

# Anti-cancer compounds / Antineoplastic Agents, chapter 42

**Neoplasm:** New and diseased form of tissue growth

**Benign (godartet) neoplasm:** Easy to separate from surrounding tissue,  
no metastases

**Malign (ondartet) neoplasm:** Invassive to surrounding tissue  
Metastases } **Cancer**

**Metastase:** Secondary tumors, different location  
Malign cells separated from primary tumor  
and spread by vascular- or lymph systh.

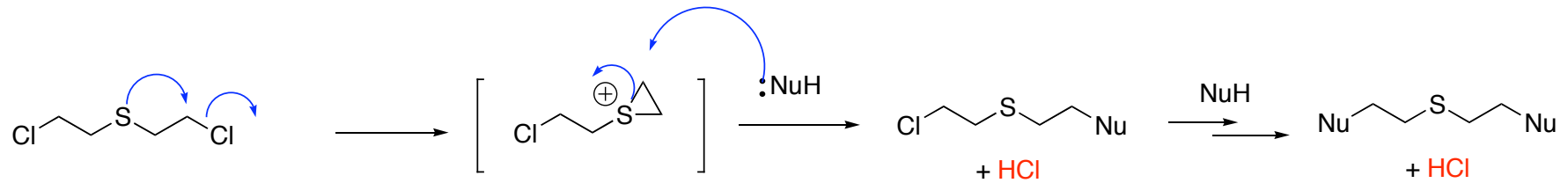
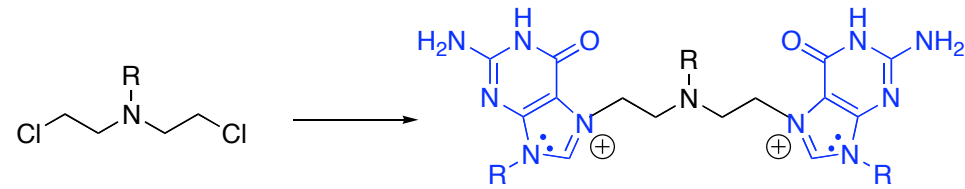
**Terminology differents types of cancer confusing**

## Cancer Therapy

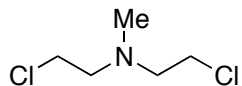
- Surgery
- Radiation
- Immunologican Therapy (interferons - Incr. prod. T-cells and B cells)
- Chemotherapy
  - Alkylation Agents
  - Antimetabolites / Nucleoside Analogs
  - Antibiotics
  - Antimitotic Agents
  - Micellaneous Antineoplastic Agents
  - Hormonal Therapy

# Alkylating Agents

- 1) Nitrogen mustards
- 2) Other alkylation agents
- 3) Pt-complexes



**Sulfur mustard**  
**Mustard gas**  
**Yprite**  
**Worlds war I (1917)**  
**Impurity smell like mustard / garlic**

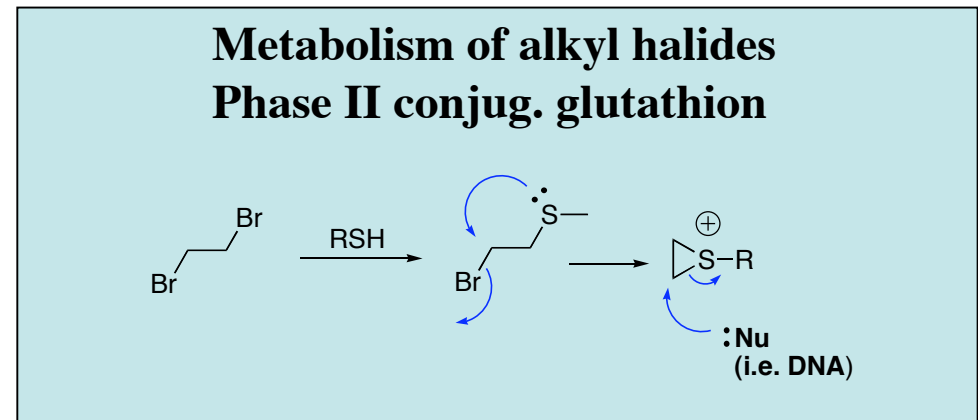


**Mechlorethamine**  
**FDA 1949**

**Rel. selective tox. to lymphoid tissue**  
**(Hodkins disease, Lymphomas)**

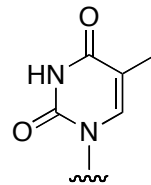
**Tox. to rapid proliferating cells (short time for DNA repair)**

**More water sol.**

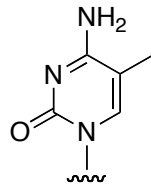


# Alkylating Agents

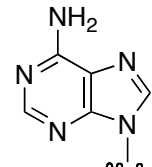
## DNA Bases - Nucleophilic Centra



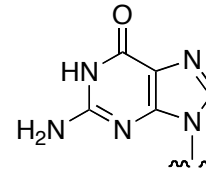
Thymin



Cytosin

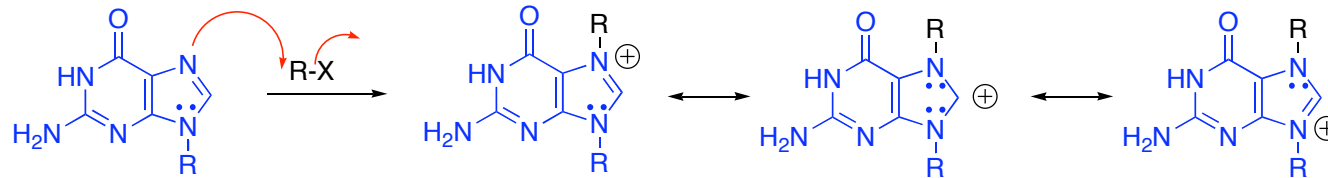


Adenine

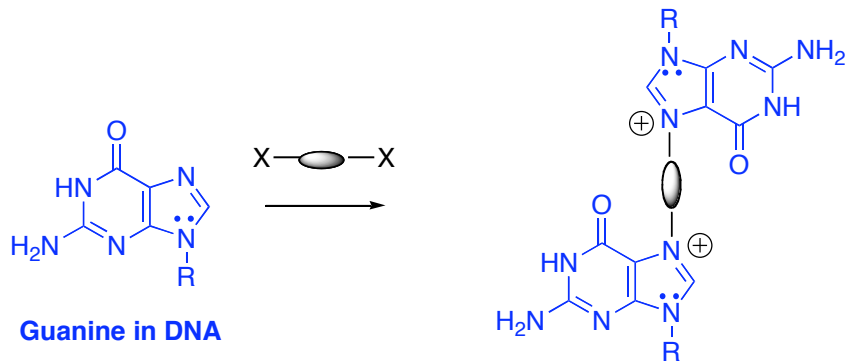


Guanine

Also O in phosphate  
may be alkylated

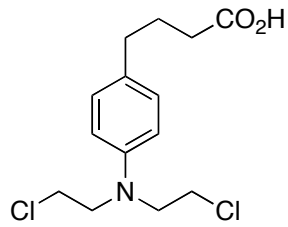


Guanine in DNA

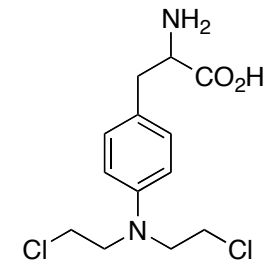


Guanine in DNA





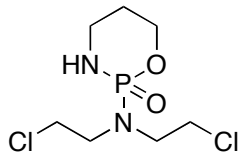
***Chlorambucil***  
Leukeran®,



***Melfalan***  
Alkeran®,  
**L-isomer**  
**Active transport mech (L-AA)**



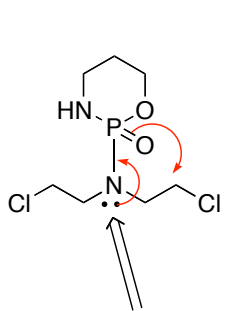
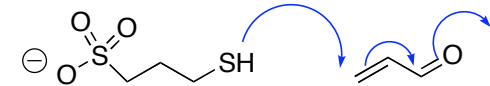
**Aryl decrease reactivity**



***Cyclophosphamide***  
Sendoxan®

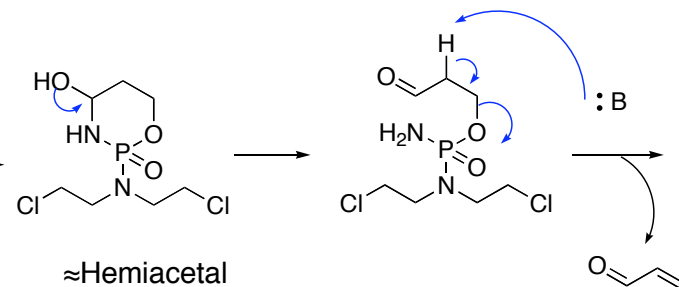
**Pro-drug**

**MESNA Co-admin.**



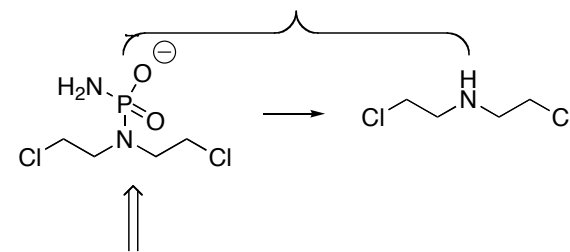
**Not nucleophilic  
cf amides**

CYP450



≈Hemiacetal

**Active compound**

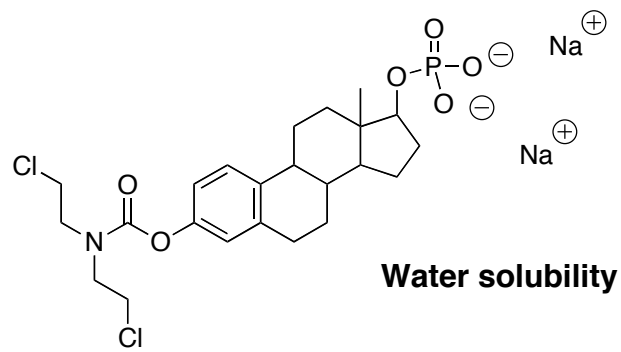


**More nucleophilic  
Neg charge (phys. pH)  
prevents delocal.**

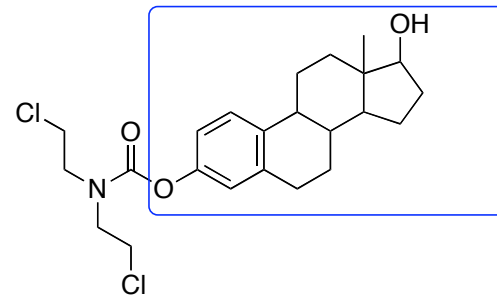
***Estramustine phosphate***

Estracyt®

Pro-drug



1) Oral absorb  
2) Fast metabol.



**Estradiol**  
Carry to cells with  
estrogenic receptors

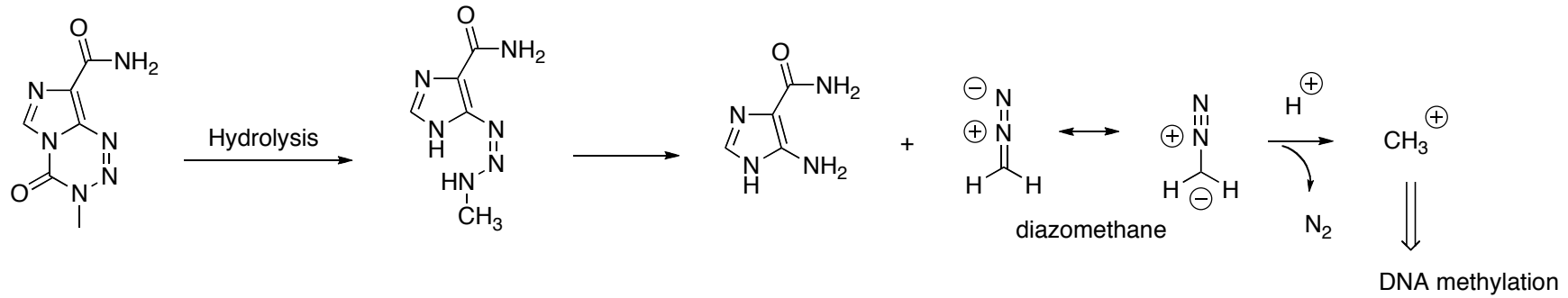
**Estrogenic (Anti-androgenic) effect prostate cancer**  
**Cleaved to active alkylating agent?**

## Alkylating Agents

- 1) Nitrogen mustards
- 2) Other alkylation agents
- 3) Pt-complexes

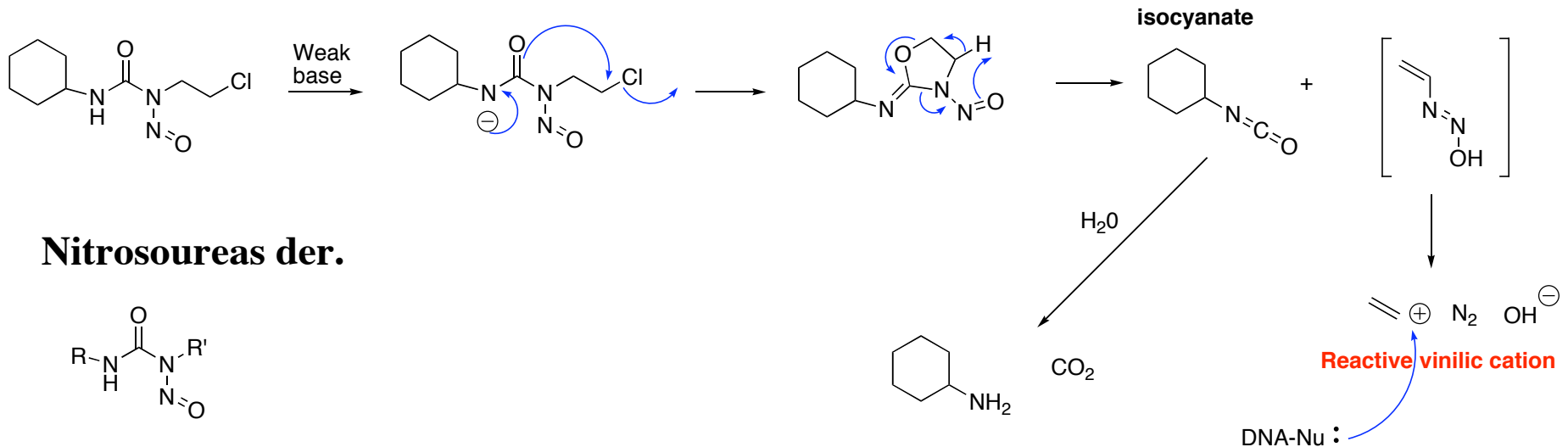
### Temozolomide

Temodal®

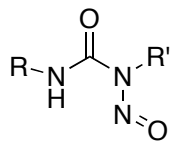


### Lomustine

Lomustine medac®

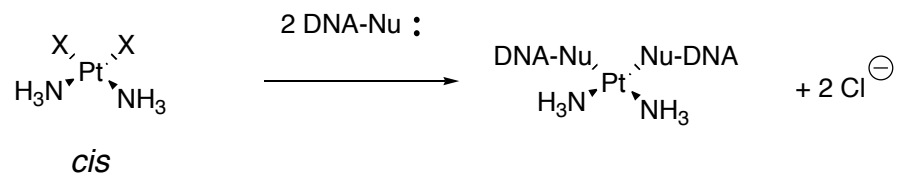
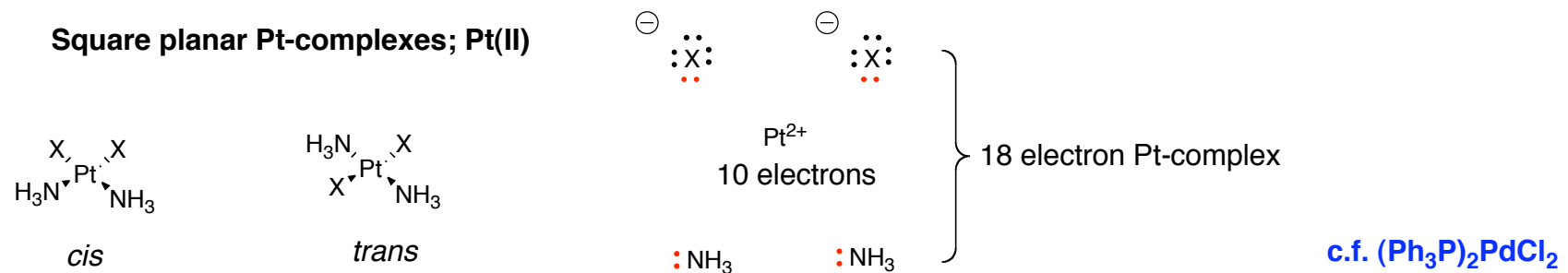


