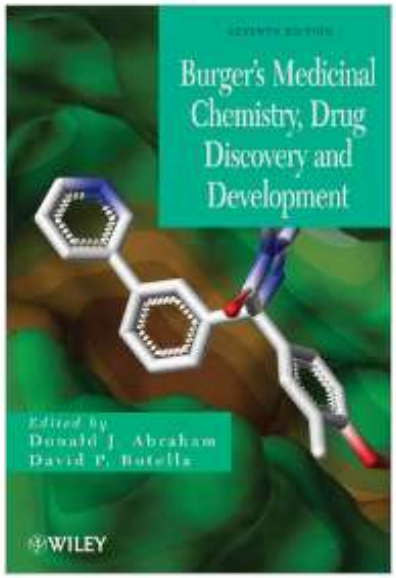
Chemotherapeutic Agents:

Drugs to Treat Neo(b/p)lastic Diseases:

Anticancer Agents

Section1

SRAmini Nov 2024



DESCRIPTION

Now in its seventh edit
established, recognized
discovery and development. This flagship reference for medicinal chemists and pharmaceutical professions has been thoroughly updated and expanded across 8 volumes to incorporate the entire process of drug development (preclinical testing, clinical trials, etc.) alongside the traditional strengths in medicinal chemistry and drug discovery.

Volume 6: Cancer.

Natural product cytotoxics.

Histone Deacetylase Inhibitors: A brief overview of their role and medicinal chemistry.

Synthetic DNA-targeted chemotherapeutic agents and related tumor-activated prodrugs.

PARP Inhibitors as Anticancer Agents.

Proteasome inhibitors.

CNS Cancers.

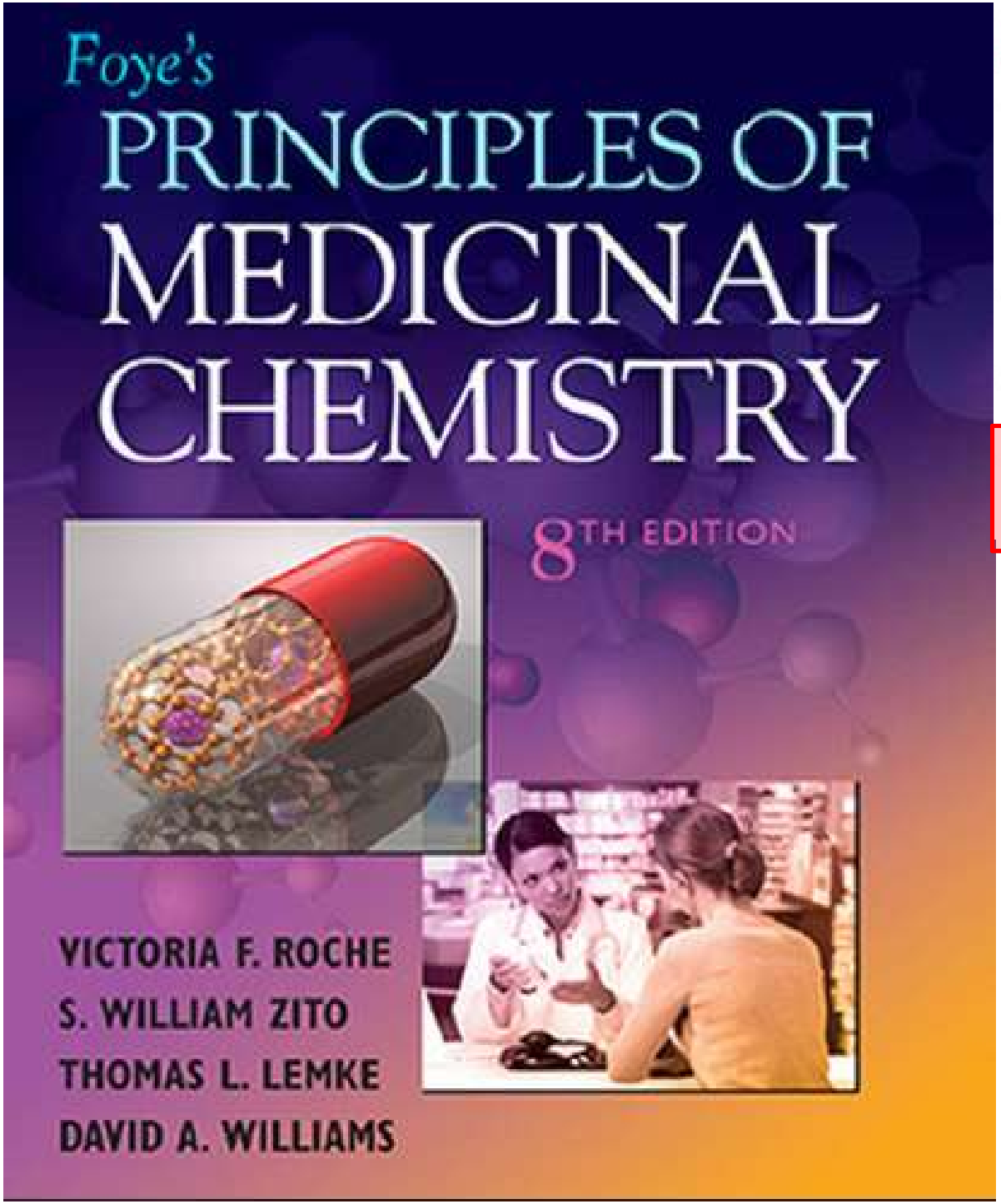
Kinase inhibitors: Approved Drugs and Clinical Candidates.

Structure-Based Design of Kinase Inhibitors: Molecular Recognition of Protein Multiple Conformations.

Cancer drug resistance-targets and therapies.

HSP inhibitors.

Gene therapy with plasmid DNA.



SECTION 7 **DRUGS IMPACTING INFECTIOUS AND NEOPLASTIC DISEASE PROCESSES**

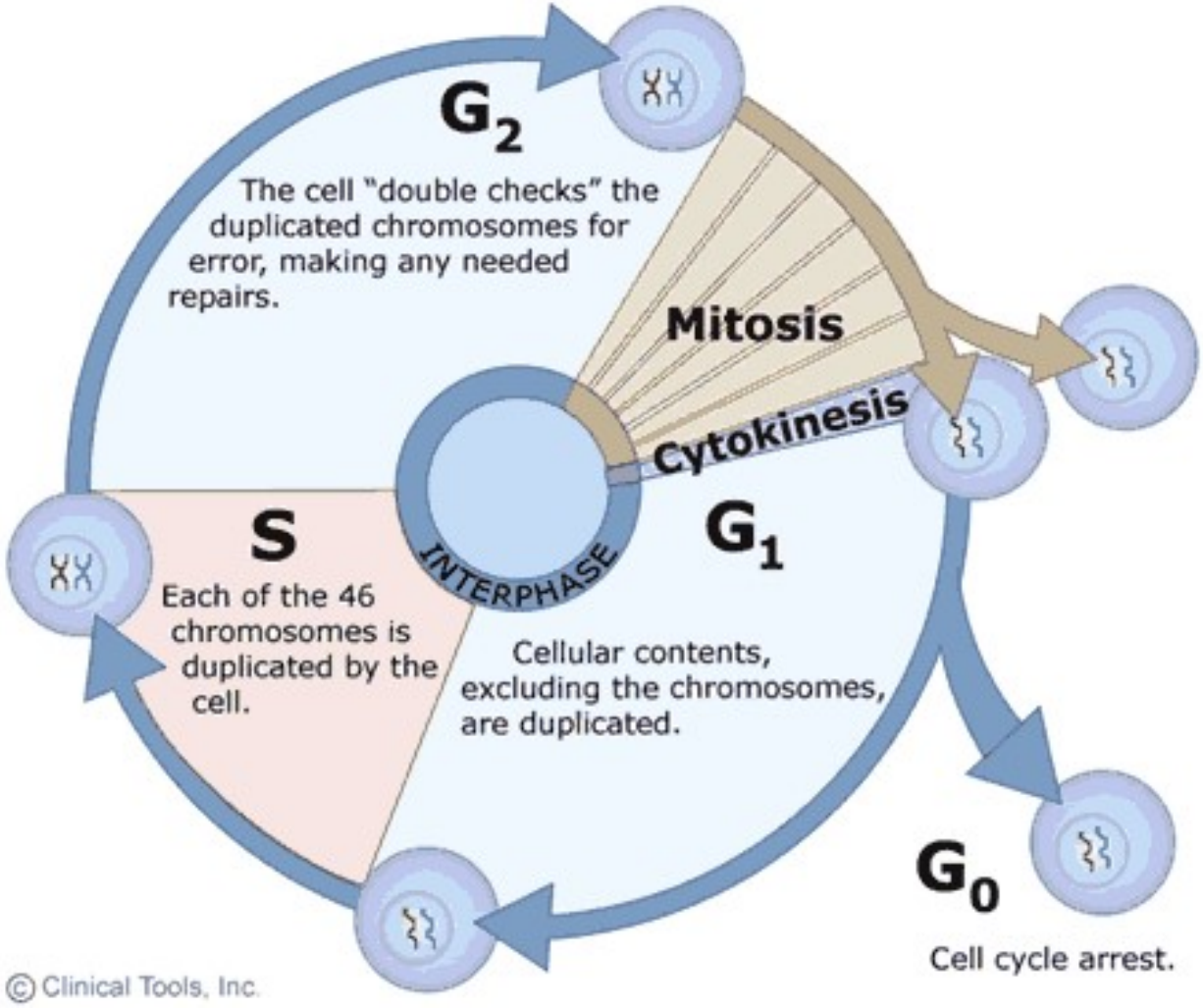
Foye's 2019

Principles of Medicinal Chemistry
by William Foye, 2019

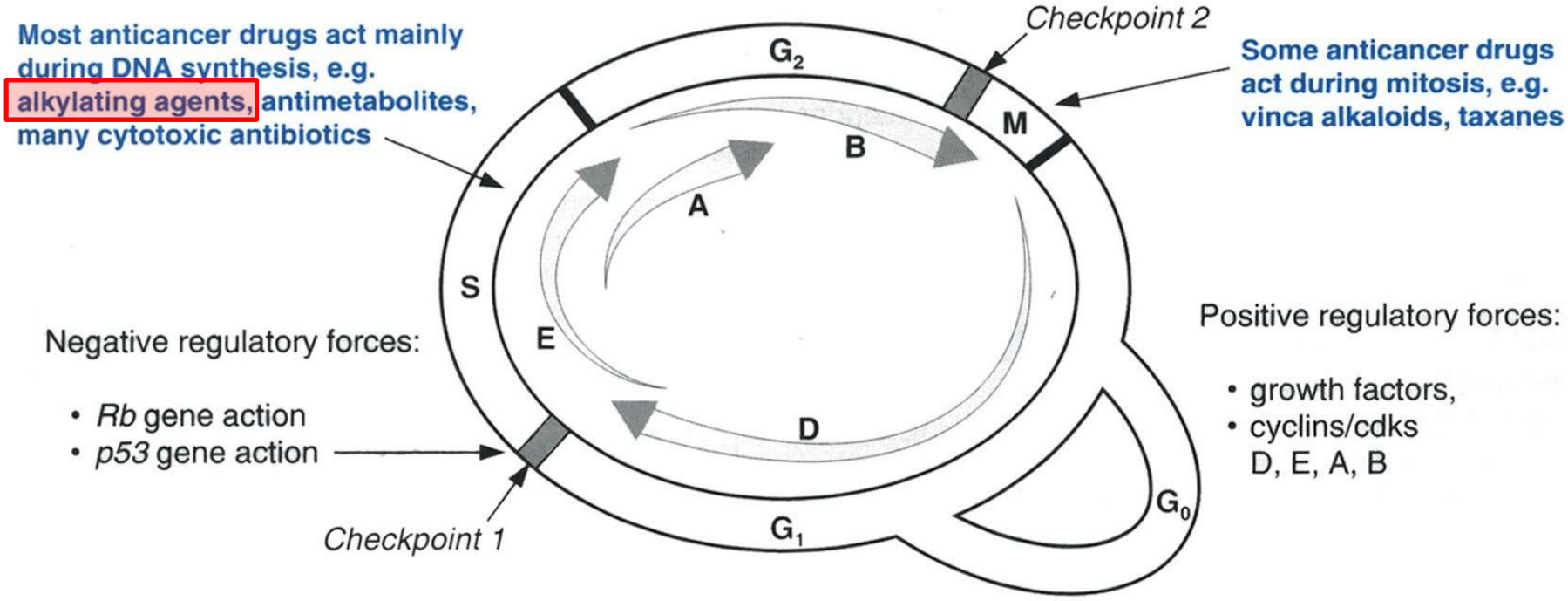
An Introduction to Medicinal Chemistry

by Graham Patrick, 2017

Normal Cell Cycle



Established Possible Targets for Anticancer Agents in Cell Cycle



[1] Rang , Dale, Ritter *Pharmacology*. 4th ed.; 1999.p.664,665,666.

Cancer Treatment

- *Treatment approaches:*
- Surgery
- Radiation therapy
- Immunologic treatment
- Hormonal therapy
- ***Chemotherapeutic agents***

❑ *Goals in:*

✓ Cure

✓ Reduce size of tumor

✓ Sensitize tumor to radiation

✓ Destroy microscopic metastases

Pharmacologic Classification of Chemotherapeutic Agents

I. DNA (cross) linking agents; mostly DNA alkylating agents

II. Antimetabolites

III. DNA topoisomerase poisons & DNA intercalating agents:

III.1. Camptothecins; III.2. Epipodophyllotoxins

III.3. Antibiotics: III.3.a. Anthracyclines; III.3.b. Anthracenediones

IV. DNA interacting miscellaneous antibiotics:

IV.1. Phenoxazine; IV.2. Glycopeptide; IV.3. Mitomycin

Pharmacologic Classification of Chemotherapeutic Agents- Contd.

V. Mitosis inhibitors: natural alkaloids

VI. Tyrosine Kinase & related inhibitors

VII. Histone deacetylase inhibitors

VIII. Immunomodulators

IX. Miscellaneous: hormonal, and specific agents

I. DNA (Cross) Linking Agents:

DNA Alkylating Agents

DNA Alkylators

DNA Methylators

Organometalics

CHAPTER 33

Drugs Used to Treat Neoplastic Diseases

Victoria F. Roche

Drugs covered or mentioned in this chapter—Continued

PYRIMIDINE ANTAGONISTS
- Capecitabine
- Floxuridine
- Fluorouracil

ANTIFOLATES
- Methotrexate
- Pemetrexed
- Pralatrexate

DNA POLYMERASE INHIBITORS
- Cladribine
- Clofarabine
- Cytarabine
- Fludarabine
- Gemcitabine
- Trifluridine/tipiracil

DNA METHYLTRANSFERASE INHIBITORS
- Azacitidine
- Decitabine
- Nelarabine

MISCELLANEOUS ANTIMETABOLITES
- Hydroxyurea
- Pentostatin

DNA CROSS-LINKING AGENTS

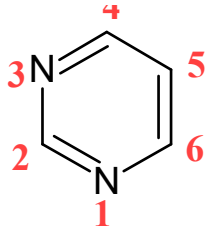
NITROGEN MUSTARDS
- Bendamustine
- Chlorambucil
- Cyclophosphamide
- Ifosfamide
- Mechlorethamine
- Melphalan
- Thiotepa

TRIAZENES AND PROCARBAZINE
- Dacarbazine
- Procarbazine
- Temozolomide

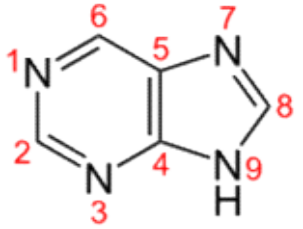
NITROSOUREAS
- Carmustine
- Lomustine
- Streptozocin

ORGANOPLATINUM COMPLEXES
- Carboplatin
- Cisplatin
- Oxaliplatin

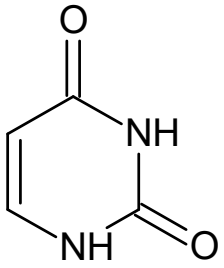
MISCELLANEOUS ANTICANCER AGENTS
- Arsenic trioxide
- Bexarotene
- Bleomycin
- Dactinomycin
- Gemtuzumab ozogamicin conjugate
- Inotuzumab ozogamicin conjugate
- Mitomycin
- Mitotane
- Trabectedin
- Tretinoin



Nucleic Acid Components

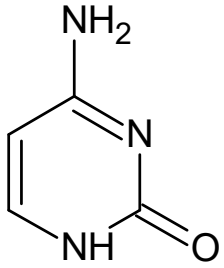


- Pyrimidines: U, C, T



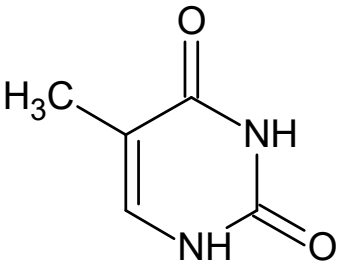
Uracil

2,4-dioxo-pyrimidine



Cytosine

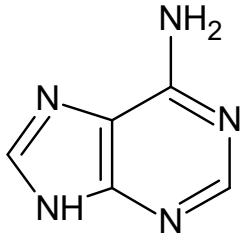
2-amino-4-oxo-pyrimidine



Thymine

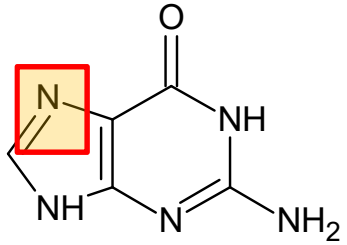
5-methyl-2,4-dioxo-pyrimidine

- Purines: A, G



Adenine

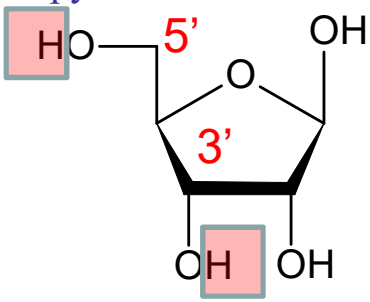
6-amino-purine



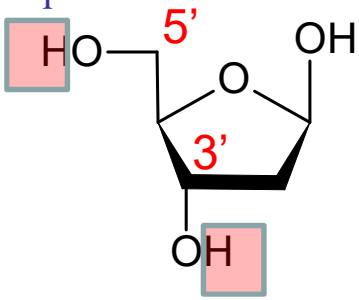
Guanine

2-amino-6-oxo-purine

- Ribose



- 2-Deoxyribose



- Phosphate Group: PO_4^{3-}: HO-P(O)(OH)-O-

Nucleotides in DNA: Structures & Nomenclatures

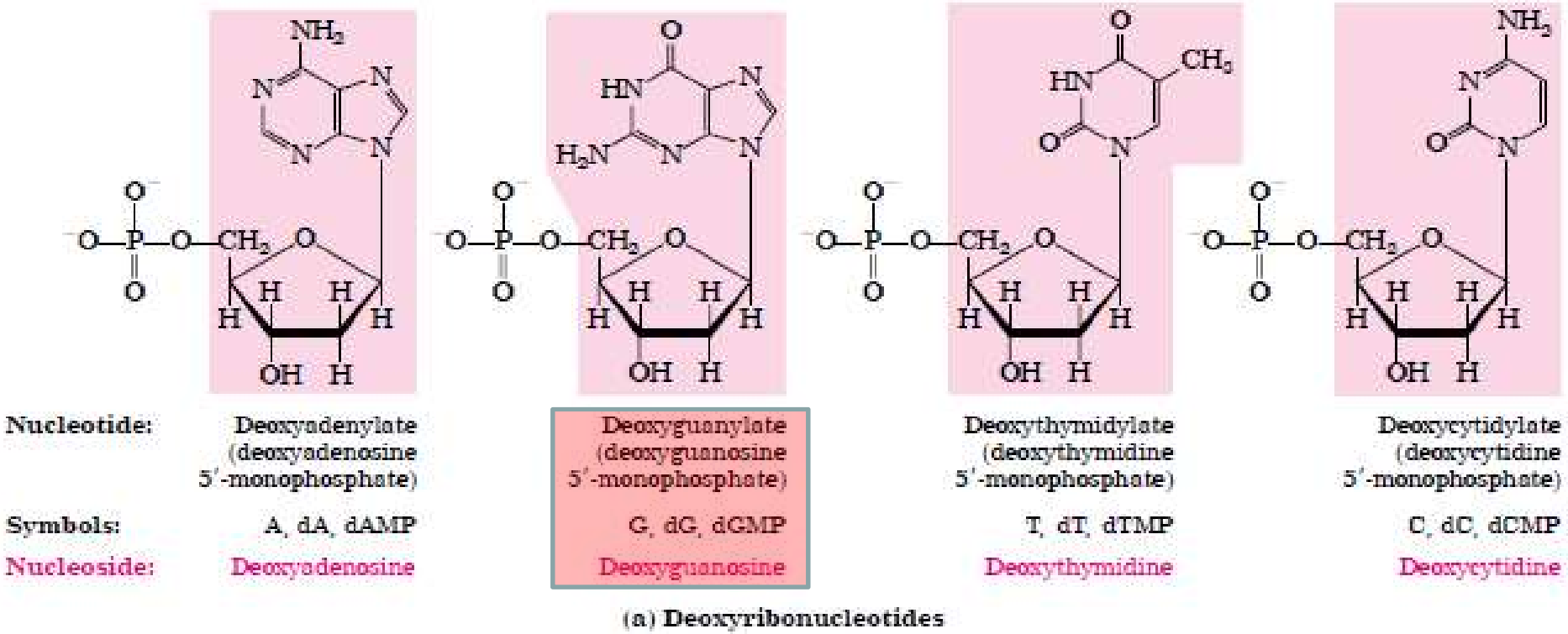
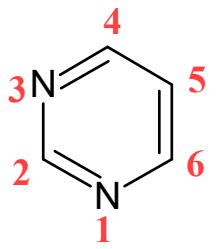
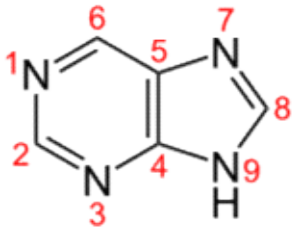


