26

Antimycobacterial Drugs

Chapter

26 Antimycobacterial Drugs

1. INTRODUCTION

Mycobacteria are designated as the *transition forms* existing between **bacteria** and **fungi.**

Mycobacterium refers to a genus of **acid-fast organisms,** usually belonging to the **Mycobacteriaceae**, that essentially includes the causative organisms of **tuberculosis** and **leprosy** natural order**.** These microorganisms are slender, nonmotile, Gram-positive rods, and fail to produce either spores or capsules. The various species invariably comprise of :

M. africanum, M. avium intracellular, M. boria, M. chelonei, M. fortuitum, M. gastri, M. gordonae, M. kanasaii, M. trivale, M. smegmatis, and *M. xenopi.*

Latest **sophisticated laboratory diagnostic methods** concerned with **mycobacterial infections,** besides the ensuing susceptible patterns to the **'antimicrobial drugs'** essentially include : (*a*) most specific radiometric methods which critically measures the evolution of $^{14}CO_2$ from a corresponding **^{14}C-labelled substrate** ; (*b*) **antigenic assays** by the **enzyme-linked immunosorbent assays (ELISA) ;** (*c*) **DNA probes ; nucleic-acid amplification techniques ;** and (*d*) the **restriction fragment length polymorphism (RFLP)** analysis of the resulting **genomic DNA.***

Metabolism of Mycobacteria : It has been established that the **'biochemical constitution'** of **mycobacteria** is of rather complex nature. The meticulous meaningful researches have discovered certain **novel chemical structures,** but the **ensuing relationship between these and the pathogenic and biologic activities of mycobacteria** yet remain to be elucidated and expatiated satisfactorily. Though copious volume of informations with respect to the precise **metabolism of mycobacteria** are available ; however, the exhaustive overall picture of the mycobacterial metabolism is far from plausible acceptable completion.

Mycosides : Smith *et al.*, (1960)** reported **mycosides** which are the **glycolipids** and **peptidoglycolipids** type specific of **mycobacteria.** McLennan *et al.* (1961)*** ascertained that they have in common the particular **terminal saccharide groups** essentially containing **rhamnoses**

*Watt B : *Rev. Med. Microbiol*, **4** : 97, 1993.

Smith DW : *Nature*, **186 : 887, 1960.

***Mclennan AP *et al.* : *Biochem. J.*, **80** : 309, 1961.

O-methylated in different strategical positions. Lederer (1967) assified the **mycosides** into *two* major classes, namely :

(*a*) **Phenolic glycolipids** — having brached-chain fatty acids, and

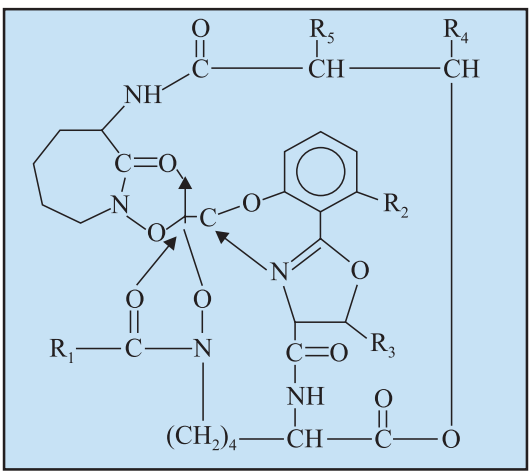
(*b*) **Peptidoglucolipids** — consisting of one mole each of : sugar moiety, fatty acid, and short peptide.

In general, the **glycolipids** and the peptidoglycolipids are held absolutely resposible for the apparent ropelike structures which is quite obvious in one of the outer layers of the **mycobacteria** on being examined by using the unique technique of **negative staining.***

Mycobactin P : Mycobactin P is a natural product, first and foremost isolated in 1946, which possesses an exceptional **iron-chelating characteristic feature.**

Mycobactin S : Mycobactin S happens to be the most active of these factors exhibiting distinct growth stimulation at a concentration as low as 0.3 ng . mL^{-1}.

Mycobactin M : Mycobactin M designates the structure of **M-type factors.**



MYCOBACTIN P : $R_1 = C_{17}H_{34}$; $R_2 = CH_3$; $R_3 = H$; $R_4 = C_2H_5$; $R_5 = CH_3$;

MYCOBACTIN S : $R_1 = C_{17}H_{34}$; $R_2 = H$; $R_3 = H$; $R_4 = CH_3$; $R_5 = H$;

MYCOBACTIN M : $R_1 = CH_3$; $R_2 = H$; $R_3 = CH_3$; $R_4 = C_{17}H_{34}$; $R_5 = CH_3$;

The latest knowledge with respect to the chemistry and functions of **mycobactins** may be exploited skilfully in a wide spectrum of approaches to the intensive and extensive search for **antimycobacterial drugs.**** In actual practice, one such approach may essentially involve critical and exhaustive screening of compounds that interfere at certain specific point in the **pathway of biosynthesis of mycobactins ;** and selecting only such compounds which inhibited exclusively the bacterial growth under **iron-limiting conditions.** Thus, one may justifiably link up the primary role of action of ***para*-aminosalicylic acid (PAS)** with the ensuing inhibition of the **mycobactin synthesis.**

It has been amply proved and established that both **tuberculosis** and the ***Mycobacterium avium* complex infection** are enhanced significantly by virtue of the fact that the relatively high number of **AIDS patients** that usually coexist specifically in the huge inner city populations, and also due to plenty of homeless shelters. In actual practice, the **antimicrobial drugs** that are solely employed for the effective

*Barksdale L and Kim KS : *Bacteriol Rev.*, **41,** 217, 1977.

Braun V *et al.* (eds) : **The Future of Antibiotherapy and Antibiotic Research, Academic Press, London (UK), 1981.

treatment of ***Mycobacterium avium*** **complex** essentially include : **rifabutin,** the new **macrolides** (*viz.*, **clarithromycin** and **azithromycin**), the **fluoroquinolones,** and **combination regimens** of **ethambutol** (or other tuberculosis drugs) with either **clarithromycin** or **azithromycin.**

2 CLASSIFICATION

The **antimycobacterial drugs** may be judiciously classified into *two* major categories, namely :

(*a*) First-Line Drugs, and

(*b*) Second-Line Drugs.

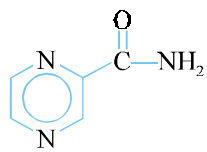
The two aforesaid categories shall now be discussed individually in the sections that follows :

2.1. First-Line Drugs

The **first-line drugs** used widely for tuberculosis are, namely : **isoniazid, rifampin, ethambutol, pyrazinamide,** and **sptreptomycin.**

The antituberculosis drugs *viz.* **isoniazid, rifampin.** and **ethambutol** have been duly treated under **'Newer Drugs for Newer Diseases'–Chapter–30 ;** whereas, **streptomycin** under **'Antibiotics'–Chapter–25,** and hence **pyrazinamide** shall be discussed as under :

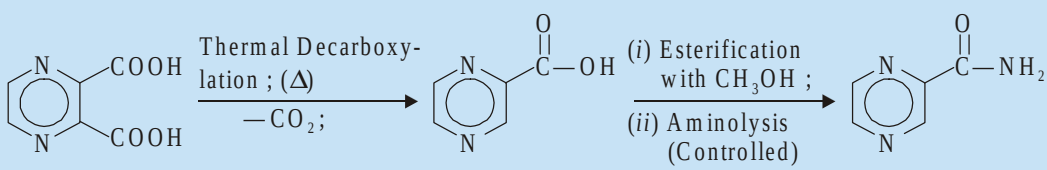
2.1.1. Pyrazinamide INN, BAN, USAN



Pyrazincarboxamide ; PZA ;

Tebrazid$^{(R)}$;

Synthesis



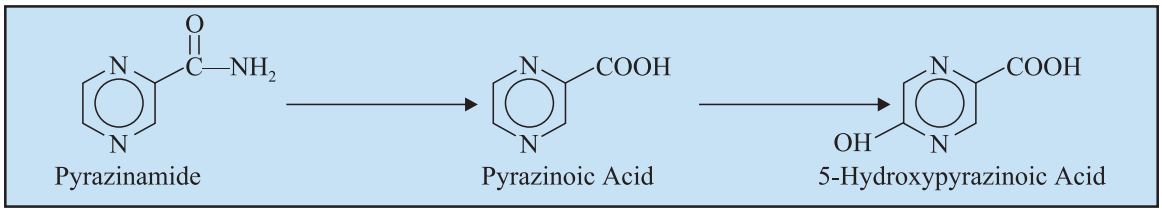
2, 3-Pyrazinedi-carboxylic acid — Pyrazinoic acid (Mono carboxylic acid) — Pyrazinamide

Thermal decarboxylation of 2, 3-pyrazinedicarboxylic acid gives rise to the formation of the corresponding monocarboxylic acid derivative as an intermediate by the loss of one mole of CO_2. The resulting product upon careful esterification with methanol followed by controlled aminolysis produces the desired **pyrazinamide.**

It is an antituberculosis drug invariably employed for the initial treatment in conjunction with **isoniazid (INH)** and **rifampin (RIF).** It is generally given along with **isoniazid,** which it potentiates significantly.

Mechanism of Action : Pyrazinamide is especially useful because it is particularly active against the **semi-dormant intracellular tubercle bacilli** which are found to be not affected by other drugs. Thus, the combined pyrazinamide therapy has remarkably reduced the **'treatment regimen'** from **9 months** to merely **6 months.** The drug is least affected by the presence of food in the gastro-intestinal (GI) tract, nor by the concurrent usage of **Al-Mg-antacids.**

The precise metabolism of **pyrazinamide** may be shown by the help of the following reactions :

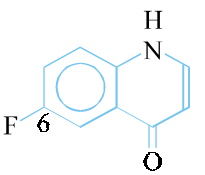


2.2. Second-Line Drugs

The **second-line drugs** for tuberculosis are found to be more toxic but may be required with certain **resistance problems.** These drugs essentially include : **fluroquinolones** (*e.g.*, **ofloxacin, ciprofloxacin**), **cycloserine, ethionosamide, aminosalicylic acid,** aminoglycosides (*viz.*, **amikacin, kanamycin**), **clofazimine,** and **capreomycin.**

A few of these imporant compounds shall now be treated in the sections that follows together with their mechanism of action wherever possible.

2.2.1. Fluoroquinolones



Fluoroquinolones designate distinctly an improvement of the earlier structural analogues, such as : **cinoxacin, nalidixic acid, oxolinic acid,** and **pipemidic acid,** for being relatively much more potent *in vitro*. Besides, the **fluoroquinolones** do exhibit a definitely **broader antibacterial spectrum,** the essentially consist of both **Gram-positive and Gram-negative microorganisms.**

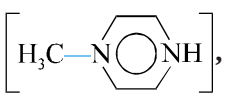
Charactersistic Features : Fluoroquinolones possess they following **characteristic features** as ennumerated below :

(1) Possess much improved pharmacokinetic properties.

(2) Newer derivatives usually get distributed much better squarely both in **body tissues** and **body fluids ;** besides, they even penetrate cells, and may be efficaciously employed in the proper treatment of systematic infections.

(3) They do exhibit an excellent bioavailability*

(4) Major factors in establishing these **characteristic features** are due to :

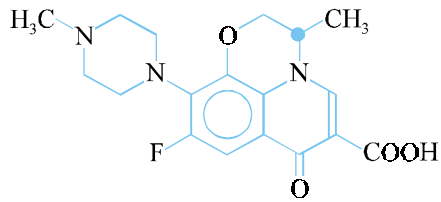
- attachment of a **Fluorine atom** at C-6 of the quinoline nucleus, and
- attachment of either **piperazinyl**  , as in **ciprofloxacin ;** or **N-methylpiperazinyl**  , as in **ofloxacin** moieties strategically positioned at C-7. Besides,

*Karabalur N and Drusano G : In : Hooper DC and Wolfson JS (eds.) : **Quinoline Antimicrobial Agents,** American Soc. for Microbiology, Washington DC, **2nd** edn, 1993.

they do possess **alkyl** or **cycloalkyl** groups at N_1 of the prevailing **1, 4-dihydro-4-oxo-3-quinoline carboxylic acid** structure specifically.*

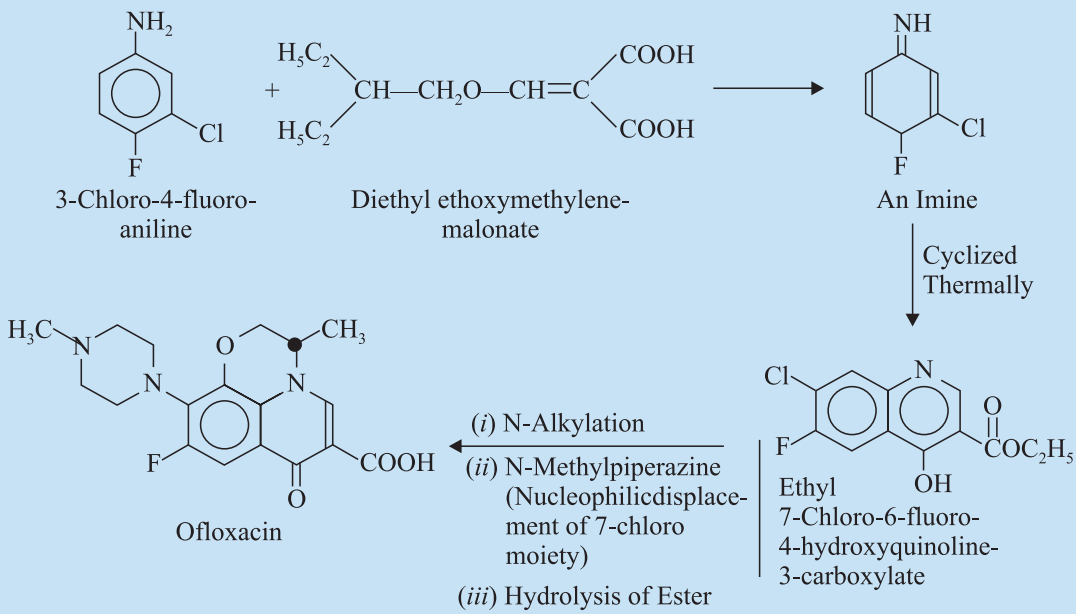
Two typical examples of the **fluoroquinolones** *viz.*, **ofloxacin** and **ciprofloxacin** shall now be treated separately in the sections that follows :

2.2.1.1. Ofloxacin INN, BAN, USAN



7H-Pyridol [1, 2, 3-*de*]-1, 4-benzoxacine-6-carboxylic acid, (±)-9-fluoro-2, 3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo ; Floxil ; Floxin ; Oflocet ; Oflocin ; Exocin ; Oxaldin ; Tarivid ; Visiren ; Flobacin ; Ofloxacine ;

Synthesis



Interaction of 3-chloro-4-fluoroaniline with diethyl ethoxy-methylene malonate yields the corresponding **imine salt,** which on being thermally cyclized gives rise to the formation of ethyl-7-chloro-6-fluoro-4-hydroxyquinoline-3-carboxylate. The resulting product on being subjected to N-alkalation, followed by the nucleophilic displacement of the 7-chloro moiety with N-methylpiperazine, and finally hydrolysis of the ester yields the desired product **ofloxacin.**

Chirality in Ofloxacin : The C-atom to which the methyl group is attached (as shown by the **dark spot**), in the **oxazine ring,** is **chiral,** and the clinically utilized drug substance is a **racemic mixture,** whereas the **(+)-isomer** almost possesses twice the activity as that of the corresponding **(–) isomer.**

*Mitscher LA *et al.* In Reference (*) above.

The **MICs*** of **ofloxacin** and **ciprofloxacin** for the organism *Mycobacterium tuberculosis* invariably vary between 0.12–2.0 mcg.mL^{-1}. Importantly, both these drygs are **bacterial in nature,** and the ensuing **MBC-MIC ratio** being from 2 to 4.

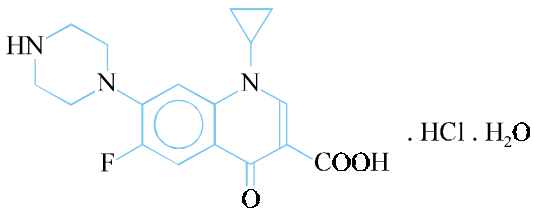
However, the MICs of **ofloxacin** are found to be a little higher, ranging between 2–16 mcg.mL^{-1} for 50% of strains, and from 8–16 mcg.mL^{-1} for 90% of strains. The MBC-MIC ratio largely varies from 1 to 8. It has been amply demonstrated that **ofloxacin** and **ciprofloxacin** invariably exhibit sufficient *in vitro* activity against such organisms as : *M. bovis, M. kansasii,* and *M. fortuitum,* but failed to show any activity against *M. chelonae.*

Ofloxacine is predominantly recognized as an **'Intermediate-spectrum Fluoroquinolone.'**

Ofloxacine fails to inhibit the **cytochrome P450.**

Dose : Adult : 400 mg twice daily.

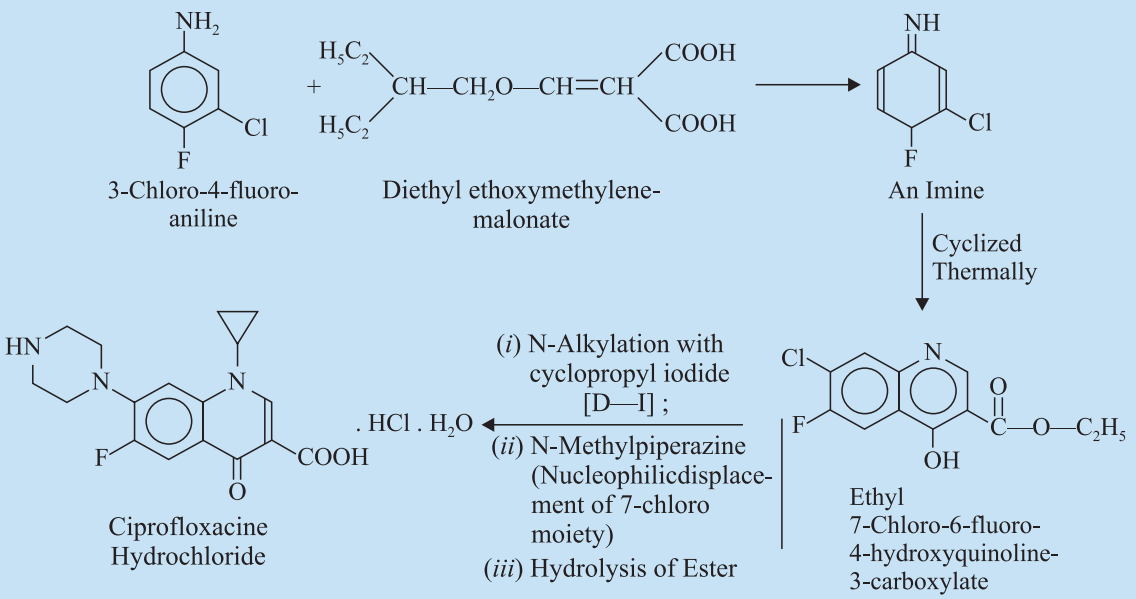
2.2.1.2. Ciprofloxacine Hydrochloride INN, BAN, USAN



2-Quinolinecarboxylic acid, 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)–, monohydrochloride, monohydrate ;

Ciloxan$^{(R)}$; Cipro$^{(R)}$;

Synthesis



*MICs : Minimum Inhibiting Concentrations.

The reaction between 3-chloro-4-fluoro aniline and diethyl-ethoxymethylene malonate yields a corresponding **imine salt.** The resulting product upon being cyclized thermally gives rise to the formation of ethyl-7-chloro-6-fluoro-4-hydroxyquinoline-3-carboxylate. This undergoes three steps of reactions sequentially :

• N-alkylation with cyclopropyl iodide,

• Nucleophilic displacement of 7-chloro moiety with the aid of N-methylpiperazine, and

• Hydrolysis of the resulting ester,

Thus, at the end it yields the official compound **ciprofloxacin hydrochloride monohydrate.**

Ciprofloxacin is the most viable and potent **second line fluoroquinlones,** effective very much against a broad spectrum of microorganisms. The most susceptible ones happen to be the aerobic **Gram-negative bacilli.**

Ciprofloxacin attains many folds higher concentration in the urine than in the plasma level. It also produces quite rapid and virtually complete clinical relief in specfic nosocomial bronchopneumonia patients. It has been frequently employed as a preoperative measure in cardiac surgery. It invariably attains levels higher than MICs meant for the commonly susceptible pathogens for at least 8 hours **Ciprofloxacin** is indicated profusely in skin, soft tissue, and skin infections, bacterial gastro-enteritis, and acute urinary-tract infections (UTIs). It also finds its usage in respiratory infections caused due to *Mycoplasma, Legionella,* as topical agent in conjunctivitis, and also in multidrug resistant tuberculosis.

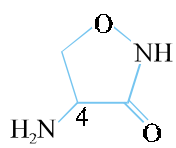
Ciprofloxacin is recognized as a **'drug of first choice'** in the treatment of typhoid fever.

MICs for **ciprofloxacin** for 50% of strains range from 1–16 mcg.mL^{-1} (with data from certain series exceeding 100 mcg.mL^{-1}).

Recently, **ofloxacin, ciprofloxacin,** and more recently **sparfloxacin** have been duly administered either with **ethambutol, pyrazinamide,** or **isoniazid (INH),** and **rifobutin,** and also in other combinations. Though one may observe certain promising results, but no specific and definite inferences may be drawn with regard to the clinical value of these new glaring approaches to the observed therapeutic efficacy.

Dose : *Adult : 750 mg once or twice daily ; or 500 mg thrice daily.*

2.2.2. Cycloserine INN, BAN



D-4-Amino-3-isoxzolidinone ; Orientomycin ; cRosina ; Farmiserina ; Micoserina ; Oxamycin ; Seronomycin ;

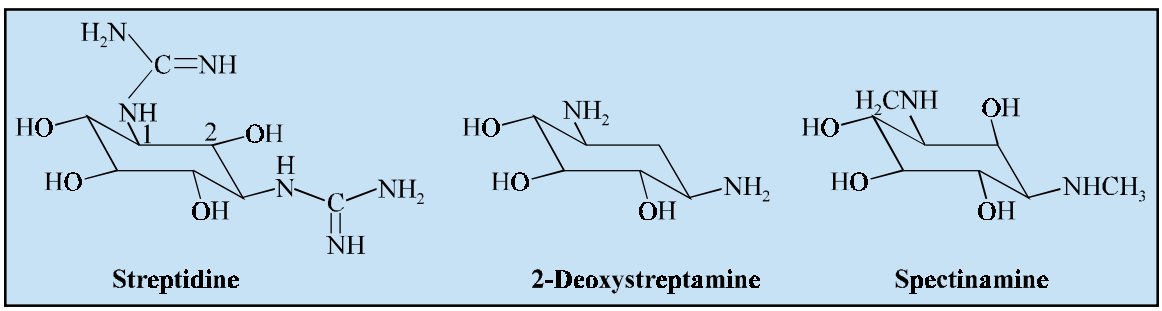
Cycloserine is an **'antibiotic' (antimycobacterial drug)** duly obtained from *S. orchidaceus.* It is a chemical analogue of D-alanine. It belongs to the **second-line tuberculostatic** drug, and it also acts as an **inhibitor of cell-wall synthesis.** It is readily absorbed *via* the oral administration, and subsequently gets distributed amongst different body tissues and the **cerebrospinal fluids (CSF).** It is found to be excreted mostly unaltered in urine *via* glomerular filtration.

Cycloserine is frequently used for the adequate treatment of **multidrug-resistant tuberculosis** along with certain other primary drugs. It also finds its application for the control and management of acute UTIs caused by **susceptible microorganisms.**

It also retains its importance for showing activity against several other microorganisms that are frequently employed in the **primary tests of fermentation broths.**

2.2.3. Aminoglycosides

The **aminoglycosides** class of antibiotics predominantly contains a pharmacophoric moiety : **1, 3-diamino-inositol** group *viz.*, **streptamine ; 2-deoxystreptamine ;** and **spectinamine** as given below :



In a broader perspective a plethora of the alcoholic functions of the **1, 3-diaminoinositol** *ie.*, the pharmacophoric moiety are strategically substituted *via* various **glucosidic bonds** studded with appropriate **characteristic aminosugars** to give rise to the production of **pseudo-oligosaccharides.**

Chemistry of Aminoglycosides : The **chemistry of aminoglycosides** *vis-a-vis* their **spectrum, potency, toxicity,** and **pharmacokinetics** represent a vital function of the specific inherent identity of the **diaminoinositil segment,** and more importantly the various arrangement as well as highly critical identity of the attachments. Perhaps the presence of several hydroxyl moieties and their ability to cause profuse hydrogen-bondings the host of **aminoglycosides** are found to be freely water soluble at most of the achievable pHs, are basic in character ; and, therefore, form respective **acid addition salts.** Consequently, these are not duly absorbed in appreciable quantum from the GI-tract ; and hence are mostly excreted both in **active form** and in **significantly higher concentrations** in the urine following injection.

Mechanism of Action : The precise **mechanism of action** of the **aminoglycosides** solely depends on their ability to combine intimately with **bacterial** (not mammalian) **ribosomes** in order to arrest the ensuing **protein synthesis.** In actual practice, one may accomplish the formation of the so called **'initiation complex', but cannot pass into, the following stages of protein synthesis.** Thus, the bondage existing between **microbial ribosomes** and **aminoglucosides** is so strong that the inhibition is severe to such an extent thereby causing ultimately a **bacterial effect.** The other accompanying drugs (in multi-drug therapy) seem to elicit noticeable inference with the specific and critical binding of **aminoacetyl-t-RNA,** that precisely **checks and prevents the phenomenon of chain elongation.** In addition, the aforesaid interference lands into **certain misreading of RNA condons,** which may lead to the production of **inappropriate proteins** in a situation whereby the prevailing **protein-synthesis** is not arrested more or less completely.

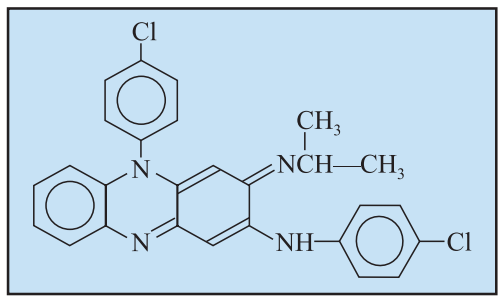
General Remarks : In a broader sense, **aminoglycosides** have gained the cognizance of being an extremely important class of **antibiotics** for the treatment of infections caused by **Gram-negative**

bacilli. It has been widely acknowledged that the treatment of most abundant **nosocomical Gram-negative bacillary infections** done with the **third-generation cephalosporins, carbapenems,** and the **new fluoroquinolones** have virtually rendered the status of the **aminoglycosides** as **'alternative drugs'** unless and until resistant strains are distinctly suspected in **specific immunosuppressed patients.**

A few typical representatives of the **second-line drugs** used as **antimycobacterial agents,** namely : **Neomycin, Kanamycin,** and **Streptomycin** have already been discussed under the chapter on **'Antibiotics'.**

However, *two* important members belonging to the class of **antimycobacterial agents** that are used widely in the cure of typical infections, such as **Clofazimine** and **Capreomycin** shall be dealt with in the sections that follows :

2.2.3.1. Clofazimine INN, BAN, USAN

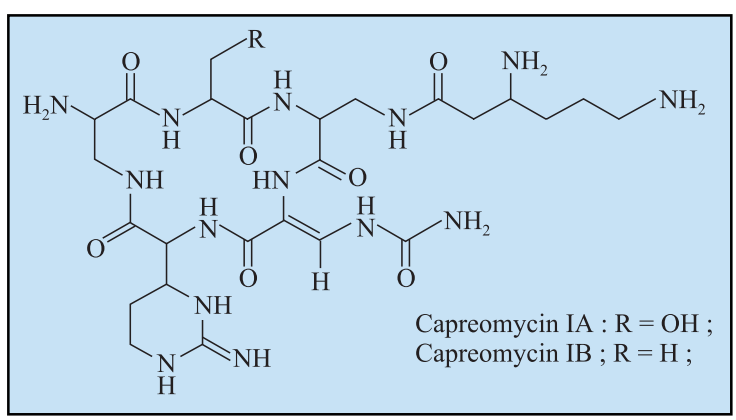


2-Phenazinamine, N, 5-bis(4-chlorophenyl)-3, 5-dihydro-3-[(1-methylethyl) imino]– ; IP ; BP ; Lamprene(R) ;

Clofazimine is used in combination with a host of other drugs for the cure and treatment of **leprosy** and **infections caused** by *Mycobacterium avium* particularly in AIDS patients. It gets bound to mycobacterial DNA and also interferes with growth. It is proved to be a **bactericidal agent** ; and may even take upto almost 50 days before exerting its **'killing effect'.** It shows **oral-systemic bioavailability** to approximately 50%. In the course of maintenance therapy the **'elimination half-life'** stands at 70 days.

Mechanism of Action : It's probable mechanism of action is its **intimate involvement in DNA binding,** it may **inferfere with template function of DNA.**

2.2.3.2. Capreomycin INN, BAN, USAN



Capreomycin is a **cyclic polypeptide complex antibiotic** having a structure very much similar to **viomycin,** and produced by *Streptomyces capreolus** as a mixture of about *four* different components. It exerts its bacteriostatic action against certain **mycobacterial strains**, such as : *M. tuberculosis ; M. bovis ; M. kansasii*, and *M. avium* by an **unknown mechanism of action.** However, its **pharmacological** and **antibacterial activities** are quite akin to the **aminoglycosides.**

It is pertinent to add here that the **capreomycin-resistant strains** are not found to be completely resistant to **kanamycin,** whereas the corresponding **kanamycin-resistant strains** are invariably resistant to **capreomycin.**

Dose : *Common daily dosage is 1 g IM.*

Note : Its usage is very much restricted to retreatment of chronic cases having predominant resistant mycobacterial flora.

Probable Questions for B. Pharm. Examinations

1. Explain the following :

(*a*) Mycobacterium

(*b*) Four latest sophisticated laboratory diagnostic methods related to mycobacterial infections

(*c*) Metabolism of Mycobacteria

(*d*) Mycobactius P, S and M.

2. How would you classify the Antimycobacterial Drugs ? Give the structure, chemical name, and uses of at least **one** most potent compound from each category.

3. Give a detailed account on **Pyrazinamide** alongwith its synthesis, mechanism of action, and uses.

4. Attempt any **two** of the following :

(*a*) Fkluoroquinolones

(*b*) Synthesis of ofloxaicin

(*c*) Chirality in ofloxacin ; MICs of ofloxacin

(*d*) Cycloserine

(*e*) Clofacimine.

5. Give a brief account of the **'Aminoglycosides'.**

RECOMMENDED READINGS

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3. Dax SI : **Antibacterial Chemotherapeutic Agents,** Blackie Academic and Professional, New York, 1997.

*Herr *et al.* : *140th Am. Chem. Soc. Meet,* Chicago, Sept. 1961.

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12. Reichman LB and Hershfield ES (eds.) : **Tuberculosis : A Comprehensive International Approach,** Marcel Dekker, Inc., New York, 1993.
13. Whelton A and Neu HC (eds.) : **The Aminoglycosides Microbiology, Clinical Use and Toxicology,** Marcel Dekker Inc., New York, 1982.

27

Antineoplastic Agents

Chapter

27 Antineoplastic Agents

1. INTRODUCTION

The past three decades have witnessed a remarkable revolution in the field of tumour chemotherapy. A spectacular wealth of basic knowledge with regard to molecular and cellular biology, better understanding of mechanisms of cellular division, tumour immunology, fundamental factors involved in both viral and chemical carcinogenesis and above all the improved investigative techniques have ultimately led to the introduction of a substantial number of newer **antineoplastic agents.**

A few years ago significant palliative results were obtained by chemotherapy in a number of human neoplasma. Today it is, however, possible to list at least certain neoplastic diseases that can be associated with a normal life expectancy after treatment with drugs alone or in combination with other modalities. These neoplasms essentially include : carcinoma in women, acute leukemia, Burkitt's lymphoma, Ewing's sarcoma, retinoblastoma in children, lymphosarcoma, Hodgkin's disease, rhabdomyosarcoma, mycosis fungoides and testicular carcinoma.

A **neoplasm,** or **tumour** is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissue and continues in the same manner after cessation of the stimuli which have initiated it.

A **malignant tumour** grows rapidly and continuously, and even when it has impoverished its host and source of nutrition, it still retains the potentiality for further proliferation. Besides, malignant tumours invade and destroy neighbouring tissues and possess no effective capsule, a malignant tumour readilty ulcerate and tend sooner or later to disseminate and form metastases.

The **causation of neoplasms** are many, for instance : the *genetic factors e.g.*, retinoblastoma is determined by a Mendelian dominant factor and so are the multiple benign tumours ; the *chemical carcinogens e.g.*, arsenic, soot, coal tar, petroleum lubricating oil ; the *polycyclic hydrocarbon carcinogens e.g.*, 1, 2, 5, 6-dibenzanthracene, 3, 4-benzpyrene.

There has been a tremendous growth in different aspects of cancer research, cancer chemotherapy *vis-a-vis* a better understanding of the intricacies of the '**tumour biology**' that has ultimately led to not only the legitimate evolution but also the explicite elucidation of the probable mechanisms of action for the **antineoplastic agents.** In fact, the various strategies involved to augment the speedy as well as meaningful progress in the develoment of **antineoplastic agents** may be accomplished as follows :

(*a*) Fundamental basis for the more rational approach in the design of newer drugs,

(*b*) Large collaborative investigations, concerted integrated research based on recent developments and advances in the clinical techniques, and

(*c*) Combination of such privileged advantages with improved preliminary screening methodologies.

As on data nearly ten differnet types of '**neoplasms'** may be '**cured**'* with the aid of chemotherapy in patients quite satisfactorily, namely : leukemia in children, Hodgakin's disease, Burkitt's lymphoma, Ewing's sarcoma, choriocarcinoma in women, lymphosarcoma, mycosis fungoides, rhabdomyosarcoma, testicular carcinoma, and retinoblastoma in children.

