Classification of Antitumor Antibiotics drugs

Many of the antineoplastic antibiotics are produced by the soil fungus *Streptomyces.*

- **Anthracyclines:** Doxorubicin, Daunorubicin, Epirubicin, Mitoxantrone, and Idarubicin.
- **Actinomycins/Chromomycins:** Dactinomycin and Plicamycin.
- **Miscellaneous:** Mitomycin and Bleomycin.

Mechanisms by which these agents target DNA is

- Intercalation,
- Alkylation, and
- Strand breakage either directly or as a result of enzyme inhibition.

Steps in Intercalation

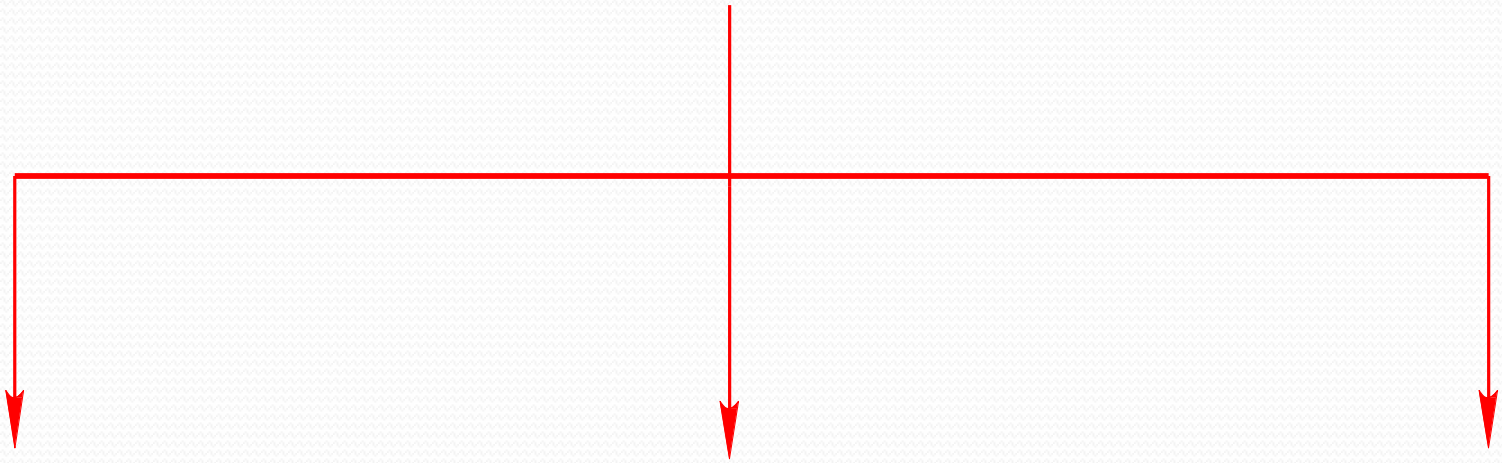
- Intercalating drugs contain a planar aromatic or heteroaromatic ring system which can slip into the double helix of DNA and distort its structure.
- Drug should induce a cavity between base pairs so that insertion may occur b/n drug and DNA.
- The interaction of the intercalator (drug) and the adjacent base pairs of DNA occurs by the overlap of *p-orbitals of the intercalator and the base pairs.*
- *The p-orbitals of the* intercalator/*intercalation species are provided by a combination* of aromatic and conjugated systems that impart the planarity required for intercalation.

❖The side chains of intercalator has a cationic ❖moiety, which may form ionic bonds with the anionic phosphate backbone in DNA.

❖The overall result of these interactions is to cause a local bend or kink or cut in DNA resulting in a local shape distortion.

❖Inhibition of topoisomerase /DNA gyrase (Topoisomerase enzymes are responsible for the unwinding and relaxation of DNA so that transcription may occur)

