Chemotherapeutic Agents:

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

SRAmini Nov2024

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:
Natural compounds: 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

Pharmacologic lassification of Chemotherapeutic Agents- Contd.

V. Mitosis inhibitors: natural alkaloids

VI. Tyrosine Kinase and related inhibitors

VII. Histone deacetylase inhibitors

VIII. Immunomodulators

IX. Miscellaneous: hormonal, and specific agents

III. DNA Topoisomerase Poisons & DNA Intercalating Agents

- Natural compounds:

✓III.1.Camptothecins: alkaloid

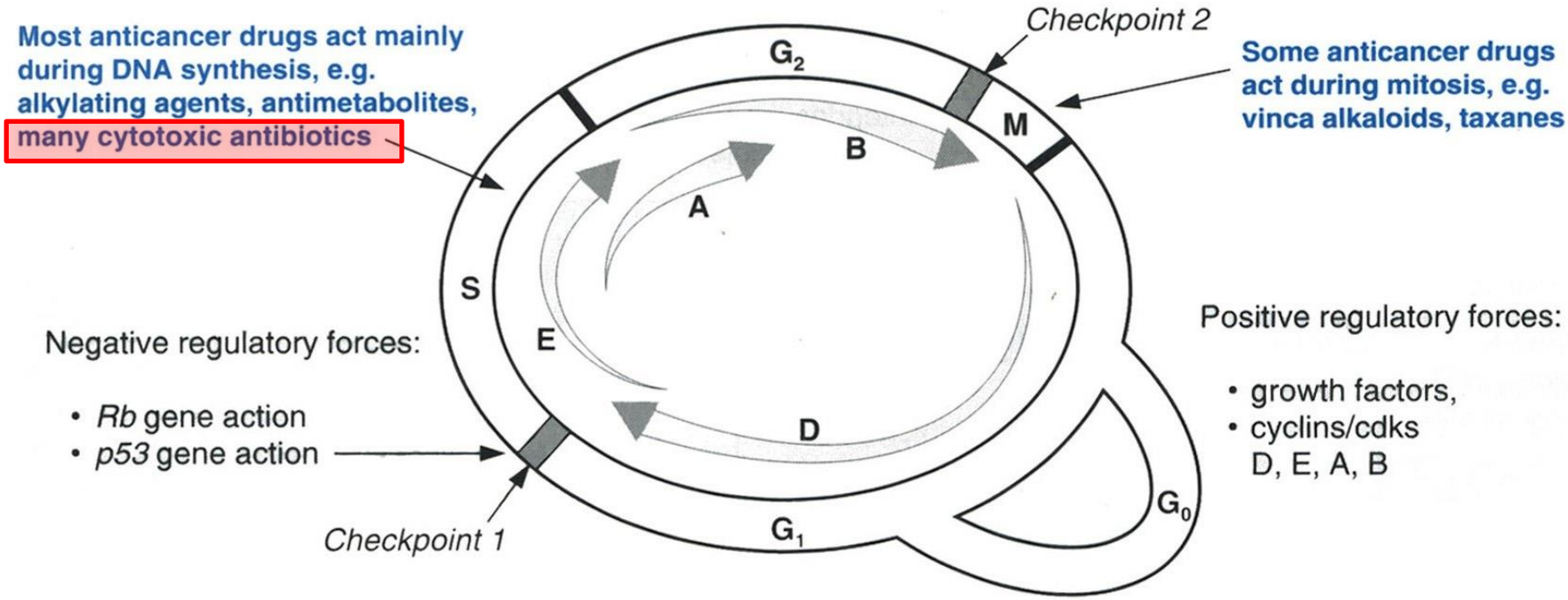
✓III.2.Epipodophyllotoxins

- Antibiotics:

✓III.3.Anthracyclines

✓III.4.Anthracenediones

Established Possible Targets for Anticancer Agents in Cell Cycle



[1] Rang , Dale, Ritter *Pharmacology*. 4th ed.; 1999.p.664-6.

A Brief Review to Topoisomerase

- Topoisomerase IIα (TopoII):

✓ 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 (TopoI):

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

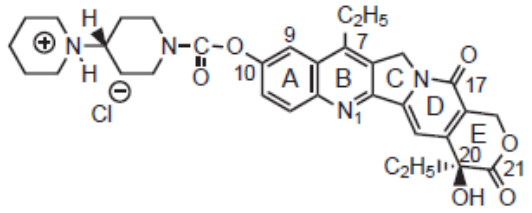
- Topoisomerase Poison:

✓ stimulate DNA cleavage reaction
✓ but inhibit the DNA resealing activity of the enzymes
✓ leaving the DNA irreversibly damaged & unable to replicate.

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

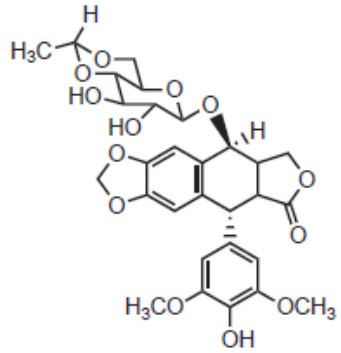
III.1. Camptothecins

Camptothecins

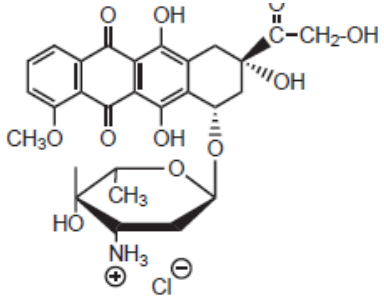


III.2. Epipodophyllotoxins

Epipodophyllotoxins

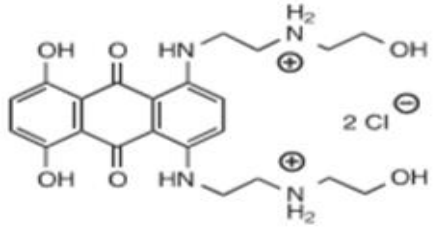


III.3. Antibiotics: anthracyclines



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:

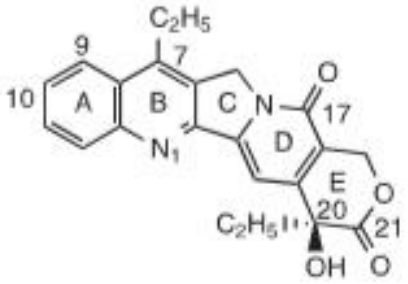
doxorubicin (adriamycin); daunorubicin

epirubicin; idarubicin; valrubicin

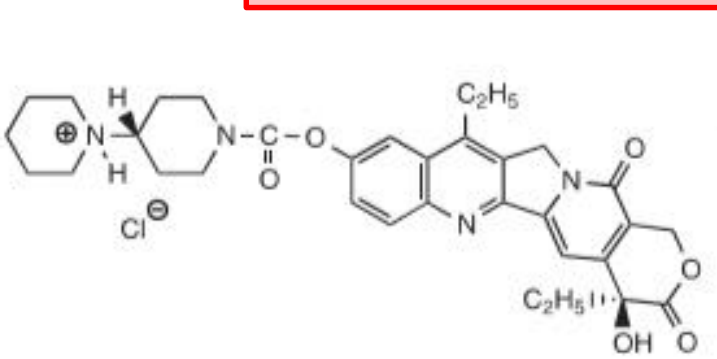
III.4. Anthracendiones: mitoxantrone

III.Topoisomerase Poisons:
III.1. Camptothecins

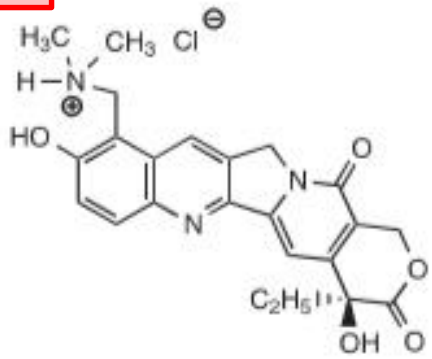
- Camptothecins: Irinotecan
  Topotecan



Camptothecin
(water-insoluble natural product)



Irinotecan hydrochloride
(Camptosar, Oinvyde)

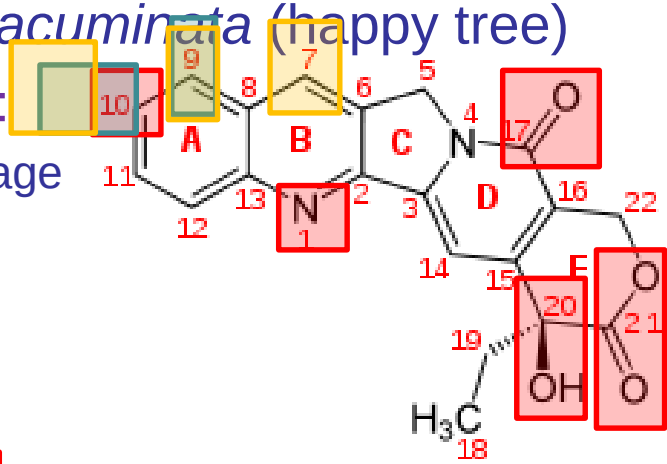


Topotecan hydrochloride
(Hycamtin)

Figure 33.25 Camptothecin topoisomerase I (TopI) poisons.

