Antibiotics and natural products

A variety of the anticancer agents available today are derived from natural sources with several of these being obtained from microbial sources (antibiotics).

Many of the antineoplastic antibiotics are produced by the soil fungus Streptomyces. Both the antibiotic and natural product classes have multiple inhibitory effects on cell growth; however, they primarily act to disrupt DNA function and cell division.

There are several mechanisms by which these agents target DNA, including intercalation, alkylation, and strand breakage either directly or as a result of enzyme inhibition.

The drug–DNA interaction is further stabilized by side chains attached to the intercalation species. The side chains often include a cationic moiety, which may form ionic bonds with the anionic phosphate backbone.

Alternative modes of stabilization may occur through a combination of van der Waals interaction or hydrogen bonds.

The overall result of these interactions is to cause a local bend or kink in DNA resulting in a local shape distortion. This may produce several effects but is often associated with inhibition of normal DNA function

Actinomycins

The actinomycins are a group of compounds that are isolated from various species of Streptomyces, all of which contain the same phenoxazone chromophore but differ in the attached peptide portion.

Dactinomycin binds noncovalently to double-stranded DNA by partial intercalation between adjacent guanine cytosine bases resulting in inhibition of DNA function.

The primary effect of this interaction is the inhibition of DNA-directed RNA synthesis and specifically RNA polymerase. DNA synthesis may also be inhibited, and the agent is considered cell cycle specific for the G1 and S phases.

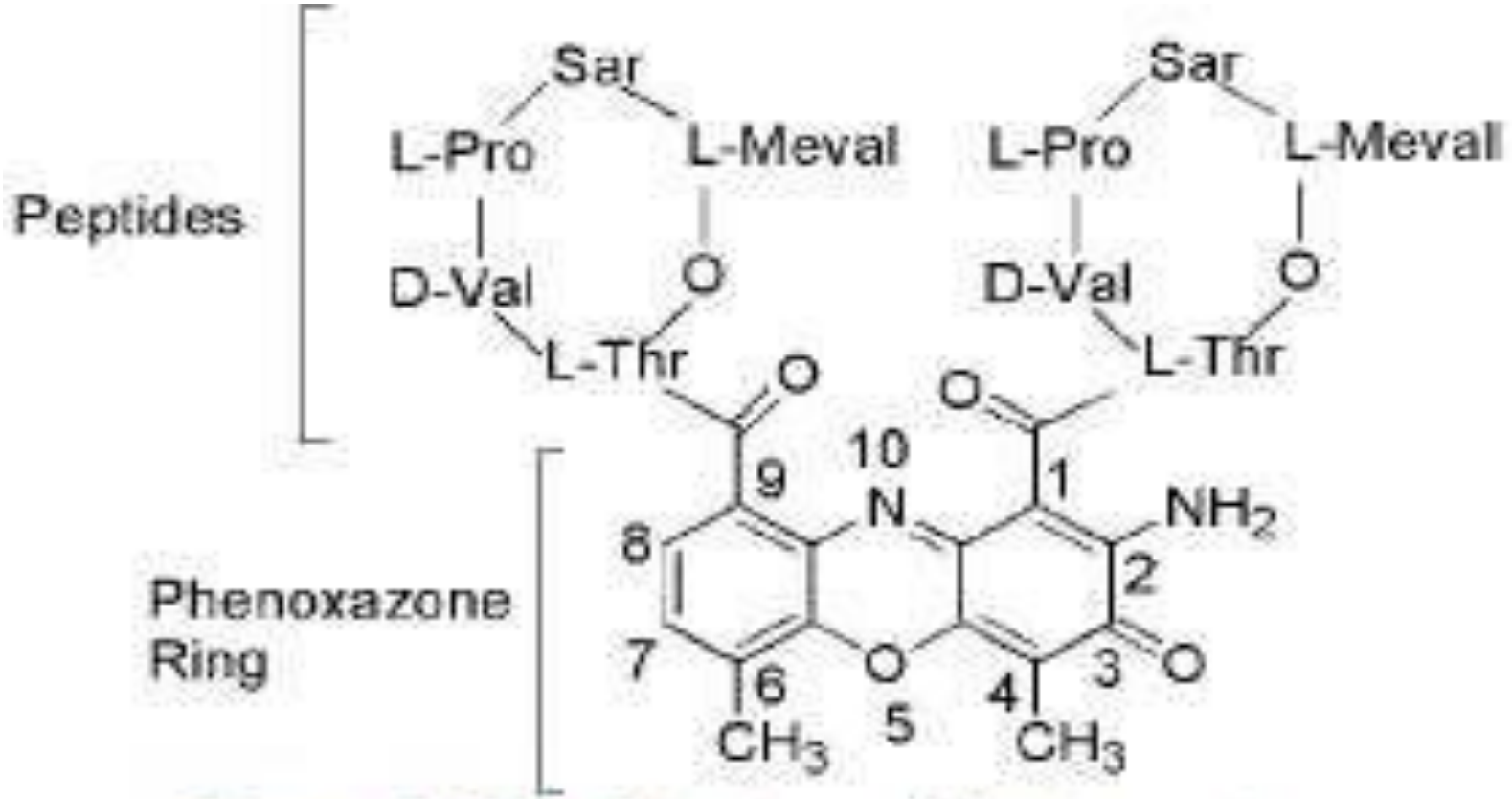
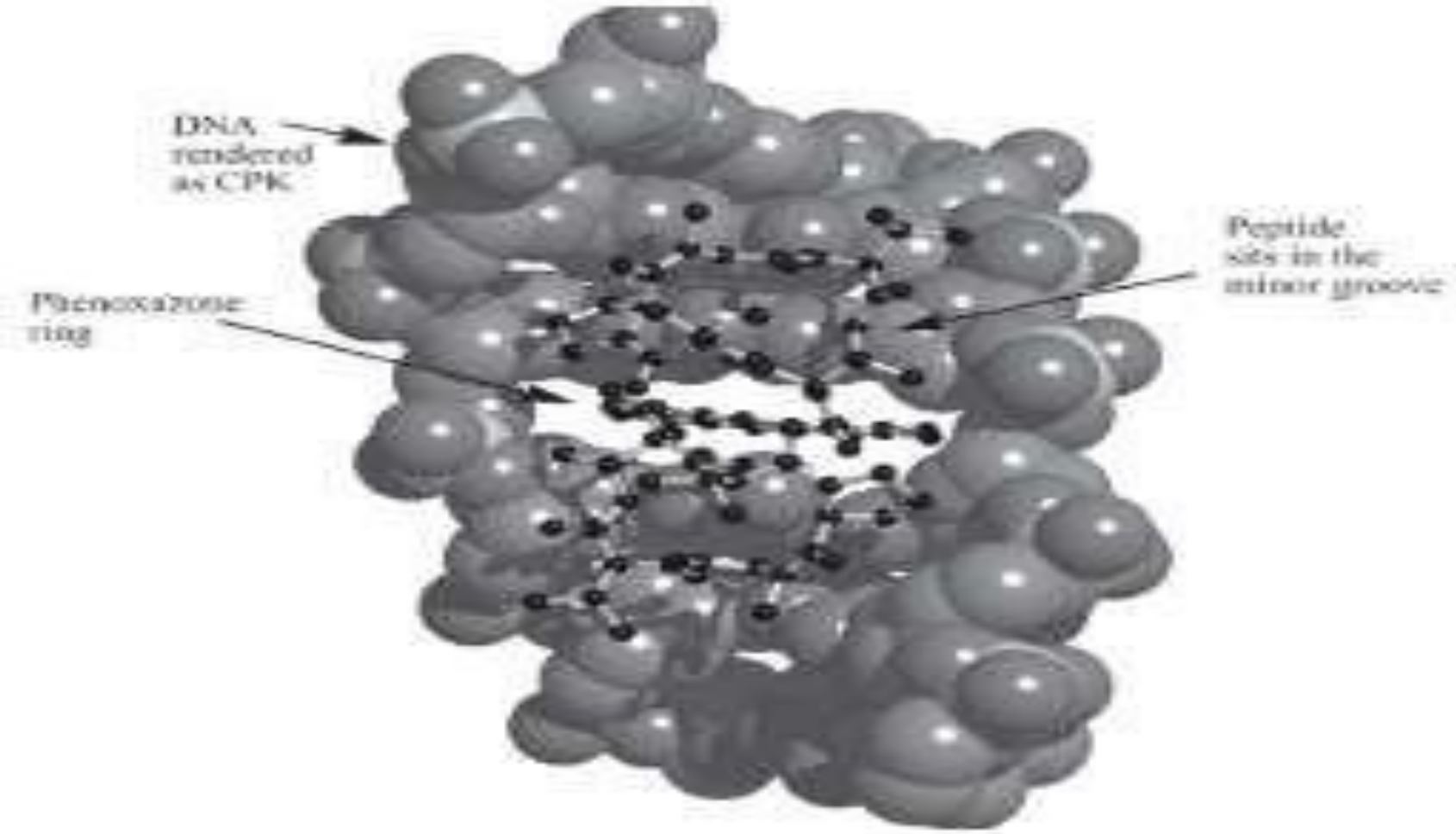