It is pertinent to raise a vital question at this point in time—**'why cancer is rather difficult to cure in comparison to other microbial infections'**. One may put forward the following plausible explanations as :

(*i*) Qualitative differences existing between the human and bacterial cells. It is well known that the bacterial cells. possess distinctive cell walls ; besides, the ribosomes also differ entirely from those of '**human cells**',

(*ii*) Quantitative differences do prevail between **normal and neoplastic human cells**, and

(*iii*) Body's immune mechanisms and other host defenses play a vital role in killing bacteria (*i.e.,* bactericidal) plus other susceptible foreign cells ; whereas they are not so prevalent in destroying cancerous cells.

Evidences of quantitative differences do exist in the natural characteristics of *proteins* observed in monitoring various essential pathways which in turn control *three* major operations, namely : (*a*) cell proliferation ; (*b*) cell differentiation ; and (*c*) induction of programmed cell death (*i.e.,* **apoptosis**)—also necessarily catering for much desired '**targets for antineoplastic agents.**** In a situation, whenever the cancerous cells overcome the **'body's suveillance mechanism'**, the chemotherapeutic agents (*i.e.,* **antineoplastic agents**) should be able to destroy, kill and thus erradicate completely each and every residual **clonogenic malignant cell,** since even one cell may refurbish and reestablish the cancerous tumour.

Incidence of Tumors :

The **incidence of tumours** vary from age, sex, geographical, ethnic, environmental, virus, radiation and hormone factors as stated below :

(*a*) **Age Incidence :** *e.g.*, *embryonic mesenchymoma* group originate and disseminate even before birth ; **sarcoma** arises in adolescence ; *carcinoma* takes place after the age of 40 years and increases with advancing years ; *bone sarcoma* occurs between 10-12 years ; *cancer of prostrate* becomes active in old age.

(*b*) **Sex Incidence :** *e.g.,* **post-cricoid cancer** is found 90% in young women ; *cancer of lower part of oesophagus* occurs in elderly men.

(*c*) **Geographical Incidence :** *e.g.*, **nasopharyngeal cancer** is common among Chinese and rare in other races ; **Cancer of mouth and tongue** is common in India ; **Cancer of bladder** is common in Egypt ; **Cancer of liver** is common in Central Africa.

(*d*) **Ethnic Incidence :** *e.g.*, uncircumsised males suffer from **penile carcinoma** and their wives often suffer from **carcinoma of cervix**.

*Cure means-an expectation of normal longevity.

Dorr RT and Von Hoff DD (eds) : **Cancer Chemotherapy Handbook, Appleton and Lange, Norwalk CT, 2nd edn., pp3-14, 1994.

(*e*) **Environmental Incidence :** *e.g.*, **bronchogenic carcinoma is** found mostly among cigarette smokers and people in industrialised areas due to air pollution and asbestos fibre inhalation.

(*f*) **Virus Incidence :** *e.g., polyoma virus* when gets in contact with host cell, it destroys it by feeding on it and releasing its DNA. Consequently, when this DNA gets in contact with host DNA, a new DNA with different genetic (genotype) material is formed. As this genotype is different, it grows differently from the normal cell leading to cancerous cells.

(*g*) **Radiation Incidence :** *e.g.*, **osteosarcoma** is found in subjects handling paints containing radium ; radiologists mostly suffer from leukemia.

(*h*) **Hormone Incidence :** *e.g.*, **breast cancer** in mice is produced by administration of large doses of *oestrogens.*

1.1. Chemotherapeutic Intervention

The various aspects of **chemotherapeutic intervention** may be discussed in an elaborated manner under the following defined categories, such as :

(*i*) Phase specificity,
(*ii*) Tumour selectivity and response,
(*iii*) Determinants of sensitivity and selectivity,
(*iv*) Requirements for 'kill',
(*v*) Combination chemotherapy,
(*vi*) Log cell-kill principle, and
(*vii*) Drug resistance.

Each of the above aspects shall now be treated individually in the sections that follows :

1.1.1. Phase Specificity

Broadly speaking the '*antineoplastic drugs*' may be categorized under *two* heads, namely :

(*a*) **Phase nonspecific drugs.** These drugs have an ability to act on the cell throughout the cell-cycle, and

(*b*) **Phase specific drugs.** The drugs act **preferentially** during one or more of the nonresting phases. In other words, they prove to be '*absolutely ineffective*' when delivered to the cell specifically during the *wrong phase.*

Figs. 27.1 and 27.2 illustrate the **cell-life cycle** and the **cell-cycle specificity** respectively as given below :

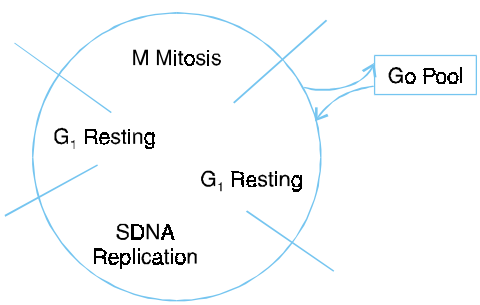


Fig. 27.1 Cell-Life cycle.

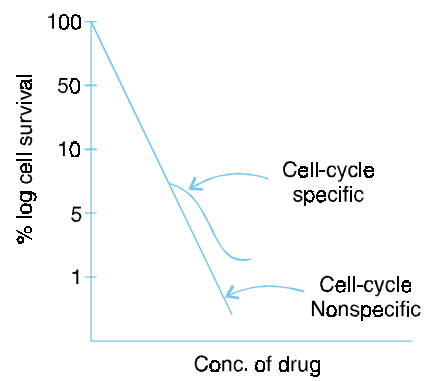


Fig. 27.2. Cell-cycle specificity.

Fig. 27.1 evidently shows a circular pictorial model actually obtained for the clockwise progression of the cell-cycle. In actual practice, however, both the duration of individual phase in the cell cycle alters appreciably guided by the cell type, and also within a single tumour. Following are some of the '**typical durations'**, for instance :

S—DNA : replication phase = 10-20 hours ;

G_2—Resting phase = 2-10 hours ;

G_1—Resting phase = highly variable due to another phase ;

M—Mitosis phase = 0.5 – 1 hours ;

G_0—Pool = Cell not active during cell division.

Salient-Features of Antineoplastic Drugs

These are as follows :

(*i*) Block the **biosynthesis** or **transcription of nucleic acids** to check cell-division through direct interference with mitotic spindles,

(*ii*) Both **mitosis phases** and cells that are engaged in **DNA-synthesis** are found to be highly susceptible to these **antineoplastic agents**, and

(*iii*) In the resting state the **not-so-fast growing tumours invariably possess good number of cells**.*

Fig. 27.2 explicitely represents the overall effects of **antineoplastic agents** upon the cell survival which is exponentially related to dose. Now, if a plot is made between **log cell survival** along the Y-axis and the **drug concentration** along the X-axis one would get a '**straight line'**. Nevertheless, these drugs usually display their cytotoxicity irrespective of the **cell-cycle-phase** ; and, hence, are known as the '**non-cell cycle phase specific drugs'.** Importantly, such other drugs *viz.*, **mitotic inhibitors** and **antimetabolites**, that particuarly act at one phase of the cell cycle only, normally display a distinct **plateau** soonafter a **preliminary low-dose exponential region**.

1.1.2. Tumour Selectivity and Response

It has been duly observed that paricularly for '**phase-specific drugs**' (see Section 1.1.1.*b*), the probability apprehended for a lethal action on a cancerous tumour cell (or nomal cell) is usually directly proportional to the actual percentage of time consumed in the '*vulnerable phase.*' In other words, one may ascertain that the real percent of time spent specifically in the vulnerable phase appears to be an important '**determinant factor**'for the susceptibility of tumours belonging to different cell types. Not withstanding to any particular growth phase one may safely generalize that such tumours having a large growth fraction one prone to chemotherapy in comparison to those having a low fraction ; and this constitutes a very ideal and equally important percept.

Examples : (*a*) **Cancerous tumors** having high growth fractions which are found to give adequate response to chemotherapy are, namely : **Hodgkin's disease**, **Burkitt's lymphoma***, **Wilm's tumour**, **acute leukemia in children**, **choriocarcinoma****, **chronic myelogenous leukemia****, **lymphocytic leukemia**, and **breast cancer**.

(*b*) **Neoplasms** (*i.e.*, **malignant tumours**) which afford a very poor response are, for instance : carcinoma of the GI-tract, malignant melanoma, and tumours of the uterus and cervix.

*Mackillop WJ *et. al. J. Natl. Cancer Inst.*, **70** : 9, 1983.

**These tumours are now considered curable to a great extent.

Salient Features. Following are some of the cardinal salient features with regard to tumour selectivity and response :

(1) Efficacy of antineoplastic drugs is increased significantly in early treatment of *newly developed small cancerous tumours* having relatively higher growth fractions.

(2) Most effective **antineoplastic drug** should invariably be expected to be of such kind which is rather specific to the phase with the longest duration *e.g.*, **S-DNA** : **replication phase** (10-20 hours), and **G_2-resting phase** (2-10 hours).

(3) Recently, investigation of the possibility of *synchronizing cancerous tumor cells* is gaining momentum so that most likely **all cells are in the same phase of the cycle.** In case, such in '*ideal situation*' may be accomplished then :

(*a*) Cancerous tumor might become more vulnerable to the suitable drugs administered at the right-time, and

(*b*) Therapeutic index of the '**drug**' may be enhanced appreciably.

(*c*) *Synchronization* is achieved by a *holding pulse* of a **mitostatic drug** which essentially holds the cells in a specified phase till such time the *out-of-phase* cells also come into that phase.

(*d*) Sudden or planned discontinuation of the '**synchronizing antineoplastic drug**' at the same time releases the cancerous cells to resume their own specific cycle *i.e.*, all commencing afresh from the same phase.

(*e*) Combination chemotherapy, the **antineoplastic drugs** are frequently administered in a particular '*sequence*', instead of simultaneously ; however, in usual practice the **first-administered antineoplastic drug** invariably stands for a **synchronizing drug**.

1.1.3. Determinants of Sensitivity and Selectivity

There are certain pivotal factors that essentially help in determining the *selectivity* of **antineoplastic drugs** required for some definite cell-types. Besides, the actual demand for *various nutrients* also varies significantly amongst different tumor types, as do they differ frequently between the **tumor cells** and the **normal cells.**

Example. A plethora of malignant tumors of need much more **asparagine** (a nonessential amino acid) in comparison to normal cells ; therefore, if by any manner the plasma asparagine gets destroyed (enzymatically), the cancerous tumor cells in turn are selectively *starved* to death.

It has been observed duly that some '**drugs**' either get metabolized in the *liver* or the *peripheral cells* thereby the various cell types substantially differ in their respective ability to metabolize these drug substances.

Example. Bleomycin—an **antineoplastic drug** usually gets metabolized much less in the *susceptible tumor cells* in relation to other cells, thereby allowing distinctly higher local concentrations. In addition to this there are a host of other antineoplastic drugs which are converted to the *active metabolites* by the aid of the prevailing '**target-cells**' (also termed as **'lethal synthesis'**) ; and the ensuing differences in the conversion rates ultimately contribute directly to **selectivity.**

Degree of variance in penetrance also account for certain critical apperent differences amongst the antineoplastic drugs.

Example. (*i*) **Neoplasms in the CNS** are more effectively curable by lipid-soluble drugs than the water-soluble ones,

(*ii*) Some drugs exhibit *greater active transport* into cancerous tumor cells than into normal cells,

(*iii*) Certain drugs show differences in '**outward transport**' as well,

(*iv*) Selectivity is also governed by tumor-cell attacking **killer T-cells, suppressor T-cells**, and **blocking factors from B-cells** which specifically guard and protect some cancerous cells from the prevailing immune attack, and

(*v*) Generally, the immune cells are established to be the most suppressed ones ; and thus two situations may arise : *first*, **antineoplastic drugs** which augment response to malignant cells and *secondly*, which antagonize it squarely.

1.1.4. Requirements for 'Kill'

Ideally, a remission (*i.e.*, reduction in intensity) normally may be accomplished with a '**kill**' ranging between 90-99% of the neoplastic cells. Interestingly, a '**kill**' amounting to 99% is supposed to leave a bear minimum of 107-108 surviving neoplastic cells to continue tumor growth, and consequently the remission would stay on 3-4 doubling times only. From these observations one may safely infer that such neoplasms against which the immune-system is absolutely ineffective, a **100% kill'** is not only a prerequisite but also necessary to cause a '**true cure**'**.**

1.1.5. Combination Chemotherapy

It has been amply tested, tried and established beyond any reasonable doubt that one may enhance the '**percent of kill'** by employing the **combination therapy** of two or even more antineoplastic agents judiciously. Of course, the usage of **radiation therapy** can also be effectively used with drugs. In reality, there exits *four* cardinal factors that may optimize such '**combinations**', namely :

(*a*) Each component drug should have certain **degree of efficacy** by itself.

(*b*) Each component drug must have an altogether different mechanism of '**cytotoxic profile'** and, preferably, command **phase specificity**.

(*c*) Each component drug should have a distinct and different **spectrum of toxicity** in comparison to the other components, so as to avoid specifically any overwhelming toxicity of a given type.

(*d*) The '**mechanism of resistance**' to each component must be invariably different to that of the other components.

1.1.6. Log Cell-Kill Principle

It has been well-defined that the efficiency of **anitneoplastic drugs** may be characterized by their inherent **log cell-kill index.** In other words, the **negative log of the fraction** of the cancerous tumor cell population which essentially survives a *single-course of treatment.*

Example. A **neoplastic drug** that eventually kills 99.9% of the malignant tumor cell population, *i.e.*, leaves 0.0001 (or 1/104) of the population is usually termed as a **4-log drug** ; whereas, a second drug which kills 99.9% is known as a **3-log drug.**

However, the **log cell-kill index** represents a very thin (tenuous) number, but it definitely serves a tremendous usefulness in rightly predicting the effects of combinations which essentially fulfil criteria (*a*) and (*b*) above (Section 1.1.5). Thus, the very close predicted effect of a combination is usually accomplished by the simple addition of the various indices obtained from the component drugs.

Example. Theoretically, a **4-log drug** together with a **3-log drug** must provide ordinarily a **7-log combination** *i.e.*, almost kills 99.99999% or leaves 1/107 of the population. Now, at this juncture a 3**rd** drug which essentially kills 99% (**2-log-drug**) may further minimize the remaining population to the extent of 1/109, that ultimately comes close to the complete eradication of a cancerous tumor noticed at an early stage.

1.1.7. Drug Resistance

It has been observed that there are certain tumour populations that seem to be heterogeneous in nature by the time the cancerous tumor is discovered after the usual **'biopsy examination' ;** whereas a few of the cells being resistant to some **antineoplastic agents** right at the very outset of the recommended treatment. The said findings hold good for certain well-established organs of the human body, such as : colon, jejunal, adrenal, kidney and liver carcinomas. A maximum of *four* different malignant cell-types have been duly recognized and identified in a single tumor.

It is, however, pertinent to mention here that a certain degree of resistance appears to be acquired in much as the same manner as in **microbial resistance**, such as :

(*a*) resistance granting '**genetic change**' taking place during treatment, and

(*b*) resistant '**daughter cells**' consequently proliferate in the prevailing environment of the antineoplastic agent.

In a nut shell, irrespective of the actual cause, the prevailing resistance invariably negates the usefulness of an **antineoplastic agent** to an appreciable extent.

In fact, there are **ten** different mechanisms of resistance that have been duly identified, namely :

(*i*) Complete loss of the '**transport system**' required essentially for the permeation of the drug into the tumor cell *e.g.*, **methotrexate**.

(*ii*) Disappearance of the enzyme necessary for the intratumor **lethal systhesis** of an essential active metabolite.

(*iii*) An enhancement in the production of the **target enzyme** *e.g.*, **methotrexate**.

(*iv*) Retardation in the *affinity for* or the **quantum of the target enzyme** *e.g.*, **methotrexate**, **fluorouracil** and **topoisomerase inhibitors**.

(*v*) **Pleiotropic drug-resistance** *i.e.*, an enhancement in the outward active transport of the antineoplastic drug, whereby the effective intracellular concentrations cannot be accomplished or maintaned.

(*vi*) **Over expression of metallothionine** in resistance to **Pt-containing drug** and some **alkylating antineoplastics**.

(*vii*) **Formation of antibodies** *e.g.*, **interferons**.

(*viii*) **Membrance of antibodies** which essentially afford resistance to natural **killer (NK) cells**.

(*ix*) Enhance **glutathione synthesis** in malignant cells being treated with anthracyclinedione cells.

(*x*) Repair of potentially **lethal DNA damage**.

2. CLASSIFICATION

Antineoplastic agents are classified under the following *seven* categories, namely :

(*i*) Alkylating Agents
(*ii*) Antimetabolites
(*iii*) Antibiotics
(*iv*) Plant products
(*v*) Miscellaneous compounds
(*vi*) Hormones
(*vii*) Immunotherapy.

2.1. Alkylating Agents

Alkylating agents are chemically reactive compounds that combine most readily with nucleophilic centres a fully saturated carbon atom of the alkylating group becoming attached to the nucleophile.

The term '**alkylating agents**' is applied to compounds which, in a sense, *alkylate* the substance with which they react, by joining it through a **covalent bond**, although a strong polar bond is not excluded from this general definition. Any '**antineoplastic agent**' whose activity is explained by such a mechanism is called an **alkylating agent**.

These are further sub-divided into *four* categories, namely :

(*i*) Mustards
(*ii*) Methanesulphonates
(*iii*) Ethylenimines
(*vi*) Nitrosoureas

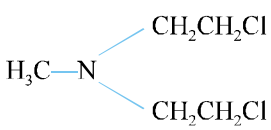
2.1.1. Mustards

After the discovery of the **antileukemic activity of mustard gas** : (Cl CH_2 $CH_2)_2S$ Bis-β-chloroenthyl sulphide (**Mustard Gas**) in human being, its clinical application for the treatment of neoplasms could not be persued further due to its high toxicity, low solubility in water, oily nature and blister-producing properties.

Nitrogen mustards were selected for the clinical application for the treatment of neoplasms because they presented fewer problems in handling, besides their respective hydrochlorides and other salts are generally stable solids having low vapour pressure and high solubility in water.

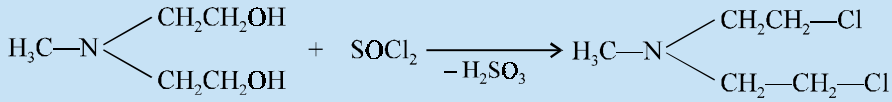
A few important **nitrogen mustards** used as **antineoplastic agents** are discussed below, for instance : **Mechlorethamine hydrochloride**, **Mephalan**, **Cyclophosphamide** and **Chlorambucil**.

A. Mechlorethamine Hydrochloride USAN



2, 2-Dichloro-N-methyldiethylamine hydrochloride USP ; Mustine Hydrochloride BP ; Mustargen(R) (Merck Sharp & Dohme) ;

Synthesis



2, 2′-(Methylimino) diethanol Thionyl chloride Mechlorethamine Hydrochloride

Chlorination of 2, 2′-(methylimino) diethanol with thionyl chloride gives rise to the desired official compound, with the elimination of sulphurous acid.

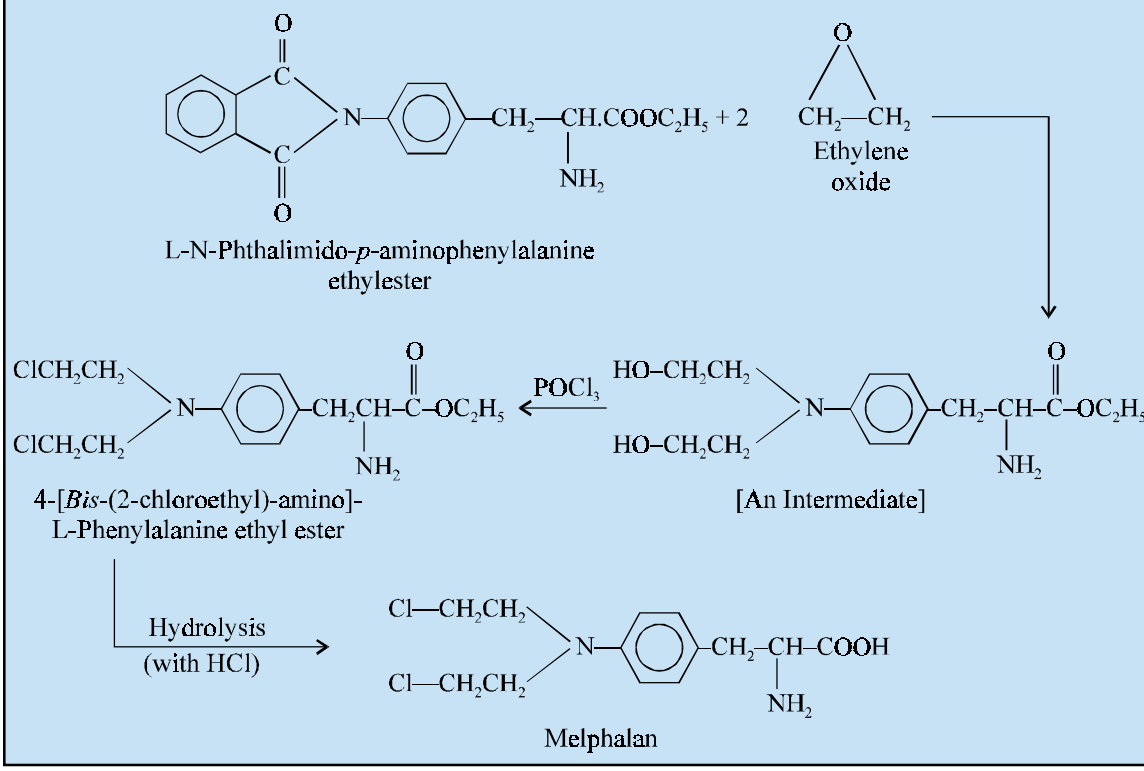
It is effective in Hodgkin's disease. Usual practice is to administer **mechlorethamine** with other **antineoplastic agents** such as **vincristine**, **prednisone** etc. It is the drug of choice for the treatment of mycosis fungoides and lymphomas.

Dose. *Single doses of 400 mcg per kg body weight or a course of 4 daily doses of 100 mcg per kg are normally administered by iv injection in a strength of 1 mg per ml in sodium chloride injection.*

B. Melphalan **USAN,**

4-[Bis (2-chloroethyl) amino]-L-phenylalanine ; L-Mustard ; L-Sarcolysin ; USP ; BP ;
Alkeran(R) (Burroughs Wellcome) ;

Synthesis

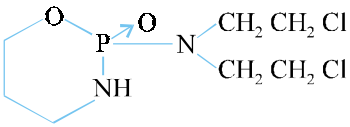


L-N-Phthalimido-*p*-aminophenylalanine ethyl ester when reacted with ethylene oxide yields an intermediate which on treatment with phosphorus oxychloride gives rise to 4-*Bis*-(2-chloroethyl)-amino-L-phenylalanine ethyl ester. This on hydrolysis with hydrochloric acid offers the desired compound.

Melphalan is very effective in preventing the recurrence of cancer in premenopausal women who have undergone radical mastectomy.

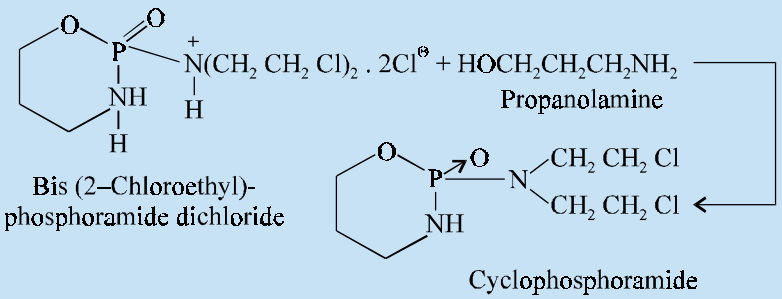
Dose. *Oral, 150 mcg per kg body weight daily for 4 to7 days, combined with prednisone 40-60 mg dialy ; 250 mg per kg daily for 4 to 5 days ; or 6 mg daily by 2 to 3 weeks.*

C. Cyclophosphamide BAN, USAN,



N, N-Bis (2-chloroethyl) tetrahydro-2H-1, 1, 3, 2-oxazaphosphorin-2-amine-2-oxide ; BP ; USP ; Cytoxan(R) (Mead-Johnson) ;

Synthesis

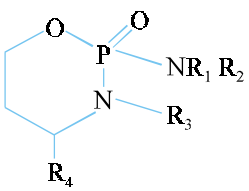


It is prepared by the interaction of bis-(2-chloroethyl) phosphoramide dichloride with propanolamine.

Cyclophosphamide is effective against acute leukemia, chronic lymphocytic leukemia and multiple myeloma. In combination with other chemotherapeutic agents it is found to cause radical cure in acute lymphoplastic leukemia in children and also in Burkitt's lymphoma. It has a positive advantage over other alkylating agents because of its activity both parenterally and orally besides its tolerance over prolonged periods in divided doses.

Dose. *Intitial, adult dose of 40-50 mg per kg, given intravenously in divided doses over 2 to 5 days ; Children : 2-8 mg per kg daily iv injection.*

Cyclophosphamide is one of the most useful antineoplastic agents and substitution at C-4 position has led to **4-phenyl cyclophosphamide** (*a*) and **4-methyl cyclophosphamide** (*b*) The most commonly used analogues of **cyclophosphamide** are **Ifosfamide** (*c*) and **Trofosfamide** (*d*) :



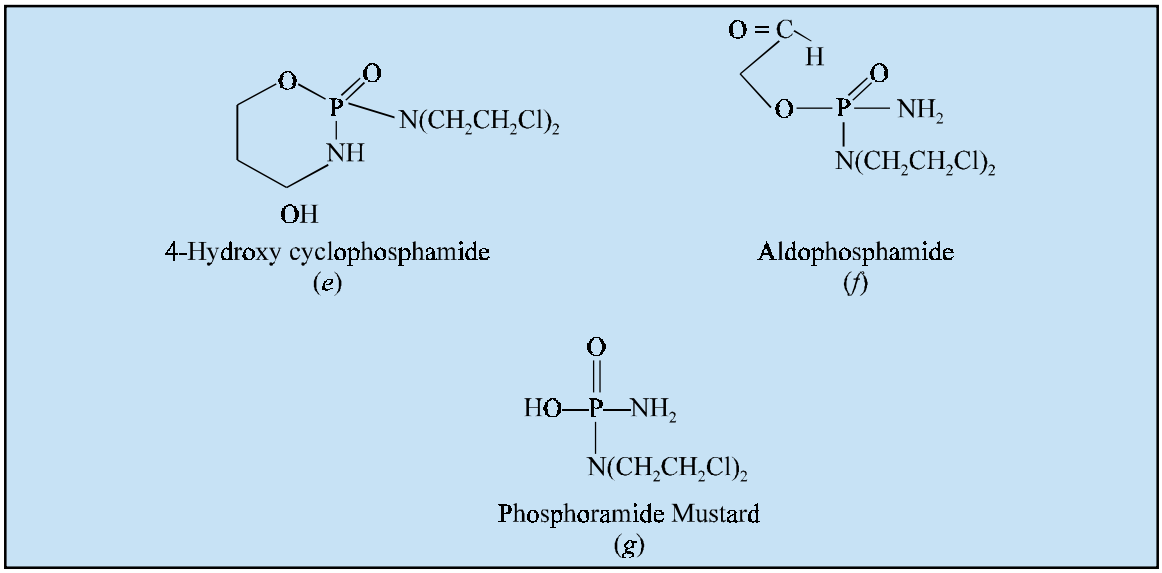
(*a*) : $R_1 = R_2 =$ —$CH_2\ CH_2\ Cl$; $R_3 = H$; $R_4 = C_6H_5$;

(*b*) : $R_1 = R_2 =$ —$CH_2\ CH_2\ Cl$; $R_3 = H$; $R_4 = CH_3$;

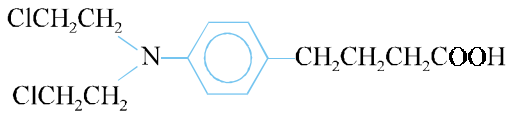
(*c*) : $R_1 = R_3 =$ —$CH_2\ CH_2\ Cl$; $R_2 = R_4 = H$;

(*d*) : $R_1 = R_2 = R_3 =$ —$CH_2\ CH_2\ Cl$; $R_4 = H$:

Enzyme catalyzed oxidation of **cyclophosphamide** yields **4-hydroxy cyclophosphamide** (*e*) and subsequent formation of **aldophosphamide** (*f*) that leads to **phosphamide mustard** (*g*) which is considered to be the ultimate alkylating agent.

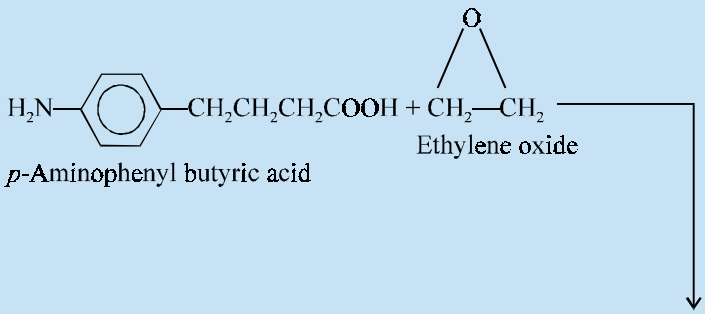


D. *Chlorambucil* USAN

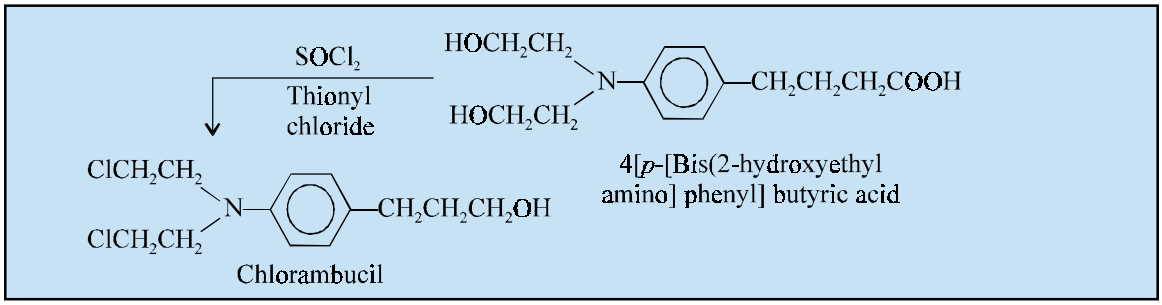


4-[*p*-Bis (2-chloroethyl) amino] phenyl] butyric acid ; Chloraminophene ; USP ; Leukeran(R) (Burroughs Wellcome) ;

Synthesis



(*Contd...*)



Chlorambucil is prepared by treating *p*-aminophenyl butyric acid with enthylene oxide to yield 4-[*p*-[Bis (2-hydroxyethyl) amino] phenyl] butyric acid which on chlorination with thionyl chloride offers the desired product.

It is indicated in treatment of Hodgkin's disease, lymphosarcoma, primary microglobulinemia and chronic lymphocytic leukemia. It has an edge over other nitrogen mustards because of its least toxicity and slowest activity.

Dose. *Usual, oral, 100 to 200 mcg per kg body weight daily (usually 4 to 10 mg as a single daily dose) for 4 to 8 weeks.*

2.1.1.1. Mechanism of Action

The mechanism of action of the drugs described under Section 2.1.1 shall be dealt with in the sections that follows :

2.1.1.1.1. Mechlorethamine Hydrochloride

The β-chloroethyl moieties lose Cl^- ions to generate carbonium and azardium (ethylerimonium ions), that are found to be extremely reactive ; and are capable of alkylating many biologically vital chemical moieties. It has been observed that in DNA they alkylate guanine moieties ; if one arm alkylates **one guanine group** and the second arm another guanine on the opposing strand of prevailing double-stranded DNA, the DNA turns into irreversibly cross-linked. It ultimately gives rise to inhibition of mitosis, besides causing chromosomal breakage. Importantly,some undifferentiated germinal cells are nonproliferative and hypertrophied during exposure to the '**drug**', whereas the rather more differentiated germinal cells usually disintegrate. Besides, some malignant growths, specifically of the lymph modes and bone marrow, seem to be more sensistive to the drug in comparison to the normal more slowly proliferative tissues.

2.1.1.1.2. Melphalan

The '**drug**' serves as a primary immunosuppressive drug. It is found to be well absorbed *via* the oral route, being also equally efficacious as administered by the IV route. The **'drug'** gets transformed into active metabolites in probably all tissues. The elimination half-life ranges between 1 to 3 hours.

2.1.1.1.3. Cyclophosphamide

The '**drug**' behaves unlike other β-chloroethylamino alkylators, and hence fails cyclize rapidly to the corresponding active ethylene imonium form unless and until activated by the hepatic enzymes. Importantly, the liver is protected by the further metabolism of activated metabolites into the corresponding inactive end products. Therefore, the '**drug**' is fairly stable in the GI-tract, well tolerated, and quite efficacious both by the oral and parenteral routes. It fails to produce any sort of '*local vasication*', necrosis, phlebitis, or even pain.

It is distributed to the tissues having **volume of distribution** v_d^{ss} more than the total body water. The '**drug**' gets metabolized by the hepatic microsomal system to the corresponding alkylating metabolites, which in turn eventually are duly converted to phosphoramide mustard and acrolein (an aldehyde). However, the relatively high doses readily induce the metabolism of **cyclophosphamide**. The plasma half-life ranges between 4 to 6 hours.

