Anti-cancer compounds / Antineoplastic Agents, chapter 38

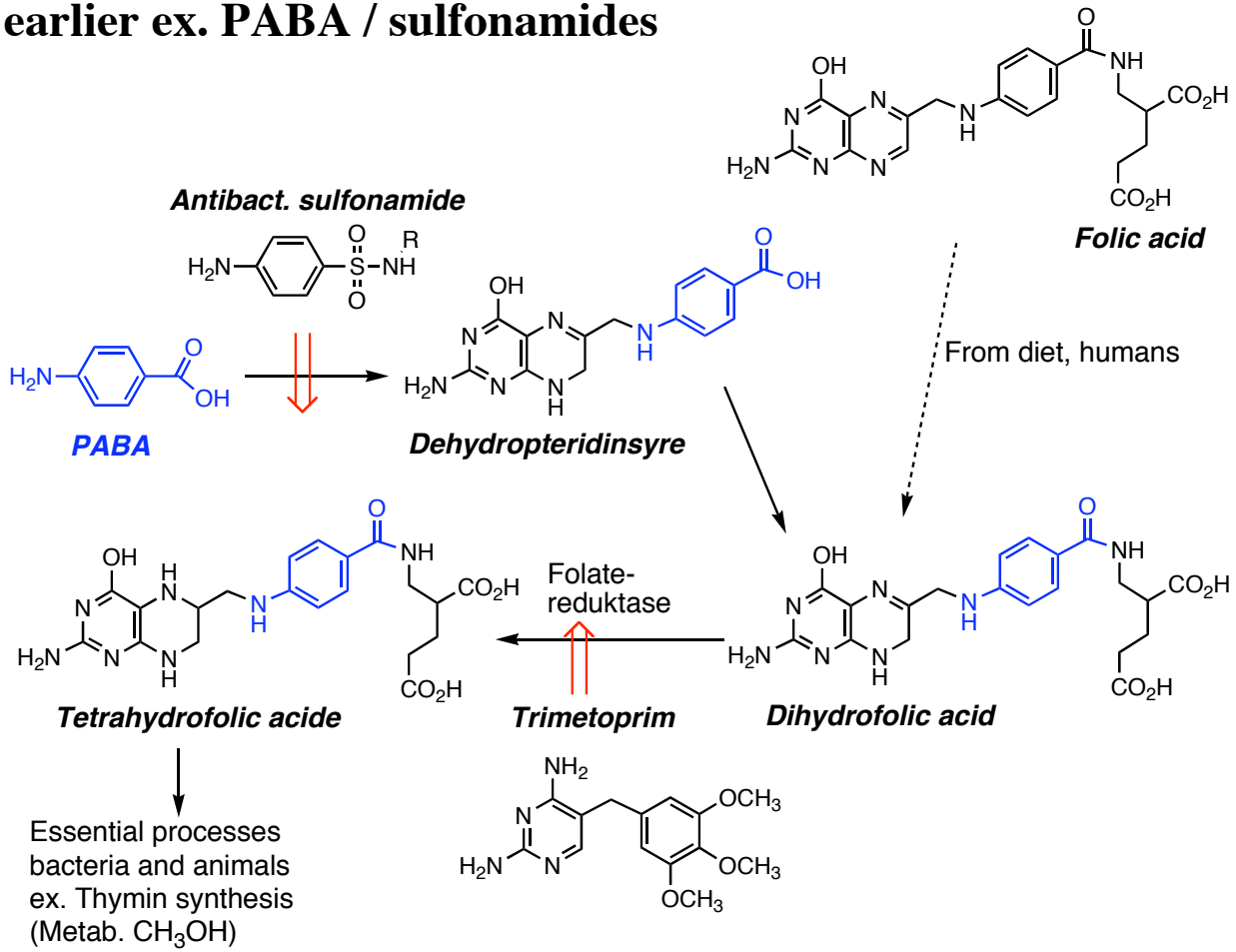
Cancer Therapy

- 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

Antimetabolites (Nucleoside Analogs, Folic acid analogs)

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

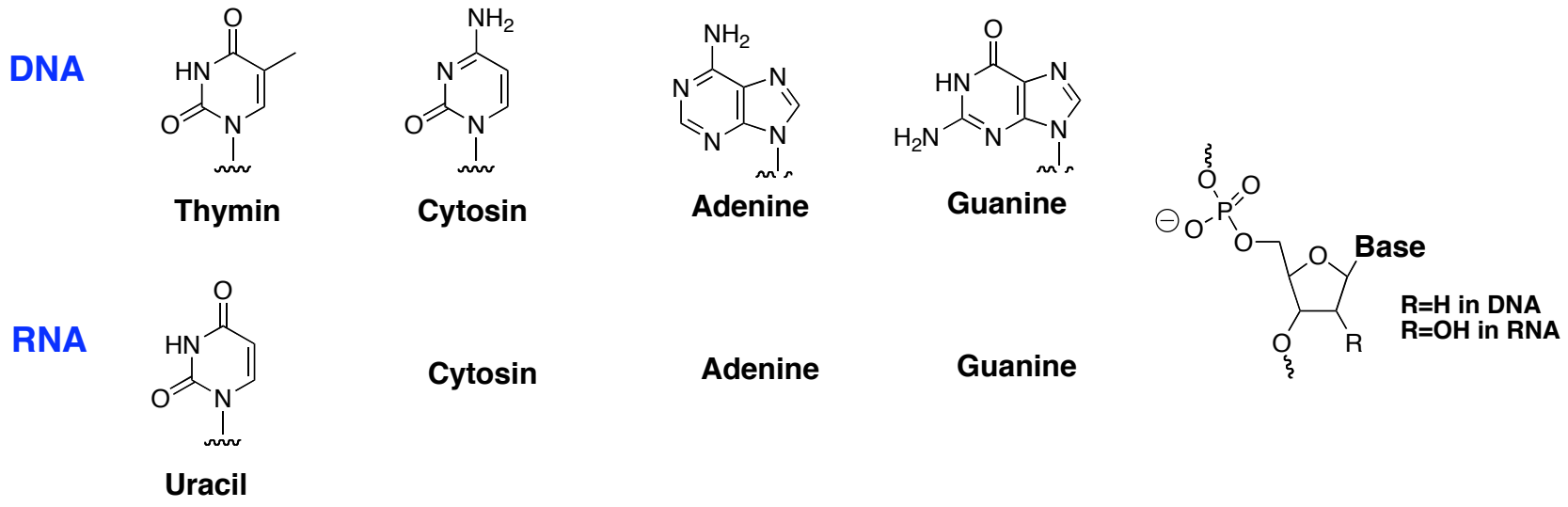
earlier ex. PABA / sulfonamides



Nucleoside analogs as antimetabolites

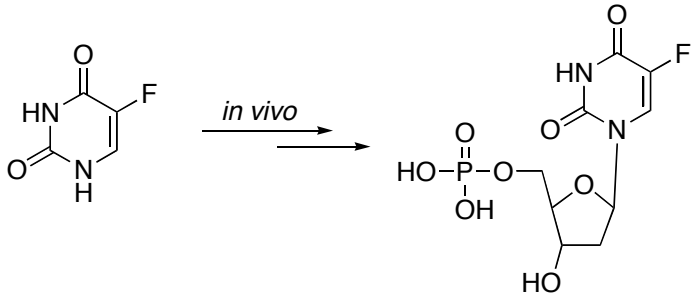
Possible mecanisms:

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

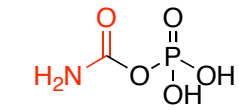


5-Fluoruracil (5-FU)

Fluorouracil®, Flurablastin®,

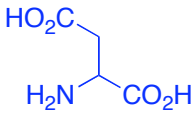


Inhibitor
Thymidylate synthetase

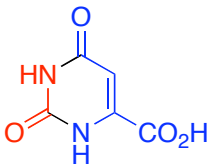


Carbamoyl phosphate

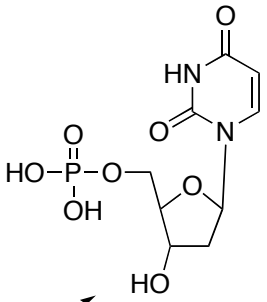
+



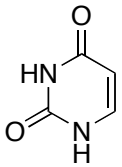
Asp



Orotic acid



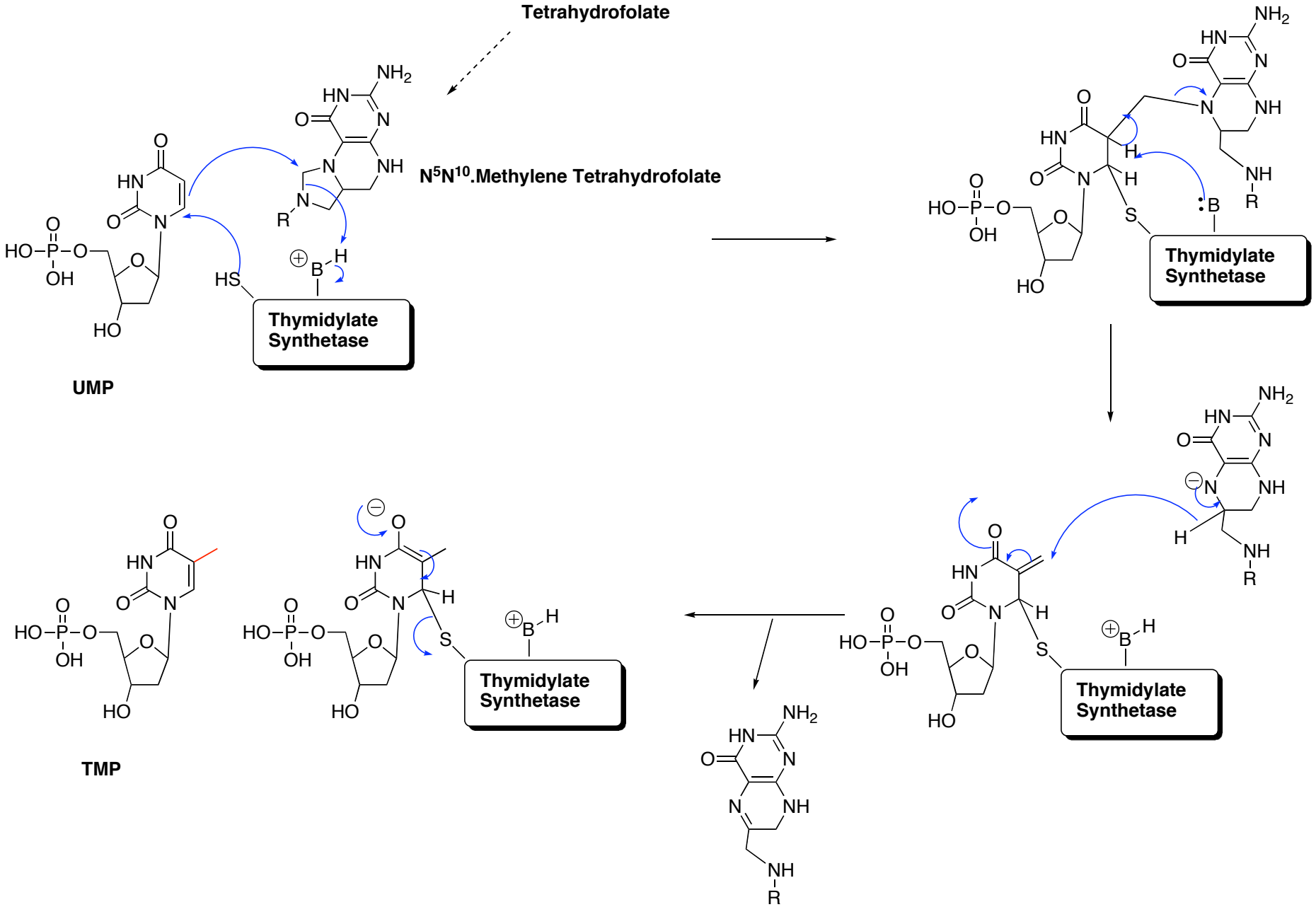
UMP

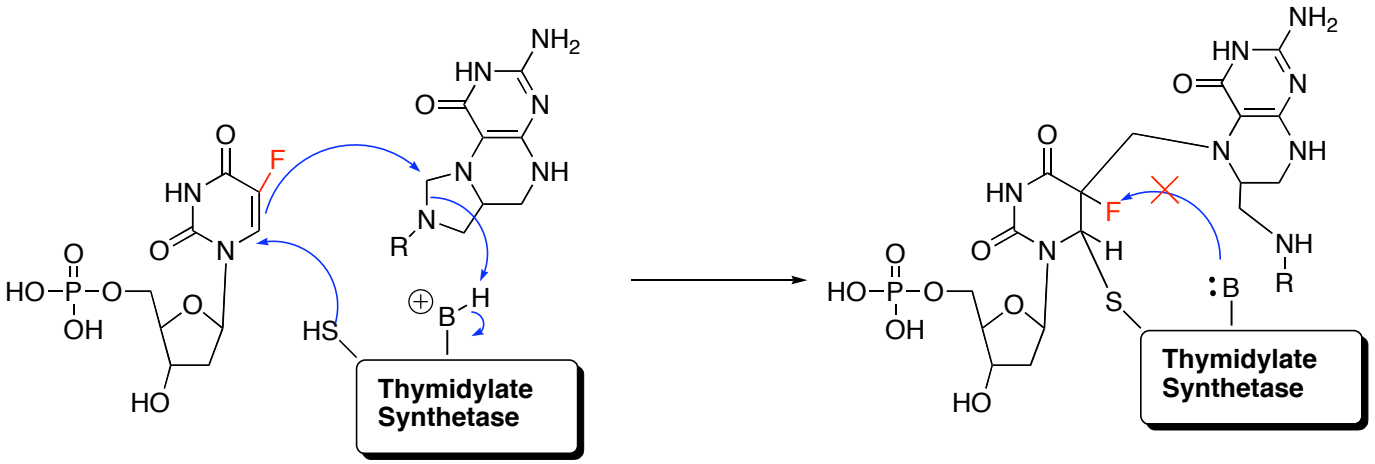


Uracil

More common route in cancer cells
5-FU more easily activated in cancer cells (?)

