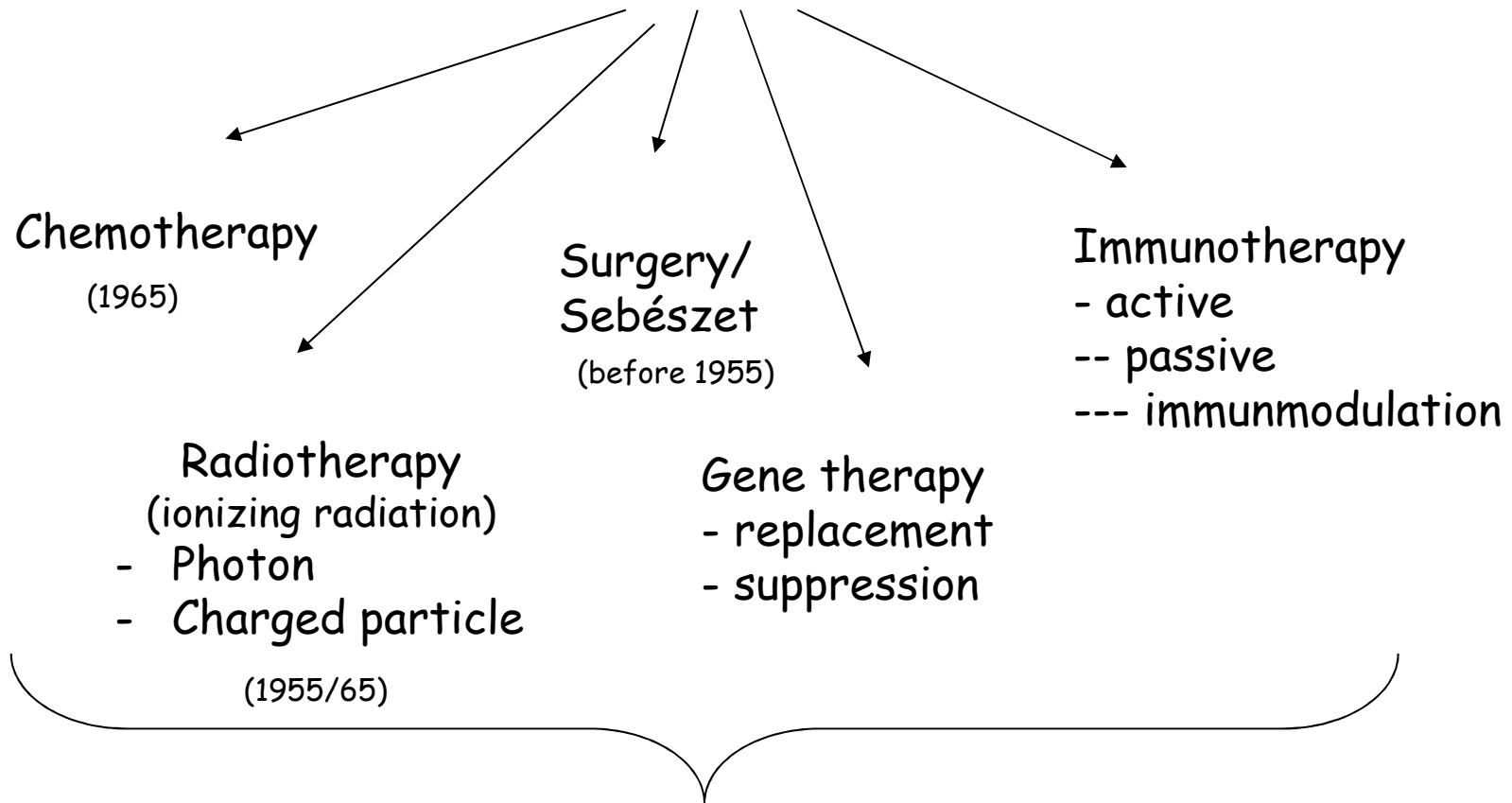


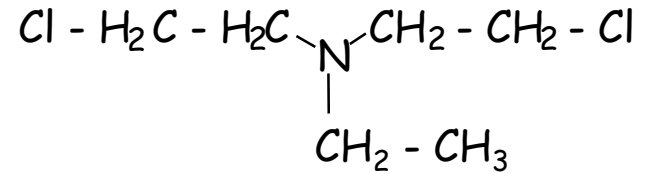
Treatment of cancer/Tumorok kezelése

(no treatment before 1940)



Combination therapy/Kombinációs terápia

Chemotherapy



First step: discovery of nitrogen mustard, as drug

1. period: 1942 - 1959, palliative, toxic side effects
2. period: 1960 - 1979, success in few cancers, toxic side effects
3. period: 1980- success in additional cancers, limited side effects

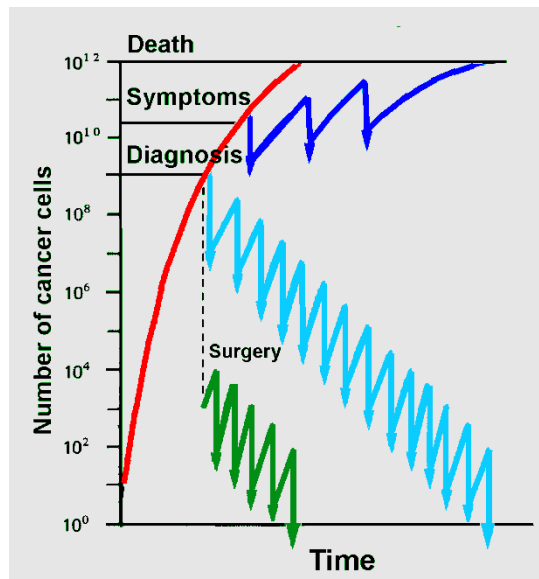
1-log-kill dose of an effective drug = the number of tumour cells is 10 times smaller after chemotherapy

e.g. 10^{12} tumour cells (1 kg)

1st combined treatment causes 3 log elimination, still 10^9 tumour cells (1 g).

2nd combined treatment causes 3 log elimination, still 10^6 tumour cells (1 mg).

"Log reduction" is a mathematical term used to show the relative number of cells, germs, microbes, etc., reduced in or on something

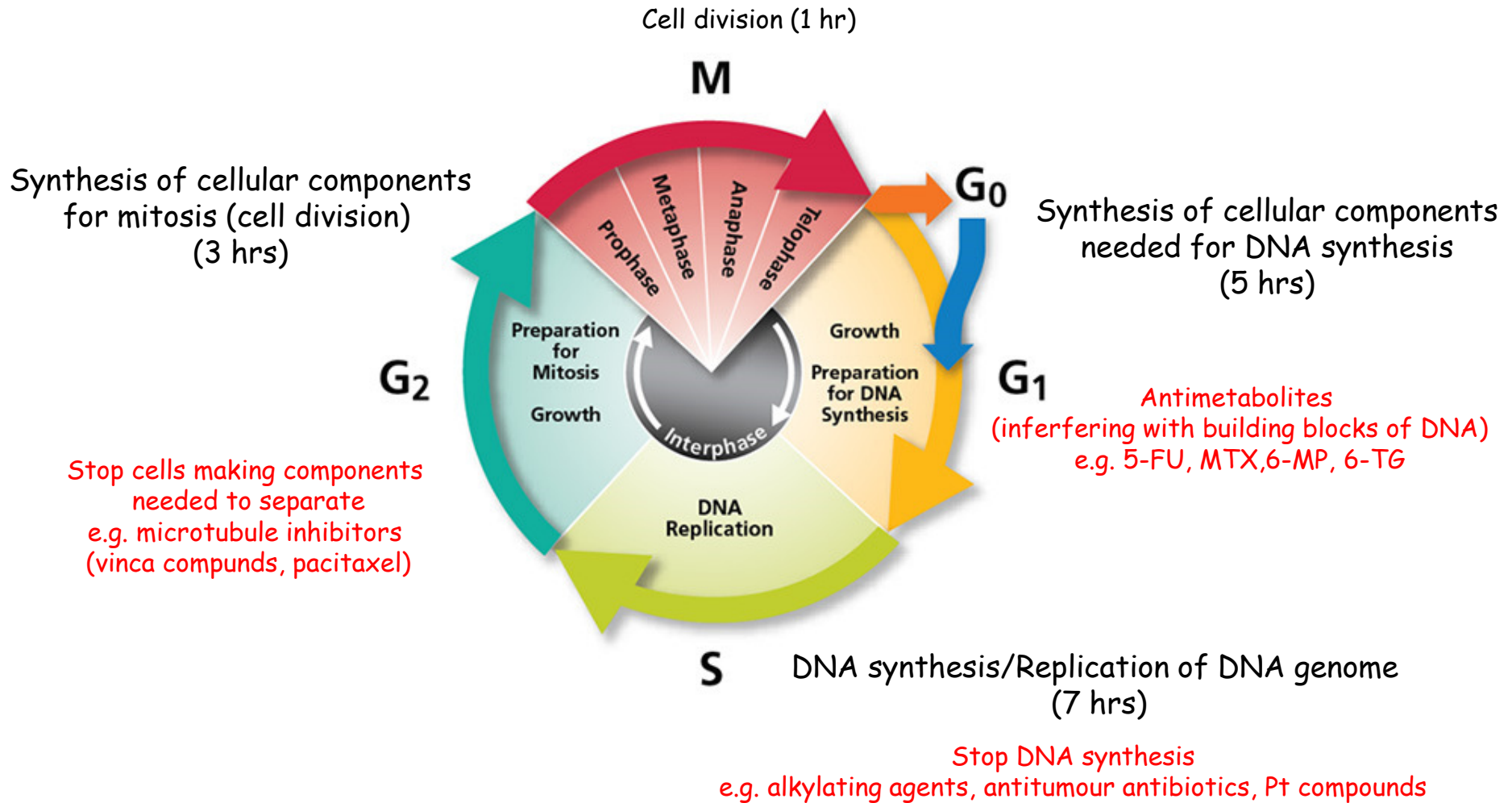


Selectivity



Side effects
(e.g. cardiotoxicity,
immunosuppression)

Cell cycle and cancer



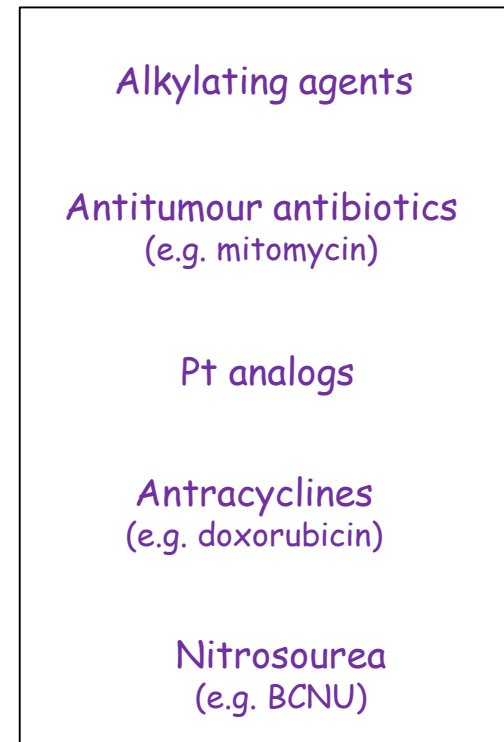
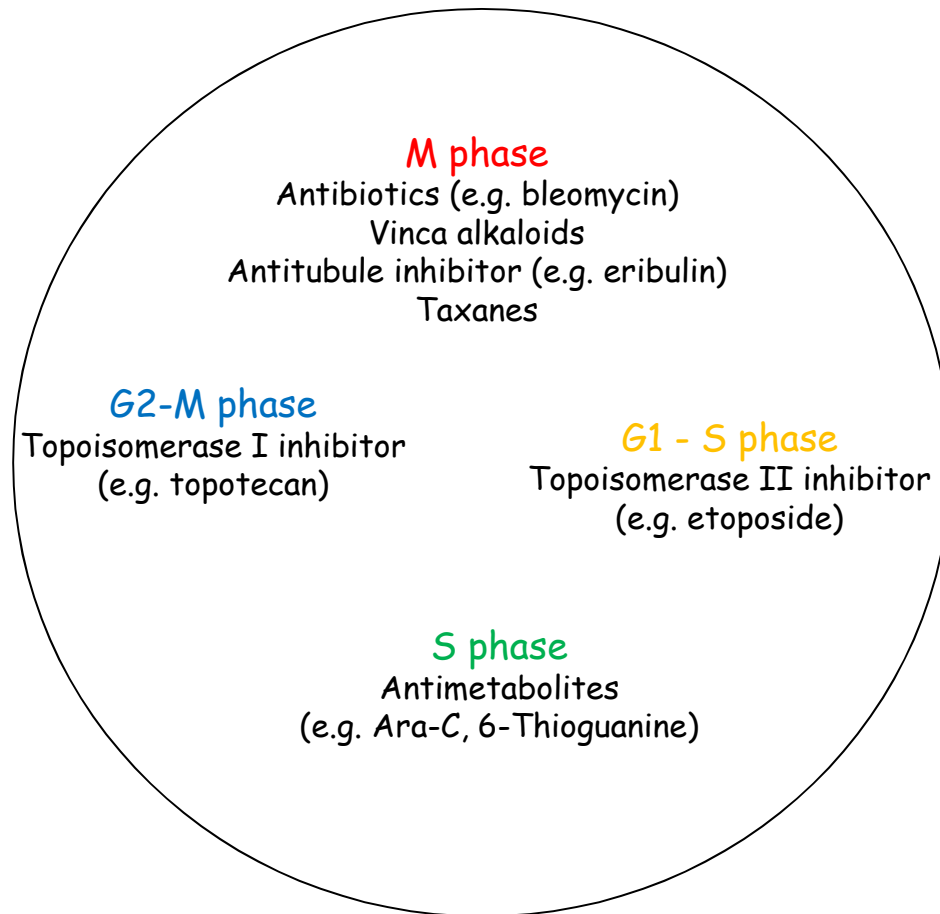
B. G. Katzung and A.J. Trevor: Basic & Clinical Pharmacology, McGraw Hill - 13th edition, 2015

<https://oncogenesandcancer.wordpress.com/cell-cycle-checkpoints-and-effect-of-oncogenes-2/>

