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PHARM

Antineoplastics

Medicinal chemistry

Mgr. Aleš Kroutil

Content of the lecture

- Cancer – the dissease
- Classification of antineoplastics
  - Alkylating agents
  - Antimetabolites
  - Antibiotics
  - Topoisomerase inhibitors
  - Hormone-based drugs
  - Kinases inhibitors
  - Monoclonal antibodies
  - Other groups

Cancer

- Cancer isn‘t only one dissease
  - Different types of tissues
  - Different mechanisms of origin
  - Loss of control on cell growth (proliferation)
- Impossible to have one compound for all types of cancer
  - cancer is a common name for >100 tumors

Classification of antineoplastics

- Classification based on a target
  - DNA
    - DNA as the molecule
    - Synthesis of DNA
  - Metabolism of cancer cells
  - Hormones
  - Immune system

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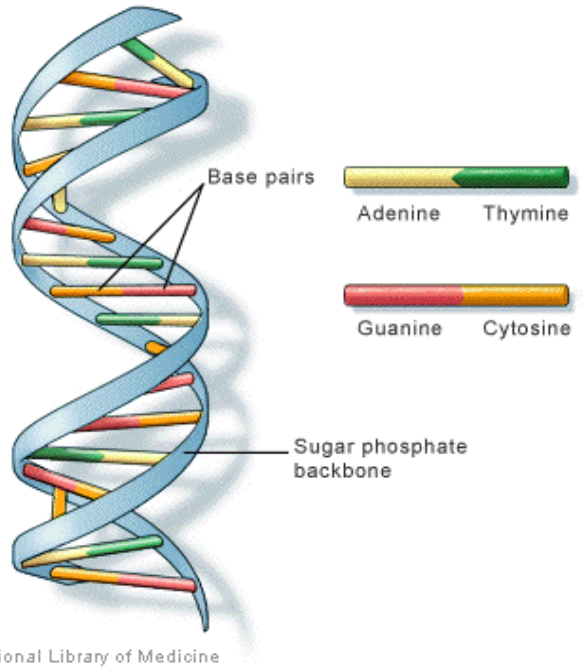
History

- Systemic chemotherapy of cancer began in the 1940s and 1950s
  - Nitrogen mustards developed from war gases
  - Antimetabolites based on early knowledge of DNA metabolism
- Large scale random screening programs
  - Natural cytotoxic products (anthracyclines, vinca alkaloids)
  - Synthetic analogs based on discovery of mechanism of action
    Topoisomerase inhibitors
- Increasing understanding of tumor physiology
  - Tumor-activated prodrugs
  - Targeted therapies
  - Monoclonal antibodies

DNA as the target of the therapy

- Modification of DNA molecule
  - Alkylating agents
  - Platinum complexes
  - Intercalators
- DNA synthesis
  - Antimetabolites
  - Enzymes inhibition



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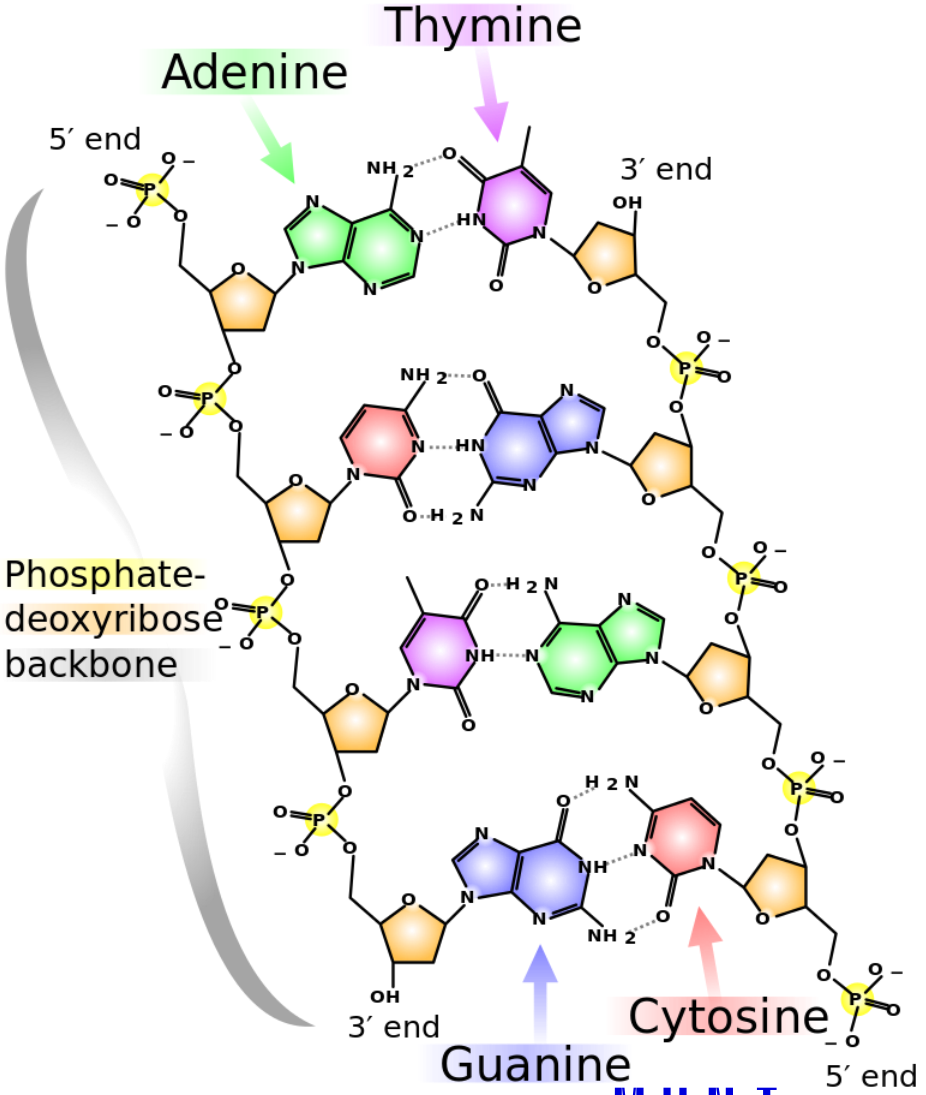

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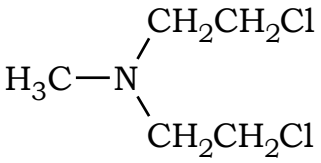
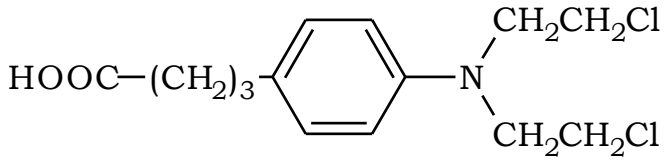
Alkylating agents

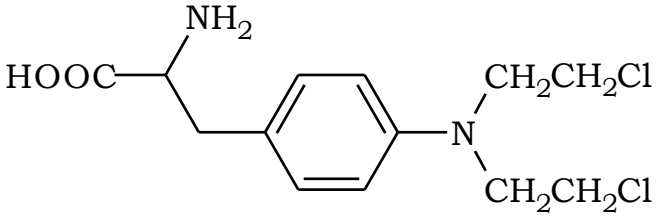
- Agents than can replace hydrogen atom by an alkyl group at physiological conditions
  - spontaneous or enzymatic origin of reactive carbenium ions
  - alkylation reaction with DNA or other molecules
- Potentially carcinogenic and mutagenic
  - the same mechanism as anticancer activity
- Severe adverse effects
  - strong effects on bone marrow – leucopenia, etc.
  - non-specific effect

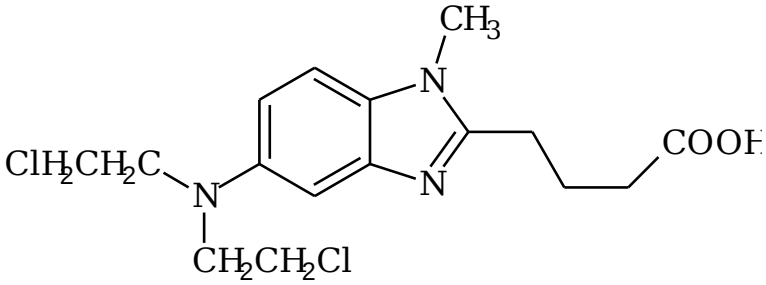
Alkylating agents – nitrogen mustards

- Based on mustard gas (yperite)
- Mechanism is interstrand cross-link between DNA purine bases
  - Mechlorethamine (1949)
  - Chlorambucil (1957)
    Therapy of leukaemias, Hodkin‘s disease
  - Melphalan (1964)
    ovarian and breast carcinoma
  - Bendamustine









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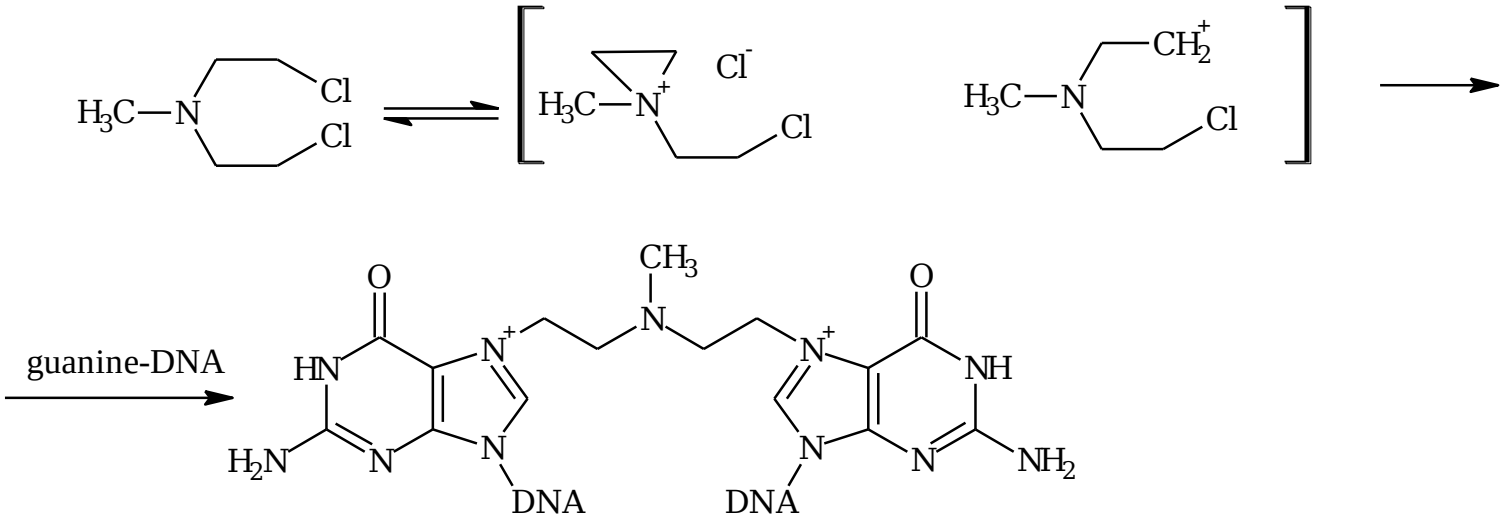
Alkylating agents – nitrogen mustards

