



Chimica Farmaceutica e Tossicologica 2

Antitumorali I parte



- Antitumorali
- Ciclo cellulare, oncogeni, oncosoppressori.
- Classificazione dei farmaci antitumorali;
- Agenti citotossici: Alchilanti

Estimated new cases

				Males	Females				
Prostate	241,740	29%			Breast	226,870	29%		
Lung & bronchus	116,470	14%			Lung & bronchus	109,690	14%		
Colon & rectum	73,420	9%			Colon & rectum	70,040	9%		
Urinary bladder	55,600	7%			Uterine corpus	47,130	6%		
Melanoma of the skin	44,250	5%			Thyroid	43,210	5%		
Kidney & renal pelvis	40,250	5%			Melanoma of the skin	32,000	4%		
Non-Hodgkin lymphoma	38,160	4%			Non-Hodgkin lymphoma	31,970	4%		
Oral cavity & pharynx	28,540	3%			Kidney & renal pelvis	24,520	3%		
Leukemia	26,830	3%			Ovary	22,280	3%		
Pancreas	22,090	3%			Pancreas	21,830	3%		
All Sites	848,170	100%			All Sites	790,740	100%		

Cancer statistics (USA, 2012)

Estimated deaths

				Males	Females				
Lung & bronchus	87,750	29%			Lung & bronchus	72,590	26%		
Prostate	28,170	9%			Breast	39,510	14%		
Colon & rectum	26,470	9%			Colon & rectum	25,220	9%		
Pancreas	18,850	6%			Pancreas	18,540	7%		
Liver & intrahepatic bile duct	13,980	5%			Ovary	15,500	6%		
Leukemia	13,500	4%			Leukemia	10,040	4%		
Esophagus	12,040	4%			Non-Hodgkin lymphoma	8,620	3%		
Urinary bladder	10,510	3%			Uterine Corpus	8,010	3%		
Non-Hodgkin lymphoma	10,320	3%			Liver & intrahepatic bile duct	6,570	2%		
Kidney & renal pelvis	8,650	3%			Brain & other nervous system	5,980	2%		
All Sites	301,820	100%			All Sites	275,370	100%		

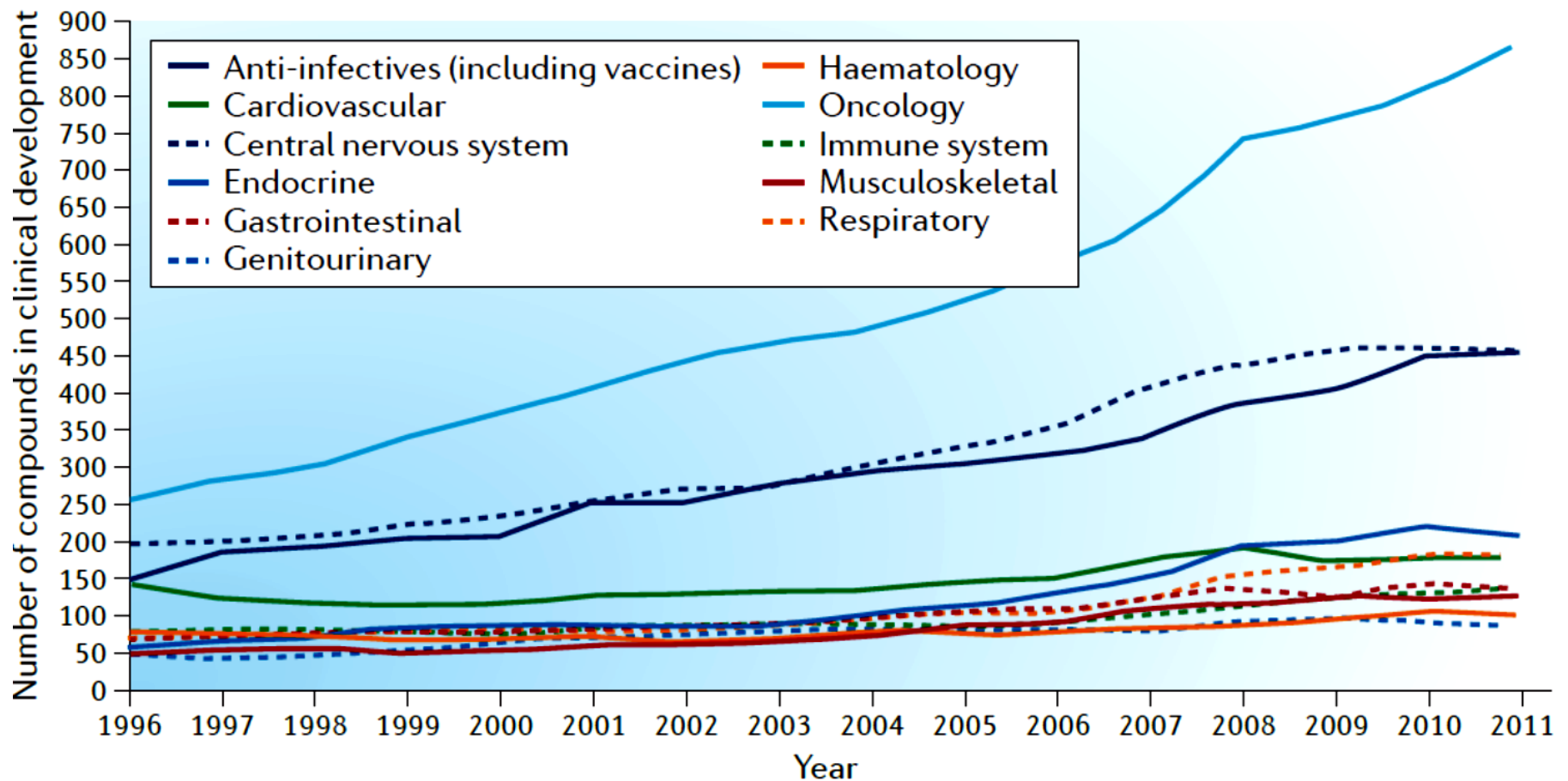
Costi di alcuni recenti farmaci AT

Table 1 – Ten current problem cancer drugs

Generic name	Trade name	Manufacturer	Indication	Delivery	Cost*	Estimated number per year†	Cost for 3 months (50%)‡
Bevacizumab	Avastin	Roche	Colon, breast	iv	£60 000	40 000	£300 million
Cetuximab	Erbix	Merck	Colon, lung	iv	£50 000	30 000	£187 million
Lapatinib	Tykerb	GSK	Breast	Oral	£40 000	4 000	£20 million
Sorafenib	Nexavar	Bayer	Renal, liver	Oral	£30 000	6 000	£22 million
Sunitinib	Sutent	Pfizer	Renal, GIST	Oral	£40 000	5 000	£25 million
Erlotinib§	Tarceva	Roche	Lung, pancreas	Oral	£40 000	30 000	£150 million
Bortezomib	Velcade	J&J	Myeloma	iv	£30 000	3 000	£11 million
Pemetrexed	Alimta	Lilly	Lung, mesothelioma	iv	£60 000	4 000	£30 million
Panitumomab	Vectibix	Amgen	Colon	iv	£45 000	20 000	£112 million
Lenalidomide	Revlimid	Cellgene	Myeloma	Oral	£70 000	1 000	£9 million

iv, intravenous; GIST, Gastrointestinal stromal tumours.

*Cost for a 1 year supply including iv infusion costs and patient management. In practice many patients will not receive a full year of drug because of failure to respond or the development of side-effects. Therefore, the package price could be considerably less. †Estimated total number of patients for current European Medicines Evaluation Agency-approved indications. All the above drugs are currently available without top-up fees in most western EU countries even though the total per capita spend on cancer in the UK is now comparable. ‡Assuming average of 3 months' drug supply as some patients will fail to respond or will develop serious side-effects and so the drug will be stopped and only 50% of patients are eligible for the drug. Total numbers estimated from CancerResearchUK statistics and labelled drug indication from the European Medicines Evaluation Agency registration file. §Erlotinib is approved for non-small cell lung cancer in Scotland.



Oncology to continue as a key area of revenue generation and investment.

From a revenue perspective, the recent success of oncology products has been indisputable, and this trend is expected to continue. For sales of innovative products in 2011 (from products launched between 2007 and 2011), 15% came from oncology and immunomodulators (data are not available for oncology alone), and the corresponding proportion of products launched in the 2012–2016 period is expected to increase to 29% in 2016.



14th Report on Carcinogens (RoC)



<https://ntp.niehs.nih.gov/go/roc14>

U.S. Department of Health and Human Services released the 14th Report on Carcinogens on November 3, 2016. The RoC is a congressionally mandated, science-based, public health document that NTP prepares for the [HHS Secretary](#). This **cumulative report** currently includes 248 listings of agents, substances, mixtures, and exposure circumstances that are known or reasonably anticipated to cause cancer in humans.

- [Press Release](#)
- [Complete Report on Carcinogens](#)
- [Fact Sheet on the 14th RoC](#)
- [Federal Register notice](#)



New Listings

Cobalt and Cobalt Compounds that Release Cobalt Ions In Vivo

- [Substance Profile](#)
- [Fact Sheet - Five Viruses](#)
- [Scientific Review](#)

Epstein-Barr Virus

- [Substance Profile](#)
- [Fact Sheet - Five Viruses](#)
- [Scientific Review](#)

Human Immunodeficiency Virus Type 1

- [Substance Profile](#)
- [Fact Sheet - Five Viruses](#)
- [Scientific Review](#)

Human T-Cell Lymphotropic Virus Type 1

- [Substance Profile](#)
- [Fact Sheet - Five Viruses](#)
- [Scientific Review](#)

Kaposi Sarcoma-Associated Herpesvirus

- [Substance Profile](#)
- [Fact Sheet - Five Viruses](#)
- [Scientific Review](#)

Merkel Cell Polyomavirus

- [Substance Profile](#)
- [Fact Sheet - Five Viruses](#)
- [Scientific Review](#)

Trichloroethylene

- [Substance Profile](#)
- [Fact Sheet](#)
- [Scientific Review](#)

Criteri di classificazione dei carcinogeni

- *Sostanze note per essere carcinogene per gli umani:*
Ci sono sufficienti evidenze di carcinogenicità da studi in vivo (animali/uomo) che indicano una relazione causa-effetto tra esposizione all'agente, sostanza o miscela e cancro.
- *Sostanze cautelativamente ritenute carcinogene per gli umani :*
 - a) Esistono evidenze, non totalmente confermate, di carcinogenicità in vivo (uomo) che indicano una credibile relazione causa-effetto benché possano esserci spiegazioni alternative;
 - b) Esistono evidenze di carcinogenicità in vivo (modelli animali) che indicano ci sia una crescente incidenza di tumori maligni e benigni in diverse specie, diversi tessuti, diverse modalità di esposizione o un'anomala frequenza di incidenza per età/tipo di tumore;
 - c) Esistono evidenze di carcinogenicità negli umani o animali, meno che sufficienti; tuttavia la sostanza o miscela rientra in una ben definita classe strutturale i cui membri erano compresi in precedenti edizioni di RoC come noti carcinogeni umani o ragionevolmente sospettati di esserlo o esistono rilevanti e convincenti informazioni sul meccanismo carcinogeno.

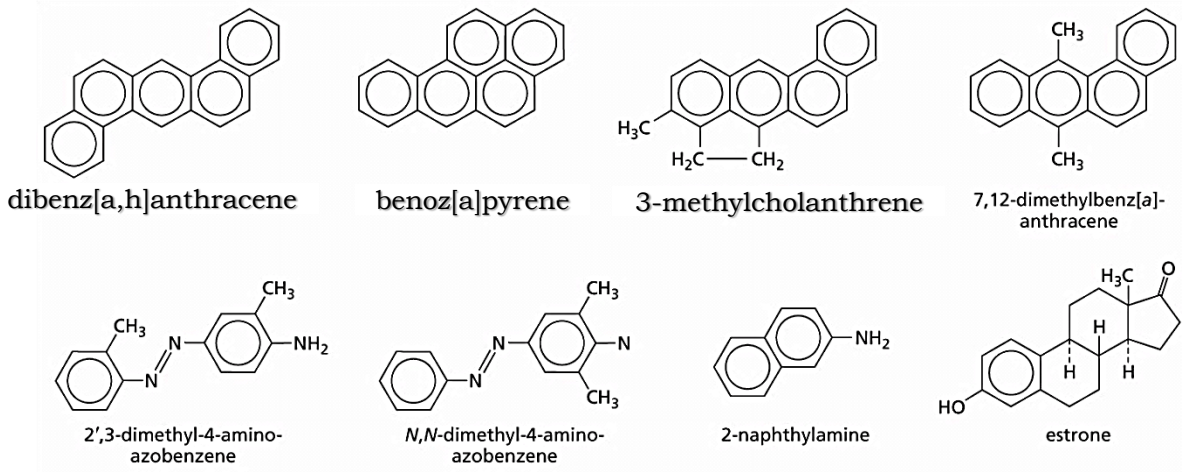


Figure 2.25 The Biology of Cancer (© Garland Science 2014)

Sostanze prodotte dalla incompleta combustione di matrici organiche.

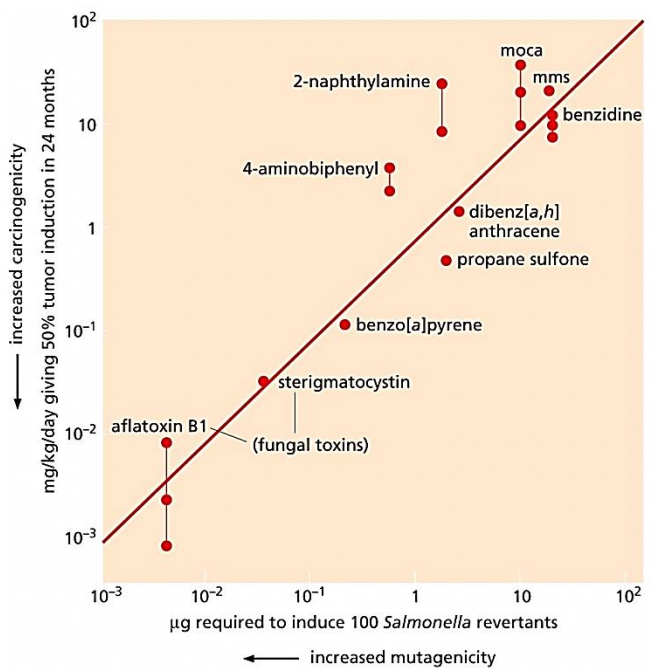


Figure 2.28 The Biology of Cancer (© Garland Science 2014)

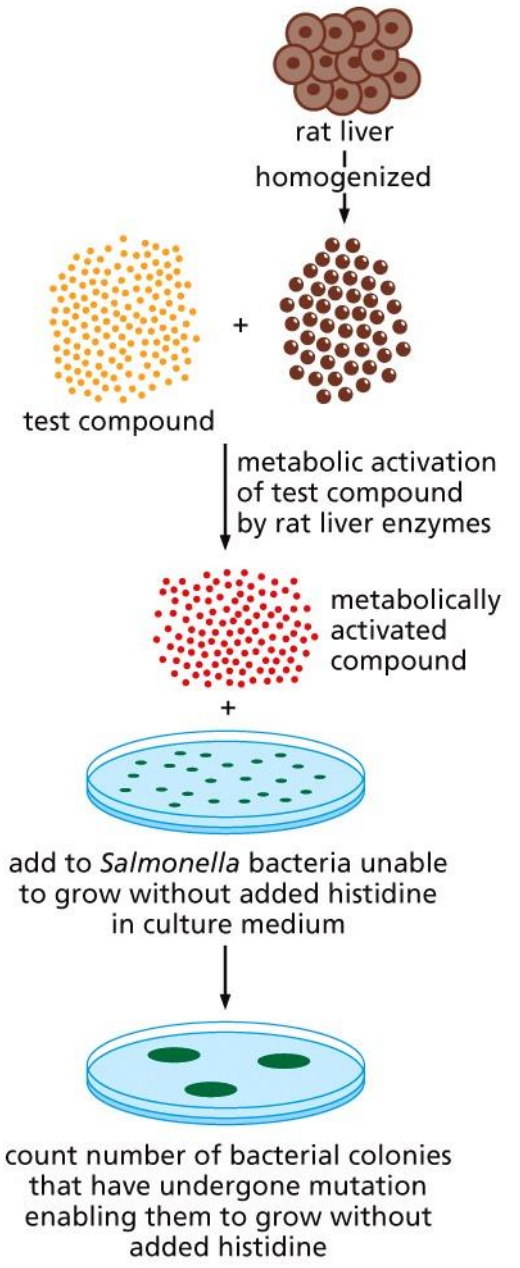
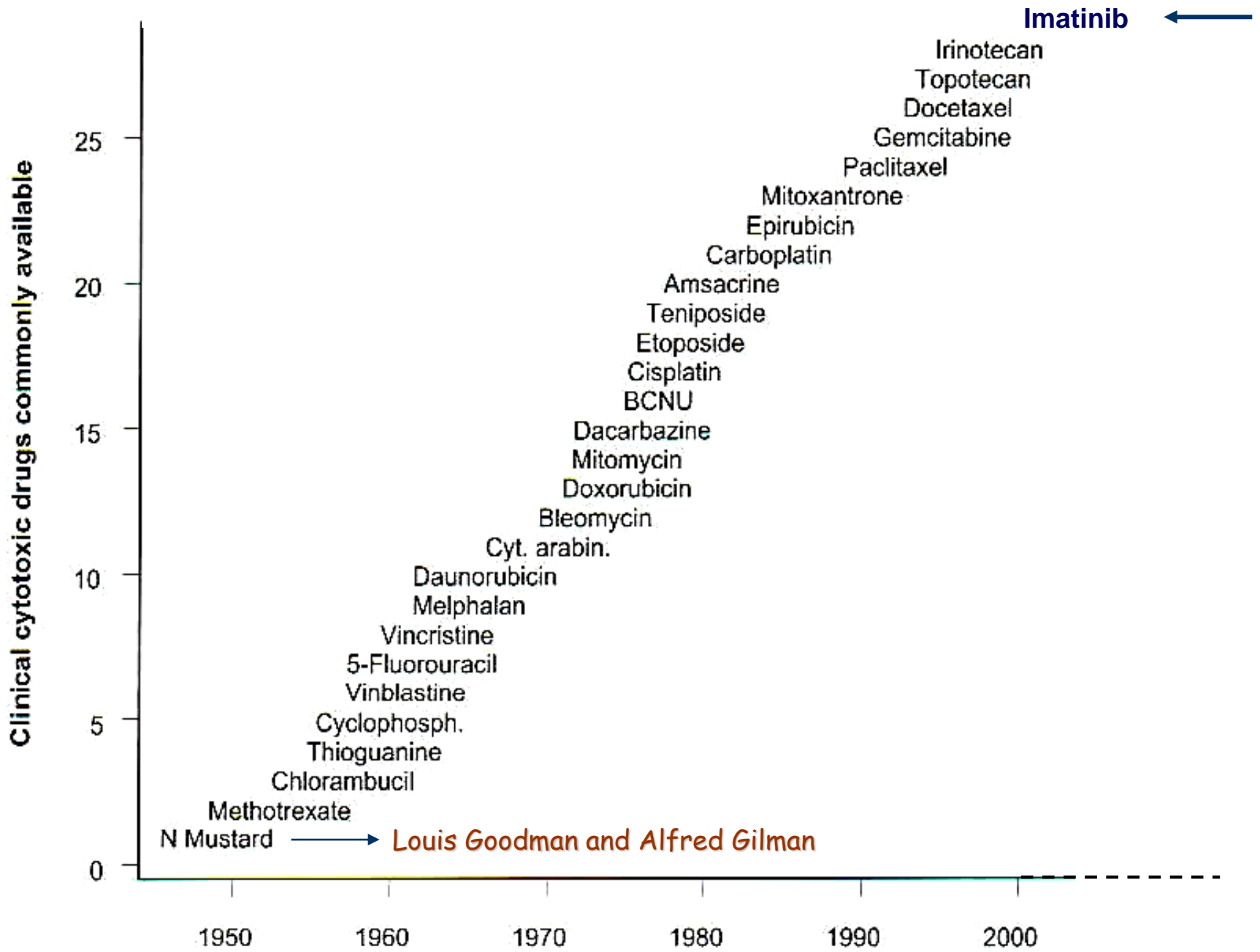


Figure 2.27 The Biology of Cancer (© Garland Science 2014)



Classificazione FARMACI ANTITUMORALI

(codice ATC*: L01-farmaci antineoplastici)

Sintetici	L01A: Agenti alchilanti	L01AA (Analoghi della mostarda azotata): Melfalan, Ciclofosfamide, Ifosfamide, Clorambucile, L01AB (Alchilsulfonati): Busulfano. L01AC (Etilenimine): Tiotepa. L01AD (Nitrosouree): Fotemustina. L01AX (altre sostanze alchilanti): Dacarbazina, Temozolomide, Pipobromano.
	L01B: Antimetaboliti	L01BA (analoghi dell'acido folico): Pemetrexed, Metotrexato, Raltitrexed. L01BB (analoghi della purina): Fludarabina, Cladribina, Mercaptopurina, Tioguanina. L01BC (analoghi della pirimidina): Citarabina, Fluorouracile, Gemcitabina, Tegafur uracile, Capecitabina.
	L01D: Antibiotici citotossici e sostanze correlate	L01DA (actinomicine): Dactinomicina L01DB (antracicline e sostanze correlate):
	Strutture varie	Derivati dell'idrazina Uree e uretani Altri

* ATC: Classificazione Anatomica Terapeutica Chimica delle specialità medicinali

CLASSIFICAZIONE DEGLI ANTITUMORALI

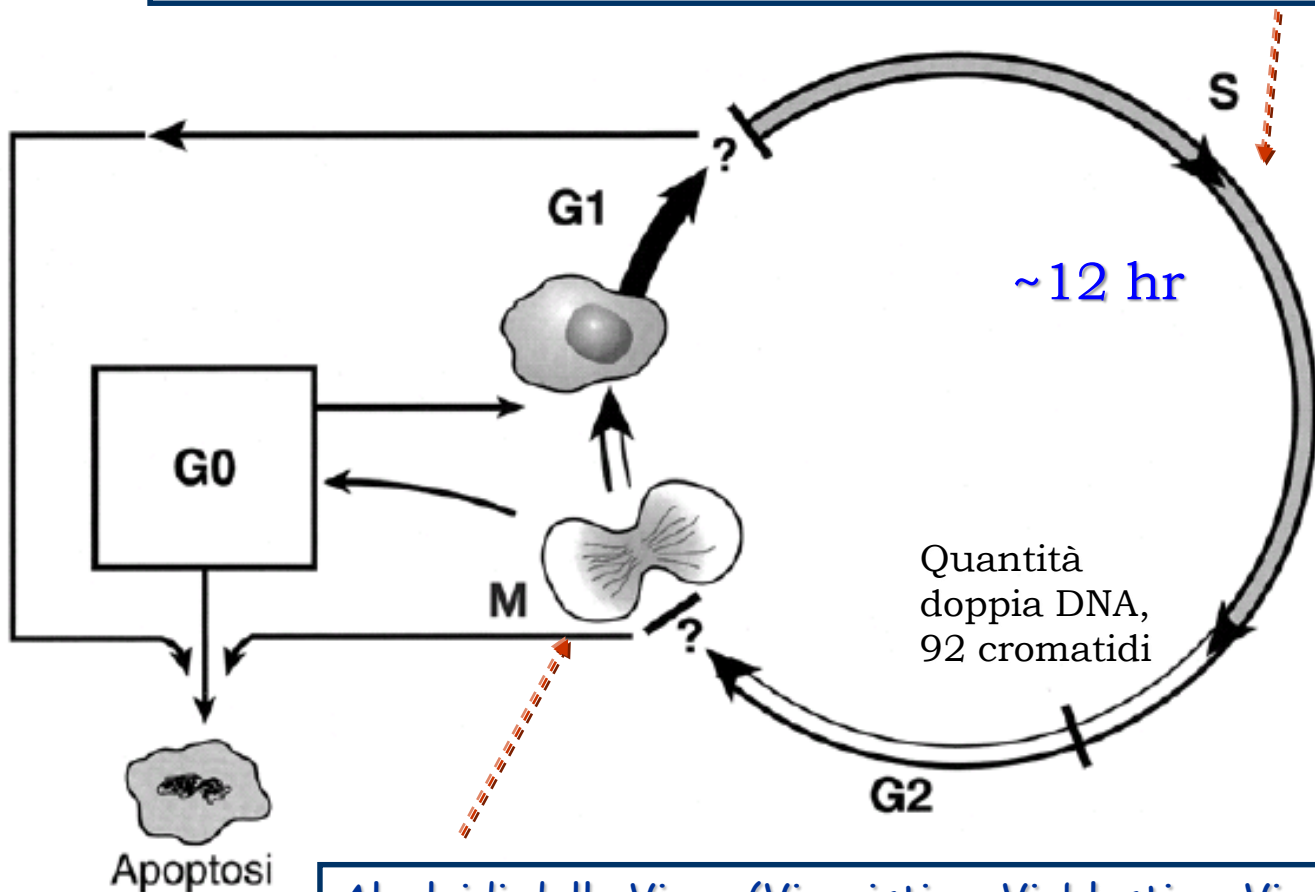
Secondo il MECCANISMO d'AZIONE

Agenti alchilanti (Radiomimetici)	Mostarde azotate Aziridine (Mitomicina) Nitrosouree (Streptozotocina) Solfonati Carbazine "Cis-platino"
Antimetaboliti Inibitori della trasduzione del segnale	Antimetaboliti purinici; Antifolici Antimetaboliti pirimidinici Inibitori di protein chinasi
Intercalanti-Inibitori Topoisomerasi	Antracicline Actinomicine Acridine Antrachinoni Mitramicina
Antimitotici	Alcaloidi della vinca Tassoli Podofillotossine
(anti)Ormoni	Sessuali (Steroidici, ipotalamici) Corticosurrenali
Immunomodulatori	Citochine (Interleuchine, interferoni) BCG, Levamisolo
Vari	Bleomicine Asparaginasi Mitotano

