Chemotherapeutic Agents:

Drugs to Treat Neoblastic Agents-

Section 3- DNA Topoisomerase Poisons & DNA Intercalating Agents

& DNA Interacting 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

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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

IV.1. Phenoxazine: Dactinomycin (Actinomycin D): Source & Chemistry: SAR

- From *Streptomyces*
- Structure:

✓ actinocin (phenoxazinone): di-benzo-oxazine: flat portion:

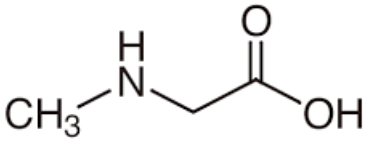
✓ possessing benzoquinoneimine

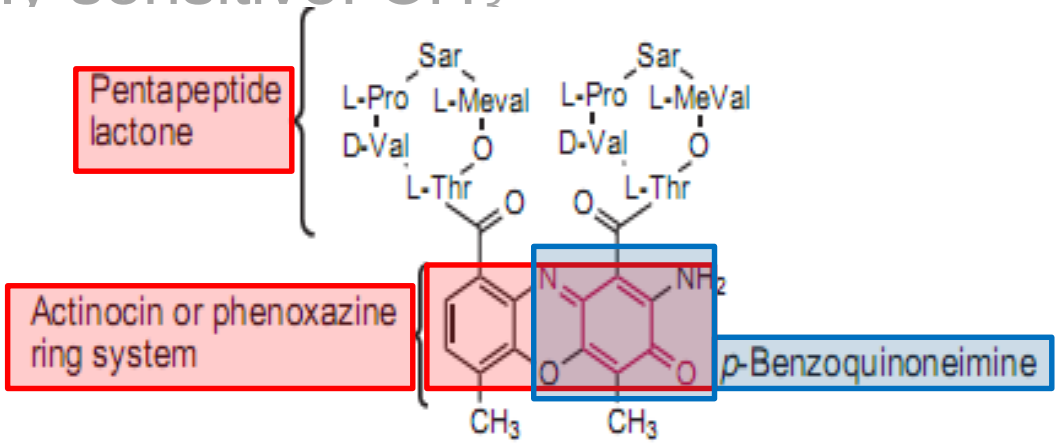
&

two symmetric pentapeptide lactone ring as substitutes on two phenyls

- Photosensitive
- Chemically sensitive: CH_3

Sar

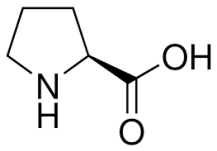




Dactinomycin

IV.1. Phenoxazine: Dactinomycin (Actinomycin D): Chemistry: More

Pro



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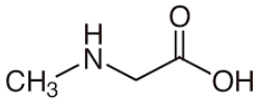

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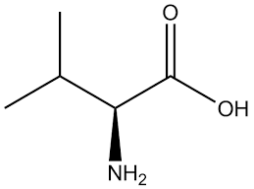

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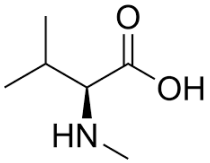
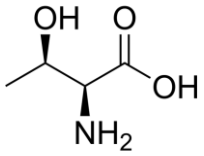
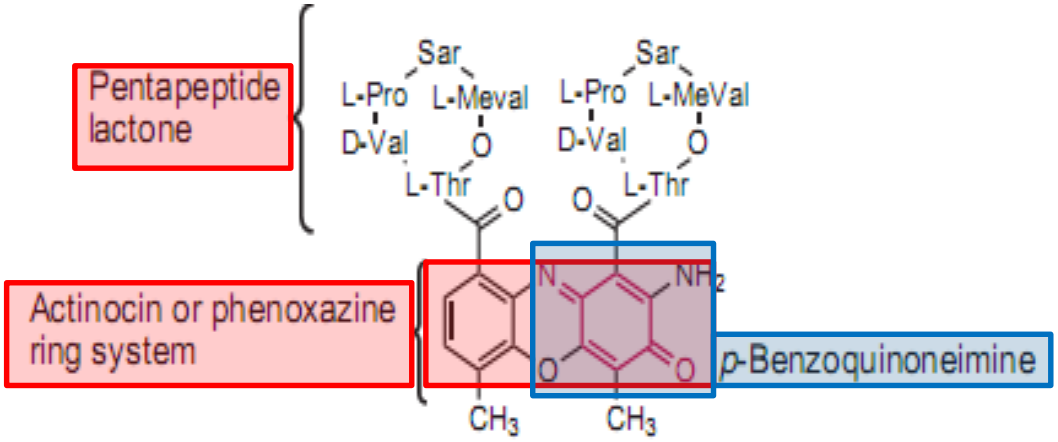


