Pharmaceutical chemistry

Antineoplastic agents

Dr. Shahlaa Zuhair Abdul-Majeed

Mustansiriyah University College of Pharmacy

Definitions

- Cancer still remains one of the most feared diseases in the modern world.

- According to the World Health Organization, it affected one person in three and caused a quarter of all deaths in the developed world during the year 2000.

- After heart disease, it is the largest cause of death. Cancer cells are formed when normal cells lose the normal regulatory mechanisms that control growth and multiplication.

- They become ‘rogue cells’ and often lose the specialized characteristics that distinguish one type of cell from another (for example a liver cell from a blood cell). This is called a loss of differentiation .

- The term neoplasm means new growth and is a more accurate terminology for the disease.

Treatment of cancer

- Most traditional anticancer drugs work by disrupting the function of DNA and are classed as cytotoxic.
- Some act on DNA directly; others (antimetabolites) act indirectly by inhibiting the enzymes involved in DNA synthesis.
- Cancer chemotherapy is now entering a new era which can be described as molecular targeted therapeutics —highly selective agents which target specific molecular targets that are abnormal or overexpressed in the cancer cell.
- The use of antibodies and gene therapy is another area of research which shows huge potential.
- Knowledge of the cell cycle is important in chemotherapy. The genetic analysis of tumours in individual patients allows the early detection and identification of cancer, as well as identifying the best treatment to be used for aparticular individual.

Drug classes

1.Alkylating Agents:

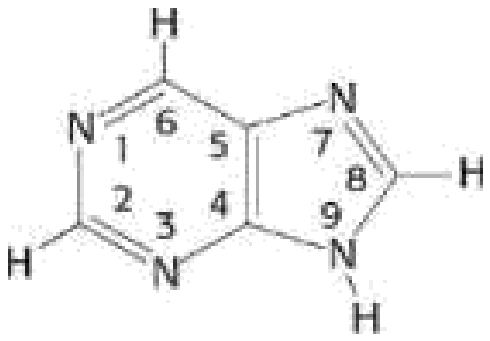
The alkylating agents are a class of drugs that are capable of forming covalent bonds with important biomolecules. The major targets of drug action are nucleophilic groups present on DNA (especially the 7-position of guanine); however, proteins and RNA among others may also be alkylated.

Alkylation of DNA is thought to lead to cell death, although the exact mechanism is uncertain. Potential mechanisms of cell death include activation of apoptosis caused by p53 activation and disruption of the template function of DNA.

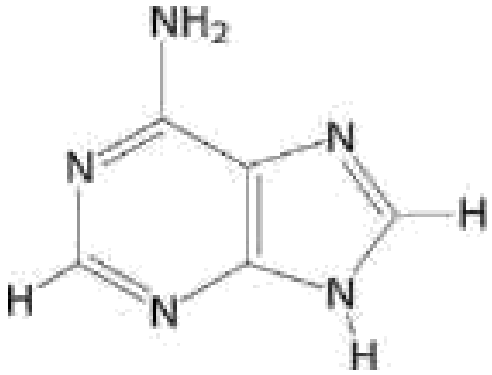
- The cancer cells have dysfunctional p53 so that even though the cell has been unable to replicate DNA error free, cell death via apoptosis does not occur.
- Cancer cells may become resistant to the effects of alkylating agents.
- There are several potential nucleophilic sites on DNA, which are susceptible to electrophilic attack by an alkylating agent (N-2, N-3, and N-7 of guanine, N-1, N-3, and N-7 of adenine, o-6 of thymine, N-3 of cytosine).
- The most important of these for many alkylating agents is the N-7 position of guanine whose nucleophilicity may be enhanced by adjacent guanine residues.