Mechanisms

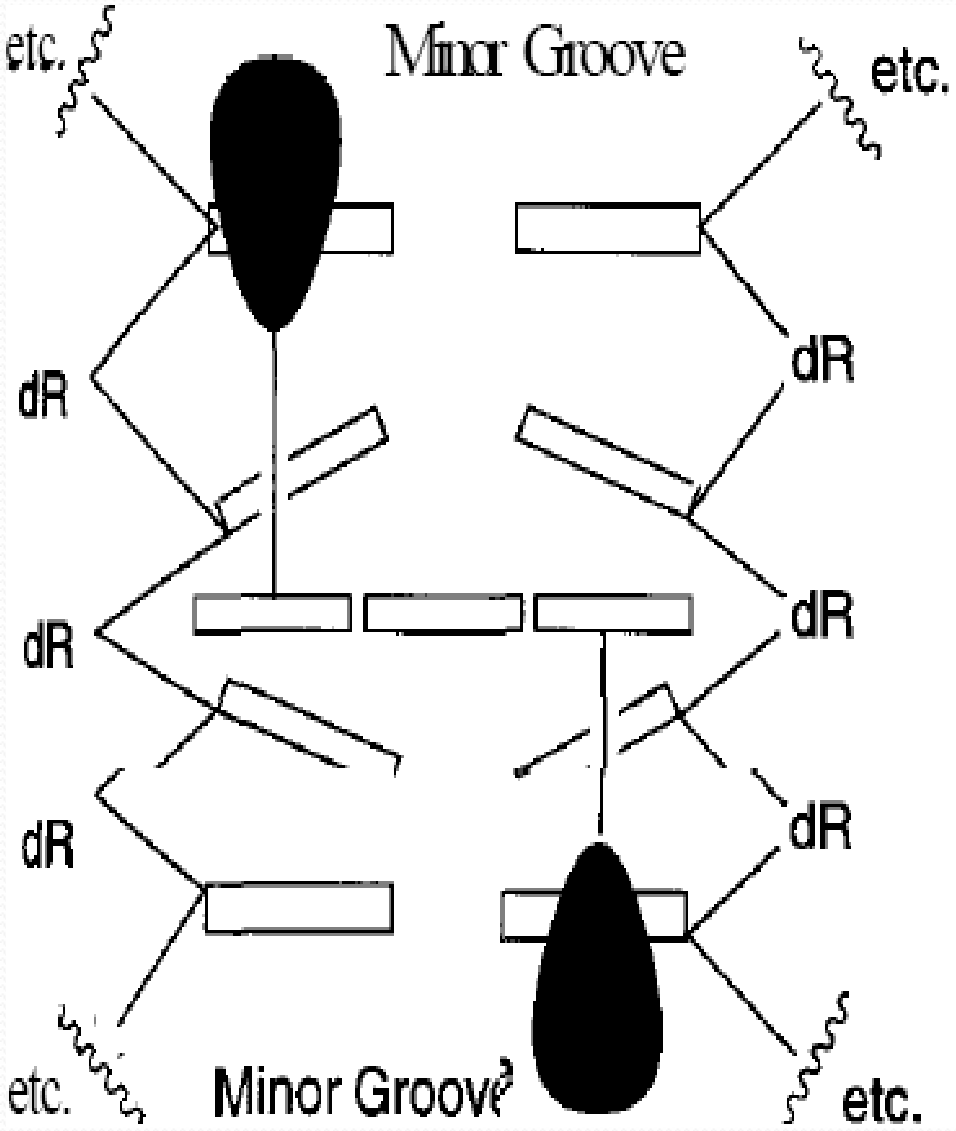


Intercalation

Alkylation

Strand breakage either directly or as a result of enzyme inhibition

Intercalation mechanism



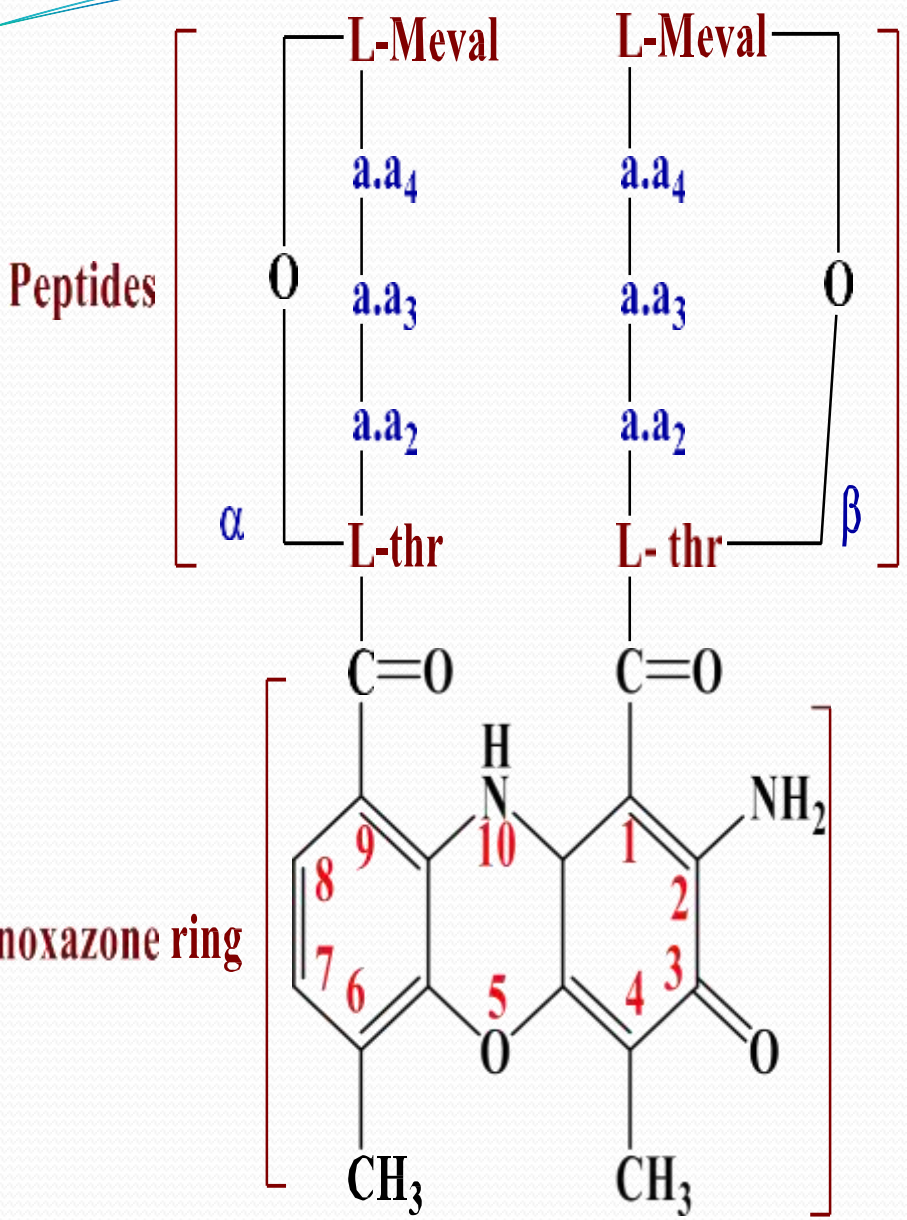
= DNA base

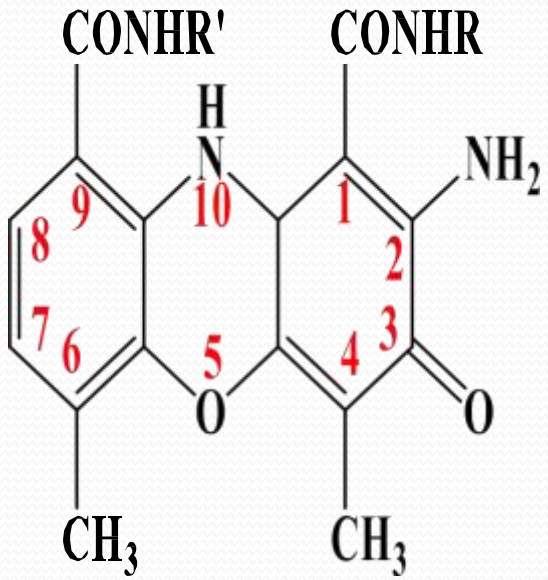
= DM ring

= DM peptide side-chain

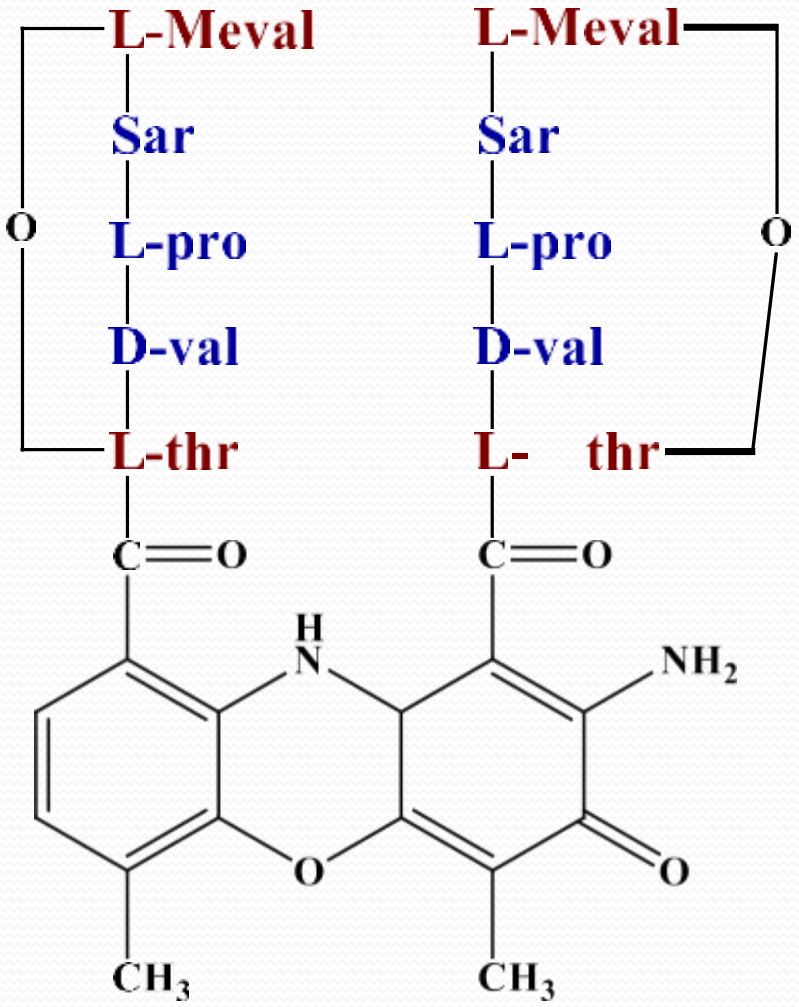
dR = Deoxyribose phosphate back bone

Antibiotics (Ab)





Actinomycin D (Dactinomycin)



Actinomycins binding tightly to double helical DNA and thereby prevents it from being an effective template for RNA synthesis. Intercalation may also result in inhibition of topoisomerase enzymes.

Note:- The main biochemical consequence of the intercalation of actinomycins into DNA is the inhibition of DNA and RNA synthesis. This inhibition eventually results in depletion of RNA and proteins and leads to cell death.

