

Anticancer agent

Introduction

- ❖ Cancer is a disease characterized by uncontrollable, irreversible, independent, and abnormal over growth of tissues.
- ❖ Cancer spreads by invasion to the surrounding tissues and by metastasis to distant sites.

Types of Cancer	Affected Area
Breast Cancer	Breast
Bladder Cancer	Urinary Bladder
Bone marrow Cancer	Shafts of long bones
Colon Cancer	Colon
Cervical Cancer	Cervix
Gynecological Cancer	Female Reproductive organs
Lung Cancer	Lung
Osteo sarcoma	metaphyseal region of tubular long bones
Wilms tumour	Kidney
Leukemia	Blood
Larynx Cancer	Larynx

Causes

Environment

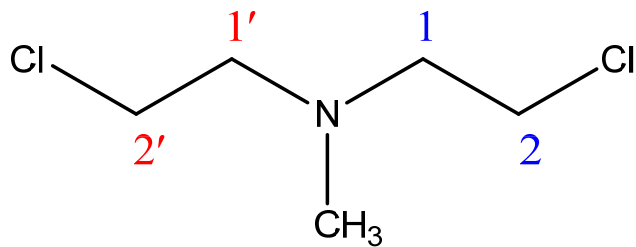
- ❖ cigarette smoke
- ❖ Chemicals
- ❖ UV light
- ❖ Viruses

Metabolic processes

- ❖ free radicals
- ❖ DNA copying and repair defects

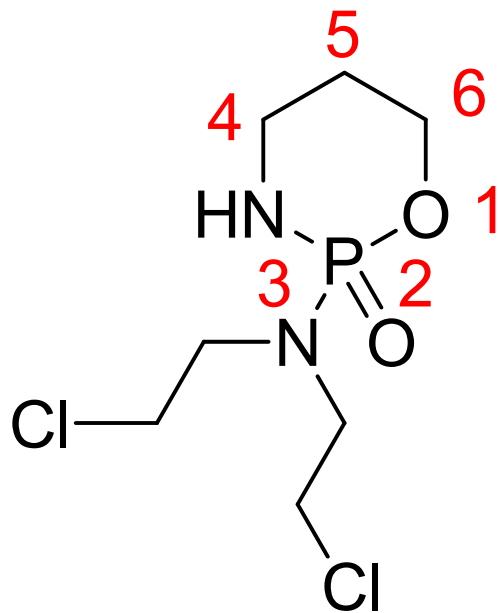
Inherited genetic mutations

Alkylating agents



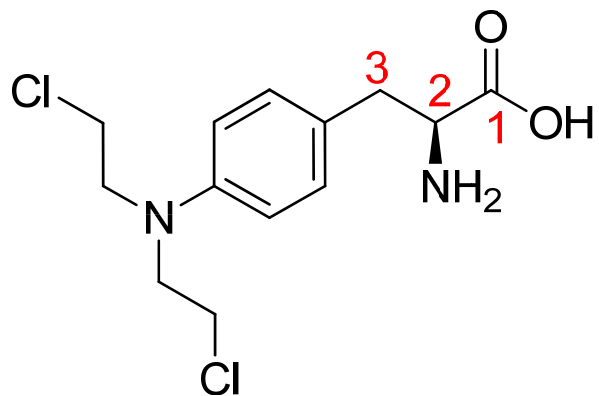
Meclorothamine

IUPAC: 2,2'-dichloro-N-methyldiethylamine



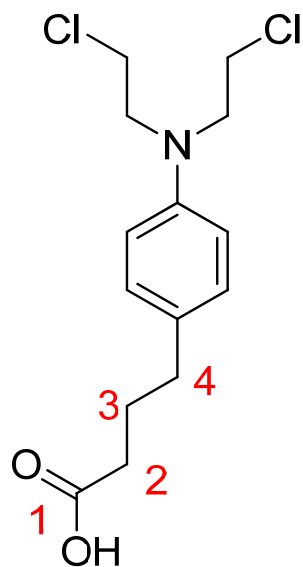
Cyclophosphamide

IUPAC: 2-[Bis(2-chloroethylamino)]-tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide



IUPAC: 3-(p-(Bis(2-chloroethyl) amino)phenyl)-L-alanine

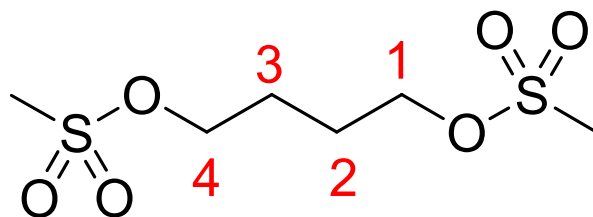
Melphalan



IUPAC: 4-(p-bis(beta-chloroethyl) aminophenyl)butyric acid

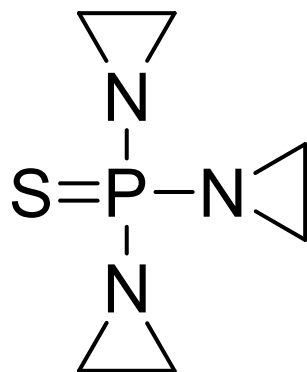
Chlorambucil

Busulfan



IUPAC: 1,4-Bis(methanesulfonyl)butane

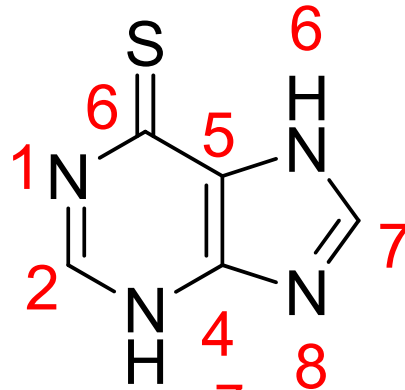
Thiotepa



IUPAC: *N,N',N''*-triethylenethiophosphoramide

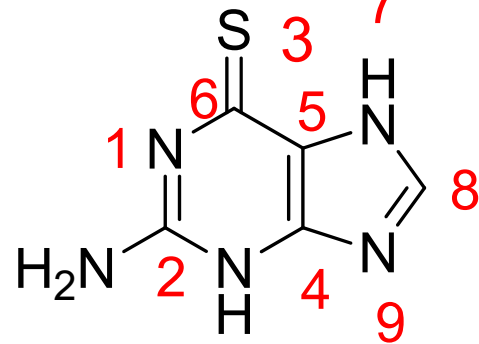
Antimetabolites

Mercaptopurine



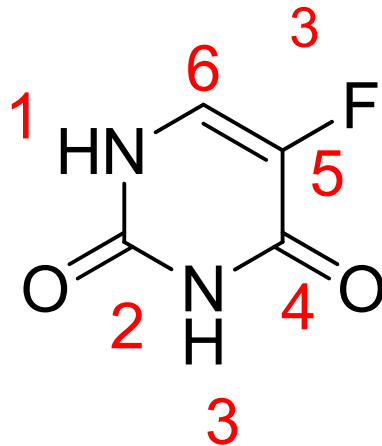
IUPAC: 6-Thioxopurine

Thioguanine



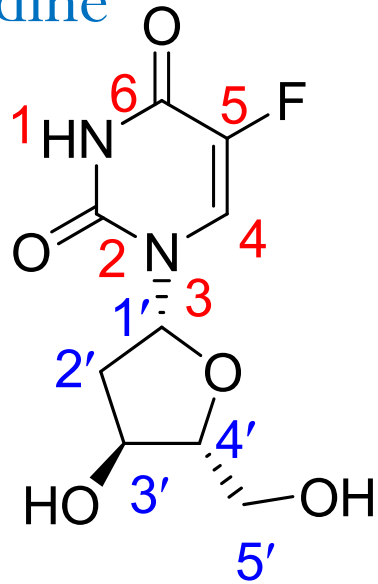
IUPAC: 2-Amino-1,7-dihydro-6H-purine-6-thione

Fluorouracil



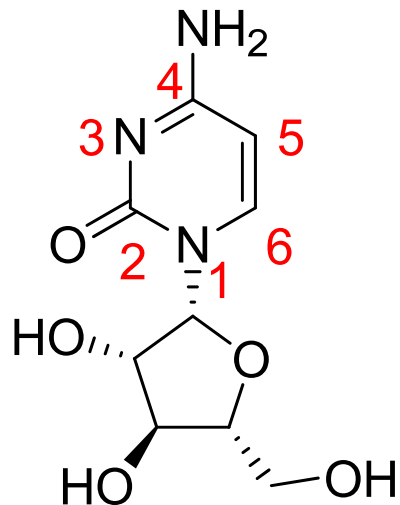
IUPAC: 5-Fluoropyrimidine-2,4-dione

Floxuridine



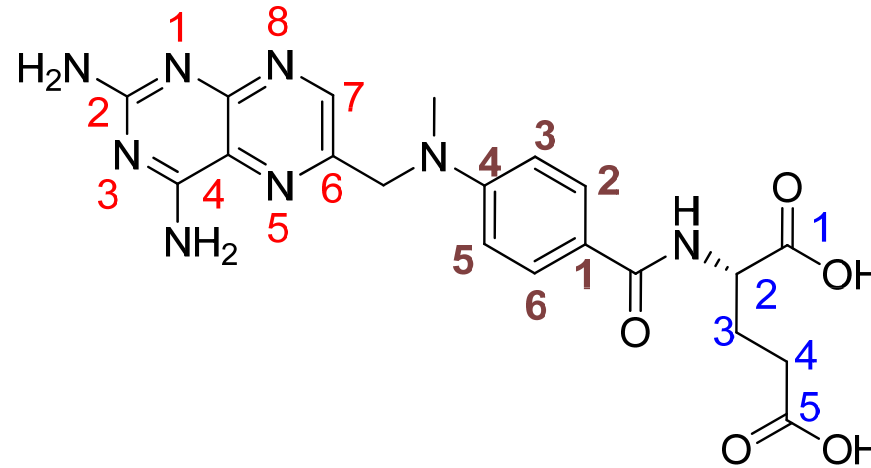
IUPAC: 1beta-D-2'-Deoxyribofuranosyl-5-fluorouracil

Cytarabine



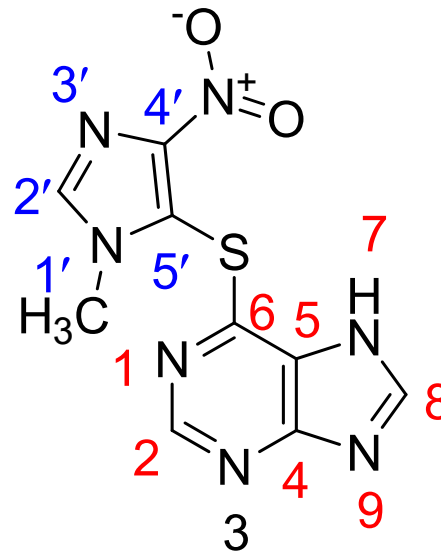
IUPAC: 4-Amino-1-beta-D-arabinofuranosyl-2(1H)-pyrimidinone

Methotrexate



IUPAC: (2S)-2-[(4- {[(2,4-diaminopteridin-6-yl)methyl] (methyl) amino} phenyl)formamido]pentanedioic acid