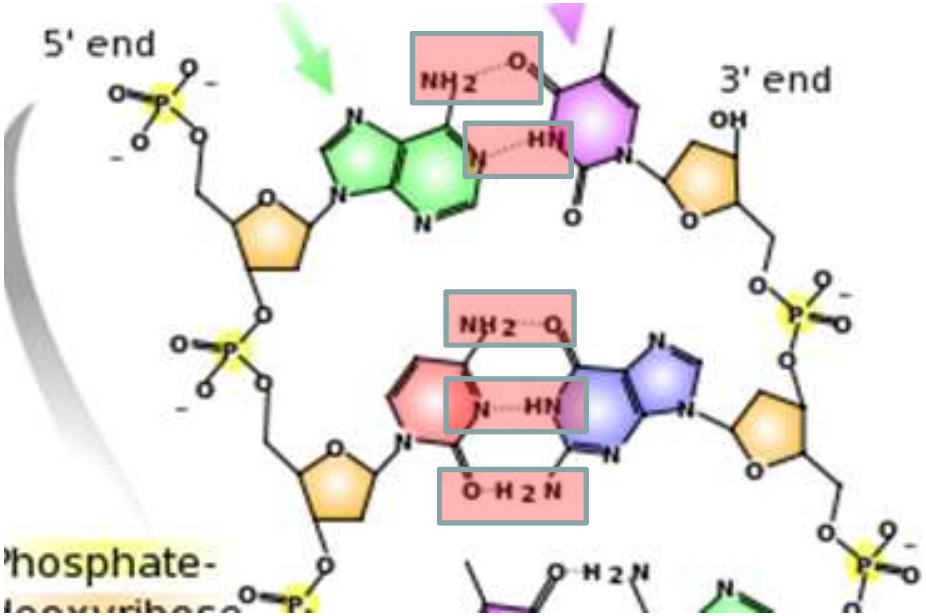
FIGURE 8–4 Deoxyribonucleotides and ribonucleotides of nucleic acids. All nucleotides are shown in their free form at pH 7.0. The nucleotide units of DNA **(a)** are usually symbolized as A, G, T, and C, sometimes as dA, dG, dT, and dC; those of RNA **(b)** as A, G, U, and C. In their free form the deoxyribonucleotides are commonly abbreviated dAMP, dGMP, dTMP, and dCMP; the ribonucleotides, AMP, GMP, UMP, and CMP. For each nucleotide, the more common name is followed by the complete name in parentheses. All abbreviations assume that the phosphate group is at the 5′ position. The nucleoside portion of each molecule is shaded in light red. In this and the following illustrations, the ring carbons are not shown.

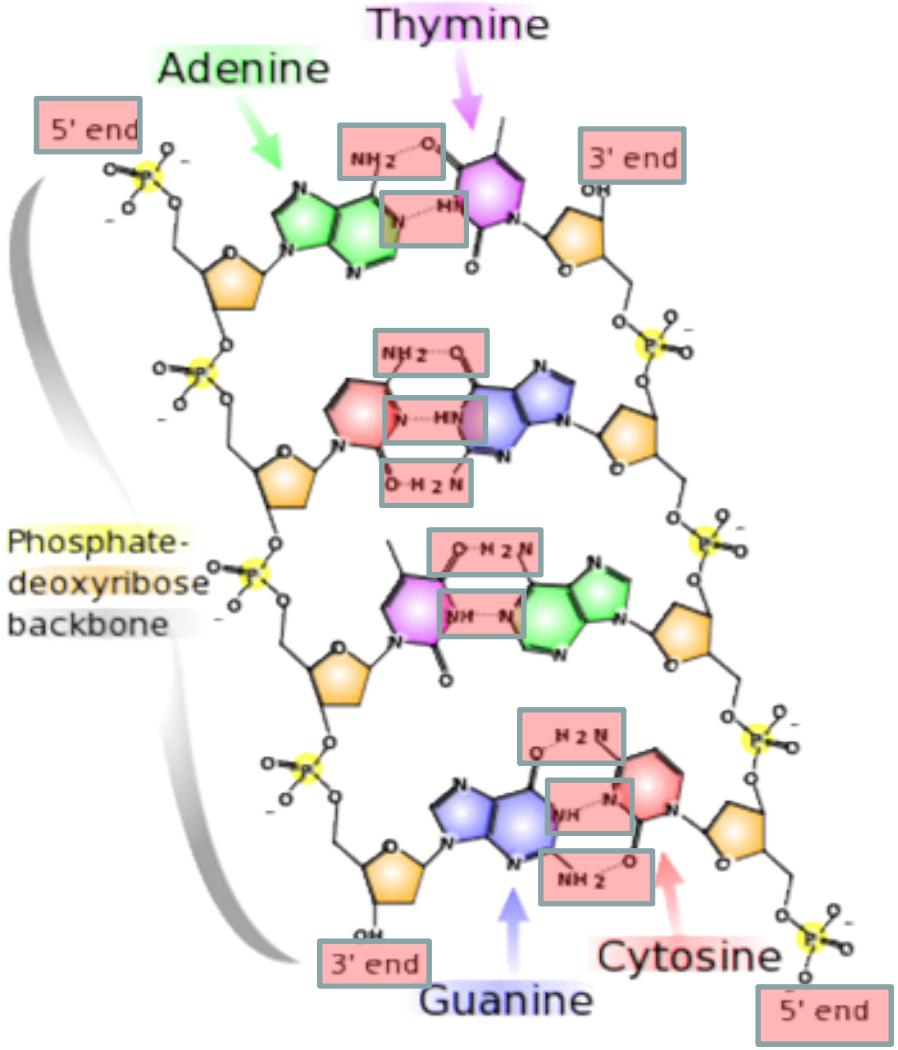
From Lehninger's 2005





Normal DNA Backbone





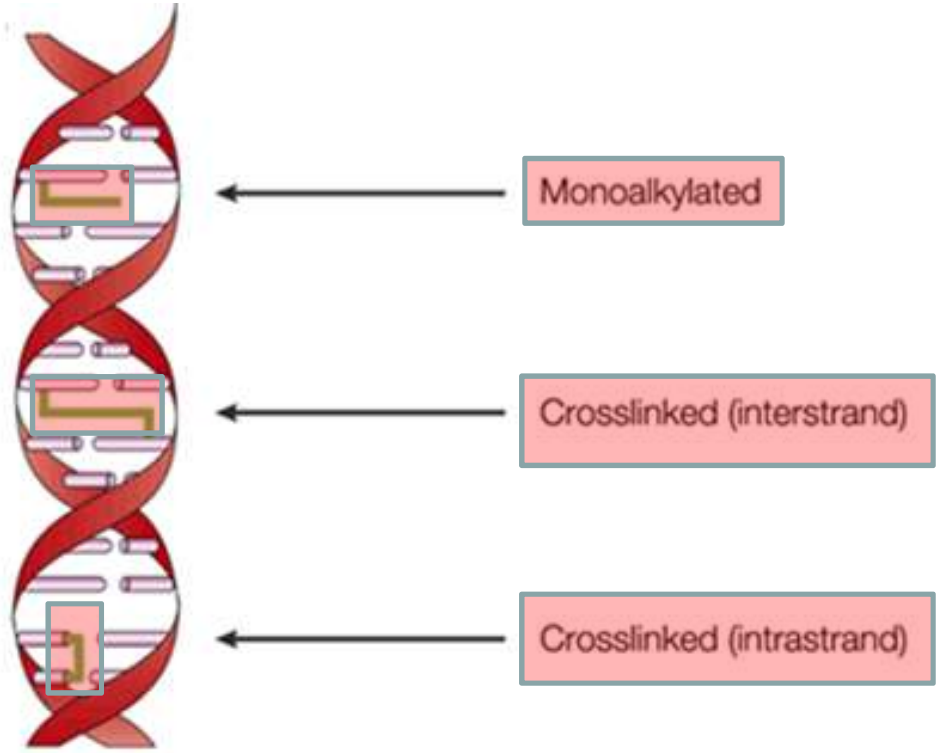
DNA Alkylating Agents in Two General Types of DNA Alkylation

- Mono-alkylation

- Bis-alkylation:

✓ inter-strand cross linking

✓ intra-strand cross linking



Nature Reviews | Cancer

DNA Alkylating Agents: Chemistry & Mechanism

- Chemistry: electrophilic:

✓ mono-functional

✓ bi-functional

- MOA: irreversible alkylation or complexation

✓ not cell cycle specific but more toxic to late G_1 & S phases

- Side effect:

✓ interaction to electron rich groups such as: -SH; -OH; -NH-

✓ in enzymes & membrane bound receptors

Chemical Classification for I. DNA (Cross) Linking Agents

I.1-Nitrogen mustards: beta halo-ethyl nitrogens:

a. beta halo-ethyl amine: aliphatic amine or aromatic amine

b. beta halo-ethyl phosphoramide nitrogen: cyclic phosphoramide

I.2-Aziridin

I.3-DNA alkylators / methylators:

a. Sulfonate ester: busulfan

b. Hydrazine: procarbazine

c. Triazene: dacarbazine

d. Tetrazine: temozolomide

e. Triazine: altretamine

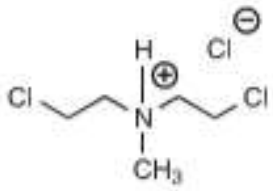
I.4-Nitroso-Ureas (NUs)

I.5- Organometallic agents: platinum agents (DNA cross linkers)

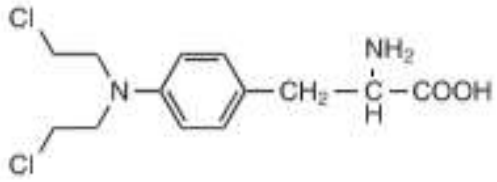
I.6. Miscellaneous antibiotic: mitomycin

DNA (Cross) Linking Agents

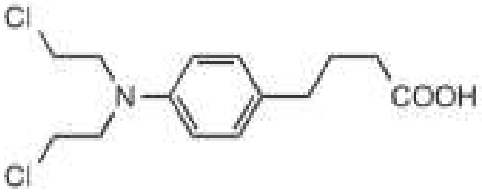
Nitrogen mustards and aziridine-mediated alkylators:



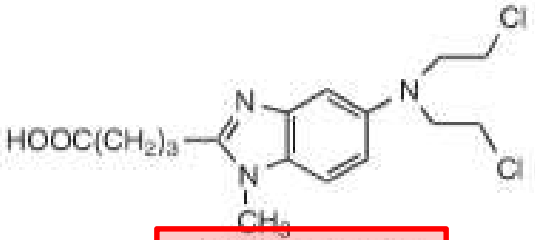
Mechlorethamine hydrochloride (Mustargen)



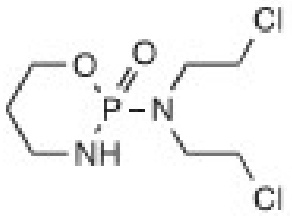
Melphalan (Alkeran)



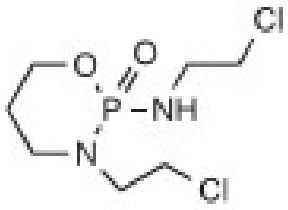
Chlorambucil (Leukeran)



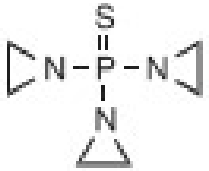
Bendamustine (Treanda)



Cyclophosphamide (Cytoxan)



Ifosfamide (Ifex)

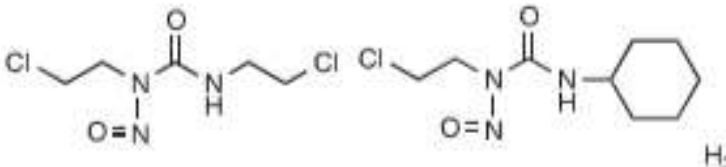


Thiotepa (Thioplex)

Figure 33.55 DNA alkylating and cross-linking agents.

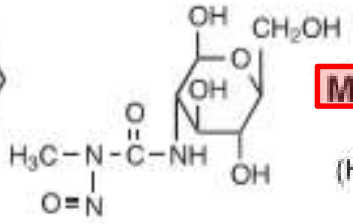
DNA (Cross) Linking Agents-Continued

Nitrosoureas:



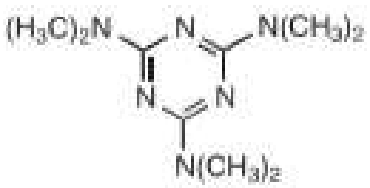
Carmustine (BiCNU)

Lomustine (CeeNU)



Streptozocin (Zanosar)

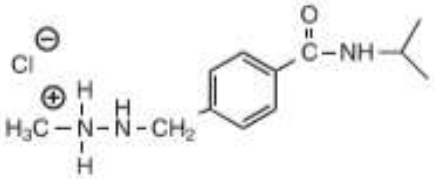
Miscellaneous DNA alkylators:



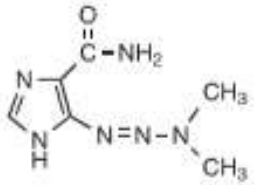
Altretamine (Hexalen)

Busulfan (Myleran)

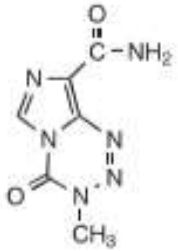
DNA methylators:



Procarbazine hydrochloride (Matulane)

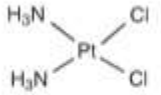


Dacarbazine (DTIC-Dome)

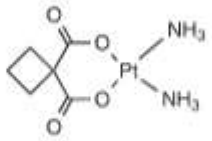


Temozolomide (Temodar)

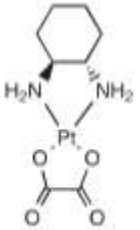
Organoplatinum complexes:



Cisplatin (Platinol-AQ)



Carboplatin (Paraplatin)

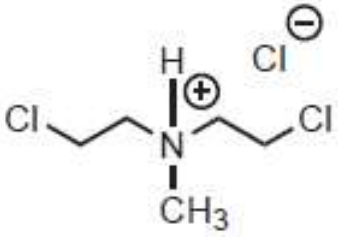


Oxaliplatin (Eloxatin)

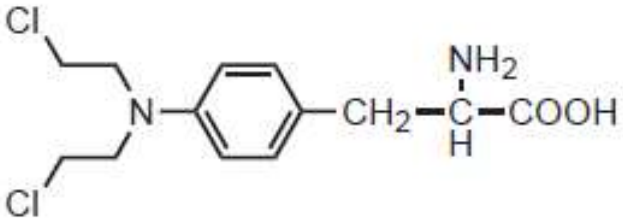
Figure 33.55 DNA alkylating and cross-linking agents.

I.1. Nitrogen Mustards:
Beta-Halo-Ethyl-Amines: Aliphatic or Aromatic Amines

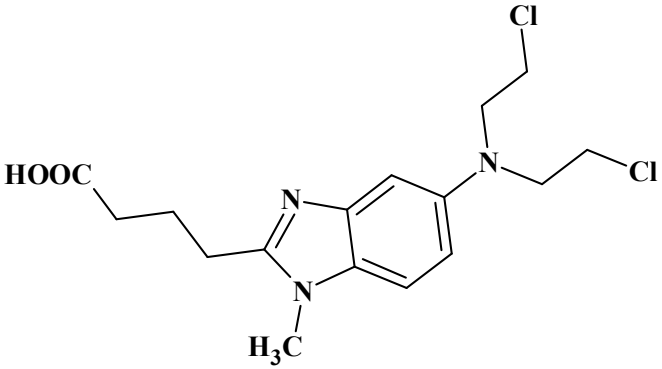
Nitrogen mustards and aziridine-mediated alkylators:

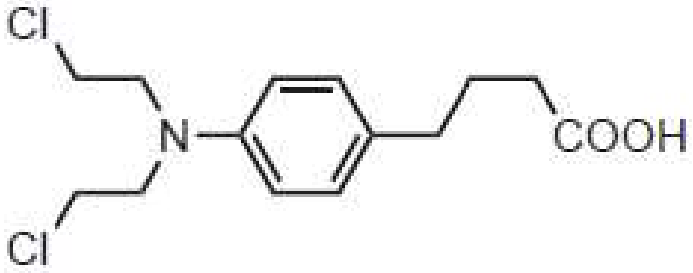


Mechlorethamine hydrochloride (Mustargen)

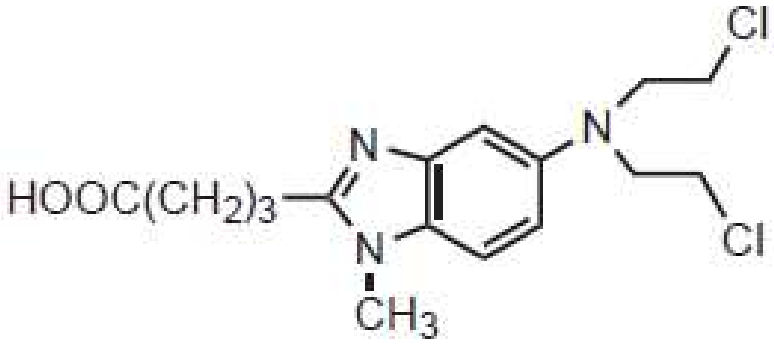


Melphalan (Alkeran)



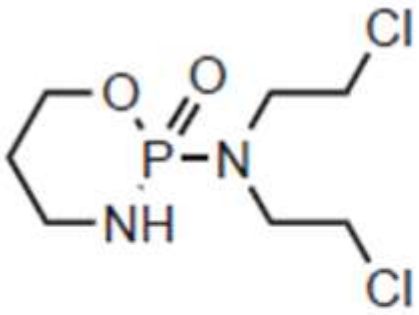


Chlorambucil (Leukeran)

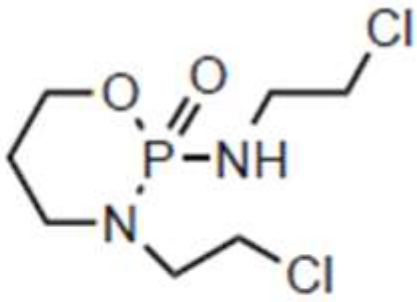


Bendamustine (Treanda)

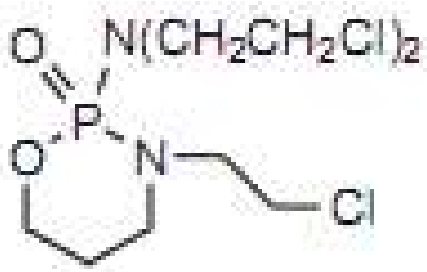
I.1. Nitrogen Mustards:
Beta-Halo-Ethyl-Phosphoramide Nitrogens



Cyclophosphamide
(Cytoxan)



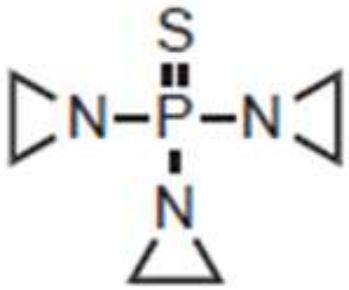
Ifosfamide
(Ifex)



