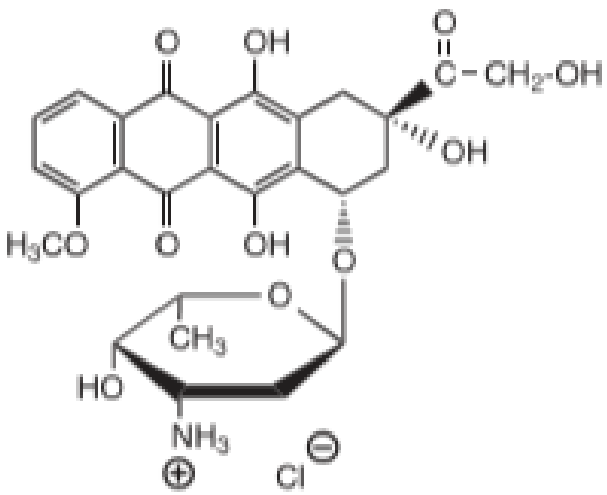
Mitoxantrone hydrochloride
(Novantrone)

Figure 33.34 Anthracycline and related anticancer agents.

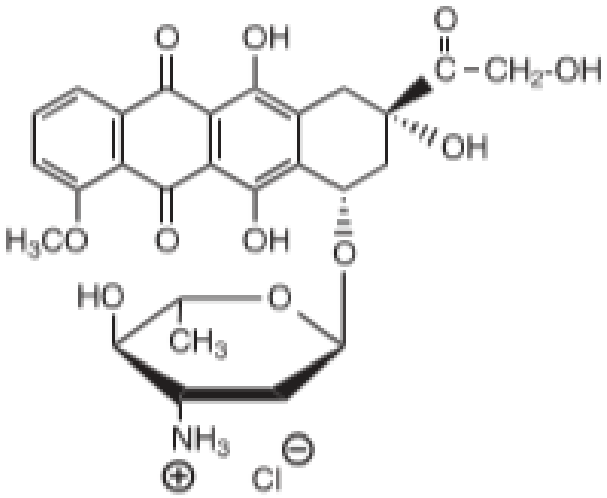
III. DNA Topoisomerase Poisons & DNA Intercalating Agents:
III. 3. Anthracyclines

- Follow SAR in each of the following structures:

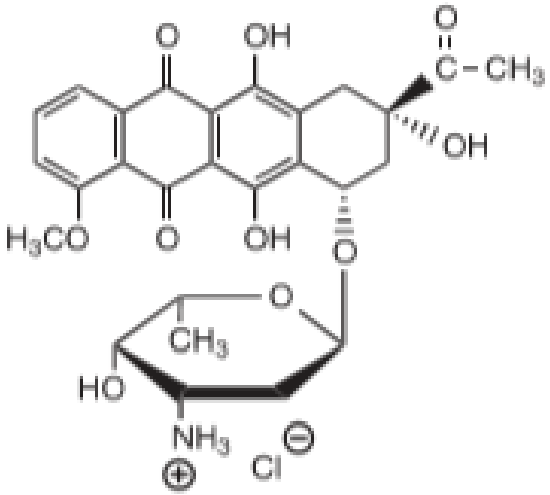
✓ Doxorubicin (Adriamycin); Epirubicin; Daunorubicin



Doxorubicin hydrochloride
(Adriamycin)



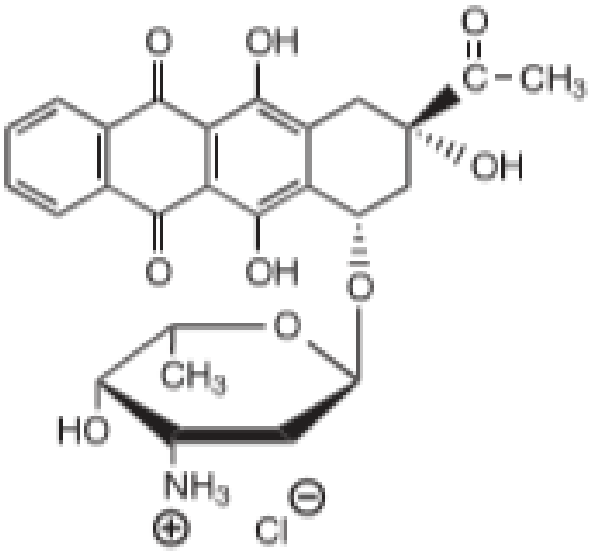
Epirubicin hydrochloride
(Ellence)



