MUNI
PHARM

Antineoplastics

Medicinal chemistry

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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

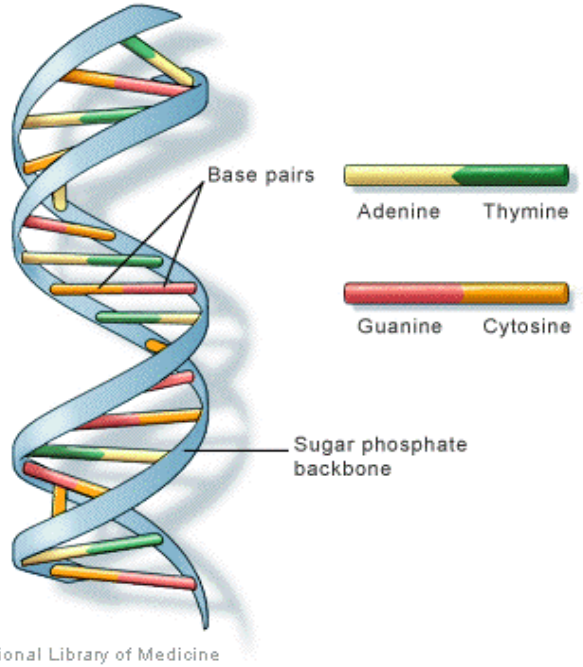
- Classification based on a target
  - DNA
    - DNA as the molecule
    - Synthesis of DNA
  - Metabolism of cancer cells
  - Hormones
  - Immune system

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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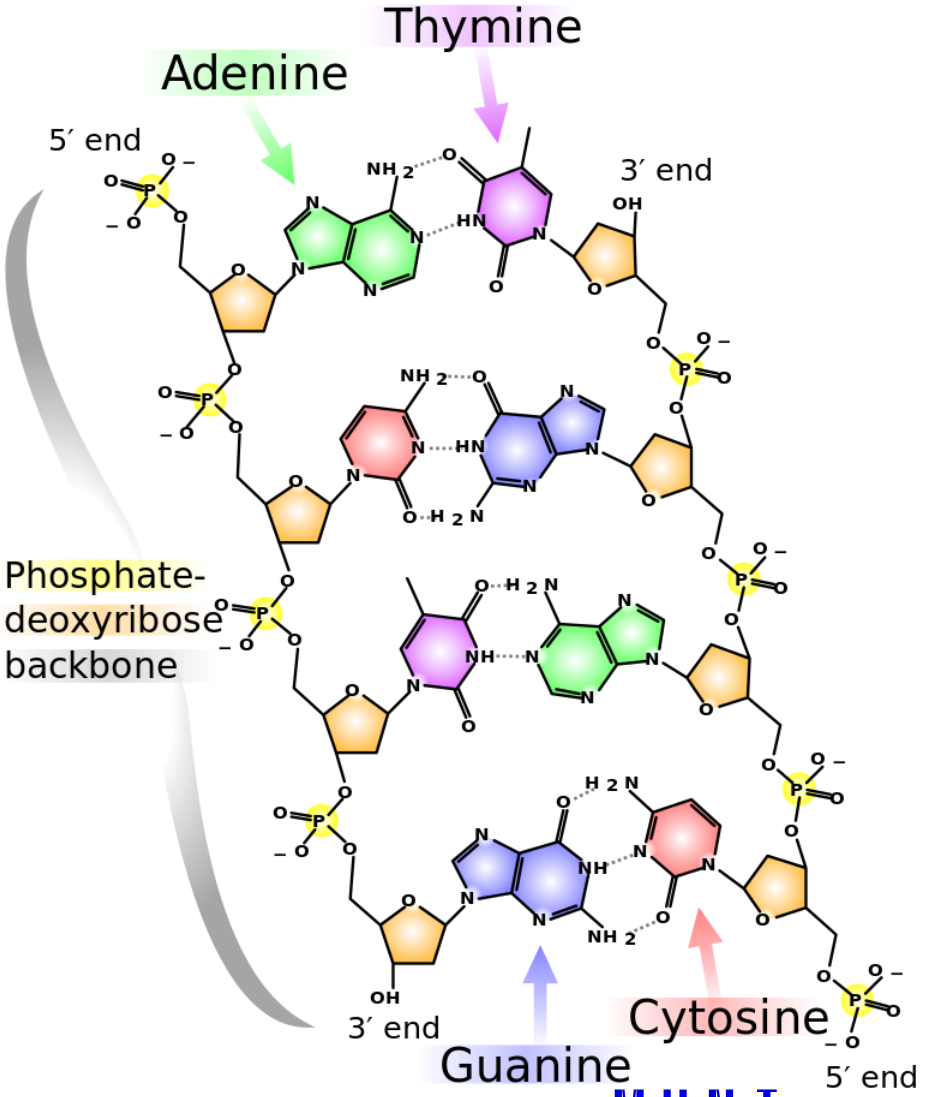

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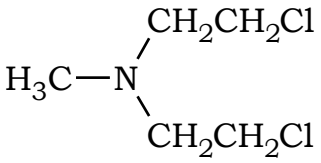
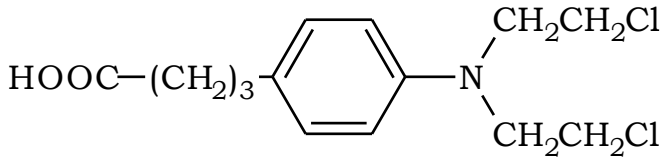
Alkylating agents

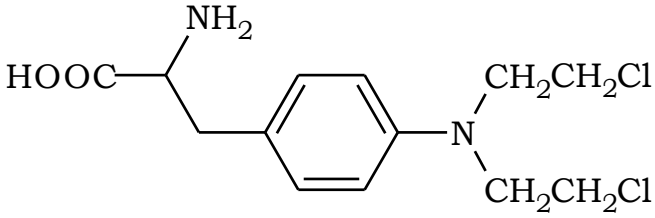
- Agents than can replace hydrogen atom by an alkyl group at physiological conditions
  - spontaneous or enzymatic origin of reactive carbenium ions
  - alkylation reaction with DNA or other molecules
- Potentially carcinogenic and mutagenic
  - the same mechanism as anticancer activity
- Severe adverse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

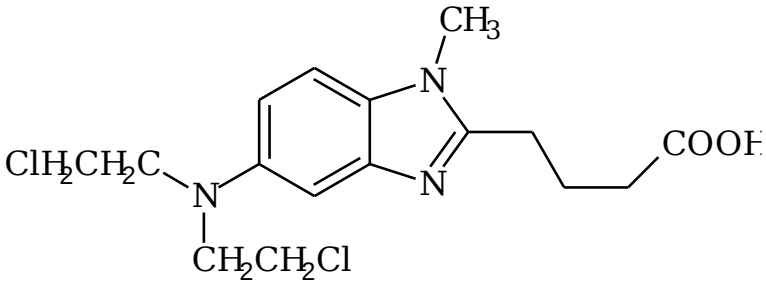
Alkylating agents – nitrogen mustards

- 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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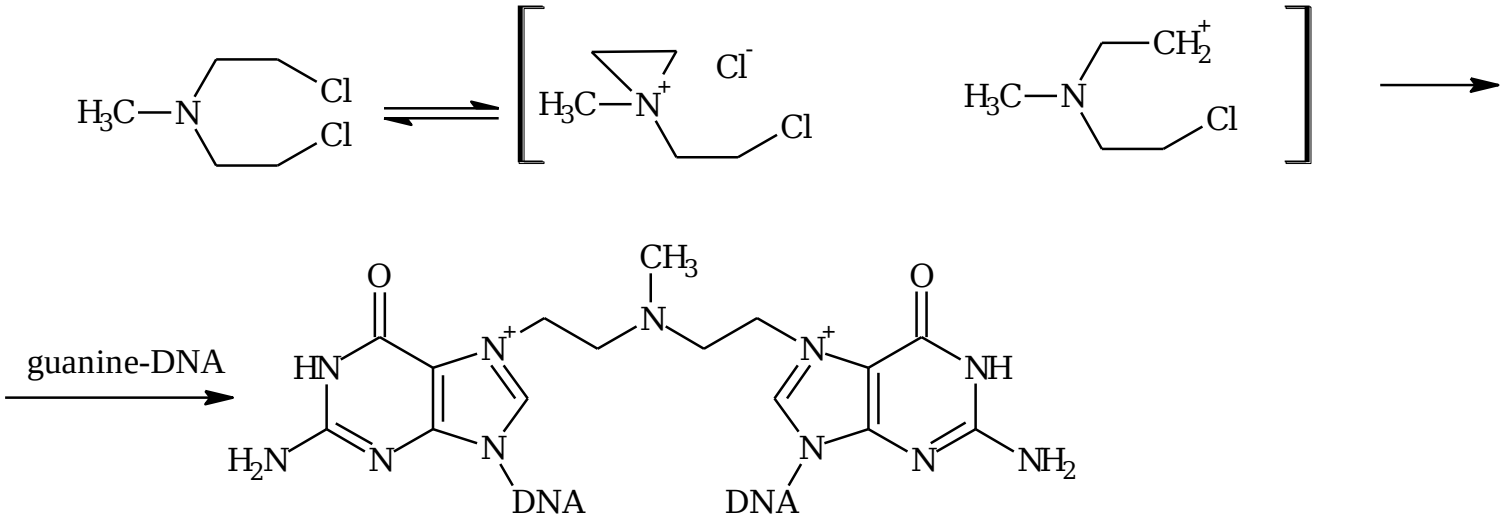
Alkylating agents – nitrogen mustards