III.1.Camptothecins: Chemistry & SAR

- Natural alkaloid from the bark of *Camptotheca acuminata* (happy tree)
- C9 or C10-amine containing pentacyclic lactones:



✓ the flat cyclic system intercalates DNA at the site of cleavage

✓ mimic **DNA base pair**

✓ chiral, extensively conjugated structure

✓ interacting points:

N1, O at C10, C17(CO), C20(OH), C21(CO)-O

✓ basic side chain at C9 or C10

✓ at physiologic pH (7.4): lactone in equilibrium with hydroxy acid

✓ limited water solubility:

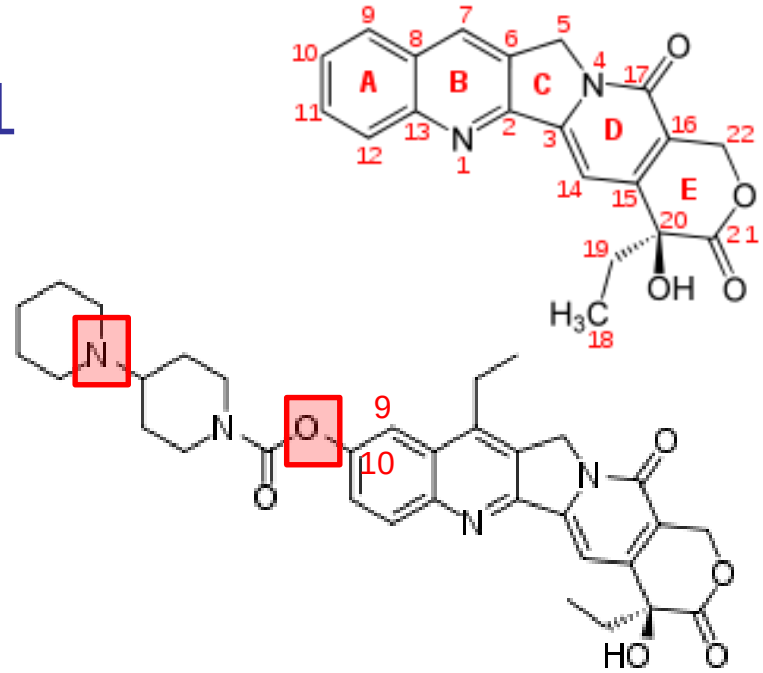
✓ sodium salt of hydrolyzed lactone: allow the formation of water soluble salts

III.1. Semisynthetic Camptothecins

- Irinotecan (camptosar®): CPT-11

✓ basic side chain at C10

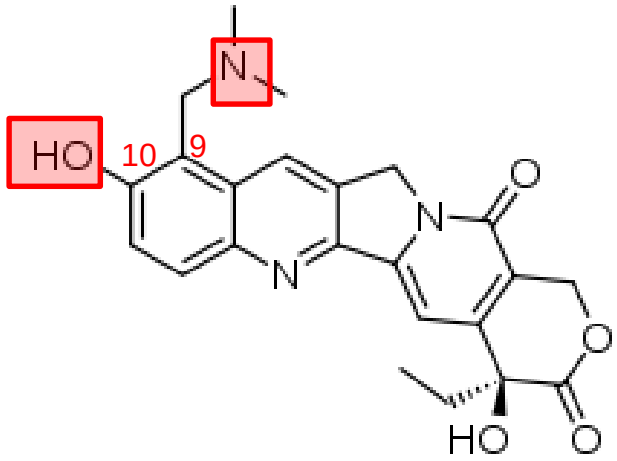
✓ Active metabolite: ?



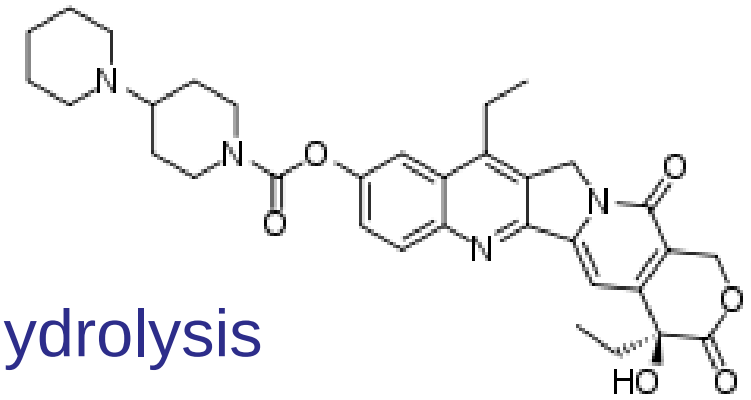
- Topotecan®:

✓ basic side chain at C9

- CYP3A4 related metabolism
- Nano-liposomal formulation



Metabolism of Irinotecan



- C21-hydrolysis

- C10:

✓ oxidation

✓ O-dealkylation:

phenolic SN38: active metabolite

✓ conjugation

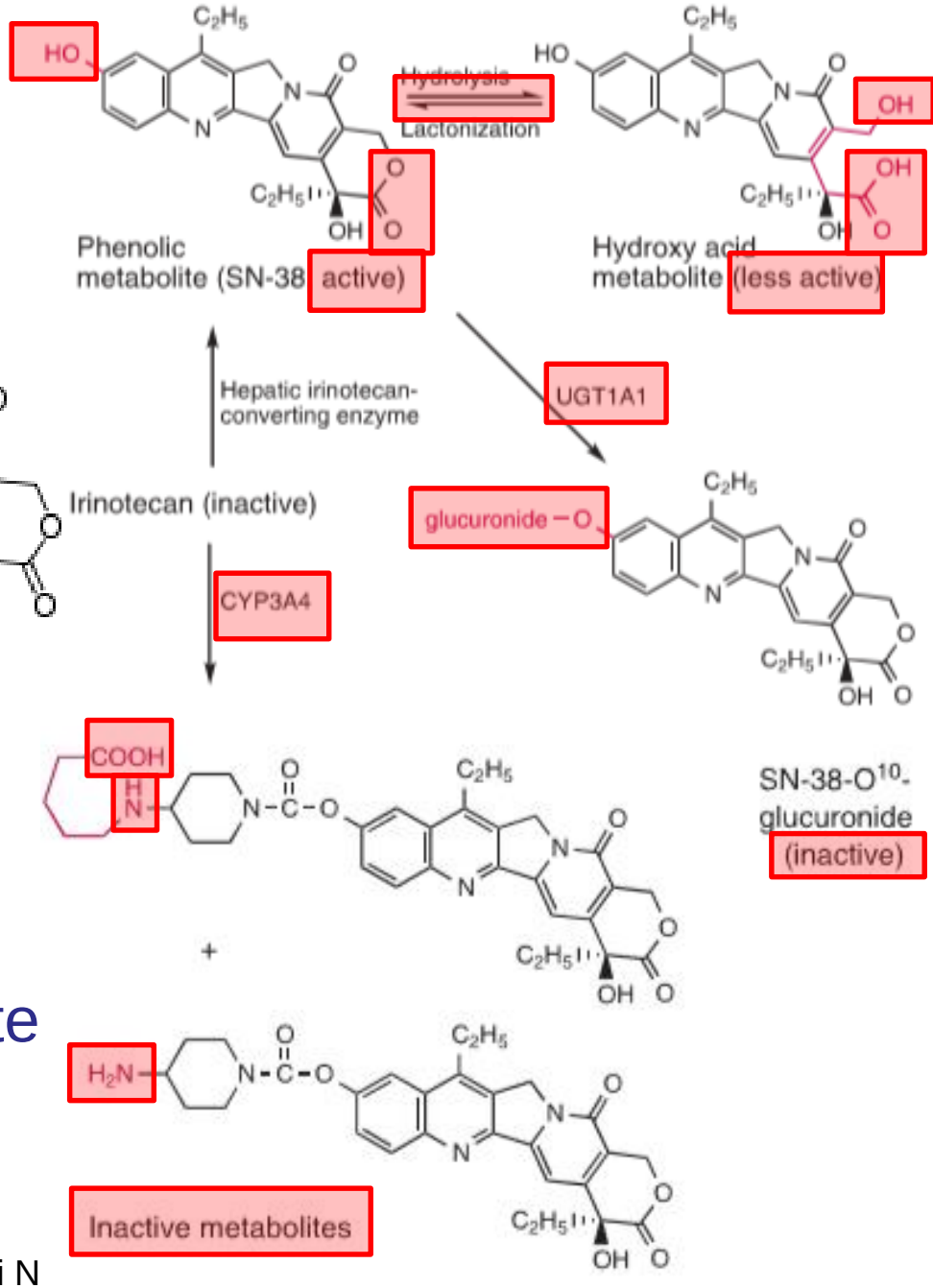
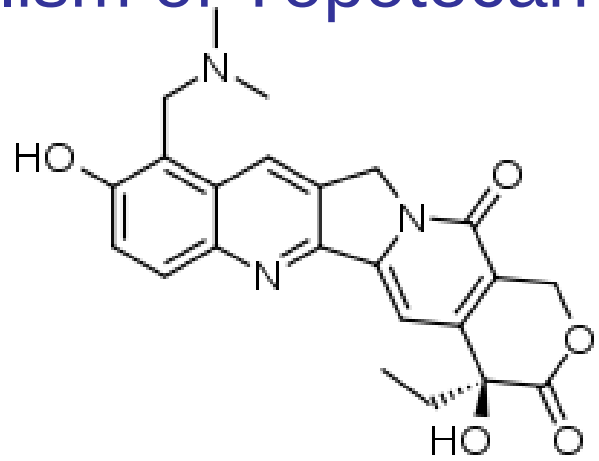
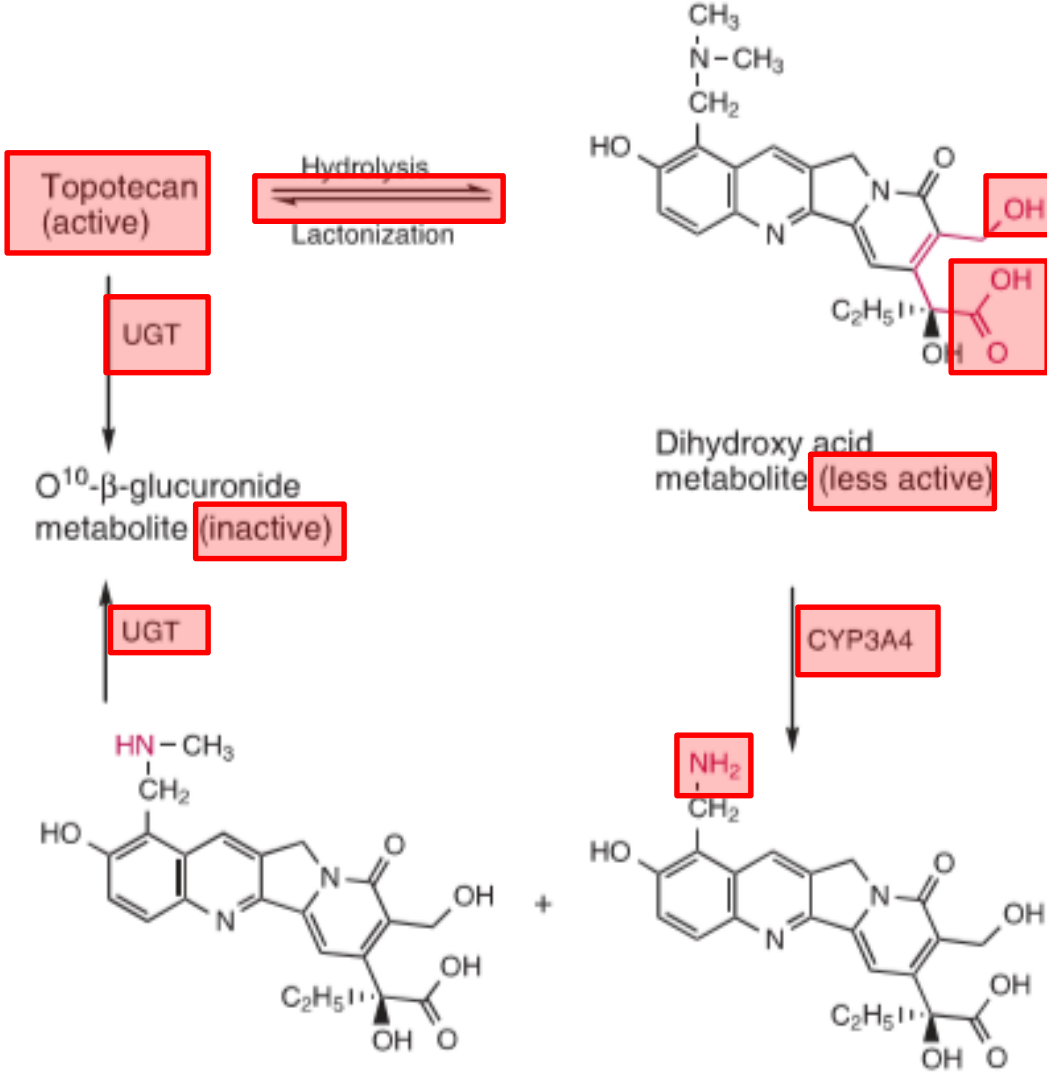