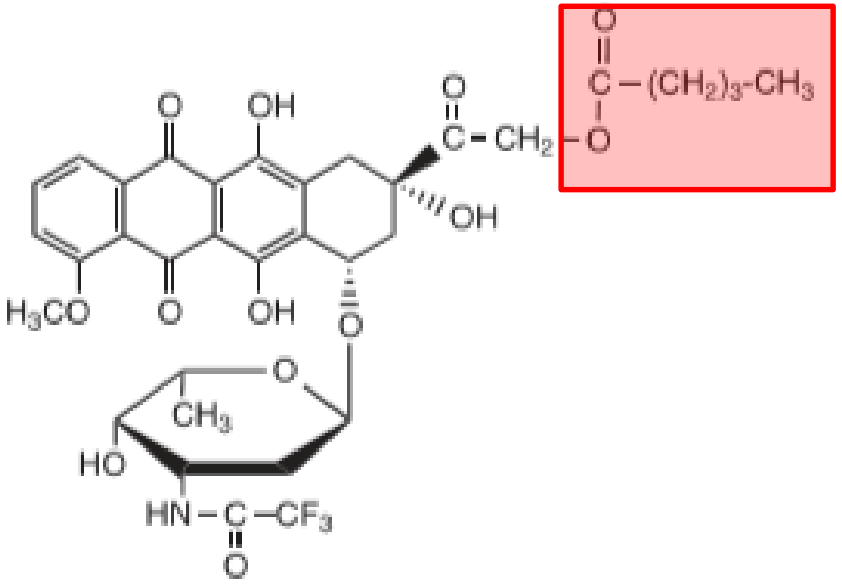
Daunorubicin hydrochloride
(Cerubidine)

III. DNA Topoisomerase Poisons & DNA Intercalating Agents:
III. 3. Anthracyclines-Contd.

- ✓ Follow SAR in each of the following structures:
- ✓ Idarubicin; Valrubicin



Idarubicin hydrochloride
(Idamycin PFS)



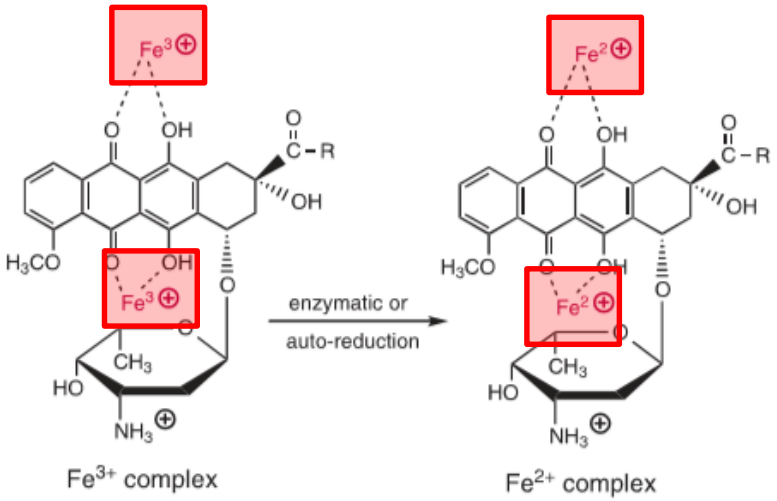
Valrubicin
(Valstar)

Free Radical Formation & Ferrous Chelation in Anthracyclines

- Superoxide radical anion: :O=O.$^-$
- Hydroxyl radical: .OH

✓ ferrous affects in [.OH]