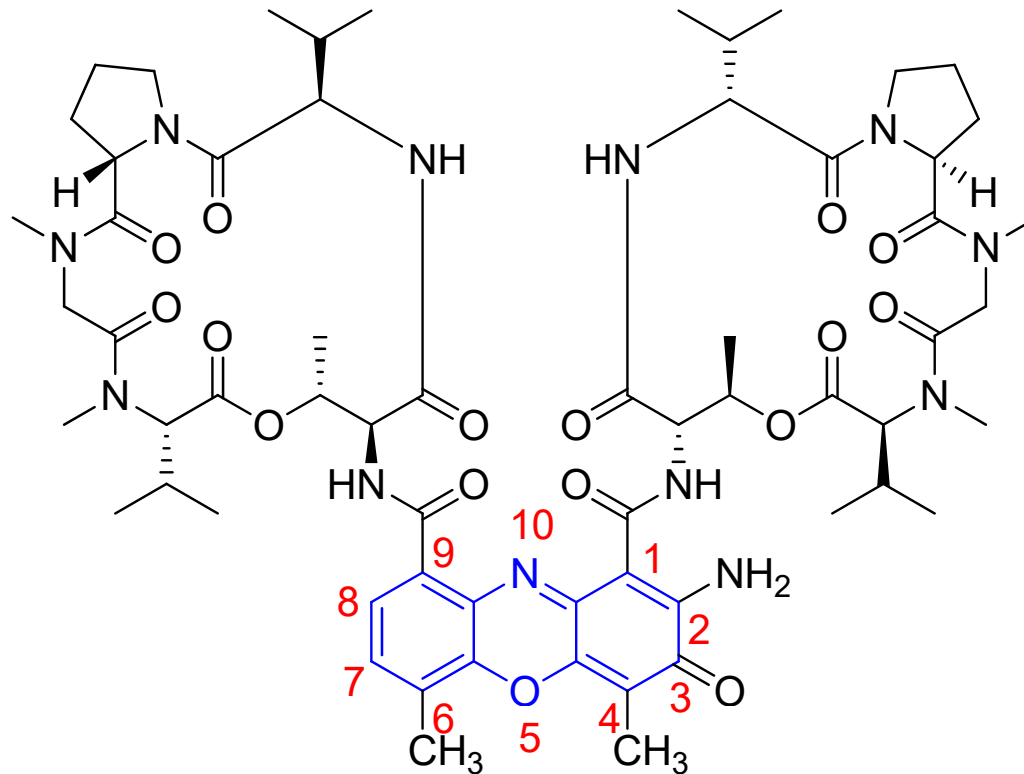
Azathioprine



6-((1'-Methyl-4'-nitro-1H-imidazol-5'-yl)thio)-1H-purine

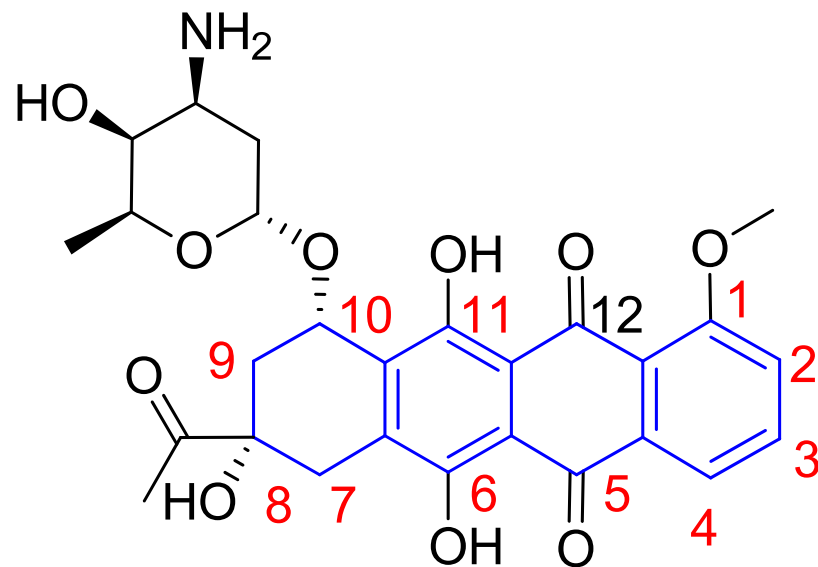
Antibiotics

Dactinomycin



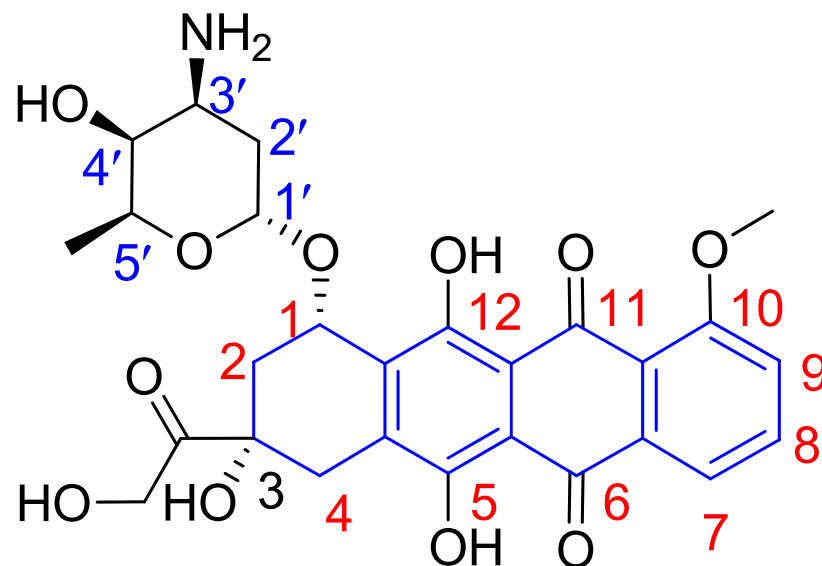
IUPAC: 2-amino-*N,N'*-bis(hexadecahydro-2,5,9-trimethyl-6,13-bis(1-methylethyl)-1,4,7,11,14-pentaoxo-1H-pyrrolo(2,1-*i*)(1,4,7,10,13)oxatetra-azacyclohexadecin-10-yl)-4,6-dimethyl-3-oxo-3H-phenoxazine-1,9-dicarboxamide

Daunorubicin



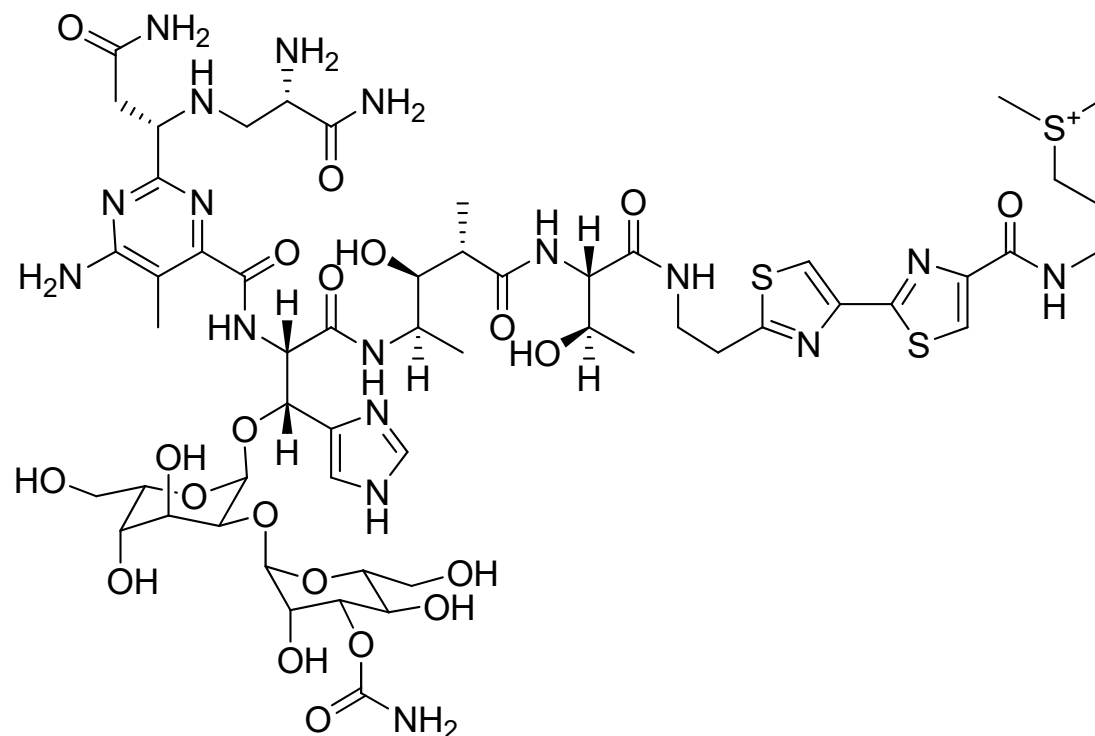
IUPAC: (8*S*-*cis*)-8-acetyl-10-((3-amino-2,3,6-trideoxy- α -L-lyxo-hexopyrannosyl)oxy)-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione

Doxorubicin



IUPAC: (1S,3S)-3-glycoloyl-3,5,12-trihydroxy-10-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-1-yl 3'-amino-2',3',6'-trideoxy- α -L-lyxohexopyranoside

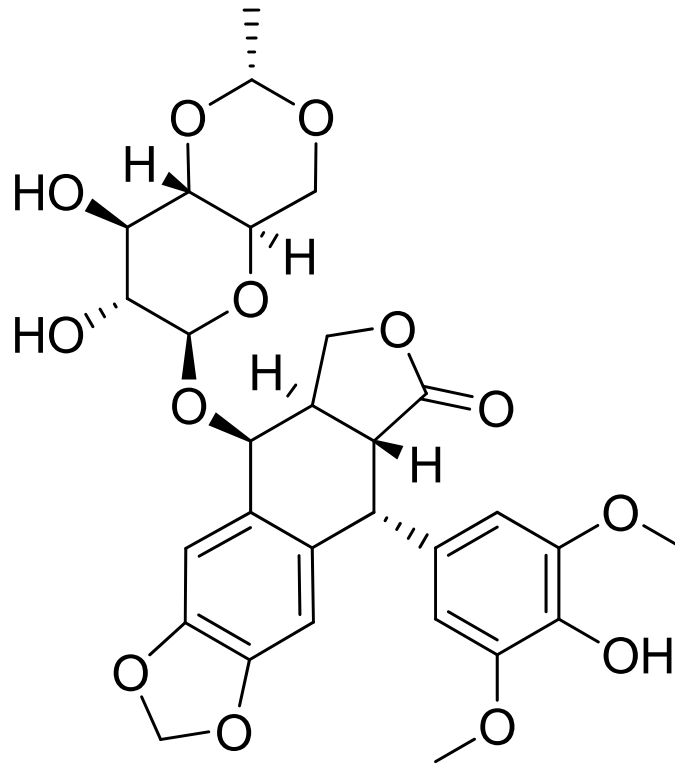
Bleomycin



IUPAC: (3- {[2-(2- {2-[(2S,3R)-2-[(2S,3S,4R)-4-[(2S,3R)-2-({6-amino-2- [(1S)-1- {[(2S)-2-amino-2-carbamoylethyl]amino} -2-carbamoylethyl]-5-methylpyrimidin-4-yl} formamido)-3-[(3- {[4-(carbamoyloxy)-3,5-dihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy} -4,5-dihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy]-3-(1H-imidazol-4-yl)propanamido]-3-hydroxy-2-methylpentanamido]-3-hydroxybutanamido]ethyl} -1,3-thiazol-4-yl)-1,3-thiazol-4-yl]formamido} propyl)dimethylsulfanium

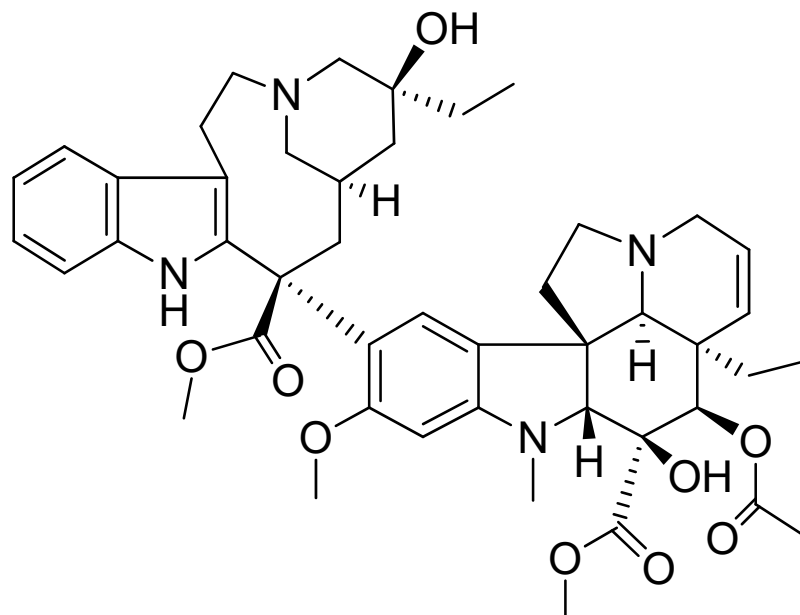
Plant products

Etoposide



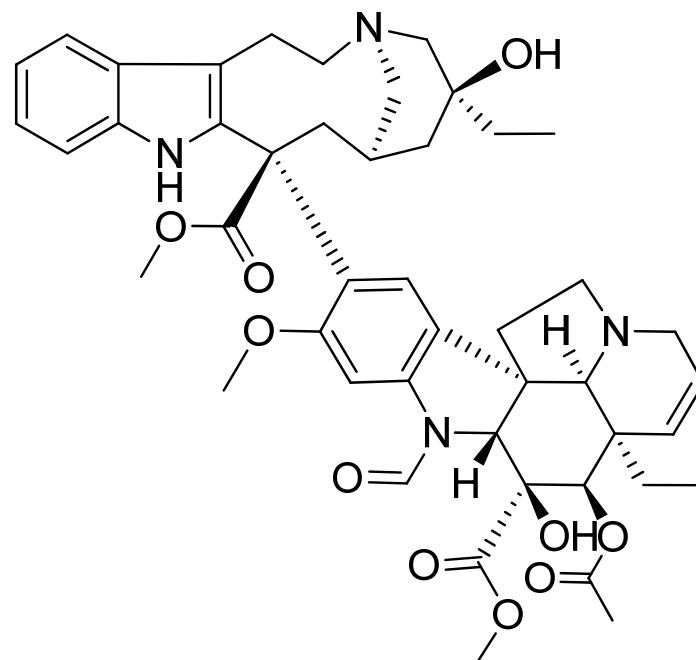
IUPAC: 9-((4,6-O-Ethylidene-beta-D-glucopyranosyl)oxy)-5,8,8a,9-tetrahydro-5-(4-hydroxy-3,4-dimethoxyphenyl)furo(3',4'':6,7)naphtho-(2,3-d)-1,3-dioxol-6(5aH)-one

Vinblastin sulphate



IUPAC: methyl (1*R*,9*R*,10*S*,11*R*,12*R*,19*R*)-11-acetyloxy-12-ethyl-4-[(13*S*,15*R*,17*S*)-17-ethyl-17-hydroxy-13-methoxycarbonyl-1,11-diazatetracyclo[13.3.1.0^{4,12}.0^{5,10}]nonadeca-4(12),5,7,9-tetraen-13-yl]-10-hydroxy-5-methoxy-8-methyl-8,16-diazapentacyclo[10.6.1.0^{1,9}.0^{2,7}.0^{16,19}]nonadeca-2,4,6,13-tetraene-10-carboxylate