La tossicità si manifesta in particolare nei confronti di tessuti a rapida proliferazione

Tessuti o sistemi coinvolti	Effetti tossici
Midollo osseo	Leucopenia e linfocitopenia con aumentato rischio di infezioni o ritorno di infezioni quiescenti Immunosoppressione Trombocitopenia con conseguenti emorragie Anemia
Apparato digerente	Ulcerazioni orali e intestinali, diarrea
Cuoio capelluto	Alopecia
Gonadi	Alterazioni del ciclo mestruale, amenorrea, infertilità. Alterazioni nella spermatogenesi, sterilità
Tessuti in rimarginazione (interventi chirurgici ecc.)	Ritardata guarigione
Massa tumorale	Nel caso di leucemia e linfomi, la rapida distruzione delle cellule tumorali può portare al rilascio in grande quantità di prodotti di demolizione degli acidi nucleici con conseguente incremento di acido urico (danni renali)
Feto	Teratogenesi

Azacitidina, Citosina arabinoside (Citarabina), Fluorouracile, Idrossiurea, 6-mercaptopurina, Antibiotici peptidici (Bleomicina), Metotressato



- **G₁ - fase intermitotica** (periodo compreso tra la mitosi e l'inizio della sintesi del DNA)
- **G₀ - subfase di G₁** (periodo di riposo (latenza) della cellula che non si sta attivando per la divisione cellulare)
- **S - fase di sintesi degli acidi nucleici** (periodo di sintesi del DNA)
- **G₂ - fase premitotica** (intervallo che precede la mitosi, sintesi dell' RNA e di materiale proteico)
- **M - fase mitotica** (periodo della mitosi)

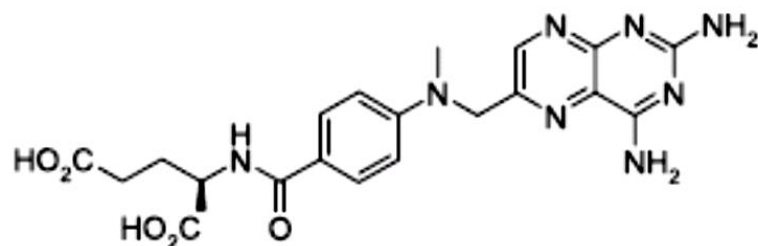
Alcaloidi della Vinca (Vincristina, Vinblastina, Vindesina), Tassolo, Lignani podofillinici (Etoposide, Teniposide)

I farmaci che agiscono in modo specifico su una determinata fase vengono definiti "ciclo cellulari specifici" (CCS).

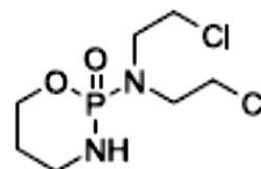
Quelli che risultano citotossici in ogni fase del ciclo vengono definiti "ciclo cellulare non specifici" (CCNS).

Esempi di farmaci CCNS (citossici)

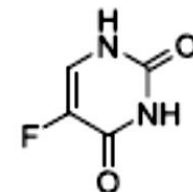
Agenti alchilanti (Busulfan, Ciclofosfamide, Clormetina, Melfalan, Tiotepa);
Nitrosouree; Antibiotici antitumorali (Actinomicina, Daunorubicina,
Doxorubicina, Mitramicina, Mitomicina); Procarbazina; Cis-platino;
Dacarbazina



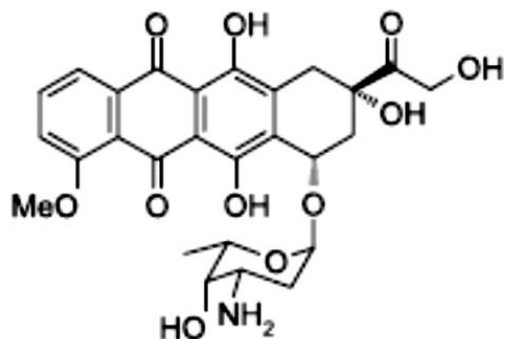
Methotrexate



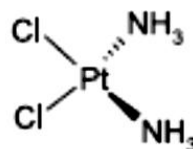
Cyclophosphamide



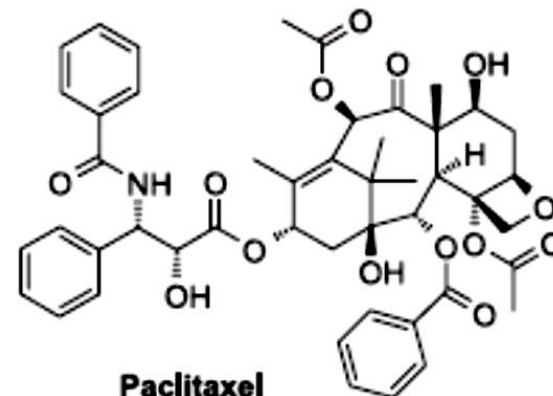
5-Fluorouracil



Doxorubicin



Cisplatin



Paclitaxel

Meccanismo d'azione comune degli agenti alchilanti: formazione di un legame covalente tra le "mostarde azotate" e DNA tramite alchilazione di basi puriniche e conseguente cross-linking inter-(intra) catene

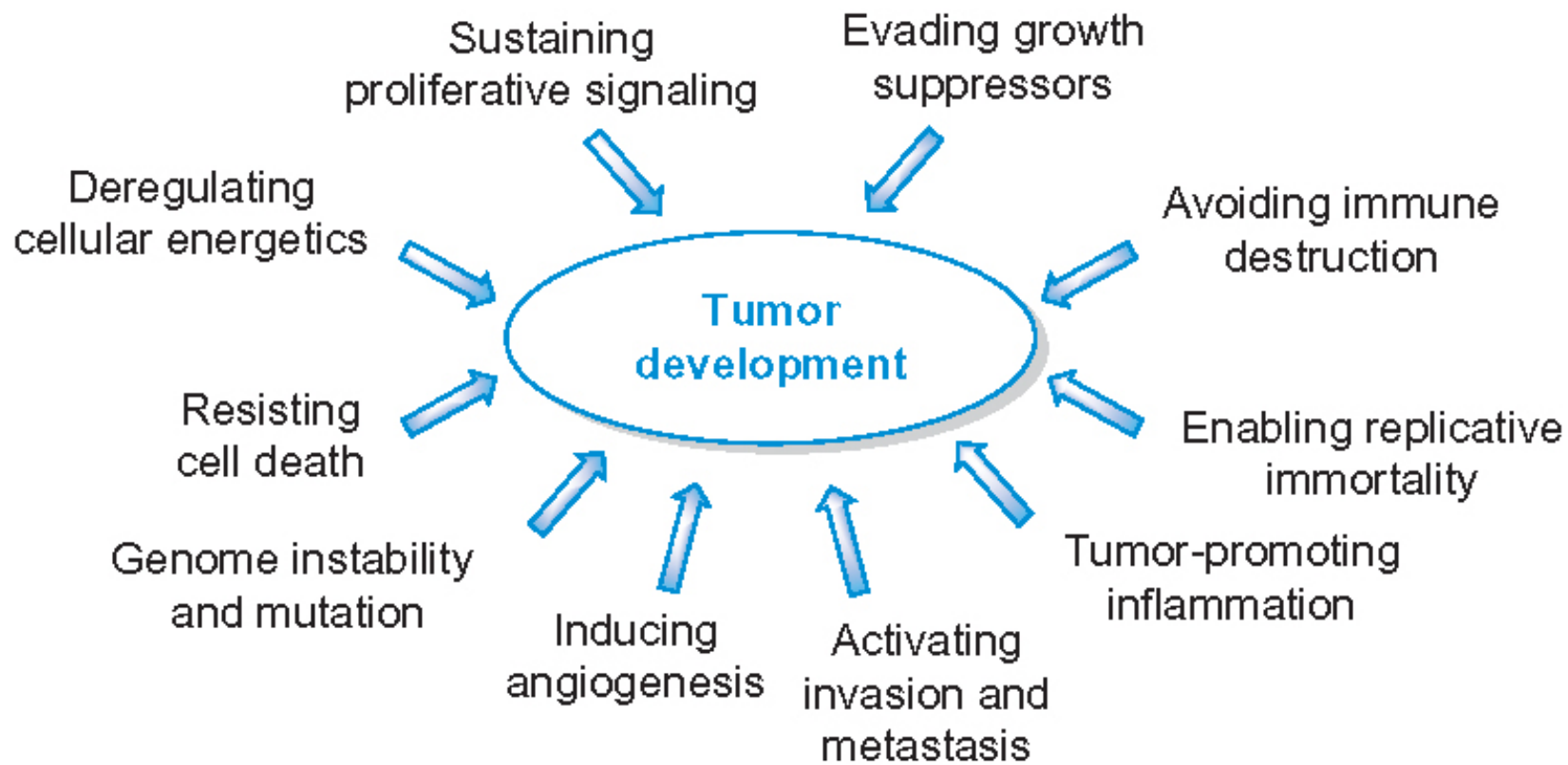
Drug	FDA approval ^a	Clinical utility ^{b,c}	Principal mode of action
Methotrexate	1953	ALL	Inhibitor of DNA precursor synthesis [13]
Cyclophosphamide	1959	Non-Hodgkin's lymphoma	DNA alkylating agent [10]
5-Fluorouracil	1962	Colorectal, gastric	Inhibitor of DNA precursor synthesis [15]
Doxorubicin	1974	Osteogenic sarcoma, Hodgkin's disease, CML, soft tissue sarcoma	Inhibitor of DNA replication, transcription, repair [20]
Cisplatin	1978	Ovarian, head and neck, lung, testicular	DNA coordinating agent [19]
Paclitaxel	1992	Ovarian, breast, small cell lung cancer	Inhibitor of microtubule assembly [21]
Imatinib	2001	CML	TKY

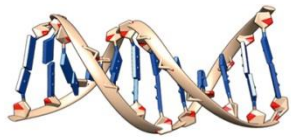
a) (<http://www.fda.gov/cder/cancer/approved.htm>);

b) *usi principali*;

c) *generalmente quale componente in multiterapia*

ALL= leucemia
linfoblastica acuta





Gene



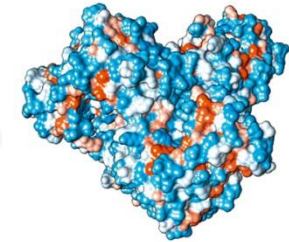
Identify a target
macromolecule



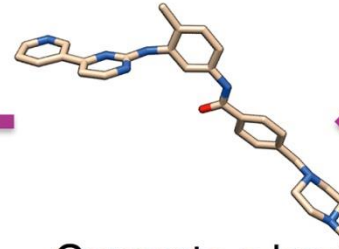
Validate
the target



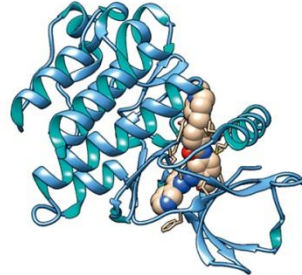
Purify and crystallize
the target



Determine the three-
dimensional structure
of the target



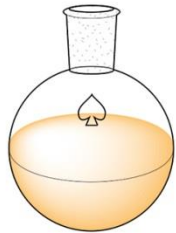
Generate a lead
compound



Target-ligand
complex structure



Design and synthesize
ligands with improved
interactions



*Lead
optimization*



Biological assays



Preclinical studies

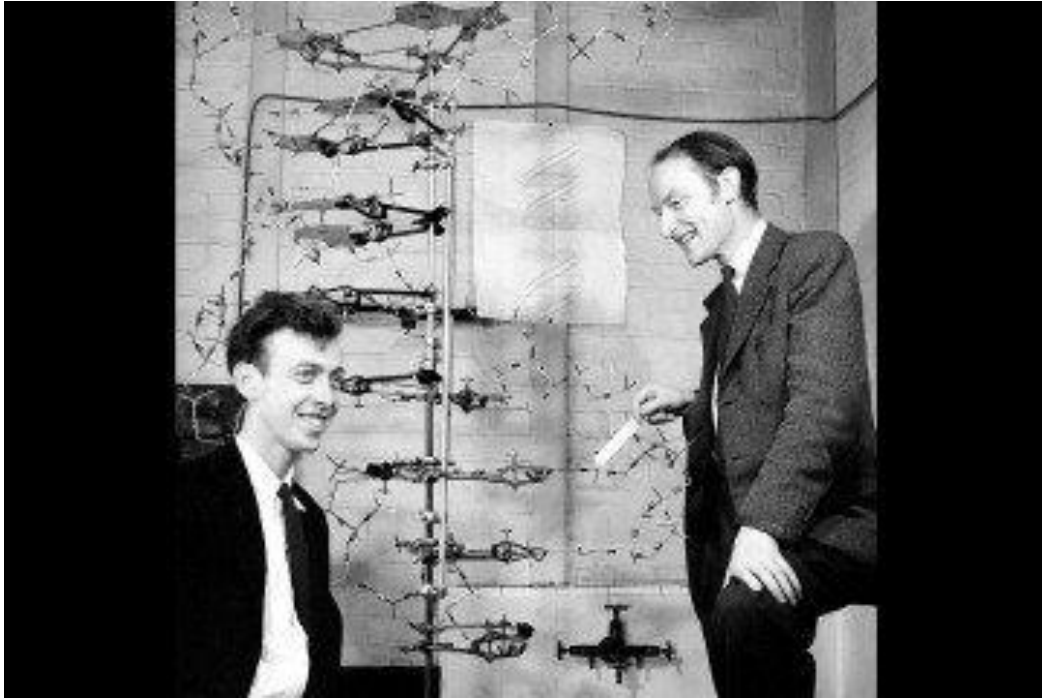


Clinical studies



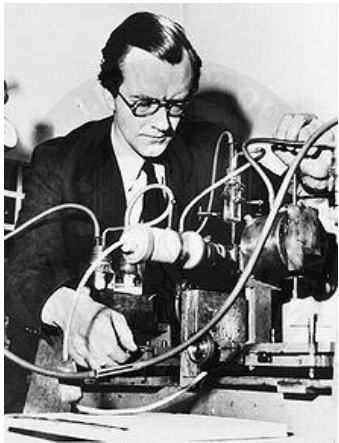
Market

Francis Compton Crick

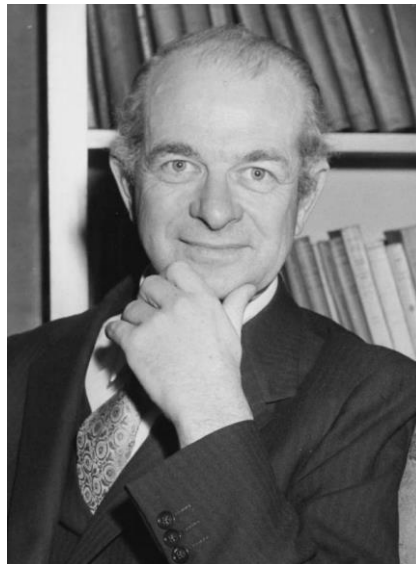


Rosalind Elsie Franklin

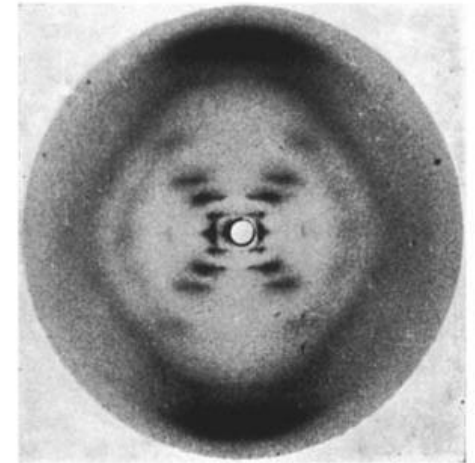
Jim Dewey Watson



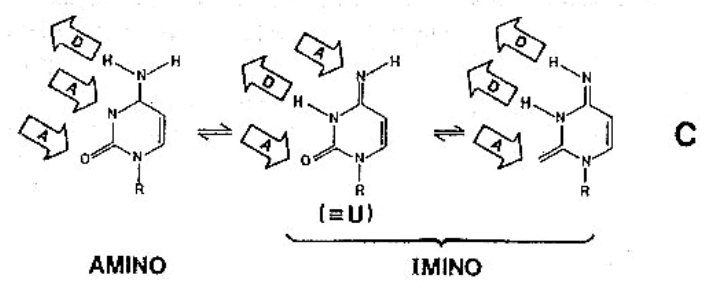
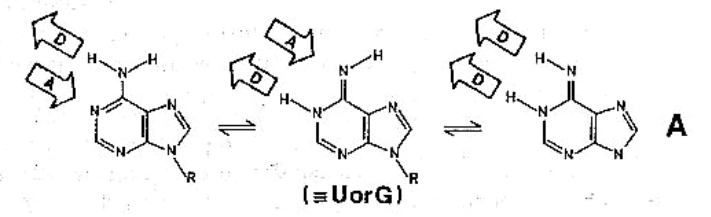
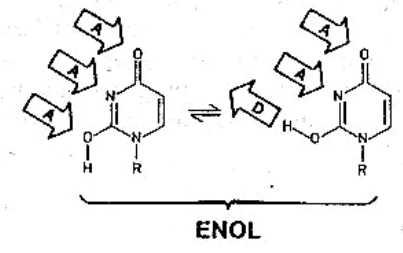
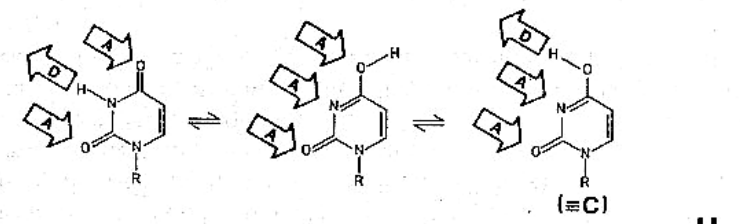
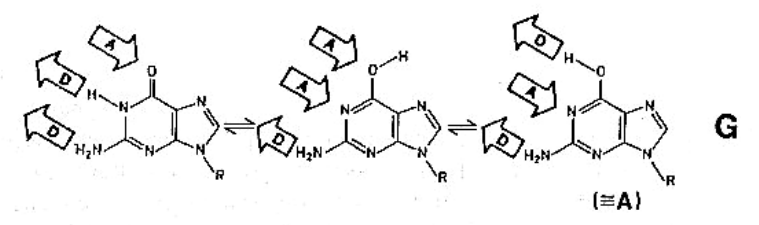
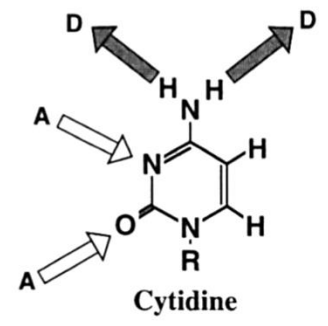
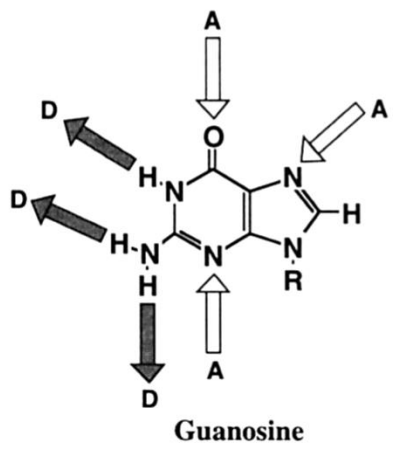
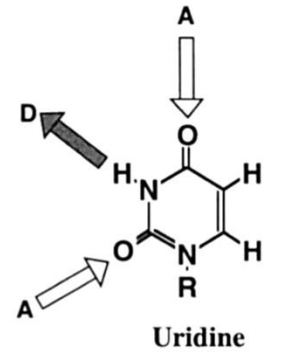
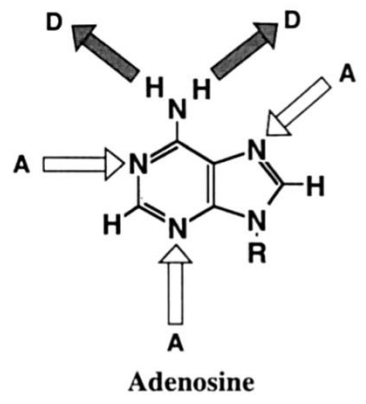
Maurice Wilkins



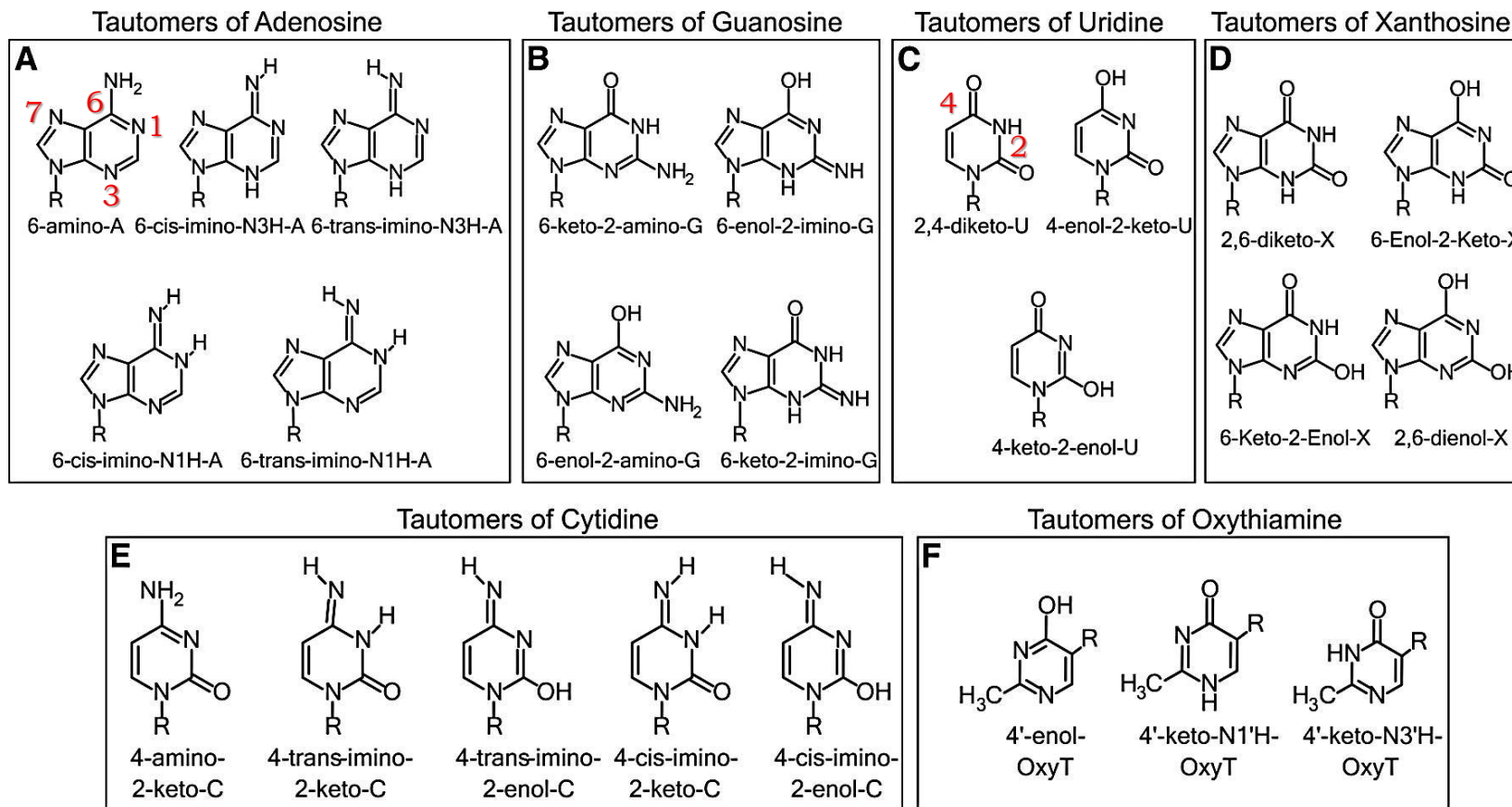
Linus Pauling



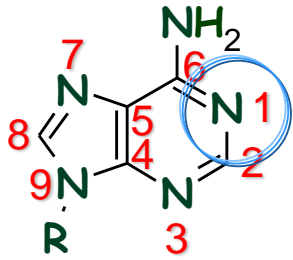
Tautomerismo keto-enolico e amino-iminico in basi nucleosidiche.