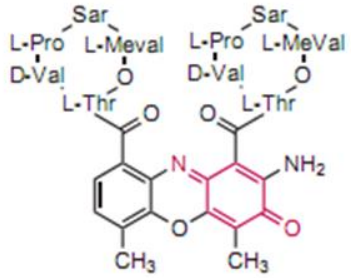
Thr





Dactinomycin

IV.1. Phenoxazine: Dactinomycin (Actinomycin D): MOA



Dactinomycin

- DNA intercalation:

✓ π stacking, hydrophobic & hydrogen bonds:
through lactone & DNA bases (especially G-C)
positioning actinocin perpendicular to the main DNA axis

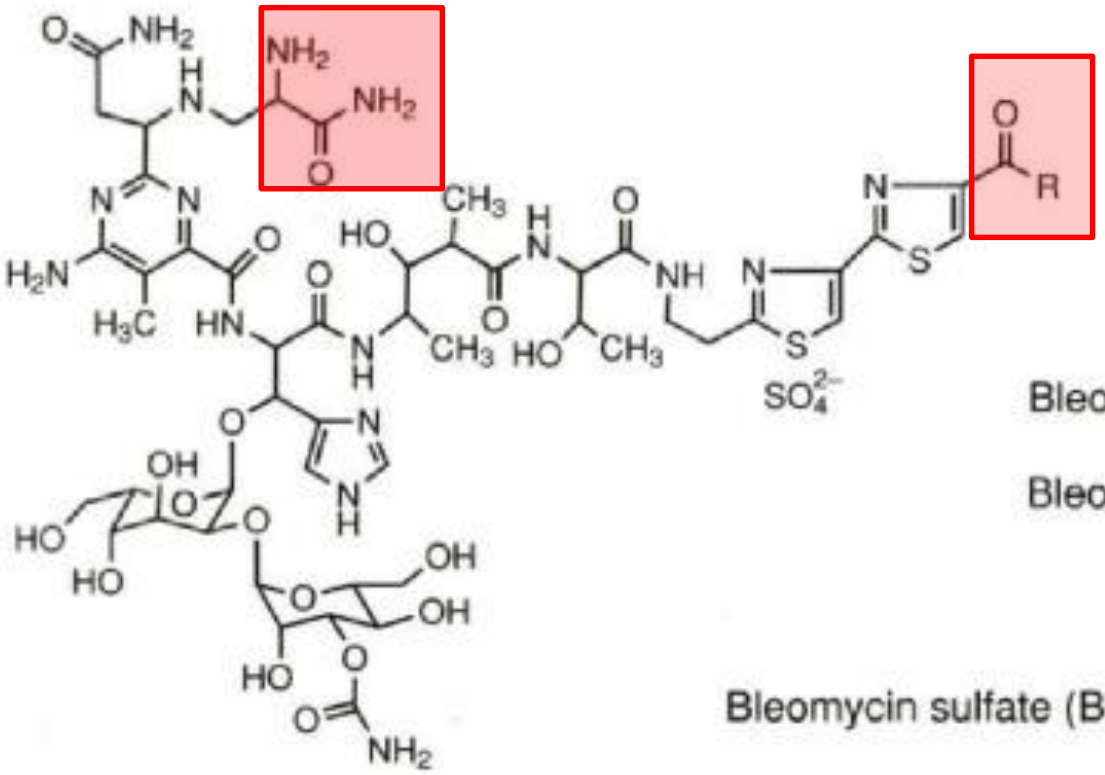
- DNA minor groove binder:

✓ hydrophobic & hydrogen bond interactions
through pentapeptide region (Thr) & protonated G-(C2-NH_2)

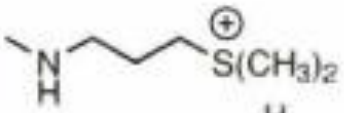
- Mostly affect on a single strand
- Pseudo-irreversible interaction to DNA
- Free radicals can be produced: next slide
- Metabolism: by NADPH reductase because of iminoquinone
- Rapid clearance: suitable dosage forms?

