

# تفریغ میدیسنال 2



المحاضرة: Cancer Part 1

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# Cancer molecular biology

- Increased knowledge of intercellular and intracellular communication has led to the development of several newer agents that have shown some effectiveness in treating several cancers, especially when used in combination with more traditional agents.
- These have included several monoclonal antibodies that target the overproduction of growth factor receptors and Tyrosine Kinase inhibitors that target the transduction process involved in growth factor stimulation
- You have to refer to the youtube lectures in your moodle.

# Cancer Types

categorized based on the functions/locations of the cells from which they originate:

- **Carcinoma**: a tumor derived from epithelial cells, those cells that line the surface of our skin and organs (80-90% of all cancer cases reported)
- **Sarcoma**: a tumor derived from muscle, bone, cartilage, fat or connective tissues.
- **Leukemia**: a cancer derived from white blood cells or their precursors.
- **Lymphoma**: a cancer of bone marrow derived cells that affects the lymphatic system.
- **Myelomas**: a cancer involving the white blood cells responsible for the production of antibodies (B lymphocytes).

كارسينوما (Carcinoma)

الخلايا الظهارية (Epithelial cells)

ورم ينشأ من الخلايا التي تُبَطِّن سطح الجلد والأعضاء. يشكل هذا النوع 80-90% من جميع حالات السرطان

ساركوما (Sarcoma)

الأنسجة الضامة والداعمة

ورم ينشأ من العضلات، أو العظام، أو الغضاريف، أو الدهون، أو الأنسجة

لوكيميا (Leukemia)

خلايا الدم البيضاء

سرطان مشتق من خلايا الدم البيضاء أو طلائعها (Precursors).

ليمفوما (Lymphoma)

خلايا مشتقة من نخاع العظم

سرطان يؤثر على الجهاز лимفاوي.

مايلوما (Myelomas)

خلايا الدم البيضاء (الخلايا البابائية)

سرطان يشمل خلايا الدم البيضاء المسئولة عن إنتاج الأجسام المضادة (B

# Antineoplastic Agents

مميزهم انهم يخلو  
alkylation  $\leftarrow$  for DNA

## Alkylating agents → make Covalent bond with nucleic acids

**(Form bonds with nucleic acids and proteins)**

## **Carboplatin, cyclophosphamide, melphalan, thiotepe**

## ▲ **Antimetabolites** المُعَدِّلُونَ الْمَعَادِلُونَ

وبعد ما تدخلتم تكتشف انهم مختلفين والفن والانقسام رجعوا

## Methotrexate, fluorouracil, gemcitabine

(similar to metabolites involved in nucleic acid synthesis)

## ▲ Natural Products

المرفقه (M-Mass)  $\leftarrow$  يفتح بفتح الماء

**doxorubicin, docetaxel, vinorelbine, topotecan**

(anti tumour antibiotics, microtubule stabilizer, mitotic inhibitor, topoisomerase inhibitor)

## ▲ Endocrine agents

الهرمون الآنتوي يزيد لا  
الآنثوي ونعالج اور الزكوي Cancer

## Anastrozole, tamoxifen, prednisolone, goserelin

(Aromatase inhibitors, oestrogen antagonist, corticosteroids, LHRH agonist)

## -Molecularly targeted agents

## Retinoids, trastuzumab, gefitinib وجودها بعض <sup>anti-body</sup> Kinase inhibitor

(gene expression, monoclonal antibody, tyrosine kinase inhibitor)