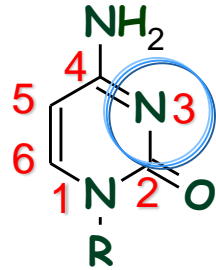
Tautomers of (A) adenosine, (B) guanosine, (C) uridine, (D) xanthosine, (E) cytidine, and (F) oxythiamine.



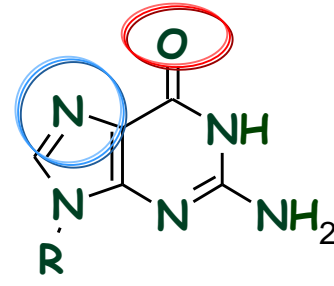
N^7 of guanine > N^1 of adenine > N^3 of cytosine > N^3 of thymine.



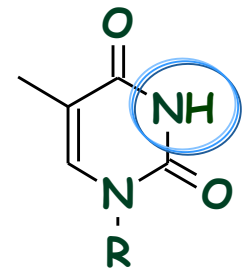
adenina



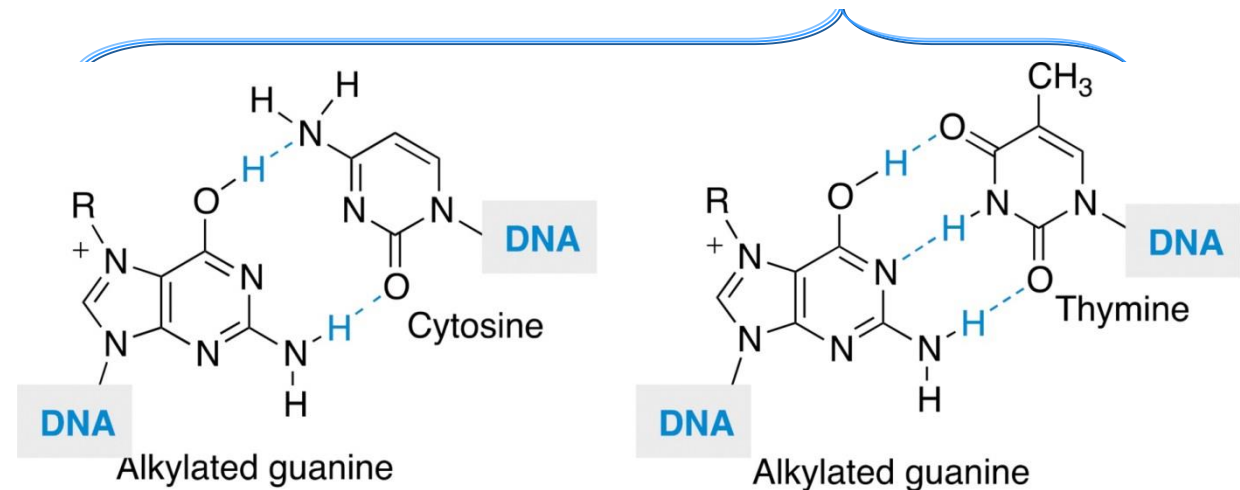
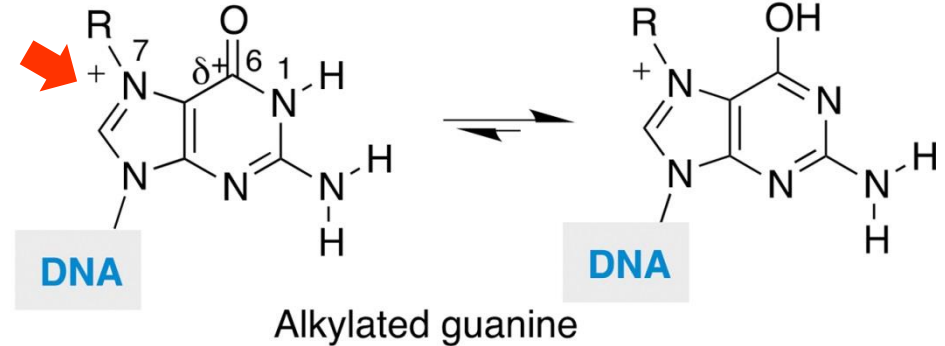
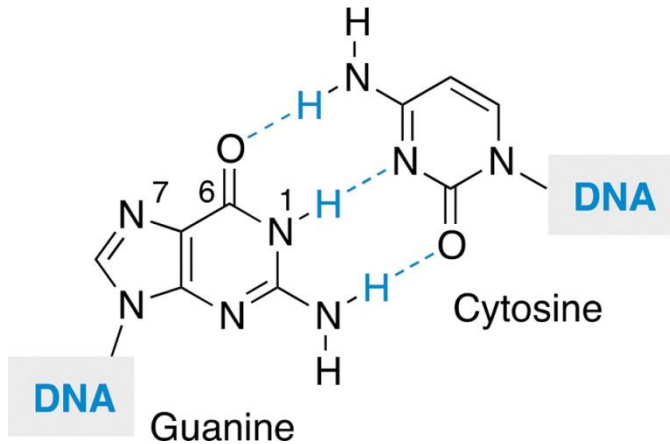
citosina



guanina

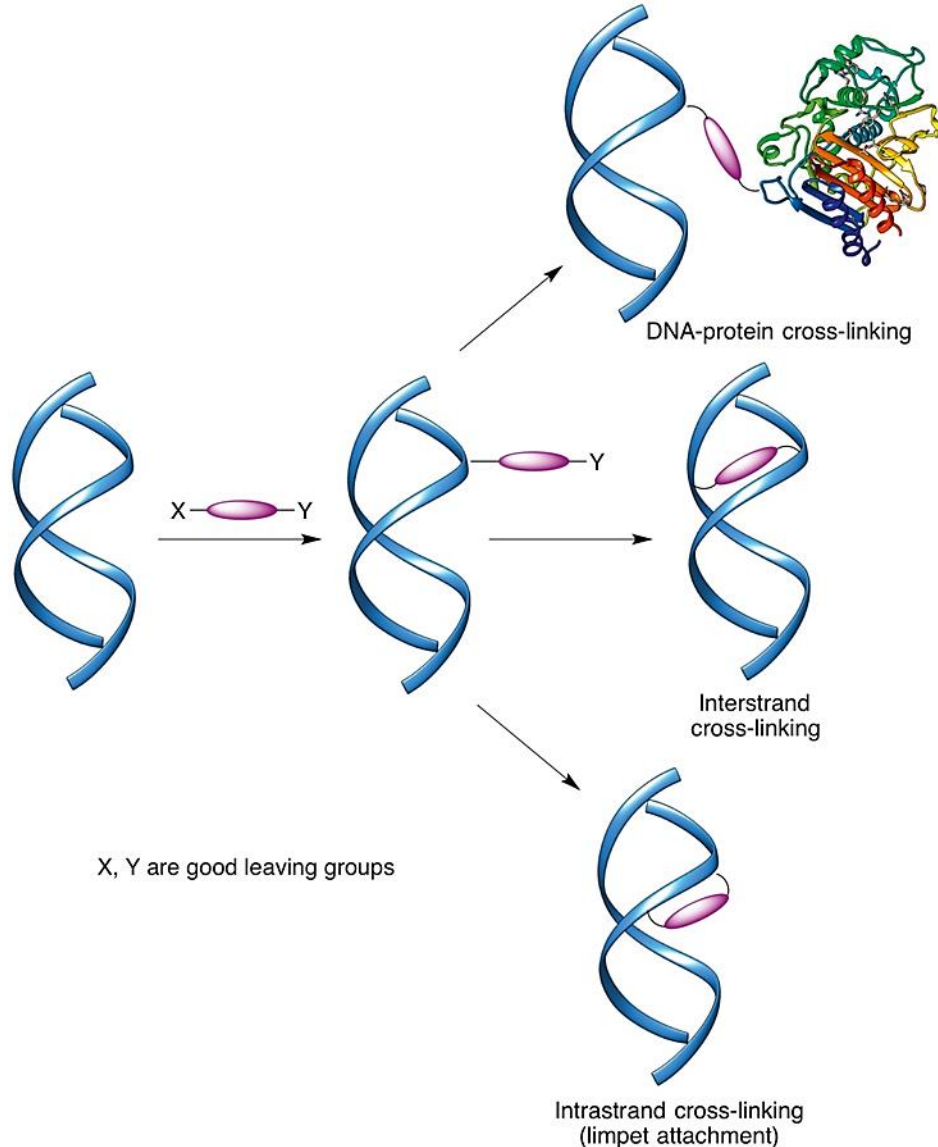


timina



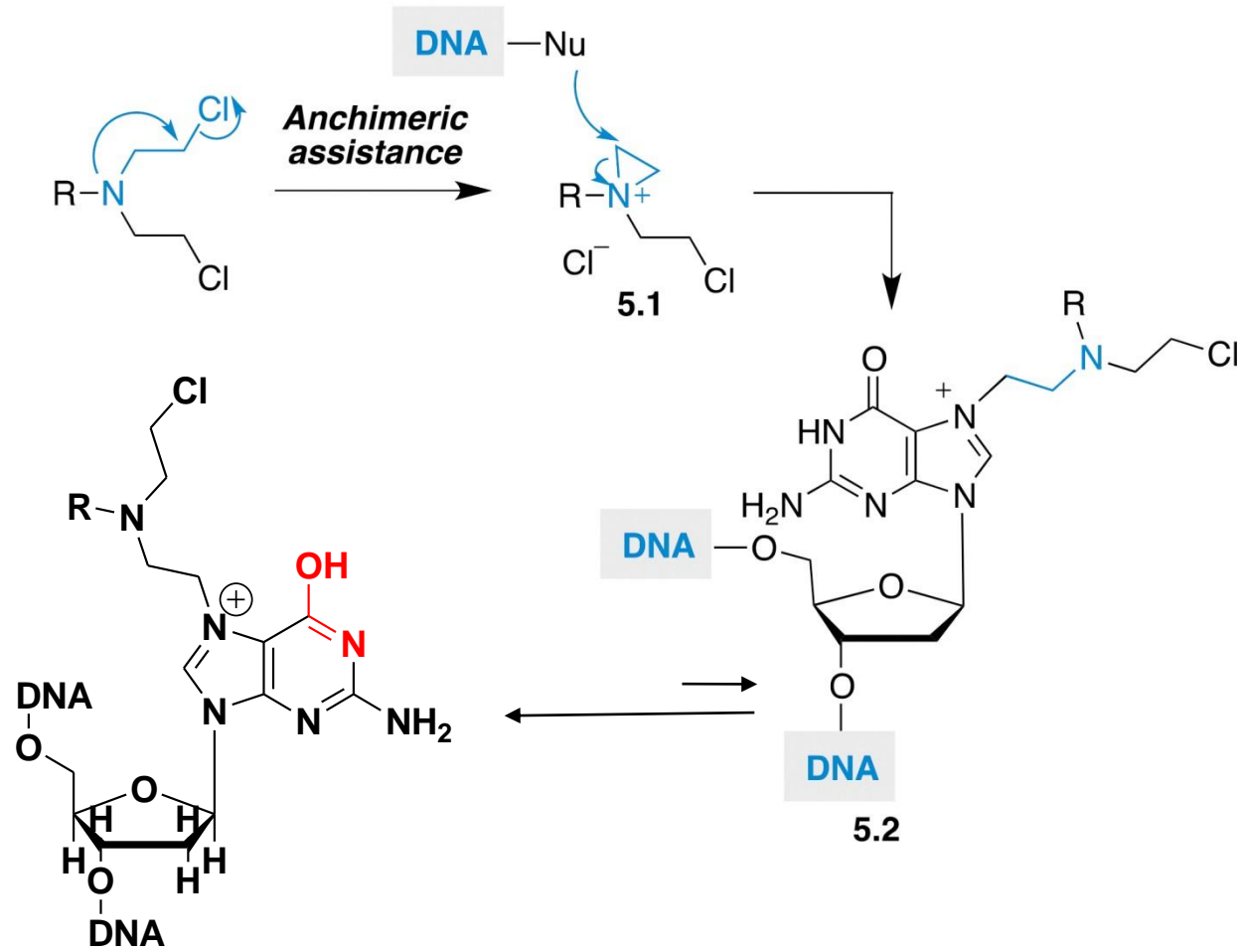
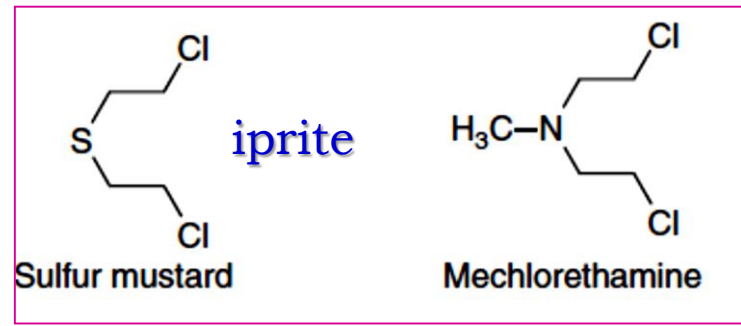
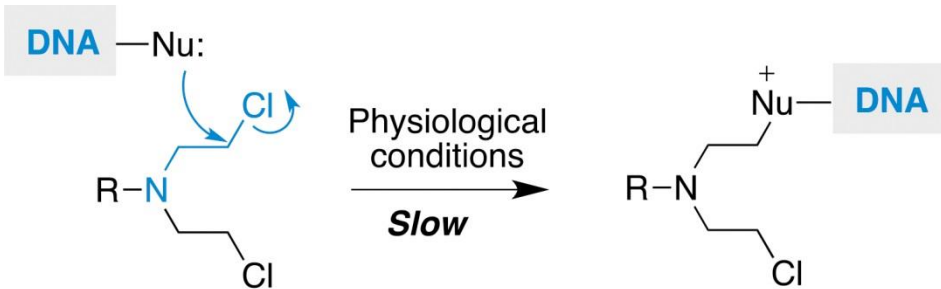
GC << GT →
mutazione

Agenti alchilanti: composti capaci di legare covalentemente un gruppo alchilco ad una biomolecola in condizioni fisiologiche (soluzione acquosa pH 7.4, 37°C);
 Agenti alchilanti il DNA, interagiscono con le cellule in ogni fase del ciclo, (> G1, S)



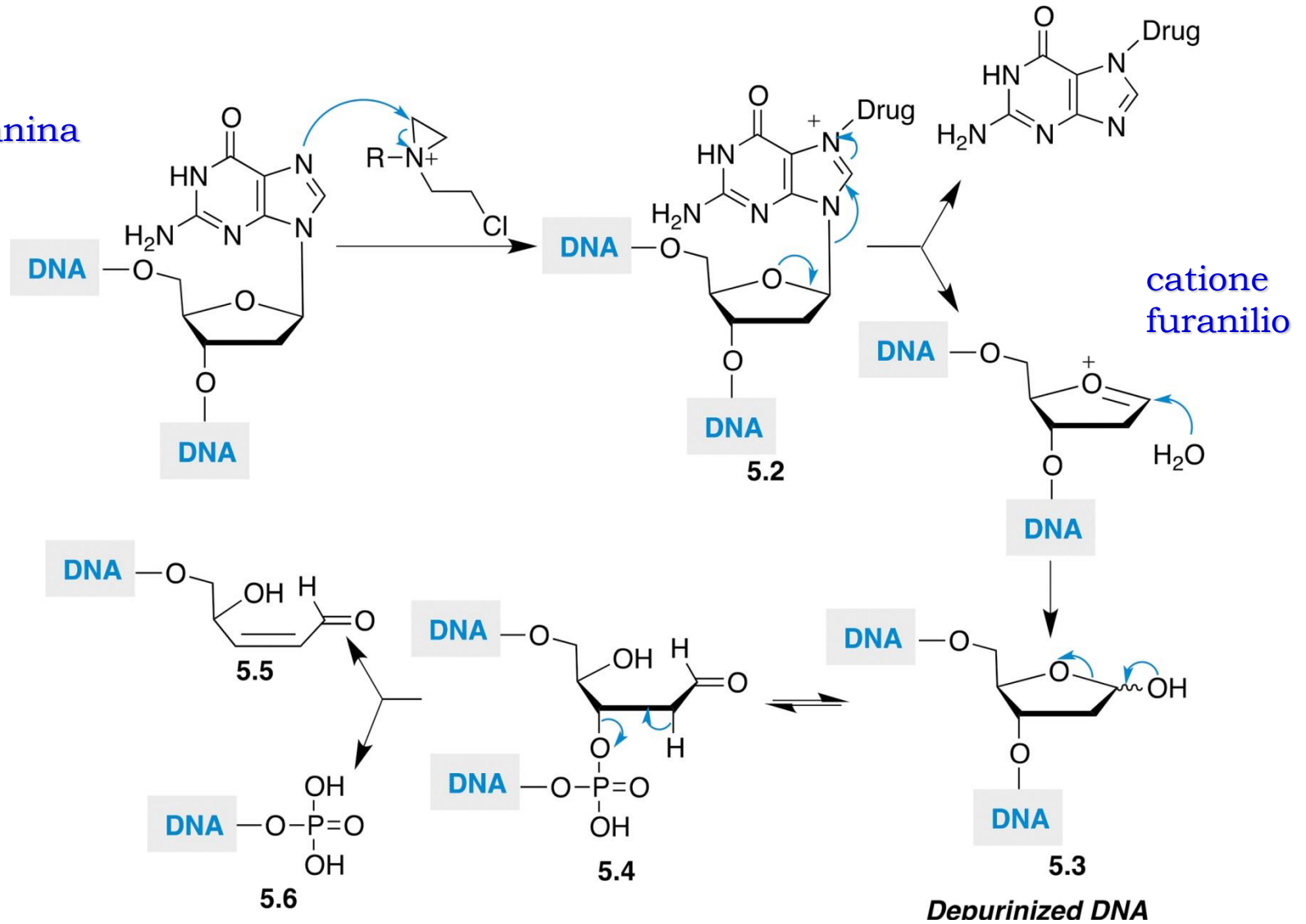
L'alchilazione

- ☒ replicazione DNA e trascrizione dell'RNA dal DNA modificato.
- induce frammentazione del DNA per reazioni idrolitiche;
- ☒ l'azione degli enzimi preposti alla riparazione del DNA quando questi tentano di rimuovere le basi alchilate;
- induce forme di accoppiamento anomale tra nucleotidi (HB tra basi);
- da alchilanti bidentati (più citotossici) formano ponti intrastrand;
- genera crosslinking tra DNA e proteine associate o tra strands complementari (interstrands) impedendo la separazione durante la replicazione o traduzione;

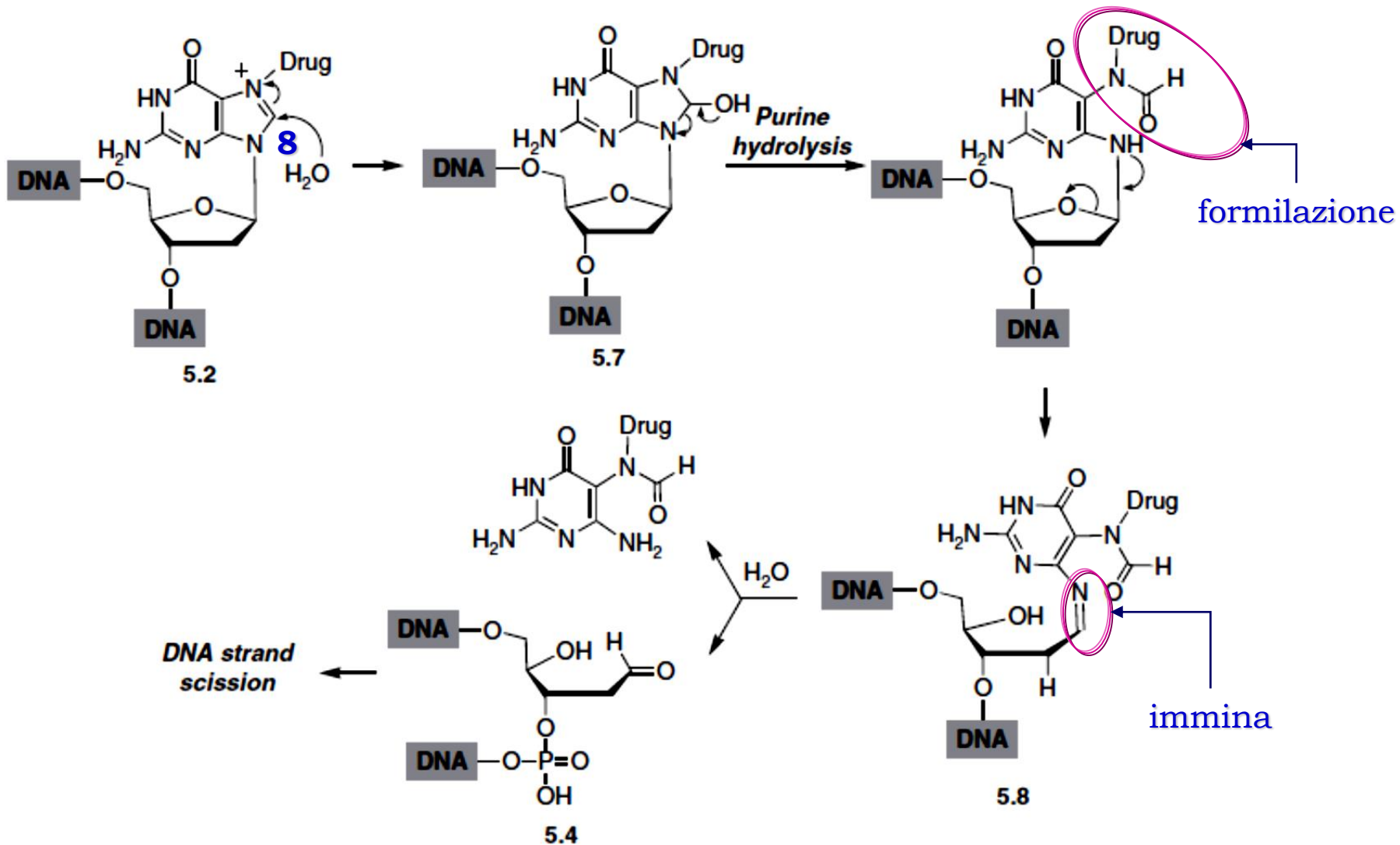


Velocità alchilazione << (t.a.) → assistenza anchimerica, sostituzione intramolecolare catione aziridinio → tensione ciclo tre termini ridotta dall'apertura. Atomo > nucleofilo N-7 guanina.