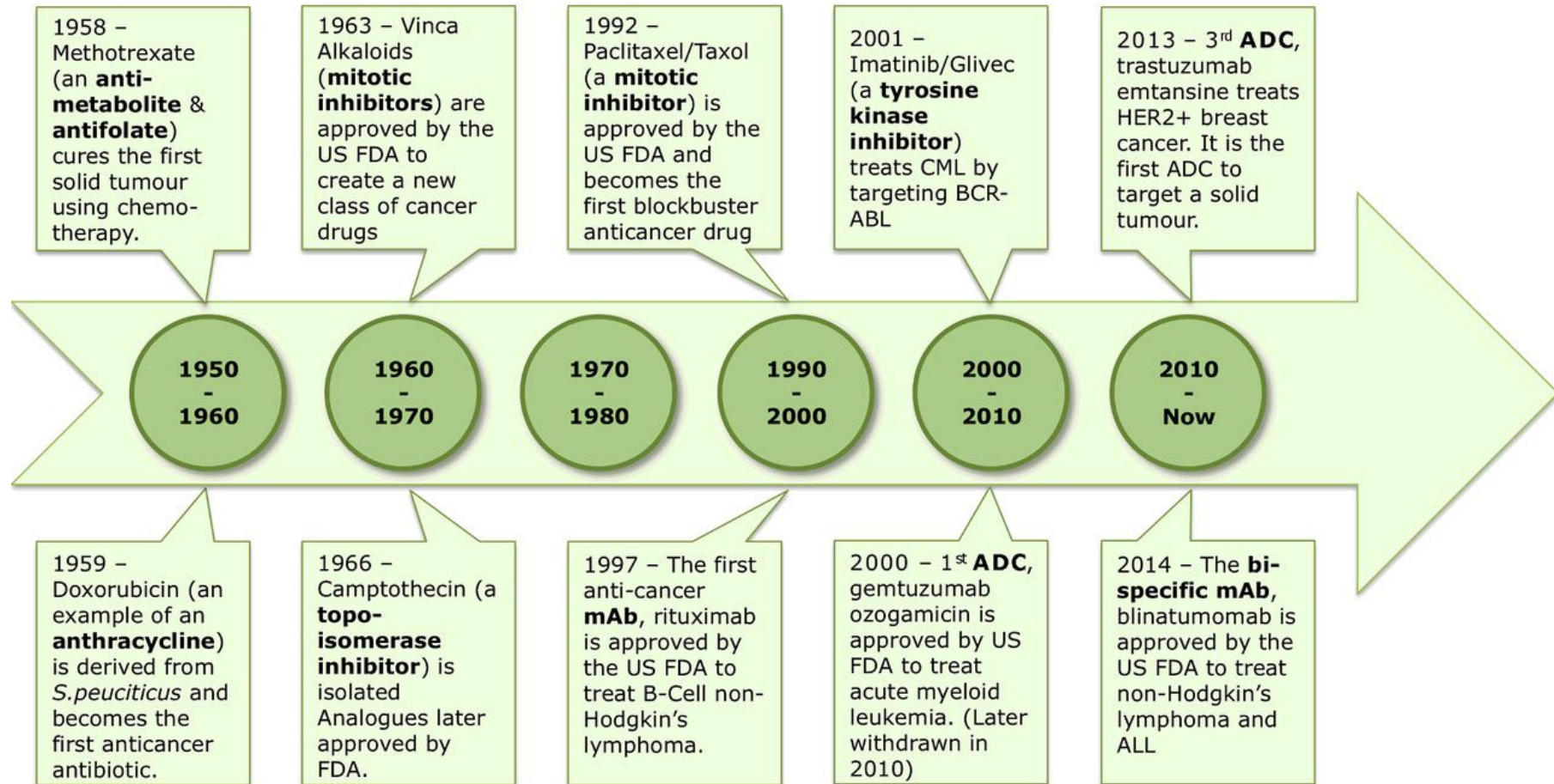
Classes of chemotherapeutic drugs

Cell-cycle-specific drugs
(CCS)

Cell-cycle-nonspecific drugs
(CCNS)



Evolution of chemotherapeutic drugs

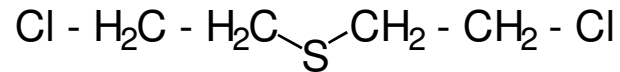


Classes of chemotherapeutic drugs

- alkylating agents
 - bis(chloroethyl)amines („mustards“)
 - nitrosourea
 - organometallic compounds
 - aziridines
 - alkylsulfonate (busulfan)
- antimetabolites (e.g. 5-F-uracil, methotrexate)
 - Folic acid analogues
 - Purine analogues
 - Pyrimidine analogues
 - Nucleoside analogues
- antibiotics (e.g. mitomycin C, daunomycin)
- microtubule damaging agents
- hormone related anticancer agents antagonists
- vitamins (A, C)

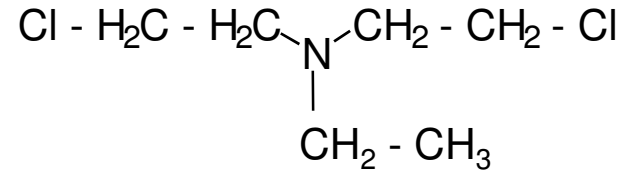
Alkylating agents

bis(chloroethyl)amines



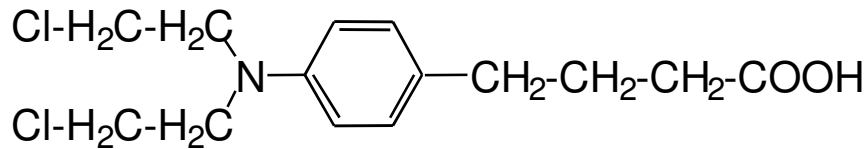
Bis(2-chloroethyl) sulfide,
[sulfur mustard, mustard gas]

(Sellei, Jány, Koller 1931)
breast cancer

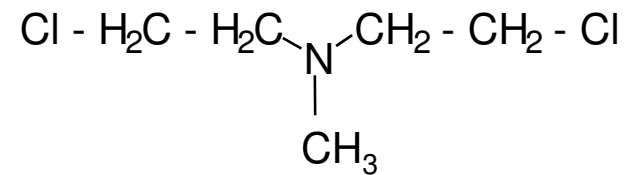


Bis(2-chloroethyl)ethylamine
[nitrogen mustard]

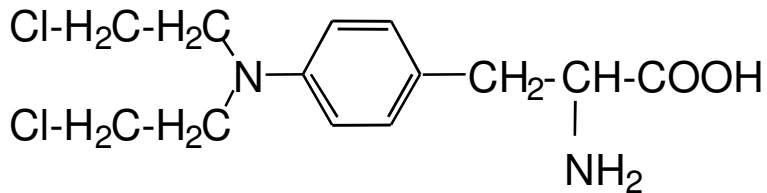
(Berenblum 1935)
melanoma



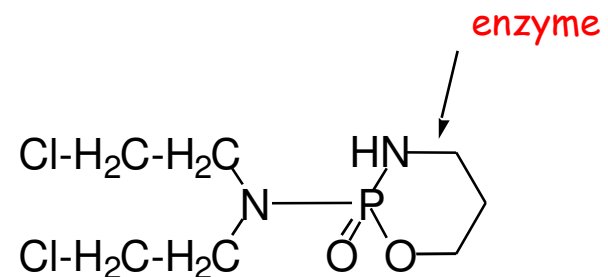
4-[bis(2-chloroethyl)amino]benzenebutanoic acid
(Chlorambucil)



Bis(2-chloroethyl)methylamine



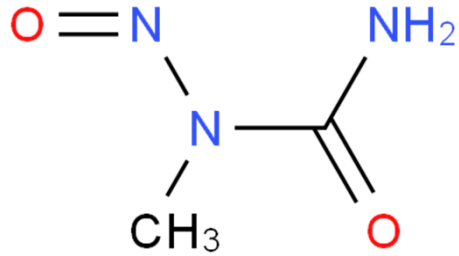
Melphalan, L - amino acid
(multiple myeloma, ovarium)



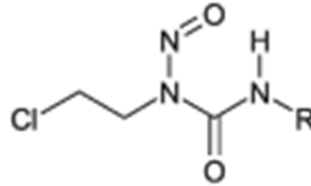
cyclophosphamide (Endoxan)
breast

Alkylating agents

N-nitrosourea

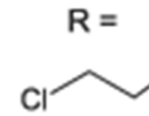


N-methyl- N- nitrosourea



N-2-chloroethyl- N- nitrosourea derivatives

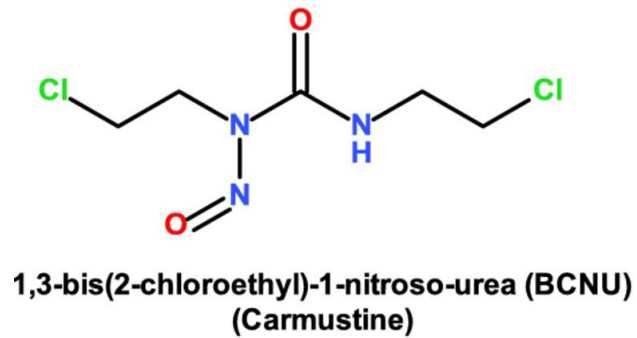
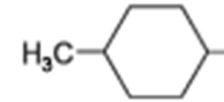
Carmustine
(BCNU)



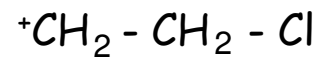
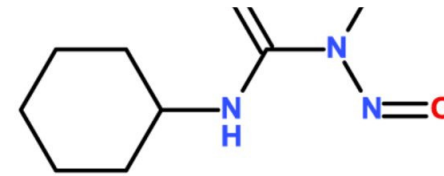
Lomustine
(LCNU)



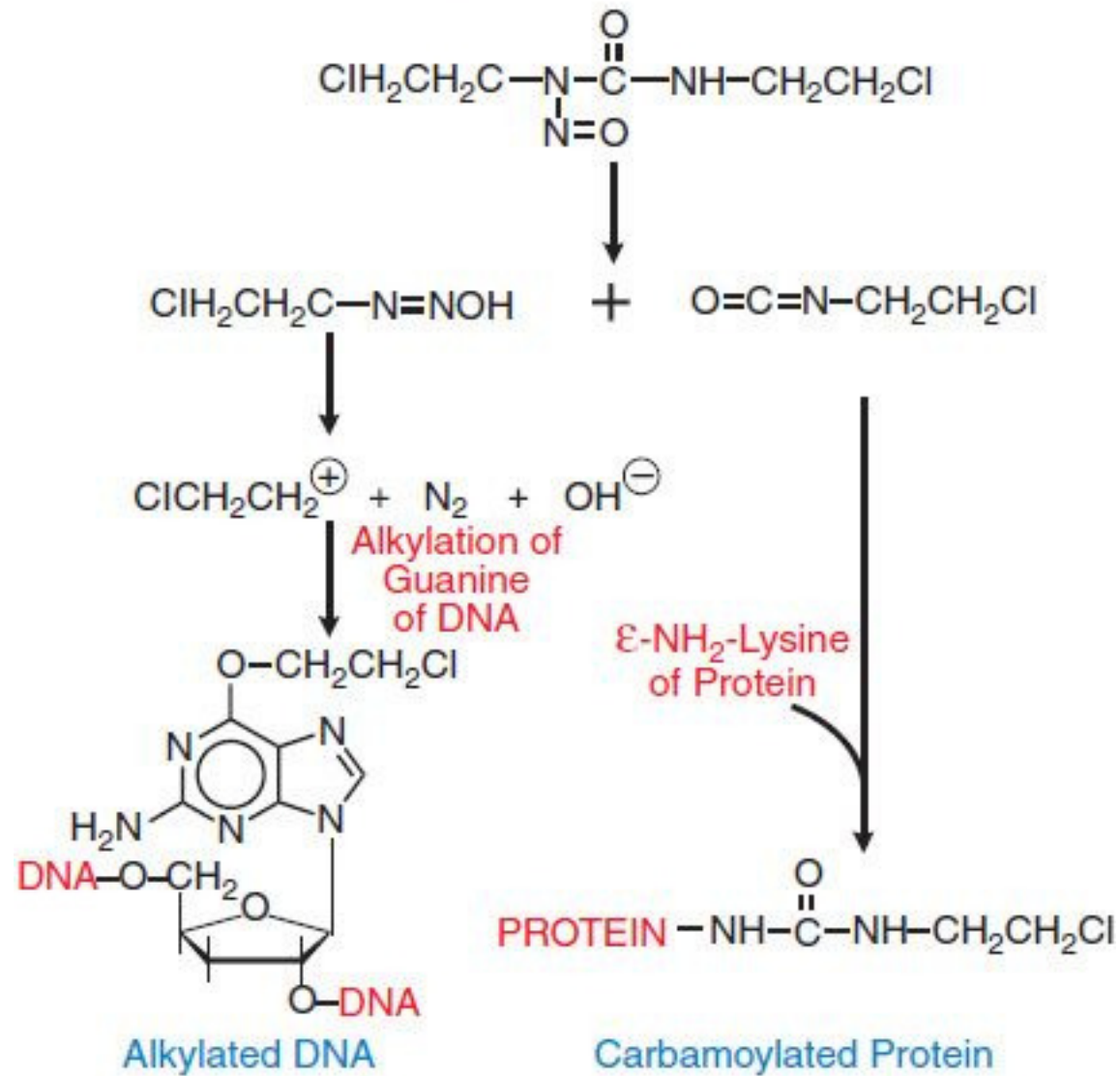
Semustine
(metilCCNU)



1-(2-chloroethyl)-3-cyclohexyl-1-nitroso-urea (CCNU)
(Lomustine)

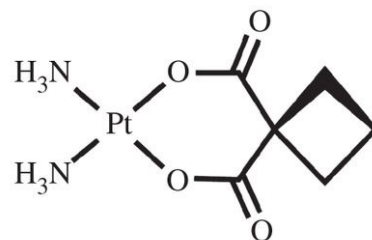


The effect of Carmustine (BCNU)