SAR

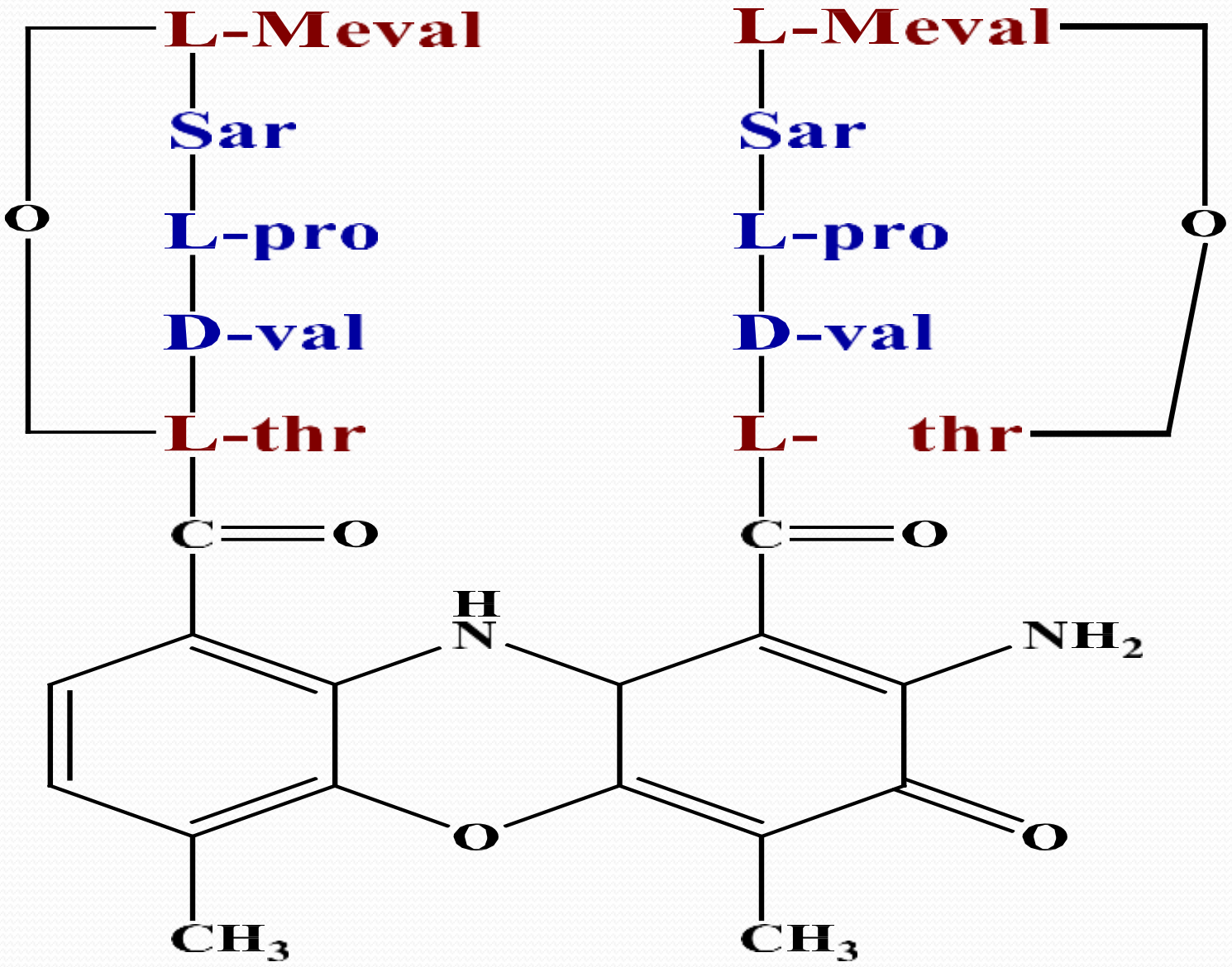
1-Changes in substituents on the actinomycins, influence their binding to DNA, usually by making it less effective.

2-Opening a lactone ring or changing the stereochemistry of an amino acid abolishes activity.

3-Replacement of the 4- and 6- methyl groups by other substituents lead to reduces the activity of actinomycins.

4-Replacement of the 2-amino group also reduces activity.

Actinomycin D (Dactinomycin)



Uses:-

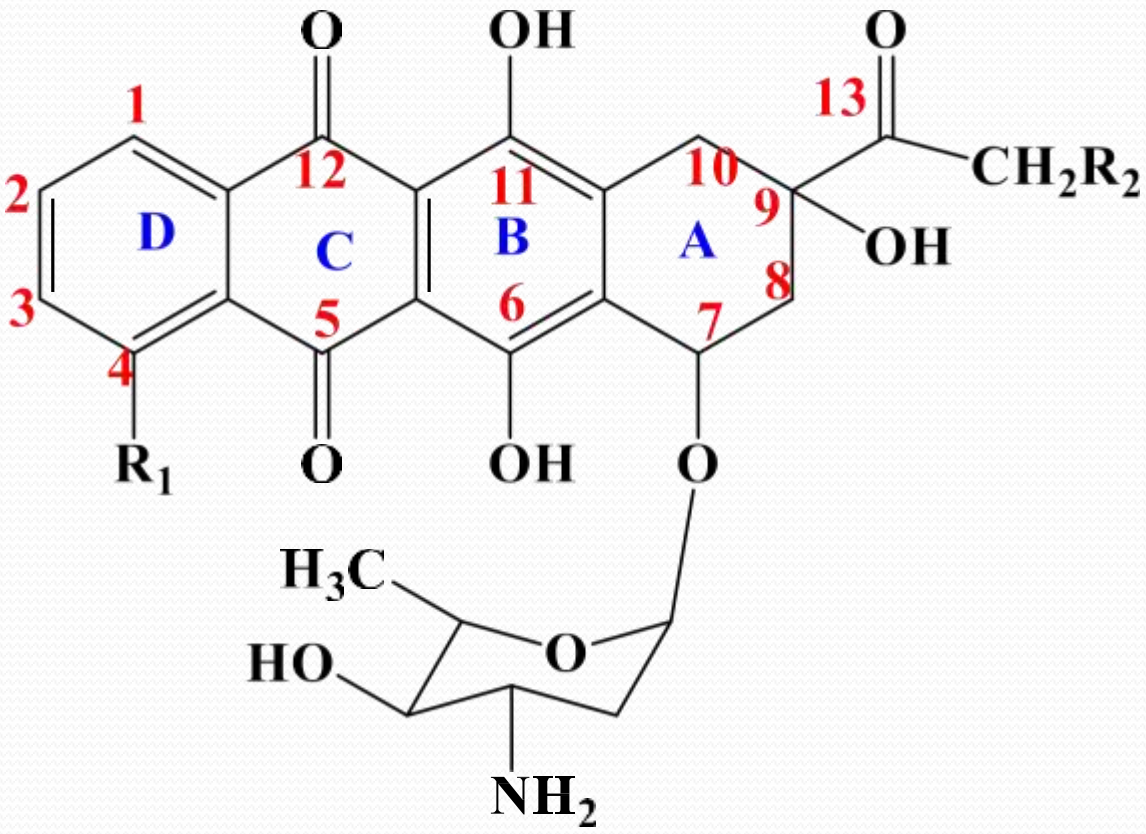
1-Used against rhabdomyosarcoma andWilm's tumor in children

2 -for live saving in women withchoriocarcinoma resistant to methotrexate.