2.1.1.1.4. Chlorambucil

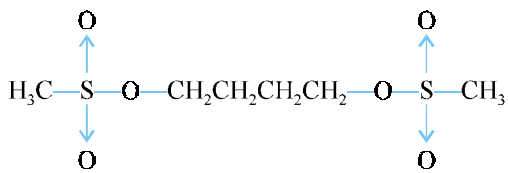
The '**drug**' is one of the slowest-acting and also least toxic currently employed nitrogen mustards. Importantly, its toxicity is manifested chiefly as bone-marrow depression ; however, in the prevailing therapeutic doses it is observed to be fairly moderate and reversible. The '**drug**' gets adsorbed well *via* the oral administration. It generally is degraded extensively *in vivo.* The elimination half-life is nearly 1.5 hour.

2.1.2. Methanesulphonates

From a mechanistic point of view the **methanesulphonates** (or the **methanesulphonate esters**) are specially interesting since the long alkylene chains separating the reductive ester groups virtually exclude the possibility of the formation of reactive intermediate ring structures. Thus, these ester groups constitute a level of direct alkylating ability which need not be mediated by cyclization. The **methanesulphonate ion** is a weakly nucleophilic group which is displaced from carbon by a more strongly nucleophilic group that is present in the biological system acted upon by the drug.

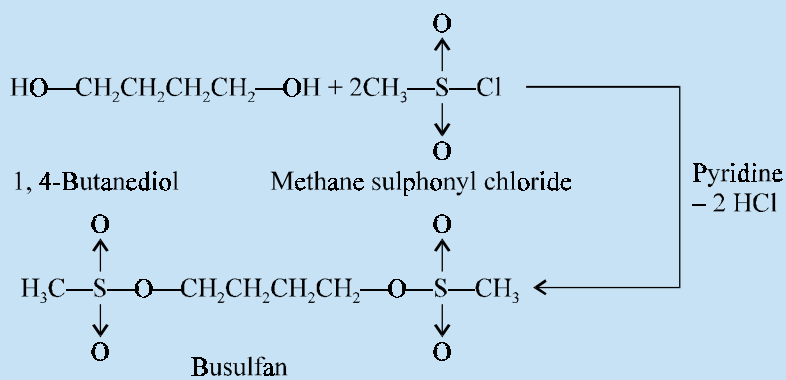
The most important alkylating agent in this group is **Busulfan** :

A. *Busalfan* USAN



1, 4-Butanediol dimethanesulphonate ; 1, 4-Di (methanesulfonyloxy) butane ; BP, USP, Mylearn(R) (Burroughs Wellcome) ;

Synthesis



It is prepared by the interaction of 1, 4-butanediol with two moles of methane sulphonyl chloride in the presence of pyridine, when the final product obtained is recrystallised either from acetone or alcohol. Busulfan is broadly used in the treatment of granulocytic leukemia.

Dose. *For granulocytic leukemia : 60 mcg per kg body weight daily orally, upto a maximum single daily dose of 4 mg and to be continued till the white-cell count falls between 15000 to 25000 per* mm^3.

2.1.2.1. Mechanism of Action

The **mechanism of action** of **busulfan** shall be discussed as under :

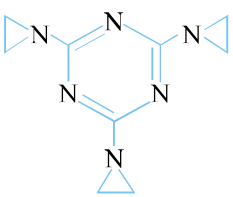
2.1.2.1.1. Busulfan

The '**drug**' is phase nonspecific. It exerts almost negligible action on rapidly proliferative tissues other than the bone marrow. However, at relatively lower dose levels granulo-cytopoesis may be suppressed quite selectively without causing any effect on erythropoises. As the '**drug**' has little effect on lymphopoesis, it is of no value in lymphocytic leukemia and malignant lymphoma. It is found to be not immunosuppressive. Its elimination half-life ranges between 2-3 hours.

2.1.3. Ethylenimines

Clossley first reported the inhibition of experimental tumours in mice by treatment with **triethylene melamine (TEM)** and this resulted in the discovery of another drug **triethylenethio phosphoramide**.

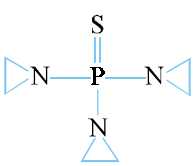
A. *Triethylenemelamine*



2, 4, 6-Tri (1-azridinyl)-S-triazine ; 2, 4, 6-Tris (ethyleneimino)-S-triazine ; 2, 4, 6-Triethyleneimino-1, 3, 5-triazine.

It is used as an adjuvant to radiation therapy of retinoblastoma and injected into the carotid artery. It is used in the palliative treatment of malignant neoplasms.

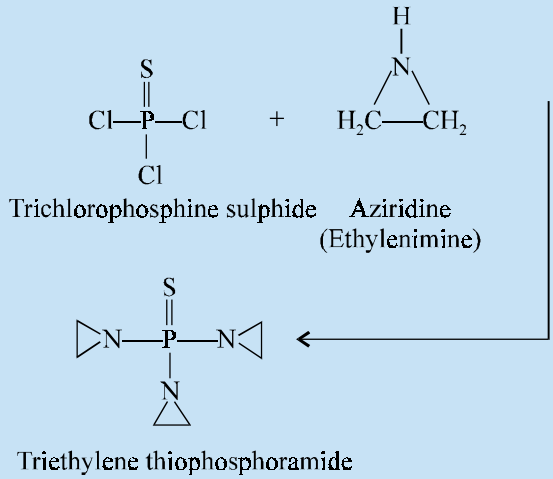
B. *Triethylenethio Phosphoramide* BAN



Tris (1-aziridinyl) phosphine sulphide ; N, N′, N″-Triethylenethio-phosphoramide ; Thiotepa USP ; BP,

Ledertepa(R) (Lederle) ; Thiofosyl(R) (Astra) ;

Synthesis



It is prepared by teating trichlorophosphine sulphide with aziridine and recrystalizing the official product from water.

It is of value in the treatment of carcinoma of breast, ovaries, colon-rectum and rectum. It is also found to be useful in the treatment of malignant lymphomas and bronchogenic carcinomas.

Dose. *Upto 60 mg in single or divided doses may be given by im injection or by instillation in adults and children over 12 years.*

2.1.3.1. Mechanism of Action

The mechanism of action of the '**drugs**' discussed under Section 2.1.3 shall now be treated individually.

2.1.3.1.1. Triethylenemelamine (Tretamine)

Its action and properties are very much akin to **thiotepa** (**triethylenethio phosphoramide**). It happens to cross blood brain barrier (BBB).

2.1.3.1.2. Triethylenethio Phosphoramide (Thiotepa)

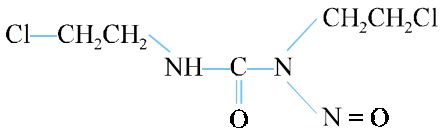
The '**drug**' exerts its action due to its alkylating characteristics. It is extensively metabolized ; and traces of unchanged drug substance are excreted in the urine, along with a large proportion of metabolites. The '**drug**' also crosses the blood-brain barrier (BBB). It has been observed that it undergoes absorption through *serous membrances*, for instance : bladder and pleura, to a certain degree.

2.1.4. Nitrosoureas

Nitrosoureas are having both practical and theoretical interest. They are very highly lipid soluble antineoplastic compounds first synthesized at Southern Research Institute, Birmingham.

A few important members of this category are discussed below, namely : **Carmustine** and **Lomustine**.

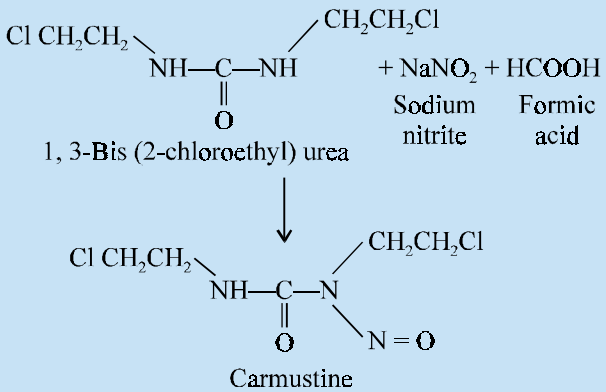
A. *Carmustine* BAN, USAN,



1, 3-Bis (2-chlorethyl)-1-nitrosourea ; BCNU ;

Carmubris(R) (Bristol),

Synthesis

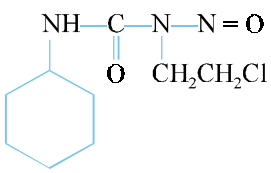


Carmustine may be prepared by interacting 1, 3-bis (2-chloroethyl) urea with sodium nitrite and formic acid. It is a low-melting white powder that undergoes decomposition at 27°C and hence it is supplied as a lypholized powder.

As it possesses the potential to cross the blood-brain-barrier, **carmustine** is employed specifically for brain tumours and other tumours, for instance leukemias, which have metastasized to the brain. A combination of **carmustine** and **prednisone** is used for the treatment of multiple mycloma. As a secondary therapy it is frequently employed in conjunction with other **antineoplastic agents** for lymphomas and Hodgkin's disease.

Dose. *A single dose by IV injection at 100 to 200 mg/m^2.*

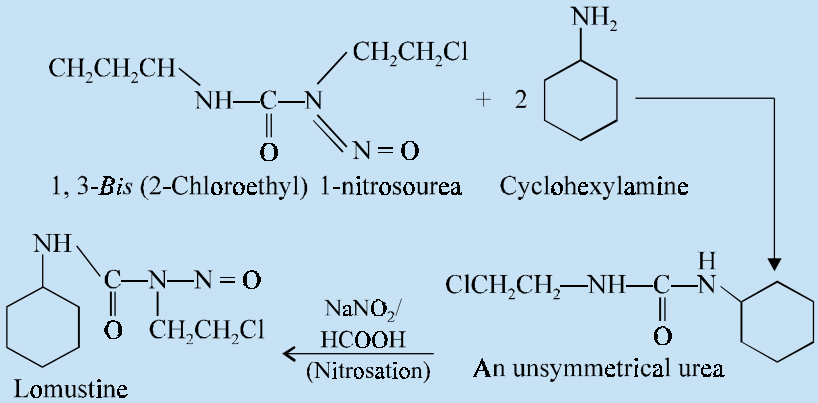
B. *Lomustine USAN*



1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea ; CCNU ;

CeeNU(R) (Bristol) ; CINU(R) (Bristol-Myers) ;

Synthesis



It is prepared by the decomposition of 1, 3-bis (2-chlorethyl)-1-nitrosourea in the presence of two equivalents of cyclohexylamine to yield an unsymmetrical urea which on nitrosation with sodium nitrite and formic acid offers the desired compound.

It is employed effectively in the treatment of primary and metastatic brain tumours. It is also used as secondary therapy in Hodgkin's disease.

Dose. *Usual dosage : 130 mg/m^2 orally every six weeks.*

2.1.4.1. Mechanism of Action

The mechanism of action of the two medicinal compounds described under Section 2.1.4. shall now be treated individually as under :

2.1.4.1.1. Carmustine

The '**drug**' most probably exerts its action due to the ability to cross-like cellular DNA. Thus the very synthesis of both DNA and RNA is ihibited. It is specifically phase nonspecific. The '**drug**' gets metabolized, *via* oral administration, practically 100% as it happens to pass through the liver ; therefore, it should be given IV. It has been observed that after IV administration, its plasma half-life is of rather shorter duration ranging between 3-30 minutes. By virtue of the fact that the '**drug**' has a high lipid solubility profile which renders it to pass through the **blood-brain barrier (BBB)** rather swiftly. Besides, the prevailing concentrations in the **cerebrospinal fluid (CSF)** varies from approximately 50-115% of those in plasma.

2.1.4.1.2. Lomustine

The '**drug**' is a chemical congener of **Carmustine** and, therefore, almost possesses the same mechanisms of action. Just like **carmustine**, it accomplishes maximum concentrations in the CSF ; and, hence, shares with carmustine a **first choice status** for the treatment of *glioblastoma.**

The '**drug**' is found to be well absorbed orally and thereby survives the first pass through the liver to be effective by the oral administration. Besides, it gets distributed evenly amongst the various tissues having a volume of distribution (v_d^{ss}) much higher than the total body water content. However, in the CSF the concentration of metabolites attains almost 150% of that normally present in plasma. It has been observed that the biotransformation usually takes place throughout the body ; the half-life is nearly 15 minutes, and the half-lives of the metabolites are 48 hour.

*A neuroglia (*i.e.*, cells and fibers forming the interstitial elements of CNS) cell tumour.

2.2. Antimetabolites

Antimetabolites are such compounds which essentially prevent the biosynthesis of normal cellular metabolites. They generally possess close structural resemblance to the metabolite which is ultimately antagonized. Thus they have a tendency to unite with the active site, as if they are the actual substrate.

In general, following are the various classes of **antimetabolites** usually employed in the treatment of cancer. They are namely :

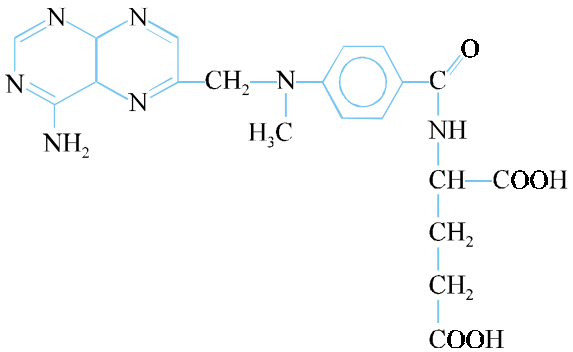
(*a*) Antifolic acid compounds
(*b*) Analogues of Purines
(*c*) Analogues of Pyrimidines
(*d*) Amino acid antagonists

2.2.1. Antifolic Acid Compounds

Antifolic acid compounds are also referred to as '**Antifolics**' or '**Folate Antagonists**' Drugs belonging to this category act by preventing the synthesis of folic acid which is required by the tissues. They bind strongly to **dihydrofolate reductase (DHFR)** thereby inhibiting the conversion of dihydrofolic acid to tetrahydrofolic acid and thus inhibit the synthesis of **purines** and **thymidines**. Antifolics kill cells by **inhibiting DNA synthesis in the S phase of the cell cycle**. Therefore, they are found to be most effective in the log growth phase.

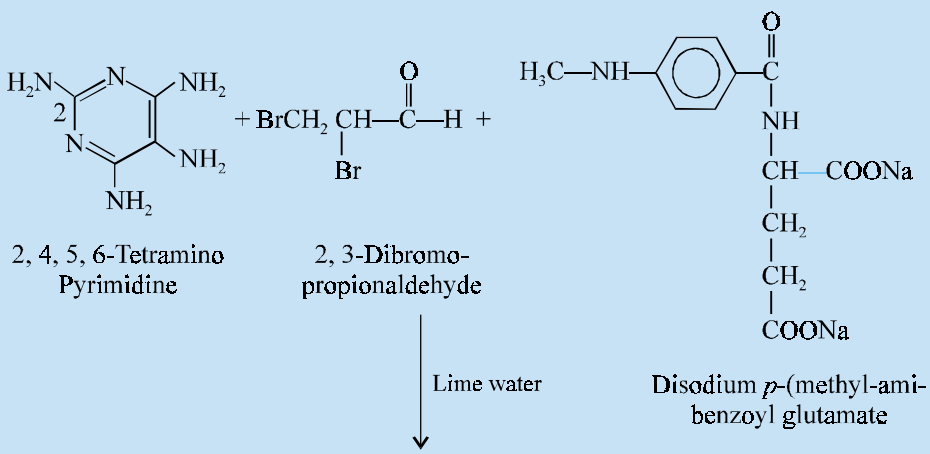
The most important drug in this group is methotrexate.

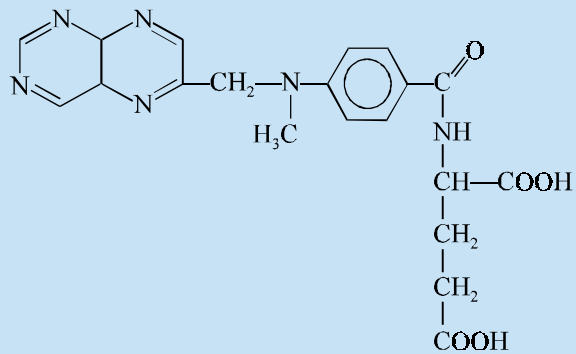
A. *Methotrexate* BAN, USAN, INN



N-[4-[[(2, 4-Diamino-6-pteridinyl) methyl] methylamino] benzoyl]-L-glutamic acid ;
BP (1973) ; USP ;
Amethopterin(R) (Lederle) ;

Synthesis





Methotrexate

It is prepared by treating together 2, 4, 5, 6-tetraaminopyrimidine ; 2, 3-di-bromopropionaldehyde, disodium *p*-(methylamino)-benzoylglutamate, iodine and potassium iodide and subsequently followed by heating with lime water.

It is the first ever **antineoplastic agent** that produced appreciable remissions in leukemia. It is extensively employed for the treatment of acute lymphoblastic leukemia. It is invariably used in combination cheotherapy for palliative management of lung cancer, breast cancer and epidermoid cancers of the head. It is frequently recommended for the treatment and prophylaxis of meningeal leukemia based on its ability to penetrate the central nervous system. It is also of value in choricarcinoma and related trophoblastic tumours of women.

Dose. *For maintenance therapy of acute lymphoblastic leukemia is 15-30 mg per m^2 body surface once or twice weekly, either orally or intramuscularly, with other agents such as mercaptopurine.*

2.2.1.1. Mechanism of Action

The mechanism of action of **methotrexate** shall be discussed as under :

2.2.1.1.1. Methotrexate

The '**drug**' exerts its action by inhibiting the enzyme **dihydrofolate reductase (DHFR)**, and thus prevents effectively the conversion of **deoxyuridylate** to **thymidylate**, that ultimately blocks the synthesis of new DNA required urgently for the cellular replication.

Interestingly, the '**drug**' in doses less than 30 mg/m^2 usually gets absorbed well by the oral administration ; however, nearly 1/3rd of an oral dose is metabolized by both **intestinal organisms** and **antibiotics** that ultimately affect the quantam absorbed. Furthermore, in doses greater than 80 mg/m^2 the amount absorbed is further reduced to the extent of 30-50%. It has been duly observed that almost 50% of the '**drug**' is bound to plasma-protein, however, it fails to gain an access to the cerebrospinal fluid (CSF) due to the glaring fact that it gets ionized overwhelmingly and outwardly transported at the *choroid plexus*. As a result it should be administered intrathecally for its judicious application in CNS.

The plasma clearance of the '**drug**' is found to be triexponential having a distribution half-life of nearly 45 minutes ; whereas, a *second-phase* of approximately extending upto 3.5 hours.* It has an elimination half-life of 6 to 69 hours. The renal tubular secretion is responsible for nearly 80% of the elimination.

*Perhaps due to an enterohepatic component—as about 10% of the '*drug*' is secreted into the **bile**.

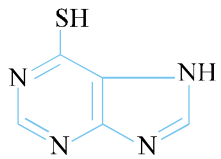
Note. The simultaneous administration of drugs like : probenecid, salicylate and other NSAIDs etc., directly interfere with its secretion ; and hence, should be avoided as far as possible.

2.2.2. Analogues of Purines

Purines are integral components of RNA, DNA and coenzyme that are synthesized in proliferaton of cancer cells. Therefore, an agent that antagonizes the purine will certainly lead to formation of false DNA and these include analogues of natural purine bases, nucleosides and nucleotides.

A few drugs belonging to this classification are, namely : Mercaptopurine and Azathiopurine :

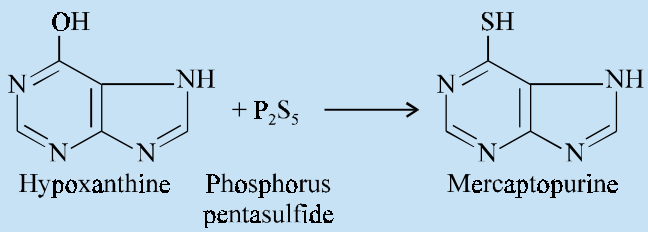
A. *Mercaptopurinum* BAN ; *Mercaptopurine* USAN ;



o-Mercapto-6-purine ; 6 MP ; BP(1973) ; USP ;

Purinethol(R) (Burroughs Wellcome) ;

Synthesis

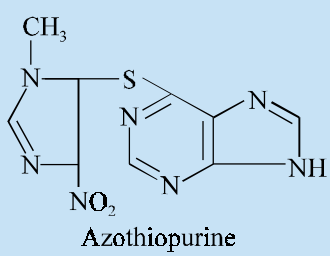


It may be prepared by the interaction of hypoxanthine with phosphorus pentasulphide.

Mercaptopurine is found to inhibit experimental orthoimmune encephalomyletis and thyroiditis and hence used in combination with vincristine, methortrexate and prednisone in the treatment of childhood leukemia. As such 6-MP may cause hyperuricamia but it is usually administered with *allopurinol*—an analogue of hypoxanthine which blocks the conversion of 6-MP to uric acid and hence the dose of 6-MP is reduced and still the desired response is obtained.

Dose. *Oral, usual, initial for children and adults : 2.5 mg per kg body weight daily, but the dosage varies as per individual response and tolerance.*

***B. Azathiopurine* BAN, USAN,**

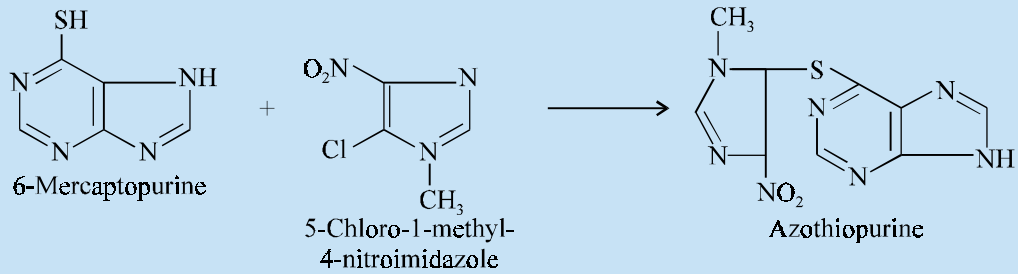


Azothiopurine

6-[1-Methyl-4-nitromidazole-5 yl] thio] purine ;BP ; USP ;

Imuran(R) (Burroughs Wellcome) ;

Synthesis



It is prepared by treating 6-mercaptopurine with 5-chloro-1-methyl-4-nitroimidazole.

The main use of **azathiopurine** is as an adjunct for the management and prevention towards the rejection of renal homotransplants.

Dose. *Usual, adult, and children : 1 to 25 mg per kg body weight daily by mouth.*

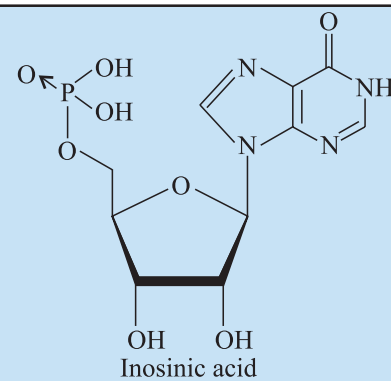
2.2.2.1. Mechanism of Action

The **mechanism of action** of the two medicinal compounds described under Section 2.2.2 shall be dealt with in the sections that follows :

2.2.2.1.1. Mercaptopurine

The '**drug**' gets converted to 6-thioinosinic acid that predominantly serves as an antimetabolite to inhibit synthesis of **adenine** and **guanine** ; besides, it also presents conversion of *purine bases* into the corresponding **nucleotides**.

It also mimics **inosinic acid** thereby causing a negative feedback suppression of the synthesis of **inosinic acid**. It has been observed that a portion of the '**drug**' gets converted to **thioguanine**, which is ultimately incorporated into both DNA and RNA to give rise to the formation of defective nucleic acids. In this manner the synthesis and functionalities of the resulting nucleic acid are impaired in various ways. It finally helps in the *inhibition of cell mitosis.*



Inosinic acid

It has been found that the systemic bioavailability of mercaptopurine *via* the oral route varies from 5-37%, due to its first-pass metabolism in the intestinal mucosa and liver, wherein the two biochemical reactions usually take place, namely : (*a*) **oxidation by xanthine oxidase** ; and (*b*) **S-**

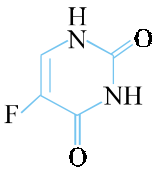
methylation. The '**drug**' gets bound to plasma protein to nearly 20%. Its volume of distribution (v_d^{ss}) is much higher in comparison to the extracellular space ; however, the access to CSF is minimal. The half-life in children is 21 minutes and in adults 47 minutes.

2.2.3. Analogues of Pyrimidines

Pyrimidine analogues have the capacity to interfere with the synthesis of pyrimidine nucleoside and hence the DNA synthesis. Aside from their **antineoplastic** effects they are also found to be equally effective in psoriasis and fungal infections.

A few characteristic compounds of this category are, namely : **Fluorouracil** and **Cytarabine**.

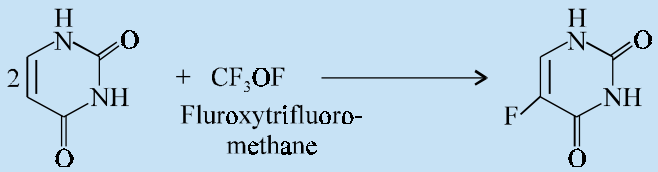
A. Fluorouracil BAN, USAN,



5-Fluoro-2, 4 (1H, 3H)-pyrimidinedione ; 2, 4-Dioxo-5-fluoropyrimidine ; USP ;

Efudex(R) (Roche) ; Fluoroplex(R) (Allergan) ;

Synthesis

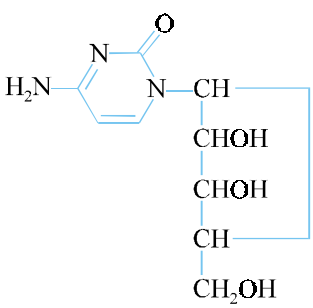


This official compound is prepared by the direct fluorination of **uracil** with **fluoroxytrifluoromethane**.

It is used in the palliative treatment of carcinoma of the breast, pancreas, prostrate, colon and hepatoma for which surgery or irradiation is not possible. It is also found to be beneficial in tropical treatment of premalignant solar keratosis.

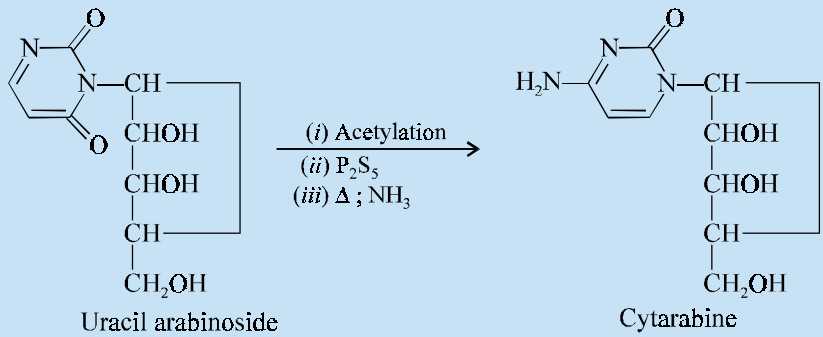
Dose. *Usual, iv injection : 1.2 mg per kg body weight daily to a maximum of 1 g daily for 3 or 4 days.*

B. *Cytarabine* BAN, USAN,



o-Amino-4-arabinofurannosyl-1-oxo-2dihydro-1, 2-pyrimidine ; Cytosine arabinoside ; USP ; Aracytin$^{(R)}$ (Upjohn) ; Cytosar-U$^{(R)}$ (Upjohn).

Synthesis



Cytarabine may be synthesized by the acetylation of uracil arabinoside followed by treatment with phosphorus pentasulphide and subsequent heating with ammonia.

It is indicated in both adult and childhood leukemia. It is specifically useful in acute granulocytic leukemia and found to be more effective when combined with **thioguanine** and **daunorubacine**.

Dose. *Usual adult, and children for leukemia : 2 mg per kg body weight intravenously per day for 0 days.*

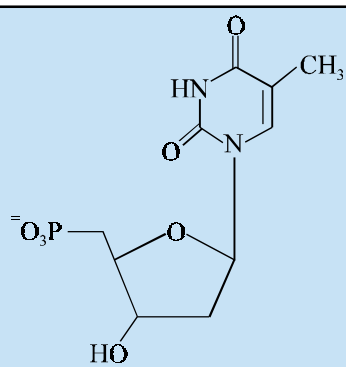
2.2.3.1. Mechanism of Action

The **mechanism of action** of **fluorouracil** and **cytarabine** discussed under Section 2.2.3 shall now be treated individually as under :

2.2.3.1.1. Fluorouracil

The '**drug**' is a congener of uracil which eventually serves both as a surrogate and as an antimetabolite of the nueleotide. Interestingly, its metabolite, **5-fluorodeoxyuridine-5′-monoplosphate (FUMP)**, blocks the synthesis of **thymidylic** and hence of **deoxyribonucleic acid (DNA**).

It also gets incorporated into the RNA directly. The '**drug**' is poorly absorbed orally and hence shows variable first-pass metabolism of the drug but the gut and the liver ; and hence, IV administration is an absolute necessity. It has been observed that nearly 60% of it gets metabolized to CO_2 ; however, more than 15% is excreted through the urine. The '**drug**' gains entry into the CSF and effusions. The plasma half-life is nearly 10 minutes ; however, the **active metabolite FUMP,** may be detectable for quite a few days at a stretch.



2.2.3.1.2. Cytarabine

The '**drug**' is a **pyrimidine nucleoside antimetabolite** which is cytotoxic to a plethora of cell-types. Precisely the induction of the enzyme **nucleotidase** into DNA inhibits polymerization *via* termination of strand synthesis. It is **S-phase specific**.

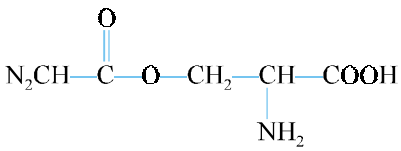
As the '**drug**' is not absorbed quite effectively by oral administration, hence its oral bioavailability is merely 0.2. Nevertheless, it penetrates right into the CSF and accomplishes a concentration upto 40% in plasma. It gets destroyed *in vivo* to an extent of 90% by **deamination**. Its plasma half-life ranges between 1-3 hours. The elimination half-life in the CSF stands at 3.5 hours. The '**drug**' undergoes **detoxification** through the entire body ; and, therefore, perhaps it may be administered even in patients with renal impairment, however, the dosage could be lowered accordingly.

2.2.4. Amino Acid Antagonists

The **amino acid antagonists** broadly act as a **glutamine antagonists** in the synthesis of formylglycinamidine ribotide from glutamine and formylglycinamide ribotide.

Example. Azaserine ;

A. Azaserine USAN,



o-Diazoacetyl-L-serine ;

CI-337$^{(R)}$ (Parke Davis) ;

Azaserine inhibits the growth of sarcoma 180 and several leukemias. In clinical trials, although there was improvement in some cases of Hodgkin's disease, acute leukemia in children and chronic lymphocytic leukemia, the results in general were not very encouraging.

2.2.4.1. Mechanism of Action

The mechanism of action of **azaserine** is discussed as under :

2.2.4.1.1. Azaserine

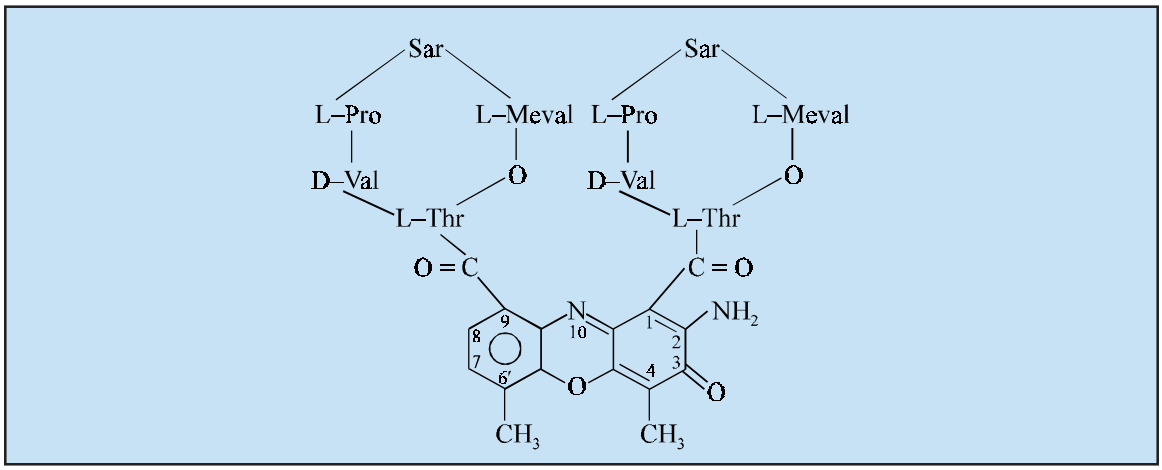
The '**drug**' is believed to be a glutamine antagonist that specifically inhiits **purine biosynthesis** and thus may exert antitumour activity.

2.3. Antibiotics

The recognitiion of **antibiotics** as an important class of **antineoplastic agents** is quite recent. Consequently, the production of **antineoplastic agents** through proper strain selection and controlled microbial fermentation conditions may ultimately optimize the formation of a particular component in an antibiotic mixture.

A few important members of this category are described below, namely ; **Dactinomycine** ; **Daunorubicin** ;

A. *Dactinomycine* USAN,



Actinomycin D ; USP ;

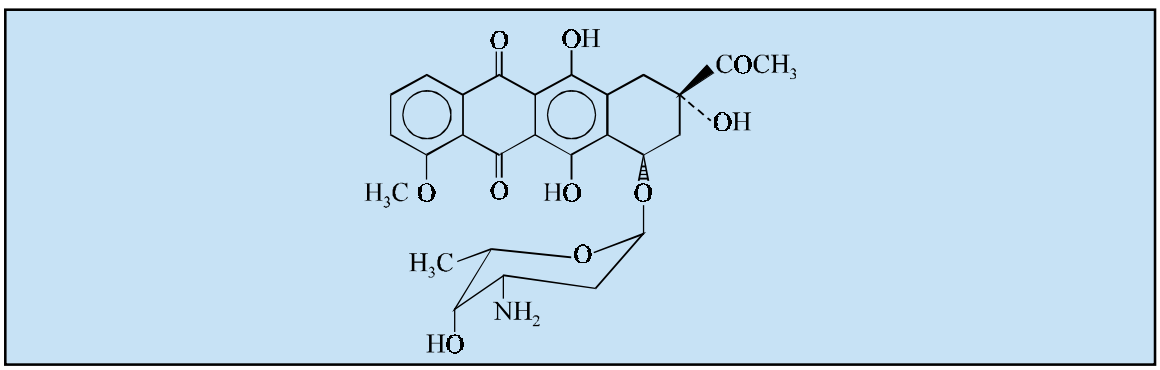
Cosmegen(R) (Merck, Sharp & Dohme).