Synth. thymine nucleotide from uracil nucleotide by thymidylate synthetase

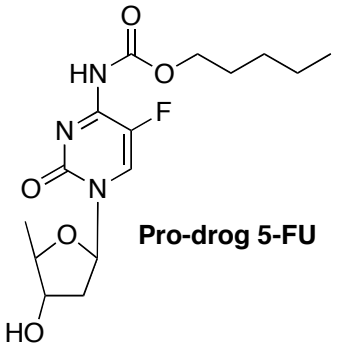




5-FU metabolite

Enzyme inhibition

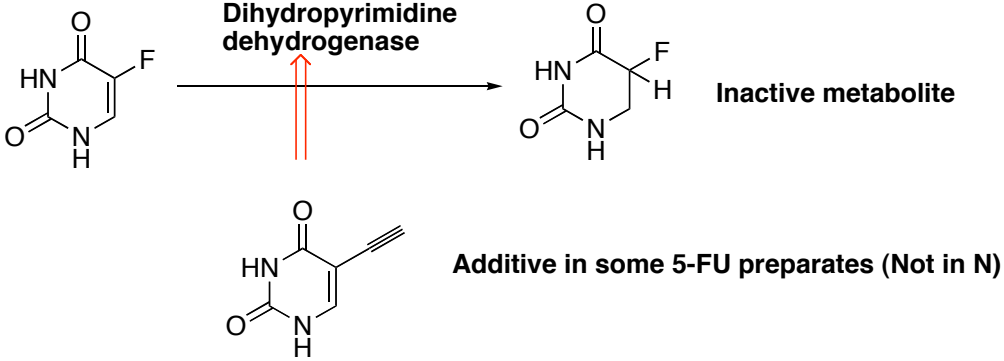
Kapecitabin
Xelodar®,



Pro-drog 5-FU

Additional mechanisms: Incorp. DNA / RNA

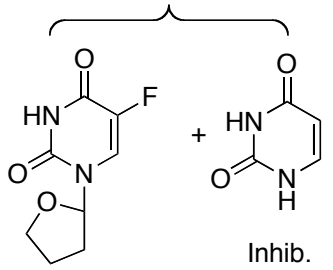
5-FU metabolism



Inactive metabolite

Additive in some 5-FU preparates (Not in N)

Tegafur
UFT®

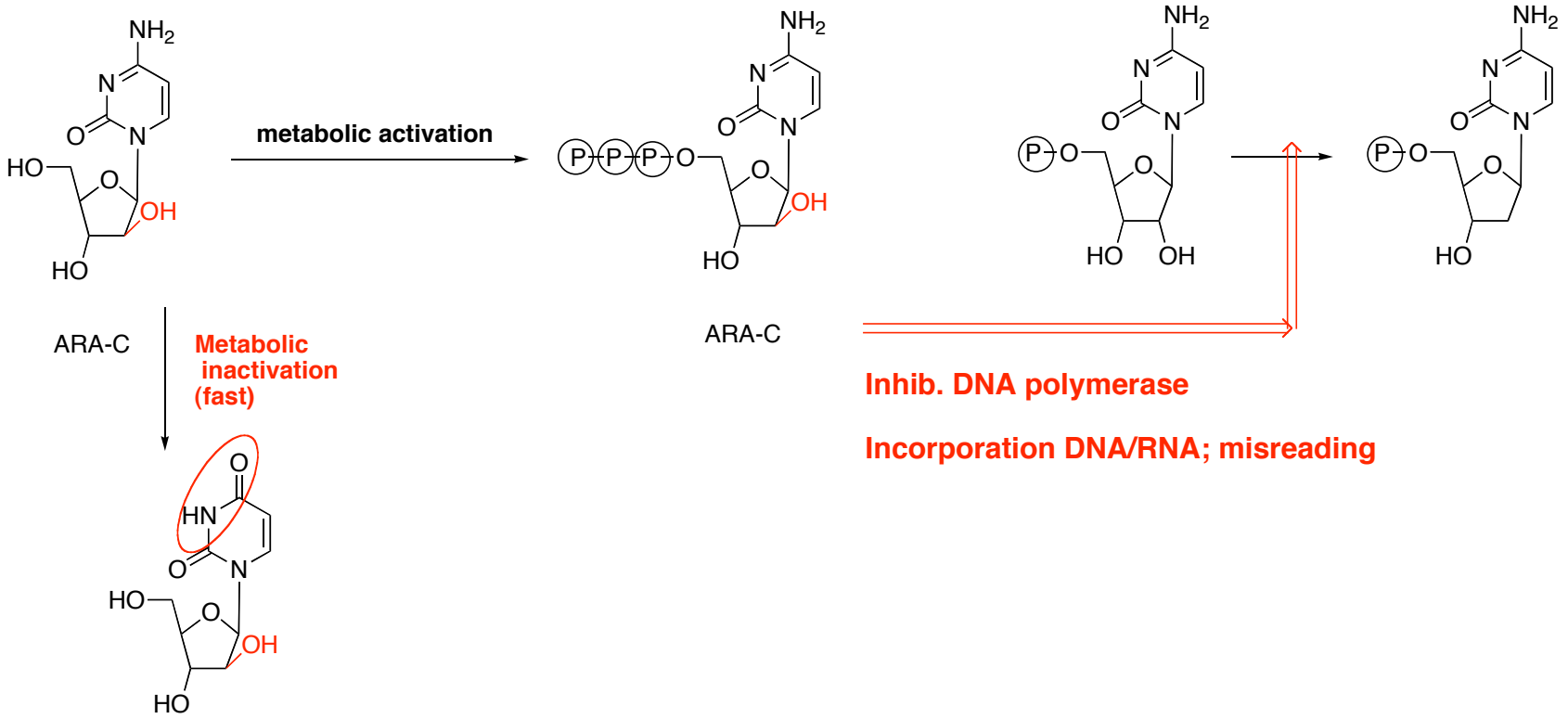


5-FU prodrug

Inhib. **Dihydropyrimidine dehydrogenase**

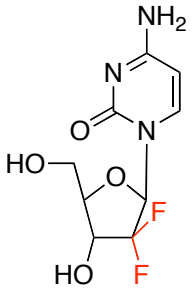
Cytarabine (ARA-C)

Cytarabin®, Cytosar®,



Gemcitasbin

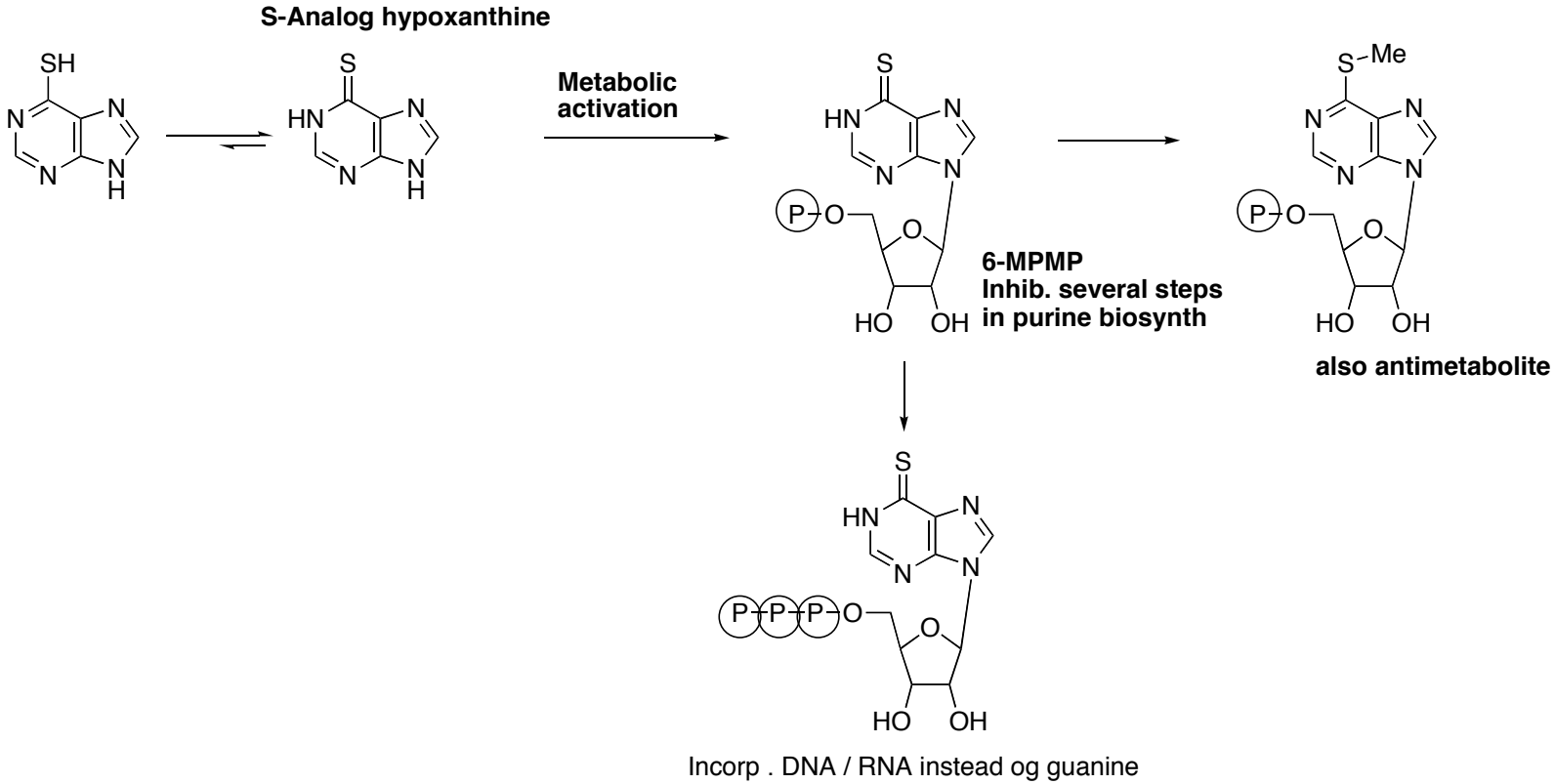
Gemzar®,

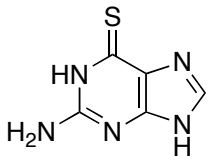


Metabolic activation (triphophate)
Incorp. DNA / RNA

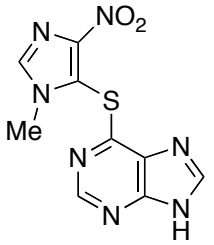
6-Mercaptopurine (6-MP)