3 -In combination with vincristin and cyclophosphamide used for solid tumorsin childrens.

- Dosage form:- powder for injection(0.5mg)0

anthracycline



1)Daunorubicin (Active against acute leukemias).

2)Doxorubicin (Adriamycin) active against broad spectrum of tumor, including both solid tumor and hematological.

3)Idarubicin.

4)Epirubicin.

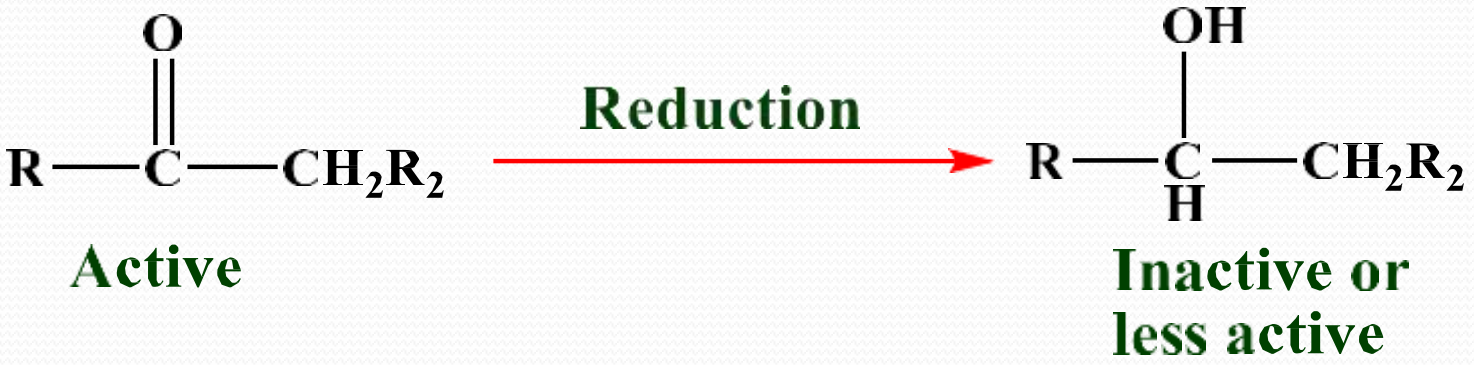
5)Valrubicin.

SAR (Anthracycline antibiotics) → Closely related to tetracycline

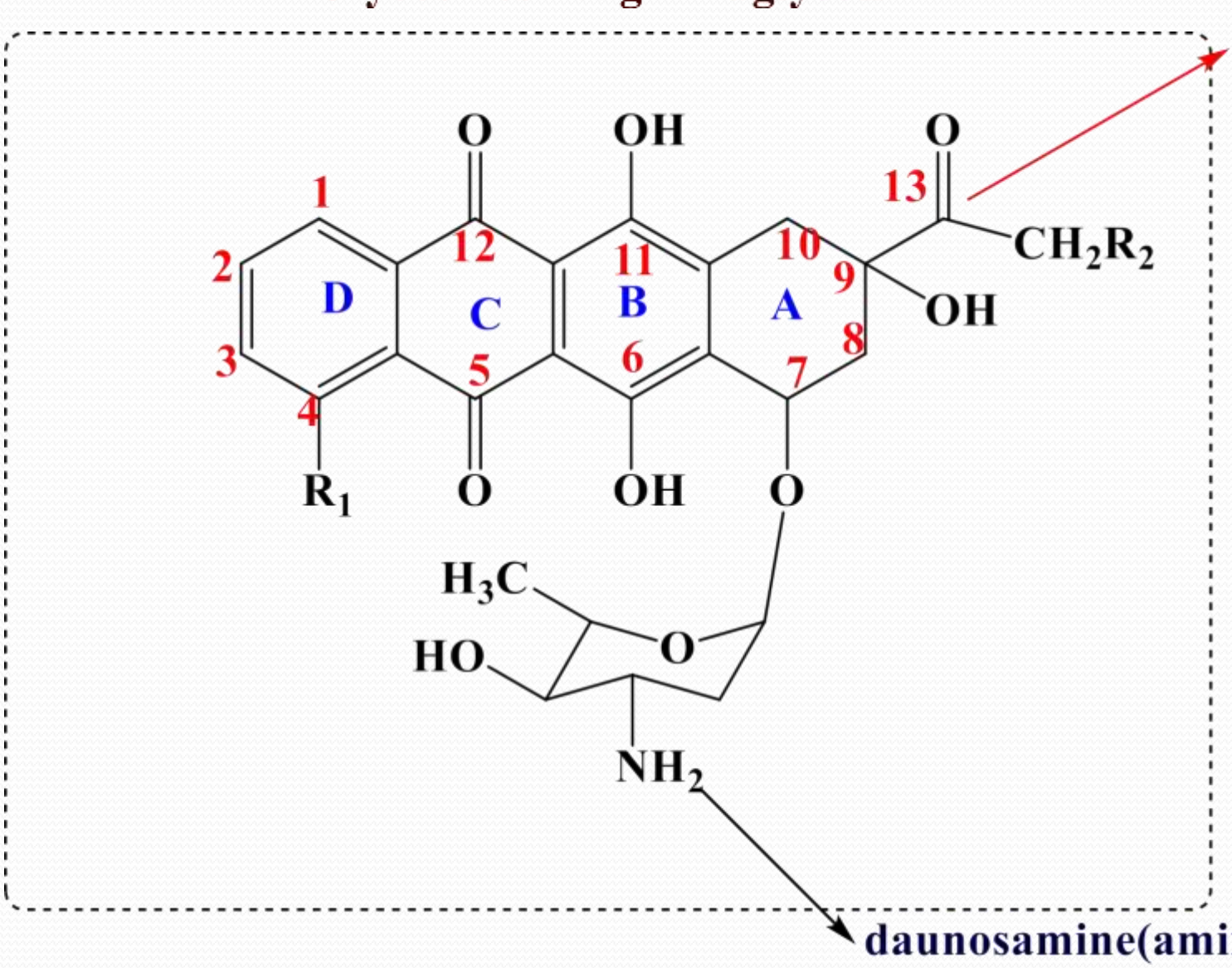
1-Complete structure is a glycoside (Sugar and aglycone) require for activity.