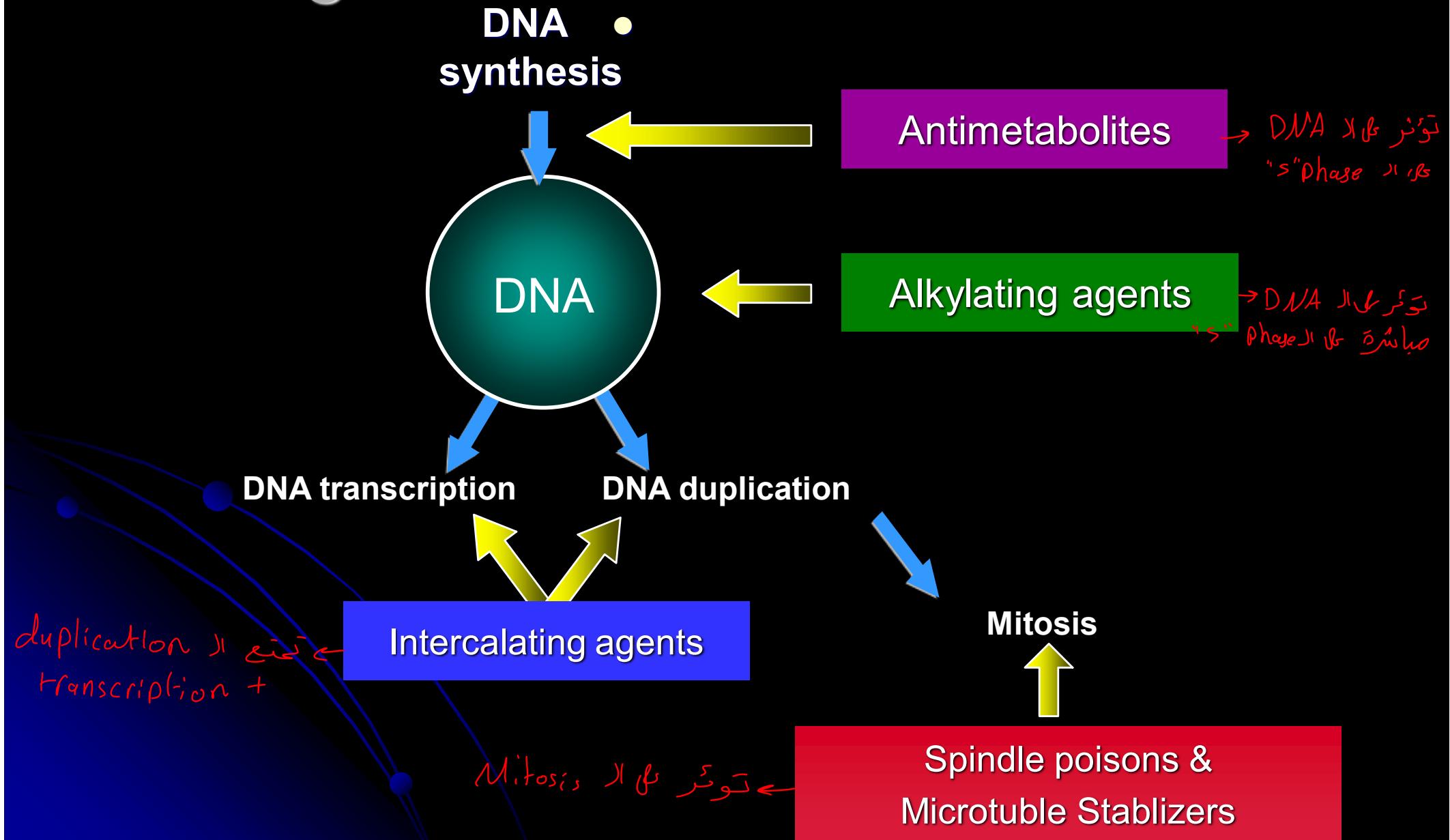
## ▲ **Biologic response modifiers**

## Interferon, thalidomide, filgrastim

زمان كانوا تأخذن الحال عطان الراهن سبب  
في صنف  $R$   $\rightarrow$  بمنتهى الخلط

بعض زرمان كانوا يأخذون Risomers كـ "الوهام" صنف الأطفال صار ينولون يتشوهمات وارتفعوا سعر الـ "الوهام" زيز "الدكتور فواز عبد الحق" بعد ما صاروا يديرون

# Sites of Action of Cytotoxic Agents – Cellular Level



# 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	<b>Miscellaneous</b>
lomustine ✓	liposomal daunomycin	thioguanine	arsenic trioxide
mechlorethamine ✓	liposomal doxorubicin	<b>Tubulin binders</b>	asparaginase
melphalan ✓	mitoxantrone	docetaxel	bleomycin
oxaliplatin	teniposide	ixabepilone	dexamethasone
procarbazine ✓	topotecan	vinblastine	hydroxyurea
temozolomide		vincristine	mitotane
thiotepa		vinorelbine	PEG-asparaginase
		paclitaxel	prednisone

side effect  
resistance

# Problems with chemotherapy

- 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:

من الـ Alkylation agent ويعتبر من الادويه القوية  
نستخرج لعلاج سرطان المبيض ويعبر عليه resistance (صاعده)  
14 طرق

ما يقدر يدخل الخلية

– Decreased drug uptake/increased efflux

– Enhanced tolerance of DNA adducts

موجورة بـ covalent bond  
الـ cancer cell مسؤولة عن رupture bond بـ  
لـ تدخل تثبيط

Enhanced repair of DNA adducts

الخلية تعالج نفسها  
enzymatic  
تحفيز بغير عصبية  
تقليل الماء  
والـ covalent bond  
وتحفيز  
تكمل الماء طبيعيا

Increased drug deactivation by intracellular glutathione

بعض (glutathione) و مسؤول عن انه يخلصنا من الموارد الساردة و بعـ اذا (cancer cell) صنعته بـ سلطنة ابر