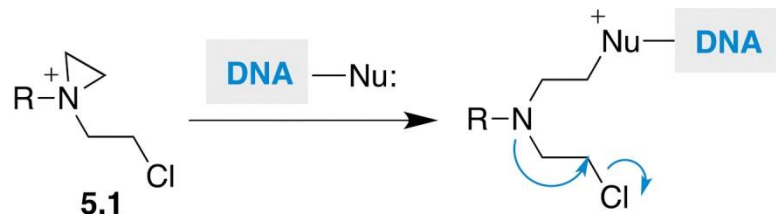
guanina



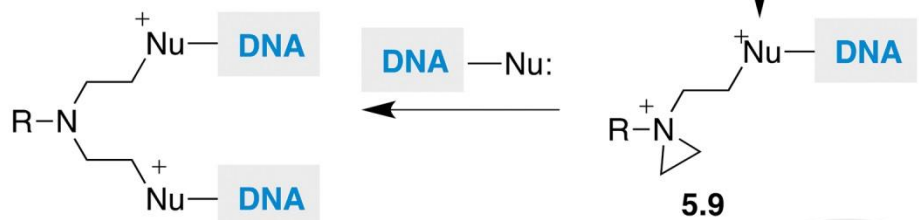
- Reazioni idrolitiche → alterazione DNA.
- cleavage (lento) legame eterosidico (5.2) induce depurinazione DNA (5.3);
- equilibrio con 5.4 → fosfato (gruppo uscente);
- riarrangiamento e frammentazione a 5.5 e 5.6



Incremento della elettrofilia in C8, adiacente alla carica positiva indotta dall'alchilazione. L'aggiunta di acqua in C8 produce 5.7 che riarrangia per formare 5.8, una immina che subisce a sua volta idrolisi per dare il frammento 5.4 e scissione del DNA.

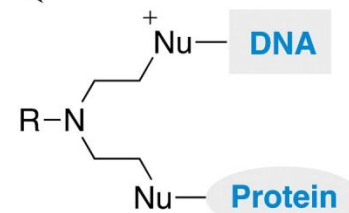


DNA monoalkylation

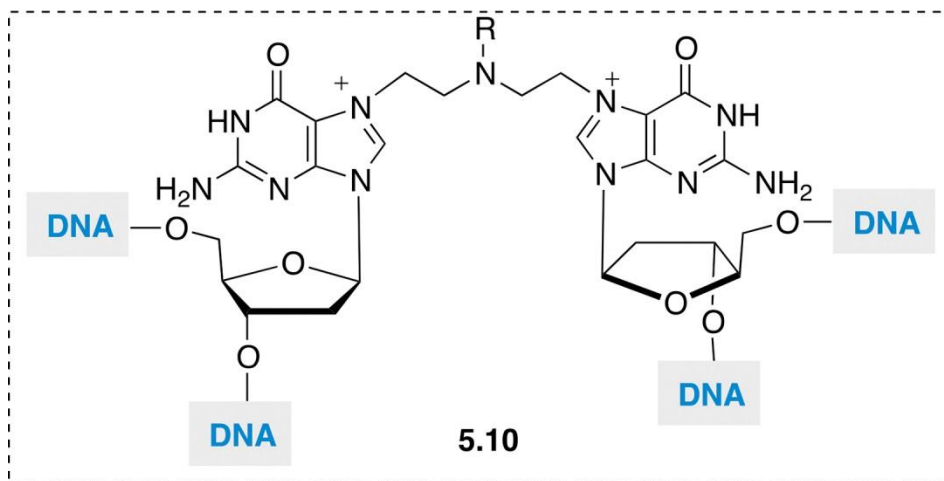


DNA dialkylation

Protein-NuH

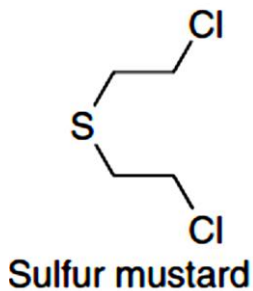


5.11





Iprite: Fritz Haber
Premio Nobel nel 1918
(processo Haber-Bosch)



1-cloro-2-[(2-cloroetil)sulfanil]etano
Iprit, Mustard gas, Yperite



Foto del 1917 in seguito alla
terza battaglia di Ypres

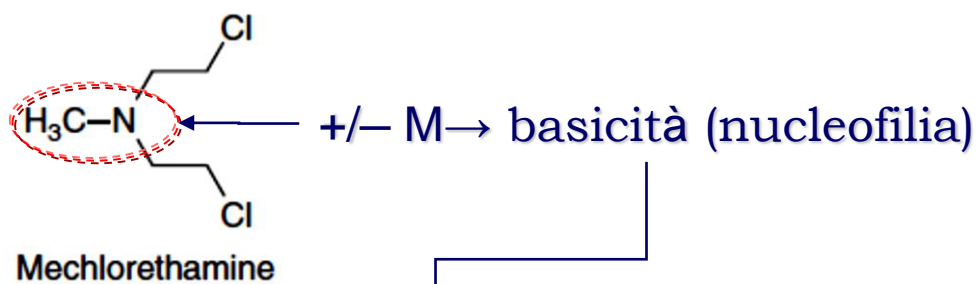
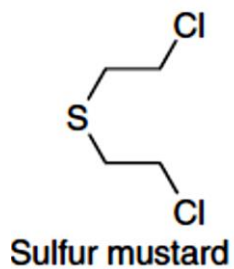


Stewart F. Alexander
danno tessuto linfoide
e mieloide



2 dicembre 1943

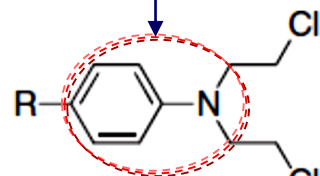
John Harvey



Clorambucile

(LEUKERAN o.s.)

Morbo di Hodgkin
non-Hodgkin
Leucemia linfocita cronica
Macroglobulinemia di Waldenström
Adenocarcinomi ovarici avanzati



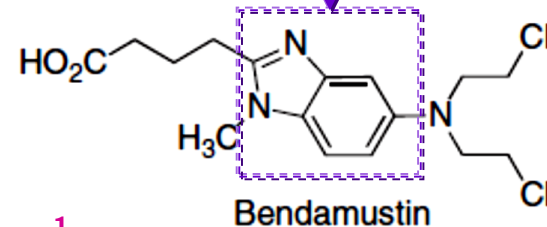
R = H 5.12 ← insol.

R = CO₂H 5.13

R = (CH₂)₃CO₂H ← Chlorambucil

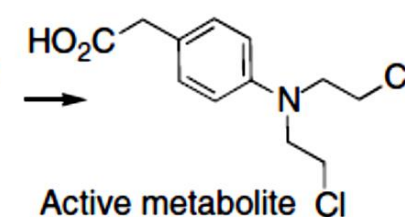
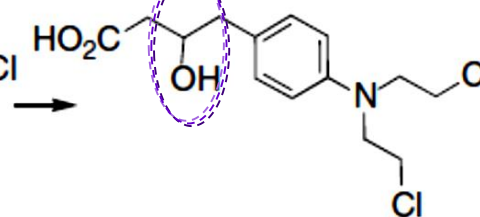
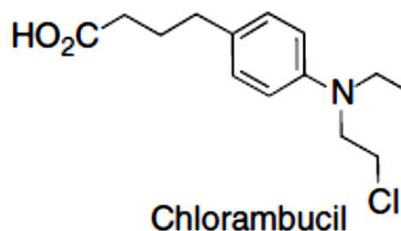
butirrato

benzimidazolo



β-idrossilazione
(cfr acidi grassi)

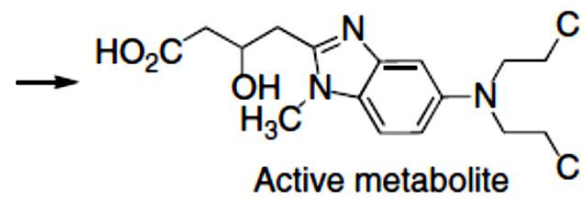
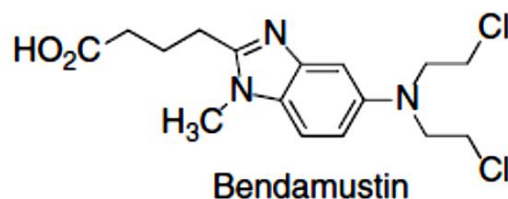
Ac. 4-[bis(2-clorettil)amino]
benzenebutanoico

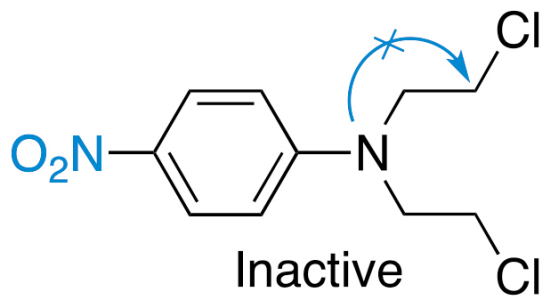


Bendamustina

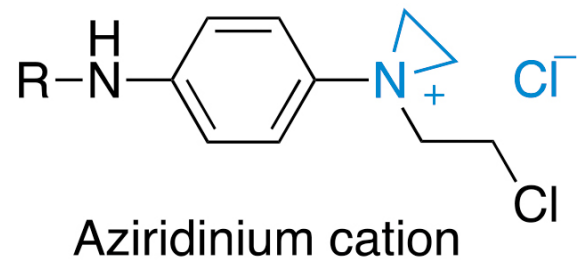
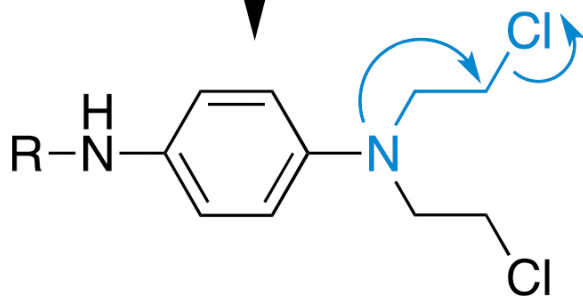
(Levact)

Morbo di Hodgkin
non-Hodgkin
Leucemia linfocita
cronica
Mieloma multiplo

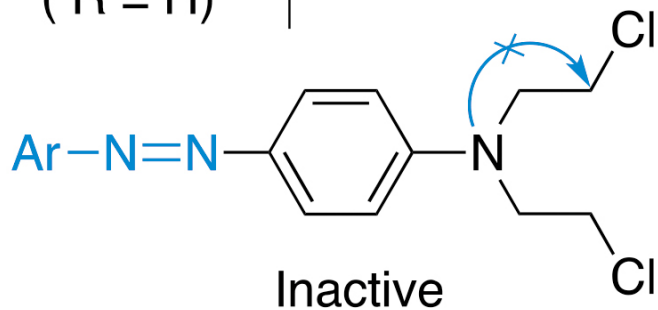




Reduction
(R = H, OH)



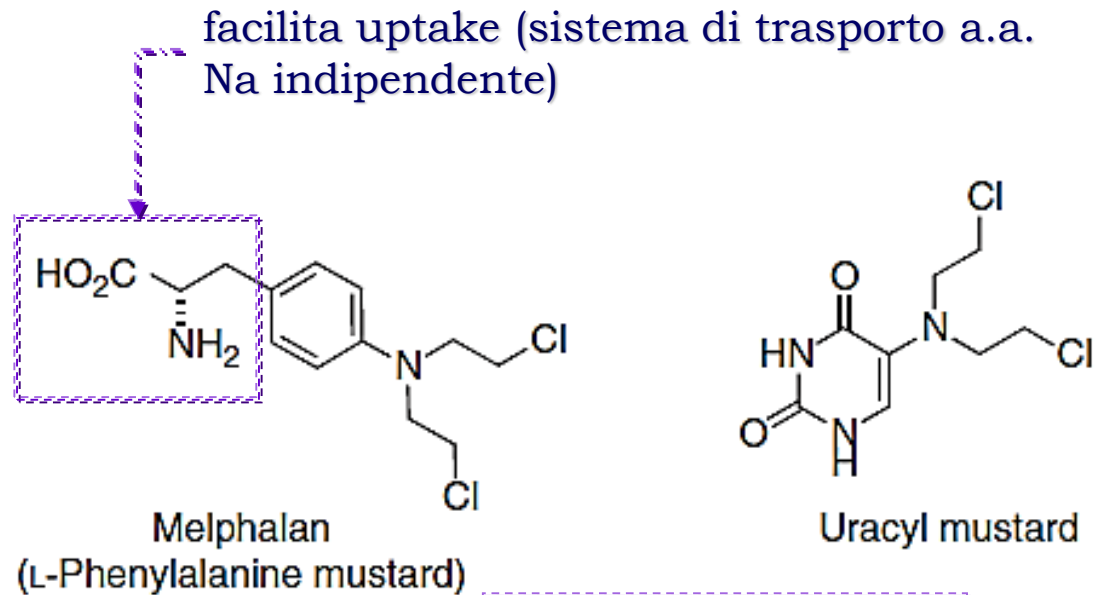
Reduction
(R = H)



Mostarde azotate sito-dirette

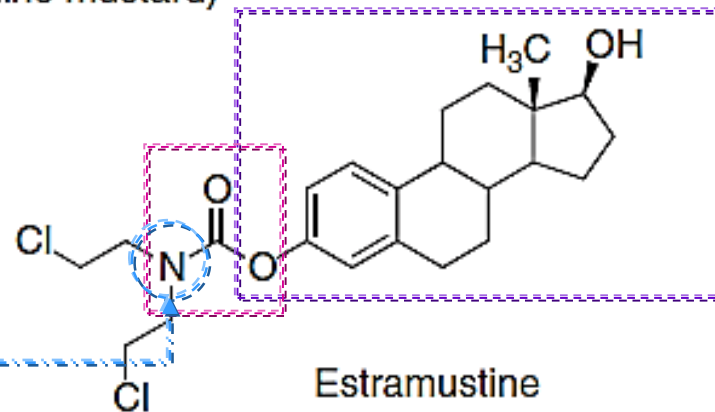
Melfalan (*ALKERAN*)

- melanoma maligno
- mieloma multiplo, carc. ovarico/mammella, sarcoma tessuti molli (arti), sarcoma di Ewing, neuroblastoma infantile.

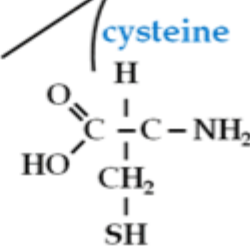
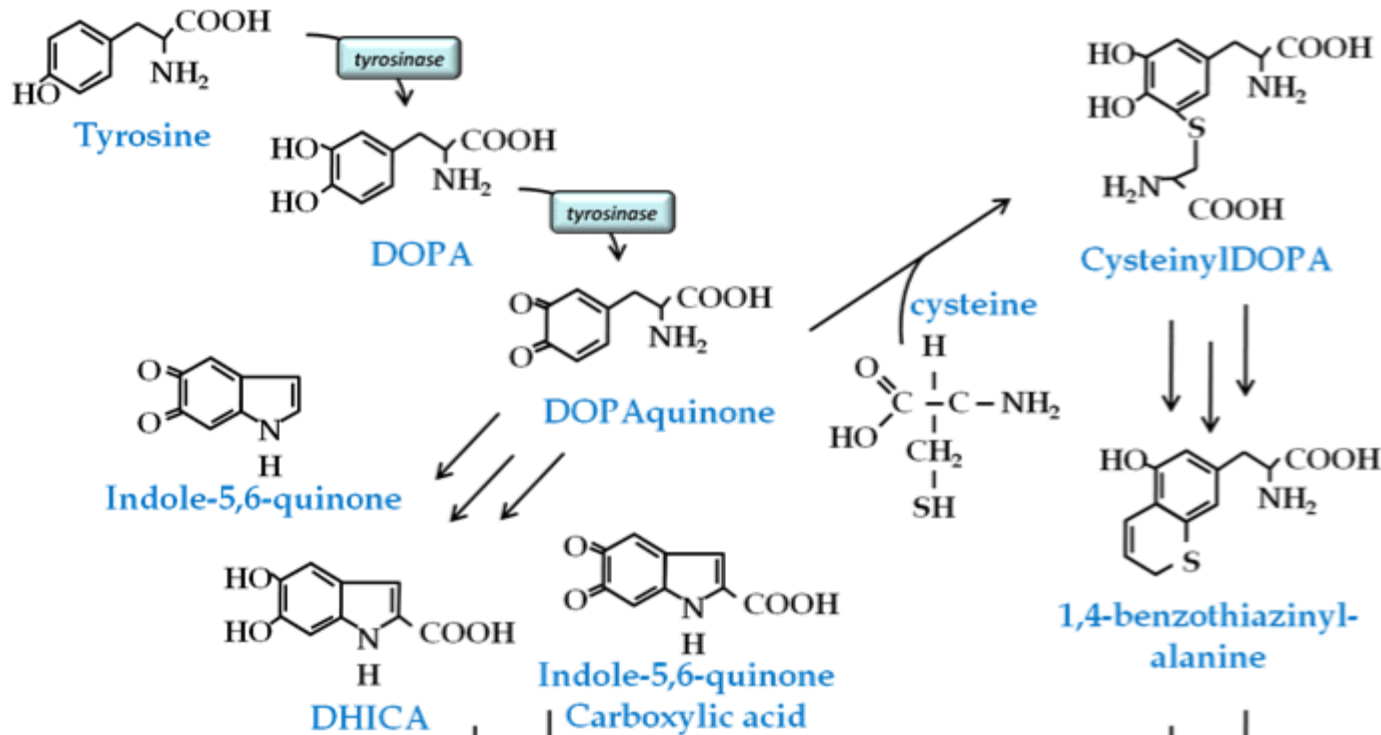


Estramustina (*Estracyt*)

- carcinomi prostatici divenuti resistenti alla estrogenoterapia (EMBP, estramustine binding protein)



non nucleofilo → no formazione ione aziridinio → no alchilante
no recettore estrogeni; citoscheletro (tubulina, antimitotico)

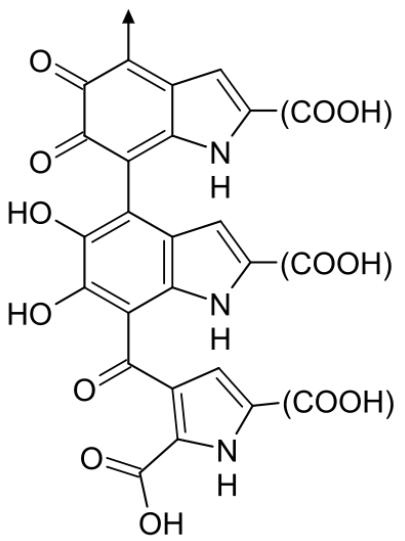


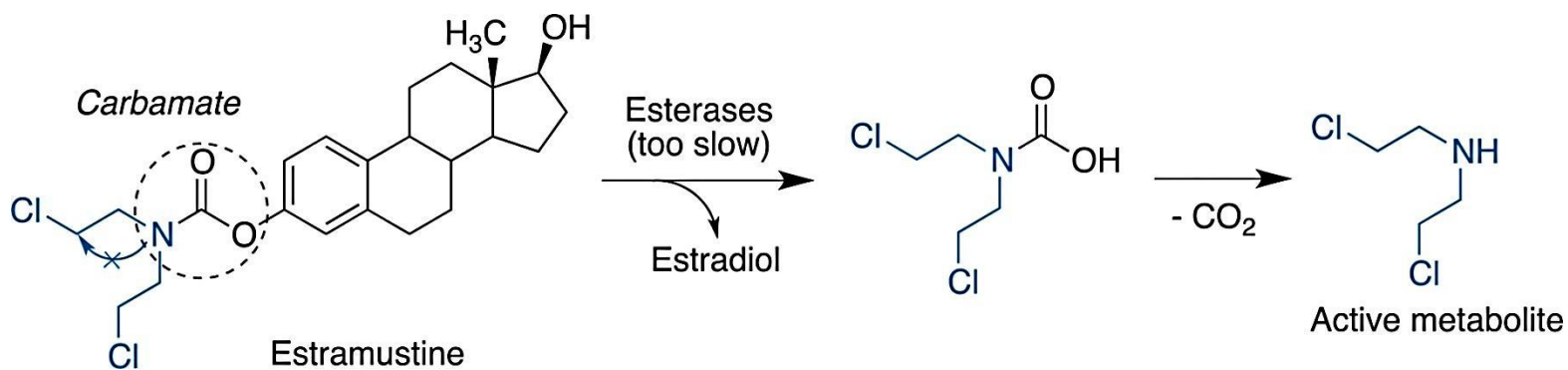
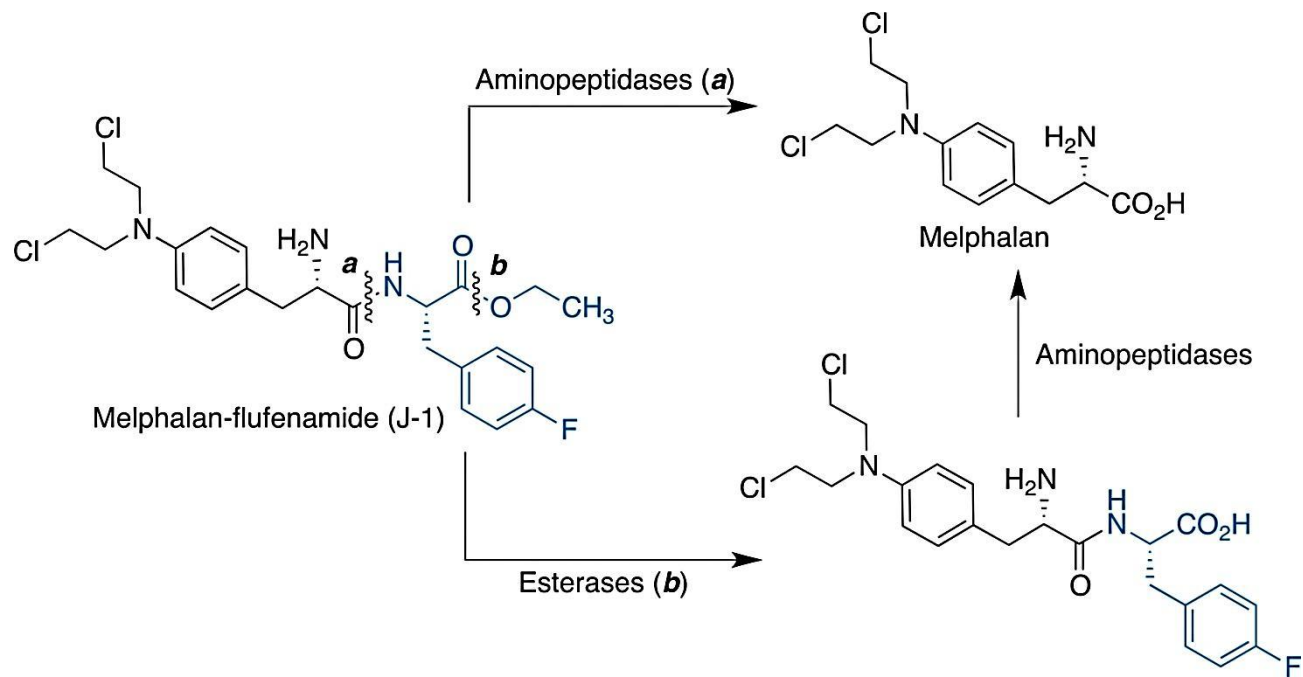
Eumelanin

(brown/black melanin)
- effective UV blocking pigment

Pheomelanin

(red/blond melanin)
- UV-permeable
- Promotes free radical formation?