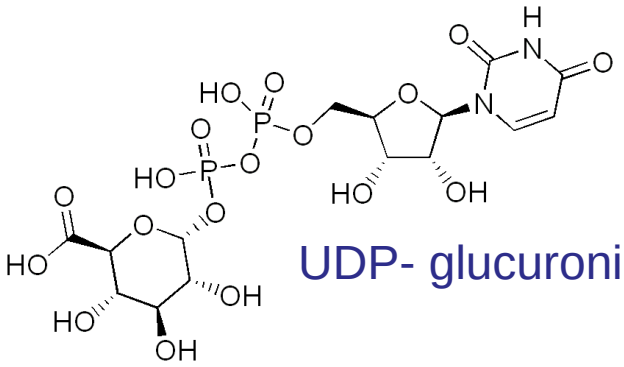
Figure 33.26 Irinotecan metabolism.

Metabolism of Topotecan





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



UDP- glucuronic acid

III. Topoisomerase Poisons: 2- Epipodophyllotoxins

- Epipodophyllotoxin: Etoposide
  Teniposide

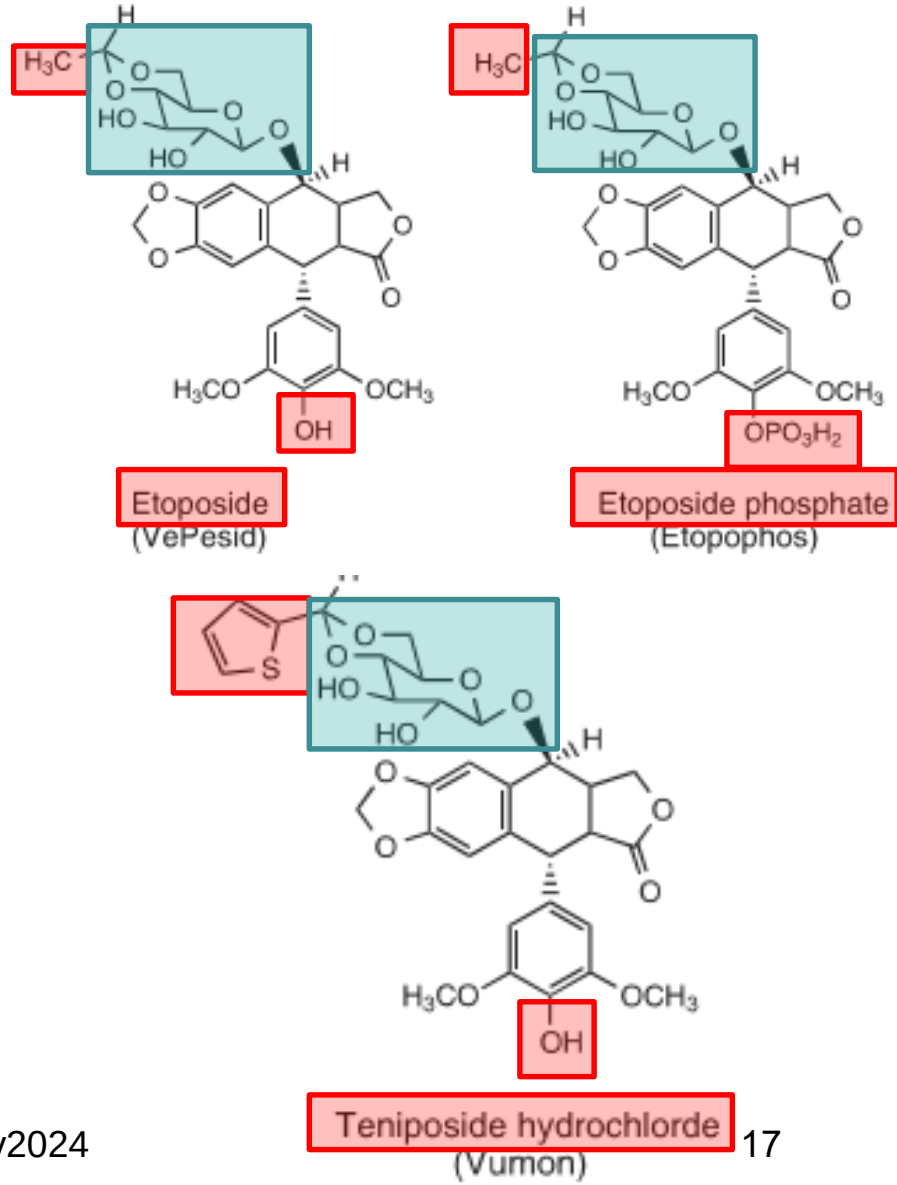


Figure 33.28 Epipodophyllotoxin topoisomerase IIα (TopIIα) poisons.

III.2. Epipodophyllotoxins: Chemistry & SAR

- Chemistry: isolated from root of mayapple

✓ semisynthetic glycosidic derivative of podophyllotoxin:

✓ tetracyclic structure: dioxolane fused to hydro-naphthalene ended to butyrolactone

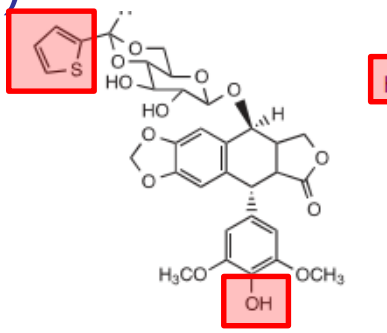
✓ substitutes at hydro-naphthalene portion:

β-D-glucopyranosyl: fused to dioxane: difference in substituent: methyl or thienyl

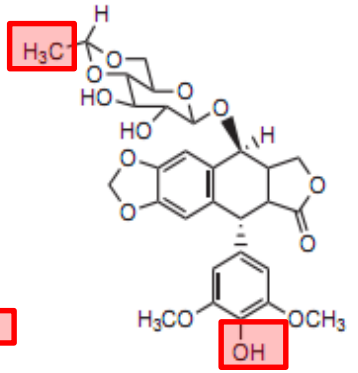
Phenolic portion: critical pharmacophore

✓ solubility enhancers: polysorbate 80 (Tween)

or polyoxymethylated castor oil (cremophore)



