Antineoplastic Agents

Antineoplastic agents describe the chemistry ,use ,metabolism and adverse effect profiles for the:

alkylating agent

antibiotic

natural products

antimetabolites and

Tyrosine kinase (TK) inhibitore

used in the ttt of cancer

Cancer defines as a grp. of diseases c¯c¯ by uncontrolled growth and the spread of abnormal cells that left untreated may lead to death.

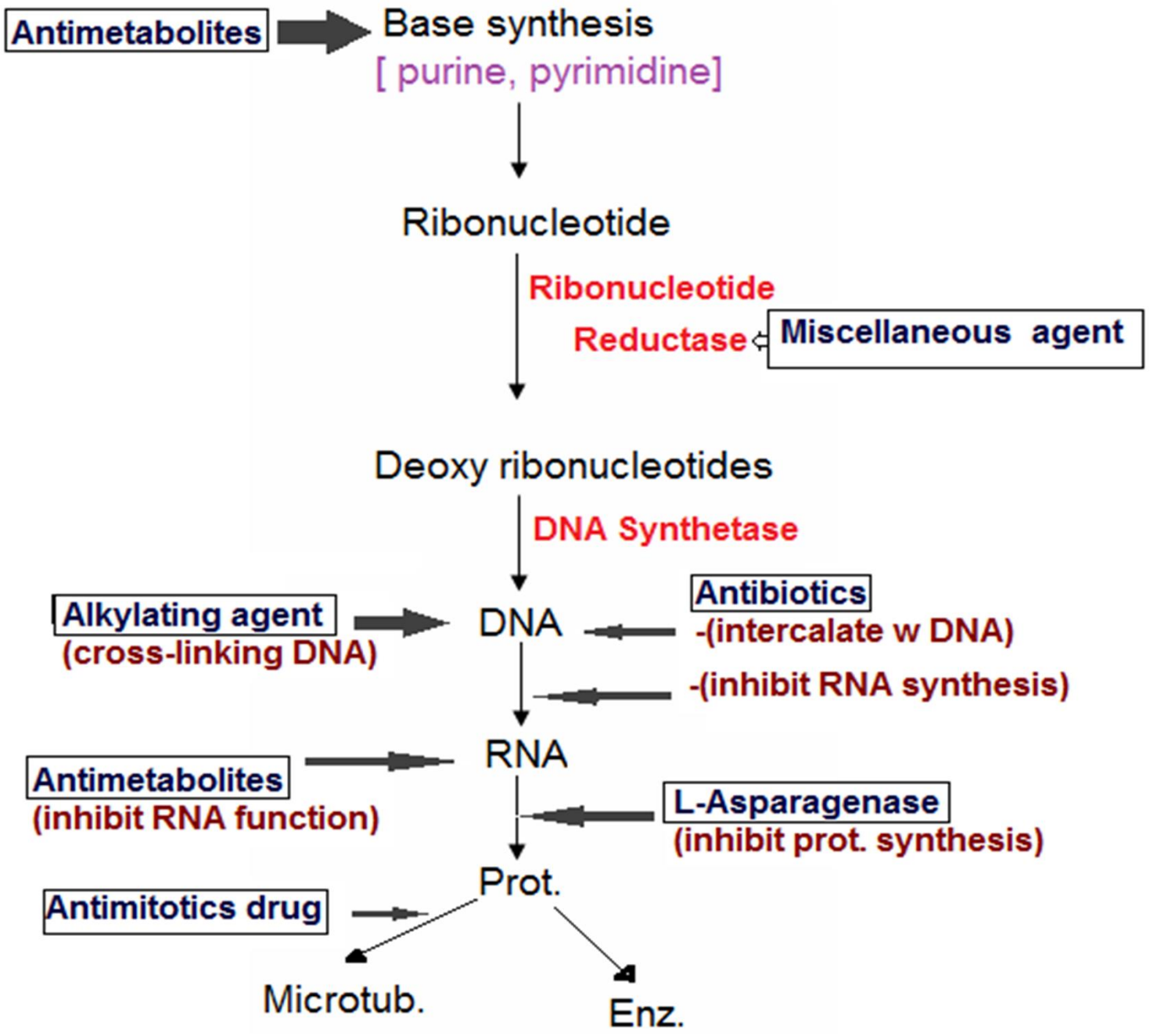
The term neoplasia ,w is the uncontrolled growth of new tissue, the product of w known as a tumor,& these tumors may be either malignant or benign.

Malignant tumors have the capability of invading surrounding tissues and moving to distant location in the body in a process known as metastasis; characteristic that benign tumors do not possess.

