Anthracyclines and Anthracenediones as a Antitumor Agents

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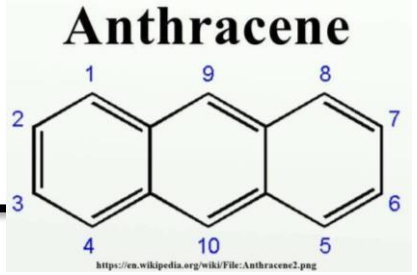
Introduction



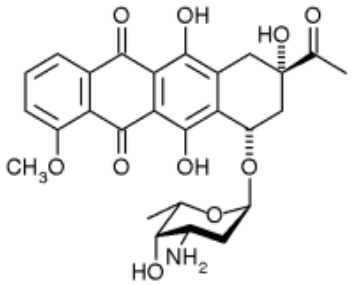
- Anthracyclines and anthracenediones are anthracene derivatives.
- The first anthracycline (daunorubicin) discovered from *Streptomyces peucetius*, a species of actinobacteria in 1960.
- The first anthracycline discovered was daunorubicin (trade name Daunomycin®), which is produced naturally by *Streptomyces peucetius*, a species of actinobacteria.
- Doxorubicin (trade name Adriamycin) was developed shortly after, and many other related compounds have followed, although few are in clinical use.
- Anthracyclines are broad-spectrum antineoplastic agents used in the treatment of hematopoietic malignancies such as acute lymphocytic (ALL) and acute myelogenous leukemia (AML), Hodgkin's and non-Hodgkin's lymphoma and multiple myeloma, as well as carcinomas of the breast, lung, ovary, stomach and thyroid, and various childhood malignancies.
- Its introduction in the 1960s and incorporation into combination regimens led to curative treatments for non-Hodgkin lymphoma (cyclophosphamide, hydroxydaunomycin [doxorubicin], Oncovin [vincristine], and prednisone [CHOP]).
- Available agents include: Daunorubicin (Daunomycin®), Doxorubicin (Adriamycin®), Epirubicin, Idarubicin, Valrubicin, Mitoxantrone
- Anthracyclines are used to treat various cancers and as of 2019 were among the most commonly used chemotherapeutic agents.

TABLE 18.1
KEY FEATURES OF DAUNORUBICIN AND DOXORUBICIN

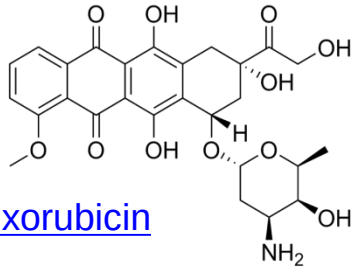
Mechanism of action	Pleiotropic effects including (1) activation of signal transduction pathways, (2) generation of reactive oxygen intermediates, (3) stimulation of apoptosis, and (4) inhibition of DNA topoisomerase II catalytic activity
Metabolism	1. Reduction of side-chain carbonyl to alcohol, resulting in some loss of cytotoxicity 2. One-electron reduction to semiquinone free-radical intermediate by flavoproteins, leading to aerobic production of superoxide anion, hydrogen peroxide, and hydroxyl radical 3. Two-electron reduction, resulting in formation of aglycone species that can be conjugated for export in bile
Pharmacokinetics	*Doxorubicin:* V_d = 25 liters; protein binding = 60–70%; CSF/plasma ratio, very low; $t_{1/2\alpha}$ = 10 min; $t_{1/2\beta}$= 1–3 hr; $t_{1/2\gamma}$ = 30 hr. Circulates predominantly as parent drug; doxorubicinol is most common metabolite, although a substantial fraction of patients form doxorubicin 7-deoxyaglycone and doxorubicinol 7-deoxyaglycone; substantial interpatient variation in biotransformation; no apparent dose-related change in clearance; clearance in men > women. *Daunomycin:* V_d, protein binding, and CSF/plasma ratio similar to doxorubicin; $t_{1/2\alpha}$ = 40 min; $t_{1/2\beta}$ = 20–50 hr. Metabolism to daunomycinol faster than for equivalent doxorubicin metabolism, although interpatient variation remains high.
Elimination	Only 50 to 60% of parent drug accounted for by known routes of elimination, which include reduction of the side-chain carbonyl by hepatic aldoketoreductases, aglycone formation, and excretion of biliary conjugates and metabolites. A substantial fraction of the parent compound is bound to DNA and cardiolipin in tissues and is slowly dissociated, contributing to prolonged disappearance. While changes in anthracycline pharmacokinetics may be difficult to demonstrate in patients with mild alterations in liver function, drug clearance is definitely decreased in the presence of significant hyperbilirubinemia or patients with a marked burden of metastatic tumor in liver.
Drug interactions	Heparin binds to doxorubicin, causing aggregation; coadministration of both drugs leads to increased doxorubicin clearance. In rodents, phenobarbital has been shown to increase, and morphine decrease, doxorubicin disappearance; drugs that diminish hepatic reduced glutathione pools (acetaminophen and BCNU) sensitize the liver to anthracycline toxicity.
Toxicity	1. Myelosuppression 2. Mucositis 3. Alopecia 4. Cardiac toxicity 5. Severe local tissue damage after drug extravasation
Precautions	1. Acute and chronic cardiac decompensation can occur. Most common is cumulative dose-related congestive cardiomyopathy, which is more frequent in patients with underlying hypertensive heart disease or those who have received mediastinal radiation with a cardiac dose > 2000 cGy. 2. Radiation sensitization of normal tissues, including chest wall and esophagus, is common and may occur many years after radiation exposure. 3. Extravasation damage to extremities has resulted in loss of limb function.

Structure Activity Relationships Anthracyclines

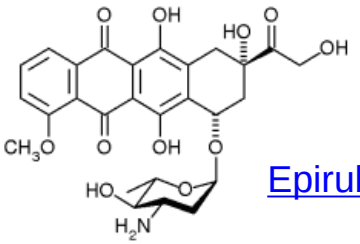
- Consist of a planar, hydrophobic tetracycline ring linked to a daunosamine sugar through a glycosidic linkage.
- (+) charged at physiologic pH, favoring intercalation into DNA.
- Quinone moieties allow to participate in electron transfer reactions and generate oxygen free radicals.
- Daunomycin and doxorubicin differ only by a single hydroxyl at position C14.
- Epirubicin is an epimer of doxorubicin having the C4′ hydroxyl group on the amino sugar in the equatorial rather than the axial position which increases lipophilicity.
- Idarubicin is a semisynthetic derivative of daunomycin (4-demothoxydaunorubicin) lacking the 4-methoxy group.



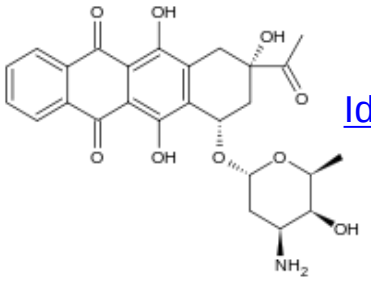
Daunorubicin, the prototypical anthracycline



Doxorubicin



Epirubicin



Idarubicin

Mechanism of Action of Anthracyclines

The anthracyclines are highly reactive in solution and create a panoply of effects on biologic systems