2-Amino group on daunosamine sugar important for activity.

3-C-13 carbonyl can reduced to alcohol generate inactive (or less active) metabolite, the larger R_2 group, the slower this reaction takes place and the more active the anthracycline as in doxorubicin.



Glycosides= sugar +aglycon

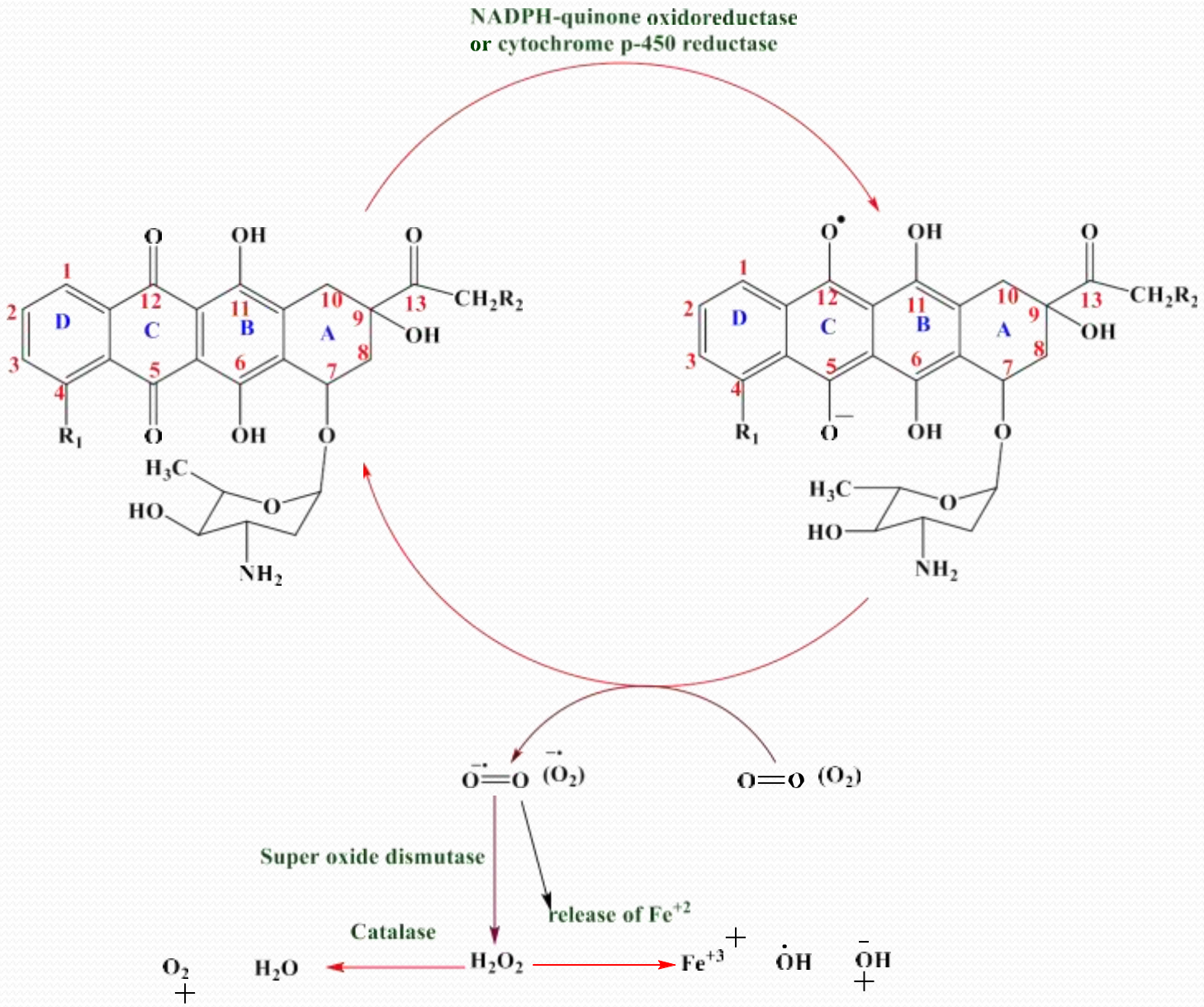


Mechanism of action

The anthracyclines are considered specific for the S phase of the cell cycle

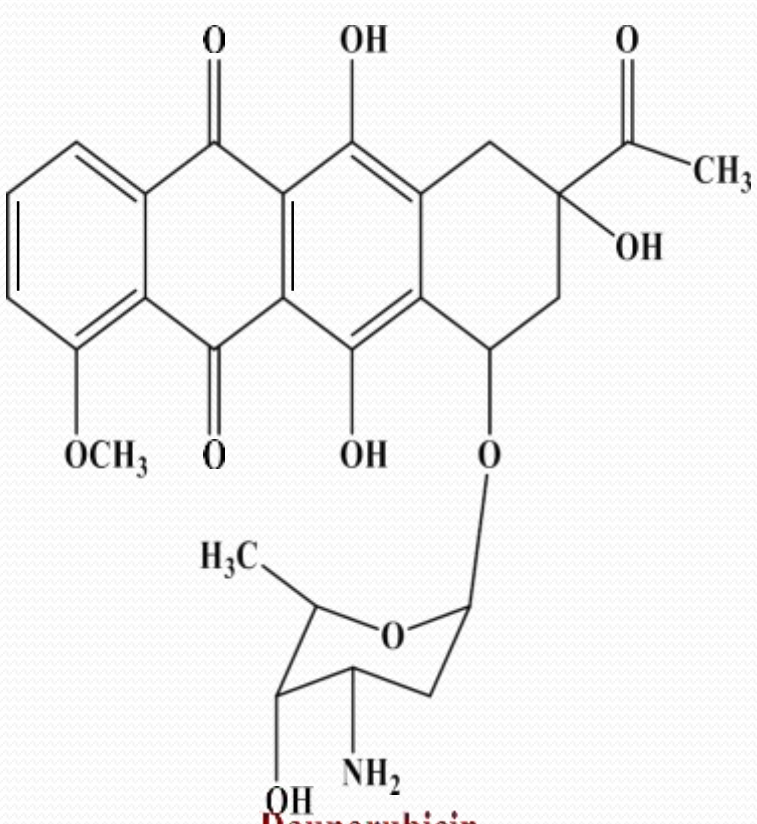
1- An intercalation into the double helical DNA, and inhibit topoisomerase II, resulting in strand breakage leading to apoptosis.

2- Free radical damage of DNAand cell membrane


NADPH-quinone oxidoreductase
or cytochrome p-450 reductase
Super oxide dismutase
release of Fe+2
Catalase
O2
H2O
H2O2
Fe+3
OH
OH

