تفريغ ميديسنال 2

المحاضرة: anti cancer 2 المحاضرة 1

الصيدلاني/ة: Layan shaher

Soul Academy

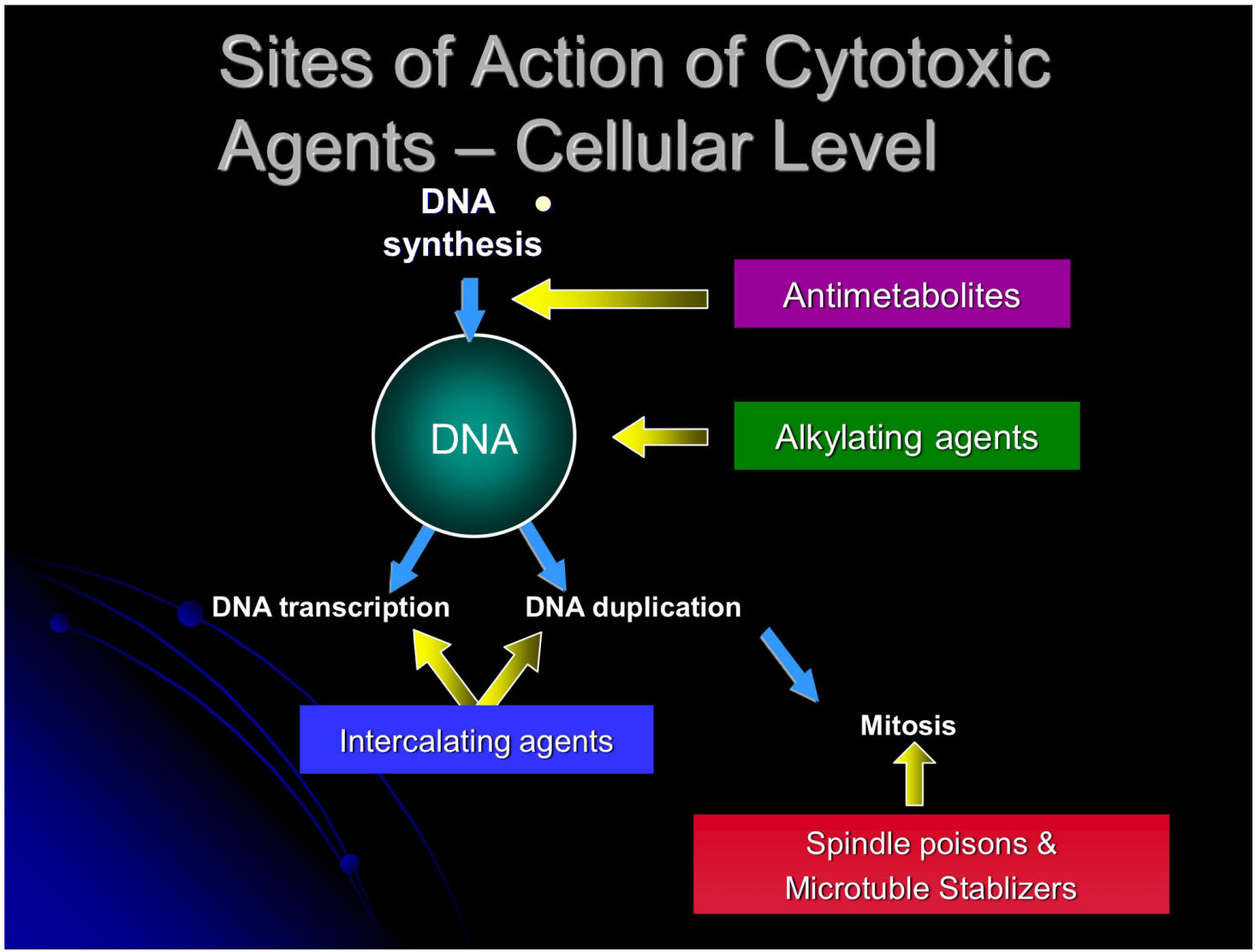
لجان الدفعات

Antineoplastic Agents

- **Alkylating agents** — Carboplatin, cyclophosphamide, melphalan, thiotepa
  (Form bonds with nucelic acids and proteins)
- **Antimetabolites** — Methotrexate, fluorouracil, gemcitabine
  (similar to metabolites involved in nucelic acid synthesis)
- **Natural Products** — doxorubicin, docetaxel, vinorelbine, topotecan
  (anti tumour antibiotics,mictotubule stabilizer, mitotic inhibitor, topoisomerase inhibiotor)
- **Endocrine agents** — Anastrozole, tamoxifen, prednisolone, goserelin
  (Aromatase inhibitors, oestrogen antagonist, corticosteroids, LHRH agonist)
- **Molecularly targeted agents** — Retinoids, trastuzumab, gefitinib
  (gene expression, monoclonal antibody, tyrosine kinase inhibitor)
- **Biologic response modifiers** — Interferon, thalidomide, filgrastim

لـ هاذا اجباري .

Sites of Action of Cytotoxic Agents –



Antineoplastic Agents

Alkylating agents	Topoisomerase inhibitors	Antimetabolites	Molecularly targeted
busulfan	dactinomycin	cytarabine	erlotinib
carboplatin	daunomycin	clofarabine	imatinib
carmustine	doxorubicin	fludarabine	sorafenib
cisplatin	etoposide	gemcitabine	sunitinib
cyclophosphamide	etoposide phosphate	mercaptopurine	tretinoin
dacarbazine	idarubicin	methotrexate	Herceptin
ifosfamide	irinotecan	nelarabine	**Miscellaneous**
lomustine	liposomal daunomycin	thioguanine	arsenic trioxide
mechlorethamine	liposomal doxorubicin	**Tubulin binders**	asparaginase