1. Poisoning of topoisomerase II

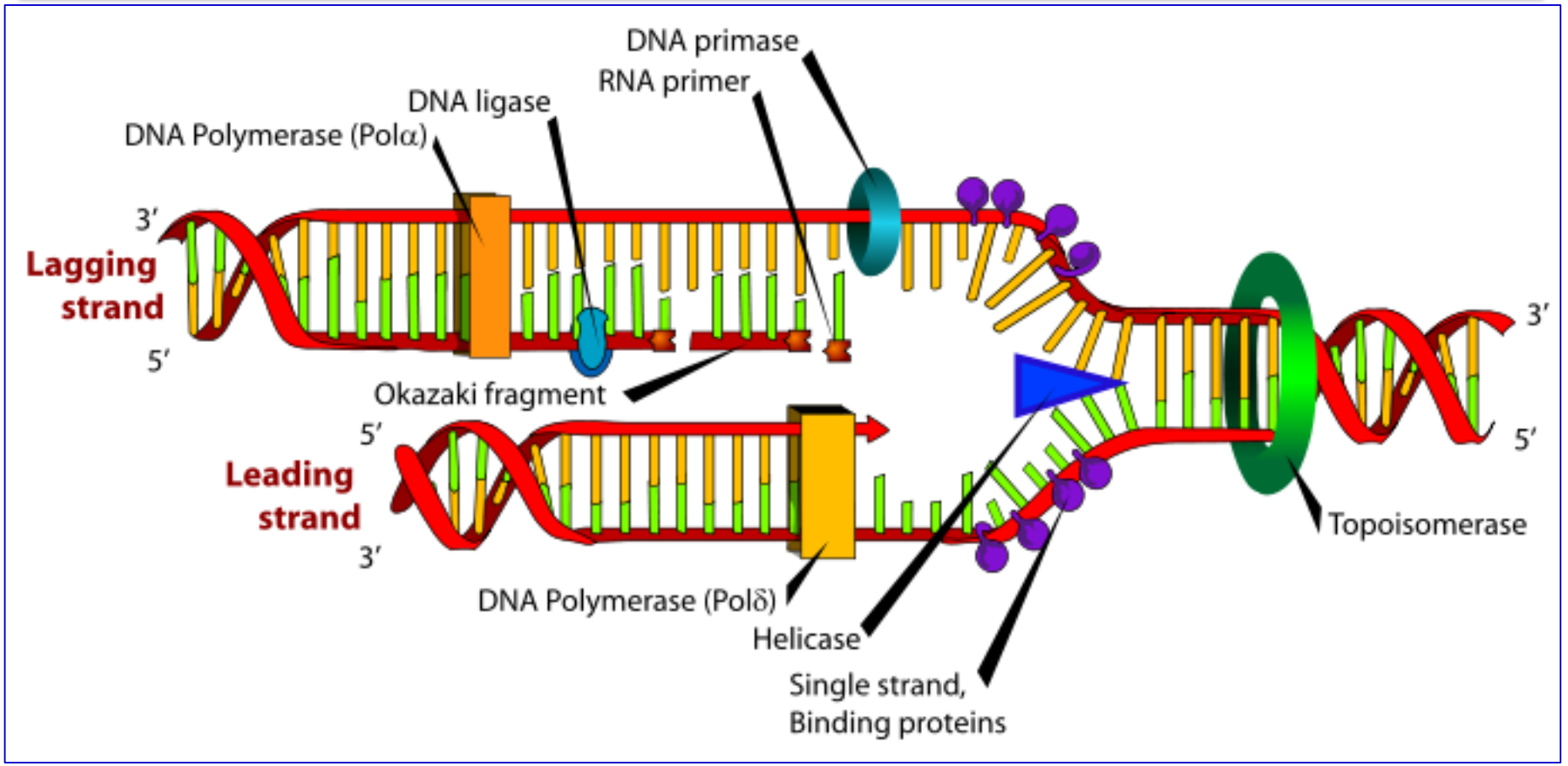
2. Intercalate with double-stranded DNA and produce structural changes that interfere with DNA and RNA synthesis

3. Generation of reactive oxygen species (ROS)

4. Activation of signal transduction pathways

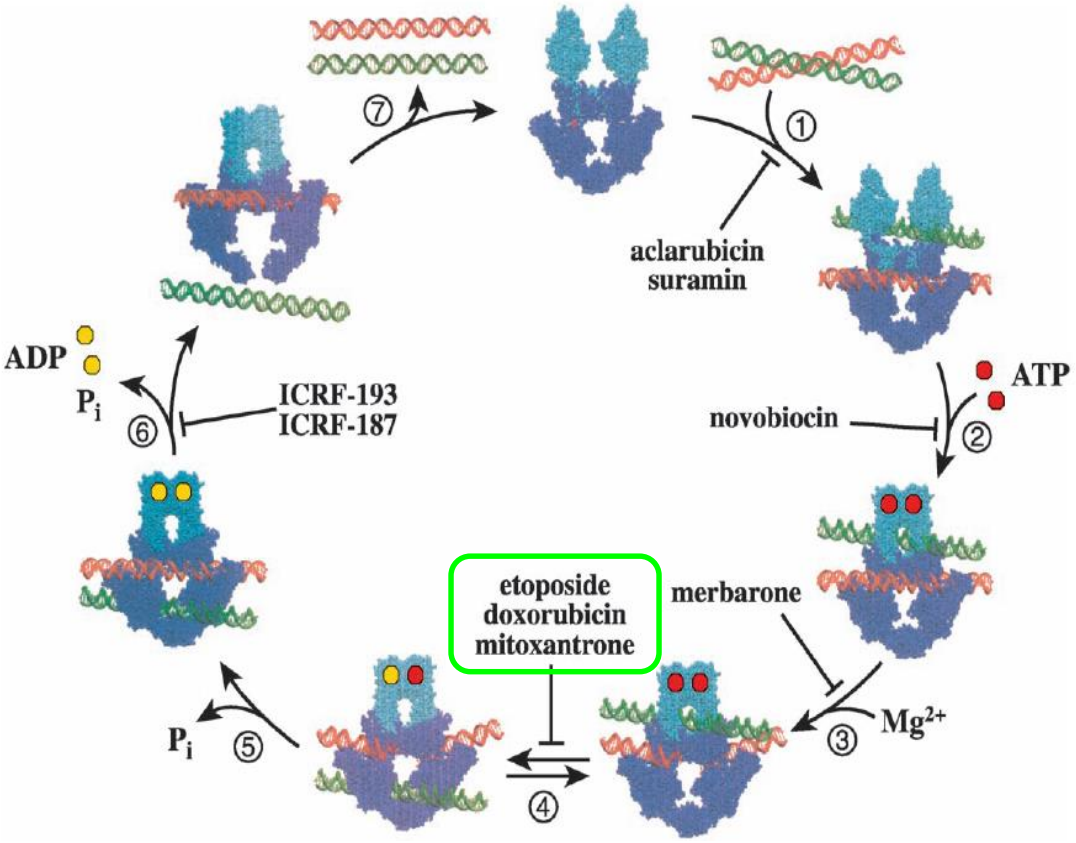
5. Stimulation of apoptosis

DNA Replication



DNA replication. The double helix is unwound by a helicase and topoisomerase. Next, one DNA polymerase produces the leading strand copy. Another DNA polymerase binds to the lagging strand. This enzyme makes discontinuous segments (called Okazaki fragments) before DNA ligase joins them together.

