

# Chemistry of Chemotherapeutic Agents

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## What is Chemotherapy ?

- The word chemotherapy means the use of any drug (such as aspirin or penicillin) to treat any disease, but to most people chemotherapy refers to drugs used for cancer treatment.

Cerebrospinal fluid drawn from between two vertebrae





# History of Chemotherapy

The first drug used for cancer chemotherapy did not start out as a medicine. Mustard gas was used as a chemical warfare agent during World War I and was studied further during World War II. During a military operation in World War II, a group of people were accidentally exposed to mustard gas and were later found to have very low white blood cell counts.

Doctors reasoned that something that damaged the rapidly growing white blood cells might have a similar effect on cancer. So, in the 1940s, several patients with advanced lymphomas (cancers of certain white blood cells) were given the drug by vein, rather than by breathing the irritating gas. Their improvement, although temporary, was remarkable.

That experience led researchers to look for other substances that might have similar effects against cancer. As a result, many other drugs have been developed

# How chemotherapy is different from other treatments



Treatments like radiation and surgery are considered local treatments. They act only in one area of the body such as the breast, lung, or prostate and usually target the cancer directly. Chemotherapy differs from surgery or radiation in that it's almost always used as a systemic treatment. This means the drugs travel throughout the body to reach cancer cells wherever they are.

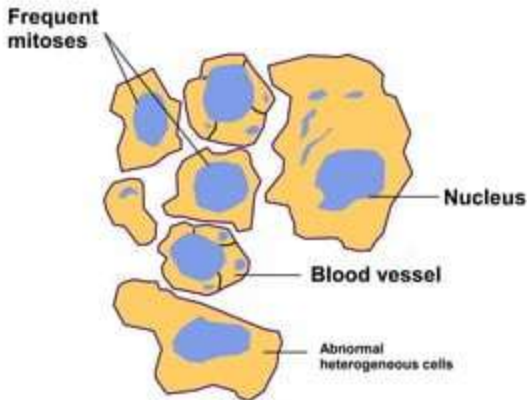
Chemotherapy is used to treat many cancers. More than 100 chemotherapy drugs are used today — either alone or in combination with other drugs or treatments. As research continues, more drugs are expected to become available. These drugs vary widely in their chemical composition, how they are taken, their usefulness in treating specific forms of cancer, and their side effects.

New drugs are first developed through research in test tubes and animals. Then the drugs are tested in clinical trials in humans to find out how safe they are and how well they work.

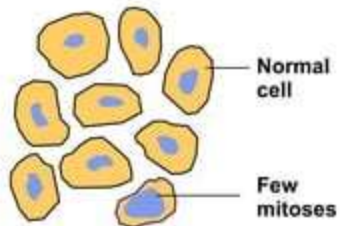


# Cancer Cells and Normal Cells

## CANCER CELLS



## NORMAL CELLS



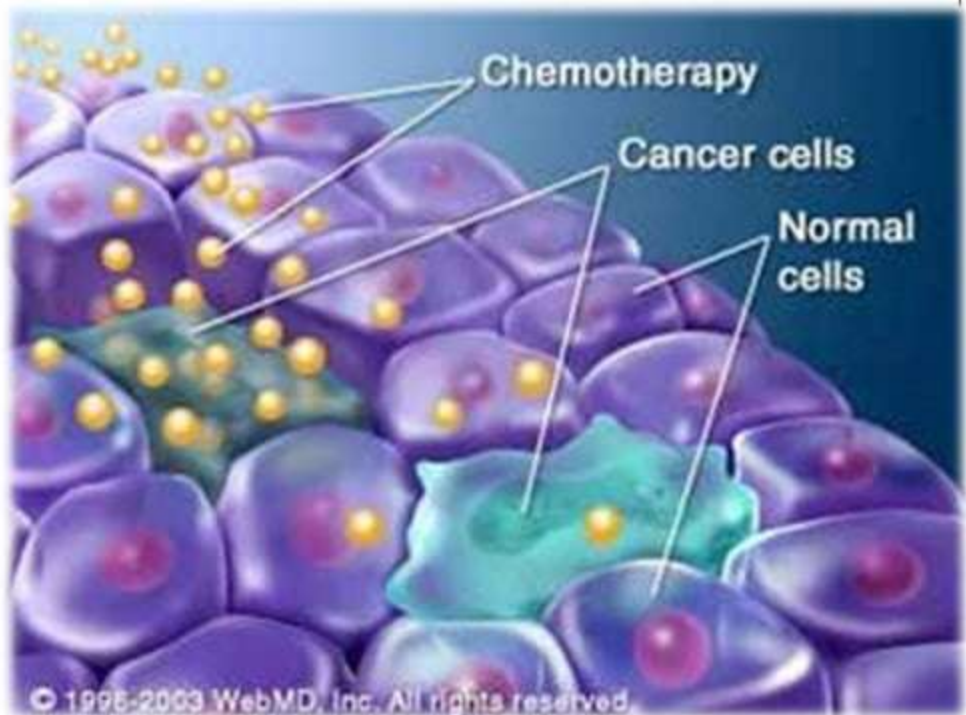
- Loss of contact inhibition
- Increase in growth factor secretion
- Increase in oncogene expression
- Loss of tumor suppressor genes