Heterocyclic nitrogen bases

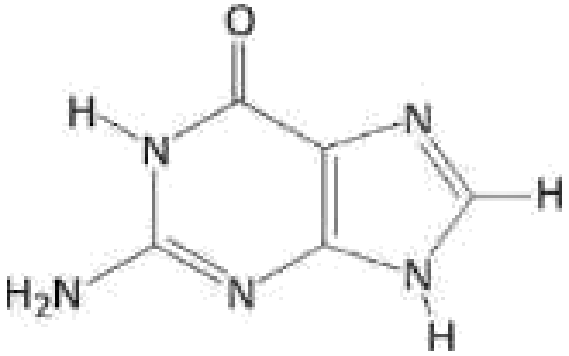
PURINES



Purine

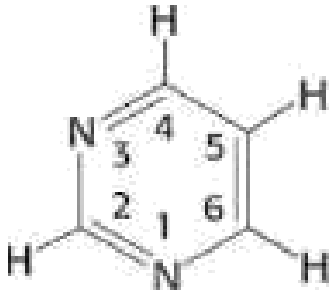


Adenine

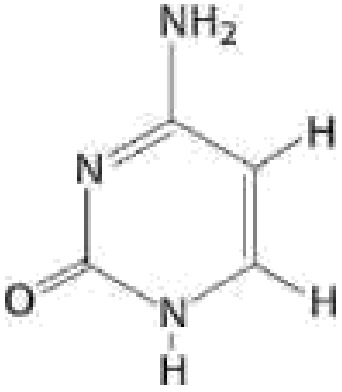


Guanine

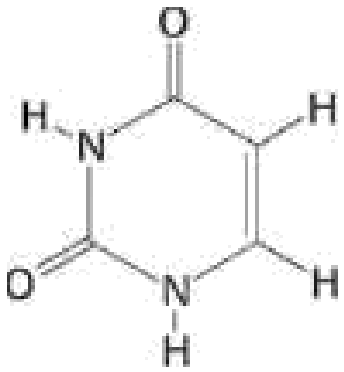
PYRIMIDINES



Pyrimidine

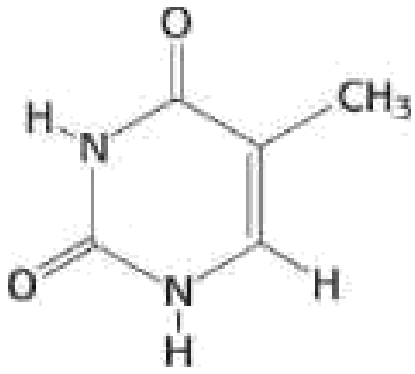


Cytosine