Trofosfamide

I.2.Aziridine

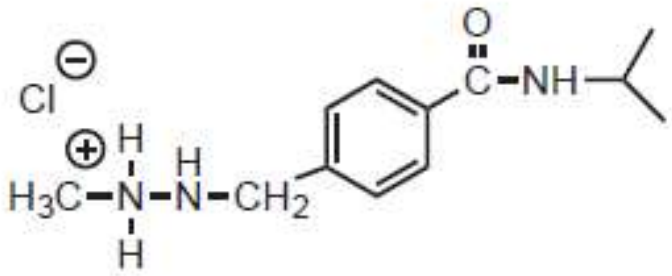
Nitrogen mustards and aziridine-mediated alkylators:



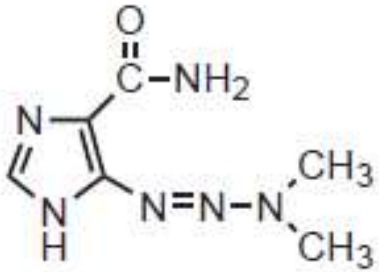
Thiotepa
(Thioplex)

I.3. DNA Alkylators/Methylators

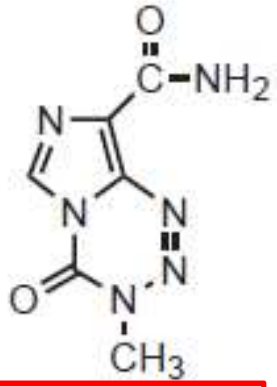
DNA methylators:



Procarbazine hydrochloride
(Matulane)



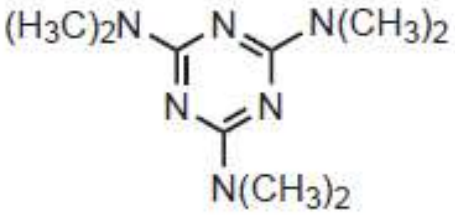
Dacarbazine
(DTIC-Dome)



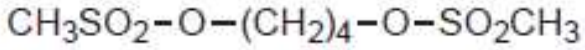
Temozolomide
(Temodar)

Miscellaneous DNA alkylators:

a. Sulfonate ester: busulfan
b. Hydrazine: procarbazine
c. Triazene: dacarbazine
d. Tetrazine: temozolomide
e. Triazine: altretamine



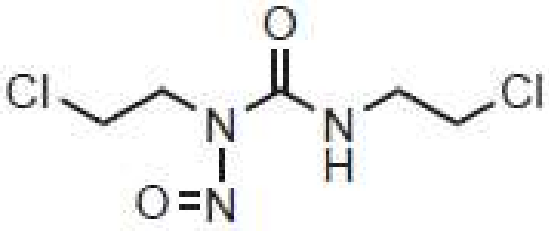
Altretamine
(Hexalen)



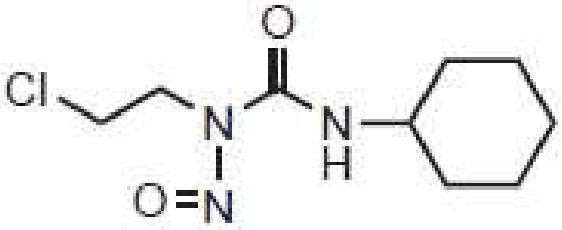
Busulfan
(Myleran)

I.4. Nitroso-Ureas

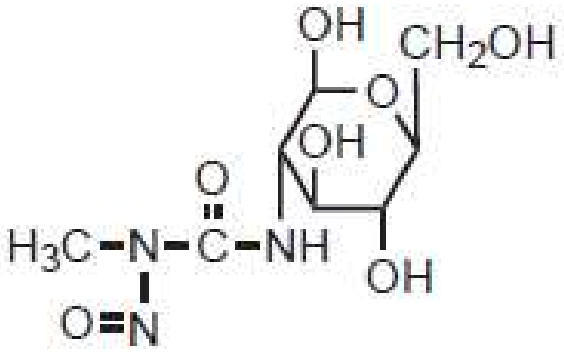
Nitrosoureas:



Carmustine (BiCNU)



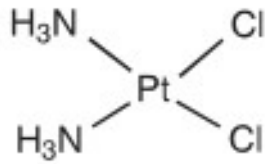
Lomustine (CeeNU)



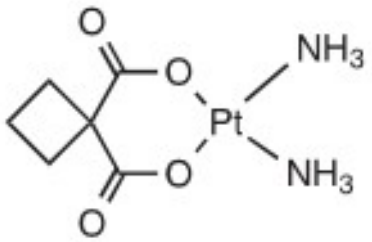
Streptozocin (Zanosar)

I.5. Organoplatinum Agents

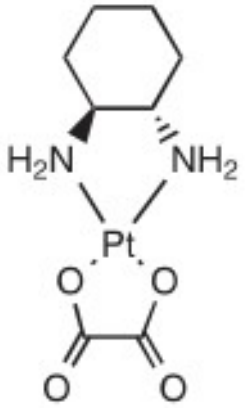
Organoplatinum complexes:



Cisplatin
(Platinol-AQ)



Carboplatin
(Paraplatin)



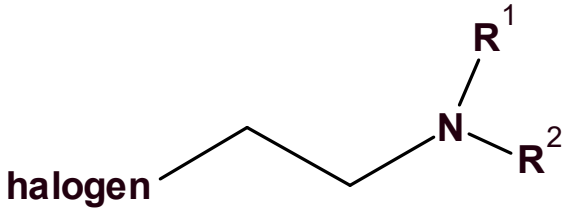
Oxaliplatin
(Eloxatin)

I. DNA (Cross) Linking Agents:

I.1-Nitrogen Mustards: Beta-Halo Ethyl Nitrogen

a. Beta-halo ethyl amine: mostly in Bis-form:

- ✓ aliphatic amine
- ✓ aromatic amine: anilinic

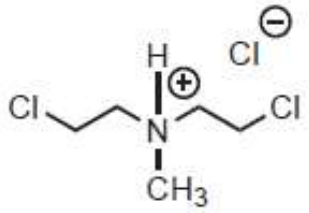


b. Beta- halo ethyl phosphoramide nitrogen

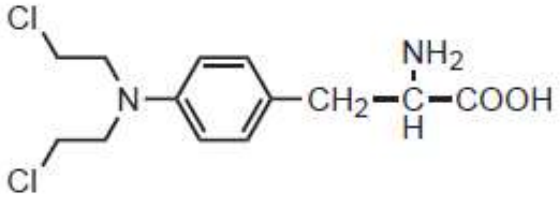
I.1. Nitrogen Mustards:
Beta-Halo-Ethylamines: Aliphatic or Aromatic Amines: SAR

Nitrogen mustards and aziridine-mediated alkylators:

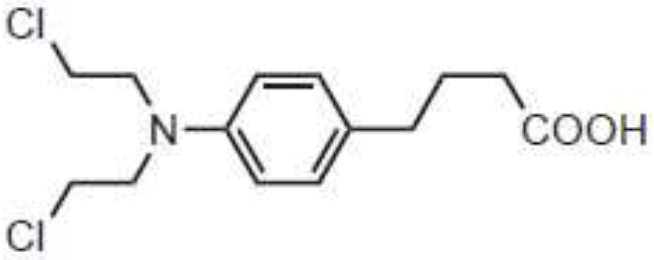
- SAR



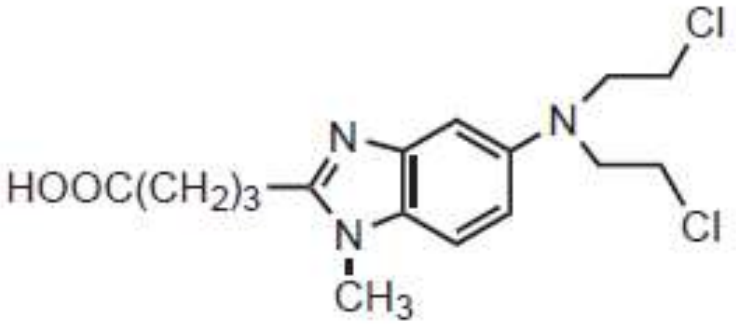
Mechlorethamine hydrochloride (Mustargen)



Melphalan (Alkeran)



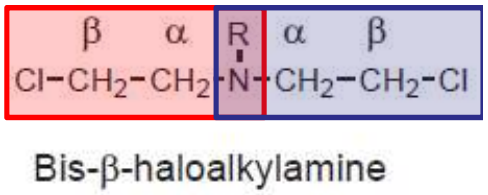
Chlorambucil (Leukeran)



Bendamustine (Treanda)

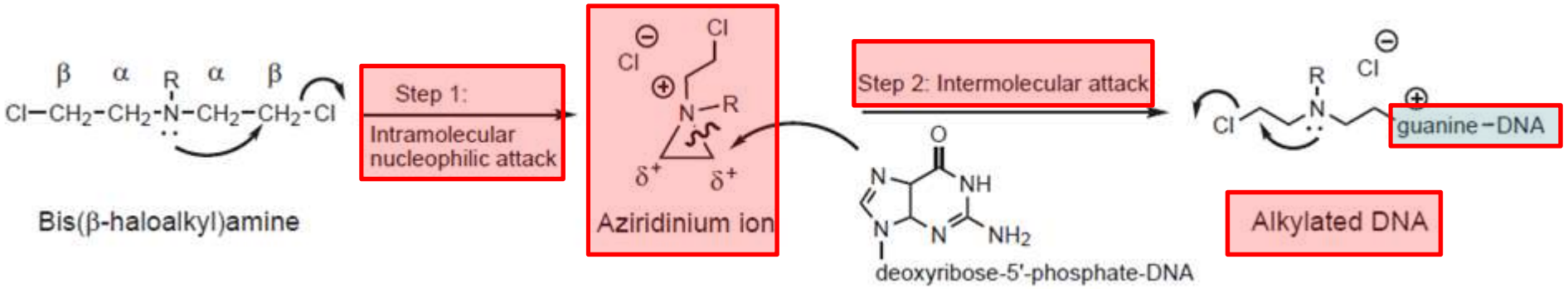
I.1. Nitrogen Mustards: MOA

- Bis- β-halo-ethyl amines (nitrogens): as prodrug:



✓ step1: intramolecular nucleophilic attack: aziridinium cation

✓ step2: intermolecular nucleophilic attack by N7-G



- Reactive intermediate: highly electrophilic aziridinium cation
- Molecular mechanism: as prodrug:

✓ DNA alkylation through G-N7

✓ hydrolytic depurination

4 to 5 steps in Mechanism of DNA Alkylation & DNA Destruction through Nitrogen Mustards

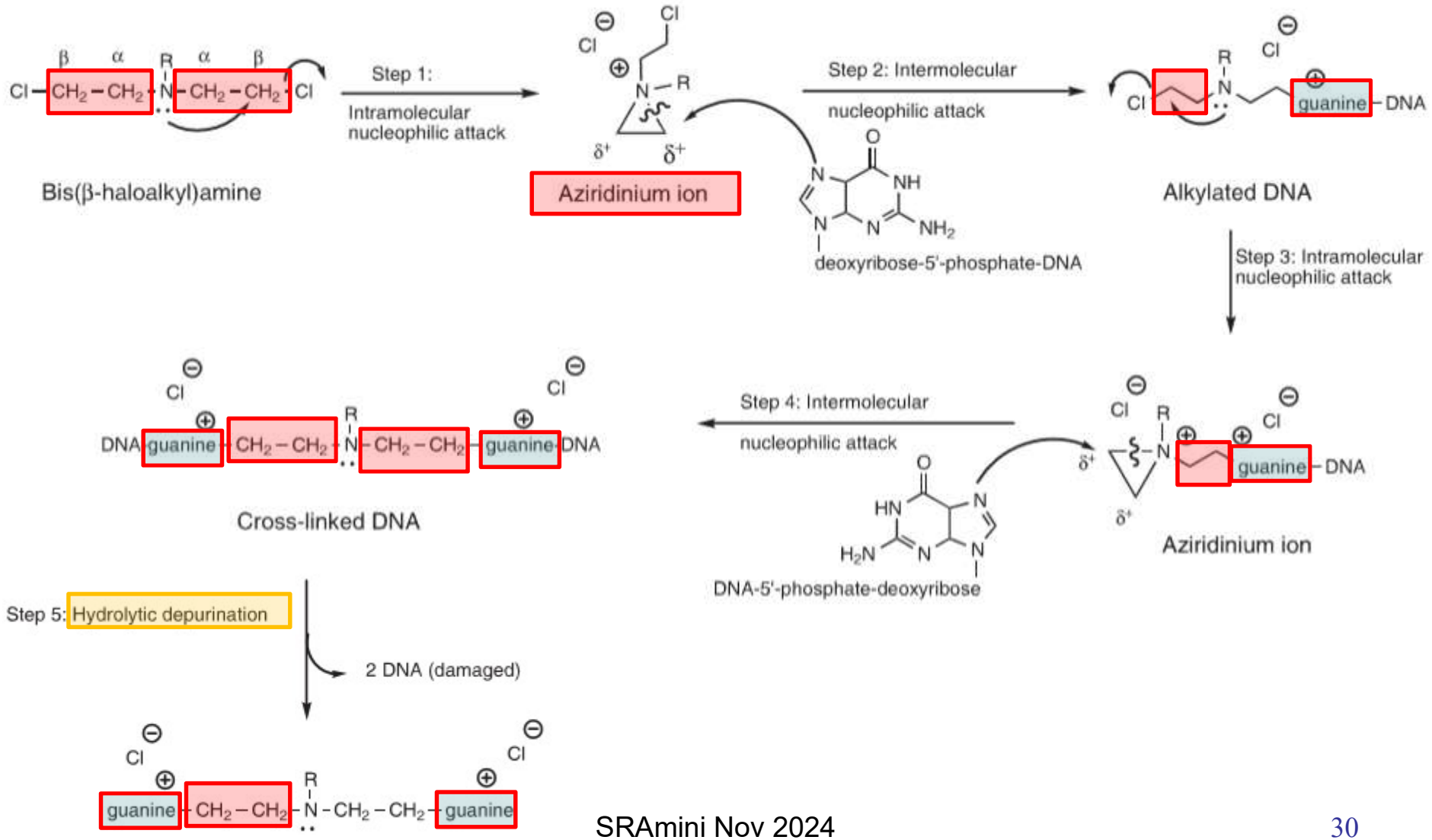


Figure 33.56 DNA destruction through nitrogen mustard-mediated alkylation.

Aqueous Inactivation or Decomposition of Nitrogen Mustards by Water

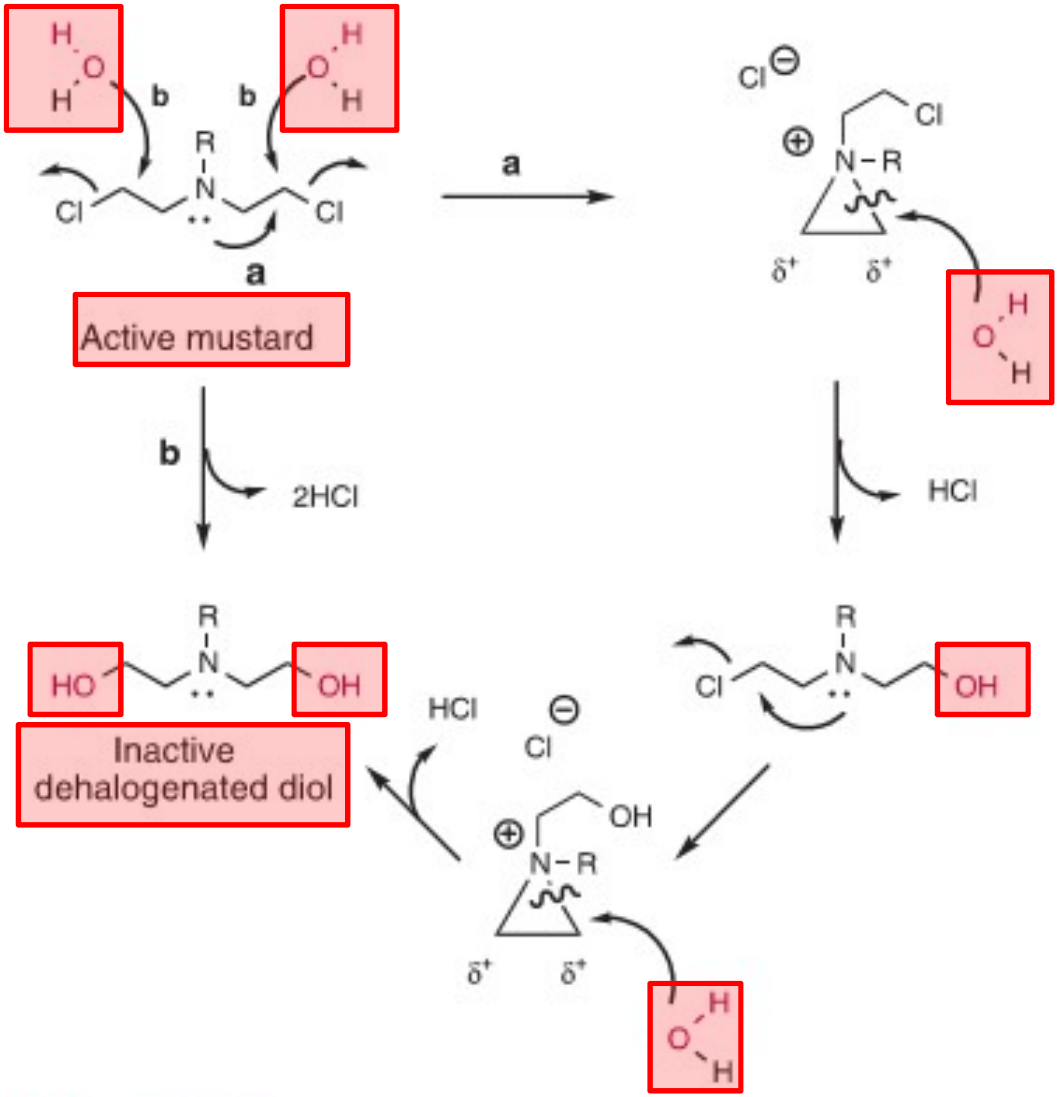
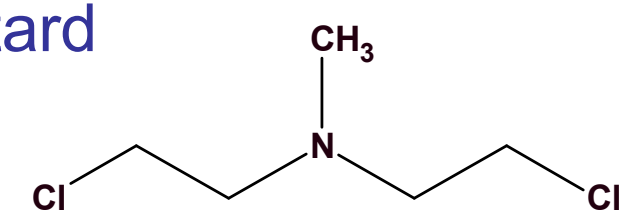


Figure 33.57 Aqueous decomposition of nitrogen mustards.

I.1. Nitrogen Mustards: Mechlorethamine:
Inactivation of Nitrogen Mustards by Sodium Thiosulfate

- Mechlorethamine: the only aliphatic mustard



✓ HCl salt

✓ pK_a= 6.1

- Even in skin contact: should be inactivated with:

✓ sodium thiosulfate ($Na_2S_2O_3$): reactant anion: $S_2O_3^{2-}$

✓ produce inactive, highly ionized & water soluble thio-sulfate ester

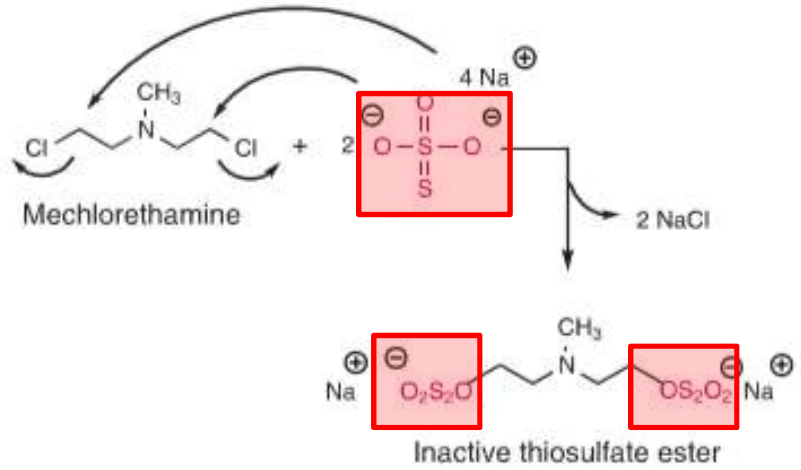
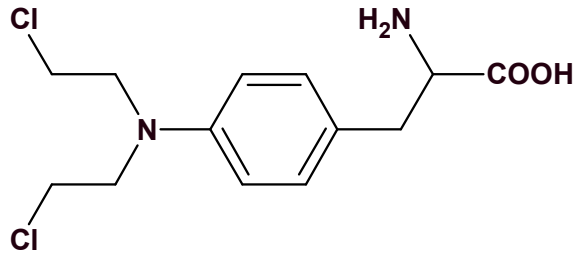


Figure 33.58 Mechlorethamine inactivation by sodium thiosulfate.

