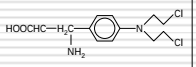
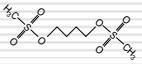
Classes of Antineoplastic Agents

ALKYLATING AGENTS

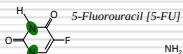


Melphalan [Nitrogen Mustard]

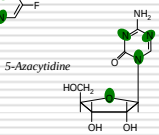


Busulfan [Alkyl sulfonate]

ANTIMETABOLITES

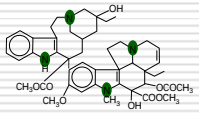


5-Fluorouracil [5-FU]



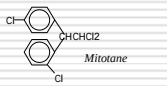
5-Azacytidine

NATURAL PRODUCTS



Vinblastine
[V. rosea Alkaloid]

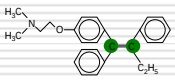
MISCELLANEOUS



Mitotane

Hydroxyurea

HORMONES & ANTAGONISTS



Tamoxifen
[Estrogen receptor antagonist]

EXPERIMENTAL & NEW AGENTS

Trastuzumab [Anti-EGFR mAb]
Rituximab [Anti-CD20 mAb]

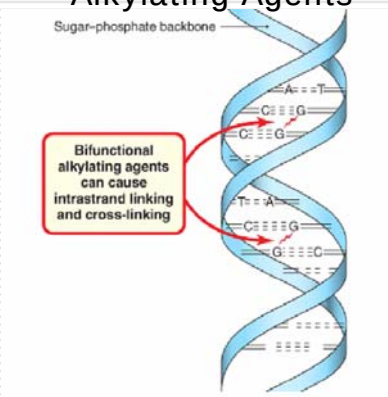
Alkylating Agents

- Alkylating agents are so named because of their ability to add alkyl groups to many electronegative groups under conditions present in cells.
- They stop tumor growth by cross-linking guanine bases in DNA double-helix strands - directly attacking DNA. This makes the strands unable to uncoil and separate. As this is necessary in DNA replication, the cells can no longer divide.
- In addition, these drugs add methyl or other alkyl groups onto molecules where they do not belong which in turn inhibits their correct utilization by base pairing and causes a miscoding of DNA.

Alkylating Agents

- Alkylating agents are cell cycle-nonspecific.
- They work by three different mechanisms all of which achieve the same end result - disruption of DNA function and cell death.
  - Attachment of alkyl groups to DNA bases, resulting in the DNA being fragmented by repair enzymes in their attempts to replace the alkylated bases, preventing DNA synthesis and RNA transcription from the affected DNA,
  - DNA damage via the formation of cross-links (bonds between atoms in the DNA) which prevents DNA from being separated for synthesis or transcription, and
  - The induction of mispairing of the nucleotides leading to mutations.

Alkylating Agents

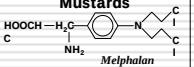


Alkylating Agents

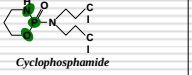
Class of alkylating agent	*Drugs in class*	*Disease*
1. Nitrogen mustards	***Mechlorethamine***	*Hod, Lym*
	Cyclophosphamide	*Leu, Lym, Solid, Soft, Mye*
	Ifosfamide	*Leu, Lym, Solid, Soft, Mye*
	Melphalan	*Mye*
	Chlorambucil	*Hod, Leu, Lym*
2. Ethyleneimines/ Methylmelamines	*Thiotepa*	*Solid*
	Hexamethylmelamine	
3. Alkyl sulfonates	*Busulfan*	*Leu*
4. Nitrosureas	*Carmustine [BCNU]*	*Hod, Lym, Mye, Solid [Brain]*
	Lomustine	*Hod, Lym, Mye, Solid [Brain]*
	Streptozocin	*Malignant insulinoma*
5. Triazenes	*Dacarbazine*	*Hod, Soft, Solid [Skin]*
	Temozolomide	*Solid [Skin], Gliomas*

Alkylating Agents

1. Nitrogen Mustards



Melphalan

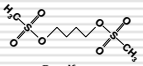


Cyclophosphamide

2. Ethyleneimines & Methylmelamines

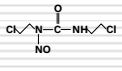
Thiotepa

3. Alkyl sulfonates



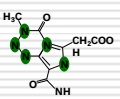
Busulfan

4. Nitrosureas



Carmustine [BCNU]

5. Triazenes



Temozolomide

Common mechanism of action:

Convertion to an active aziridine. Nucleophilic attack of unstable ring by electron donor [-SH, -N, =O] Alkylation

Alkylating Agents

Common mechanism of action:

Convertion to an active aziridine
Nucleophilic attack of unstable ring by electron donor [-SH, -N, =O]
Alkylation

1

Possible consequence 1:

Keto to Enol switch of nucleotide =
Formation of G-T bonds & intrastrand bonds

DNA breakage

2

3

Possible consequence 2:

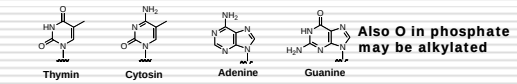
Labilization of the imidazole ring of guanine =
Excision of nucleotide.

