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Antineoplastics

Medicinal chemistry

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Content of the lecture

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

Cancer

- Cancer isn't only one disease
 - 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

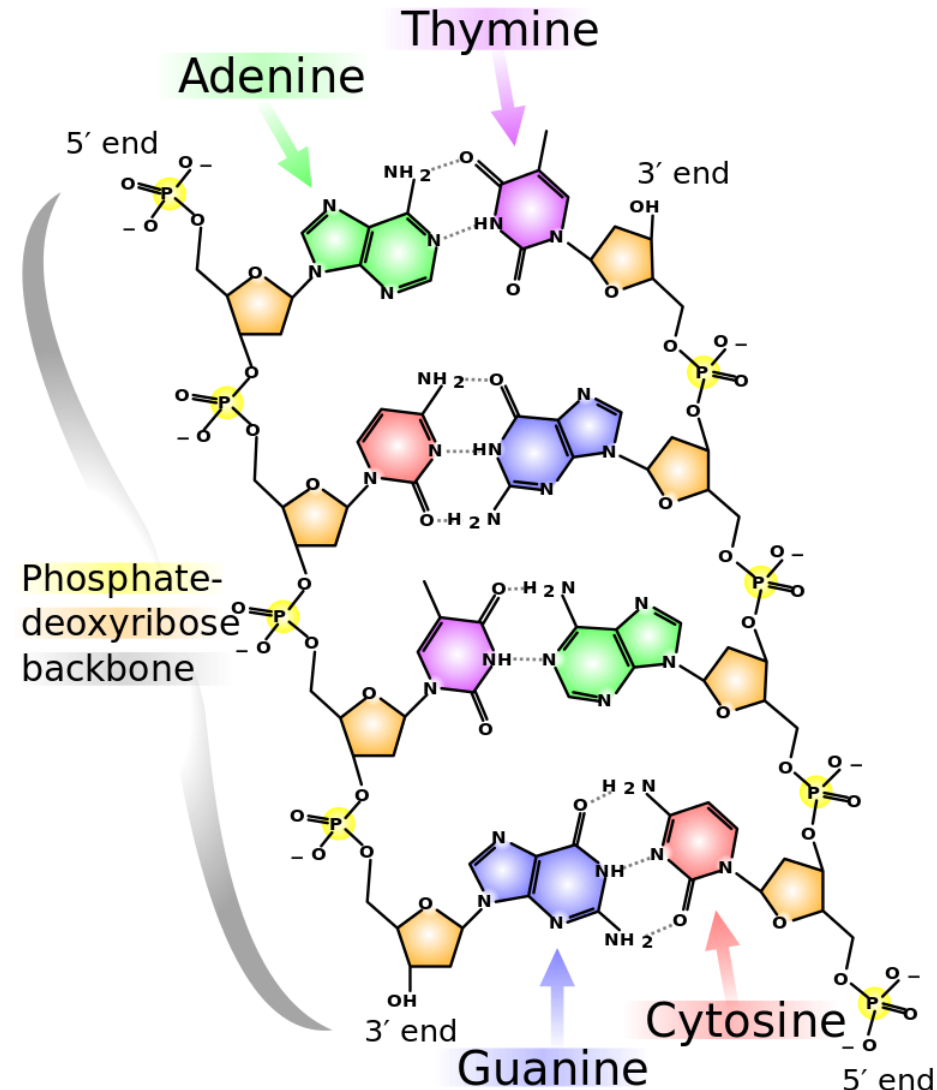
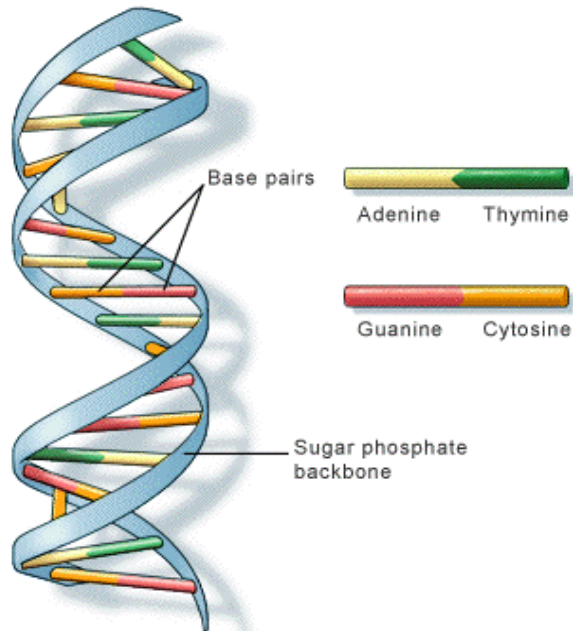
- Classification based on a target
 - DNA
 - DNA as the molecule
 - Synthesis of DNA
 - Metabolism of a cancer cells
 - Hormones
 - Immune system

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



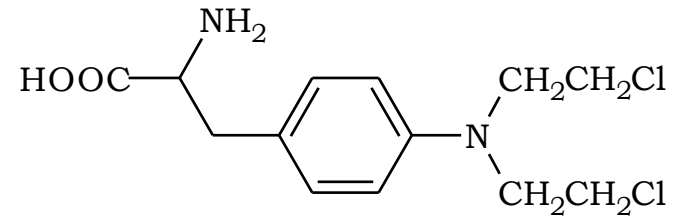
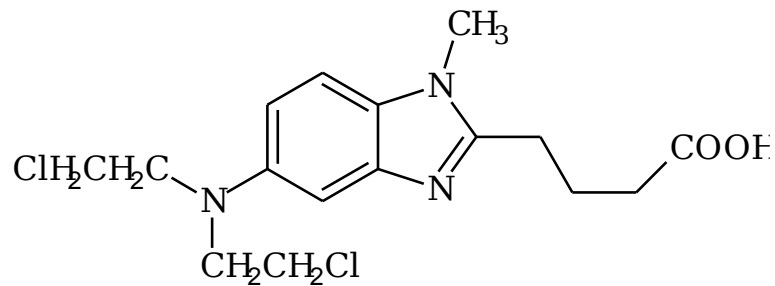
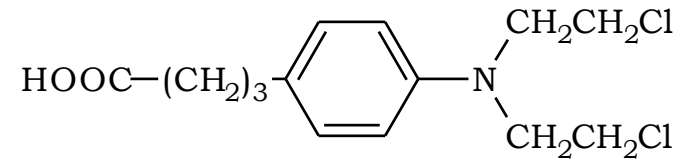
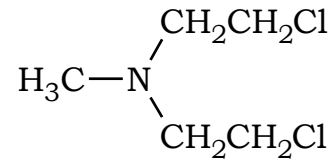
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Alkylating agents

- 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

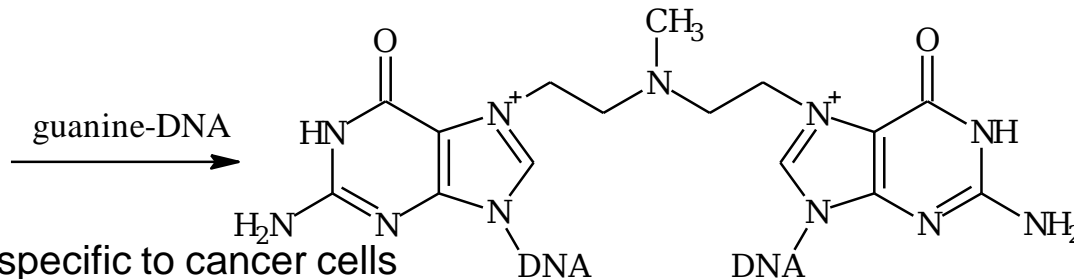
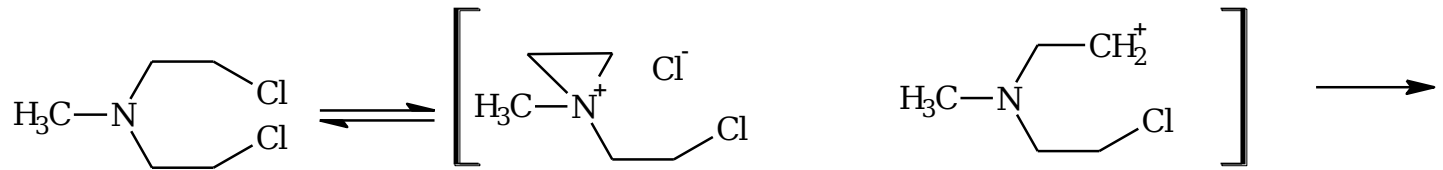
Alkylating agents – nitrogen mustards

- 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



Alkylating agents – nitrogen mustards

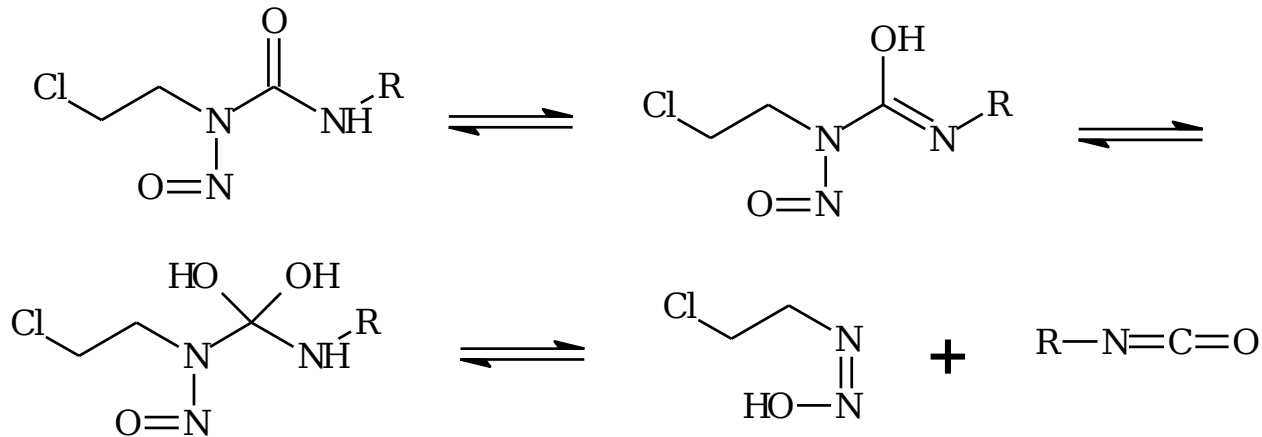
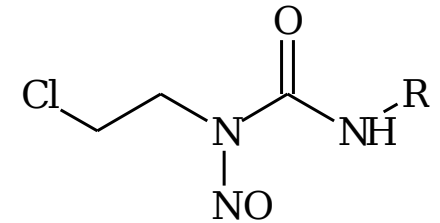
– Mechanism of alkylation