melphalan	mitoxantrone	docetaxel	bleomycin
oxaliplatin	teniposide	ixabepilone	dexamethasone
procarbazine	topotecan	vinblastine	hydroxyurea
temozolomide		vincristine	mitotane
thiotepa		vinorelbine	PEG-asparaginase
		paclitaxel	prednisone

Problems with chemotherapy

اهم مشاكل الـ Chemotherapy هي مش بين الـ SE والـ SE مرتبطة بـ الخلايا اللي العادية حياة سريعة مثل الشعر والخلايا الـ Bone marrow وخلايا الـ GI اللي بتتسبب الـ SE لادوية السرطان.

- **Treatments are non-specific, attack healthy cells as well as normal cells since cancer cells are derived from normal cells.**
- **Cancers can develop resistance: for example with platinum-drugs, cancer cells became resistant by many ways:**

  - **Decreased drug uptake/increased efflux**
  - **Enhanced tolerance of DNA adducts**
  - **Enhanced repair of DNA adducts**
  - **Increased drug deactivation by intracellular glutathione**

المشكلة الحقيقية عندي بتكون بالمقاومة مش الـ SE اللي تعتبر عادية.

ب المقاومة الـ Resistance:

① الدوا اللازم يدخل للخلية وما يطلع.

② اللازم يعمل coupled مع DNA اذا ما عملت هي صار عندي Resist

③ الخلايا ممكن يصير فيها انزيمات تعتم الخلايا وتقل Repair فاذا كان عندي هاذ الـ Repair عالية فرح يصير عندي Resist

④ عندي الرجلوتاثيون بخفضا من ادوية الكيماوية الضارة موجود بالكبد فممكن يصير يتخلص منه الدوا فرح يصير عندي Resist

مثل اللي دخنت 90 سنة وما عاندت بتكون الـ Repair عندها عالية

⑤ اللازم نعرف اذا ممكن المريض يجيب عما ما يلدقي نتيجة بالعلاج وهاي بتكون بسبب الـ Resistance مثل دوا Imatinib

مثل الـ Imatinib اللازم اعمل منه 2 و 3 generation للدوا الـ 1st صار عندو مقاومة لانو صارت الخلية السرطانية تختر حالها.