Teniposide hydrochlorde (Vumon)



Etoposide (VePesid)

Proposed Interaction Sites of Etoposide to TopoII

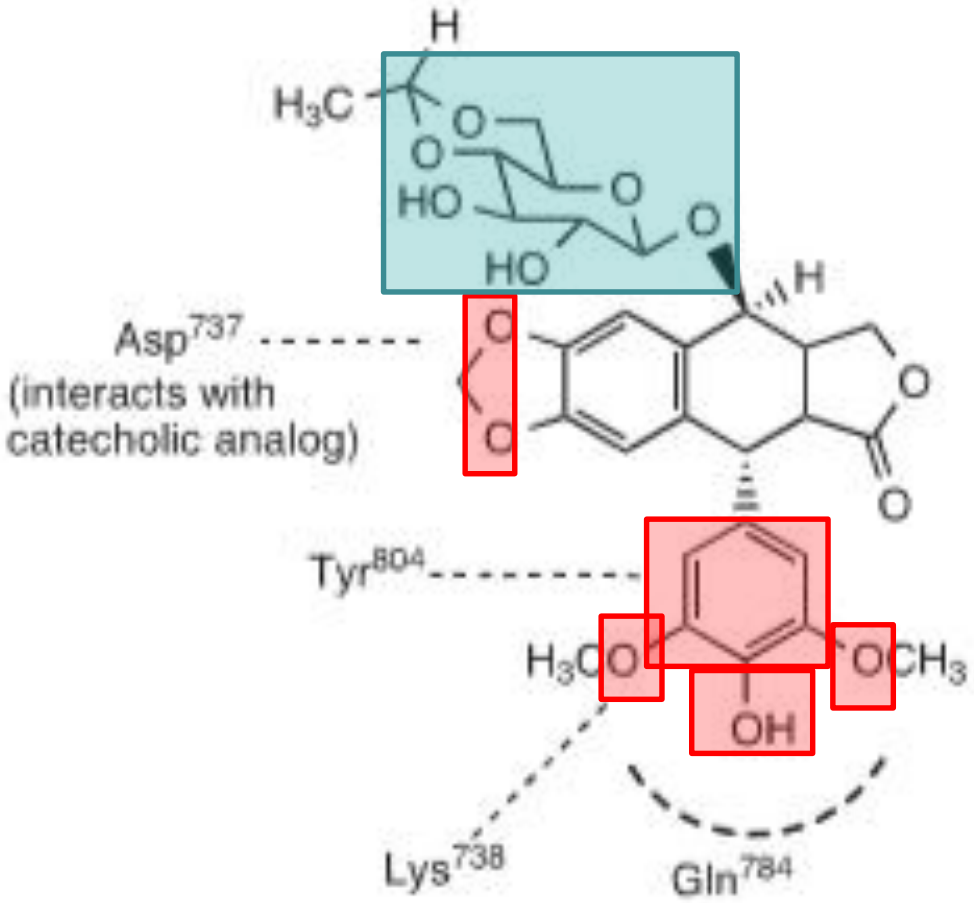
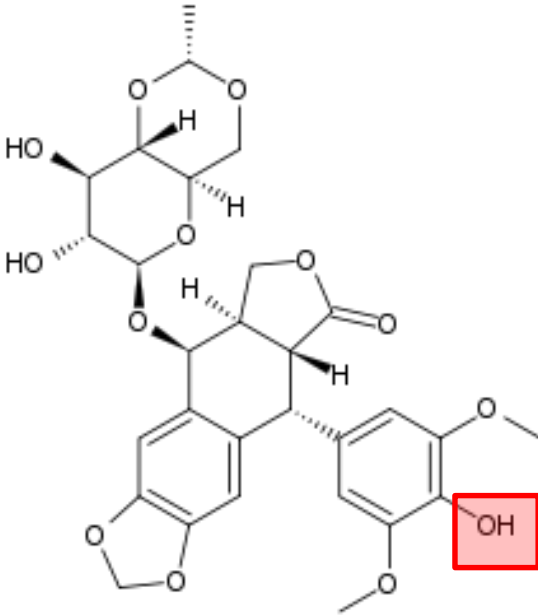


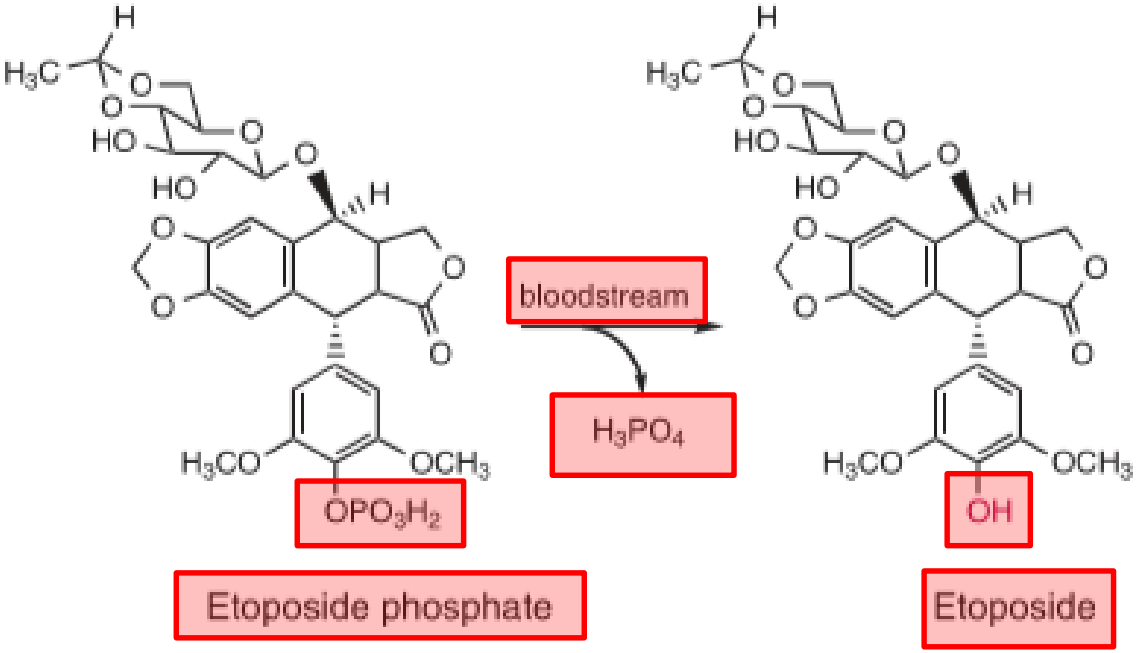
Figure 33.29 Proposed etoposide-TopIIα binding interactions.

III.2. Epipodophyllotoxin: Etoposide

- VP-16®:
- Semisynthetic: water insoluble
- Etoposide phosphate:

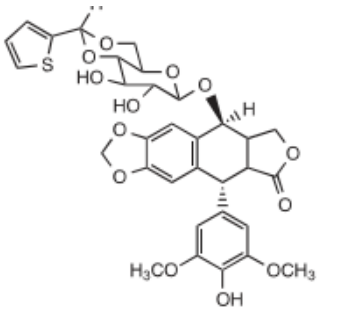
✓ prodrug of etoposide: water soluble



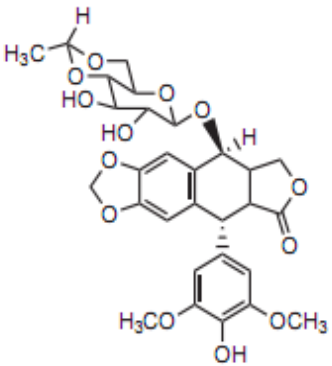


Metabolism of Epipodophyllotoxin

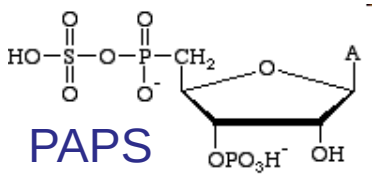
- Lactone hydrolysis:
- ✓ hydroxy acid metabolite
- Phenolic OH: conjugation:
- ✓ Sulfonation
- O-de-alkylation: ortho-quinone



Teniposide hydrochlorde (Vumon)



Etoposide (VePesid)