- Mechanism of alkylation



- Not specific to cancer cells
- Affects all dividing cells

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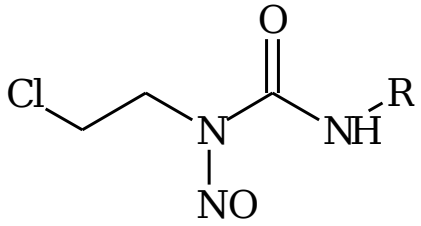
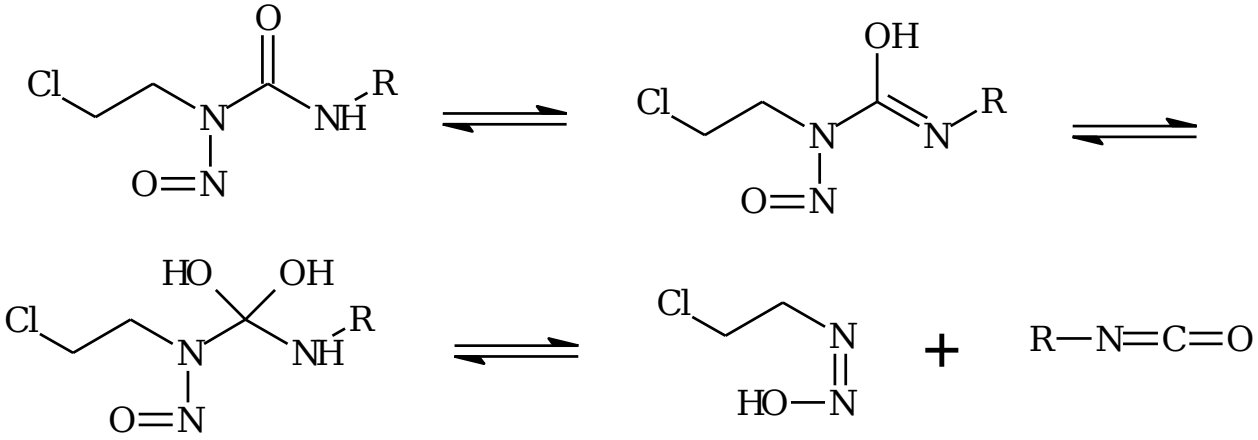
Alkylating agents – nitrosourea derivatives

- Active after metabolic activation
- Alkylating and carbamoylating activity
- Some derivatives active against brain cancers





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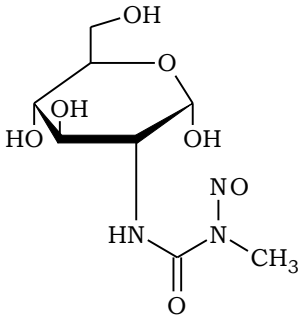
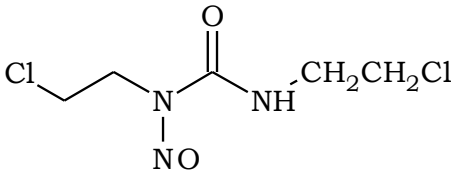
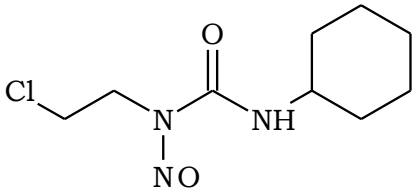
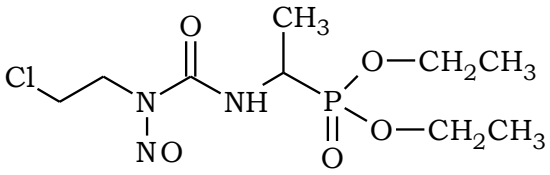
Alkylating agents – nitrosourea derivatives

- Streptozocine
  - antibiotics, isolated from *Streptomyces achromogenes*
  - pancreatic cancer
- Carmustine
  - high lipophilicity – effective against brain tumours
- Lomustine
  - simlar to carmustine, available after oral administration
- Fotemustine
  - primarily for brain tumours therapy









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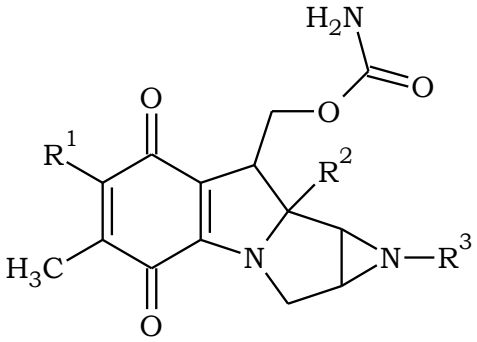
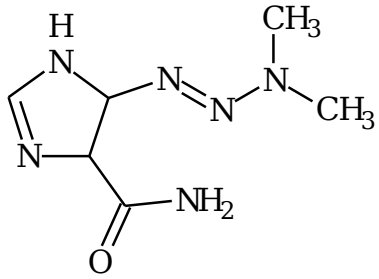
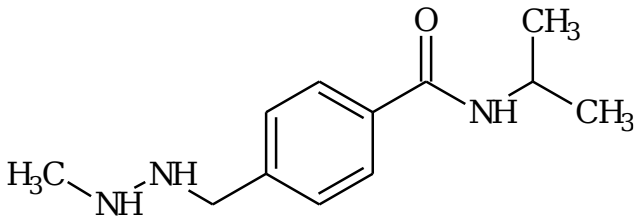
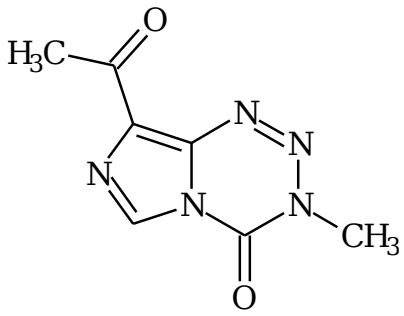
Alkylating agents – aziridines, triazines

- Mitomycines
  - effective after bioactivation
  - GIT and gynecological carcinomas
- Dacarbazine
  - malignant melanoma, etc.
- Procarbazine
  - effective in brain tumours
- Temozolomide
  - very good oral bioavailability
  - brain tumours









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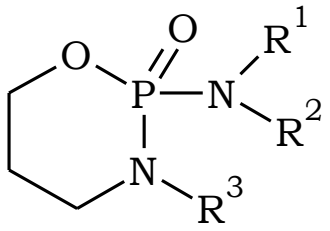
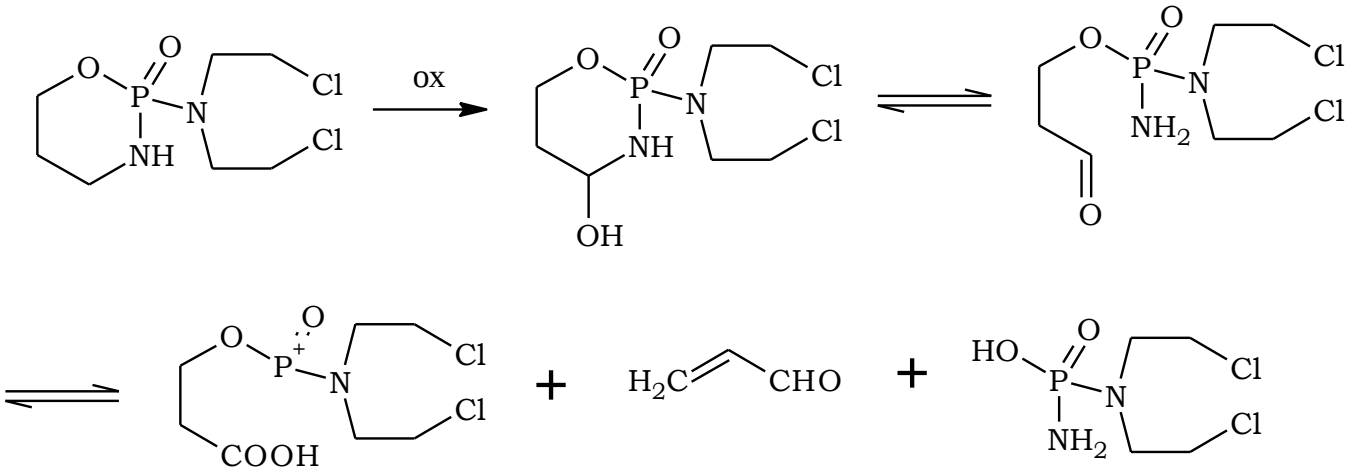
Alkylating agents - phosphamides

– Active after metabolic activation





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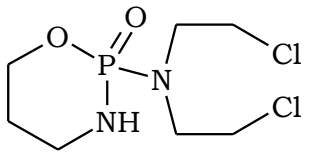
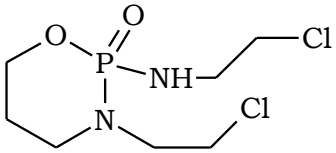
Alkylating agents - phosphamides

- Cyclophosphamide
  - good oral bioavailability
  - widely used for therapy of different tumours
  - leukaemias, solid tumours (breast, ovarian, testis)
- Iphosphamide
  - similar therapeutic spectrum as cyclophosphamide





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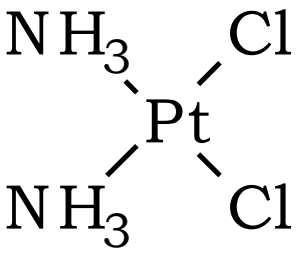
Platinum coordination compounds

- Coordination compounds
  - organic compounds as ligands
  - neutral complexes
  - geometrical isomerism – only *cis* derivatives are effective
- Platinum in oxidative state II or IV as the central atom
  - coordination number 4 in Pt(II) complexes
  - coordination number 4 in Pt(IV) complexes
- Alkylation-like mechanism of action

Platinum coordination compounds

- Cisplatin
  - First time synthesised by Peyron in 1845
  - Discovery of its anticancer efficacy by serendipity
  - Start of clinical evaluation in 1971
  - Marketed in 1978
  - Therapy of testicular cancer was the first indication
    - 80% efficacy in comparison with 5% of previous methods
  - Still widely used in therapy in combination with other antineoplastics
  - Severe side effects
    - nefrotoxicity
    - neurotoxicity
    - strong emetogenic effect



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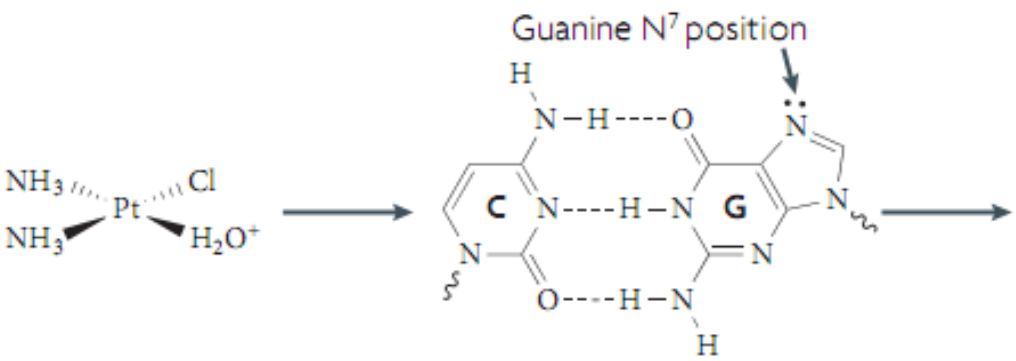
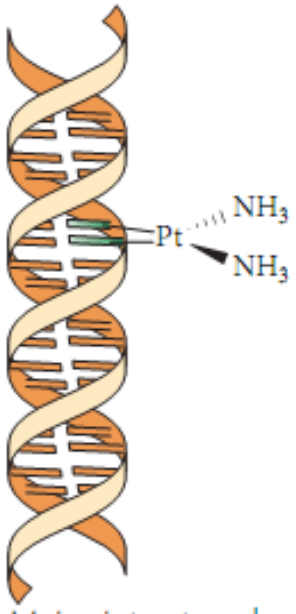
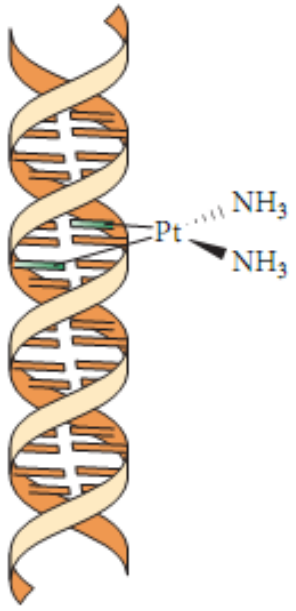
Platinum coordination compounds