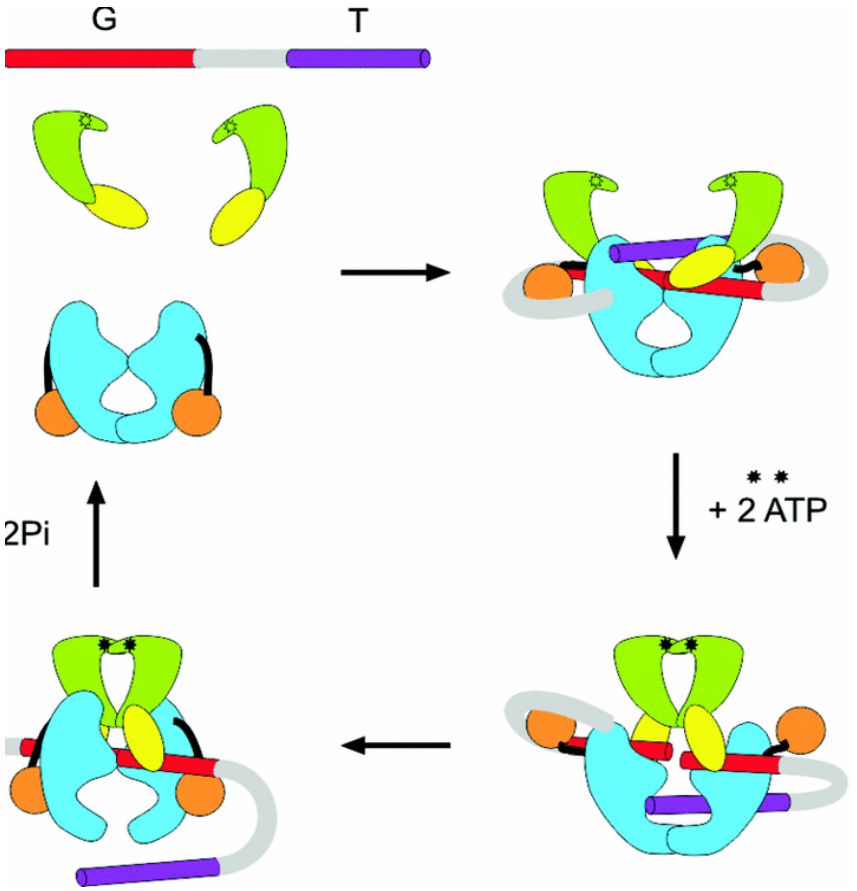
Topoisomerase II Poisoning

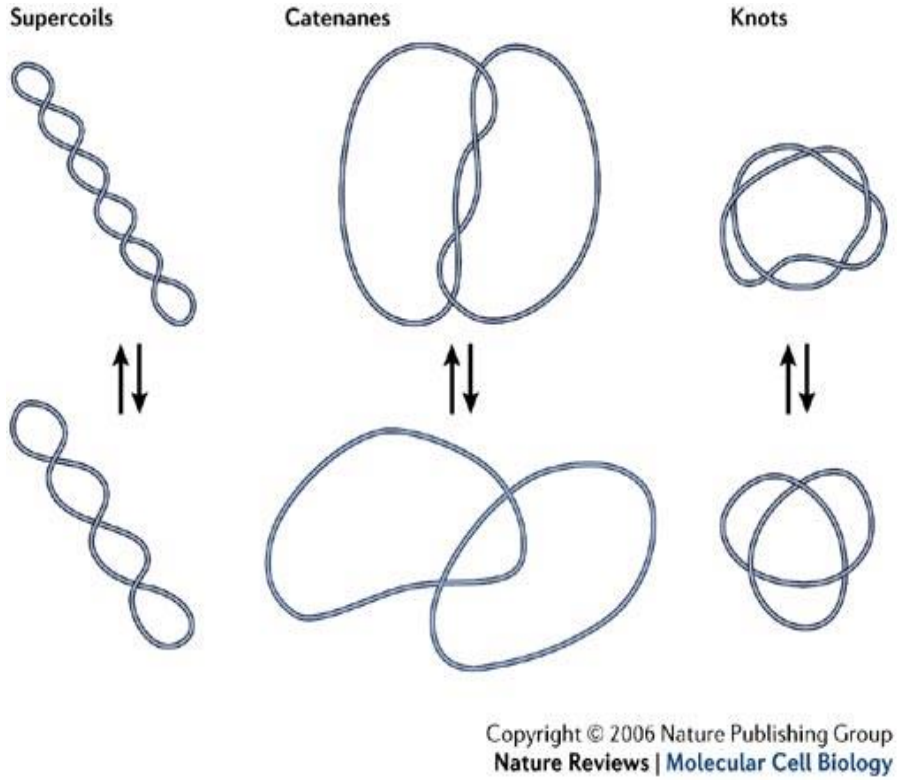


- Topoisomerase II temporary breaks the deoxyribose-phosphate backbone of both strands of the DNA to relax supercoils ahead via. Transport one DNA duplex through another and decatenation of intertwined sister chromatids .
- **TopoIIα**-cell-cycle regulated and abundant in proliferating cells
- **Topo IIβ** -predominates in quiescent cells

(Step 1) The catalytic cycle is initiated by enzyme binding non-covelently to two double-stranded DNA segments called the G segment (in red) and G duplex-topo II complex bind at the crossover region with the transported T segment (in green). (Step2)Next, two ATP molecules are bound, which is associated with dimerization of the ATPase domains. (Step 3) Mg^{2+}-dependent cleavage of the G dupex form a phosphotyrosine linkage. (Step 4) The T segment is transported through the break in the G segment, which is accompanied by the hydrolysis of one ATP molecule. (Step 5) The G segment is then religated and the remaining ATP molecule is hydrolyzed. (Step 6) dissociation of the two ADP molecules, the T segment is transported through the opening in the C-terminal part of the enzyme and followed by closing of this gate. (Step 7) Finally, the N-terminal ATPase domains reopen, allowing the enzyme to dissociate from DNA. Data from Berger et al. (1996), Baird et al. (1999), Brino et al. (2000), and Hu et al. (2002).