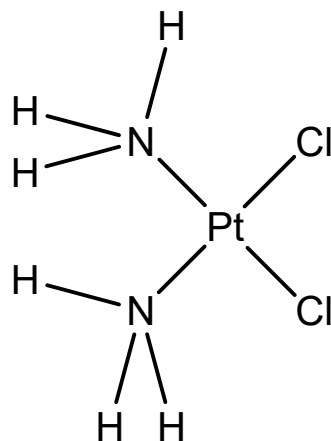
Vincristin



IUPAC: 2-(2,4-difluorophenyl)-1,3-bis(1,2,4-triazol-1-yl)propan-2-ol;methyl (1R,9R,10S,11R,12R,19R)-11-acetyloxy-12-ethyl-4-[(13S,15S,17S)-17-ethyl-17-hydroxy-13-methoxycarbonyl-1,11-diazatetracyclo[13.3.1.04,12.05,10]nonadeca-4(12),5,7,9-tetraen-13-yl]-8-formyl-10-hydroxy-5-methoxy-8,16-diazapentacyclo[10.6.1.01,9.02,7.016,19]nonadeca-2,4,6,13-tetraene-10-carboxylate

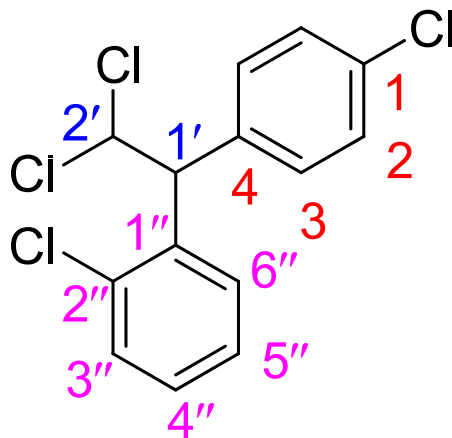
Miscellaneous

Cisplatin



IUPAC: Cis-diamminedichloroplatinum(II)

Mitotane



IUPAC: 1-chloro-4-[2,2-dichloro-1'-(2''-chlorophenyl)ethyl]benzene

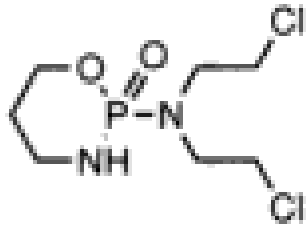
The Classification of Anticancer Drugs

A. Drugs acting directly on cells (Cytotoxic drugs)

1. Alkylating agents:

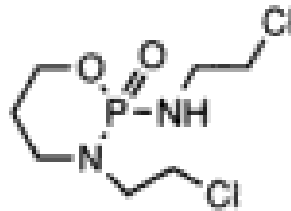
- These compounds produce highly reactive carbonium ion intermediates which transfer alkyl groups to cellular macro molecules by forming covalent bonds.
- Alkylation results in cross linking/
~~abnormal base pairing/scission of DNA~~

mustard



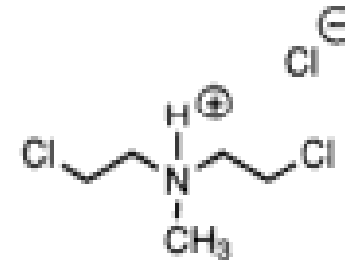
Cyclophosphamide
(Gytoxan)

Breast cancer,
Multiple
myeloma



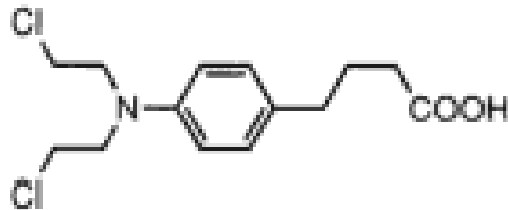
Ifosfamide
(Ifex)

head and neck carcinomas,
osteogenic sarcoma



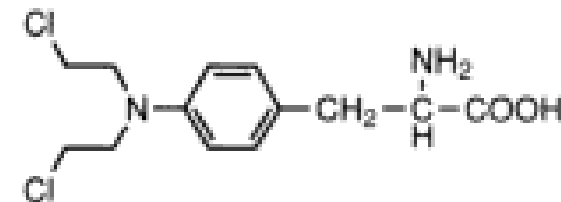
Mechlorethamine
hydrochloride
(Mustargen)

Hodgkin's disease,
T-cell lymphoma



Chlorambucil
(Leukeran)

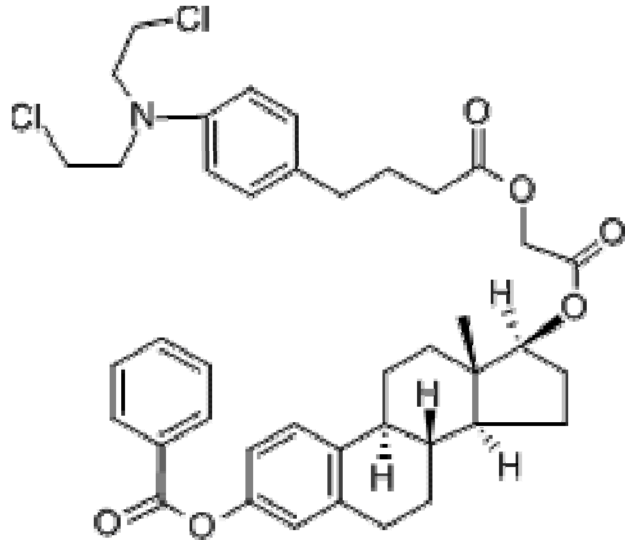
Chronic lymphocytic
leukemia



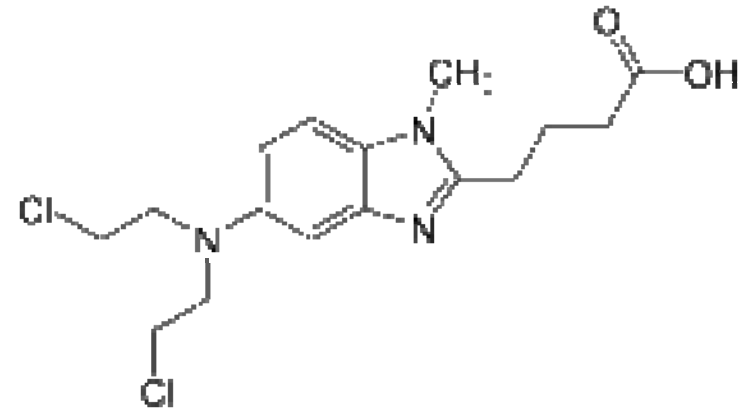
Melphalan
(Alkeran)

Multiple myeloma,
Ovarian cancer, Breast
cancer

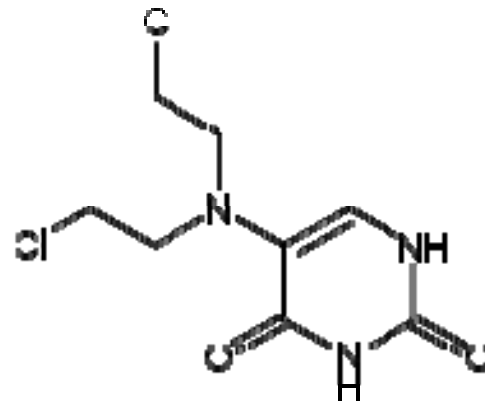
Recent drugs based on Nitrogen mustard



Bestrabucil (phase I trial)
[Chlorambucil derivative]



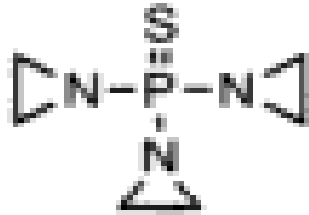
Bendamustine



Uramustine (Nitrogen mustard+Uracil
Derivative)

Triazolo

ine



Thiotepe
(Thioplex)



Ovarian cancer, Breast
cancer
Lymphoma

Alkyl sulfonate



Busulfan
(Myleran)

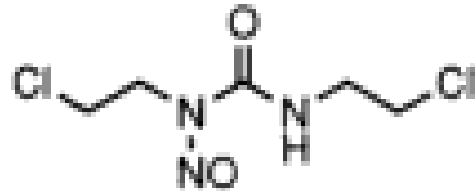


Chronic Myeloid
Leukemia

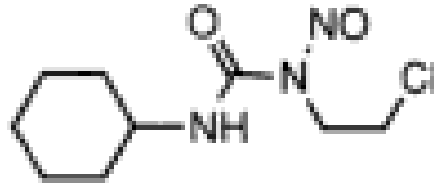
nitrosoureas

reas

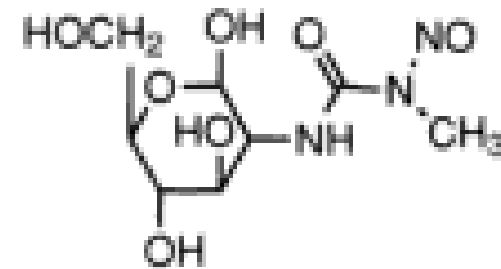
:- meningeal leukaemias and brain tumours (can cross BBB)



Carmustine
(BiCNU)

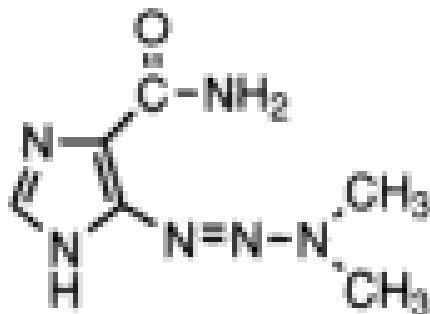


Lomustine
(CeeNU)



Streptozocin
(Zanosar)

Triazine



Dacarbazine
(DTIC-Dome)

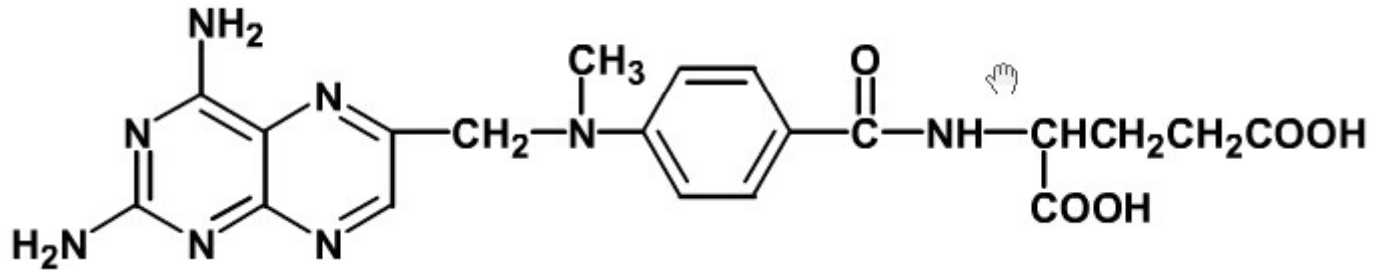


Malignant melanoma;
Hodgkin's disease.

2. Antimetabolites

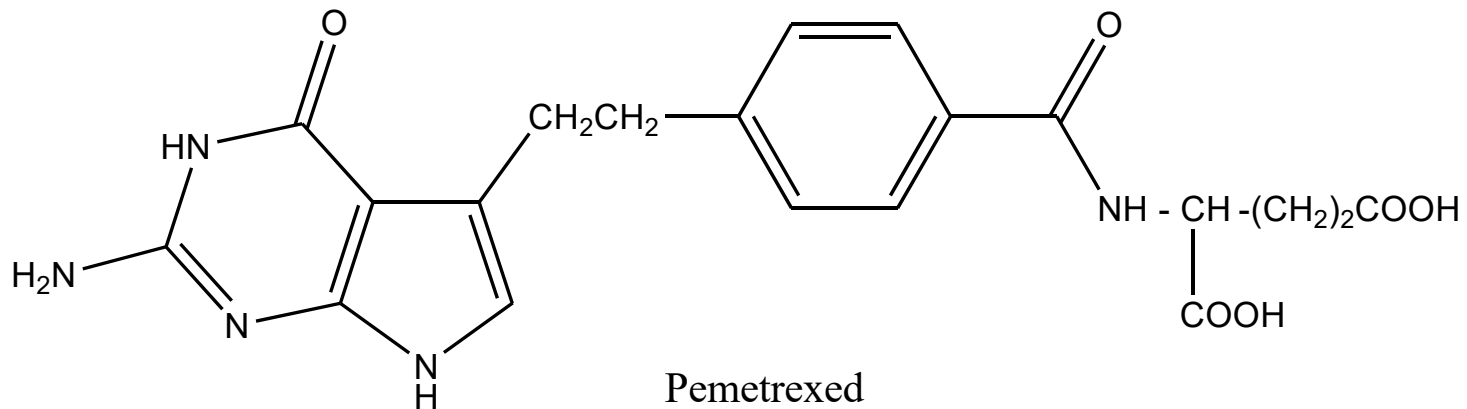
- These are analogues related to normal components of DNA or of coenzymes involved in nucleic acid synthesis.
- They competitively inhibit utilization of the normal substrate or get themselves incorporated forming dysfunctional macromolecules.
- Several of the useful drugs used in antimetabolite therapy are purines, pyrimidines, folates, and related

antagonist



Methotrexate
(NEOTREXATE)

Acute lymphoblastic leukemia,
Lung cancer.