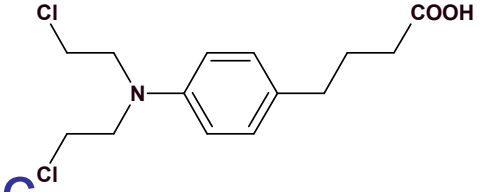
I.1. Nitrogen Mustards: Melphalane

- Melphalane: phenylAlanin Mustard: PAM (L-PAM); Alkeran®
- ✓ aromatic mustard: less reactive than aliphatic
- ✓ L-Phe act as homing device

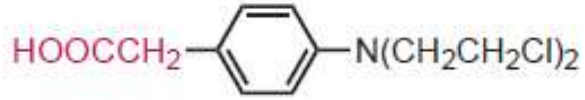


- Cell penetration: active transport & facilitated diffusion
- Dosage form: oral
- ✓ SE: mutagenic: to induce leukemia

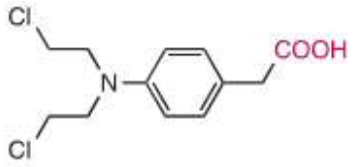
I.1.Nitrogen Mustards: Chlorambucil



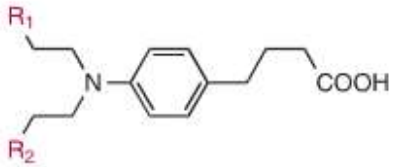
- Chlorambucil: Leukeran®
- ✓ aromatic mustard: less reactive than aliphatic
- Cell penetration: facilitated diffusion > active transport
- Dosage form: oral
- Active Metabolite: Phenyl Acetic acid Mustard: PAM
- Inactive metabolites: ?



Phenylacetic acid mustard (an active chlorambucil metabolite)

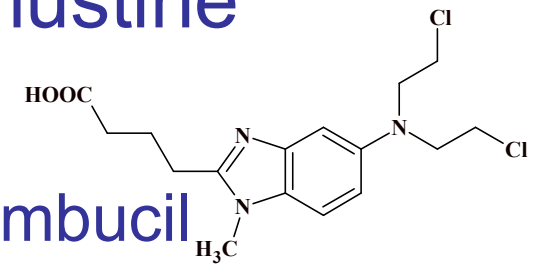


Phenylacetic acid mustard (active chlorambucil metabolite)

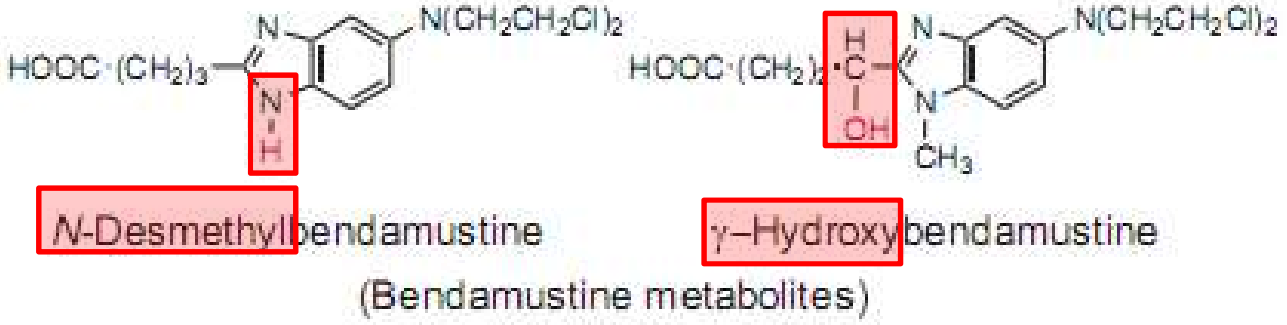


Inactive chlorambucil hydrolysis products
(R_1= OH, R_2 = Cl [monohydroxy])
(R_1 = R_2 = OH [dihydroxy])

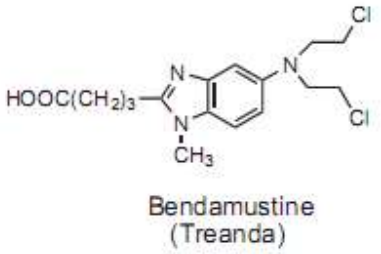
I.1. Nitrogen Mustards: Bendamustine



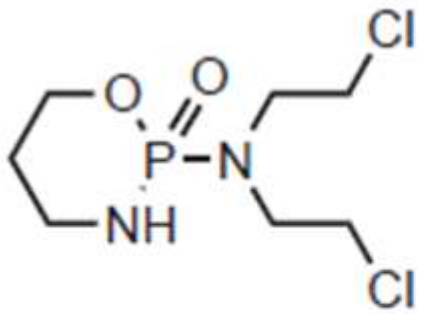
- Bendamustine: Treanda®
- ✓ N-methyl benz-imidazole analogue of chlorambucil
- Purine like ring substitution: promote antimetabolite
- ✓ provides extra MOA in addition to DNA alkylation
- Metabolism: active but clinically insignificant
- ✓ N-demethylation
- ✓ γ-hydroxylation



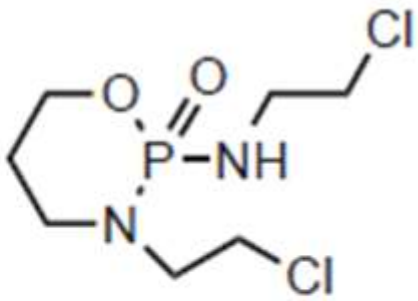
- Dosage form: only IV
- Can induce p53-mediated stress response
- Can induce apoptosis



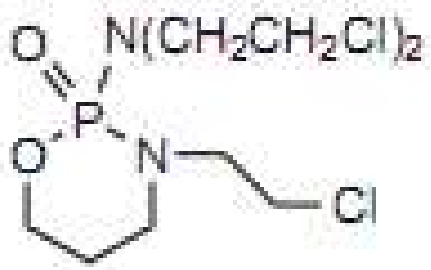
I.1. Nitrogen Mustards:
Beta-Halo-Ethyl-Amines (Nitrogens): Phosphoramide: SAR



Cyclophosphamide
(Cytoxan)



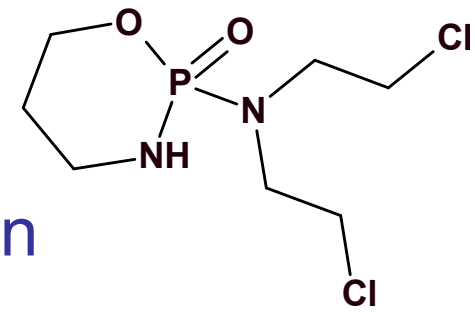
Ifosfamide
(Ifex)



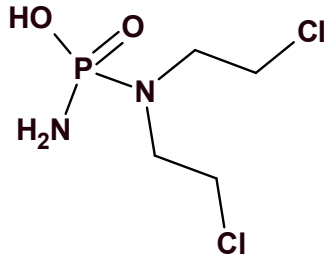
Trofosfamide

I.1. Nitrogen Mustards: Phosphoramides: Cyclophosphamide

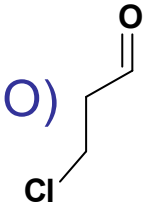
- Cyclophosphamide: CTX; Cytoxan®

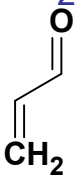


- Chemistry: oxazaphosphorine
- Chiral prodrug: CYP450 related bio-activation
- Metabolic & non-metabolic activation processes.
- Active metabolites: phosphoramide mustard (pK_a= 4.75)

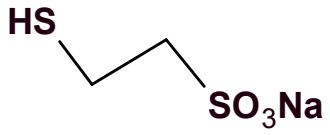


- Toxic metabolites:
  - ✓ Chloro-acetaldehyde (Cl-CH_2-CHO)
  - ✓ Acrolein (CH_2=CH-CHO)





- Adjuvant in therapy: mercaptoalkyl sulfonate natrium: Mesna; MESNA



Cyclophosphamide Bio-Activation

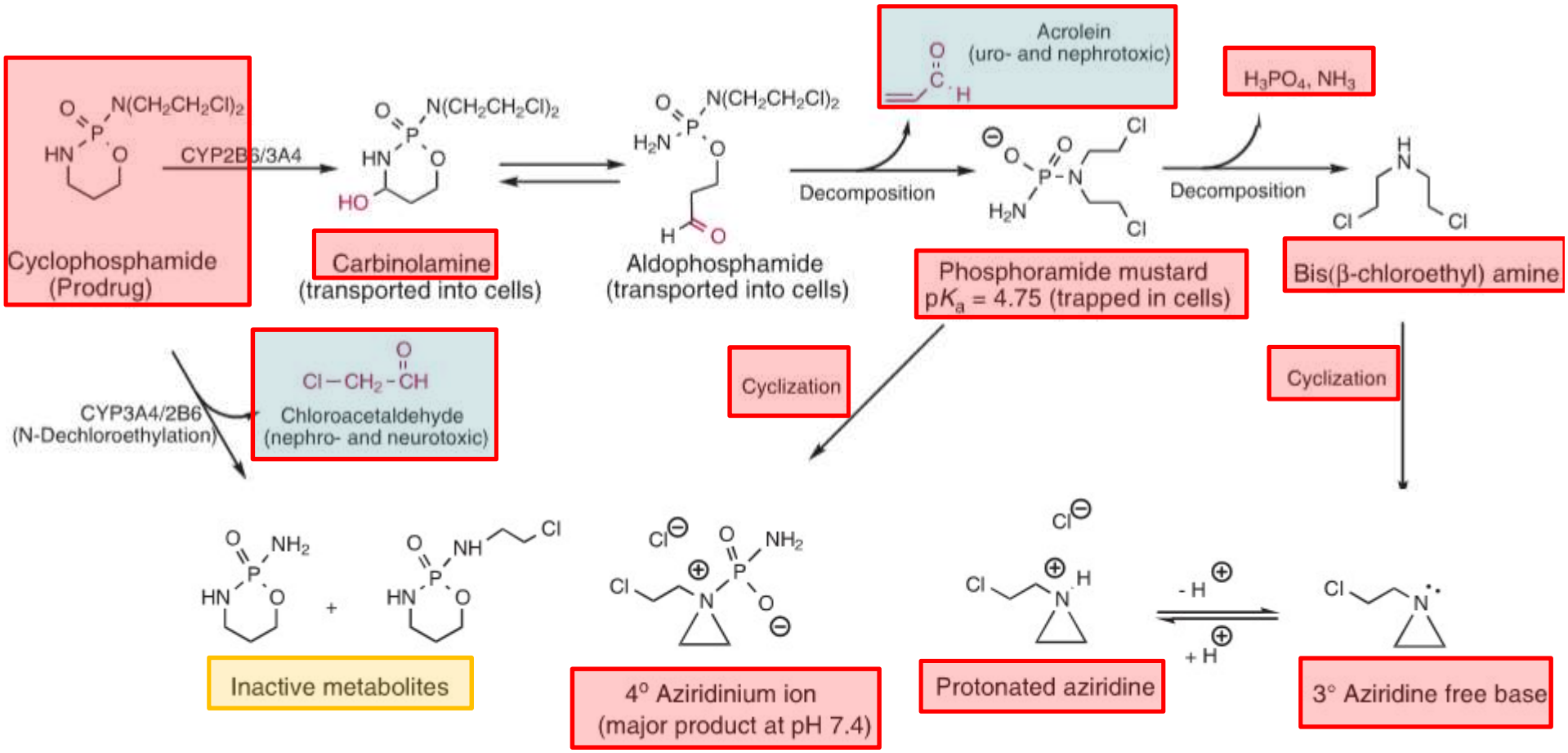


Figure 33.59 Cyclophosphamide metabolism.

Interaction of Cys & GSH to Acrolein

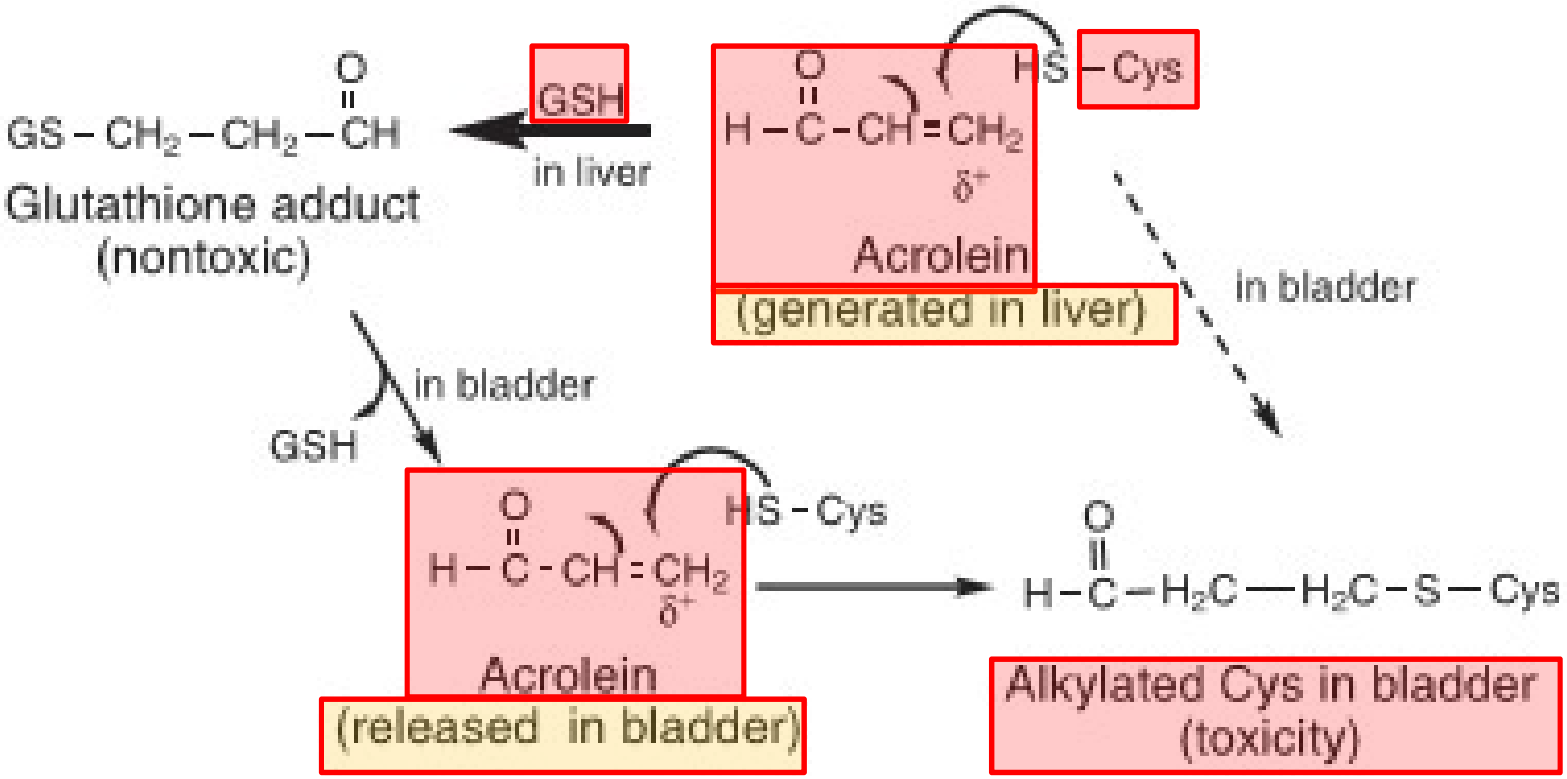


Figure 33.60 GSH conjugation with acrolein.

Acrolein Detoxification By Mesna

- Consider activation of Di-Mesna by Glutathione dehydrogenase
- Follow MESNA adduct product

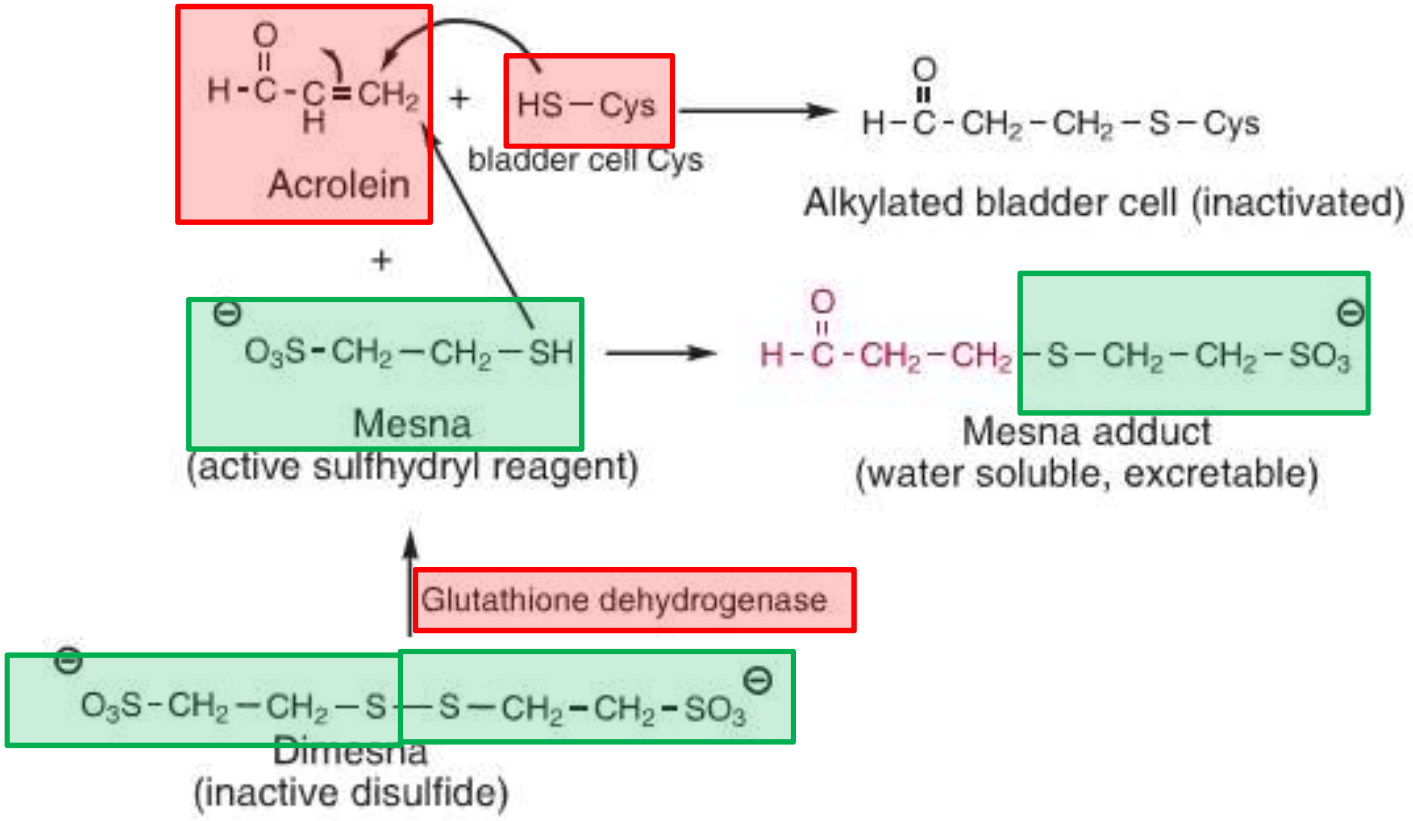


Figure 33.61 Acrolein detoxification by mesna.