Possible consequence 3:
[Nitrogen mustards]

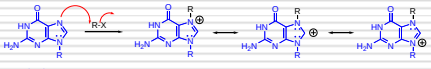
Crosslinking of both DNA strands = DNA breakage.

Alkylating Agents

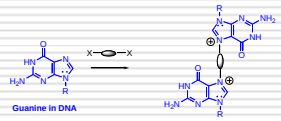
DNA Bases - Nucleophilic Centre



Also O in phosphate may be alkylated



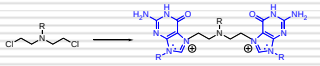
Guanine in DNA

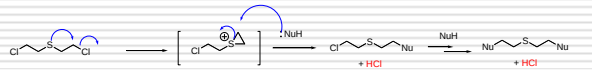


Guanine in DNA

Alkylating Agents

1) Nitrogen mustards
2) Other alkylation agents

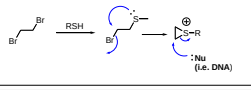




Sulfur mustard
Mustard gass
Yprite
Worls war I (1917)
Impurity smell like mustard / garlic

Mechlorethamine
FDA 1949

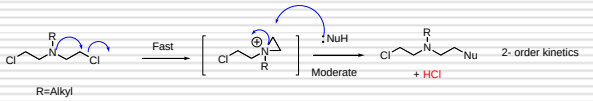
Metabolism of alkyl halides
Phase II conjug. glutathion



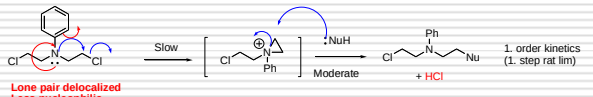
Rel. selective tox. to lymphoid tissue
(Hodkins disease, Lymphomas)
More water sol.

Tox. to rapid proliferating cells (short time for DNA repair)

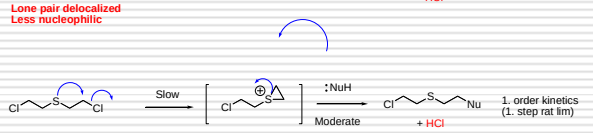
Alkylating Agents



R=Alkyl



Lone pair delocalized
Less nucleophilic



less stable than N-aanalog

Alkylating Agents

Chlorambucil
Leukeran®,

Melfalan
Alkeran®,

Aryl decrease reactivity

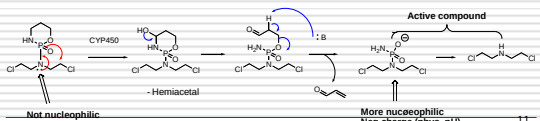
L-isomer
Active transport mech (L-AA)

Cyclophosphamide
Sendoxan®

Pro-drug

Ifosfamide
Holoxan®

Pro-drug



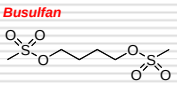
Not nucleophilic cf amides

More nucleophilic
Neg charge (phys. pH) prevents delocal

Alkylating Agents

1) Nitrogen mustards
2) Other alkylation agents

Busulfan

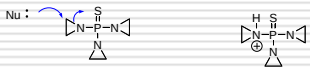


Not reg. N
Mono or dialkylation
Better leav. gr, not 3-embered ring intermed
cf dimethyl sulfate

Thiotepa

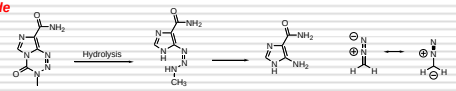
Not reg. N

Even more reactive at low pH

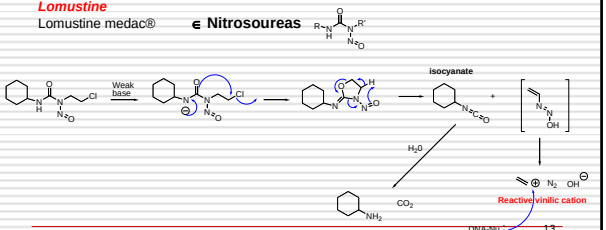


Alkylating Agents

Temozolomide
Temodal®

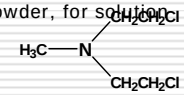


Lomustine
Lomustine medac® ∈ **Nitrosoureas**

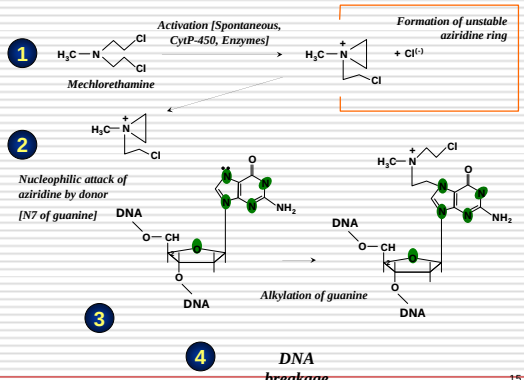


Mechlorethamine

- Chemical Formula
  $C_5H_{11}Cl_2N$
- Trade Name — Mustargen
- Dosage Forms
  - Powder — Topical
  - Injection, powder, for solution — Intravenous



Mechlorethamine



Mechlorethamine

Pharmacology

- Mechlorethamine also known as mustine, nitrogen mustard, and HN_2, is the prototype anticancer chemotherapeutic drug.
- Successful clinical use of mechlorethamine gave birth to the field of anticancer chemotherapy.
- The drug is an analogue of mustard gas and was derived from toxic gas warfare research.
- It belongs to the group of nitrogen mustard alkylating agents.
- Alkylating agents work by three different mechanisms all of which achieve the same end result - disruption of DNA function and cell death.