- Mechanism of alkylation



- Not specific to cancer cells
- Affects all dividing cells

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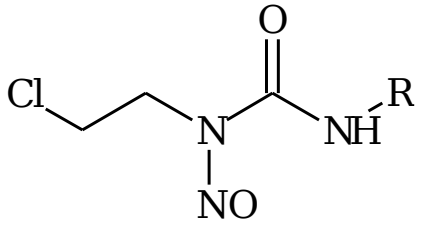
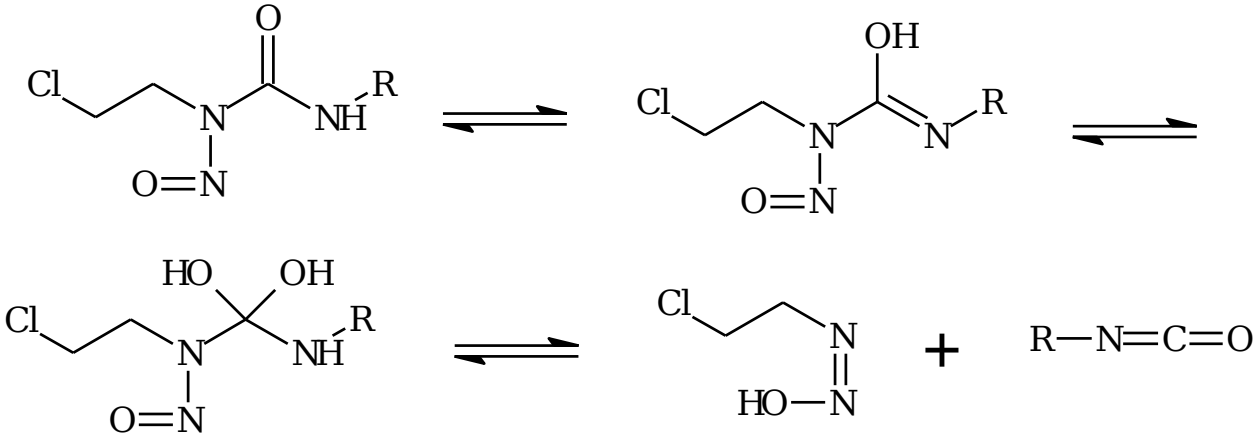
Alkylating agents – nitrosourea derivatives

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





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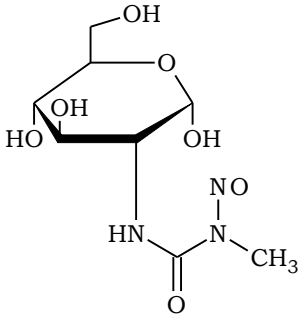
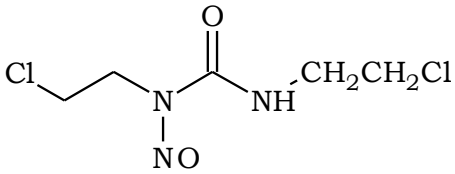
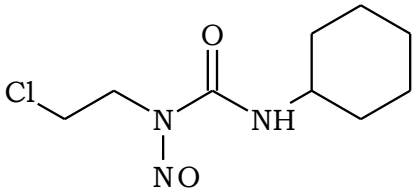
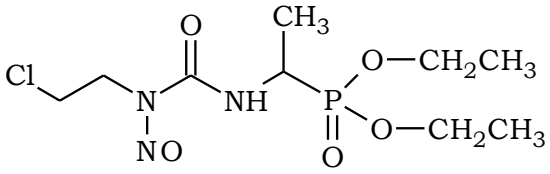
Alkylating agents – nitrosourea derivatives

- 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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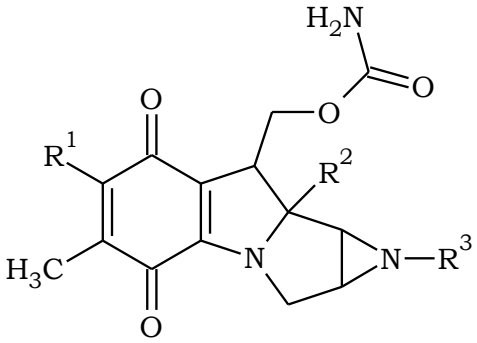
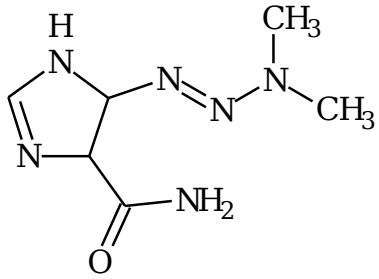
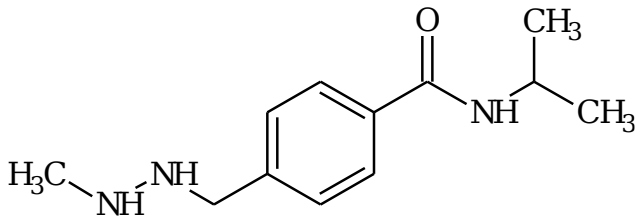
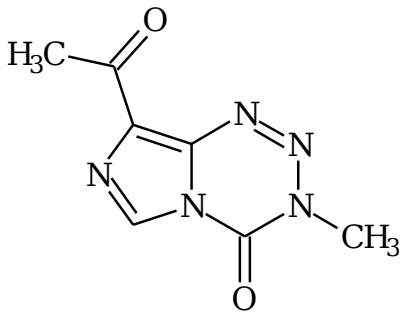
Alkylating agents – aziridines, triazines

- 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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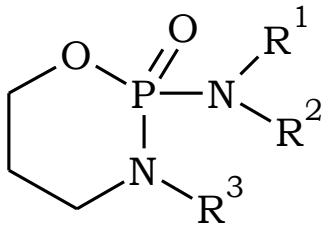
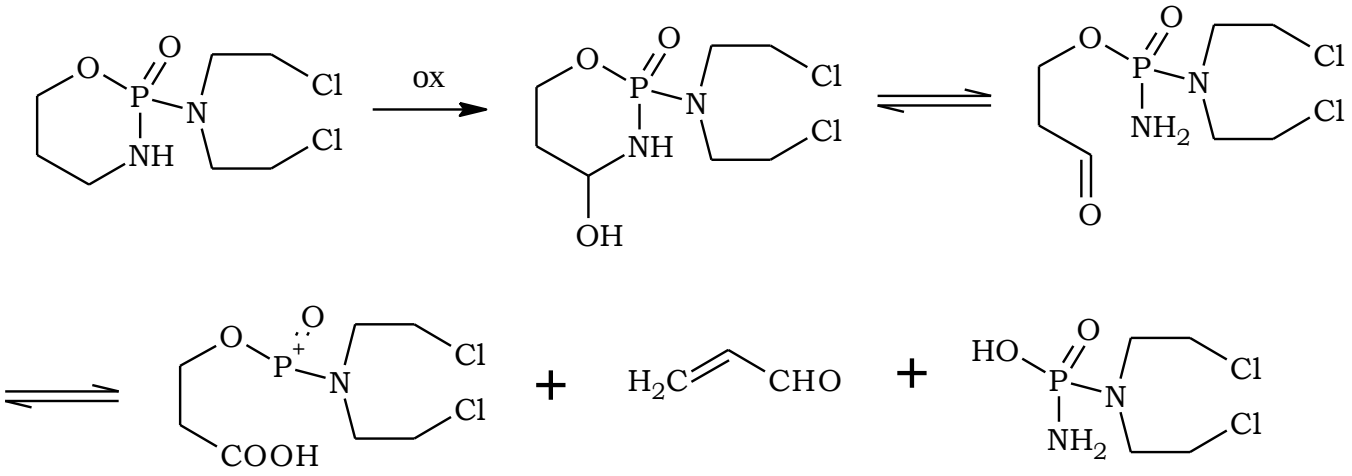
Alkylating agents - phosphamides

– Active after metabolic activation





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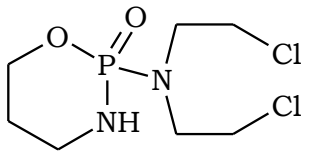
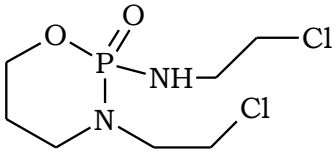
Alkylating agents - phosphamides

- 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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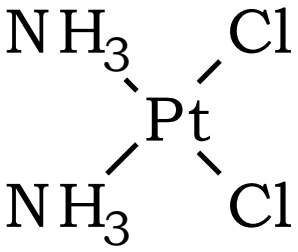
Platinum coordination compounds

- 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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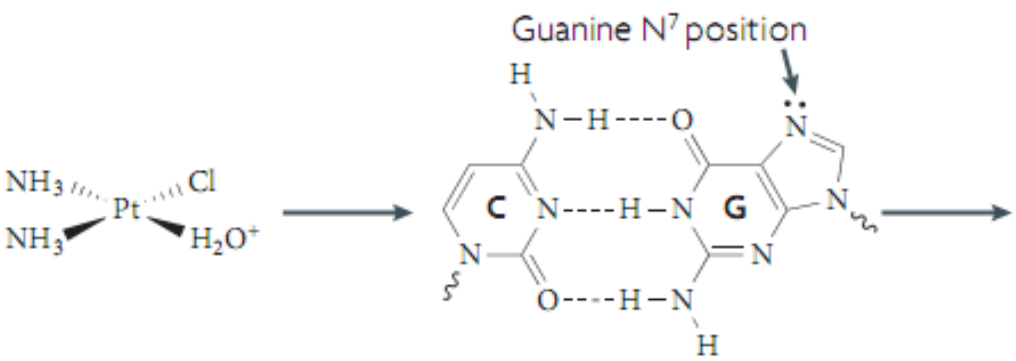
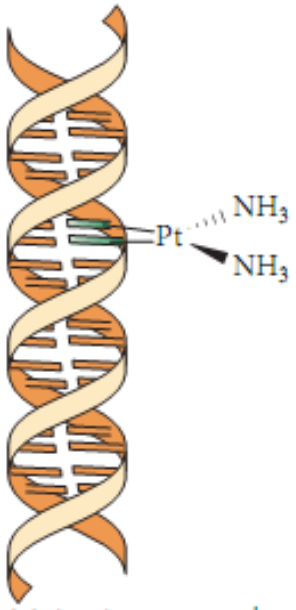
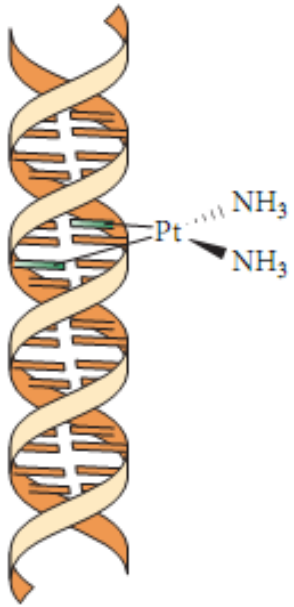
Platinum coordination compounds