### Nitrosoureas der.



# Alkylating Agents

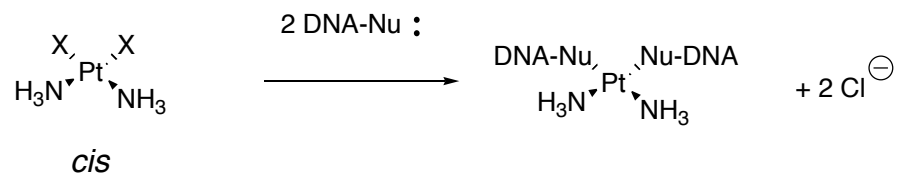
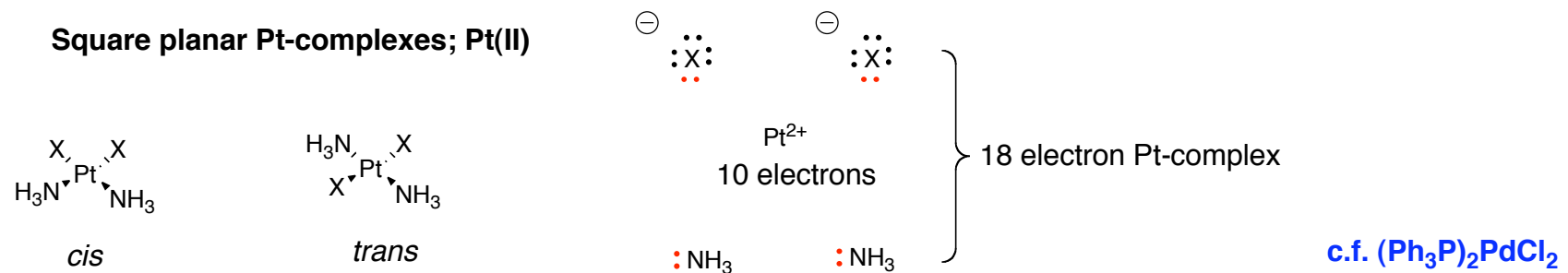
- 1) Nitrogen mustards
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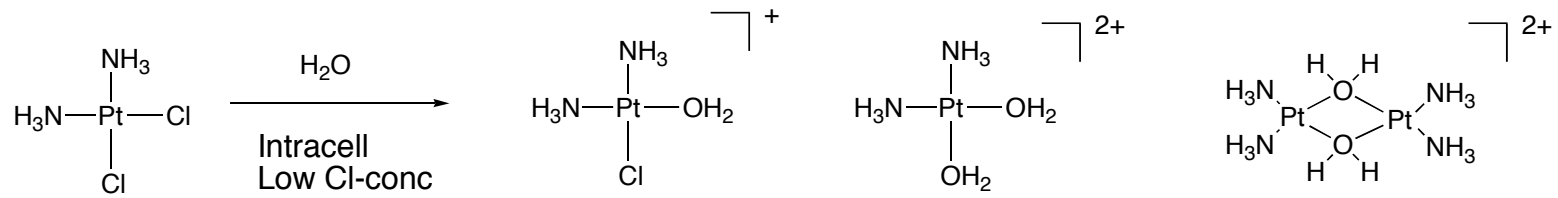
(Complexes with trans isomers are more readily recognized and repaired)

# Alkylating Agents

- 1) Nitrogen mustards
- 2) Other alkylation agents
- 3) Pt-complexes



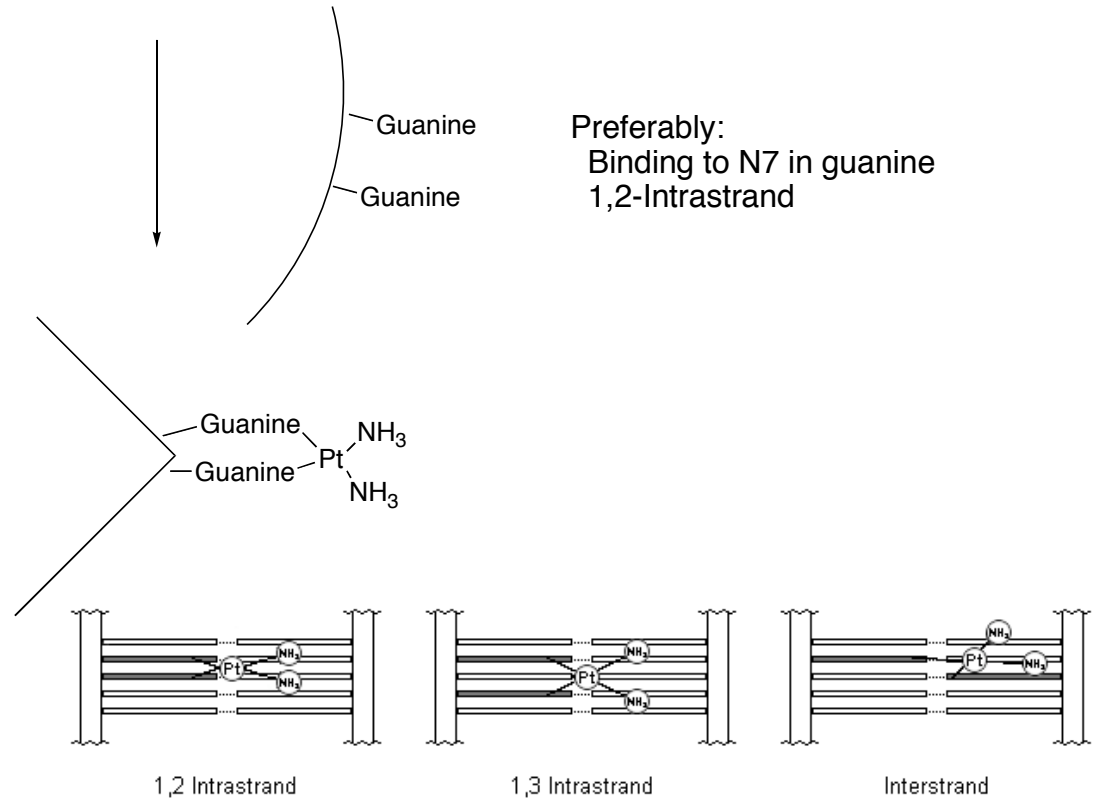
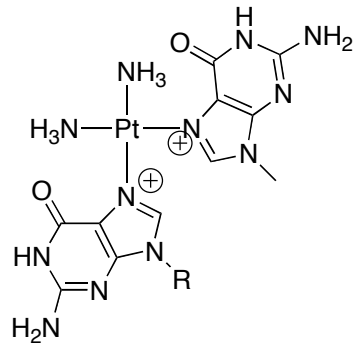
(Complexes with trans isomers are more readily recognized and repaired)



Pt(II) [as Pd(II)] electrophilic  
Nucleophilic subst.

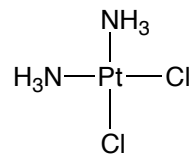
Most probably

Preferably:  
Binding to N7 in guanine  
1,2-Intrastrand



**Cisplatin**

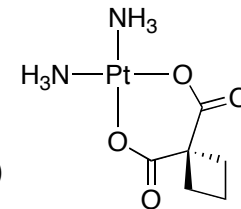
Platinol® Platistin®



**Carboplatin**

Carboplatin® Carbosin® Paraplatin®

More stabile comp. (reacts less readily with water)



# Anti-cancer compounds / Antineoplastic Agents, chapter 42

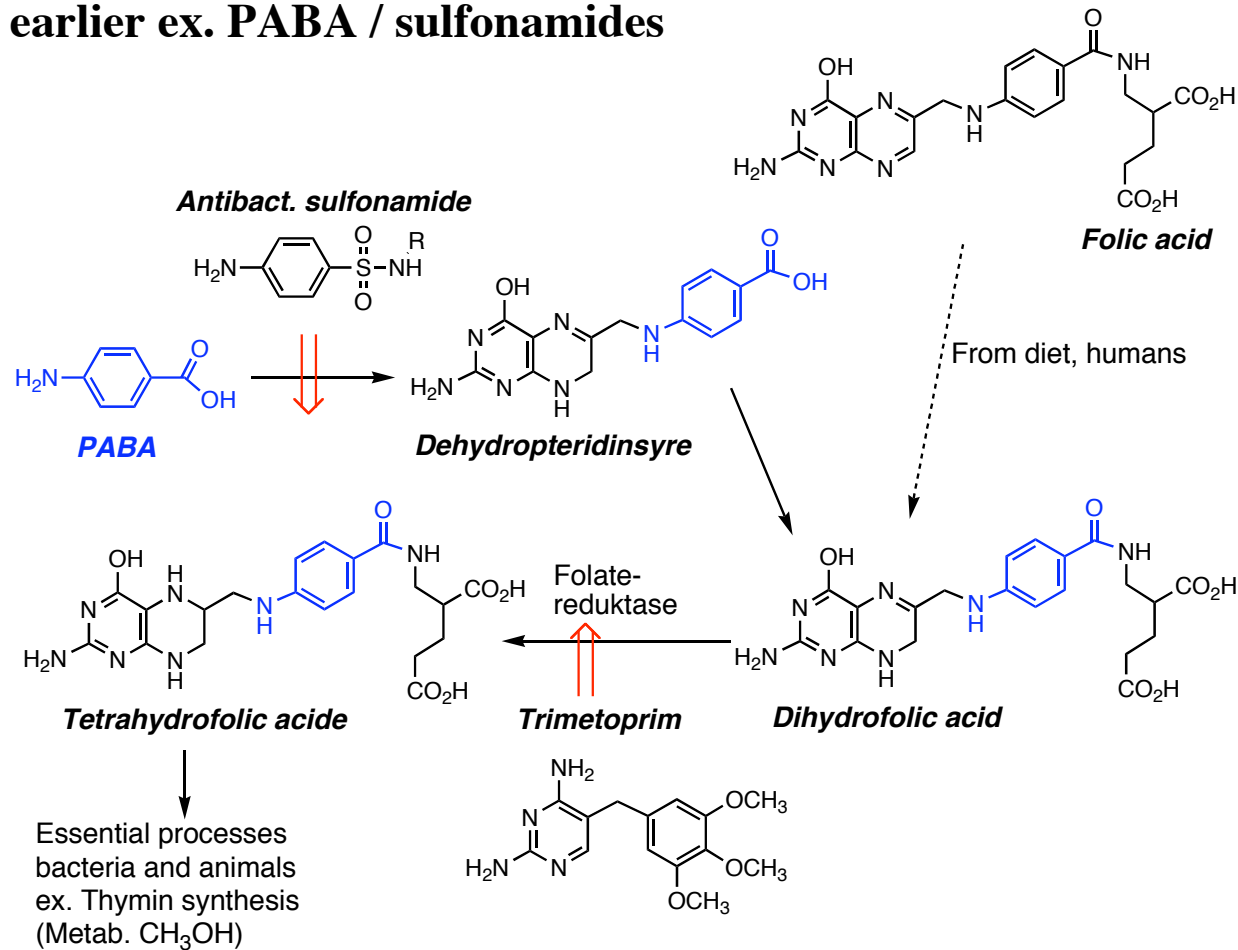
## Cancer Therapy

- Surgery
- Radiation
- Immunological Therapy (interferons - Incr. prod. T-cells and B cells)
- Chemotherapy
  - Alkylation Agents✓
  - Antimetabolites / Nucleoside Analogs
  - Antibiotics
  - Antimitotic Agents
  - Miscellaneous Antineoplastic Agents
  - Hormonal Therapy

# Antimetabolites (Nucleoside Analogs, Folic acid analogs)

**Antimetabolites:** Prevents synthesis of normal cellular metabolites  
Often close structural similarities metabolite and antimetabolite

earlier ex. PABA / sulfonamides



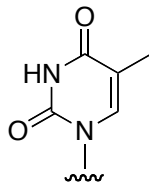


# Nucleoside analogs as antimetabolites

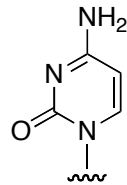
## Possible mechanisms:

- Incorporation DNA or RNA; misreading
- Inhibition of DNA polymerase
- Inhibition of Kinases
- Inhib. of enzymes involved in pyrimidine / purine biosynthesis