Ideal cytotoxic drugs should:

- **Selectively target cancer cells without causing damage to normal cells.**
- **Reduce size of tumors + minimize risks of metastases.**

- **unfortunately, most of the available agents are not selective, they also affect rapidly-proliferating normal tissues (bone marrow, gastro intestinal epithelium, hair cells, …), causing serious side-effects (bone marrow suppression, nausea, vomiting, …).**

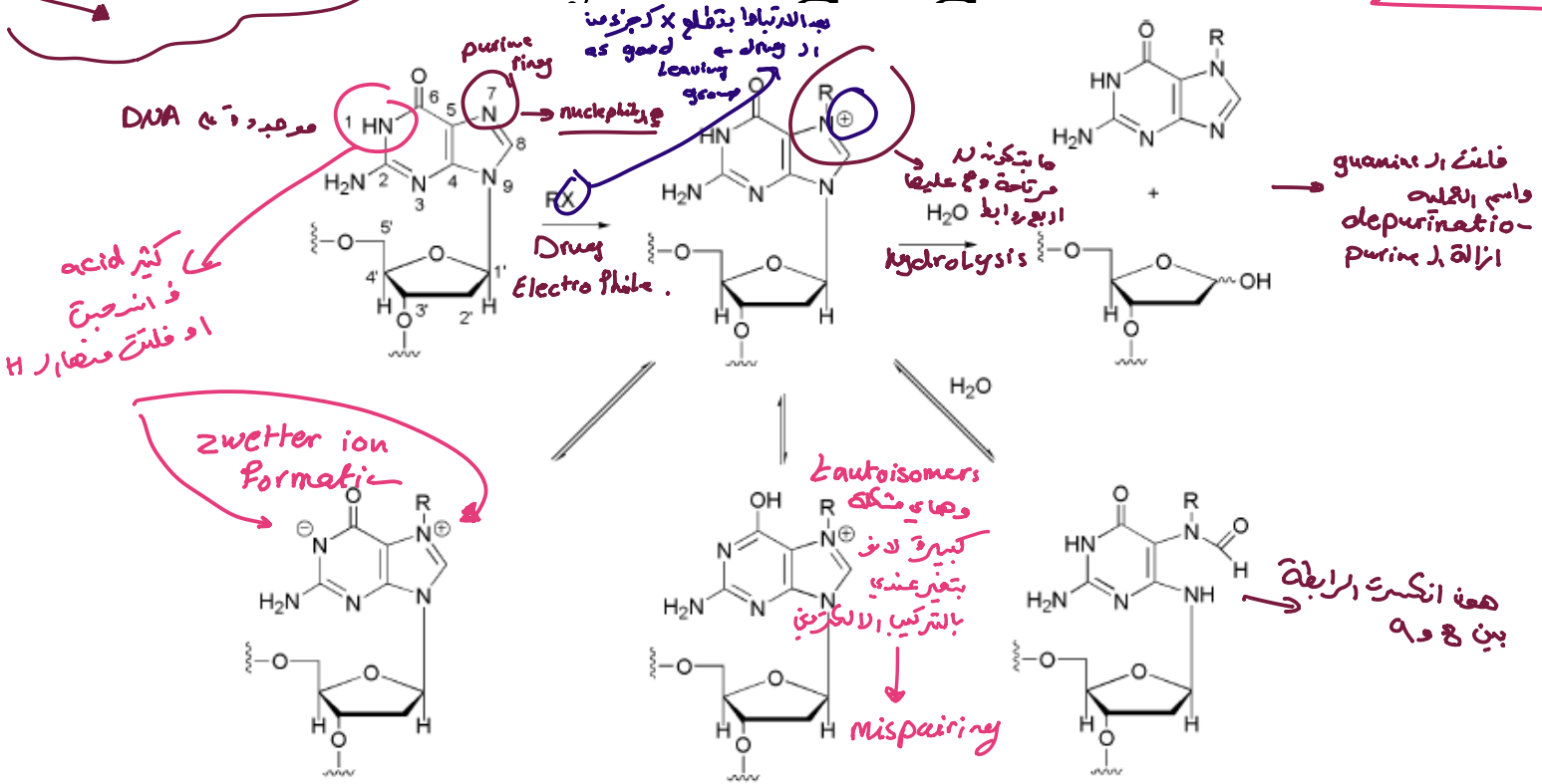
Alkylating Agents

- 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)

- 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.