● 5

- Oncogene expression is rare
- Intermittent or coordinated growth factor secretion
- Presence of tumor suppressor genes



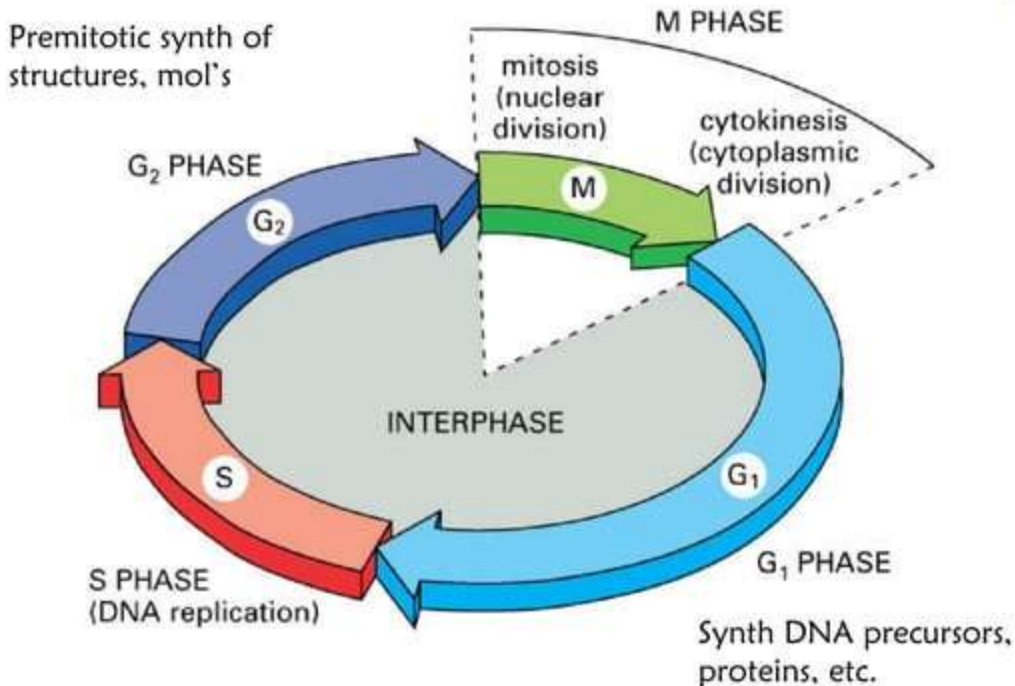
# How Chemotherapy works



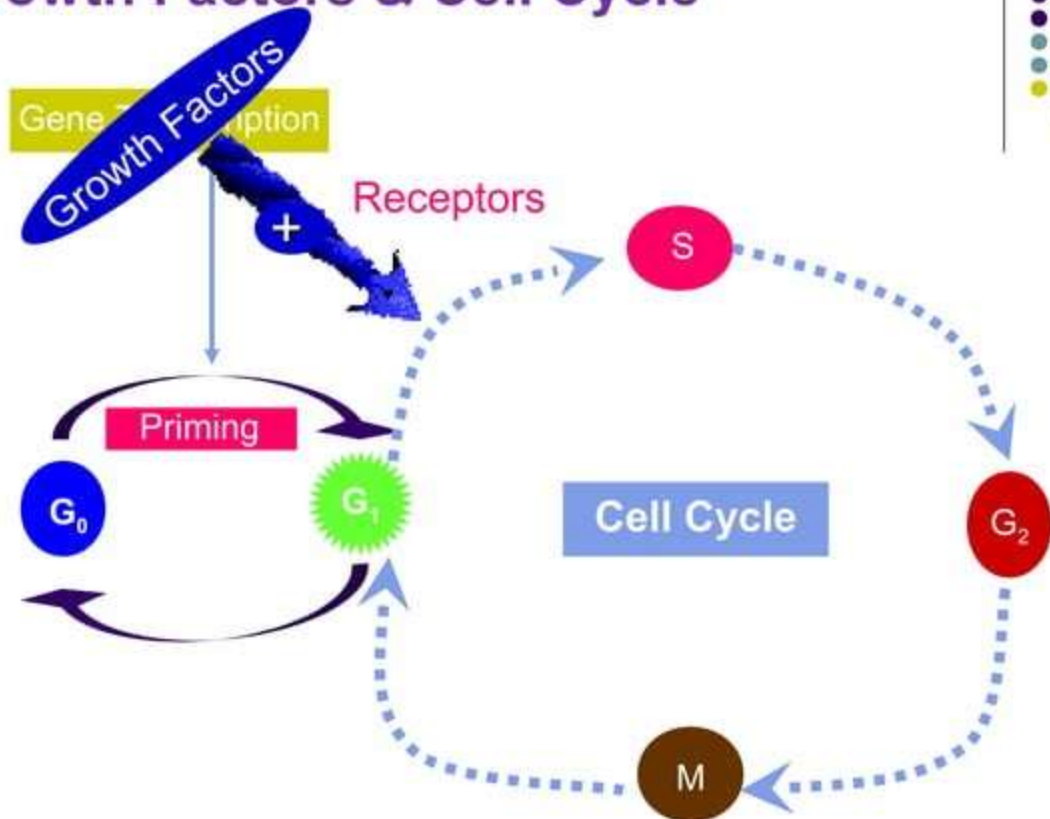


# How Chemotherapy works

## Cell Cycle Phases



# Growth Factors & Cell Cycle







# Goal of Chemotherapy

- Cure
- Control
- Palliation

## Chemotherapy that given with other treatments

- Adjuvant chemotherapy
- Neoadjuvant chemotherapy





# How is Chemotherapy given ?

## Systematic Chemotherapy

- Oral – taken by mouth
- Intravenous – infused through a vein
- Intramuscular – injected into a muscle
- Subcutaneous – injected under the skin




# The Negative Aspects of Chemotherapy



There are several downsides to chemotherapy. One of which is the broad “target” range of the chemicals used. Since the chemicals target all cells undergoing rapid cell division, the process had been known to target other cells besides the cancerous target, most notoriously the cells responsible for hair growth.

Also, since some cancerous tumours have stopped dividing and growing, there are tumours immune to chemotherapy.

**Other side effects exist, and usually cease after treatment, but rarely have long term effects. They include:**



Abdominal pain

Acid indigestion

Bladder Problems

Dizziness

Weight gain/ weight loss

Vomiting

Diarrhoea

Anemia

Depression of the immune system

Hemorrhage

# Chemotherapy Today



Despite all of the negative effects and problems with chemotherapy, research is continuing and successfully improving chemotherapeutic treatments.

Today, there are over forty different types of chemotherapy, and it is certain that thanks to this breakthrough therapy, many lives have been improved and undoubtedly many more will be in the years to come.