لـ تدخل ابر الخلية



# 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.

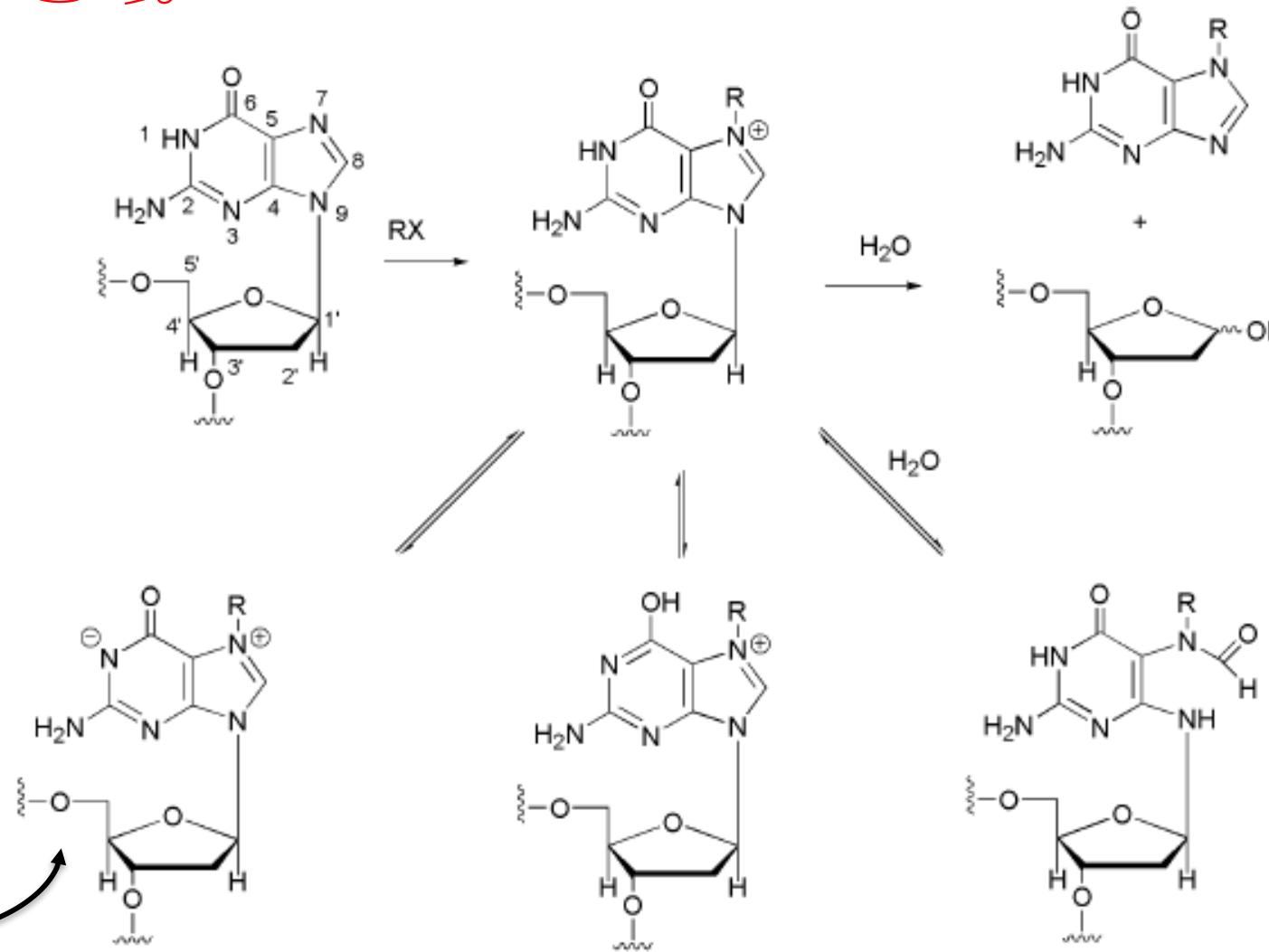
عمل ال alkylating agent على DNA ينطوي على formation of covalent bonds with nucleophilic groups present on DNA.

ويؤدي إلى apoptosis عن طريق p53 activation.



Caption لفظاً  
عنوان المحتوى  
عنوان المحتوى

# 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 to 8 giving rise to a zwitterionic form that may also mispair





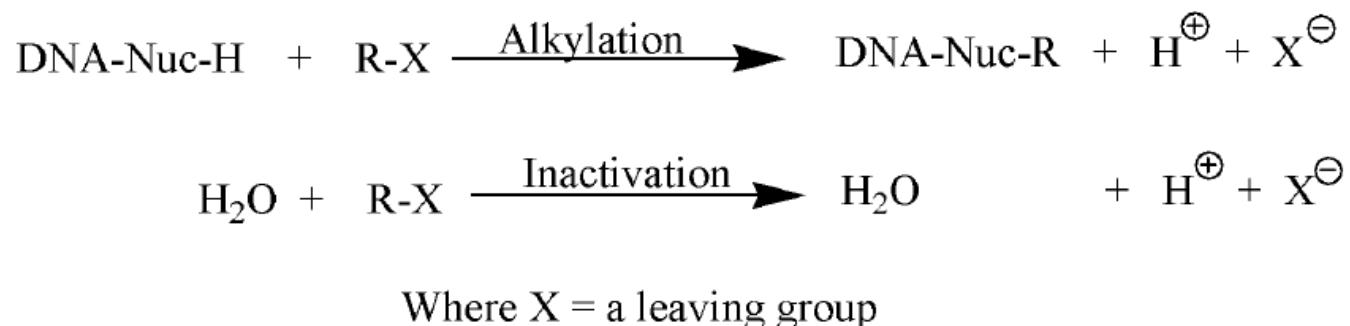
# Resistance to alkylating agents

- 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.