- Mechanism of action
  - Intrastrand covalent bond to DNA purine bases
  - Reactivity of „leaving ligands“





Major intrastrand crosslink



Minor interstrand crosslink

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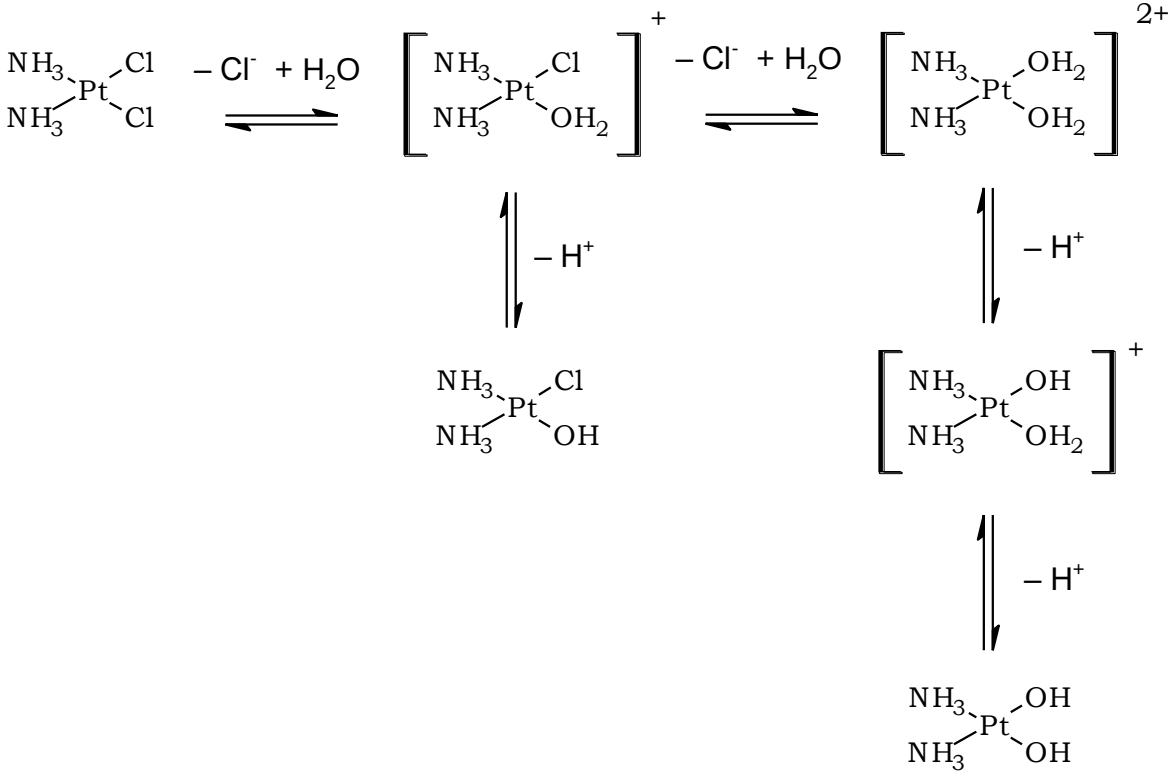
Platinum coordination compounds

- Mechanism of action
  - activation – aquacomplexes – very reactive



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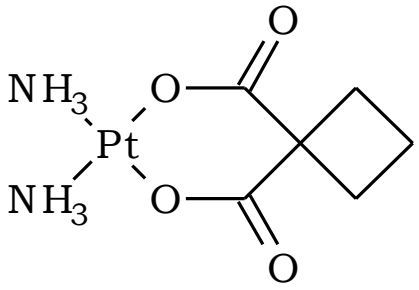
Platinum coordination compounds

- Carboplatin
  - Reduced toxicity, but also less effective
  - Significantly less nephrotoxic
  - Cross-ressistance with cisplatin
  - Similar indications as cisplatin



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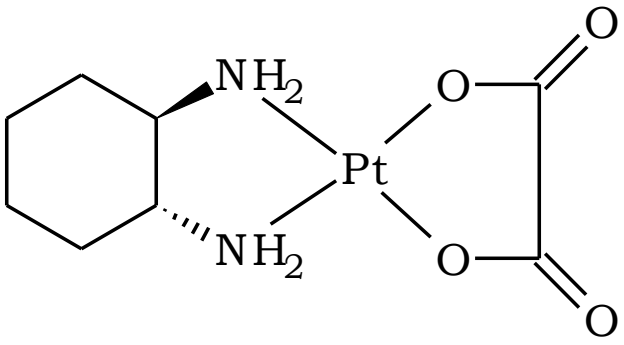
Platinum coordination compounds

- Oxaliplatin
  - First registration in 1996
  - Lack of nephrotoxicity
  - Dose limitting toxicity is neurotoxity
    Peripheral neuropathy
  - Therapy of colorectal cancer in combination with 5-fluorouracil



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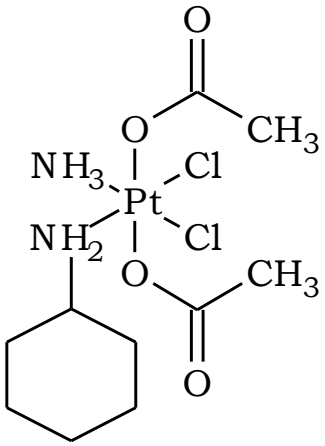
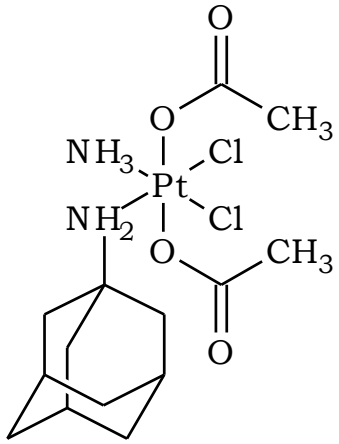
Platinum coordination compounds

- Orally available compounds
  - Platinum in oxidative state IV
  - Increased stability in GIT due to reduced reactivity
  - Reduction to platinum(II) compounds in cells (activation)
  - Overcomming resistance to cisplatin



satraplatin



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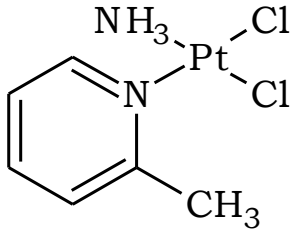

picoplatin

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Antimetabolites – folic acid