The catalytic cycle of DNA topoisomerase II

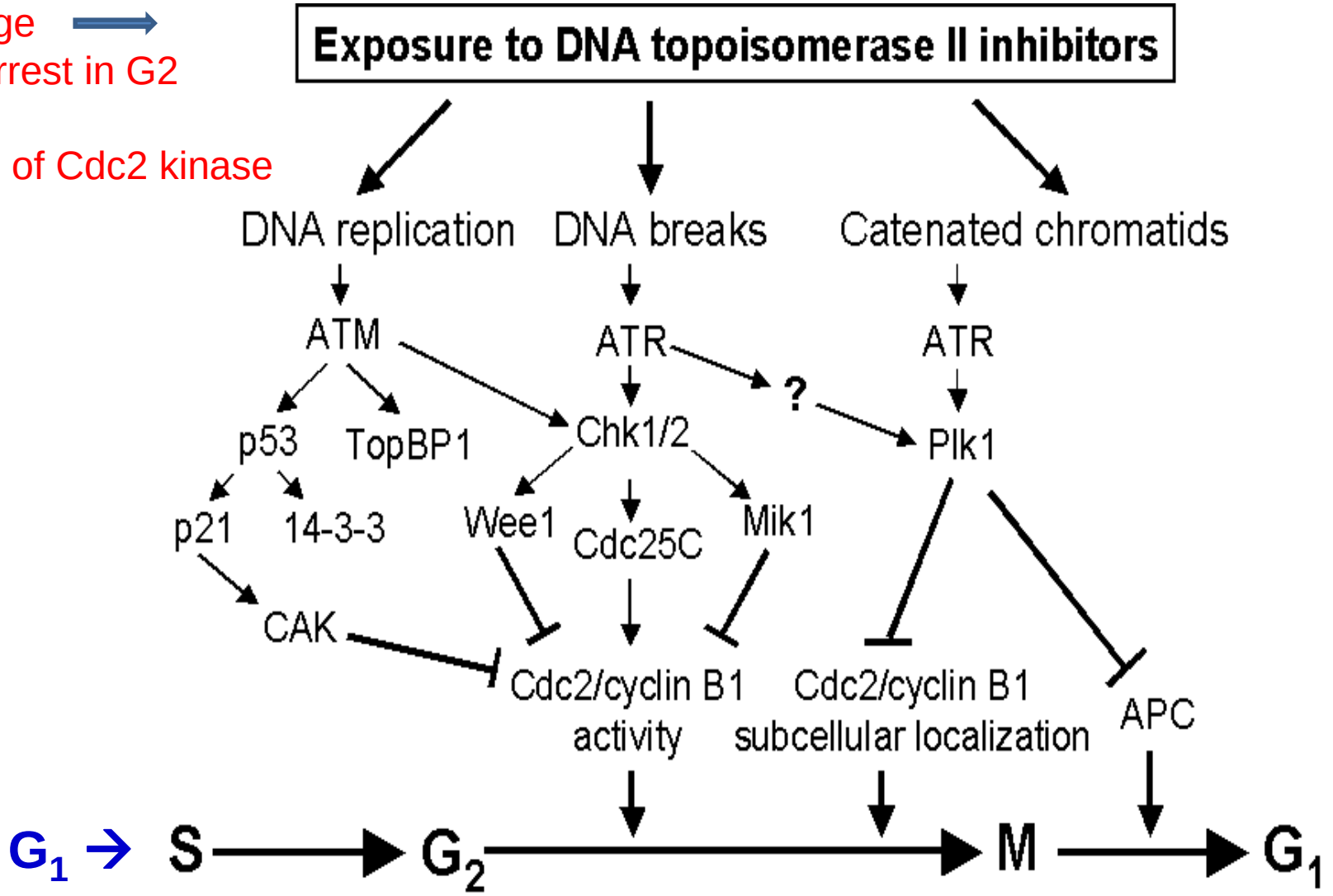




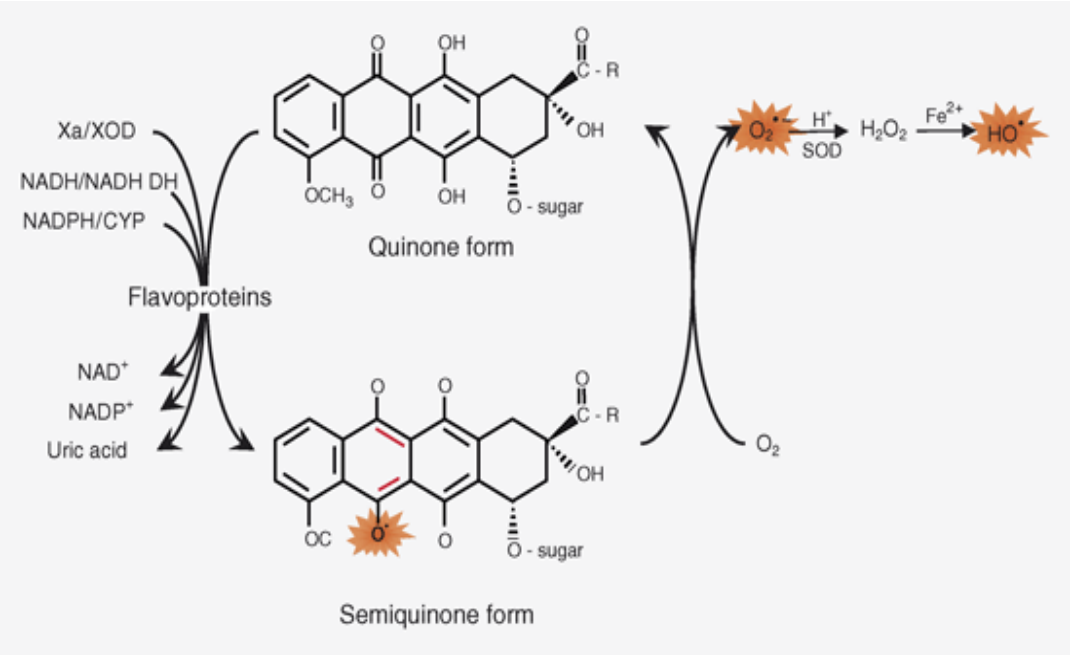
Mechanisms associated with G2 arrest in cells exposed to topo II inhibitors

DNA damage ⟶
cell cycle arrest in G2

Inactivation of Cdc2 kinase



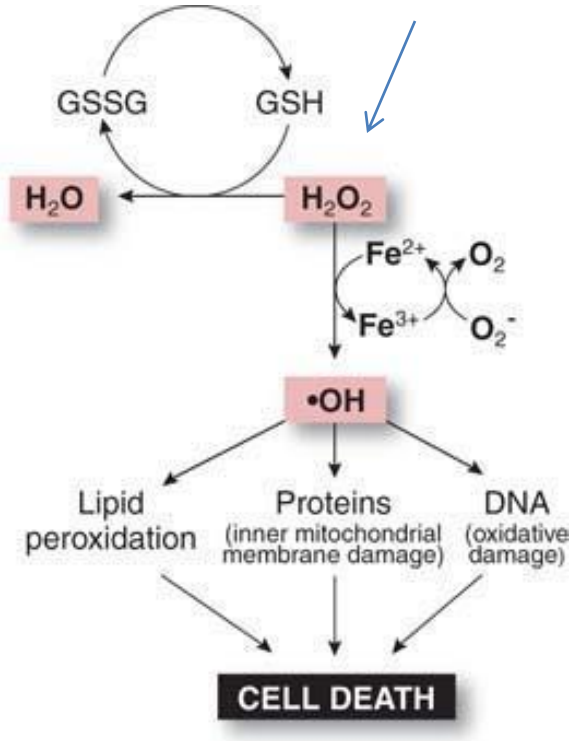
Generation of Reactive Oxygen Species (ROS)



ROS (produced by one & two-electron reduction) damage to intracellular macromolecules, including lipid membrane DNA bases and thiol-containing transport proteins