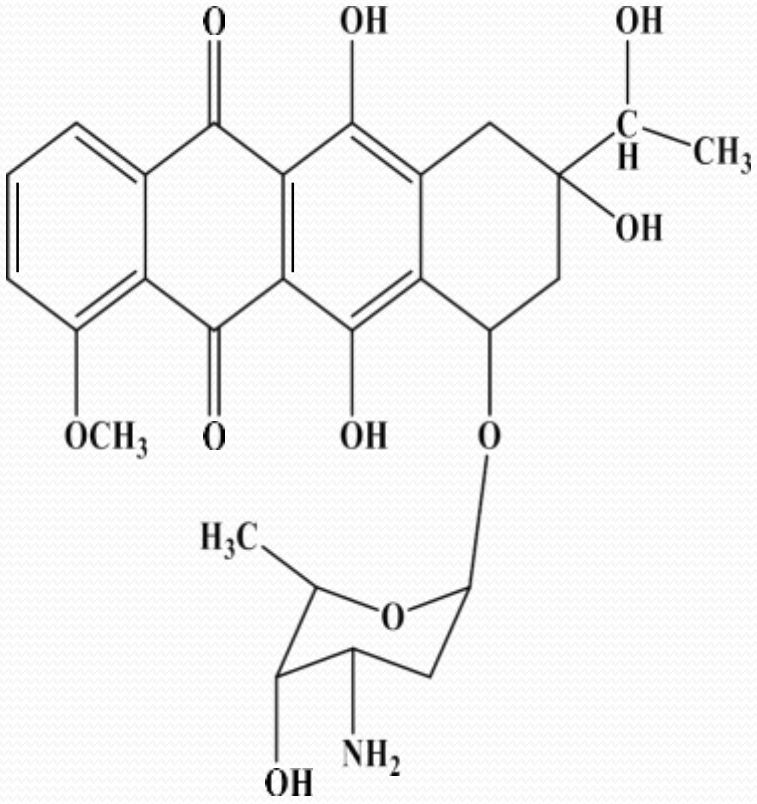
Products:-

Daunorubicin Hydrochloride



Daunorubicin

more active than daunorubicinol



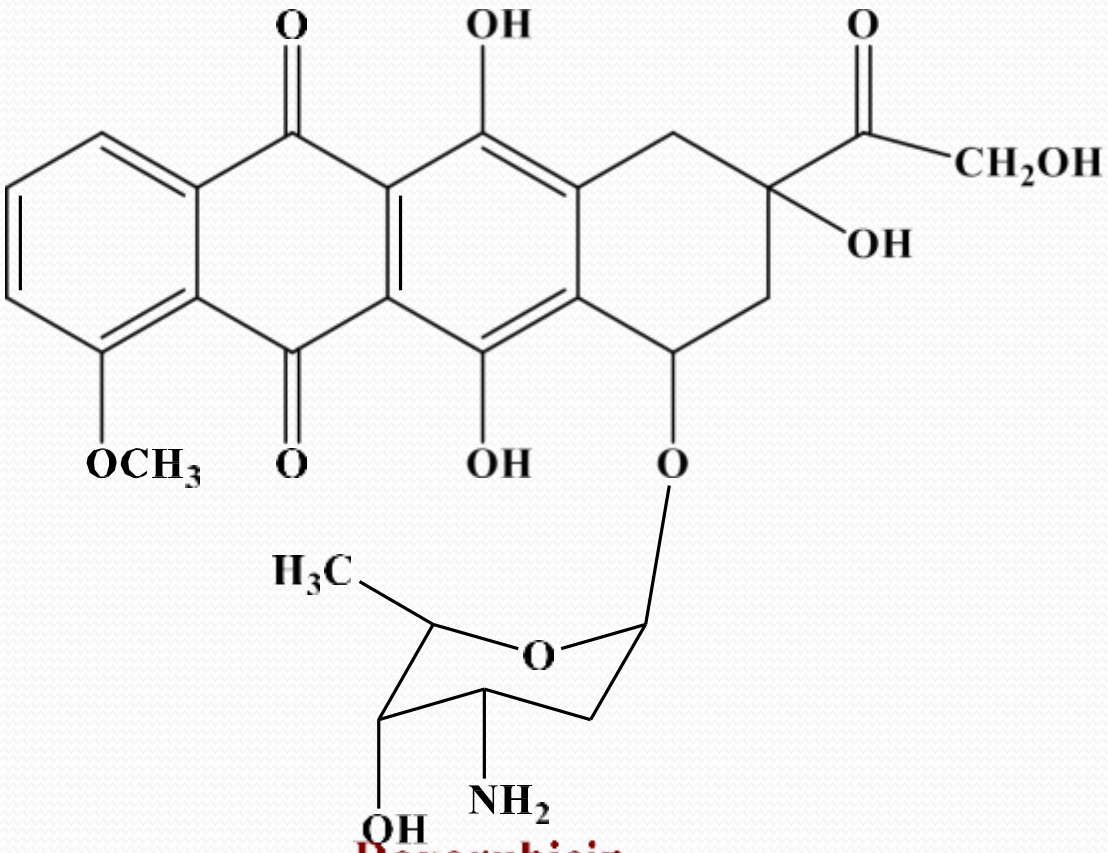
Daunorubicinol

one-tenth as active as daunorubicin

Uses: - Used in treatment of acute lymphocytic and granulocytic leukemia.

S/E: - cardiotoxicity

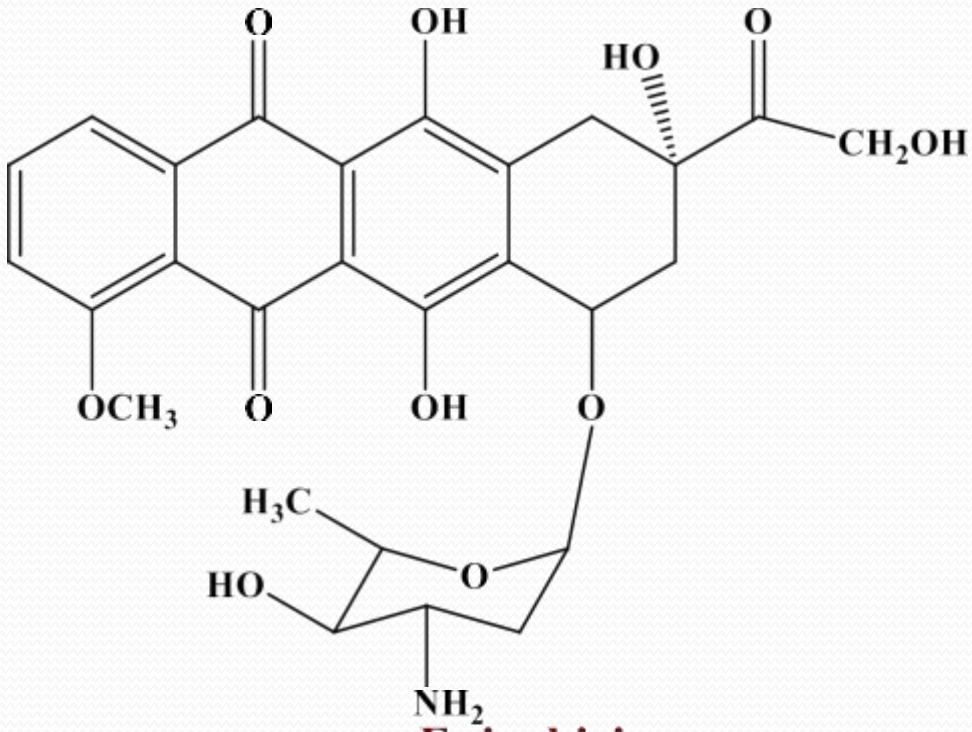
Doxorubicin Hydrochloride•



Doxorubicin

Uses:- is widely used in treating various cancers, including leukemias, soft and bone tissue sarcomas, Wilms