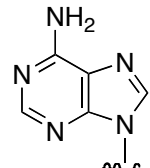
**DNA**



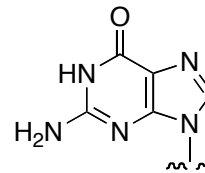
**Thymin**



**Cytosin**

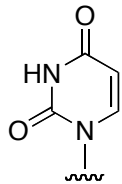


**Adenine**



**Guanine**

**RNA**

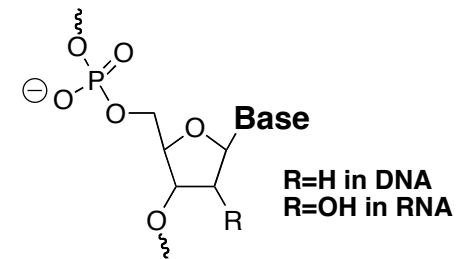


**Uracil**

**Cytosin**

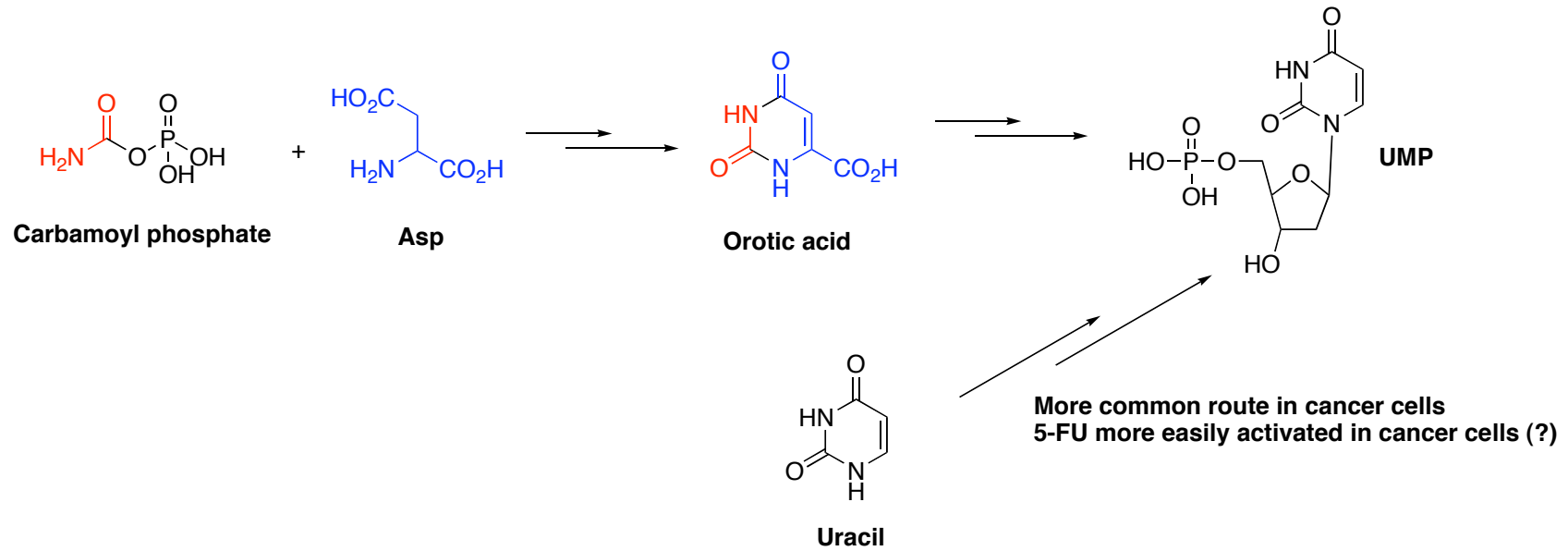
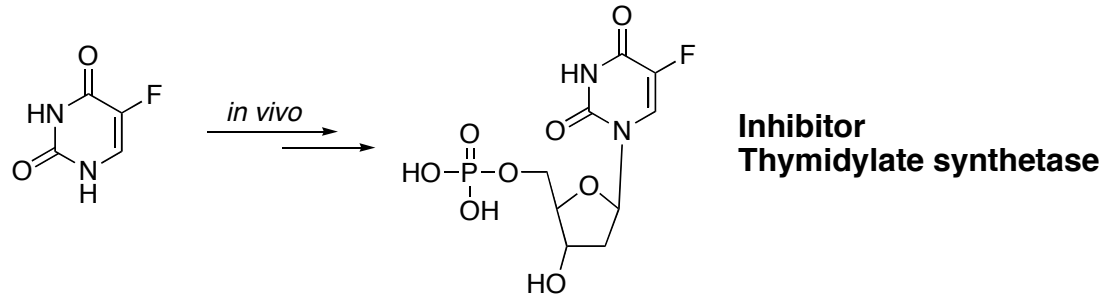
**Adenine**

**Guanine**

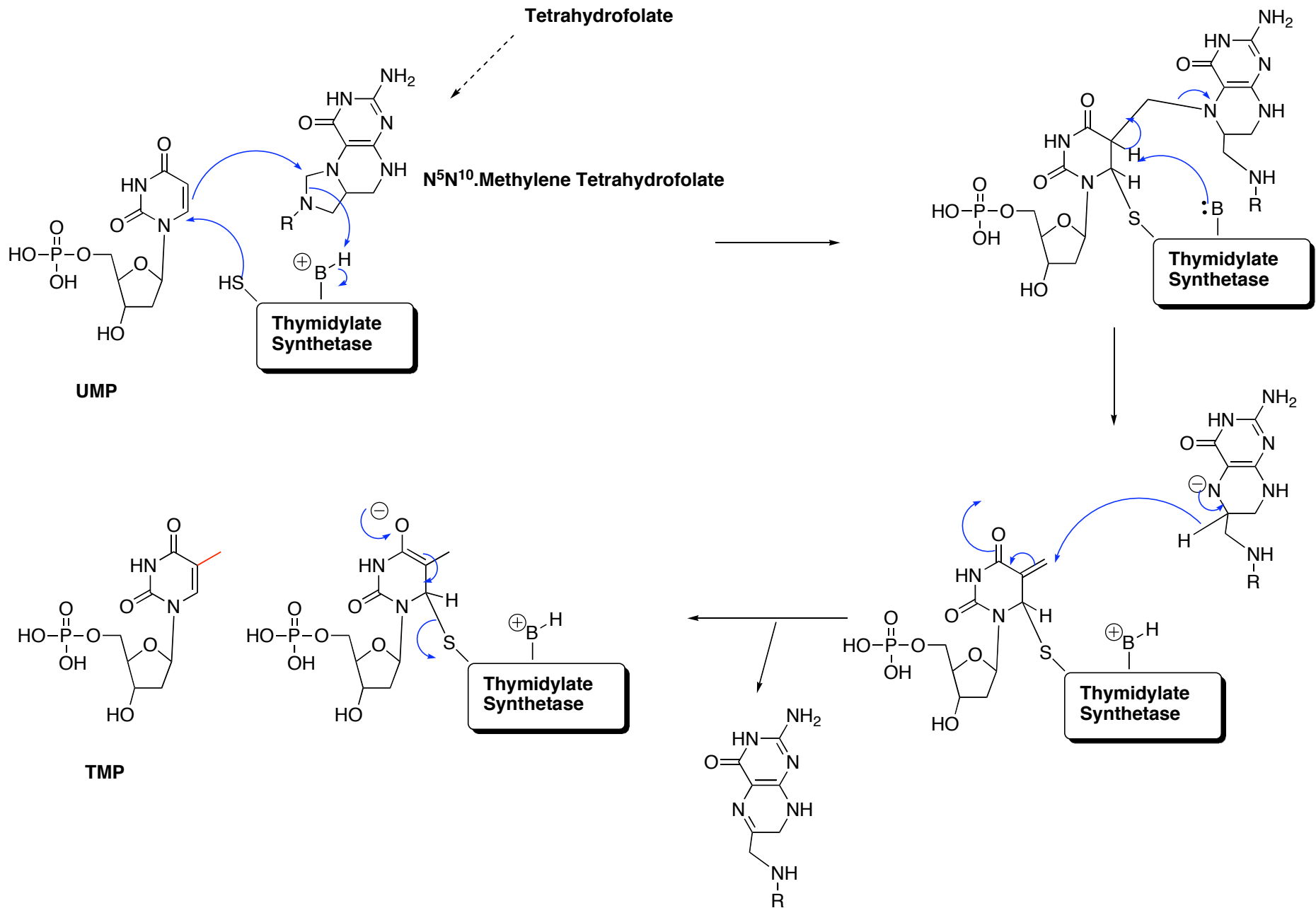


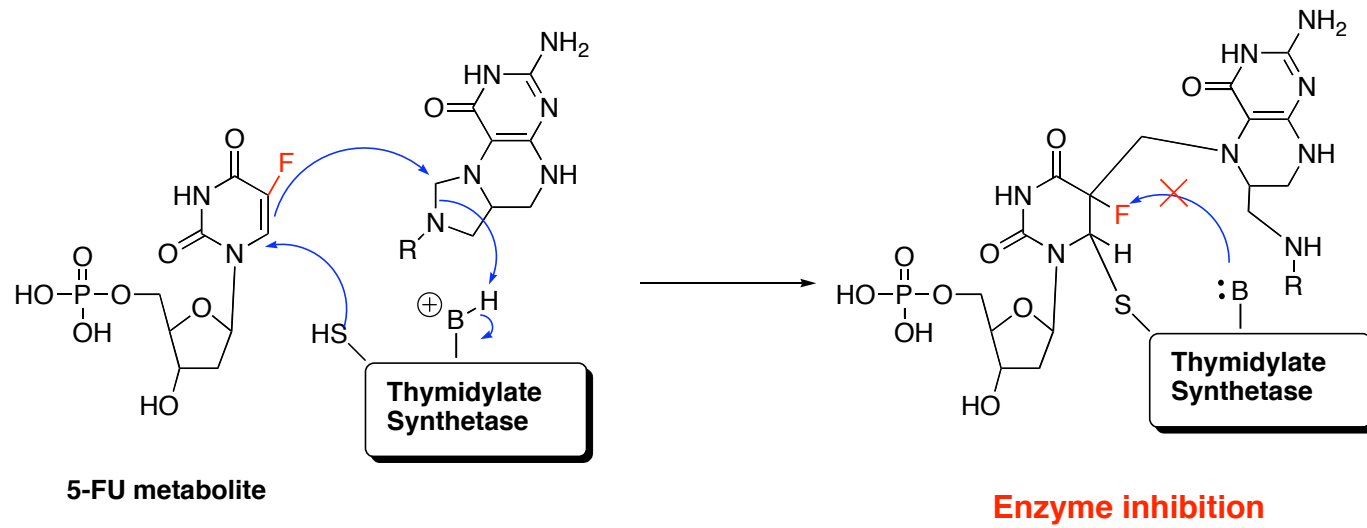
**5-Fluorouracil (5-FU)**

Fluorouracil®, Flurablastin®,



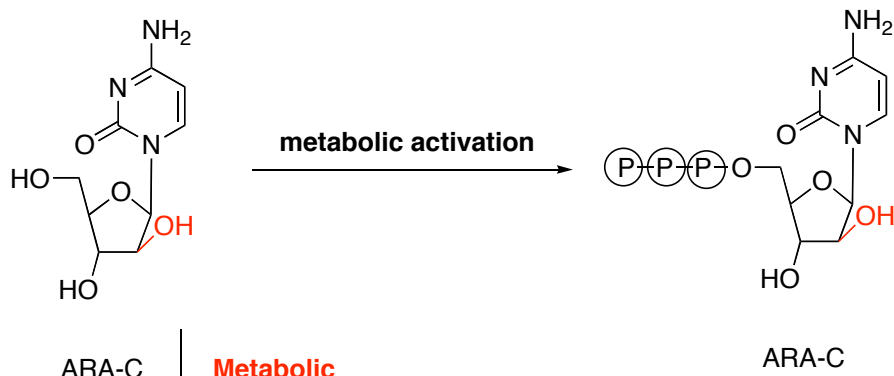
# Synth. thymine nucleotide from uracil nucleotide by thymidylate synthetase



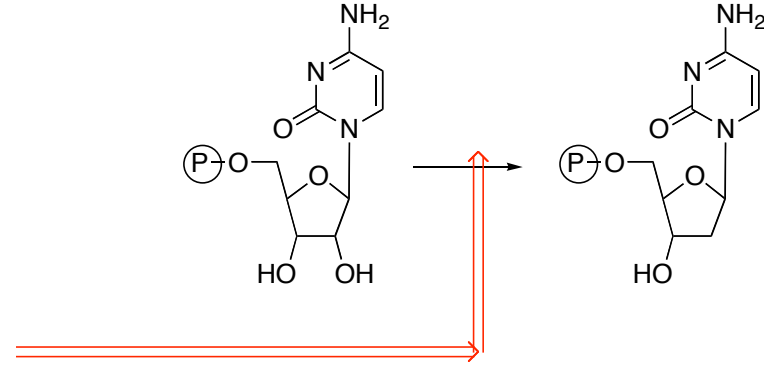
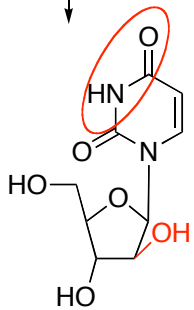


**Additional mechanisms: Incorp. DNA / RNA**

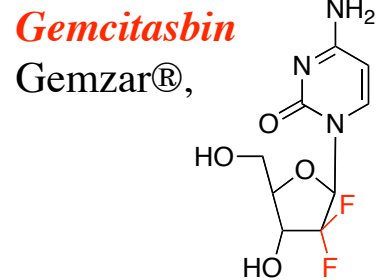
**Cytarabine (ARA-C)**  
Cytarabin®, Cytosar®,



Metabolic inactivation (fast)

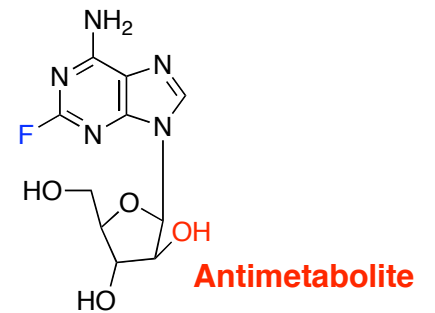


Inhib. DNA polymerase  
Incorporation DNA/RNA; misreading



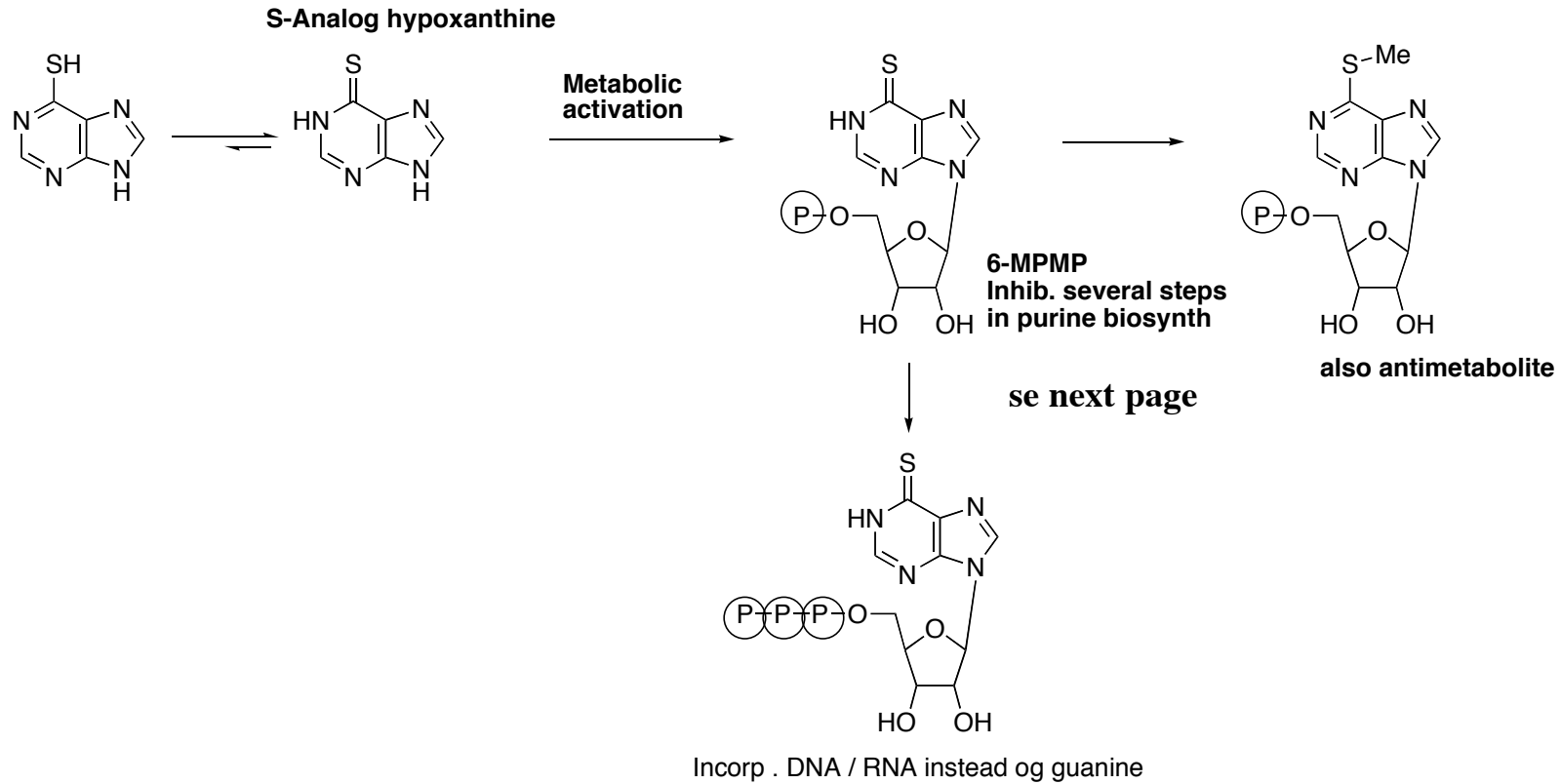
Metabolic activation (triphosphate)  
Incorp. DNA / RNA