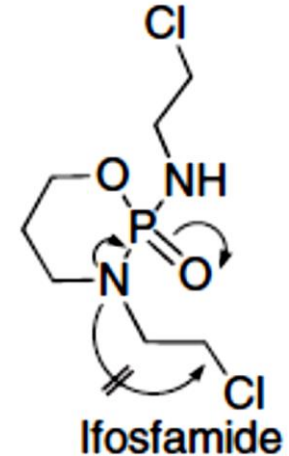
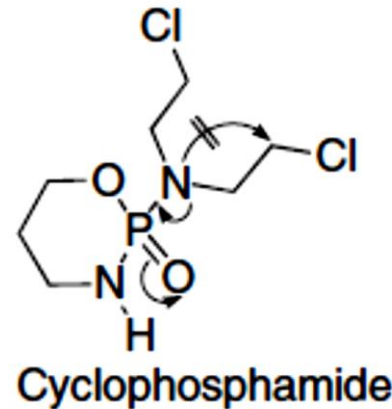


Ciclofosfamide

(Endoxan Baxter)

- Trattamento citostatico.

(RS)-N,N-bis(2-chloroethyl)-1,3,2-oxazaphosphinan-2-amine 2-oxide



Sviluppo di alchilanti (mostarde azotate) come prodrug sito-diretti capaci di essere attivati metabolicamente e selettivamente da cellule tumorali (**alti livelli di fosforamidasi**); *attivazione metabolica reale CYP e non idrolitica*.

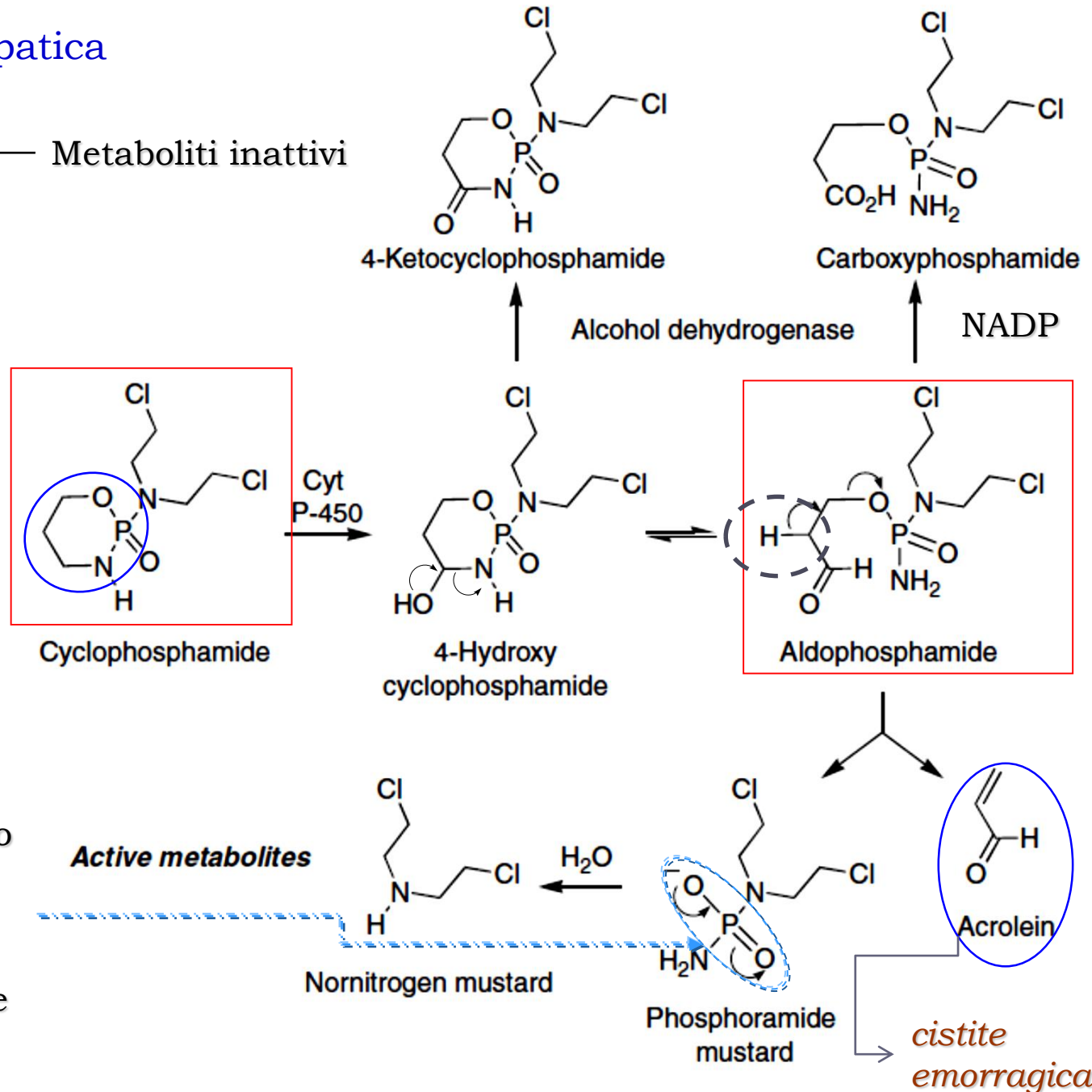
In entrambi i composti l'effetto -I del gruppo fosforamidico previene l'attivazione dello ione aziridinio.

1958-Ciclofosfamide: Hodgkin's, linfomi, leucemie, cancro ovarico (in associazione), cancro al seno, granulomatosi, artrite reumatoide, lupus.

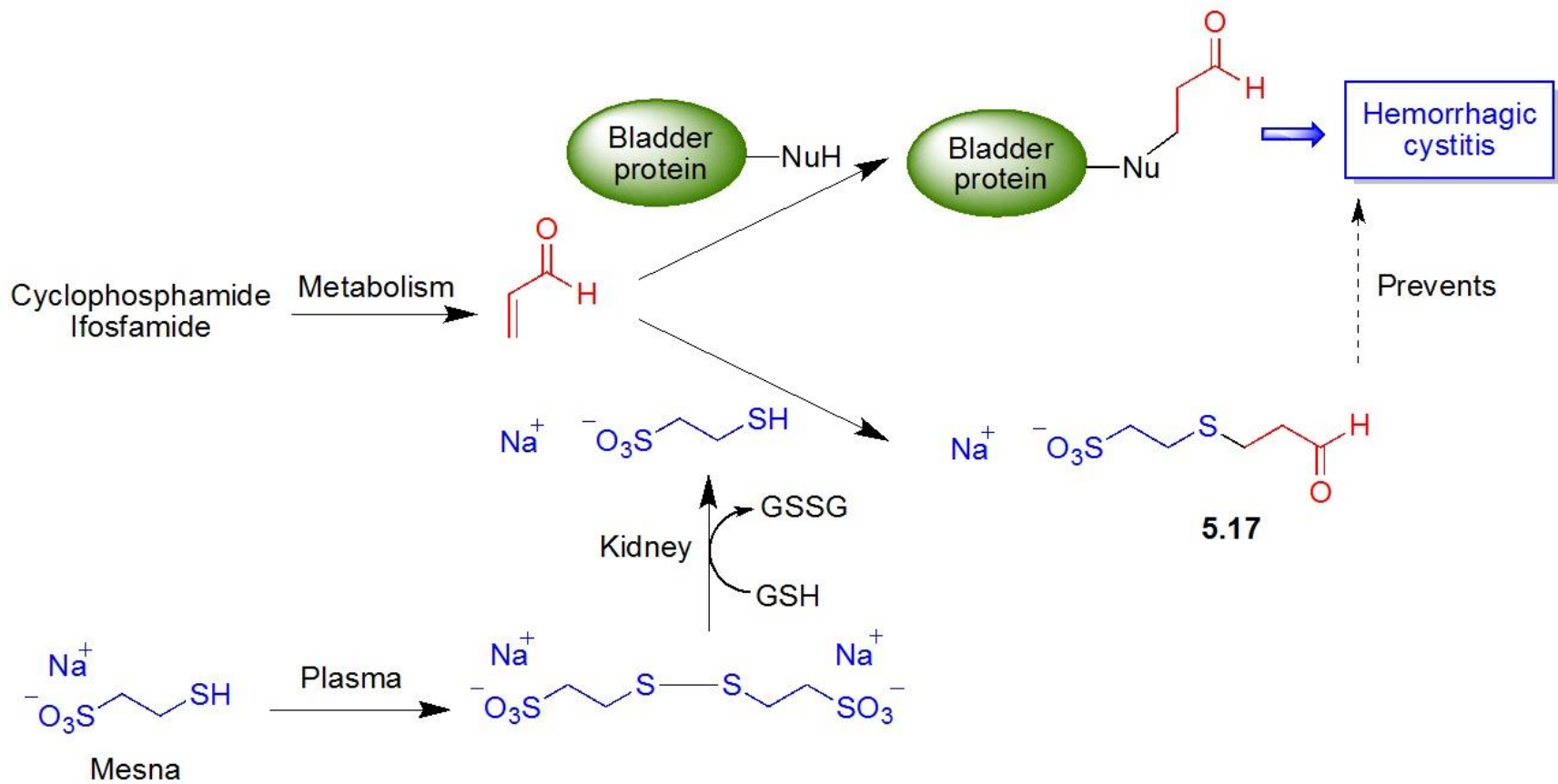
Ifosfamide: cancro testicolare. Attività immunosoppressiva a dosi ridotte.

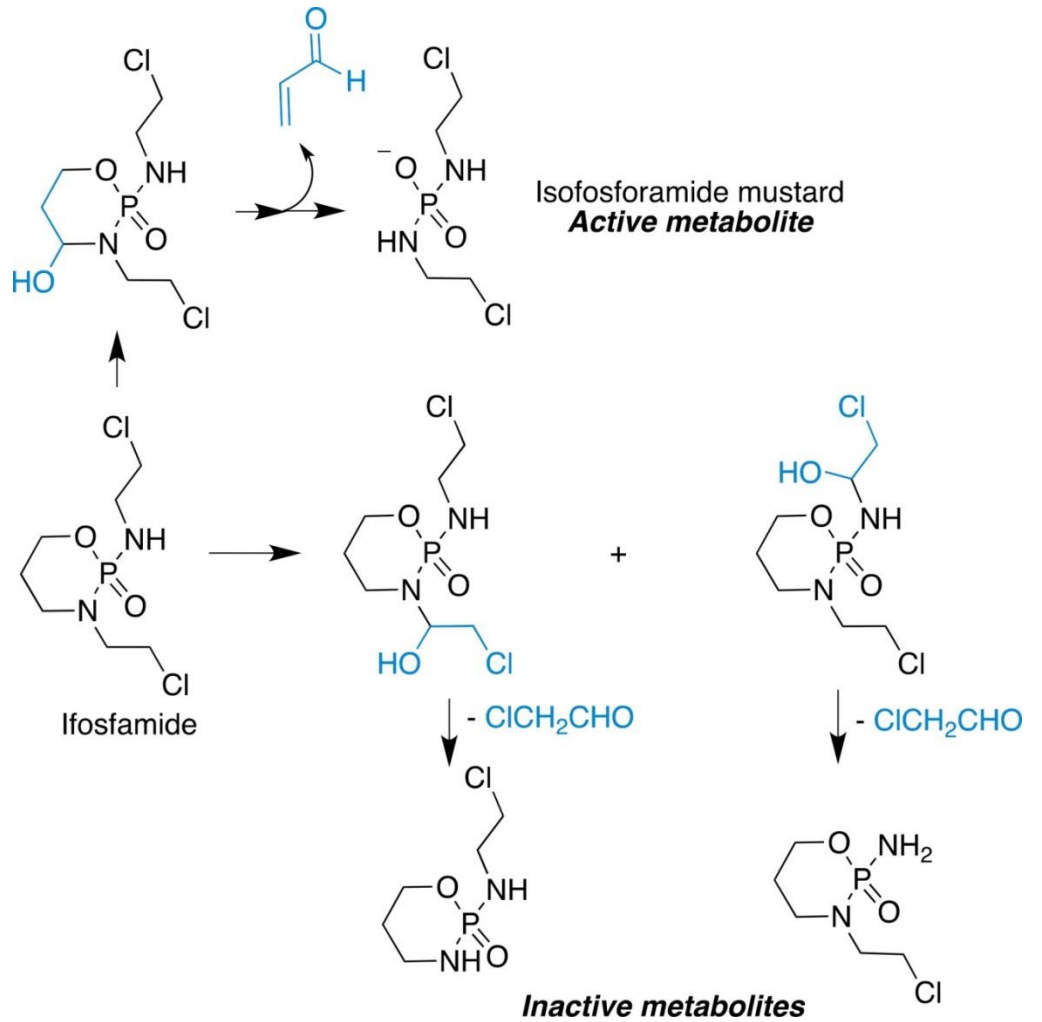
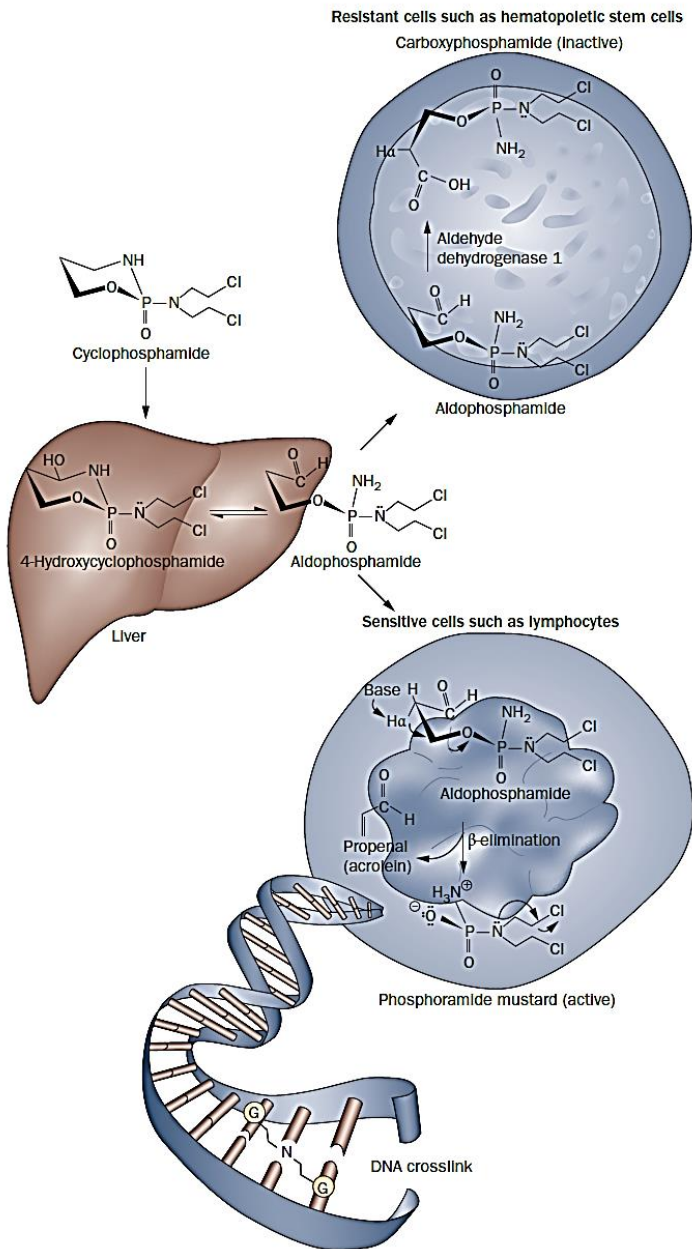
Scarsa tossicità epatica

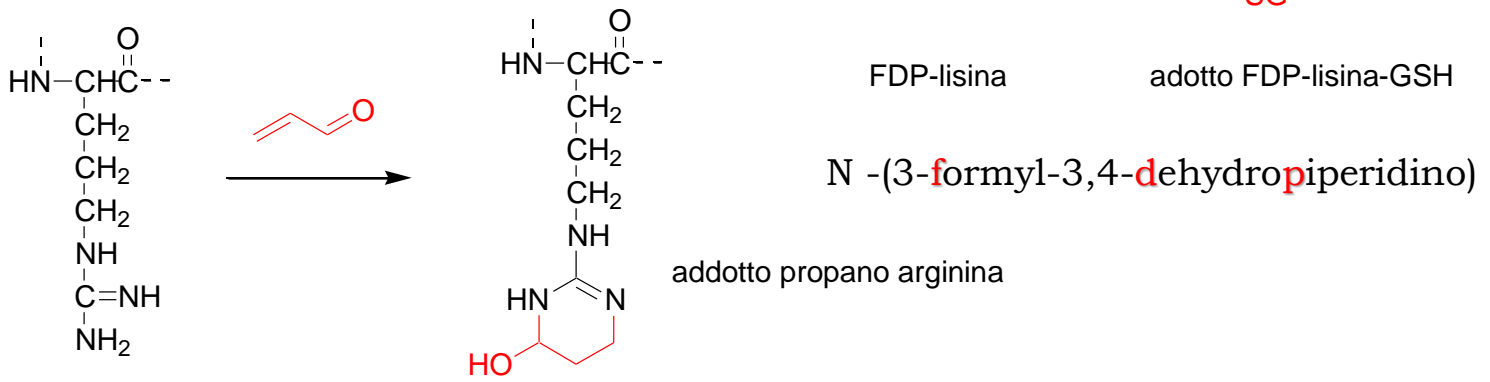
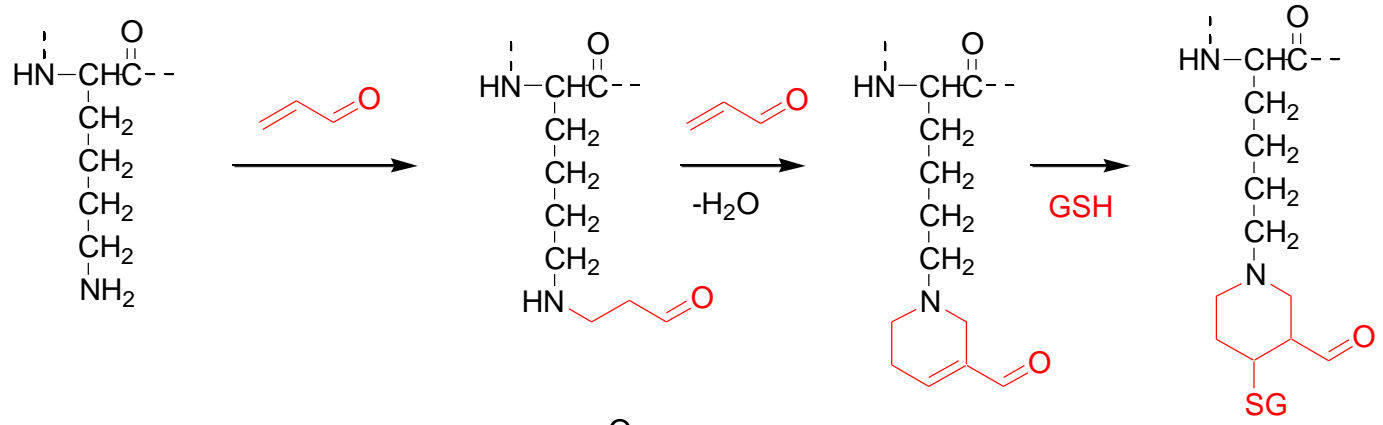
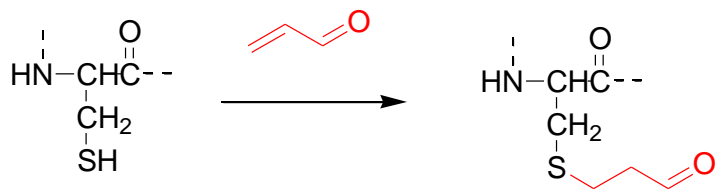
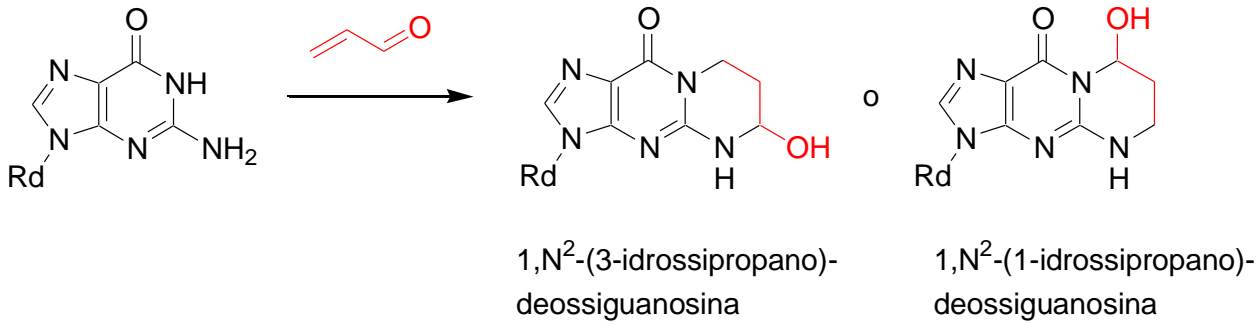
Metaboliti inattivi



La carica negativa dell'O del fosforamidato bilancia l'effetto elettronattrattore di P=O e permette l'attivazione del catione aziridinio

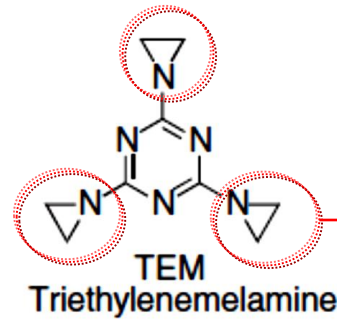
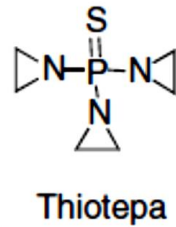
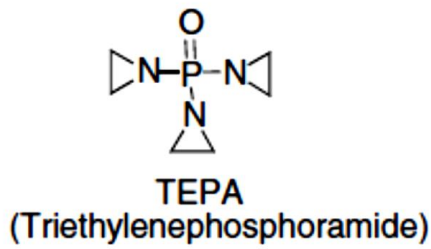






Aziridine (Etilenimmine)