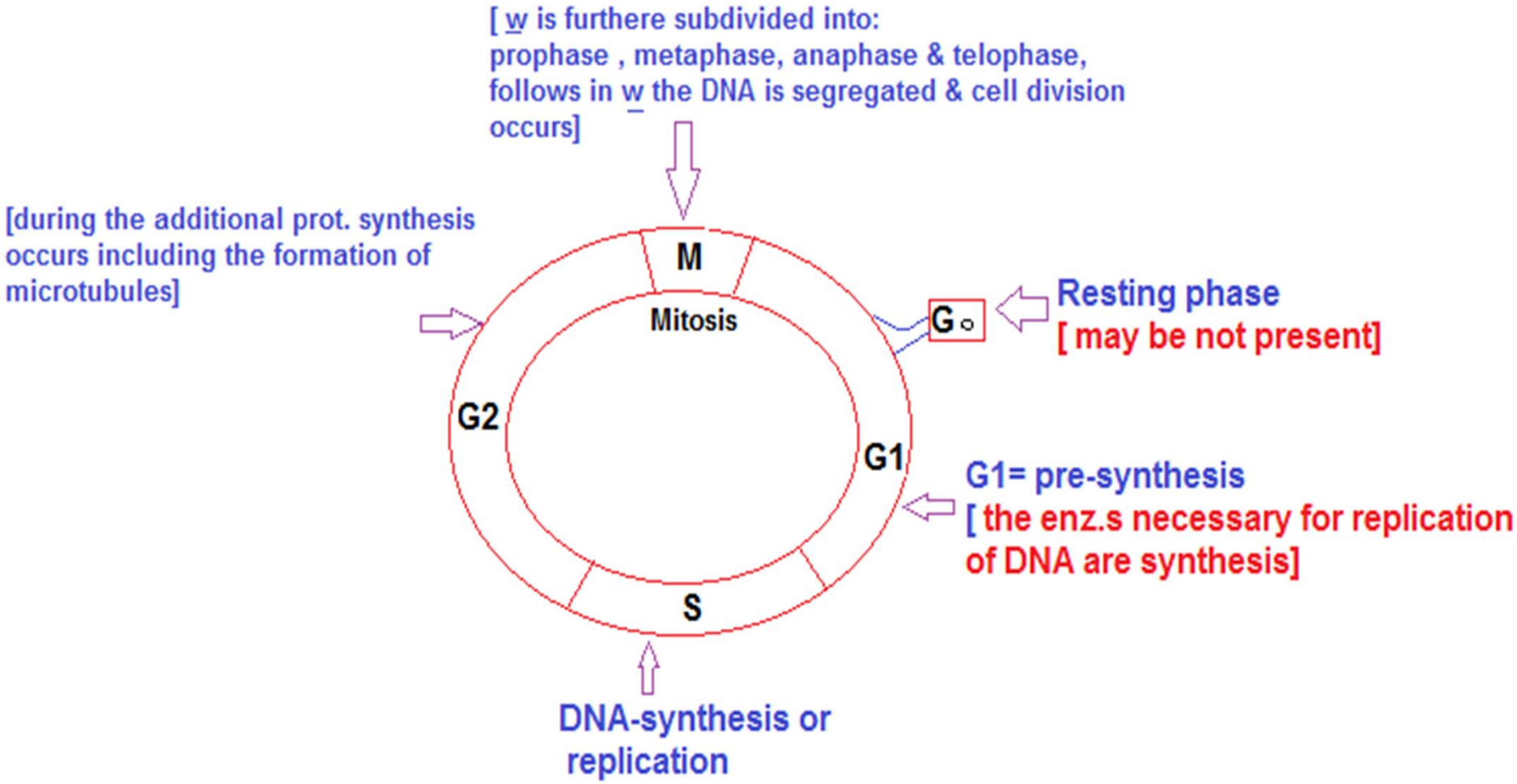
- *ttt of malignant tumors or cancer has generally involved initially surgical removal followed by radiation and/or chemotherapy if necessary*

The term *chemotherapy* refers to drugs that are used to kill cells and includes both antibiotics and agents used in ttt of cancer, but it used for anticancer agent that also called antineoplastic agents.

Traditional chemotherapy has been based on principle of selective toxicity, this has been dificult to achieve in the case of cancer cells b these cells utilize the biochemical pathways used by normal cells.


Antimetabolites
Base synthesis
[purine, pyrimidine]
Ribonucleotide
Ribonucleotide
Reductase
Miscellaneous agent
Deoxy ribonucleotides
DNA Synthetase
Alkylating agent
(cross-linking DNA)
DNA
Antibiotics
-(intercalate w DNA)
-(inhibit RNA synthesis)
RNA
Antimetabolites
(inhibit RNA function)
L-Asparagenase
(inhibit prot. synthesis)
Prot.
Antimitotics drug
Microtub.
Enz.

The process of cell division occur through a serious of phases that are known as a (cell cycle).