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





Major intrastrand crosslink



Minor interstrand crosslink

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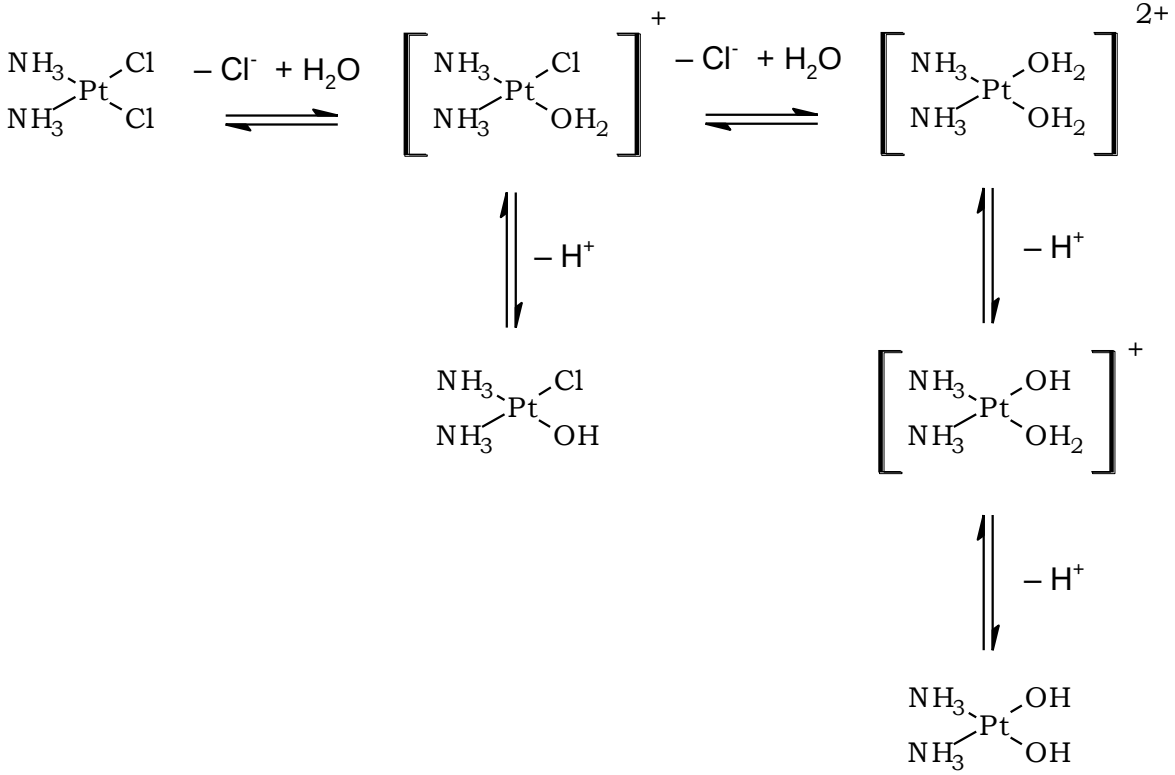
Platinum coordination compounds

- Mechanism of action
  - activation – aquacomplexes – very reactive



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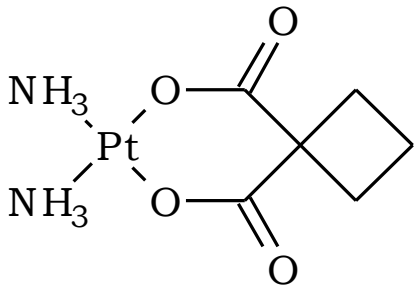
Platinum coordination compounds

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



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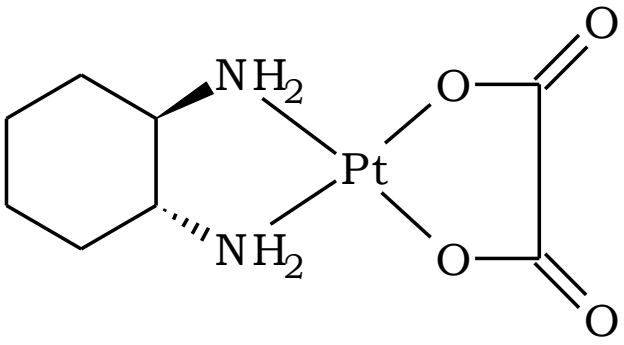
Platinum coordination compounds

- 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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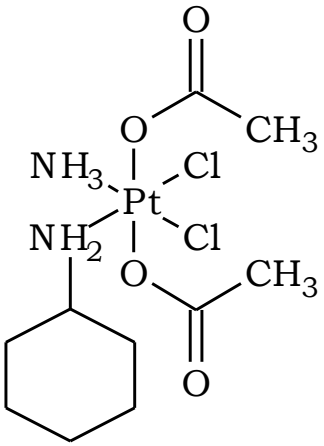
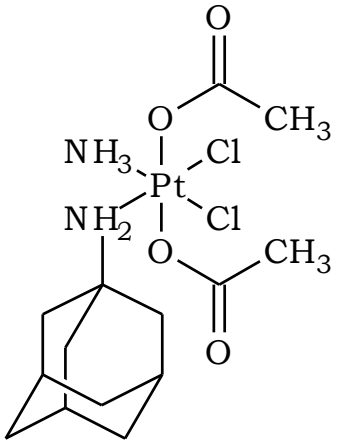
Platinum coordination compounds

- 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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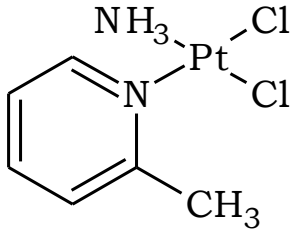

picoplatin

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Antimetabolites – folic acid