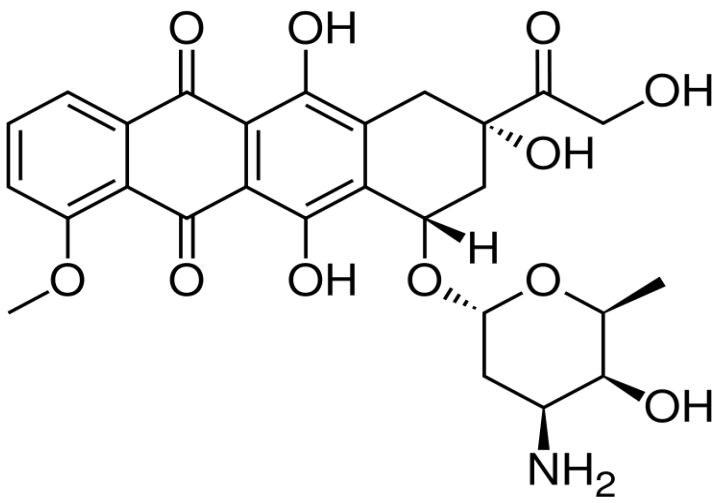
Anthracene donate e^-

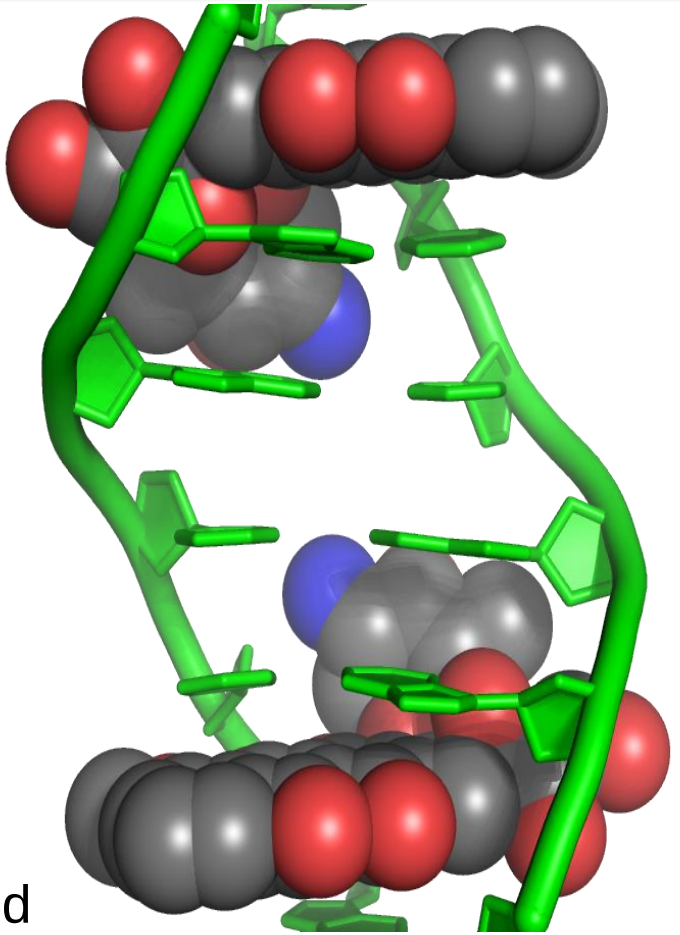
$O_2 \longrightarrow O_2^{\cdot -}$



ROS Formation

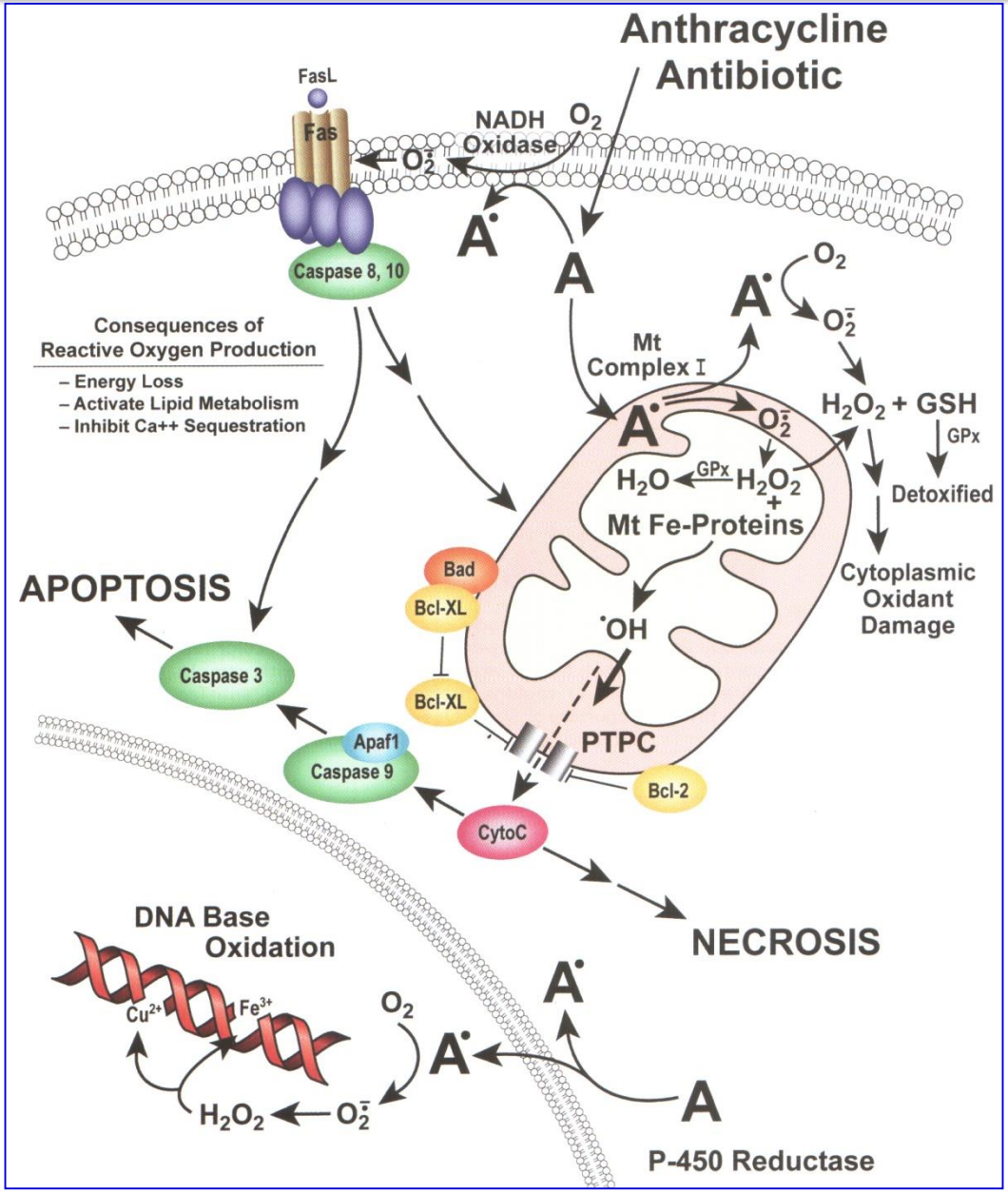
Intercalation with Double-stranded DNA





- The planar ring intercalates into DNA.
- The side chain provide an important H-binding function.
- The daunosamine sugar binds to the minor groove A.
- And play a critical role in base recognition and sequence specificity.

General Mechanism of Action



Activity of Anthracyclines

- The anthracyclines are use against both solid and hematologic malignancies.
- Doxorubicin is one of the most active agents in the treatment of breast cancer.
- Single-agent activity is similar to that of paclitaxel and is comparable with combination therapy.
- Doxorubicin has limited but demonstrable activity against thyroid cancer, ovarian cancer, and small-cell lung cancer.
- It also has demonstrated activity against endometrial carcinoma, cancer of the testis, prostate, cervix, and head and neck, and multiple myeloma.
- Daunomycin is used mostly for the treatment of acute lymphocytic and myelocytic leukemias.
- Idarubicin is used predominantly in the treatment of adult acute myelogenous leukemia.
- Epirubicin has broad-spectrum antitumor activity in preclinical models.
- In the clinic, it has activity against melanoma, breast, colorectal, renal, gastric, pancreatic, hepatocellular and ovarian, and lung cancers and soft-tissue sarcomas.

Clinical Pharmacology of Anthracycline

- Doxorubicin (Adriamycin®, Rubex®) i.v. dose of 40 to 75 mg/m^2 as a single agent.
- Daunorubicin (Cerubidine®) i.v. dose of 30 to 60 mg/m^2 daily for 3 days.
- Idarubicin i.v dose of 12 mg/m^2 daily for 3 days in combination with cytosine arabinoside for the treatment of acute myelogenous leukemia.
- In i.v. administration, anthracyclines are rapidly cleared from the plasma, where they reach all tissues except the brain and testes.
- Approximately 75% of the drug remaining in the plasma is bound to plasma proteins.
- Within tissues, the drugs are tightly bound to DNA.
- Tissue concentrations of anthracycline correlate with content of DNA and are 10- to 500-fold greater than plasma.
- Anthracyclines are metabolized in the liver and excreted in the bile and to a lesser extent through the kidneys.
- Epirubicin, reduction of the 13-keto group to the enol by aldoketoreductase, produces active metabolites.

Mechanisms of Resistance by Cancer Cells

1. Decreased drug accumulation due to transport by P-glycoprotein (P170), the *mdr*1 gene product, and MRP1 (multidrug resistance associated protein 1), the *mrp*-1 gene product.