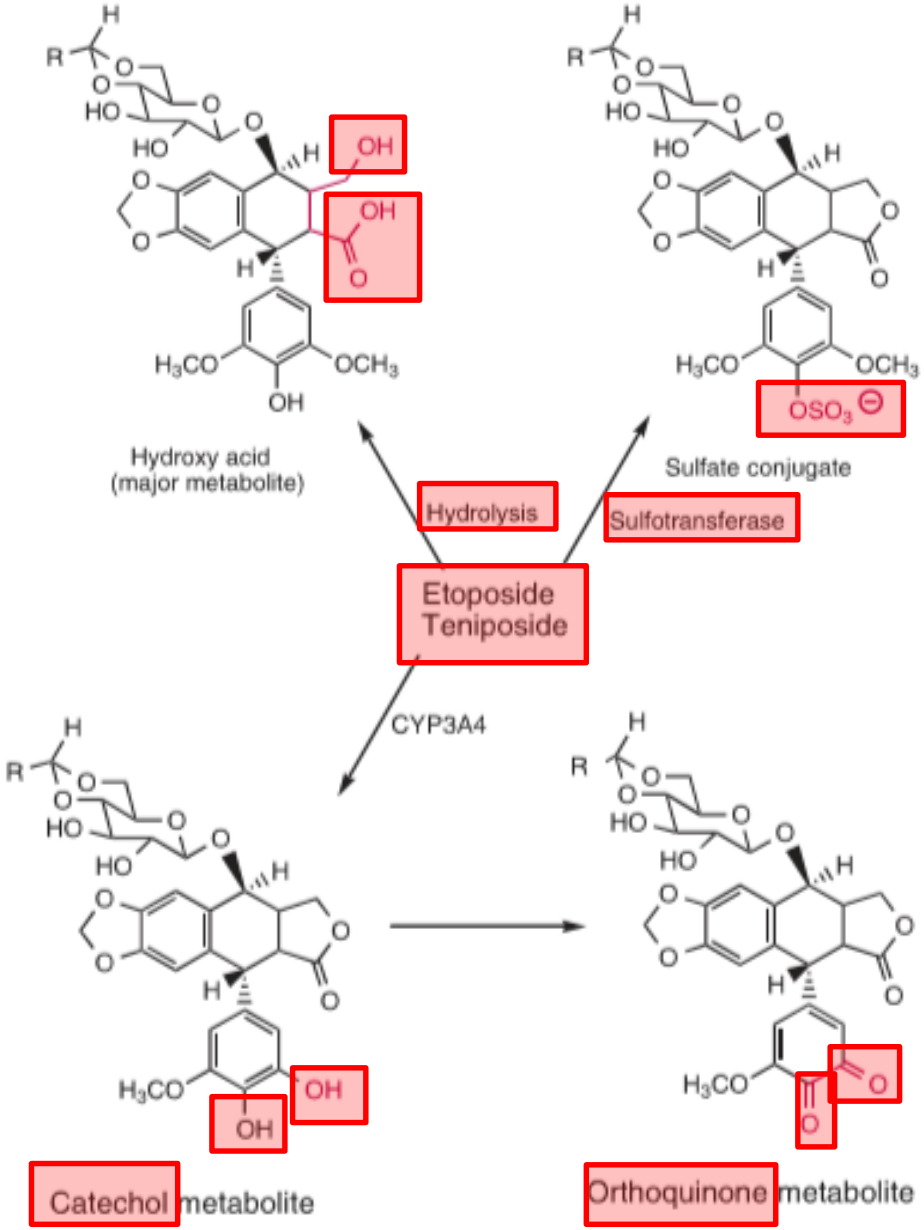


Figure 33.30 Epipodophyllotoxin metabolism.

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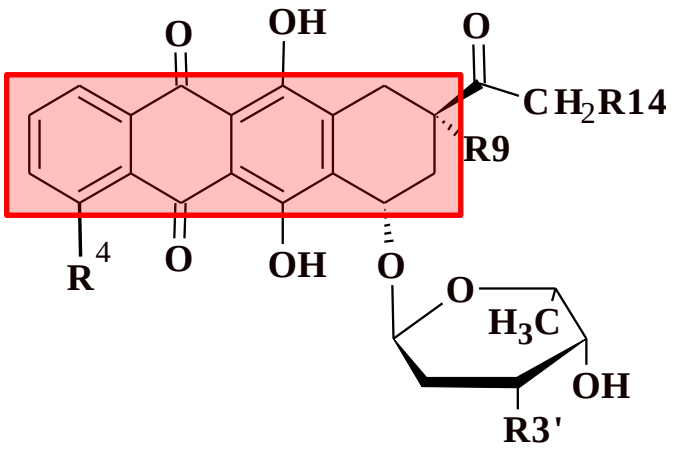
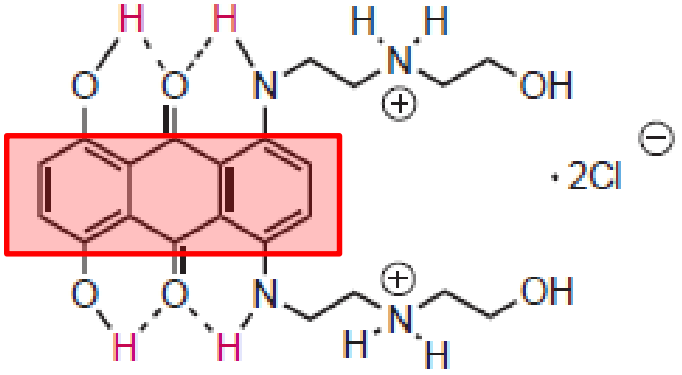
III. DNA Topoisomerase Poisons&DNA Intercalating Agents: III. 3. Anthracyclines; III. 4. Anthracenediones

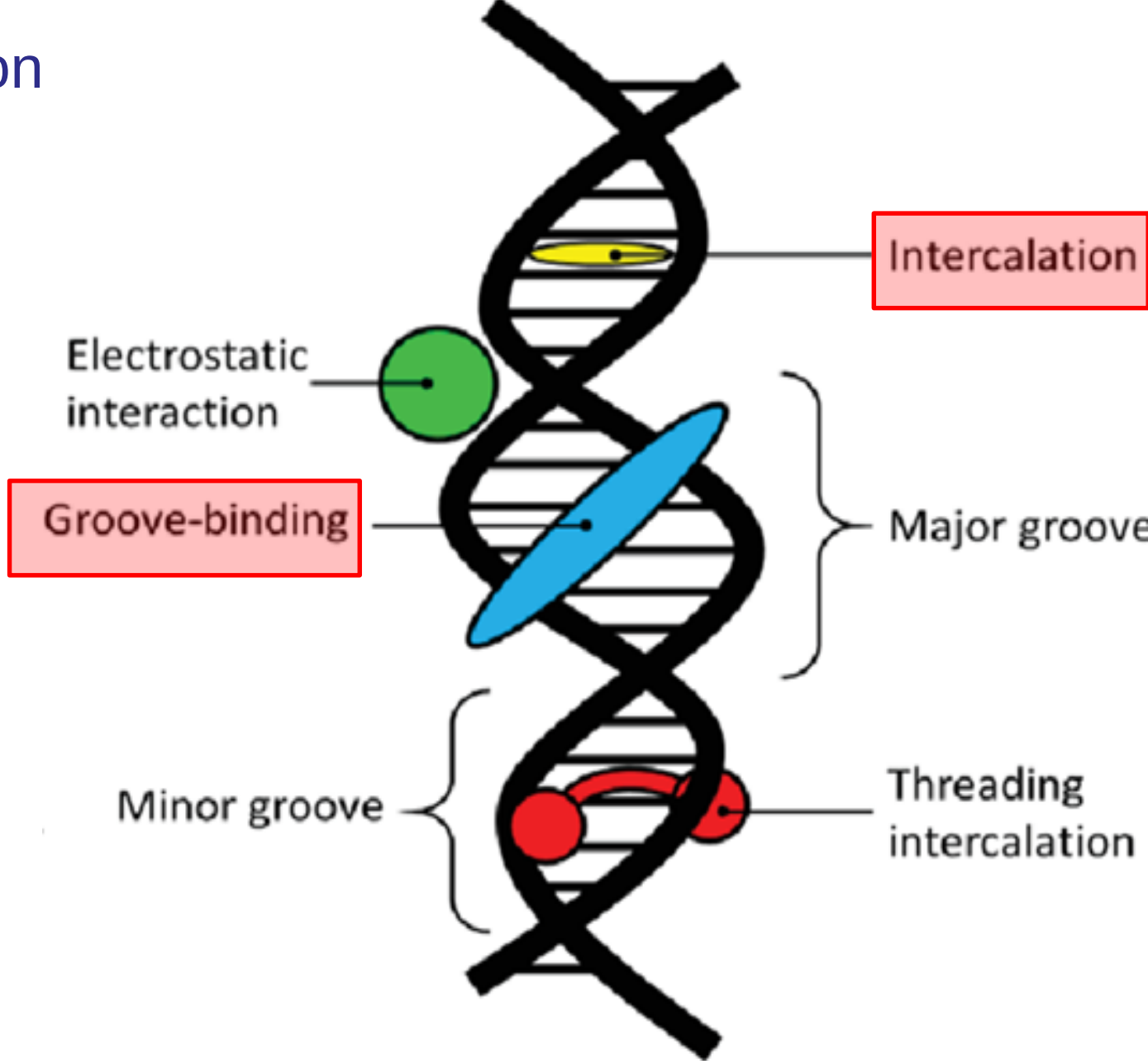
III. 3. Anthracyclines:



III. 4. Anthracenediones:



DNA Intercalation & DNA Groove Binding in Schematic



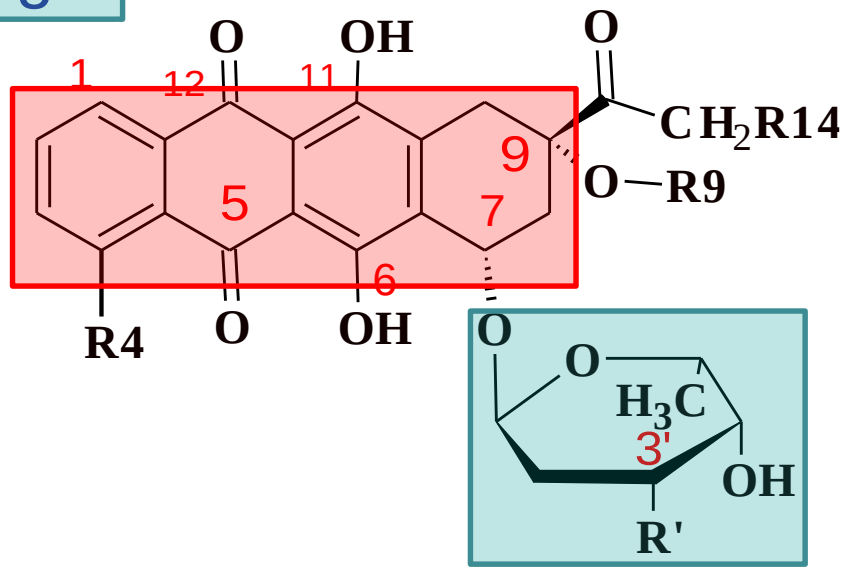
III. 3. Anthracyclines: Source & Structure