Such as hormonotherapy, immunotherapy

# Chemotherapeutic agents



**Chemotherapeutic agent:** acts to reduce the number of bacteria present

## Classification of Chemotherapeutic agents

1. Alkylating agents
2. Antimetabolites
3. Plant derivatives
4. Anti-tumor antibiotics





# 1. Alkylating agents

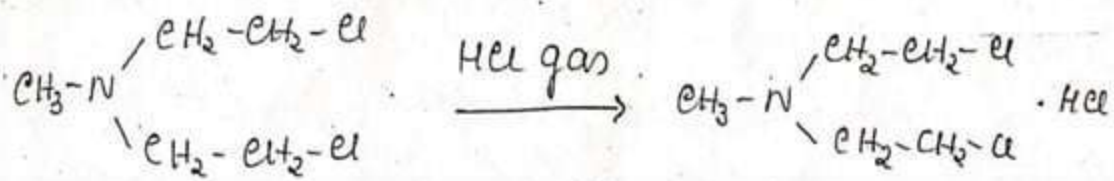
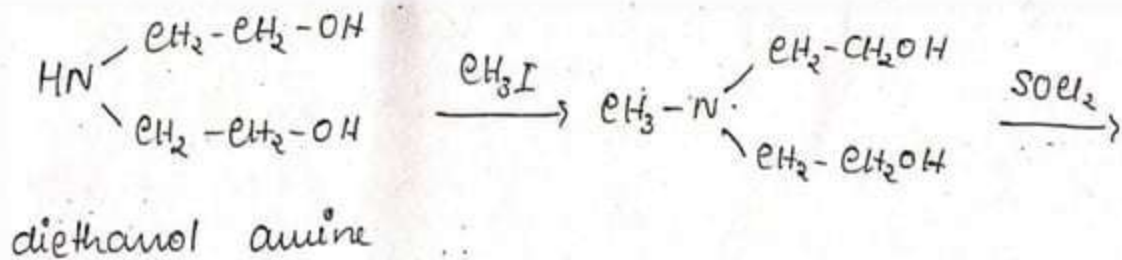
Alkylating agents directly damage DNA to prevent the cancer cell from reproducing. As a class of drugs, these agents are not phase-specific; in other words, they work in all phases of the cell cycle. Alkylating agents are used to treat many different cancers, including leukemia, lymphoma, Hodgkin disease, multiple myeloma, and sarcoma, as well as cancers of the lung, breast, and ovary.

Because these drugs damage DNA, they can cause long-term damage to the bone marrow. In rare cases, this can eventually lead to acute leukemia. The risk of leukemia from alkylating agents is “dose-dependent,” meaning that the risk is small with lower doses, but goes up as the total amount of the drug used gets higher. The risk of leukemia after getting alkylating agents is highest about 5 to 10 years after treatment.

## **Examples:**

Mechloromethanamine, Nitrogen mustards, Busulfan

# Mechloromethanamine







## 2. Antimetabolites

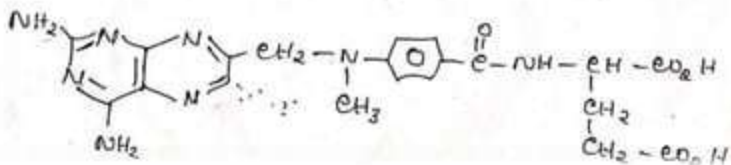
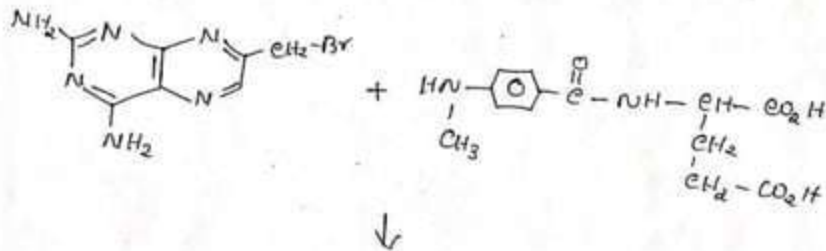
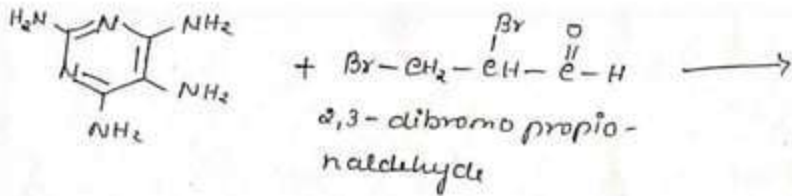
Antimetabolites are a class of drugs that interfere with DNA and RNA growth by substituting for the normal building blocks of RNA and DNA.