الخطوات المطلوبة

لهم إني

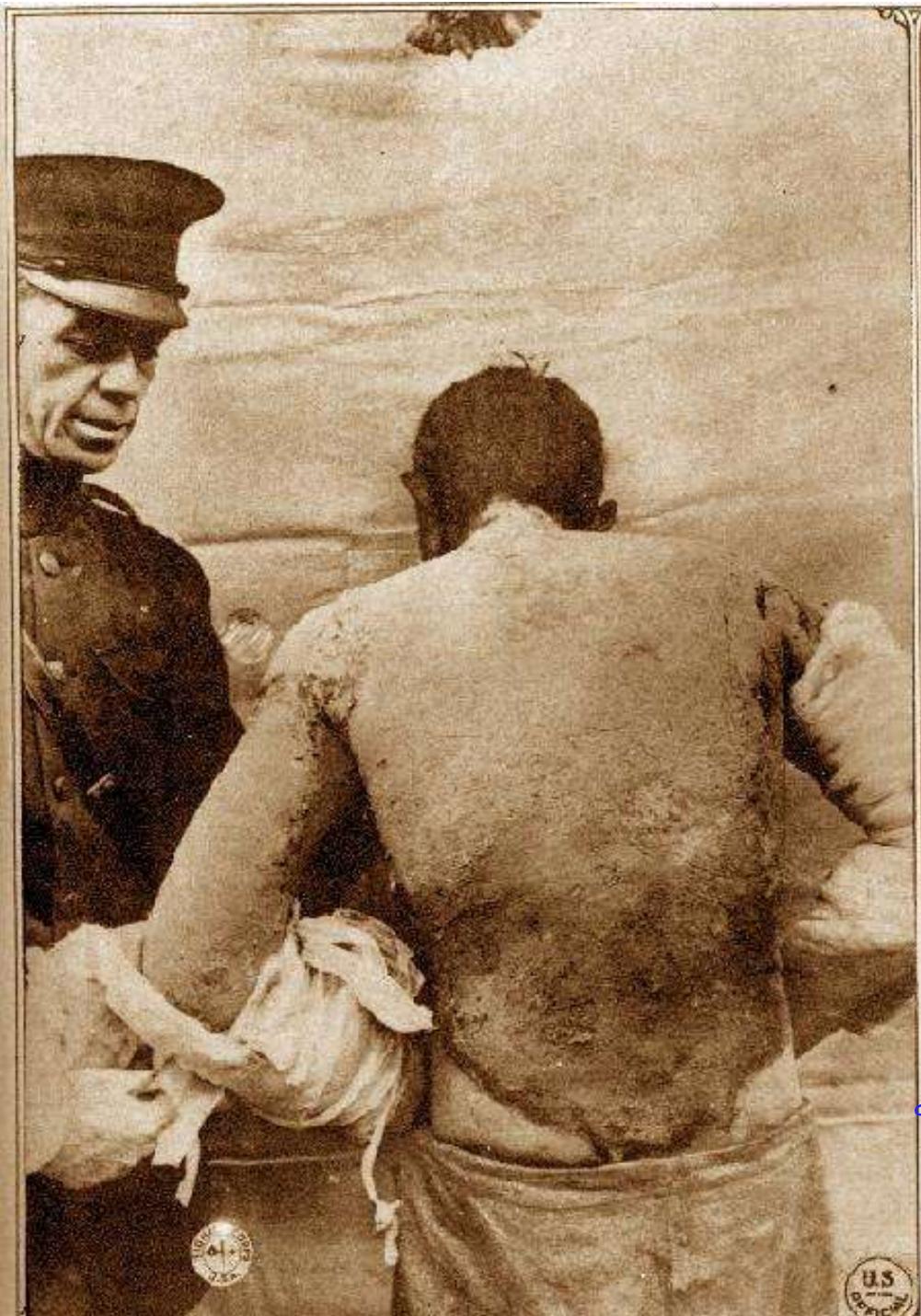
- The general mechanism for alkylation involves nucleophilic attack by  $\text{--N}=\text{}$ ,  $\text{--NH}_2$ ,  $\text{--OH}$ ,  $\text{--O--PO}_3\text{H}$  of DNA and RNA