- Not specific to cancer cells
- Affects all dividing cells

Alkylating agents – nitrosourea derivatives

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



Alkylating agents – nitrosourea derivatives

– Streptozocine

- antibiotics, isolated from *Streptomyces achromogenes*
- pancreatic cancer

– Carmustine

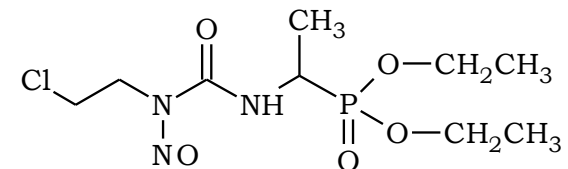
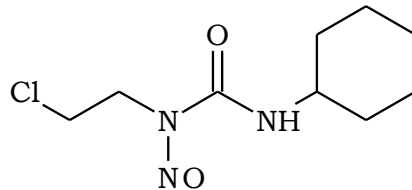
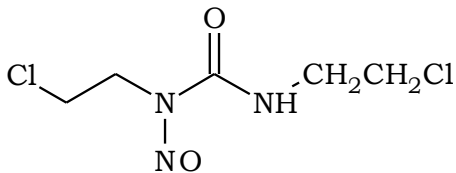
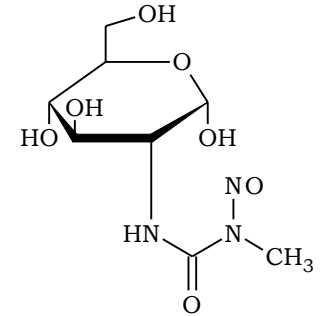
- high lipophilicity – effective against brain tumours

– Lomustine

- similar to carmustine, available after oral administration

– Fotemustine

- primarily for brain tumours therapy



Alkylating agents – aziridines, triazines

– Mitomycines

- effective after bioactivation
- GIT and gynecological carcinomas

– Dacarbazine

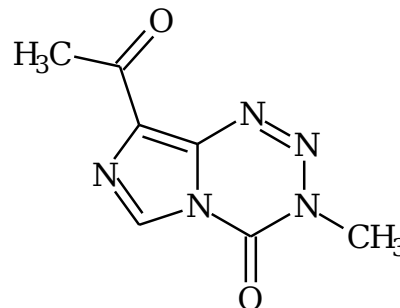
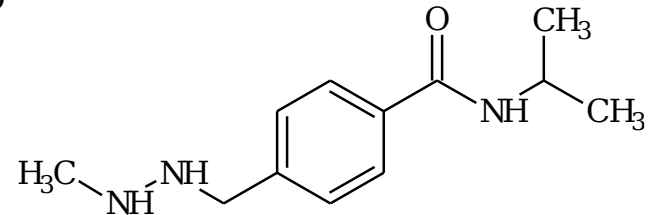
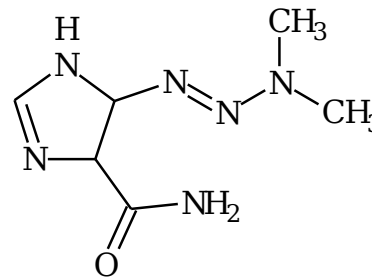
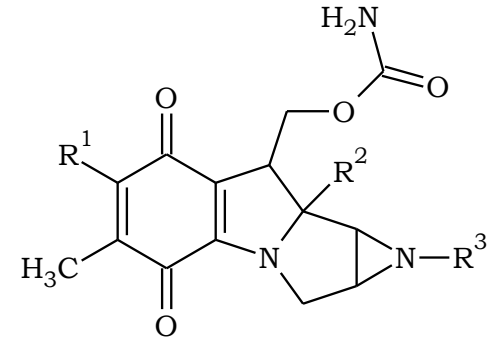
- malignant melanoma, etc.

– Procarbazine

- effective in brain tumours

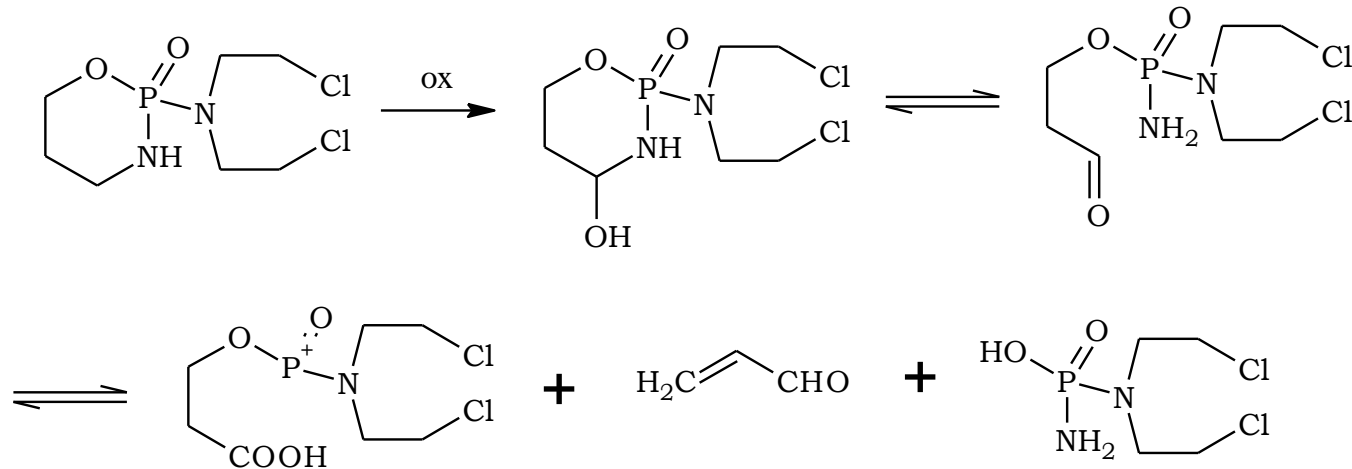
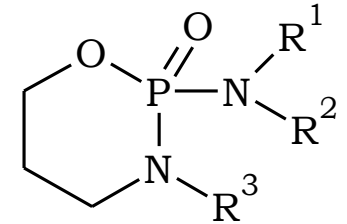
– Temozolomide

- very good oral bioavailability
- brain tumours



Alkylating agents - phosphamides

– Active after metabolic activation



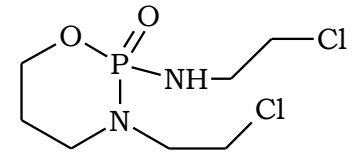
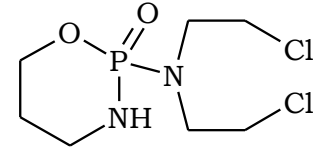
Alkylating agents - phosphamides

– Cyclophosphamide

- good oral bioavailability
- widely used for therapy of different tumours
- leukaemias, solid tumours (breast, ovarian, testis)

– Iphosphamide

- similar therapeutic spectrum as cyclophosphamide



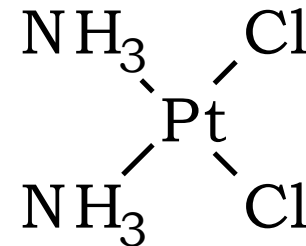
Platinum coordination compounds

- 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

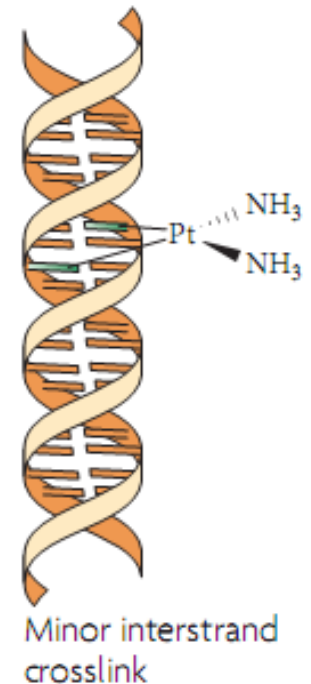
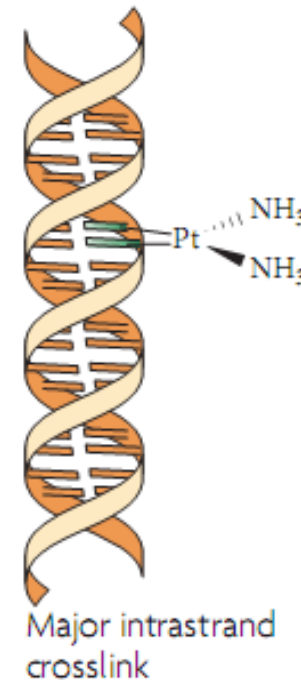
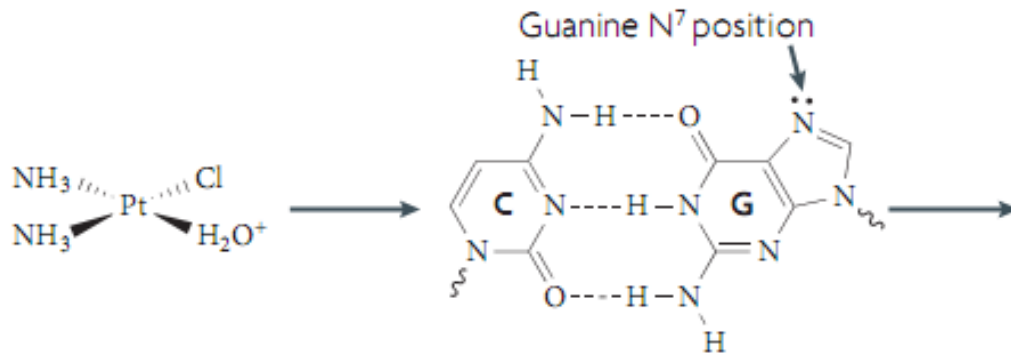
- First time synthesised by Peyron in 1845
- Discovery of its anticancer efficacy by serendipity
- Start of clinical evaluation in 1971
- Marketed in 1978
- Therapy of testicular cancer was the first indication
 - 80% efficacy in comparison with 5% of previous methods
- Still widely used in therapy in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