Figure 10.11 • Structure of dactinomycin.

Dactinomycin-DNA Complex



The drug has been found to bind to single-stranded DNA and double-stranded DNA without adjacent GpC sequences. It has been suggested that binding to single-stranded DNA may occur as the strands separate during transcription, and this may be responsible for the inhibition of RNA polymerase.

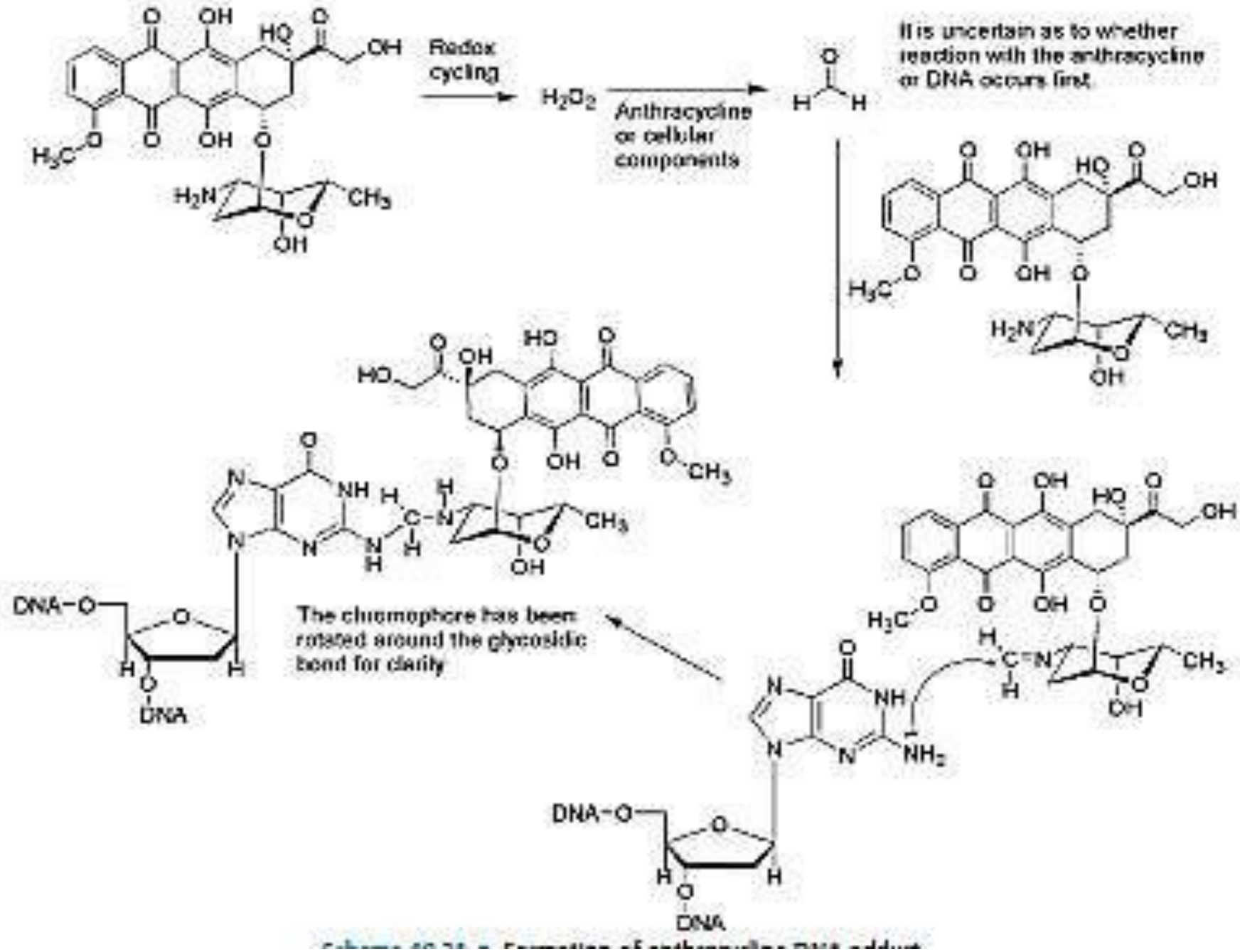
There are several mechanisms of its action that are responsible for its cytotoxic and antitumor action, these being associated with DNA functionality, leading to RNA and, consequently, protein synthesis inhibition.

Anthracyclines

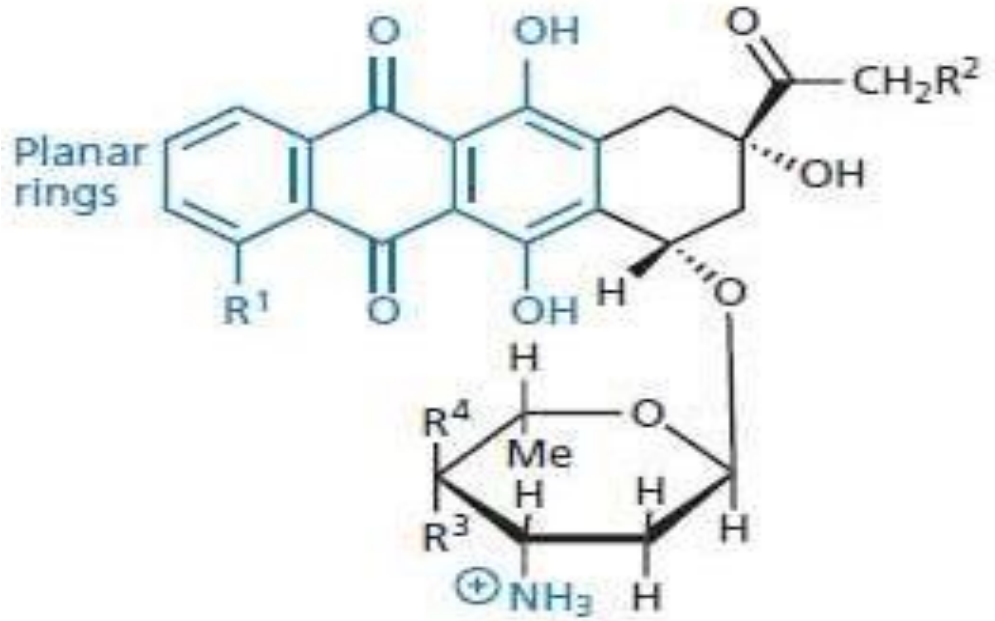
The anthracycline antibiotics are characterized by a planar oxidized anthracene nucleus fused to a cyclohexane ring that is subsequently connected via a glycosidic linkage to an amino sugar.

The mechanism by which the anthracyclines exhibit their cytotoxic effects initially focused on the ability of the compounds to associate with DNA resulting from intercalation of their planar ring system reinforced by auxiliary binding of the amino sugar.

The amino sugar seems to play an especially important role and compounds lacking this functionality failed to inhibit the enzyme. The formation of covalent bonds between anthracyclines and DNA also is supported by several studies in which formaldehyde is produced by oxidation of cellular components or other anthracycline molecules.