# NITROGEN MUSTARDS



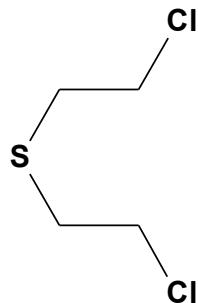
- The nitrogen mustards are compounds that are chemically similar to sulfur mustard or mustard gas developed and used in World War I. The term “mustard” comes from the similarity in the **blisters** produced by the compound and those seen upon exposure to the oil of black mustard seeds.
- Investigation of sulfur mustard revealed that it possessed antineoplastic properties but because the compound existed as a gas at room temperature, handling and administration of the material were difficult.
- Conversion of the sulfide to a tertiary amine allowed for the formation of salts, which exist as solids at room temperature allowing for easier handling and dosing. The term mustard was then extended to the nitrogen analogs (nitrogen mustards) given their chemical similarity.
- 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 (see figure next page).
- Nucleophilic attack can then occur at the aziridinium carbon to relieve the small ring strain and neutralize the charge on nitrogen.
- This process can then be repeated provided a second leaving group is present



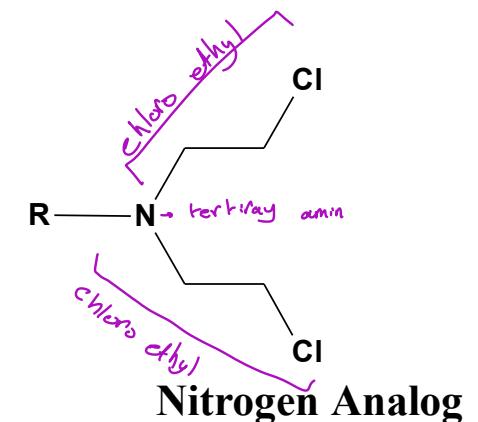
Lieut. Col. William Mook, an army skin expert, treating a soldier burned by mustard gas <sup>greased</sup> || is given a

بالحرب العالمية تم إثبات  
هذه العاد وصار نتاجه ذلك  
حرف جديه للجنود و  
صار في ملائمه بالانسجة  
الجلدية، تم تعزيزه هكذا  
لوجه ترمي المسترة وبغلو  
الارطاط قرروا يجربوا يهنجوا  
Clinically analogus  
Cultured  $\rightarrow$  gas Sulphur-mustard  
واما في

(chemical weapon) not  
used clinically



## Sulfur Mustard (goes)



هي اول analogous دواء اخذ ده من اول sulfur Mustard يحيط بهم الدبلون و هو اضفعت من Sulfur Mustard Clinically فبل اربعين دقيقة واستعمله tablets و powder و ointment حقن حقن