Platinum coordination compounds

– Mechanism of action

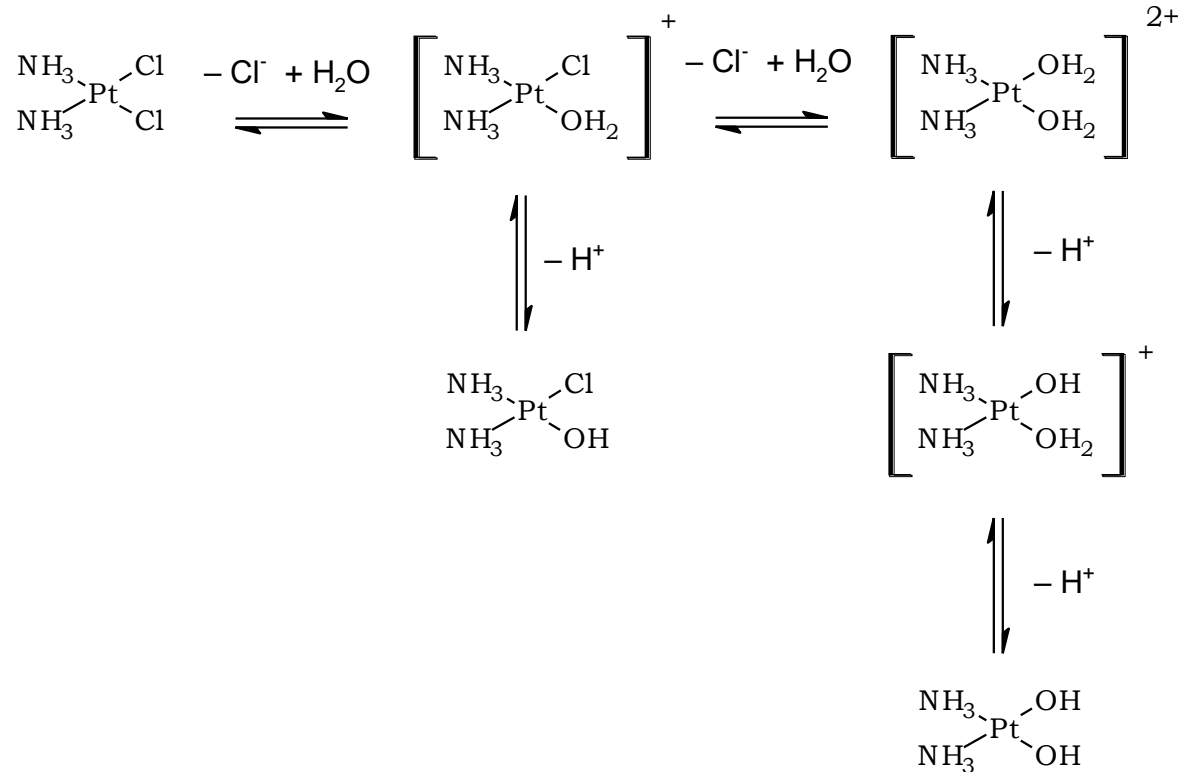
- Intrastrand covalent bond to DNA purine bases
- Reactivity of „leaving ligands“



Platinum coordination compounds

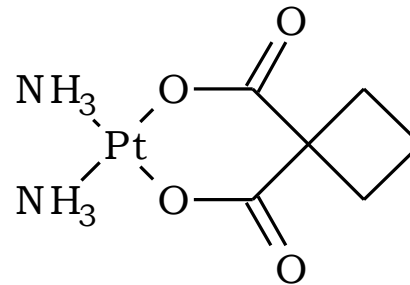
– Mechanism of action

– activation – aquacomplexes – very reactive



Platinum coordination compounds

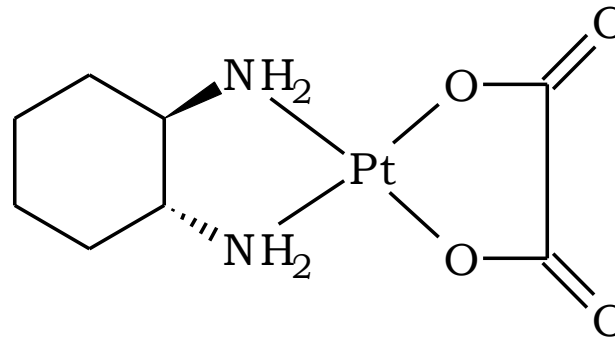
- Carboplatin
 - Reduced toxicity, but also less effective
 - Significantly less nephrotoxic
 - Cross-resistance with cisplatin
 - Similar indications as cisplatin



Platinum coordination compounds

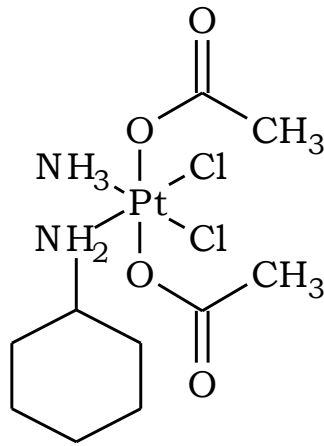
– Oxaliplatin

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

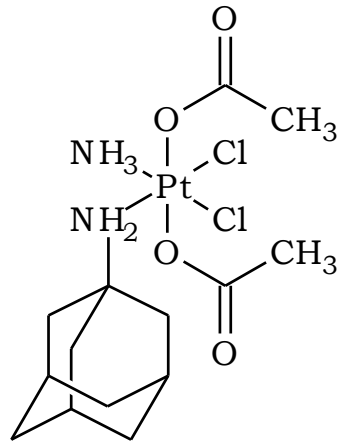


Platinum coordination compounds

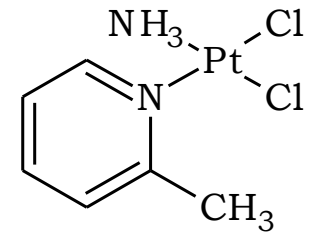
- Orally available compounds
 - Platinum in oxidative state IV
 - Increased stability in GIT due to reduced reactivity
 - Reduction to platinum(II) compounds in cells (activation)
 - Overcoming resistance to cisplatin



satraplatin



LA-12



picoplatin

Antimetabolites – folic acid

Folic acid is needed for biosynthesis of nucleic acids

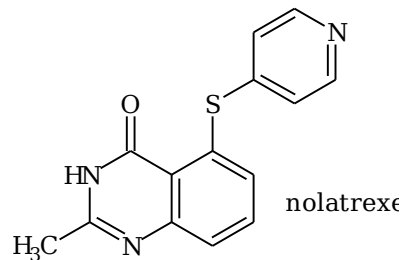
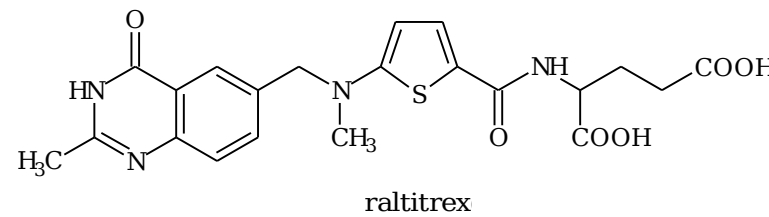
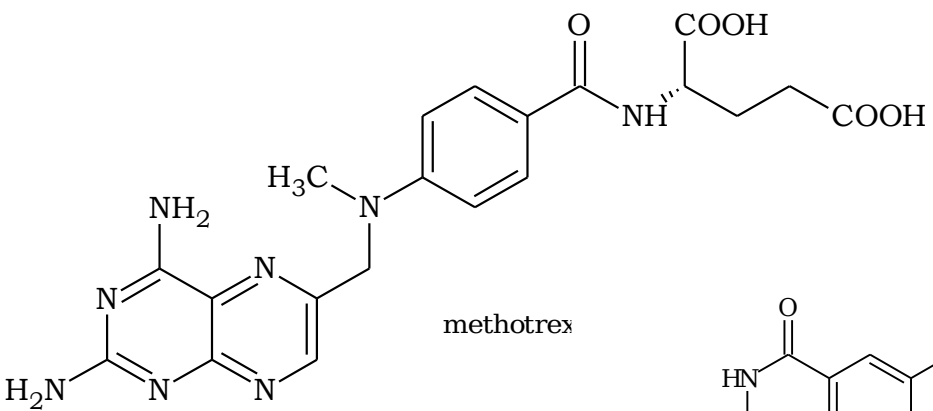
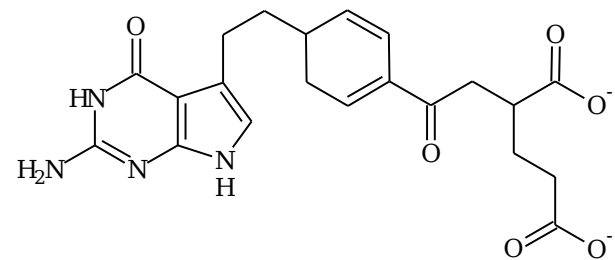
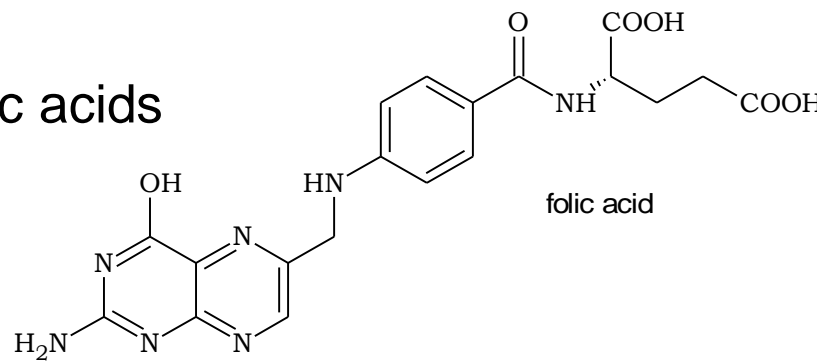
Source for one-carbon fragments

Methotrexate
immunosuppressive agent
inhibition of tetrahydrofolate reductase

Pemetrexed
inhibition of more enzymes

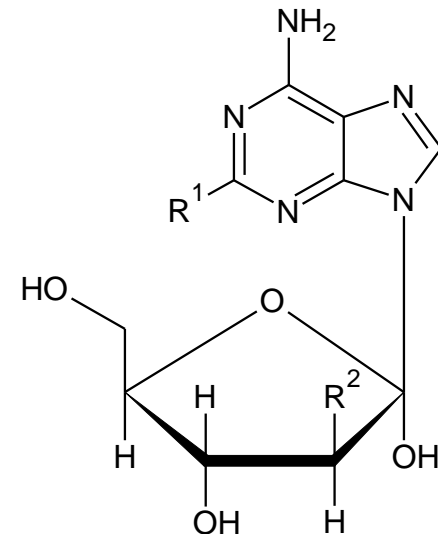
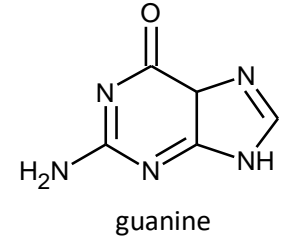
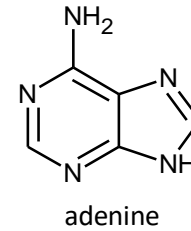
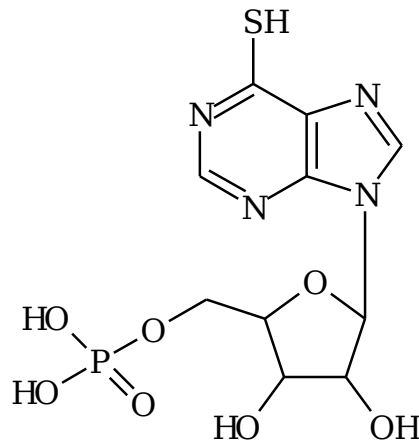
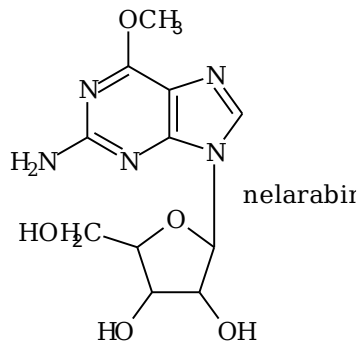
Raltitrexed