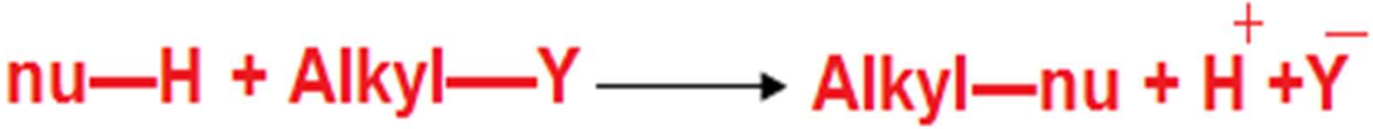
Note:

during the entire cycle,movement from one phase to the next is driven by prot.s known as cyclins & their associated cyclin-dependant kinase.

1- Alkylating agents :

r¯ class of drugs that r¯ capable of formation covalent bond w¯ important biomolecules[DNA, RNA & Prot.]

the major targets of drug action r¯ nucleophilic grp.s p¯ on DNA(especially 7-position of guanine),RNA & prot.that alkylated by substitution RX.[nu. Atom displaces a leaving grp. from alkylating agent]



Y = leaving grp.
nu-H = DNA,RNA,Prot.

Alkylating agents:

** r thought to be effective from G°--M & r⁻ therefore ,not specific cell-cycle.

** from those agents that possess two reactive functionalities both interstand & intrastrand cross-linking becomes possible.

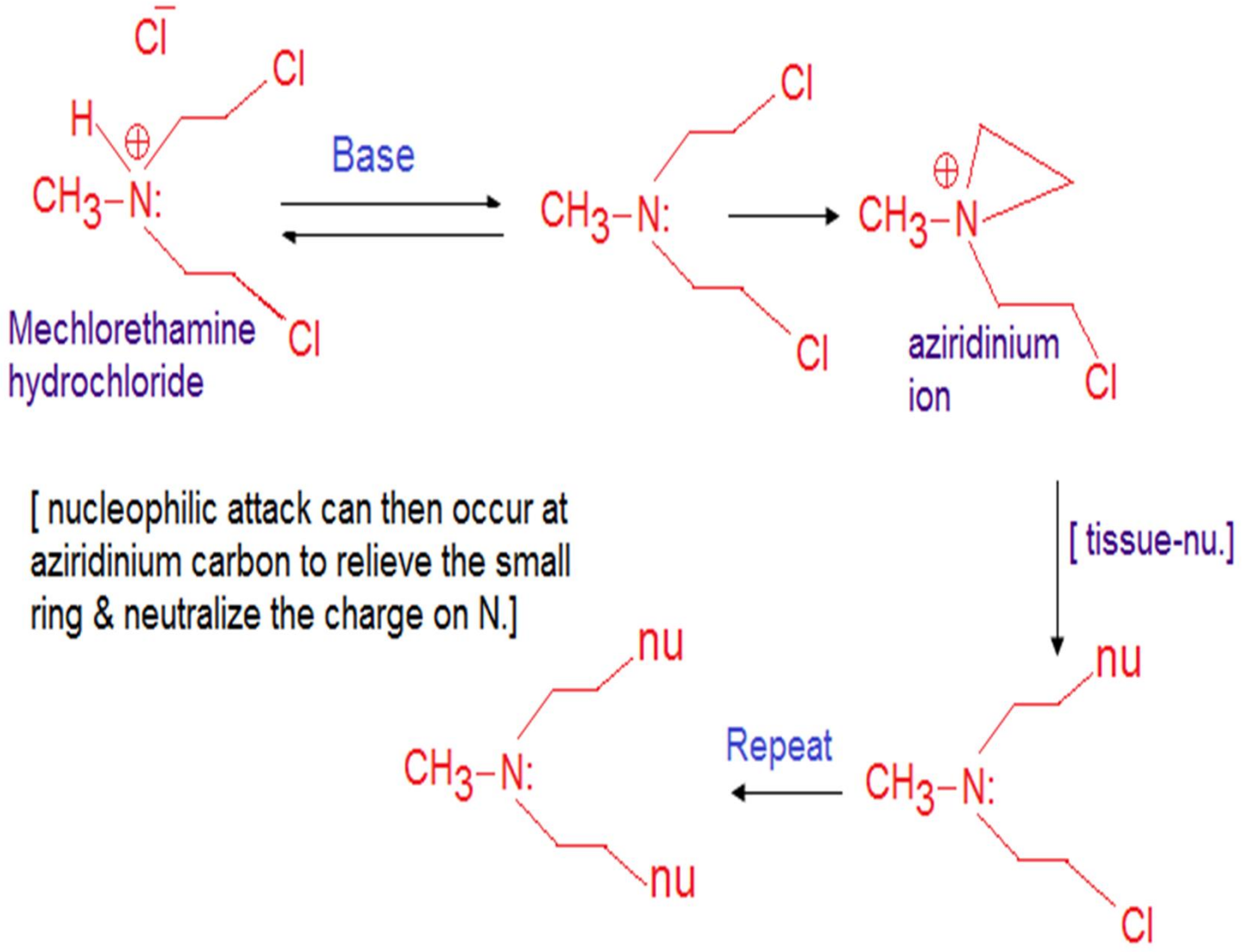
*** the RX rate depend on the nucleophilicity of the atom (S,N,O) w is greatly enhanced ,if the nucleophile is ionized[increase the reactiWn compared w⁻ unionized form]

O^- is more nucleophilic than OH.