- Folic acid is needed for biosynthesis of nucleic acids

Source for one-carbon fragments

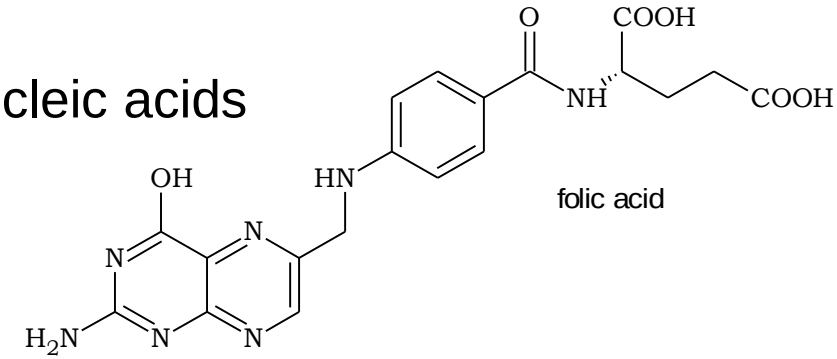
- Methotrexate

immunosuppresive agent
inhibition of tetrahydroflate reductase

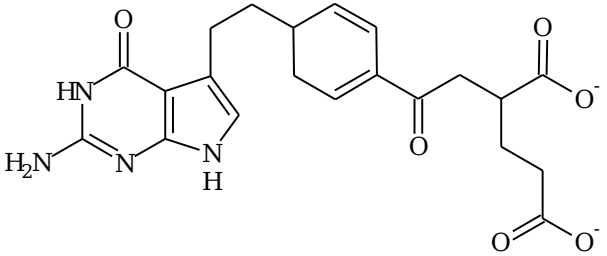
- Pemetrexed

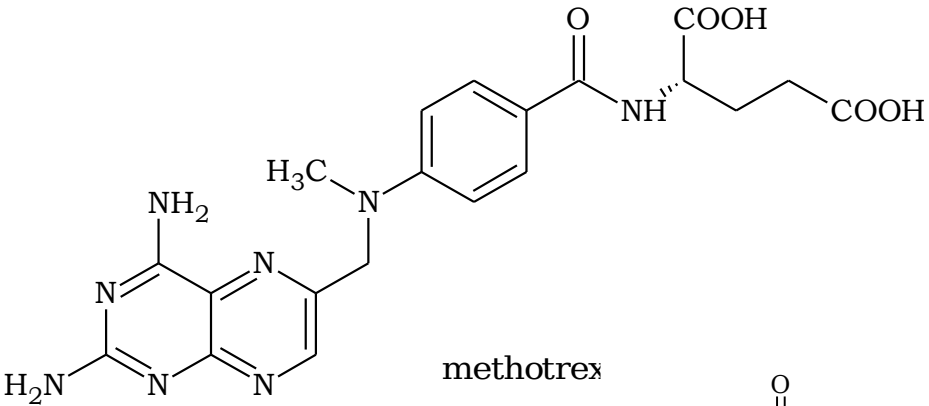
inhibition of more enzymes

- Raltitrexed
- Nolatrexed

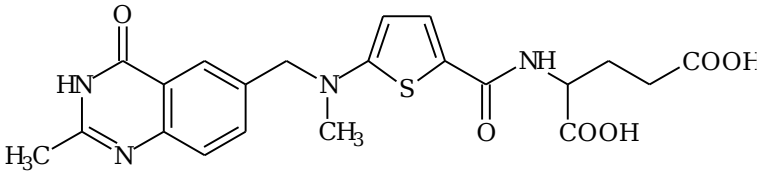


folic acid

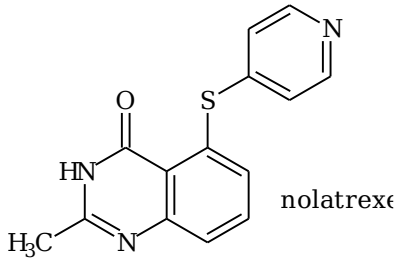




methotrex

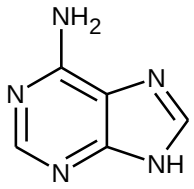


raltitrex

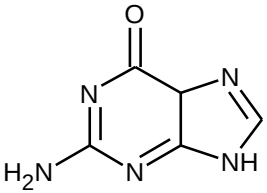


nolatrexe

Antimetabolites – purine bases



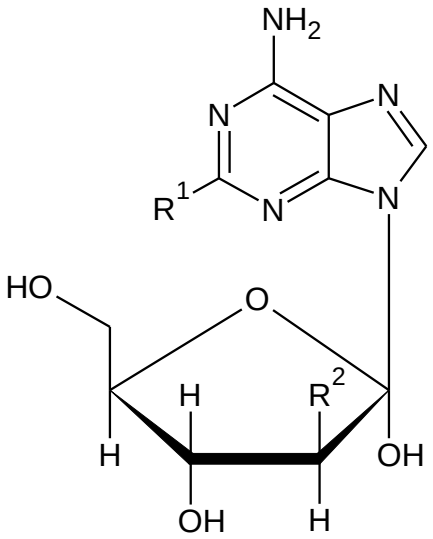
adenine

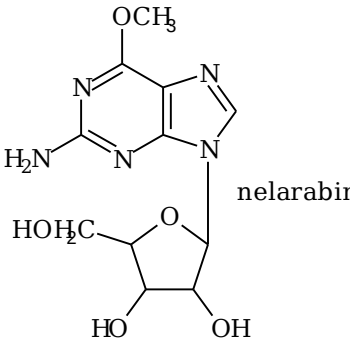


guanine

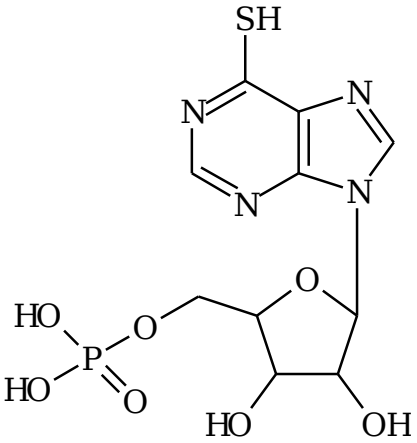
- R^1 = H; R^2 = OH – vidarabine (antivirotics)
- R^1 = F; R^2 = OH – fludarabine (leukaemia)
- R^1 = Cl; R^2 = H – kladribine (leukaemia)
- R^1 = Cl; R^2 = F – klofarabine (leukaemia)

- Activation by phosphorylation
  - Nelarabine
  - Mercaptopurine





nelarabin



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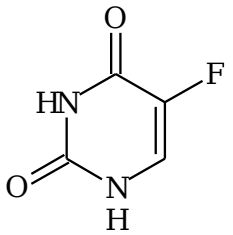
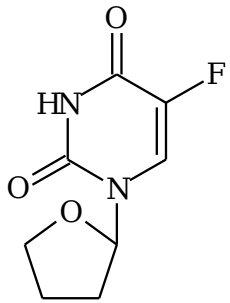
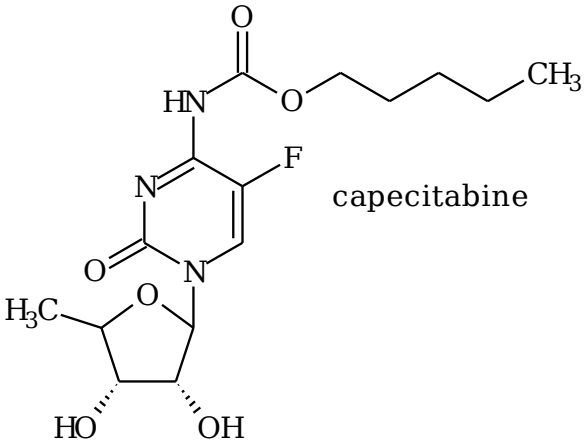
Antimetabolites – pyrimidine bases



- Uracile derivatives 5-halogene substitution
  - fluorine, event. bromine
  - iodine derivatives are antivirotics
  - 5-fluorouracil
    - i.v. administration
    - inhibition of RNA ant protein synthesis
    - breast, GIT and colorectal carcinomas
  - capecitabine
    - 5-fluorouracil prodrug



tegafur



capecitabine

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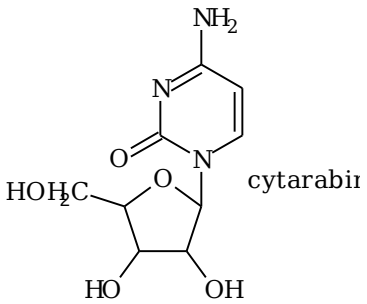
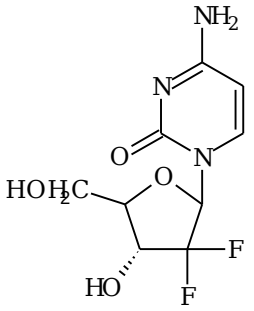
Antimetabolites – pyrimidine bases

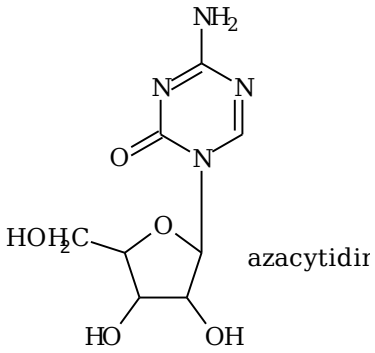
- Cytidine derivatives
  - cytarabine
    - arabinose instead of ribose
    - false nucleotide in DNA
    - i.v. administration
    - therapy of leukaemias
  - gemcitabine
    - bioactivation by phpsphprylation
    - pancreatic, bronchial, breast and bladder carcinoma
  - azacytidine
    - myelodysplastic syndrome



cytarabin



gemcitabine

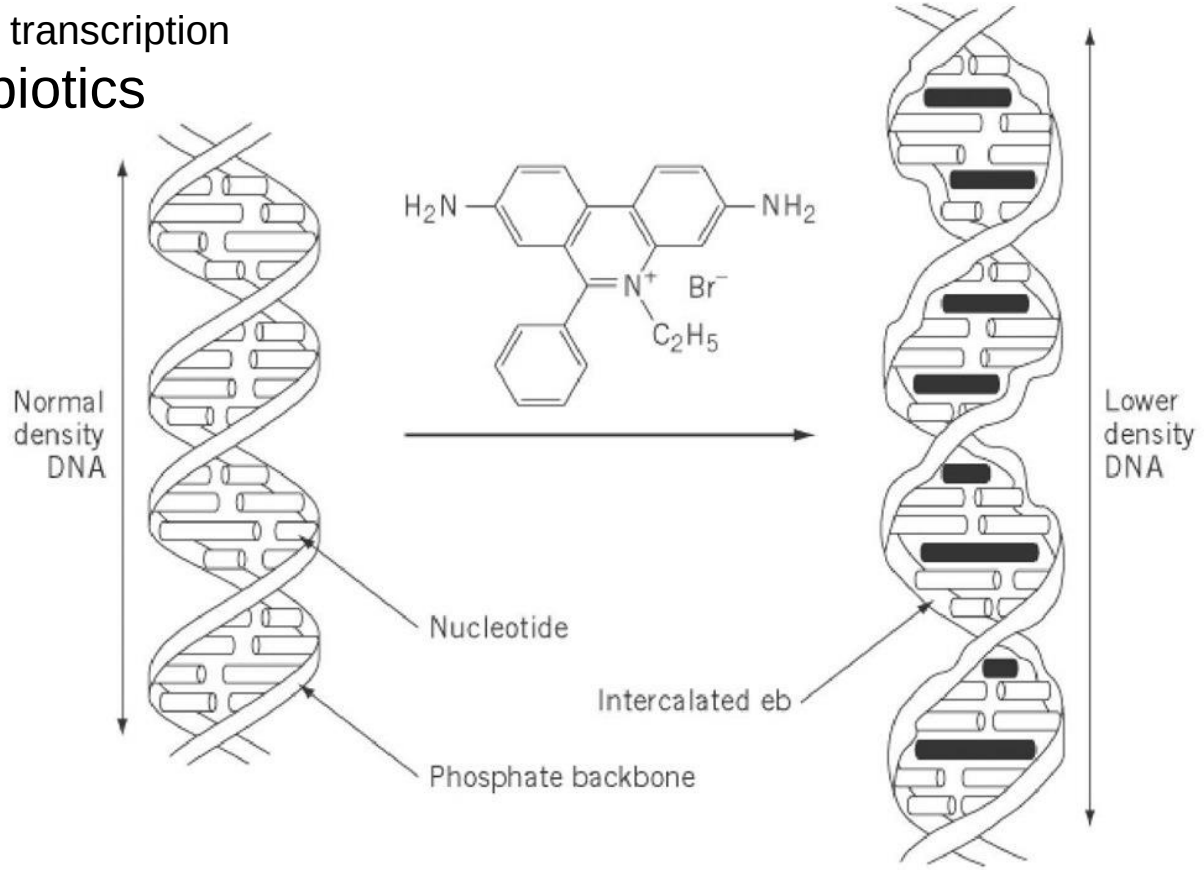


azacytidin

MUNI PHARM

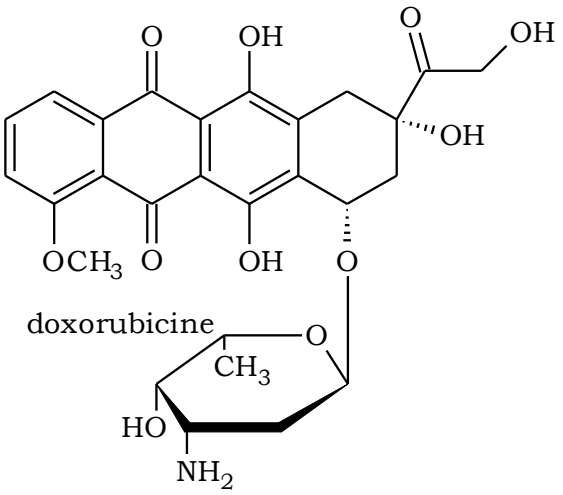
Intercalating agents

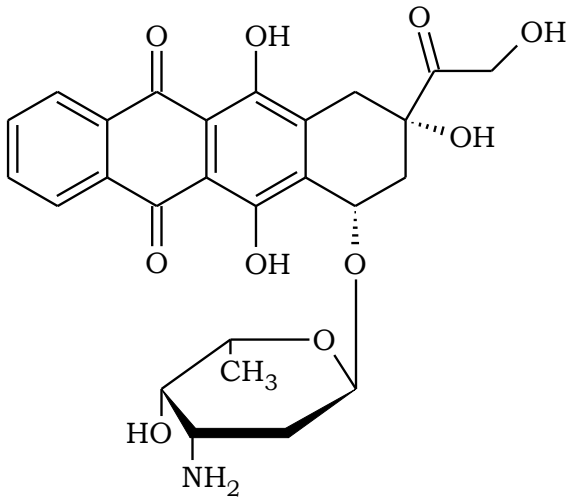
- Different structures
- Antibiotics ant its derivatives, synthetic compounds
- Intercalation
  - the compound inserts into DNA double helix
  - it blocks replication and transcription
- Anthracycline antibiotics



Intercalating agents

- Anthracycline antibiotics
  - doxorubicine
    - wide spectrum of cancer types
    - cardiotoxicity, myelosupression
  - epirubicine
    - epimere of doxorubicine
    - reduced toxicity
  - idarubicine
    - increased lipophilicity
    - acute myeloid leucaemia