The first **antibiotic** to be isolated from a species of *Streptomyces* was Actinomycin A and many related antibiotics including **Actinomycin D** were latter obtained. **Actinomycin C** was the first to be tried on neoplastic diseases. **Actinomycin D** is commercially available as **Dactinomycine**. It is found to the acitve against **L-1210, P-1534, P-388 and adenocarcinoma strains**. It binds to DNA thereby preventing DNA transcription.

It is used in the treatment or rhabdomyosarcoma in children and methotrexate-resistant choricarcinoma in women. It has also been used to inhibit immunoligical response particularly the rejection of renal transplants.

Dose. *Adults, iv, 0.01 mg (10 mcg) per kg body weight ; Children : 0.015 mg (15 mcg) per kg body weight for not more than 5 days.*

B. *Daunorubicin* BAN ; *Daunorubicin Hydrochloride* USAN



5,12-Naphthacenedione, (8S-*cis*)-8-acetyl-10-[(3-amino-2,3,6-trideoxy)-α-1-lyxo-hexanopyranosyl) oxy]-7, 8, 9, 10-tetrahydro-6, 8, 11-trihydroxy-10-methoxy, hydrochloride ;

Ondena(R) (Bayer).

Anthracyclines constitute another complex and bigger family of antibiotics. They mostly occur as **glycosides of the anthracyclinones** (aglycone residue). They act by intercalation with the DNA in both normal and neoplastic cells.

Daunorubicin is useful in the treatment of acute lymphoblastic leukemia in children. It is normally employed in combination therapy, for instance : with cytosine arabinoside in the treatment of myclogenous leukemia ; with **cytarabine** in the treatment of non-lymphoblastic leukemia in adult.

Dose. For acute mycloblastic leukemia : 45 to 60 mg per m^2 body-surface daily for 3 days by injecting a solution in sodium chloride injection into a fast-running infusion of sodium chloride.

2.3.1. Mechanism of Action

The **mechanism of action** of **dactiromycin** and **daunorubicin** will be dealt with individually as under :

2.3.1.1. Dactinomycin

The '**drug**' specifically inhibits the **DNA-dependent RNA-polymerase.** Interestingly, the drug also significantly potentiates **radiation recall** (otherwise known as '**radiotherapy**'). It also serves as a *secondary (efferent) immunosuppressive agent.* It has been demonstrated that almost 50% of the dose is excreted in fact into the bile and 10% into the urine ; the half-life is nearly 36 hour. The drug does not pass the **blood-brain barrier (BBB)**.

2.3.2. Daunorubicin Hydrochloride

The '**drug**' intercalates into DNA, inhibits **topoisomerase** II, yields oxygen radicals, and ultimately inhibits DNA synthesis. It can invariably prevent and check cell division in doses that virtually fail to interfere directly with the nucleic acid synthesis.

It has been observed that the oral absorption is reasonably poor ; and, therefore, it must be administered IV. The half-life of distribution is about 45 minutes and of elimination, nearly 19 hours. The active metabolite, **daunorubicinol**, has a half-life of almost 27 hours. The '**drug**' gets metabolized largely in the liver, and also secreted right into the bile (ca 40%).

CAUTION : **Dosage should be lowered in instances where liver or renal insufficiencies occur.**

2.4. Plant Products

Plant products have been used extensively in the treatment of malignant disease since thousands of years, but the studies of Dustin in 1938 on the cytotoxicity of colchicin heralded the start of the search for **natural antineoplastic drugs**. Today a large number of chemical constituents isolated from naturally occurring plant products have proved to the quite efficacious as **antitumour agents**.

An attempt is made here to review the action, clinical usefulness, their sources and the classification is done based on their chemical nucleus ; *viz.*,

(*a*) Imides and Amides

(*b*) Tertiary Amines

(*c*) Heterocyclic Amines

(*d*) Lactones

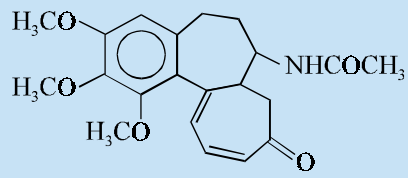
(*e*) Glycosides

2.4.1. Imides and Amides

Examples. Colchicine ; **Narciclasine** ;

A. Colchicine

Colchicine occurs as the major alkaloid of the autumn crocus, *Colchicum autumnale* and the African climbing Lily, *Gloriosa superba* Linn., (Family : *Liliaceae*).



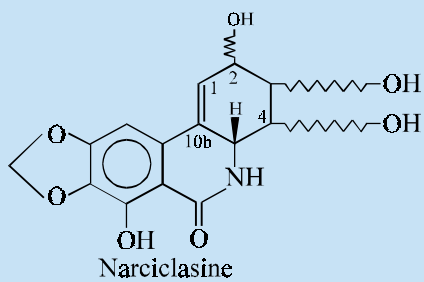
Colchicine

It arrests mitosis at the metaphase preventing anaphase and telophase. It was observed that colchicine diminishes deoxy-cytidylate aminohydrolase activity in Ehrlich ascites cells suggesting thereby that its action on mitosis and DNA synthesis could be by this method only. It is mainly used in terminating acute attacks of gout.

However, its derivative, **demecoloine** (**Colcemid**) is found to be active against myelocytic leukemia.

B. ***Narciclasine***

Narciclasine, an alkaloid isolated from the bulbs of **narcissus**, possesses antimitotic activity against S-180 in ascites form suggesting thereby that it acts essentially as a metaphasic or preprophasic poison.



Narciclasine

Both chemical and spectral studies suggest the above structure of narciclasine, but unlike other members of the **amaryllidaceae group of alkaloids** it possesses no basic properties.

2.4.1.1. Mechanism of Action

The **mechanism of action** of **colchicine** and **narciclasine** described under Section 2.4.1 will be treated as under :

2.4.1.1.1. Colchicine

The precise mechanism of action of this '**drug**' is not yet known, although it is believed to minimize appreciably leukocyte motility, phagocytosis, and also **lactic acid production**, thereby lowering the deposition of **urate crystals** and the **inflammatory response.** In fact, all these effects combinedly relate to the **interference of colchicine** upon the cellular mitotic spindles progressively.

It is found to be absorbed very well after oral administration ; and almost 31% gets bound to plasma protein. It is usually eliminated by the faecal and urinary routes.

CAUTION. ***The 'drug'*** **must be given with great caution particularly to debilitated and aged patients ; and also for those who have a history of cardiac, renal, hepatic, GI, or hematological problems.**

2.4.1.1.2. Narciclasine

The '*drug*' exert its action due to its inherent antimitotic agent. It also inhibits protein synthesis. It is regarded to be the most active antitumour agent of the *Amaryllidaceae* alkaloids.

2.4.2. Tertiary Amines

It includes a good number of dimeric, acyclic and phenanthro compounds and a few of them are discussed below :

(*i*) Dimeric indole alkaloids : *e.g.,* Vinblastine ; Vincristine ;

(*ii*) Dimeric tetrahydroisoquinolines : *e.g.,* Thalicapine ; Thalidasine ;

(*iii*) Acyclic tertiary amines : *e.g.,* Solapalmitine ; Solapalmitenine ;

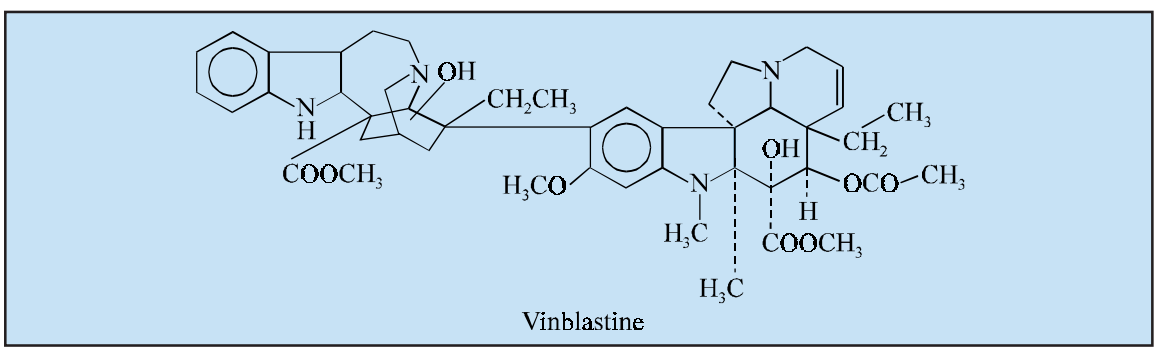
(*vi*) Phenanthroquinilizidines : *e.g.,* Cryptoleurine ;

(*v*) Phenanthroindolizidines : *e.g.,* Tylophorine ; Tylocrebrine ; Tylophorinine ; Phenanthroindolizidine ;

2.4.2.1. *Dimeric Indole Alkaloids*

So far about 72 alkaloids have been isolated from *Vinca rosea* Linn, genus *Catharanthus roseus* (**Family** : *Apocynaceae*). Out of these 24 dimeric alkaloids only six possess **antineoplastic activity** but specifically two *i.e.*, **vincristine**, **vinblastine**, are used clinically in human neoplasms. These are cell-cycle specific agents.

A. *Vinblastine* BAN



Vinblastine

Vincaleucoblastine ; Vinblastine Sulfate USP ; Vinblastine Sulphate BP ;

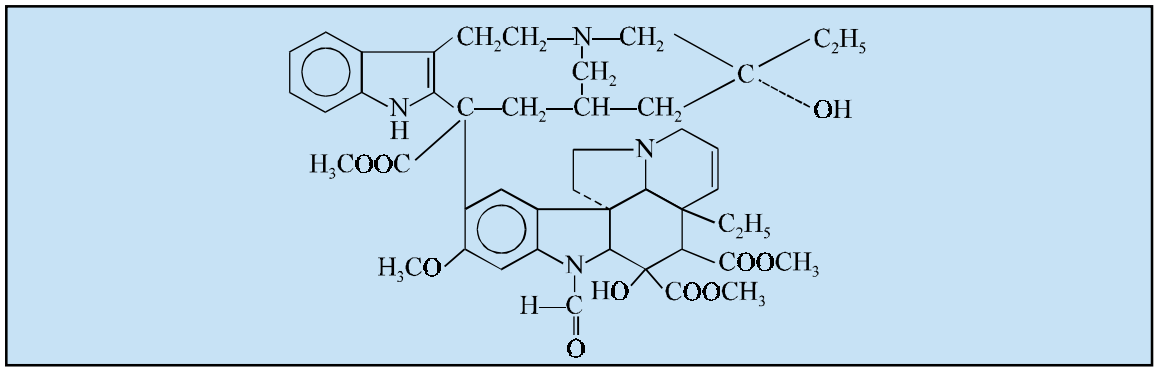
Velban$^{(R)}$ (Lilly) ;

The alkaloid **vinblastine** is made up of two moieties namely : **catharanthine** and **vindoline** which is found to occur in the plant.

It is used in the treatment of Hodgkin's disease, monocytic a drug of third choice in the treatment of neuroblastoma, breast tumours and mycosis fungoides. It is combined with vincristine in the treatment of lymphocytic and myeloblastic leukemia in children.

Dose. *Intravenously as a solution containing 1 mg per ml in sodium chloride injection.*

B. *Vincristine* BAN ; *Vincristine Sulfate* USAN :



Vincristine Sulfate USP : Vincristine Sulphate BP ;

Oncovin(R) (Lilly) ; Vincasar PFS(R) ;

It is employed for the treatment of acute leukemia in children, neuroblastoma, Wilm's tumour and rhabdomyosarcoma. It is found to induce remission in lymphosarcoma and Hodgkin's disease. It is also used in combination therapy with **daunomycin** and **prednisone** in dramatic remission of leukemia.

Dose. *Intravenously as a solution containing 0.01 to 1 mg per ml in sodium chloride injection.*

2.4.2.1.1. Mechanism of Action

The **mechanism of action of vinblastine** and **vincristine sulfate** shall be treated as under :

2.4.2.1.1.1. Vinblastine

The '**drug**' specifically interferes with the assembly of the microtubules, by effectively combining with tubulin, thereby causing a mitotic arrest in the metaphase. Besides, there exists enough supportive evidence that vinblastine exerts its antitumour effect significantly with glutamate and aspartate metabolism. It is, however, pertinent to mention here that the extent of antineoplastic spectrum and the degree of toxicity are distinctly different in comparison to vincristine, that incidently also interacts with tubulin. It has been found that in plasma the '**drug**' is almost 75% protein bound. It usually manifests a **three-compartment kinetics,** of which the second-phase essentially exhibit a half-life ranging between 1–1.5 hours, and an elimination half-life varying between 18-40 hours. Vinblastine is metabolized extensively by the liver ; and, therefore, the dosage regimen has got to be reduced by almost 50% in such patients who have confirmed impaired liver function.

2.4.2.1.1.2. Vincristine Sulfate

The '**drug**' progressively gets combined to the protein tubulin, and subsequently provides a check upon the assembly of microtubules, thereby causing a complete disruption of various cellular processes, including essentially mitosis and spindle formation. Besides, vincristine appreciably suppresses the strategic syntheses of proteins and RNA.

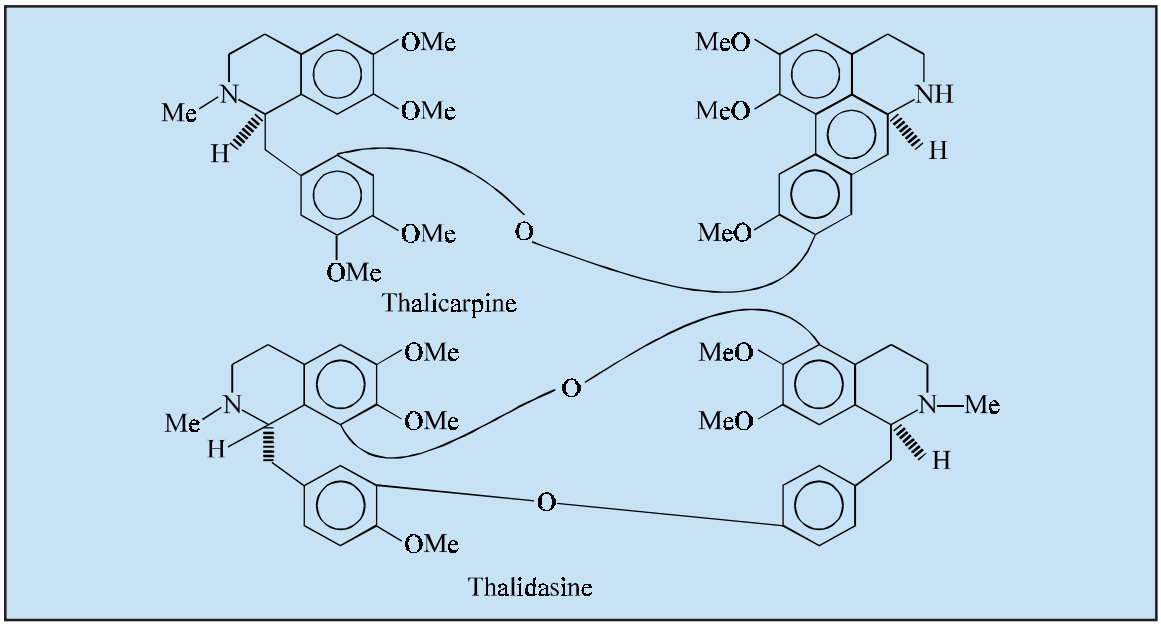
It manifests a three-compartment kinetics, having the half-lives of 0.08, 2.3 and 8.5 hour respectively.It is usually secreted directly into the bile upto 70%. Nearly 12% gets excreted in urine. As the '*drug*' cannot penetrate into the brain ; therefore, it has a little usage for the CNS leukemias.

2.4.2.2. *Dimeric Tetrahydroisoquinolines*

In fact only two alkaloids have been isolated from the roots of *Thalictrum dasycarpum* (Family : *Ranunculaceae*) by systematic fractionation namely : **thalicarpine** and **thalidasine**.

A. *Thalicarpine*

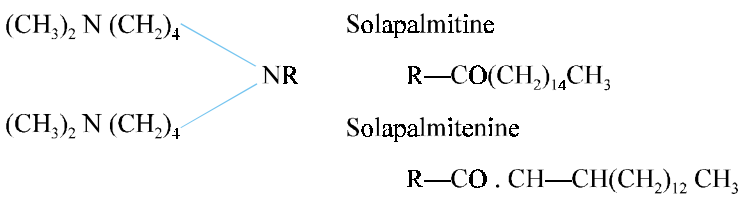
It has also been isolated from *Thalictrum minus* Linn., *Thalictrum revoluctum* and *Hernandia ovigera* (**Family** : *Hernandiaceae*).



Both these compounds have shown activity in mice, dog and rats against Walker 256 carcinomas.

2.4.2.3. *Acyclic Tertiaryamines*

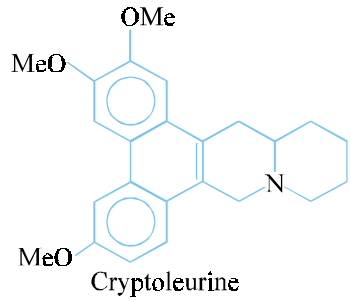
The Bolivian plant *Solanum tripartitum* (**Family** : *Solanaceae*) gave two alkaloids, namely : **solapalmitine** and **solapalmitenine**.



Both these alkaloids have shown *in vivo* activity against Walker 256 and their therapeutic indices do not call for further clincial studies.

2.4.2.4. Phenanthroquinolizidines

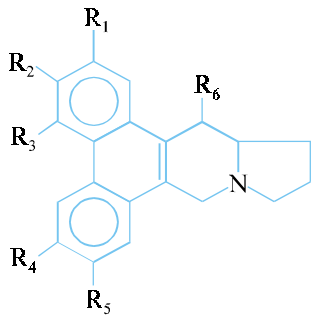
Cryptoleurine has been isolated from *Bochmeria cylindrica* (Family : *Urticaceae*) and it is found to possess highly specific cytotoxic action against **Eagle's KB carcinoma** but inactive against many experimental tumours. A number of its analogues have been synthesized for antineoplastic studies.



Cryptoleurine

2.4.2.5. *Phenanthroindolizidines*

Four alkaloids have been isolated from *Tylophora crebriflora* (**Family** : *Asclepiadaceae*) by **systematic** fractionation, namely : **Tylophorine** ; **Tylocrebrine**, **Tylophorinine**, and **Phenanthroindolizidine**.



Tylophorine : $R_1 = R_2 = R_4 = R_5 = OCH_3$ & $R_3 = R_6 = H$;

Tylocrebrine : $R_1 = R_6 = H$ & $R_2 = R_3 = R_4 = R_5 = OCH_3$;

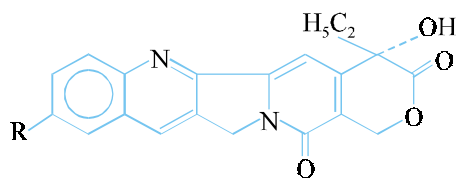
Tylophorinine : $R_1 = R_3 = H$; $R_6 = OH$ & $R_2 = R_4 = R_5 = OCH_3$;

Phenanthroindolizidine : $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = H$;

Tylophorine is active against C-755 and W-256 and tylocrebrine against C-755, P-388, lymphocytic leukemia and L-1210.

2.4.3. Heterocyclic Amines

These alkaloids namely : **camptothecin**, **hydroxycamptothecin** and **methoxy camptothecin** were isolated from the Chinese tree *Camptotheca acuminata* (**Family** : *Nyssaceae*).



Camptothecin : R = H ;

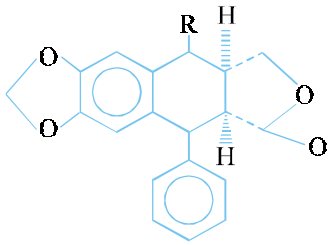
Hydroxycamptothecin : R = OH ;

Methoxycamtothecin : $R = OCH_3$;

Both **camptothecin** and **hydroxycamptothecin** are found to be active against rodent leukemia and solid tumours.

2.4.4. Lactones

Podophyllotoxin and **deoxypodophyllotoxin** are the two alkaloids obtained from the Himalayan shrub *Podophyllam emodi* and the May Apple *Podophyllum peltatum* (**Family** : *Berberidaceae*).



Podophyllotoxin : R = OH ;

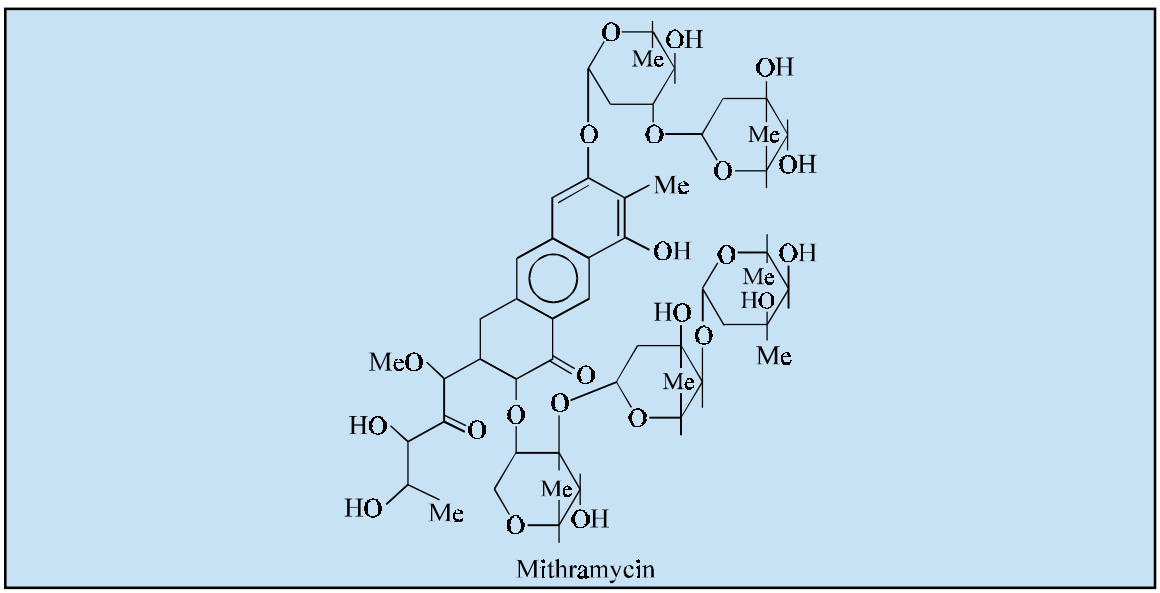
Deoxypodophyllotoxin : R = *o*-glucosyl ;

Podophyllotoxin is an aromatic lactone that arrests the **metaphase activity in the DNA synthesis**.

2.4.5. Glycosides

Two glycosides that possess antineoplastic properties are discussed here, namely : **Mithramycin** (**Aureolic Acid**) and **β-Solamarine**.

A. *Mithramycin* BAN, USAN,



Plicamycin ; Aureolic Acid ; USP ;

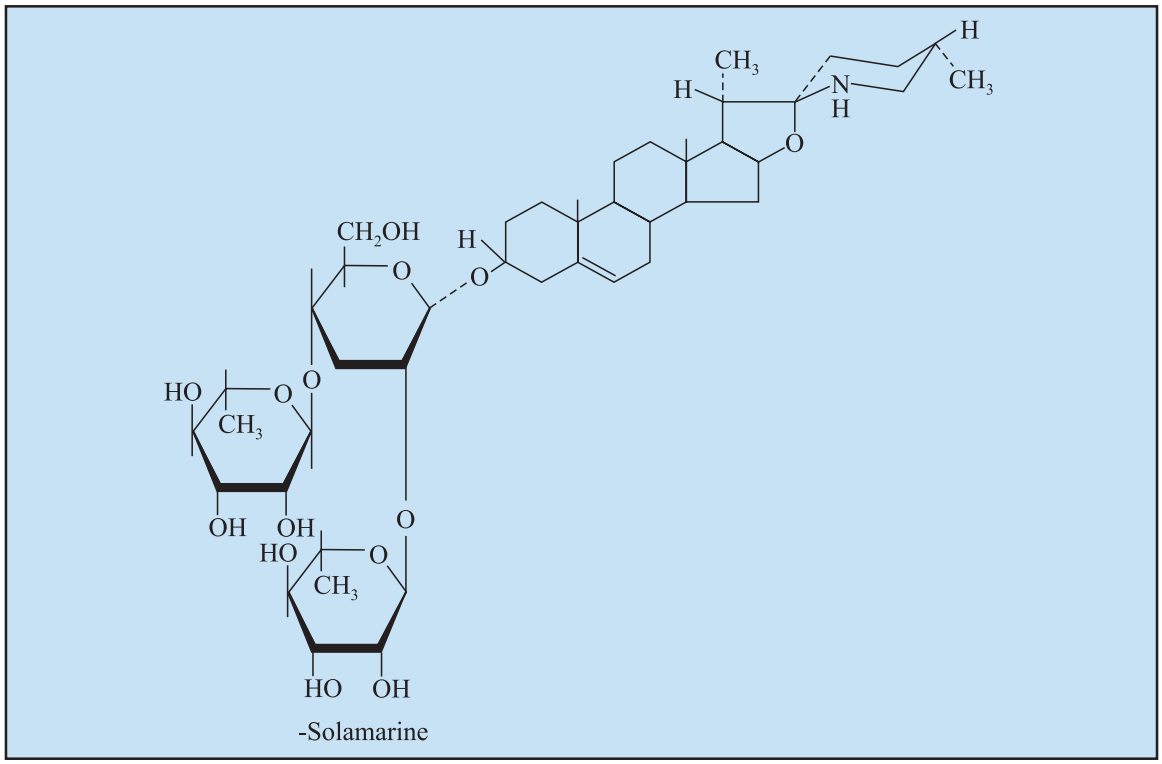
Mithracin$^{(R)}$ (Pfizer-Roarig ; Dome) ;

It is isolated from *Streptomyces argillaceus.* It is employed in the treatment of breast cancer, malignant lymphomas and carcinoma of the stomach.

Dose. *For hypercalcamia and hypercalcuria : usual 25 mcg per kg daily by slow iv infusion for 3 or 4 days.*

The steroidal alkaloidal glycoside **β-solamarine** is isolated from woody night-shade *Solanum dulcomara* Linn., (**Family** : *Solanaceae*).

It is found to be active against S-180, strain.



-Solamarine

2.4.5.1. Mechanism of Action

The mechanism of action of medicinal compound discussed under Section 2.4.5 shall be treated separately in the sections that follows :

2.4.5.1.1. Mithramycin (Plicamycin)

The '*drug*' exerts its action by getting itself bound to **guanine-rich DNA** and thereby helps in inhibiting **DNA-dependent RNA polymerase**. It predominantly acts during the S-phase. As it is found to suppress *osteoclast activity**, it is invariably employed to treat *malignant hypercalcemia*** that is both unresponsive to *conventional treatment* and other severe, *refractory hypercalcemias*.

2.5. Miscellaneous Compounds

There are various compounds that exert **neoplastic activity** both belonging to synthetic and natural origins. A few such compounds are described below :

Examples : Cisplatin, **Imidazole Triazines**, **Hycanthone**, **Pipobroman**,

***A. Cisplatin* BAN, USAN,**

cis—[Pt $(NH_3)_2$ Cl_2]

Cisplatine ; *cis*-Dichlorodiamine platinum ;

Platinex(R) (Bristol-Meyers) ; Neoplatin(R) (Mead-Johnson) ;

---

* A device for fracturing bones for therapeutic purposes.

**Neoplasms which essentially cause dissolution of bone salts.

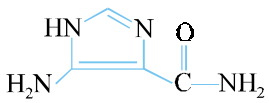
The effectiveness of transition-metal complexes, particularly platinum complexes, as experimental **antineoplastic agents** has been reported in recent years. **Cisplatin** is the prototype platinum complex having **antineoplastic activity**.

It is employed in combination with **vinblastine** and **bleomycin** for the treatment of metastatic testicular tumours. It is also used for the remission of metastaticovarian tumours when given either alone or in combination with **doxorubicin**. It also exhibits activity against a host of other tumours, such as : cervical cancer, neck and head cancer, penile cancer, bladder cancer and small-cell cancer of the lung.

Dose. *Usual, for metastatic testicular tumours 20 mg/m^2 iv daily for five days, followed every 3 weeks for 3 courses : for metastatic ovarian tumours 50 mg/m^2 iv once every 3 weeks.*

B. *Imidazole Triazines :*

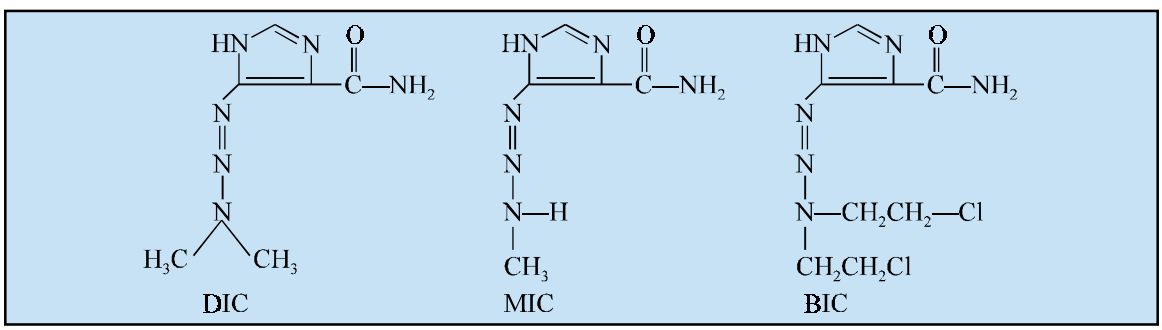
Windans and Langenbeck (1923) first described the synthesis of 5-aminoimidazole-4-carboxamide (AIC) which they later on used for the synthesis of purines :



AIC

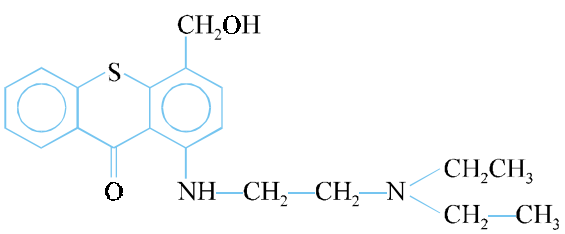
Its structural modification resulted into the synthesis of the following *three* compounds, namely :

5-(3, 3-dimethyl-1-triazeno) imidazole-4-carboxamide **(DIC)** ; 5-3, 3-bis (2-chloroethyl)-1-triazeno) imidazole-4-carboxamide **(BIC)** ; 5-(3-monomethyl-1-triazeno) imidazole-4-carboxamide **(MIC)** ;



DIC (NSC 45388) is found to be active against mouse leukemia L 1210, sarcoma 180 and adenocarcinoma. BIC was found to be most potent suggesting thereby that halo-substitution are often more potent in antineoplastic activity. At present **DIC** is mostly employed in malignant malanoma. It is used in combination with **adriamycin**, **bleomycin** and **vinblastine** in the treatment of Hodgkin's diseases and in sarcomas with **adriamycin**.

***C. Hycanthone* USAN**

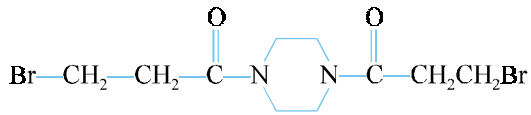


[(Diethlamino-2-ethyl) amino]-1-hydroxymethyl-4-thioxanthenone-9 ;

Etrenol(R) (Winthrop) ;

Hycanthone, which was earlier identified as an antischistosomal drug, found to possess antineoplastic activity in animals. It is comparatively non-toxic. Besides, it is an intercalating agent which inhibits both DNA and RNA synthesis.

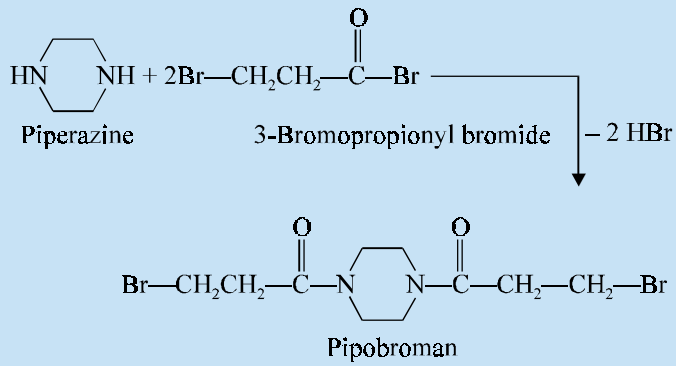
D. *Pipobroman* USAN,



Bis-(bromo-3-propionyl)-1, 4-piperazine ; USP,

Vercyte(R) (Abbott) ;

Synthesis



It is prepared by the interaction of piperazine with two moles of 3-bromopropionyl bromide.

It is used in patients with chronic granulocytic leukemia refractory to busulfan. It is also employed for the treatment of polycythemia vera.

Dose. *Usual, initial : 1 to 1.5 mg per kg body weight daily.*

E. *Asparaginase* USAN *; Colaspase* BAN ;

L-Asparaginase amidohydrolase :

Leunase(R) (May & Baker) : Elspar(R) (Merck, Sharp & Dohme) ; Crasnitin(R) (Bayer) ;

It is a preparation from *Escherichia coli* containing the enzyme L-asparaginase amidohydrolase.