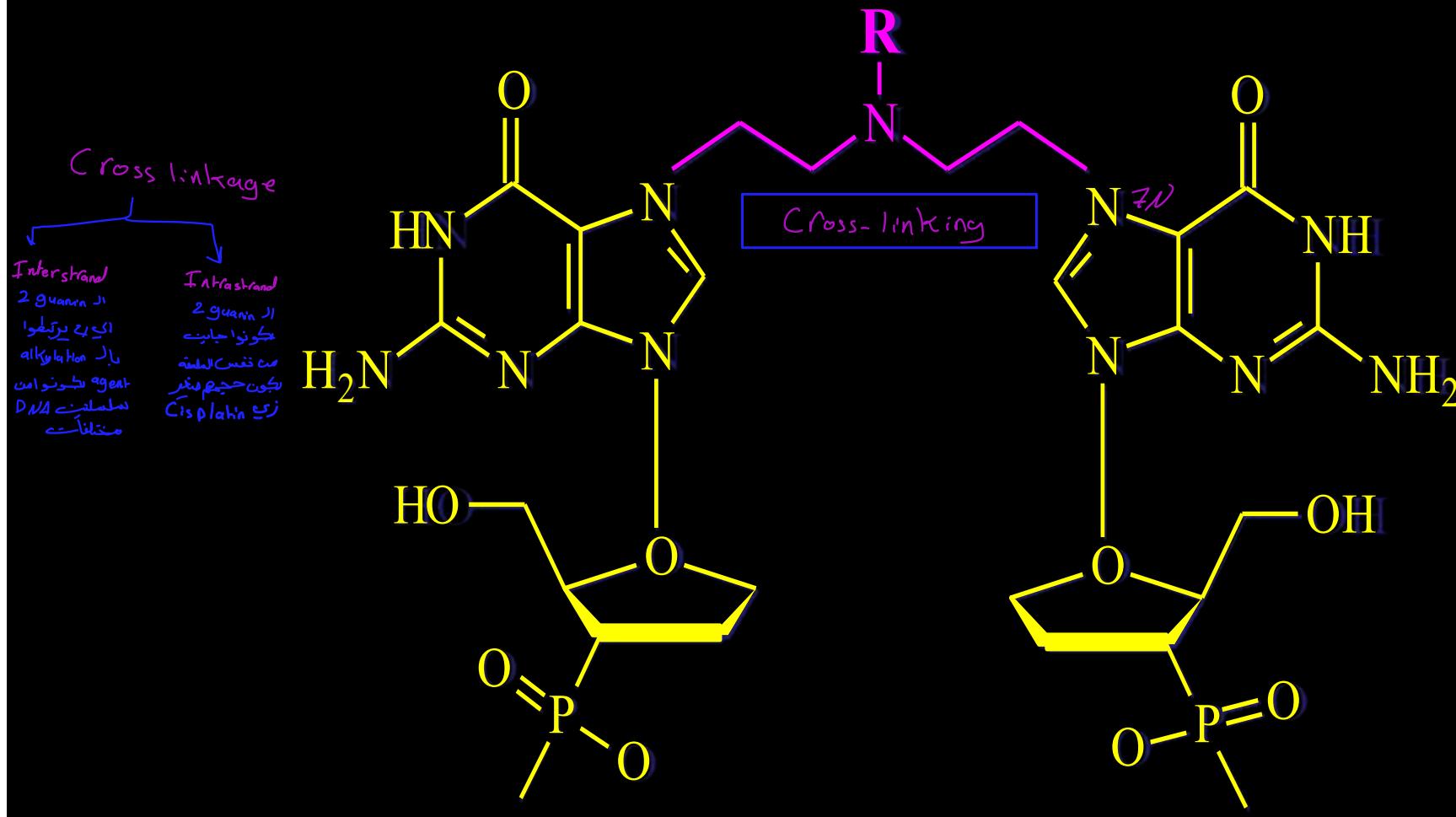
e – *circa* 1914

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





# An Example of DNA Crosslinking



**Crosslinking:** Joining two or more molecules by a covalent bond. This can either occur in the same strand (intrastrand crosslink) or in the opposite strands of the DNA (interstrand crosslink). Crosslinks also occur between DNA and protein. DNA replication is blocked by crosslinks, which causes replication arrest and cell death if the crosslink is not repaired.