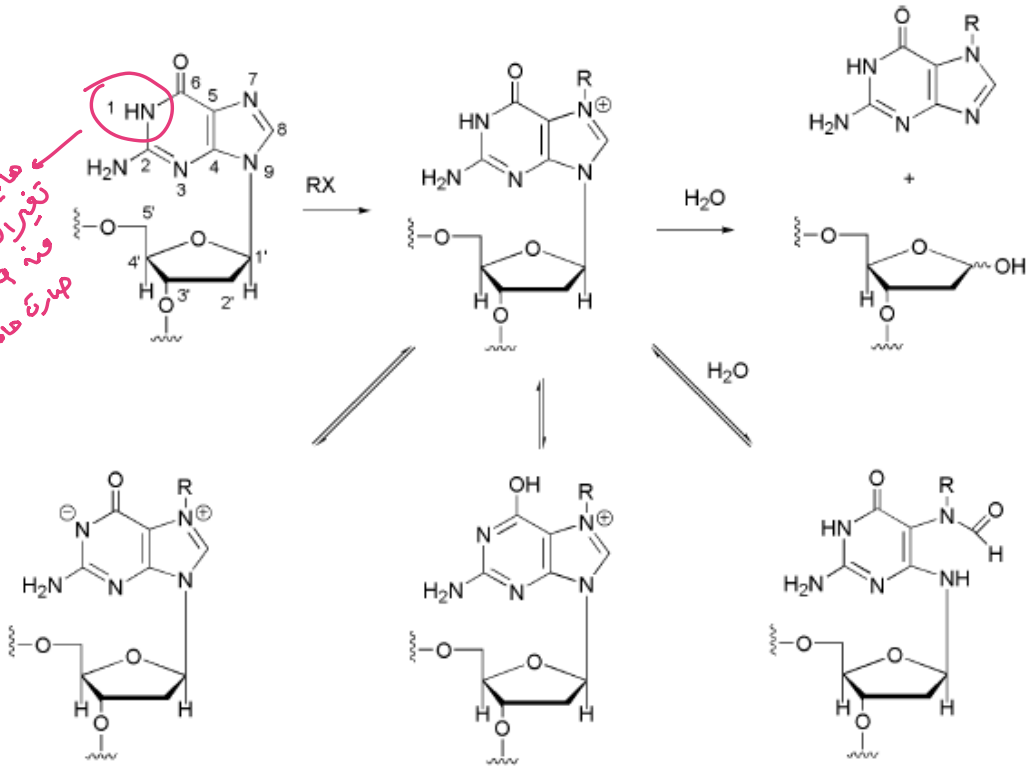
Alkylating Agents



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

Alkylation converts the base to an **effective leaving group** so that attack by water leads to depurination and the loss of genetic information if the resulting depurination is not repaired by the cell

Alkylating Agents



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

Additionally, alkylation has been proposed to result in **altered base pairing** away from the normal G-C, A-T hydrogen bonds because of alterations in tautomerization. The alkylation also leads to increased acidity of the N-1 nitrogen reducing the pKa from 9 to 7-8 giving rise to a zwitterionic form that may also mispair

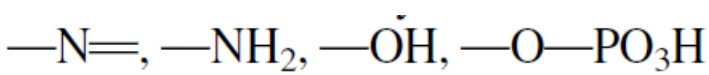
Classification of Alkylating Agents

- BisChloroethylAmines Cyclophosphamide,ifosfamide, Chlormethine, Chlorambucil, Sarcolysine
- Nithrosoureas
- Carmustine,Lomustine
- Ethyeneammonium or Aziridines
- Thiotepa, triethylene melamine
- Alkysulfonates:Busulfan

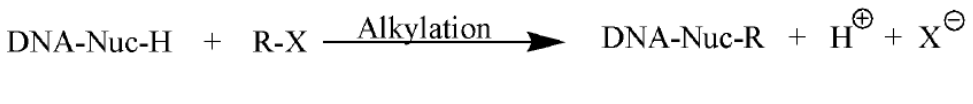
Resistance to alkylating agents

- In many cases, however, 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.
- In this way, cancer cells may become resistant to the effect of alkylating agents.
- Another possibility is that the cancer cells, like normal cells, have various mechanisms by which alkylated DNA bases can be excised.