It is used in patients suffering from acute lymphocytic and other leukemias.

Dose. *Intravenously : 1000 units per kg body weight daily for 10 days following treatment with vincristine or prednisone.*

2.5.1. Mechanism of Action

The **mechanism of action** of certain medicinal compounds discussed under Section 2.5 shall now be dealt with individually as under :

2.5.1.1. Cisplatin

The '**drug**' essentially cross-links DNA ; and, therefore, behaves like alkylating antineoplastic agents. In general, the platinum complex acts as a potent inhibitor of DNA polymerase. Based on adequate

supportive evidences it has been duly established that there exists a bondage between DNA and platinum complex, wherein the two Cl^- ions are duly displaced by N or O atoms of purines. This evidence is fully substantiated by concrete experimental findings, such as : (*a*) **enhanced sedimentation coefficient** ; (*b*) **hyperchromicity shown by the DNA-UV-spectrum** ; and (*c*) **selective and specific reaction occurring between the Pt-complex and guanine over other bases**.*

Cisplatin is *not* well absorbed by oral administration, and hence, must be given IV. The '*drug*' gets bound to plasma proteins to the extent of 90%. It fails to cross the blood-brain barrier (BBB). It gets secreted chiefly *via* renal route, partly by tubular secretion ; however, the overall pattern is found to be '**nonlinear**' in nature. It has been observed that the prevailing distribution half-life of the unbound drug is 25-49 minutes and the elimination half-life of total Pt ranges between 58-73 hours, which may get extended upto 240 hours in *anuria*.**

Note. Sodium thiosulphate decomposes cisplatin and complxes with Pt, and in this manner affords protection against renal damage and certain other toxicity.

2.5.1.2. Pipobroman

The '**drug**' exerts its action due to its alkylating properties. Importantly, it is invariably held in reserve for usage in such patients who have virtually turned refractory to **X-irradiation** and **busulfan** in the severe case of **leukemia** and **phlebotomy**.***

CAUTION : It should not be used in pregnancy.

2.5.1.3. Asparaginase

It has been observed that the ensuing protein synthesis in a good number of normal and malignant cell types depends partially on **exogenous asparagine** ; and in a few cells like-*leukemic cells* and *lymphoblasts* is dependent almost completely. Consequently, the enzymatic destruction of asparagine by the enzyme asparaginase duly injected into plasma usually deprives the dependent cells of the essential asparagine thereby causing predominantly *three* vital effects, namely : (*i*) **partial cell-death** ; (*ii*) **arrest cell growth** *;* and (*iii*) **tumour regression**.

Asparaginase (the **enzyme**) is found to protect certain tissues and malignant tumours from some known **antimetabolites**, such as : **methotrexate**, **ara-C**, presumably by directly preventing DNA synthesis.

Ervinia (Porton) *asparaginase* is observed to be less sensitizing in comparison to that obtained from *E. coli*. Besides, Ervinia asparaginase is designated as an '**orphan drug**' which is virtually reserved for usage particularly in patients who are found to be allergic to **asparaginase** obtained from *E. coli.* Interestingly, both enzymes do exhibit **immunosuppressant activity.**

The '**drug**' exhibits extremely poor extravascular tissue penetration ; and, therefore, gets cleared from plasma in a quite sluggish and unpredictable manner. Nevertheless, the elimination is *biphasic*, having an inital half-life of 4-9 hours and a terminal half-life ranging betwen 1.4 to 1.8 day.****

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* Sartorelli AC and Johns DJ (eds) : **Handbook of Experimental Pharmaeology**, Vol. 38, Pt. 2, Springer = Verlag, New York, pp. 829-838, 1975.

**Absence of urine formation.

*** The surgical opening of a vein to withdraw blood.

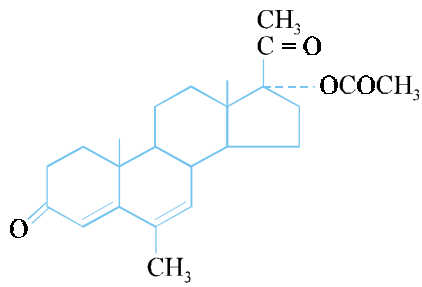
****Physicians' Desk Reference**, Medical Economics, Oradell N.J., 33**rd** edn., (p. 749) 1979.

2.6. Hormones

Hormones has the ability to suppress mitosis in lymphocytes and this effect is duly utilized in the treatment of neoplastic diseases. **Adrenocorticosteroids** specifically are effective in the treatment of leukemia in children and in the management of hemolytic anaemia and hemorrhagic complications of thrombocytopenia that mostly occur in malignant lymphomas and chronic lymphocitic leukemia. Acute lymphoblastic leukemias in children are better treated with corticosteroids rather than antimetabolities and remission take place more rapidly. The **hormones** have been beneficial in breast cancer and other carcinomas although palliative effects are of short duration.

A few important compounds are discussed here, namely : **Megestrol ; Mitotane and Testolactone ;**

A. *Megestrol* BAN, ; *Megestrol Acetate* USAN :



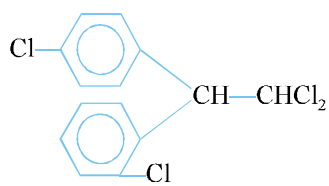
17-(Acetoxy-6-methyl-pregna-4, 6-diene-3, 20-dione, Megesterol Acetate BP (1973) :

Ovarid(R) (Glaxo) ; Megestat(R) (Bristol) ; Megace(R) (Mead-Johnson) ;

It is indicated for the palliative treatment of endometrial carcinoma and advanced breast cancer when other methods of medication are not effective.

Dose. *Usual, 160 mg/day in four equal doses in breast cancer, ; 40-320 mg/day in equal divided doses in endometrial cancer.*

B. *Mitotane* USAN ;



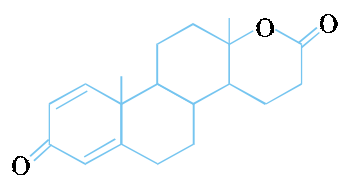
1, 1-Dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl) ethane ; *o, p*-DDD ; USP ;

Lysodren(R) (Bristol) ;

It is indicated mainly for the treatment of inoperable adrenal cortical carcinoma.

Dose. *Usual, 8-10 g per day, divided into 3 or 4 equal doses.*

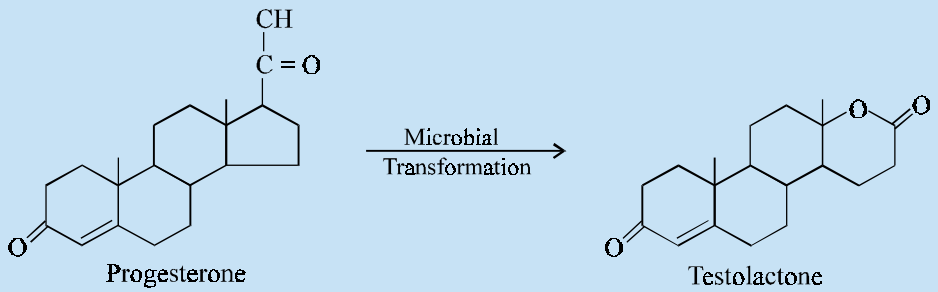
C. *Testolactone* USAN ;



1-Dehydrotestololactone USP ;

Teslac(R) (Squibb) ;

Synthesis



It may be prepared by microbial transformation of progesterone.

It is invariably employed in the palliative treatment of advanced breast cancer in postmenopausal women.

Dose. *Usual, 250 mg 4 times per day by mouth or 100 mg intramuscularly thrice weekly.*

2.6.1. Mechanism of Action

The **mechanism of action** of some drug substances discussed under section 2.6 shall be treated individually in the section that follows :

2.6.1.1. Magestrol Acetate

It is well established that not only normal, but also well-differentiated neoplastic target cells to possess a plethora of strategically located '**hormone receptors** ; and eventually they bank upon the hormones for stimulation.* Importantly, the rather comparatively less differentiated neoplastic cells invariably become independent of the ensuing '**hormonal control**' and thereby lose their specific receptors eventually. Evidently, a few malignant tumours are solely hormone dependent and responsive to hormone-based therapy, on the contrary others are independent and naturally altogether unresponsive. Hence, magestrol acetate exert its action on hormone dependent tumours *e.g.*, endometrial carcinoma and breast cancer.

2.6.1.2. Mitotane

The '**drug**' is found to be toxic to the adrenal cortex and, therefore, it is exclusively indicated for the treatment of *inoperable adrenal cortical carcinoma.* It is metabolized in the liver. Approximately 40% of a single oral dose gets absorbed ; whereas, the '**drug**' gets excreted in urine in the form of an **unidentified metabolite** ranging between 10-25%, and almost 60% is excreted absolutely unchanged in faeces. The remainder of the '**drug**' gets stored in the adipose tissues *in vivo.*

2.6.1.3. Testolactone

The '**drug**' obtained *via* microbial transformation of progesterone** is found to be devoid of any androgenic activity in the usual recommened dosage regimens.

2.7. Immunotherapy

It is now an established fact that the human body continually produces cells having neoplastic potential which are destroyed by our immune surveillance system. The very formation of tumours suggests

* Fried J *et. al. J. Am. Chem. Soc.* **75 :** 5764, 1953.

that this system is impaired. In other words, suppression of body's immune system by these agents easily results to development of serious viral, bacterial and fungal infections.

Biochemical modulation of the action of some of the **antineoplastic agents** has more or less provided a means of improving their specificity for tumour cells. **Biological modifiers specific antibodies** such as **interferons**, **interleukins** and agents that might affect or arrest cancerous growth by inducing terminal differentiation have been also applied but there exists only limited evidence till date that these agents can affect widely disseminated cancers, It may, however, be ascertained confidently that treatment with biological response-modifiers amalgamated with improved form of chemotherapy will ultimately lead to significant enhancement both in the arrest and even cure of wider spectrum of neoplasma.

One important member of this group is discussed here, namely : **Interferon Alfa-2*a* recombinant**.

A. *Interferon Alfa-2a, Recombinant*

It is prepared on a large scale from a strain of *E. coli* having essentially a plasmid produced by the technique of genetic engineering, otherwise known as recombinant DNA technology, consisting of an interferon alfa-2*a* gene from human leukocytes.

It is employed in subjects above the age of 18 years for the treatment of hairy cell leukemia.

Dose. *In hairy cell leukemia the dose of interferon alfa-2a and alfa-nl is 3 million units daily by deep intramuscular or subcutaneous injection until there is improvement or for up to 24 weeks, then redcued to a maintenance dose of 3 million units 3 times a week.*

2.7.1. Mechanism of Action

The **mechanism of action** of the **interferon alfa-2*a*, recombinant** is discussed as under :

2.7.1.1. Interferon Alfa-2a, Recombinant

The **'drug'** enhances class I histocompatibility molecules on lymphocytes, increases the production of **ILs-1 and -2**,* regulates antibody responses, and above all enhances **NK cell**** activity. Besides, it also inhibits cancerous tumour-cell growth by virtue of its inherent ability to inhibit protein anabolism (synthesis) *in vivo*. The '**drug**' is antiproliferative ; and, therefore, may also serve as immunosuppressive. It is, however, pertinent to state here that the prevalent action of the **'drug'** upon the **NK cells** is believed to be the most important and critical factor for its prevailing **antineoplastic profile.**

The '**drug**' also exhibits antiviral activity, specifically against the RNA viruses. Furthermore, it appreciably enhances the strategic targetting of monoclonal antibody-tethered cytotoxic drugs to the corresponding malignant cells.

The '**drug**' is not absorbed when administered through mouth. However, by IV route it exclusively disappears within a span of 4 hours, but by the IM or sub-cutaneous route disappearance gets prolonged to 6-7 hours.

Probable Questions for B. Pharm. Examinations

1. What is a neoplasm ? What are the causations of neoplasm ? Give the structure, name and uses of at least **three** potent drugs employed as antineoplastic agents belonging to :

(*a*) Natural plant source

(*b*) Synthetic drugs.

---

* Mediate most of the toxic and therapeutic effects.

**Natural killer cells.

2. How would you classify the **'antineoplastic agents'** ? Give the structure, chemical name and uses of **one** important member from each category.

3. Mustards, methanesulphonates, ethylenimines and nitrosoureas constitute **four** vital categories of the **'Alkylating Agents'** employed for the treatment of neoplasms. Discuss the synthesis of the following drugs :

(*a*) Chlorambucil

(*b*) Busulfan

(*c*) Triethylene melamine

(*d*) Carmustine.

4. (*a*) How would you classify **'Antimetabolities'** ?

(*b*) Give the structure, chemical name and uses of the following :

(*i*) Methotrexate

(*ii*) Meracaptopurine

(*iii*) Fluorouracil

(*iv*) Azaserine.

(*c*) Discuss the synthesis of any **one** drug stated above.

5. 'Recognition of **antibiotics'** as an important class of *antineoplastic agents* is quite recent'. Justify the statement with reference to the following drugs :

(*a*) Dactinomycine

(*b*) Daunorubicin.

6. Classify the **'plant products'** employed in the treatment of malignant disease. Give structure, name and uses of **one** potent drug from each category.

7. Discuss the synthesis of the following :

(*a*) Pipobroman

(*b*) Lomustine

(*c*) Cytarabine.

8. Give a comprehensive account of **'hormones'** that are potent as antineoplastic agents. Support your answer with suitable examples.

9. Give a brief account of the following :

(*a*) Immunotherapy in cancer

(*b*) Pharmacokinetics, pharmacodynamic and mode of action of antineoplastic agents.

10. Discuss the following with regard to antineoplastic agents :

(*a*) Dimeric tetrahydroisoquinoline

(*b*) Acyclic tertiaryamine

(*c*) Phenanthroquinolizidine

(*d*) Phenanthroindolizidine.

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28

Antipsychotics (Tranquilizers)

Chapter

28 Antipsychotics (Tranquilizers)

1. INTRODUCTION

In general, **antipsychotics** (**tranquilizers**) are primarily employed for the treatment of symptoms in mental diseases, their overall influence being to free the mind from passion or disturbance and thus clam the mind *i.e.,* they cause sedation without inducing sleep.

Tranquilizers are drugs essentially used in the management and, treatment of psychoses and neuroses. They specifically exert their action on the lower brain areas to produce emotional calmness and relaxation without appreciable hypnosis sedation euphoria or motor impairment. In addition many of these drugs also display clinically beneficial actions, for instance skeletal muscle relaxants, antihypertensive, antiemetic and antiepileptic properties.

One school of thought even suggested that these drugs may be divided into *two* categories, namely : **major tranquilizers** (for **psychoses**) and **minor tranquilizers** (for **neuroses**) ; however, such an arbitrary categorization stands invalid because of their overlaping characteristic features.

More recently **antipsychotics** may be defined as—**'drugs' which ameliorate mental aberrations* that are invariably characteristic feature of the psychoses.**

Positive symptoms of psychoses essentially comprise of a host of disorders, such as : mild behavioural changes anxiety, delusions, hallucinations, and sclizzophrenias. Negative symptoms are usually designated by cognitive deficits, social withdrawl, apathy, and anhedonia.

Interestingly, '**psychoses**' may be organic which could be either trigger off or directly related to a variety of reasons, namely :

(*i*) particular toxic chemical influence *e.g.,* **delirium**—due to central anticholinergic drugs,

(*ii*) a N-methyl-D-aspartate (NMDA) antagonist *e.g.,* **phencylidine**.

(*iii*) a particular disease process *eg.,* **dementia** (cognitire deficit including memory impairment, and

(*iv*) idiopathic conditions *i.e.,* disease without clear pathiogenesis, as of spontaneous origin.

In a broader perspective the typical **'antipsychotics'** should ideally possess the following cardinal requirements, such as :

(*a*) high lipid solubility,

***Aberration :** Deviation from the normal.

(*b*) affinity for protein-binding (92–99%),

(*c*) large volume of distribution (v_d^{55}) *i.e.*, greater than 7 L.kg^{-1},

(*d*) variance in oral bioavailability (25–35%), and

(*e*) short plasma half-life between 10–20 hours.

It is, however, pertinent to mention here that though these drugs have a relatively shorter plasma half-life but their duration of action is much longer ; their metabolites may be found in the urine weeks even after the last terminal dosage ; and finally a good proportion of the drug are adequately sequestered in the various tissues.

2. CLASSIFICATION

Antipsychotics may be classified under the following categories, namely :

(*a*) Reserpine and Related Alkaloids

(*b*) Alkylene Diols

(*c*) Diphenylmethane Compounds

(*d*) Phenothiazine Compounds

(*e*) Dibenzazepines

(*f*) Butyrophenones

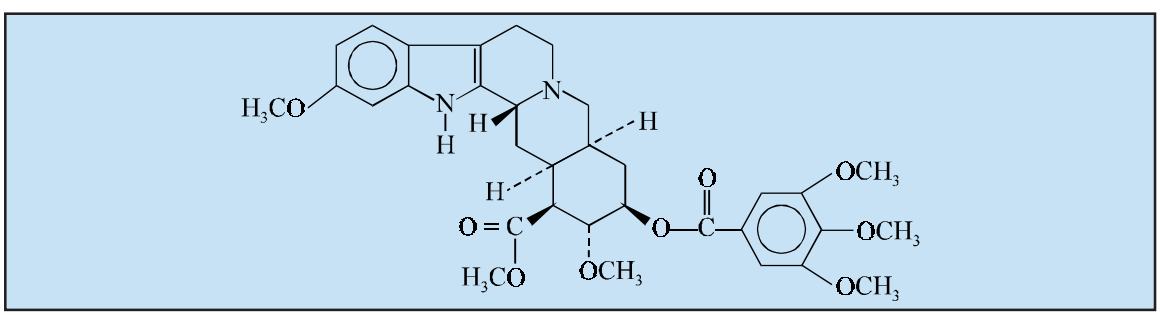
(*g*) Azaspirodecanediones

2.1. Reserpine and Related Alkaloids

The roots of *Rauwolfia serpentina*, a climbing shrub indigenous to India, and named after the German botanist **Rauwolf,** contains an alkaloid **Reserpine** which was reported to possess both tranquilizing and hypotensive properties.

Examples : Reserpine and **Deserpidine**.

A. *Reserpine* BAN, USAN, INN,



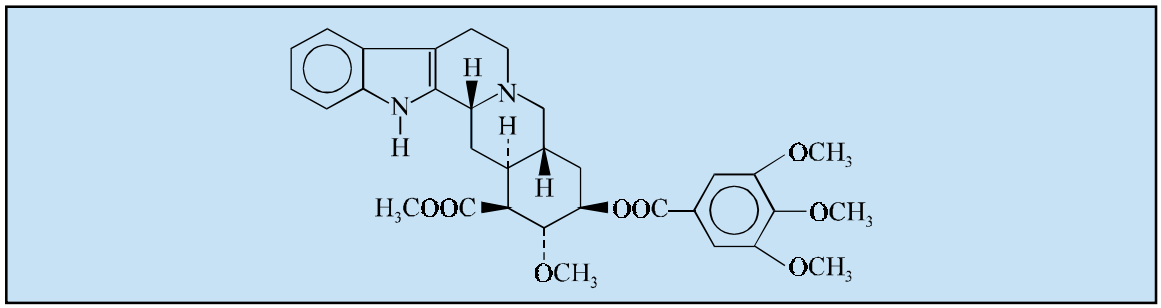
Methyl 18 β-hydroxy-11,17 a-dimethyoxy-3β, 20α-yohimban-16β-carboxylate 3,4,5-trimethoxybenzoate (ester) ; BP ; USP ; Int. P ;

Serpasil$^{(R)}$ (Ciba-Geigy) ; SK-Reserpine$^{(R)}$ (Smith Kline & French) ; Sandril$^{(R)}$ (Lilly) ;

It has central depressant and sedative actions and a primarily peripheral antihypertensive effect accompanied by bradycardia. It is also used for the management and treatment of hypertensive specifically in patients with mild labile hypertension associated with tachycardia.

Dose. *As sedative in anxiety states and chronic psychoses : 0.1 to 1 mg daily doses. For hypeprtension-in adults : 250 to 500 mcg daily for about 2 weeks ;*

B. *Deserpidine* INN, USAN ; *Desipraminum* BAN ;



II-Desmethoxyreserpine ; BP ; USP ;

Harmonyl(R) (Abbott) ; Pertofram(R) (Ciba-Geigy) ;

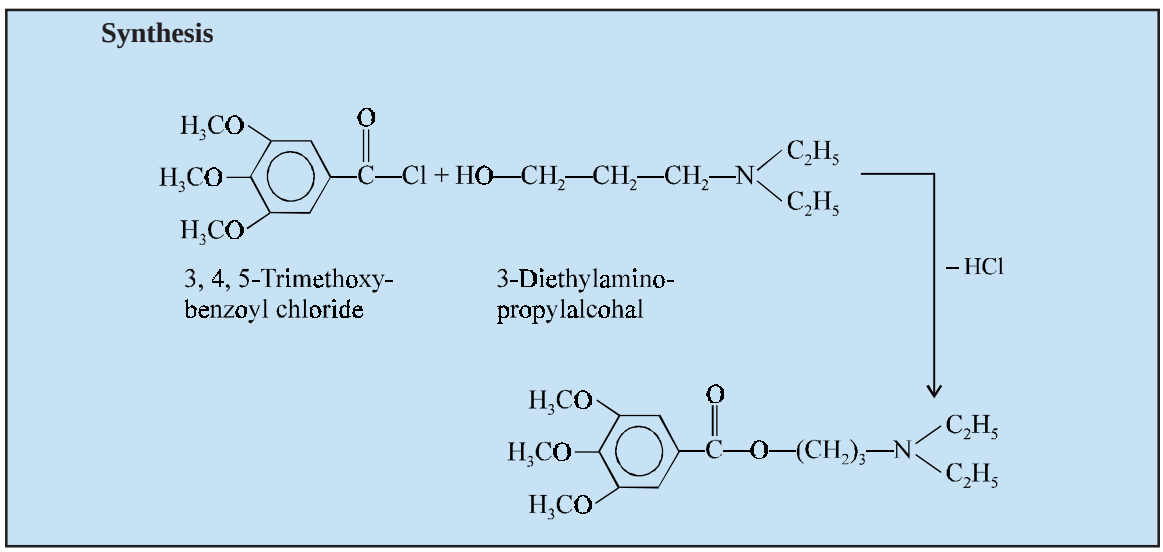
Its actions and uses are very much similar to those described under reserpine.

Dose. *For psychiatric treatment : Average, initial, 500 mcg daily with a range of 0.1 to 1 mg ; For antihypertension ; initial 0.75 to 1 mg daily subsequently reduced to a maintenace dose of about 250 mcg per day.*

Miller and Weinberg (1956) observed that even the simple tertiary amines having the trimethoxybenzoyl group exhibits the reserpine-like activity.

Example : 3-Diethylamino propyl ester of 3, 4, 5-trimethoxy benzoic acid.

Synthesis



It is prepared by the interaction of 3, 4, 5-trimethoxybenzoyl chloride with 3-diethylaminopropyl alcohol with the elimination of hydrochloric acid.

It is found to possess about 1/3rd the activity of **reserpine**.

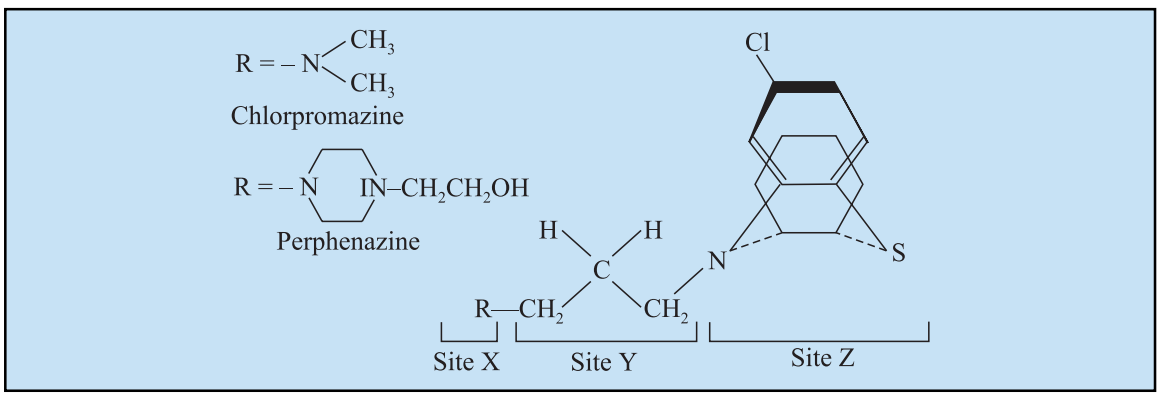
2.1.1. Mechanism of Reaction

The mechanism of reaction of the '**drug**' discussed under Section 2.1 shall be treated separately as under :

2.1.1.1. Reserpine

The '**drug**' exerts its action to cause significant inhibition of both **neuronal** and **chromaffin granule transporters**. Consequently, the **catecholamine accumulation** gets blocked appreciably. As a net overall effect the depletion is rather slower and less complete in the adrenal medulla in comparison to other tissues. Therefore, the strategic prevention of such storage ability/capacity, the '**drug**' at its initial primary state affords a distinct **catecholamine** release. Subsequently, a marked and pronounced '*depletion of transmitter*' commences that usually prolongs for days through weeks. The effects of reserpine seem to be irreversible absolutely.

Reserpine exerts its antihypertensive action by virtue of its adrenergic neutronal blockade consequent to depletion of the catecholamines-containing granudles of the postganglionic sympathetic neuron. It, however, depletes both brain **catecholamines** and **seritonins**.



Phenothiazines exert their antipsychotic potency by interacting with a receptor at three marked sites X, Y, Z to produce a singificant response. The order of specific structural requirement at these sites is YZX. However, a three-carbon chain at site Y affords an optimal antipsychotic activity.

The apparant variance in the efficacy of oral administration of **reserpine** is due to the fact that it gets absorbed very poorly as well as erratically from the ensuing GI tract. Importantly and characteristically the '*drug*' bears a relatively longer latency of onset, and followed by a prolonged duration of action.

Note. Combinations of resperpine, with a diuretic enhances the efficacy of the former significantly.

2.1.1.2. Deserpidine

It essentially possesses almost similar phermacological activity and mechanism of action of that of **'reserpine'** discussed under Section 2.1.1.1 above.

2.2. Alkylene Diols

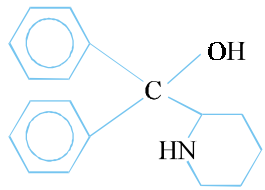
Alkylene diols are also referred to as **'propanediol carbamates'** have been used as tranquilizer. Two mportant members of this classification, namely : **meprobamate** and **tybamate** have been discussed in the Chapter-8 on **'Muscle Relaxants'** in this book.

2.3. Diphenylmethane Compounds

A number of **diphenylmethane** derivatives have been synthesized that exhibit antipsychotic activities.

A few such compounds are described below, namely : **Pipradrol** ; **Captodiame** ; **Hydroxyzine** ; **Benactyzine** ;

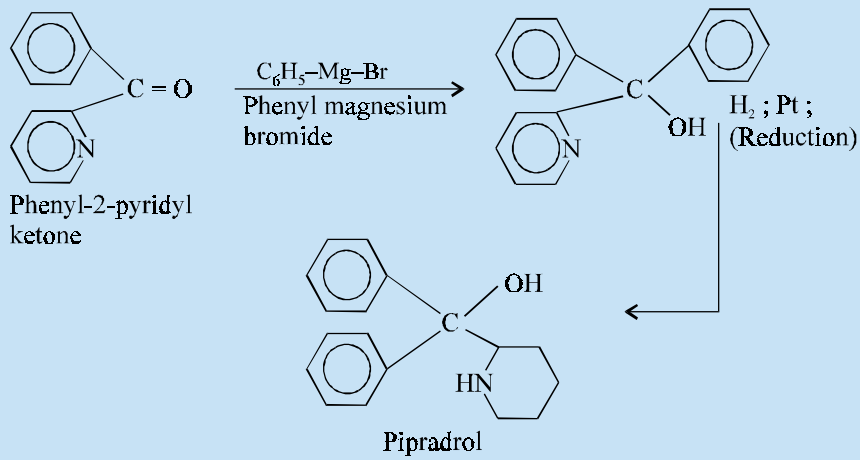
A. *Pipradrol* INN, BAN, *Pipradrol Hydrochloride* USAN,



α, α-Diphenyl-2-piperidine methanol ; Pipradrol Hydrochloride BP ;

Meratran(R) (Merrell Dow) ;

Synthesis

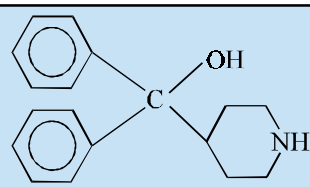


It is synthesized by **Grignard reaction** of phenyl-2-pyridyl ketone with phenyl magnesium bromide followed by catalytic reduction to get the official compound.

It is used for the treatment of functional fatigue and various types of depressions.

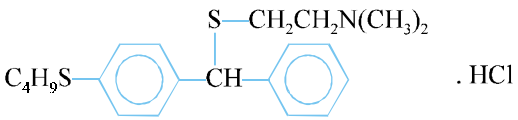
Dose. *Usual, 2.5 mg twice daily.*

The corresponding 4-piperidyl derivative pipradrol is also a **tranquilizer** used under the name of **Azacyclonal**.



The drug is prepared from phenyl ketone exactly in the same manner as that of **pipradrol**. It has the same application as that of its isomer.

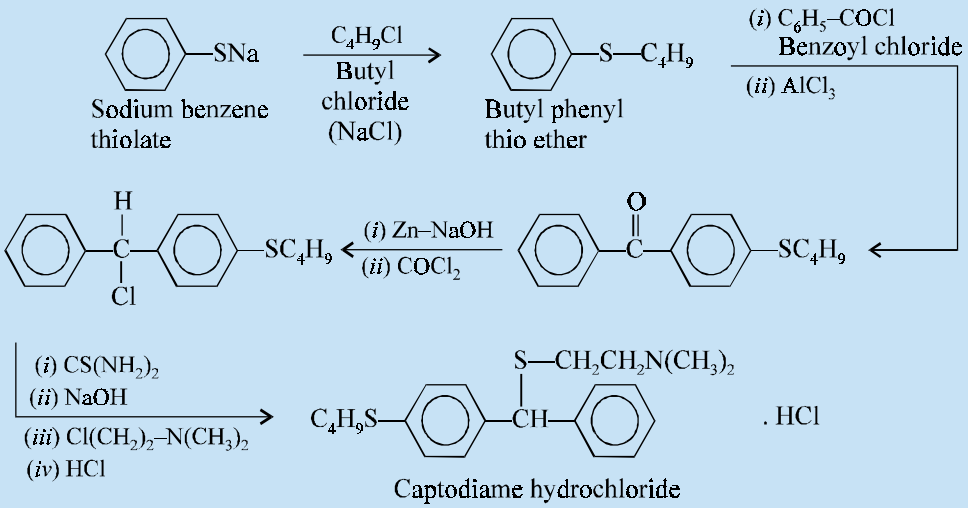
B. *Captodiame* INN, BAN ; *Captodiame Hydrochloride* USAN ;



2-[*p*-(Butylthio)-α-phenylbenzylthio]-N, N-dimethylethylamine hydrochloride ;

Covatin(R) (Warner-Lambert) ;

Synthesis

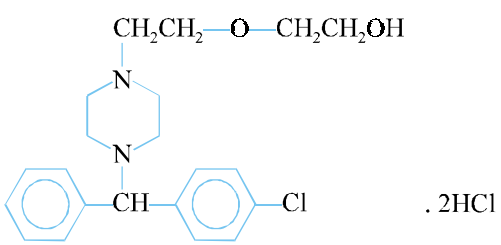


Butylphenyl thioether is first prepared by the interaction of sodium benzenethiolate and butyl chloride. The resulting product on treatment with benzoyl chloride and aluminum chloride yields butyl-p-benzoyl phenyl thioether. This on reaction with zinc and sodium hydroxide and carbonyl chloride yields an intermediate. The intermediate on treatment with thiourea, sodium hydroxide, 2-dimethyl amine ethyl chloride and hydrochloric acid gives rise to the desired compound.

It is used for the treatment of anxiety and tension. It is an excellent nonhypnotic sedative.

Dose. *For anxiety and tension : 50 mg three times per day.*

C. *Hydroxyzine* INN, BAN ; *Hydroxyzine Hydrochloride* USAN ;

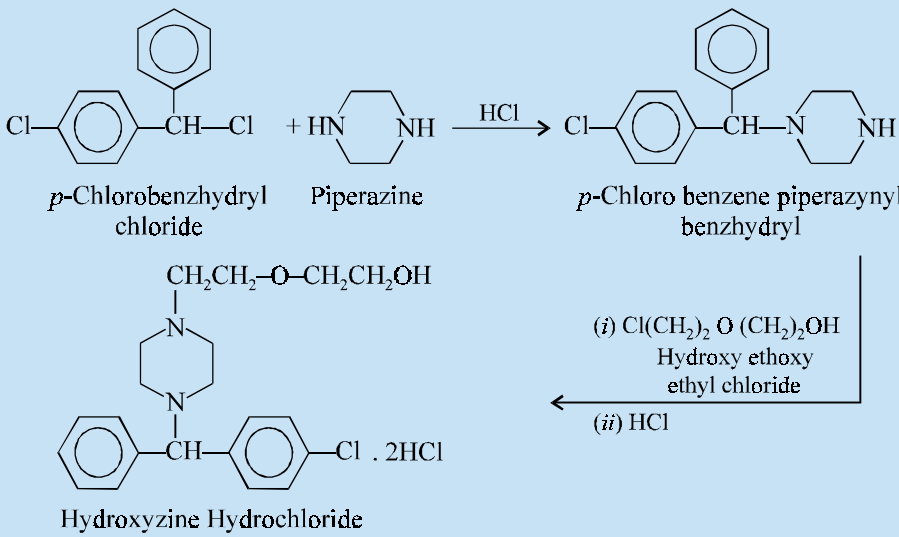


Ethanol, 2-[2-[4-chlorophenyl) phenyl methyl]-1-piperazinyl]ethoxy]-, dihydrochloride ;

Hydroxyzine Hydrochloride USP ;

Atarax(R) (Roerig) ; Orgatrax(R) (Organon) ;

Synthesis

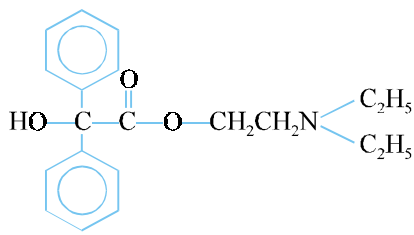


It is prepared by interacting p-chloro benzhydryl chloride with piperazine to obtain p-chlorobenzene piperazynyl benzhydryl which is subsequently treted with β-hydroxy ethoxy ethyl chloride to give the hydroxyzine base. They official compound may be finally obtained by treating with hydrochloric acid.