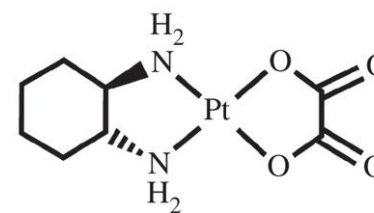


Alkylating agents

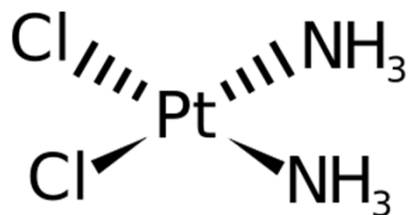
Organometallic compounds



carboplatin

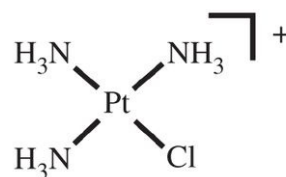


oxaliplatin

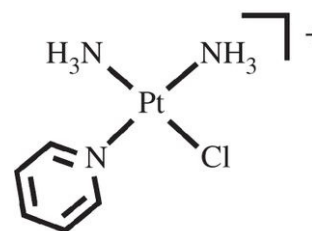


Cisplatin

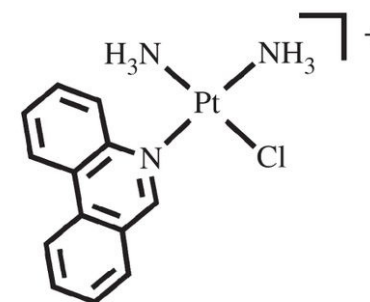
(*cis*-diammino-dichloro-platinum(II))



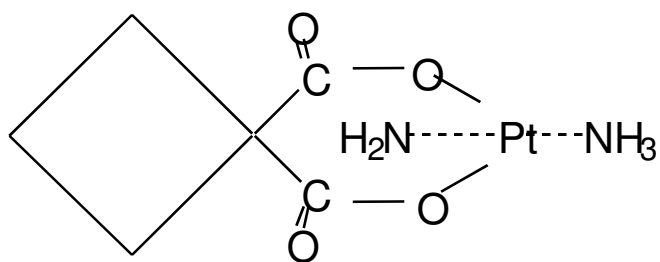
triamminechloro-
platinum(II)



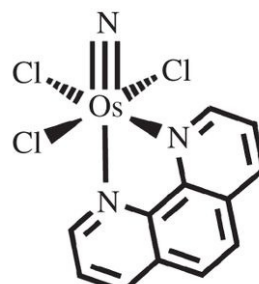
pyriplatin



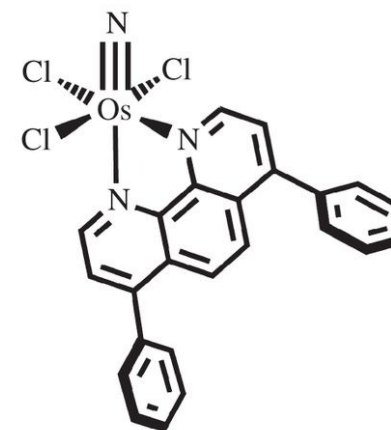
phenanthriplatin



cis-diammino-1,1-cyclobutane
dicarboxylate platinum(II)

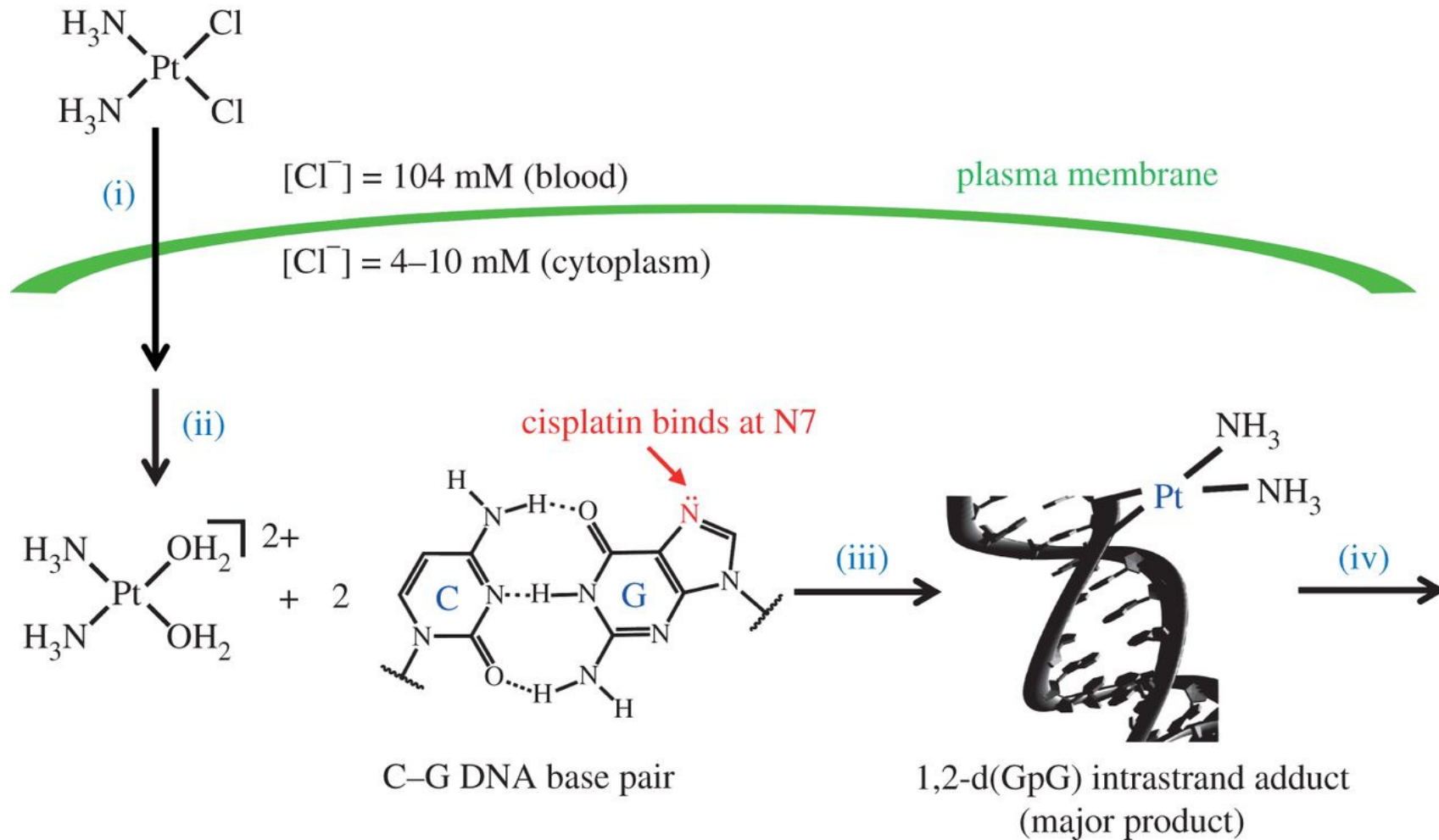


Os-1

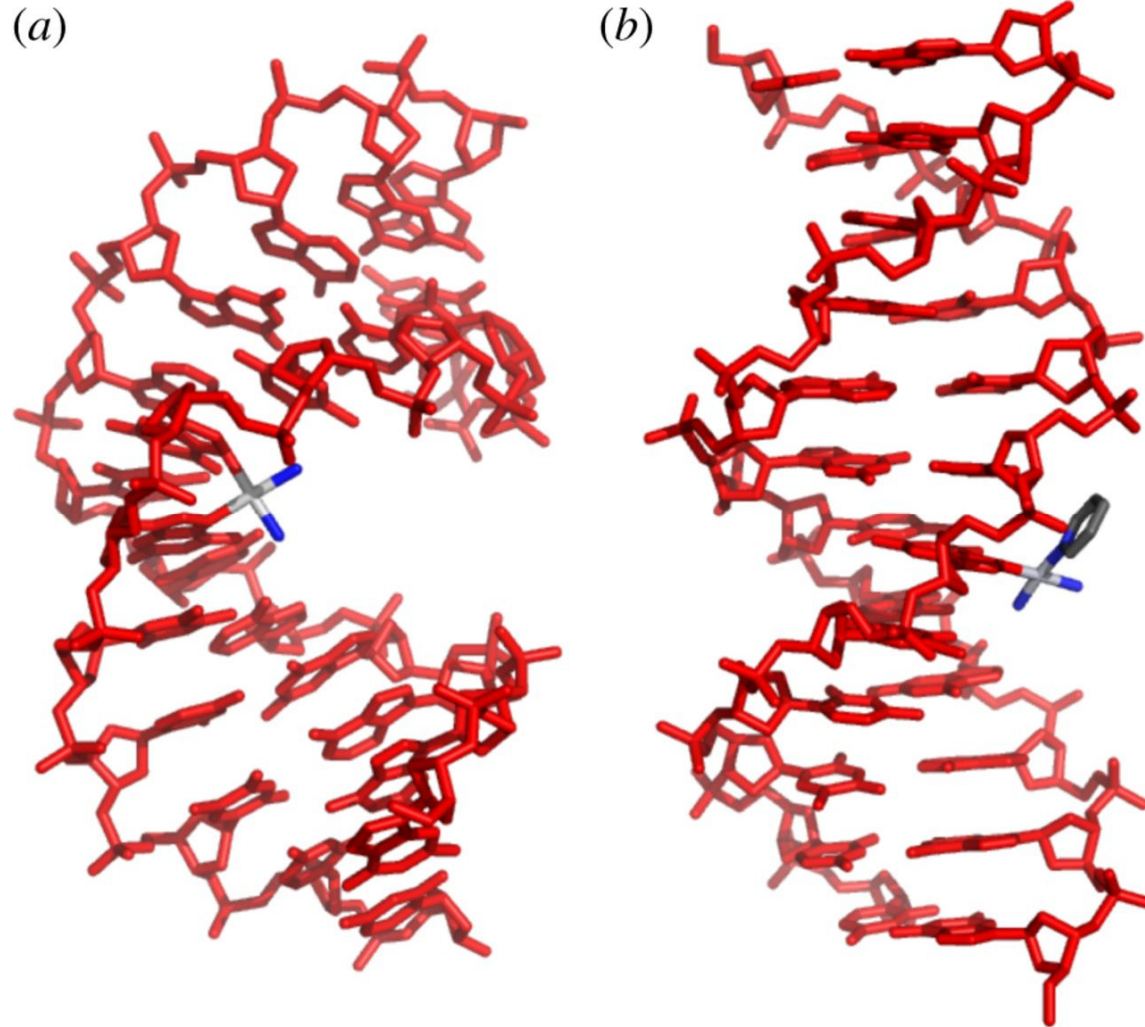


Os-2

Mechanism of action of cisplatin: (i) cellular uptake, (ii) activation, (iii) DNA platination, and (iv) cellular processing leading to apoptosis



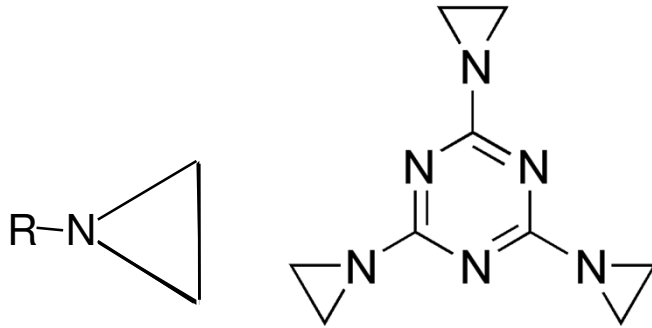
The crystal structures of duplex DNA oligonucleotides platinated with either (a) cisplatin, PDB: 1AIO or (b) pyriplatin, PDB: 3CO3



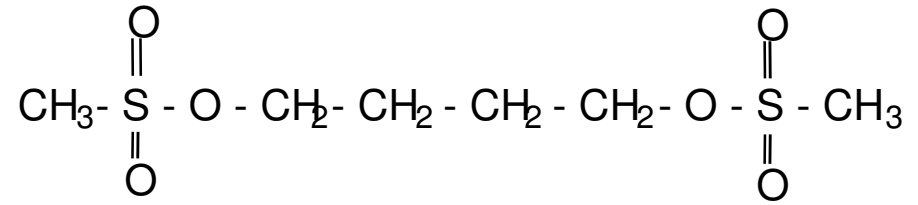
T. C. Johnstone et al. *Phil. Trans. R. Soc. A* 2015; 373: 201401850
© 2015 The Author(s) Published by the Royal Society. All rights reserved.

Alkylating agents

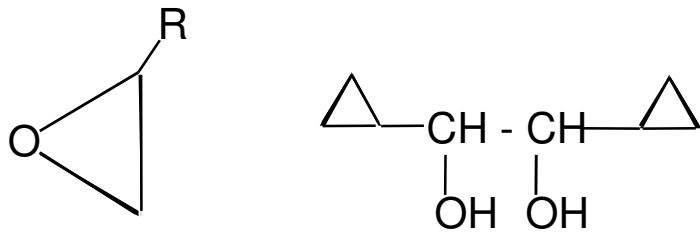
aziridines, epoxides, alkylsulfonates



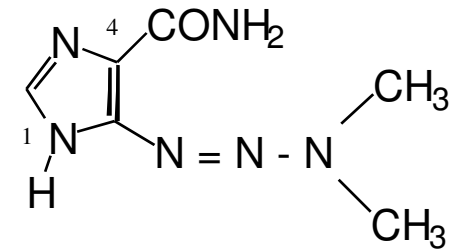
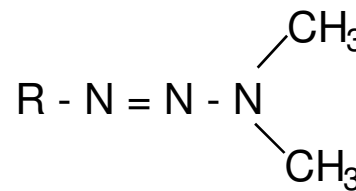
aziridines/ethylene imine
(e.g. triethylenemelamine, TEM)