H.W? can represent H_2O as nucleophilic ,although it present in greatest abandance in the body.

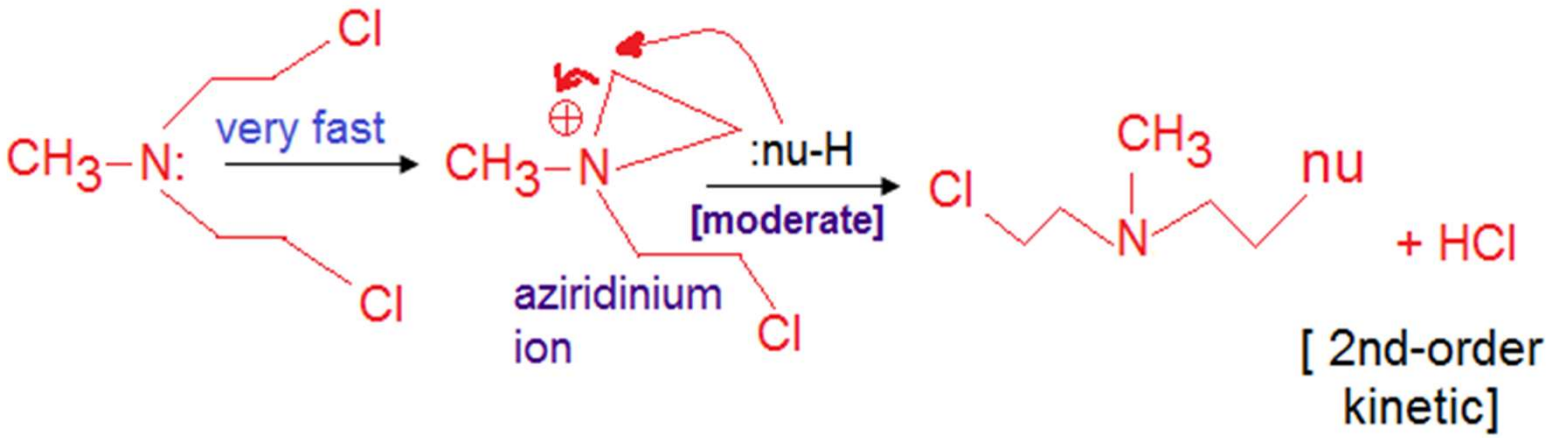
N-mustards:

∧ N-mustards r¯ cpds ∧at chemically simillar to sulfur mustard or mustard gas developed and used in warld war. ∧ term “mustard” comes from the similarity in the blisters produced by the cpd & those seen upon exposure to the oil of black mustard seeds.