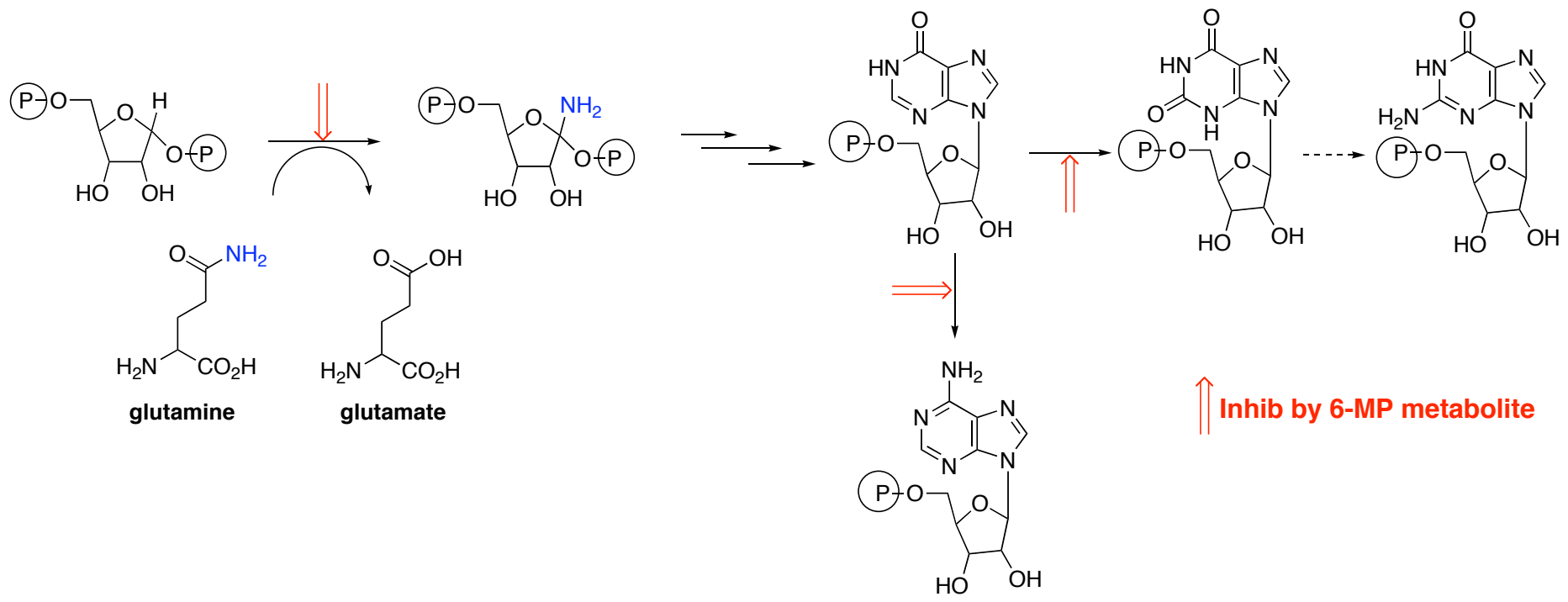
**Fludarabine**  
Fludara®  
Not good substrate for adenosine deaminase



## 6-Mercaptopurine (6-MP)

Puri-Nethol®



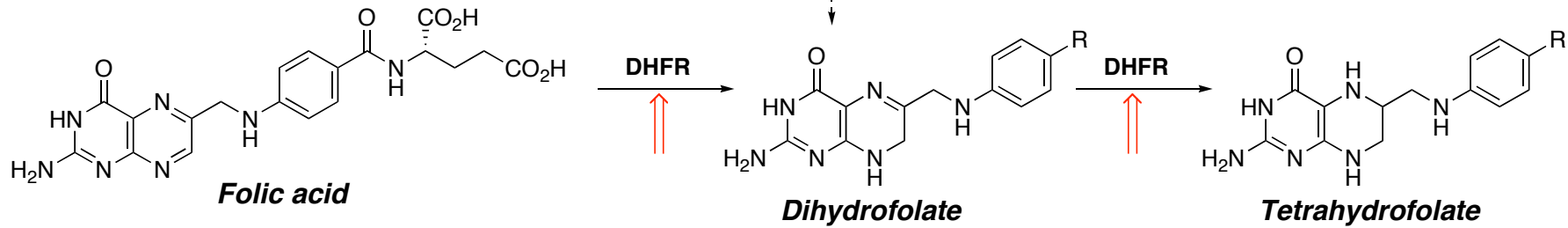


↑↑ Inhib by 6-MP metabolite

# Folic Acid analogs as antimetabolites

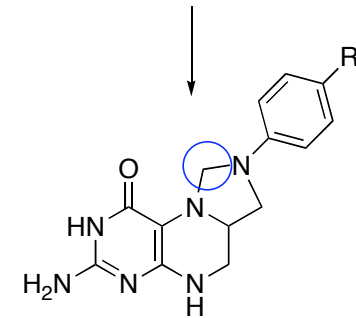
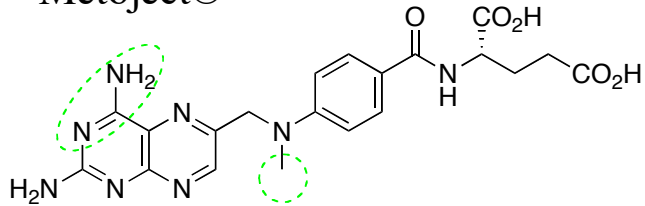
**PABA**

Microorganisms



**Metotrexat**

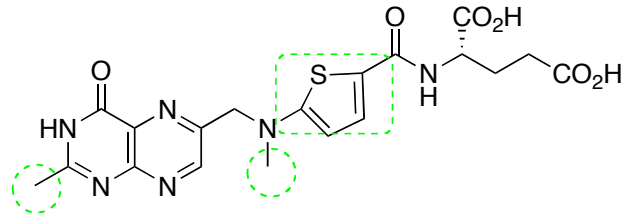
Metoject®



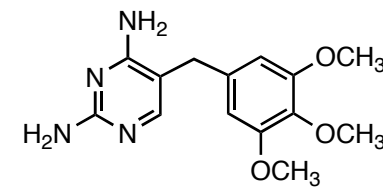
**Thymine synth**

**Raltitrexed**

Tomudex®



**Trimetoprim**





- Chemotherapy**

- Alkylation Agents** ✓

- Antimetabolites / Nucleoside Analogs** ✓

- Antibiotics**

- Antimitotic Agents**

- Micellaneous Antineoplastic Agents**

- Hormonal Therapy**

**Metabolites from microorg., too toxic as antibiotics - anticancer comp.**

- Bleomycins**

- Actinomycins**

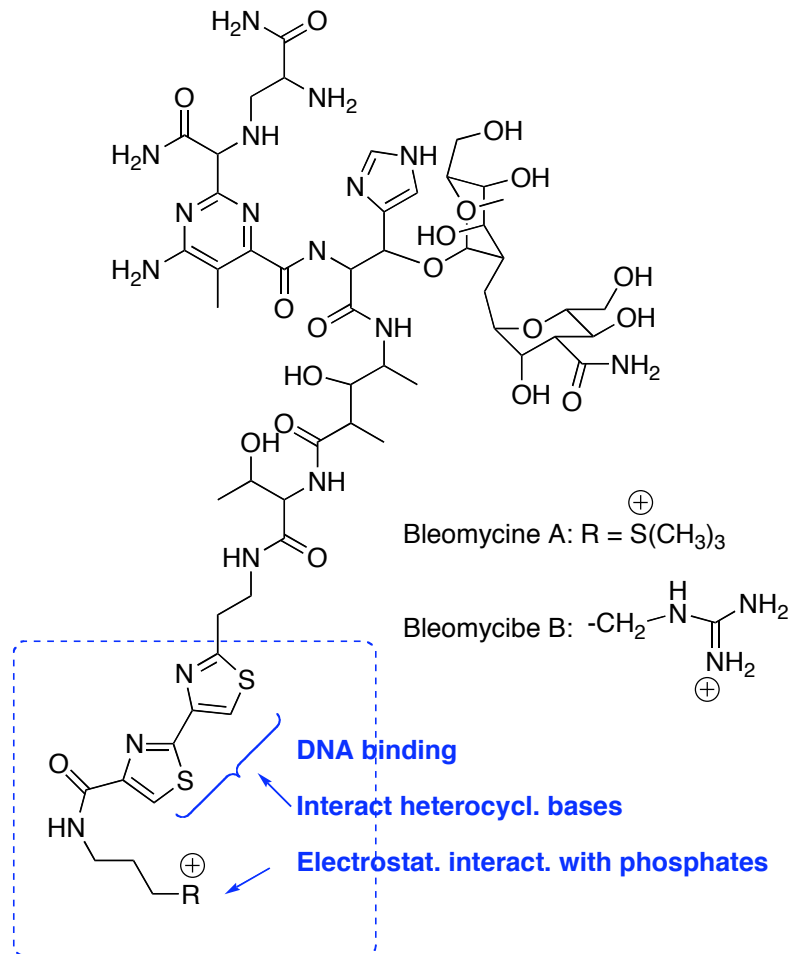
- Mitomycins**

- Antracyclins**

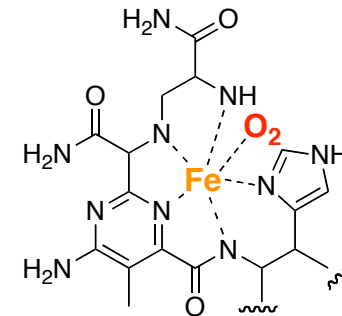
- Coformycins**

# Bleomycins

Isolated from *Streptomyces verticillius*  
Naturally occurring as Cu-chelates



1) Binds Fe(II) inside cells



2) Bleomycin complexed Fe(II) reduce  $O_2$

3)  $\bullet OH$  radicals produced

4) Cleavage of DNA

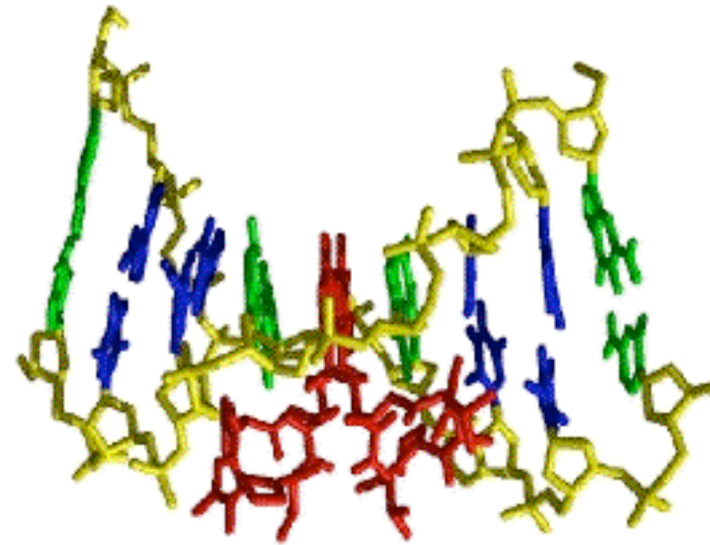
*Bleomycin*  
Bleomycin Baxter®

# Actinomycins

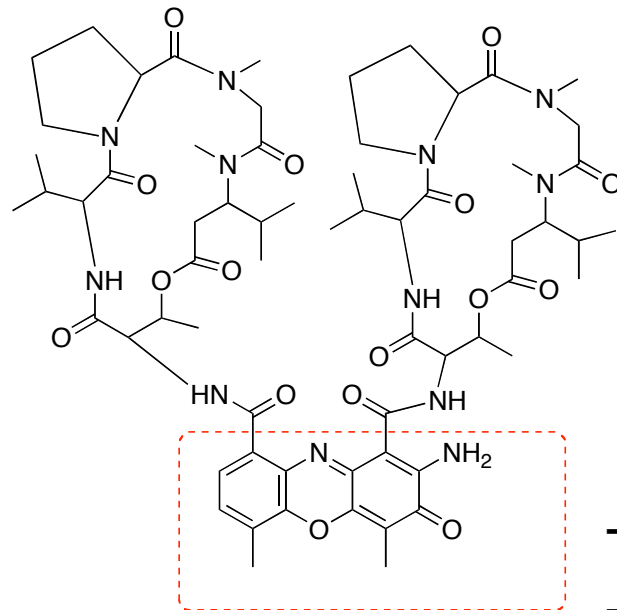
Isolated from *Streptomyces* sp.

*Dactinomycin (Actinomycin D)*

Cosmegen®



red: actinomycin D  
green: G,C bases  
blue, A,T bases  
yellow, phosphate/sugar backbone



**Planar, aromatic rings  
Intercalate between G-C base pairs  
( $\pi$ - $\pi$  stacking interact)**



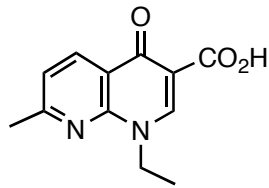
- Affects DNA topoisomerase II (Unwinding)
- May also promote DNA cleavage (nucleases)

## Quinolones (antibact, chapt 38)

Inhib DNA-synthesis; **DNA-gyrase (prokaryoter)** unwinding DNA before replic..