2. Downregulation or mutations in topoisomerase II.

3. Increases in drug-neutralizing species, such as glutathione or glutathione transferase.

4. Mutations in *p53.*

5. Overexpression of anti-apoptotic molecules, such as Bcl-2.

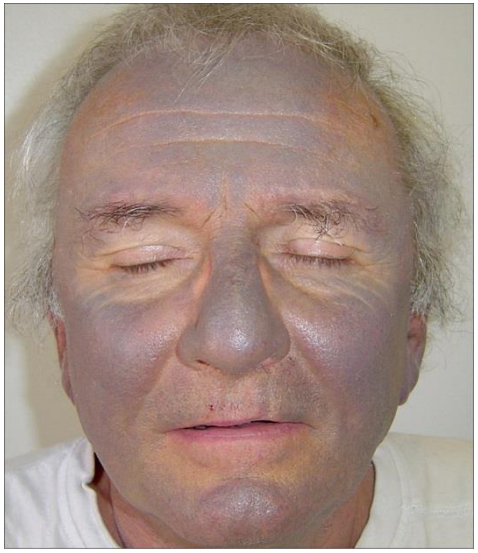
6. Loss of DNA mismatch repair genes, such as *MLH1* (contribute to withstand the cytotoxic effects).

***MutL homolog 1, colon cancer, nonpolyposis type 2 (*E. coli*)**, also known as **MLH1**, is a human gene located on Chromosome 3. It is a gene commonly associated with hereditary nonpolyposis colorectal cancer.

Toxicity & Drug Interaction

Toxicity

1. Myelosuppression (dose-limiting toxicity)
2. Mucositis
3. Extravasation
4. Alopecia
5. Cardiotoxicity
6. Nausea, vomiting
7. Increased skin pigmentation



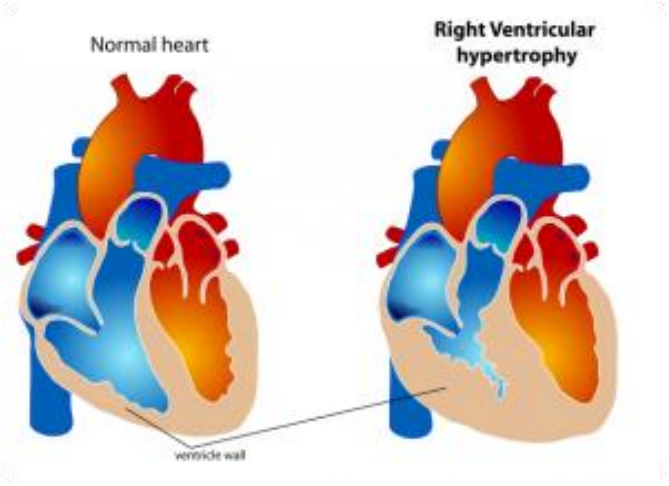
Drug Interactions

1. Heparin increase the clearance of Doxorubicin.
2. Phenobarbital increase and Morphine decrease disappearance.
3. Drug which reduce the glutathione in liver that increase the anthracycline toxicity.

Lists the Incidence of Congestive Heart Failure

List of incidence of clinically detectable congestive heart failure as a junction of cumulative doxorubicin dose of 40 to 75 mg/m^2 as a bolus injection every 3 to 4 weeks.

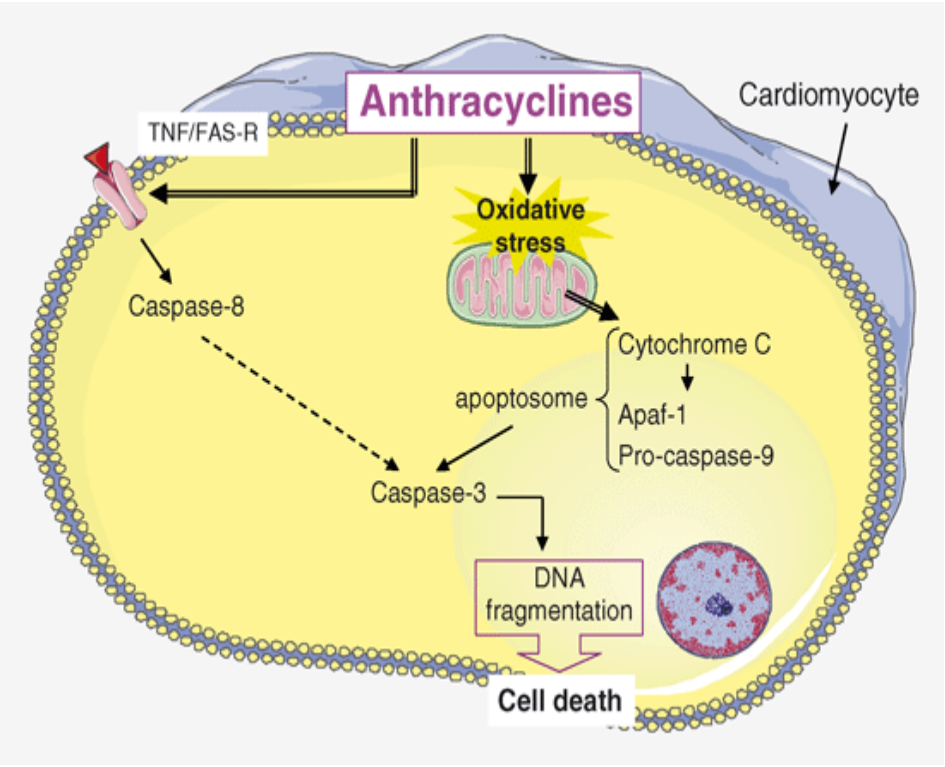
Cumulative Dose (mg/m^2)	Incidence of Congestive Heart Failure (%)
< 350	< 1
550	7
600	15
700	30
Modified from VonHoff DD et al.	