It is employed for pre-and postoperative sedation. It has also been used successfully in the treatment of anxiety, tension and agitation.

Dose. *Adult, IM injection as the hydrochloride in doses of 25 to 100 mg every 4 to 6 hrs ; Children : 1 mg per kg body weight im for pre-and postoperative sedation.*

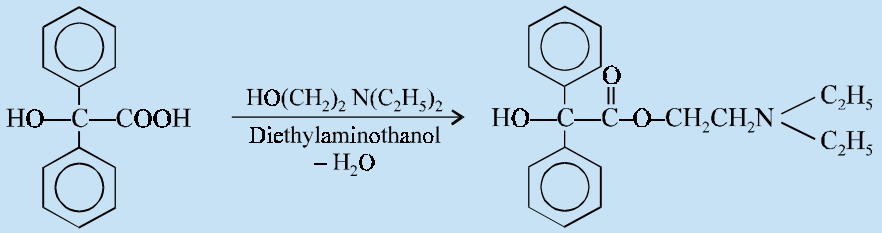
D. *Benactyzine* BAN ; USAN ; *Benctyzine Hydrochloride* INN ;



2-Diethylaminoethyl benzilate ; BPC (1959) ;

Suavitil(R) (Dumax) ; Nutinal(R) (Boots) ; Cevanol(R) (ICI) ; Parasan(R) (Medix) ;

Synthesis



Benzilic acid Benactyzine

It may be prepared by treating benzilic acid with diethylamne ethanol resulting the official compound with the elimination of a molecule of water.

2.3.1. Mechanism of Action

The mechanism of action of some of the medicinal compounds described under Section 2.3 shall now be dealt with individually in the sections that follows :

2.3.1.1. Pipradrol Hydrochloride

The '**drug**' exerts its action as a stimulant of the central nervous system. Perhaps this could be the reason it is invariably included in multingredient preparations of combat antipsychotic profile to a great extent.

2.3.1.2. Captodiame Hydrochloride

The '**drug**' exerts its therapentic action to combat various types of anxiety disorders *viz.*, generalized anxiety disorders, panic attacks, phobic disorders, obsessive-compulsive disorder, post-tranmatic stress disorder, and mixed anxiety and depressive disorders. Perhaps the **'drug'** acts as a atypical antisychotic agent by virtue of its reduced tendency to produce the extrapyramidal effects.

2.3.1.3. Hydroxyzine Hydrochloride

The '**drug**' exhibits antichloinergic action ; and, therefore, its overall effects may be additive with those of **atropine** and other **belladona alkaloids**. Likewise, a host of other therapeutically potent sedative drugs it essentially requires a stringent precautionary measure with regard to its dose adjustment in such subjects who are on other **CNS-depressant drugs**. In the same vein, when employed as a preanaesthetic medication with other agents *e.g.,* **barbiturate(s)**, **mepreidine**, the dosage regimen need to be adjusted on an individual basis cautiously.

Note. The potentiating effect of this drug should always be taken into consideration when it is employed in conjunction with CNS-depressants for instance : barbiturates and narcotics.

2.3.1.4. Benactyzine Hydrochloride

The **'drug'** is found to show its action as an antidepressant as well as antimuscarinic activity. However, the antidepressant therapy has mainly been accomplished either *via* the **monoamine oxidase (MAO)** inhibitors or *via* the **reversible inhibitors (RIMAs)**.

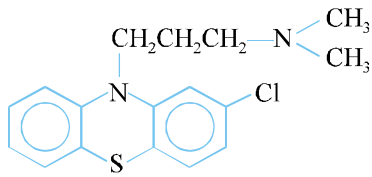
2.4. Phenothiazine Compounds

The discovery of **phenothiazine** as an anthelmintic dates back to 1883, however, its antithistaminic activity was revealed in 1937. The comintuous search for better drugs ultimately resulted into the synthesis of **chlorpromazine** in the famous **Rhone-Poulenc Laboratories in France** in the year 1950 which was

found to possess remarkable ameliorative effect on anxiety, agitation and psychoses. This ultimately led to the synthesis of a host of structural analogues of **chlorpromazine** that were found to be useful as antipsychotics.

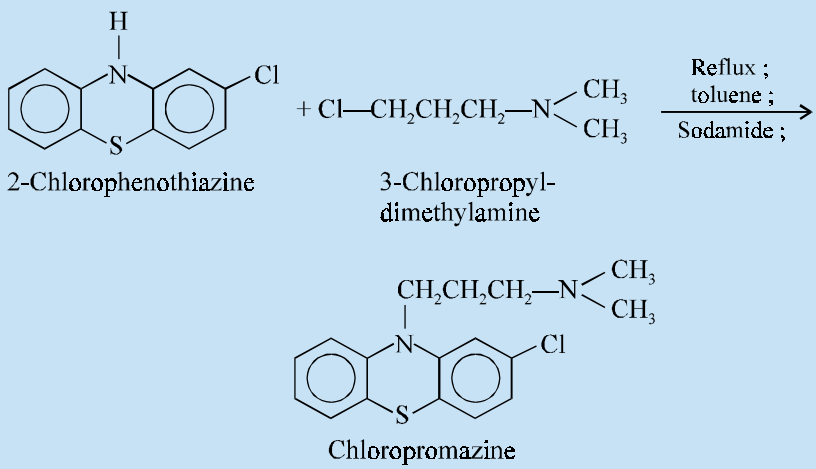
A few typical examples from this class of compounds are discussed here, namely ; **Chlorpromazine**, **Perphenazine**, **Thioridazine**.

A. *Chlorpromazine* INN, BAN, USAN,



2-Chloro-10-[3-(dimethylamino) propyl] phenothiazine ; BPC (1973) ; USP ; Thorazine(R) (Smith Kline French) ; Promapar(R) (Parke-Davis) ; Megaphen(R) (Bayer) ; Promacid(R) (Knoll) ;

Synthesis

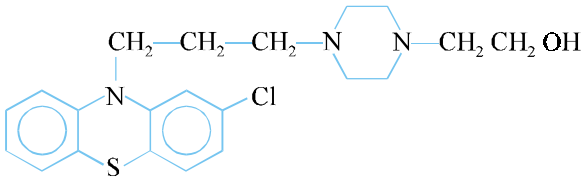


It is prepared by refluxing a toluene solution of 2-chlorophenothiazine and 3-chloropropyl dimethylamine in the presence of sodamide for several hours, followed by filtration and removal of toluene under reduced pressure.

It enjoys the reputation for being the **tranquilizer** of the **phenothiazine compounds**. It is found to be effective in the management of manifestations of psychotic disorders and manic depressive illness (*manic pahse*), apprehension and anxiety and prior to surgery. It is also used for the treatment of moderate to severe agitation.

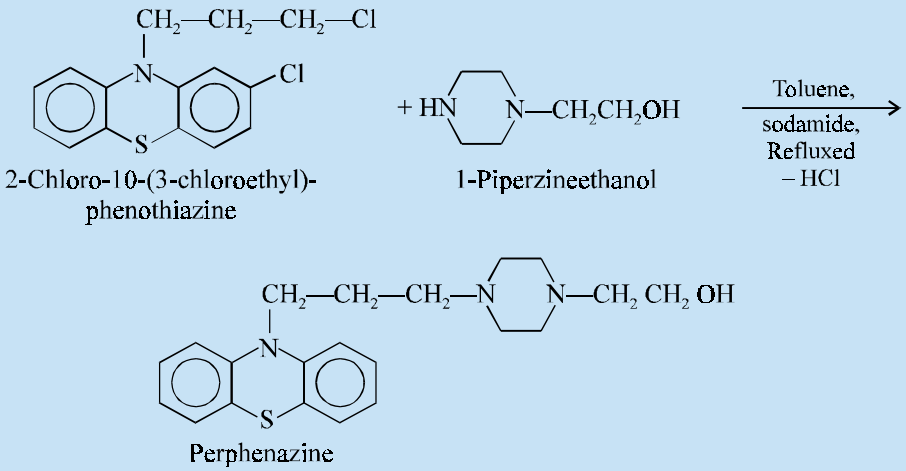
Dose. *Tranquilizer : Adults, oral, usual, 10 to 50 mg 2 or 3 times daily to a total dose of 1 g daily when indicated ; 1m, 25 to 50 mg repreated in 1 hour upto a total dose of 1 g per day ; Children, oral, 0.55 mg/kg every 4 to 6 hours ; im, 0.55 mg/kg every 6 to 9 hours.*

B. *Perphenazine* INN, BAN, USAN,



Piperazineethanol, 4-[3(2-chloro-10-phenothiazine-10 yl) propyl]- ; BP (1973) ; USP ; Trilafon$^{(R)}$ (Schering-Plough) ;

Synthesis

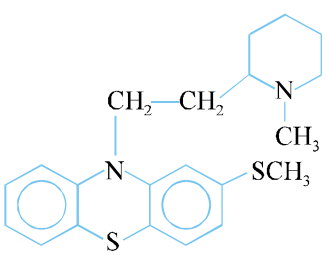


It is prepared by refluxing a toluene solution of 2-chloro-10-(3-chloro-propyl) phenothiazine with 1-piperazineethanol in the presence of sodamide.

It is used for the mangement and treatment of neuroses.

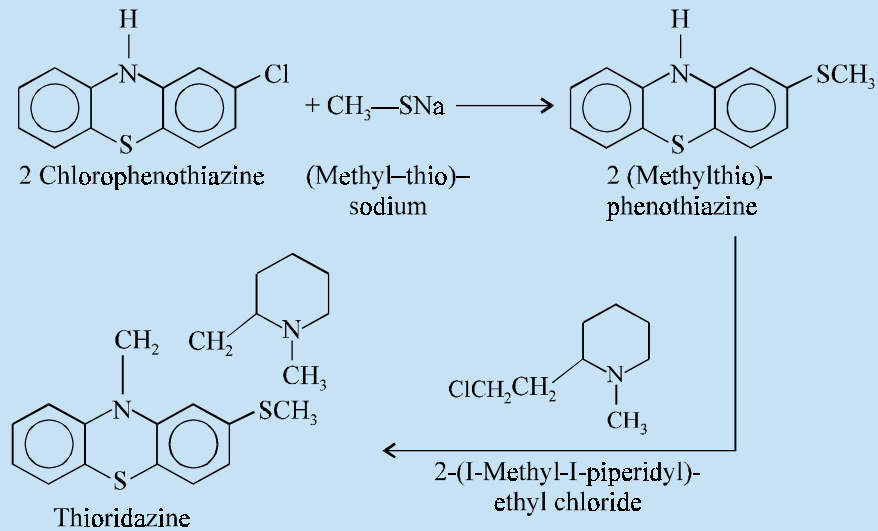
Dose. *Usual, oral, nonhospitalized patients, 2 to 8 mg thrice daily ; hospitalized patients, 8 to 16 mg 2 to 4 times a day ; im, 5 to 10 mg initially, followed by 5 mg in 6 hours.*

C. *Thioridazine* INN, BAN, USAN,



10[2-Methyl-2-piperidyl) ethyl]-2-(methylthio)-phenothiazine ; BP (1973) ; USP ; Mellaril$^{(R)}$ (Sandoz) ;

Synthesis



It is prepared in two steps. First step being the preparation of 2-(methylthio) phenothiazine by the interaction of 2-chlorophenothiazine with (methyl-thio) sodium. The second step involves the condensation of the resulting product with 2-(1-methyl-1-piperidyl) ethyl chloride to obtain the official compound.

Its actions and uses are very much identical to those of **chlorpromazine** discussed earlier.

Dose. *Usual, initial, for psychoses : 50 to 100 mg 3 times daily ; for nonpsychotic emotional disturbances for instance tension and anxiety : 30 to 200 mg per day ; for children having behavioural disorders : 1 mg per kg body weight per day in divided doses.*

2.4.1. Mecha]nism of Action

The mechanism of action of drugs described under Section 2.4 shall now be dealt with as below :

2.4.1.1. Chlorpromazine Hydrochloride

The '**drug**' shows its effectiveness for the control and management of symptoms associated with mild alcohol withdrawl, moderate to acute agitation, and observed hyperactivity or apparent aggressiveness particularly in mentally disturbed children by exerting its action on the CNS.

The '**drug**' shows volume of distribution (v_d^{ss}) after a single oral administration to be 80.6 L kg^{-1}, whereas a reduction to 21.8 L kg^{-1} (upto 25%) *via* IM administration. Hence, the 4-fold difference actually reflects directly upon the low availability *via* the oral route (32%). Almost 100 metabolites of chlorpromazine (CPZ) in humans are known, of which only two are found to be **active** in humans, namely : (*i*) **11-hydroxy CPZ** ; and (*ii*) **17-hydroxy-CPZ**.

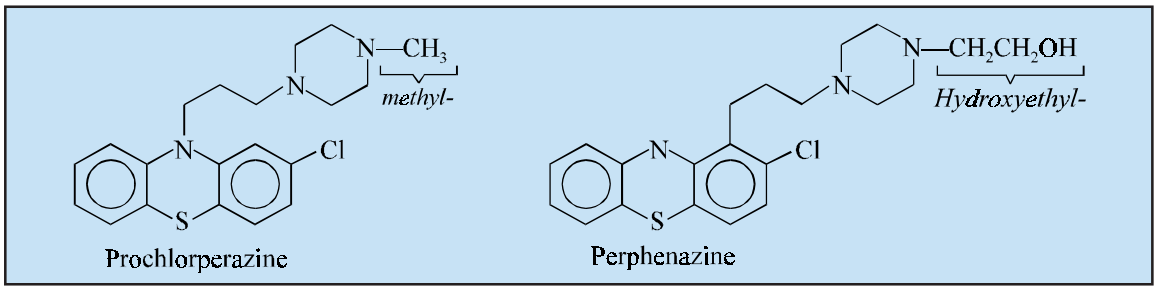
The effective plasma concentration of **CPZ** specifically in severe schizophrenic subjects have been demonstrated to vary from 30—300 ng. mL^{-1}, and plasma levels from 750-1000 ng. mL^{-1}.

CAUTION. Levarterenol and phenylephrine are employed invariably for the control and management of hypotension.

2.4.1.2. Perphenazine

The '**drug**' exerts its action very much similar to the one described under chlorpromazine (Section 2.4.1.1).

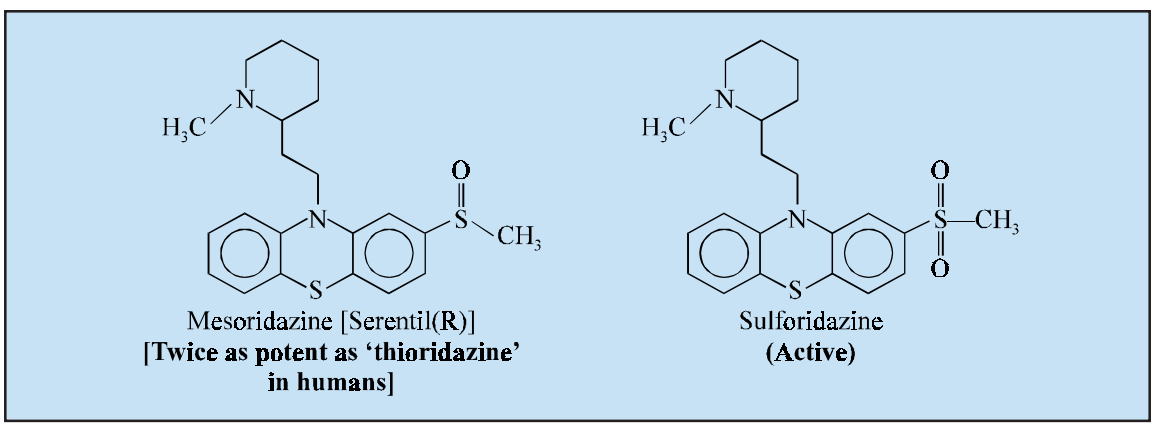
SAR of Perphenazine. It differs chemically from **prochlorperazine** only with respect to the substitution of a hydroxyethyl (—C_2H_5OH) moiety for the methyl moiety of the latter drug as shown below :



2.4.1.3. Thioridazine Hydrochloride

The '**drug**' exerts its bear minimum antimetic activity and thereby gives rise to minimal **extrapyramidal stimulation (EPS)**. Drowsiness and sedation are predominantly less intense in this '**drug**' in comparison to either **CPZ** and other similar drug substances.

The half-life seems to be particularly to a *multiphasic status i.e.*, having an *early phase* ranging between 26-36 hours ; and a definitive *late phase* varying between 26-36 hours. The '**drug**' gets bound to plasma protein to the extent of 96-99%. Importantly, **thioridazine** gets sulfoxidized *in vivo* into the metabolities **mesoridazine** plus a small quantum of **sulforidazine,** both of which are **active** pharmacologically.

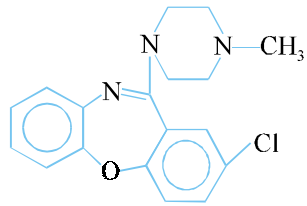


2.5. Dibenzazepines

Dibenzazepine analogous constitute another category of antisychotics which have gained recognition in late sixties.

A few important member of this class are described here, namely ; **Loxapine** ; **Clozapine** ;

A. *Loxapine* BAN, USAN, INN,



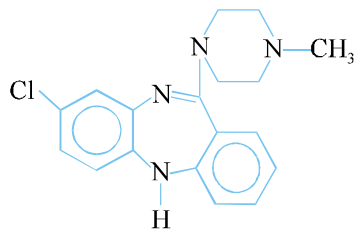
Dibenz [b, f][1, 4] oxazepine, 2-chloro-11-(4-methyl-1-piperazinyl)-;

Loxitane(R) (Lederle) ;

Its antipsychotic actions are similar to those of **chlopromazine**.

Dose. *Usual, oral, for psychoses : 20 to 50 mg per day initially, split in 2 to 4 divided doses.*

B. *Clozapine* INN, BAN, USAN,



5 H-Dibenzo [*b, e*][1, 4] diazepine, 8-chloro-11-(4-methyl-1-piperazinyl)-;

Clozaril(R) (Sandoz) ;

It is a **dibenzodiazepine derivative**. It is an unusual antipsychotic agent which hardly produces any extrapyramidal symptoms. It possesses the ability to suppress symptoms of tardive dyskinesia.

2.5.1. Mechansim of Action

The mechanism of action of **loxapine** and **clozapine** shall now be described as under :

2.5.1.1. Loxapine Succinate

The exact mechanism of action of this '**drug**' is not yet established. It has been observed that the absorption soonafter oral administration is almost complete. Furthermore, the '**drug**' after distribution to tissues invariably gets metabolized and subsequently excreted *via* urine and faeces, largely in the first 24 hours. By virtue of the fact that it may give rise to possible **anticholinergic activity,** it must be employed with great caution in such patients who have either a history of *glaucoma* or *urinary retention* problems.

2.5.1.2. Clozapine

The '**drug**' is found to very effective and relatively rapid-acting in the treatment of schizophrenia perhaps due to several of its CNS effects that essentially differ from a host of other members of antipsychotics. It is also believed beyond any reasonable doubt that the antipsychotic actions of this '**drug**' are basically of more complex nature in comparison to other antipsychotic drugs. In addition to the above observations the '**drug**' specifically blocks **dopamine** D-2 and 0-1 receptors essentially in the *mesolimbic** and *mesocortical brain regions*, which may also involve covertly and overtly **cholinergic**, **seretonergic** and **noradrenergic** systems.

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* Medium sized border of a part.

Contrary to the usual activity of antipsychotics, **clozapine** exhibits *regional specific anti-dopaminergic profile* having, relatively mild antagonism on the extrapyramidal dopaminergic action ; and this could be responsible for its low prepensity to produce extrapyramidal side effects *e.g.*, dystonias, tardive dyskinesia.* It also causes greater blockade of dopamine D-1 receptors ; and however, it is not yet established whether such action precisely contributes to its antipsychotic therapeutic activity.

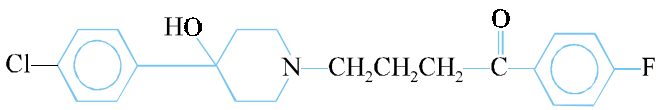
Clozapine gets absorbed rapidly from the GI tract and extensively metabolized during the first pass through the liver. The peak plasma levels usually take place in about 1.5 hour after a single oral dosage. It has been observed that there exists a **sixfold interindividual variability** in steady state plsma concenrations in subjects administered with high dosage regimen of this **'drug'**. The **'drug'** and its metabolites are excreted mostly in the urine.

2.6. Butyrophenones

Janssen and coworkers synthesized a number of **butyrophenones** having antipsychotic potency similar to **chlorpromazine** :

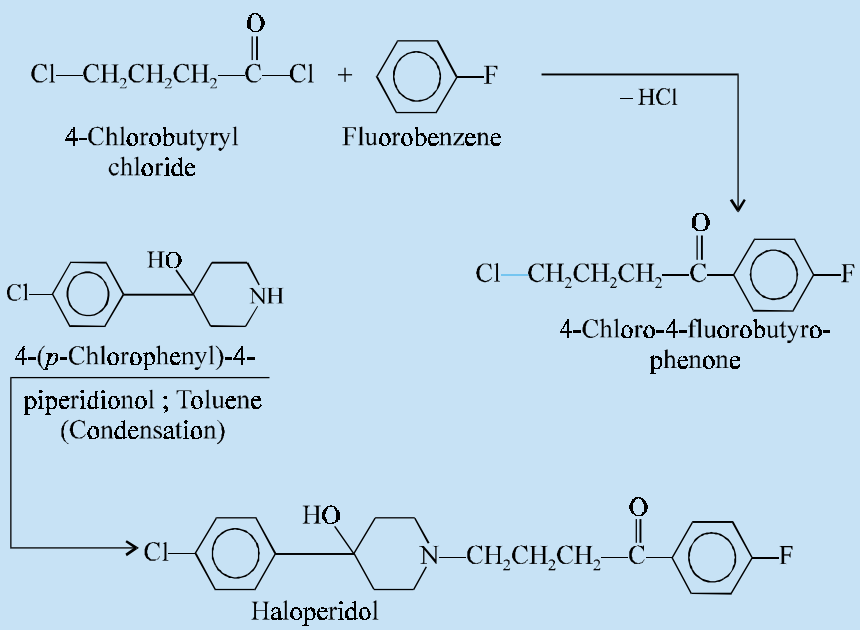
Examples : Haloperidol ; **Droperidol** ;

A. *Haloperidol* INN, BAN, USAN,



4-[4-(*p*-Chlorophenyl)-4-hudroxypiperidino]-4′-fluorobutyrophenone ; BP (1973) ; USP ; Haldol(R) (McNeil) ; Aloperidin(R) (Janssen) ; Serenace(R) (Searle) ;

Synthesis



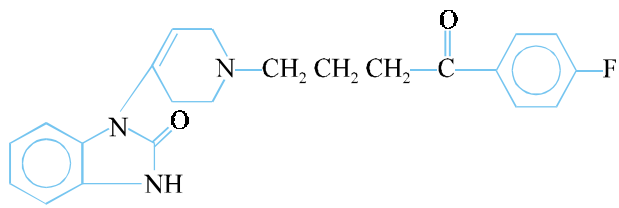
*A condition of slow, rhythmical, automatic sterotyped movements, either generalized or in single muscle groups. These occur as an undesired effect of therapy with **phenothiazine**s (psychotropic drugs).

4-Chloro-4′-fluorobutyrophenone is first prepared by the **Friedel-Craft's reaction** between 4-chlorobutyl chloride and fluorobenzene which is subsequently condensed with 4-(*p*-chloro-phenyl)-4-piperidinol in toluene to give the official compound.

It is useful in the treatment of anxiety, tension, moderate to severe agitation, hostility, and hyperactivity. It also finds its usefulness in schizophrenia, psychotic reactions related to organic brain syndromes and in *Gilles de la Tourette's disease* (unusual barking).

Dose. *Usual, adult, oral, 0.5 to 5 mg 2 or 3 times daily ; Intramuscular, 3 to 5 mg ;*

B. *Droperidol* INN, BAN, USAN,



1-[1-[3-(*p*-Fluorobenzoyl) propyl]-1,2,3,6-tetrahydro-4-pyridyl]-2-benzimidazolinone ; USP ;

Inapsine$^{(R)}$ (Janssen) ;

It is employed for the control of agitated patients in acute psychoses. It is normally used in conjunction with an analgesic for instance fantanyl citrate or phenoperidine hydrochloride to maintain the patient in a state of neuroleptanalgesia whereby he is calm and indifferent to his surroundings and able to cooperate with the surgeon.

Dose. *Premeditation : iv or im, 2.5 to 10 mg 30 to 60 minute before induction ; Induction : usual, IV, 2.5 mg per 20 to 25 lb. ; maintenance : usual, IV : 1.25 to 2.5 mg.*

2.6.1. Mechanism of Action

The mechanism of action of the medicinal compounds discussed under Section 2.6 shall now be treated individually in the sections that follows :

2.6.1.1. Haloperidol

The '**drug**' exhibits its activity by calming down excessive motor activity quite prevalent in '*hyperactive children*' having conduct disorders, such as : aggressivity, mood lability, impulsivity, poor frustration tolerance, and difficulty in sustaining attention.

Haloperidol shows bioavailability extending upto almost 60% *via* oral administration. Interestingly, its elimination half-life *via* oral route varies between 12-38 hours, which eventually gets lowered between 10-19 hours after IV administration. The usual therapeutic plasma concentrations ranges between 3-10 ng mL^{-1}.

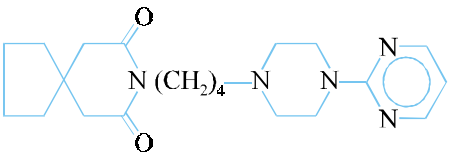
2.6.1.2. Droperidol

The '**drug**' exhibits relatively low therapeutic potency, medium extrapyradimal toxicity, high sedative effect, and above all high hypotensive action. However, it is most frequently employed in the form of its combination [**Innovar$^{(R)}$**] along with the narcotic agent **fentanyl** [**Sublimaze$^{(R)}$**] preanaesthetically.

2.7. Azaspirodecanediones

Azaspirodecanediones have gained prominence as antipsychotic agents recently. In mid-eighties a member of this family, namely, **buspirone** was introduced in the United States and is discussed here.

A. *Buspirone* INN, BAN ; *Buspirone Hydrochloride* USAN,



8-Azaspiro [4, 5] decane-7, 9-dione, 8-4-[4-(pyramidinyl)-1-piperazinyl]butyl]-;

Buspar$^{(R)}$ (Mead Johnson) ;

It is found to be useful in the treatment of anxiety and its effectiveness is fairly comparable to that of **diazepam**. It alleviates anxiety without producing sedation or functional impairment. It neither promotes abuse nor physical dependence.

2.7.1. Mechanism of Action

The mechanism of action of **buspirone hydrochloride** will be discussed as under :

2.7.1.1. Buspirone Hydrochloride

The exact mechanism of its anxiolytic effect has not yet been established ; but however, seems to be altogether different in comparison to the **barbiturates** and the **benzodiazepines.** Most probably the '**drug**' essentially involves *multiple transmitter systems,* specifically those of the first-pass metabolism.

Buspirone attains peak plasma concentrations ranging between 1-6 mg mL^{-1}, usually take place within a span of 40-90 minutes. The '**drug**' gets bound to plasma protein to nearly 95% ; and excretion through urine varies between 29-63%, while through faeces between 18-38%. The elimination half-life of the unchanged drug is approximately between 2-3 hours.

Probable Questions for B. Pharm. Examinations

1. What are **'antipsychotics'** ? Classify them by giving examples of **one** potent compound from each category.
2. (*a*) Name the **two** major alkaloids isolated from the roots of *Rauwolfia serpentina* ued as **'antipsychotics'.**

   (*b*) Give their structure, chemical name and uses.

   (*c*) Discuss the synthesis of 3-diethylamino propyl ester of 3,4,5-trimethoxy benzoic acid given by Miller and Weinberg.

   (*d*) What is the relative potency of compound in (*c*) and that of Reserpine ?
3. Discuss the synthesis of the following **diphenylmethane analogues** as 'antipsychotics' :

   (*a*) Benactyzine

   (*b*) Captodiame
4. How would you synthesize **Perphenazine** and **Thioridazine** belonging to the phenothiazine group of **'antipsychotics'** ?

5. Describe **dibenzazepines** as potent 'antipsychotics'. Give the structure, chemical name and uses of **two** such drugs.
6. (*a*) Give the structure, chemical name of the following :
   (*i*) Haloperidol
   (*ii*) Droperidol.
   (*b*) Discuss the synthesis of any **one** drug.
7. Elaborate the 'mode of action' of the following **'antipsychotics'** :
   (*a*) Reserpine
   (*b*) Chlorpromazine and Perphenazine.
   (*c*) Loxapine
   (*d*) Haloperidol
   (*e*) Buspirone.
8. Give a comprehensive account of **'antipsychotics'.** Support your answer with the most potent drugs by providing structures, chemical names and uses adequately.

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29

Antiviral Drugs

Chapter

29 Antiviral Drugs

1. INTRODUCTION

Viruses are obligate parasites having the operational characteristics of an exogenous submicroscopic unit capable of multiplication only inside specific cells.

The size range is considerable, ranging from an approximate diameter of 200 micrometers (μm) vaccinia down to 10 (μm) for foot and mouth disease. They can be seen and identified-only with the aid of an electron microscope.

In general, viruses are essentially made up of a nucleic acid core having either **deoxyribonucleic acid (DNA)** or **ribonucleic acid (RNA)** that provides the genetic material and also forms the basis for classification of viruses.

The viruses may be conceived as particles attaching themselves to particular '**receptors**' of the succeptible cells. These receptors may be chemical configurations that combine with either viruses or allied substances of similar composition. After due attachment the viruses gain entry into the cell and subsequently multiply. Thus the newly constituted viruses are eventually realised from the cell to *paraciticize other cells of the host.* In such transformation the metabolic activity of the host cell is modified in some manner.

A number of diseases are caused by different types of viruses which are enumerated briefly as under :

S.No.	Species	Indications
1	**Herpes simplex (virus types 1 & 2)**	Eye infections, skin diseases, encephalitis and genital infections
2	**Influenza A, B & C viruses**	Influenza A, B and C
3	**Rabies viruses**	Rabies, encephalitis
4	**Enteroviruses (polio, Coxsackle A, B echovirus)**	Poliomyelitis
5	**Parainfluenza virus**	Parainfluenza
6	**Variola, Vaccinia**	Smallpox (variola), Cowpx (vaccinia)
7	**Variclla-zoster**	Variclla (zoster), herpes zoster (shingles)
8	**Rhiniviruses**	Respiratory diseases

1.1. Replication and Transformation

Viruses, in general, utilize only the **enzyme-system of the host-cell** for two purposes, namely : *first*, to synthesize DNA ; and *secondly*, to replicate virus, thereby enabling it to perform their usual metabolic activities. They may carry out either the transformation or the replication processes of the cell at the same time. By virtue of the fact that viruses are **obligate intracellular parasites,** therefore, their replication phenomenon solely depends on the *host's cellular processes*.

2. CLASSIFICATION

Antiviral drugs are broadly classified on the basis of their **specific mode of action** as stated below :

(*a*) Substances that inhibit early stages of viral replication

(*b*) Substances that interfere with viral nucleic acid replication

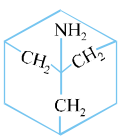
(*c*) Substances that affect translation on cell ribosomes

2.1. Substances That Inhibit Early Stages of Viral Replication

A number of **antiviral drugs** that block particular **viruscoded enzymes** produced in the host cells which are vitally required for viral replication have been included in the therapeutic armamentarium for the treatment of viral infections.

Examples : Amantadine hydrochloride ; **Interferon** ;

A. *Amantidine Hydrochloride* USAN ; *Amantadinum* BAN ;

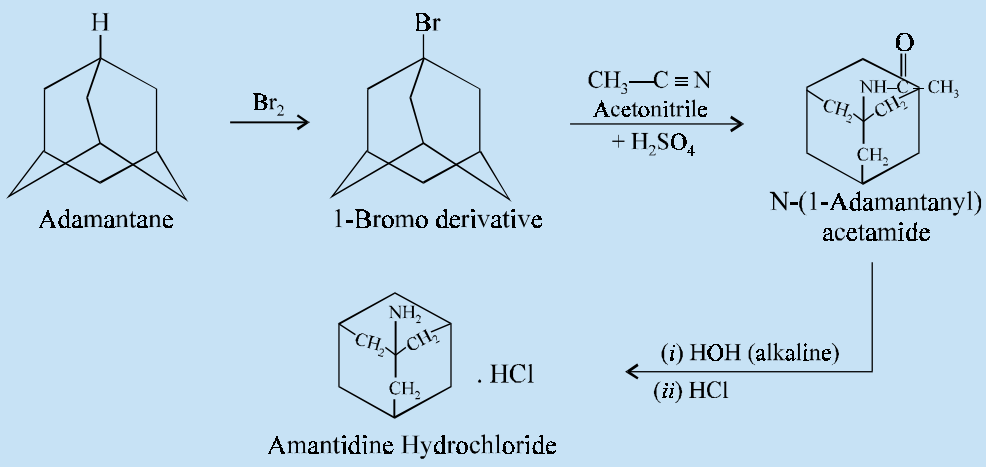


. HCl

1-Admantanamine hydrochloride ; Amantidine Hydrochloride USP ;

Symmetrel(R) (Geigy) ;

Synthesis



It is prepared by brominating adamantane and treating the resulting bromo derivative with acetonitrile in the presence of sulphuric acid to obtain N-(1-adamantanyl) acetamide. This on alkaline hydrolysis and treatment with hydrochloric acid affords the official compound.