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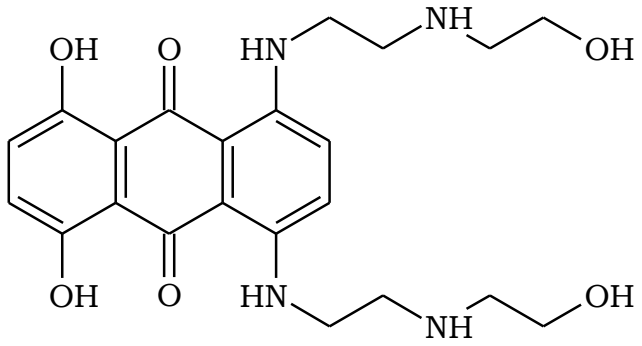
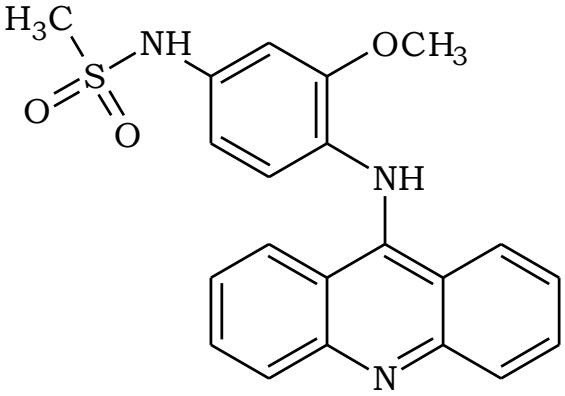
Intercalating agents

- Synthetic compounds
  - mitoxantrone
    - acute myeloid leucaemia, breast and other carcinomas
  - amsacrine
    - poor solubility
    - inhibition of topoisomerase

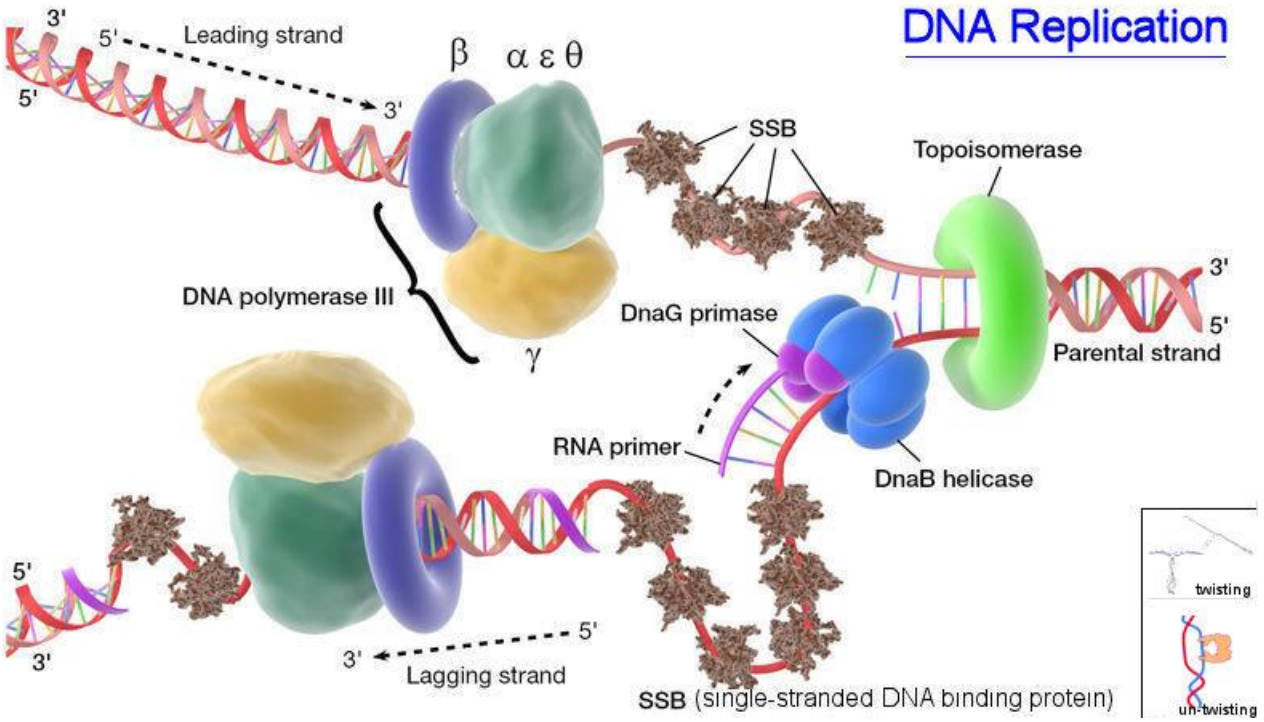




MUNI PHARM

Topoisomerase inhibitors

- Topoisomerases
  - control of topological arrangement of replicated DNA
  - inhibition of topoisomerase causes stable bonding of it to DNA
- Camptothecin and its analogues
- Podophylotoxine derivatives
- Some anthracyclines



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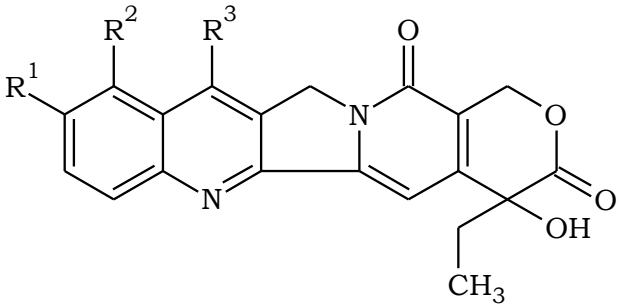
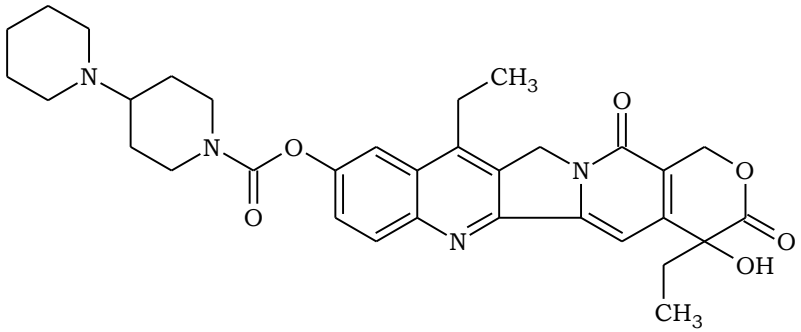
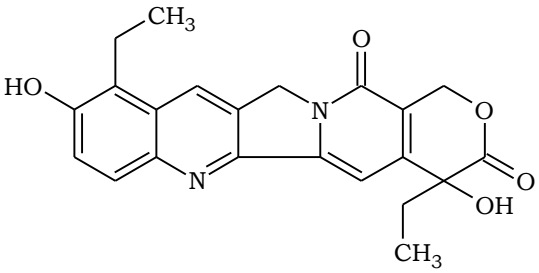
Topoisomerase inhibitors – camptothecins

- Camptothecin and its derivatives
  - pentacyclic structure
  - lactone ring is necessary for anticancer activity
- Irinotecane
  - good inhibitor
  - inhibes acetylcholinesterase too
  - advanced colorectal carcinoma
- Topotecane
  - i.v.administration
  - metastatic ovarian carcinoma, NSCLC



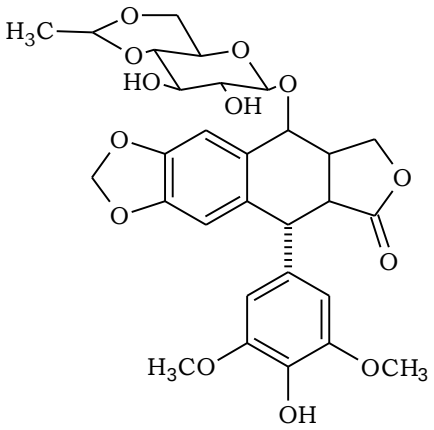


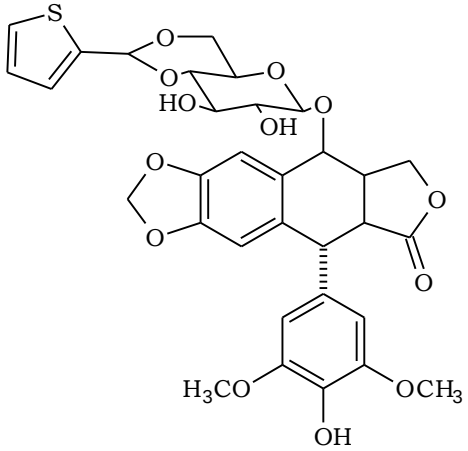


MUNI PHARM

Topoisomerase inhibitors – podophylotoxins

- Podophylotoxine is unusable fot the therapy, in clinical use are semisynthetical derivatives
- Etoposide
  - p.o. administration
  - lung carcinomas, leukaemias
- Teniposide
  - parenteral administration only
  - mitosis inhibitor



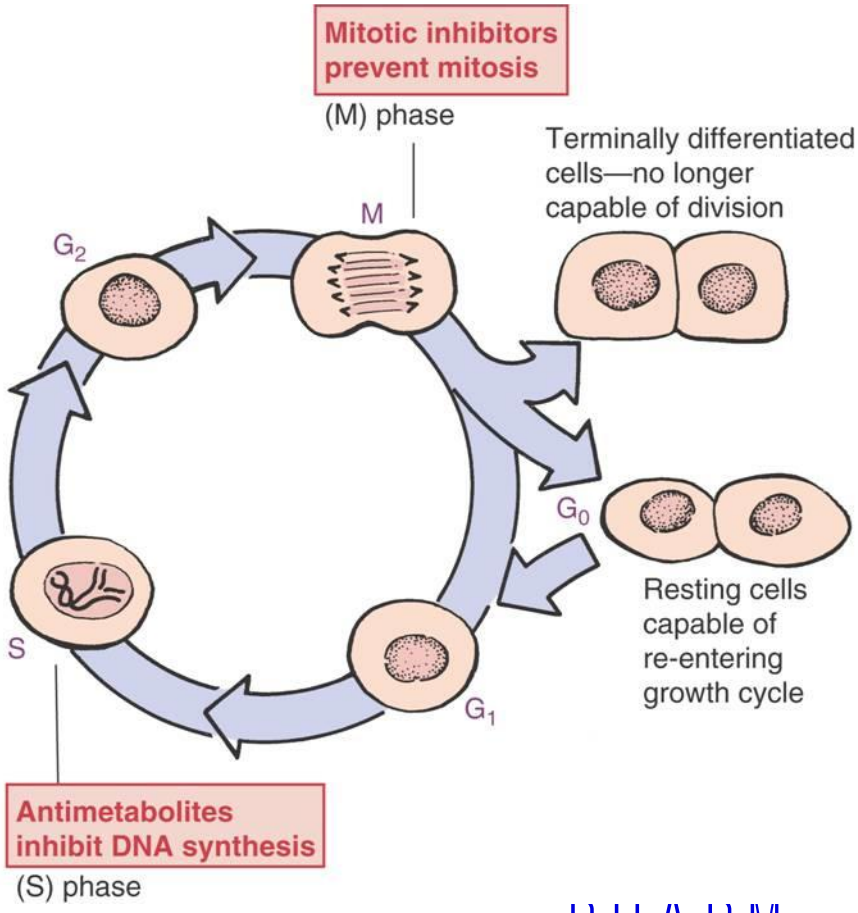


MUNI PHARM

Mitosis inhibitors

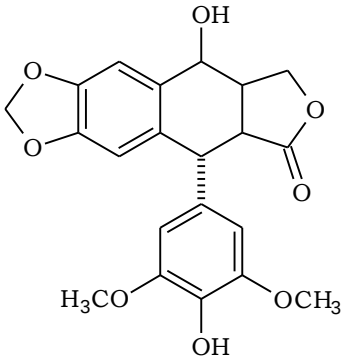
- Natural compounds of different structures
- Block of mitosis in M-phase
- Bonding to microtubules