## Alkylating Agents (Covalent DNA binding drugs)

\* (الدكتورة جاكل سوائل سلوك طلبتم على الترتيب

## باد ۱ تغیر المترکیب الالکترونی

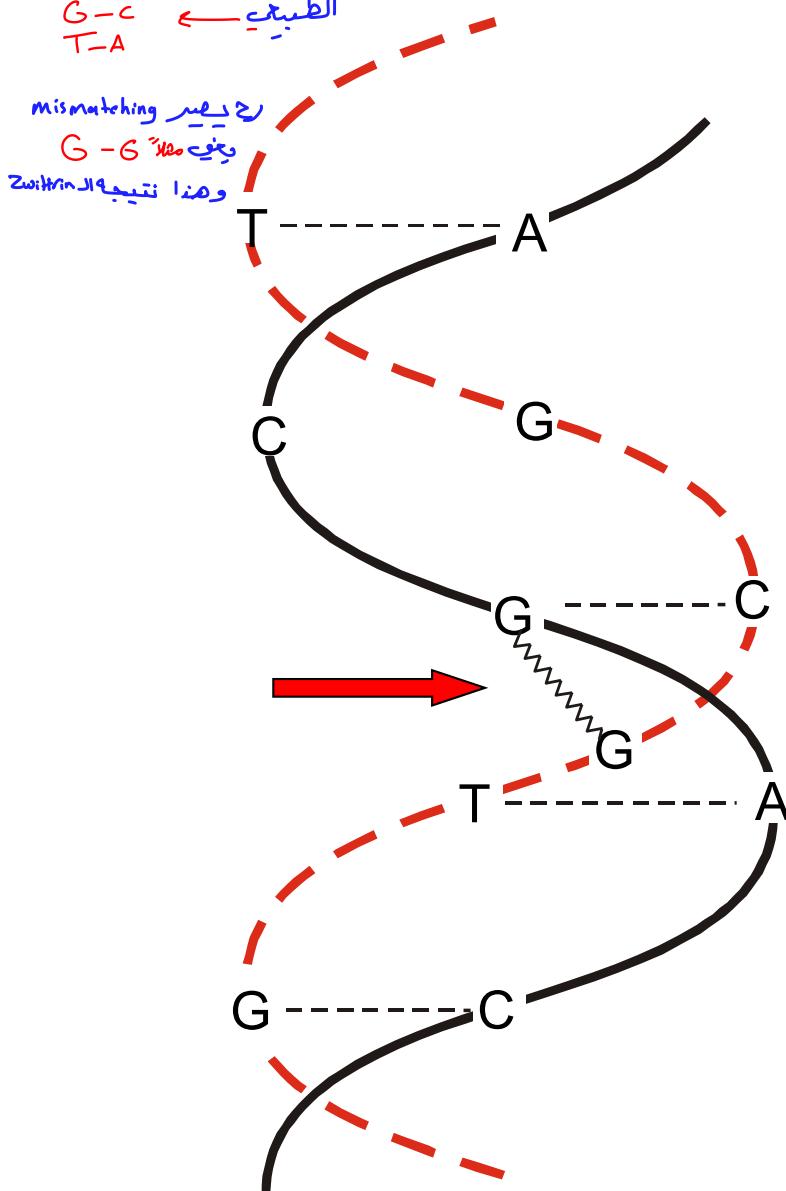
## ا) H-B مارٹ متریک بالسکل

$$\frac{G-C}{T-A} \leftarrow \text{ الطبيعي}$$

mismatching rule ✓

## ج - ج ملحوظ

وهذا نتيجة الـ **T**



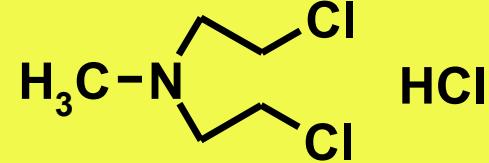
1. The first class of chemotherapy agents used.
2. They stop tumour growth by cross-linking guanine nucleobases in DNA double-helix strands - directly attacking DNA.
3. This makes the strands unable to uncoil and separate.
4. As this is necessary in DNA replication, the cells can no longer divide.
5. Cell-cycle nonspecific effect  
 $\xrightarrow{\text{M, S, G}_1, G_2, G_0}$   
التأثير على جميع مراحل الدورة الخلوية
6. Alkylating agents are also mutagenic and carcinogenic

الـ ١١) Chemotherapy! هي تحتوى على  
ـ ١٢) alkylating agent بتأثيرهم على اطفال  
ـ ١٣) مستاد هيليك السيرية! ليرتاحذهم بفضل  
ـ ١٤) ادفأ ما تتوجب وبعد ٥ سنوات عيادة المبيض ما  
ـ ١٥) تكون متاخر

## Cancer Chemotherapy

### Chapter 55. B.G. Katzung

## Mechlorethamine (or Chlormethine)



## Mechlorethamine HCl - Mustargen®

- Mechlorethamine is highly reactive, in fact, too reactive and therefore. In cases of extravasation (drug escapes from the tumor into the underlying tissue), the antidote sodium thiosulfate  $\text{Na}_2\text{S}_2\text{O}_3$  (a strong nucleophile) may be administered.  $\rightarrow$  antidote  $\left[ \text{S}-\text{S}-\text{O}^- \right]$  Strong Nucleophile
- It is capable of reacting with electrophilic sites on the mustard, and once reaction has occurred, the resulting adduct has increased water solubility and may be readily eliminated (Scheme 10.4).
- Cancer patients are at an increased risk of extravasation because of the fragility of their veins resulting from radiation, previous chemotherapy treatments, or malnutrition.

1) radiation أعشاب  
 2) previous chemotherapy treatments أدوية الكيمياء  
 3) malnutrition الغذاء الم 缺乏





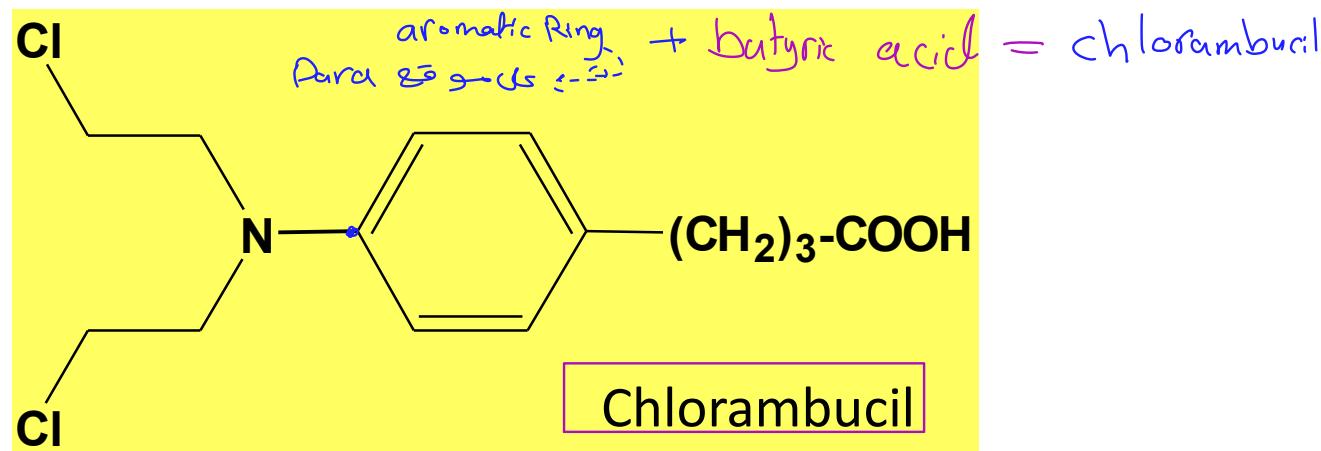


## Theoretical rationales used to improve nitrogen mustards

-Substituting an aromatic ring for methyl group can be predicted to increase chemical stability and thereby decrease the rate of alkylation because of electron-withdrawing effect.