✓ fenton reaction



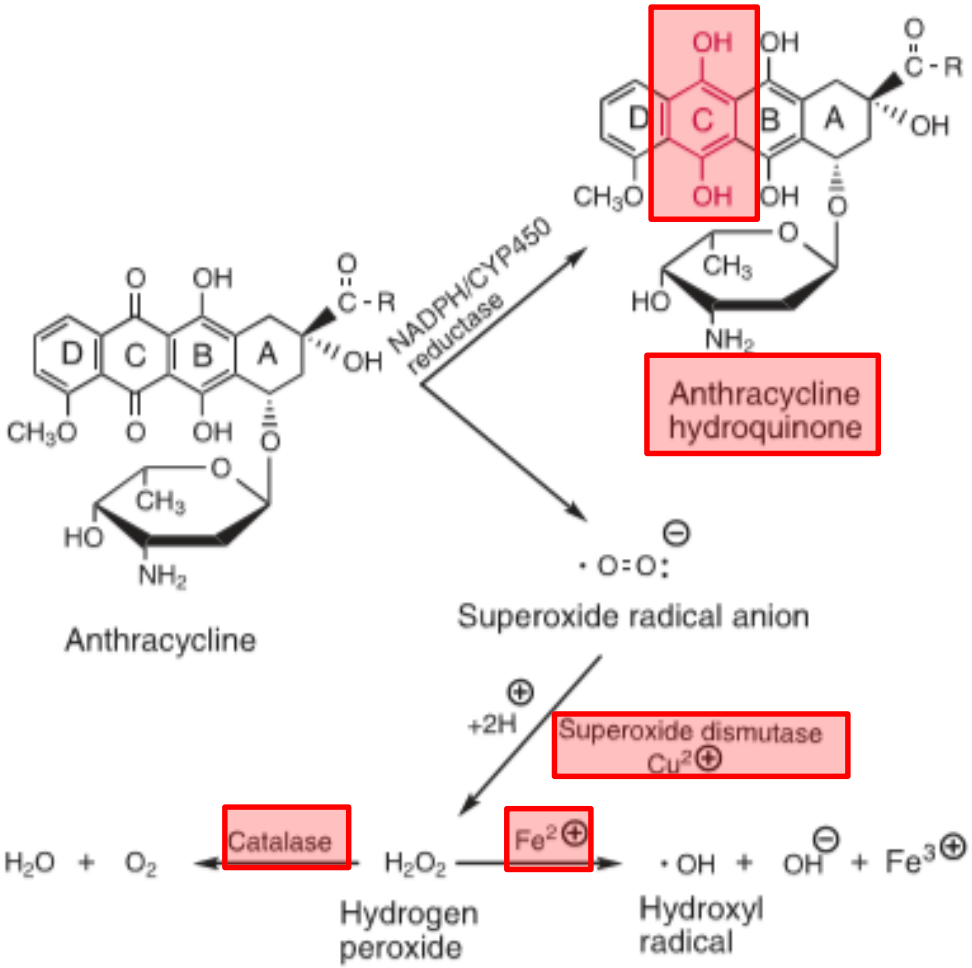
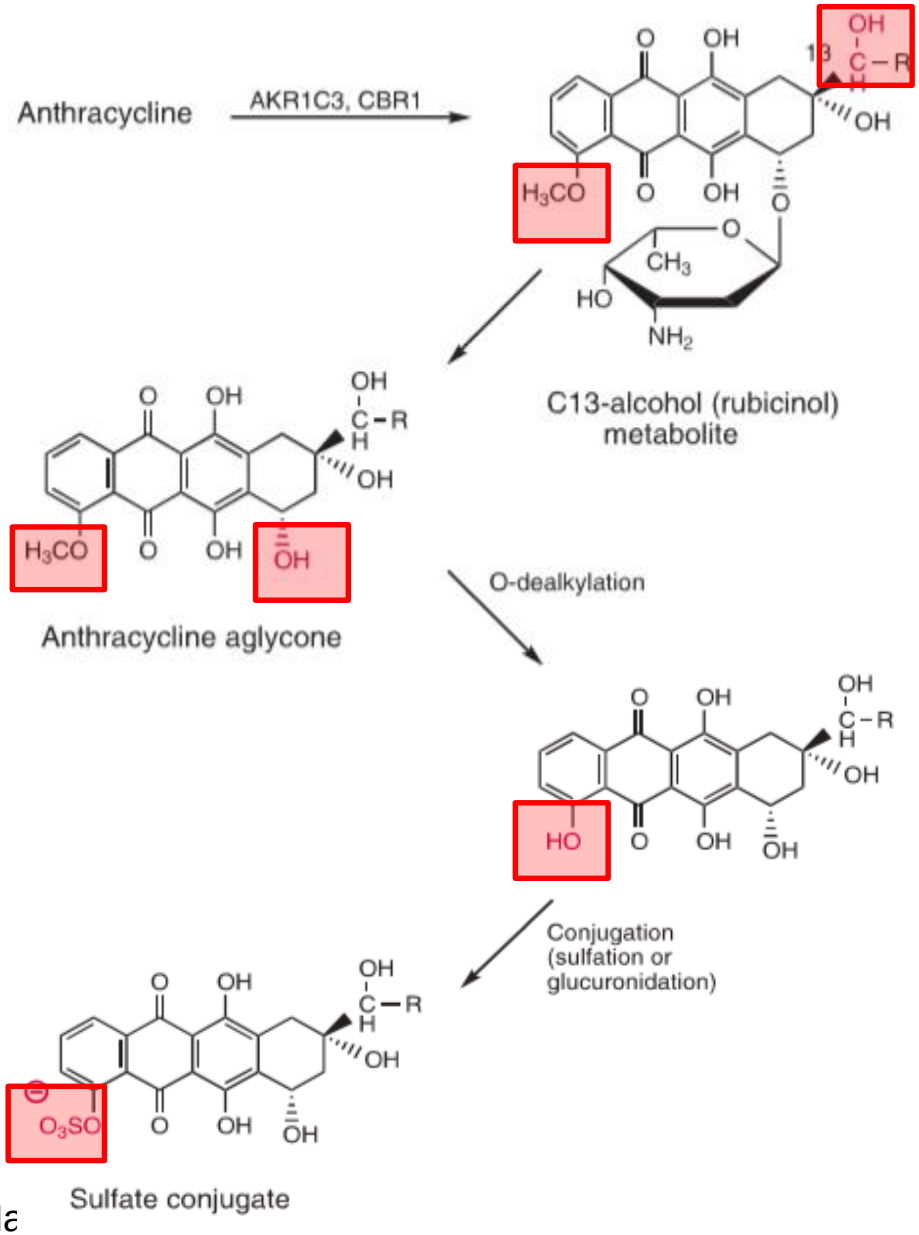


Figure 33.32 Anthracycline-mediated free radical formation.

Metabolism of Anthracyclines

- Rubicinols by:
- ✓ Aldo Keto Reductase (AKR)
- ✓ CarBonyl Reductase (CBR)
- ✓ affected by C14: CH_3 / CH_2OH

- 7-hydroxy / deoxy derivative:
- ✓ aglycone derivative



SRAmini Ma

Figure 33.33 Anthracycline metabolism (AKR, aldo-keto reductase; CBR, carbonyl reductase).