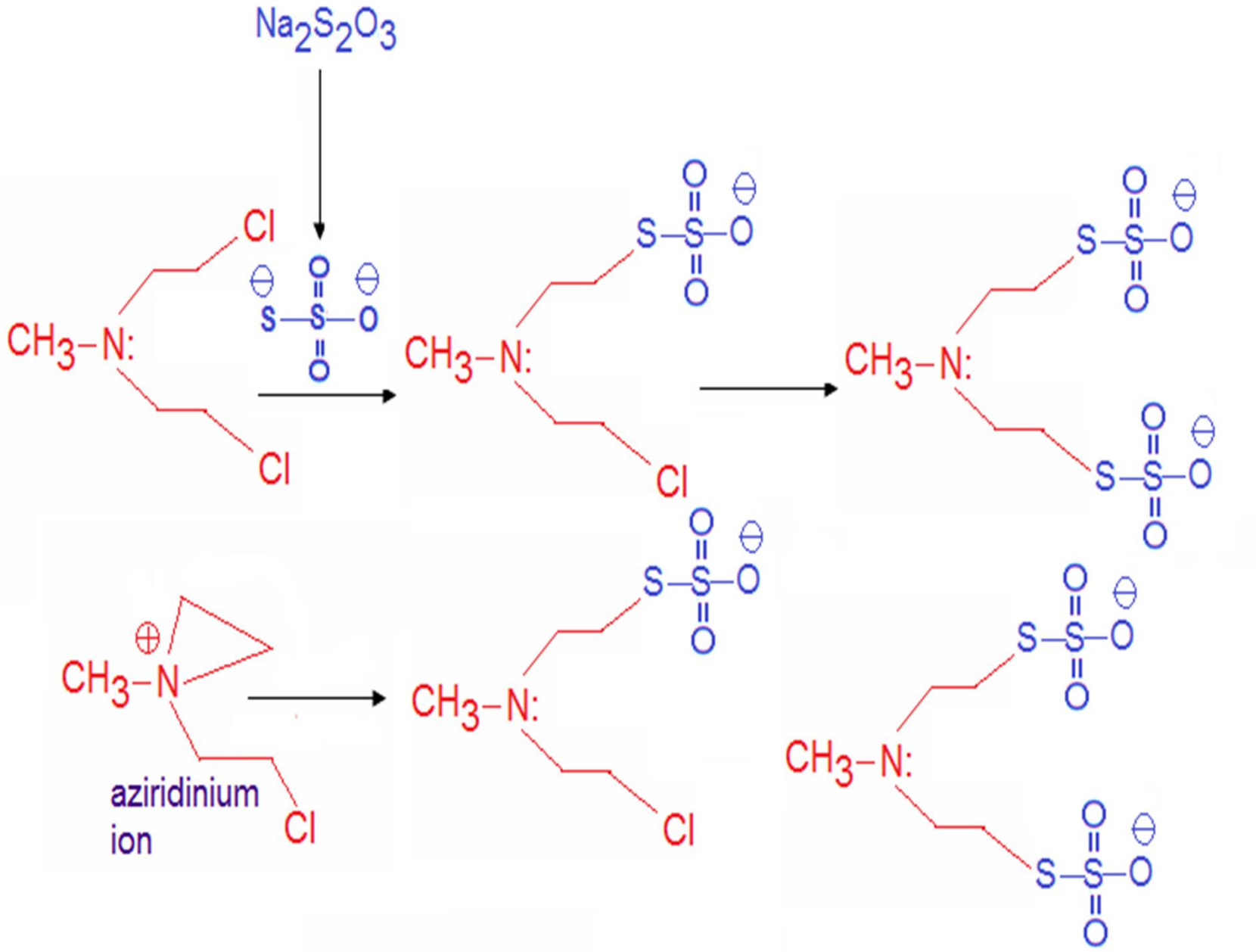
* di alkylating agent: 1:2

Mechlorethamine is highly reactive,in fact, too reactive and therefore non selective, making it unsuitable for oral admin.& necessitating direct injection into the tumor.



[reactive intermediat p- CH3]

In cases of extravasation (drug escapes from the tumor into the underlying tissue), the antidot $Na_2S_2O_3$
a strong nucleophile, may be administrated. It is capable of reacting w^- electrophilic sites on the mustard, and once RX has occurred, the resulting adduct has increased water solubility & may be readily eliminated.

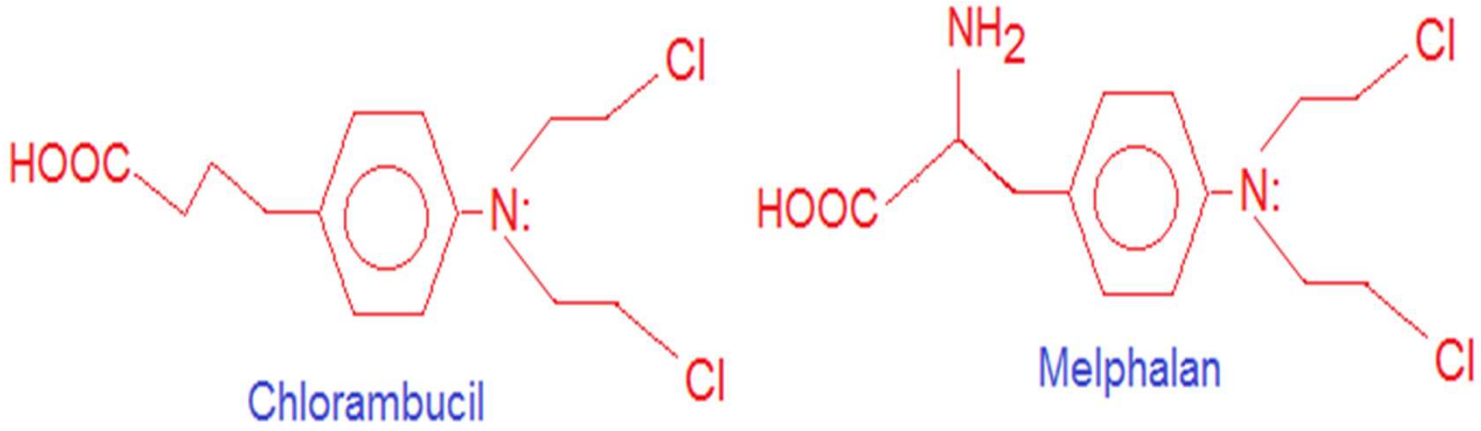

Na2S2O3
Cl
CH3–N:
Cl
S–S–O
CH3–N:
Cl
S–S–O
S–S–O
CH3–N:
S–S–O
CH3–N
aziridinium
ion
Cl
S–S–O
CH3–N:
Cl
S–S–O
S–S–O
CH3–N:
S–S–O