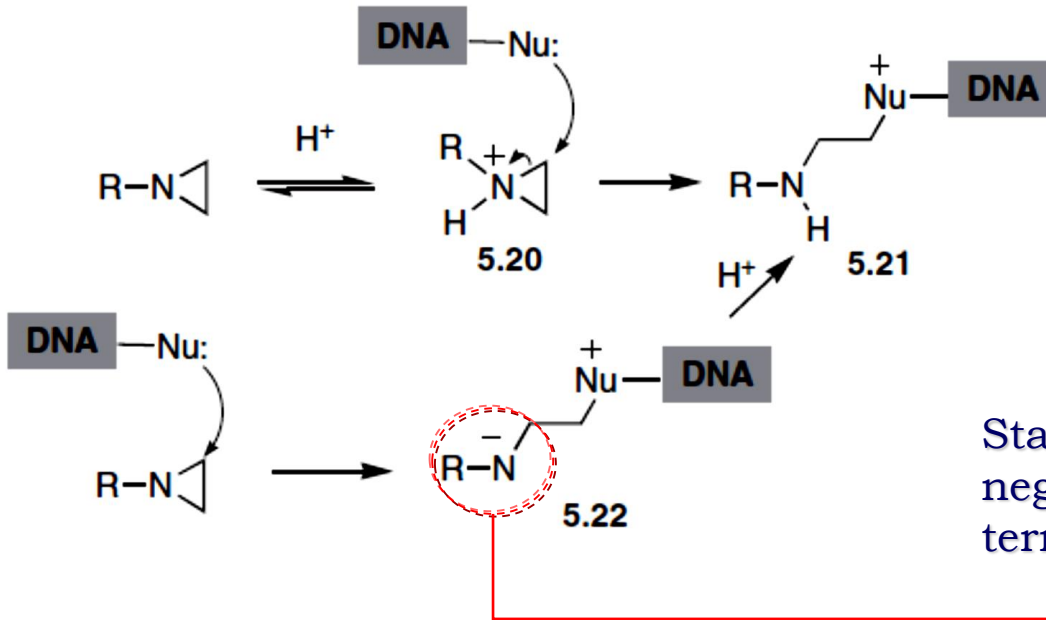
Generalmente legate a gruppi -I



Tiotepa (Thioplex)

- adenocarcinoma della mammella.
- adenocarcinoma dell'ovaio
- carcinoma papillare superficiale della vescica

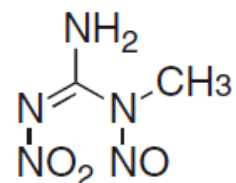
Due aziridine sono necessarie per una buona attività citotossica (terzo o quarto nucleo non necessari) → cross-linking



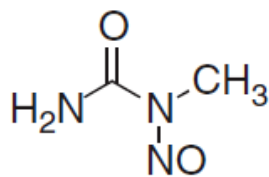
Stabilizzazione della carica negativa su N ed apertura ciclo tre termini

N-Nitrosouree

(random screen NCI-1959)

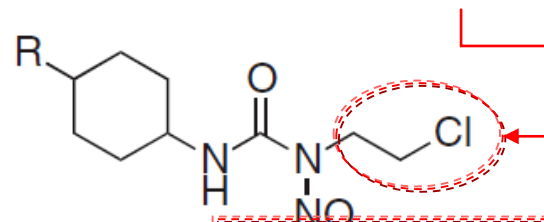


1-Methyl-3-nitro-1-nitrosoguanidine

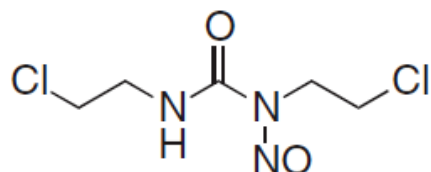


N-Methyl-N-nitrosourea (MNU)

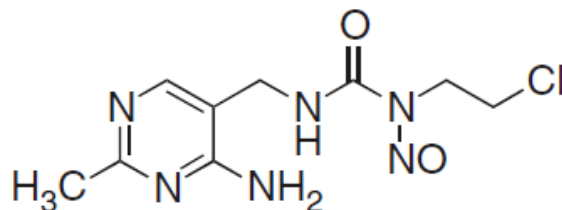
Catena cloroetilaminica*
aumenta l'attività



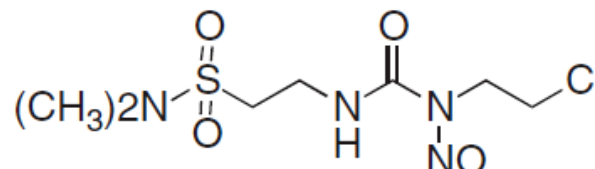
R = H Lomustine (CCNU)
R = CH₃ Semustine



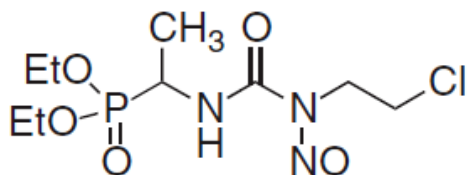
Carmustine (BCNU)



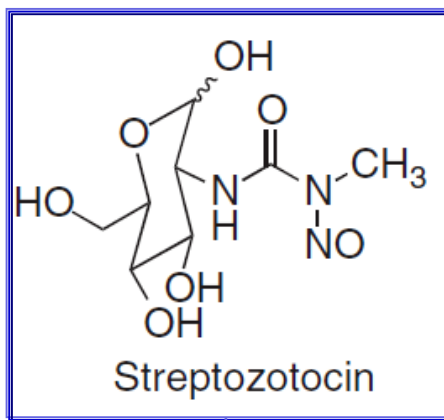
Nimustine (ACNU)



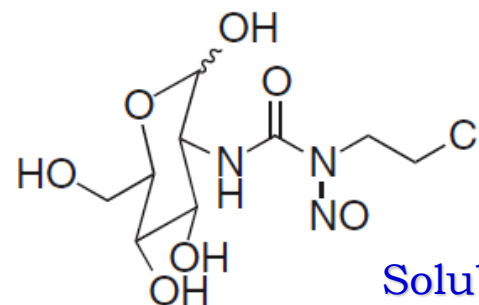
Tauromustine



Fotemustine
Solubile acqua



Streptozotocin



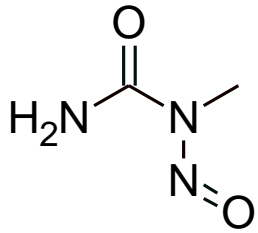
Chlorozotocin

Solubile acqua

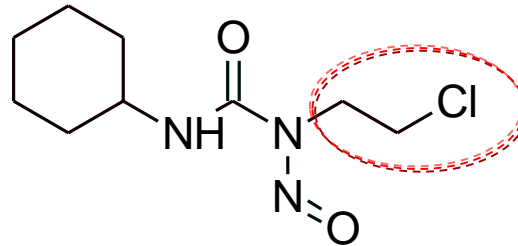
1967. Prodotto di origine naturale (*S. achromogenes*)

* > lipofilia (BBB) tumori cerebrali

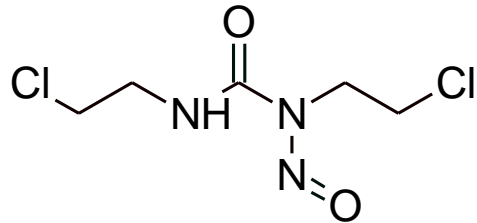
N-Nitrosouree (NCI-1959)



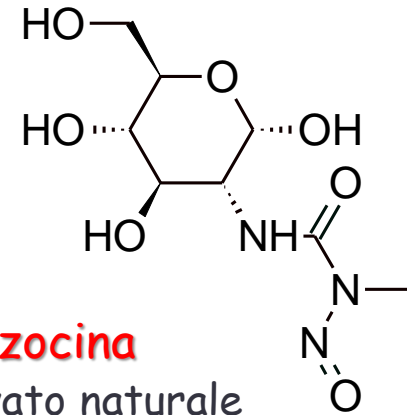
N-metil-N-nitrosourea



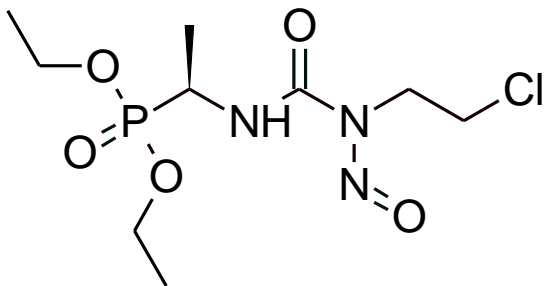
N-(2-cloroetil)-N'-cicloesil
-N-nitrosourea
Lomustina



N, N' bis-(2-cloroetil)-N-nitrosourea
Carmustina (Gliadel)
glioma ad alto grado di malignità

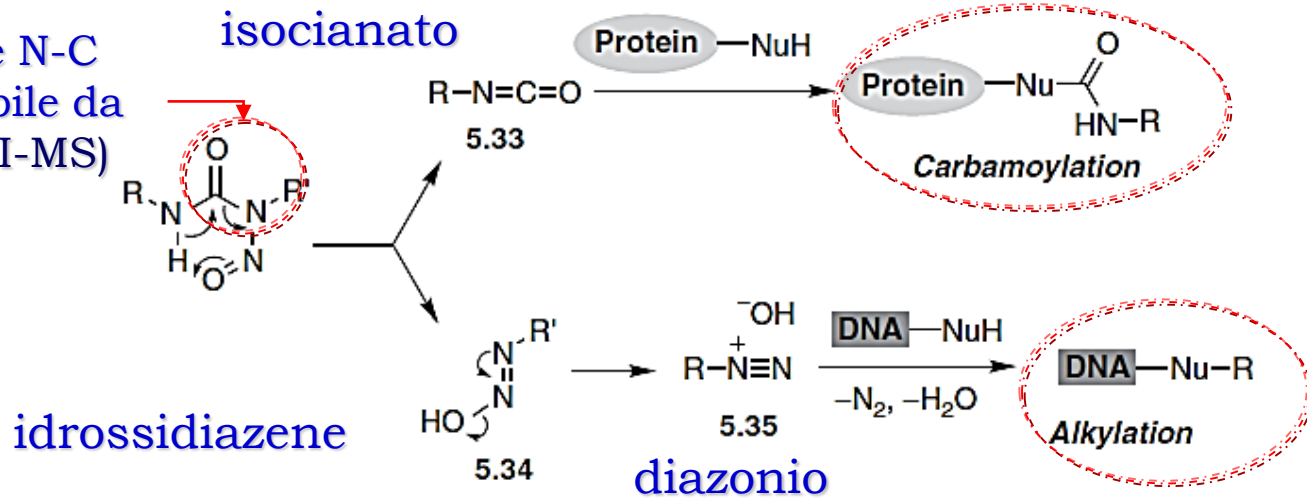


Streptozocina
(**Zanosar**, derivato naturale
della 3-D-glucosammina)



dietil-1-(3-(2-cloroetil)-3-nitrosoureido) etilfosfonato
Fotemustina (Muphoran)
Melanoma maligno disseminato, comprese le
localizzazioni cerebrali.

Legame N-C
reso labile da
NO (ESI-MS)



**Inib. riparaz.
DNA**

**Attiv.
antitumorale**

FIGURE 5.25 Thermal decomposition of nitrosoureas.

Forme tautomeriche
N-nitrosouree

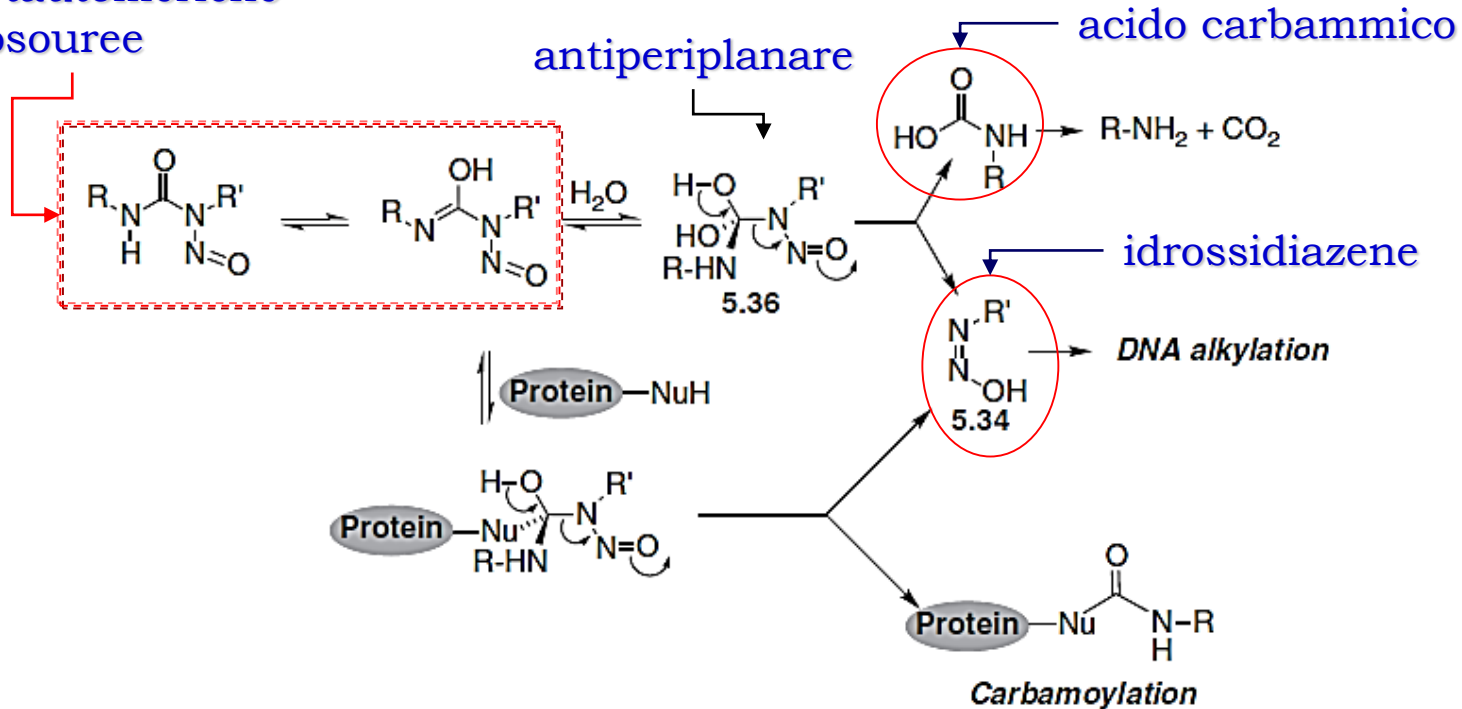
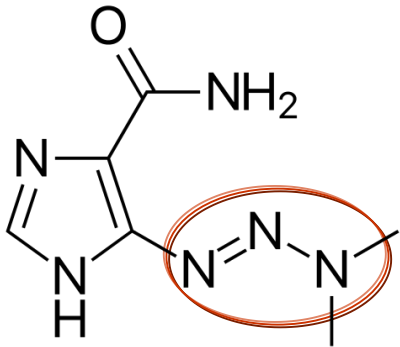


FIGURE 5.26 Decomposition of nitrosoureas in water solution.

Proalchilanti Triazinici



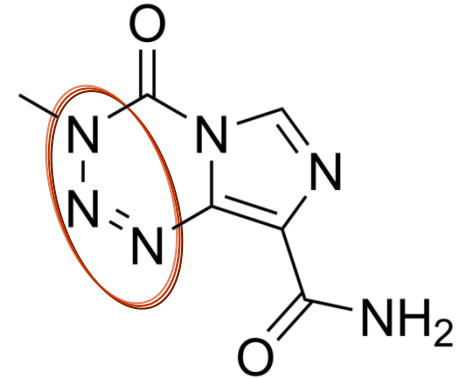
Dacarbazina (DTIC)

(equivalenti)

5-(3,3-dimetil-1-triazenil)

imidazolo-4-carbossiammide

melanoma maligno metastatico

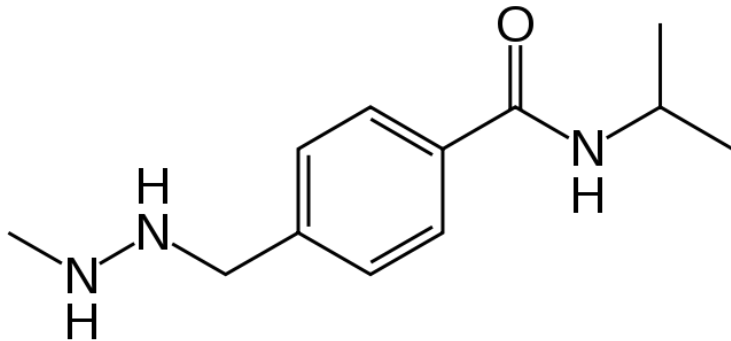


Temozolomide (TMZ) (Temodal)

4-metil-5-oxo-2,3,4,6,8-pentazabicyclo[4.3.0]nona-

2,7,9-triene-9-carbossiammide

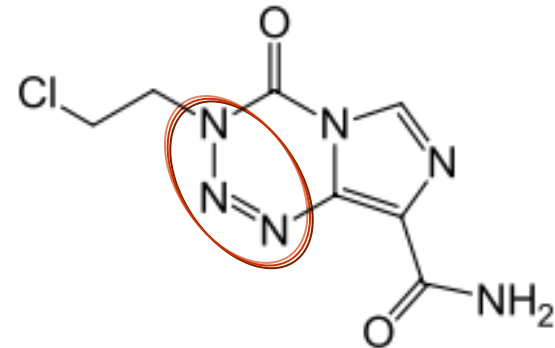
glioblastoma multiforme



Procarbazina (Natulan)

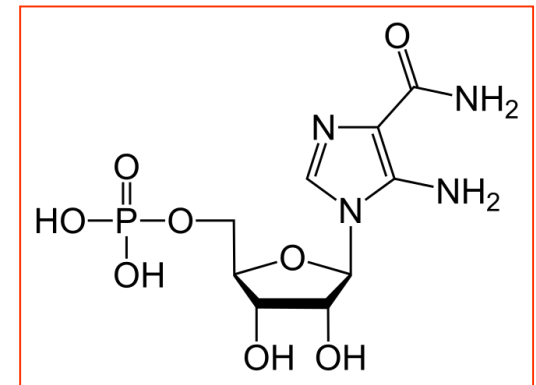
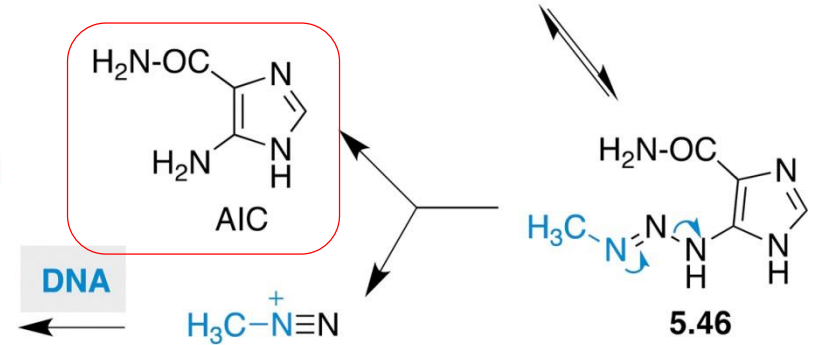
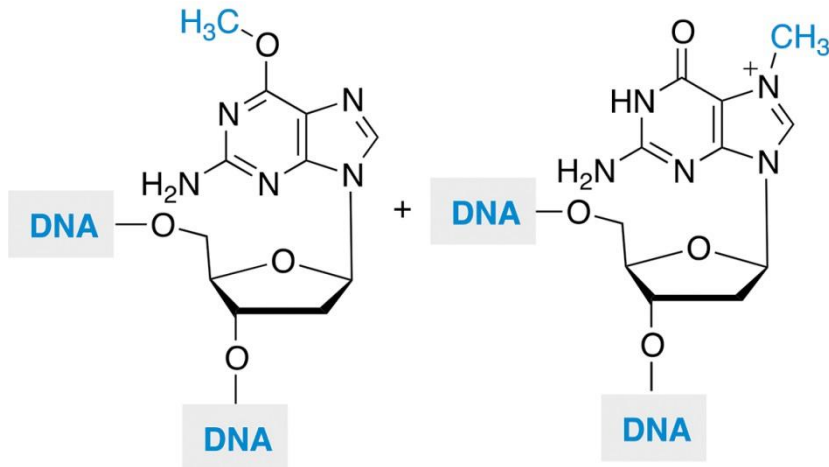
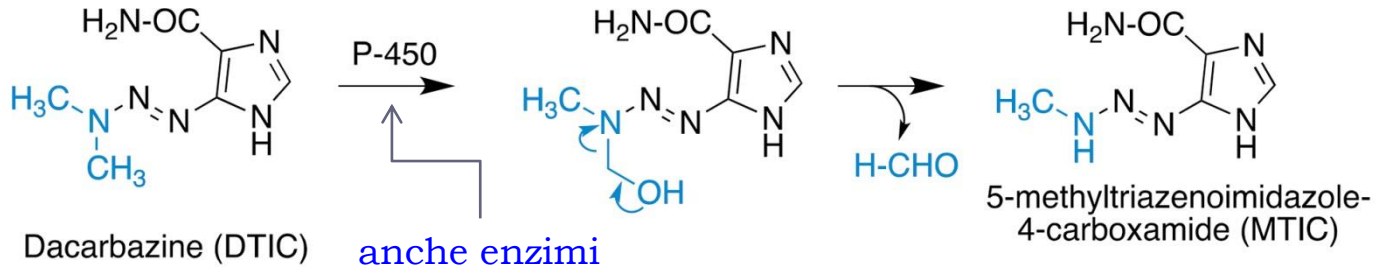
N-isopropil-4-[(2-metilidrazino)metil]benzamide

Hodgkin, linfosarcoma, reticolosarcoma



Mitozolomide (MTZ)

3-(2-cloroetil)-4-oxo-3,4-diidroimidazo[5,1-d][1,2,3,5]tetrazino-8-carbossiammide



L'intero processo di attivazione della DTIC è molto rapido con comparsa di AIC (principale metabolita urinario e intermedio biosintesi purine) dopo 15' dall'infusione ev.