butane-1,4-diy dimethanesulfonate (busufan)
since 1959

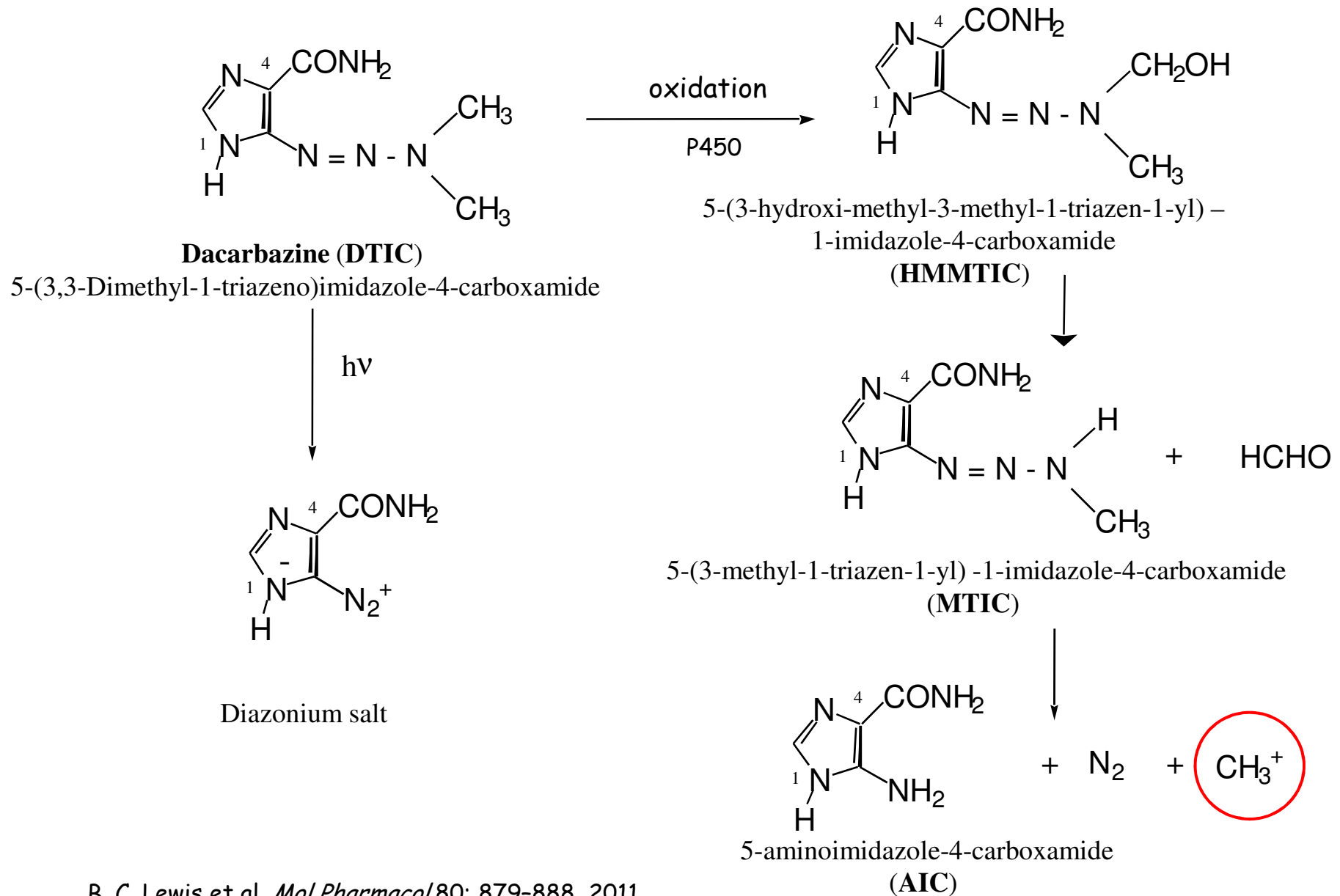


epoxide (e.g. dianhydrogalactitol, DAG)

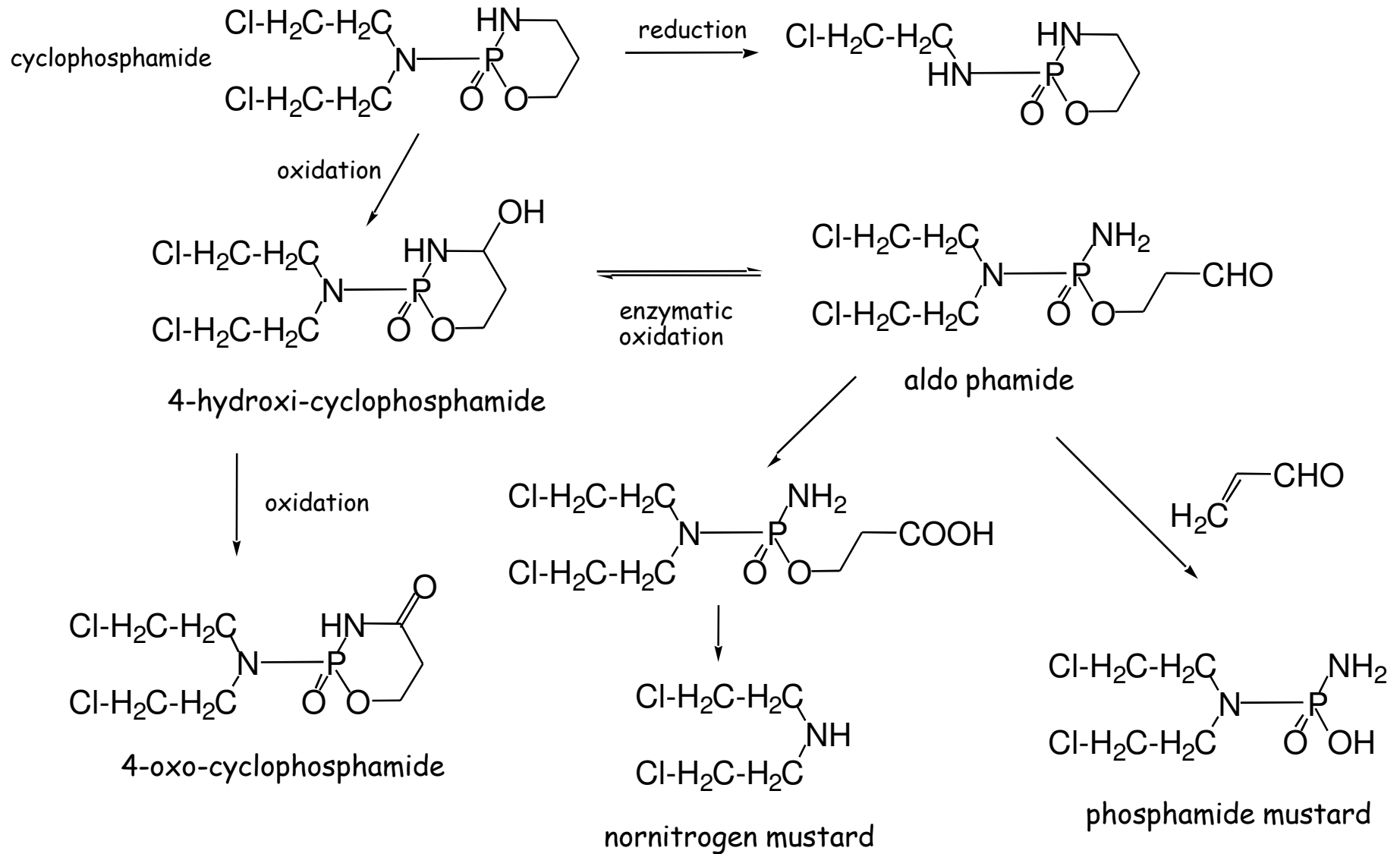


(e.g. 5-(3,3-Dimethyl-1-triazenyl) imidazole-
- 4-carboxamide, Dacarbazine, DTIC)

The metabolism of DTIC



The metabolism of cyclophosphamide



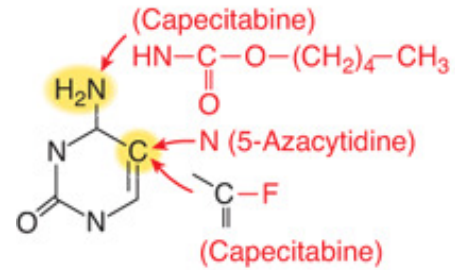
Classes of chemotherapeutic drugs

- alkylating agents
 - bis(chloroethyl)amines („mustards“)
 - nitrosourea
 - organometallic compounds
 - aziridines
 - alkylsulfonate (busulfan)
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 - Folic acid analogues
 - Purine analogues
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- hormone related anticancer agents antagonists
- vitamins (A, C)

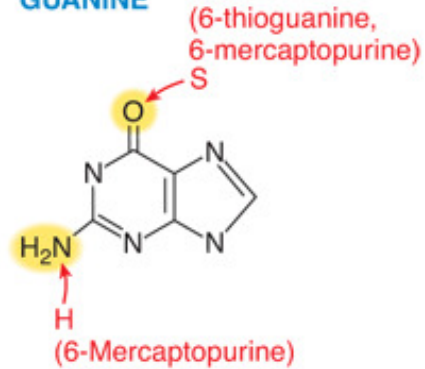
Modifications for metabolites

Base

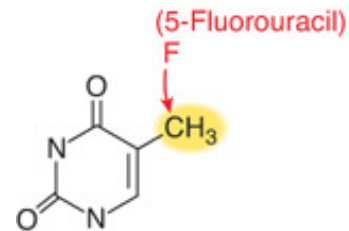
CYTOSINE



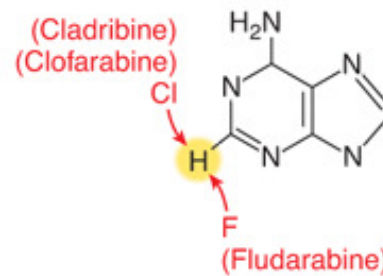
GUANINE



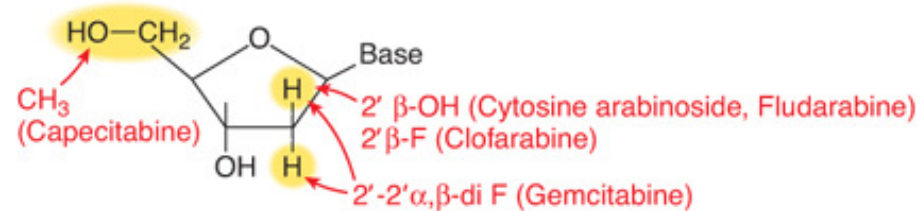
THYMINE



ADENINE

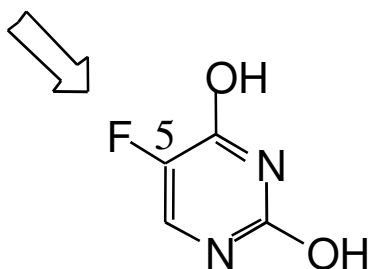


Desoxyribose

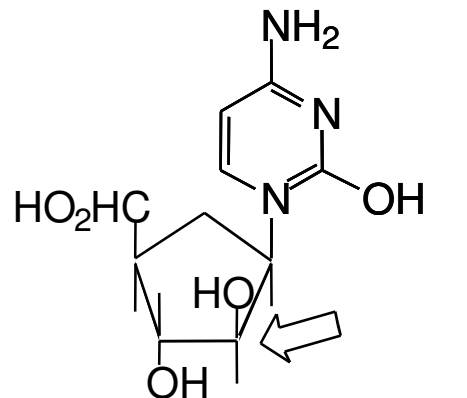


Antimetabolites

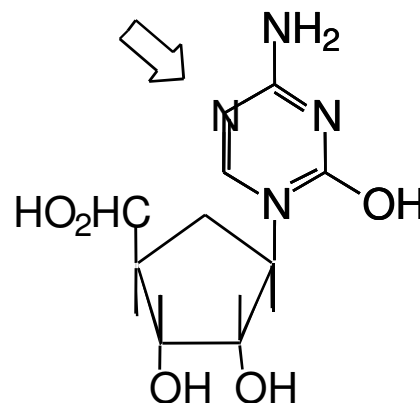
Pyrimidine analogues



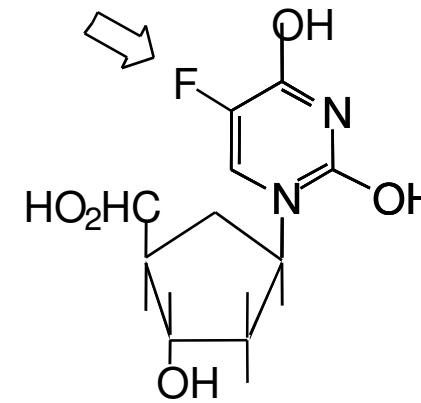
5 - fluorouracil
(Cl, Br, I)



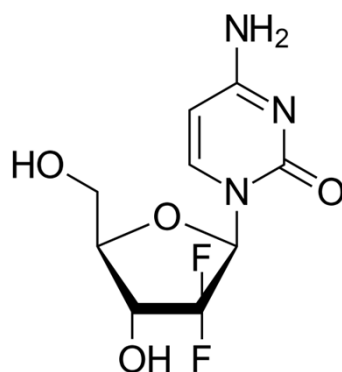
cytosine arabinoside
(Ara-C)



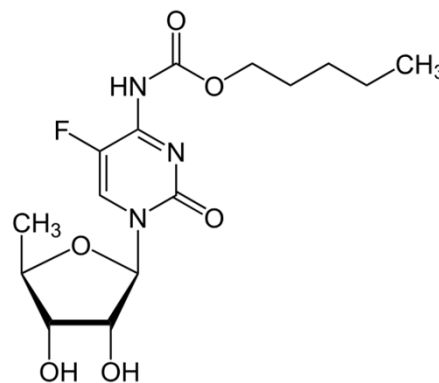
5-azacytidine



5-fluorodeoxyuridine



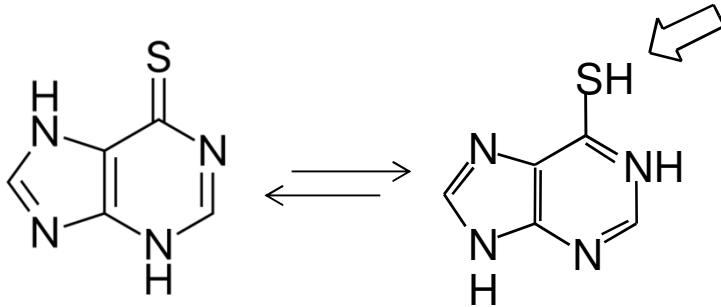
Gemcitabine (1995)



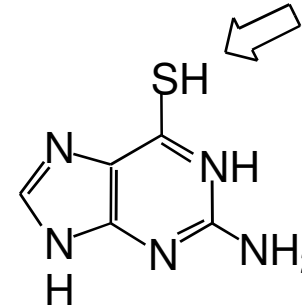
Capecitabine (1998)