Pemetrexed

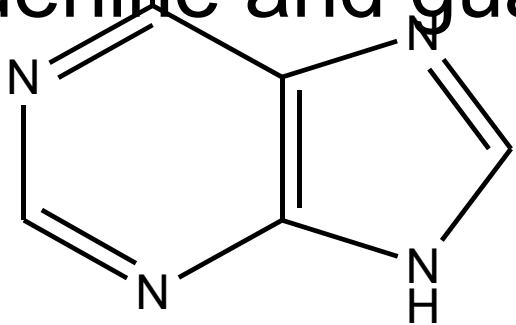
antagonist

○ These are highly effective antineoplastic drugs.

○ They are converted in the body to the corresponding

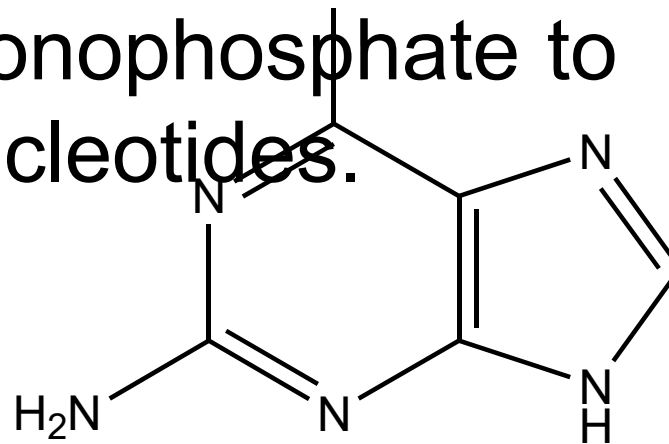
monoribonucleotides which inhibit the

conversion of inosine monophosphate to adenine and guanine nucleotides.



6-mercaptopurine

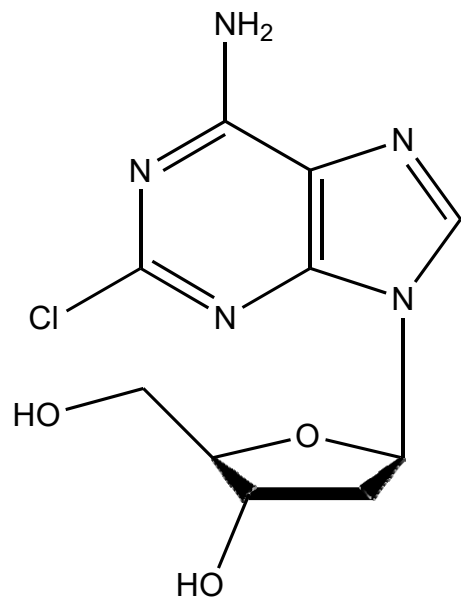
Childhood acute leukemia



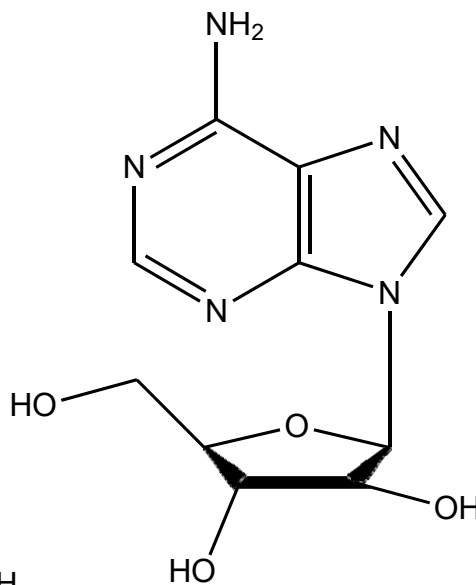
Thioguanine

Adult acute leukemia

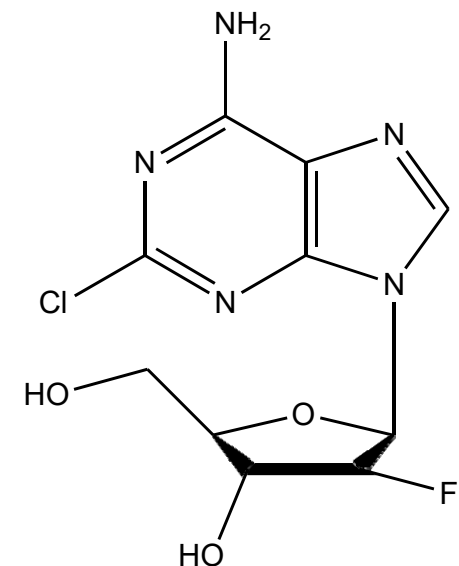
□ Recent drugs based on purines and related compounds:



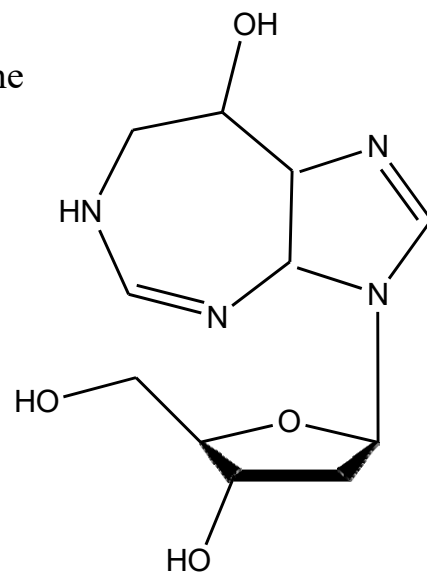
Cladribine



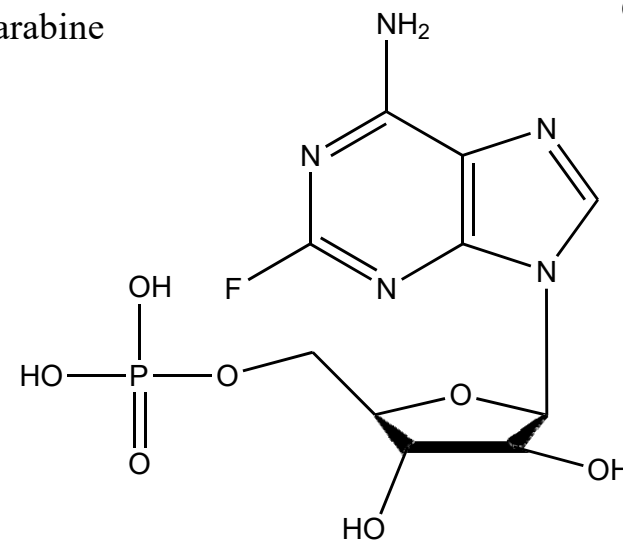
Vidarabine



Clofarabine



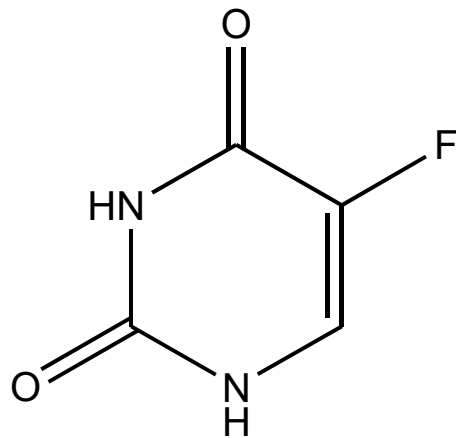
Pentostatin



Fludarabine

antagonist

- Pyrimidine analogues have varied applications as antineoplastic, antifungal and antipsoriatic agents.



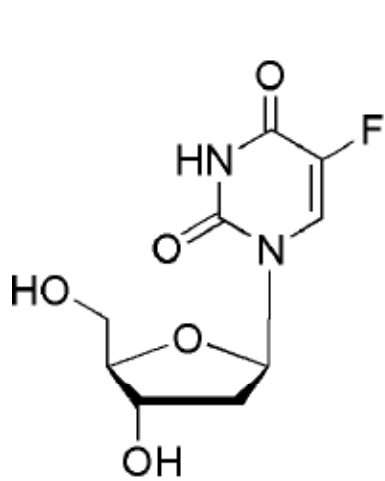
5-Fluorouracil

Adenocarcinoma,
Skin cancer

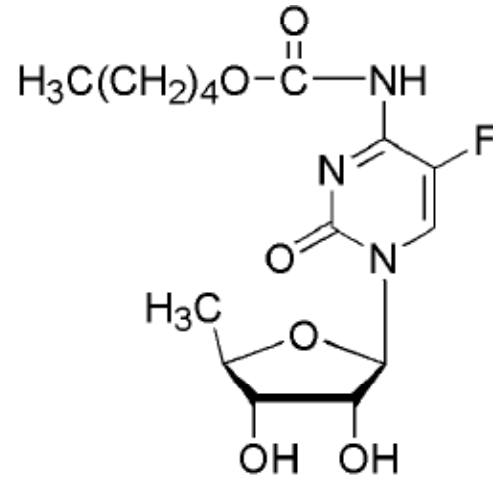
- 5-Fluorouracil is converted in the body to the corresponding nucleotide 5-fluoro-2-deoxyuridine monophosphate, which inhibits thymidylate synthase and blocks the conversion of deoxyuridilic acid to deoxythymidylic acid.

- This leads to elective failure of

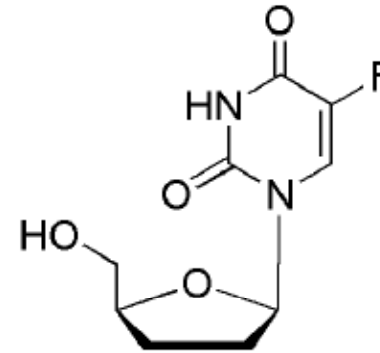
Recent drugs



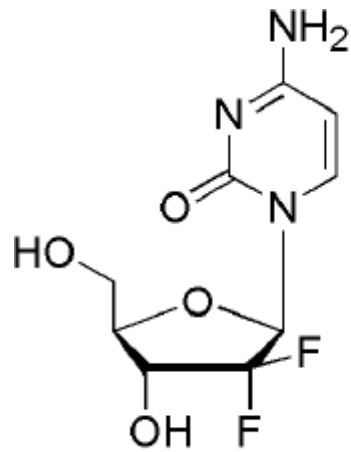
Floxuridine



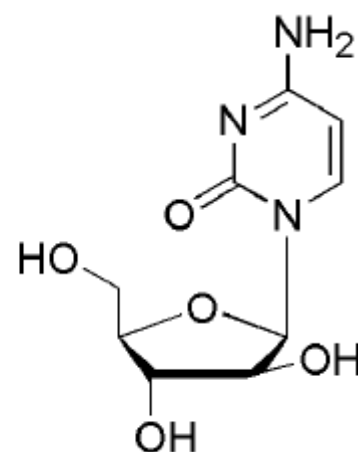
Capecitabine



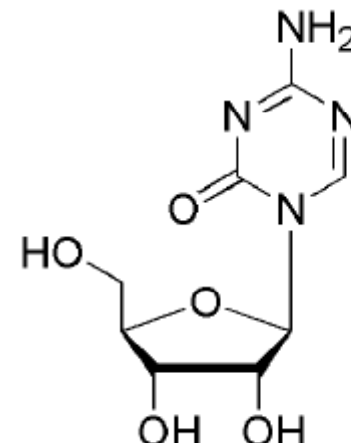
Tegafur



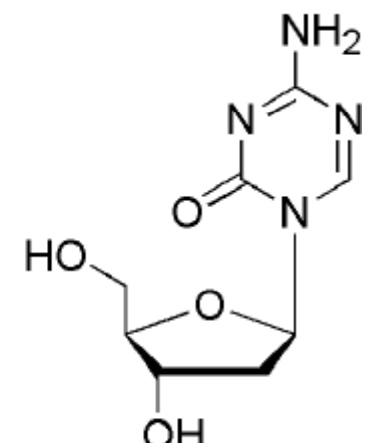
Gemcitabine



Cytarabine



5-Azacytidine



Decitabine

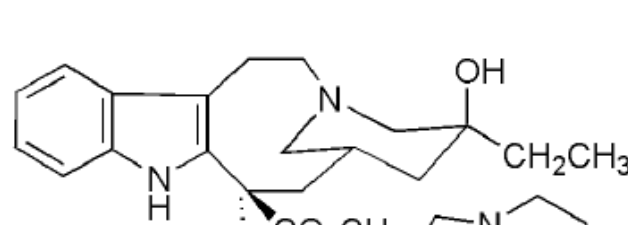
3. Natural anticancer agents:



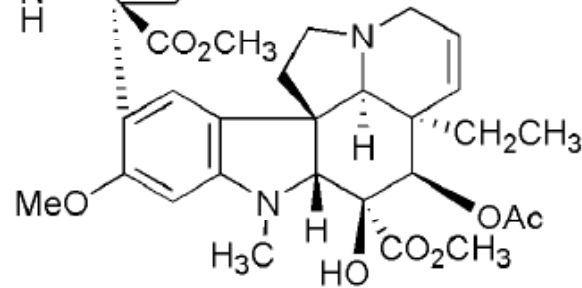
Vinca alkaloids

- These are mitotic inhibitors, bind to microtubular protein-'tubulin', prevent its polymerization and assembly of microtubules, cause disruption of mitotic spindle and interfere with cytoskeletal function.
- The chromosomes fail to move apart during mitosis: metaphase arrest occurs.
- They are cell cycle specific and act in the mitotic phase.