Puri-Nethol®

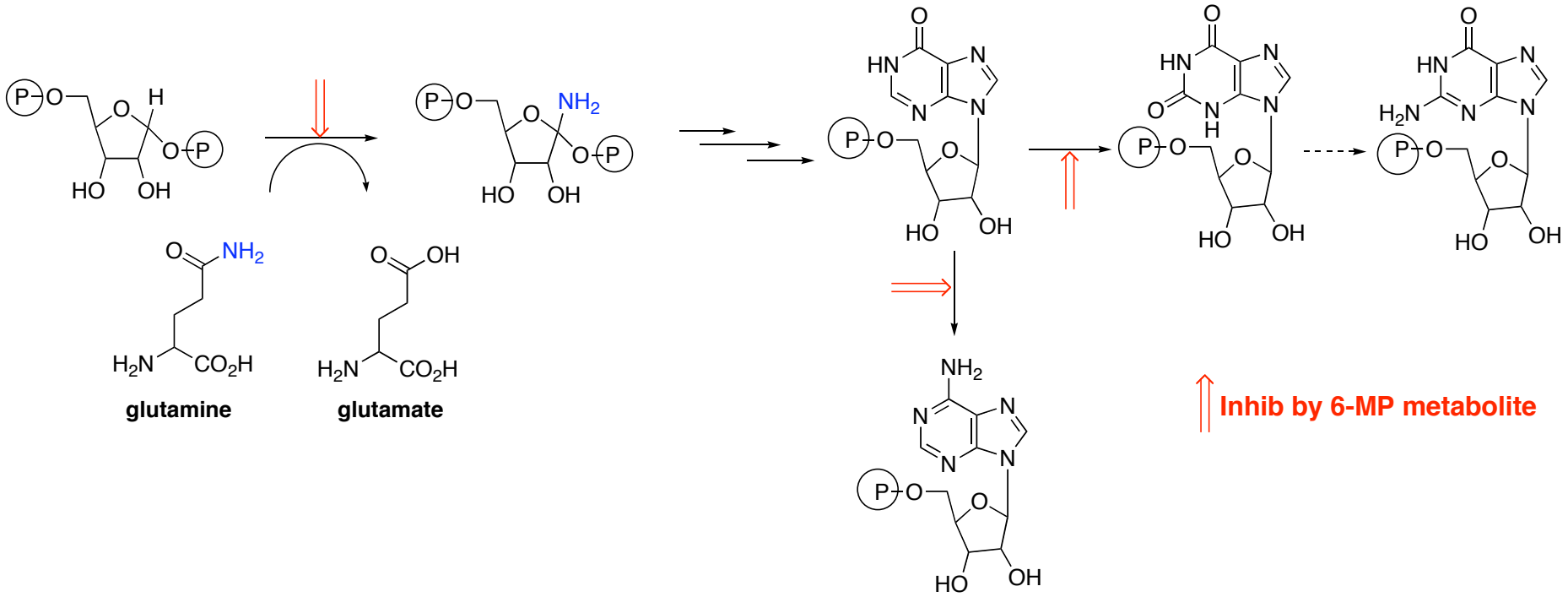




6-thioguanine (not drug in N)
≈ 6-MP activity

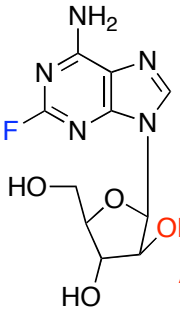


6-MP pro-drug
used before



Fludarabine

Fludara®

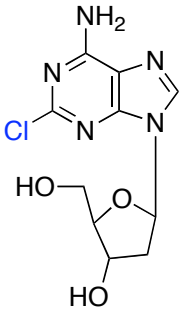


Not good substrate for adenosine deaminase

Antimetabolite

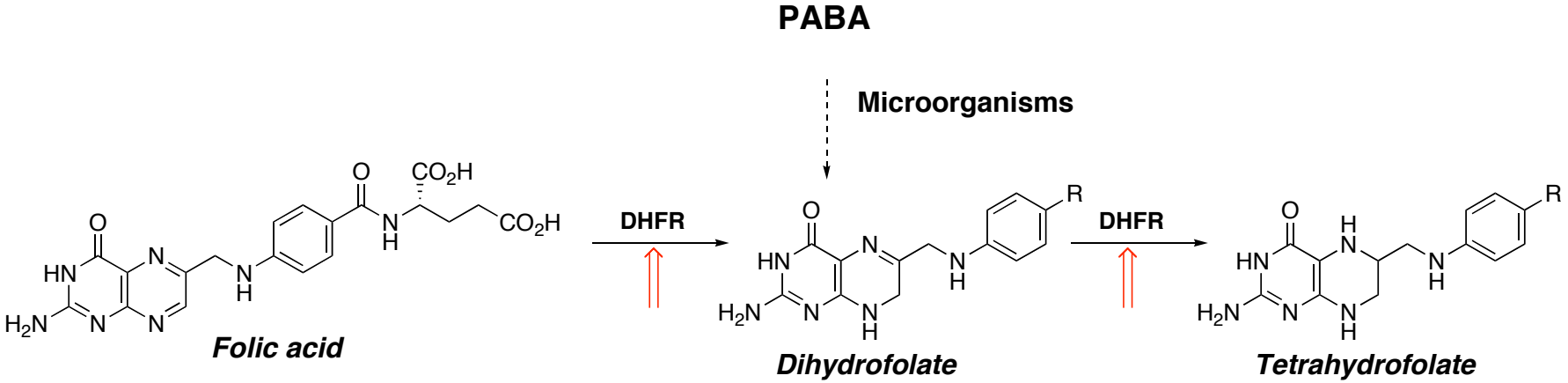
Cladribin

Leustatin®



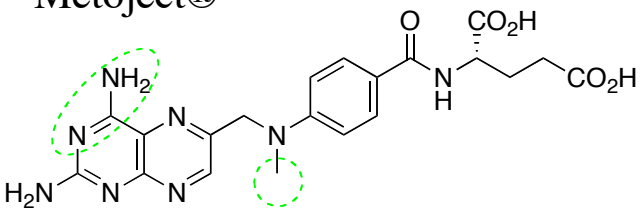
Not really antimetabolite
Inhib. repair enzymes

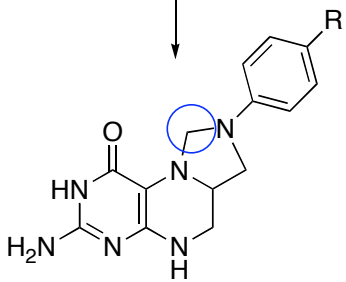
Folic Acid analogs as antimetabolites



Metotreksat

Metoject®

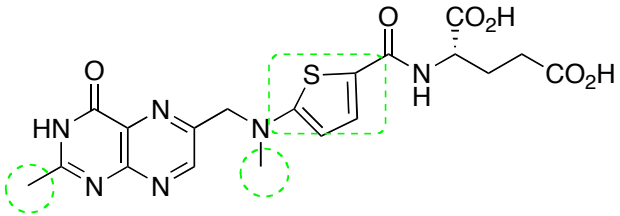




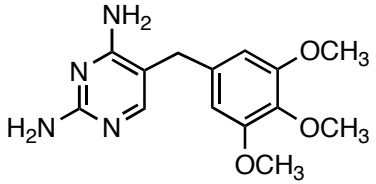
Thymine synth

Raltitrexed

Tomudex®



Trimetoprim



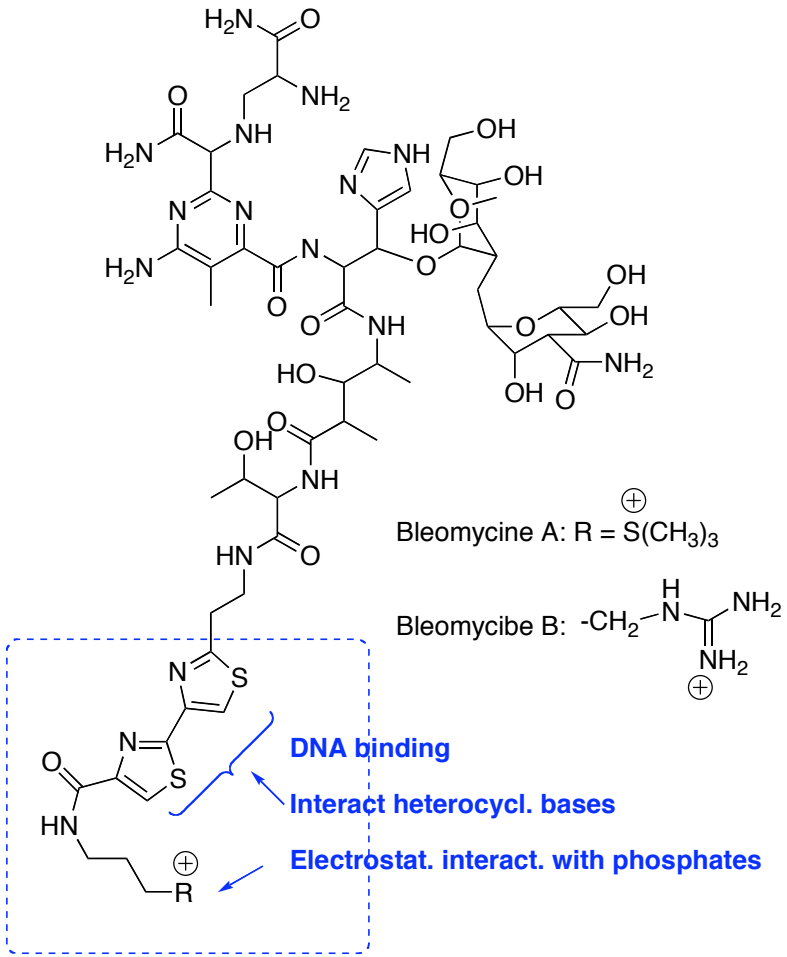
- **Chemotherapy**
  - **Alkylation Agents √**
  - **Antimetabolites / Nucleoside Analogs √**
  - **Antibiotics**
  - **Antimitotic Agents**
  - **Micellaneous Antineoplastic Agents**
  - **Hormonal Therapy**

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

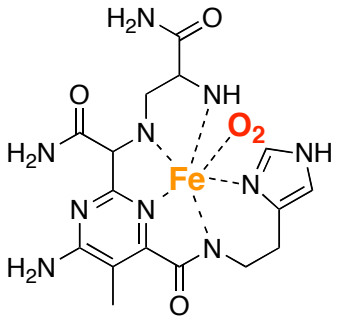
- **Bleomycins**
- **Actinomycins**
- **Mitomycins**
- **Antracyclins**
- **Coformycins**

Bleomycins

Isolated from Streptomyces verticillius
Naturally occuring as Cu-chelates



1) Binds Fe(II) inside cells



2) Bleomycin complexed Fe(II) reduce O_2

3) •OH radicals produced

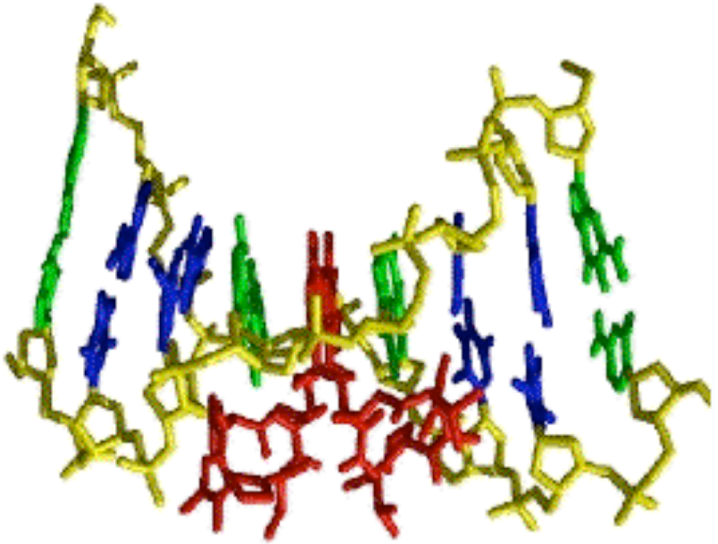
4) Cleavage of DNA

Bleomycin
Bleomycin Baxter®

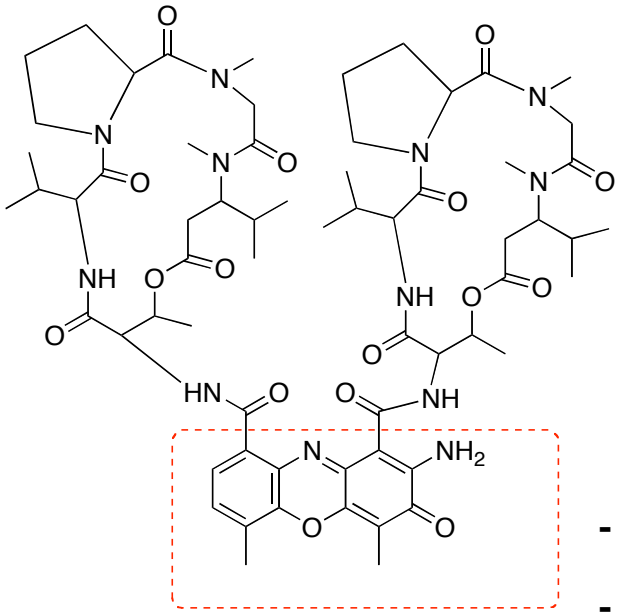
Actinomycins

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
(π–π stacking interact)

⇓

- Affects DNA topoisomerase II (Unwinding)

- May also promote DNA cleavage (nucleases)

Quinolones

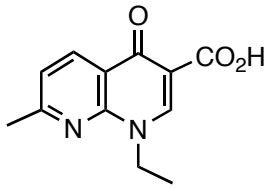
Inhib DNA-synthesis; DNA-gyrase (prokaryoter) uwounding DNA before replic..