Detoxification of Chloro-Acetaldehyde by NAC

- NAC: N-Acetyl Cysteine: $HS\text{-}CH_2\text{-}CH(NHCOCH_3)COOH$

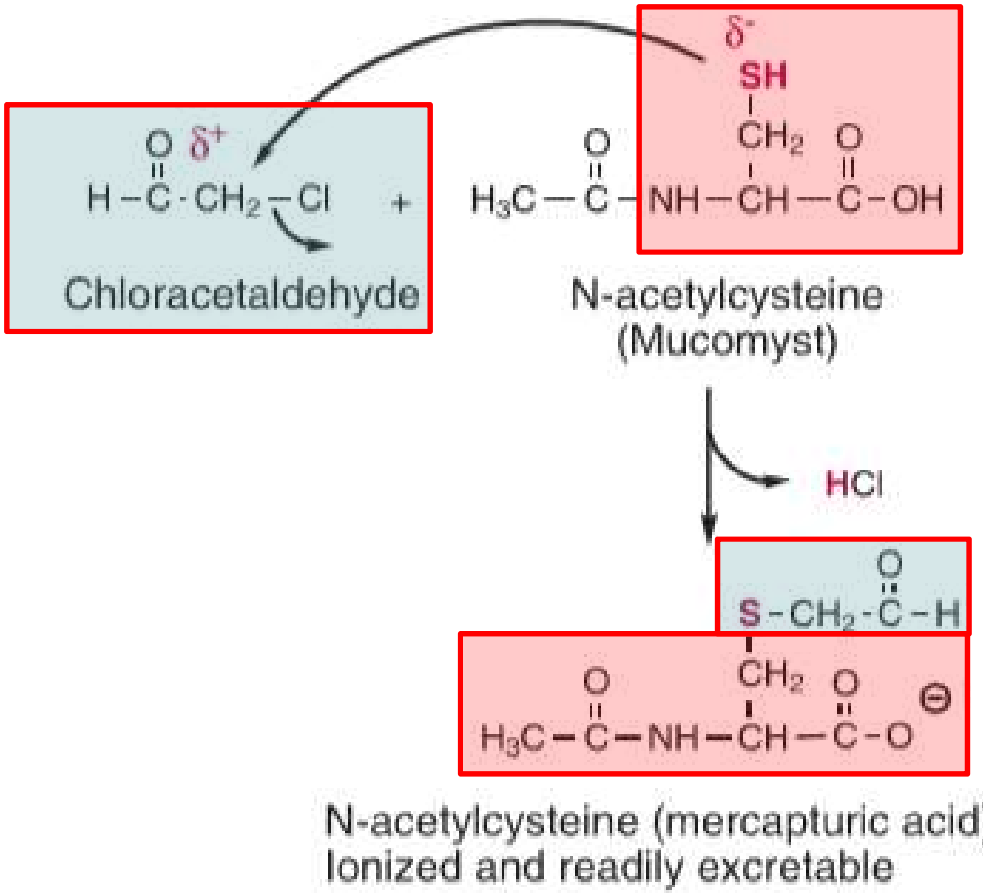
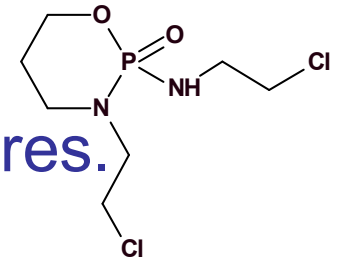


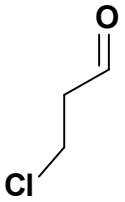
Figure 33.63 Chloroacetaldehyde detoxification by N-acetylcysteine.

I.1. Nitrogen Mustards: Phosphoramides: Ifosfamide

- Ifosfamide: Ifex®
- Cyclophosphamide analogue: compare the structures.



- CYP450 related bio-activation: slower rate: due to steric reasons



- Active metabolites:
- Toxic metabolite: chloro-acetaldehyde: > cyclophosphamide
- Nephrotoxicity & neurotoxicity
- Adjuvant in therapy: Mesna

Bio-Activation of Ifosfamide

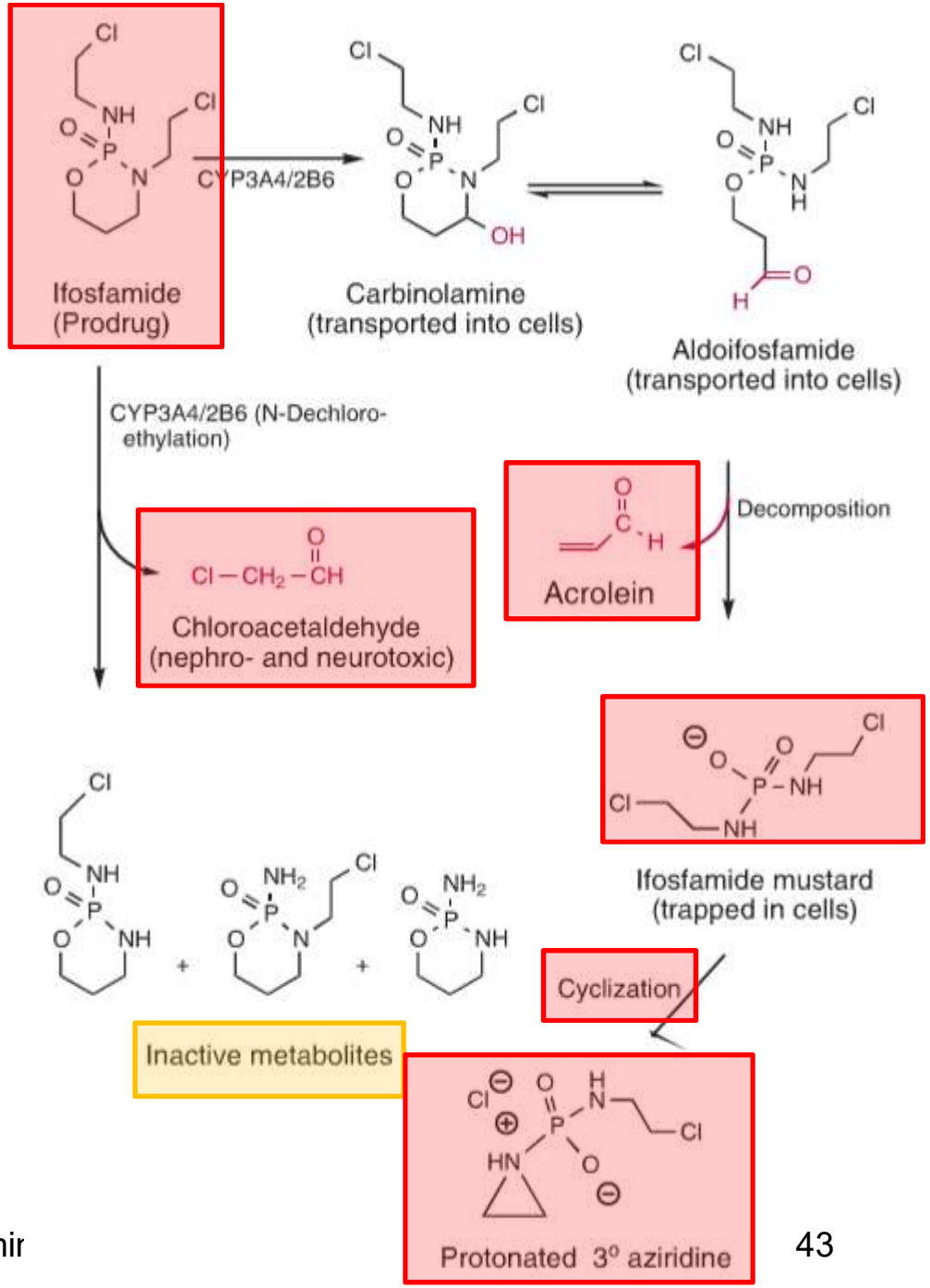
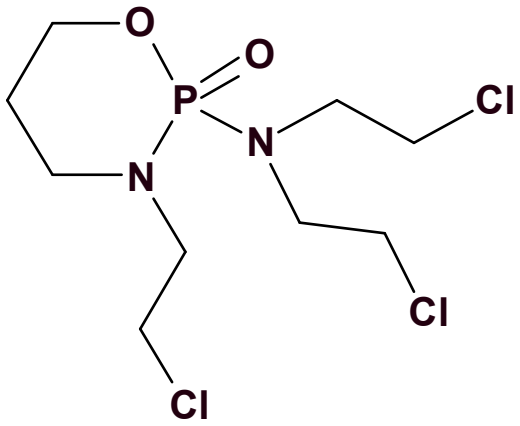
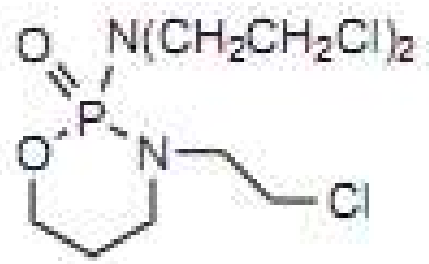


Figure 33.62 Ifosfamide metabolism.

I.1. Nitrogen Mustards: Phosphoramides: Tr-e/o-fosfamide

- Compare the structure to cyclophosphamide & ifosfamide.





Trofosfamide

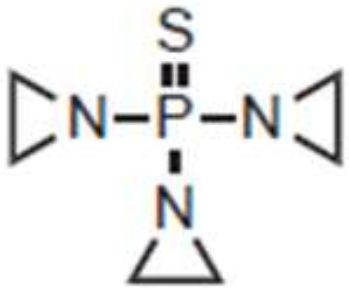
- Dechloro-ethylation:

✓ bioactivation to cyclophosphamide & ifosfamide

I.2.Aziridine

- SAR

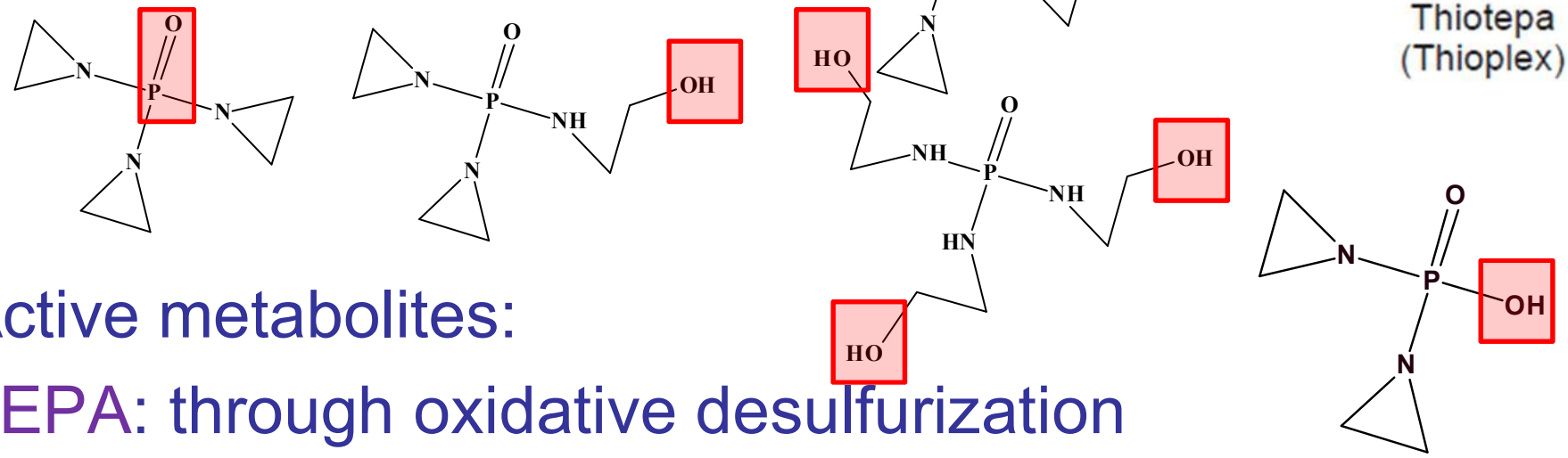
Nitrogen mustards and aziridine-mediated alkylators:



Thiotepa
(Thioplex)

I.2. Aziridin DNA Alkylating Agents: Thio/TEPA

- Thiotepa; TEPA: Tri-Ethylene-thio-PhosphorAmide
- Chemistry: tertiary aziridine
- Metabolites:



- Active metabolites:

✓ TEPA: through oxidative desulfurization

✓ aziridinium ion

- MOA: weak alkylator
- SE: CNS penetration

DNA Alkylation by Thiotepa

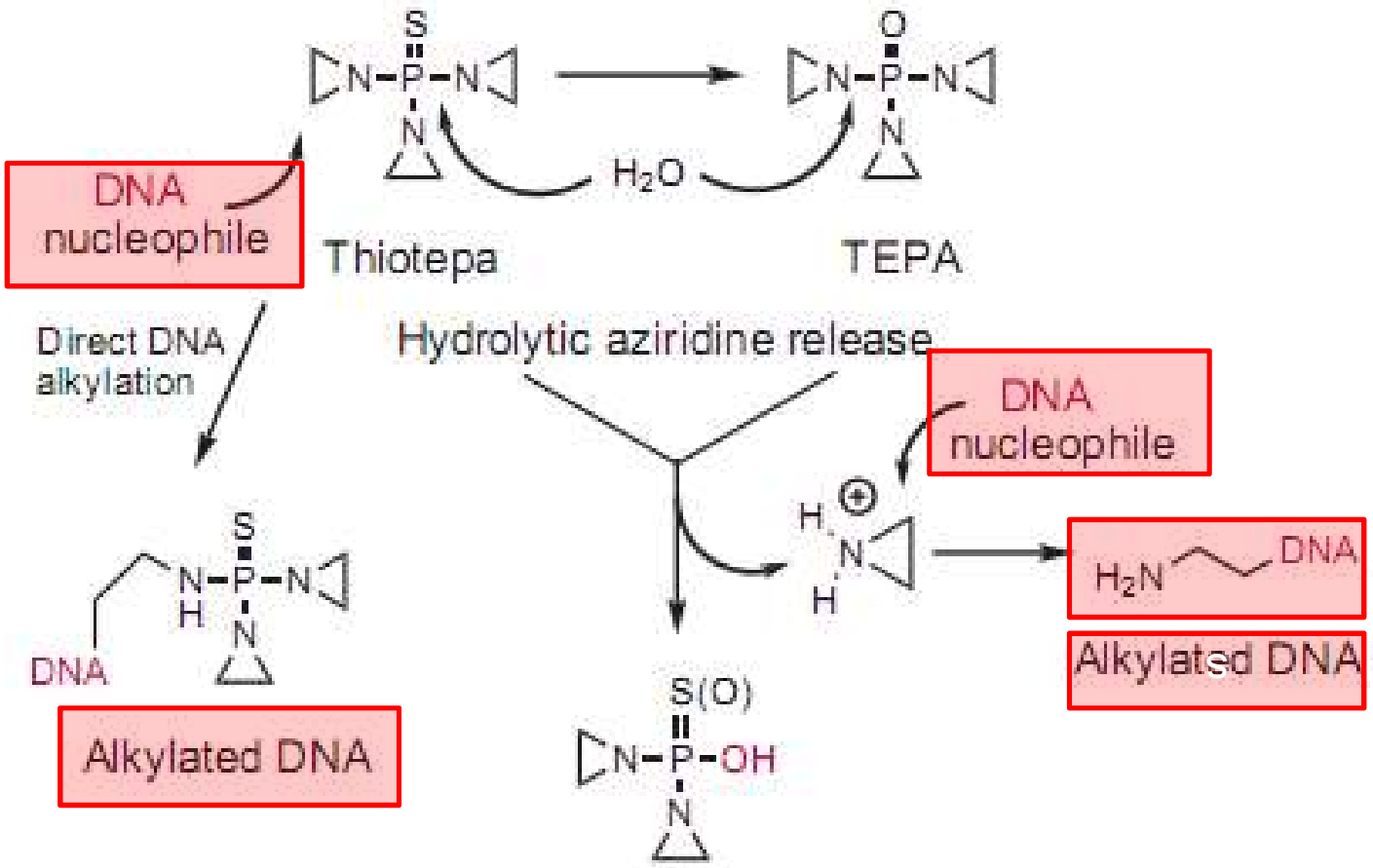
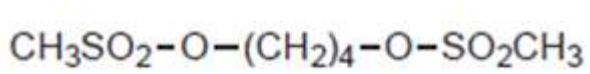


FIGURE 37.8 Mechanism of thiotepa DNA alkylation.

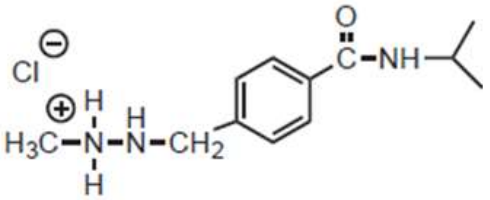
I.3. DNA Alkylators:
Chemical Classification: Subclass “a” to Subclass “e”

a. Sulfonate ester: busulfan
b. Hydrazine: procarbazine
c. Triazene: dacarbazine
d. Tetrazine: temozolomide
e. Triazine: altretamine



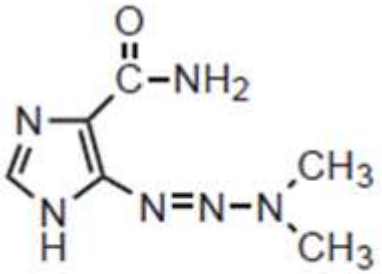
Busulfan
(Myleran)

DNA methylators:

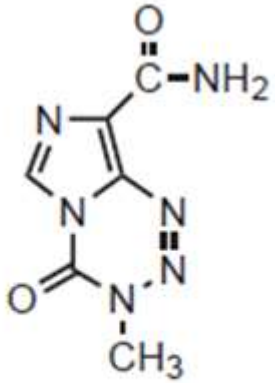


Procarbazine hydrochloride
(Matulane)

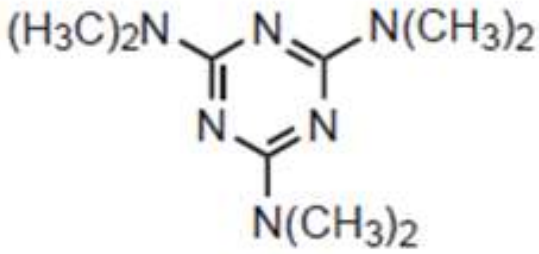
DNA methylators:



Dacarbazine
(DTIC-Dome)



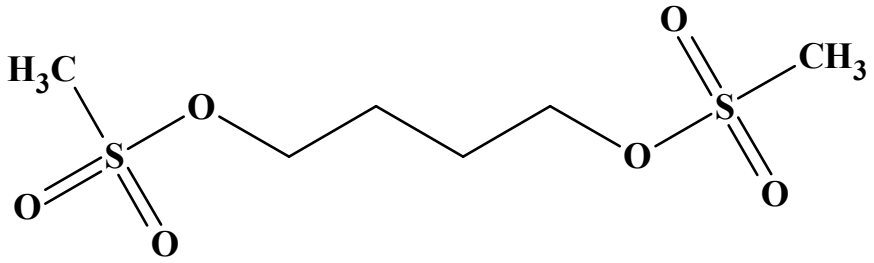
Temozolomide
(Temodar)



Altretamine
(Hexalen)

I.3.a. DNA Alkylators: Sulfonate Ester: Busulfan

- Busulfan: Myleran®: a sulfonic acid ester



- SAR
- MOA:
- Mono- or di-alkylated adduct to N7- Guanine in DNA
- also cystein alkylation
- provide cross linker: how?

- Metabolite: ?

DNA Cross-Alkylation by Busulfan

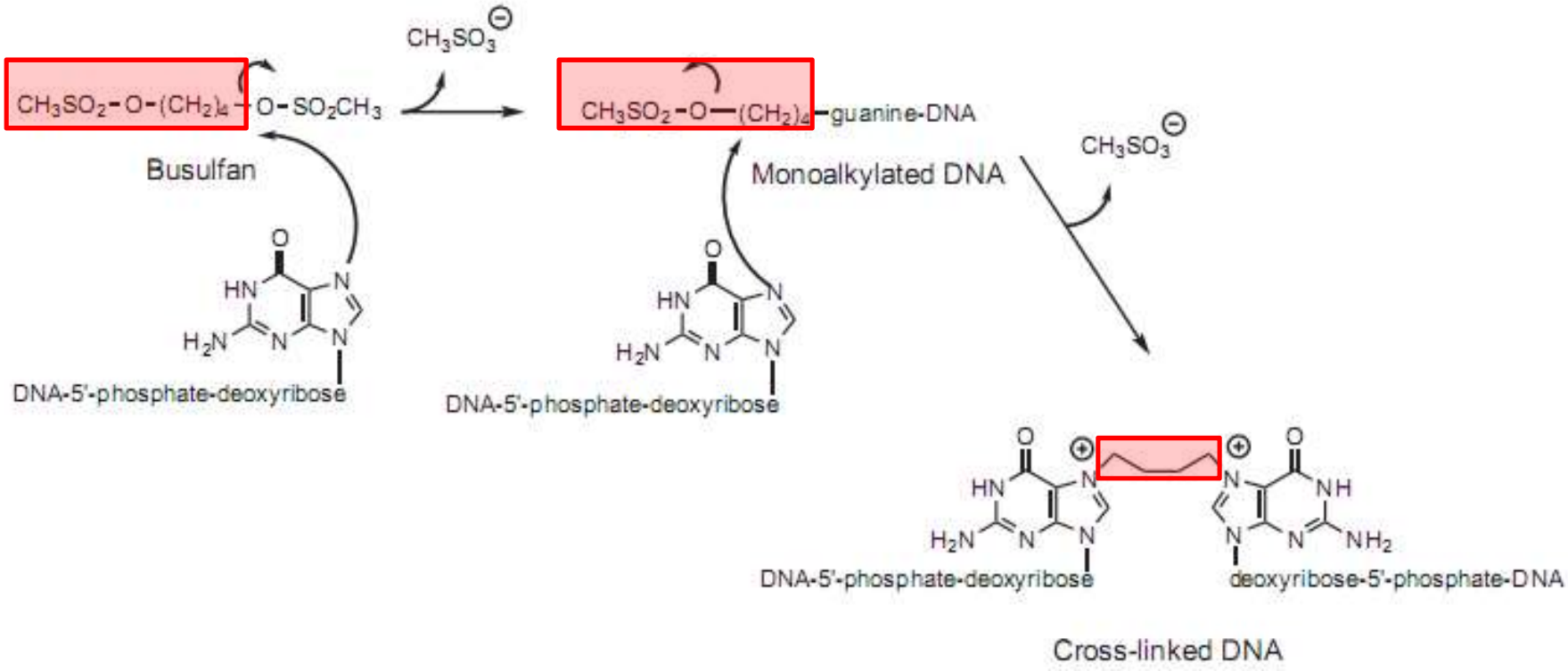


FIGURE 37.13 Busulfan-mediated DNA alkylation.