Nolatrexed



Antimetabolites – purine bases

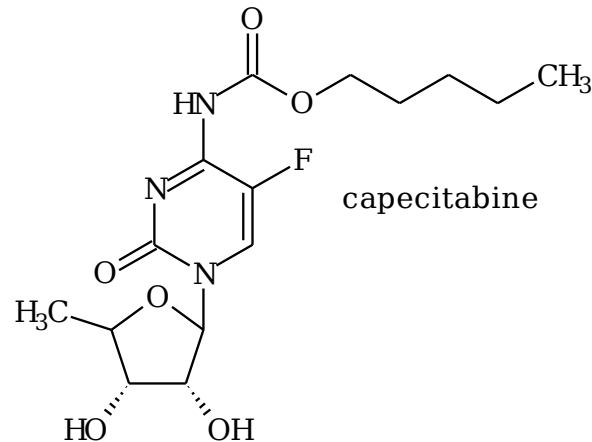
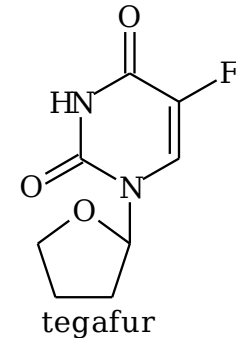
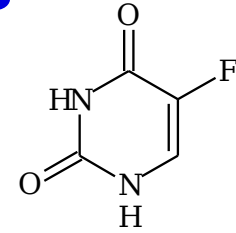
- $R^1 = H$; $R^2 = OH$ – vidarabine (antivirotics)
- $R^1 = F$; $R^2 = OH$ – fludarabine (leukaemia)
- $R^1 = Cl$; $R^2 = H$ – cladribine (leukaemia)
- $R^1 = Cl$; $R^2 = F$ – clofarabine (leukaemia)
- Activation by phosphorylation
 - Nelarabine



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



Antimetabolites – pyrimidine bases

– Cytidine derivatives

– cytarabine

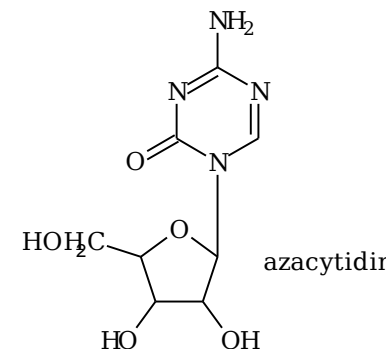
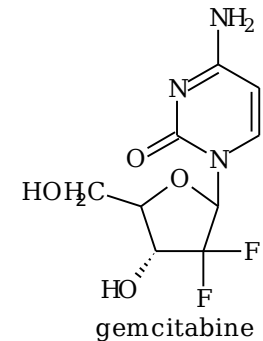
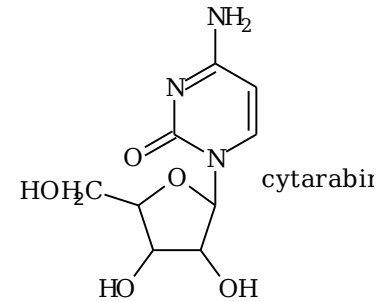
arabinose instead of ribose
false nucleotide in DNA
i.v. administration
therapy of leukaemias

– gemcitabine

bioactivation by phosphorylation
pancreatic, bronchial, breast and bladder carcinoma

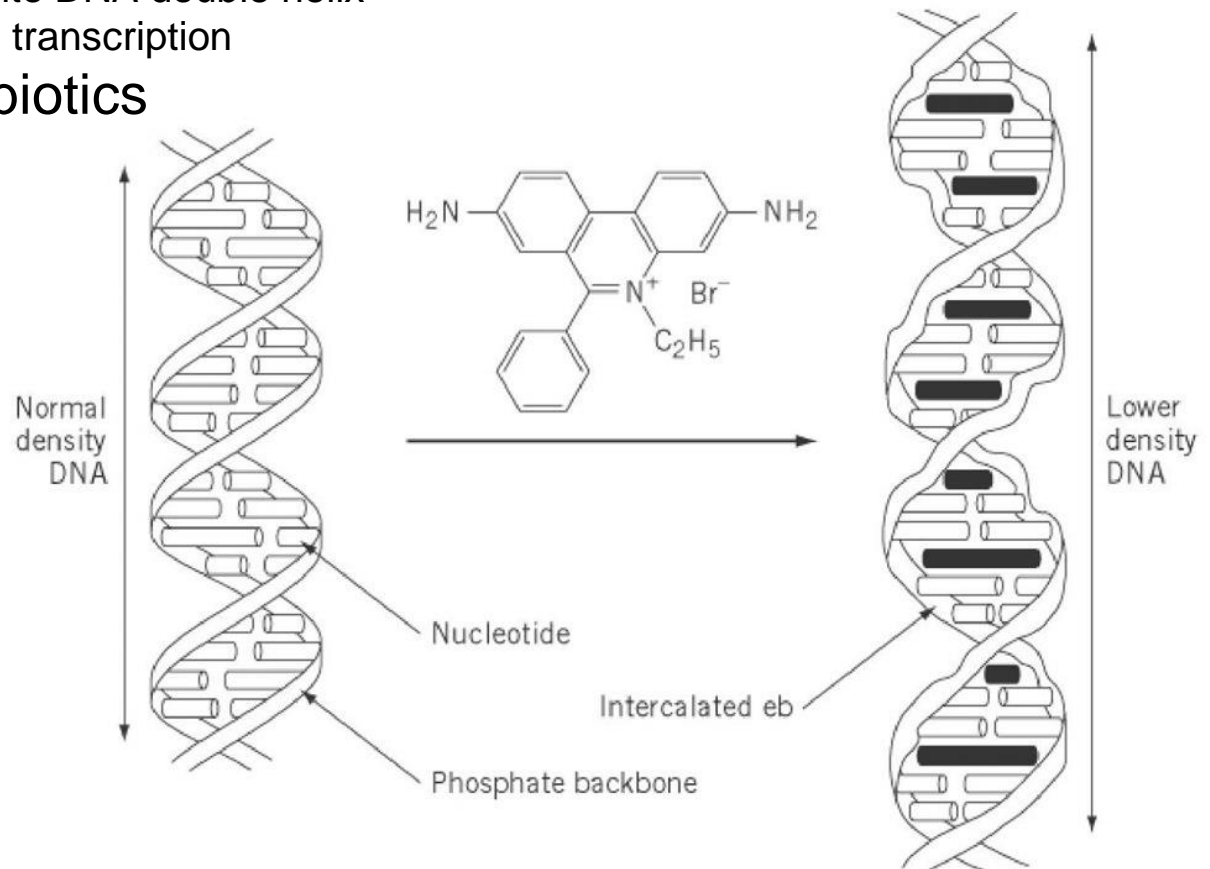
– azacytidine

myelodysplastic syndrome



Intercalating agents

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



Intercalating agents

– Anthracycline antibiotics

– doxorubicine

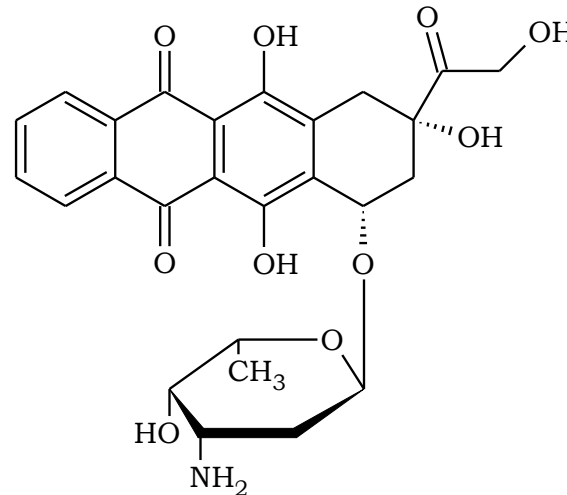
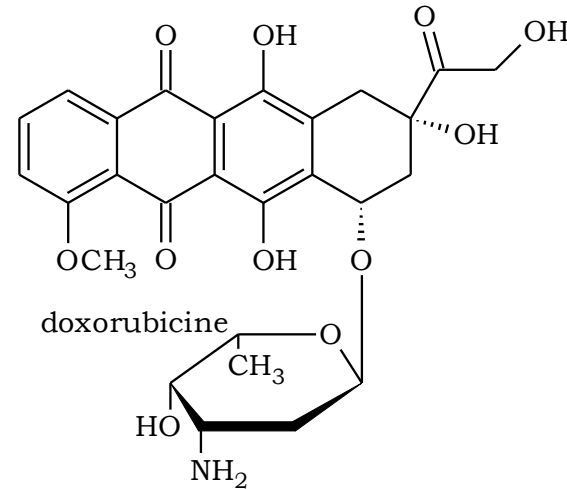
wide spectrum of cancer types
cardiotoxicity, myelosuppression