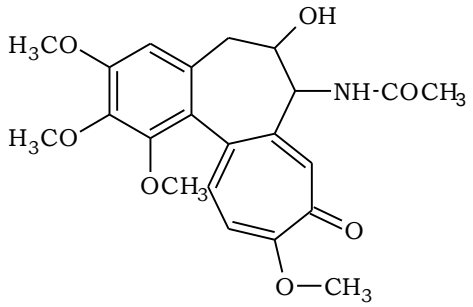
- Colchicum alkaloids
- Podophylotoxins
- Vinca-alkaloids
- Taxanes
- Epothilones

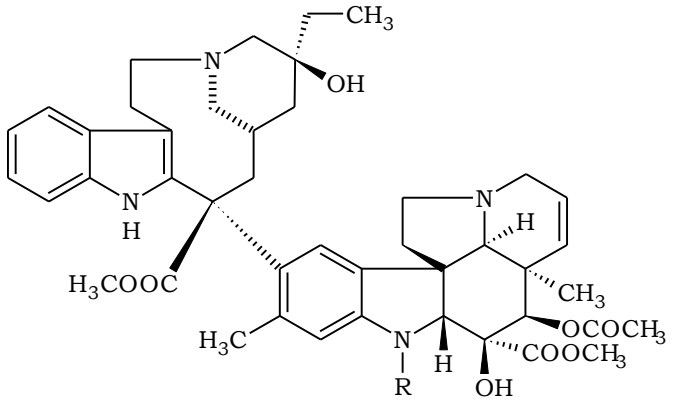


Mitosis inhibitors

- Colchicine
  - not used in therapy
- Podofylotoxin derivatives
  - glycosides
- Vinca alkaloides
  - vinblastine (CH_3)
    - parenteral administration
    - leukaemias, some solid tumours
  - vincristine (CHO)
    - acute leukaemia
  - vinorelbine
    - lung carcinoma (NSCLC)
    - metastatic breast carcinoma







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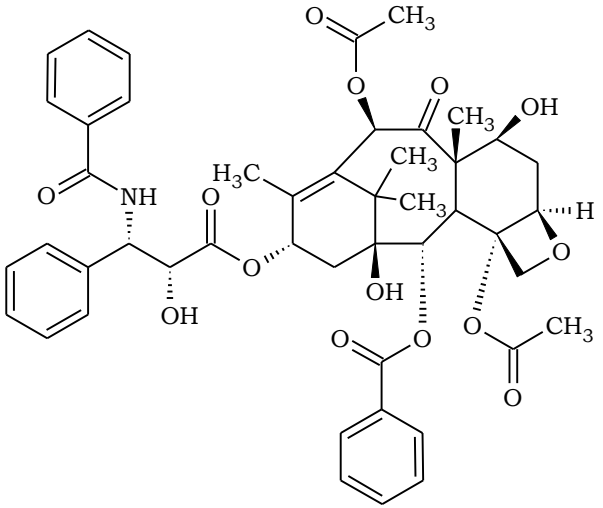
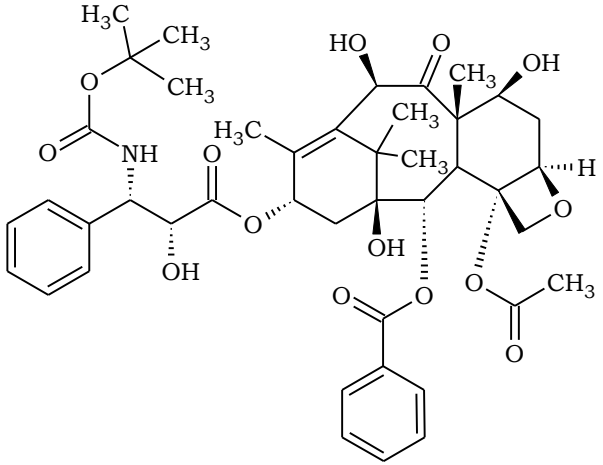
Mitosis inhibitors – taxanes

- Taxus brevifolia
  - stabilisation of microtubules
- National Cancer institute programme
  - technological problems, toxicological problems
- Paclitaxel
  - parenteral administration, poor solubility
  - advanced uterine carcinoma
  - breast and lung carcinoma
- Docetaxel
  - better efficacy in comparison with paclitaxel
  - indications the same as paclitaxel





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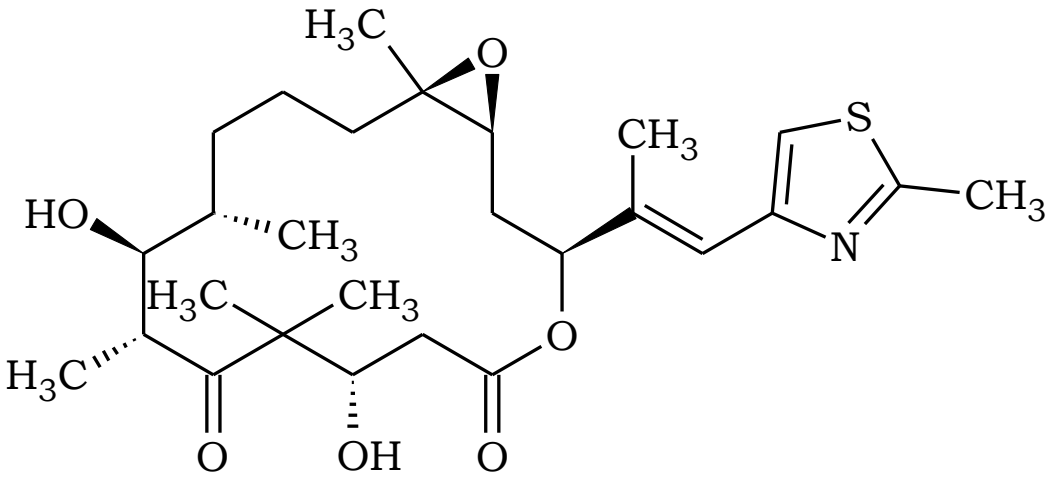
Mitosis inhibitors – other structures

- Epothilones
  - taxanes-like mechanism of action
- Ixabepilone
  - advanced breast carcinma
  - hepatic carcinoma



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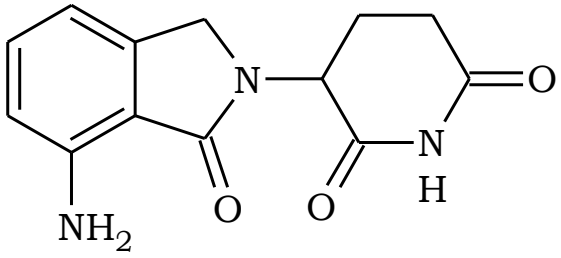
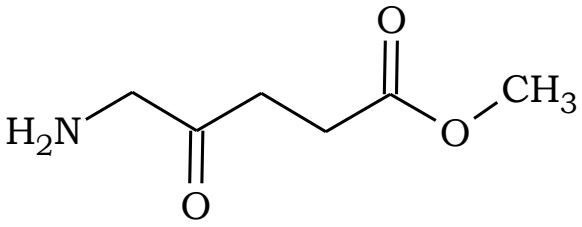
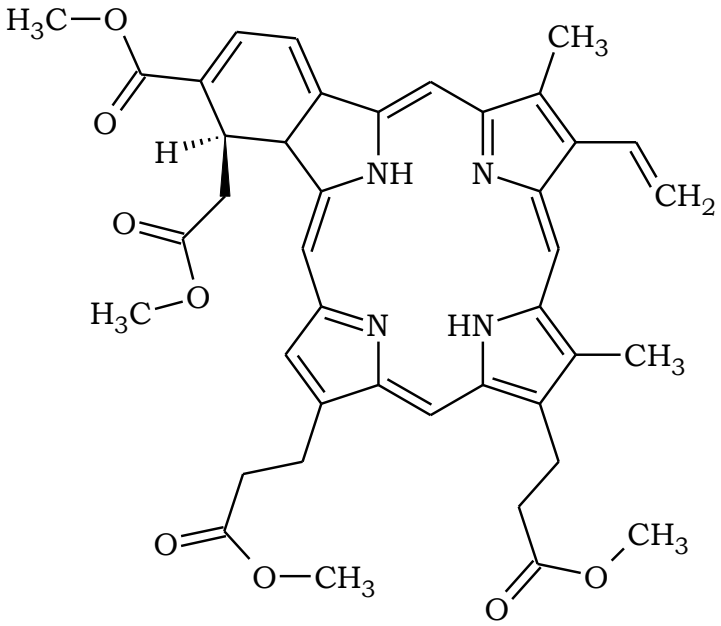
Other antineoplastics

- Lenalidomide
  - based on thalidomide
  - inhibition of cytokines
  - inhibition of angiogenesis
- Photosensitizers
  - Aminolevulinic acid
    Precursor of porphyrins
  - Porphyrins