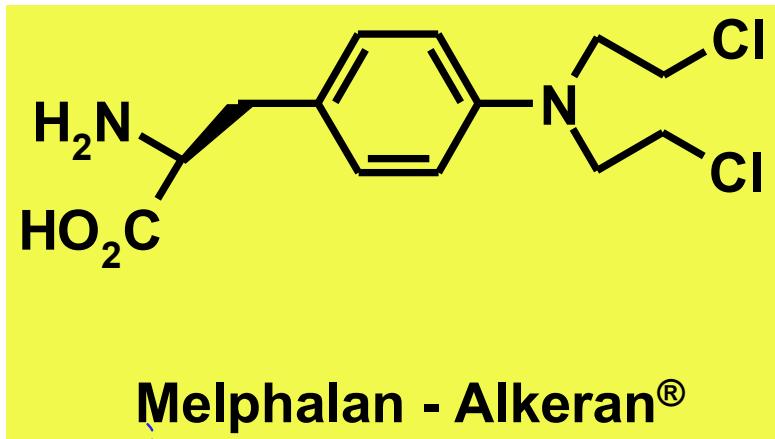
This also, will lead to good oral bioavailability, tissue distribution, before alkylation is widespread.

E.g. Chlorambucil, and melphalan.



4-(*p*-bis(2-Chloroethylamino)phenyl)butyric acid.

# Nitrogen Mustards



**Melphalan - Alkeran®**

Side effect  
alkylation agent

① Oral or IV, severe bone marrow suppression resulting in infection and bleeding

② Dosage reduction may be necessary in renal failure as measured by BUN

③ Known to cause chromosome abnormalities



IV

tab

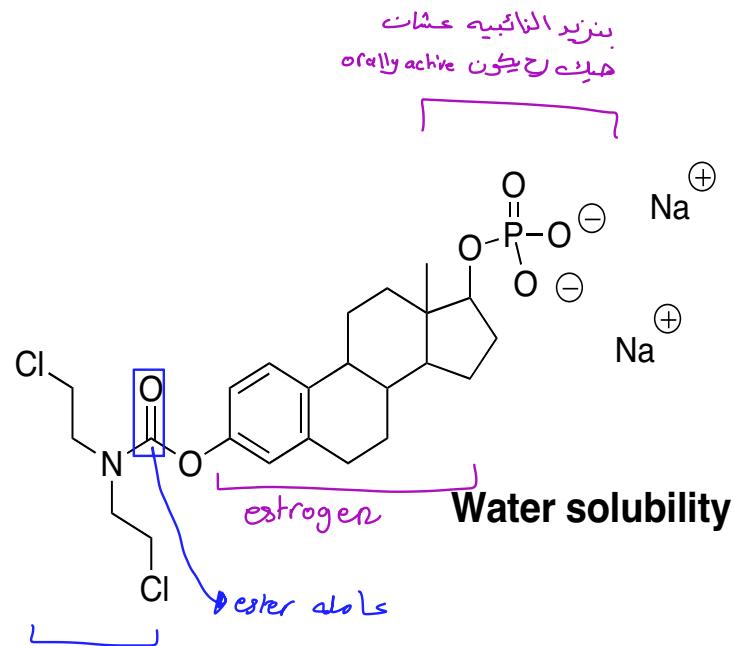


# Nitrogen Mustards

To increase selectivity, nitrogen mustards was bonded with natural carrier e.g. **estrامustine** which is active against prostate cancer, another examples is the bonding with <sup>2</sup> antimetabolites e.g. uracil mustard.

## Estramustine phosphate

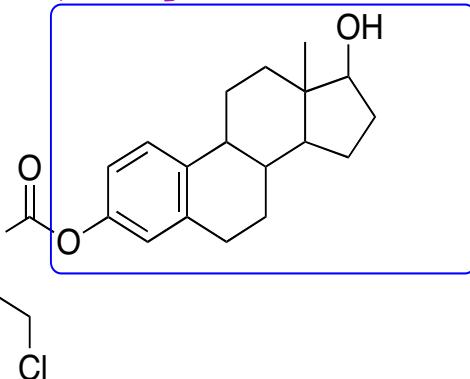
Estracyt®



Pro-drug

بنزيل الناتئي عصات  
زوج بعمل العلاج لـ  
Prostate Cancer

[estrogen +  
Prostate Cancer]



Main comp. plasma

Estradiol  
Carry to cells with  
estrogenic receptors

Estrogenic (Anti-androgenic) effect prostate  
cancer  
Cleaved to active alkylating agent?