– epirubicine

epimere of doxorubicine
reduced toxicity

– idarubicine

increased lipophilicity
acute myeloid leucaemia



Intercalating agents

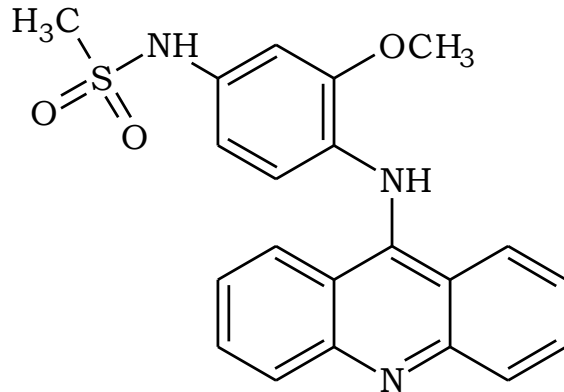
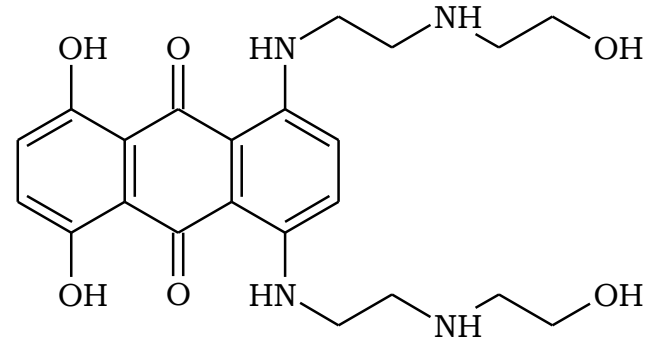
– Synthetic compounds

– mitoxantrone

acute myeloid leucaemia, breast
and other carcinomas

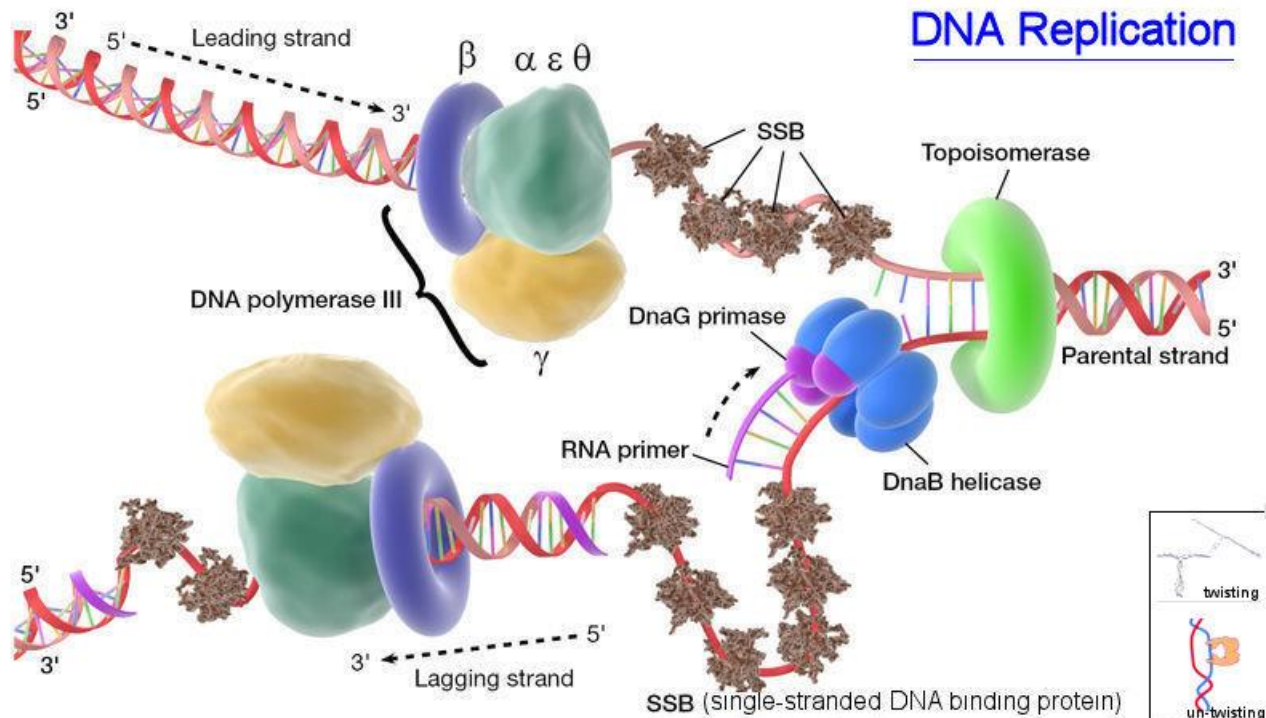
– amsacrine

poor solubility
inhibition of topoisomerase



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



Topoisomerase inhibitors – camptothecins

– Camptothecin and its derivatives

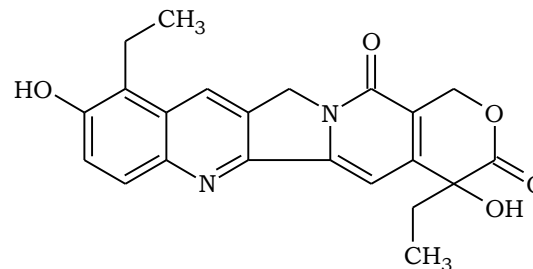
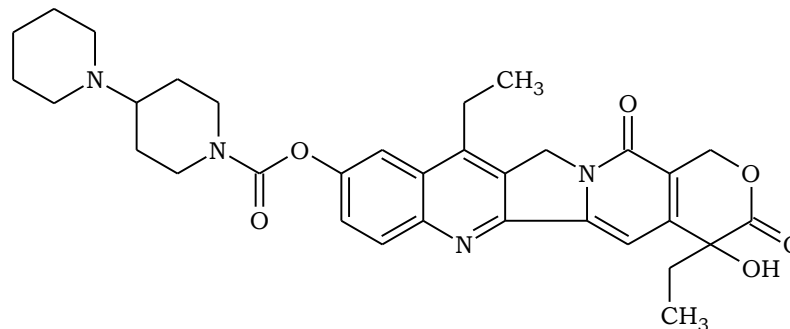
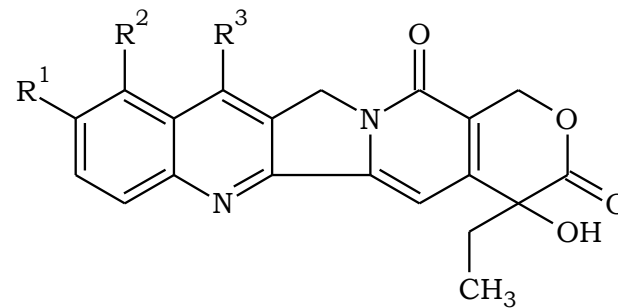
- pentacyclic structure
- lactone ring is necessary for anticancer activity

– Irinotecan

- good inhibitor
- inhibes acetylcholinesterase too
- advanced colorectal carcinoma

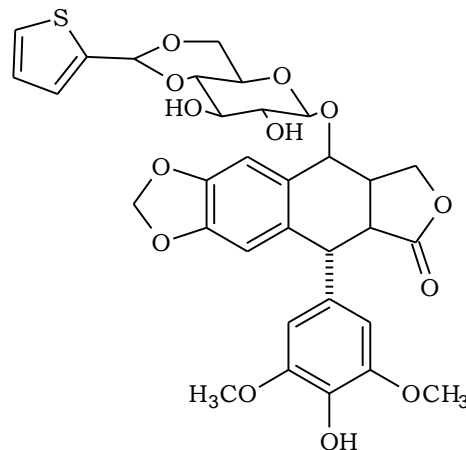
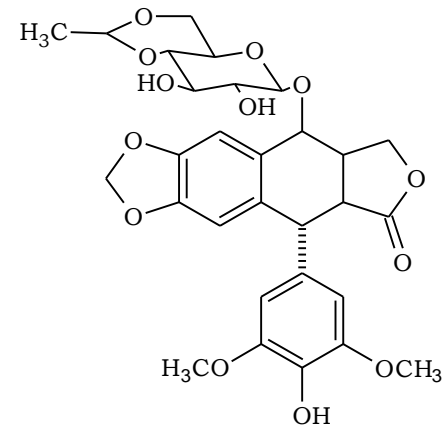
– Topotecan

- i.v. administration
- metastatic ovarian carcinoma, NSCLC



Topoisomerase inhibitors – podophylotoxins

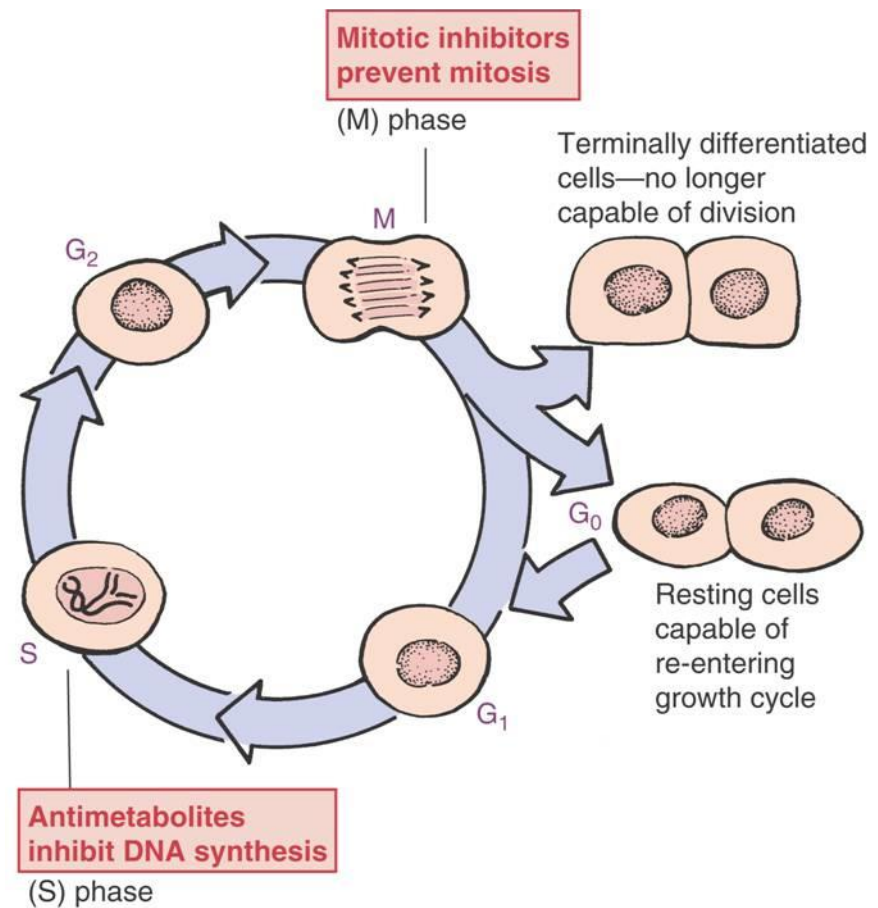
- Podophylotoxine is unusable for the therapy, in clinical use are semisynthetic derivatives
- Etoposide
 - p.o. administration
 - lung carcinomas, leukaemias
- Teniposide
 - parenteral administration only
 - mitosis inhibitor