- Folic acid is needed for biosynthesis of nucleic acids

Source for one-carbon fragments

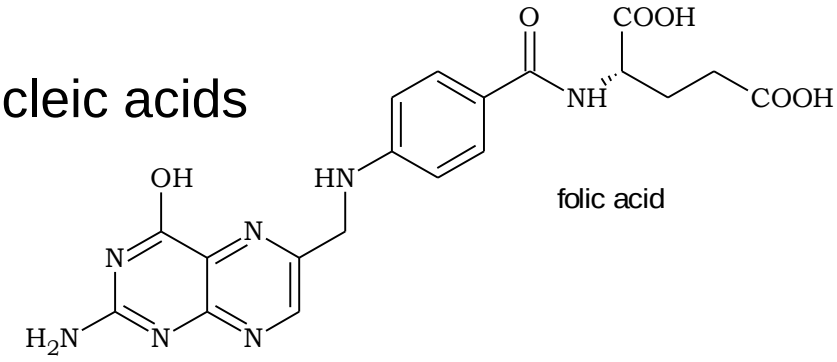
- Methotrexate

immunosuppresive agent
inhibition of tetrahydroflate reductase

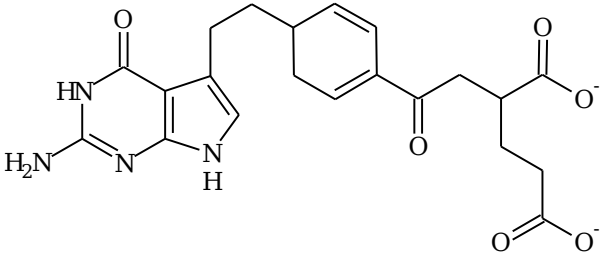
- Pemetrexed

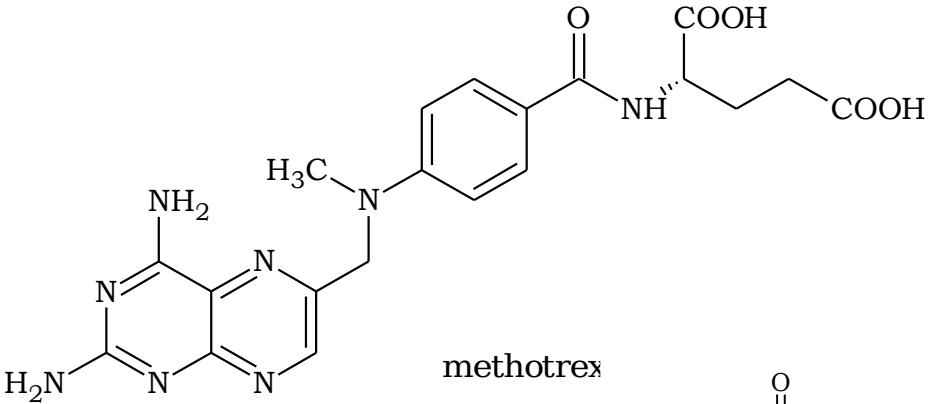
inhibition of more enzymes

- Raltitrexed
- Nolatrexed

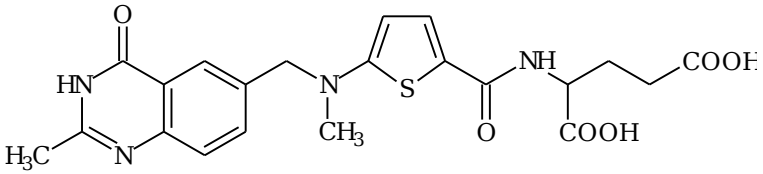


folic acid

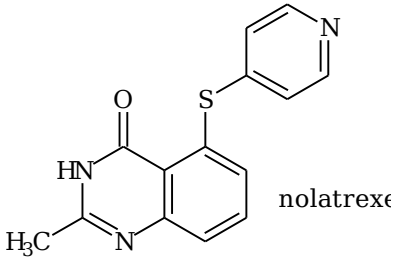




methotrex

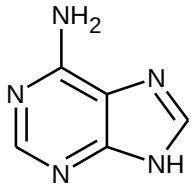


raltitrex

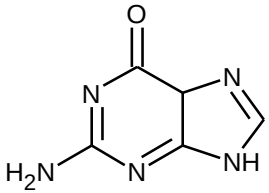


nolatrexe

Antimetabolites – purine bases



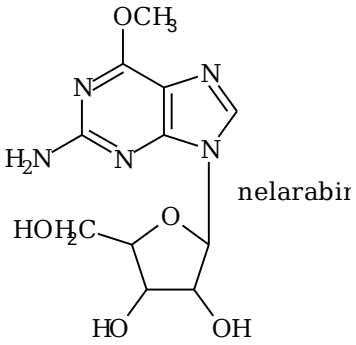
adenine

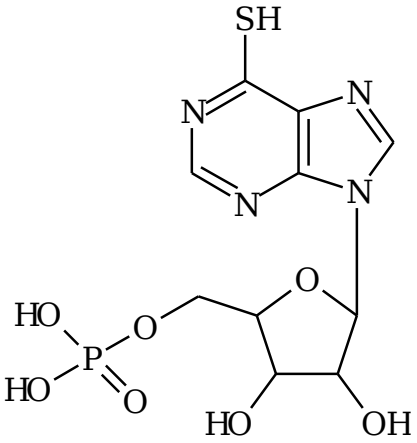


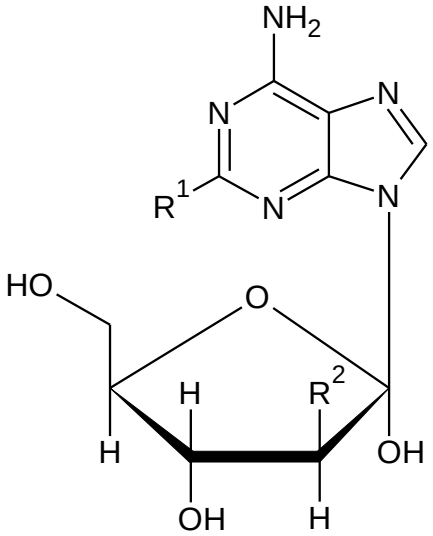
guanine

- 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







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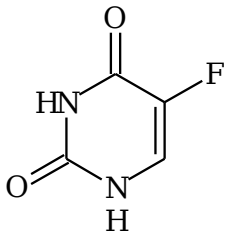
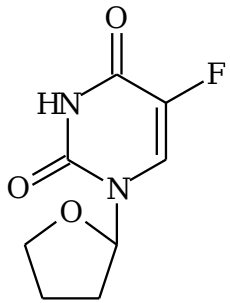
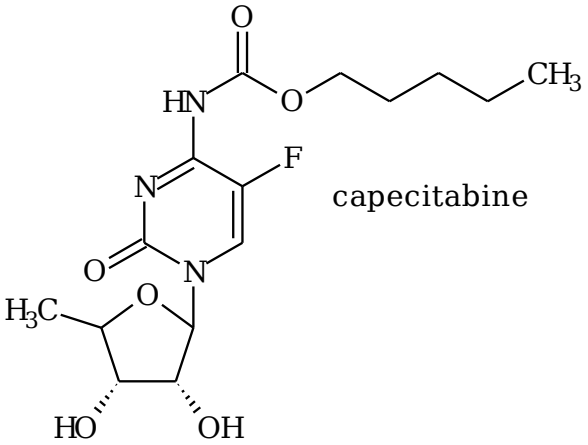
Antimetabolites – pyrimidine bases



- 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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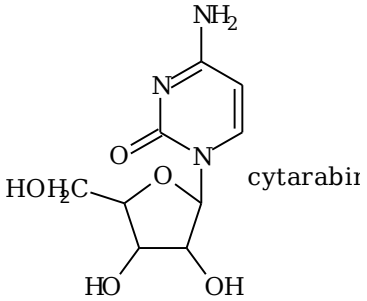
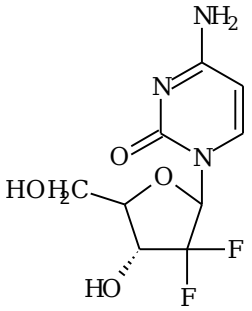
Antimetabolites – pyrimidine bases

- 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



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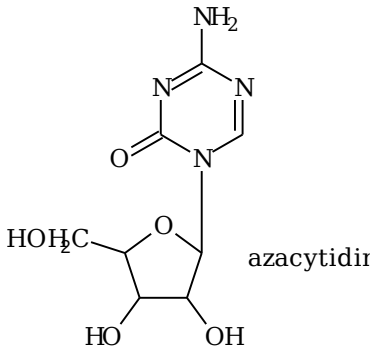
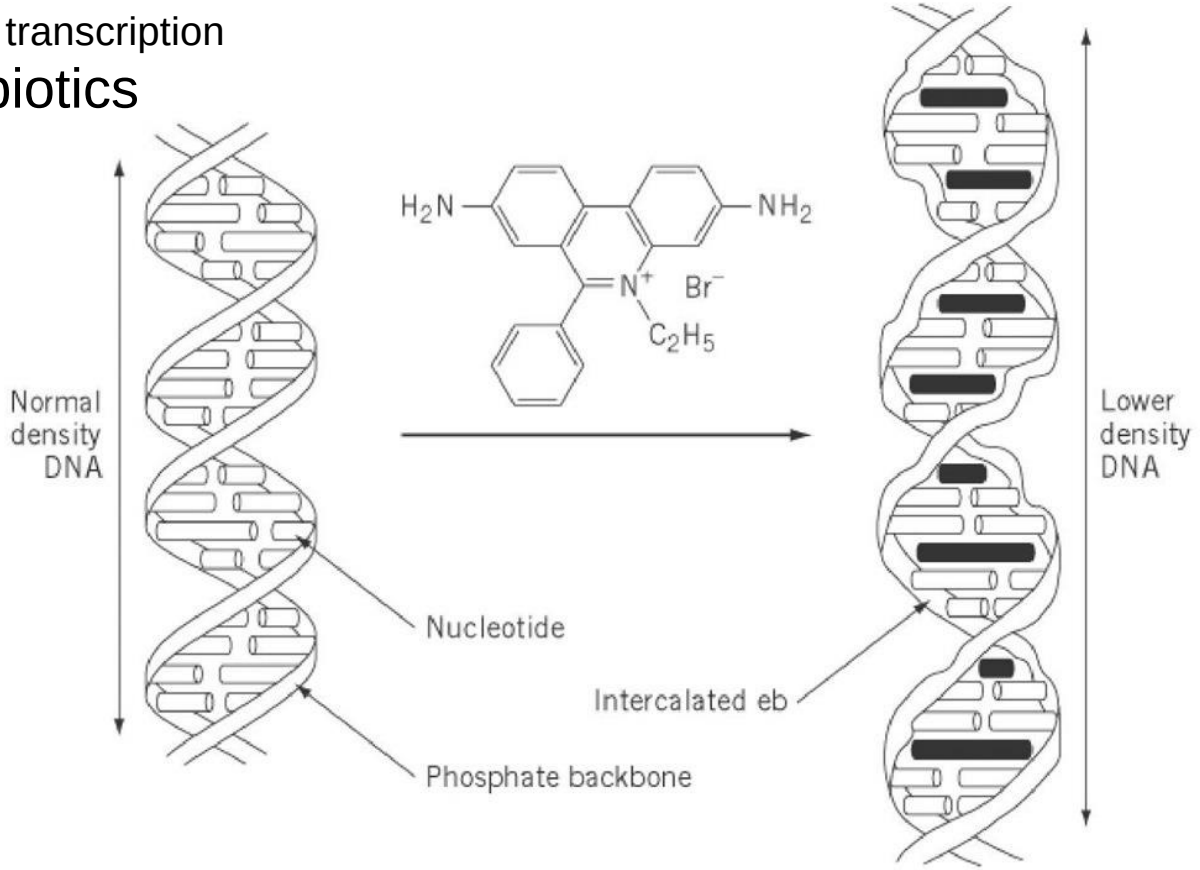


azacytidin

MUNI PHARM

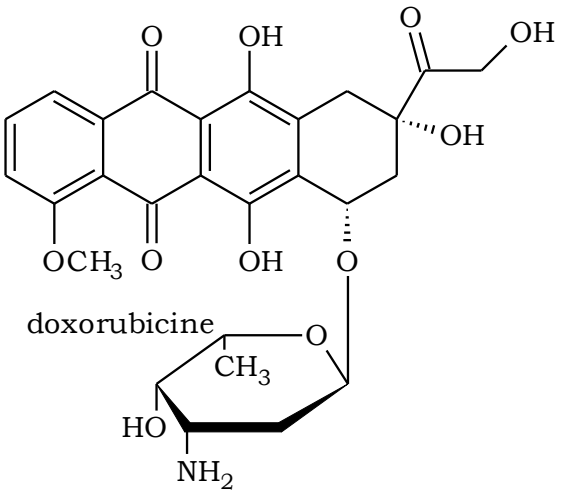
Intercalating agents

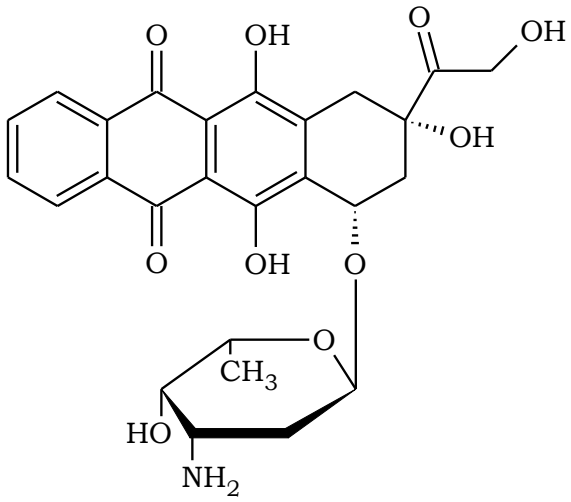
- Different structures
- Antibiotics ant its derivatives, synthetic compounds
- Intercalation
  - the compound inserts into DNA double helix
  - it blocks replication and transcription
- Anthracycline antibiotics