IV.2. Glycopeptide: Bleomycin

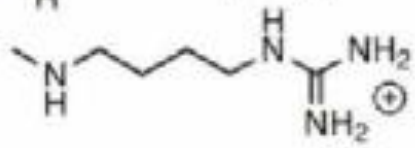
- Blenoxane®
- Sulfate salt



Bleomycin A_2 R =



Bleomycin B_2 R =



Bleomycin sulfate (Blenoxane)

IV.2. Glycopeptide: Bleomycin: Source & Chemistry & SAR

- From *Streptomyces*
- Chemistry: glycopeptide:
- Flat aromatic rings: provide DNA base pair interaction:

✓ bi-thiazole; pyrimidine; imidazole

- amide groups
- polyamine:

✓ amino-acetamide: critical

✓ compare related metabolite

- Di-saccharide: polyol:

✓ hydrophilic

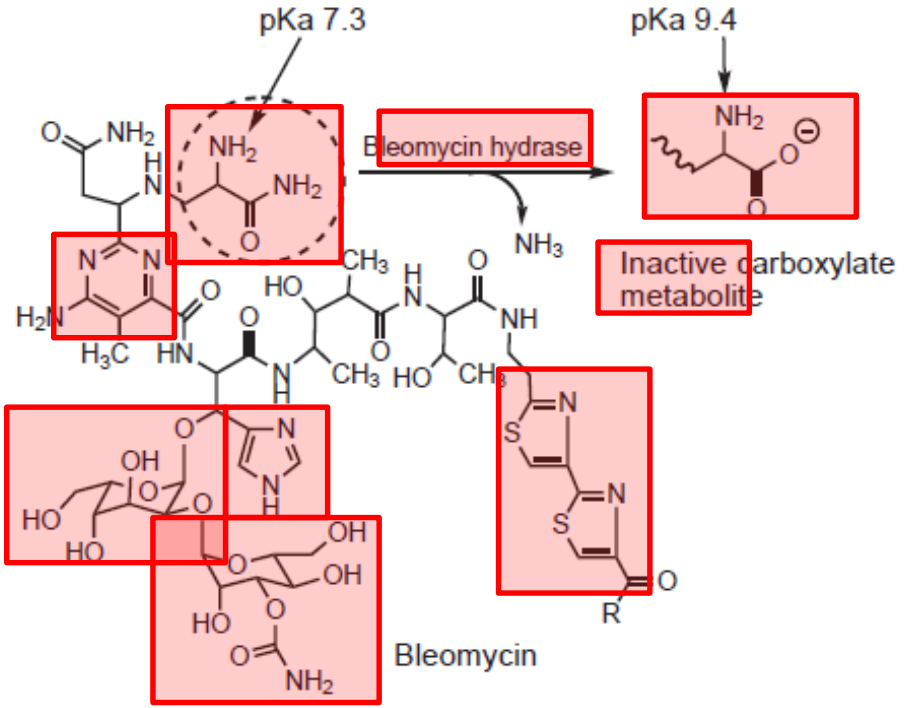


FIGURE 37.29 Bleomycin hydrase-mediated inactivation of bleomycin.