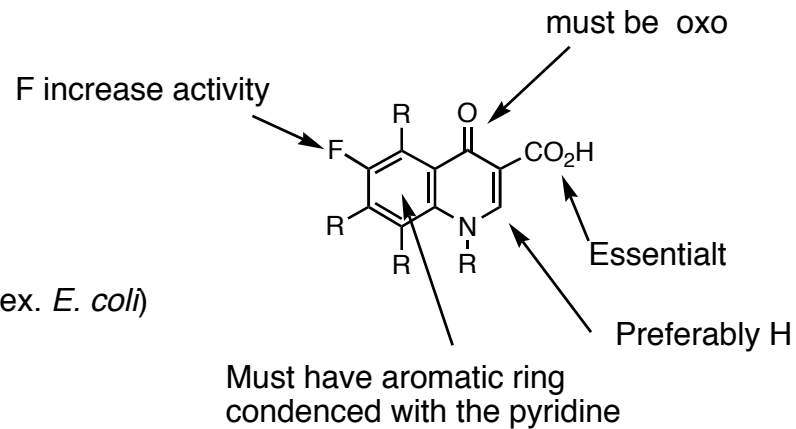
**DNA-topoisomerase (humans)**, anticancer compds. ex. anthracyclines

**Parent comp.**  
Nalidixic acid



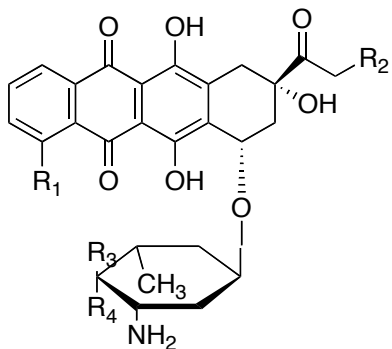
Urinary tract infect. earlier  
effect on Gram-negative bacteria (ex. *E. coli*)

**Moderne quinolones**



# Antracyclines

Isolated *Streptomyces* sp, several semisynth analogs



## *Doxorubicin*

Doxorubicin® Adriamycin® Caelyx®

$R_1 = \text{OMe}, R_2 = \text{OH}, R_3 = \text{H}; R_4 = \text{OH}$

## *Daunorubicin*

Cerubidin®  $R_1 = \text{OMe}, R_2 = \text{H}, R_3 = \text{H}; R_4 = \text{OH}$

## *Idarubicin*

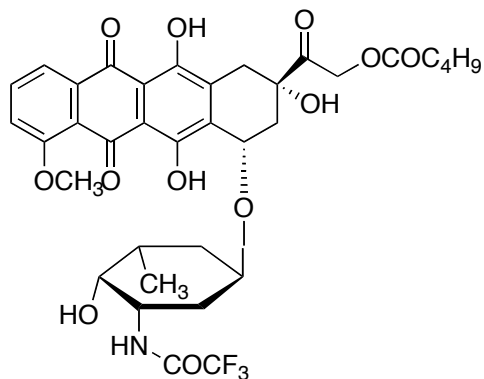
Zavedos®  $R_1 = \text{H}, R_2 = \text{H}, R_3 = \text{H}; R_4 = \text{OH}$

## *Epirubicin*

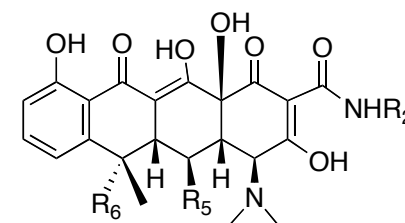
Farmorubicin®

$R_1 = \text{OMe}, R_2 = \text{OH}, R_3 = \text{OH}; R_4 = \text{H}$

## *Valrubicin*

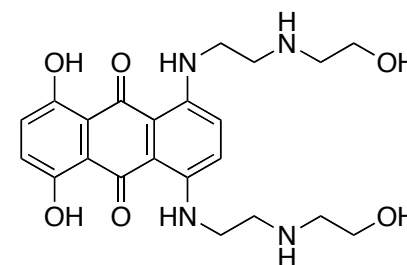


# Antibacterial Tetracyclines



## *Mitoxantrone*

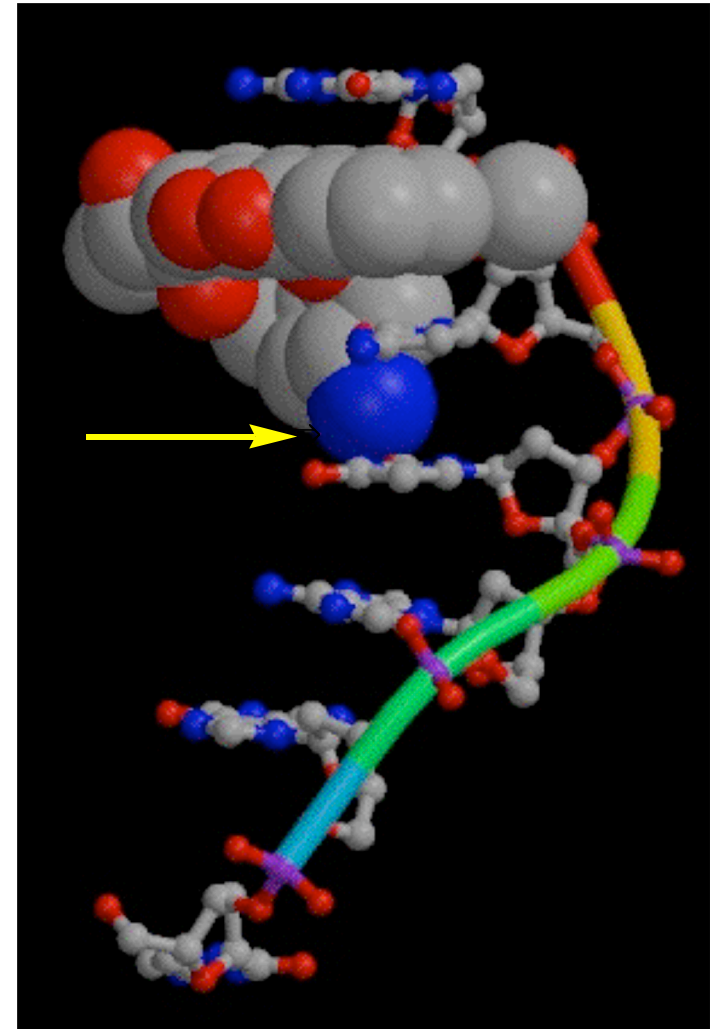
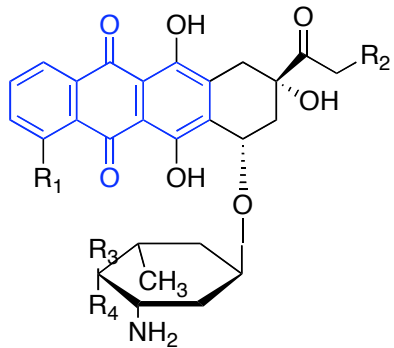
Novantrone®



**Mechanism  $\approx$  Actinomycins (Intercalation)**

**Also interact aminosugar - phosphate**

**Antraquinone - red/ox react:**  
**prod. reactive oxygen radicals**



*DNA-Daunomycin Complex*

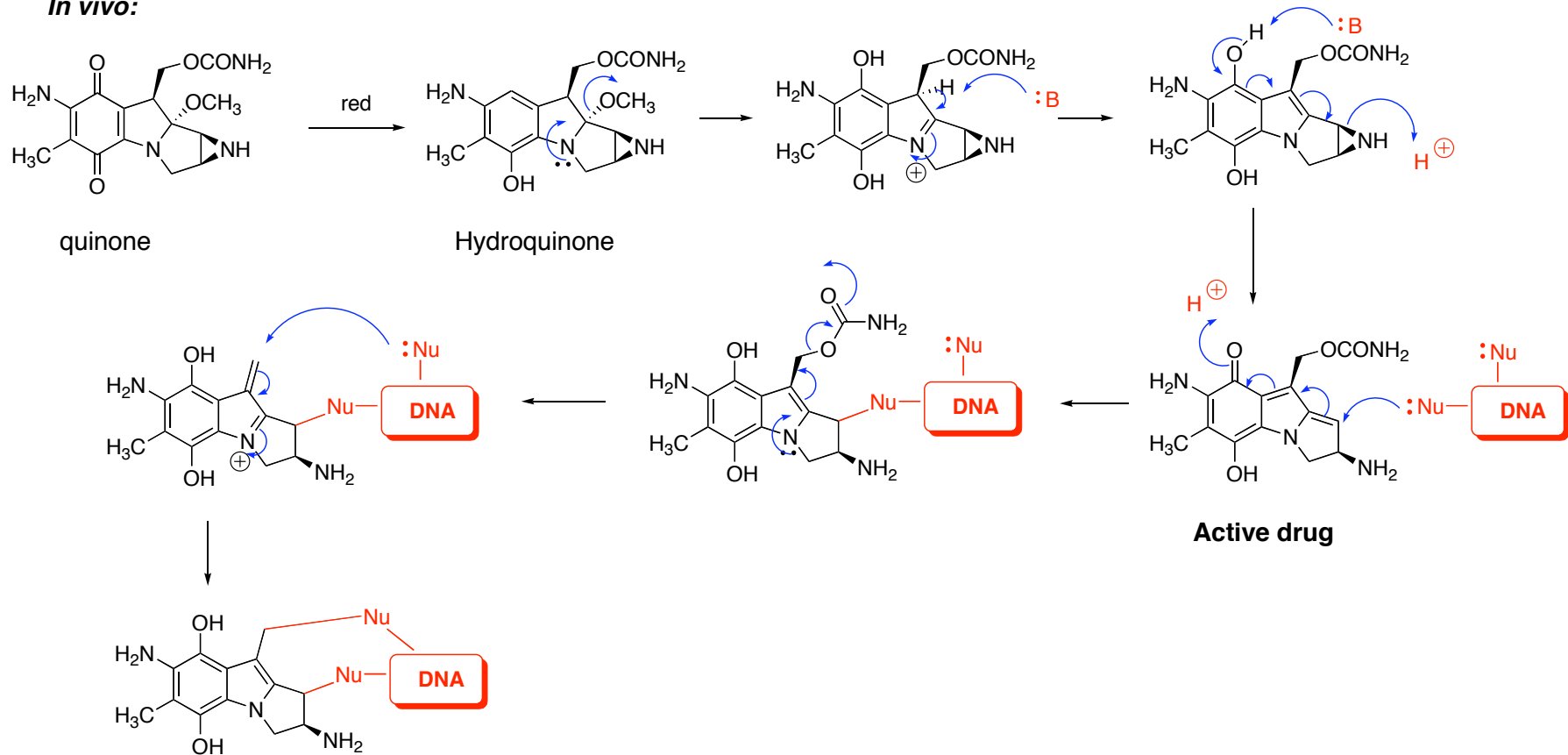
# Mitomycins

Isolated *Streptomyces sp.*

## Mitomycin C

Mutamycin®

*In vivo:*



- Chemotherapy**

- Alkylation Agents** ✓

- Antimetabolites / Nucleoside Analogs** ✓

- Antibiotics** ✓

- Antimitotic Agents**

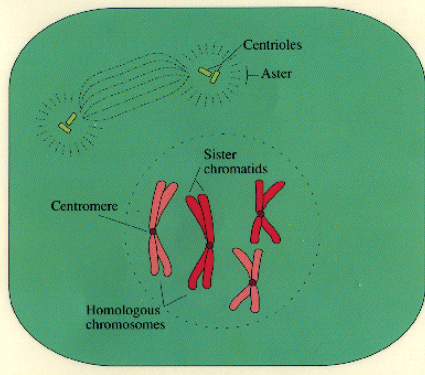
- Micellaneous Antineoplastic Agents**

- Hormonal Therapy**

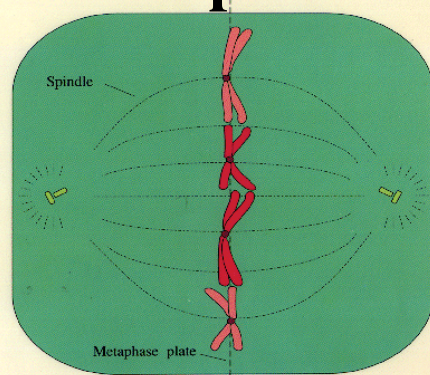


# Mitosis

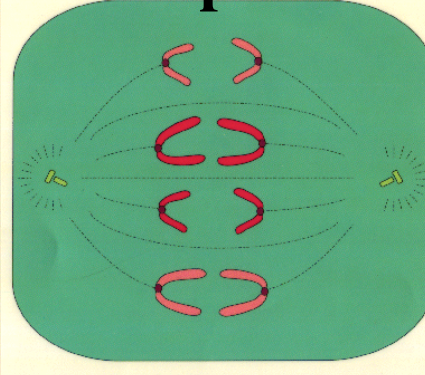
## Prophase



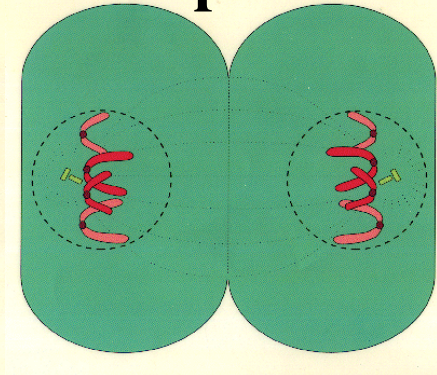
## Metaphase



## Anaphase



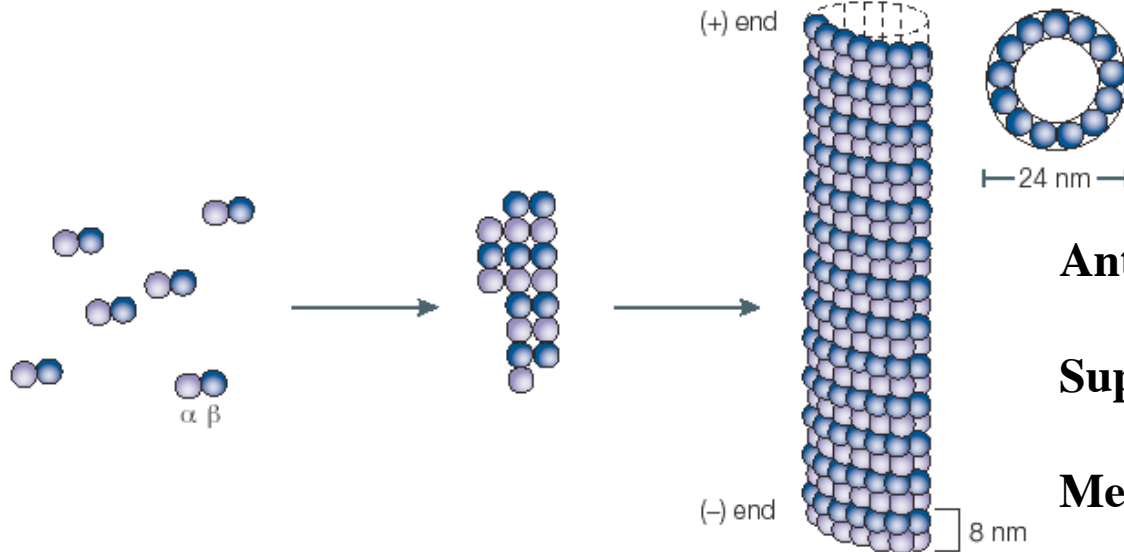
## Telophase



$\alpha$ - and  $\beta$ -tubulin heterodimers

Microtubule nucleus

Microtubule



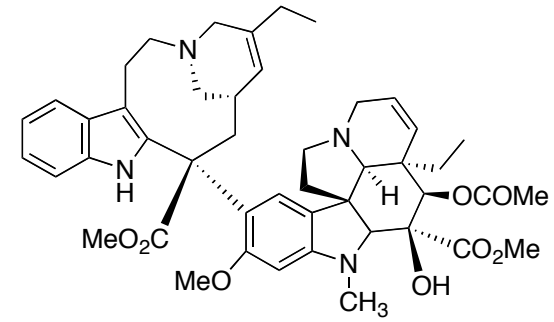
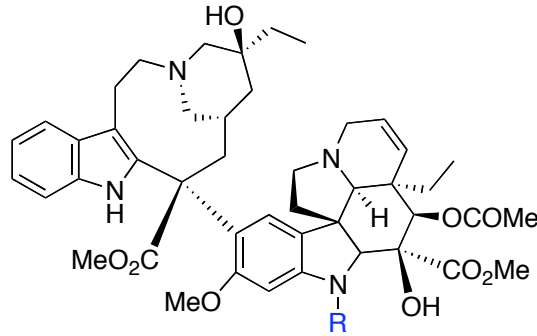
**Antimitotic agents bind to microtubuli**

**Supression of microtubuli dynamics**

**Metaphase arrest**

Figure 1 | **Polymerization of microtubules.** Heterdimers of  $\alpha$ - and  $\beta$ -tubulin assemble to form a short microtubule nucleus. Nucleation is followed by elongation of the microtubule at both ends to form a cylinder that is composed of tubulin heterodimers arranged head-to-tail in 13 protofilaments. Each microtubule has a so-called plus (+) end, with  $\beta$ -tubulin facing the solvent, and a minus end (-), with  $\alpha$ -tubulin facing the solvent.