Intercalating agents

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

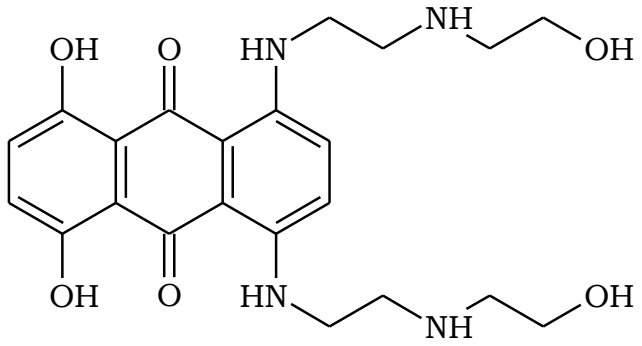


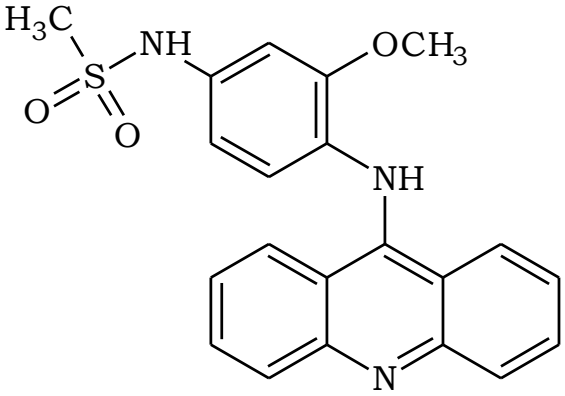


MUNI PHARM

Intercalating agents

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

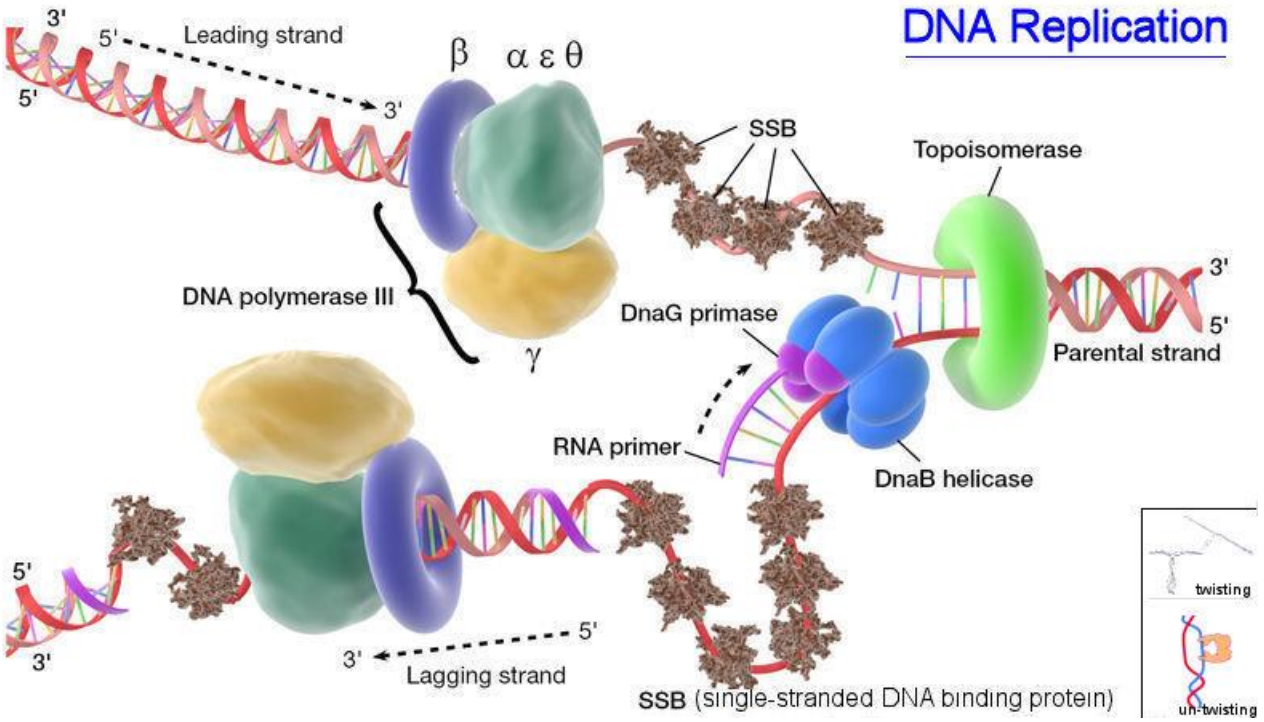




MUNI PHARM

Topoisomerase inhibitors

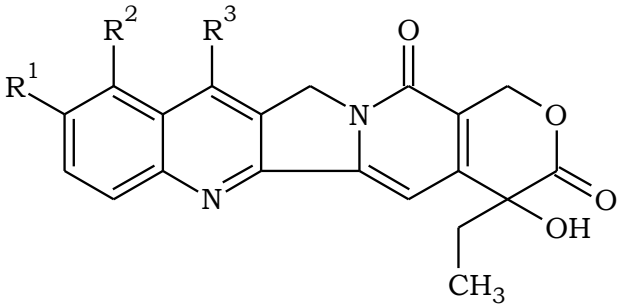
- Topoisomerases
  - control of topological arrangement of replicated DNA
  - inhibition of topoisomerase causes stable bonding of it to DNA
- Camptothecin and its analogues
- Podophylotoxine derivatives
- Some anthracyclines

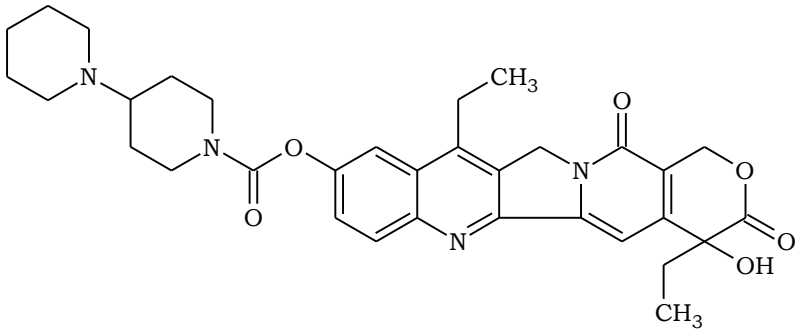


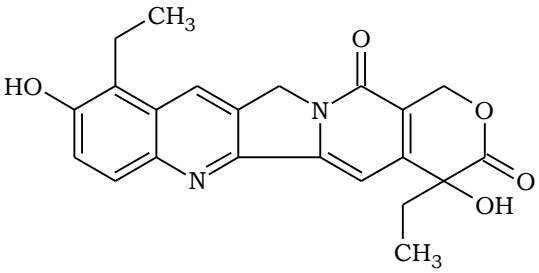
MUNI PHARM

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



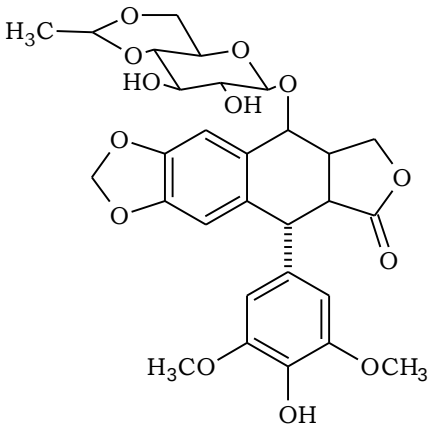


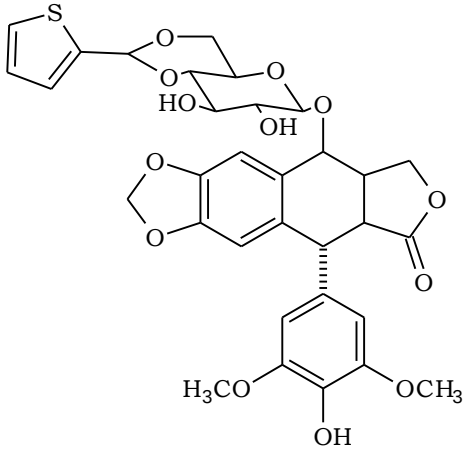


MUNI PHARM

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



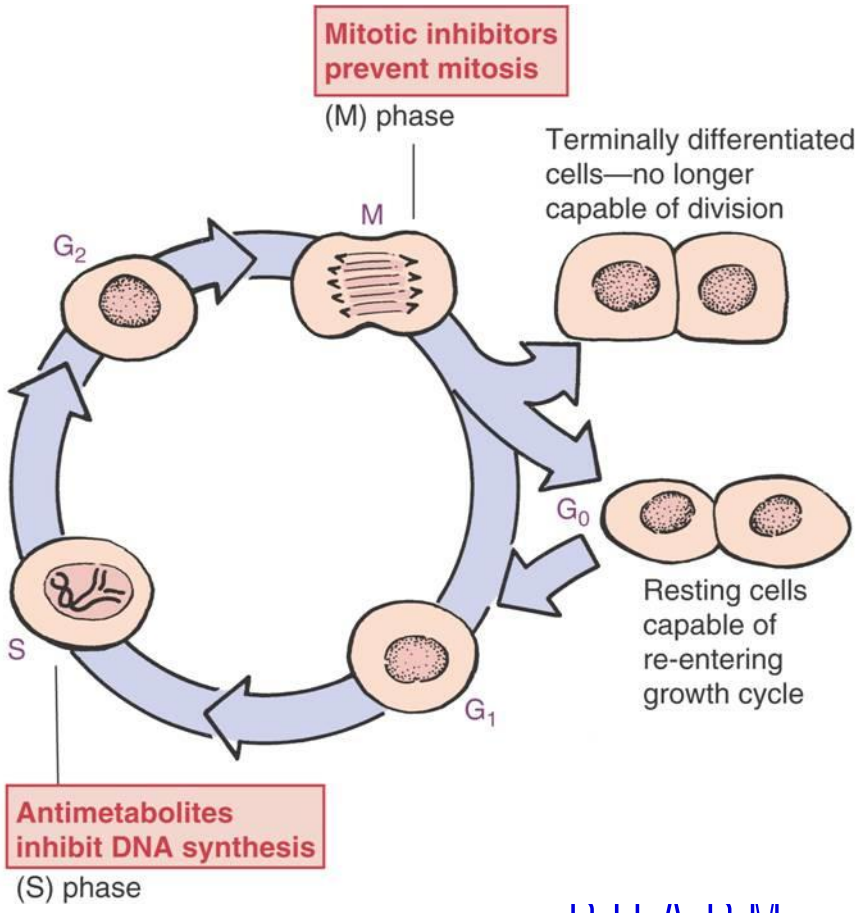


MUNI PHARM

Mitosis inhibitors

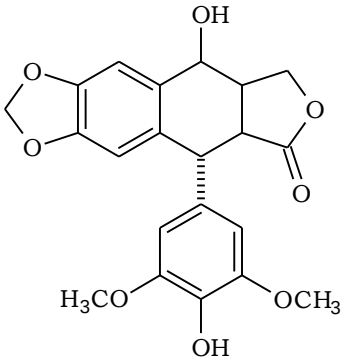
- Natural compounds of different structures
- Block of mitosis in M-phase
- Bonding to microtubules