Uracil

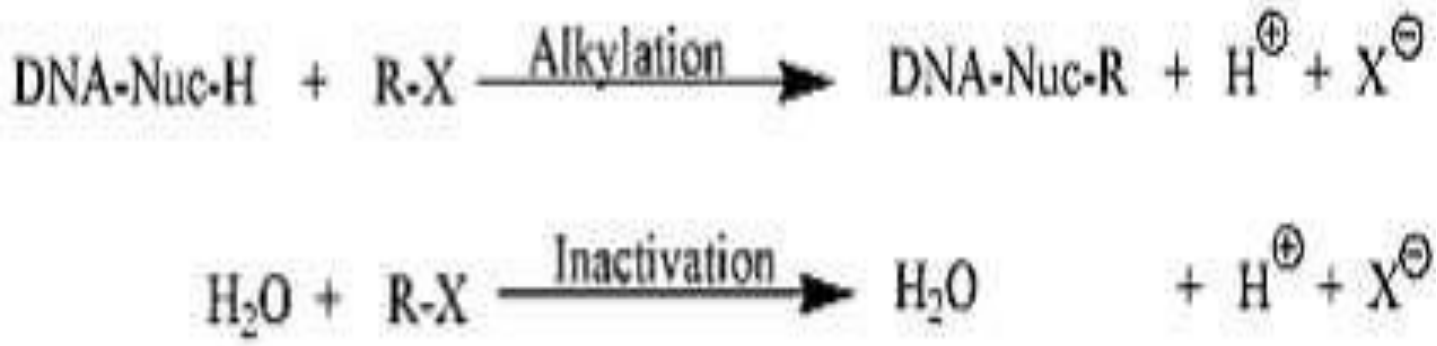
RNA

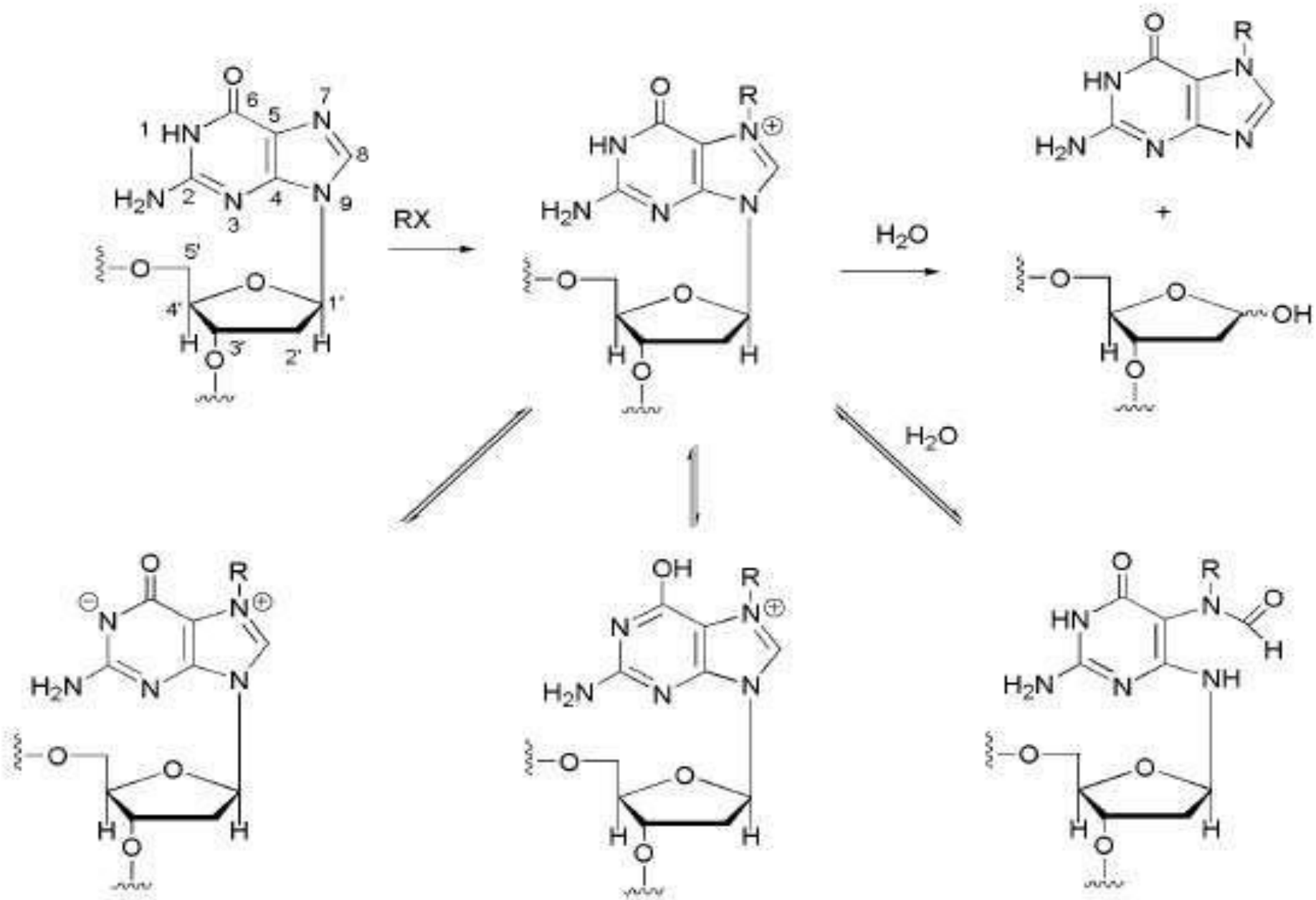


Thymine

DNA

- The general mechanism for alkylation involves nucleophilic attack by –N=, -NH_2, -OH, -O-PO_3H of DNA and RNA, while additional nucleophiles (-SH, COOH, etc.) present on proteins may also react.