lenalidomide

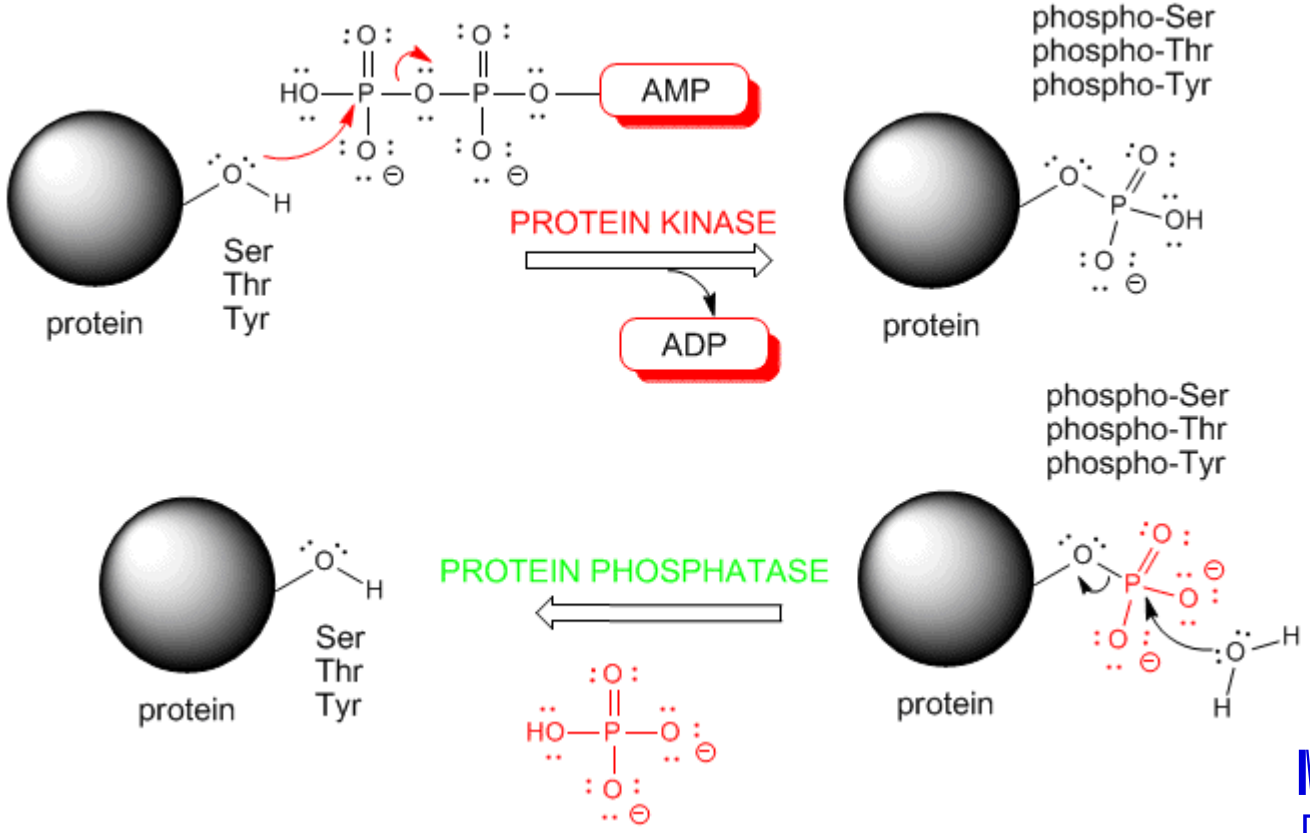




MUNI PHARM

Kinases inhibitors

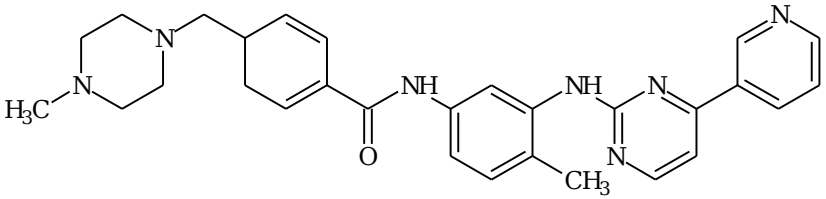
- Protein Kinases
  - Key regulators of cell function
  - By adding phosphate groups to substrate proteins, they direct the activity, localization and overall function of many proteins, and serve to orchestrate the activity of almost all cellular processes.

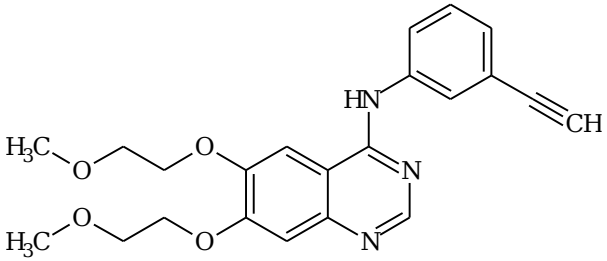


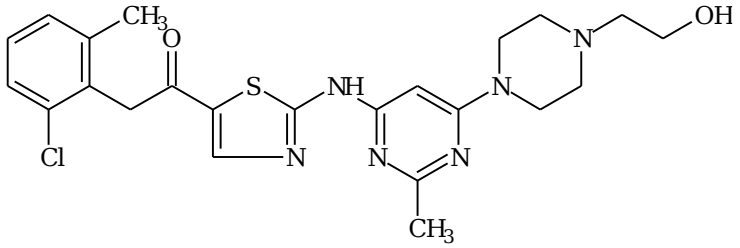
MUNI PHARM

Kinases inhibitors – tyrosinekinase inhibitors

- Imatinib
  - chronic myelogenous leukaemia
  - oral administration
- Erlotinib
  - oral administration
  - advanced or metastatic lung carcinoma
- Dasatinib
  - chronic myelogenous leukaemia
  - oral administration



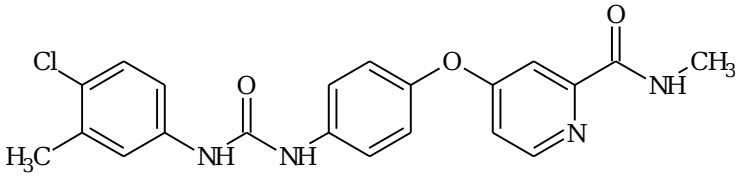


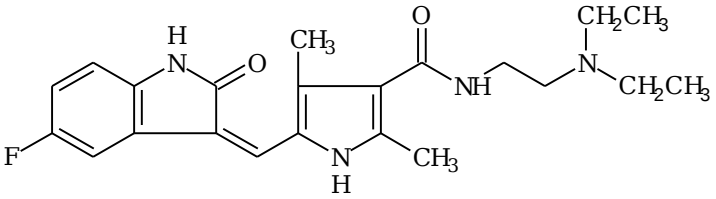


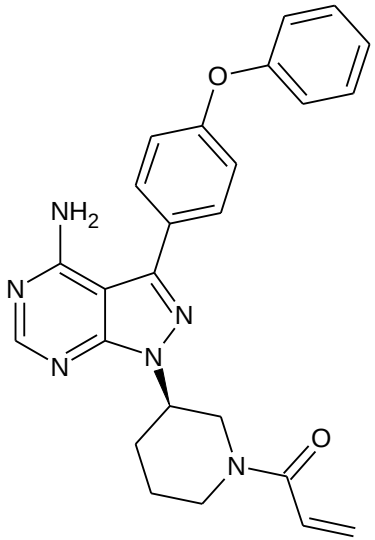
MUNI PHARM

Kinases inhibitors – tyrosinekinase inhibitors

- Sorafenib
  - multiple-kinases inhibitor
  - advanced kidney carcinoma
  - liver carcinoma
- Sunitinib
  - inoperable gastric tumours
  - advanced kidneys carcinoma
- Ibrutinib
  - Lymphoma
  - Chronic lymphocytic leukaemia



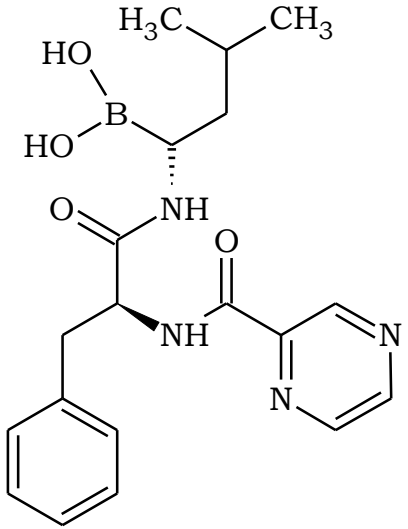


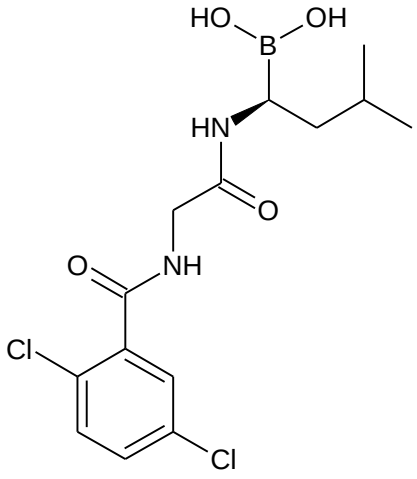


MUNI PHARM

Proteasome inhibitors

- Bortezomib
  - proteasomes eliminate singaling and regulating proteins
  - cancer cells are more sensitive to proteasome inhibition
  - therapy of advanced multiple myeloma
- Ixazomib
  - multiple myeloma (bone marrow cancer), in combination chemotherapy with lenalidomide and dexamethasone

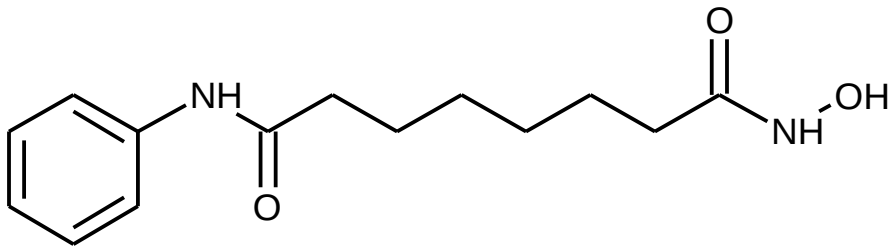




MUNI PHARM

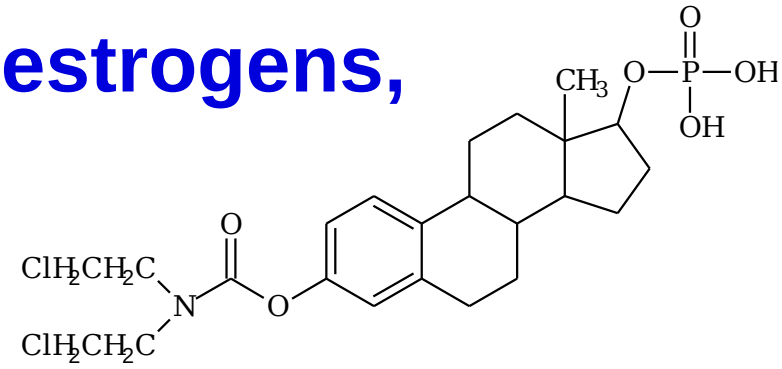
Histonedeacetylase inhibitors

- DNA is surrouded by histones and creates nucleosomes
  - protection of DNA
- Histones are basic proteins
- Acetylation and deacetylation regulate accessibility of DNA for some enzymes
- Inhibitors of histone deacetylase are used for treatment of haematological cancers
- **Vorinostat**

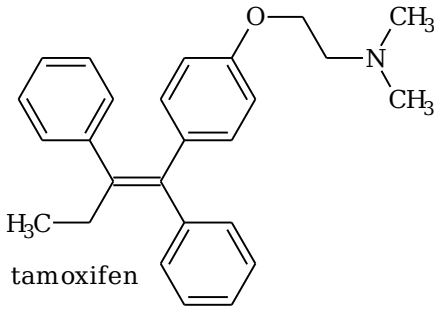


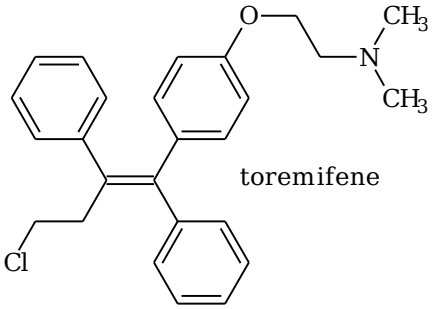
MUNI PHARM

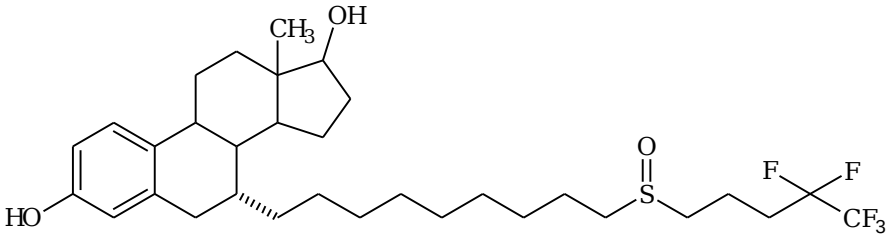
Hormone-based drugs – estrogens, antiestrogens



- Estramustin-phosphate
  - alkylation mechnism
  - main mechanism is hormonal
  - therapy of prostate carcinoma
- Tamoxifene
  - antiestrogen
  - parcial agonistic activity
  - estrogen-dependent breast carcinoma
- Toremifene
  - very similar indications as tamoxifene
- Fulvestrant
  - inactivator of estrogen receptors – strong bonding resulted in receptor destruction
  - high lipophilicity