Antimetabolites

Purine analogues

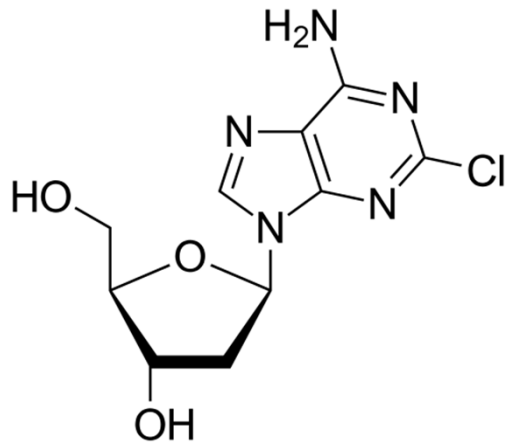


6 - mercaptopurine (1953)

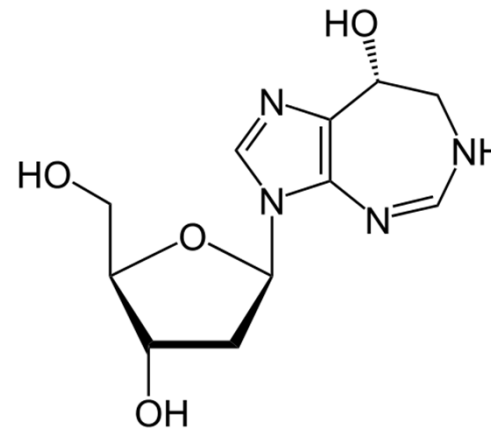


6 - thiaguanine (1949)

Inhibition of adenosine deaminase



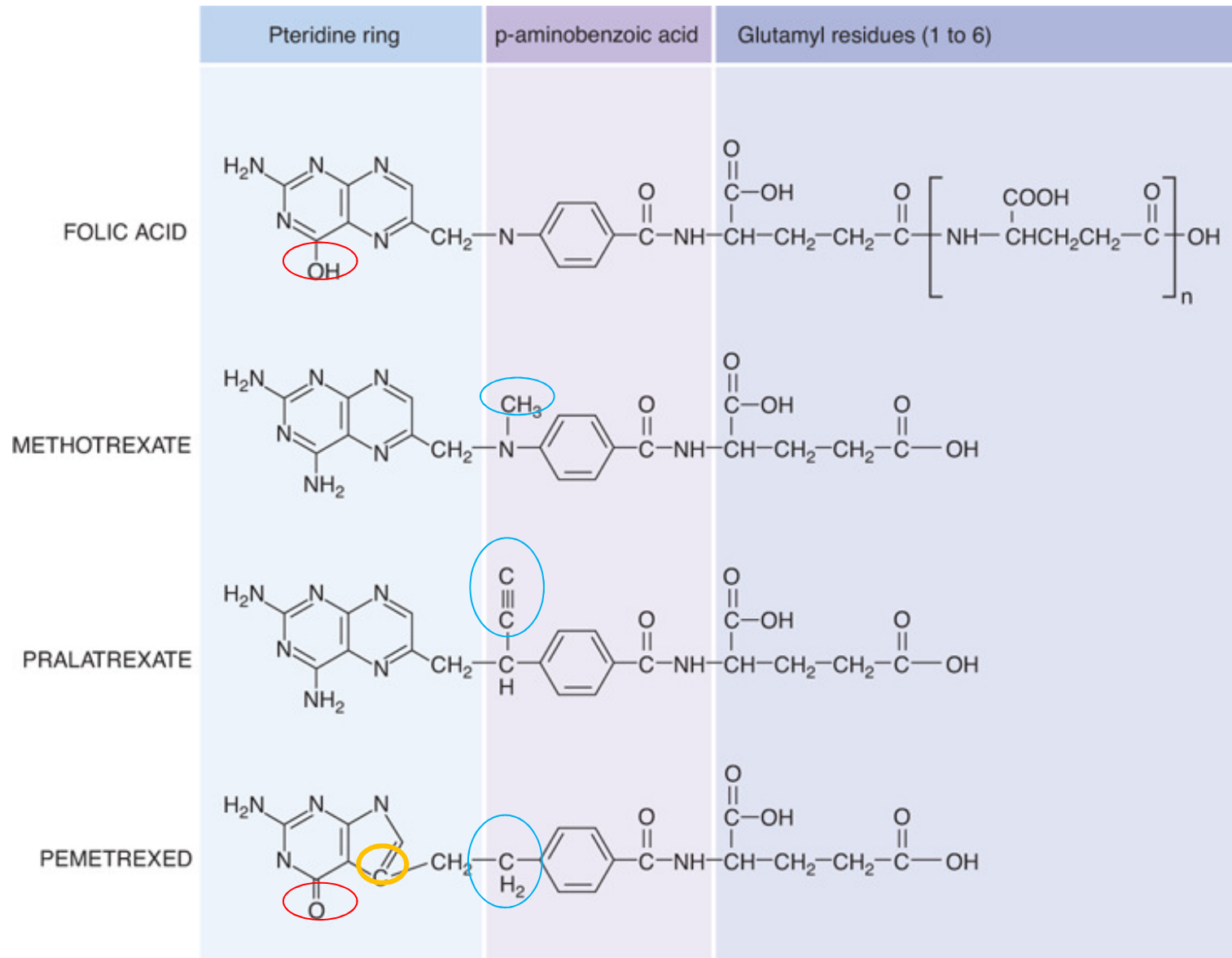
2-chloro-2'-deoxyadenosine
Cladribine (2001)



(8R)-3-(2-deoxy-β-D-erythro-pentofuranosyl)-
3,4,7,8-tetrahydro-imidazo[4,5-d][1,3]diazepin-8-ol;
(Pentostatin)

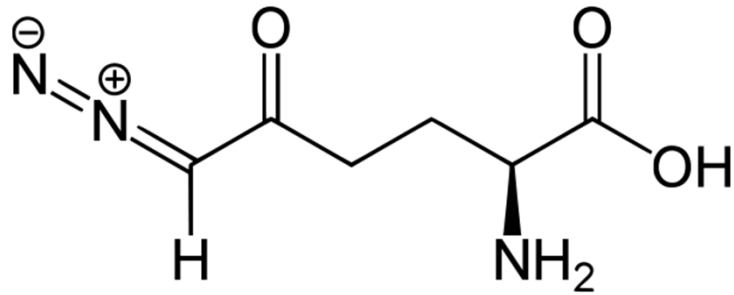
Antimetabolites

Folic acid analogues



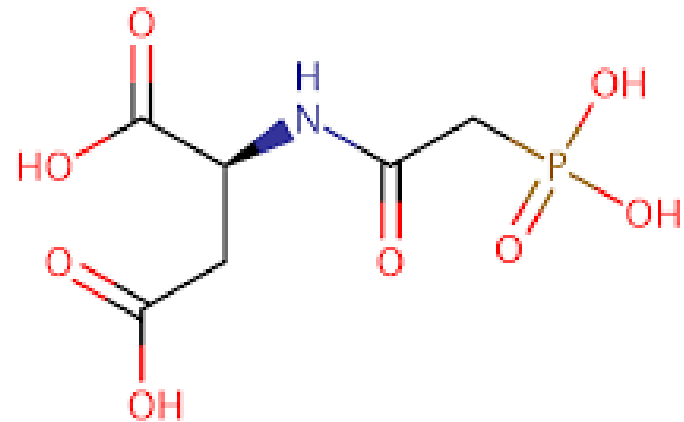
Source: L. L. Brunton, B. A. Chabner, B. C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12ed.
www.accesspharmacy.com
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Antimetabolites

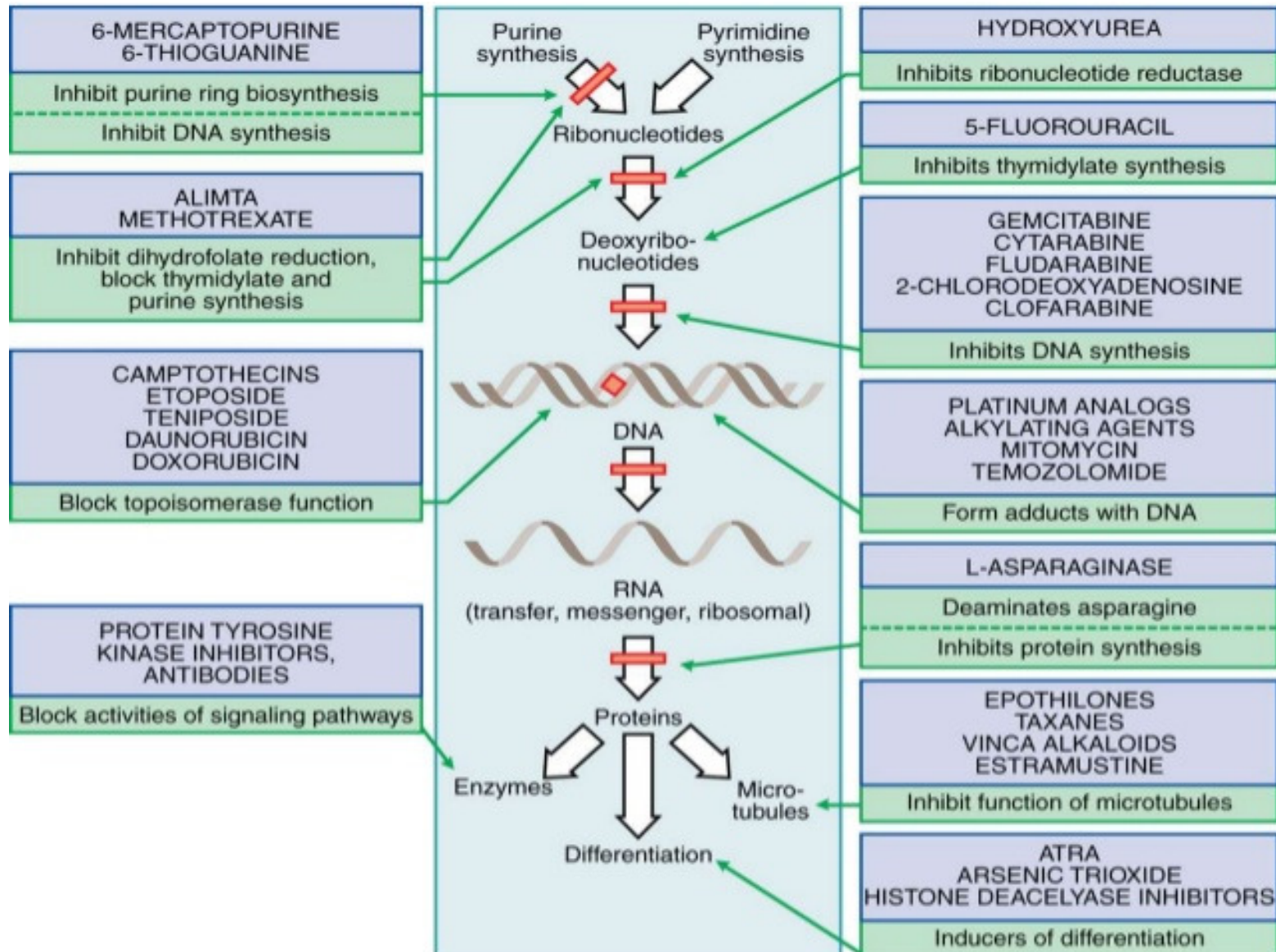


6-Diazo-5-oxo-L-norleucine
(DON)

Glutamine antagonist, isolated from *Streptomyces*
in Peruvian soil (1956, H. W. Dion et al.)



N-(phosphonacetyl)-L-Asp
(PALA)

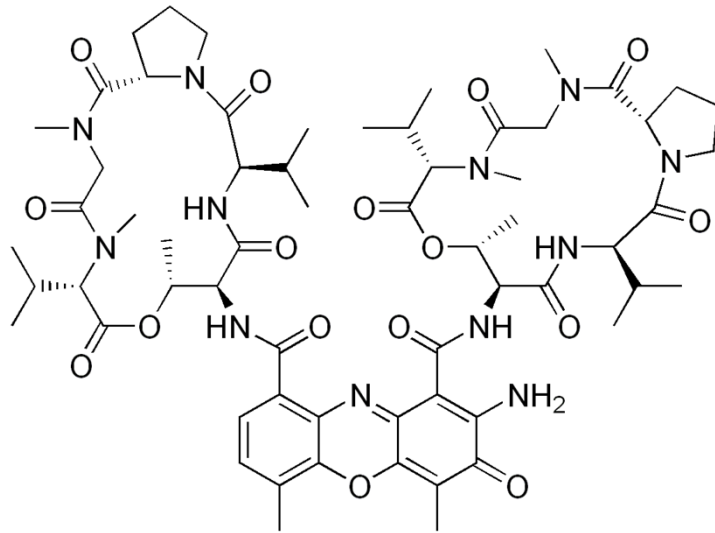


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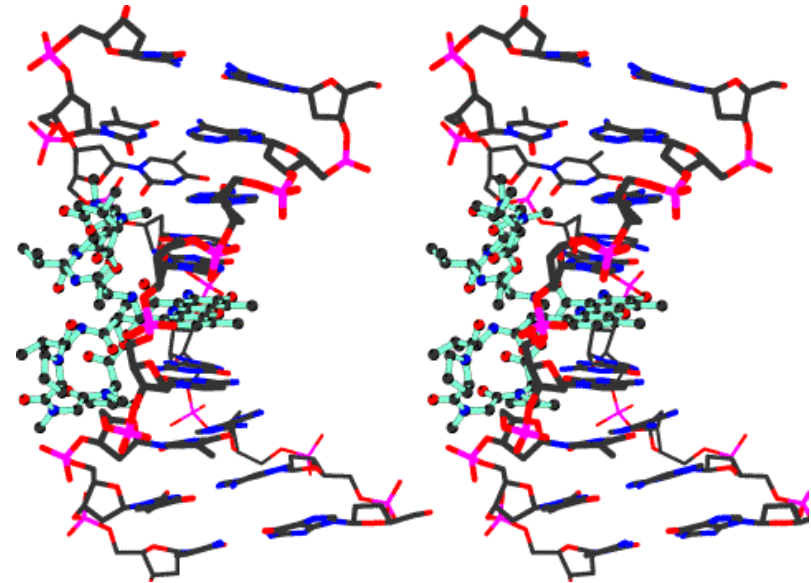
Antibiotics

Selman A. Waksman, (1940)
microbial origin (*Streptomyces rochei*)