# Vinca alkaloids



**Vinorelbine, Navelbine®**

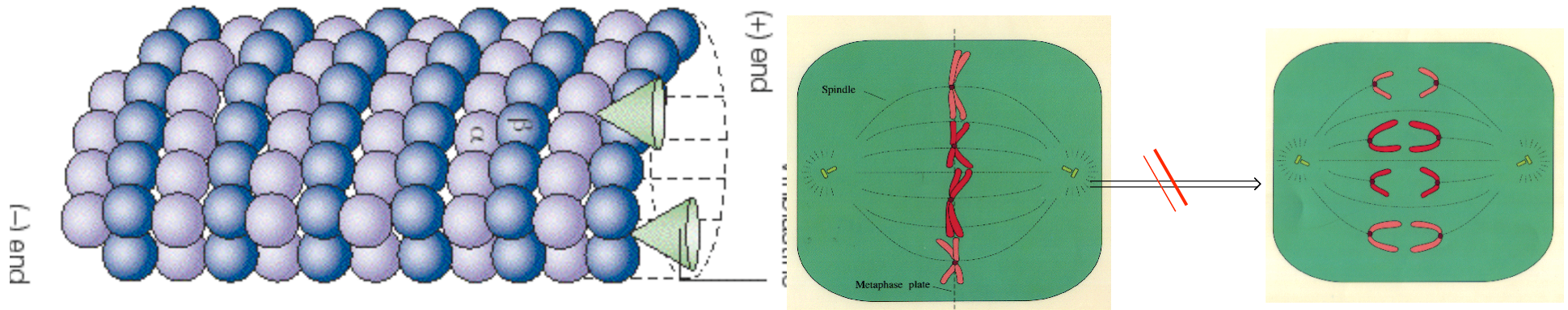
R=-Me: **Vinblastin, Velbe®**

R=-CHO: **Vinkristin, Vincristine®**

Vinca alkaloids (Indols)  
from *Vinca rosea*  
(*Catharantus roseus*)  
Madagascar Periwinkle

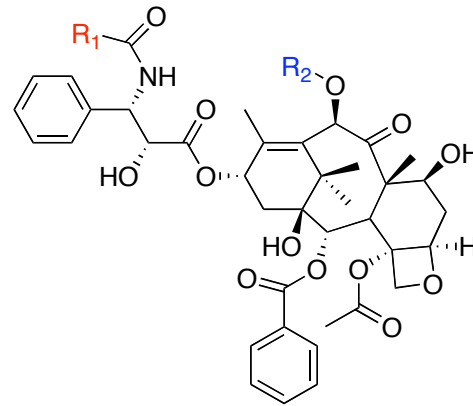
Binds to microtubuli- Supression of microtubuli dynamics-  
Metaphase arrest

Depolymerization of microtubuli high conc.



# Taxanes

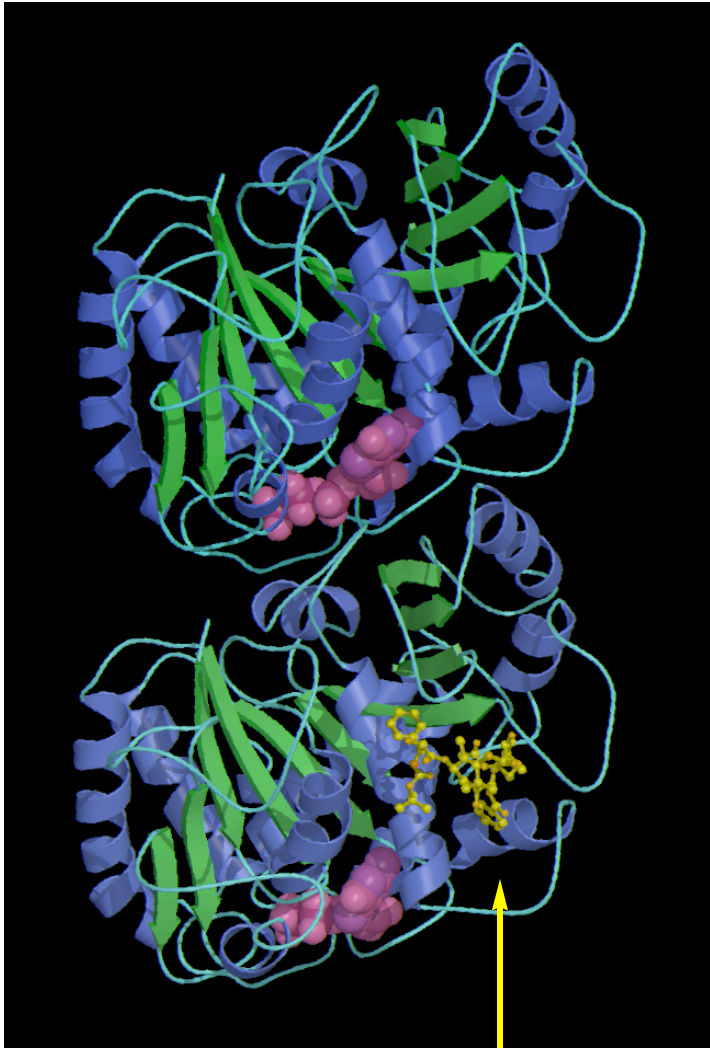
First isolated from bark of Western / Pacific yew (*Taxus brevifolia*)  
NIH screening of plant extracts 1960s



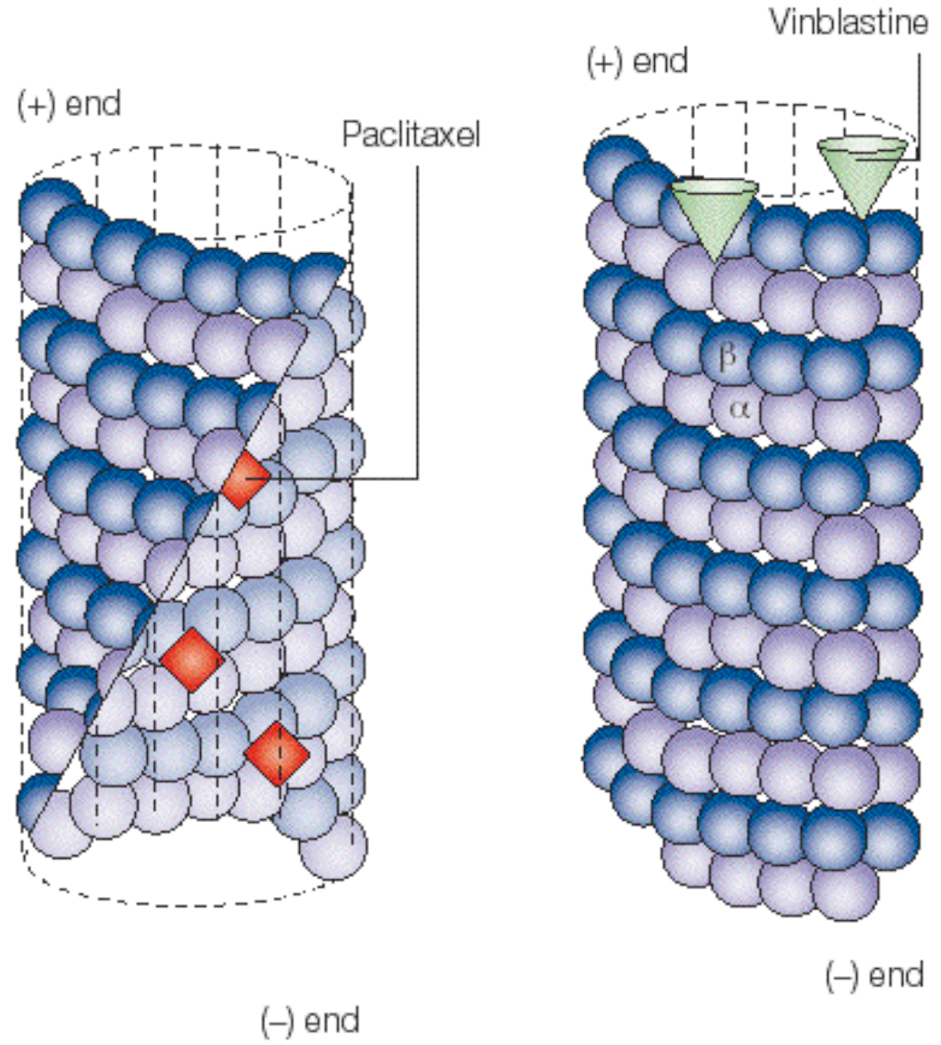
$R_1 = -\text{Ph}$ ,  $R_2 = -\text{COMe}$ : **Palitaxel**, **Taxol®**  
 $R_1 = -\text{OBu}^t$ ,  $R_2 = -\text{H}$ : **Dodetaxel**, **Taxotere®** **Semisynthetic**

Mecanism  $\approx$  Vinca alkaloids, different binding sites



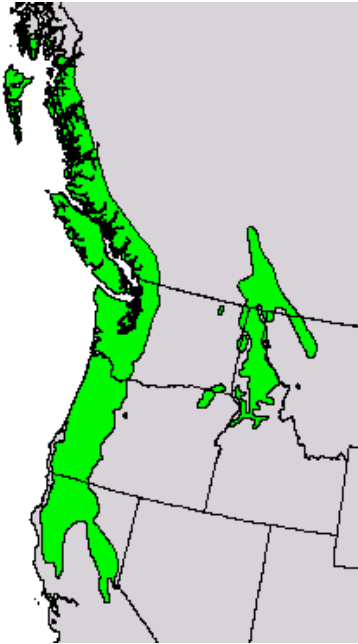


**Paclitaxel**



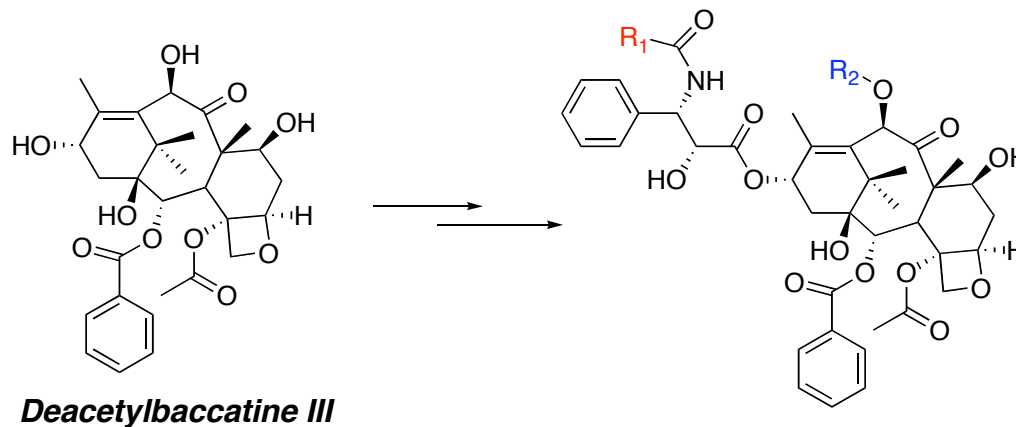
## Availability

Dried inner bark of Western / Pacific yew (*Taxus brevifolia*): 0.01 - 0.04%  
1 kg Taxol - 900 kg bark (2000 - 3000 trees)



-Other *Taxus* sp: Also palitaxel in needles (renewable source)

-Semisynth from deacetylbaaccatin III (0.1% in needles *Taxus baccata*)



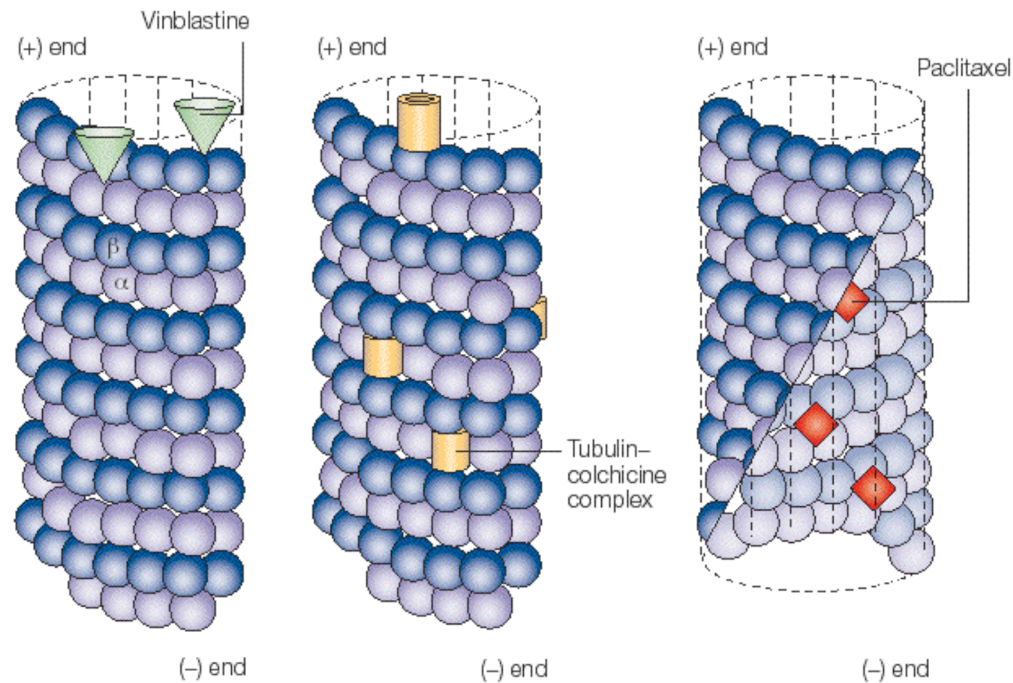
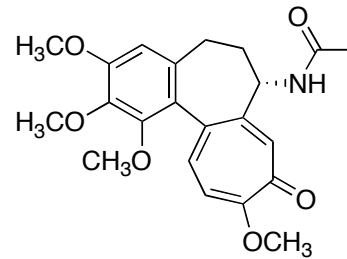
(-Total syntheses)