- From Streptomyces: semi-synthetic derivatives
- Chemistry:

✓ aglycon region: tetracyclic quinone: anthraquinone

✓ glycon region: C7: glycosidic bond:

daunosamine: amino(3'-NHR)-sugar



III. 3. Anthracyclines: SAR

- Aglycon region: anthraquinone: anthracycline-one: tetracyclic region:

✓ three aromatic rings fused to one non-aromatic ring: A to D

✓ coplanar geometry

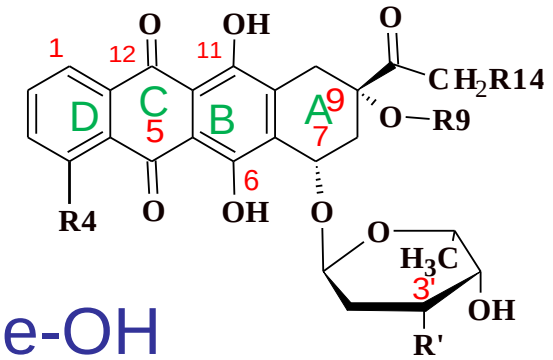
✓ make reddish urine

✓ R4-H or OCH_3

✓ C5,C12-quinone(O); C6,C11-hydroquinone-OH

✓ C9-α-OR9: C9-α-OH

✓ C9-ß-$COCH_2$R14: R14-H or R14-OH or R14-O-CO-R



- Glycon region: pyran (sugar structure): 3'-NH_2 or 3'-$NHCOCF_3$

✓ proper positioning & stabilization of drug at its biding site

- DNA interaction sites: …: next slide
- DNA topoisomerase interaction sites: …: next slide

III. 3. Anthracyclines: Proposed Interaction Points

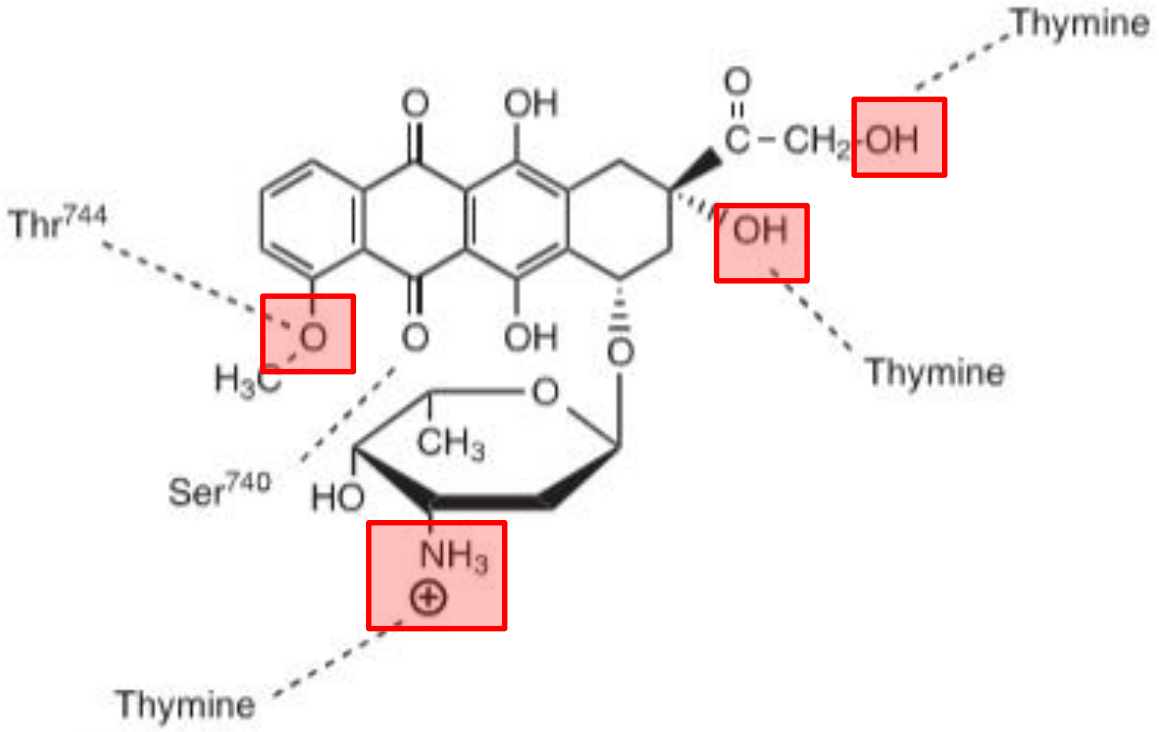
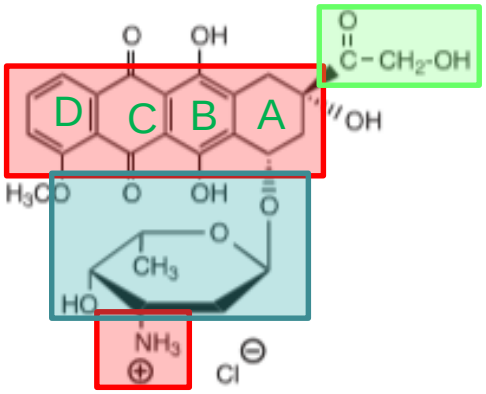
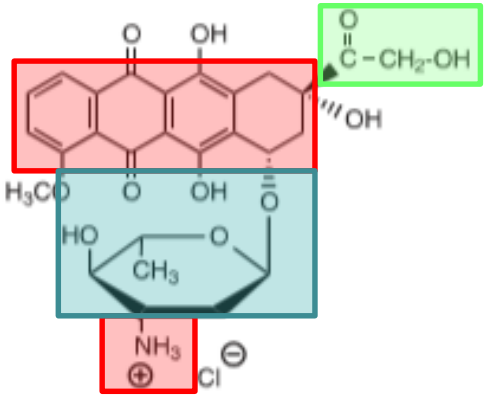


Figure 33.31 Proposed interaction between doxorubicin, DNA, and topoisomerase IIα.

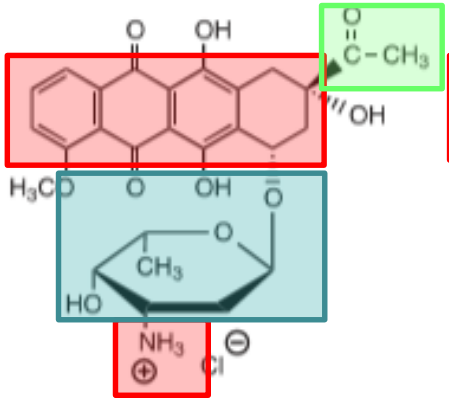
III. DNA Topoisomerase Poisons & DNA Intercalating Agents:
III. 3. Anthracyclines:1st, 2nd & 3rd Generations



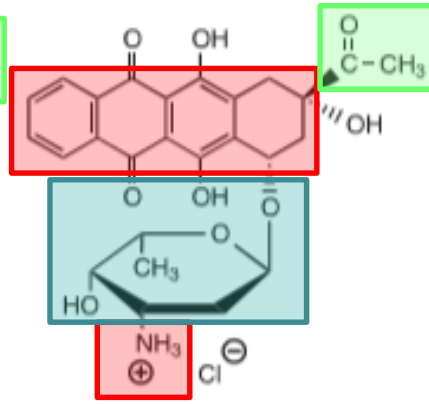
Doxorubicin hydrochloride
(Adriamycin)



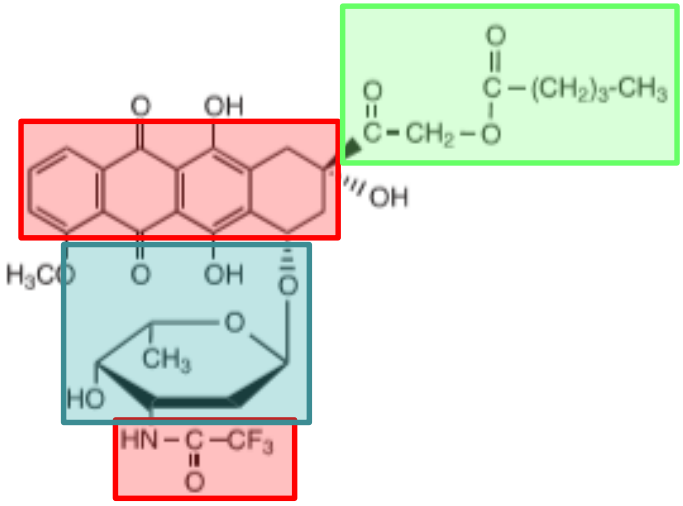
Epirubicin hydrochloride
(Ellence)



Daunorubicin hydrochloride
(Cerubidine)



Idarubicin hydrochloride
(Idamycin PFS)



Valrubicin
(Valstar)

Figure 33.34 Anthracycline and related anticancer agents.