Actinomycin D, (Dactinomycin) (1964)
The first antibiotic with anticancer effect

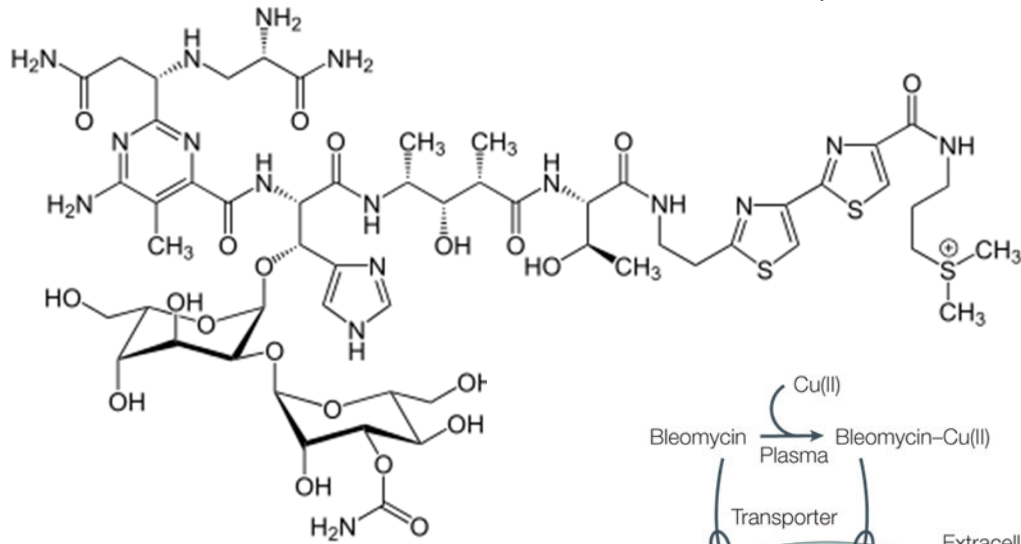
Hollstein, U.: "Actinomycin. Chemistry and mechanism of action". Chemical Reviews. 74 (6): 625-652 (1974)



DNA binding, inhibit transcription

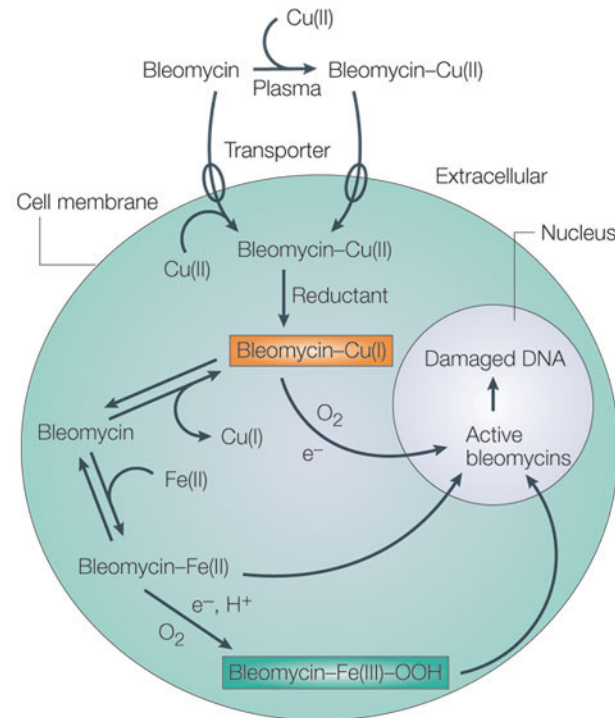
<http://crystal.res.ku.edu/~crystal/research/amd.html>

Antibiotics



bleomycin
(1962)

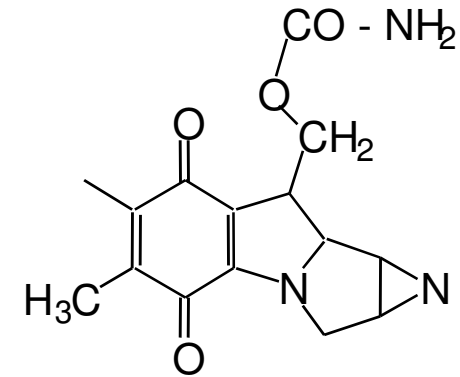
from *Streptomyces verticillus*



J. Chen & J.A. Stubbe:
Nature Reviews Cancer 5, 102-112 (2005)

Nature Reviews | Cancer

mitomycin C
[liver, kidney, bladder]



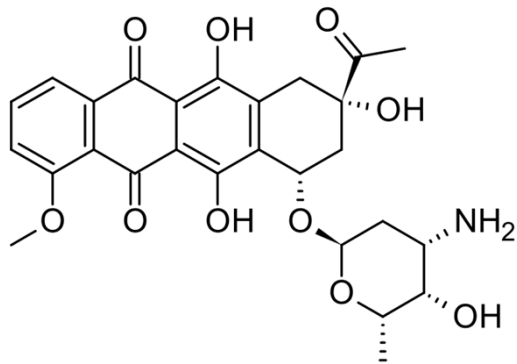
from *Streptomyces caespitosus*

bi- or tri-functional ALKYLATING AGENT
cross-linking of DNA and
inhibition of DNA synthesis.

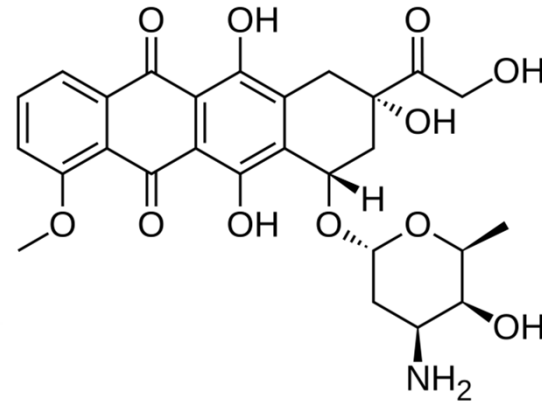
https://pubchem.ncbi.nlm.nih.gov/compound/mitomycin_C

Antibiotics - anthracyclines

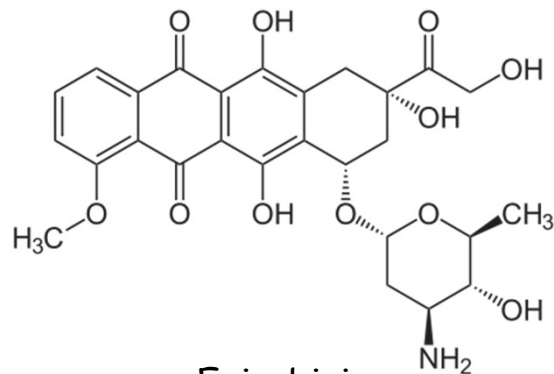
From *Streptomyces peucetius* (1960s)



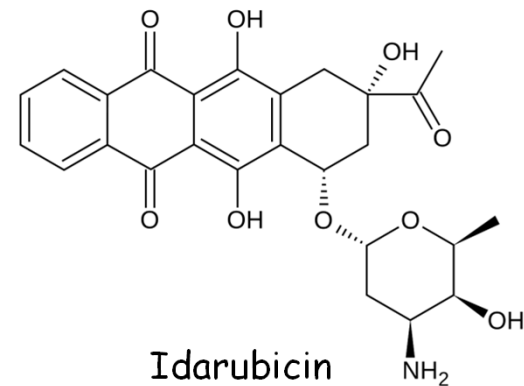
Daunomycin/daunorubicin



Doxorubicin



Epirubicin



Idarubicin

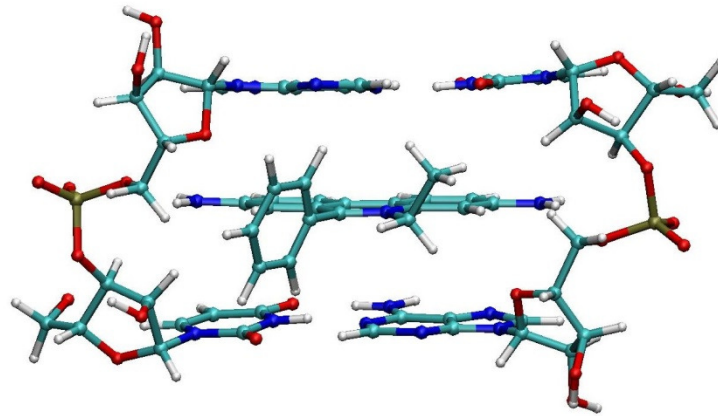
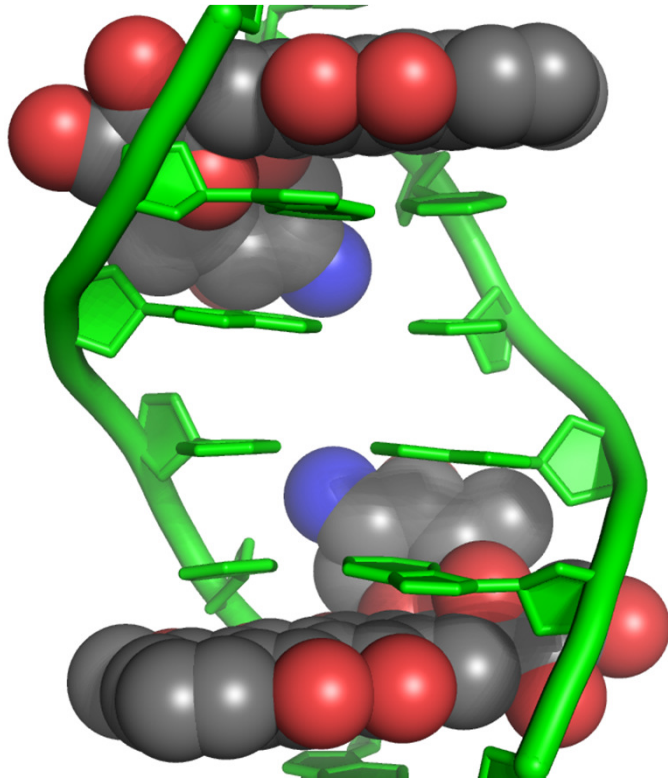


Combination therapy treatment: Colon carcinoma, breast cancer
(5-fluorouracil, doxorubicin, ciklofoszfamid), acute childhood leukemia

Minotti, G. et al. "Anthracyclines: Molecular Advances and Pharmacologic Developments in Antitumor Activity and Cardiotoxicity". *Pharmacological Reviews*. **56**: 185-229 (2004)

Antibiotics - anthracyclines

Aromatic polyketones,
Structure: four rings, 7,8,9,10- tetrahydro tetracen - 5,12-kinon



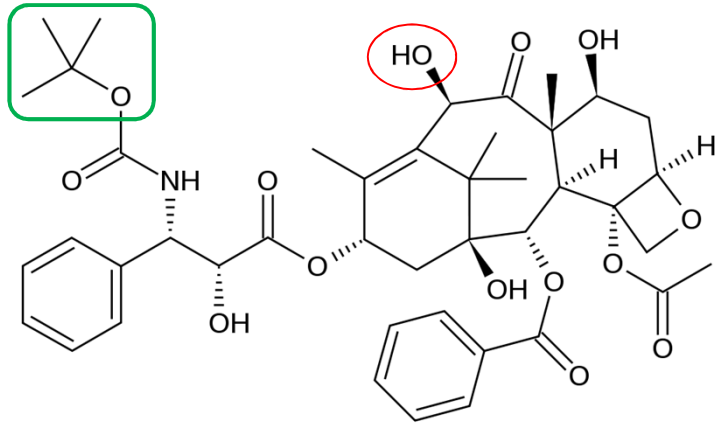
[https://en.wikipedia.org/wiki/Intercalation_\(biochemistry\)#/media/File:DNA_intercalation2.jpg](https://en.wikipedia.org/wiki/Intercalation_(biochemistry)#/media/File:DNA_intercalation2.jpg)

Diagram of two doxorubicin molecules intercalating DNA, from
<http://www.rcsb.org/pdb/explore/explore.do?structureId=1D12>

Classes of chemotherapeutic drugs

- alkylating agents
 - bis(chloroethyl)amines („mustards“)
 - nitrosourea
 - organometallic compounds
 - aziridines
 - alkylsulfonate (busulfan)
- antimetabolites (e.g. 5-F-uracil, methotrexate)
 - Folic acid analogues
 - Purine analogues
 - Pyrimidine analogues
 - Nucleoside analogues
- antibiotics (e.g. mitomycin C, daunomycin)
- **microtubule damaging agents**
- hormone related anticancer agents antagonists
- vitamins (A, C)

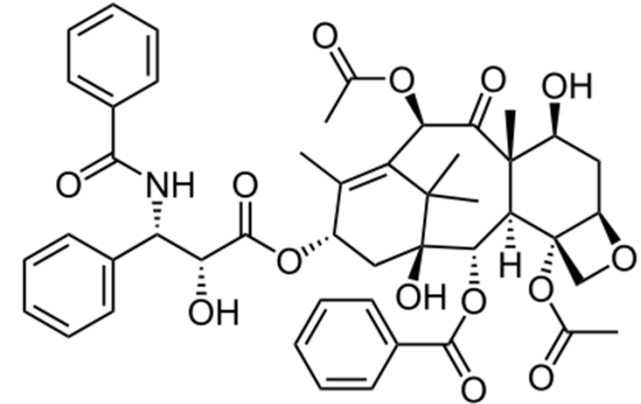
Antimitotic compounds: taxanes



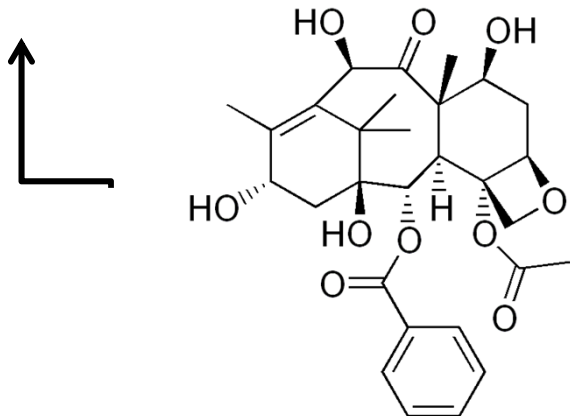
Docetaxel
(semisynthetic analog) patented 1986



Taxus brevifolia
(Pacific Yew)