5-aminoimidazolo-4-carbossamide ribonucleotide (AICAR) **Acadesine**. proprietà anti-ischemiche (fase 3)

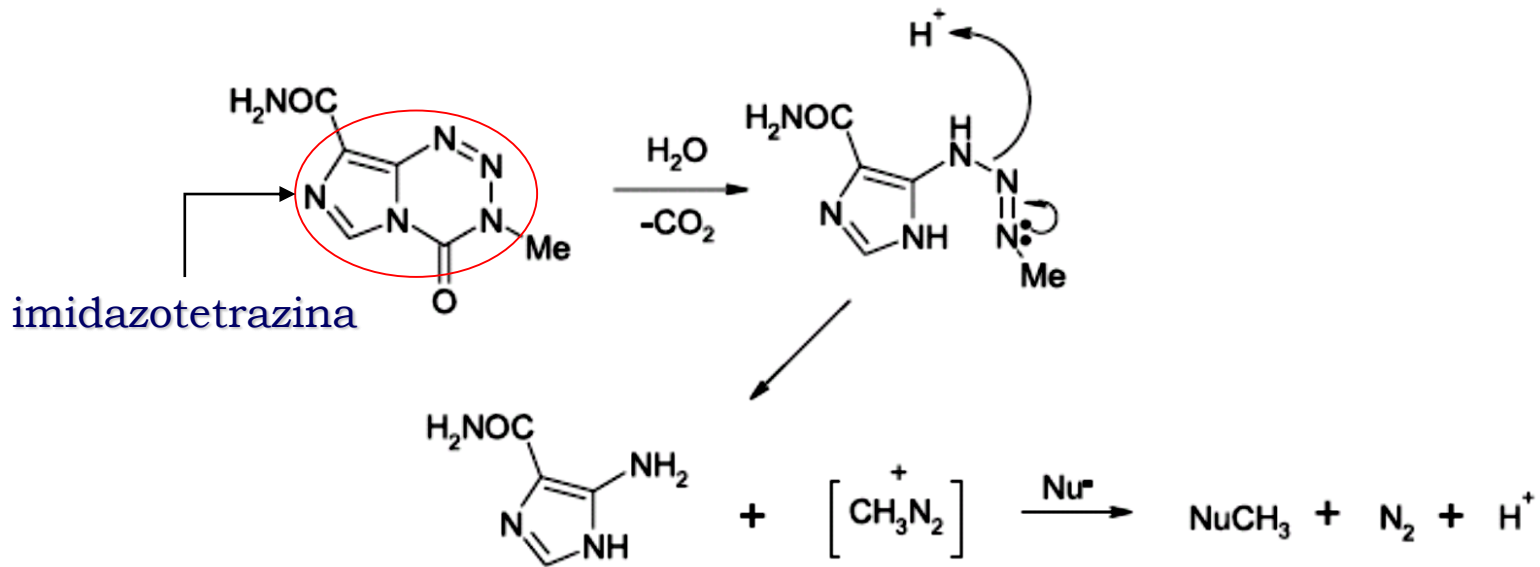
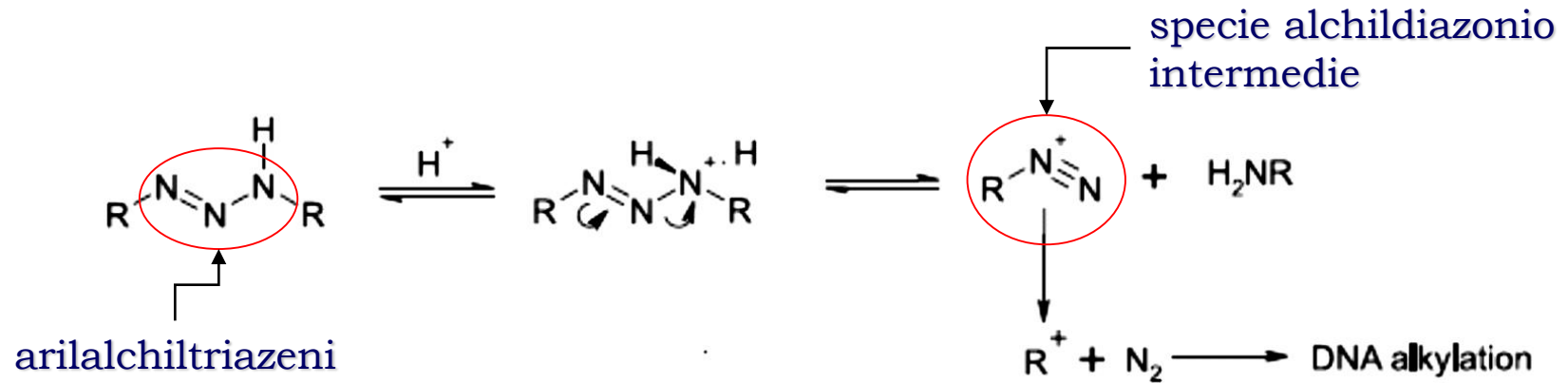
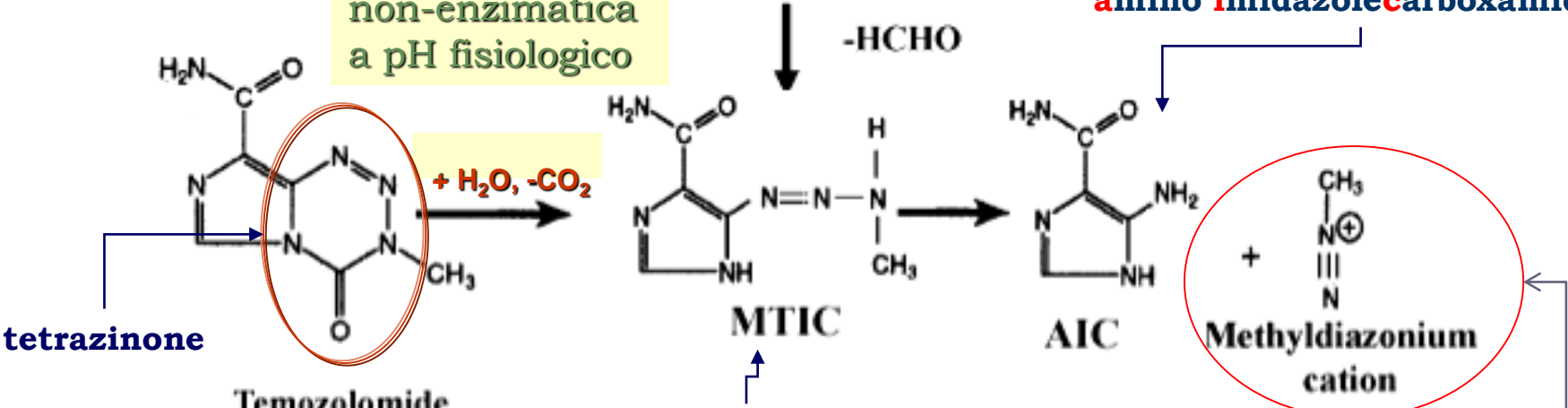


Fig.3 Decomposition of antitumor drug temozolomide

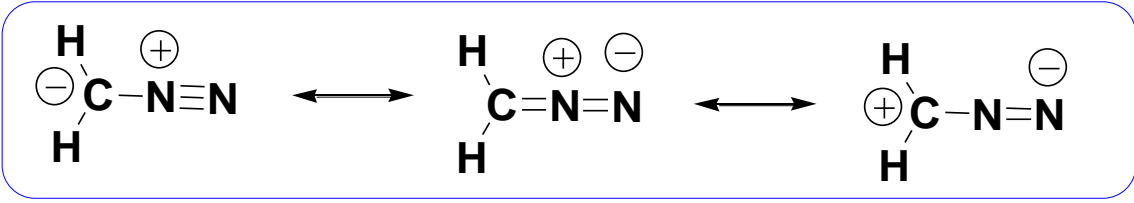
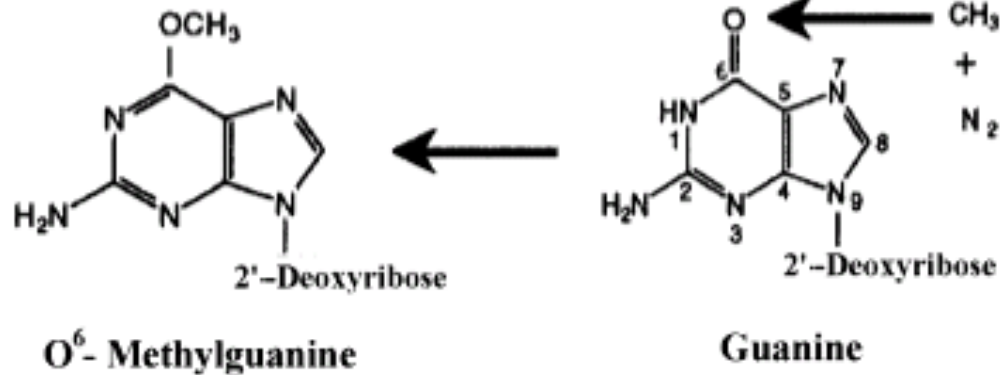
Conversione non-enzimatica a pH fisiologico

Dacarbazina

amino imidazolecarboxamide



Tumori cerebrali

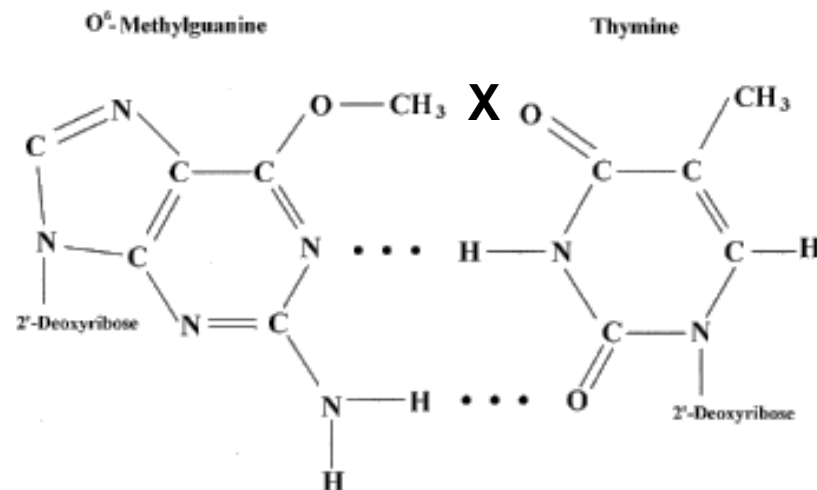


$+ H^+$

Basi metilate formate in vivo dalla DTIC

O^6 -methylguanine		6–8%
N^7 -methylguanine	→	70%
N^1 -methyladenine		15%
N^3 -methyladenine		10%
N^3 -methylcytosine		Rare

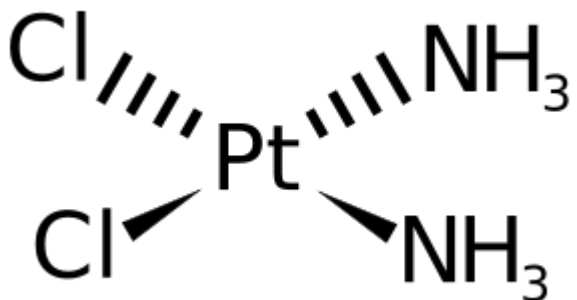
O^6 -metilguanina è la principale responsabile dell'effetto antineoplastico e mutagenico della DTIC perché è capace di determinare un accoppiamento errato delle basi



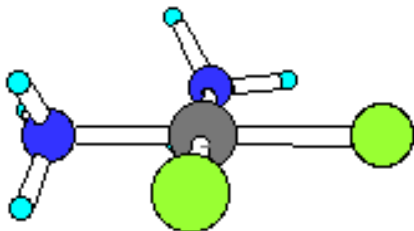
DIAMMINO-DICLORO-PLATINO

(cis-[PtCl₂(NH₃)₂], Citoplatino, Platinex, Platamine)

Carcinoma: **del testicolo avanzato o metastatico**; ovarico avanzato o metastatico; della vescica avanzato o metastatico; a cellule squamose della testa e del collo avanzato o metastatico polmonare non a piccole cellule avanzato o metastatico polmonare a piccole cellule avanzato o metastatico.



cis-diamminodichloroplatinum(II)



1845: Michele Peyrone, prima sintesi;
1913: Nobel a Alfred Werner per la corretta identificazione della configurazione planare quadrata e degli isomeri cisplatino e transplatino;
1965: Rosenberg → attività antiproliferativa del cisplatino; crescita filamentosa cellule tumorali simile a quella osservata con le mostarde azotate.
1971: fase 1, fase 2, elevata tossicità;
1973: Wallace e Holland, tumore testicoli;
1978: app. FDA

The "Accidental" Cure—Platinum-based Treatment for Cancer: The Discovery of Cisplatin

1960-5: cisplatin {cis-[PtCl₂(NH₃)₂]};

- migliaia di composti preparati e testati ma pochi in uso clinico;
- fatturato mondiale circa 2 MD dollari;
- altri complessi con metalli diversi come Ru e Au e metalloceni (Ti, Nb, Mo, Re);
- Cisplatino è prima scelta chemioterapica nel 90% dei tumori testicolari;
- presente in protocolli di trattamento di cancro ovarico, testa-collo, melanoma, linfoma e altri.



Barnett Rosenberg (biofisico Università del Michigan), architettura citoscheletro (fusi mitotici) durante divisione cellulare simile linee di forza campo (elettro) magnetico;

Crescita *E. coli* in ammonio cloruro applicando tensione con elettrodi al Pt; le cellule apparvero lunghe, filamentose e incapaci a dividersi. Il campo elettrico applicato non aveva alcun ruolo bensì la formazione di nuovi complessi idrolitici del Pt. Si testano composti coordinati a altri 10 metalli di transizione ma il sale di Pt era il più efficace.

I complessi cis-[PtCl₂(NH₃)₂] (**Pt (II)**) e cis-[PtCl₄(NH₃)₂] (**Pt (IV)**) sono testati vs 150 tipi di sarcoma in modello animale (topo); l'attività è straordinaria, i topi sopravvissero e dopo 6 mesi non mostrano alcun segno del tumore.

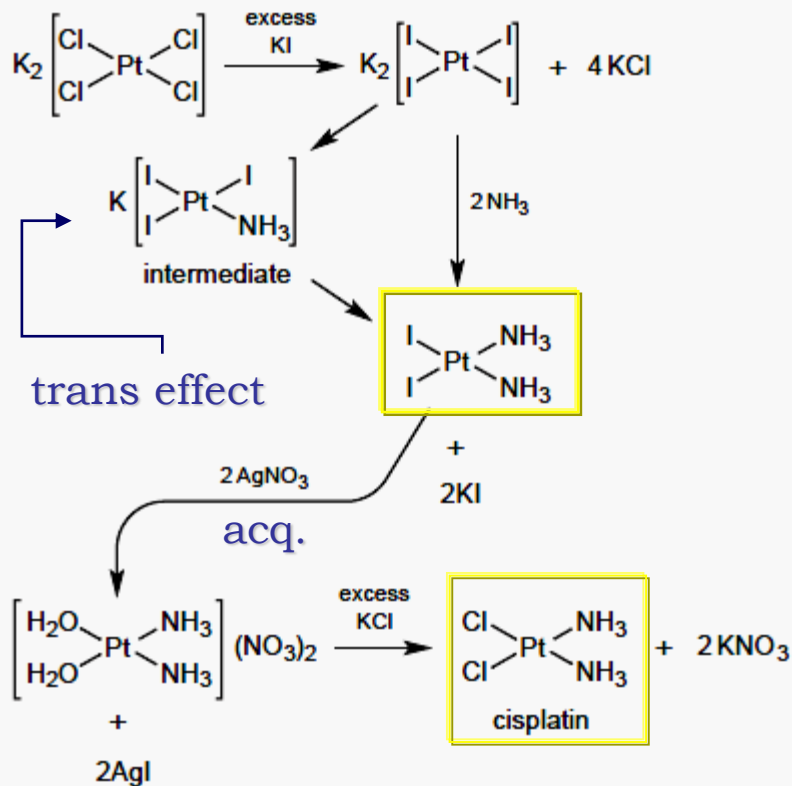
<http://www.cancer.gov/research/progress/discovery/cisplatin>;

<http://www.cancer.gov/research/progress/250-years-advances>

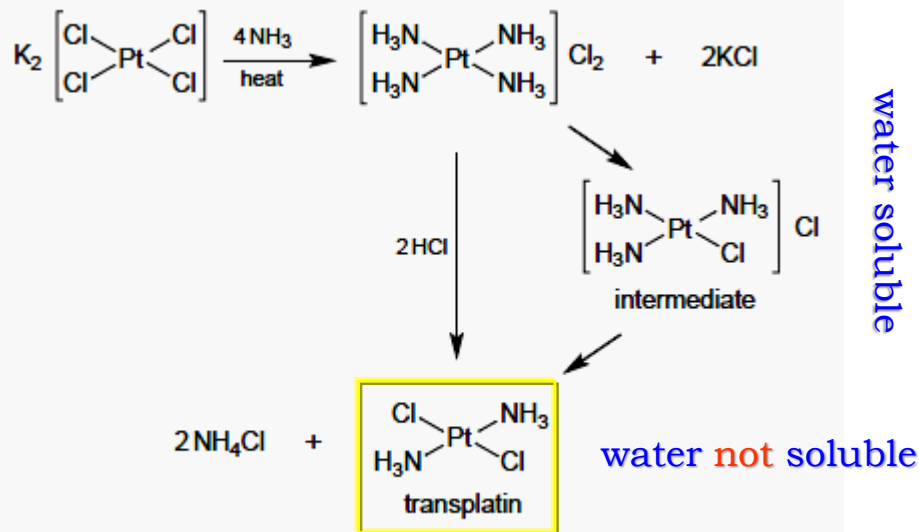
Barnett Rosenberg

Sintesi di Dhara (1970)

K tetracloroplatinato(II)



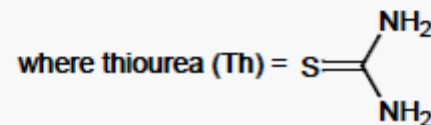
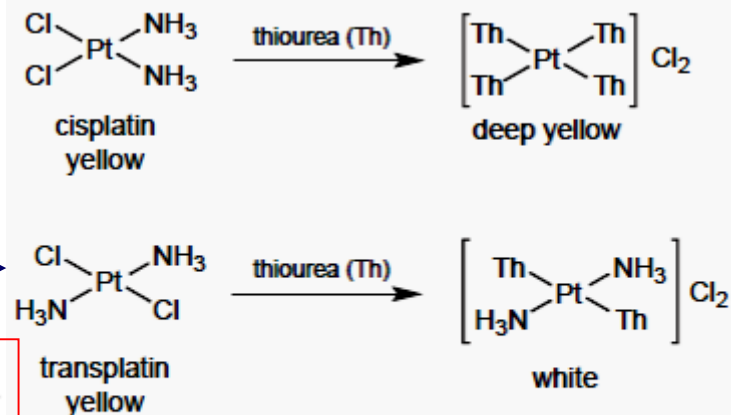
water soluble



Scheme II. Synthetic scheme for the synthesis of transplatin (25).

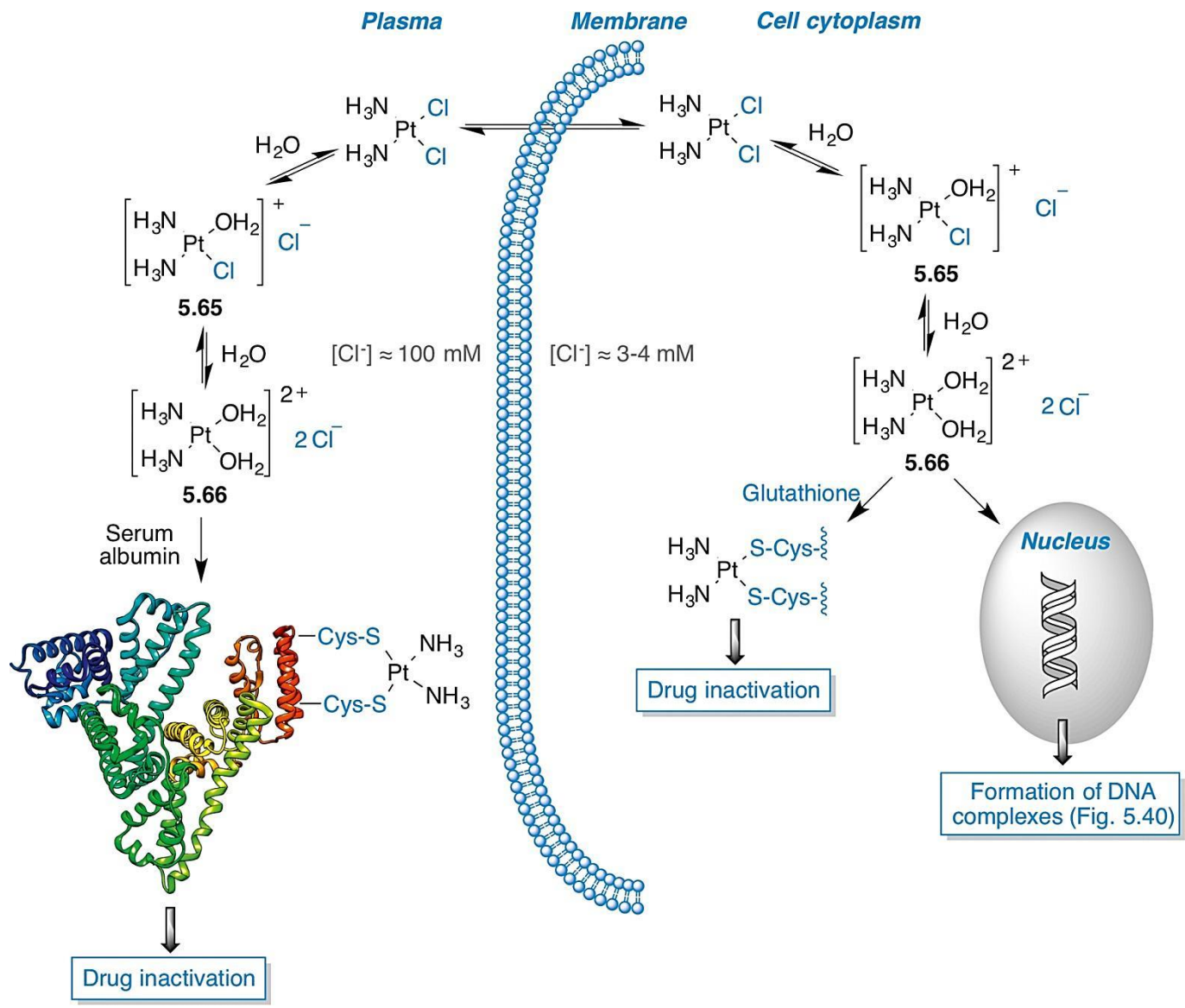
Test di Kurnakow.

Nel complesso cis la tiourea sostituisce i ligandi Cl e successivamente i ligandi NH₃ per formare un addotto tetraureidico giallo solubile. Nel complesso trans la tiourea sostituisce solo i ligandi Cl per formare un composto bianco insolubile

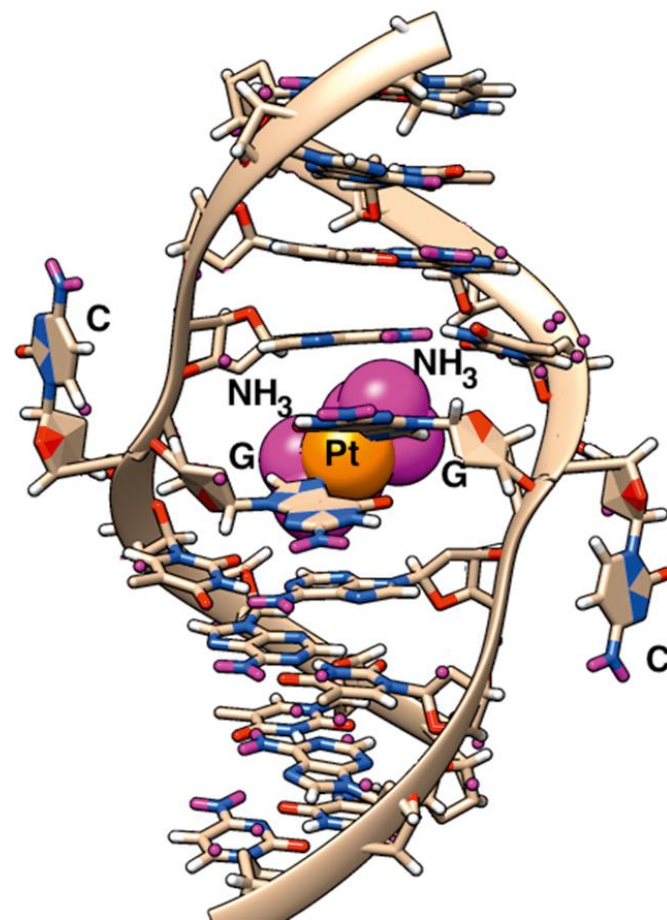
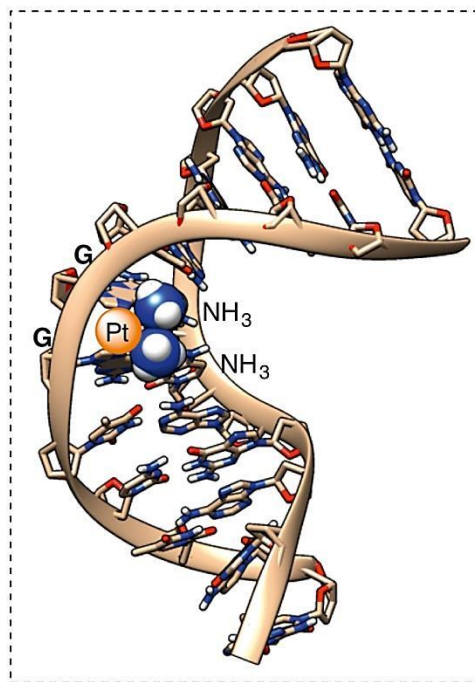
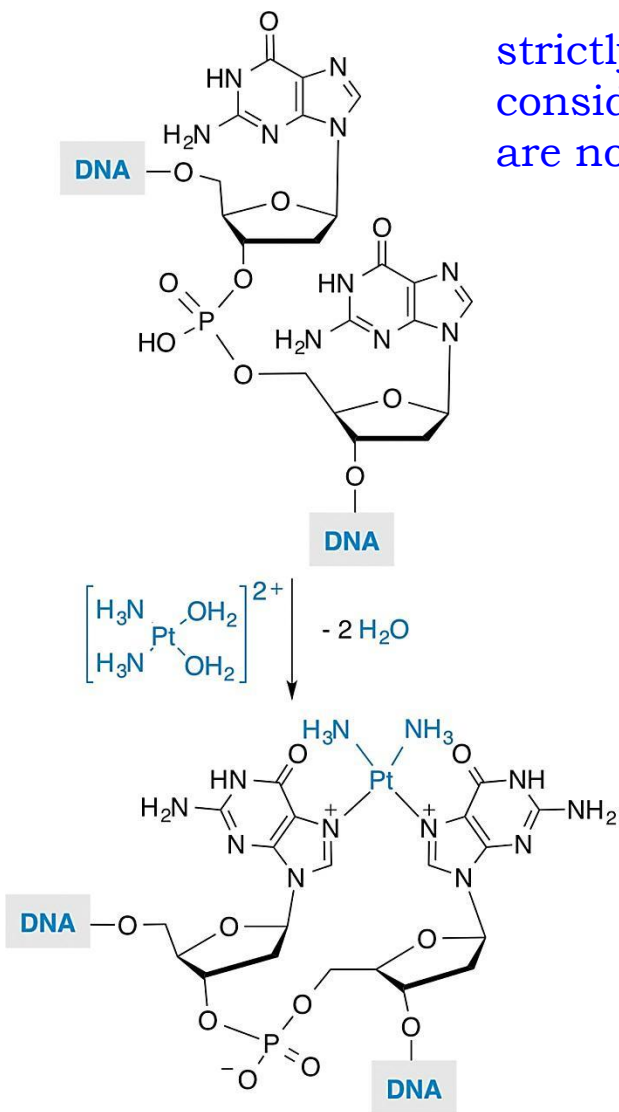


Effetto trans (la velocità di sostituzione di un ligando in un complesso con metallo a configurazione planare quadrata o ottaedrica è dipendente dal sostituente opposto (trans).