It is useful only as *prophylactic against A_2 influenza virus* (*Asian Flu*). It broadly prevents the entry of certain viruses into the cell.

Dose. *Usual, 100 mg twice daily ; For children, 1 to 9 years of age, 4-9 mg/kg and 9 to 12 years of age 100 mg twice daily.*

B. *Interferon* α-2B :

Intron(R) (Parke-Davis) ; Wellferon(R) (Burroughs Wellcome) ;

Though '**interferon**' was first reported in 1957 by Issacs and Lindenmann but it was recognized as an **antiviral drug** in 1980.

It is the protein formed by the intersection of animal cells with viruses capable of conferring on animal cells resistance to virus infection.

In general, **interferons** are made up of a mixture of relatively small proteins with molecular weights varying from 20,000 to 1,60,000. These are basically glycoproteins that display specific antiviral properties with species-related characteristics. So far three different categories of **interferons** have been isolated, characterized and studied in an elaborated manner :

These are namely :

(*a*) Alpha (α)–secreted by human leukocytes

(*b*) Beta (β)-secreted by human fibroblasts

(*c*) Gamm (γ)-secreted by lymphoid cells

It is broadly employed for the treatment of herpes zoster, herpetic–keratitis, herpes genitalis, chronic hepatitis, common cold and influenza. It also finds its usefulness in lung carcinoma, breast cancer, multiple myclomas. It is also recommended as a prophylactic agent in cytomegalovirus infection in renal transplant patients.

2.1.1. Mechanism of Action

The mechanism of action of the various medicinal compounds discussed under Section 2.1 shall be treated separately below :

2.1.1.1. Amantidine Hydrochloride

The '**drug**' is a narrow-spectrum antiviral active against almost all influenzae. A virus strains, certain C virus strains ; however, not found effective against B strains. It has been observed that the peripheral and central effects of the anticholinergic drugs are enhanced by concomitant use of **amantidine**.

The '**drug**' fails to undergo metabolism and almost a major portion (90%) is practically excreted unchanged in the urine. The half-life is nearly 20 hours. It attains levels in the cerebral spinal fluid (CSF) to the extent of 60% of the plasma concentration.

2.1.1.2. Interferon α-2B

The '**drug**' belongs to a family of proteins ranging between 15,000–27,000 (MW) which are found to be secreted by the lymphocytes in response to acute viral infections. It has been observed that they invariably get bound to cellular proetins. In this way, they actually exert a plethora of effects that

may essentially include induction of certain enzymes, for instance : **2, 5A synthetase,** which particularly inhibits viral replication and inhibition of cell proliferation. Besides, they augment **immune-regulating activity** which includes expression of **HLA-major histocompatibility antigens** that ultimately turn out to be the targets of **cytotoxic T lymphocytes**.

The peak-serum level is attainable within 3–12 hour after injection. The elimination half-life ranges between 2–3 hours, and serum levels are undetectable after 16 hours. It is found that the hepatitis C replication rates are in the trillious a day, having viral half-life of nearly 5 hours. Therefore, there exists a predominant inherent mismatch between pharmacokinetic and pharmacodynamic characteristic features which ultimately ends up in enhancing the prevailing **replication rate of the virus above the baseline.**

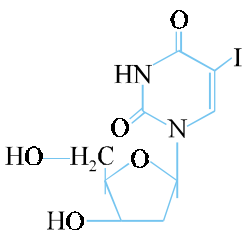
Note. More recently interferons may also be indicated for antiinflammatory, antifibrinogenic, and antineoplastic conditions.

2.2. Substances That Interfere With Viral Nucleic Acid Replication

A good number of **antiviral drugs** exert their effect against DNA viruses either by interfering with their replication due to its similarity of structure to the nucleotide structures in natural DNA virus or by interfering with the nucleic acid replication of the virus, specifically inhibiting the early steps in DNA synthesis.

A few important compounds shall be discussed here, namely : **Idoxuridine**, **Acyclovir**, **Vidarabine**, **Ribavirin**.

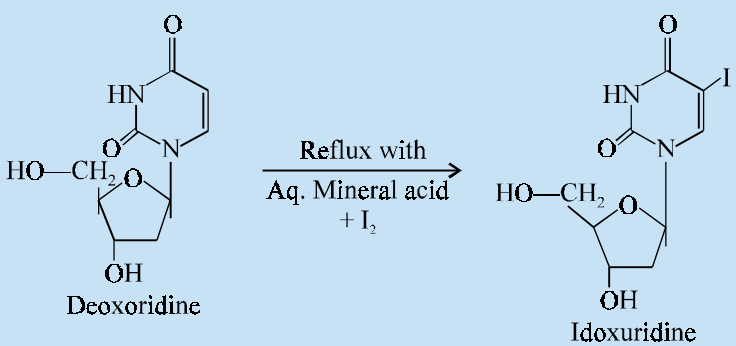
A. *Idoxuridine* INN, BAN, USAN,



2-Deoxy-5-iodouridine ; BP ; USP ;

Stoxil(R) (Smith, Kline & French) ; Herplex Liquifilm(R) (Allergan) ;

Synthesis

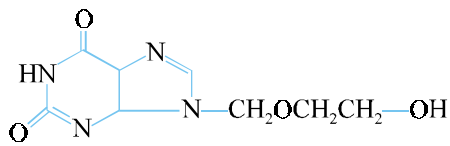


It is prepared by refluxing a solution of **deoxuridine** in aqueous mineral acid in the presence of iodine.

It is an **antimetabolite of thymidine ;** and, therefore, may be incorporated into deoxyribonucleic acid in place of thymidine, thus interfering with usual nuclear metabolism. It is solely employed for the topical therapy of *herpes simplex keratitis* of the eye. It has also been administered intravenously for the treatment of herpetic encephalitis.

Dose. *Topical, as a 0.5% ointment 4 to 16 times a day, or 0.1 ml of a 0.1% solution every 1 to 2 hours, to the conjunctiva.*

B. *Acyclovir* USAN ; *Aciclovir* INN ;



6H-Purin-6-one, 2-amino-1, 9 dihydro-9-[2-hydroxyethoy)-methyl]– ;

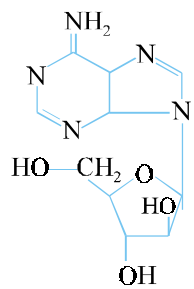
Zovirax(R) (Burroughs Wellcome) ;

It is used for the treatment of cold sore caused by labial herpes, herpes simplex virus Type I and Type II responsible for genital herpes. It also affects the isolated of EB viruses and varicella-zoster significantly.

Herpetic keratitis and herpes genitalis are treated effectively by using an ointment containing 5% acyclovir.

Dose. *For herpes virus infections in immunosupressed patients : up to 10 mg per kg body–weight every 8 hours.*

C. *Vidarabine* BAN, USAN,



β-D-Arabinofurannosyl-9-adenine ; USP ;

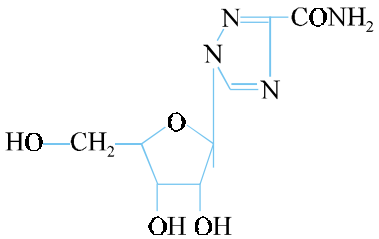
Vira-A(R) (Parke–Davis) ;

It is specifically employed for the treatment of herpes simplex virus infections belonging to Types 1 and 2 encephalitis.

It is also found to be beneficial both in varicella-zoster infections and neonatal herpes.

Dose. *For encephalitis due to herpes simplex : 15 mg per kg body–weight per day for 10 days ; which is infused at a constant rate over a period of 12 to 24 hours.*

D. *Ribavirin* INN, USAN ; *Trivabirin* BAN ;



1-β-D-Ribofuranosyl-1H-1, 2, 4-triazole-3-carboxamide ;

Virazole$^{(R)}$ (ICN) ;

It possesses broad–spectrum antiviral activity against both DNA and RNA viruses. It exerts its maximum activity against influenza A and B and the parainfluenza group of measles, hepatitis and viruses. It is also reported to inhibit *in vitro* replication of HTLV-III, which is concerned with AIDS.

Dose. *For viral hepatitis, influenza and herpes virus infections : upto 1 g per day in divided doses.*

2.2.1. Mechanism of Action

The mechanism of action of various drugs described under Section 2.2 shall be dealt with separately as follows :

2.2.1.1. Idoxuridine

The '**drug**' is a **nucleic acid synthesis inhibitor**, which specifically acts as an antiviral agent against **DNA viruses** by the aid of its direct interference with their replication phenomenon given their similarity of structure. As a first and foremost step the '**drug**' undergoes phosphorylation largely by the host cell **virus-encoded enzyme thymidine kinase** into an active triphosphate form. Consequently, kinase the phosphorylated drug entity is found to inhibit **cellular DNA polymerase** surprisingly to a much lower extent in comparison to **HSV-DNA polymerase,** that is required as an absolute necessity for the ultimate synthesis of DNA. Subsequently, the triphosphate form of the drug is appropriately introduced in the course of viral nucleic acid synthesis aided by an altogether **false pairing system** which critically replaces thymidine. The overall net outcome upon *transcription* is the generation of faulty viral proteins which finally give rise to **'defective viral particles'.***

2.2.1.2. Acyclovir

In this particular instance the '**drug**' aid inside an infected cell to get converted into a '**triphosphate**', which is subsequently incorporated directly into DNA. In fact, this phenomenon terminates elongation of the DNA, and thereby prevents viral replication mechanism significantly. It fails to eradicate latent herpes. It is observed to be unpredictable to a certain extent as a '**topical prophylactic agent**' against particularly the recurrent infections caused by **HSV–1** and **HSV–2**.

The '**drug**' gets bound to protein in plasma between 9–33%. The drug is usually excreted through urine either by oral IV administration between a range of 62–91% and 9–20% respectively. The normal usual half-life is about 2.5 hours which may get extended upto 19.5 hours in patient having renal failure.

*Farah A *et al.* (eds) : **Handbook of Experimental Biology**, Vol. : 38(2), Springer–Berlin, pp : 272–347, 1975.

2.2.1.3. Vidarabine

The '**drug**' gets converted by the help of cellular enzymes into corresponding mono-, di-, and tri-phosphate structural analogues which strategically interfere with viral nucleic acid replication phenomenon, particularly jeopordizing the very preliminary steps involved in DNA–synthesis. It has been observed that the antiviral effect is, in certain instances, proved to be much superior to that of **idoxuridine** and **cytarabine**.

Vidarabine is deaminated quite rapidly by the enzyme **adenine deaminase** that is usually found in serum and RBC. Interestingly, this enzyme helps in the conversion of this '**drug**', into its principal metabolite termed as **arabinosyl hypoxanthine (ara–HX)**, which displays weak **antiviral activity**.*

2.2.1.4. Ribavirin

The '**drug**' is duly converted to metabolites which critically cause inhibition of the 5′ capping of viral *m*RNA ; so that finally the viral protein synthesis of both DNA and RNA viruses are affected directly and significantly. The **triphosphate** is believed to be the **active metabolite** that is formed invariably in lung and liver than in other tissues. Perhaps that could be a plausible explanation for its optimal activity against infections in these organs specifically. It fails to pass the blood-brain barrier (BBB). It has been found that the '**drug**' and its known metabolites are duly excreted in the urine upto 50% and faeces upto 15%. The plasma half-life stands at 9.5 hours, whereas the plasma half-life in erythrocytes is approximately 40 days.

Ribavirin specifically inhibits *in vitro* replication of **HIV-1**, which is essentially involved in AIDS.

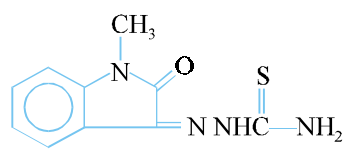
Note. Interestingly, till date viral strains susceptible to ribavirin have not been found which may develop drug resistance, as could be observed with other antiviral agents, *e.g.*, acyclovir, idoxuridine, and bromovinyldeoxy uridine (BVDU).

2.3. Substances That Affect Translation on Cell Ribosomes

There are a few specific compounds that directly interfere with the translation of RNA message into protein synthesis on the cell ribosome thereby resulting a defect in protein inclusion into the virus. In short, virus DNA gets enhanced host-cells are mutilated and ultimately infectious virus is not generated.

Examples : Methisazone ; **Arildone** ;

A. *Methisazone* USAN ; *Metisazone* INN ;

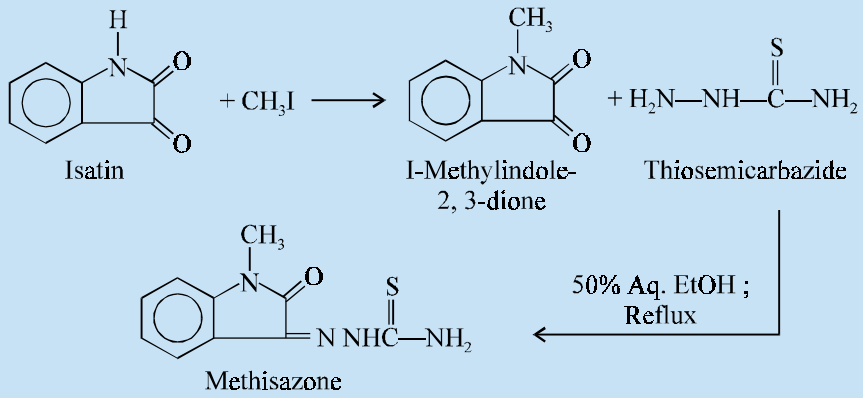


1-Methyl-indole-2, 3-dione-3-(thiosemicarbazone) ;

Marboran(R) (Burroughs Wellcome) ;

*Chao DL and AP Kimbali, *Cancer Res.*, **32**, 1721 (1972).

Synthesis

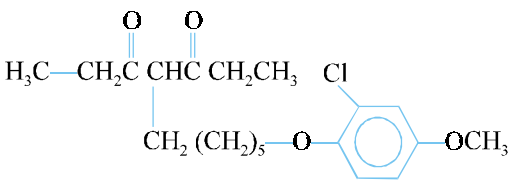


1-Methylindole-2, 3-dione is first prepared by reacting isatin with methyl iodide, which is then treated with thiosemicarbazide in 50% aqueous ethanol and refluxed for several hours to obtain **methisazone**.

It possesses prophylactic value against smallpox and alastrim. In conjunction with gamma globulin it shows its usefulness against eczema vaccinatum and vaccinia gangrenosa.

Dose. *Oral, 1.5 to 3.0 g twice daily for 4 days ; as a prophylactic against smallpox-it should be administered before the 8th or 9th day of the 12-day incubation period.*

B. *Arildone* INN, USAN ;



4-[6-(Chloro-4-methoxyphenoxy) hexyl]-3, 5-heptanedione ;

Win 38020(R) (Winthrop) ;

It is found to be useful against both DNA and RNA viruses, for instance herpes virus, parainfluenza virus and respiratory *syncytial viruses**. It is also used as a prophylactic in renal transport patients and to minimise herpes simplex virus infections.

2.3.1. Mechanism of Action

The mechanism of action of the medicinal compounds discussed under Section 2.3 shall be treated individually in the sections that follows :

2.3.1.1. Methisazone

The '**drug**' once enjoyed the fame of being used as a prophylaxis for smallpox.

2.3.1.2. Arildone

The '**drug**' has been demonstrated to be exerting practically little effect when applied topically in the control, management and treatment of genital herpes.

*Viruses of the nature of a synctium *i.e.*, a multinucleated mass of protoplasm such as a striated muscle fiber.

Probable Questions for B. Pharm. Examinations

1. (*a*) Give brief account of viruses.

(*b*) What are the various diseases caused by different types of viruses ?

(*c*) Replication and transformation in viruses.

2. Classify the **'antiviral drugs'** on the basis of their **mode of action.** Give the structure, chemical name and uses of at least **one** potent drug from each category.

3. How would you synthesize the following :

(*a*) Amantadine hydrochloride

(*b*) Methisazone.

4. **Interferon** was recognized as an **'antiviral drug'** in 1980. Discuss its merits.

5. Give the names of **three** important drugs that specifically interfere with *viral nucleic acid replication.* Discuss the synthesis of **one** such drug selected by you.

6. Give the structure, chemical name and uses of two important **'antiviral drugs'** that affect translation on cell ribosomes. Discuss the synthesis of any **one** drug.

7. Discuss the following in details :

(*a*) Important **'antiviral drugs'**.

(*b*) Mode of action of **'antiviral drugs'.**

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30

Newer Drugs for Newer Diseases

Chapter

30

Newer Drugs for Newer Disease

1. INTRODUCTION

The quest for **'better medicines for a better world'** is indeed an eternal process world wide to help the suffering mankind from dreadful and fatal ailments. The accelerated growth and spectacular advancement of science and research specifically during the past three decades, has not only contributed some really **'wonder drugs'** to the therapeutic armamentarium, but also paved the way for their availability internationally through approved and recognised government agencies.

The history of medicine reveals that some of the most potent compounds were made known to the world by the traditional healers and herbal practitioners belonging to Ancient Greek, Rome, China, Egypt, Tibet, India and Africa. The guardians of these ancient system of medicines made use of the medicinal plants, herbs and shrubs available locally to treat a variety of diseases ranging from mild fever to acute mental disorders. With the passage of time, such age–old but classical treatment started gaining popularity even outside the countries of origin by virtue of their startling therapeutic efficacy.

The advent of modern sophisticated technological techniques have helped the scientists of various disciplines to isolate, purify and characterize the medicinally active constituents present in a vast number of medicinal plants all over the world. Aside, scientists in the research laboratories have successfully synthesized tailor–made–biologically active prototype compounds possessing better therapeutic effects, lesser toxicity and fewer side effects. Scientific knowledge, thus generated, were skillfully communicated across the globe through scientific literatures, research journals and internet so that positive contributions might prove beneficial in a particular specialized field of interest.

In short, such scientific oriented investigations though may not help in the establishment of potent remedies from plant sources, yet the expository information of the various components along with the physical and chemical characteristics profusely stimulate ingenous ventures.

2. NEWER DRUGS

A host of **newer drugs** both from the natural origins and synthetic routes have been isolated/ synthesized, purified, characterized and schematically evaluated for various biological responses.

A number of **newer drugs** that have been found to be useful for the treatment of newer diseases are discussed here briefly :

(*i*) Prostaglandins and other Eicosanoids

(*ii*) Antilipedemic Drugs

(*iii*) Hormone Antagonists

(*iv*) Antimycobacterial Drugs

(*v*) Antithyroid Drugs

(*vi*) Cardiac Steroids and Related Inotropic Drugs

(*vii*) Heparin

(*viii*) Radiosensitizer

(*ix*) Cromakalim

(*x*) Drugs to Combat AIDS

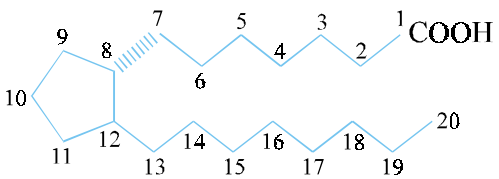
2.1. Proistaglandins and other Eicosanoids

Earlier observation that human seminal fluid exerts direct muscle contractions of uterine tissues was thought to be caused by an acidic vasoactive substance produced in the prostate gland, that was subsequently named as **prostaglandin** (referred to as **PG**). It was revealed later on that the acidic substance contained a number of structurally similar prostaglandin products.

Prostaglandins (IGA through PGF) are a group of **cyclopentane derivatives** formed from 20-carbon polyunsaturated fatty acids. They exert a good number of physiologic properties. They are usually termed as **"local hormones"** because of the *two* cardinal facts, namely : *first*, they influence biologic processes near their point of release ; and *secondly*, they display mechanisms for their inactivation near the locus of release.

2.1.1. Nomenclature

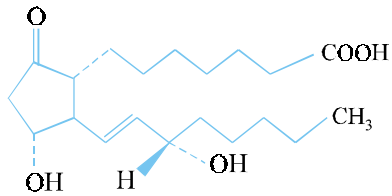
Prostaglandin (PG) is based on the following hypothetical compound **prostanoic acid :**



A-type compounds	:	α, β-unsaturated ketones ;
E-type compounds	:	β-hydroxyketones with *keto* moiety at C-9 and an α-OH at C-11 ;
F-type compounds	:	1, 3-diols ;
α-designation	:	Having stereochemistry of the OH at C-9, below ; and, therefore ; on the same side (*cis*) of the cyclopentane ring as the OH at C-11 ;
PGF_2	:	PG of F series (containing 2 ring OH functions) having the OH at C-9 in the α-configuration and 2 double-bonds at C-5 and C-13,
$PG1_2$	:	Contains a furan ring (consisting of C-6 and C-7 from the side chain and the C-9 α-oxygen) fused to the cyclopentane ring.
TXA_2	:	Origin from thrombocytes containing thromboxane A_2.
LTC_4	:	Origin from leukocytes containing leukotriene C_4.

A few typical examples are described below, namely : **Aloprostadil** ; **Epo-prostenol** ; and **Misoprotol** ;

A. *Alprostadil* INN, BAN, USAN,



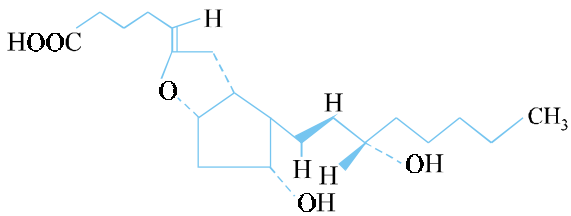
Prost-13-en-1-oic acid, 11, 15-dihydroxy-9-oxo, -(11α, 13E, 15S)- ; Prostaglandin E_1 ; PGE_1 ; Prostaglandin E_1 USP ;

Prostin VR(R) (Upjohn) ;

It is employed temporarily to maintain potency of the *ductus arteriosus* in the management of congenital heart disease. It also finds its usefulness in peripheral vascular disease.

Dose : *For congenital heart disease : by IV drip starting with doses of 100 nanograms per kg body weight per minute.*

B. *Epoprostenol* INN, BAN ; *Epoprostenol Sodium* USAN ;



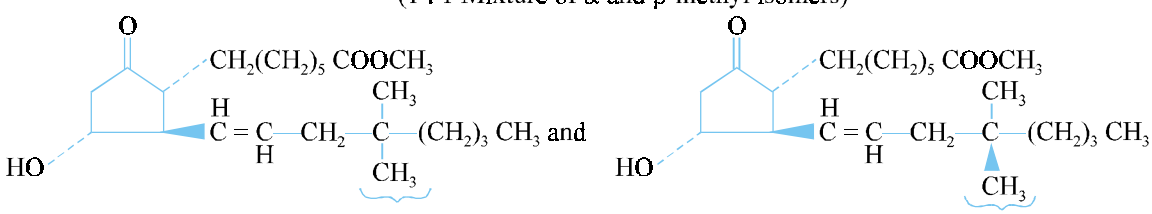
Prosta-5, 13-dien-1-oic acid, 6, 9-epoxy-11, 15-dihydroxy-, (5z, 9α, 11α, 13E, 15S)- ; PGI_2 ; PGX ; Prostacyclin ; Prostaglandin I_2 ; Prostaglandin X ;

Cyclo-Prostin(R) (Upjohn) ;

It has been employed as an anticoagulant in dialysis procedures. It has also been used in pre-eclampsia, and in the haemolytic–uraemic syndrome and thrombotic thrombocytopenic purpura.

C. *Misoprostol* INN, BAN, USAN,

(1 : 1 Mixture of α and β-methyl isomers)



Prost-13-en-1-oic acid, 11, 16-dihydroxy-16-methyl-9-oxo-, methyl ester ; (11α, 13E)-(±)- ;

Cytotec(R) (Searle) ;

It is used orally as a potent gastric antisecretory and gastroprotective agent.

Dose : *Oral, 100-200 mcg 4 times daily to check gastric ulceration in susceptible individuals who are taking NSAIDS.*

2.1.2. Mechanism of Action

The **mechanism of action** of the drugs described under Section 2.1.1 shall be dealt with appropriately in the sections that follows :

2.1.2.1. Alprostadil

The '**drug**' helps to *maintain the potency of the ductus arteriosus of the faetus.* It has been observed that soon after birth, prostaglandin production falls and ductus get closed. Nevertheless, in the events involving congenital heart defects, for instance : tetralogy of Fallot, transposition of the great vessels, pulmonary atresia, pulmonary stenosis, tricuspid atresia, or imperfect artic arch, coarctation of the aorta, it is almost a primary and necessary urgent requirement that the ductus should remain patent unless and until corrective surgical measures may be carried out effectively. Therefore, in such instances, timely infusion of **alprostadil** (PGE) definitely helps in maintaining patency pending surgical manipulations.

The '**drug**' is also employed for treating erectile dysfunction by injection right into corpora cavernosa of the penis (Edex) or alternatively by direct insertion of a suppository into the urethra (MUSE). It exerts its action by relaxation of trabecular smooth muscle and also by reasonable dilatation of the cavernous arteries.

2.1.2.2. Epoprostenol Sodium

The '**drug**' causes vasodilation and prevents platelet aggregation. The endogenous substance is known as **prostacyclin,** which is a product of arachidonic acid metabolism having a very shot half-life. Soonafter IV infusion it gets hydrolyzed rapidly to the more stable but much less active **6-keto-prostaglandin $F_{1\alpha}$ (6-oxo-prostaglandin $F_{1\alpha}$).** Contrary to host of other **prostaglandins**, this '**drug**' is not inactivated in the pulmonary circulation.

2.1.2.3. Misoprostol

The '**drug**' not only inhibits gastric acid secretion but also enhances mucosal resistance appreciably. It is believed that the '**drug**' essentially sustains as well as derives its therapeutic supremacy particularly in the GI tract by enhancing duly mucous and bicarbonate secretion by the gastric epithelium by augmenting epithelial regeneration ; besides by increasing specifically the mucosal blood flow thereby enhancing the mucosal protection to a great extent.

Misoprostol is rapidly (T_{max} , 12 minutes) and largely absorbed. It has a terminal half-life ranging between 20-40 minutes, with 80% almost excreted in the urine.

Note. It does not prevent the therapeutic benefit of NSAIDs specifically in the treatment of rheumatoid arthritis.

2.1.3. Future Developments

A plethora of **prostaglandin analogoes** are presently under active investigation to combat various human ailments. Some specific areas of common interest being gastroprotection in antiulcer therapy, management and control of coronary artery or cerebrovascular diseases, control of facility and above all the progress for **antiasthamatics**. Likewise, **eiscosanoids** offer a bright prospect for the treatment of immune system disorders and hypertension. It is very much sure that the application of **eicosanoids** as potent therapeutic drugs in the near future shall dominate the search for newer drugs for newer diseases.

2.2. Antilipemic Drugs

According to a current medical dictionary antiatherosclerotics may be defined as '**a form of simple intimal arteriosclerosis with atheromatous deposits within and beneath the intima**'.

In fact, due recognition and efforts for the management and treatment of atherosclerosis and the evolution of **antilipedemic drugs** dates back to a couple of centuries. Previously it was believed that fatty deposition in walls of arteries mostly take–place either in middle or in old ages, but now it has been observed that it may happen at any age whether child or youngesters.

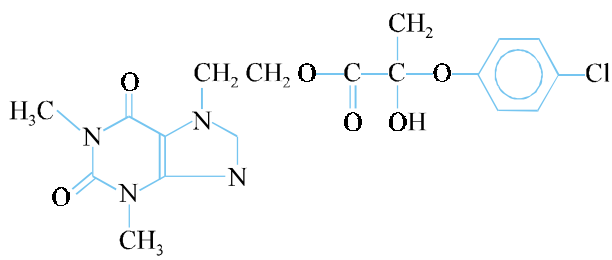
Many scientists have laid primary stress of such abnormalities on blood serum contents, for instance : **cholesterol**, **triglycerides**, **phopholipids** and **free fatty acids (FFA)**. Recent studies have revealed that patients with elevated blood-cholesterol generally have the plasma cholesterol bound in the form of **β-lipoproteins** which becomes higher than in 'normal individual'. These **β-lipoproteins** have a higher molecular weight and a higher proportion of cholesterol that the corresponding **α-lipoproteins** that are higher in 'normal blood'.

It is, however, pertinent to mention here that every individual suffers from atherosclerosis to a certain extent, but its incidence is more abundant in affluent countries. Perhaps the various general factors that contribute towards its frequent occurrence are, namely : emotional stress, excessive smoking, hypertension, unbalanced diet and obesity, lack of endurance type physical activity and above all sustained high–serum–cholesterol levels. More recently some specific factors are found to be responsible for this ailment, such as-immunologic and autonomic factors, coagulation and blood flow, genetic make–up and most importantly endocrinologic aberration.

Developed countries and affluent nations are footing a big chunk of their resources in their health–care–systems to combat **coronary artery disease (CAD)** and **coronary heart disease (CHD)**.

A few important antilipidemic drugs which have gained recognition by virtue of their clinical significance are described here, for instance : **Theofibrate** ; **Probucol** ; and **Gemfibrozil** ;

A. *Theofibrate* USAN : *Etofyline Clofibrate* INN ;

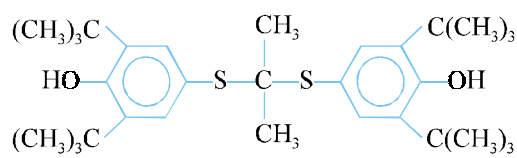


Propionic acid, 2-(4-chlorophenoxy)-2-methyl-, 2-(1, 2, 3, 6-tetrahydro-1, 3-dimethyl-2, 6-dioxo-7H-purin-7-yl) ethyl ester ;

Duolip$^{(R)}$ (L.Merckle, Germany) ;

It has been used in the treatment of hyperlipidaemias.

B. *Probucol* INN, BAN, USAN,



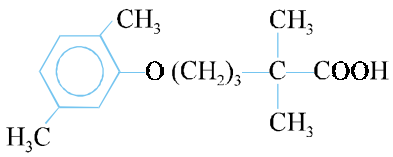
Phenol-4, 4′-[(1-methylethylidene) *bis* (thio)] *bis* [2, 6-*bis* (1, 1-dimethylethyl)]- ;

Lorelco$^{(R)}$ (Merrell Dow) ;

It is employed as an adjunct to diet, to reduce elevated serum-cholesterol concentrations, particularly in type II, hyperlipoproteinamia.

Dose : *Usual, 500 mg with meals, morning and evening.*

C. *Gemfibrozil* INN, USAN,



Pentanoic acid, 5-(2, 5-dimethylphenoxy)-2, 2-dimethyl)- ;

USP ; Lopid$^{(R)}$ (Parke–Davis) ;

It is used in the treatment of hyperlipidaemia.

Dose : *Usual, 0.8 to 1.2 g per day in divided doses.*

2.2.1. Mechanism of Action

The mechanism of action of various medicinal compounds discussed under Section 2.2 shall be treated separately in the sections that follows :

2.2.1.1. Theofibrate

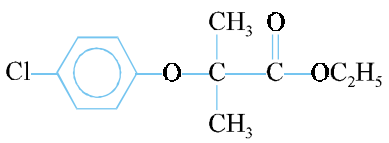
The '**drug**', being a structural analogue of **fibric acid**, acts on the **lipoprotein metabolism**. It also reduces elevated plasma concentration of **cholesterol** to a much lesser extent, but the overall effect is variable in nature. Its mechanism of action is not quite explicite and clear. It may also cause *regression of xanthomas.*

2.2.1.2. Probucol

The '**drug**', which is a highly lipid soluble sulphur containing *bis*-phenol, and is quite capable of minimizing **LDL-cholesterol** even upto 20% without causing any significant difference in the triglyceride levels. It has been amply-proved that it has the inherent double-action on enhancing bile acid secretion in one hand while on the other increasing the degradation of **LDL-apo B**. Besides, probucol also lowers **HDL** as a component of the overall cholesterol reduction.

2.2.1.3. Gemfibrozil

The '**drug**' happens to be a structural analogue of **clofibric acid.** Contrary to **clofibrate** it helps to raise **HDL levels** but at the same time triglyceride levels are reduced appreciably. Interestingly, the '**drug**' is invariably employed in *diet-refractory hypertriglyceridemia.**



Clofibrate [Atromid-S]

*An increased blood triglyceride level.

2.3. Hormone Antagonists

Hormones may be defined as—'**substances secreted by the endocrine, or ductless glands that essentially serve to integrate various metabolic processes**'.

It is interesting to observe that hormones do represent a widely diverse category of compounds, for instance ;

Amino acid derivatives *e.g.*, **thyroxine**, **epinephnine** ;

Steroids-*e.g.*, **testosterone**, **progesterone**, **cortisone**, **hydrocortisone** ;

Polypeptides/proteins-*e.g.*, **corticotropin**, **calcitonin**, **insulin** ;

While, hormones are solely responsible for the reproductive system, they are also the causative substances for the growth and development of cancers related to breast, prostate and uterine.

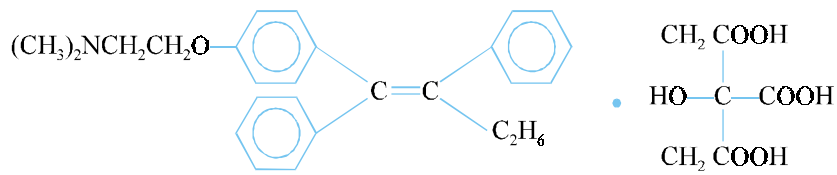
A few typical examples of **hormone antagonists** are discussed below.