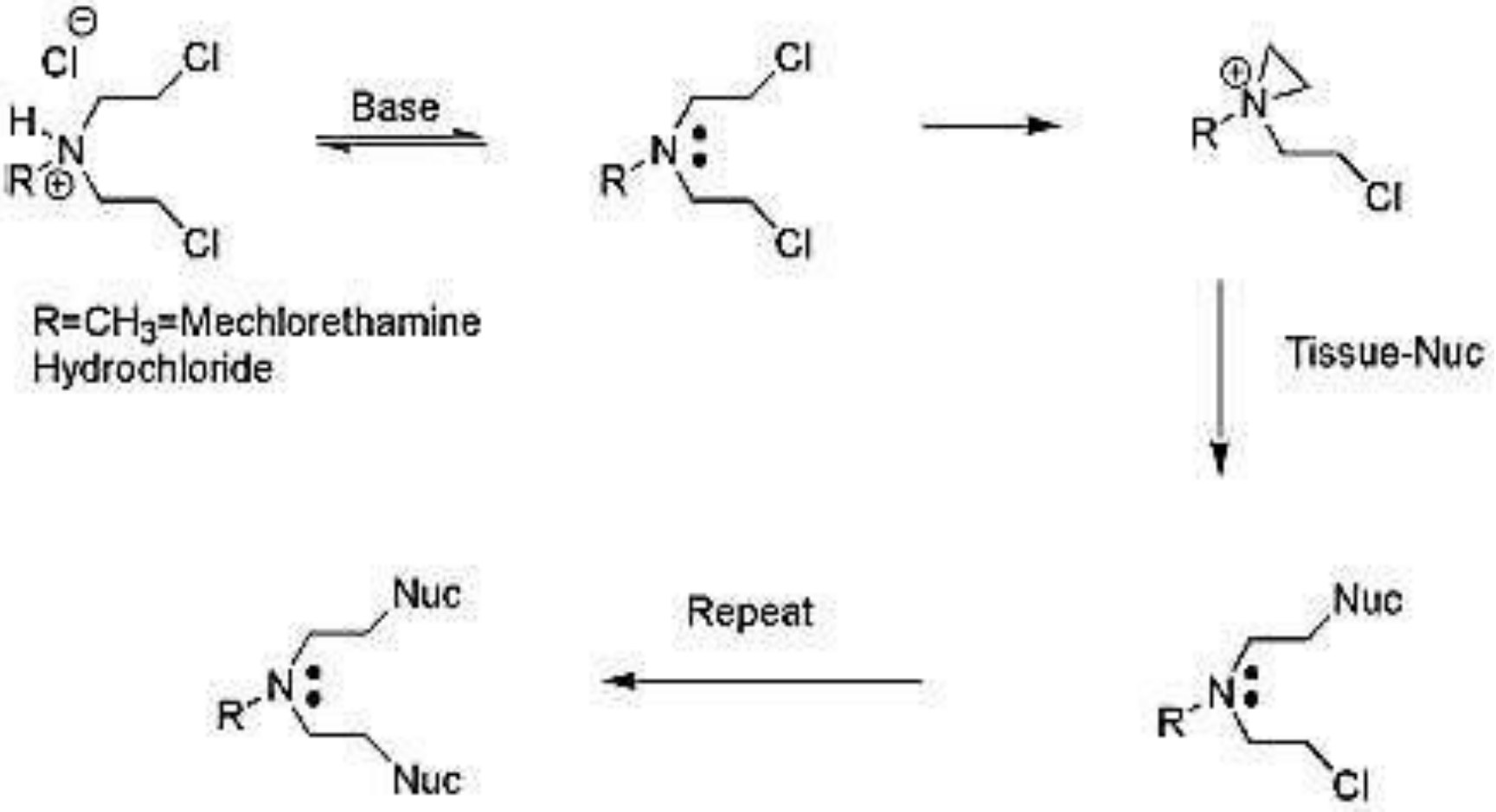


Scheme 10.1 • Alkylation of guanine N-7 and subsequent depurination of DNA.