These agents damage cells during the S phase. They are commonly used to treat leukemias, cancers of the breast, ovary, and the intestinal tract, as well as other types of cancer.

### **Examples :**

5-fluorouracil (5-FU) , Hydroxyurea,  
Methotrexate, Thioguanine

# Methotrexate





### 3. Plant derivatives

Mitotic inhibitors are often plant alkaloids and other compounds derived from natural products. They can stop mitosis or inhibit enzymes from making proteins needed for cell reproduction.

These drugs work during the M phase of the cell cycle but can damage cells in all phases. They are used to treat many different types of cancer including breast, lung, myelomas, lymphomas, and leukemias. These drugs are known for their potential to cause peripheral nerve damage, which can be a dose-limiting side effect.

**Examples :**

Taxanes, Vinca alkaloids, vinorelbine



## 4. Anti-tumor antibiotics

### **Anthracyclines**

Anthracyclines are anti-tumor antibiotics that interfere with enzymes involved in DNA replication. These drugs work in all phases of the cell cycle. They are widely used for a variety of cancers. A major consideration when giving these drugs is that they can permanently damage the heart if given in high doses. For this reason, lifetime dose limits are often placed on these drugs.

### **Examples :**

Daunorubicin, Doxorubicin, Idarubicin

# Side effects of chemotherapeutic agents



Different drugs have different side effects. It's often better to use moderate doses of 2 drugs that will cause bearable side effects, rather than very high doses of a single drug that might cause severe side effects and maybe permanently damage an important organ. But there are exceptions to this rule, and a single chemotherapy drug may be the best option for some people with certain types of cancer.

Doctors try to give chemotherapy at levels high enough to cure or control the cancer, while keeping side effects at a minimum. They also try to avoid multiple drugs that have similar side effects



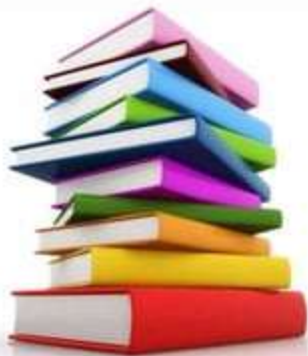
## Conclusion

- Here I conclude the chemotherapeutic agents can produce serious multisystemic side effects, which directly impinge on the patient's preoperative care. It is the anaesthetist's responsibility to be aware of these potential complications. A thorough preoperative assessment and postoperative management plan is required for all patients with a history of previous exposure to chemotherapeutic agents.



## Reference :

- Medicinal Chemistry by Ashutosh Kar
- Medicinal Chemistry by Alka L. Gupta
- Drugs – G.L. David Krupadam D, Varaprasad Rao
- Internet





shutterstock

**Questions**



**More information:**





## Hormonotherapy

Drugs in this category are sex hormones, or hormone-like drugs, that change the action or production of female or male hormones. They are used to slow the growth of breast, prostate, and endometrial (uterine) cancers, which normally grow in response to natural hormones in the body. These cancer treatment hormones do not work in the same ways as standard chemotherapy drugs, but rather by preventing the cancer cell from using the hormone it needs to grow, or by preventing the body from making the hormones.