b the lack of selectivity of Mechlorethamine lead to:-

attempts to improve on the agents by reduce the reactivity by reducing the nucleophilicity of N, thereby slowing aziridinium cation formation.

[by replacing weak donating grp. Me by e- withdrowing grp.(attachment N to phenyl ring).

Chlorambucil & Melphalan.

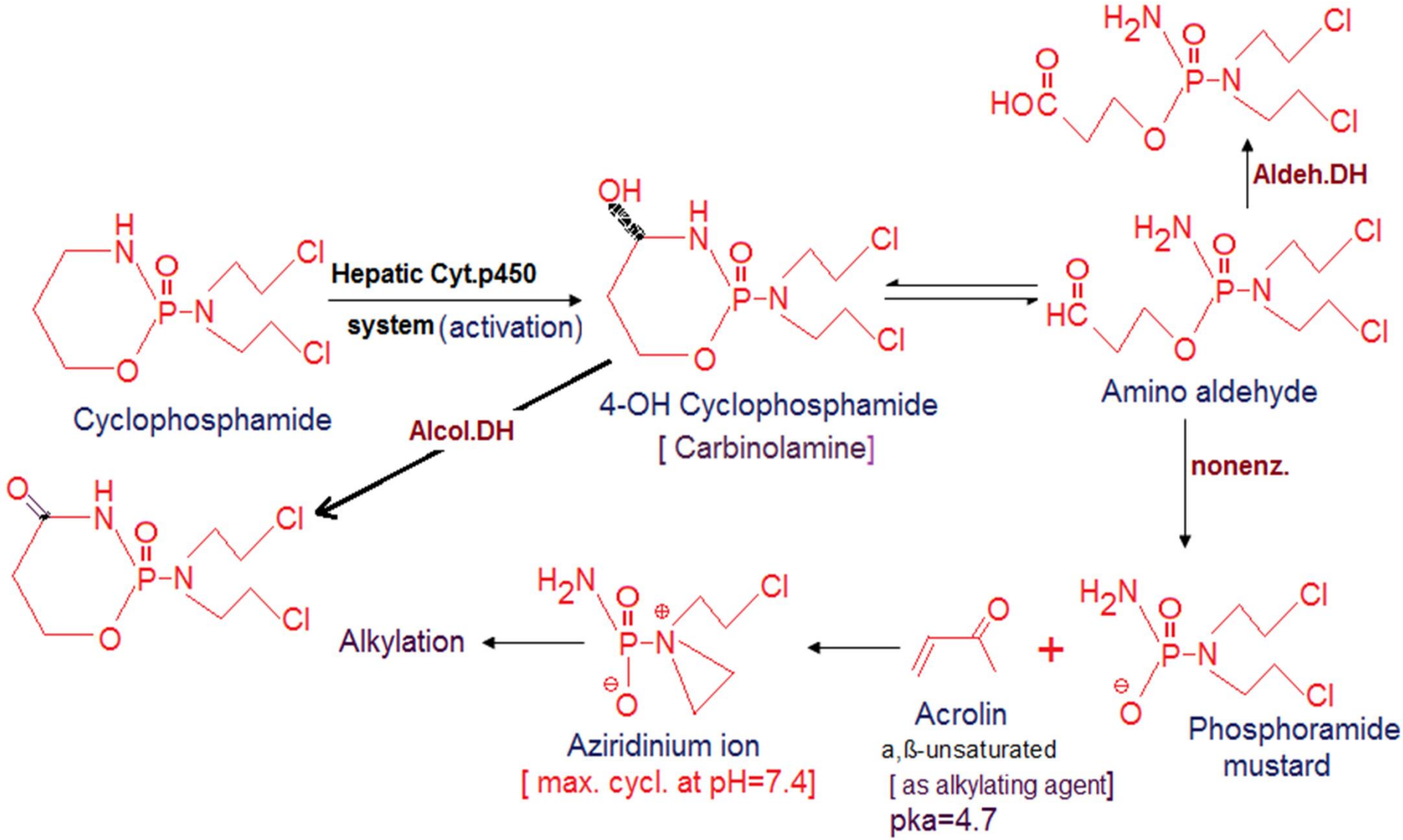


Reactivity was reduced such these cpds. Was administered orally.