Mitosis inhibitors

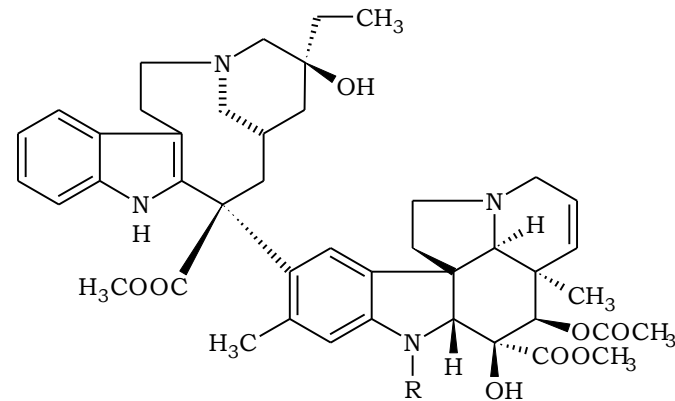
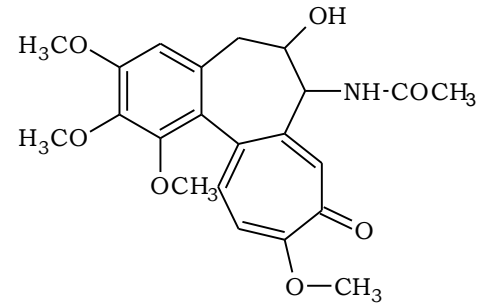
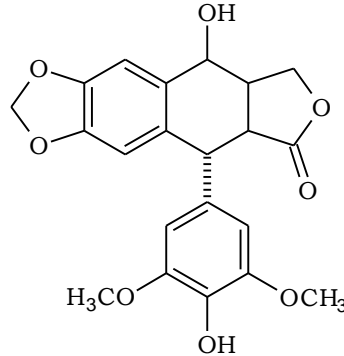
- Natural compounds of different structures
- Block of mitosis in M-phase
- Bonding to microtubules

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



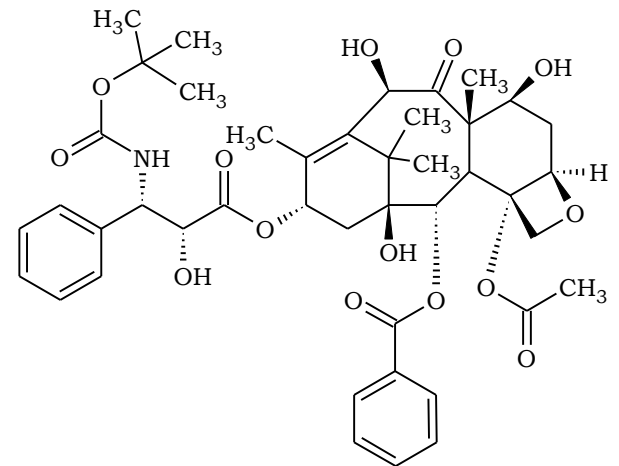
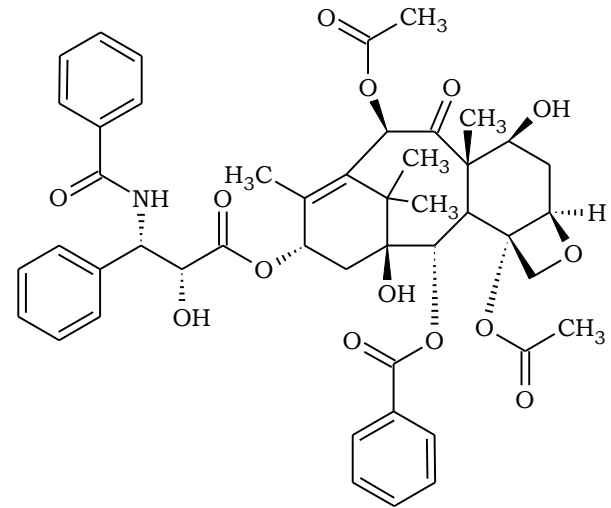
Mitosis inhibitors

- Colchicine
 - not used in therapy
- Podofylotoxin derivatives
 - glycosides
- Vinca alkaloides
 - vinblastine (CH₃)
 - parenteral administration
 - leukaemias, some solid tumours
 - vincristine (CHO)
 - vinorelbine
 - lung carcinoma (NSCLC)
 - metastatic breast carcinoma



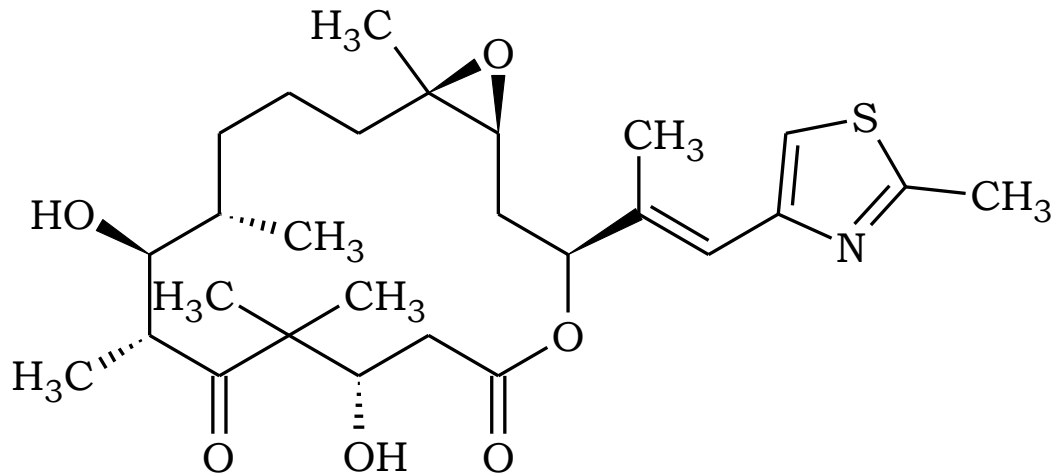
Mitosis inhibitors – taxanes

- *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



Mitosis inhibitors – other structures

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



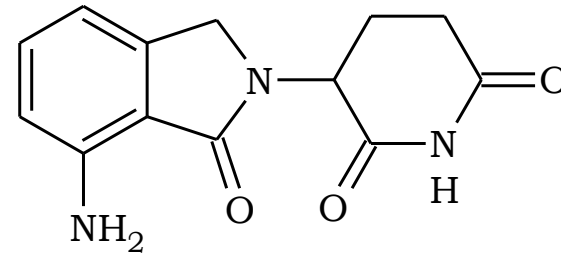
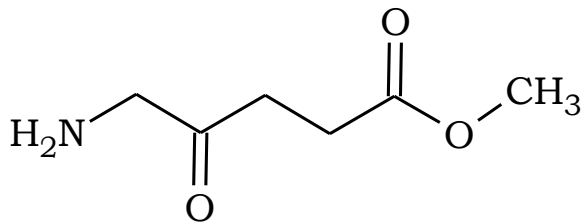
Other antineoplastics

– Lenalidomide

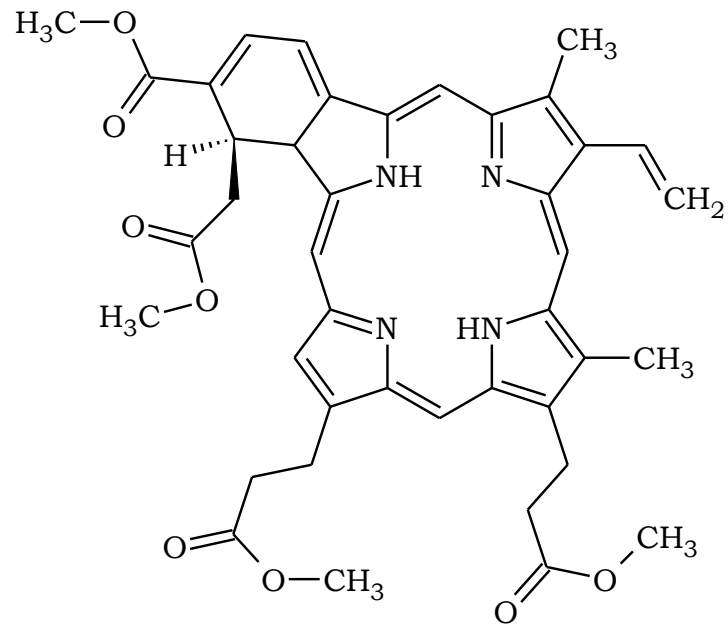
- based on thalidomide
- inhibition of cytokines
- inhibition of angiogenesis