tumor, neuroblastoma, small cell lung cancer, and ovarian and testicular cancer.

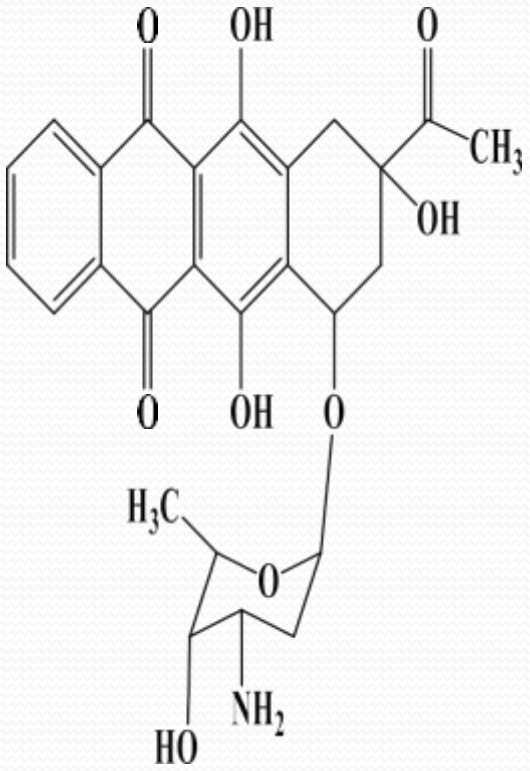
Epirubicin hydrochloride•



Epirubicin

Epirubicin is the 4'-epimer of doxorubicin
exhibits a lower level of cardiotoxicity compared with doxorubicin

Idarubicin hydrochloride•



Idarubicin

lacks the 4-methoxy group and terminal side-chain alcohol of doxorubicin making it the most lipophilic of the four major anthracyclines and it is considered less cardiotoxic than doxorubicin.