In Melphalan, attachment mustard functionality to a phenylalanine moiety was not only an attempt to reduce reactivity but also an attempt to increase entry into cancer cell by utilization of carrier-mediated uptake.

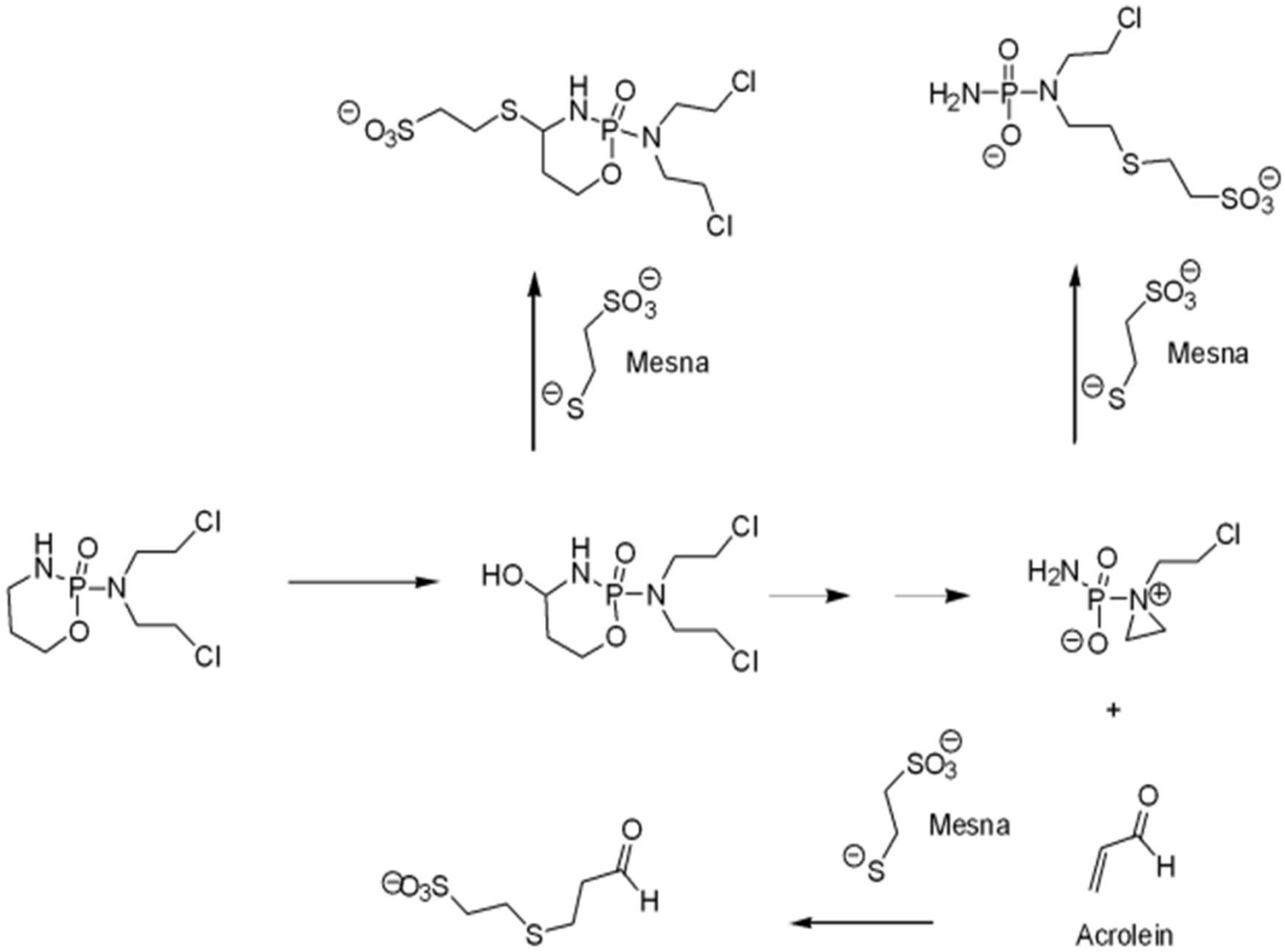
- but selectivity uptake by cancer cells has not been demonstrand

Attachment of more highly e-withdrowing functionalities was utilized in cyclophosphamide & Ifosfamide.



It believed the drug selectively activated in cancer cells b they were believed to contain high levels of phosphoramidase enz

To decrease the incidence of kidney & bladder toxicity,the –SH containing agent mesna may be administrated & functions to react with the electrophilic species that may be present in the kidney.How?



Scheme 10.6 • Detoxification of cyclophosphamide by mesna.