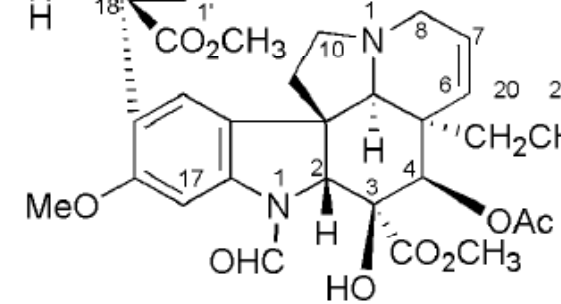
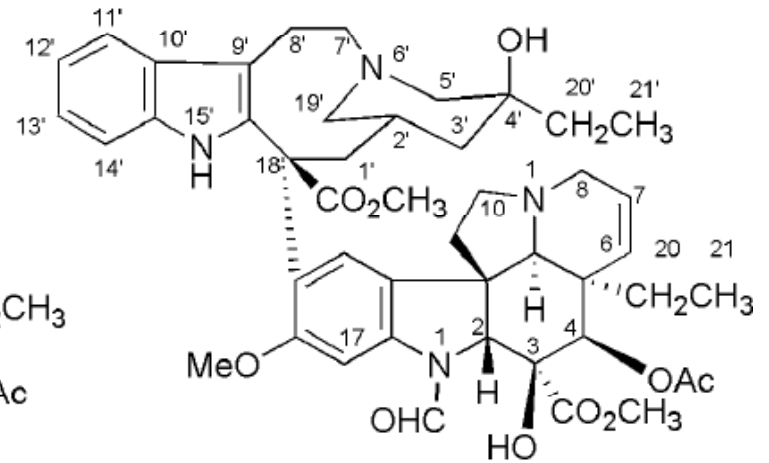
Catharanthine Subunit



Vindoline Subunit

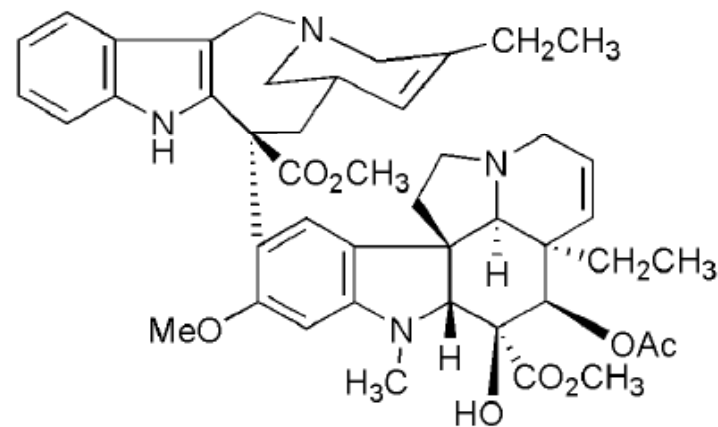


Vinblastine



Vincristine

Hodgkin's disease,
Acute lymphocytic
leukemia,
Lung cancer

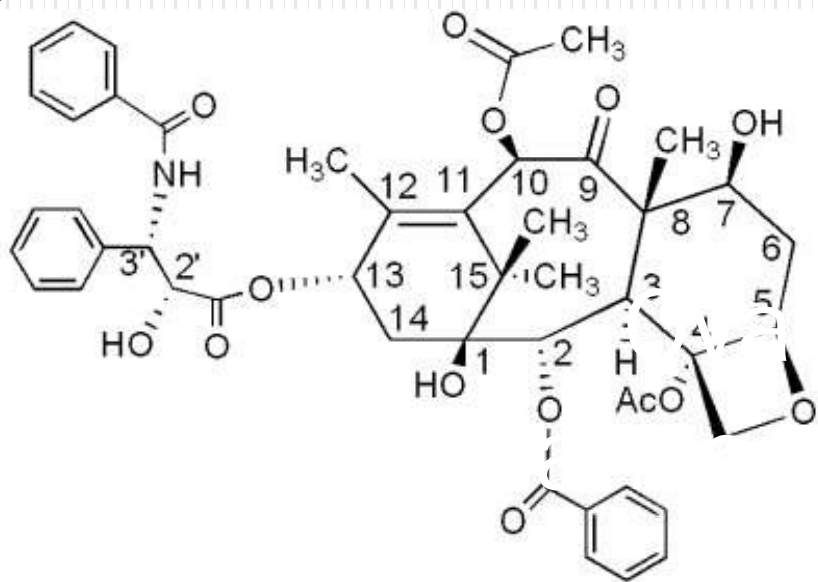


Vinorelbine

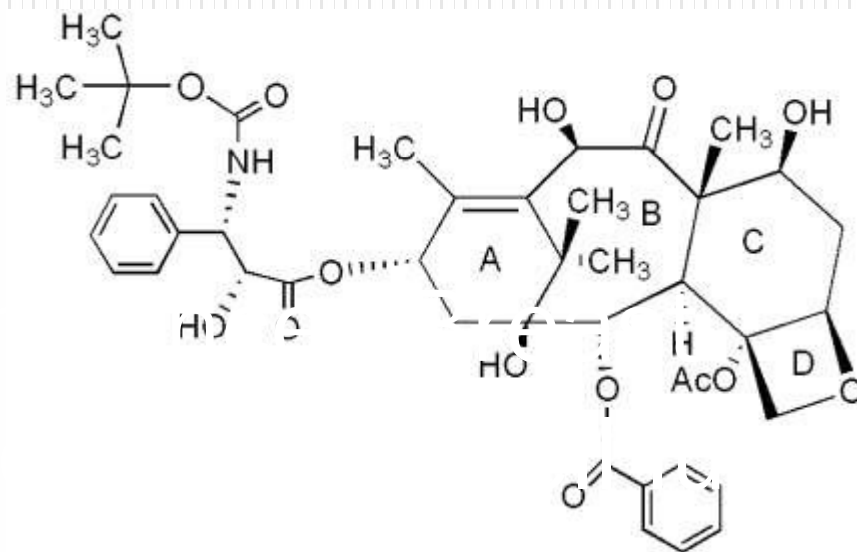
es



- First isolated from bark of Western / Pacific yew (*Taxus brevifolia*)
- It is used for treatment of lung, ovarian and breast cancer.
- Taxanes hyperstabilize microtubule structure (freeze them). Taxanes binds to the β subunit of tubulin, the resulting microtubule/ Taxanes complex does not have the ability to disassemble. This adversely affects cell function because the shortening and lengthening of microtubules

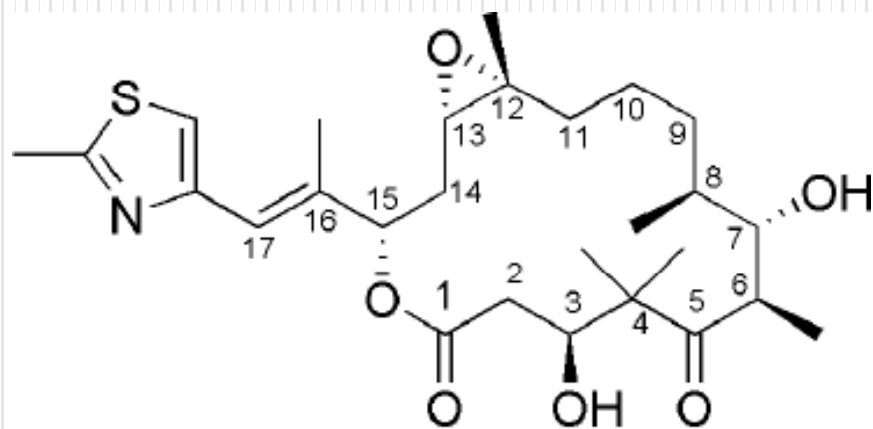


Paclitaxel

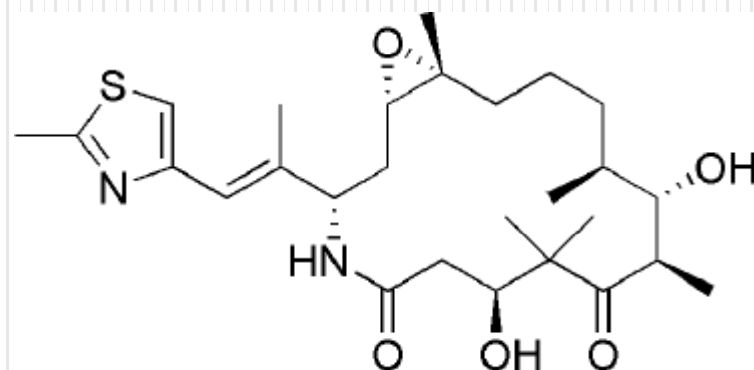


Docetaxel

Semi-synthetic derivatives



Epothilone B



Ixabepilone

Podophyllin

oxin

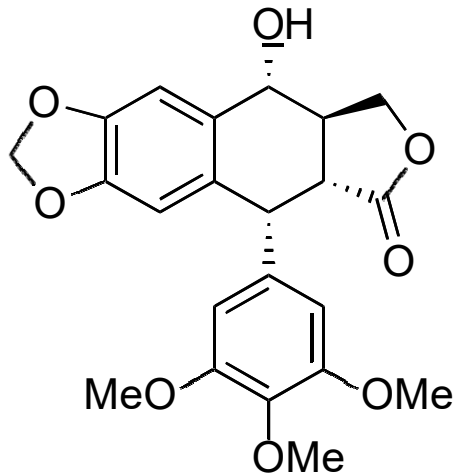
Small cell lung cancer, Non-Hodgkin's lymphomas, Kaposi's sarcoma, Cervical cancer



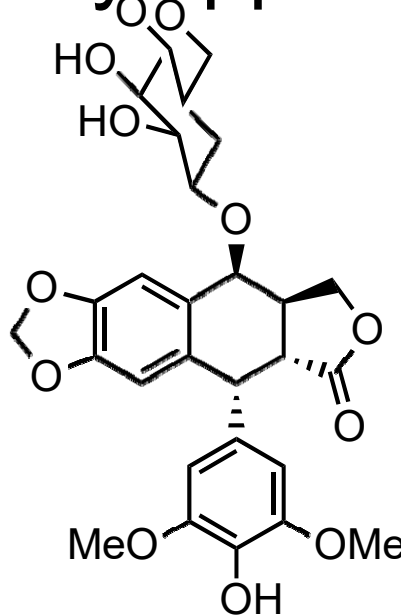
Podophyllum peltatum

- Affects DNA

Mayapple



Podophyllotoxin



Etoposide

topoisomerase II
(not intercalating)
DNA strand
breakage

Etoposide (Semi-synthetic)

Eposin® Etopofos®
Vepesid®

analogues

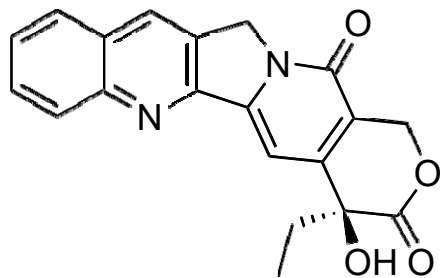
- First isolated *Camptotheca acuminata* (Chinese tree).
- Inhibits DNA topoisomerase

DNA strand

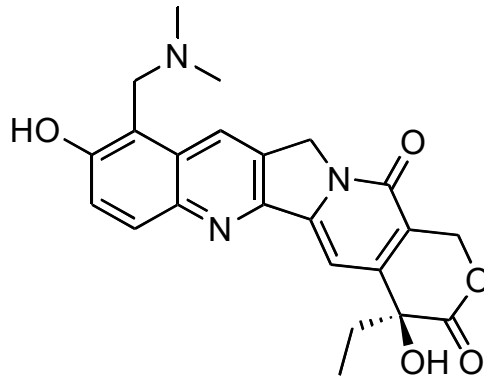
Ovarian cancer, Small cell lung cancer



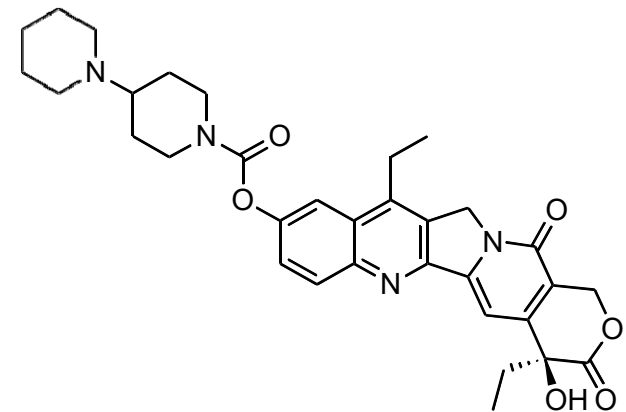
breakage



Camptothecin,
toxic, Lead comp.