I.3.b.DNA Alkylators: Hydrazine: Procarbazine

- Procarbazine
- CYP450 related bi
- Metabolites:

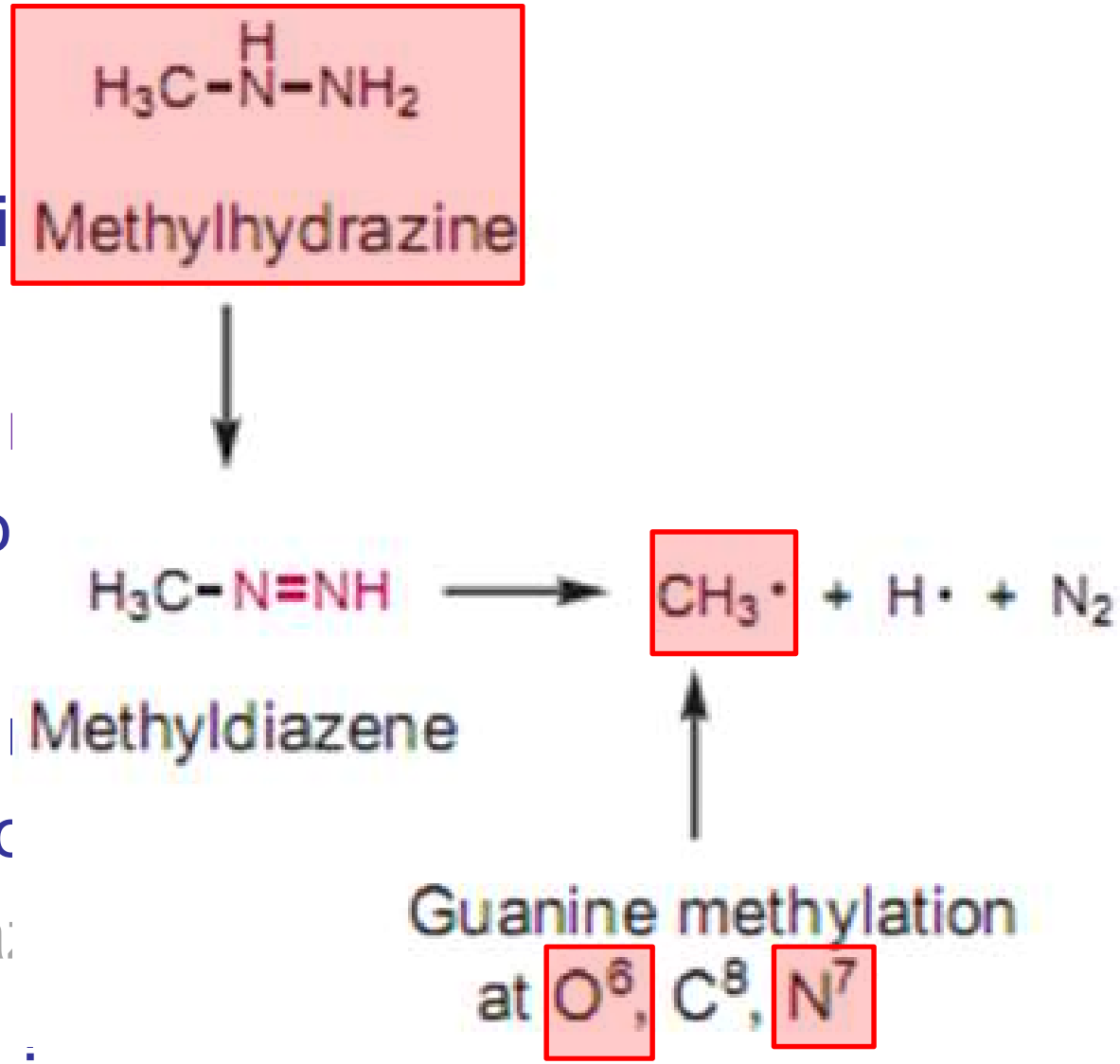
✓ active metabolite: I

+ N_2 + hydro

- SAR
- MOA: free radical I

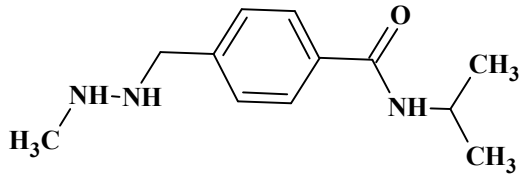
✓ guanine methylatic

- Resistant to hydra
- Drug interactions:



I.3.b.DNA Alkylators: Hydrazine: Procarbazine

- Procarbazine
- CYP450 related bioactivation
- Metabolites:



✓ active metabolite: methyl radical / carbocation

+ N_2 + hydrogen radical + aldehyde (?)

- SAR
- MOA: free radical mechanism:

✓ guanine methylation: at O_6 or N_7 or C_8

- Resistant to hydrazines & triazenes:
- Drug interactions: ?

Bio-Activation of Procarbazine- Pathway1- Minor Pathway

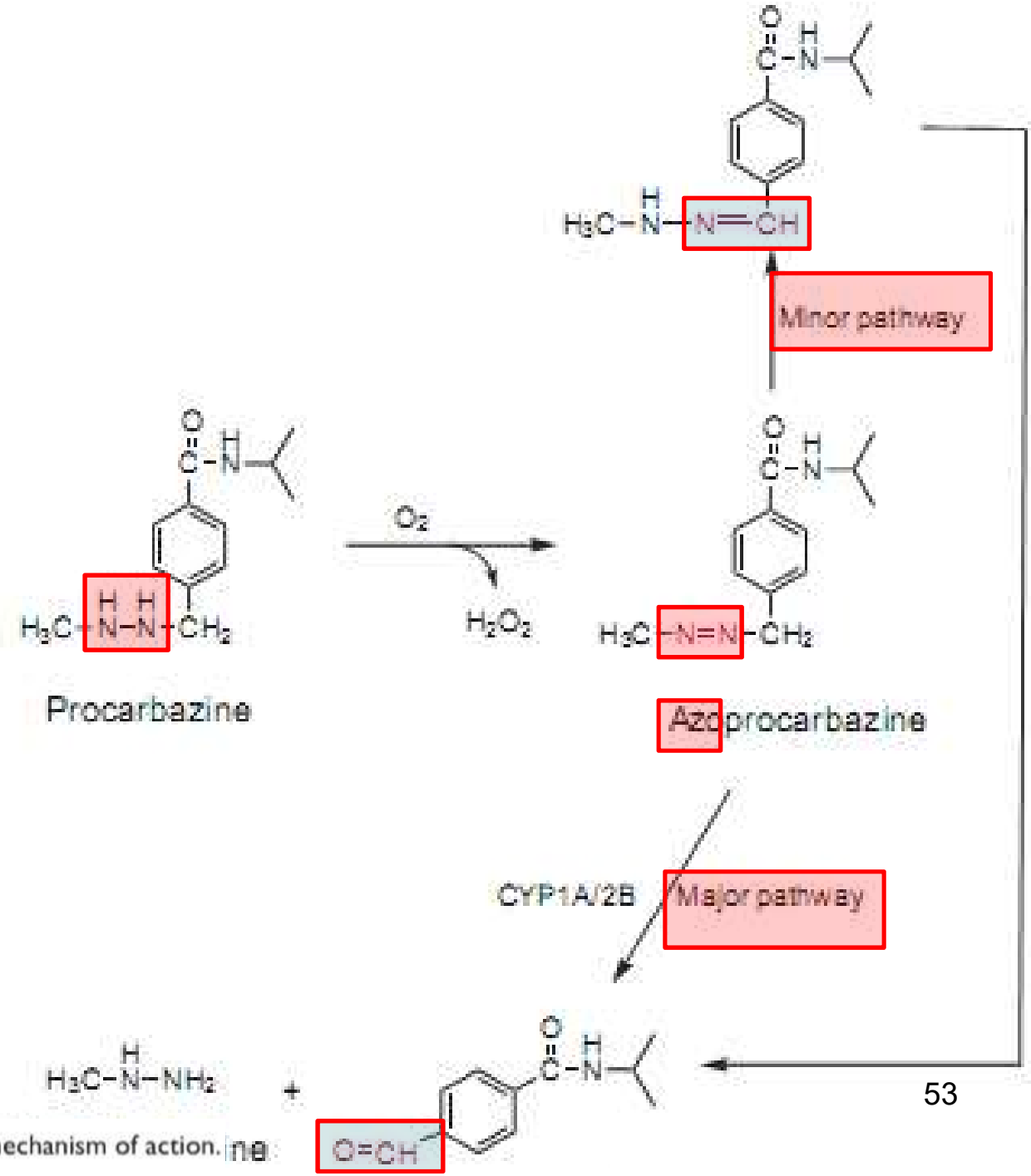


Figure 33.65 Procarbazine metabolism and mechanism of action.

Bio-Activation of Procarbazine- Pathway 2- Major Pathway

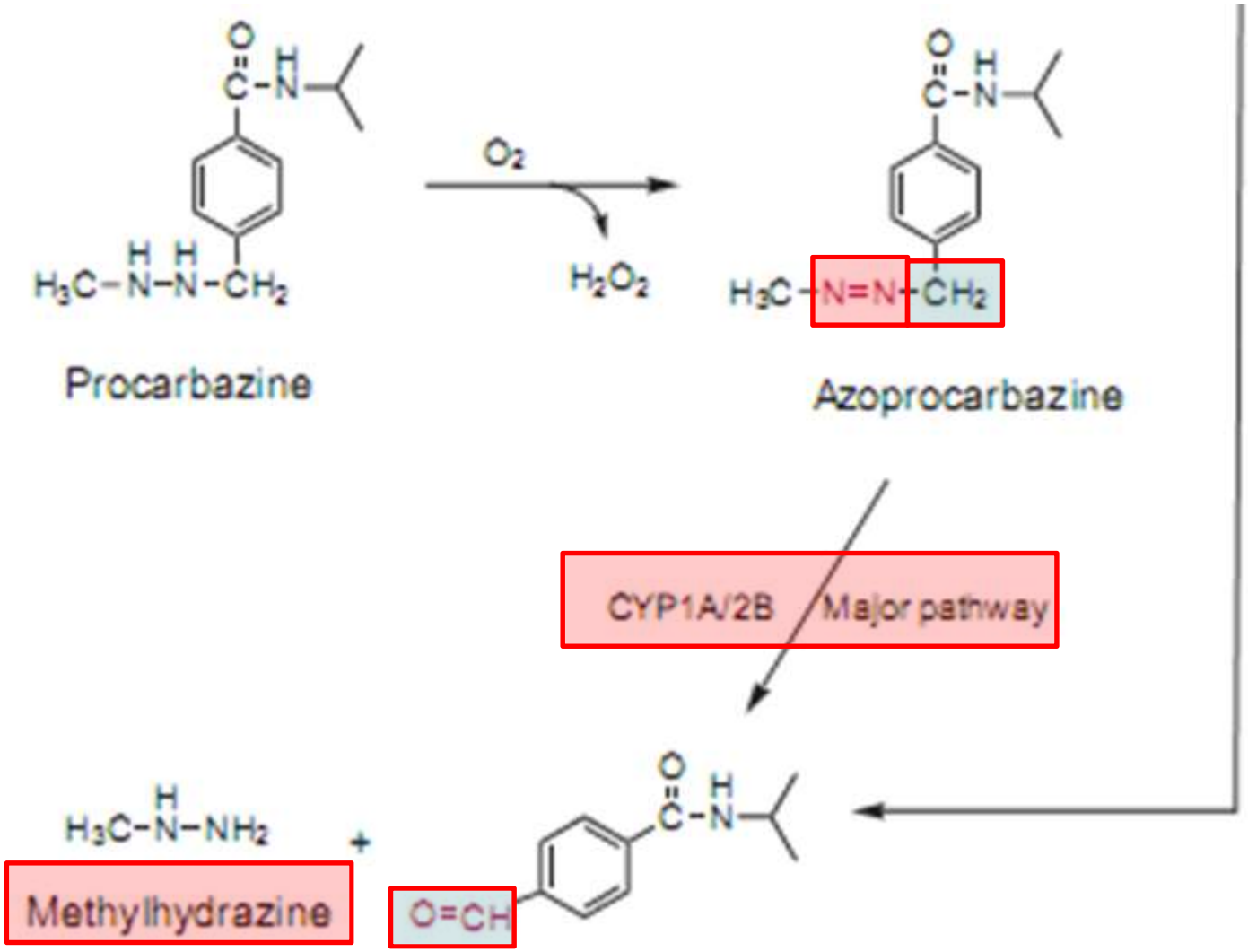


Figure 33.65 Procarbazine metabolism and mechanism of action.

Bio-Activation of Procarbazine- Pathway 2- Major Pathway- Contd.

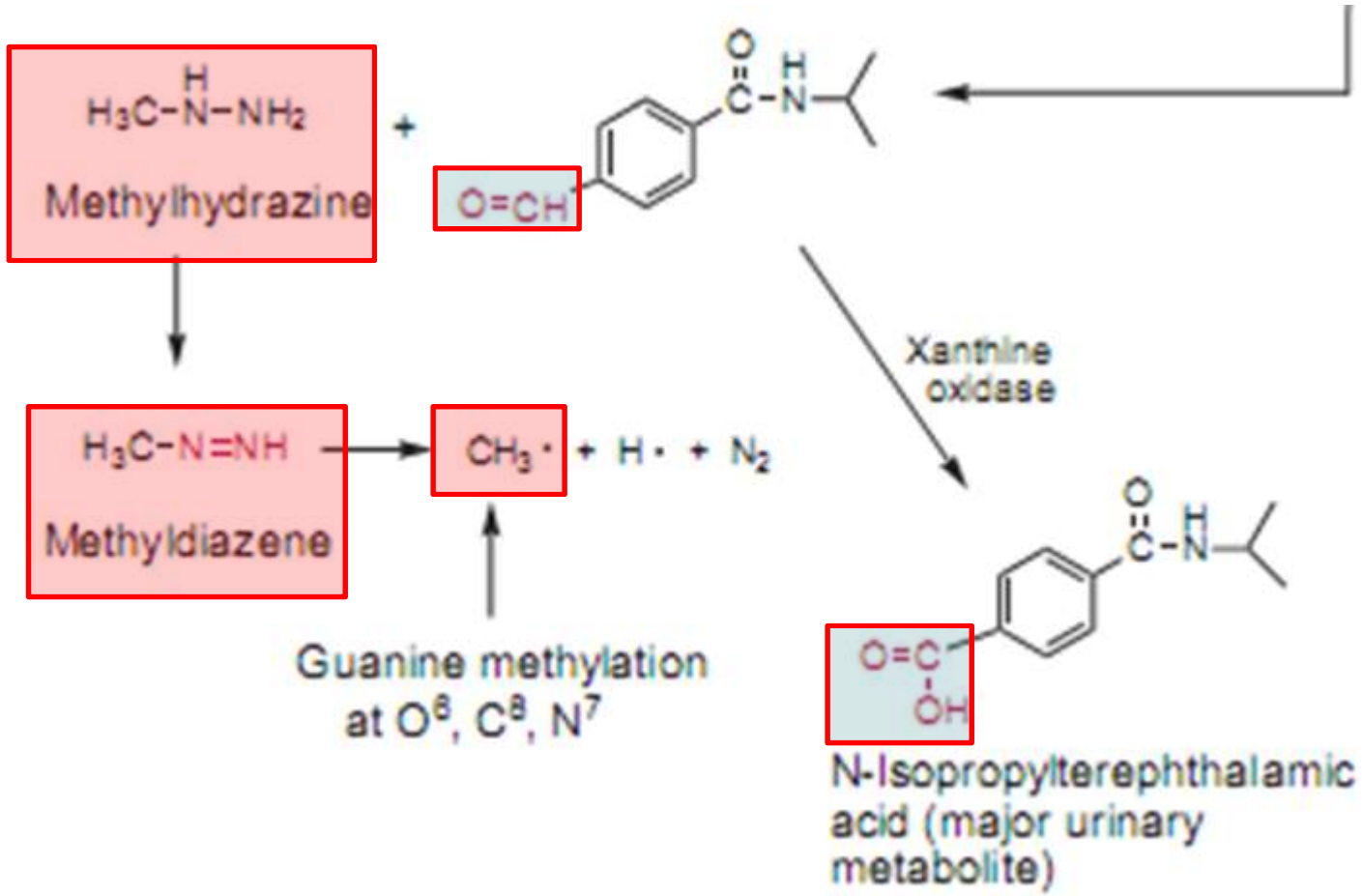
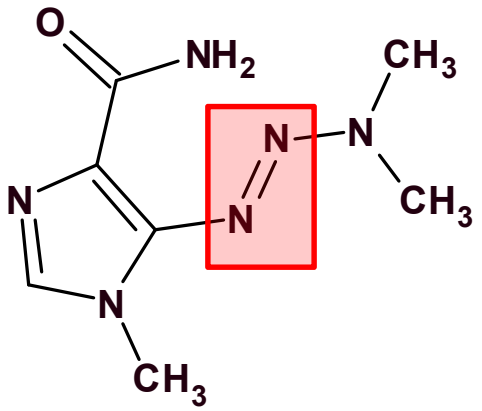


Figure 33.65 Procarbazine metabolism and mechanism of action.

I.3.c. DNA Alkylators: Triazene: Dacarbazine

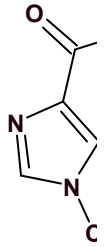
- Dacarbazine: DTIC®



- CYP450 related bio-activation:
- Metabolites:

✓ active metabolite: methyl carbocation

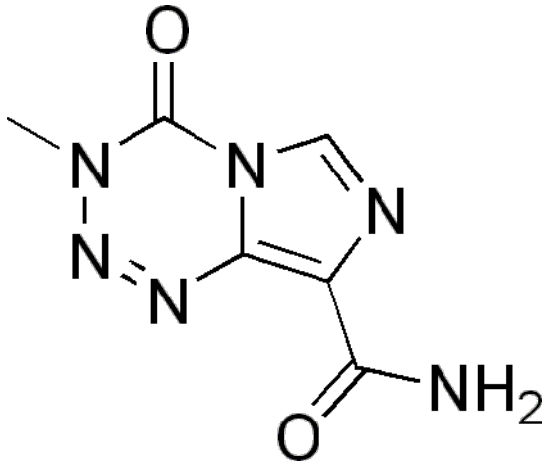
+ N_2 + diazomethane



- SAR
- MOA: Guanine (N7- or O6) methylation

I.3.d. DNA Alkylators:Tetrazine: Temozolomide

- Chemistry: imidazolotetrazine



- Bio-activation

  not related to CYP450:

  non-enzymatically produce MTIC
- SAR
- MOA: Guanine (N7- or O6-) alkylation

Bio-Activation of Dacarbazine (Triazene) & Temozolomide (Tetrazine)

- Follow the common pathways.