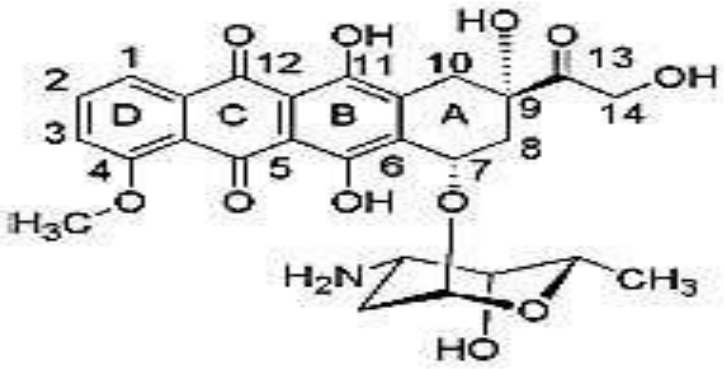

Redox cycling
H_2O_2
Anthracycline or cellular components
It is uncertain as to whether reaction with the anthracycline or DNA occurs first
The chromophore has been rotated around the glycosidic bond for clarity
DNA-O
DNA

The anthracyclines.

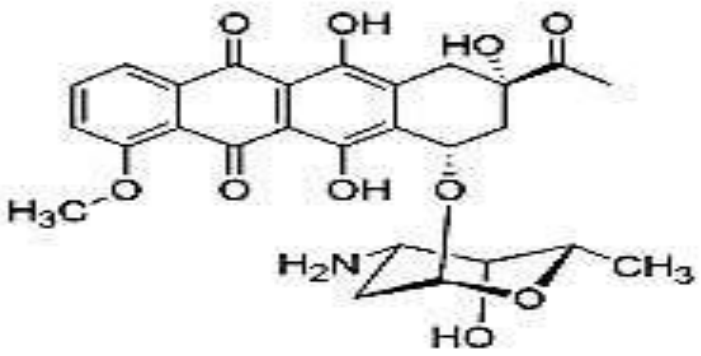


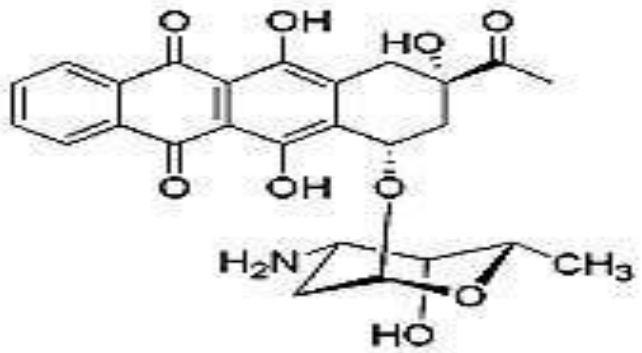
Anthracyclines	R^1	R^2	R^3	R^4
Doxorubicin	OMe	OH	OH	H
Epirubicin	OMe	OH	H	OH
Daunorubicin	OMe	H	OH	H
Idarubicin	H	H	OH	H

Doxorubicin

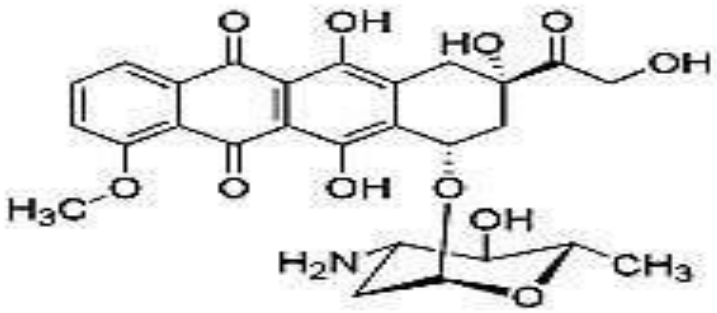


Daunorubicin

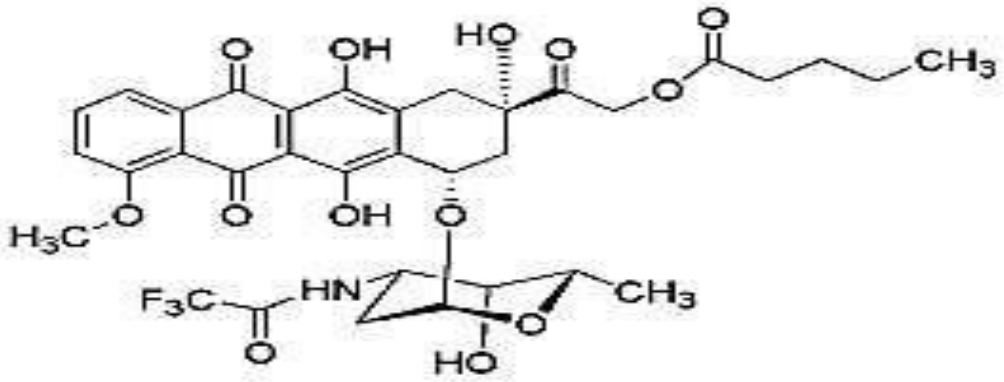




Idarubicin



Epirubicin



Valrubicin

Figure 10.13 • Structure of the anthracycline antibiotics.