Topotecan
Hycamtin®

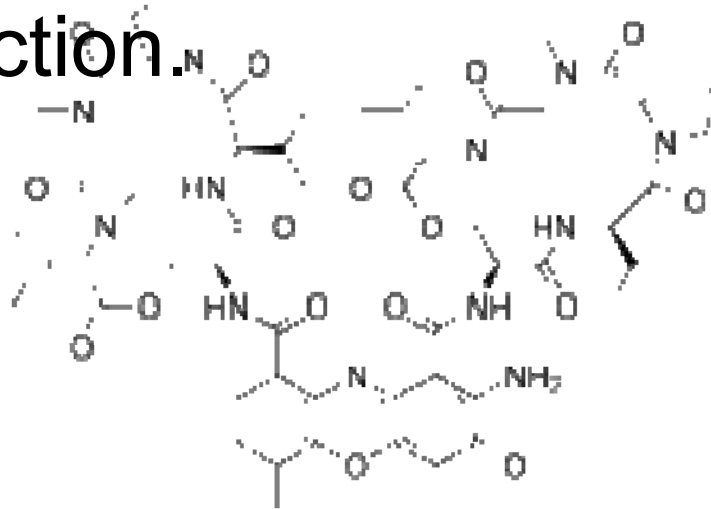


Irinotecan
n
Campto®

Semisynthetic

Antibiotics

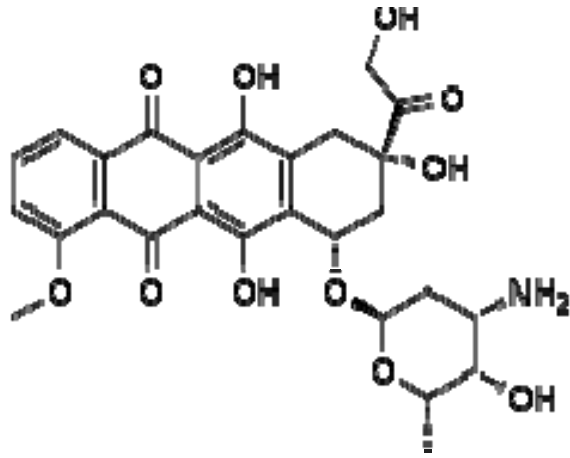
- These are products obtained from microorganisms and have prominent antitumour activity.
- Practically all of them intercalate between DNA strands and interfere with its template function.



Actinomycin D



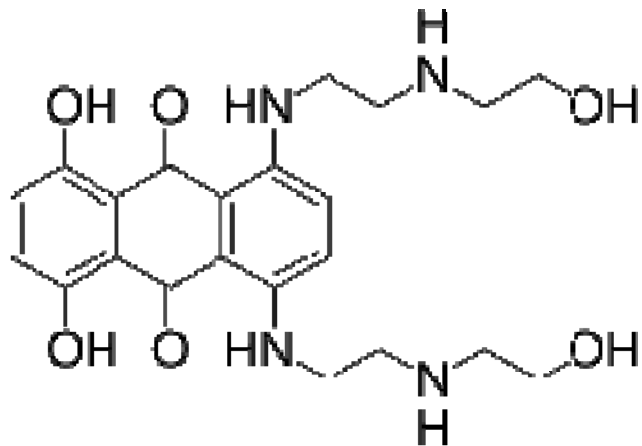
Wilms' tumour,
Rhabdomyosarcoma



Doxorubicin



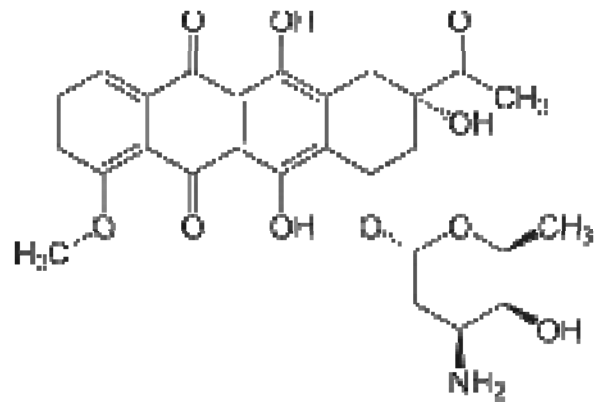
Kaposi's sarcoma,
Small cell lung cancer,
Breast cancer,
Malignant lymphomas



Mitoxantrone



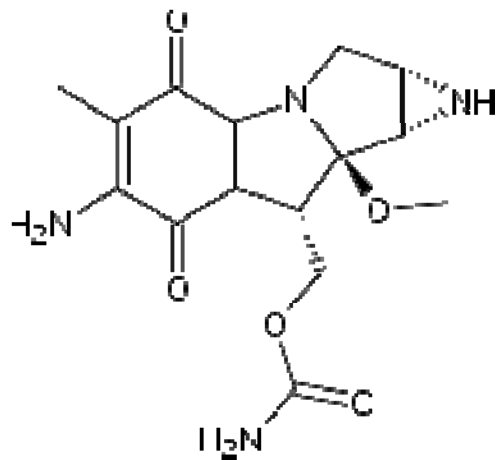
Prostate cancer,
Multiple sclerosis



Daunorubicin



Kaposi's sarcoma,
Acute myeloid leukemia

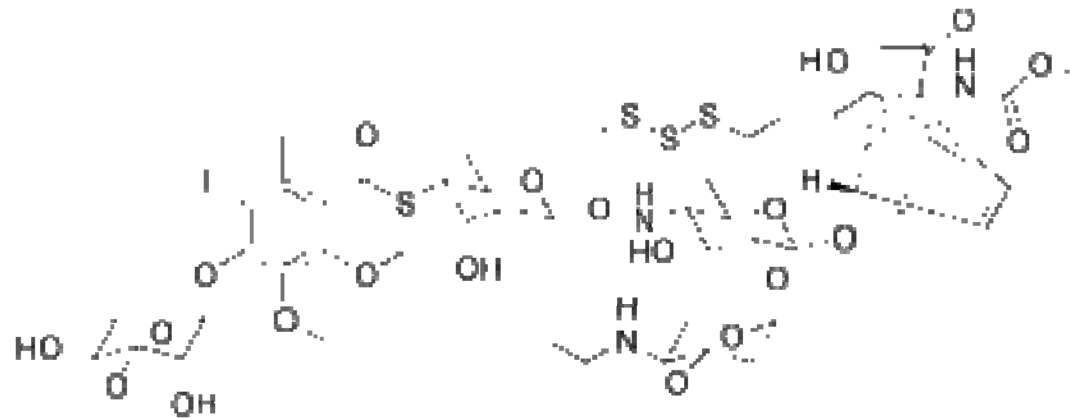


Mitomycin

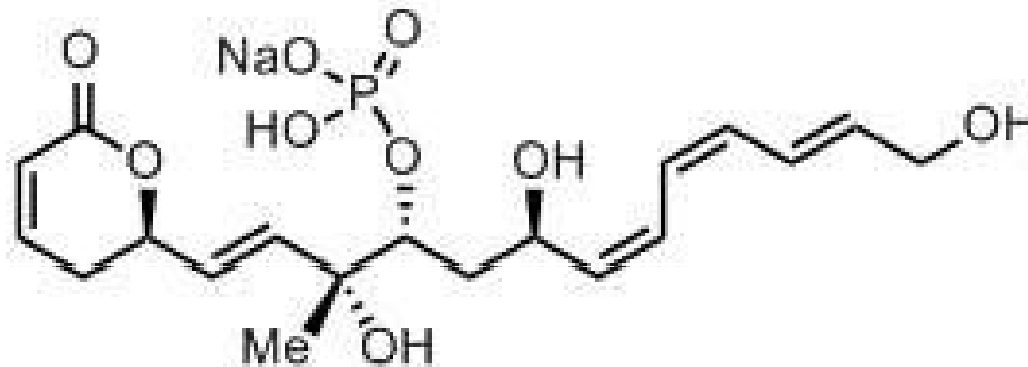


Carcinomas of the cervix
Breast, lung, stomach

Recent anticancer antibiotics drugs:

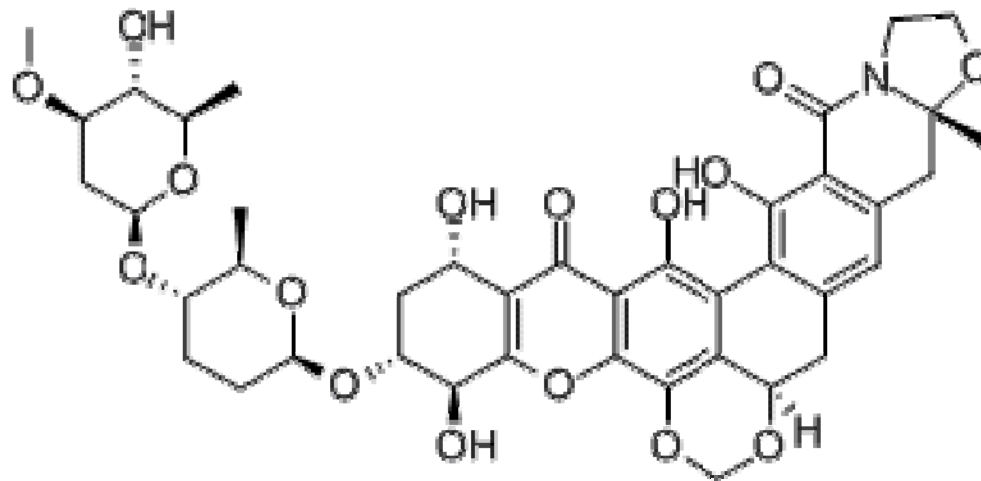


Calicheamicin

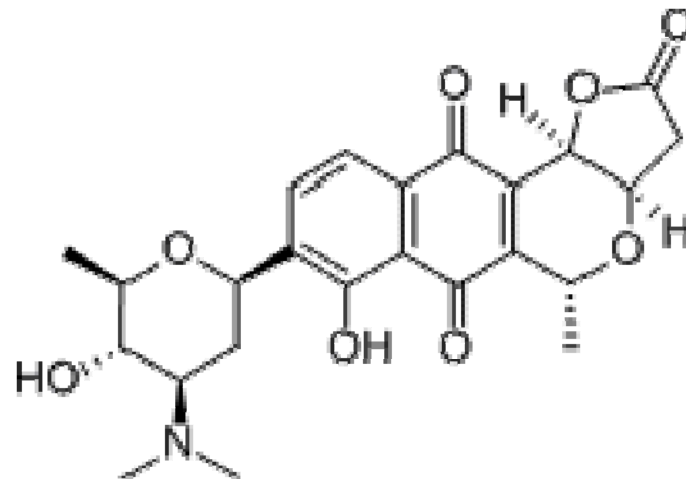


Fostriecin (Priclinica

|
)



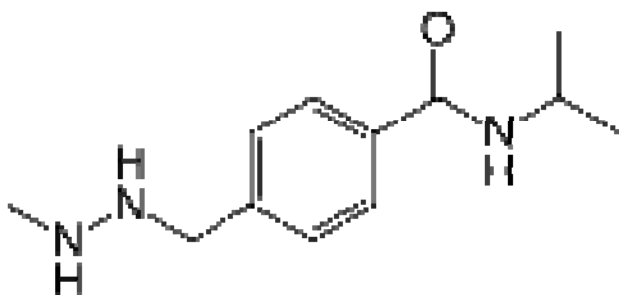
Kigamicin C (priclinical)



Lactoquinomycin A

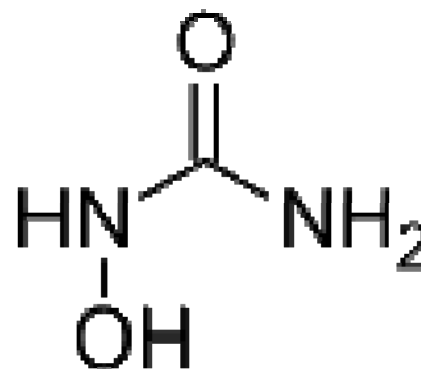
○ 5. Miscellaneous :

○ These drugs have been developed by random synthesis and testing for anti tumour activity.