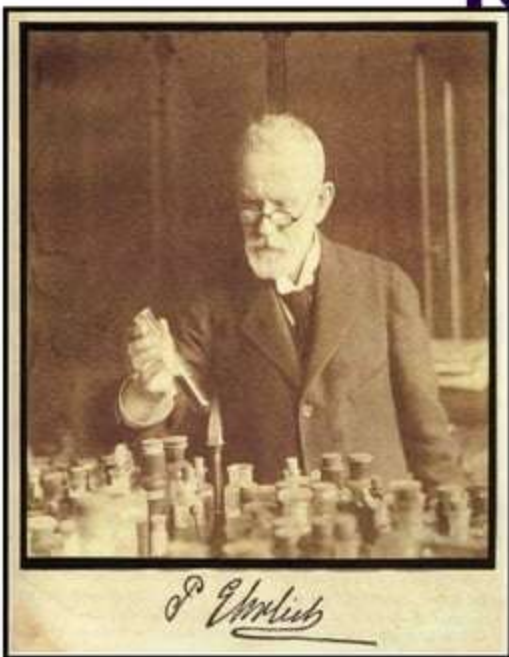
# Immunotherapy

Some drugs are given to people with cancer to stimulate their natural immune systems to recognize and attack cancer cells. These drugs offer a unique method of treatment, and are often considered to be separate from chemotherapy. Compared with other forms of cancer treatment such as surgery, radiation therapy, or chemotherapy, immunotherapy is still fairly new.

There are different types of immunotherapy. Active immunotherapies stimulate the body's own immune system to fight the disease. Passive immunotherapies do not rely on the body to attack the disease; instead, they use immune system components (such as antibodies) created outside the body.



# Paul Ehrlich 1854 - 1915

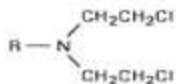


**Father of  
Chemotherapy**

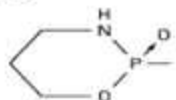
- **Salvarsan for Treatment of Syphilis**
- **Nobel Prize 1908**
- **“Magic Bullet Concept”**



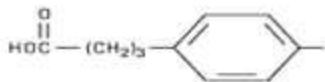
### BIS(CHLOROETHYL)AMINES



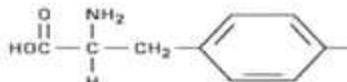
Where R is:



**Cyclophosphamide**

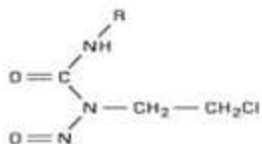


**Chlorambucil**

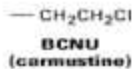


**Melphalan**

### NITROSOUREAS



Where R is:

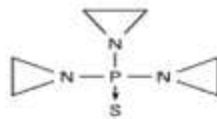


**CCNU**  
(*lomustine*)

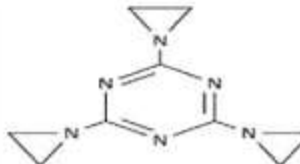


**Methyl-CCNU**  
(*semustine*)

### AZIRIDINES

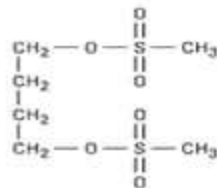


**Thiotopa**



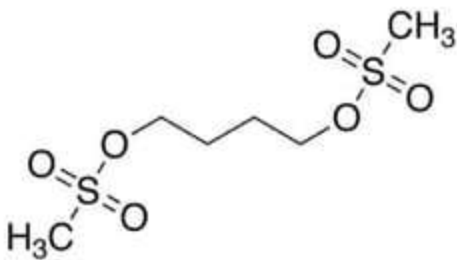
**Triethylenemelamine**

### ALKYLSULFONATE

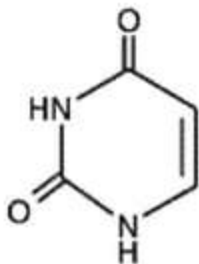


**Busulfan**

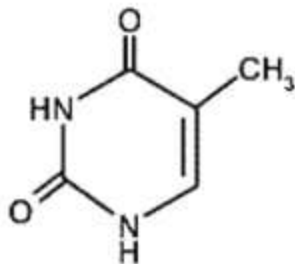
# Alkylating agents



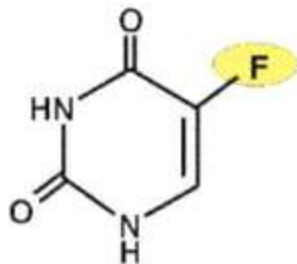
# Antimetabolites



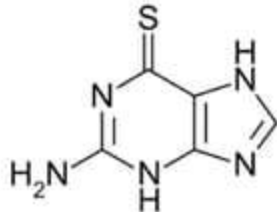
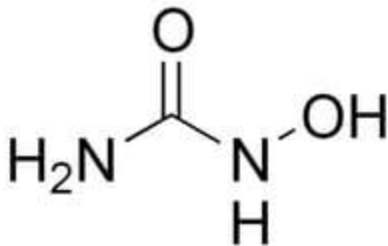
Uracile