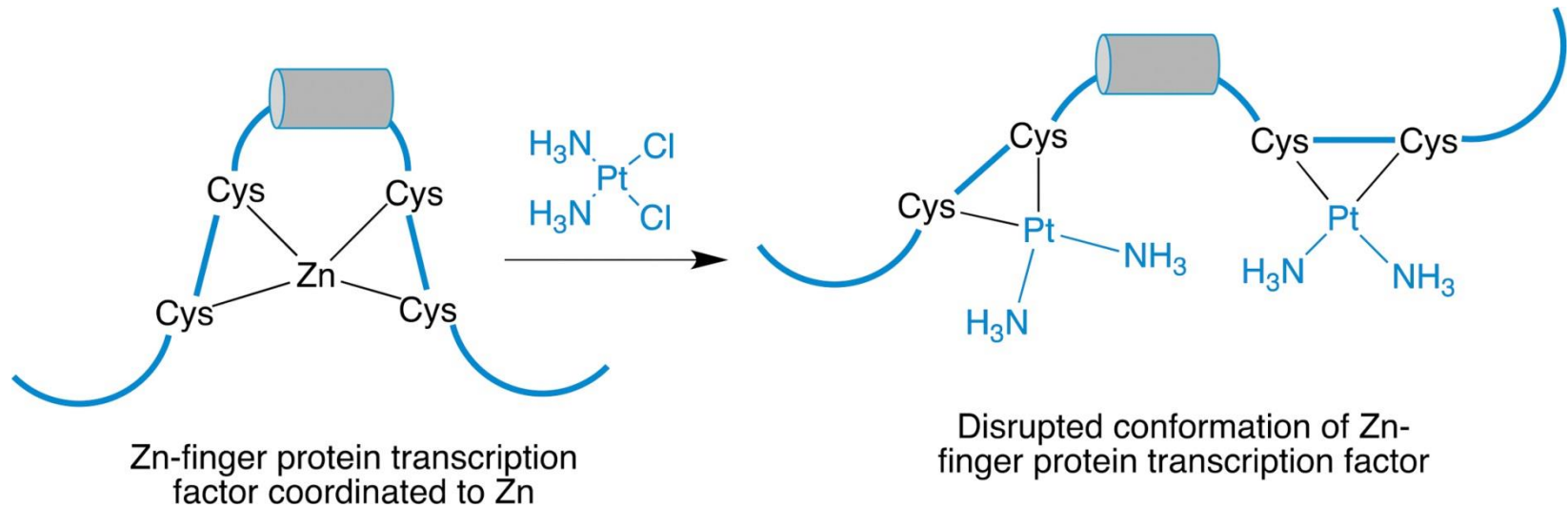
CO, CN⁻, C₂H₄ > PR₃, H > CH₃, SC(NH₂)₂ > C₆H₅, NO₂⁻, I⁻, SCN⁻ > Br⁻, Cl⁻ > py, NH₃, OH⁻, H₂O.



strictly speaking, Pt coordination with DNA bases cannot be considered an alkylation reaction, cisplatin and its analogs are normally studied among the alkylating agents.

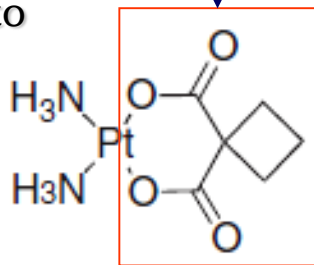


Zn^{++} è essenziale per coordinare amminoacidi, come cisteina e istidina, di proteine che interagiscono con i domini di binding del DNA formando una struttura densa cromatinica. La sostituzione dello ione zinco con platino altera irreversibilmente la conformazione della DNA-polimerasi, enzima fondamentale di trascrizione.



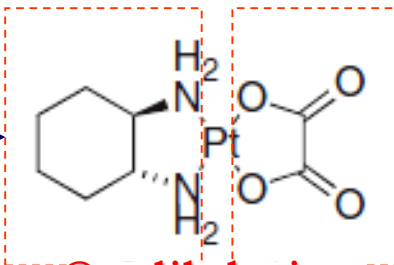
- **la elettroneutralità** facilita il trasporto attraverso la membrana, benchè la forma attiva possa essere carica dopo lo scambio di ligando;
- la presenza di almeno **due buoni gruppi uscenti**, preferenzialmente in **cis**;
- la presenza di ligandi carrier inerti, generalmente amine non terziarie che stabilizzano gli addotti via HB con basi vicine.

Ciclobutan
dicarbossilato



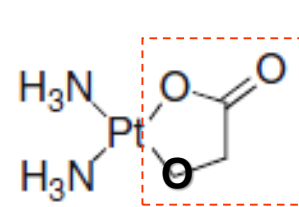
Carboplatino (equiv.)

diaminocicloesano



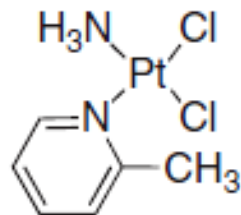
Oxaliplatino
(equiv.)

ossalato

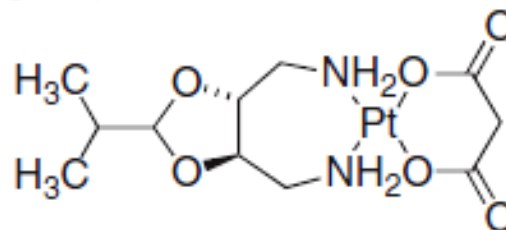


Nedaplatino
(equiv.)

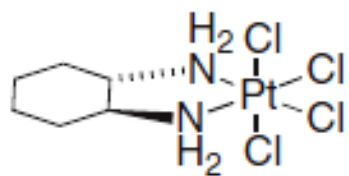
glicolato



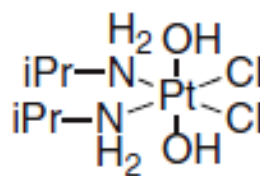
ZD-0473



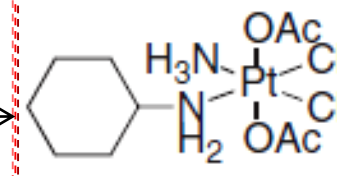
SKI 2053R



Tetraplatin

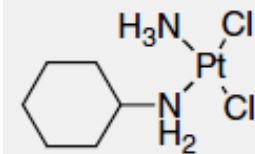


Iproplatin



Satraplatin (JM 216)

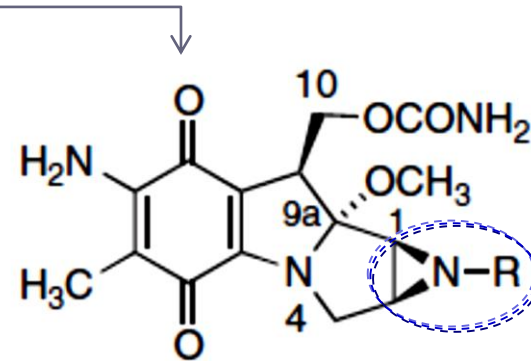
complessi Pt (VI)



JM 118
(active species)

Mitomicine (agenti alchilanti attivati per riduzione metabolica) (Mitomycin-C)

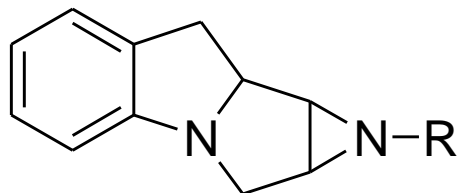
Chinone con potenziale di riduzione simile ai substrati delle reduttasi;



R = H Mitomycin C

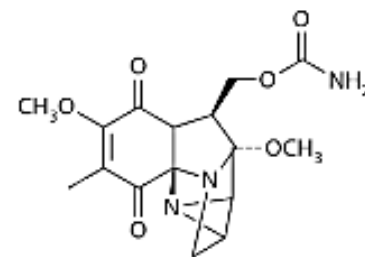
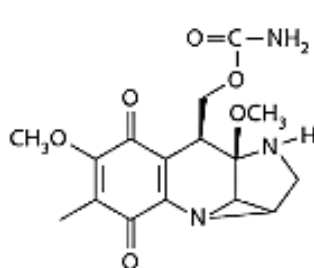
R = Me Porfiromycin ← Fase III

Antitumorale chinonico di origine naturale (*Streptomyces caespitosus*);
Tumori ipossici (la bioriduzione del chinone ad idrochinone non può essere invertita da O₂)



sistema azirino[2,3:3,4]
pirrolo[1,2-a]indolico

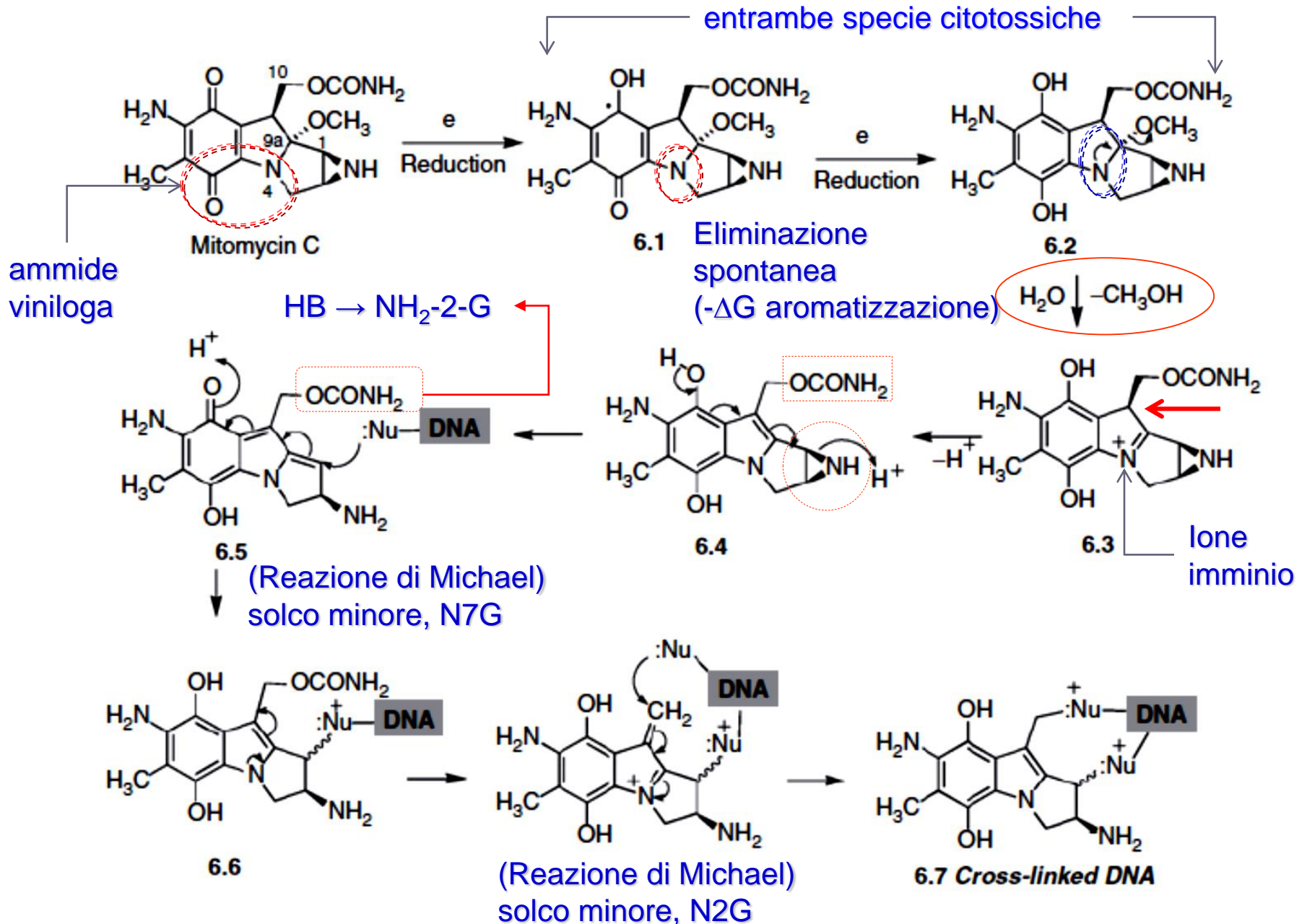
A-type			B-type			G-type		
Mitomycin	X	Z	Mitomycin	X	Y	Mitomycin	X	Y
A	CH ₃ O	H	B	CH ₃ O	H	G	H ₂ N	CH ₃
C	H ₂ N	H	D	H ₂ N	H	H	CH ₃ O	H
F	CH ₃ O	CH ₃	E	H ₂ N	CH ₃	K	CH ₃ O	CH ₃
Porfiromycin	H ₂ N	CH ₃	I		H			
M	CH ₃ NH	H	J	CH ₃ O	CH ₃			
			L	CH ₃ NH	H			

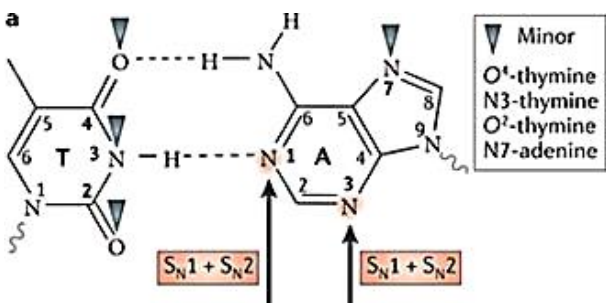


Anticancer Agents from Natural Products, Second Edition (2011)

a cura di Gordon M. Cragg, David G. I. Kingston, David J. Newman

Attivazione bioriduttiva (linee cellulari tumorali iperesprimono NAD(P)H chinone ossidoreduttasi)



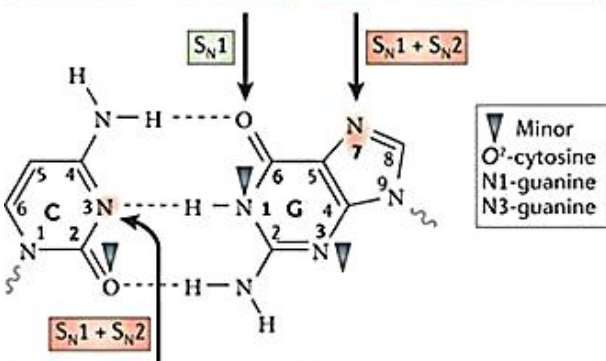


- N1-adenine
- Toxic (replication block)
- Mutagenic (A→T transversion)

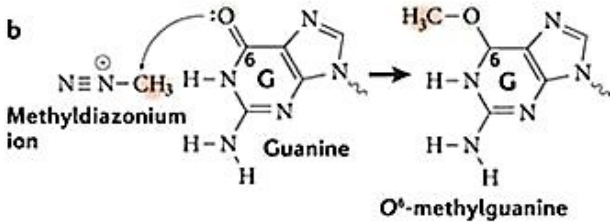
- N3-adenine
- Toxic (replication block)
- Mutagenic (A→T transversion)

- O⁴-guanine
- Toxic (replication block)
- Mutagenic (G→A transition)

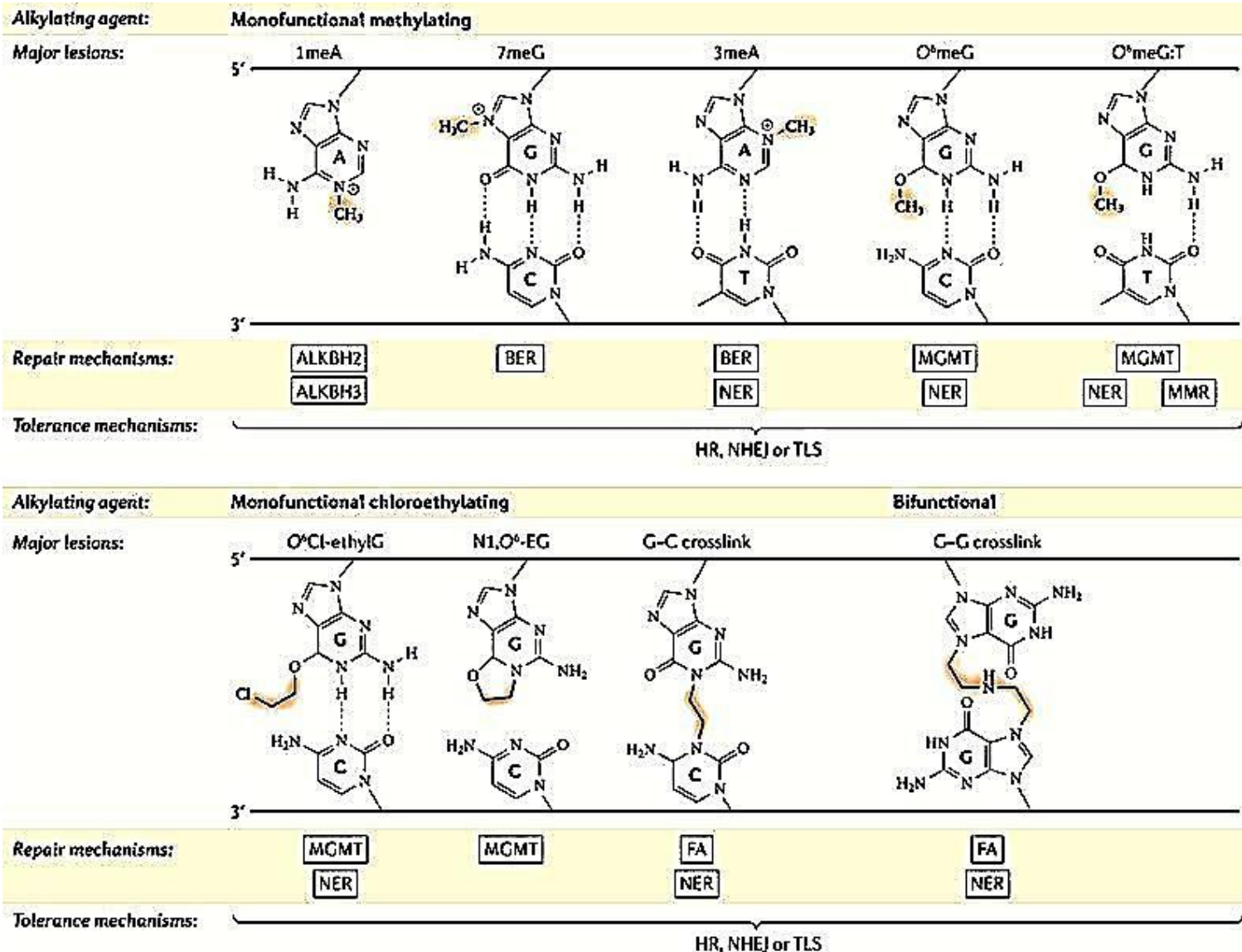
- N7-guanine (after depurination)
- Toxic (replication block)
- Mutagenic



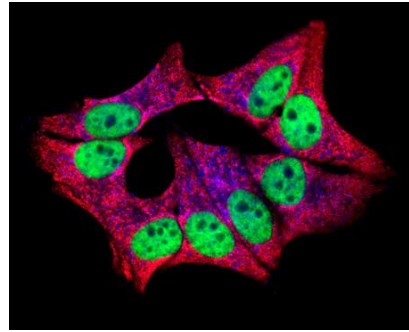
- N3-cytosine
- Toxic (replication block)
- Mutagenic (C→T transition)



a Monofunctional				Lesions¹
<p>Triazene</p> <p>Dacarbazine Metastatic melanoma Hodgkin's lymphoma Sarcoma</p> <p>Procarbazine Malignant gliomas Hodgkin's lymphoma</p> <p>Temozolomide Malignant gliomas</p> <p>Nitrosourea</p> <p>Streptozotocin Pancreatic islet cell cancer</p>				<p>7meG 3meA O⁶meG</p>
<p>Chloroethylating Nitrosoureas</p> <p>ACNU (Nimustine) Brain tumors Solid tumors</p> <p>BCNU (Carmustine) Brain tumors Lymphomas Melanoma</p> <p>CCNU (Lomustine) Brain tumors Lymphomas Melanoma</p> <p>Fotemustine Metastatic melanoma</p>				<p>7-alkylG O⁶Cl-ethylG N1,O⁶-EG G-C x-link G-G x-link</p>
b Bifunctional				Lesions
<p>Nitrogen mustards</p> <p>Mechloroethamine -CH₂CH₂COOH Chlorambucil</p> <p>Cyclophosphamide</p> <p>Melphalan</p> <p>Bendamustine</p> <p>Lymphomas, leukemias, multiple myeloma, ovarian cancer and solid tumors</p>				<p>7-alkylG O⁶alkylG G-G x-link G-A x-link</p>
<p>Aziridines</p> <p>Altretamine Recurrent ovarian cancer</p> <p>Mitomycin C Breast cancer Gastrointestinal tumors</p> <p>Thiotepa Breast, ovarian and bladder carcinomas</p>				<p>7-alkylG O⁶alkylG G-G x-link G-A x-link</p>



Red structures are alkyl modifications. ALKBH, AlkB homologue; BER, base excision repair; FA, Fanconi anaemia; HR, homologous recombination; MGMT, O 6-methylguanine-DNA methyltransferase; MMR, mismatch repair; NER, nucleotide excision repair; NHEJ, non-homologous end joining; TLS, translesion DNA synthesis.



HeLa cells



Rebecca Skloot
The Immortal Life of
Henrietta Lacks (2011)



Biospecimen policy: Family matters
Nature, 500,141–142, (08 August 2013)