Nitrogen mustards

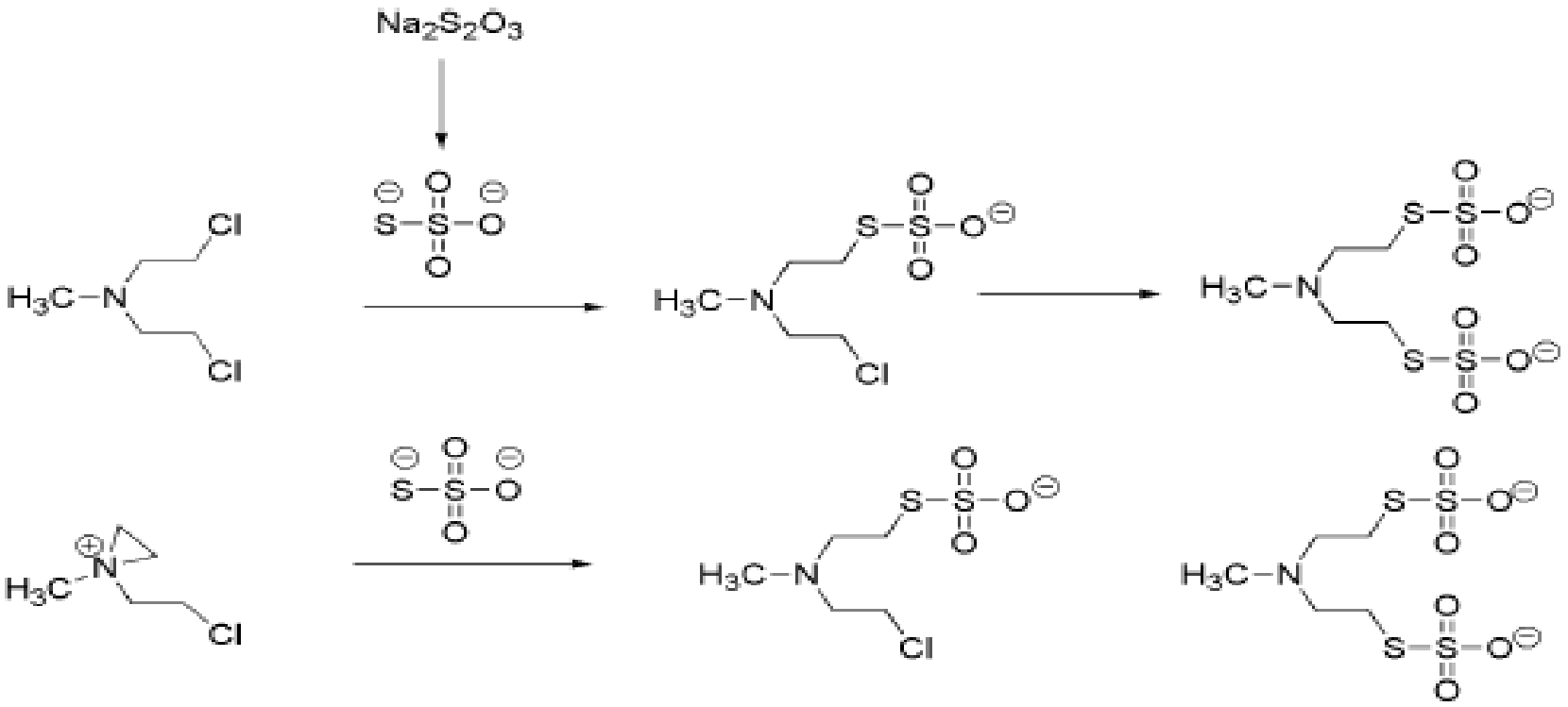
- Mustards such as mechlorethamine are classified as dialkylating agents in that one mustard molecule can alkylate two nucleophiles.
- The initial acid–base reaction is necessary to release the lone pair of electrons on nitrogen, which subsequently displaces chloride to give the highly reactive aziridinium cation.
- Nucleophilic attack can then occur at the aziridinium carbon to relieve the small ring strain and neutralize the charge on nitrogen. Mechlorethamine is highly reactive, in fact, too reactive and therefore nonselective, making it unsuitable for oral administration and necessitating direct injection into the tumor.

Alkylation of nucleophilic species by nitrogen mustards.



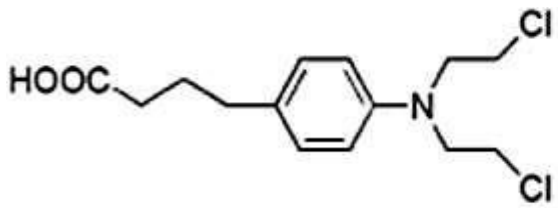
Thiosulfate inactivation of mechlorethamine.