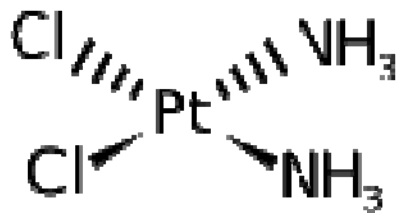
Procarbazine

Hodgkin's disease,
Non-Hodgkin lymphomas,
Oat cell carcinoma of lung



Hydroxyurea

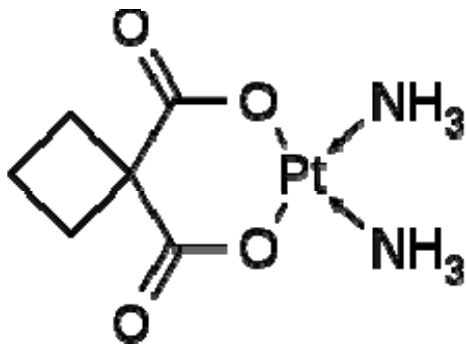
Chronic myeloid leukaemia,
Psoriasis, Polycythaemia



Cisplatin



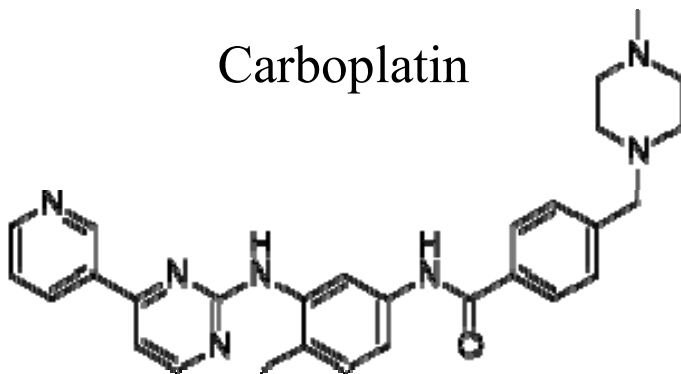
Metastatic testicular
and
Ovarian carcinoma



Carboplatin



Squamous carcinoma of
head
and neck,
Small cell lung cancer,
Seminoma

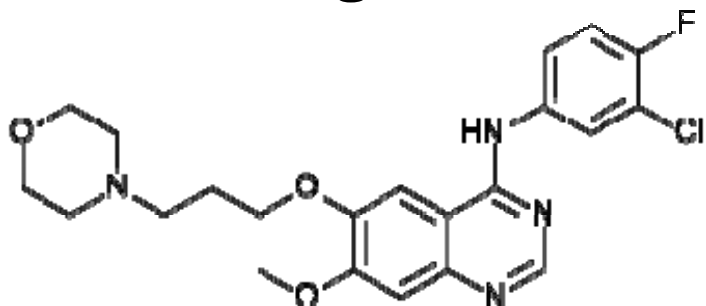


Imatinib

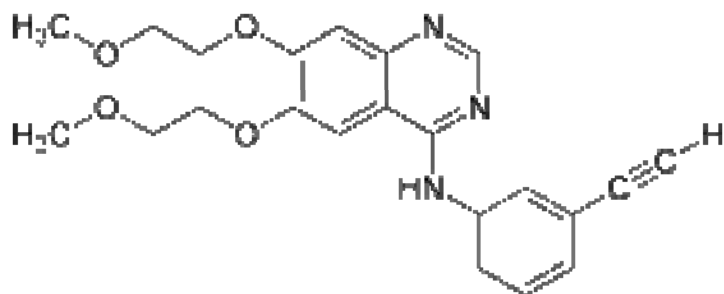


chronic myeloid
leukaemia

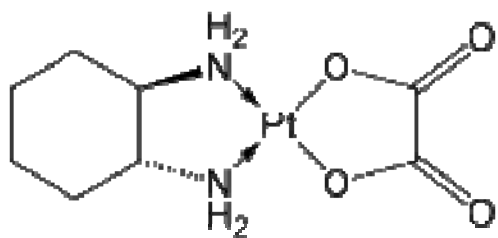
Recent drugs



Gefitinib



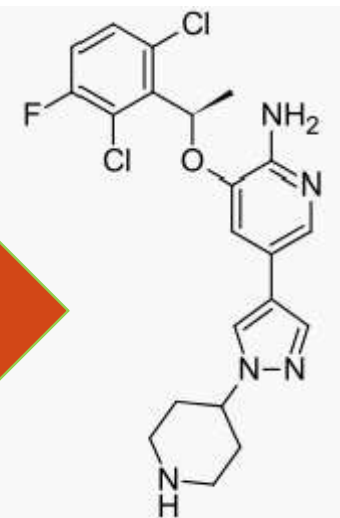
Erlotinib



Oxaliplatin

Non-
Small
Cell lung
cancer

(PROTEIN
KINASE
INHIBITORS)



Crizotinib

Ovarian
carcinoma,
Seminoma

B. Drugs acting on Hormones

- It involves the manipulation of the endocrine system through exogenous administration of specific hormones, particularly steroid hormones, or drugs which inhibit the production or activity of such hormones.
- Because steroid hormones are powerful drivers of gene expression in certain cancer cells, changing the levels or activity of certain hormones can cause certain cancers to cease growing, or even undergo cell death.

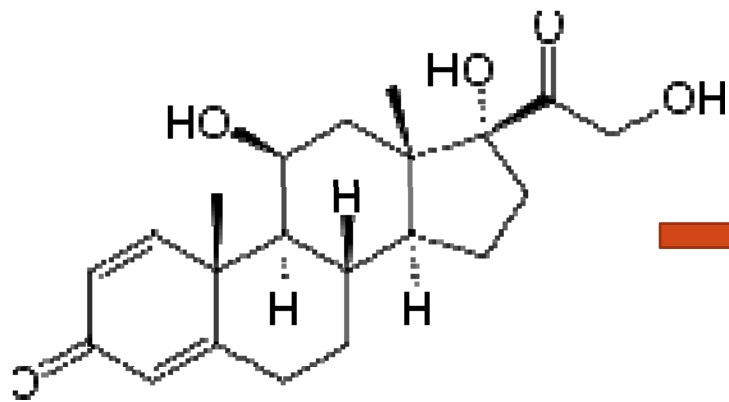
Corticosteroids

:

- Corticosteroids are strong anti-inflammatory drugs.
- They are used to reduce swelling that causes cancer pain.

Examples

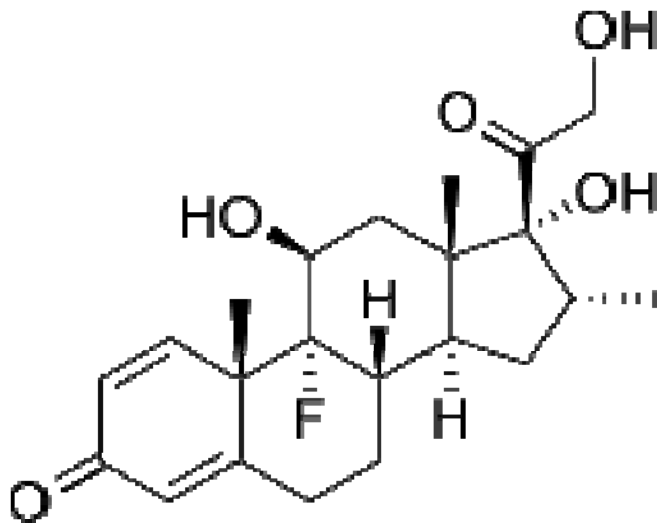
Generic Name	Brand Name
dexamethasone	Dexamethasone Intensol
hydrocortisone	Cortef
methylprednisolone	Medrol
prednisolone	Orapred, Pediapred, Prelone
prednisone	Prednisone Intensol



Prednisolone



palliation of lymphomas
and leukemias



Dexamethasone

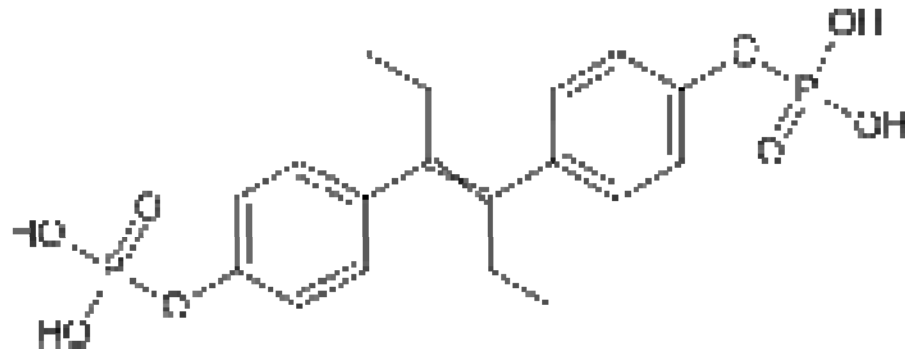


haematological
malignancies

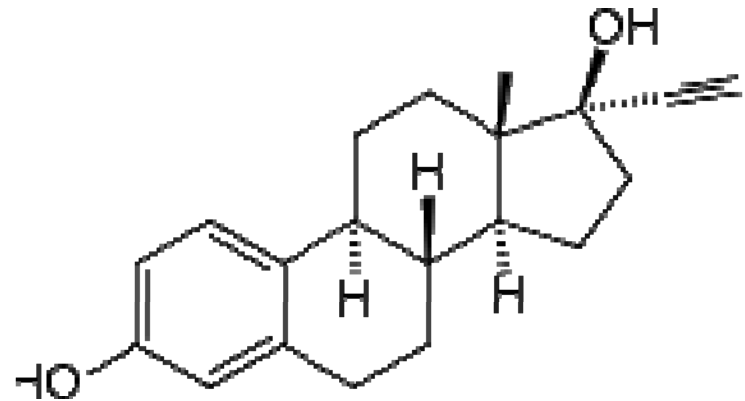
2.

Estrogens

- The agonist is occasionally used to treat prostate cancer through suppression of testosterone production.



Fosfestrol

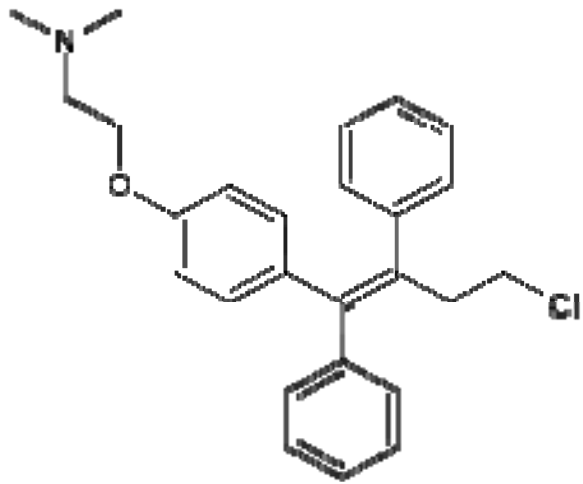


Ethinylestradiol

carcinoma
prostate

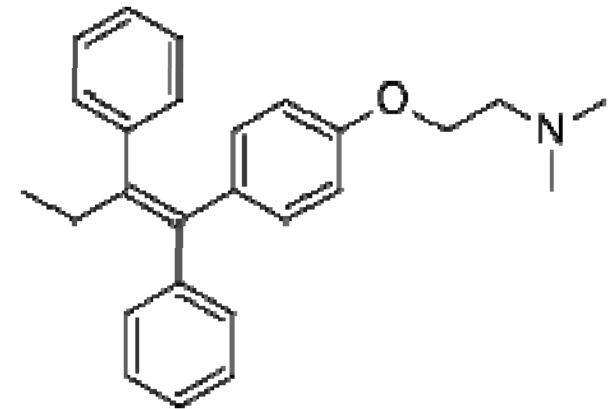
3. Selective estrogen receptor modulators

- Acts by selective antagonism of the estrogen receptor.



Toremifene

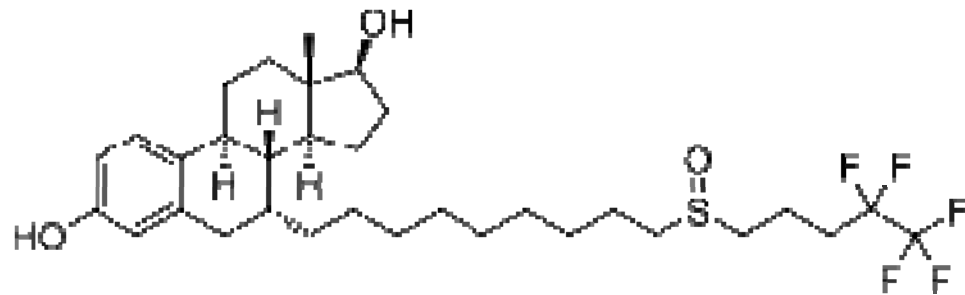
Breast cancer

A thick red double-headed arrow points from the Toremifene structure on the left to the Tamoxifen structure on the right, with the text "Breast cancer" centered within the arrow.

Tamoxifen

4. Selective estrogen receptor down regulators

- Estrogen receptor down regulators blocks the effects of estrogen in breast tissue.



Fulvestrant



Metastatic
breast
cancer

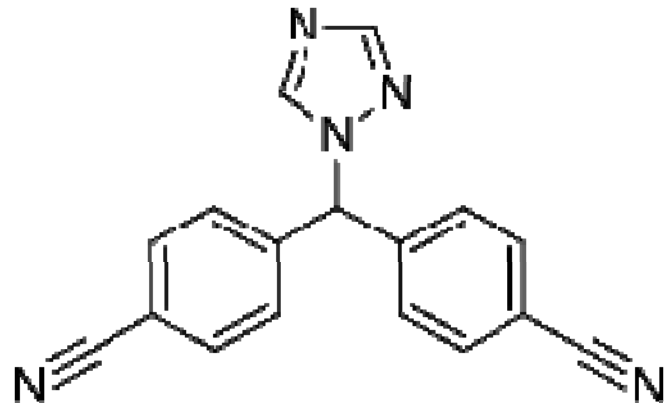
5. Aromatase inhibitors

- Aromatase is the enzyme that synthesizes estrogen.

- Aromatase inhibitors (AIs) are a class of drugs used in the treatment of breast cancer and ovarian cancer in postmenopausal women.