Synthetic Analogue of the Anthracyclines

- Mitoxantrone is a simplified, synthetic analogue of the anthracyclines where the tetracyclic ring system has been 'pruned' back to the planar tricyclic system required for intercalation.
- There are two identical substituent chains present which make the molecule symmetrical and easier to synthesize. The sugar ring is lacking because it is thought to be responsible for cardio toxic side effects.
- However, the amino substituent that is normally present on the sugar is still present within the substituent chains.
- Structure– activity relationship (SAR) studies on mitoxantrone identify a pharmacophore involving one of the phenol groups, a carbonyl group, and the amino group in the side chain.
- Because the molecule is symmetrical, there are two such pharmacophores, but activity remains much the same for analogues containing only one.

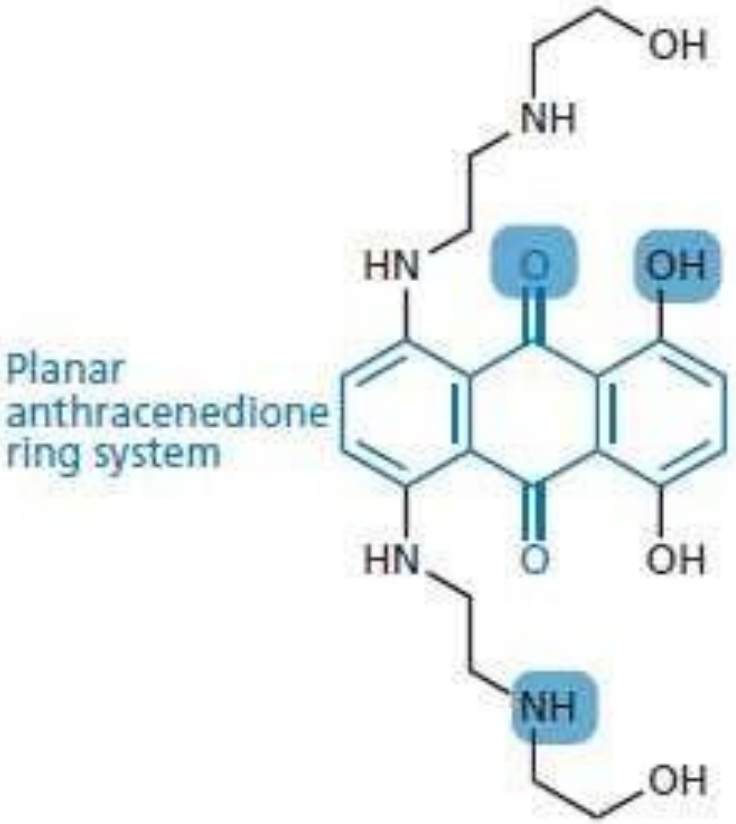
It was also demonstrated that the amino group linking the side chain to the tricyclic ring system was important to activity.

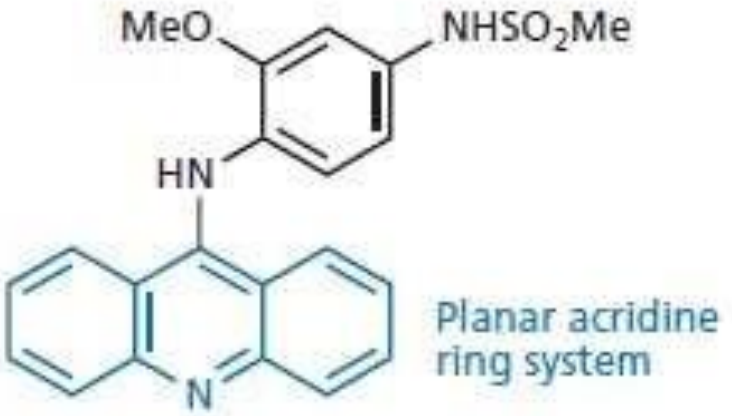
Mitoxantrone intercalates DNA preferentially at guanine–

cytosine base pairs such that the side chains lie in the minor groove of DNA, and it is thought to interact with topoisomerase II in a similar fashion to doxorubicin.

Other mechanisms of action have been proposed, including inhibition of microtubule assembly and inhibition of protein kinase C .

- Amsacrine contains an acridine tricyclic system capable of intercalating into DNA. It also stabilizes topoisomerase-cleavable complexes.





Amsacrine (m-AMSA)

Mitoxantrone (pharmacophoric groups highlighted in boxes) and amsacrine.

Epipodophyllotoxins

The epipodophyllotoxins are semisynthetic derivatives of podophyllotoxin, which is isolated from the may apple (mandrake) root and functions as an inhibitor of microtubule function.

Chemical modification has led to compounds with a different mechanism of action, which involves inhibition of topoisomerase enzymes. The change in mechanism was associated with:

- Removal of the 4-methyl group of podophyllotoxin.
- The addition of the glycosidic portion of the molecules. Etoposide acts on topoisomerase II stabilizing the cleavable complex leading to single- and double-strand breaks.