– Photosensitizers

- Aminolevulinic acid
Precursor of porphyrins
- Porphyrins



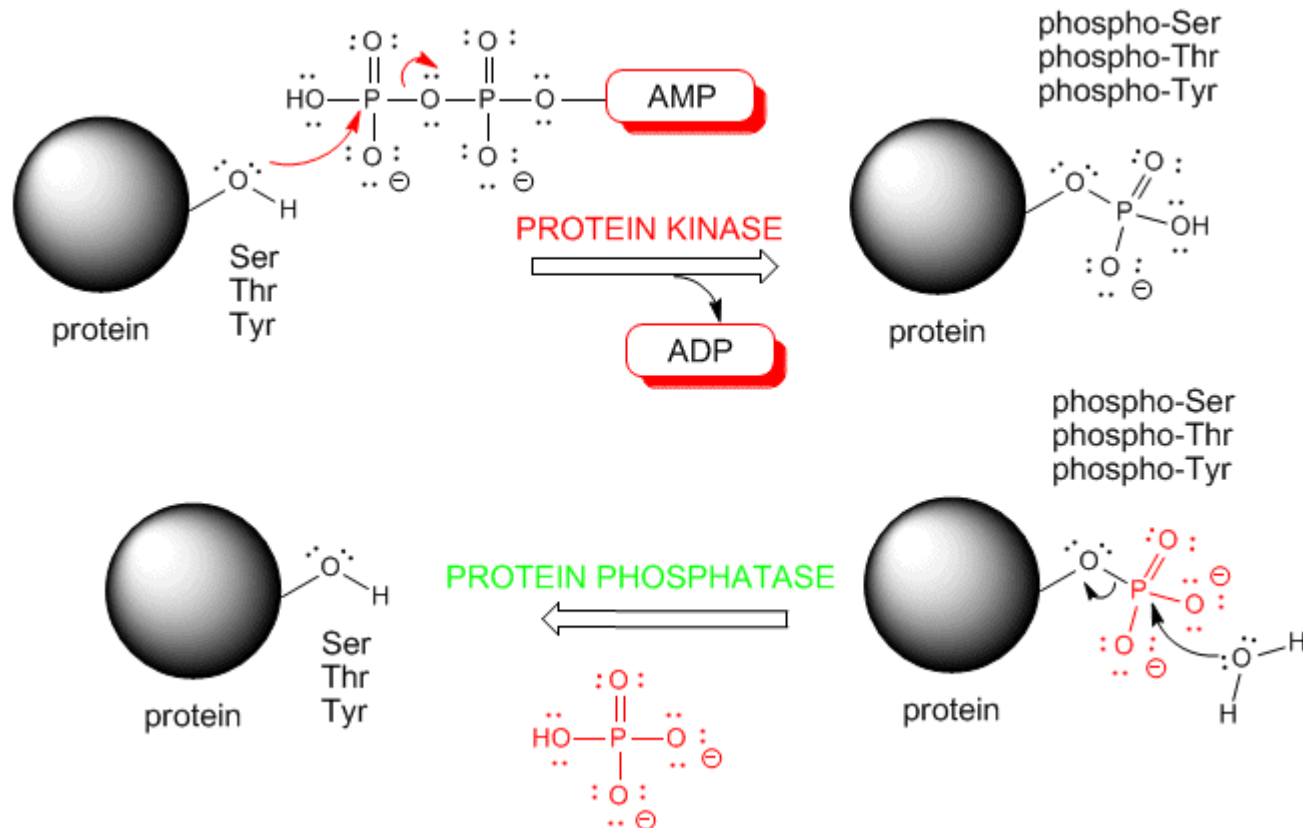
lenalidomide



Kinases inhibitors

– Protein Kinases

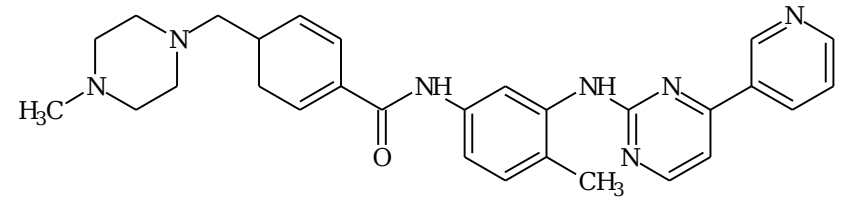
- Key regulators of cell function
- By adding phosphate groups to substrate proteins, they direct the activity, localization and overall function of many proteins, and serve to orchestrate the activity of almost all cellular processes.



Kinases inhibitors – tyrosinekinase inhibitors

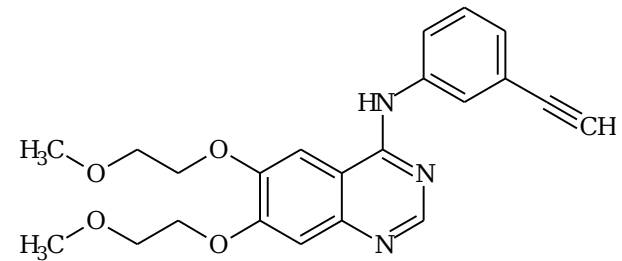
– Imatinib

- chronic myelogenous leukaemia
- oral administration



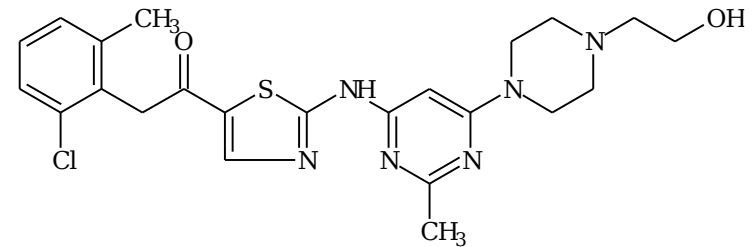
– Erlotinib

- oral administration
- advanced or metastatic lung carcinoma



– Dasatinib

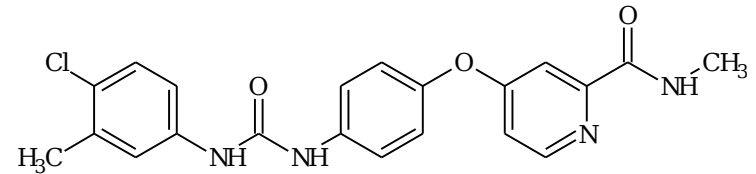
- chronic myelogenous leukaemia
- oral administration



Kinases inhibitors – tyrosinekinase inhibitors

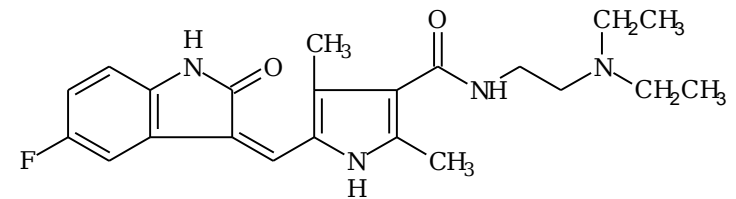
– Sorafenib

- multiple-kinases inhibitor
- advanced kidney carcinoma
- liver carcinoma



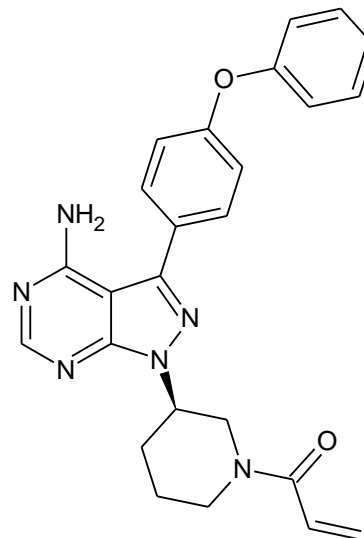
– Sunitinib

- inoperable gastric tumours
- advanced kidneys carcinoma



– Ibrutinib

- Lymphoma
- Chronic lymphocytic leukaemia



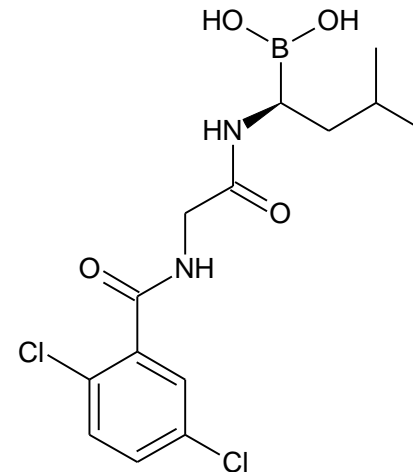
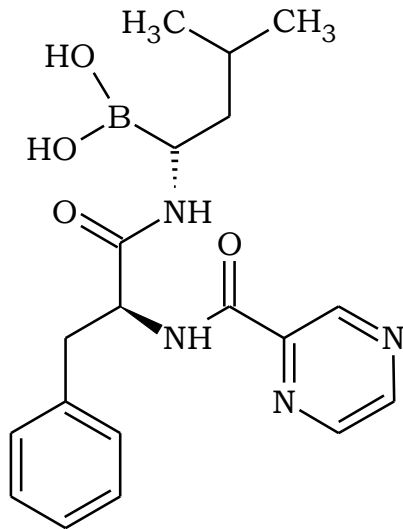
Proteasome inhibitors

– Bortezomib

- proteasomes eliminate signaling and regulating proteins
- cancer cells are more sensitive to proteasome inhibition
- therapy of advanced multiple myeloma

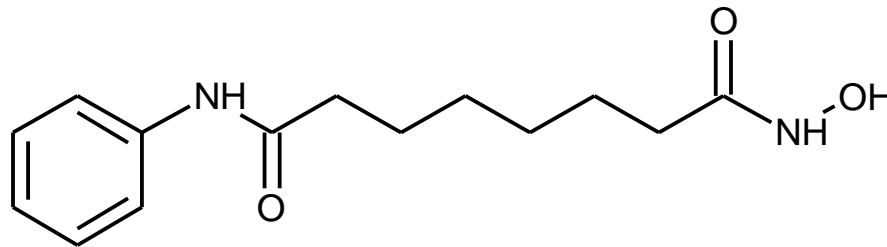
– Ixazomib

- multiple myeloma (bone marrow cancer), in combination chemotherapy with lenalidomide and dexamethasone



Histone deacetylase inhibitors

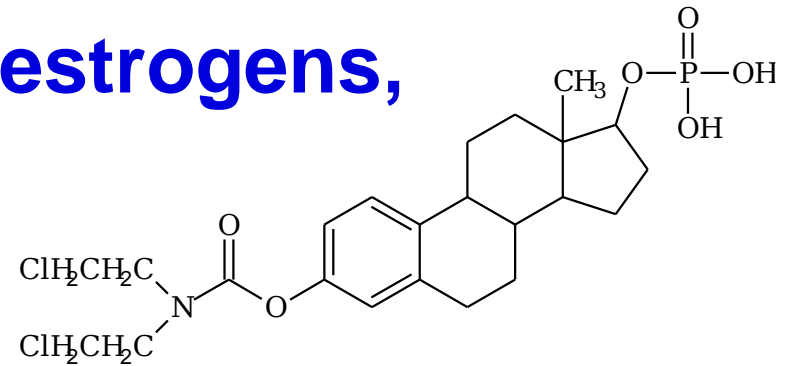
- DNA is surrounded by histones and creates nucleosomes
 - protection of DNA
- Histones are basic proteins
- Acetylation and deacetylation regulate accessibility of DNA for some enzymes
- Inhibitors of histone deacetylase are used for treatment of haematological cancers
- **Vorinostat**



Hormone-based drugs – estrogens, antiestrogens

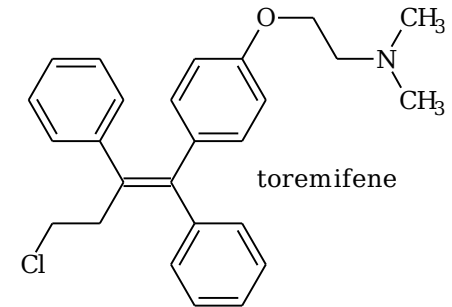
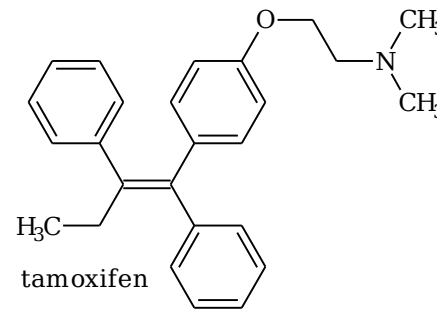
– Estramustin-phosphate

- alkylation mechanism
- main mechanism is hormonal
- therapy of prostate carcinoma



– Tamoxifene

- antiestrogen
- partial agonistic activity
- estrogen-dependent breast carcinoma