DNA-topoisomerase (humans), anticancer compds. ex. doxorubicin

Unique mecanism, no cross resistance

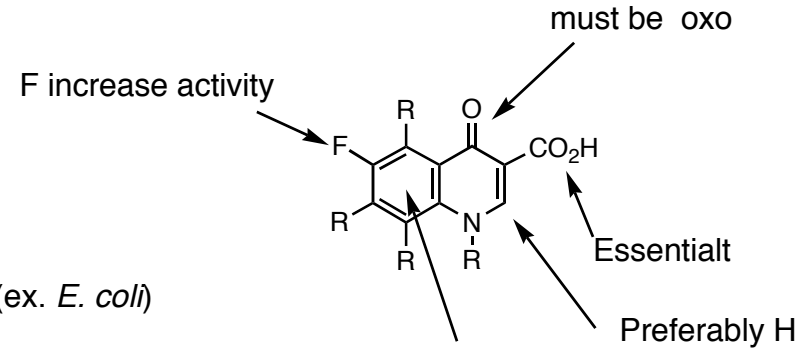
Broad spectrum: G+ and G- ; also mycobactria, clamydia

Parent comp.
Nalidixic acid



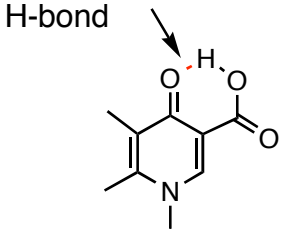
Urinary tract infect. earlier
effect on Gram-negative bacteria (ex. *E. coli*)

Moderne quinolones



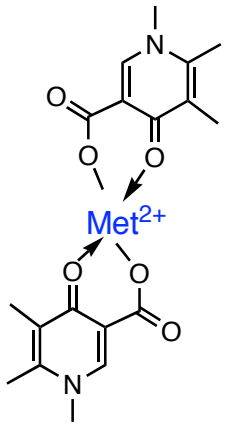
Must have aromatic ring
condenced with the pyridine

Intramolek.
H-bond



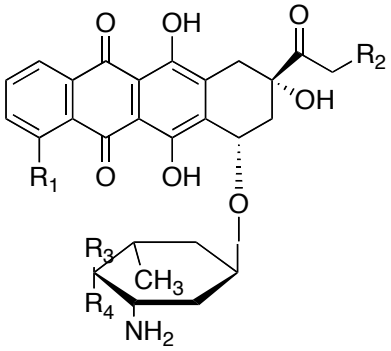
pKa ca 5.5 - 6.5
(Benzoic acid pKa 4.2)

Chelater with
Ca^{2+}, Mg^{2+}, Zn^{2+}, Fe^{2+}, Fe^{3+}, Bi^{3+}



Antracyclines

Isolated *Streptomyces sp*, several semisynth analogs



Doxorubicin

Doxorubicin® Adriamycin® Caelyx®

R_1 = OMe, R_2 = OH, R_3 = H; R_4 = OH

Daunorubicin

Cerubidin® R_1 = OMe, R_2 = H, R_3 = H; R_4 = OH

Idarubicin

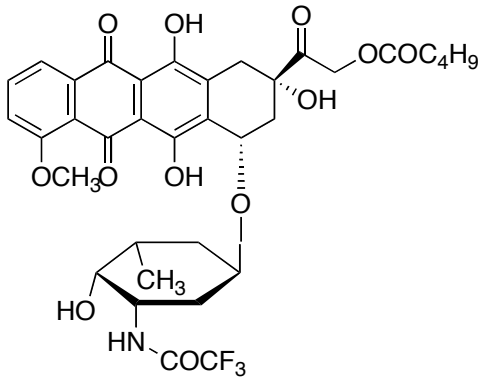
Zavedos® R_1 = H, R_2 = H, R_3 = H; R_4 = OH

Epirubicin

Farmorubicin®

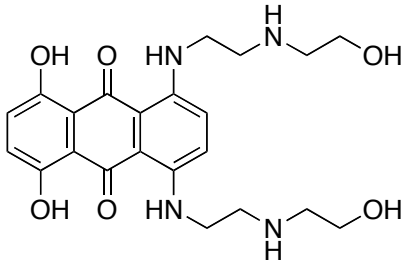
R_1 = OMe, R_2 = OH, R_3 = OH; R_4 = H

Valrubicin

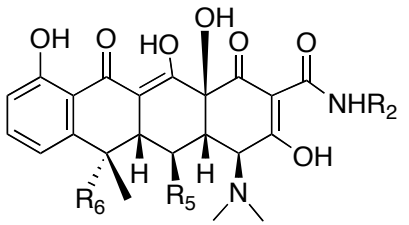


Mitoxantrone

Novantrone®



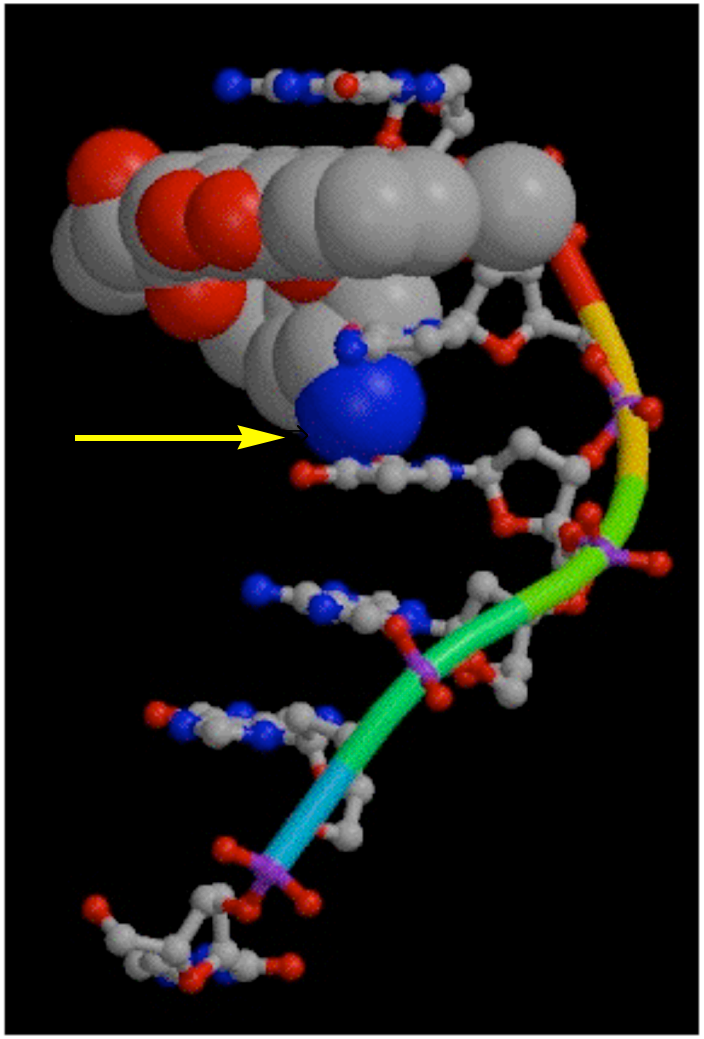
Antibacterial Tetracyclines



Mechanism ≈ Actinomycins (Intercalation)

Also interact aminosugar - phosphate

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



DNA-Daunomycin Complex

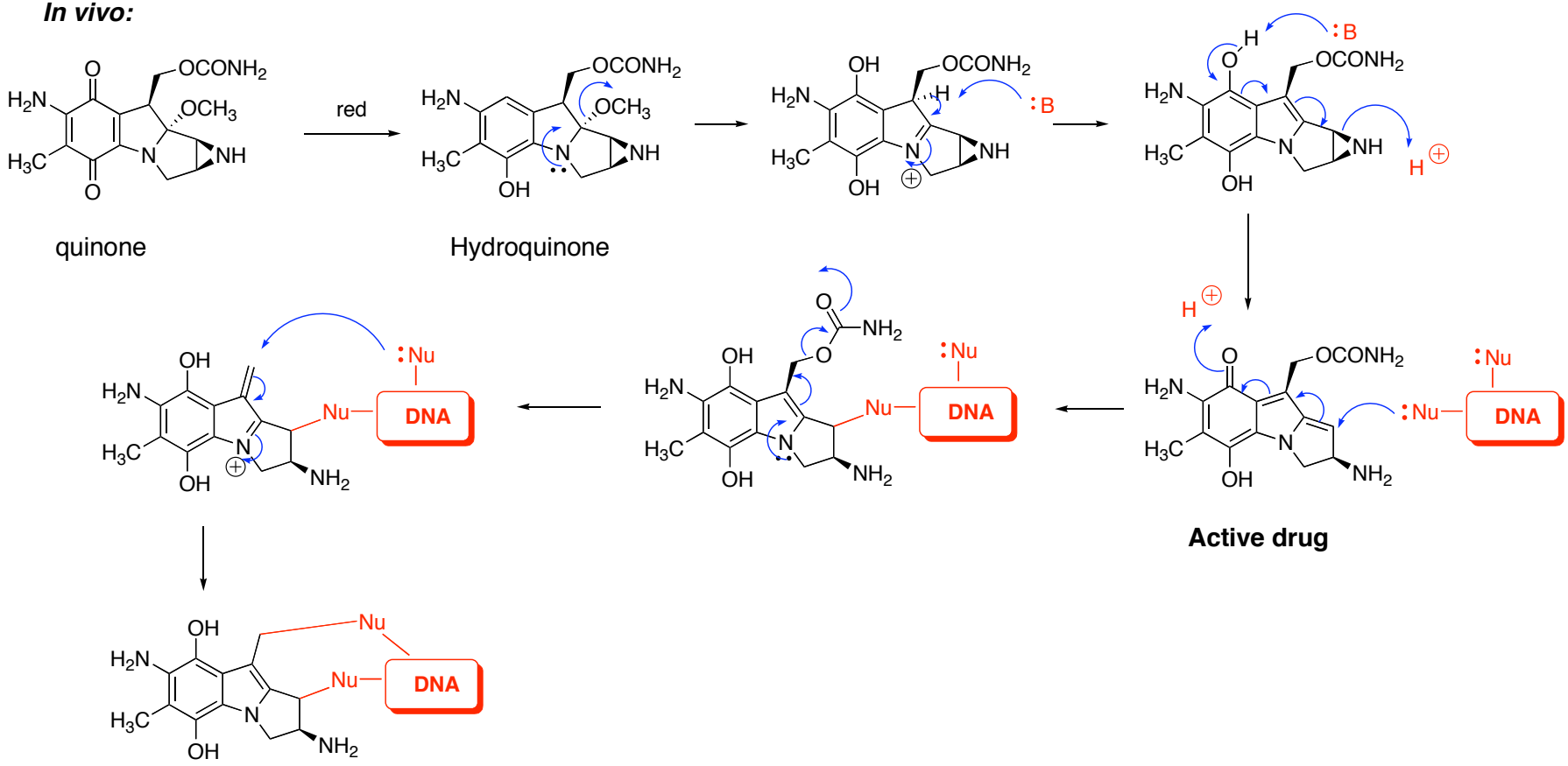
Mitomycins

Isolated *Streptomyces sp*,

Mitomycin C

Mutamycin®

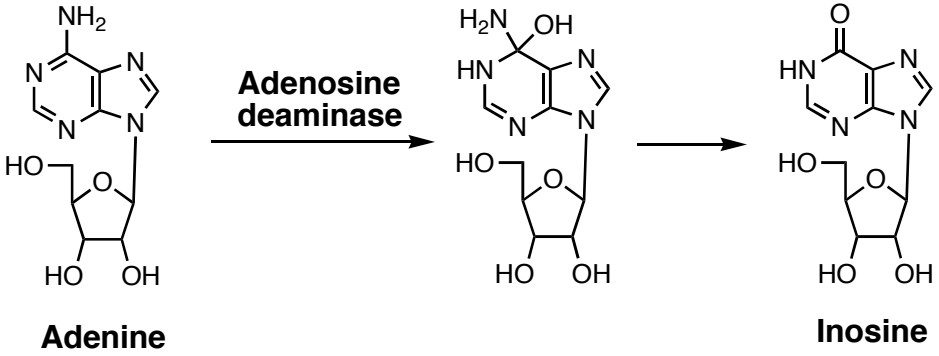
In vivo:



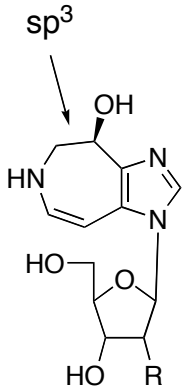
Conformycins

Isolated *Streptomyces sp*,

Also metab. of anticancer / antiviral adeninederiv.