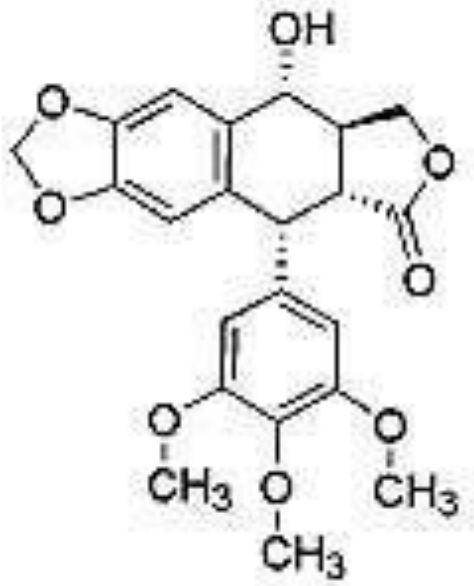
The etoposide-topoisomerase II complex then binds DNA, and strand cleavage occurs; the ligation step is inhibited.

The glycosidic moiety of the epipodophyllotoxins, which is lacking in podophyllotoxin, is associated with converting these compounds from tublin binders to topoisomerase inhibitors.

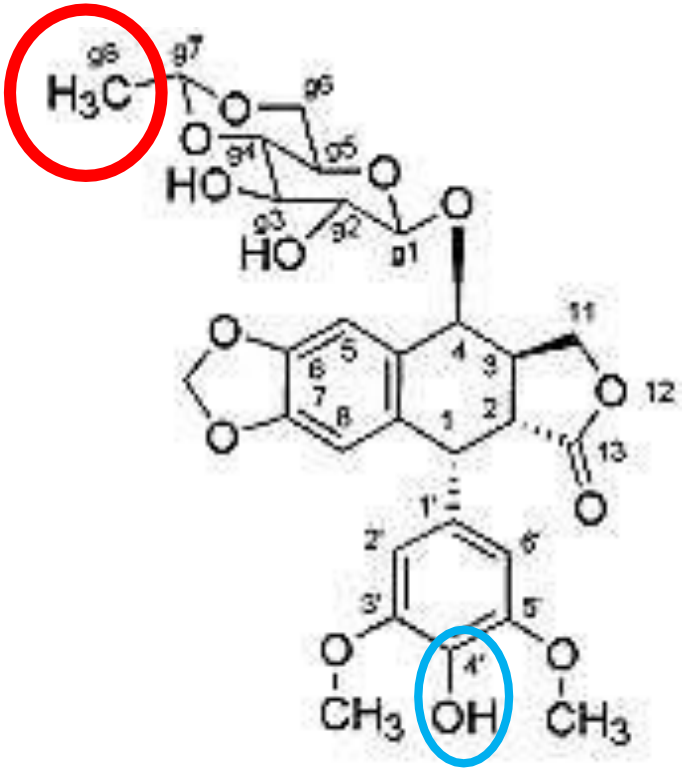
- Replacement of the glycosidic 8-methyl group with thiophene gives tenoposide, which is 10-fold more potent than etoposide. The glycosidic moiety is not an absolute requirement for activity, and other more active compounds are known in which it has been replaced.
- The 4`-OH group is important for the activity of the compounds, and loss of this functionality results in greatly reduced levels of strand breaks.

- Etoposide is one of the few natural product derivatives that can be administered orally.
- Etoposide phosphate is a prodrug of etoposide and is converted to the parent by the action of phosphatases.
- Metabolism involves opening of the lactone ring to give the hydroxy acid as the major metabolite.
- Epimerization occurs at C-3 to give the cis-lactone, which may also undergo hydrolysis to give the hydroxy acid.
- Glucuronidation and sulfation of the 4`-OH give products that are inactive.
- Active metabolites are formed as a result of CYP3A4 mediated oxidative-O-demethylation of the 3`-methoxy group to give the catechol followed by oxidation to give the quinone.