Anthracyclines: Free Radical Formation

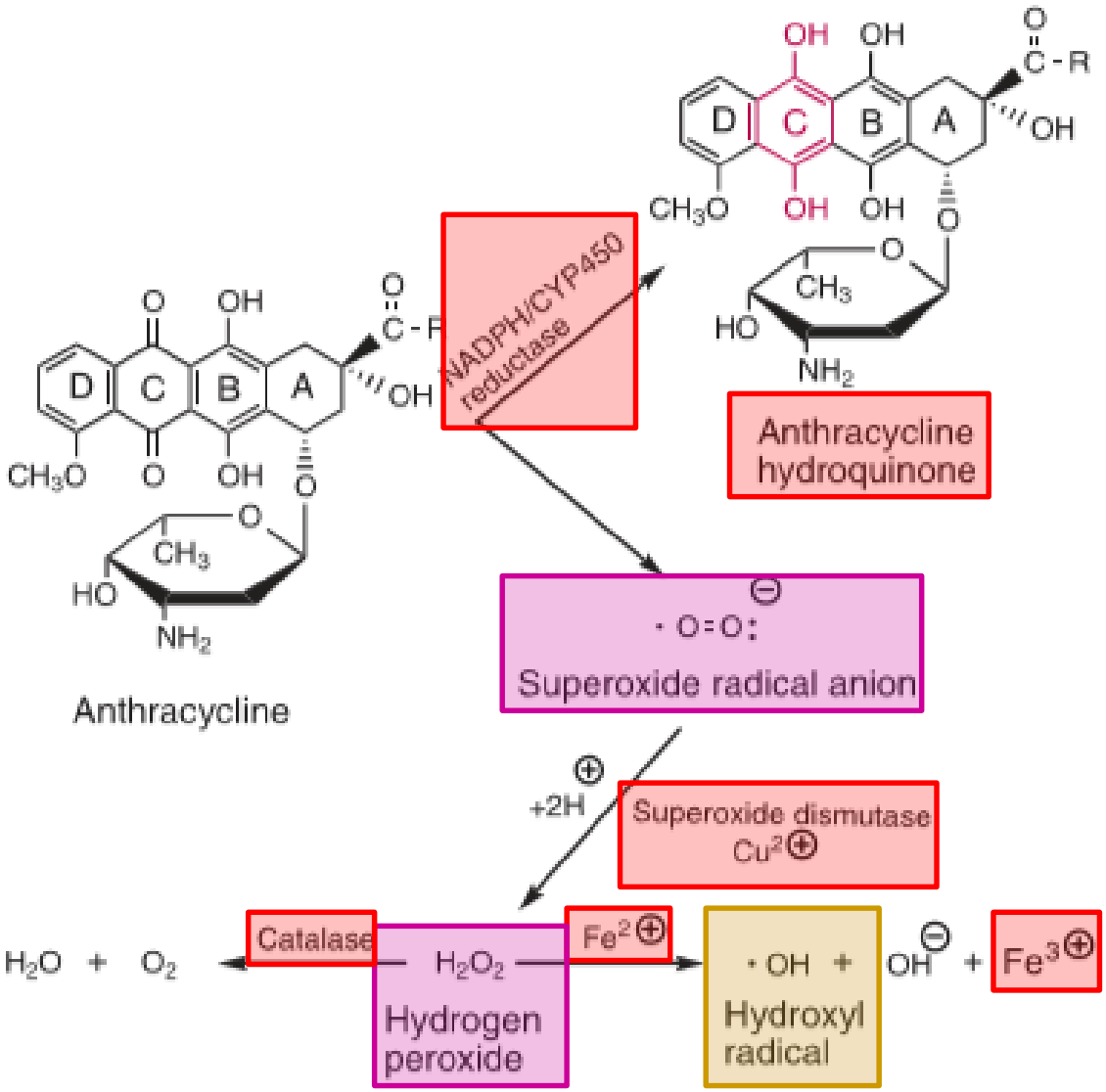


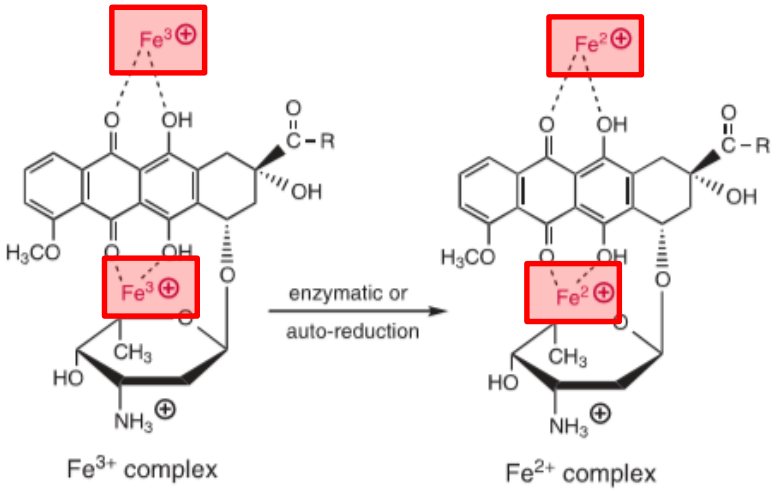
Figure 33.32 Anthracycline-mediated free radical formation.

Free Radical Formation & Ferrous Chelation in Anthracyclines

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

✓ ferrous affects in [.OH]

✓ fenton reaction



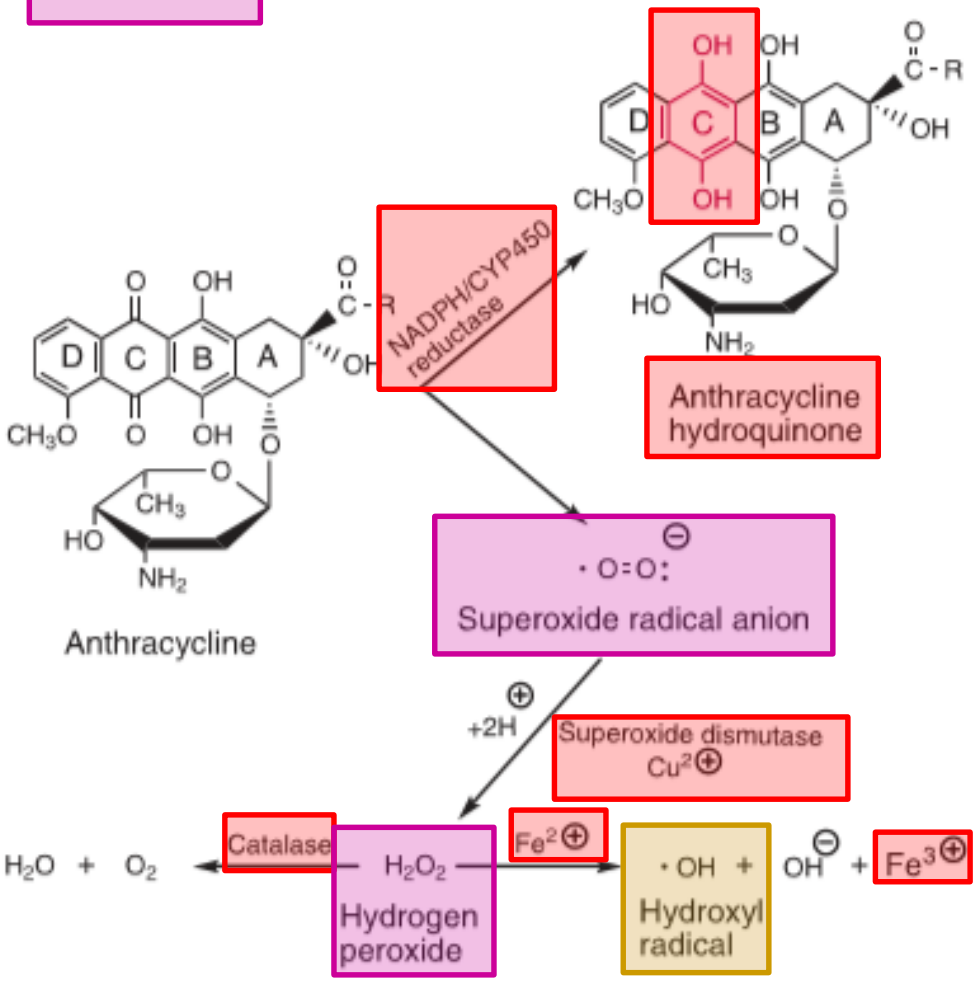


Figure 33.32 Anthracycline-mediated free radical formation.