Adenine **Inosine**



R=OH: Coformycin
R=H: DEoxycoformycin (Pentostatin)

Ex. transition state analogs

- **Chemotherapy**
  - **Alkylation Agents √**
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  - **Antimitotic Agents**
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  - **Hormonal Therapy**

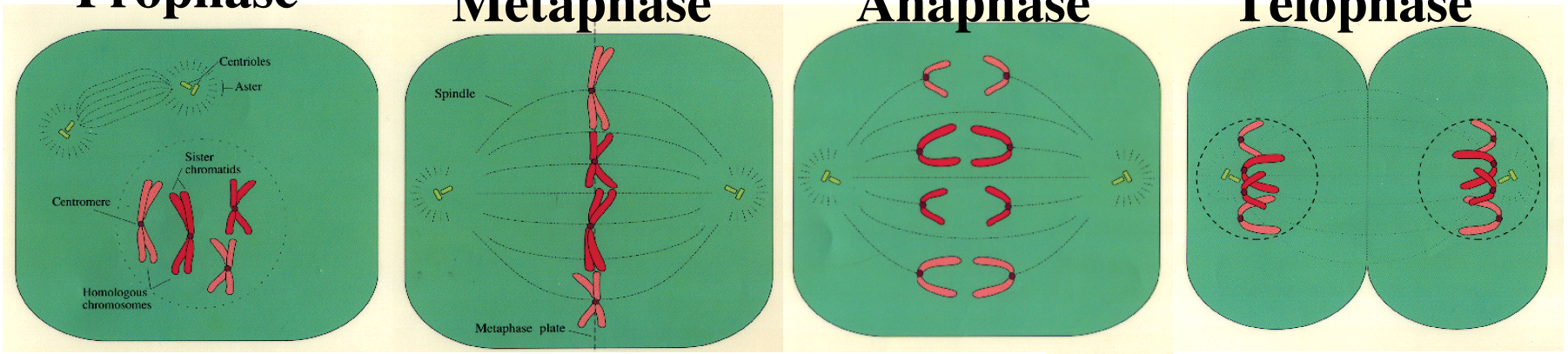
Mitosis

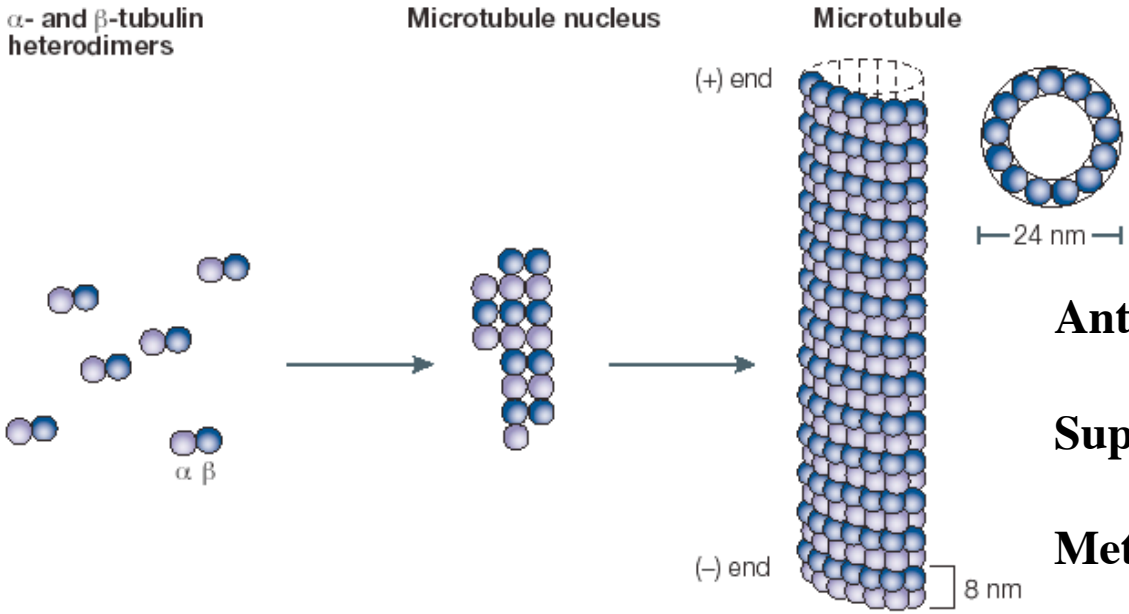
Prophase

Metaphase

Anaphase

Telophase





Antimitotic agents bind to microtubuli

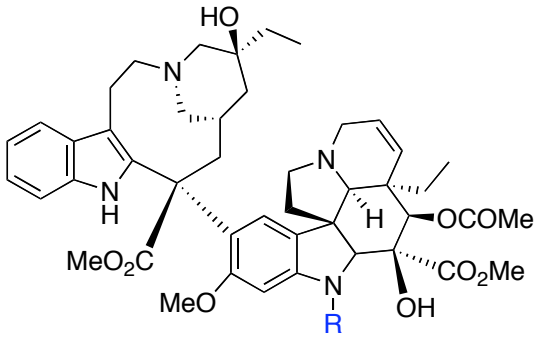
Supression of microtubuli dynamics

Metaphase arrest

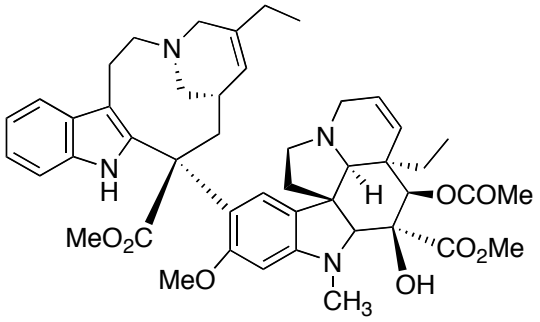
Figure 1 | **Polymerization of microtubules.** Heterdimers of α- and β-tubulin assemble to form a short microtubule nucleus. Nucleation is followed by elongation of the microtubule at both ends to form a cylinder that is composed of tubulin heterodimers arranged head-to-tail in 13 protofilaments. Each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

Vinca alkaloids

Vinca alkaloids (Indols) from Vinca rosea (Catharantus roseus) MadagaskarPerivinkle



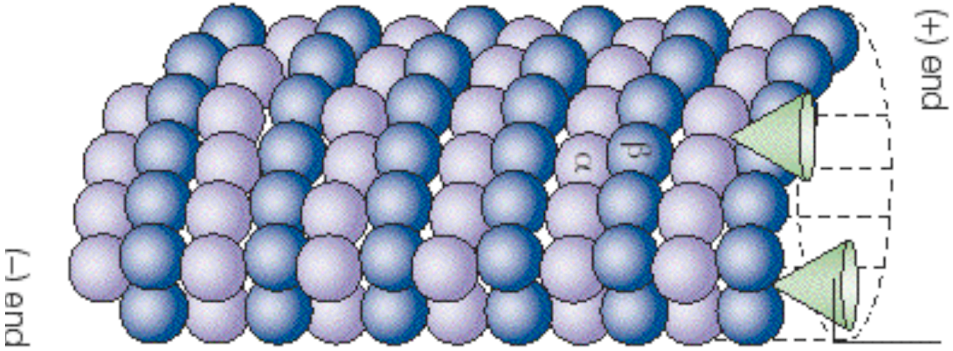
R=-Me: *Vinblastin*, *Velbe®*
R=-CHO: *Vinkristin*, *Vincristine®*

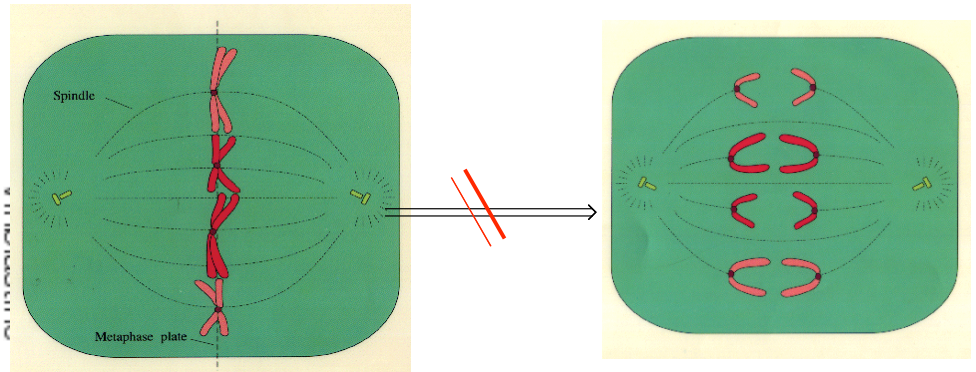


Vinorelbine*, *Navelbine®

Binds to microtubuli- Supression of microtubuli dynamics- Metaphase arrest

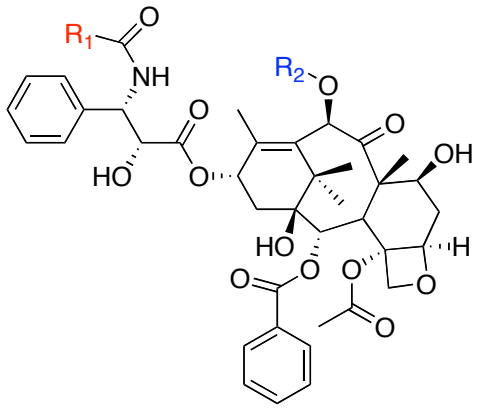
Depolymerization of microtubuli high conc.





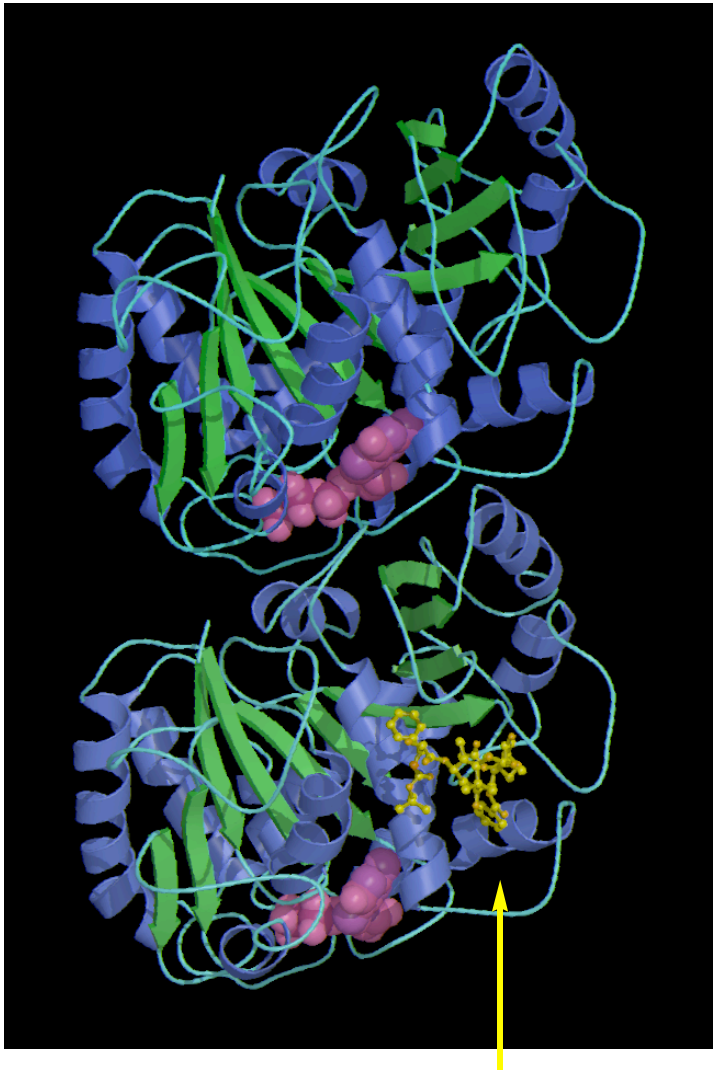
Taxanes

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

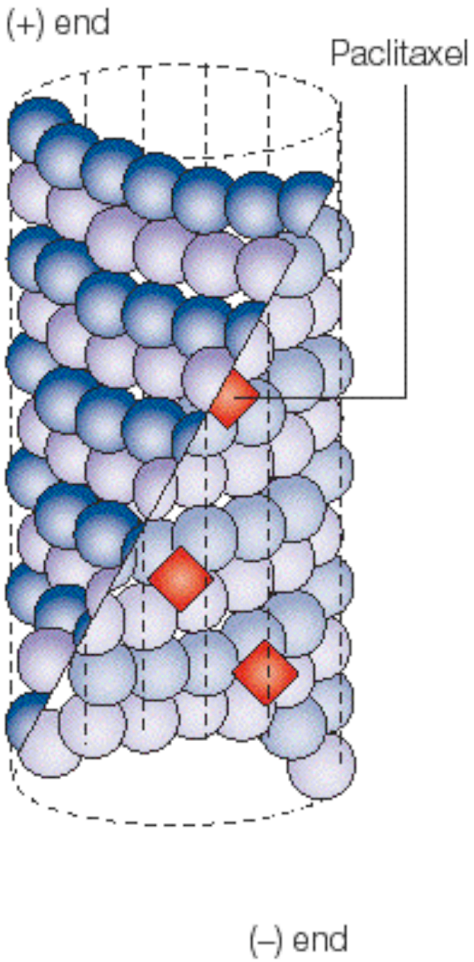


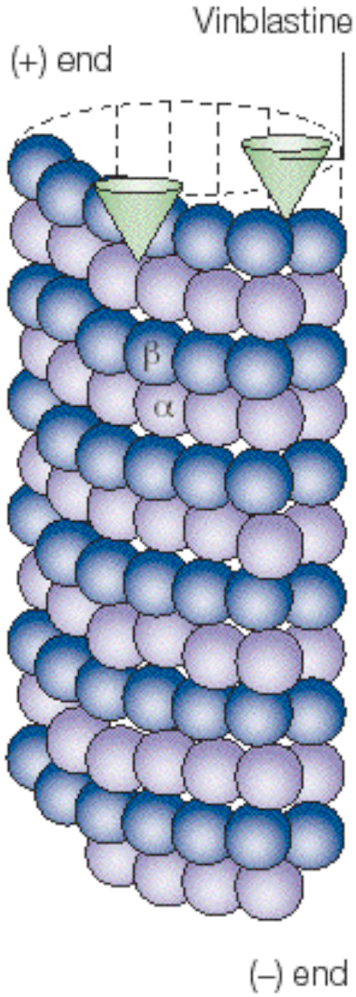
R_1 = -Ph, R_2 = -COMe: *Palitaxel*, *Taxol®*
R_1 = -OBu^t, R_2 = -H: *Dodetaxel*, *Taxotere®* *Semisynthetic*