Sulfonic acid functionality serves to help concentrate the material in the urine, and neucleophilic sulfahydryl grp. May react w⁻ carbinolamine ,aziridine cation, chlorosubstituents of cyclophosphamide or via conjugate addition of acroline. this inactivation & detoxification may also be accomplished by other thiol containing proteins such as GSH. Increase levels of prot. May occur as cancer cell become resistant to these alkylating agent.

Ifosfamide contain similar functionality & also requires activation by liver CYP system. Although ʌ agents r̄ similar, ʌere r̄ differences in ʌ metabolism & activity of ʌ agents.

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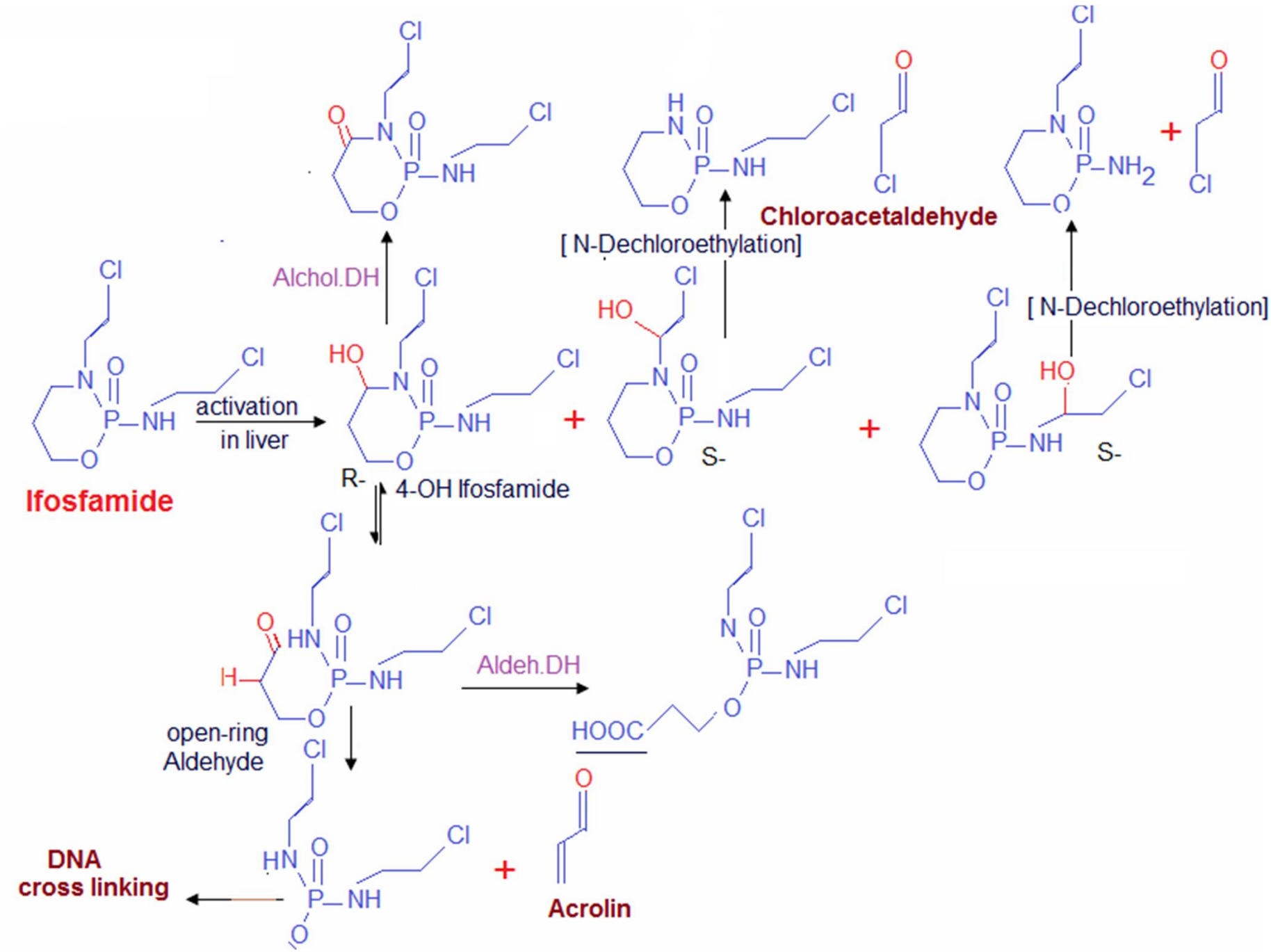
Ifosfamide
activation
in liver
Alchol.DH
R-
4-OH Ifosfamide
[N-Dechloroethylation]
Chloroacetaldehyde
S-
[N-Dechloroethylation]
S-
open-ring
Aldehyde
Aldeh.DH
DNA
cross linking
Acrolin