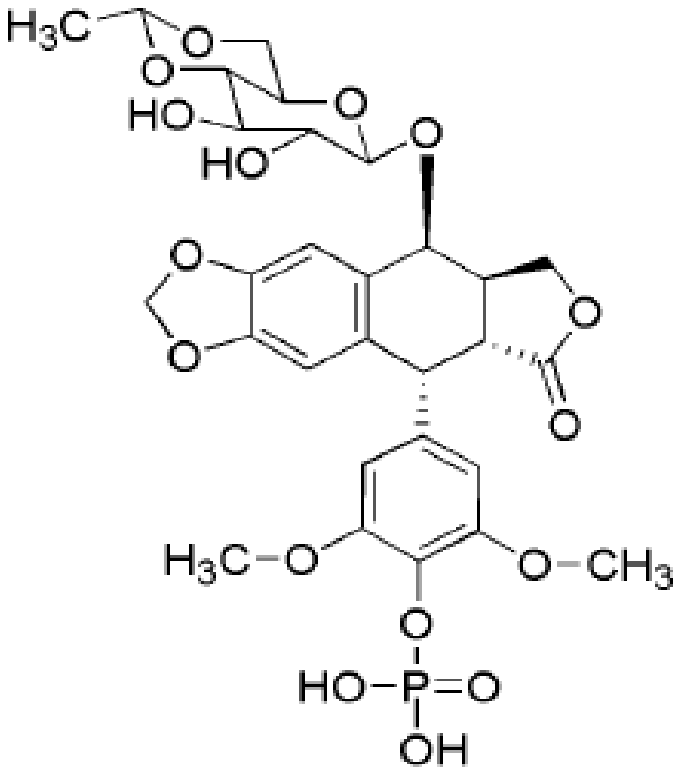
Epipodophyllotoxins



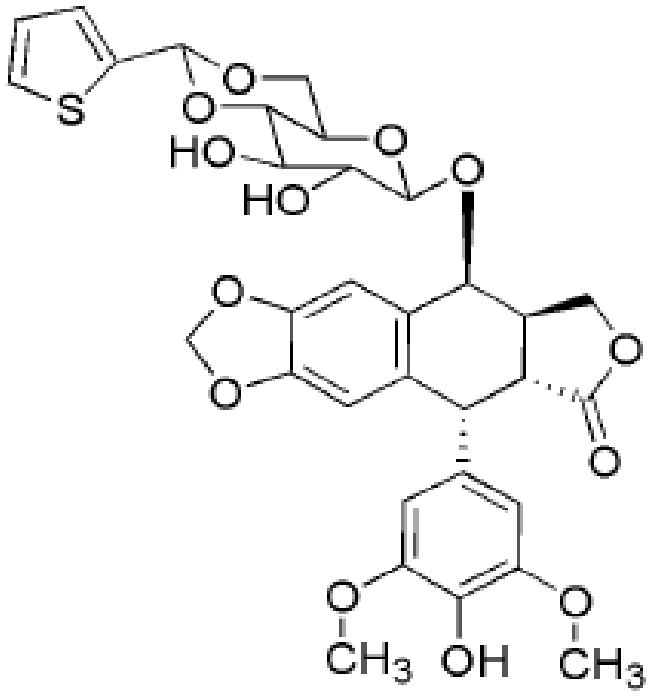
Podophyllotoxin



Etoposide



Etoposide Phosphate



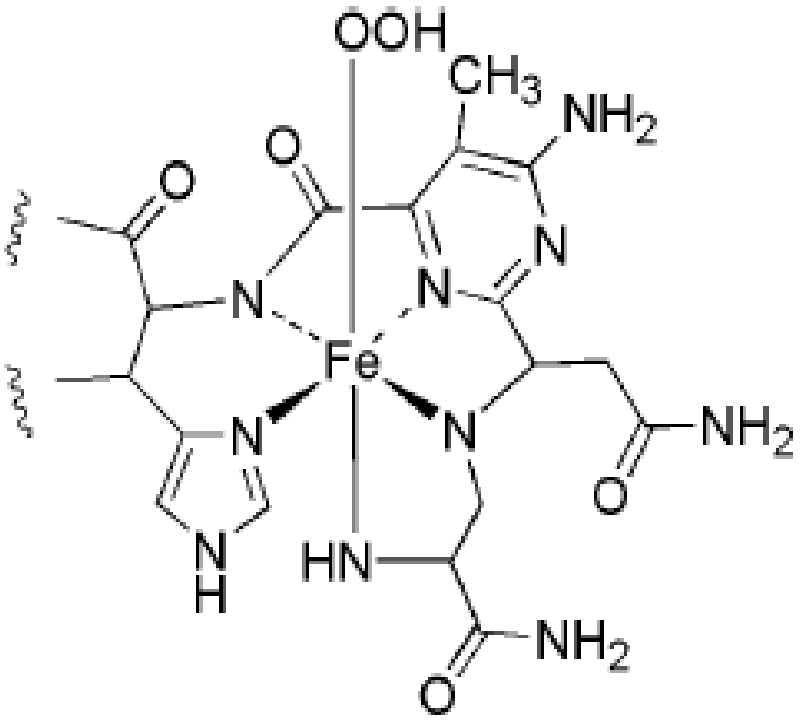
Teniposide

Bleomycin

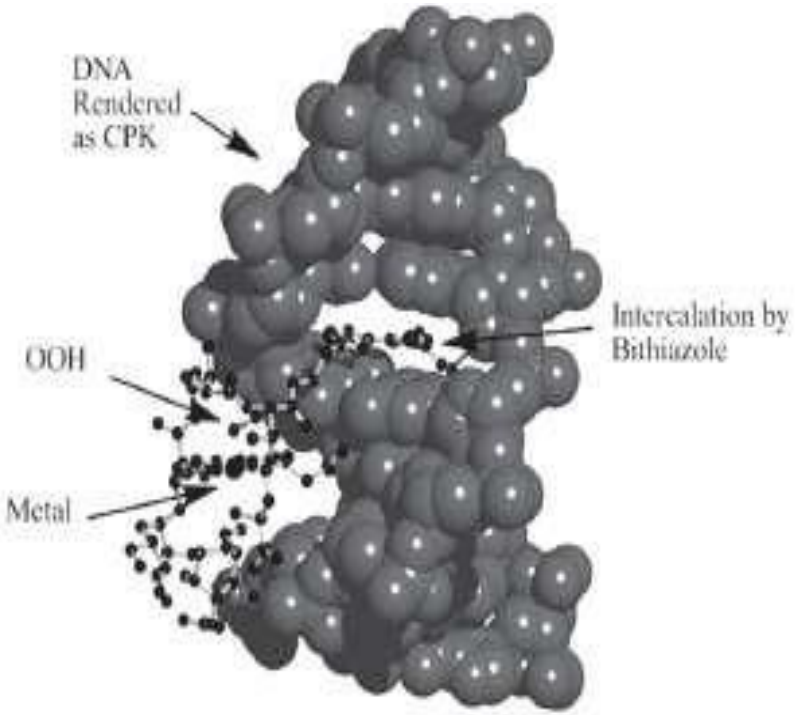
Bleomycin is a glycopeptide antibiotic complex isolated from Streptomyces verticillus initially by Umezawa.