Mecanism ≈ Vinca alkaloids, different binding sites



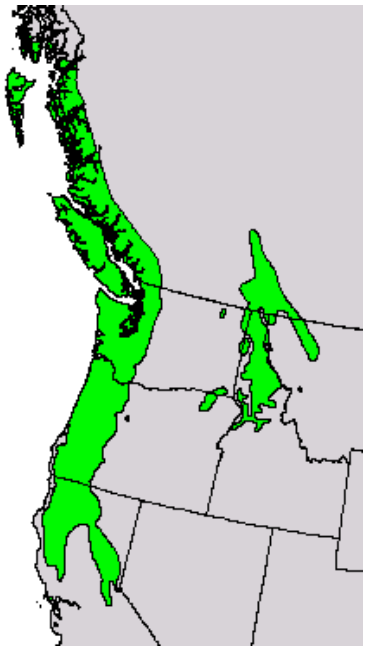
Palitaxel





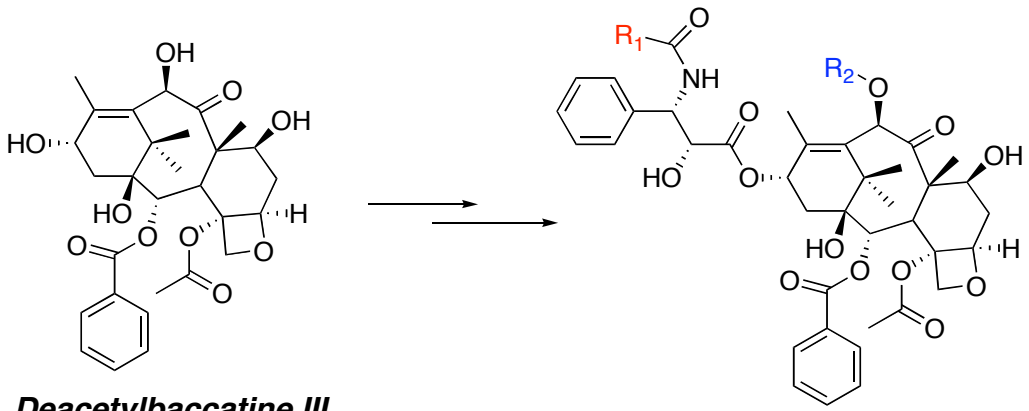
Availability

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 deacetylbaccatin III (0.1% in needles *Taxus baccata*)

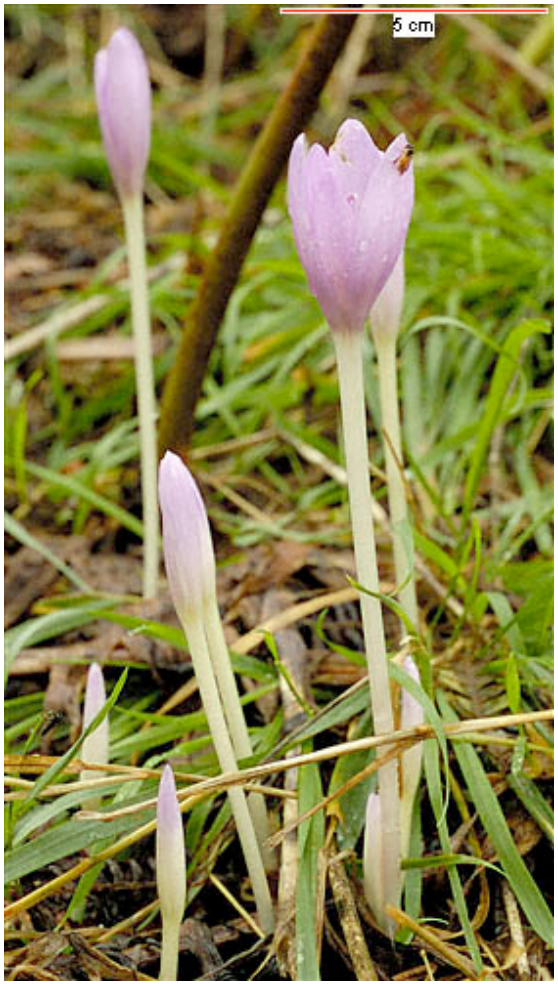


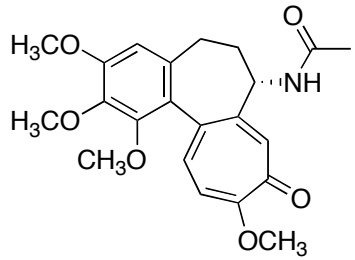
Deacetylbaccatine III

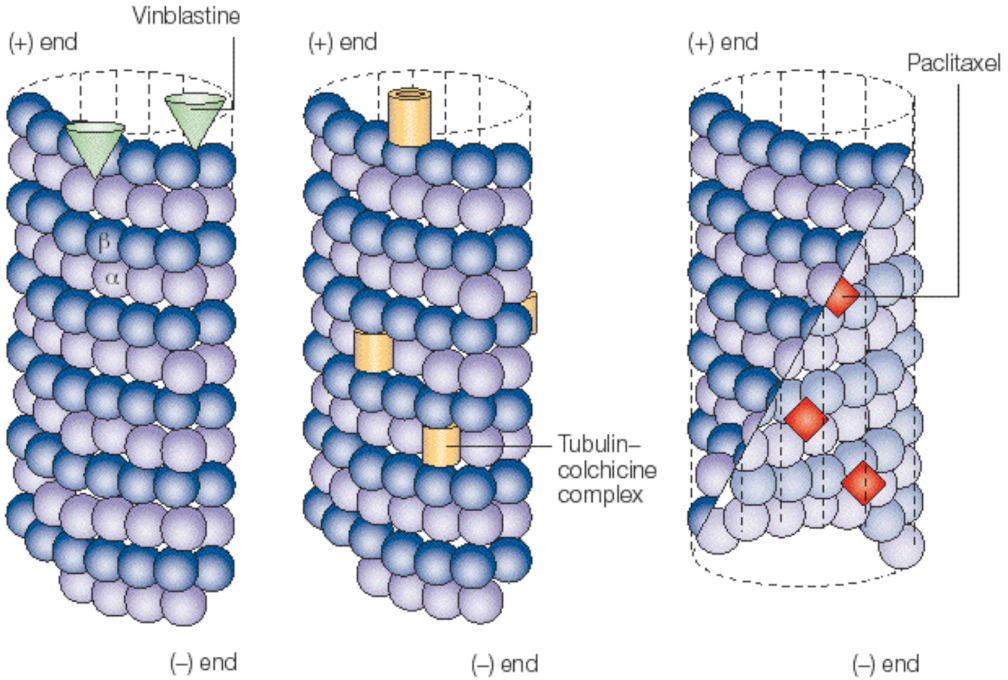
(-Total syntheses)

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)

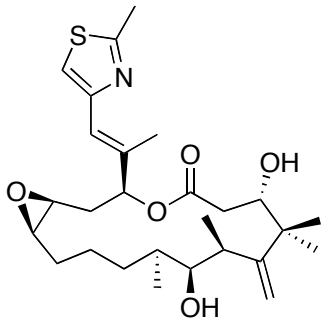




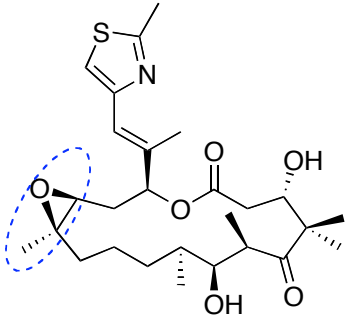


Comming next? - Epothilones

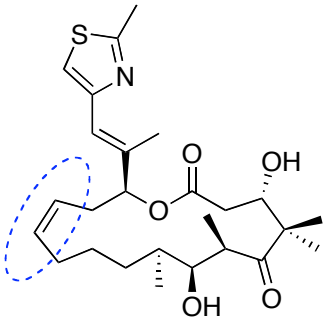
Isolated from *Myxobacteria* (Epothilone A - F + synth. analogs)



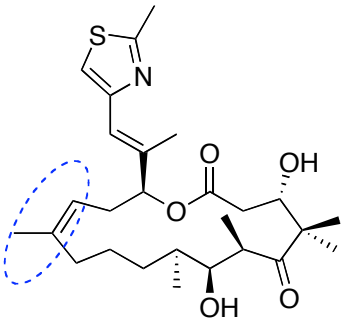
Epothilone A



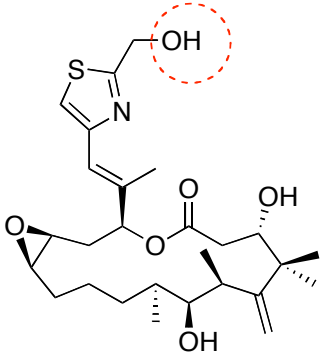
Epothilone B



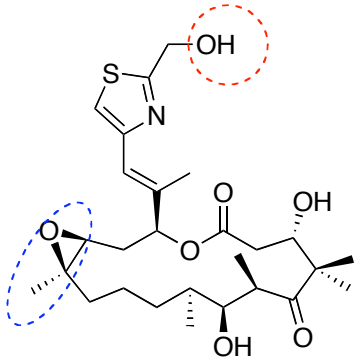
Epothilone C



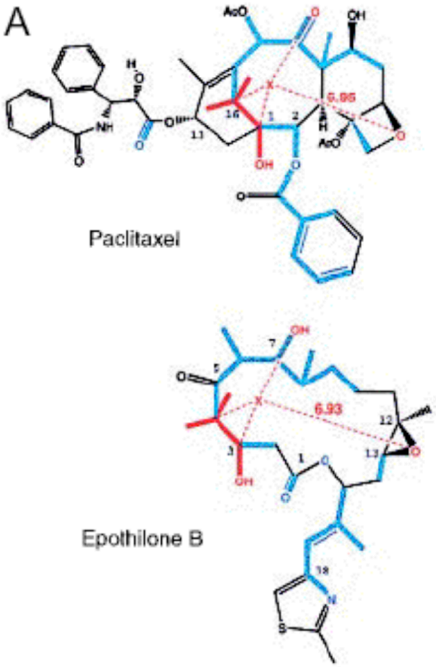
Epothilone D

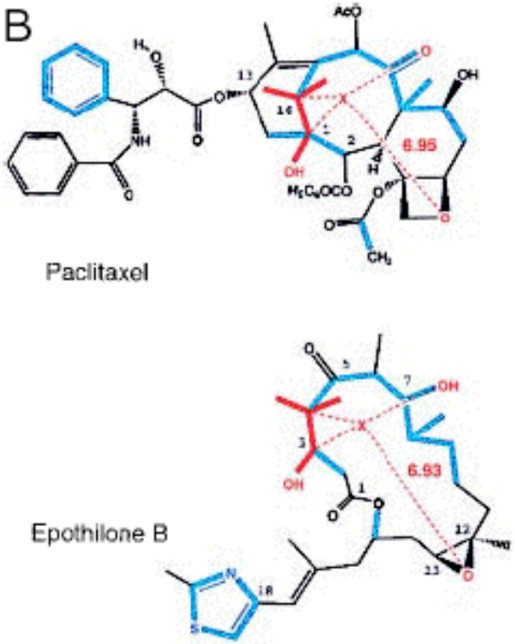


Epothilone E



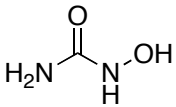
Epothilone F





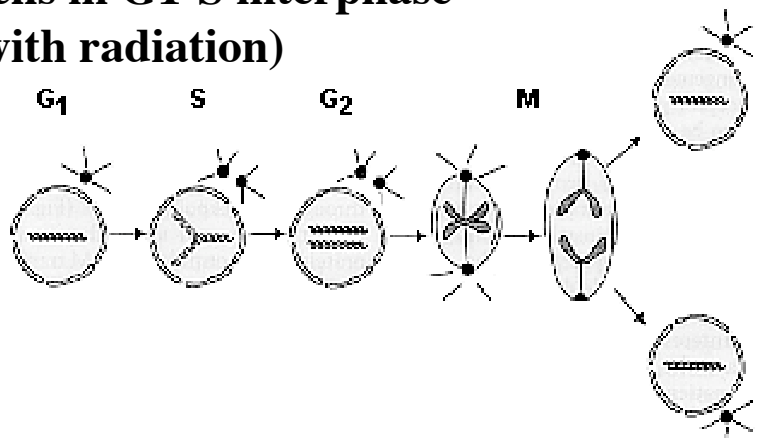
- **Chemotherapy**
  - **Alkylation Agents √**
  - **Antimetabolites / Nucleoside Analogs √**
  - **Antibiotics √**
  - **Antimitotic Agents √**
  - **Micellaneous Antineoplastic Agents**
  - **Hormonal Therapy**