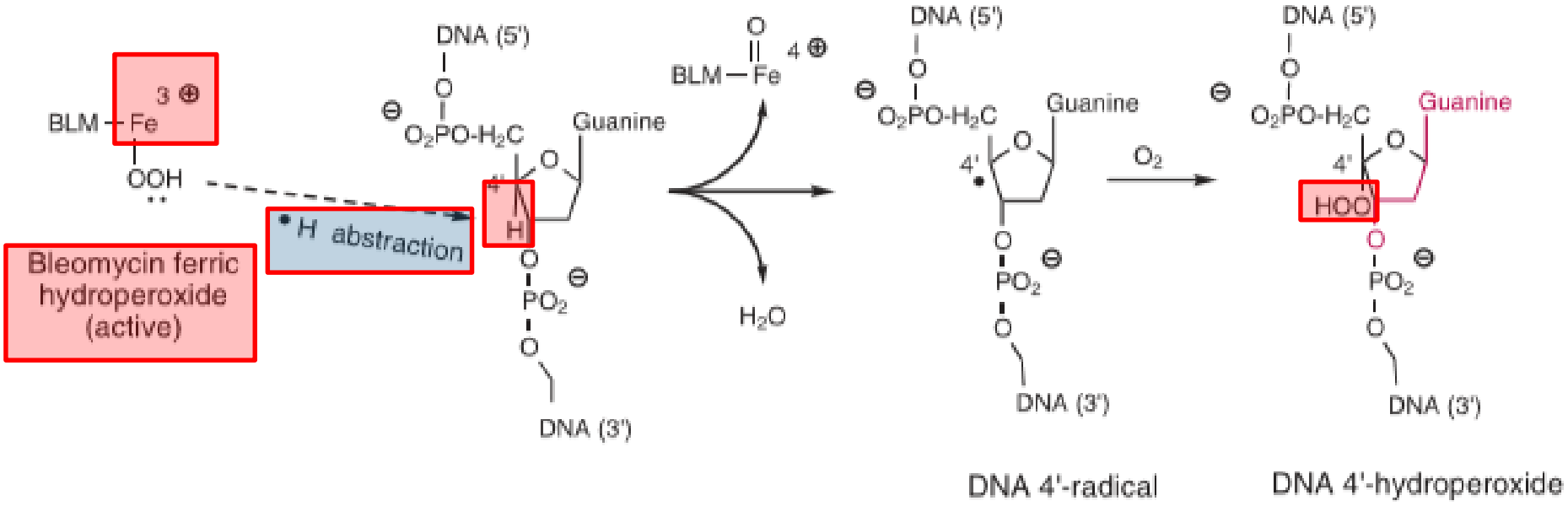
IV.2. Glycopeptide: Bleomycin: MOA

- Capability of:

✓ providing electron rich region for cation (Fe^{2+}): to form chelate

✓ producing free radical: G-C: DNA destruction: formation of propenal as a 3-carbon linear structure (next slide)

- Sensitivity/stability: due to hydrase activity in target tissue/organ
- Active metabolite: Bleomycin ferric hydroperoxide