- The general mechanism for alkylation involves nucleophilic attack by



of DNA and RNA

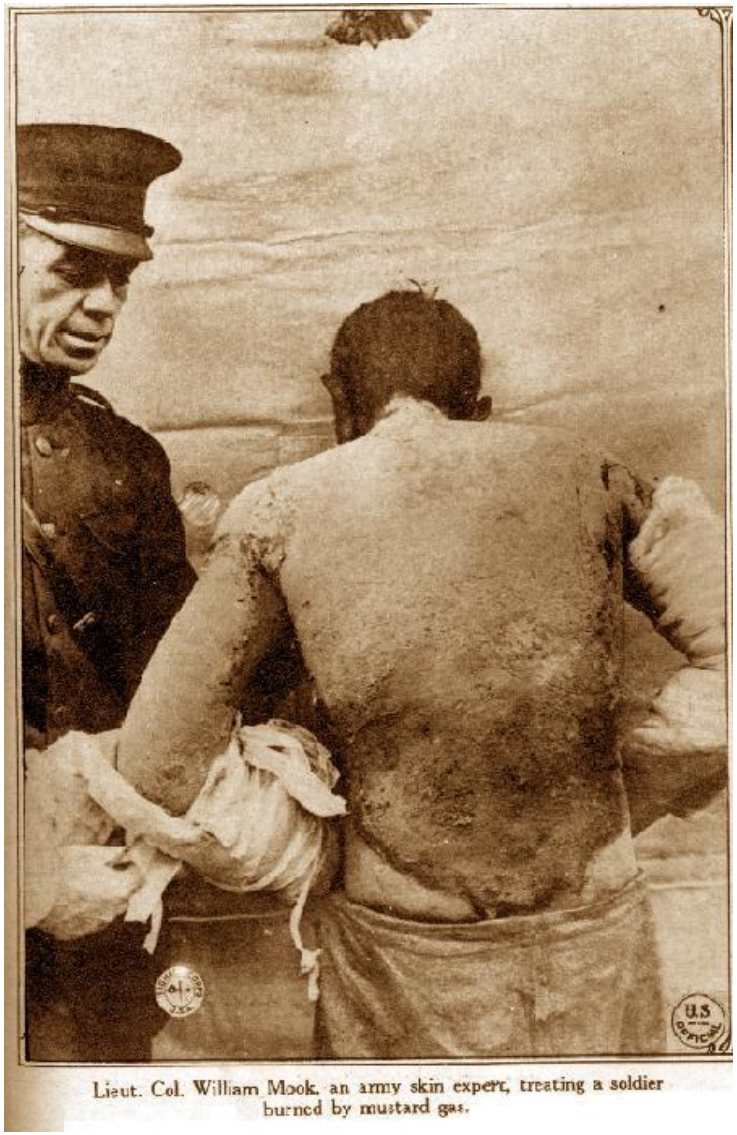


Where X = a leaving group

Scheme 10.2 ● General reaction for alkylation and inactivation of alkylating agents.

NITROGEN MUSTARDS

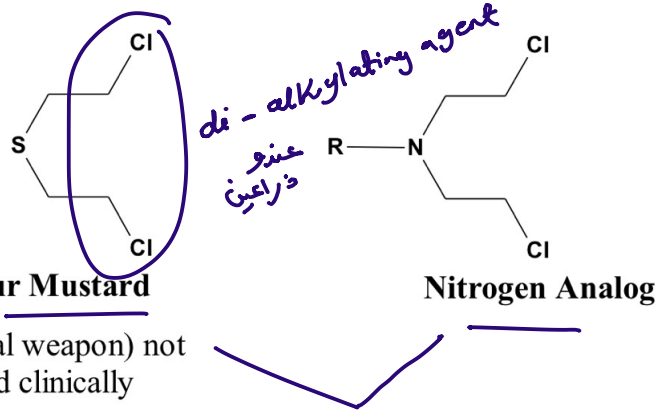
- The nitrogen mustards are compounds that are chemically similar to sulfur mustard or mustard gas developed and used in World War I. The term “mustard” comes from the similarity in the blisters produced by the compound and those seen upon exposure to the oil of black mustard seeds.
- Investigation of sulfur mustard revealed that it possessed antineoplastic properties but because the compound existed as a gas at room temperature, handling and administration of



Lieut. Col. William Mook, an army skin expert, treating a soldier burned by mustard gas.