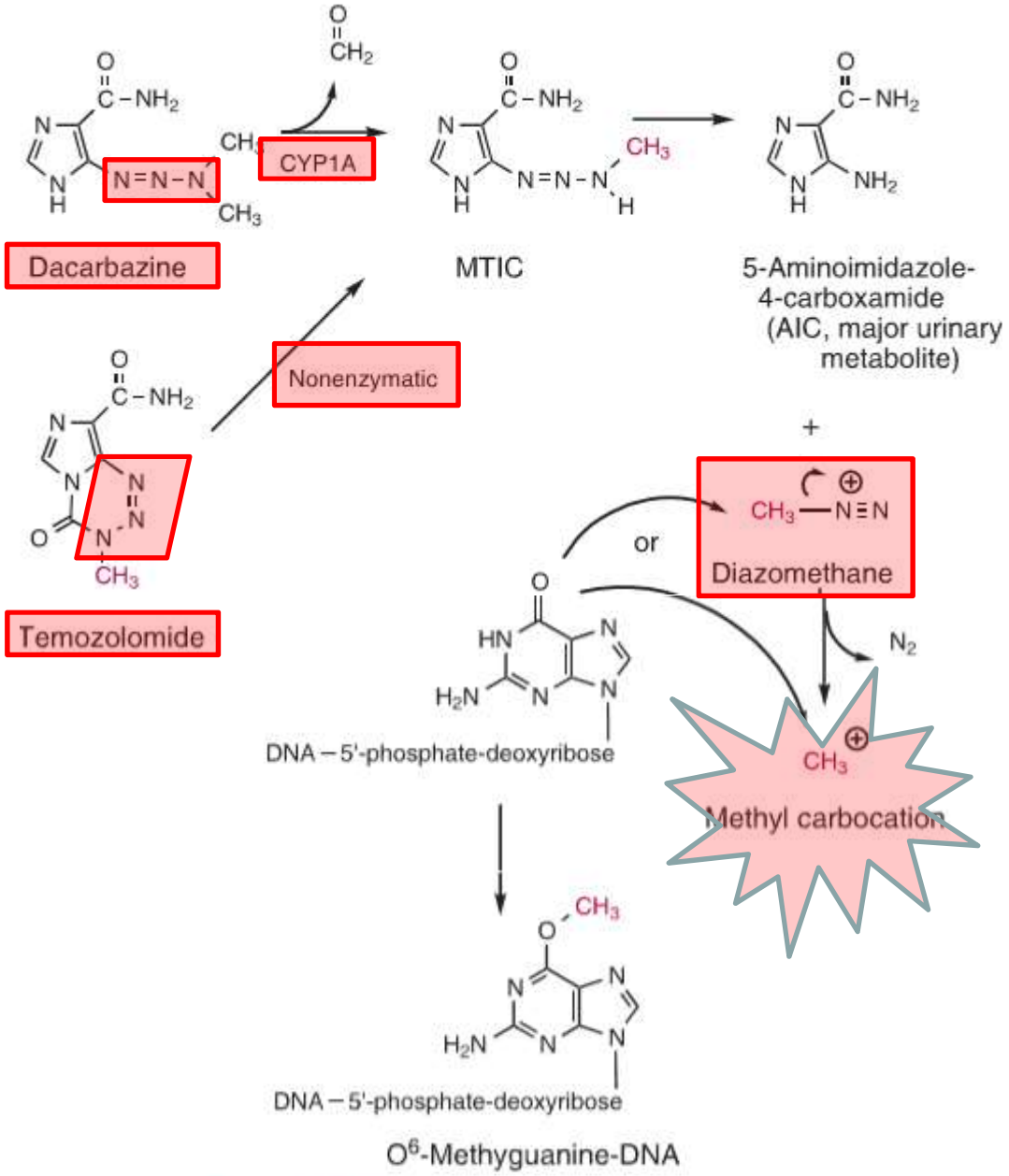


Figure 33.64 Metabolic activation of triazenes.

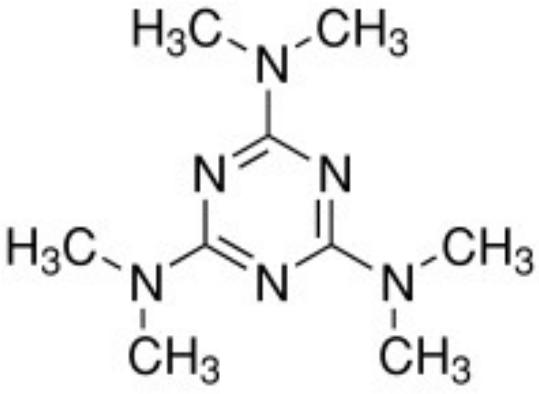
I.3.d. DNA Alkylators: Triazine: Altretamine

- SAR:

✓ chemistry:

6- membered triazine ring

- Prodrug: CYP-related bio-activation
- MOA: ?



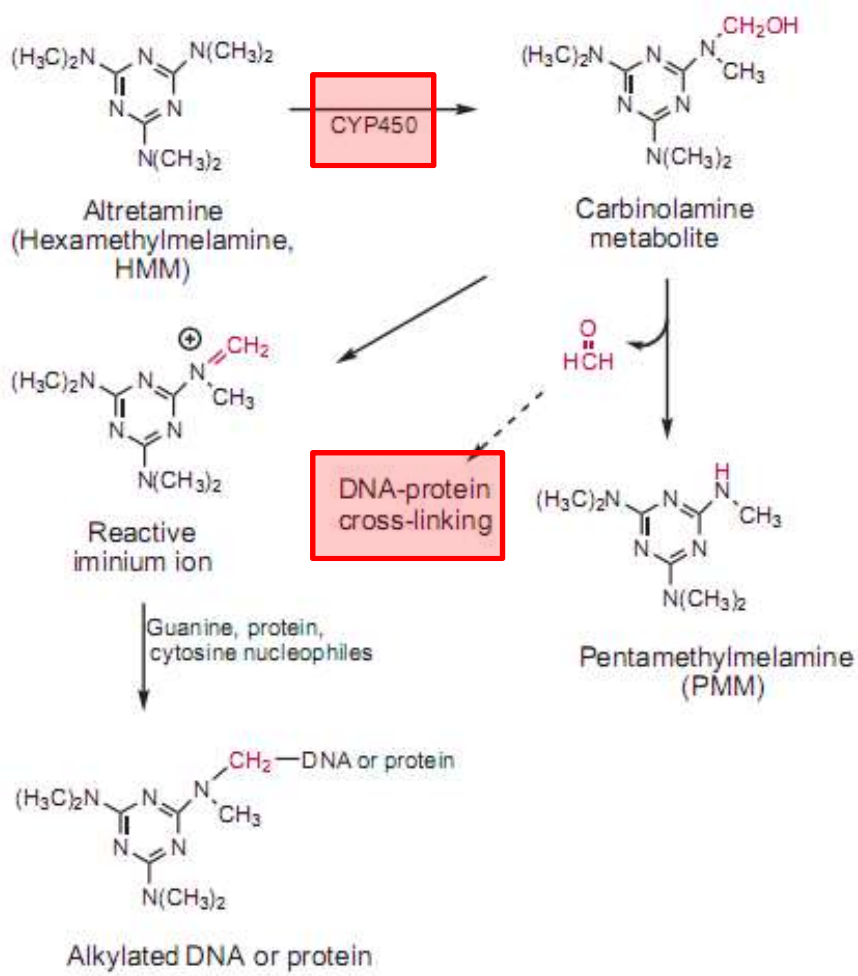
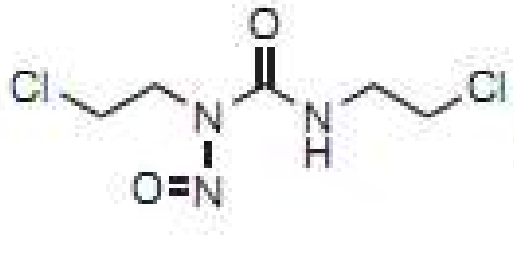


FIGURE 37.12 Altretamine metabolism and mechanism of action.

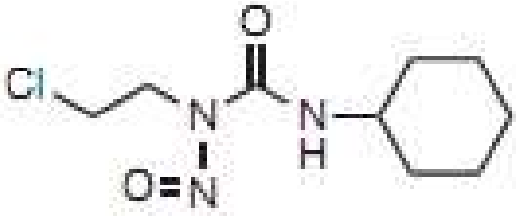
I.4. Nitroso-Ureas (NUs)

- SAR

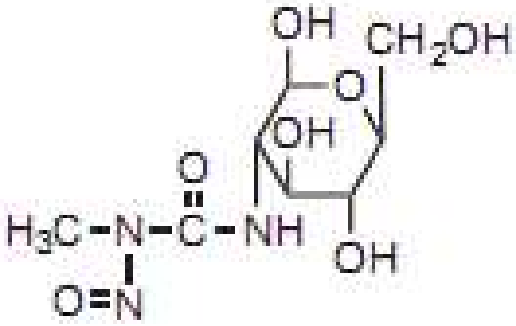
Nitrosoureas:



Carmustine
(BiCNU)



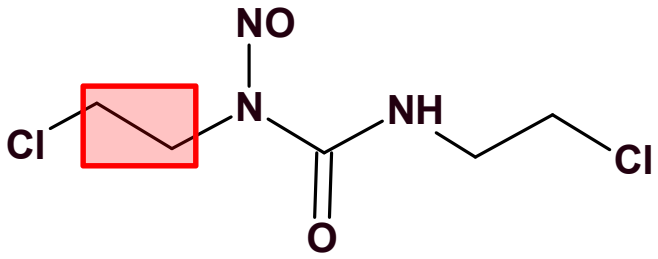
Lomustine
(CeeNU)



Streptozocin
(Zanosar)

I.4. Nitrosoureas (NUs): Carmustine

- Carmustine: BCNU®; BiCNU®



- Metabolites:

✓ active electrophiles: chloro/hydroxyl ethyl carbocation

✓ other metabolites: isocyanate + N_2

✓ theory of ~~vinyl-carbocation~~ as active metabolite is retracted

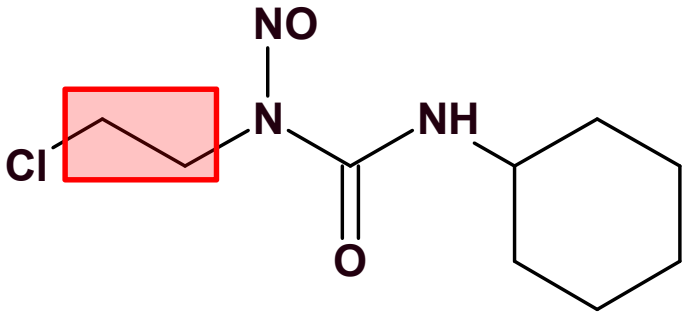
- MOA:

✓ DNA alkylation & DNA cross links by N_7, or O_6-Guanine

✓ also protein-(Lys) carbamylation

I.4. Nitrosoureas (NU): Lomustine

- Lomustine: CCNU®



- Crosses BBB
- Metabolites:

✓ active electrophiles: chloro/hydroxyl ethyl carbocation

✓ other metabolites: isocyanate + N_2

✓ theory of ~~vinyl-carbocation~~ as active metabolite is retracted

- MOA:

✓ DNA alkylation & DNA cross links

✓ also protein-(Lys) carbamylation

NU
Bio-activation

- Pathway A
- H- release from urea moiety.
- SAR

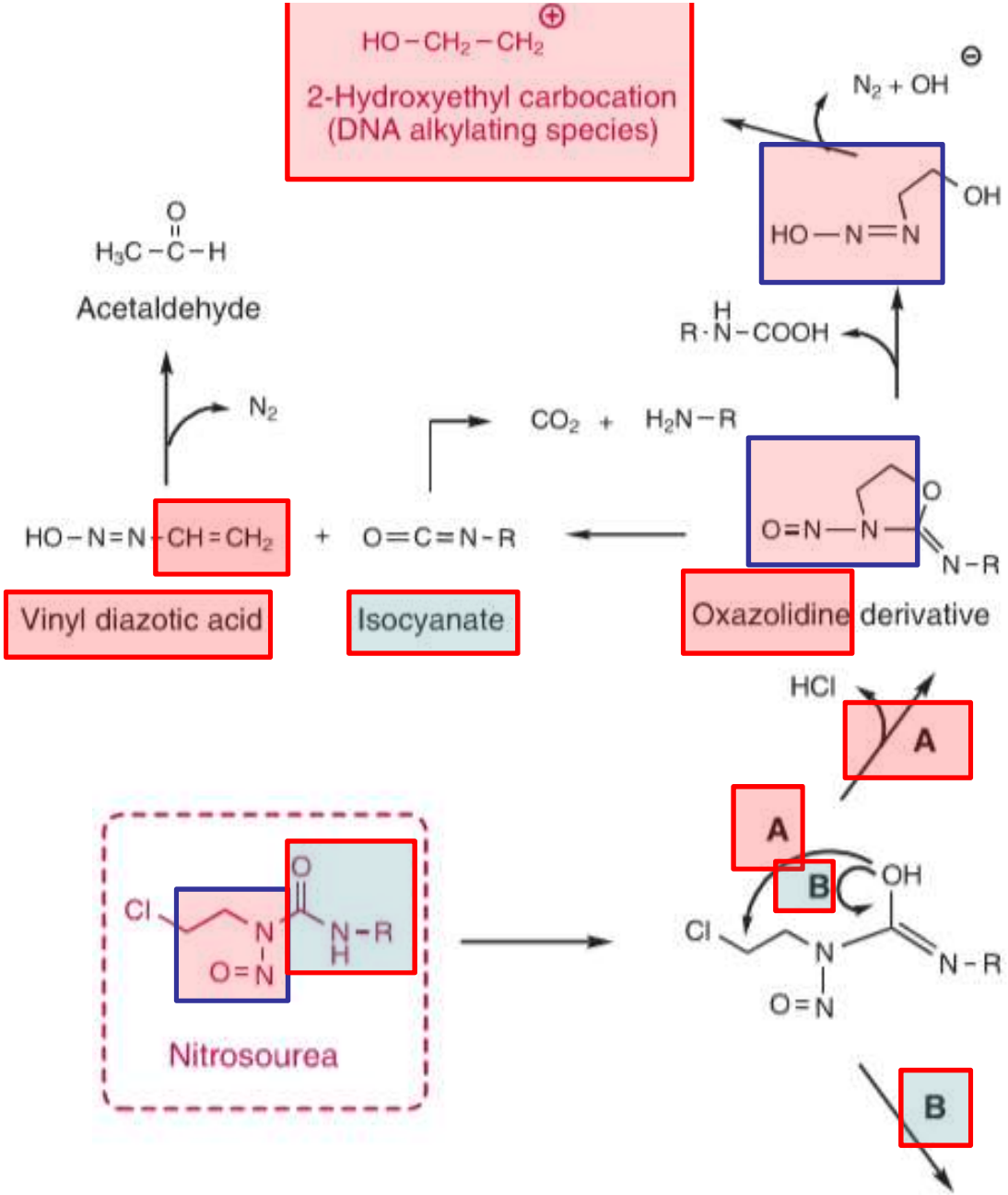


Figure 33.66 Nitrosourea decomposition to cytotoxic electrophiles.

NU
Bio-activation

- Pathway B

- H-release from urea moiety.

- SAR

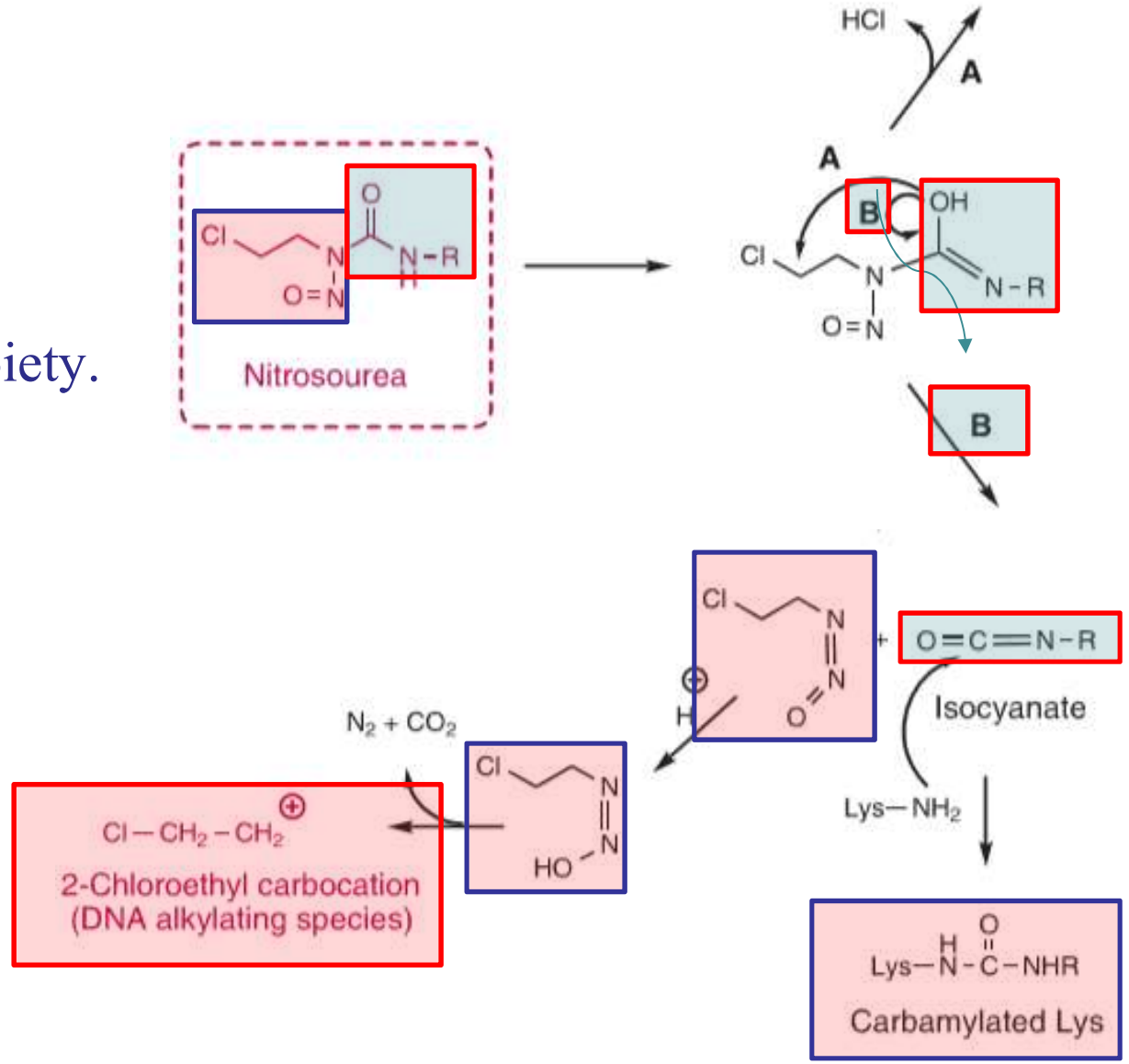


Figure 33.66 Nitrosourea decomposition to cytotoxic electrophiles.

DNA Cross Linking of NU Active Metabolites

- Follow G(N7)-alkylation.
- Follow C-cross linked DNA.
- Follow G(O6)-alkylation.

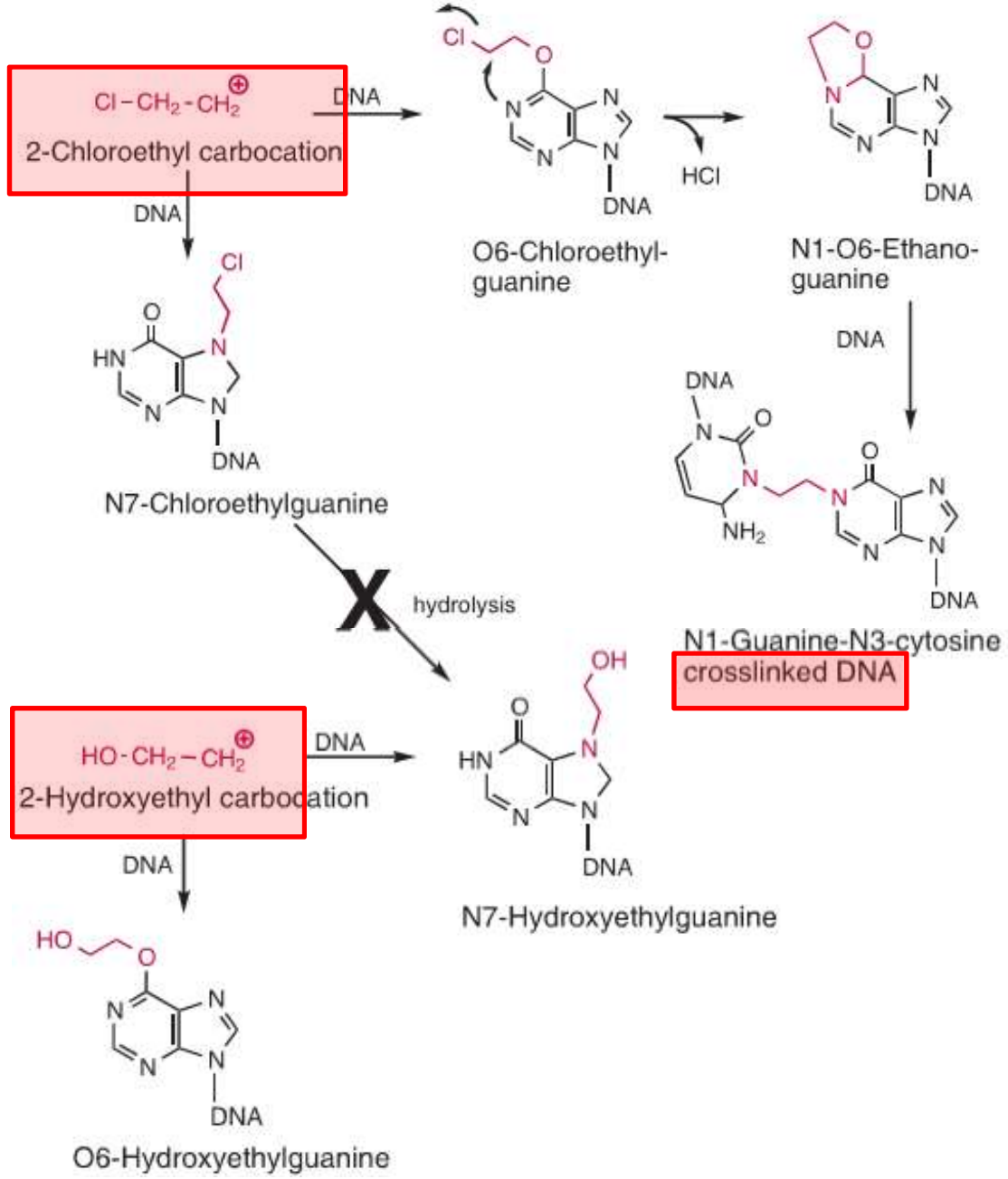
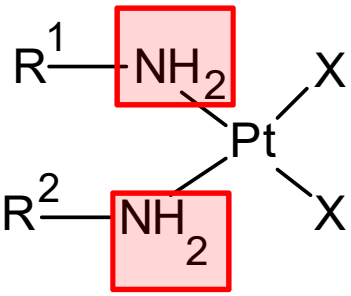


Figure 33.67 DNA cross-linking by 2-chloroethyl carbocation.