- In cases of extravasation (drug escapes from the tumor into the underlying tissue), the antidote sodium thiosulfate ($Na_2S_2O_3$), a strong nucleophile, may be administered

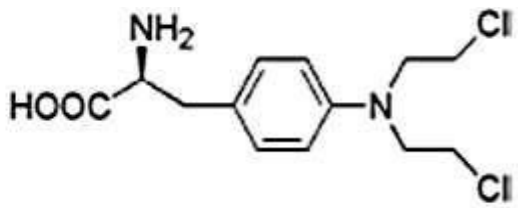


Chlorambucil and Melphalan

- The lack of selectivity of mechlorethamine led to attempts to improve on the agent.
- One rationale was to reduce the reactivity by reducing the nucleophilicity of nitrogen, thereby slowing aziridinium cation formation.
- This could be accomplished by replacement of the weakly electron-donating methyl group with groups that were electron withdrawing (-I). This is seen in the case of chlorambucil and melphalan by Attachment of nitrogen to a phenyl ring.



Chlorambucil

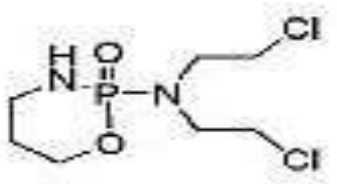


Melphalan

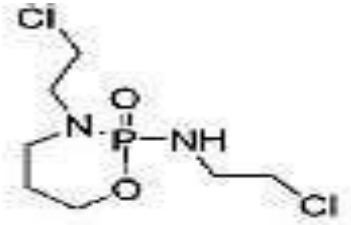
- Reactivity was reduced such that these compounds could be administered orally. In the case of melphalan, attachment of the mustard functionality to a phenylalanine moiety was not only an attempt to reduce reactivity but also an attempt to increase entry into cancer cells by utilization of carrier mediated uptake.
- Melphalan was found to utilize active transport to gain entry into cells, but selective uptake by cancer cells has not been demonstrated.

Cyclophosphamide and Ifosfamide

- Attachment of more highly electron-withdrawing functionalities was utilized in the case of cyclophosphamide and ifosfamide. In these cases, aziridinium cation formation is not possible until the electron- withdrawing function has been altered.
  - The drug could be selectively activated in cancer cells because they were believed to contain high levels of phosphoramidase enzymes.
  - This would remove the electron-withdrawing phosphoryl function and allow aziridine formation to occur.