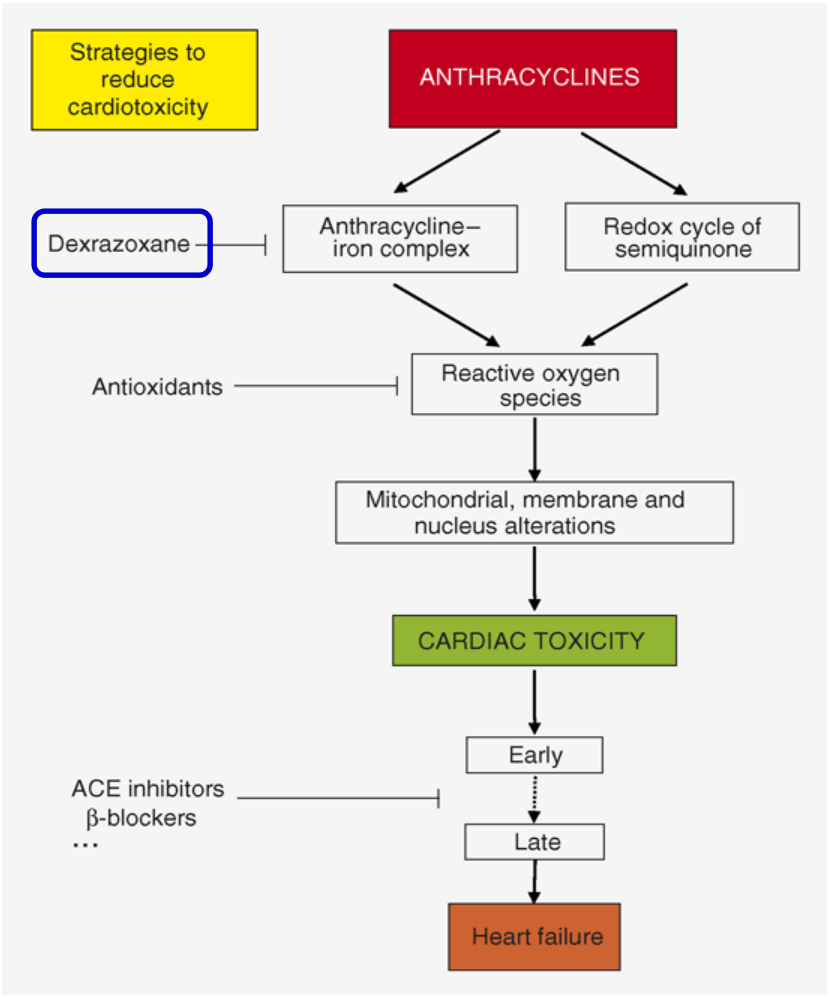


Cardiotoxicity of Anthracyclines-1

- Notorious for causing cardiotoxicity.
- Caused by many factors, which may include interference with the ryanodine receptors of the sarcoplasmic reticulum in the heart muscle cells, from free radical formation in the heart, or from buildup of metabolic products of the anthracycline in the heart.
- The cardiotoxicity often presents as ECG changes (especially change in the frequency of QRS complex) and arrhythmias, or as a cardiomyopathy leading to heart failure (sometimes presenting many years after treatment).
- This cardiotoxicity is related to a patient's cumulative lifetime dose.
- A patient's lifetime dose is calculated during treatment, and anthracycline treatment is usually stopped (or at least re-evaluated by the oncologist) upon reaching the maximum cumulative dose of the particular anthracycline.
- There exists evidence that the effect of cardiotoxicity increases in long-term survivors, from 2% after 2 years to 5% after 15 years.

Cardiotoxicity





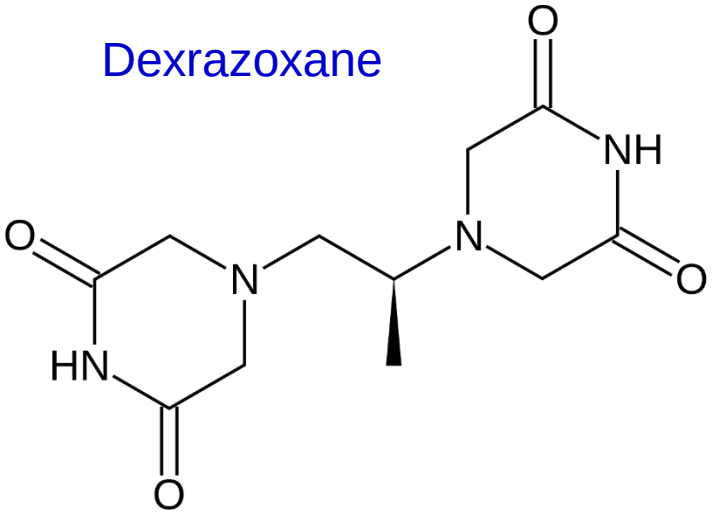
Cardiac toxicity manifested by arrhythmia (부정맥), tachycardia (빈맥), and congestive heart failure (울혈성심부전).

Cardiotoxicity of Anthracyclines-2

- In addition to staying below the cumulative doses, various prevention measures may be employed by the oncologist in order to reduce the risk of cardiotoxicity.
- Cardiac monitoring are recommended at 3, 6, and 9 months.
- Other measures include the use of Dexrazoxane hydrochloride, the use of liposomal preparations of doxorubicin when appropriate, as well as the administration of doxorubicin over longer infusion rates.
- As a derivative of EDTA, dexrazoxane chelates iron and thus reduces the number of metal ions complexed with anthracycline and, consequently, decrease the formation of superoxide radicals.

- Dexrazoxane 염산염은 심장 보호제.
- 1972년 유진 허먼 (Eugene Herman)에 의해 발견.
- 덱사라족산의 IV 투여 시 HCl로 pH를 조정해서 산성 상태임.

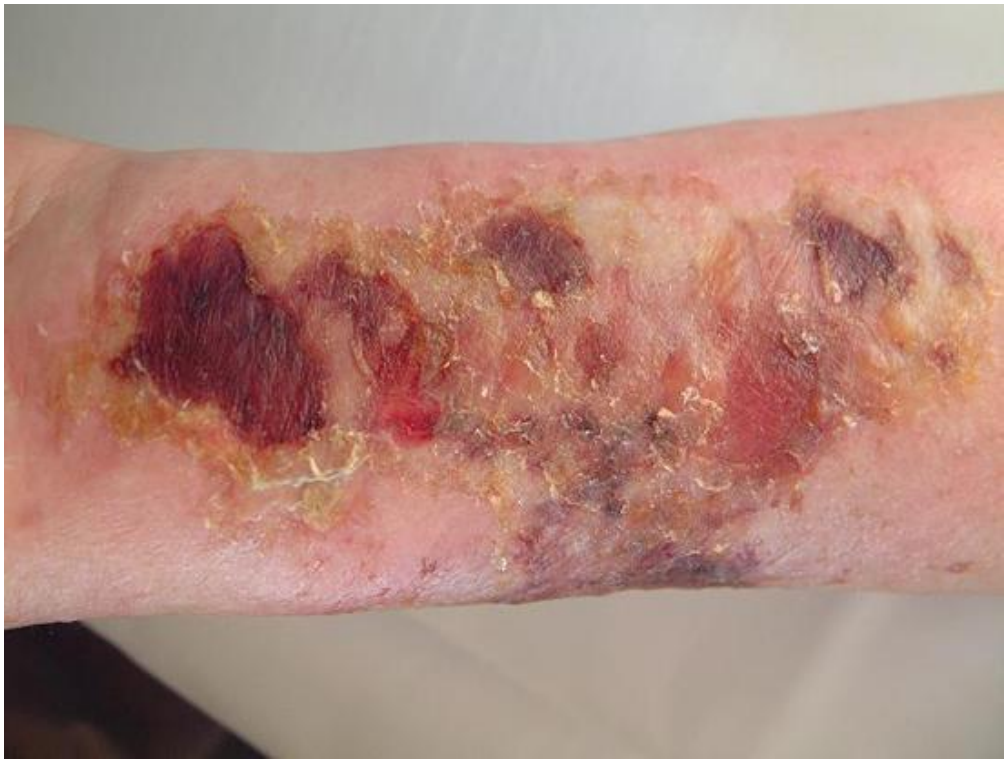
Dexrazoxane



Cardiotoxicity of Anthracyclines-3

- Dexrazoxane is a cardioprotectant that is sometimes used to reduce the risk of cardiotoxicity; it has been found to reduce the risk of anthracycline cardiotoxicity by about two-thirds, without affecting response to chemotherapy or overall survival.
- The liposomal formulations of daunorubicin and doxorubicin are less toxic to cardiac tissue than the non-liposomal form because a lower proportion of drug administered in the liposome form is delivered to the heart.
- Longer infusion rates will result in a reduced plasma level and a much lower left ventricular peak concentration

Extravasation



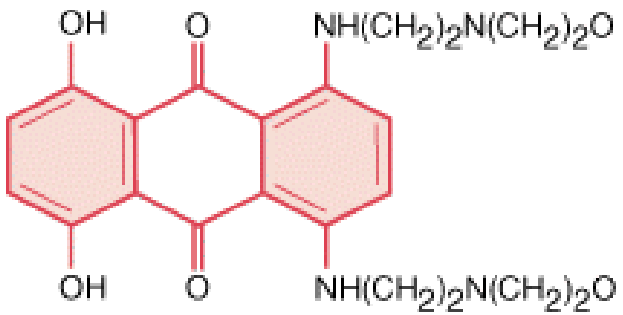
Doxorubicin Analogs: Idarubicin and Epirubicin