- As breast and ovarian cancers require estrogen to grow, Aromatase inhibitors are taken to either block the production of

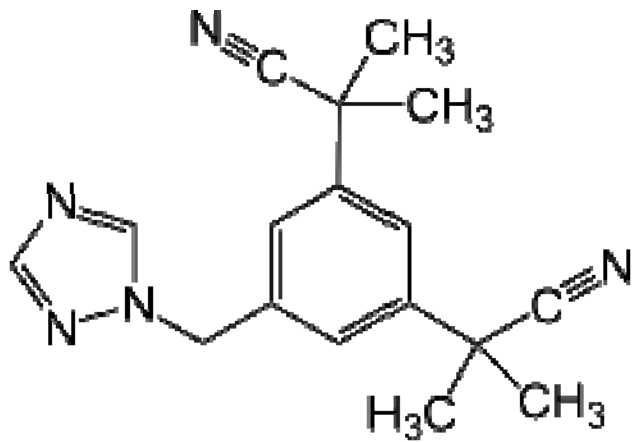
~~estrogen or block the action of estrogen on~~



Letrozole



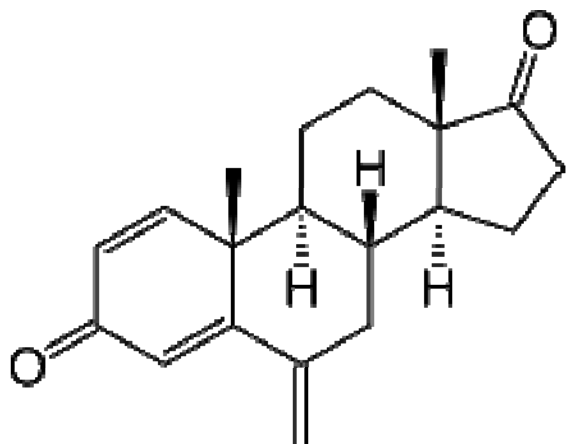
Breast cancer



Anastrozole



Breast cancer

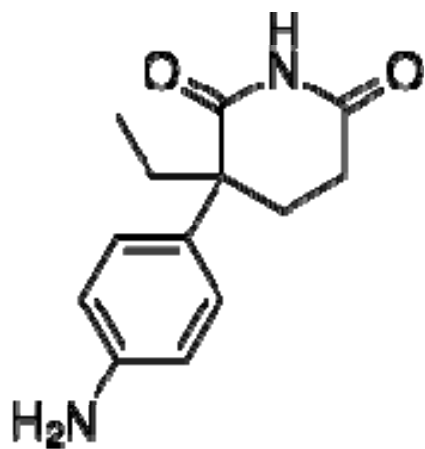


Exemestane

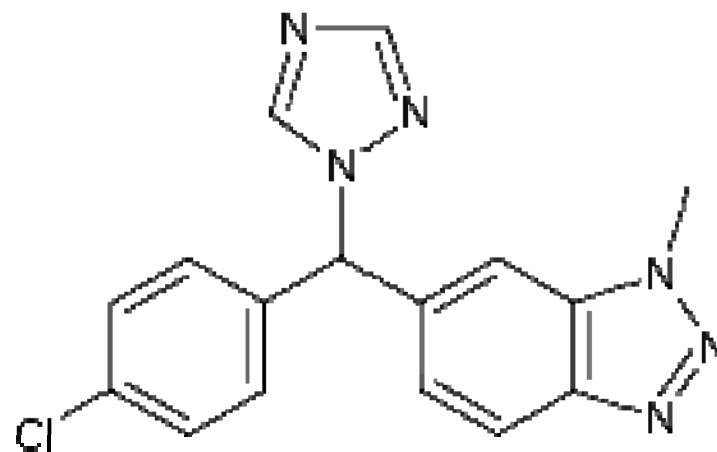


Early stage of breast cancer

Recent drug



Aminoglutethimide



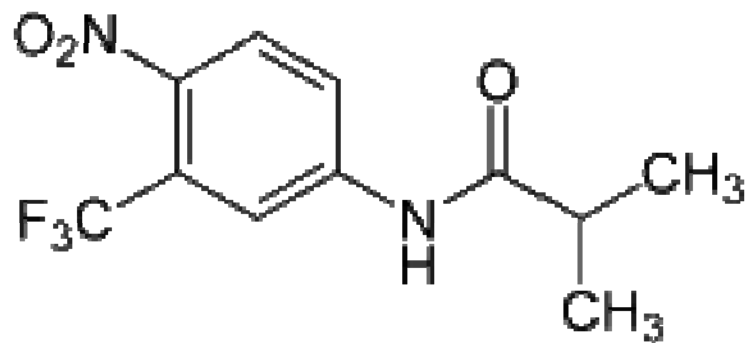
Vorozole

6. Antiandrogen

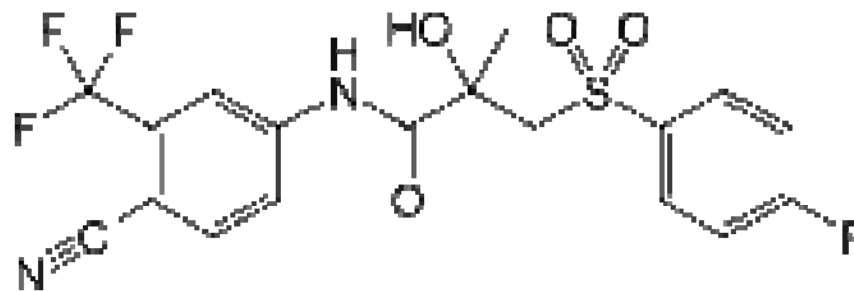
- Antiandrogens, or androgen antagonists, first discovered in the 1960s, prevent androgens from expressing their biological effects on responsive tissues.

- Antiandrogens alter the androgen pathway by blocking the appropriate receptors, competing for binding sites on the cell's surface, or affecting androgen production.

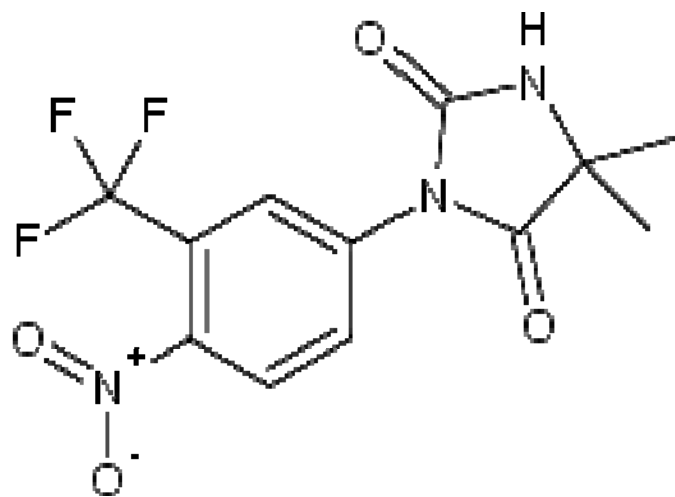
- Antiandrogens are most frequently used to treat prostate cancer.



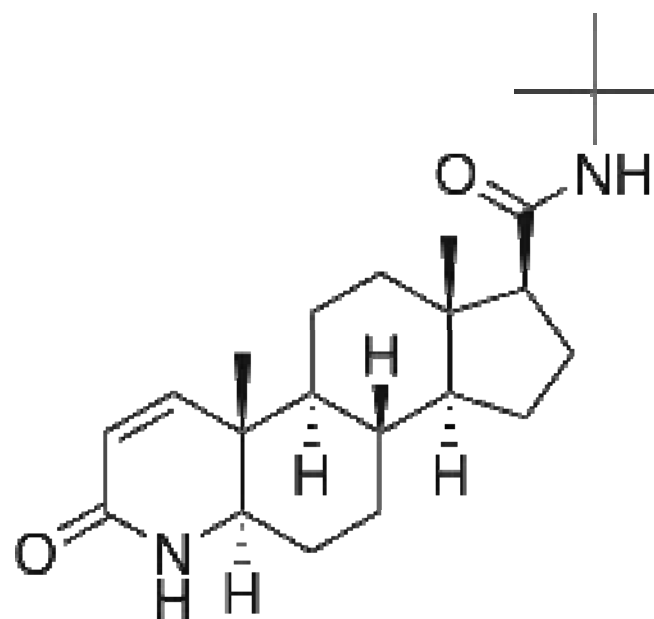
Flutamide



Bicalutamide

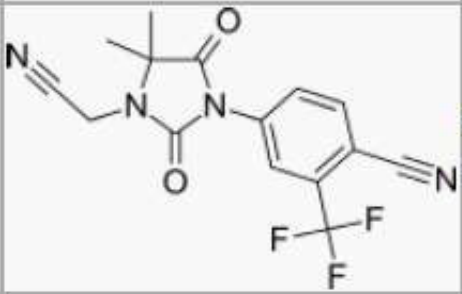
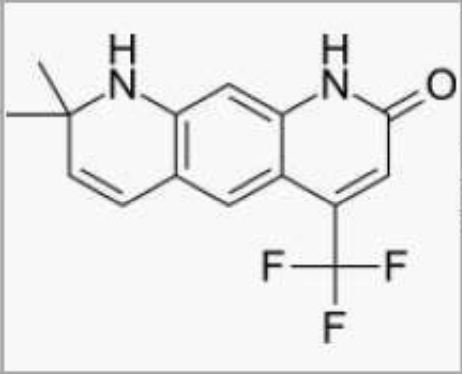
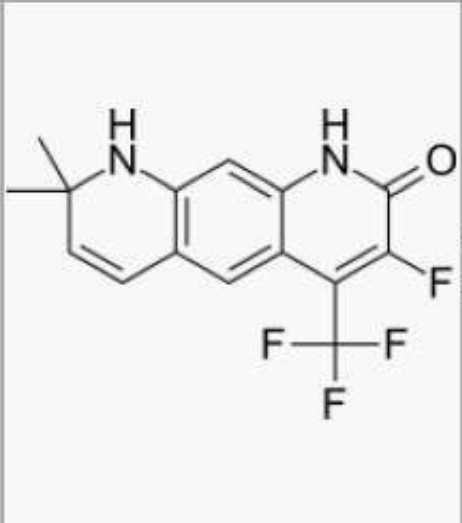


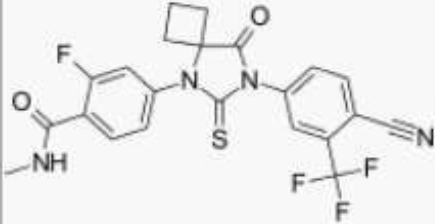
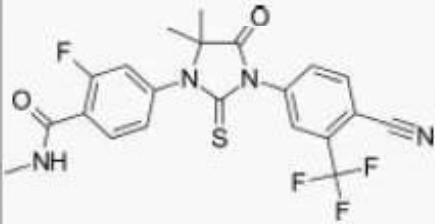
Nilutamide

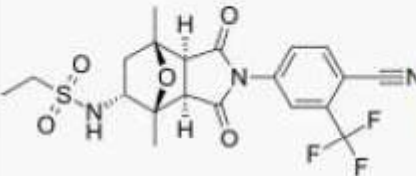
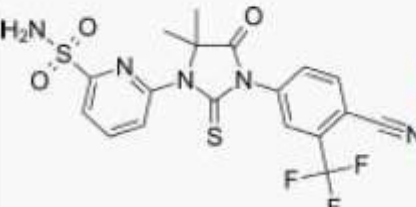


Finasteride

development status of antiandrogen drugs:

Name of compound	Structure	Company	Stage of development
RU58642		Roussel-Uclaf SA	Preclinical – no further developments since 1998
LG120907		Ligand Pharmaceuticals	Preclinical
LG105		Ligand Pharmaceuticals	Preclinical

RD162	 <p>The chemical structure of RD162 features a central 1,2,4-thiazolidine-5-one ring system. The nitrogen at position 2 is substituted with a cyclobutane ring. The nitrogen at position 4 is substituted with a 4-fluorophenyl group. The sulfur atom at position 3 is substituted with a 4-(trifluoromethyl)phenyl group. The carbonyl oxygen at position 5 is also substituted with a 4-(trifluoromethyl)phenyl group.</p>	Medivation	Preclinical
Enzalutamide (Xtandi)	 <p>The chemical structure of Enzalutamide is very similar to RD162, but instead of a cyclobutane ring at the 2-position of the thiazolidine ring, it has a methyl group.</p>	Medivation	Approved

BMS-641988	 <p>The chemical structure of BMS-641988 features a bicyclic core consisting of a piperidine ring fused to a five-membered ring containing a nitrogen atom and two carbonyl groups. A propylsulfonamide group is attached to the piperidine ring. The nitrogen atom of the five-membered ring is substituted with a 4-cyano-2,2-difluorophenyl group.</p>	Bristol-Myers Squibb	Phase I clinical – trial terminated
CH5137291	 <p>The chemical structure of CH5137291 features a central five-membered ring containing a nitrogen atom and a sulfur atom, with a carbonyl group attached to the nitrogen. This central ring is substituted with a 2-sulfamoylpyridin-5-yl group and a 4-cyano-2,2-difluorophenyl group.</p>	Chugai Pharmaceutical Co., Ltd.	Preclinical

Recently Approved Drugs by FDA

Drugs	Uses
	2014
Belinostat	Peripheral T-cell lymphoma
Ramucirumab	Gastric cancer
Ibrutinib	Chronic lymphocytic leukemia
Idelalisib	Relapsed Chronic lymphocytic leukemia
Ceritinib	Non-small cell lung Cancer

Drugs	Uses
	2013
Obinutuzumab	Chronic lymphocytic leukemia
Afatinib	Metastatic non-small cell lung cancer
Ibrutinib	Mantle cell lymphoma
Trametinib	Metastatic melanoma
Pomalidomide	Relapsed and refractory multiple myeloma
Lenalidomide	Mantle cell lymphoma
Regorafenib	Gastrointestinal stromal tumor
Dabrafenib	Metastatic melanoma
Denosumab	Prostate cancer

References

1. *Wilson and Gisvold's* textbook of organic medicinal and pharmaceutical

chemistry, Twelfth Edition, Charles Owens Wilson, Ole

2. *Gisvold's* *Essentials of Medical Pharmacology*, Sixth Edition, K.D TRIPATHI

3. Foye's Principles of medicinal chemistry, Sixth Edition, Thomas L.

Lemke, David A. Williams

4.

<http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm>

Thank You!