- **Hydroxyurea**
- **Podophyllotoxines**
- **Camptothecins**
- **Compounds for photodynamic therapy**
- **Tyrosine-Kinase Inhibitors**



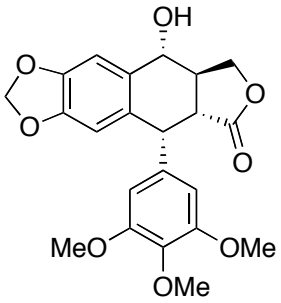
Hydroxykarbamid®

Inhib. ribonucleotide diphosphate reductase
Arrest cells in G1-S interphase
(combi with radiation)



Podophyllotoxines

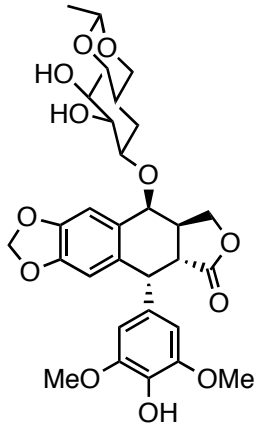
From *Podophyllum peltarum*
May apple



Podophyllotoxin

Antiviral, veneric warts

Toxic - lead for anticancer drugs



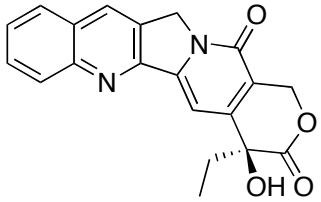
Etoposide

Etoposide
Eposin® Etopofos®
Vepesid®

Affects DNA topoisomerase II (not intercalating)
DNA strand breakage

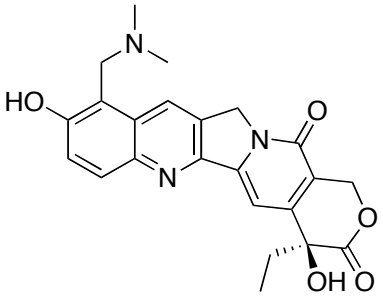
Camptothecins

First isolated *Camptotheca acuminata* (Chinese tree)
NIH screening
Later found in several plants

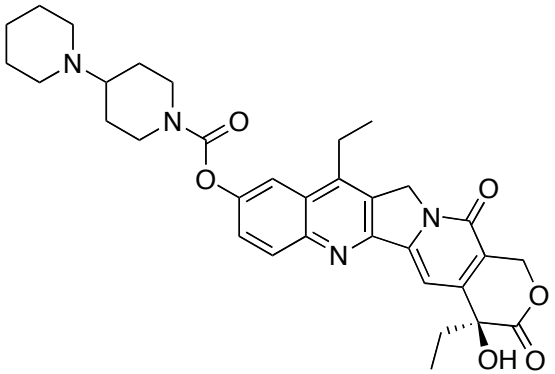


Camptothecin,
toxic, Lead comp.

Topotecan
Hycamtin®



Irinotecan
Campto®

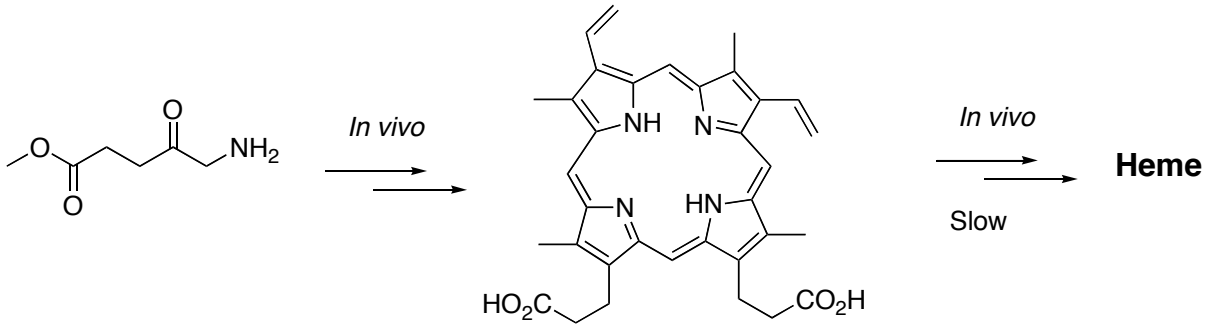


Semisynth. inhib. DNA topoisomerase II, DNA strand breakage

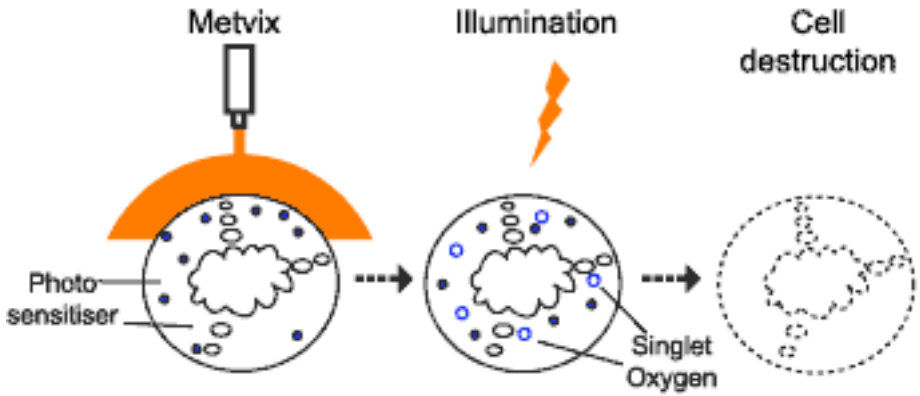
•Compounds for photodynamic therapy

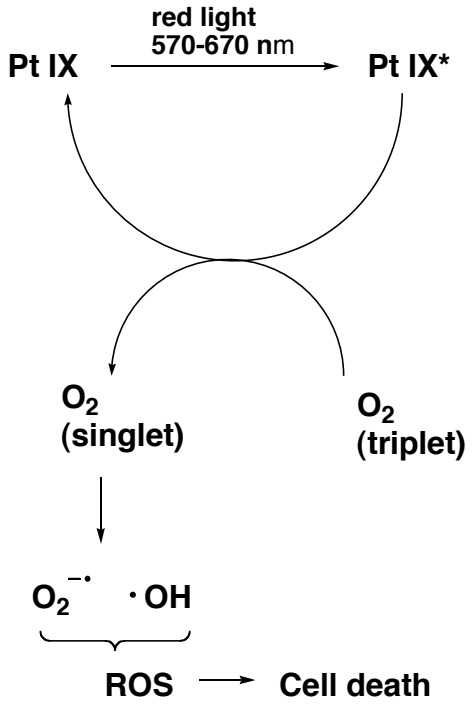
Metylaminolevulinat

Metvix® **PhotoCure**



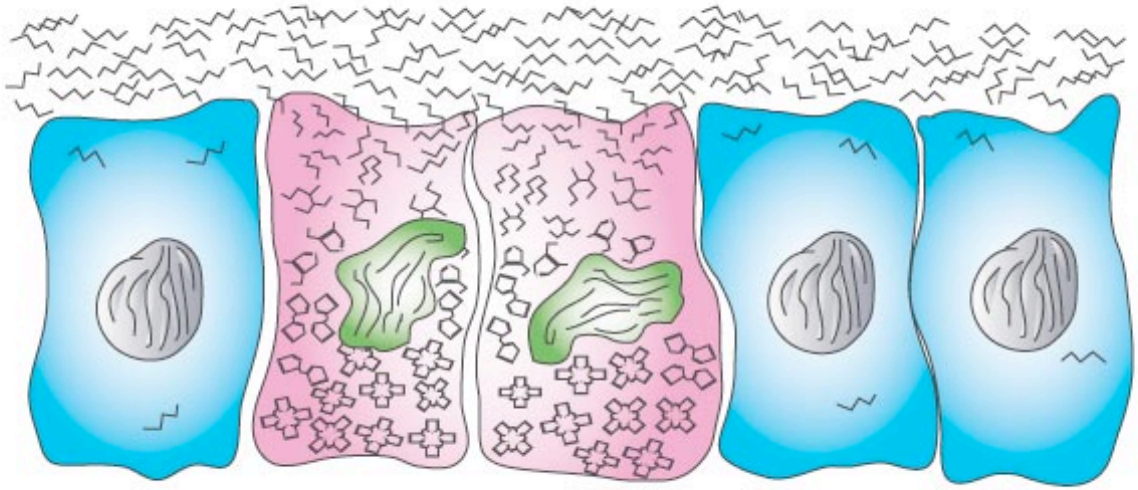
Protoporphyrine IX (Pt IX)





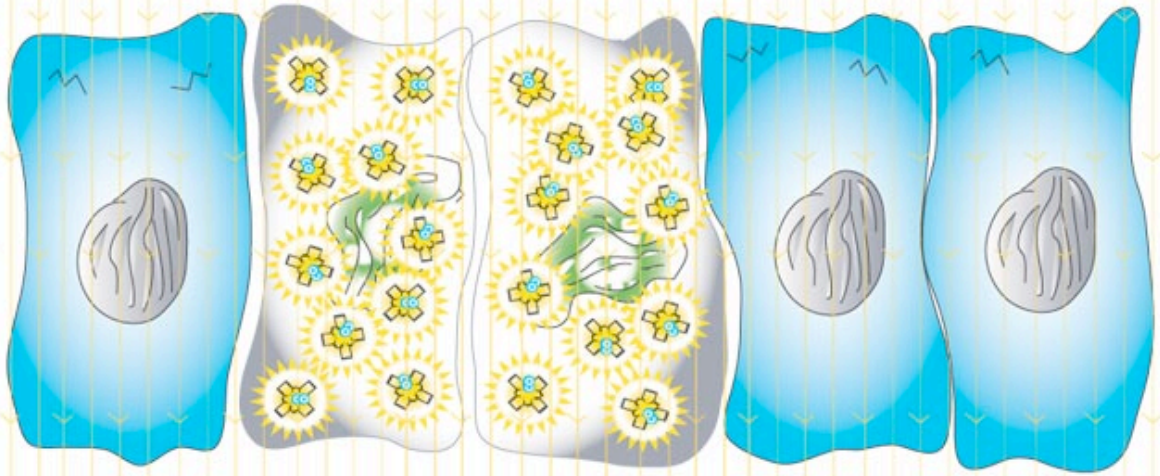
Shore Laser & Esthetics

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

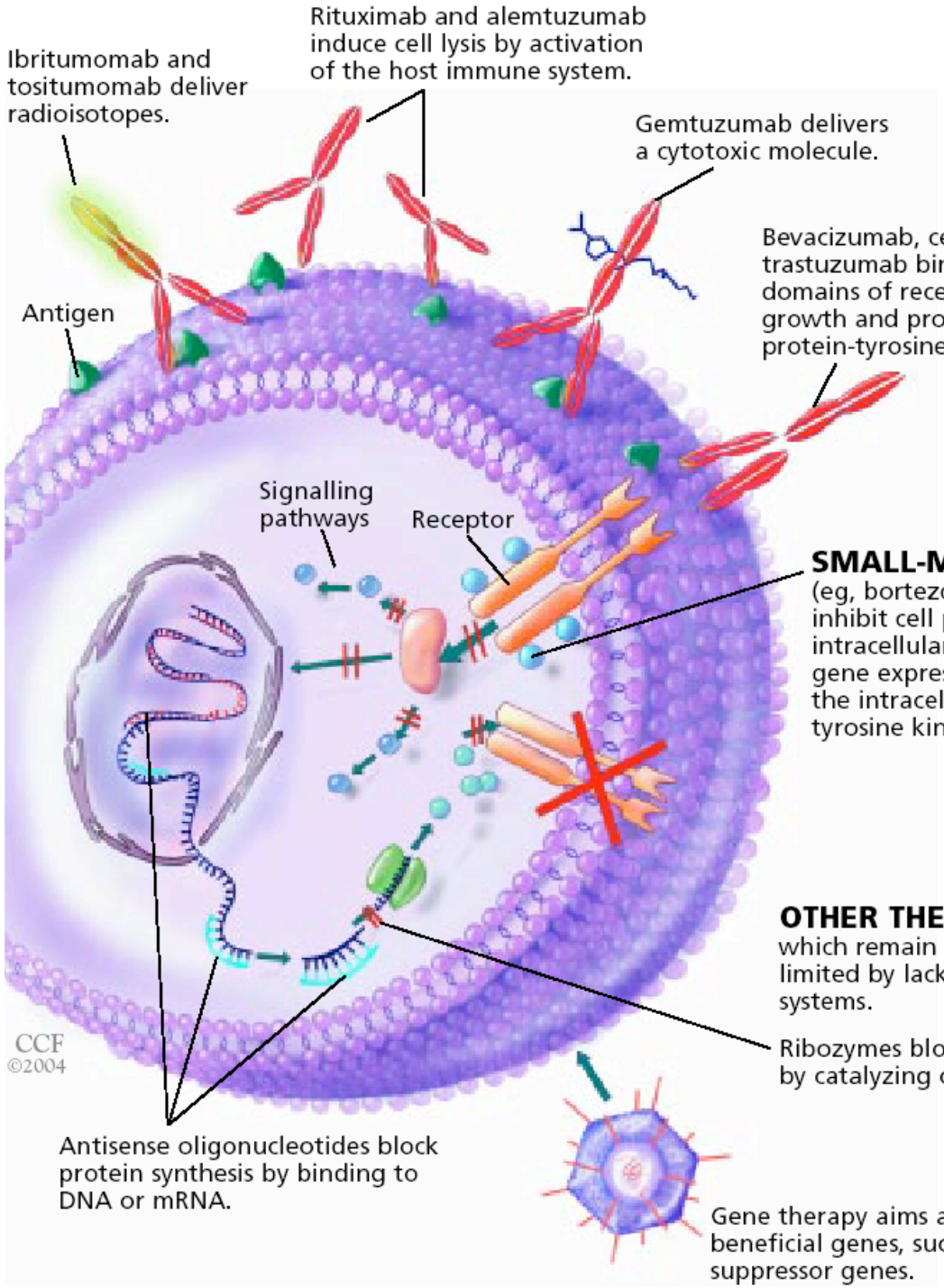


and Protoporphyrin IX, a powerful photosensitizer, is synthesized and concentrated.