# Colchicine

From Meadow-saffron, *Colchicum autumnale* (Tidløs) seeds

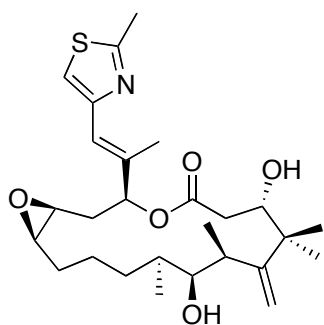
Binds to microtubuli - metaphase arrest, too toxic too be used in cancer treatment

Used to treat gout (podagra)

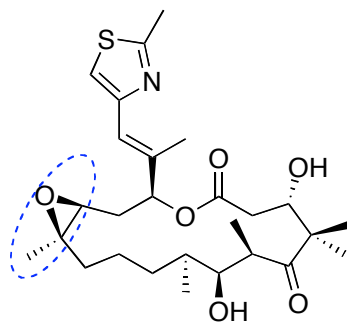


# Coming next? - Epothilones

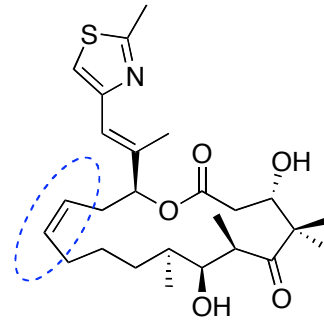
Isolated from *Myxobacteria* (Epothilone A - F + synth. analogs)



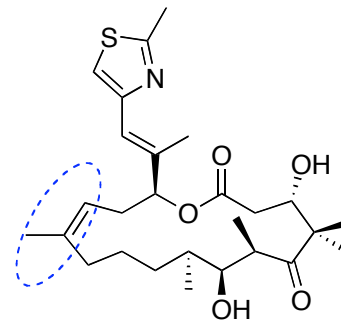
**Epothilone A**



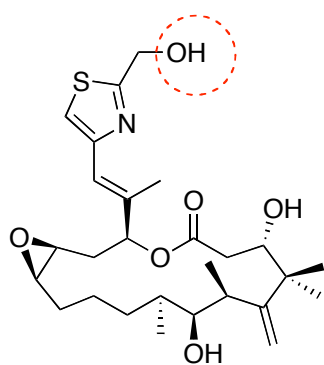
**Epothilone B**



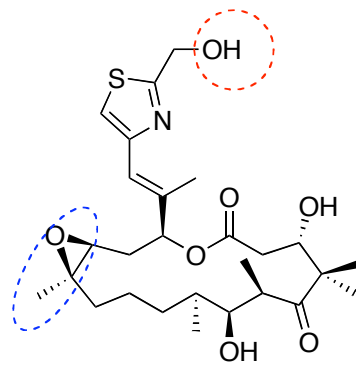
**Epothilone C**



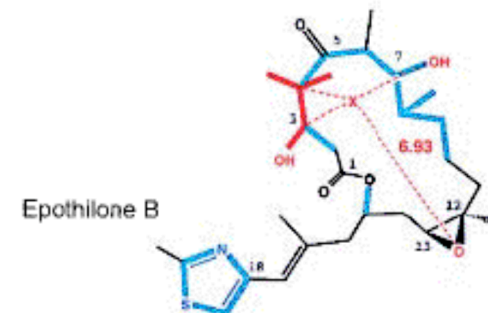
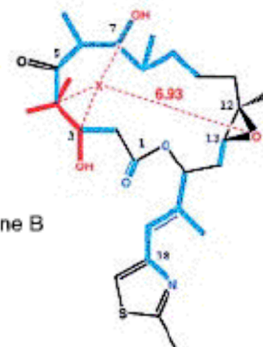
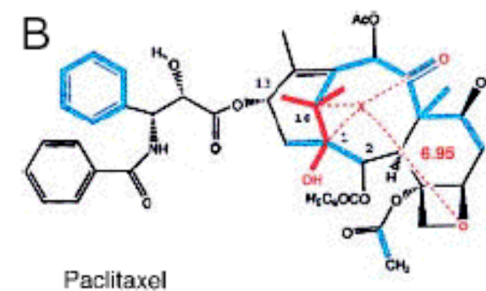
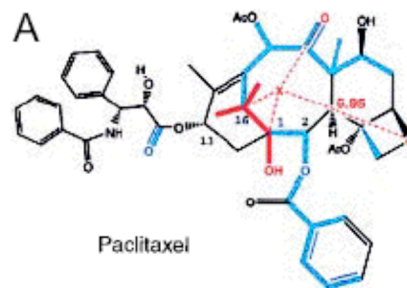
**Epothilone D**



**Epothilone E**



**Epothilone F**



- **Chemotherapy**

- **Alkylation Agents** ✓

- **Antimetabolites / Nucleoside Analogs** ✓

- **Antibiotics** ✓

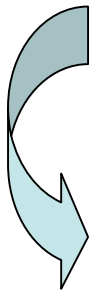
- **Antimitotic Agents** ✓

- **Micellaneous Antineoplastic Agents (selected comp.)**

- **Hormonal Therapy**

- **Compounds for  
photodynamic therapy**

- **Tyrosine-Kinase Inhibitors**

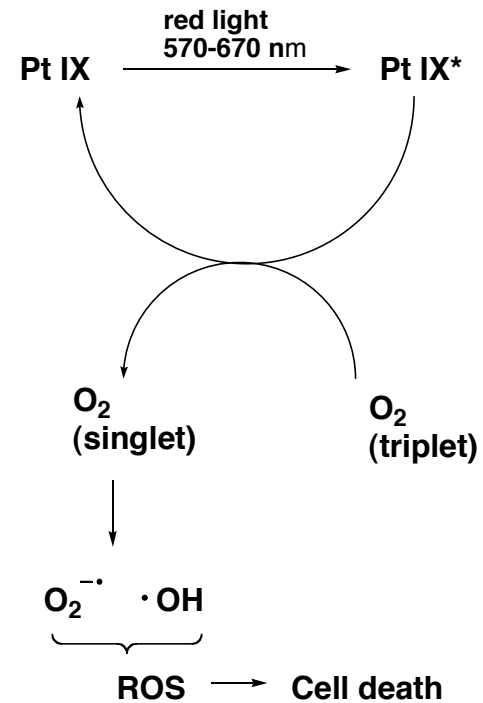
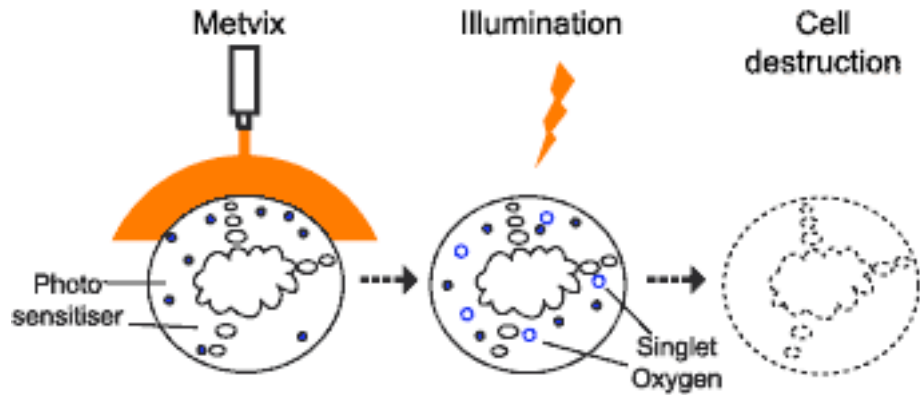
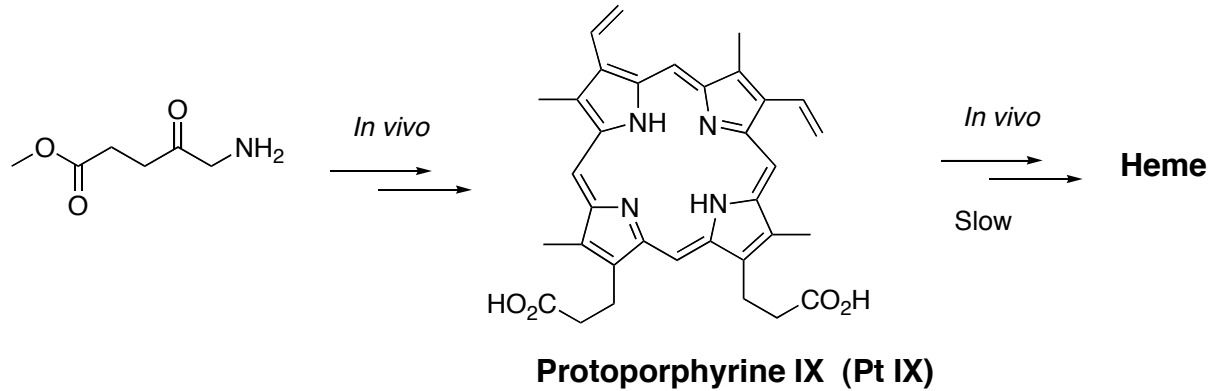




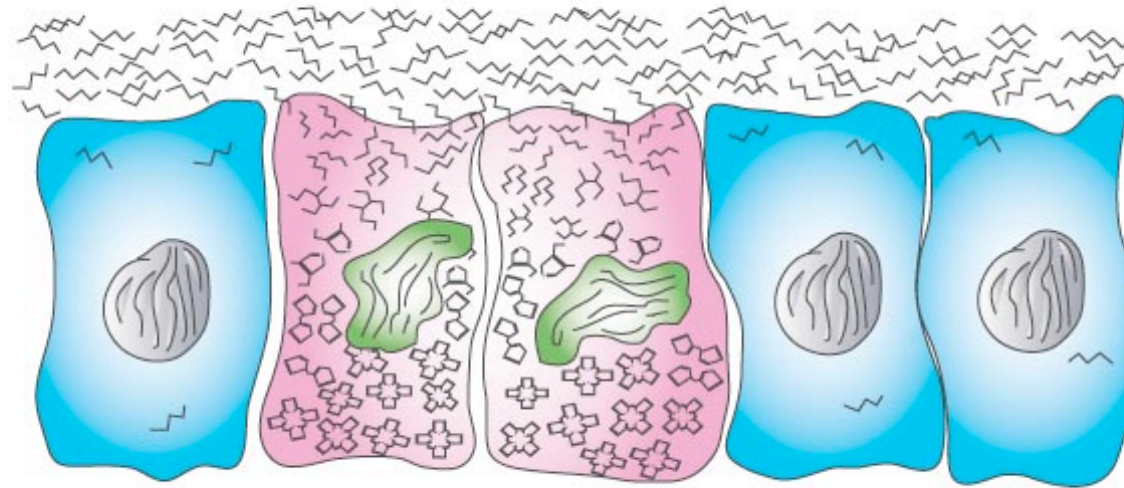
# •Compounds for photodynamic therapy

*Methylaminolevulinat*

Metvix® PhotoCure

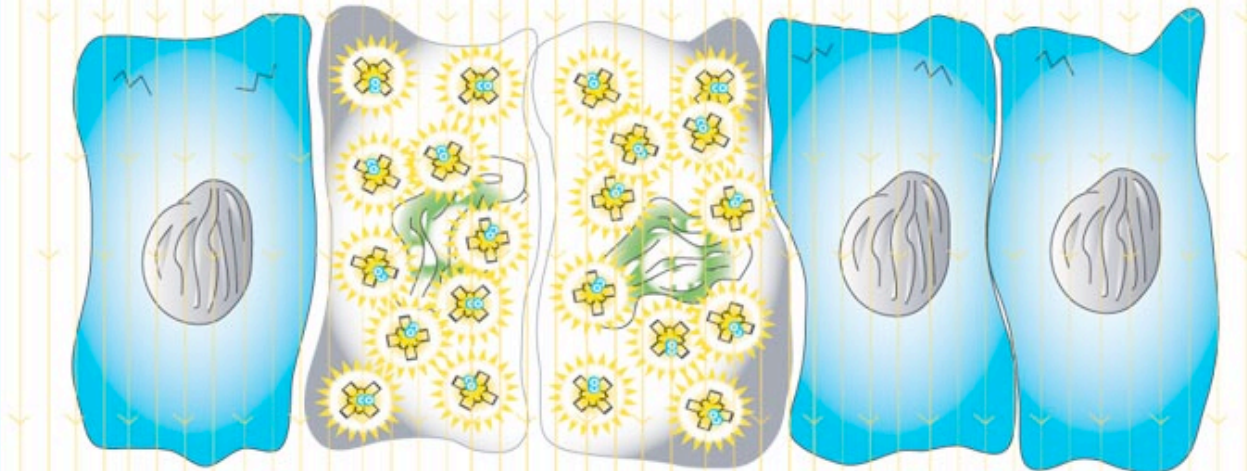


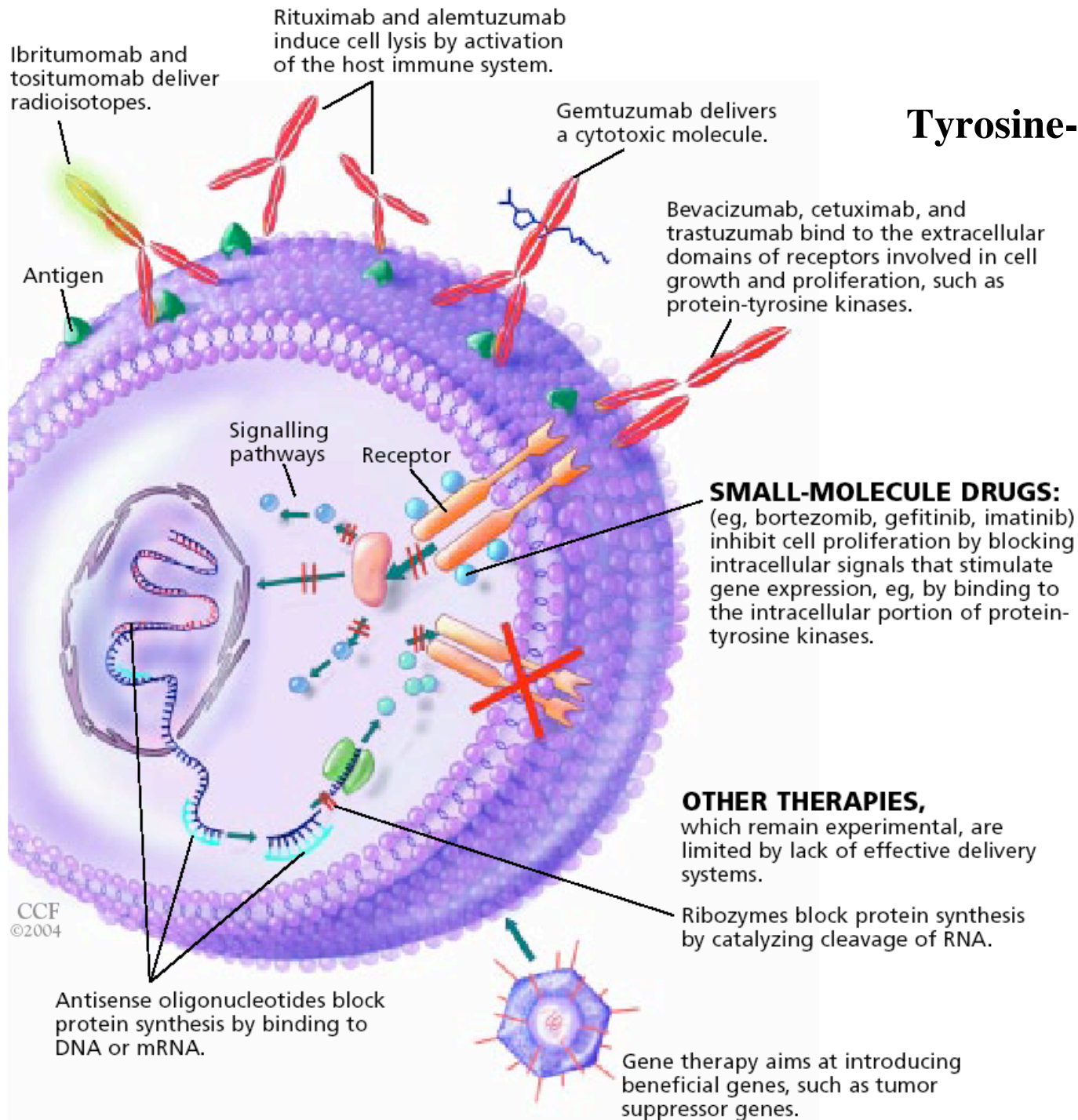
Topical 5-ALA is preferentially taken up by abnormal or metabolically active cells



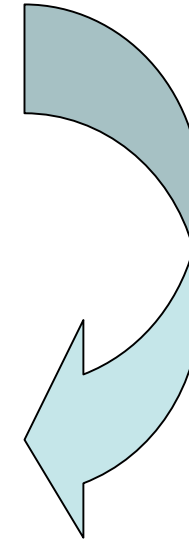
and Protoporphyrin IX, a powerful photosensitizer, is synthesized and concentrated.