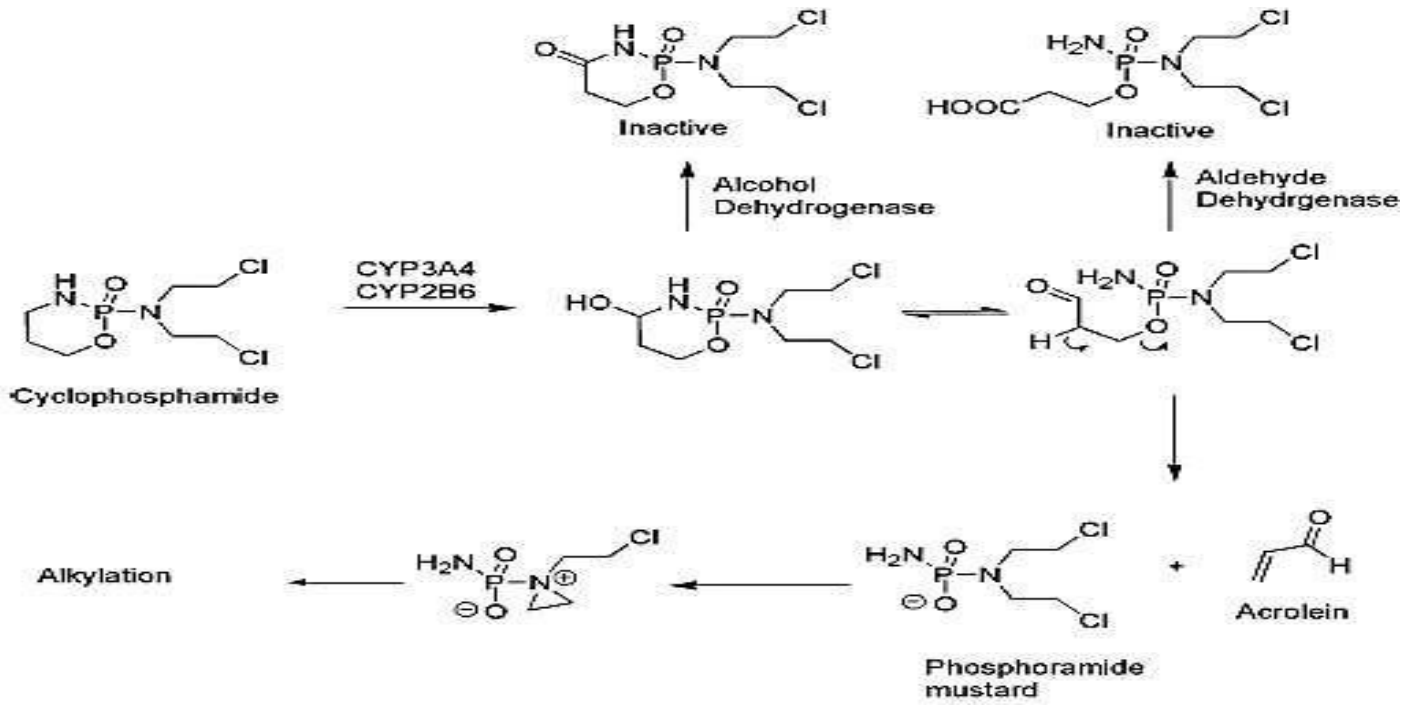
Cyclophosphamide

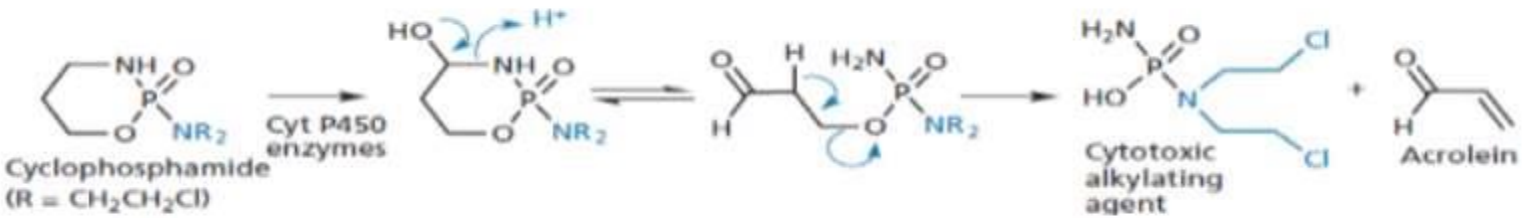


Ifosfamide

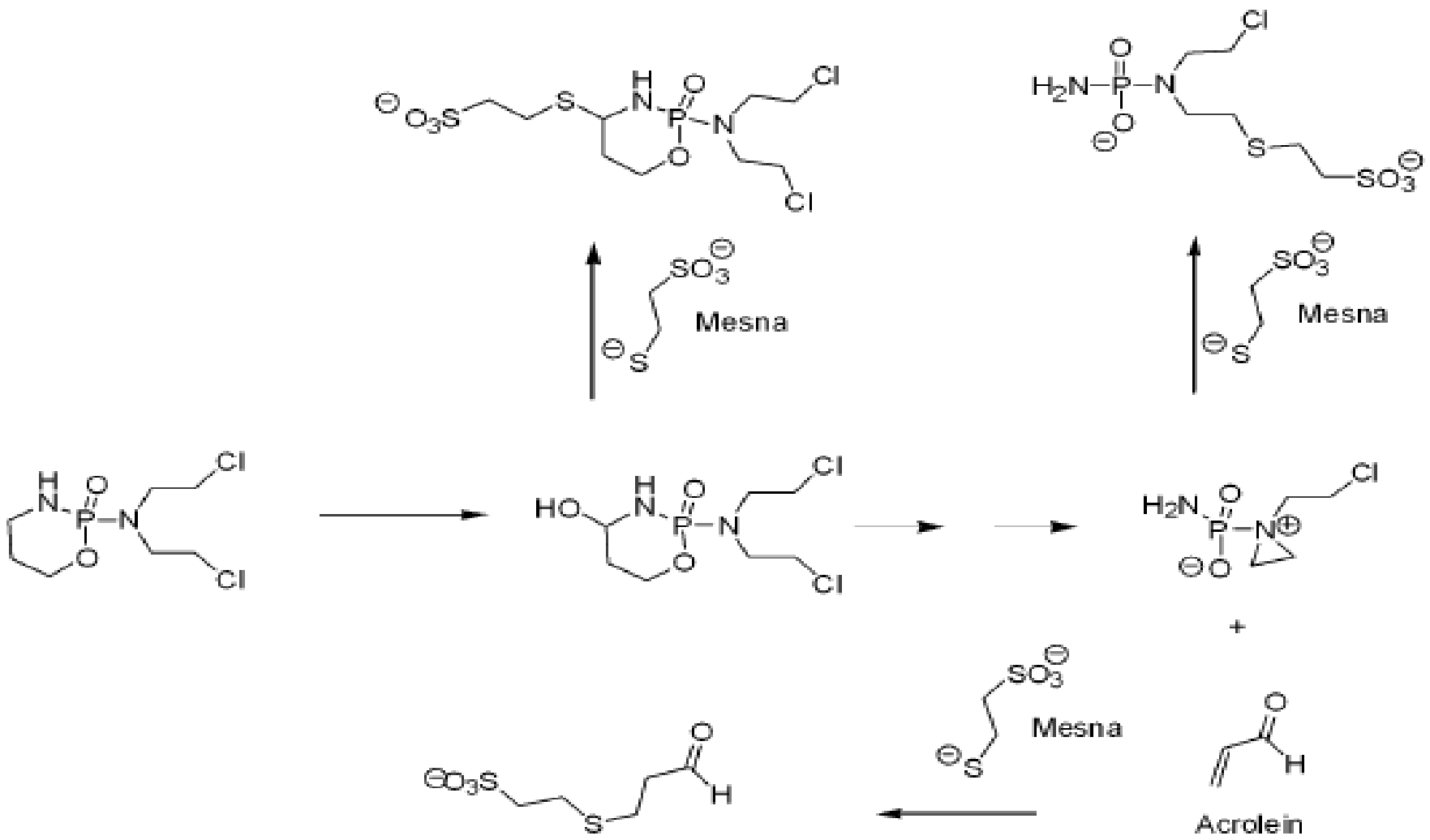
- The drug was activated by cytochrome P450 (CYP) isozymes CYP2B6 and CYP3A4/5 to give a carbinolamine that could undergo ring opening to give the aldehyde.
- The increased acidity of the aldehyde -hydrogen facilitates a retro-Michael decomposition
- The ionized phosphoramide is now electron-releasing via induction and allows aziridinium cation formation to proceed.
- To decrease the incidence of kidney and bladder toxicity, the sulfhydryl (MSH) containing agent mesna may be administered and functions to react with the electrophilic species that may be present in the kidney.

Metabolic and chemical activation of cyclophosphamide





Detoxification of cyclophosphamide by mesna.



- There are differences in the metabolism and activity of the agents.
  - Both are administered as racemic mixtures as a result of the presence of a chiral phosphorus atom.
  - There appears to be little difference in the metabolic fate of the R- and S-isomers of cyclophosphamide.
  - In the case of ifosfamide, the R-isomer is converted to the required 4-hydroxy-ifosfamide 2 to 3 times faster than the S-isomer.

- The S-isomer undergoes preferential oxidation of the side chain to give N-dechloroethylation, which removes the ability of the agent to cross-link DNA and also produces the neurotoxic and urotoxic chloroacetaldehyde.
- An additional difference between cyclophosphamide and ifosfamide is the larger alkylating species that ultimately results after metabolic activation of ifosfamide. This results in the reactive form of ifosfamide having a higher affinity for DNA than the analogous form of cyclophosphamide and differences in the interstrand and intrastrand links that ultimately result.