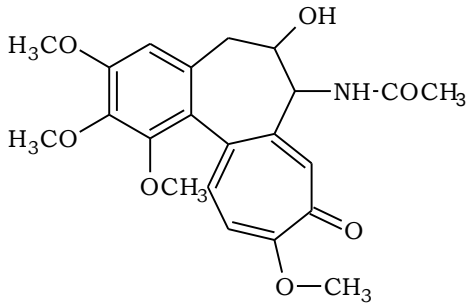
- Colchicum alkaloids
- Podophylotoxins
- Vinca-alkaloids
- Taxanes
- Epothilones

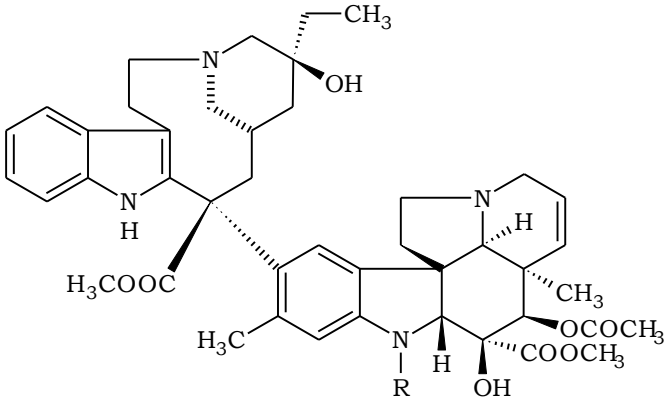


Mitosis inhibitors

- 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



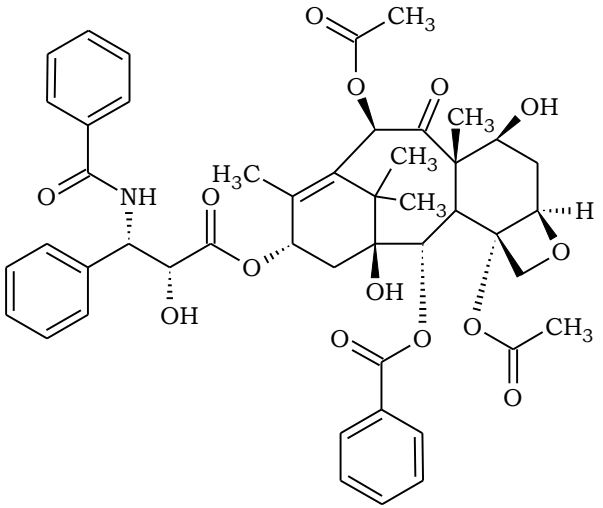


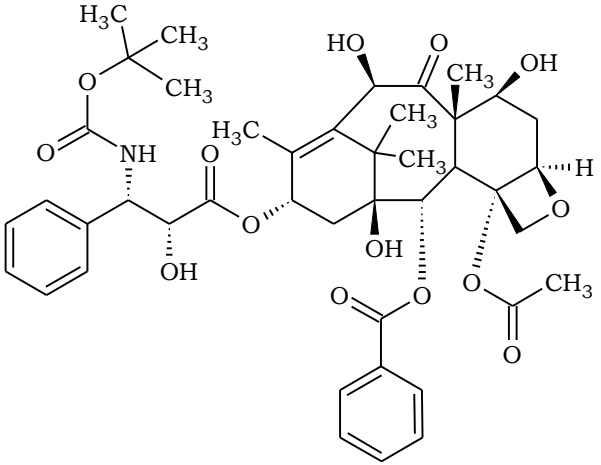


MUNI PHARM

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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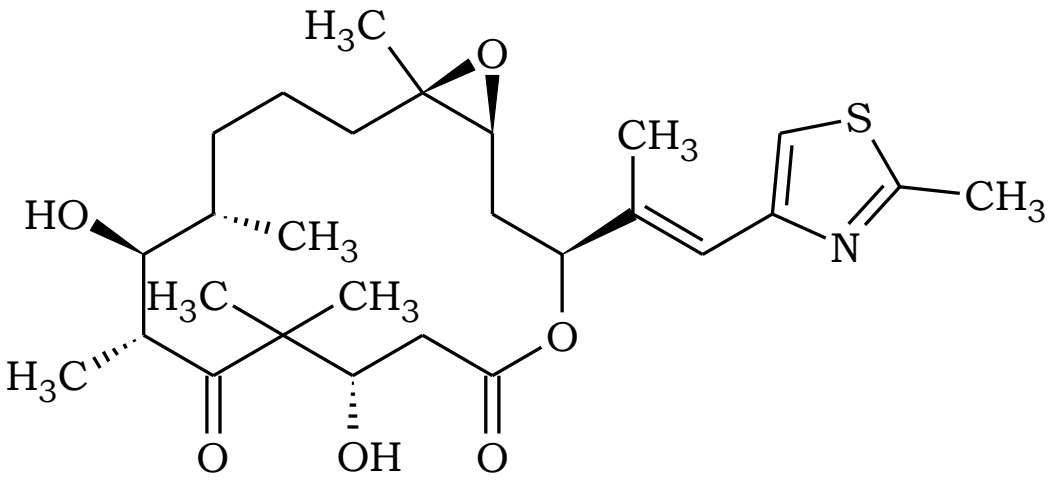
Mitosis inhibitors – other structures

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



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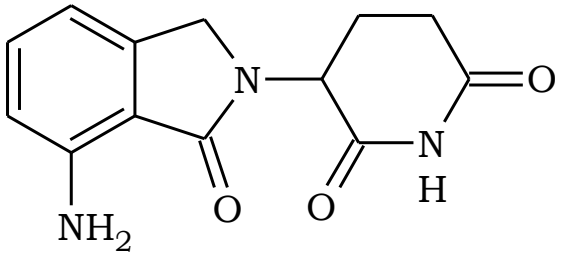
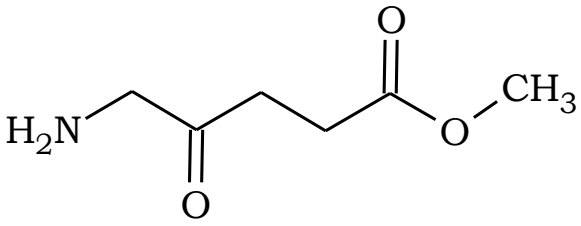
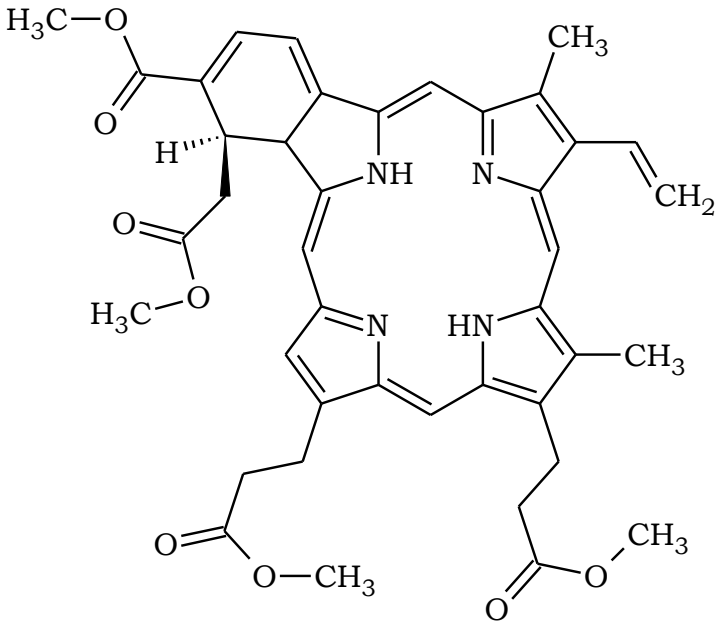
Other antineoplastics