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

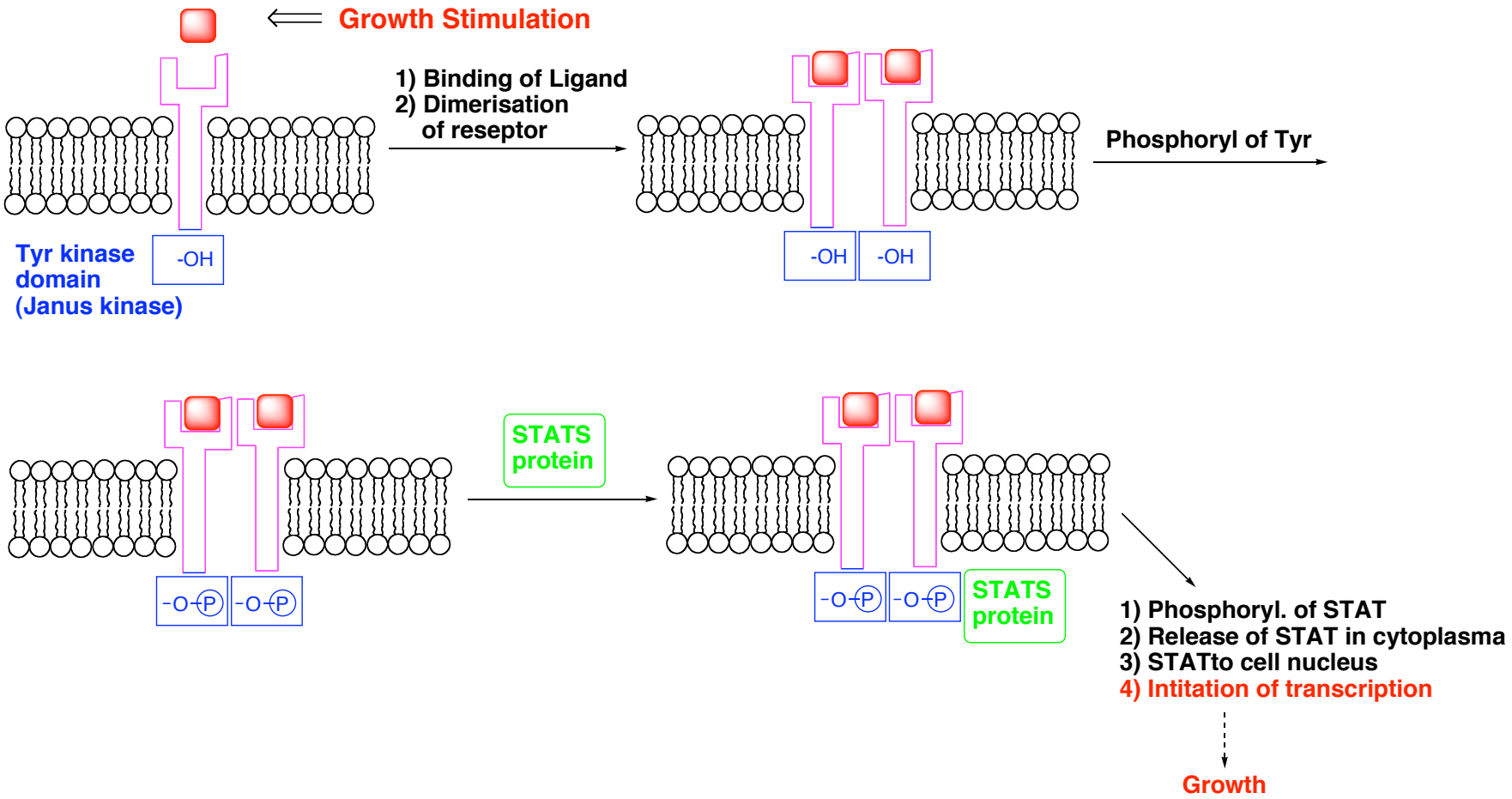


Tyrosine-Kinase Inhibitors



Enzyme coupled receptors - Catalytic receptors (Chapter 4)

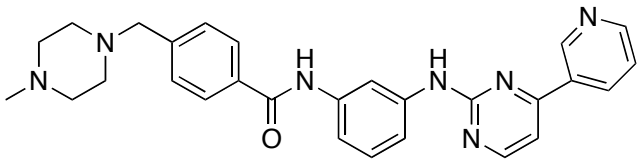
Ligands: Peptide hormones



Imatinib

Glivec®

Leukemia types



Gefitinib

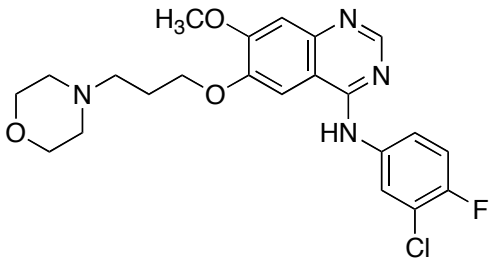
Iressa® - Not in N.

Lung cancer

Side effect: Intestinal lung disease (may be fatal)

0.3 % US

2% Japan



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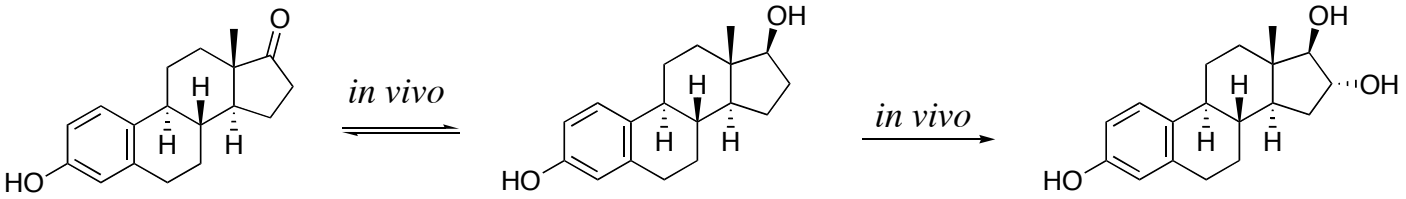
  - **Antibiotics √**
  - **Antimitotic Agents √**
  - **Micellaneous Antineoplastic Agents √**
  - **Hormonal Therapy**

Estrogens and agonists

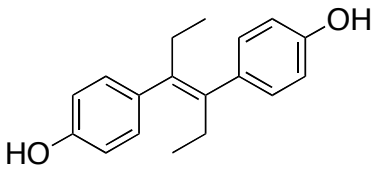


Estrone
(Low activity)

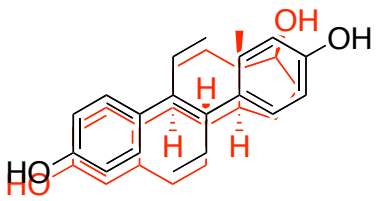
Estradiol

Estriol
(low activity)

(fast metabolism)



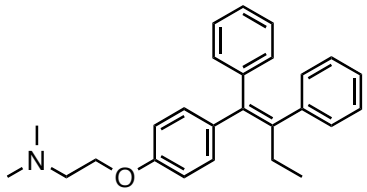
Diethylstilbestrol
Estrogene agonist, used as drug before



Overlap estradiol

Antiestrogens

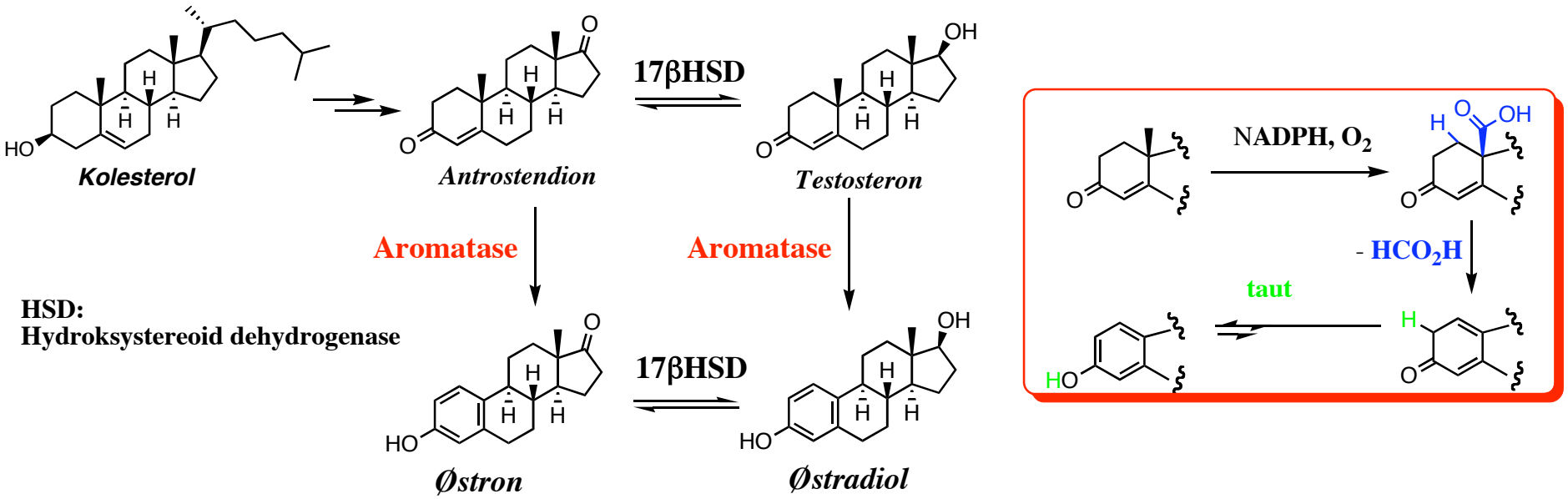
Tamoxifen
Nolvadex® Tamoxifen®



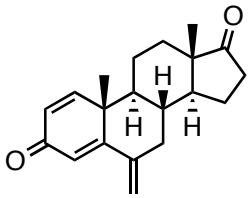
Breast cancer
(estrogen depend.)

Aromatase Inhibitors

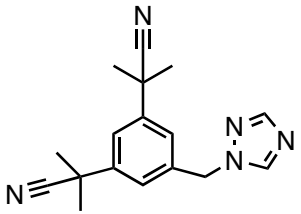
Estrogen depend. breast cancer
Inhib. estrogen biosynth.



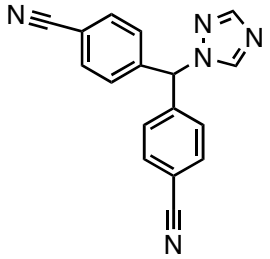
Exemestan
Aromasin®



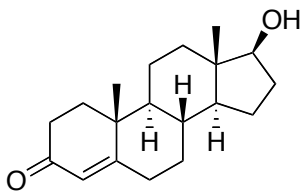
Anastrosol
Arimidex®



Letrozol
Femar®

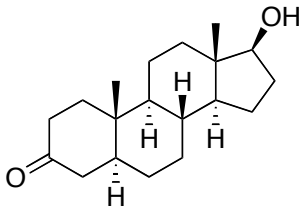


Androgens



Testosterone

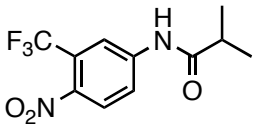
5α-reduktase



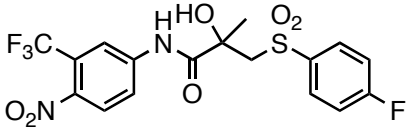
5α-Dihydrotestosterone (5DHT)
More active

Anti-androgens

Flutamid
Eulexin® Flutamid®
Prostate cancer



Bicalutamid
Casodex®
Prostate cancer (less tox.)



5α-Reductase Inhibitors

Finasterid
Proscar®
benign prostate