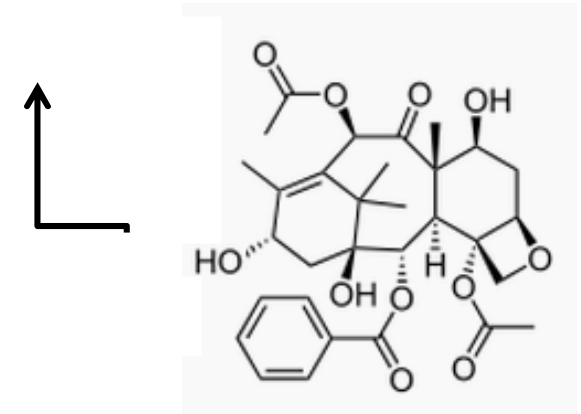
Paclitaxel



10-Deacetylbaccatin

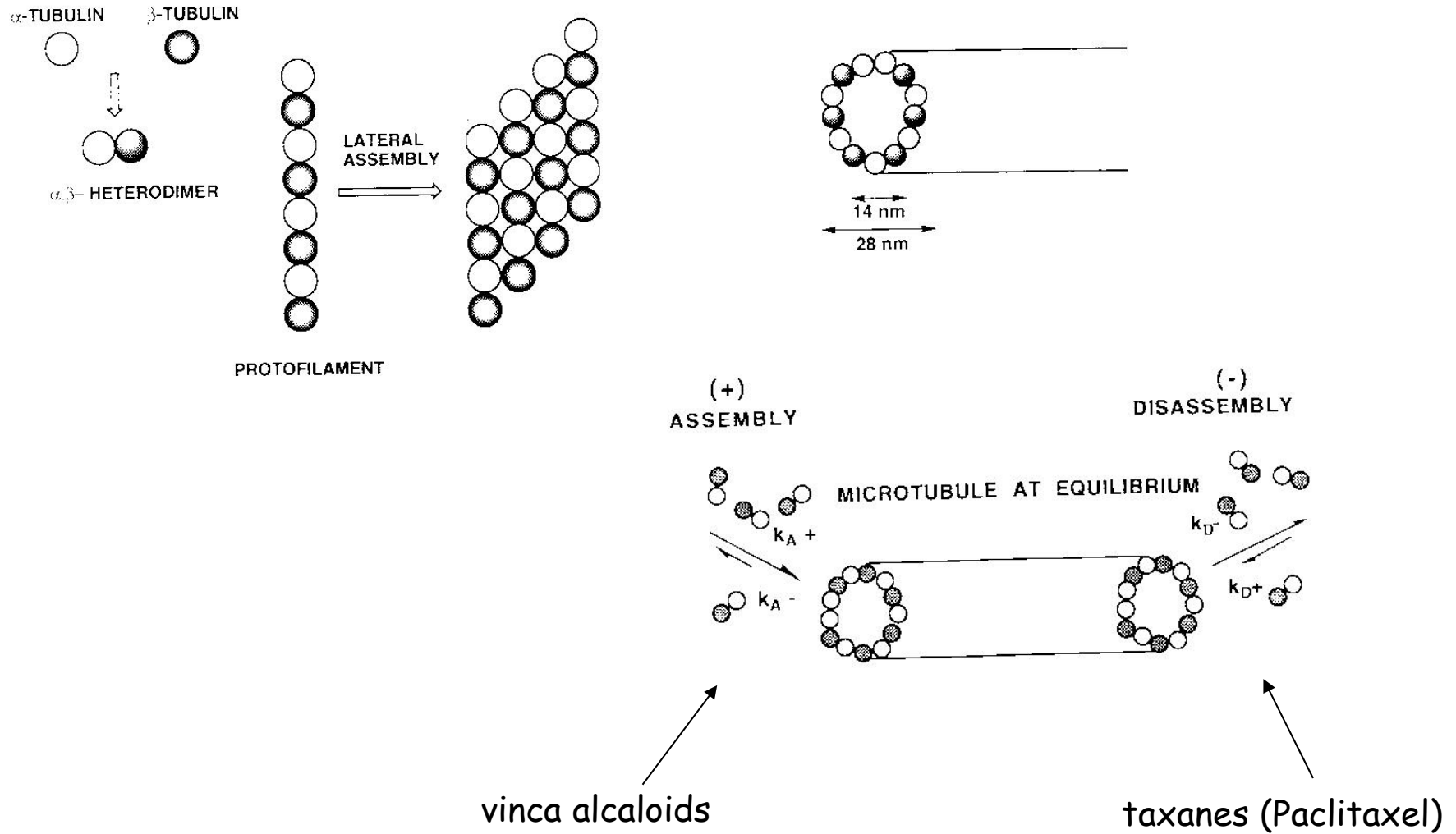


Taxus baccata (European yew)

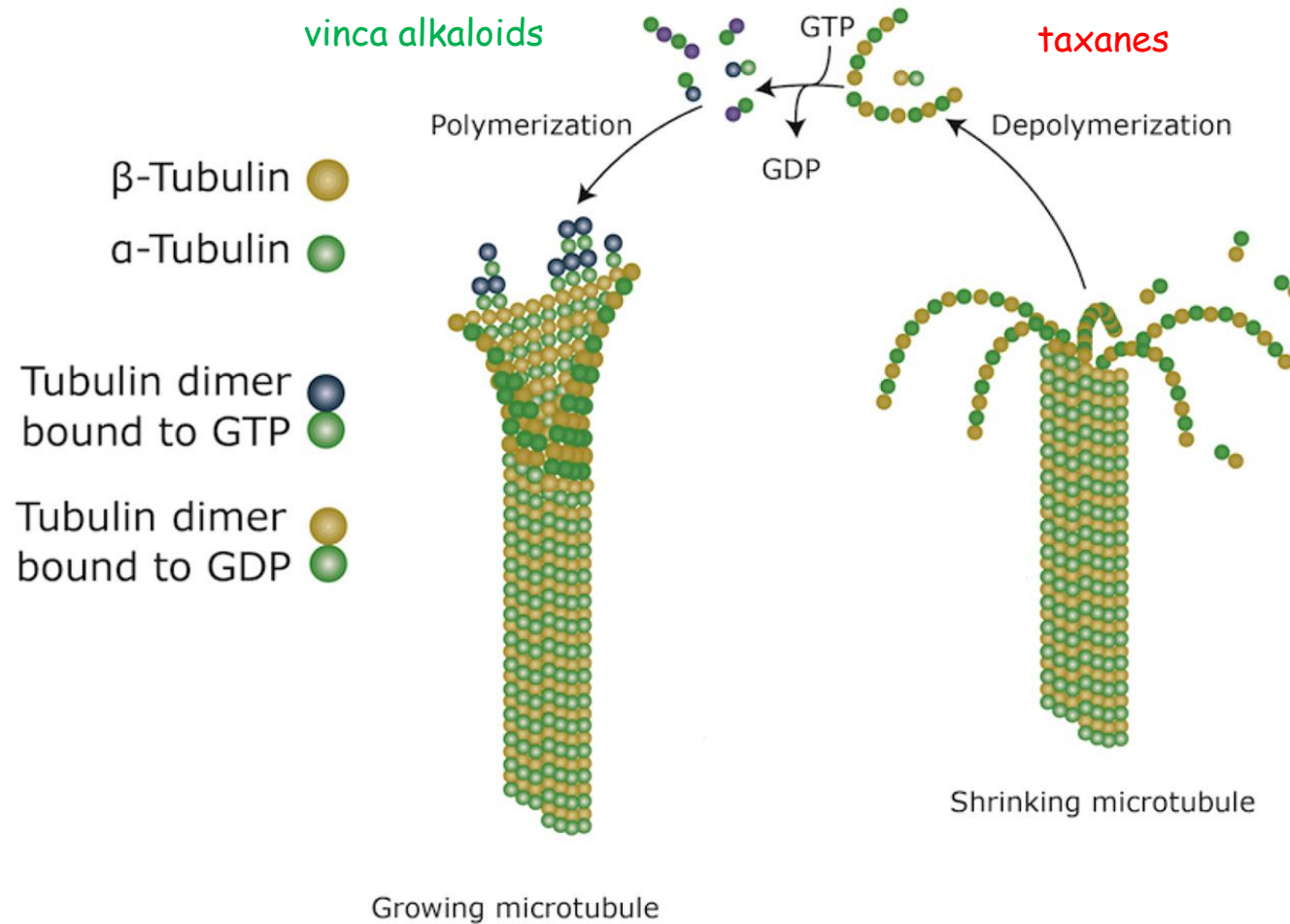


Baccatin III

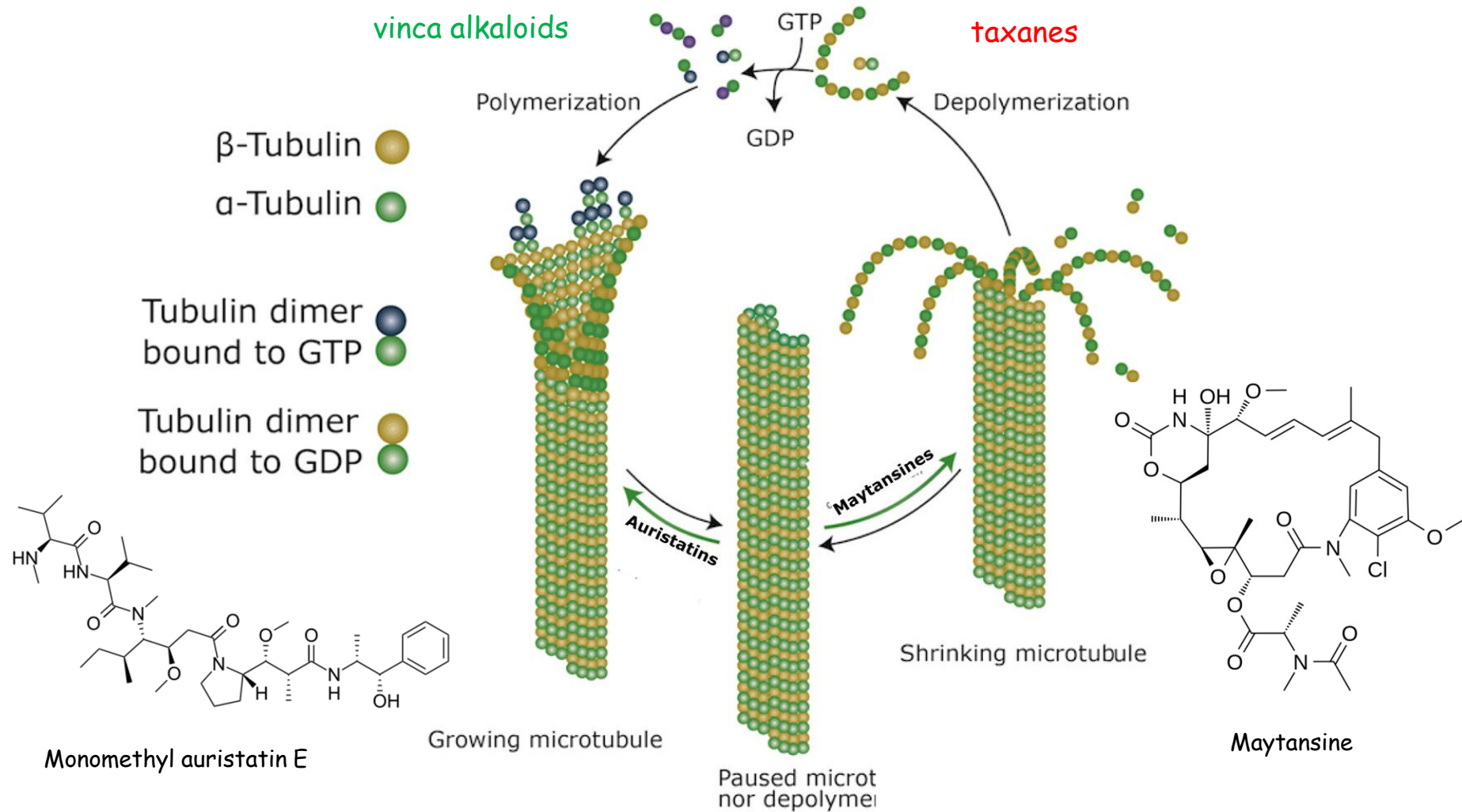
Mechanism of action: tubuline polymerisation



Effect of vinca alkaloids and taxanes on microtubule formation



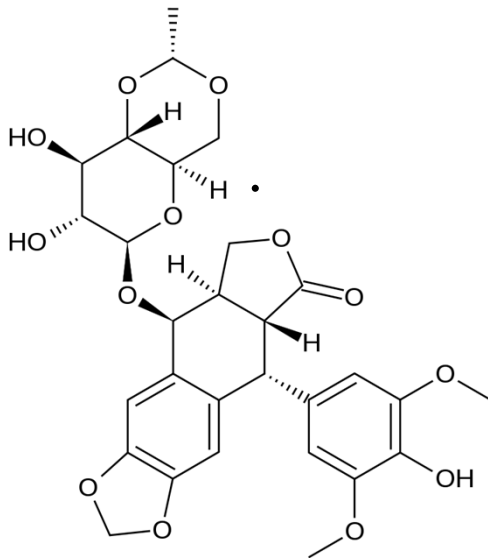
Effect of auristatins/maytansines on microtubule formation



Topoisomerase inhibitors

Topoisomerase - 1 inhibitors

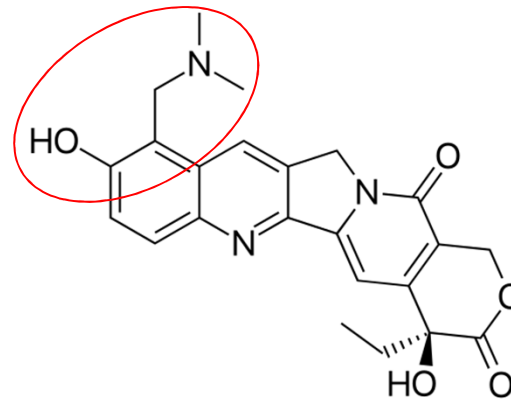
Etoposide
Teniposide



Etoposide (1983)

Topoisomerase - 2 inhibitors

Topotecan
Irinotecan



Topotecan (1996, ovarian, 2007, cervical)
(Camptothecin analogue)