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



lenalidomide

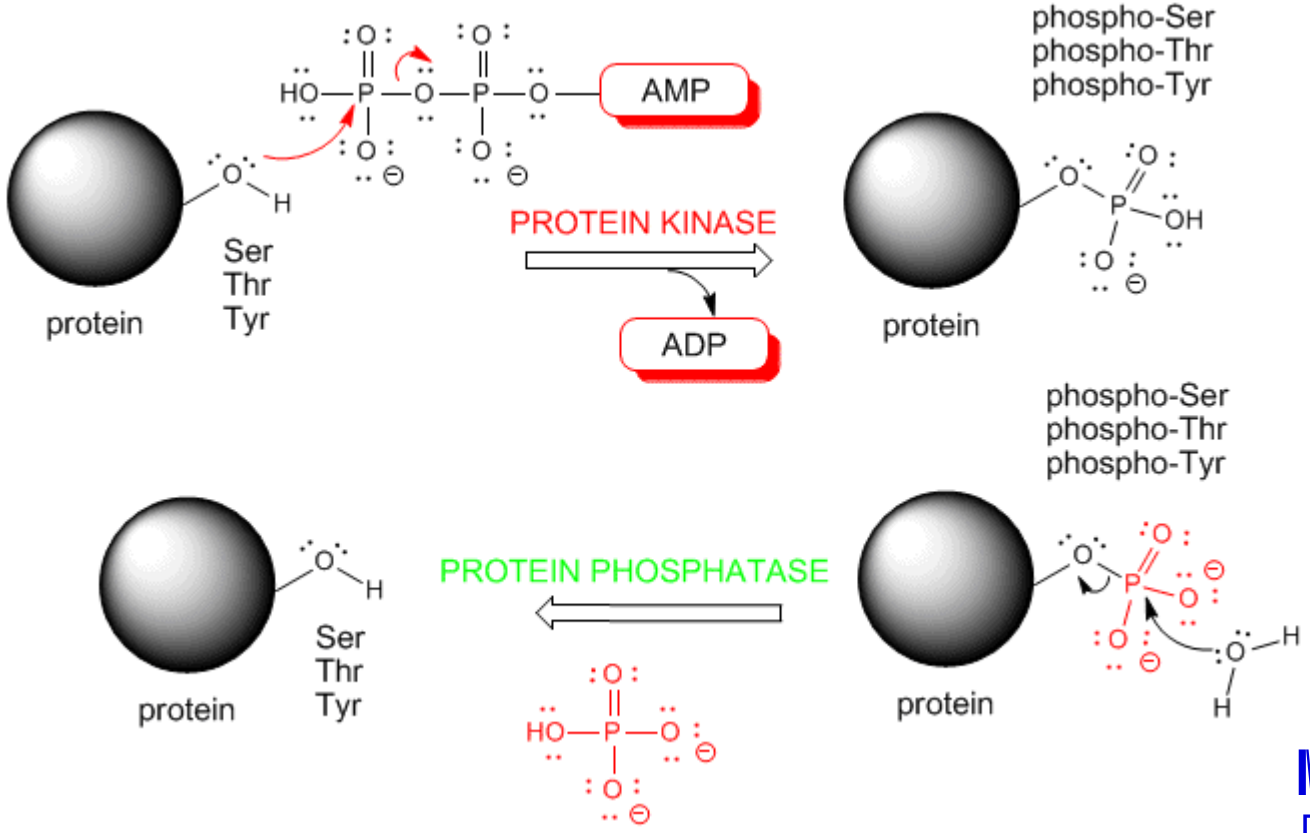




MUNI PHARM

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.



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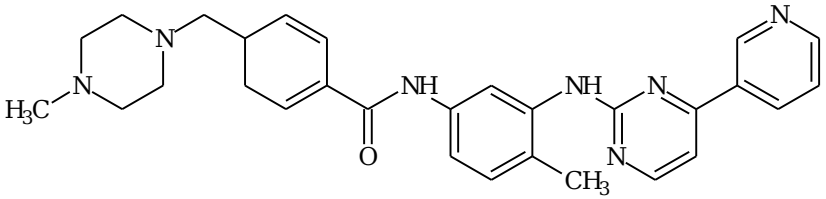
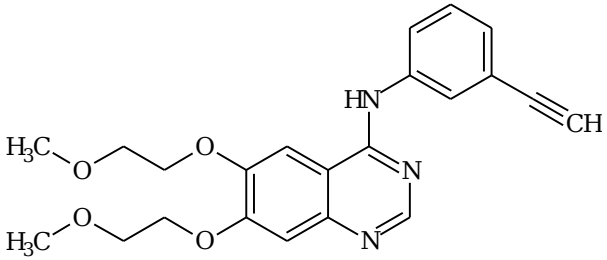
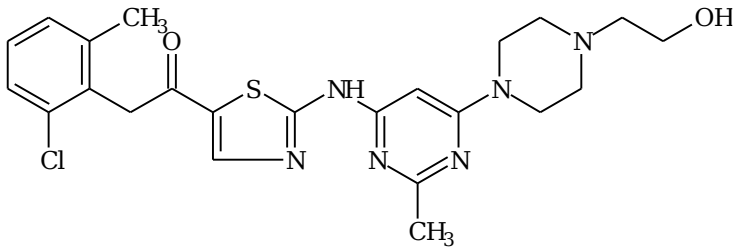
Kinases inhibitors – tyrosinekinase inhibitors

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



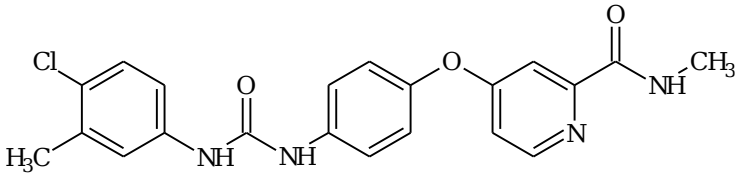


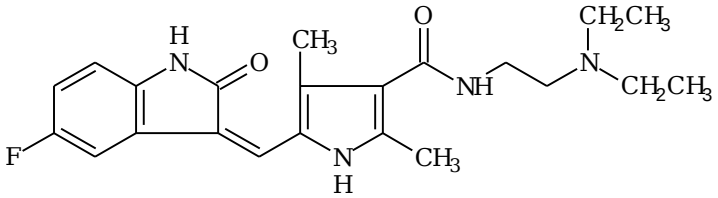


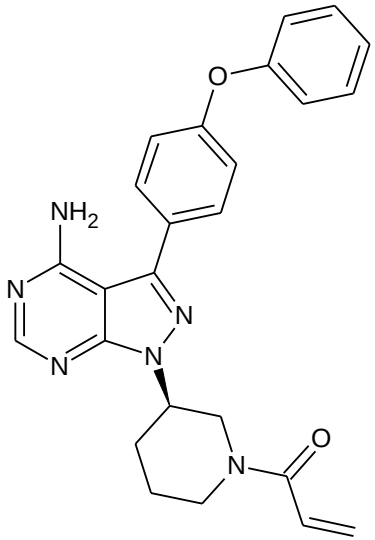
MUNI PHARM

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



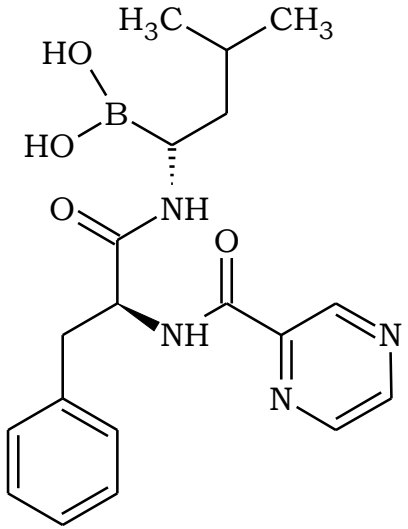


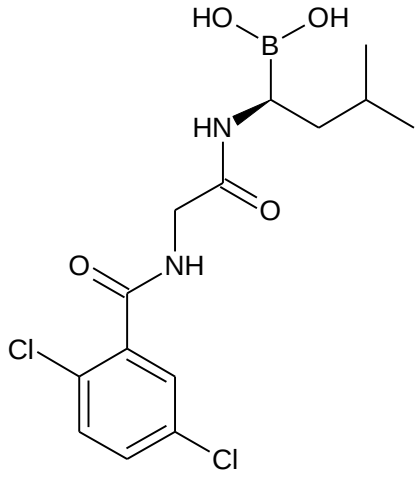


MUNI PHARM

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

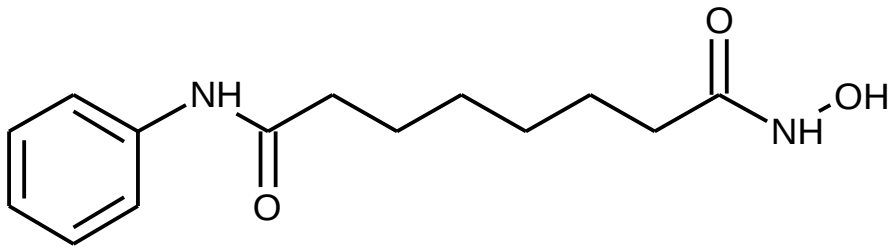




MUNI PHARM

Histonedeacetylase inhibitors

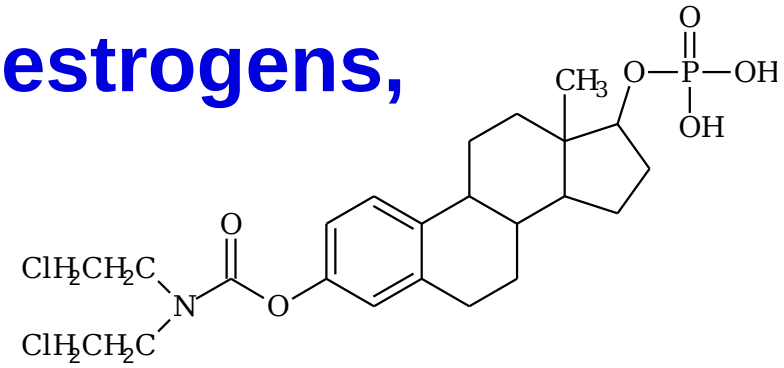
- DNA is surrouded by histones and creates nucleosomes
  - protection of DNA
- Histones are basic proteins
- Acetylation and deacetylation regulate accessibility of DNA for some enzymes
- Inhibitors of histone deacetylase are used for treatment of haematological cancers
- **Vorinostat**

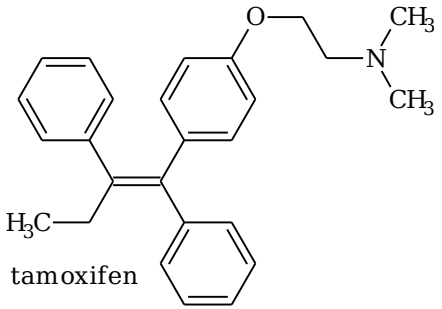


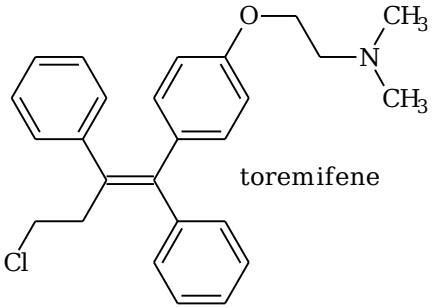
MUNI PHARM

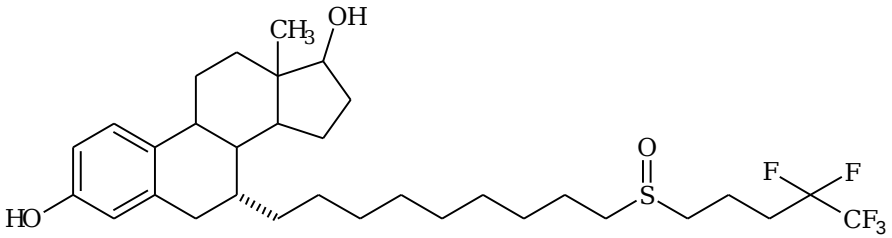
Hormone-based drugs – estrogens, antiestrogens