IV.2. Glycopeptide: Bleomycin: Bleomycin Induced DNA Cleavage

- Electron rich region(form chelate)& free radical: formation of propenal

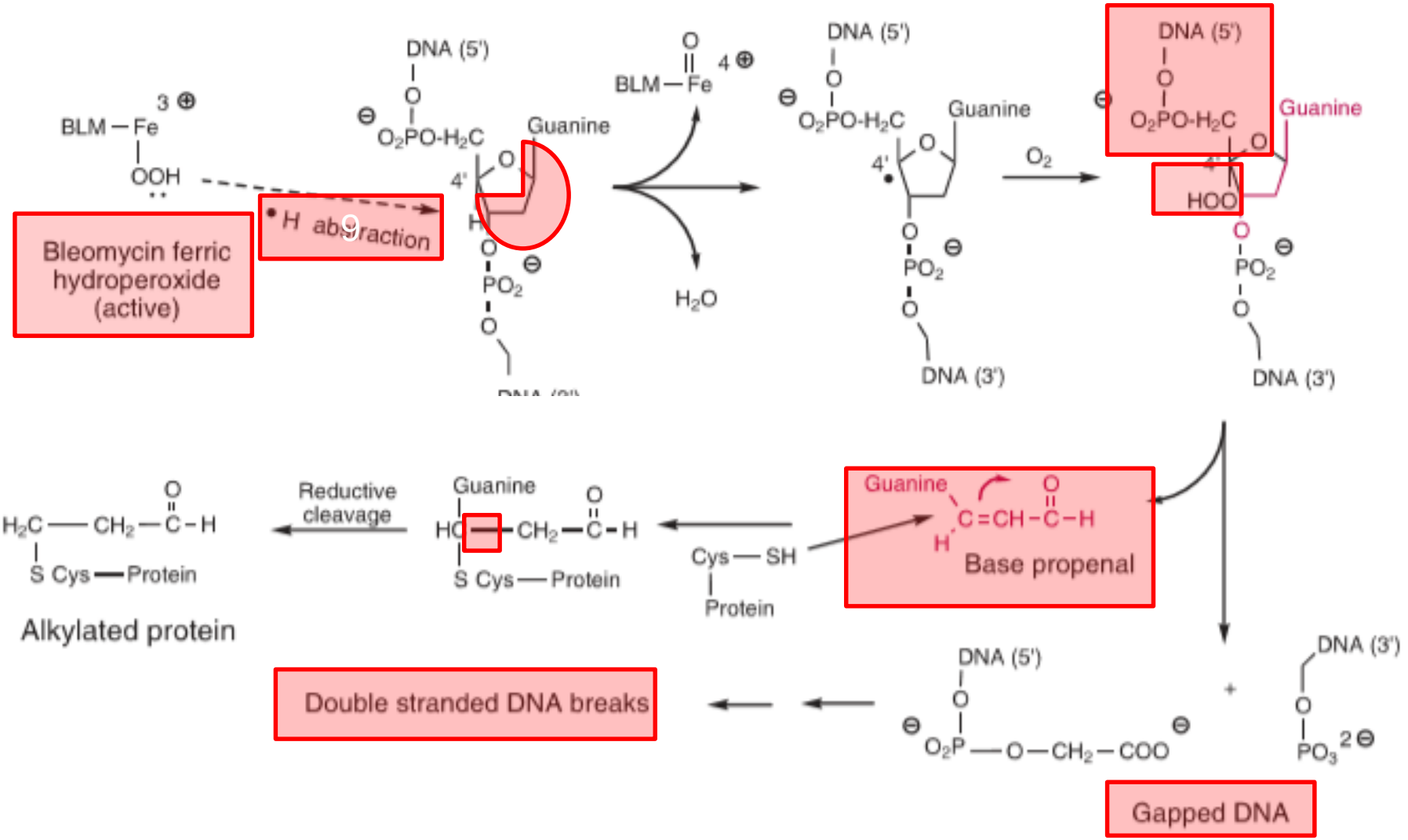
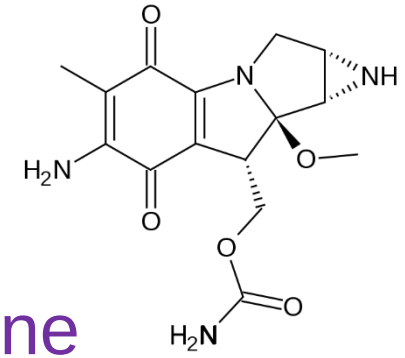


Figure 33.72 Mechanism of bleomycin-induced damage of DNA and proteins.

IV.3. Mitomycin C: Source, MOA & SAR



- M(u or i)tamycin: from *Streptomyces*
- MOA: DNA interaction & alkylation:

✓ bio-reductive alkylation: quinone-hydroquinone

cytotoxic hydroxy radicals: fenton reaction

✓ mono / dialkylation of DNA; cross linking

✓ GC rich regions of DNA: G-(C2-NH_2); Cytosine (C4-NH_2)

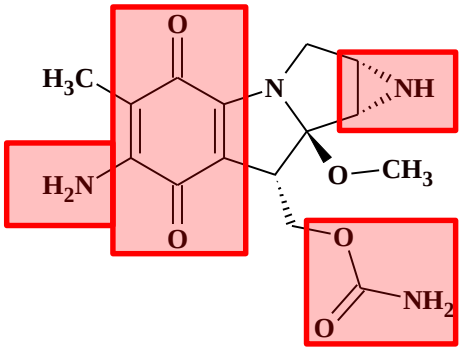
- SAR: several functional groups:

✓ amino quinone ring: can be reduced to hydroquinone

✓ aziridine ring

✓ carbamoyl methylene

- Dosage form: IV inj.