Mechlorethamine

Absorption

- Partially absorbed following intracavitary administration, most likely due to rapid deactivation by body fluids.

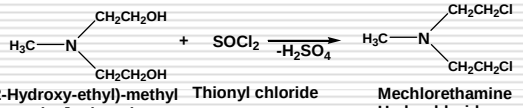
Toxicity

- Symptoms of overexposure include severe leukopenia, anemia, thrombocytopenia, and a hemorrhagic diathesis with subsequent delayed bleeding may develop. Death may follow.

Biotransformation

- Undergoes rapid chemical transformation and combines with water or reactive compounds of cells, so that the drug is no longer present in active form a few minutes after administration.

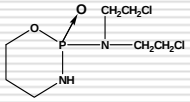
Synthesis of Mechlorethamine



2-[(2-Hydroxy-ethyl)-methyl -amino]-ethanol — **Thionyl chloride** — **Mechlorethamine Hydrochloride**

Cyclophosphamide

- Chemical Formula $C_7H_{15}Cl_2N_2O_2P$
- Trade Name — Cytoxan, Neosar
- Dosage Forms
  - Solution — Intravenous
  - Powder, for solution — Intravenous
  - Tablet — Oral



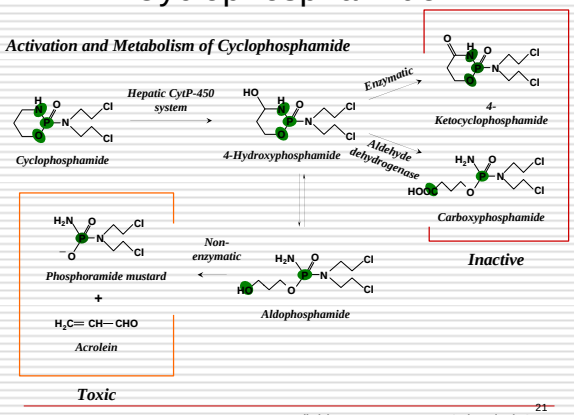
Cyclophosphamide

Pharmacology

- Cyclophosphamide is an antineoplastic in the class of alkylating agents and is used to treat various forms of cancer.
- Toxicity
  - infection, myelosuppression, and cardiac toxicity
- It is a "prodrug"; it is converted in the liver to active forms that have chemotherapeutic activity.
- The active metabolite is **4-hydroxycyclophosphamide**
- The main effect of cyclophosphamide is due to its metabolite phosphoramide mustard. This metabolite is only formed in cells which have low levels of ALDH.

Cyclophosphamide

Activation and Metabolism of Cyclophosphamide

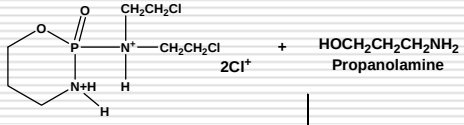


Cyclophosphamide

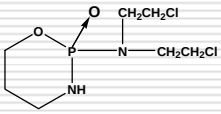
Side Effects

- Chemotherapy-induced nausea and vomiting (CINV)
- Bone marrow suppression
- Stomach ache
- Diarrhea
- Darkening of the skin/nails
- Alopecia (hair loss)
- Lethargy

Synthesis of Cyclophosphamide



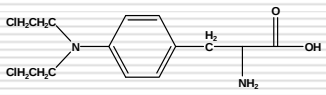
Bis(2-Chloroethyl)-phosphoramide dichloride



Cyclophosphoramide

Melphalan

- Chemical Formula — $C_{13}H_{18}Cl_2N_2O_2$
- Trade Name — Alkeran
- Dosage Forms
  - Tablet — Oral



Melphalan

- Melphalan is an antineoplastic in the class of alkylating agents and is used to treat various forms of cancer.
- An alkylating nitrogen mustard that is used as an antineoplastic in the form of the levo isomer - melphalan, the racemic mixture - **merphalan**, and the dextro isomer - **medphalan**;
- Toxic to bone marrow, but little vesicant action; potential carcinogen.

Melphalan

Toxicity

- Vomiting,
- Ulceration of the mouth,
- Diarrhea, and
- Hemorrhage of the gastrointestinal tract;
- The principal toxic effect is bone marrow suppression.

Biotransformation

- Melphalan is not actively metabolised, it spontaneously degrades to mono and dihydroxy products.

Synthesis of Mephlan