Chemical Warfare – *circa* 1914

- Two most common agents:
  - Chlorine gas
  - Mustard gas



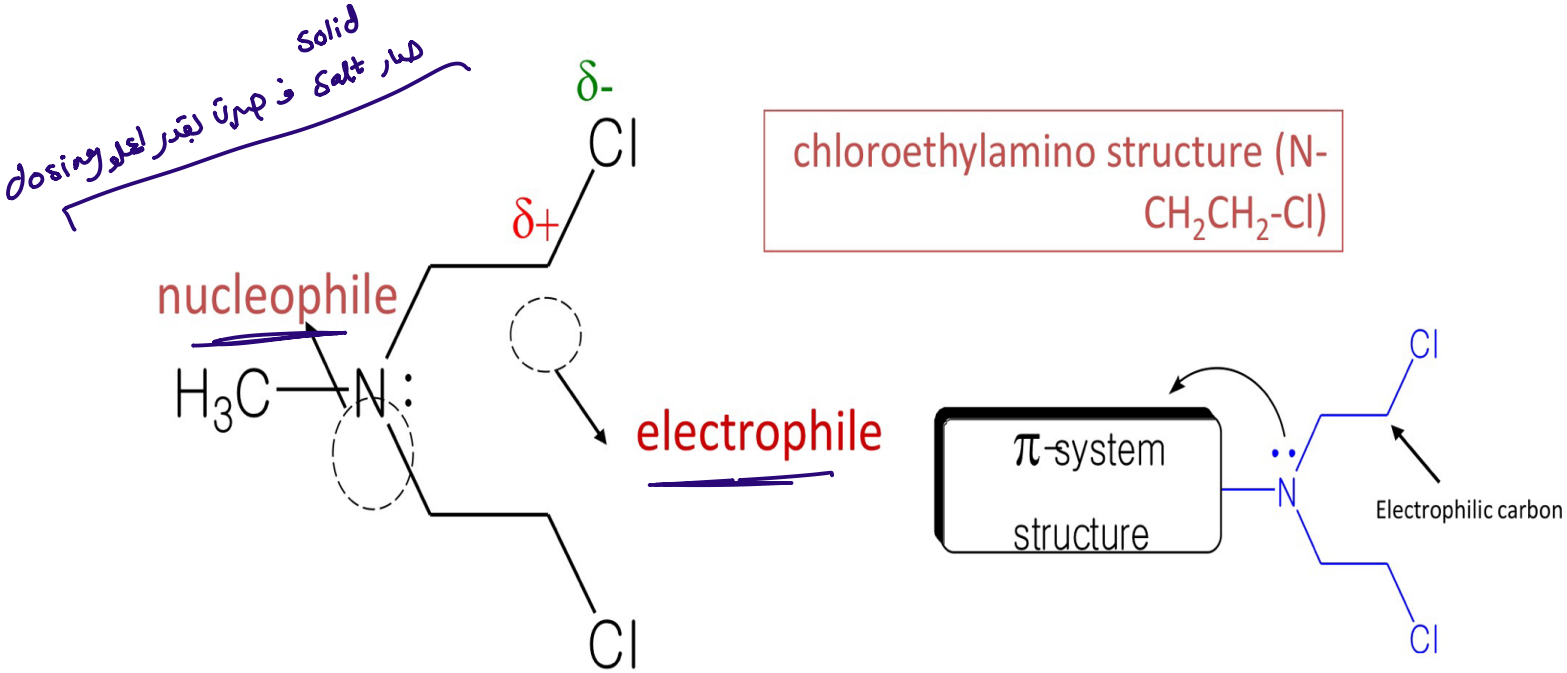
Sulfur Mustard

(chemical weapon) not used clinically

Nitrogen Analog

R group يختلف بـ
وهو اصبح prodrug

Nitrogen Mustard



Mechlorethamine (or Chlormethine)