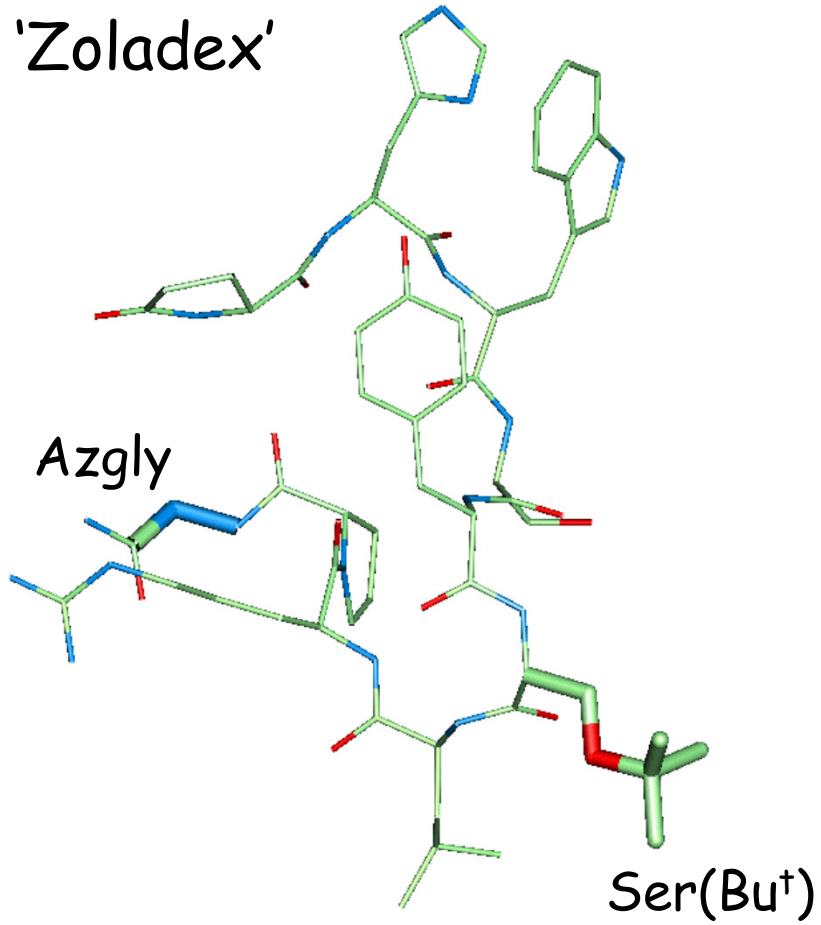
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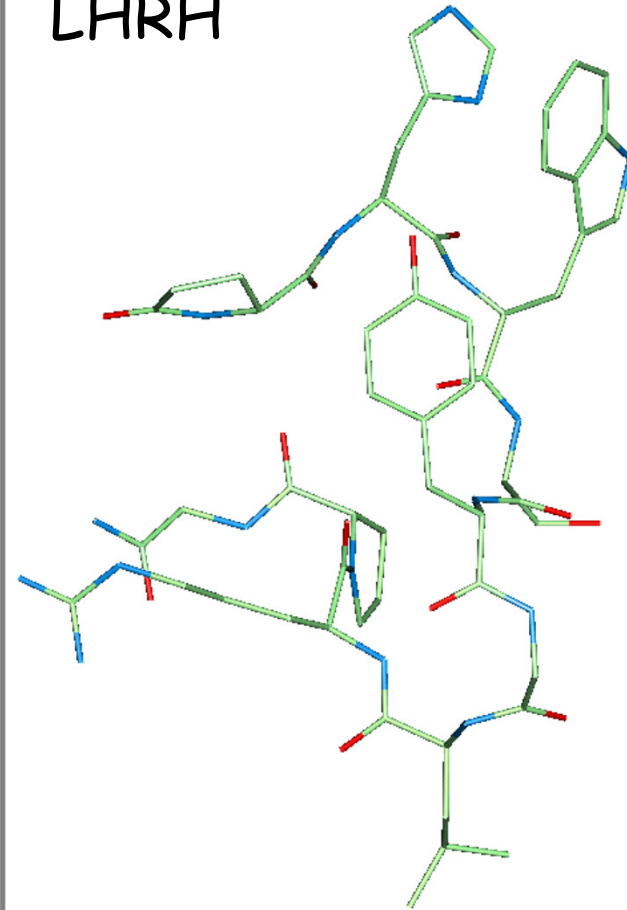
History

- 1890 Beatson/Schinzinger discovery: removal of the ovarium by surgery was helpful in the treatment of breast cancer
- 1958 Identification of estrogen receptor (E.W.Jensen, U. Chicago)
- 1960- Combined chemotherapy could be efficient in the treatment of breast cancer
- 1966 Isolation of estrogen receptor
- 1970- Introduction of tamoxifen
- 1971-72 Verification the role of LHRH (Schally/Guilleman)
- 1970- Synthesis of LHRH analogues, 'Zoladex' treatment equal to the removal of ovarium
- 1990 Permission for using 'Zoladex' (3.6mg) in advanced breast cancer patients
- 1999-2000 „NIH Consensus Statement“ : removal of ovarium could be an efficient treatment in women before menopausa, if the tumour is hormone sensitive.
- 2001 „St. Gallen Consensus“: LHRH analogues themselves or in combination with tamoxifen could be useful for treatment in women before menopausa, if the tumour is hormone sensitive.
- 2002 'Zoladex' 3.6mg: 100 countries, 70 000 patients/year

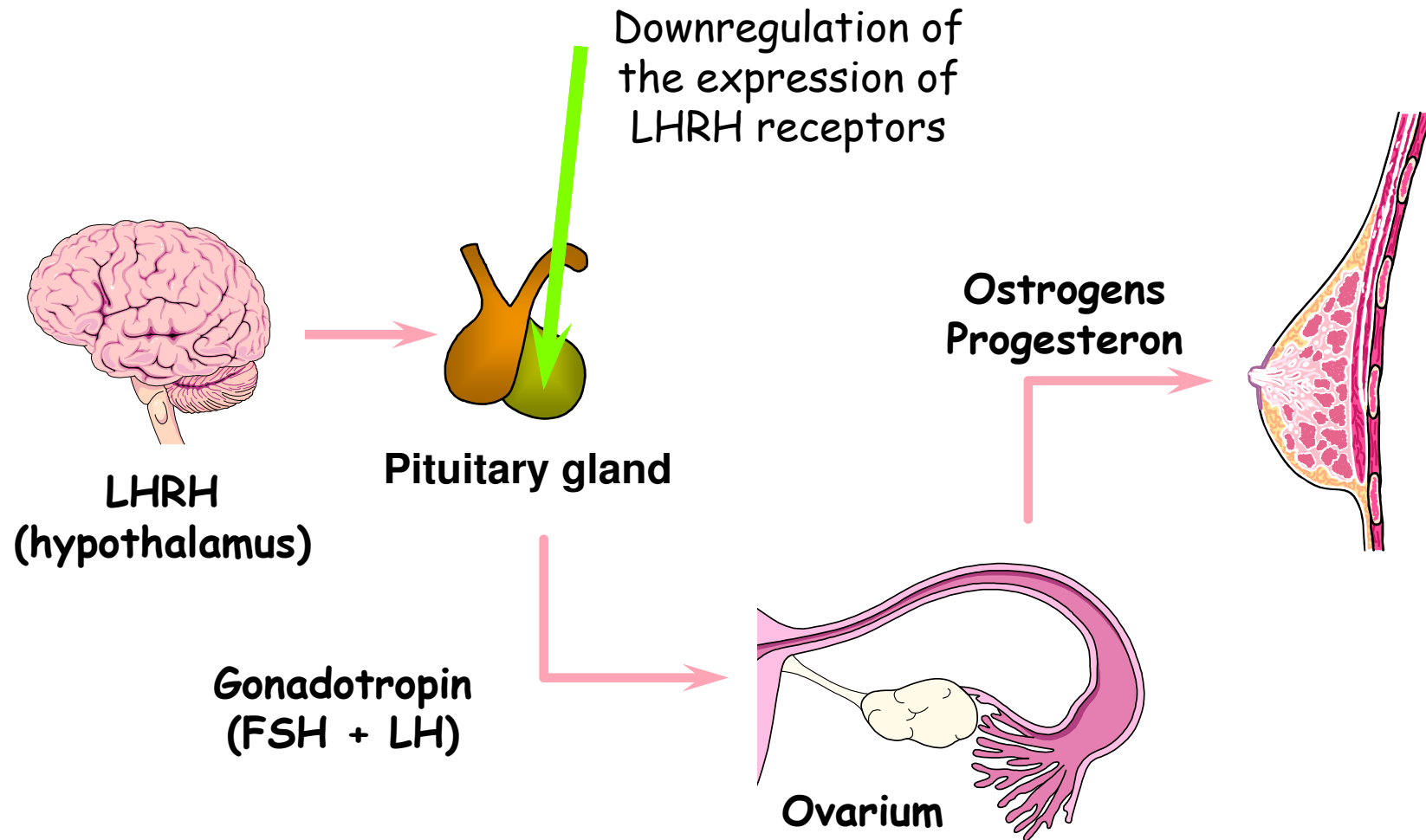
'Zoladex'



LHRH

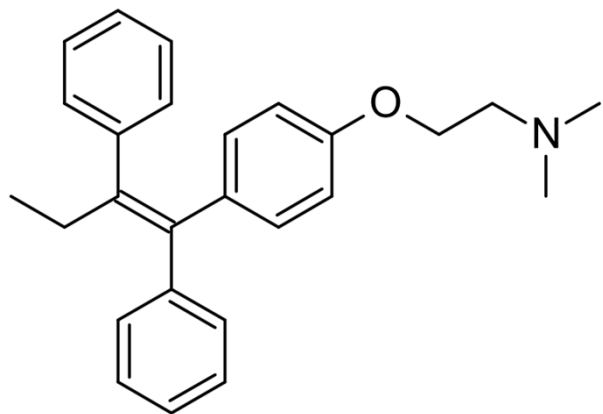


Mechanism of action



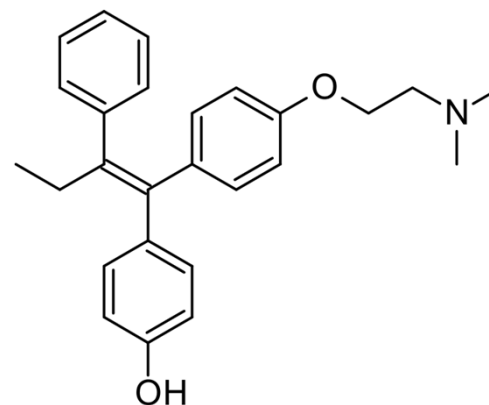
Hormone related anticancer agents antagonists

advanced estrogen receptor (ER)-positive
breast cancer

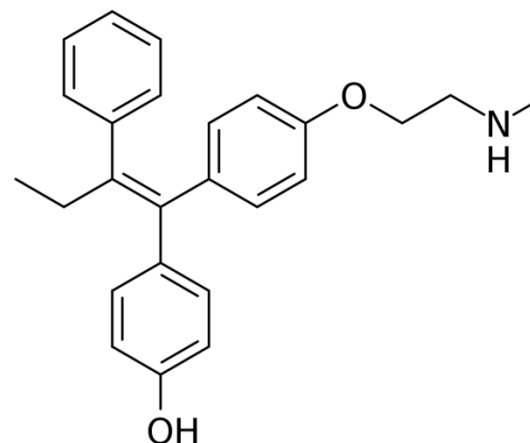


Tamoxifen (TMX), 1967
[pro-drug]

Liver
(P450 enzymes)



4-hydroxytamoxifen



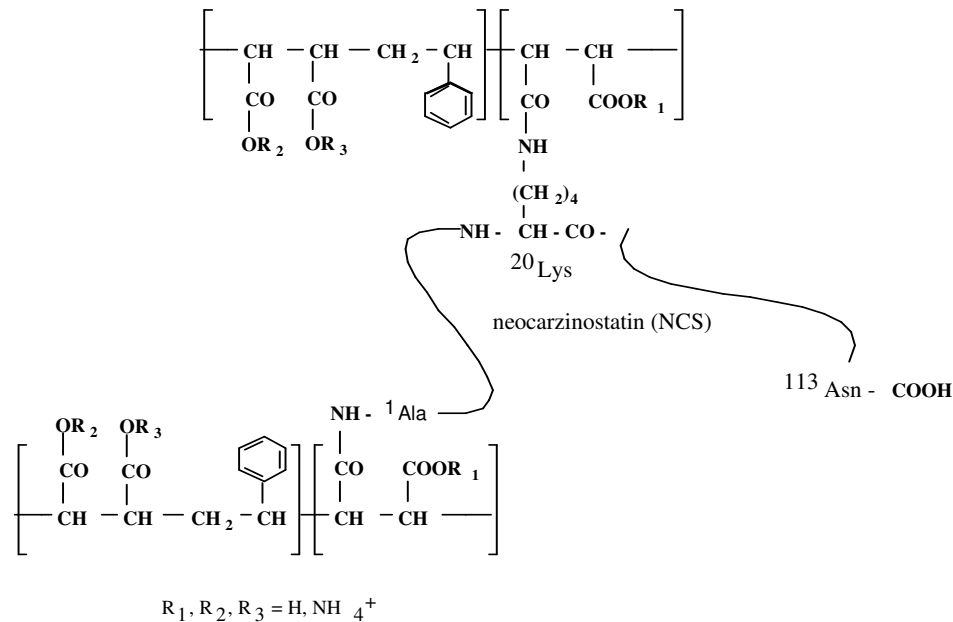
N-desmethyl-4-hydroxytamoxifen

J.A. Begam, S. Jubie, M.J. Nanjan:
Estrogen receptor agonists/antagonists in breast cancer therapy:
A critical review.
Bioorg Chem. 71:257-274 (2017). doi: 10.1016/j.bioorg.2017.02.011.

Polymer therapeutics

Poly(Glu_{1.4-1.8} Ala_{4.1-5.8}, Lys_{3.2-4.2} Tyr_{1.0}),
 Random copoly- alpha-amino acid, Mw = 7 250 D, Multiplex sclerosis,
 1997 Copaxone, TEVA Pharmaceuticals, Israel

Neocarzinostatin - copoly(styrole,maleic acid), SMANCS/Lipoidol®, Mw = 16 000 D
 Hepatocarcinoma,
 1995 Kuraray Ltd, Japan



Maeda, H. et al. (1985) *J.Med.Chem.* . 28: 455-461.

L-asparaginase - poly(ethylene glycol) (PEG), USA

Point of attack of antitumour agents