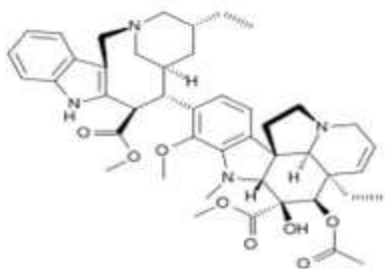
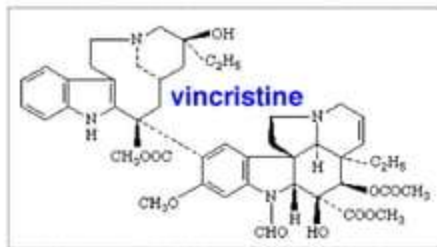
Thymine



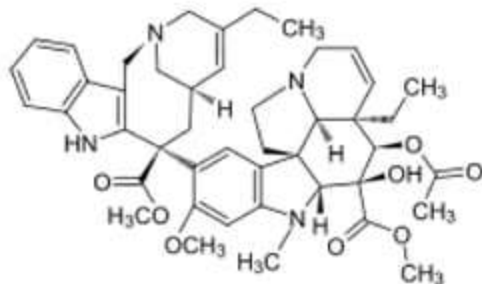
5-Fluoro-Uracile



# Plant derivatives

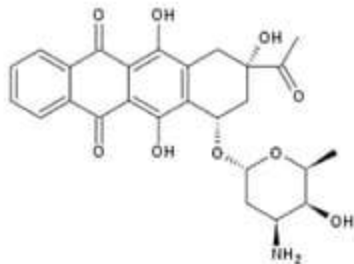
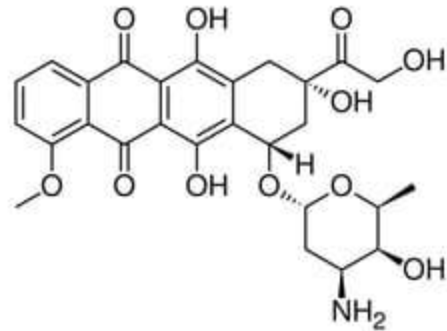
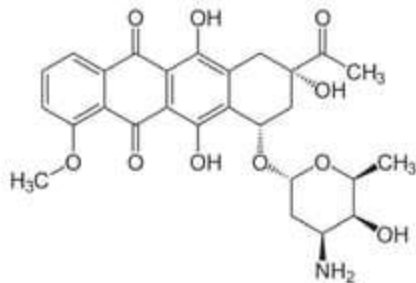


vinorelbine





# Antitumor antibiotics





## D. Other Alkylating agents

### Currently used:

**Procarbazine** → Hodgkin's, brain tumors

**Dacarbazine** → malignant melanoma, hodgkin's lymphoma

**Temozolomide** → malignant gliomas

## Newer Agents:

### Trofosfamide

- Prodrug of ifosfamide
- Orally active
- Metastatic soft tissue sarcomas

### Prednimustine

- Ester of prednisolone and chlorambucil
- Better drug delivery
- CLL, NHL, Ca breast
- S/E: myelosuppression, fluid retention





## **Uramustine**

- Derivative of nitrogen mustard and uracil
- Non Hodgkin's lymphoma

## **Bendamustine**

- Benzimidazole ring and nitrogen mustard
- Inhibits mitotic checkpoints & induces mitosis
- Partial cross resistance to other nitrogen mustards
- Approved for CLL
- Hodgkin's lymphoma NHL, multiple myeloma, breast Ca
- S/E: myelosuppression, nausea, vomiting, hypersensitivity reactions