I.5. Organometallic Agents: Organo-Platinum Agents

- Chemistry:



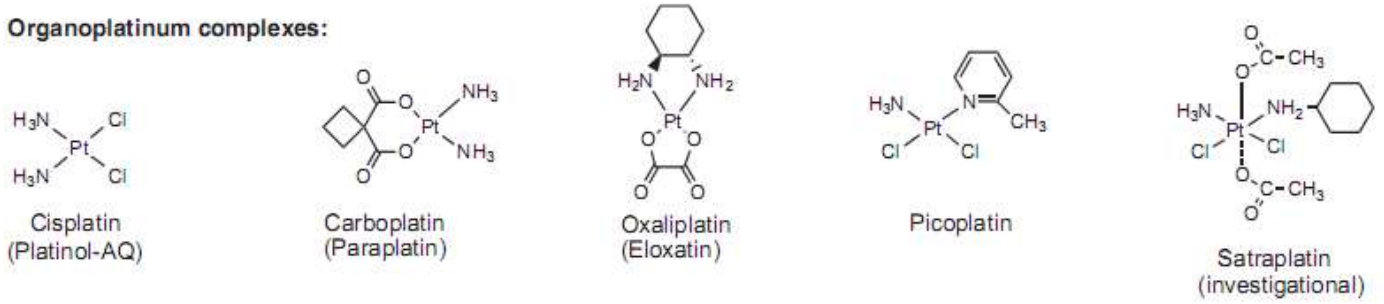
✓ Cisplatin: X = Cl; R^1 & R^2 = H

✓ Carboplatin: X = O-OCC(cyclobutyl)CO-O; R^1 & R^2 = H

✓ Oxaliplatin: X = O-CO-CO-O; R^1 & R^2 = trans(1,2-cyclohexyl)

✓ Satraplatin: X = ?; R^1 & R^2 = ?

- SAR:

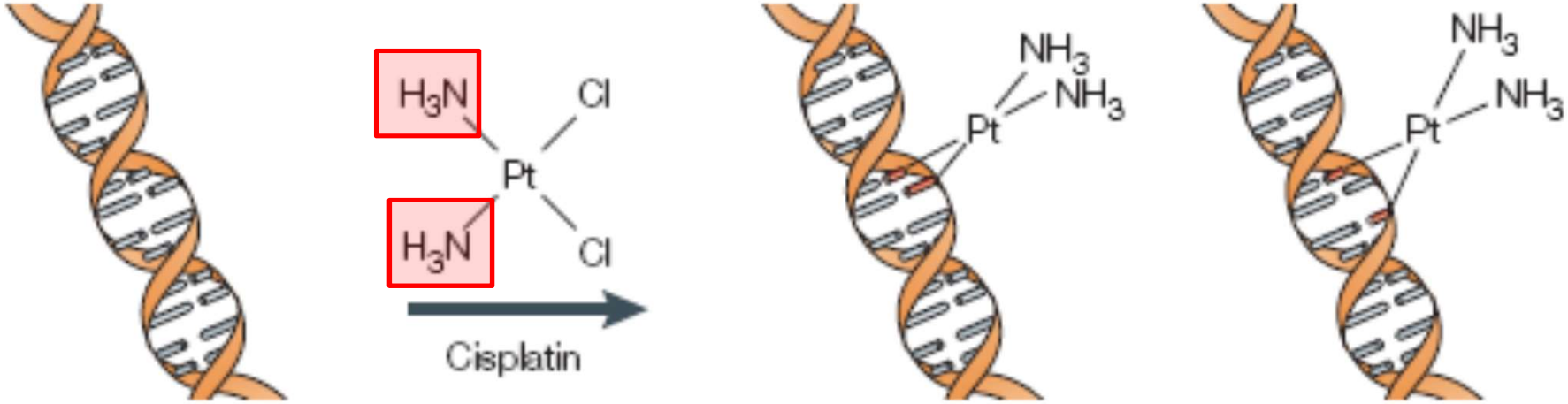


- MOA: cross electrophilic reaction with Guanine of DNA:

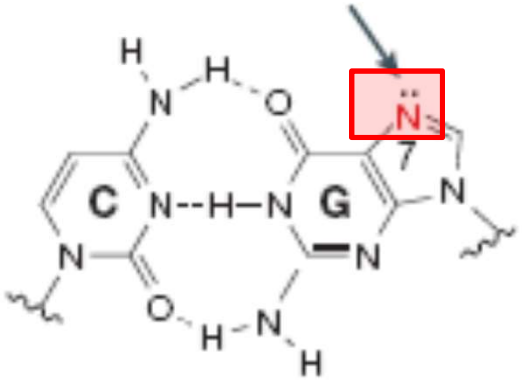
✓ link to N7-Guanine, adjacent Gs to provide G-X-G

✓ intrastrand > interstrand crosslink

DNA Cross Linking by Platin Complex



Guanine N^7 position



Replication inhibition
Transcription inhibition
Cell-cycle arrest
DNA repair
Cell death

DNA Interaction/Cross Link by Cis-Platin Complex

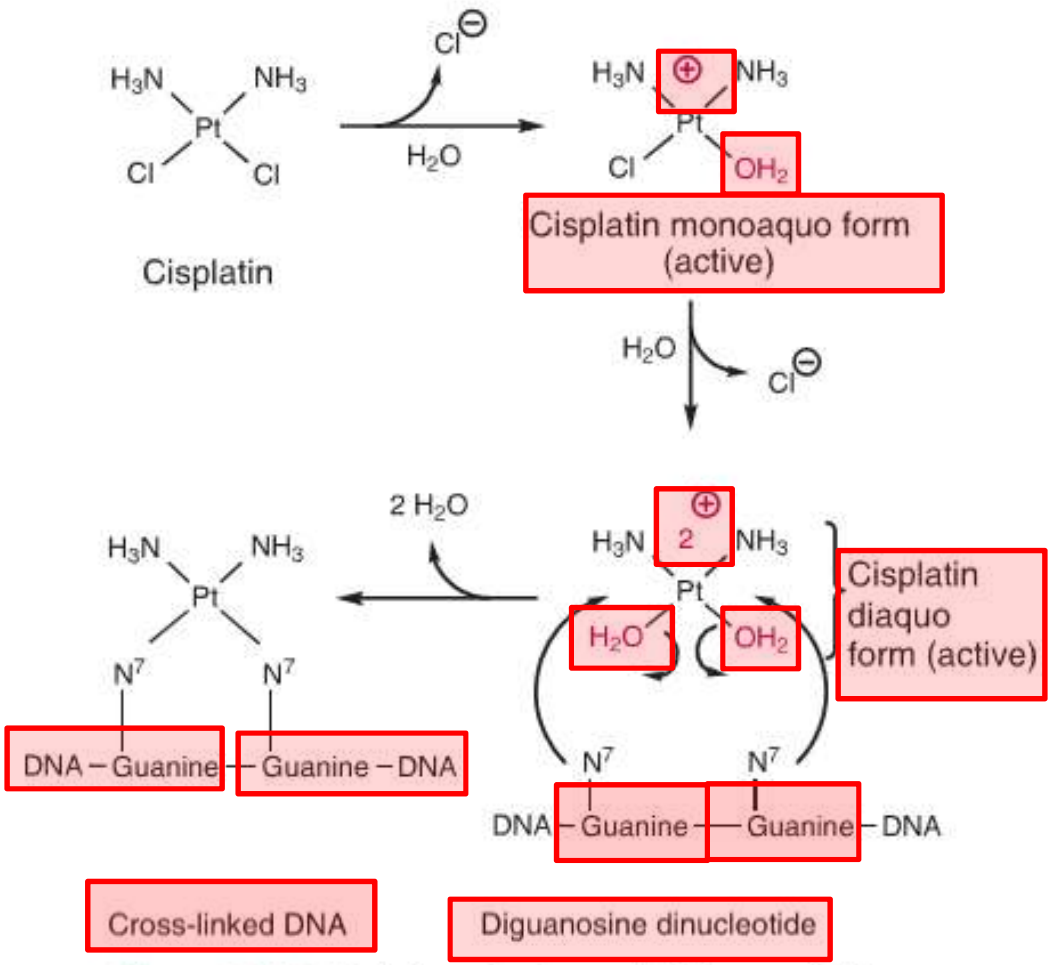
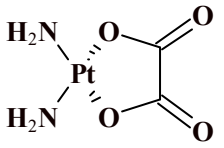


Figure 33.68 Cisplatin activation and DNA cross-linking.

Activation of Oxaliplatin

- Site of action: narrow minor groove



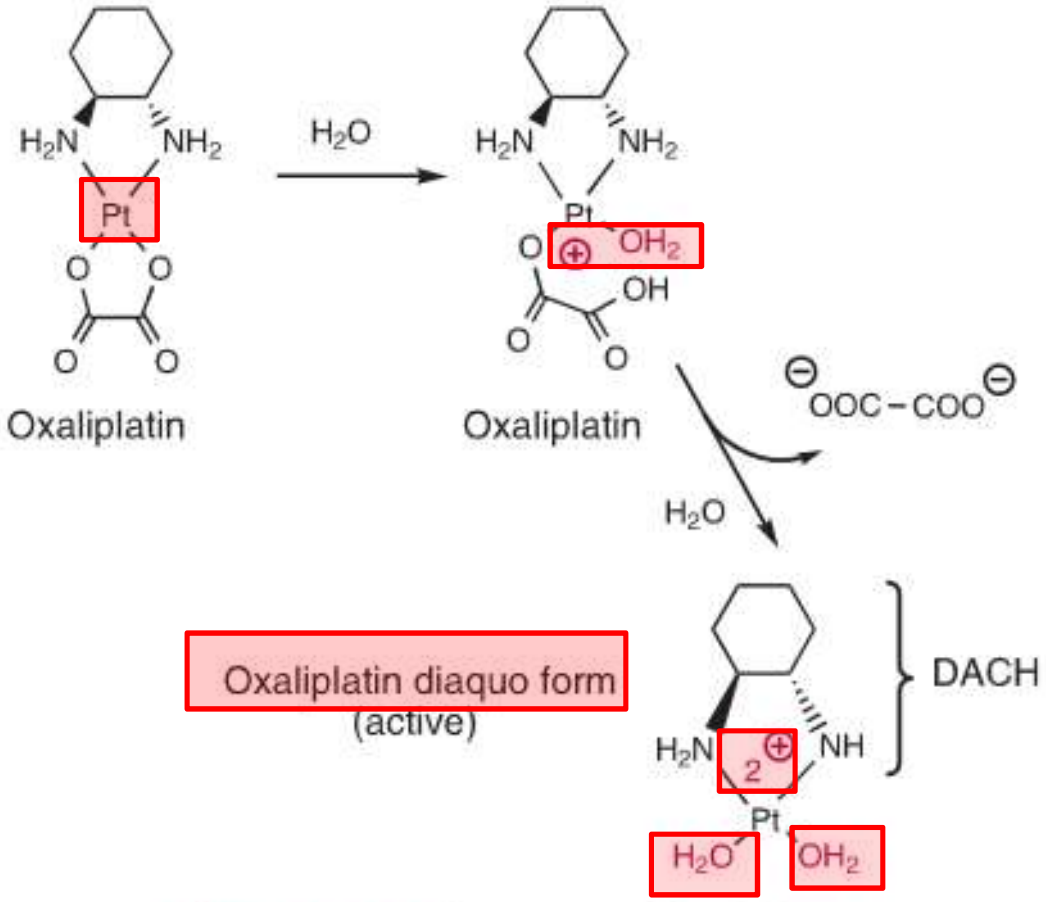


Figure 33.71 Activation of oxaliplatin.

Cisplatin Inactivation by Sulfur or Oxygen Groups: Thiols & Sulfate Anions: Amifostine & Thiosulfate Salt

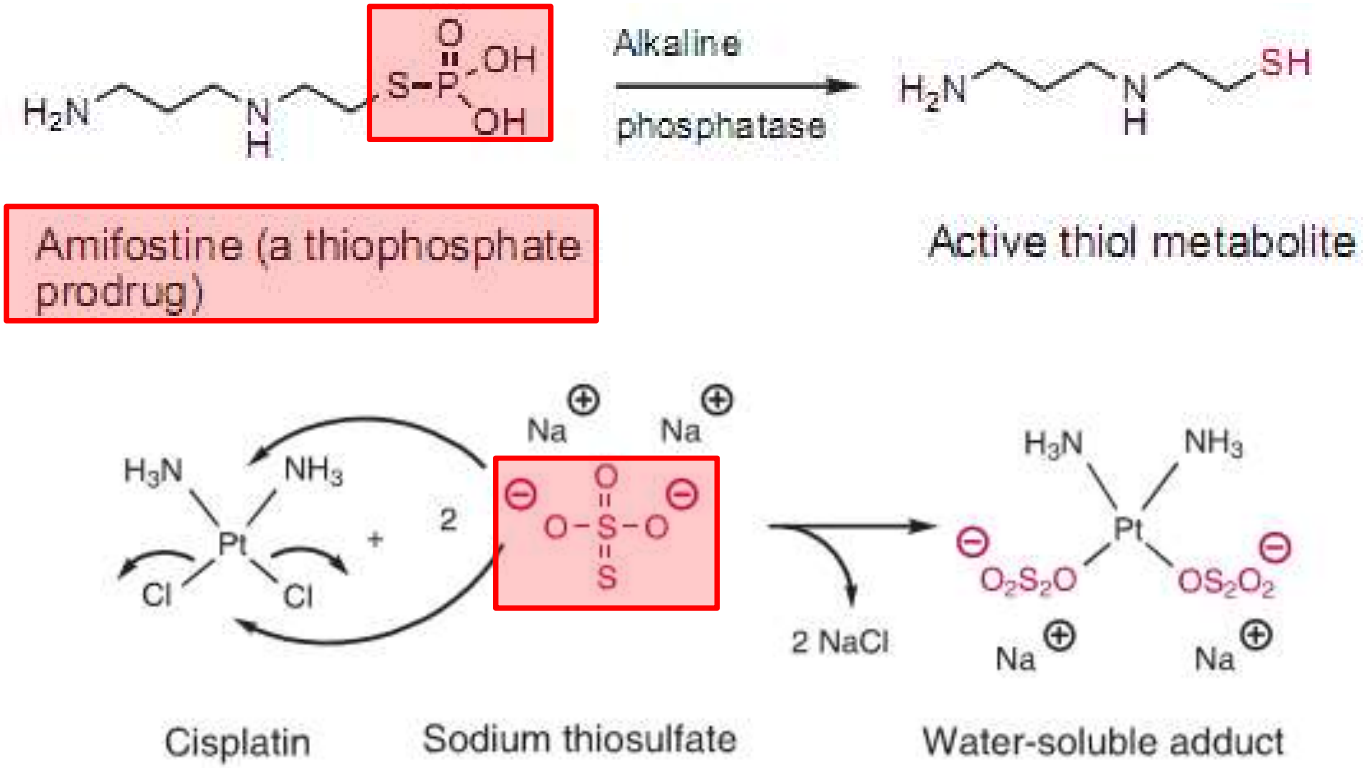


Figure 33.69 Cisplatin inactivation by sodium thiosulfate.

Amifostine: to Decrease Risk of Ototoxicity of Cisplatin

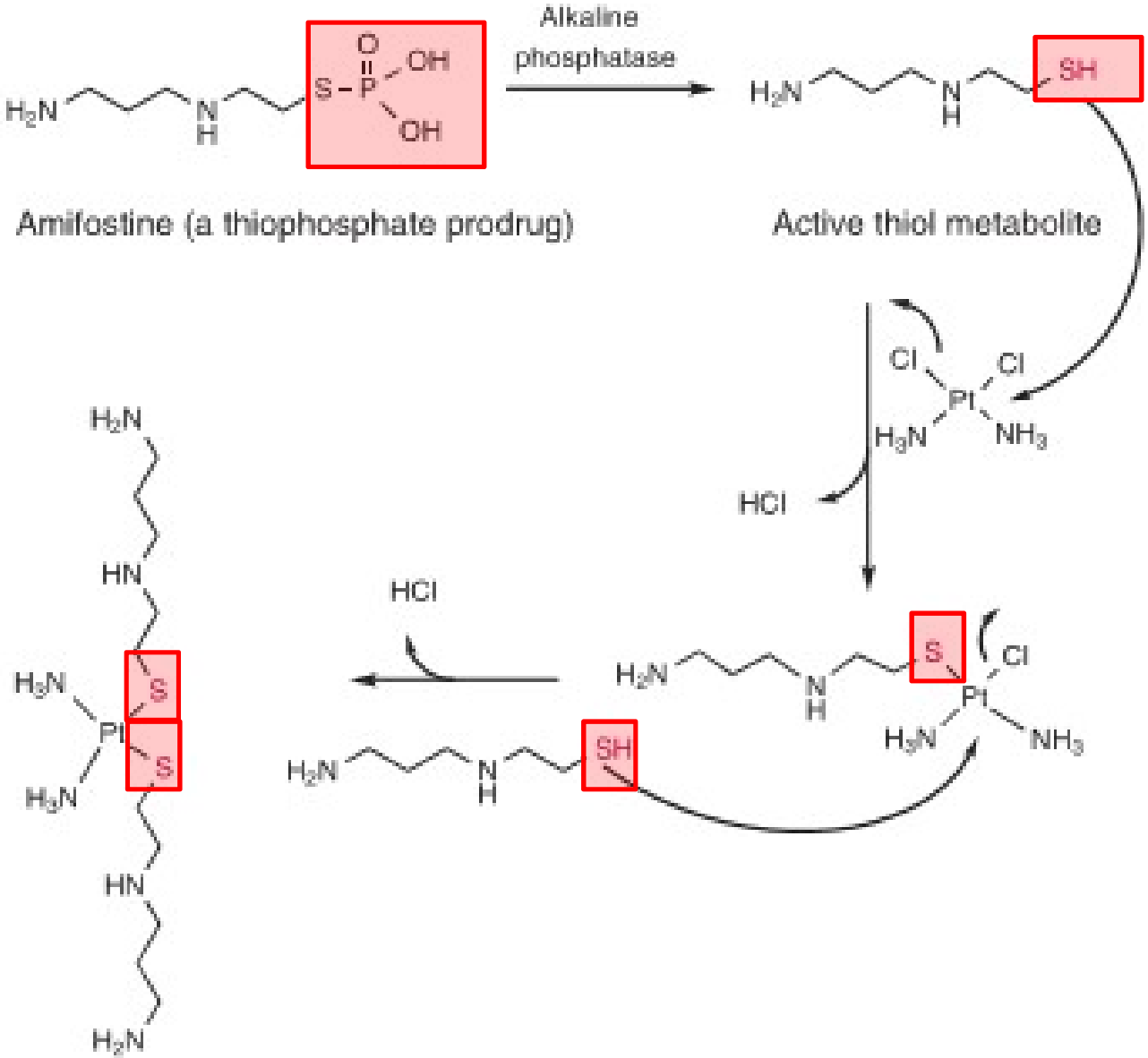


Figure 33.70 Amifostine activation and reaction with cisplatin.