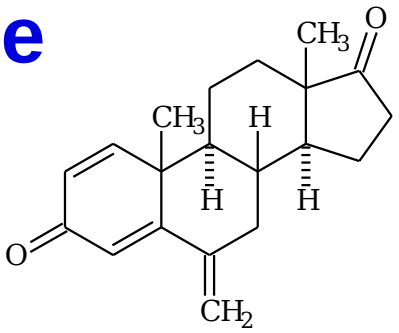


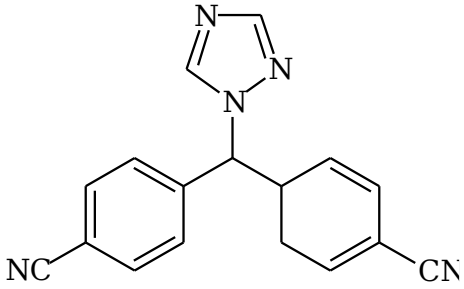


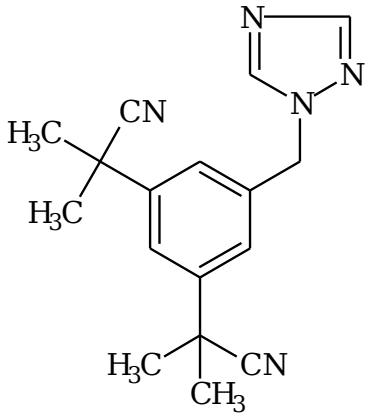
MUNI PHARM

Hormone-based drugs – aromatase inhibitors

- Inhibition of estrogen synthesis
- Exemestane
  - p.o. administration
  - advanced breast carcinoma in post-menopausal patients
- Letrozol
  - good oral availability (lipophilic)
  - first-line therapy of advanced breast carcinoma
- Anastrozol
  - similar therapeutic profile as letrozol



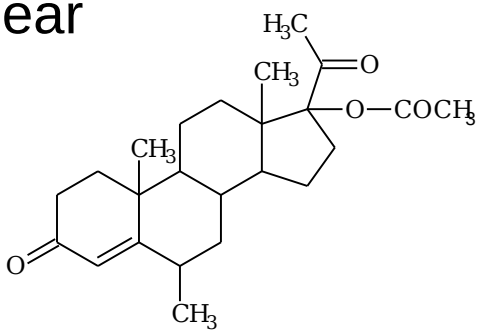


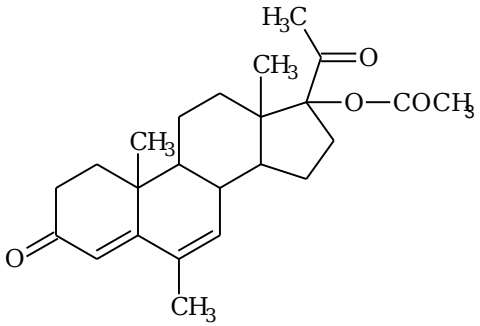


MUNI PHARM

Hormone-based drugs – gestagenes

- Mechanism of antineoplastic activity is stil not clear
- Medroxyprogesterone-acetate
- Megestrol-acetate
  - metastasis of breast carcinoma
  - advanced endometric carcinoma

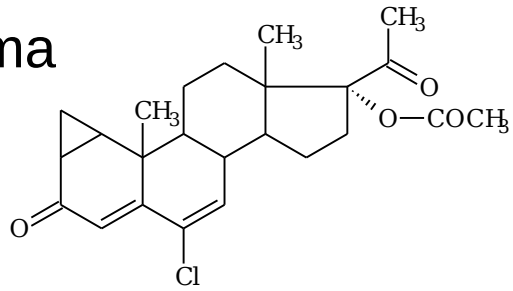


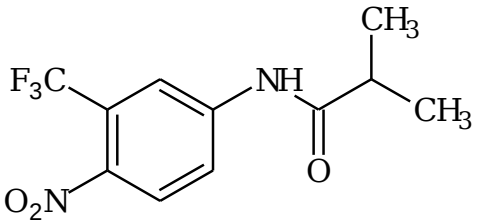


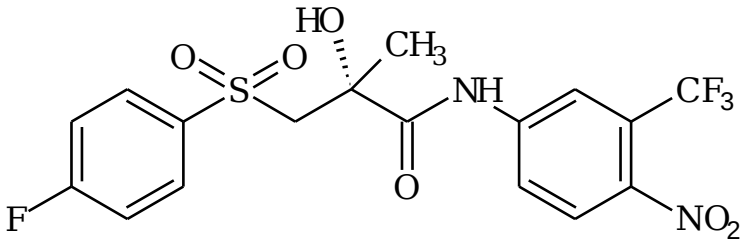
MUNI PHARM

Hormone-based drugs – antiandrogens

- Therapy of hormone-dependent prostate carcinoma
- Cyproterone-acetate
  - competitive antagonist
- Flutamide
  - advanced prostate carcinoma
  - p.o. administration
- Bicalutamide
  - higher afinity to androgen receptors than flutamide
  - longer half-time



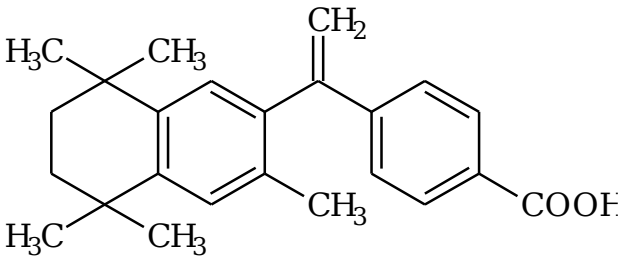




MUNI PHARM

Retinoids

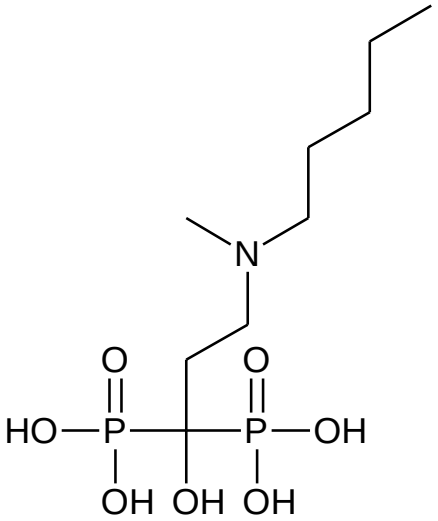
- Mostly used in dermatology
- Bexarotene
  - advanced skin lymphoma
  - orally available

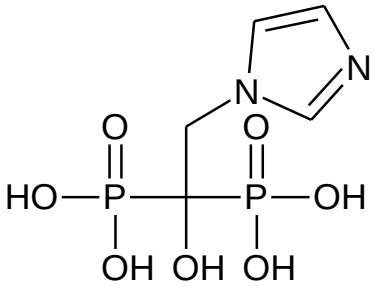


MUNI PHARM

Bisphosphonates

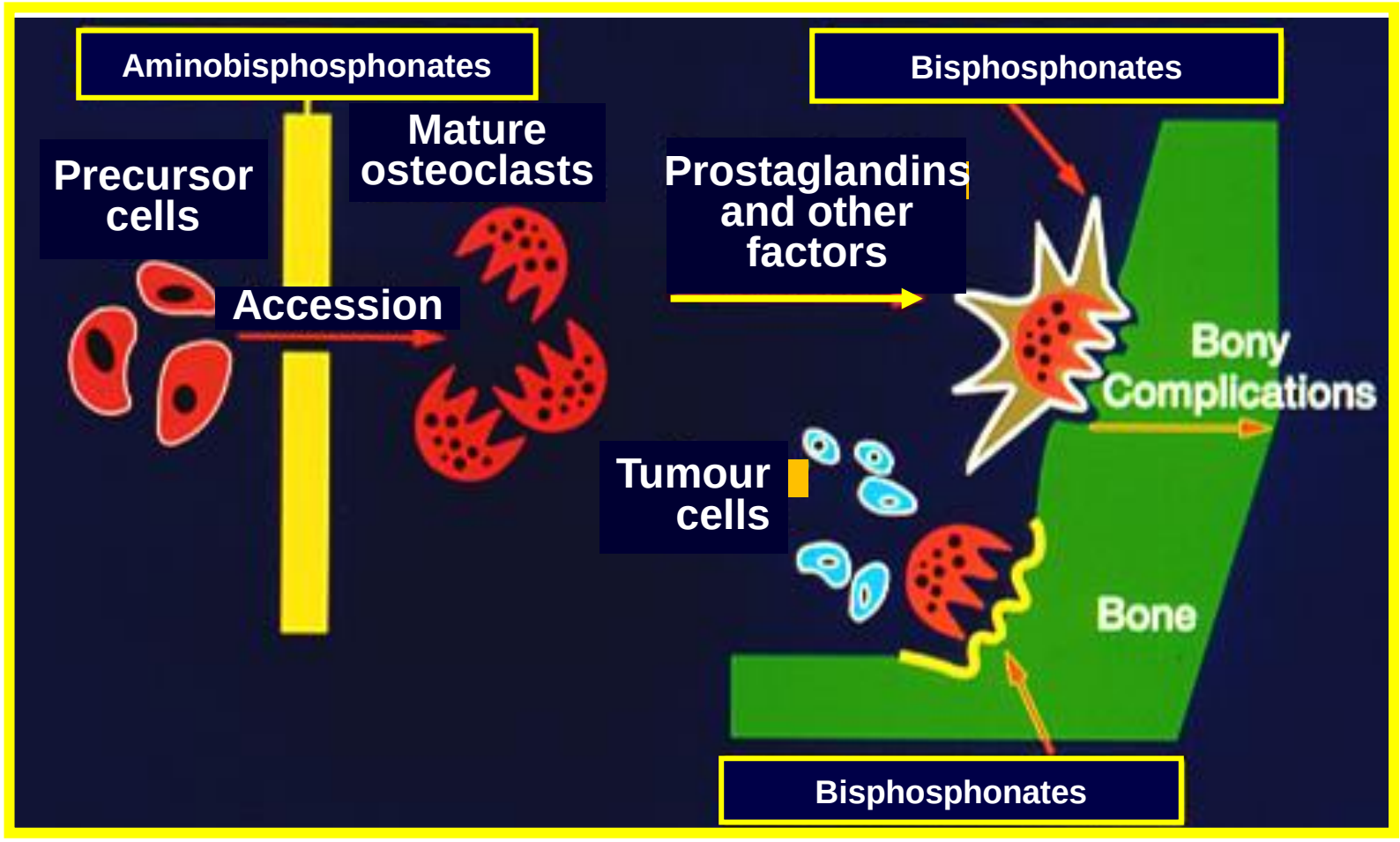
- Therapy of bone metastasis
  - Typical for breast, prostate and lung cancer
  - Prevention of bone breakdown
- Mechanism of action
  - Inhibition of osteoclast activity
  - Induction of osteoklast apoptosis
- Ibandronic acid
  - Oral administration - daily
  - i. v. bolus every 3 months
- Zoledronic acid
  - Intravenous administration every 4 weeks





MUNI PHARM

Bisphosphonates



MUNI PHARM

Monoclonal antibodies

- Antibodies against specific antigenes, exprimed on surface of cancer cells
- INN names – suffix –mab
  - Umab – prepared on human cells
  - Omab – prepared on mice cells
  - Amab – prepared on rat cells
  - Emab – prepared on hamster cells
  - Imab – prepared on primates cells
  - Zumab – humanized monoclonal antibody
- Bevacizumab – colon carcinoma (angiogenesis)
- Rituximab – breast carcinoma
- Cetuximab – colon carcinoma
- Trastuzumab – metastatic breast carcinoma