The Protoporphyrin IX-laden cells are illuminated, creating reactive singlet oxygen, sparing the adjacent normal cells.



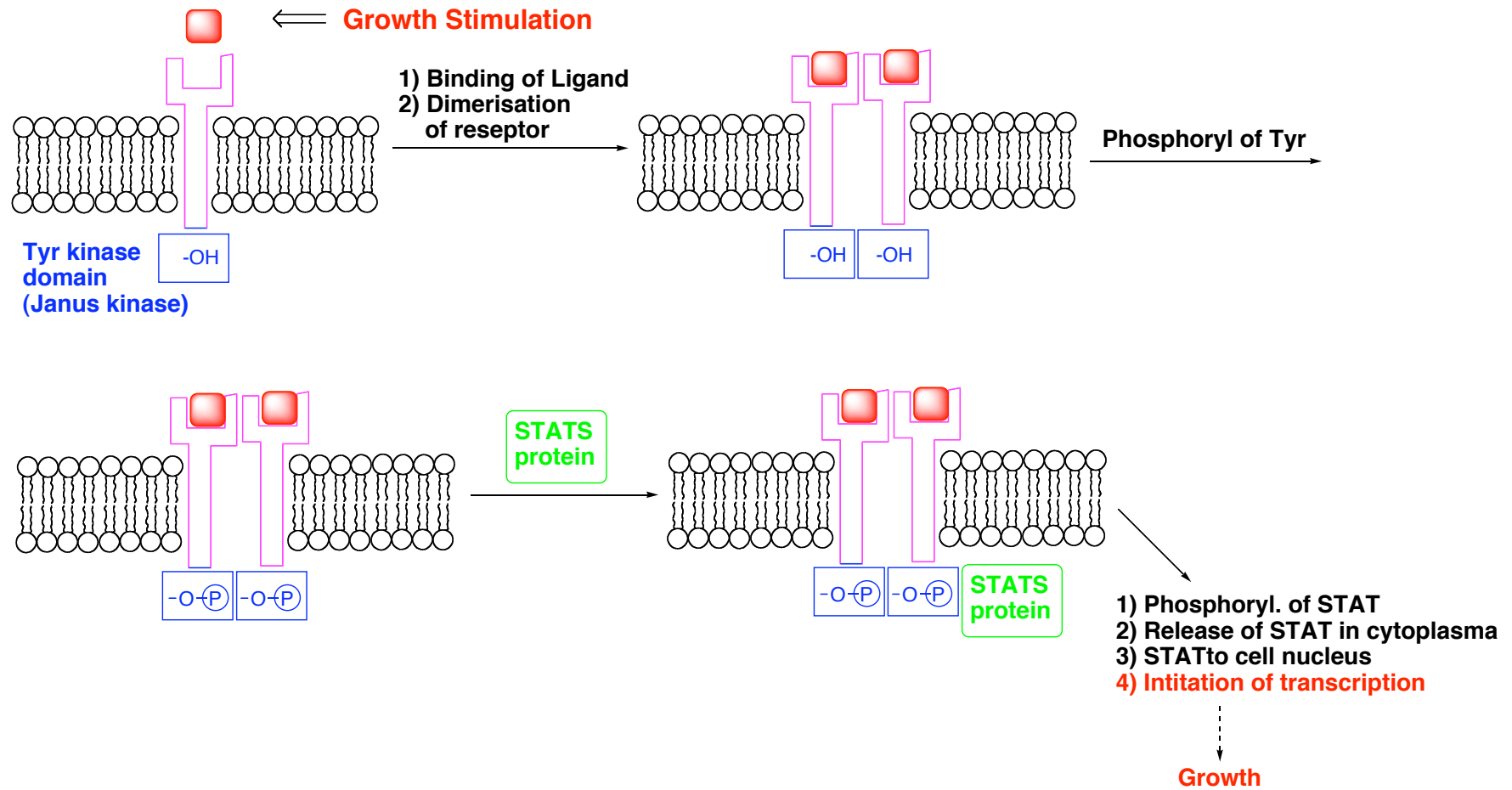


## Tyrosine-Kinase Inhibitors



# Enzyme coupled receptors - Catalytic receptors (Chapter 4)

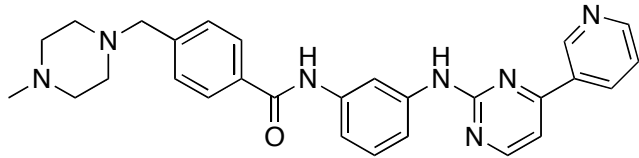
Ligands: Peptide hormones



## *Imatinib*

Glivec®

Leukemia types



## *Gefitinib*

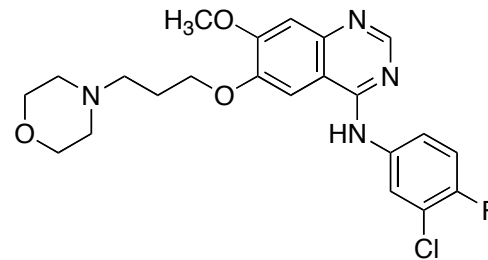
Iressa® - Not in N.

Lung cancer

Side effect: Intestinal lung disease (may be fatal)

0.3 % US

2% Japan



- Chemotherapy**

- Alkylation Agents** ✓

- Antimetabolites / Nucleoside Analogs** ✓

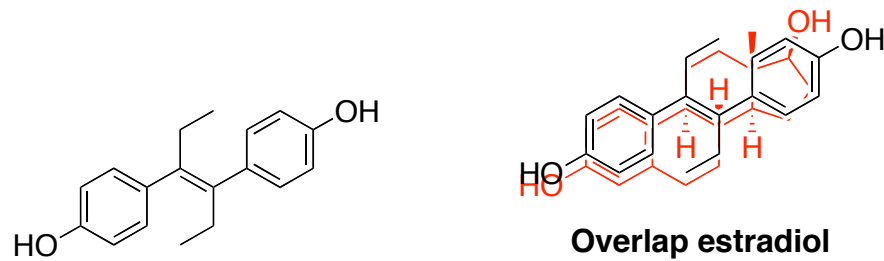
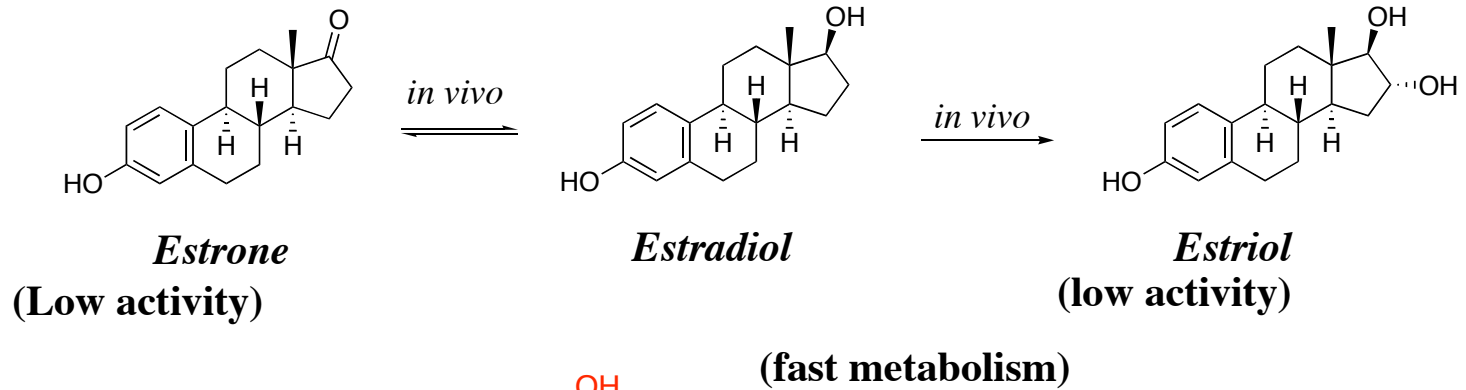
- Antibiotics** ✓

- Antimitotic Agents** ✓

- Micellaneous Antineoplastic Agents** ✓

- Hormonal Therapy**

## Estrogens and agonists



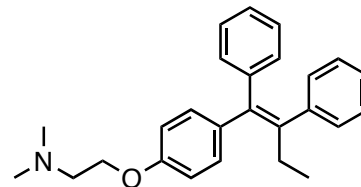
### *Diethylstilbestrol*

Estrogene agonist, used as drug before

## Antiestrogens

### *Tamoxifen*

Nolvadex® Tamoxifen®

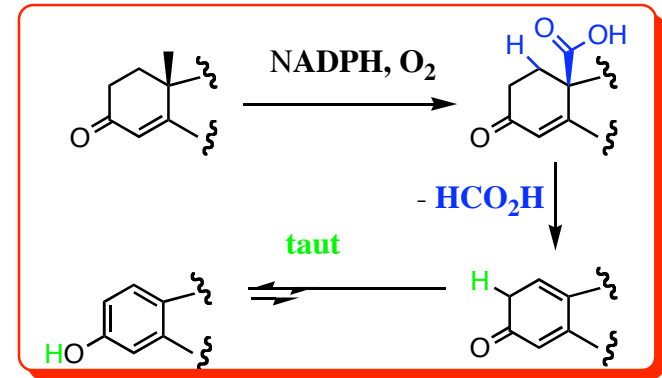
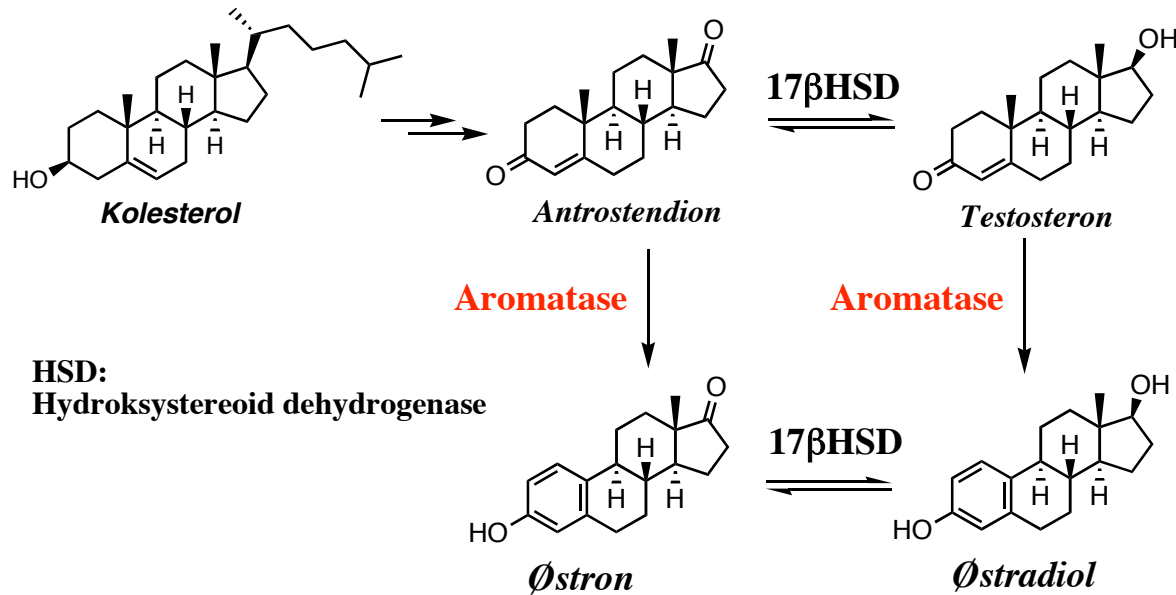


**Breast cancer**  
(estrogen depend.)

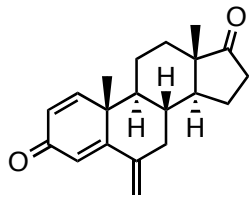


# Aromatase Inhibitors

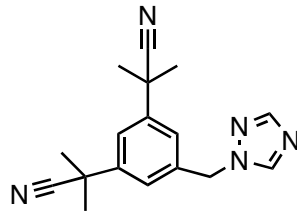
Estrogen depend. breast cancer  
 Inhib. estrogen biosynth.



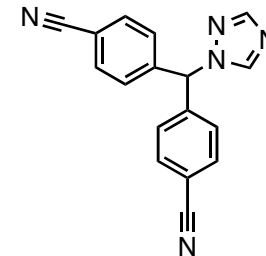
**Exemestan**  
 Aromasin®



**Anastrozol**  
 Arimidex®

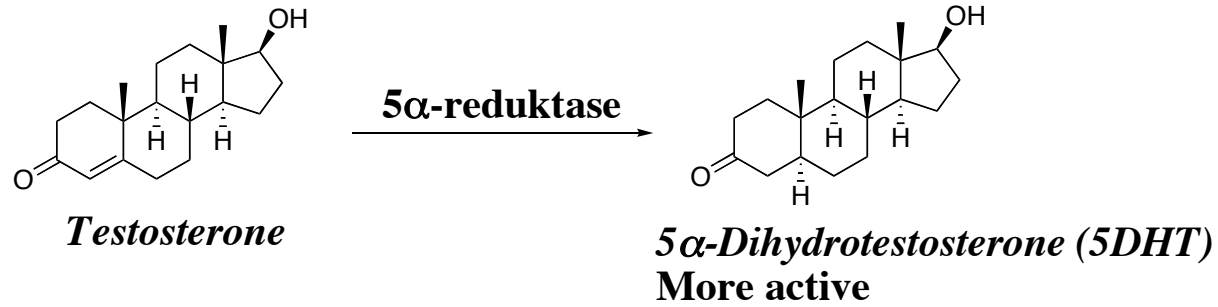


**Letrozol**  
 Femar®





# Androgens



## 5 $\alpha$ -Reductase Inhibitors

*Finasterid*  
Proscar®