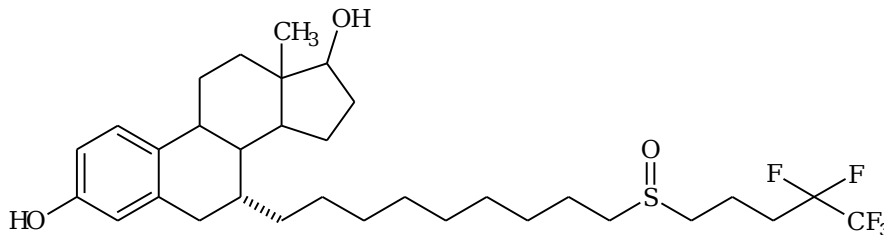


– Toremifene

- very similar indications as tamoxifene

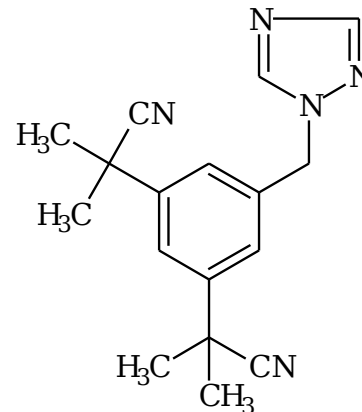
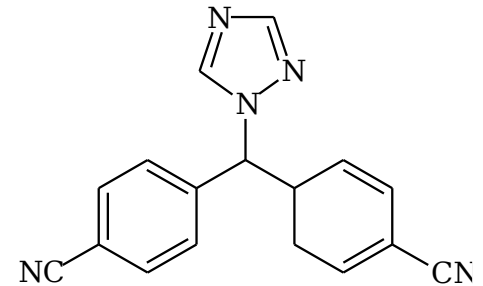
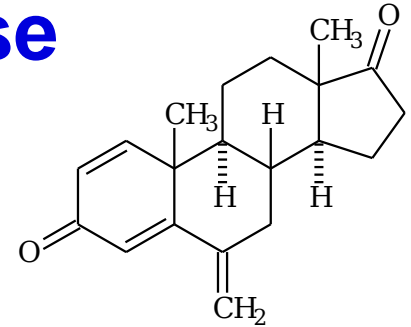
– Fulvestrant

- inactivator of estrogen receptors – strong bonding resulted in receptor destruction
- high lipophilicity



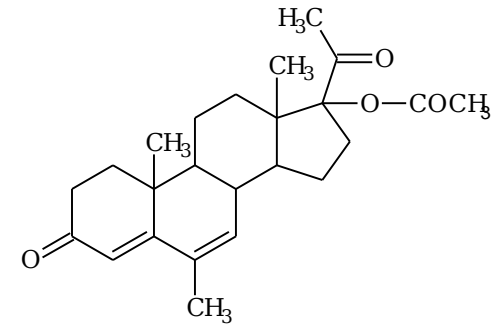
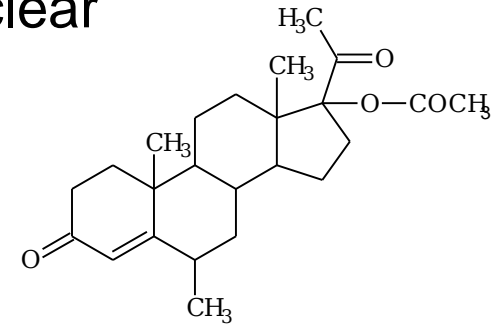
Hormone-based drugs – aromatase inhibitors

- 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



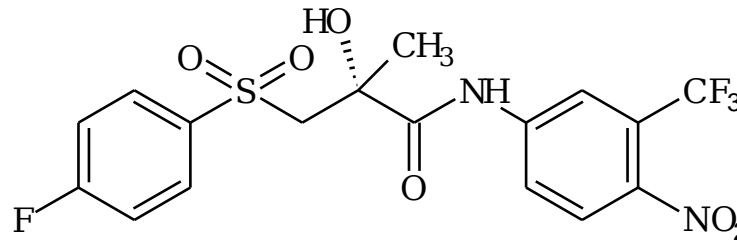
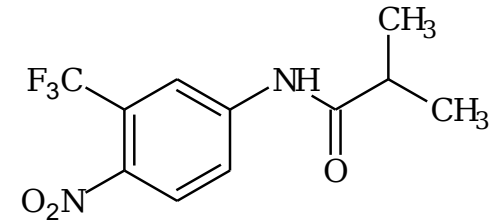
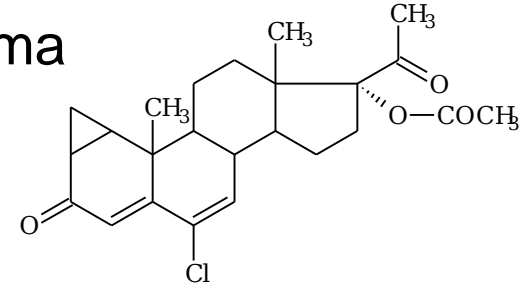
Hormone-based drugs – gestagenes

- Mechanism of antineoplastic activity is still not clear
- Medroxyprogesterone-acetate
- Megestrol-acetate
 - metastasis of breast carcinoma
 - advanced endometrial carcinoma



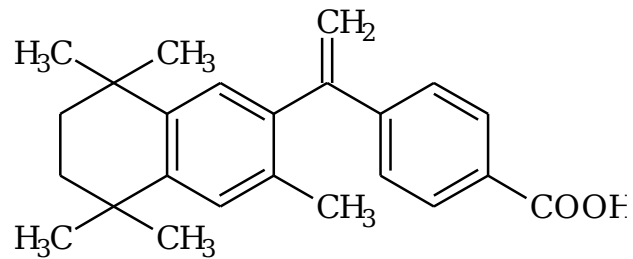
Hormone-based drugs – antiandrogens

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



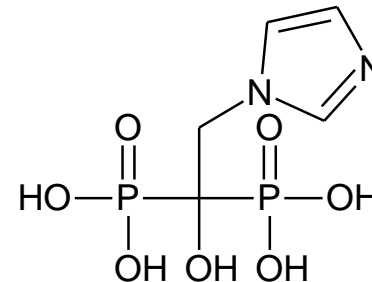
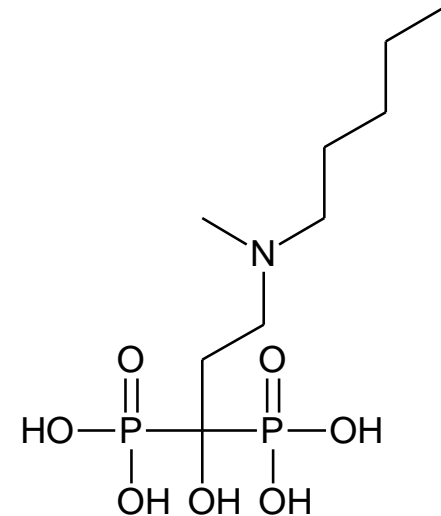
Retinoids

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

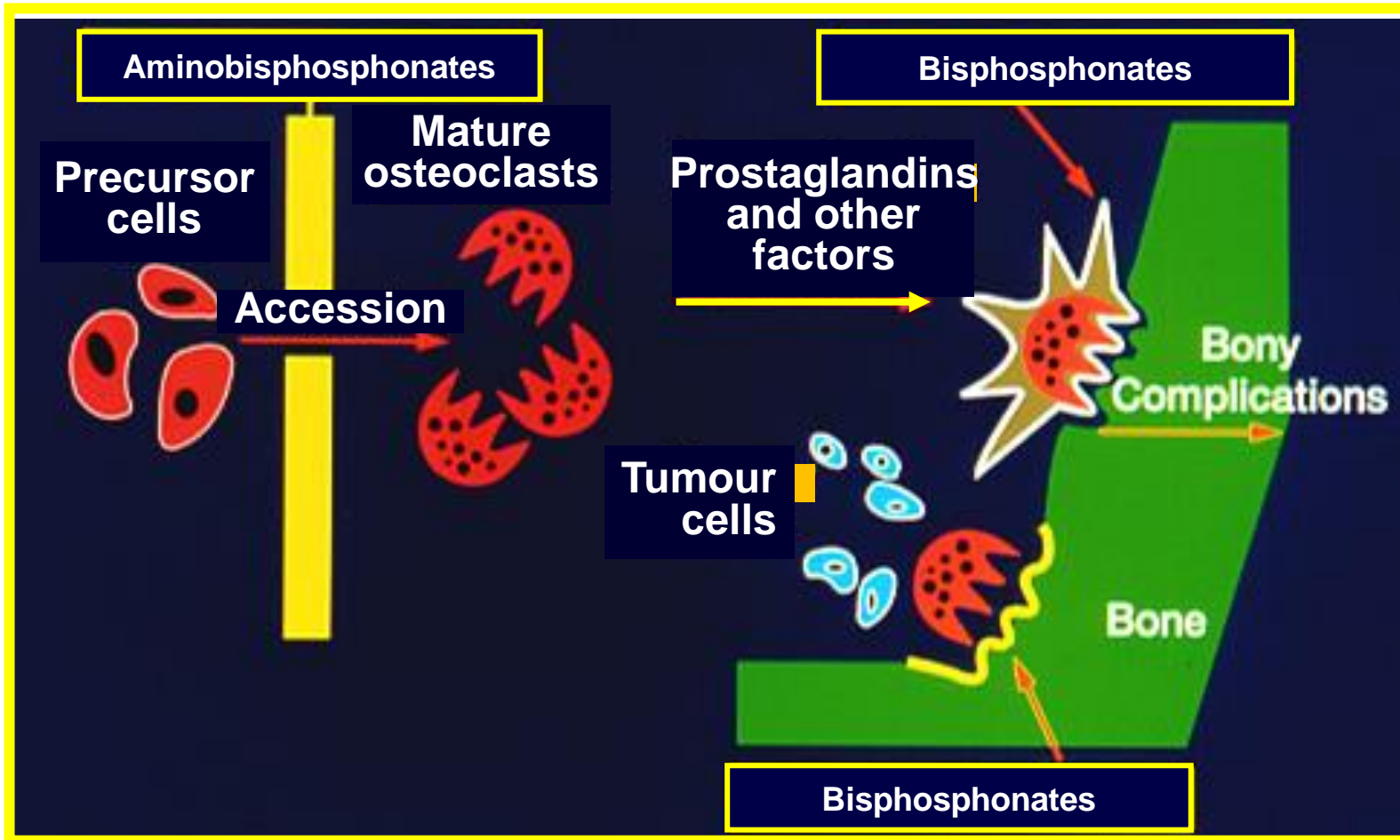


Bisphosphonates

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



Bisphosphonates



Monoclonal antibodies

- Antibodies against specific antigens, expressed 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