Bleomycin binds Fe^{+2} through multiple interactions with the amino terminal end of the peptide chain.

Bleomycin may itself initiate the release of iron necessary for this complexation. Interaction with DNA subsequently occurs through the bithiazole portion of the molecule, which intercalates between G-C base pairs with a preference for genes undergoing transcription.



Structure of the bleomycin-Fe-O_2



Representation of the bleomycin-DNA complex. (Reprinted with permission from Zhao, C., et al.: J. Inorgan. Biochem. 91:259, 2002.)

Bleomycin

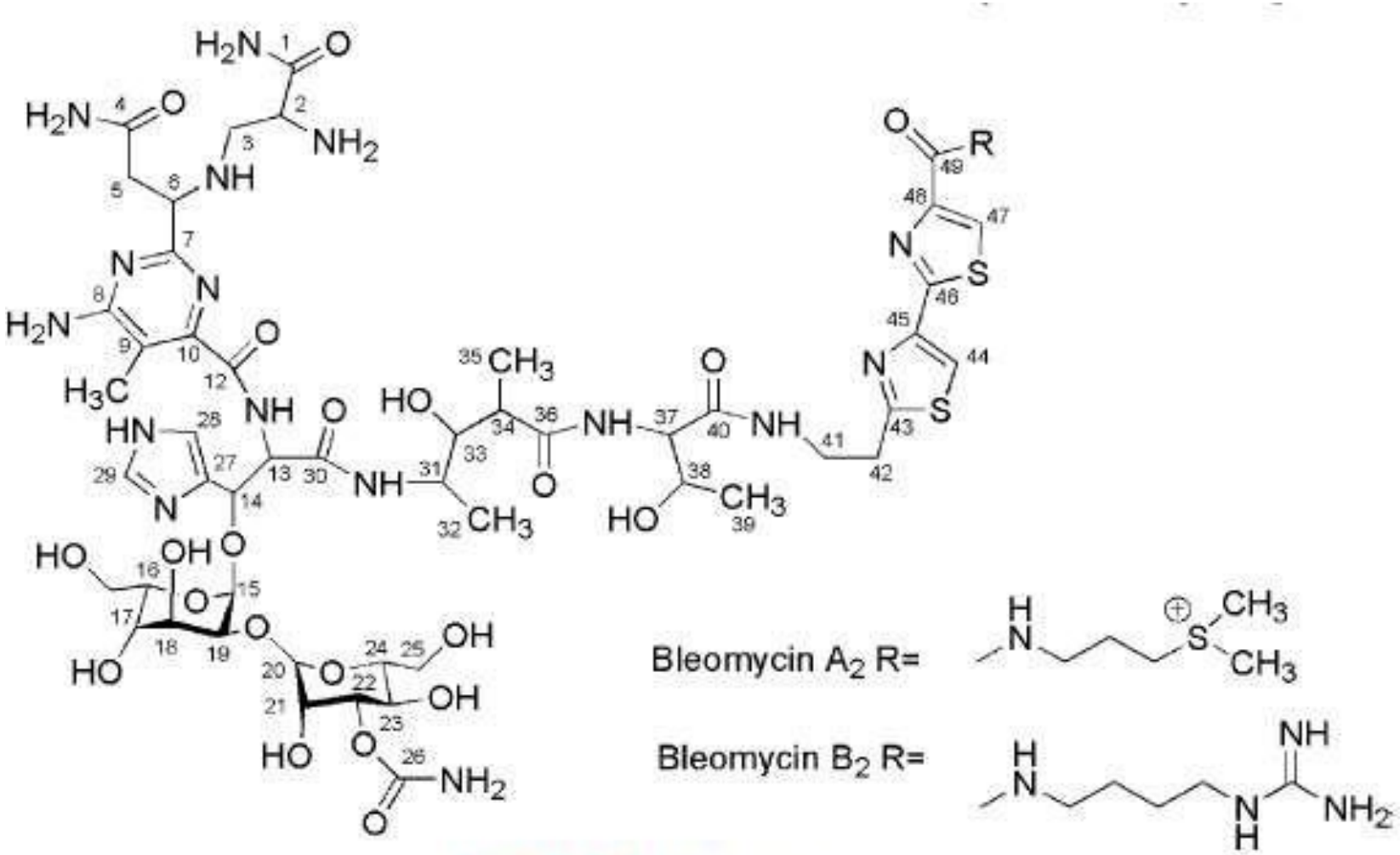
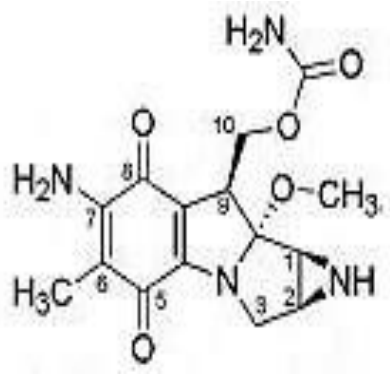


Figure 10.18 • Structure of bleomycins.

Mitomycin c



- Mitomycin C is considered the prototype of the bioreductive alkylating agents.
- Mitomycin is sometimes included as an alkylating agent but is included here because it is a naturally occurring material.
- The drug contains what would appear to be reactive functionalities, including the quinone and aziridine functionalities, both or which would be thought to be susceptible to nucleophilic attack; however, the reactivity of these functionalities is reduced because of steric and electronic effects in the parent molecule.

Alkylation of DNA by mitomycin C.