- 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





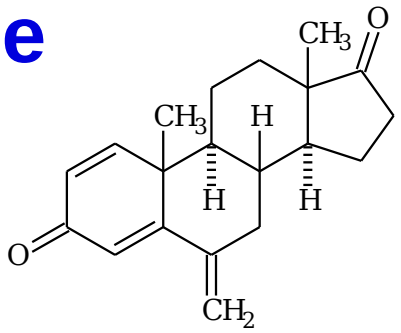


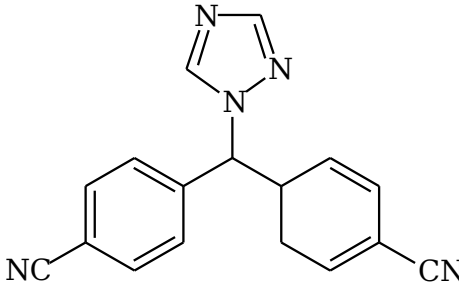


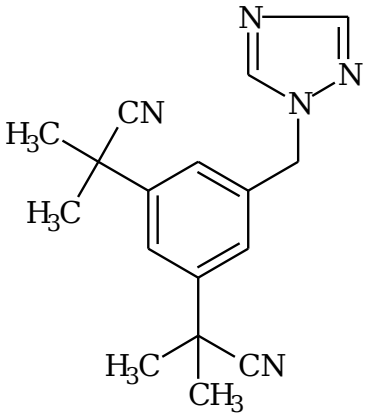
MUNI PHARM

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



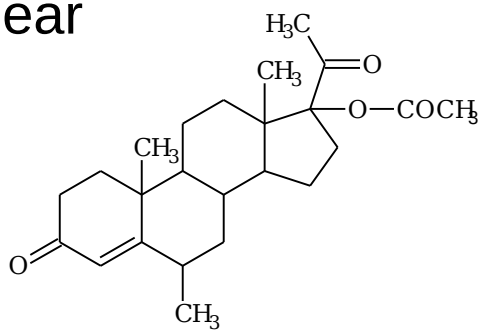


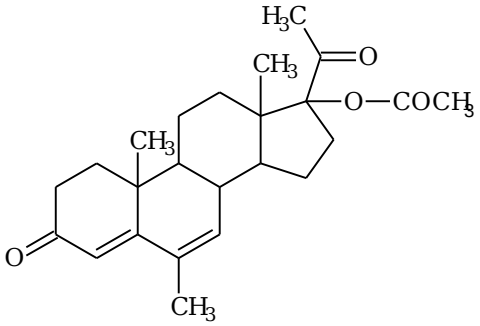


MUNI PHARM

Hormone-based drugs – gestagenes

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

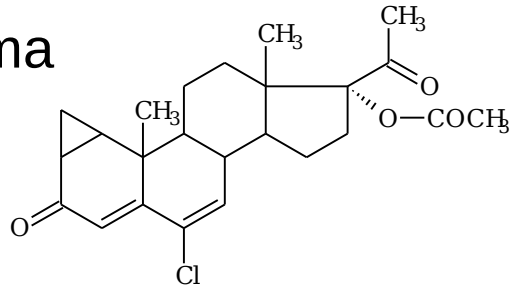


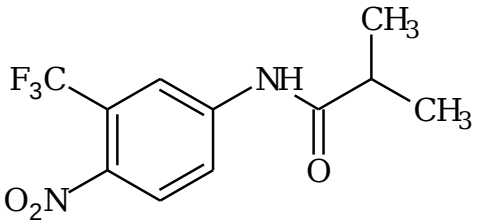


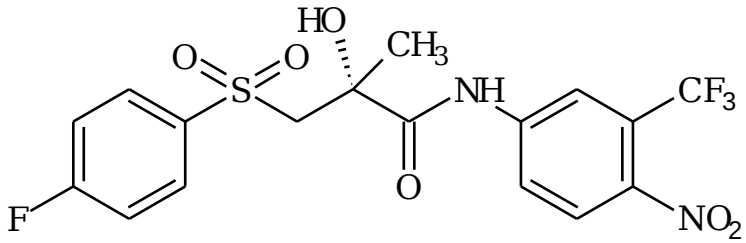
MUNI PHARM

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



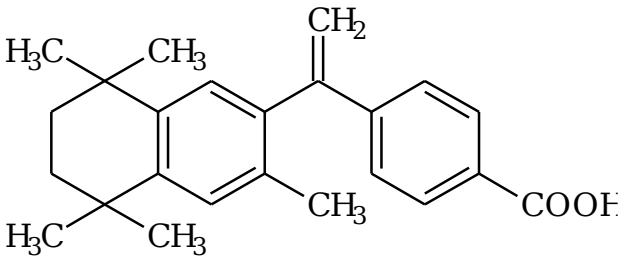




MUNI PHARM

Retinoids

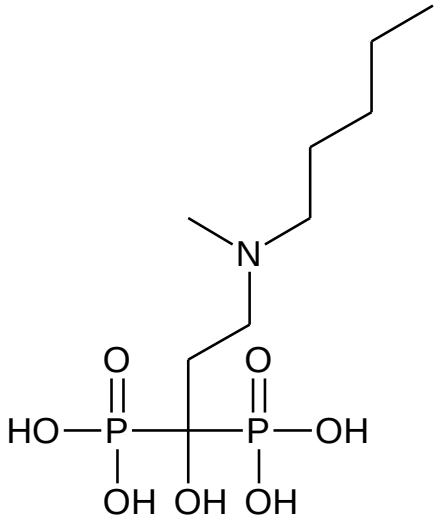
- Mostly used in dermatology
- Bexarotene
  - advanced skin lymphoma
  - orally available

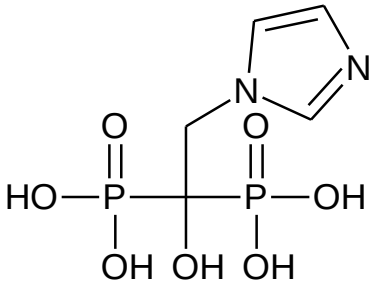


MUNI PHARM

Bisphosphonates

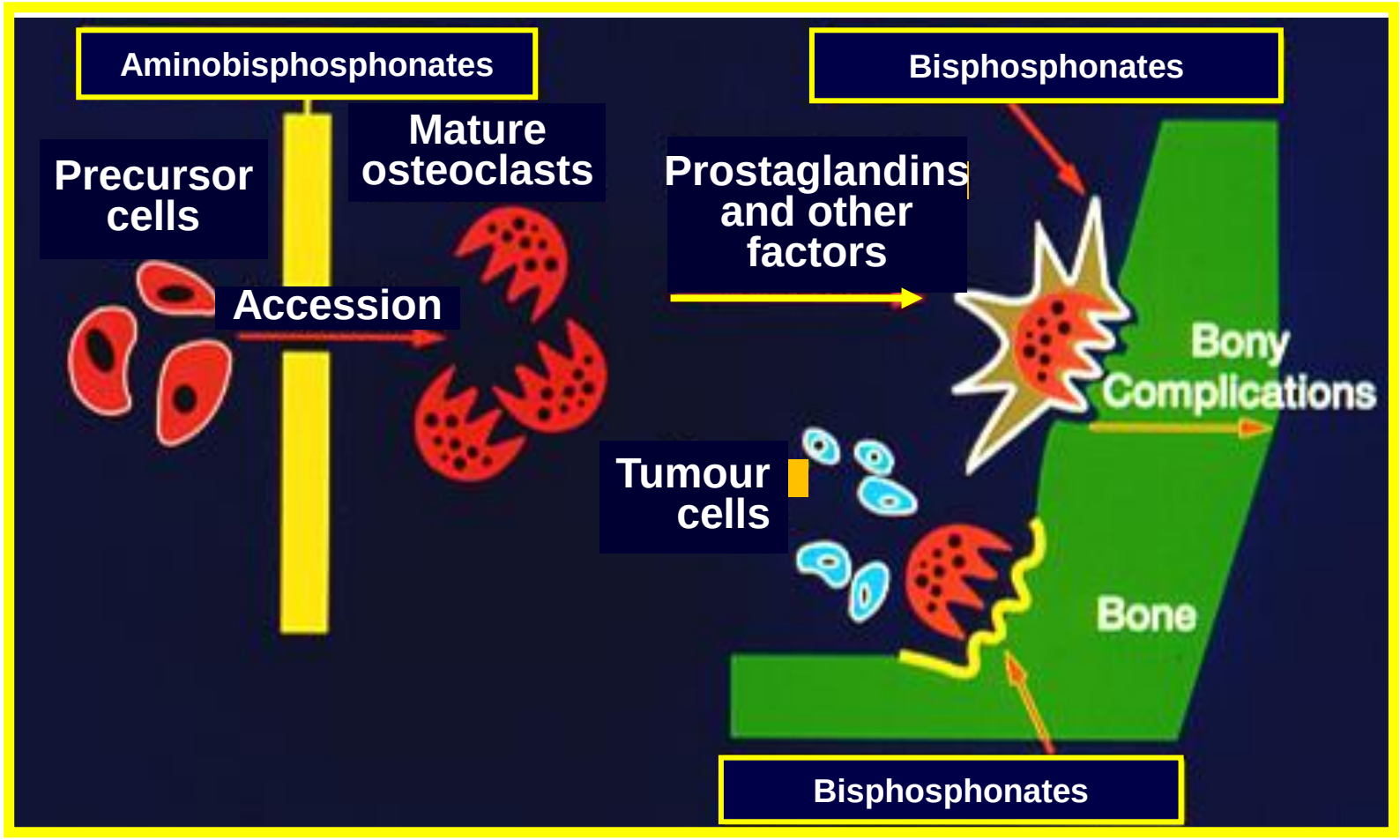
- Therapy of bone metastasis
  - Typical for breast, prostate and lung cancer
  - Prevention of bone breakdown
- Mechanism of action
  - Inhibition of osteoclast activity
  - Induction of osteoklast apoptosis
- Ibandronic acid
  - Oral administration - daily
  - i. v. bolus every 3 months
- Zoledronic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