TABLE 18.5
KEY FEATURES OF ANTHRACYCLINE ANALOGS

	Idarubicin	Epirubicin
Mechanism of action	DNA strand breakage mediated by topoisomerase II; free radical–induced injury; induction of apoptosis	Same
Mechanism of resistance	1. Multidrug resistance mediated by *MDR*1 or *MRP* 2. Topoisomerase II mutations 3. Altered apoptotic response	Same
Dose/schedule (mg/m^2)	10–15 IV q3wk 10 IV × 3 d (leukemia) 45 PO q3wk	90–110 IV q3wk
Pharmacokinetics		
Elimination half-life		
Parent compound	11.3 hr	18.3 hr
13-ol metabolite	40-60 hr	21.1 hr
Other metabolite		12.1 hr (epiglucuronide)
Oral bioavailability	30%	
Metabolism	Primary metabolite, 13-epirubicinol, is cytotoxic and exceeds level of parent compound in plasma	Primary metabolites are glucuronides of parent and 13-ol
Excretion	80% excreted in urine as 13-ol	Primarily parent compound, 13-ol, and glucuronides
Toxicity	1. Leukopenia 2. Thrombocytopenia 3. Cardiotoxicity (less than doxorubicin)	1. Leukopenia 2. Thrombocytopenia 3. Cardiotoxicity equal to doxorubicin
Drug interactions	None established	None established
Precautions	None established	Possible dose reduction in hepatic dysfunction

Doxorubicin Analogs: Anthracenediones (Mitoxantrone)

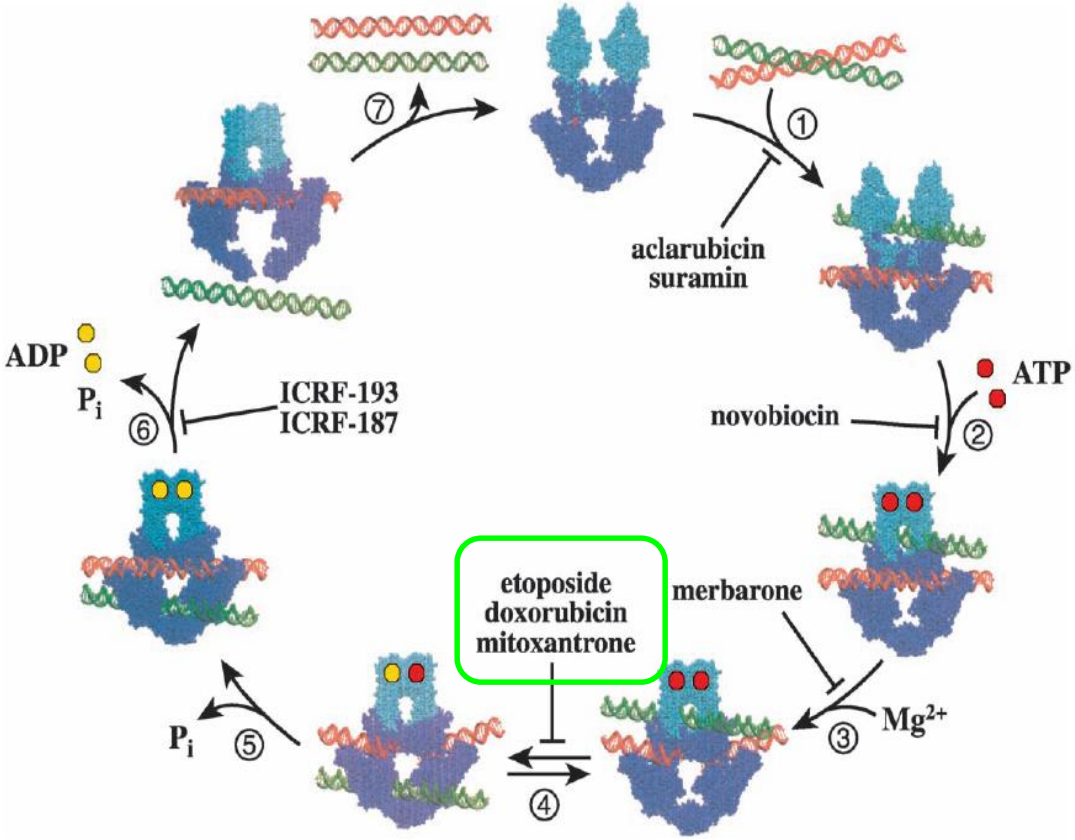
- Synthesized by chemists at American Cyanamid Laboratories in 1970.
- Mitoxantrone, the most active compound in the anthracenedione series.
- A planar tetracyclic compound with two symmetrical aminoalkyl side arms but no glycoside substituents.
- Its shows less cardiac toxicity and less potential for extravasation injury and less nausea and vomiting.
- But it is narrow spectrum of activity.



Mitoxantrone

Mechanism of Action

- Mitoxantrone produces double-stranded DNA breaks through the poisoning of topoisomerase II.
- Unlike the anthracyclines, mitoxantrone is less likely to participate in one-electron reduction reactions and is therefore less effective in forming free radicals.



Clinical Pharmacology (Anthracenediones)

- Mitoxantrone is given by i.v. injection at a dose of 12 mg/m^2 for 3 days with cytosine arabinoside to patients with acute myelogenous leukemia and 12 to 14 mg/m^2 once every 3 weeks to patients with solid tumors.
- The drug is given over 30 min and is rarely associated with extravasation injury.
- Like the anthracyclines, a high proportion of the drug is found in tissues tightly bound to DNA and in the plasma bound to plasma proteins.
- Mitoxantrone is metabolized to the monocarboxylic and dicarboxylic acids formed by oxidation on the terminal hydroxyl groups on the alkyl side chain.
- The majority of the drug is excreted in the feces, with less than 10% recovered in the urine.
- Myelosuppression is dose limiting.
- Mucositis, nausea and vomiting, and alopecia are less common than with doxorubicin.
- Cardiotoxicity is seen at cumulative doses exceeding 160 mg/m^2 in patients not receiving prior therapy with an anthracycline or other cardiotoxic drug.

Activity of Mitoxantrone

- Mitoxantrone is indicated for the treatment of acute leukemias and is also used to treat breast cancer.
- Used in combination with cytosine arabinoside, response rates in acute myelogenous leukemia range from 50% to 70%.
- Mitoxantrone produces an overall response rate of 17% to 35% in metastatic breast cancer
- Used in combination with 5-flurouracil and leucovorin, the response rate was 45% to 65%.
- Mitoxantrone has activity similar to that of doxorubicin in patients with previously treated breast cancer but produces significantly less cardiac toxicity (less than doxorubicin).

Mechanism of Resistance:

- Unlike the anthracyclines, mitoxantrone is not transported avidly by P-glycoprotein or MRP1.
- Resistance occurs through alterations in topoisomerase II, and possibly through expression of unique transport proteins.

Toxicity of Mitoxantrone

- Primary advantages of mitoxantrone in comparison with doxorubicin: much reduced incidence of cardiac toxicity, the mild nausea and vomiting that follows intravenous administration, and the minimal alopecia.

- Early trials: occasional episodes of cardiac failure, primarily in patients who had not been helped by prior doxorubicin.

- Other toxicities: reversible leukopenia; mild thrombocytopenia; nausea and vomiting; and, rarely, abnormal liver enzymes in patients receiving dose levels appropriate for solid tumors.

Conclusion

- Anthracyclines is the most effective anticancer regimens.
- The anthracyclines are indicated for use against both solid and hematologic malignancies.
- Its act via poisoning of topoisomerase II, production of ROS.
- Its resistance mainly occur by enhanced drug efflux by P170 glycoprotein.
- All anthracyclines produce cardiac damage that can result in serious and even life-threatening complications.
- Cardiac function can be monitored during treatment with anthracyclines by electrocardiography, echocardiography, or radionuclide scans.
- Mitoxantrone is a search for anthracycline analogs with less cardiac toxicity but narrow spectrum (lesser activity against breast cancer); useful in the palliative therapy of hormone-resistant prostate cancer and is effective in combination therapy for the lymphomas and leukemias.