Anthracyclines: Metabolism

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

- C7-O-dealkylation:
- ✓ C7-hydroxy or C7-deoxy derivative:
- ✓ aglycone derivative

- S

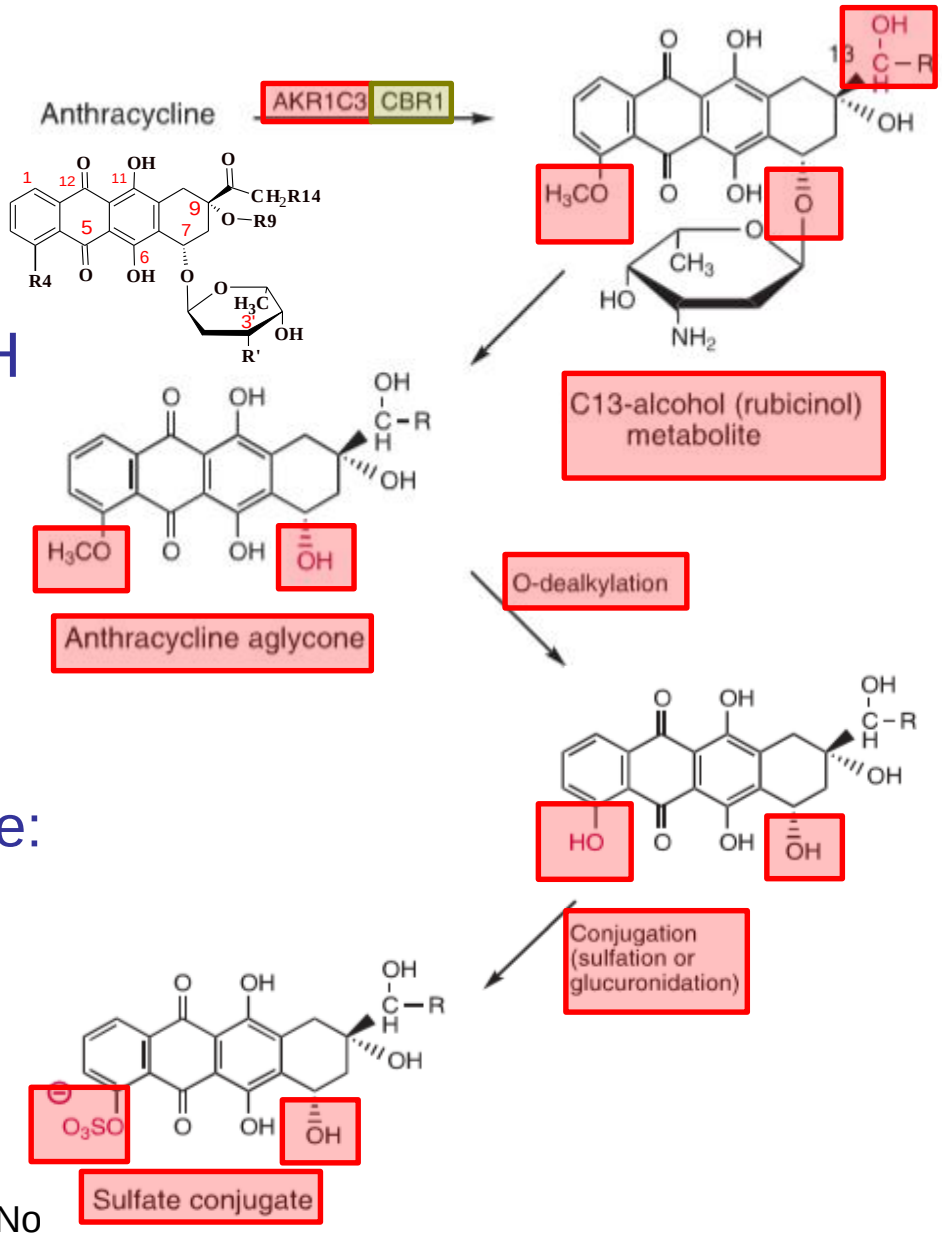


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Figure 33.33 Anthracycline metabolism (AKR, aldo-keto reductase; CBR, carbonyl reductase).

Cardiotoxicity by Anthracyclines

- Acute:

✓ caused by: superoxide radical anion(.O-O^-) &hydroxyl radical

✓ more in tissues with low catalase

✓ ferrous affects in [.OH]

✓ fenton reaction

- Chronic:

✓ caused by rubicinols & 7-hydroxy or 7-deoxy metabolites

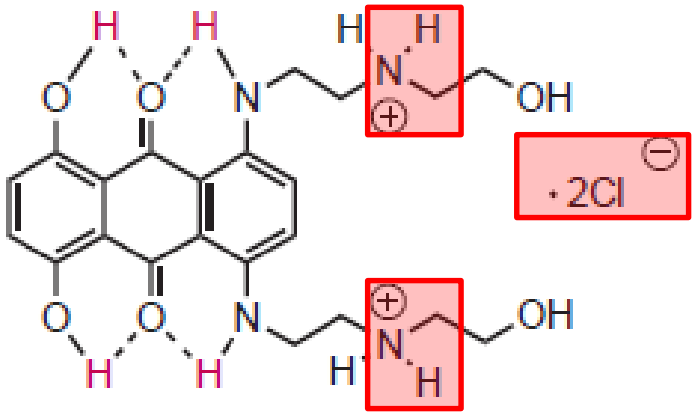
depends on Aldo-Keto Reductase(AKR) & carbonyl reductase(CBR)

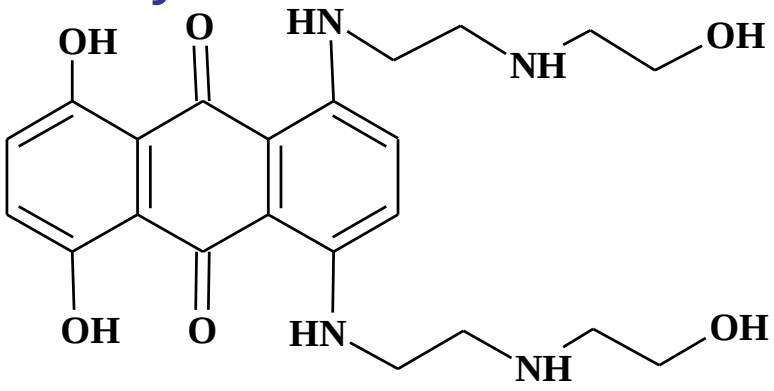
generates ROS & change in $[Ca]_i$ in cardiomyocytes

✓ TopIIß inhibition in myocardium: may facilitate ROS formation

III.4. Anthracendione: SAR

- Mitoxantrone: as di-hydrochloride salt: di-HCl
- Anthracendione: tricyclic: aromatic rings: flat portion
- ✓ how is ability to chelate Fe^{2+}?
- Compare to anthracyclines: no sugar moiety
- Amine possessing chain instead of … in anthracycline:
- ✓ hydroxy-ethylene-amino-ethylene amine
- Significantly decreased cardiotoxicity risk





Metabolism of Mitoxantrone

- N-dealkylation & CYP oxidation inactivation
- Naphthoquinoxaline: active metabolite

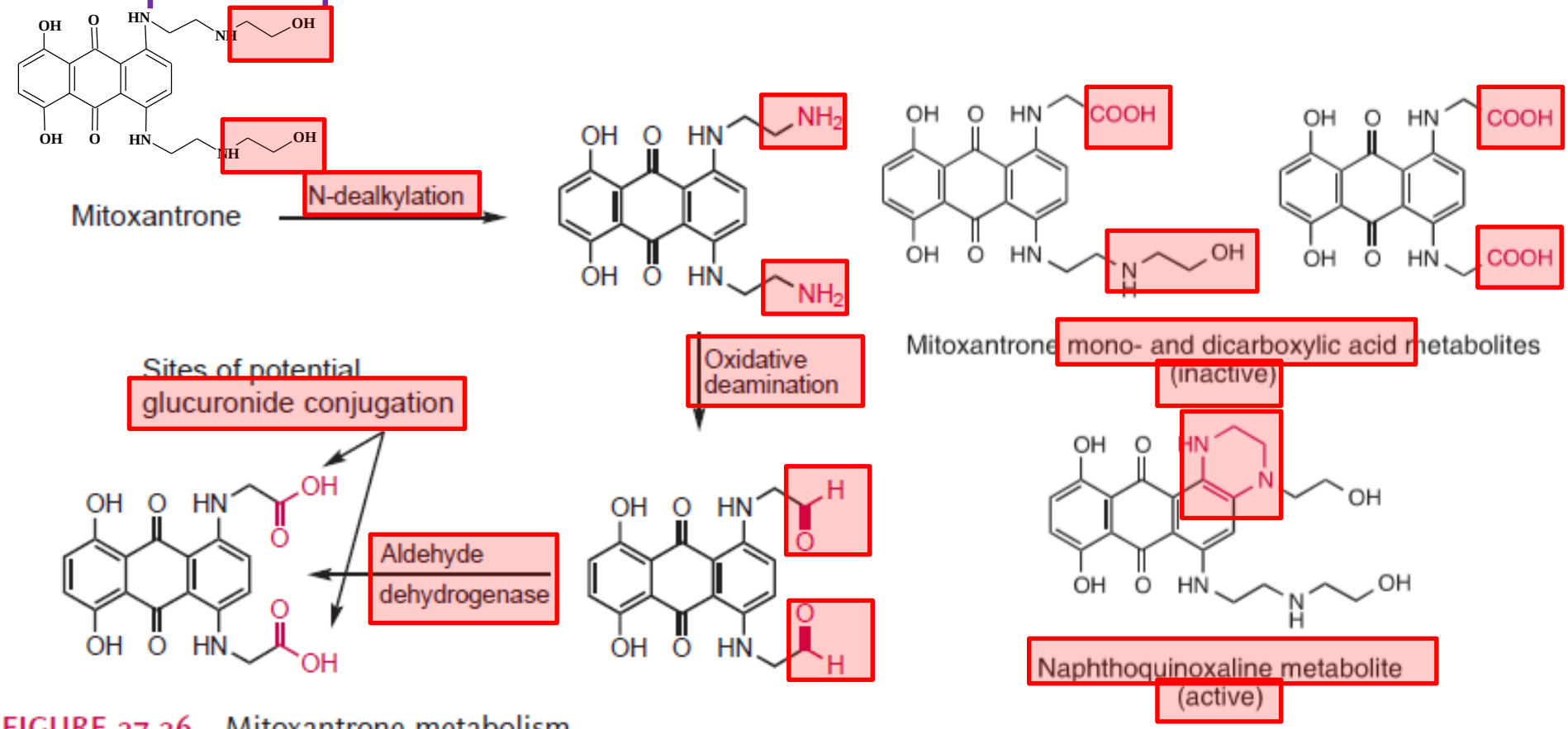


FIGURE 37.26 Mitoxantrone metabolism.