Mitomycin: MOA & Metabolism

- Follow pharmacophores.

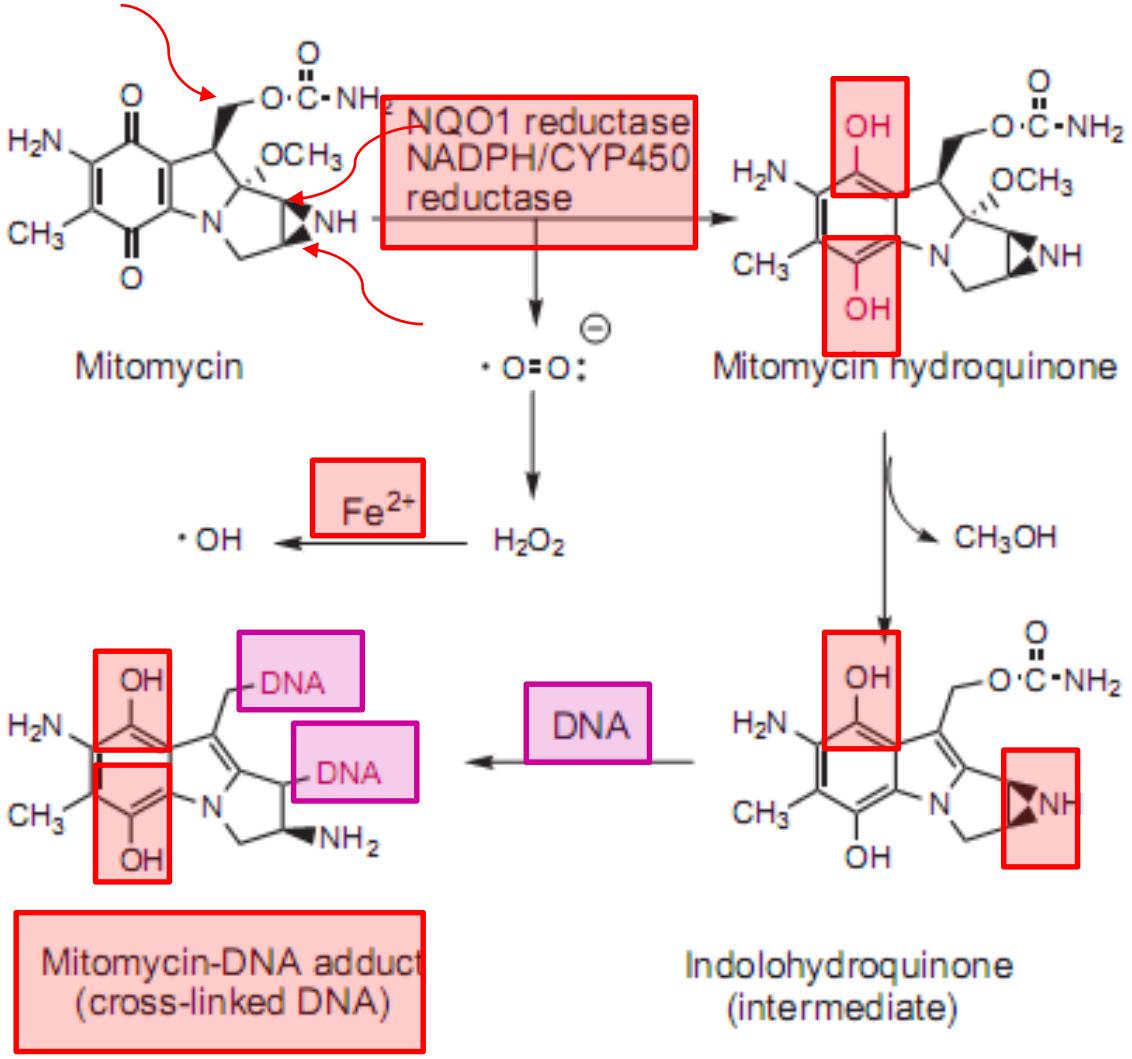


FIGURE 37.27 Mitomycin metabolism.