2.3.1. Antiestrogens

Antiestrongens are such compounds which block the **oestrogen activity**. Compounds belonging to this category are essentially the structural analogues of the **oestrogen triphenylethylene**.

Example : Tamoxifen citrate ; **Nitromifene citrate** ;

A. *Tamoxifen Citrate* USAN ; *Tamoxifene* BAN ;



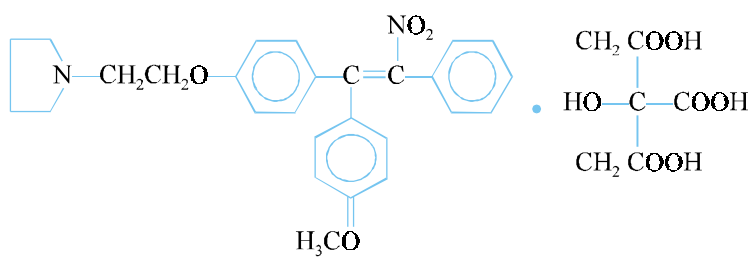
(Z)-2-[*p*-(1, 2-Diphenyl-1-butenyl) phenoxy]-N, N-dimethylethylamine citrate (1 : 1) ; Tamoxifen Citrate USP ;

Nolvadex$^{(R)}$ (Sturat) ;

It is employed as an alternative to **androgens** and **oestrogens** in the management of breast cancer. It is also used to stimulate ovulation in infertility.

Dose : *For breast cancer : oral, 10 to 20 mg of tamoxifen twice daily (or 20 to 40 mg daily) ; For stimulating ovulation : usual, 10 mg of tamoxifen two times per day on day 2, 3, 4 and 5 of the menstrual cycle, alternatively : single daily doses of 20 to 80 mg may be employed on the same days.*

B. *Nitromifene Citrate* USAN



1-[2-[*p*-[α-(*p*-Methoxyphenyl)-β-nitrostyryl] phenoxyl] ethyl] pyrrolidine citrate (1 : 1) ;

CN 5518(R) (Parke-Davis) ;

Nitromifene gets converted to its corresponding phenolic metabolite (methoxy moiety changes to phenclic OH group) which displays a high affinity for the **oestrogen receptor**.

2.3.1.1. Mechanism of Action

The mechanism of action of drugs described under Section 2.3.1 shall be treated individually as follows :

2.3.1.1.1. Tamoxifen citrate

The '**drug**' is found to exert its action by competing with **estrogens** for the **cytosol estrogen receptors**, which eventually affords more or less complete blockade of the ensuing estrogen effect in the '**target tissue**'. However, tumours having essentially **negative receptor assays** do not respond to it.

Oncologists make use of this specific antiestrogen, tamoxifen, in depriving the malignant process of the source of these hormones, therefore, shows a much better, safer and potentially useful method of treatment.

The bioavailability *via* the oral administration of this '**drug**' ranges between 25–100%. The half-life of a single dose stands at 18 hours, but it is only 7 hours at a steady state.

2.3.1.1.2. Nitromifene Citrate

The '**drug**' exerts its action after undergoing demethylation to the corresponding phenol.

2.3.2. Antiandrogens

Antiandrogens normally prevents the binding of **dihydrotestosterone** to **androgen receptors** particularly in target tissues. They may be further classified into *two* categories, namely :

(*a*) Non-steroidal Antiandrogens

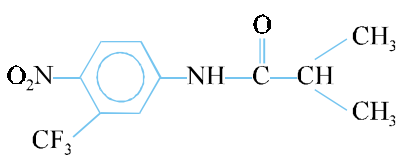
(*b*) Steroidal Antiandrogens

which shall be dealt separately as under with specific examples.

2.3.2.1. Nonsteroidal Antiandrogens

These compounds do not possess a steroidal nucleus and androgenic properties as such, but their metabolites exhibit antiandrogenic properties. **Example : Flutamide** ;

A. *Flutamide* INN, BAN, USAN,



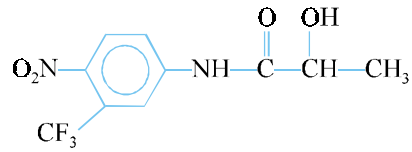
Propionamide, 2-methyl-N-[4-nitro-3-(trifluoromethyl) phenyl]- ;

Sebatrol(R) (Schering–Plough) ;

It has been used to improve urine flow in benign prostatic enlargement.

Dose : *300 mg per day.*

Mechanism of Action. Flutamide being an orally active and potent competitive inhibitor of specific **nuclear androgen receptors** in target tissues *e.g.*, seminal vesicles, adrenal cortex and prostate. Its pharmacological action is mainly on account of its major metabolite, *2-hydroxyflutamide*, as given below :



2-Hydroxyflutamide (major metabolite)

It has been observed that nearly 50% of the **'drug'** gets eliminated in the urine within a span of 3 days. Interestingly, the *hydroxylated metabolite* has a half-life which ranges between 6-22 hours depending on the dosage administered.

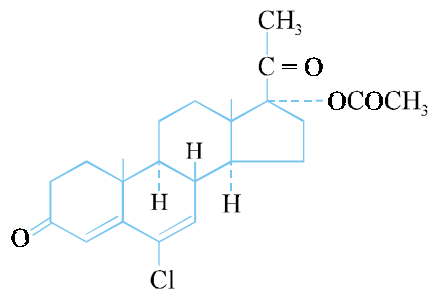
Caution. The 'drug' causes a high incidence of gynecomastia* and GI-discomfort to a certain extent.

2.3.2.2. Steroidal Antiandrogens

In early sixties cyproternone acetate was first discovered to possess antiandrogen activity. A few other compounds were found to exhibit similar properties.

Example. Chlormadinone Acetate ;

A. *Chlormadinone* INN, BAN ; *Chlormadinone Acetate* USAN



Pregna-4, 6-diene-3, 20-dione, 17-(acetyloxy)-6-chloro- ; Chlormadinone acetate BP (1968) ; Progestin(R) (Syntex) ;

It is used in the treatment of functional uterine bleeding. It also exerts very slight oestrogenic activity.

Mechanism of Action. Chlormadinone acetate is an orally active progestogen having distinct and potent antiandrogenic activity, which has been used in combination as an oral contraceptive. It serves as a **hormonal antineoplastic agent**.

2.3.3. Aldosterone Antagonists

The **mineralocorticoid-aldosterone** essentially monitors the electrolyte balance in the body by enhancing the excretion of K^+ and the retention of Na^+. Thus, **aldosterone antagonists** are usually employed for the effective treatment of edematous ailments and hypertension.

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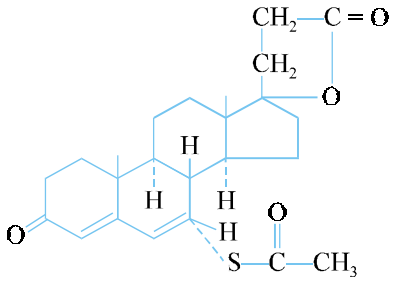
*Enlargement of breast tissue in the male.

Example : Spironolactone ;

A. *Spironolactone* INN, BAN,



17-Hydroxy-7α-mercapto-3-oxo-17α-pregn-4-ene-21-carboxylic acid, γ-lactone acetate ; BP (1973) ; USP ;

Aldactone$^{(R)}$ (Searle) ;

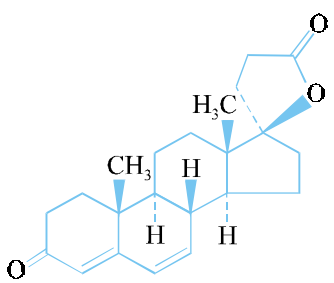
It is employed in the treatment of refractory oedema associated with congestive heart-failure, cirrhosis of the liver or the nephrotic syndrome. It is frequently administered along with diuretics like thiazides and frusemide whereby it adds to their natriuretic but retards thir kaliuretic effects, hence conserving potassium.

Dose : *Usual, initial, 100 mg per day in divided doses ; For children : 3 mg per kg body weight per day, in divided doses.*

Mechanism of Action. Spironolactone particularly competes with aldosterone at its receptor sites, that eventually triger the synthesis of the prevailing enzyme(s) which predominantly catalyze Na^+ transport when stimulated duly. Therefore, it predominantly **reverses** these electrolyte alterations by specifically causing blockade in the renal tubular action of the hormone. Thus, by initiating the inhibition of Na^+ reabsorption the drug produces significant diuresis and thereby minimizes K^+ excretion.

It has been well established that the '**drug**' exerts its action by reasonably blocking the sodium–retaining effects of **aldosterone** upon the distal convoluted tubule, thereby it corrects meticulously one of the most vital mechanisms solely responsible for the production of edema, but it may be noted with great emphasis that **spironolactone** is effective only in the presence of **aldosterone** specifically.

The '**drug**' gets metabolized rapidly after oral administration. However, the metabolites are usually excreted mostly in the urine and also in the bile to a certain extent. Interestingly, the most vital metabolite, **canrenone,** attains the peak plasma levels within a short span of 2–4 hours after oral administration of the '**drug**'.



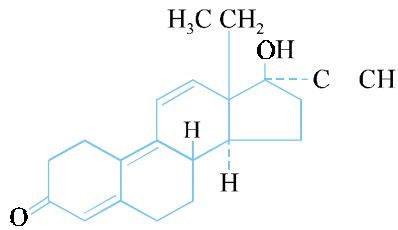
Canrenone

2.3.4. Antiprogestational Steroids

Antiprogestational steroid gained significant interest by virtue of their potential as an antifertility agent.

Example : Cestrinone ;

***Cestrinone* INN, USAN,**



13-Ethyl-17-hydroxy-18, 19-dinor-17α-pregna-4, 9, 11-trien-20 yn-3-one ;

RU-2323(R) (Roussel) ;

It has been employed as a contraceptive. It has also been used in male subjects for the suppression for spermatogenesis.

Summary

The various hormone antagonists not only help in giving a vivid picture of hormonal control mechanisms but also serve as immensely viable tool for the management and control of hormone–dependent cancer. This has, in fact, generated enough interest towards the development of newer and altogether safer **hormone antagonists**.

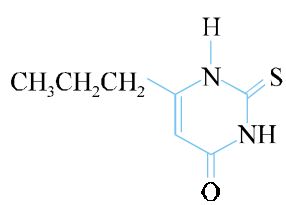
2.4. Antithyroid Drugs

In the morbid state produced by excessive secretion of the thyroid gland *i.e.,* **hyperthyroidism**, the only remedial measure is surgery. However, for pre-surgery treatment the patient must be administered with antithyroid drugs to abolish hyperthyroidism to a considerable extent.

Thiourea was initially found to exhibit an antithyroid activity but had to be abandoned due to their high toxicity. Later on, it was revealed that similar activity was shown by 2-thiouracil derivatives and 4-keto-2-thiopyrimidines ; more precisely 6-alkyl-2-2 thiouracils and their congeners display meaningful clinical characteristics.

A few typical examples are described here, namely, **Propylthiouracil** ; **Methimazole** ;

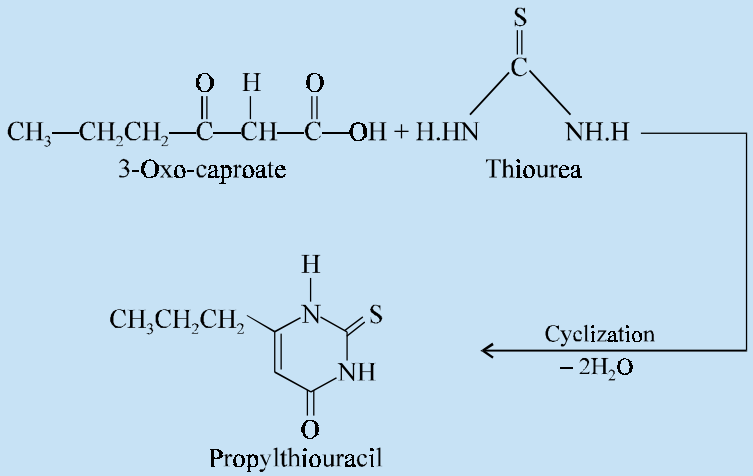
A. *Propylthiouracil* INN ;



6-Propyl-2-thiouracil ; BP ; USP ; Int., IP ;

Tietil(R) (Pharmacia, Sweden) ;

Synthesis

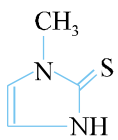


It is prepared by the condensation (cyclization) of 3-oxo-caproate with thiourea and elimination of two mole of water.

Polythiouracil is used in the preparation of the hyperthyroid patient for surgery. It is also employed in the complete management and treatment of hyperthyroidism spread over a period ranging from 6 months to 3 years.

Dose : *For hyperthyroidism in adults, initially 200 to 300 mg per day in 3 divided doses ; when the patient attains normal basal metabolic rate (euthyroidism) the dose is usually reduced to a maintenance dose fo 50 to 75 mg daily in 2 to 3 divided doses. In children : over 10 years old, initial, 150 to 300 mg per day in 4 divided doses until the child becomes euthyroid, then usually 100 mg daily in 2 divided doses, for maintenance.*

B. *Thiamazole* INN, *Methimazole* BAN, USAN ;



1-Methylimidazole-2-thiol ; Methimazole USP ;

Tapazele(R) (Lilly) ;

It is an antithyroid substance that retards the formation of thyroid hormone. It acts by reducing the formation of iodotyrosines and, therefore, of thyroxine tri-iodothyroxine. It is also used in the preparation of patients for subtotal thyroidectomy.

Dose : *Usual, initial, 5 to 20 mg every 8 Hrs.-when condition gets stabilized (1-2 months)-the dose is reduced to a maintenance dose of 5 to 15 mg per day ; For children : initial, 400 mcg per kg body weight per day in divided doses.*

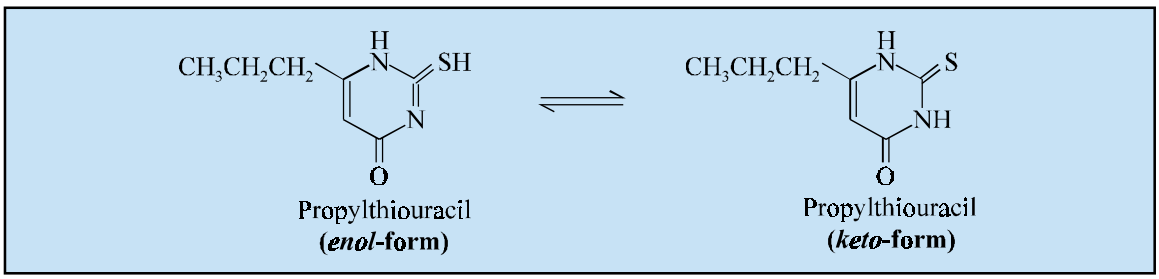
2.4.1. Mechanism of Action

The mechanism of action of the medicinal compounds discussed under Section 2.4 shall now be dealt with individually as follows :

2.4.1.1. Propylthiouracil

The '**drug**' fails to cause interference with the release or usage of accumulated thyroid hormone ; and the time-gap that essentially elapses between the very initial stage of medication together with the manifestations of its **antithyroid activity** entirely depends upon the quantum of thyroid hormone present in the gland (**thyroid**). The resulting marked and pronounced **hyperplasia*** of the **thyroid gland** which follows soonafter its administration, in fact, is a consequence of a **compensatory enhancement of thyroprotein release** as a result in the **thyroid hormone titer value of the blood**.

Propylthiouracil undergoes **tautomerism** as follows :



Because the thiol group (SH) does not invariably occur in medicinal compounds, S-glucuronide products have been duly reported for only a few drugs *e.g.*, **propylthiouracil****, undergo conjugation with **glucuronic acid**.

The '**drug**' gets absorbed by the oral route to the extent of 75%. As the drug lowers the metabolic rate ; therefore, the dosage regimen must be regulated accordingly so as to avoid accumulation as far as possible.

2.4.1.2. Methimazole

The '**drug**' is found to be almost 10 fold as potent as **propylthiouracil**, besides being more prompt in eliciting an antithyroid response. It also distinctly exhibits a much more prolonged action in comparison to propylthiouracil. The plasma half-life varies between 6—8.5 hours in *hyperthyroid* patients, but 8—18 hours in *hypothyroid* ones ; and, therefore, as the '**drug**' decreases the metabolic rate, its own metabolism gets slowed appreciably which may ultimately result into **'accumulation'** unless and until the dosage is readjusted accordingly.

2.5. Antimycobacterial Drugs

There are two dreadful diseases produced by the species *Mycobacterium,* namely ; tuberculosis caused by the organisms *Mycobacterium tuberculosis* and leprosy produced by *Mycobacterium leprae*. Unfortunately both these diseases have afflicted the mankind throughout the recorded history.

In this context, the *two* categories of **antimycobacterial drugs** shall be discussed individually as under :

(*a*) Antitubercular Drugs

(*b*) Antileprotic Drugs

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*Excessive proliferation of normal cells in the normal tissue arrangement of an organ. (**SYN** : *Hypergenesis*).

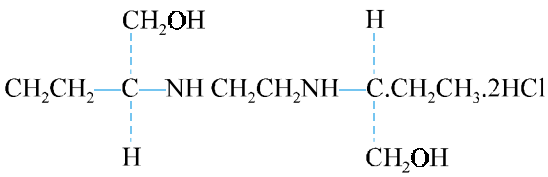
Lindsay RH *et al. Pharmacologit* **18 : 113, 1976.

2.5.1. Antitubercular Drugs

The first ever breakthrough in **antitubercular chemotherapy** took place in the year 1938 with the historical fact that sulphanilamide exhibited week bacteriostatic properties. This observation triggered off the extensive and intensive research towards the synthesis of a number of antitubercular agents which was subsequently followed by certain **antitubercular antibiotics**.

A few such important antitubercular drugs shall be discussed here, namely : **Ethambutol** ; **Isoniazid** ; **Ethionamide** ; **Streptomycin** ; **Capreomycin Sulphate** ; **Rifampicin** ;

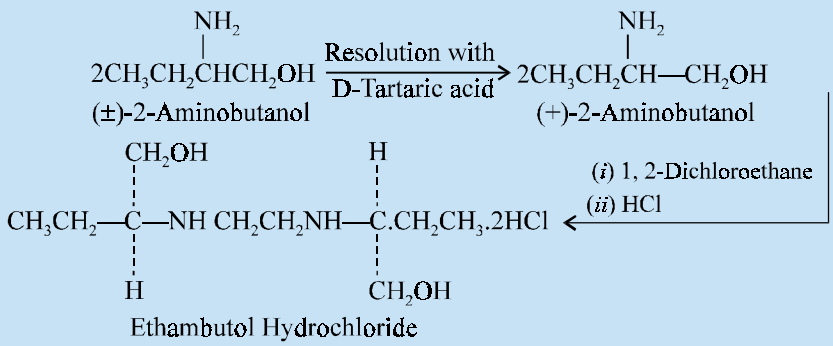
A. *Ethambutel* INN, *Ethambutolum* BAN ; *Ethambutol Hydrochloride* USAN ;



1-Butanol, 2, 2′-(1, 2-ethanediyldiamino) *bis*-, dihydrochloride, [S–(R*, R*)] ; Ethambutol Hydrochloride BP ; USP ;

Myambutol(R) (Lederle) ;

Synthesis

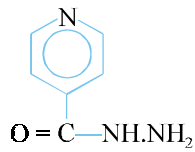


It is prepared by first resolving (±)-2-aminobutanol *via* its tartrate and the (+)-enantiomorph is condensed with 1, 2-dichloroethane in a suitable dehydro-chlorinating atmosphere. The resulting ethambutol is dissolved in an appropriate solvent and treated with hydrochloric acid to obtain the official compound.

It may be used alone to clear the sputum of mycobacteria within a span of 12 weeks in many cases, but bacterial resistance usually takes place in 35% of cases, and thus leading to frequent relapses. Therefore, it is employed in combination with **isoniazid**, **pyrazinamide**, **cycloserine** or **ethionamide**-such relapses are uncommon.

Dose : *15 to 25 mg/kg once a day ; low dose for new cases and high dose for use in patients that have had previous antitubercular therapy.*

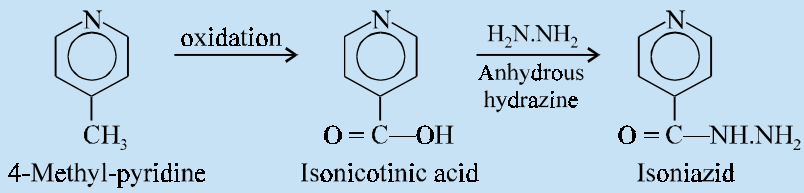
B. *Isoniazid* INN, USAN ; *Isoniazide* BAN ;



4-Pyridinecarboxylic acid, hydrazide ; BP ; USP ; Eur. P. ; Int. P, IP ;

Continazin(R) (Pfizer) ; Dimacrin(R) (Winthrop) ; INH(R) (Ciba—Geigy) ; Nydrazid(R) (Squibb) ;

Synthesis

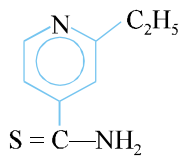


It is prepared by first carrying out the oxidation of 4-methylpyridine to obtain isonicotinic acid which upon heating with anhydrous hydrazine yields the desired compound.

It is considered to be the drug of choice for the treatment of tuberculosis. It has also been employed as a prophylactic for those who were constantly exposed to tubercular patients. It is invariably used in combination with other antitubercular drugs to achieve better clinical response, to allow lower doses of other active agent(s), and above all to retard the emergence of resistant tubercle bacilli.

Dose : *Adult, oral or im, for active tuberculosis, 5 to 7 mg/kg/day singly or in divided doses ; for prophylaxis-300 mg daily ; For children : treatment, 10 to 30 mg/kg day in 2 divided doses, as prophylaxis 10 mg/kg day.*

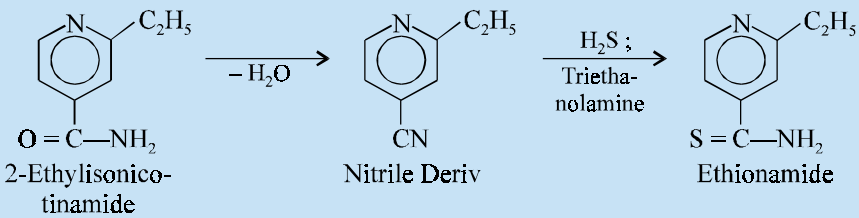
C. *Ethionamide* INN, BAN, USAN,



4-Pyridinecarbothioamide, 2-ethyl- ; BP ; USP ; Eur. P ; IP ;

Tractor-SC(R) (Ives) ; Iridocin(R) (Bayer) ; Trescatyr(R) (May & Baker) ;

Synthesis



It is prepared by dehydrating 2-ethylisonicotinamide to the corresponding nitrile analogue which is then reacted with hydrogen sulfide in the presence of triethanolamine to afford the official compound.

It is used only when the usual combination of **PAS**, **streptomycin** and **INH** are either intolerable or ineffective.

Dose : *500 mg to 1 g per day in 3 or 4 divided doses, to be administered with meals.*

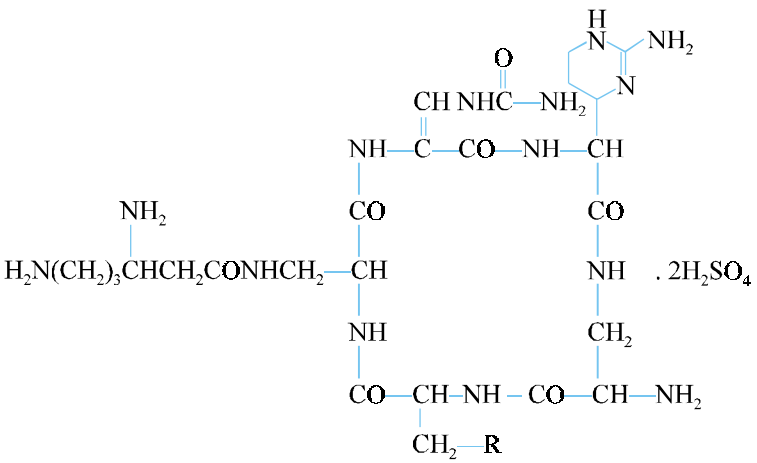
Besides, these synthetic compounds discussed above, a number of *antitubercular antibiotics* have also gained significant recognition over the past few decades. A few typical members of this particular category of compounds are described below :

Example : Streptomycin ;

D. *Streptomycin* INN, *Sterptomycin Sulphate* BAN, *Sterptomycin Sulfate* USAN ;

It has been described under the chapter on **'Antibiotics'**.

E. *Capreomycin* INN, BAN ; *Capreomycin Sulfate* USAN ;



Capreomycin IA : R = OH ;
Capreomycin IB : R = H ;

Capreomycin Sulphate ; Capreomycin Sulphate BP ; Capreomycin Sulfate USP ;

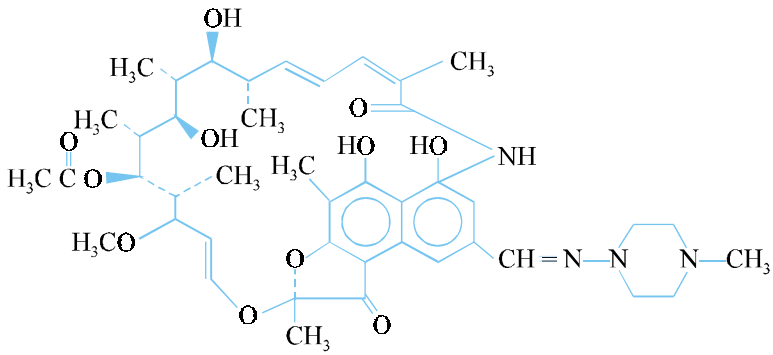
Capstat Sulfate(R) (Lilly) ;

It is a strongly basic antibiotic having a cyclic peptide structure isolated from *Streptomyces capreolus.* Out of the four capreomycins deignated as IA, IB, II*a* and II*b*, only IA and IB are found to be clinically useful.

Capreomycin resembles viomycin both chemically and pharmacologically. It is considered to be second-line antitubercular drug used in combination with other such agents. It is frequently used in place of **streptomycin** when either the patient is sensitive to it or the strain of *M. tuberculosis* is resistant to it.

Dose : *Administered by deep IM injection, usual, daily : 1 million units, equivalent to about 1 g of capreomycin with a maximum of 20,000 units (20 mg) per kg body weight.*

F. *Refampicin* INN, BAN ; *Rifampin* USAN ;



Rifamycin, 4-0-[2-(diethylamino)-2-oxoethyl]- ; Rifampicin BP, Rifampin USP ;

Rifmactane(R) (Ciba–Geigy) ; Rifadin(R) (Marrell Dow) ;

Rifampicin-a semisynthetic derivative of naphthalene was produced by *Streptomyces mediterranei.*

It is used solely in the treatment of tuberculosis. It is interesting to observe that the rate of development of resistance of the mycobacterium is low. However, it is always employed in combination with other antitubercular drugs.

Dose : *Oral, 600 mg daily m 1 to 3 divided, taken 1 hour be used in combination with at least one other antitubercular drug.*

2.5.1.1. Mechanism of Action

The **mechanism of action** of the drug substances discussed under Section 2.5.1 shall now be dealt with separately in the sections that follows :

2.5.1.1.1. Ethambutol Hydrochloride

The '**drug**' exerts its action against tubercle bacilli resistant to either isoniazid or streptomycin. It has been observed to act specifically upon the proliferating cells, evidently by causing interference with the synthesis of RNA. Importantly, when the '**drug**' is employed singly for the treatment of tuberculosis, it may help in clearing the sputum of myobacteria within a span of three months in most of the subjects ; however, bacterial resistance usually takes place in nearly 35% of cases, and relapses occur frequently. Certainly the combination with either ioniazid or other prevalent **tuberculostatic drugs**, the incidence of relapses occur seldomly.

The oral bioavailability ranges between 75–80%. It gets well distributed into most tissues and fluids but definitely less in CSF. The volume of distribution stands at 1.6 $mL.g^{-1}$. As much as 80% of the '*drug*' gets eliminated in the wine. The half-life is 3-4 hours but may extend upto 8 hours in renal failure.

2.5.1.1.2. Isoniazid

The '**drug**' exerts its action as a **tuberculocidal** particularly to the **growing organisms** (*tubercle bacilli*) and considered to be the most effective agent in the therapy of tuberculosis, and **not on the resting organisms.** It has since been well established that the **'drug'** gains an easy access to **all organs**

and to **all body fluids**, including CSF, thereby rendering it of extremely special status and value in the management and treatment of tuberculosis, meningitis together with other diseases related to extrapulmonary manifestations.

Interestingly, the manner by which the '**drug**' acts as bactericidal, may be explained by the fact that it causes the bacilli to lose lipid component by a still not fully elucidated mechanism. However, the most widely accepted and reasonably justified theory suggests that the principal effect of **isoniazid** is accomplished ***via* inhibition of the synthesis of mycotic acids.***

It has been observed critically that a **mycobacterial-catalase-peroxidase enzyme complex** is necessarily required for the bioactivation of **isoniazid**.** Consequently, a reactive species, usually produced *via* the action of these enzymes on the drug is supposed invariably to attack a *very specific enzyme* needed urgently for carrying out the *mycolic acid synthesis in mycobacteria.**** Furthermore, the observed resistance to **INH**, believed to vary between 25—50% of the '*clinical isolate*' of the **INH-resistant strains**, is intimately associated with the apparent loss of catalase and peroxidase activities, both of which are legitimately encoded by a single gene, **kat G.****** Recently, the actual predicted target for the action of **INH** has been duly recognized and identified as an *enzyme* which catalyze the **NADH-specific reduction of 2-*trans*-enolyacyl carrier protein**, which is otherwise proved to be an essential step in the fatty acid elongation *i.e.*, lengthening the carbon-chain ; and subsequently the aforesaid '*enzyme*' is encoded adequately by a very specific gene, *inh A*, present in *M. tuberculosis.*******

Isoniazid is chiefly acetylated by the liver, and th rate of acetylation varies appreciably. The half-life in '**fast-acetylators**' ranges between 1—1.5 hours ; and in relatively slow ones, it varies between 2-5 hours.

Note. IM injection of INH may cause local irritation.

2.5.1.1.3. Ethionamide

The '**drug**' is regarded to be a **secondary drug** employed usually for the treatment of tuberculosis. It gets absorbed rather rapidly and completely soonafter oral administration. Importantly, it gets largely distributed throughout the body and metabolized extensively into the **inactive forms** predominantly which are ultimately excreted through the urine. It is found that almost 1% of the '**drug**' appears in the urine in an unchanged form.

SAR of Ethionamide : The *two* structural modifications to the corresponding **INH-series**, namely :

(*a*) isosteric replacement of the carbonyl (—C(=O)—) function in INH with (—C(=S)—) ; and (*b*) 2-ethyl substitution, increases **antituberculostatic activity** in the **thioisonicotinamide series** to a considerable extent.

*Quomard A *et al. Antimicrob. Agents Chemother*, **35** : 1035, 1991.

Youatt J *et al. Am. Rev. Respir, Dis.*, **100, 25, 1969.

***Johnsson K *et al. J Am. Chem. Soc.*, **116** : 7425, 1994.

****Zhang Y *et al., Nature*, **358**, 591, 1992.

*****Dessen A *et al. Science*, **267,** 1638, 1995 ; Benerjee A *et al.Science*, **263,** 227, 1994.

2.5.1.1.4. Streptomycin Sulfate

It has already been discussed under **Chapter 23** Section 4A.

2.5.1.1.5. Rifampin

The '**drug**' exerts its predominant activity against two vital pathogenic organisms *viz*., *Mycobacterium tuberculosis* and *Mycobacterium leprae*. Bearing in mind the glaring fact that the rate of development of resistance of the causative organism, mycobacterium, is rather at a low ebb, it is invariably employed in combination with other antitubercular drugs.

Rifamycin is found to afford induction of the specific **hepatic drug-metabolizing enzyme system** ; and, therefore, accelerates the metabolism of **digitoxin**, **methadone**, **phenytoin**, **β-blockers**, **verapamil**, **oral contraceptives**, **chloramphenicol**, **theophylline**, besides—**oral anticoagulants**, **estrogens**, **tolbutamide**, **barbiturates** and itself.

The '**drug**' has proved to be *teratogenic* in laboratory animals ; and, hence, must be refrained particularly in pregnancy.

It is absorbed almost 100% after oral administration ; however, the food present in the stomach may delay its absorption considerably. It gets widely distributed in the body and even into the CSF. In plasma almost 98% is protein-bound. The volume of distribution (v_d^{ss}) stands at 0.9 $mL.g^{-1}$. Biotransformation in the liver helps in the elimination of almost 85% of the '*drug*'. An active and primary metabolite, **deacetylrifampin,** gets secreted right into the bile where it is effective therapeutically.

Cautions : (1) Risk of hepatotoxicity gets increased when used in combination with INH.

(2) Imparts distinct reddish-orange colour in urine, faeces, sweat, saliva and even tear.

(3) Soft transparent and clear '*contact lenses*' may be stained permanently.

2.6. Cardiac Steroids and Related Inotropic Drugs

A plethora of drugs are known that are found to be affecting the force of cardiac contractions. These drugs find there enormous use for the treatment of congestive heart failure by prolonging the life span of patients through pumping sufficient blood to sustain body requirements.

The **inotropic drugs** may be classified into the following *four* heads, namely :

(*a*) Cardiac Steroids

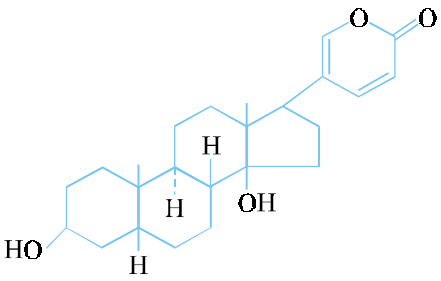
(*b*) Phosphodiesterase Inhibitors

(*c*) Adenylate Cyclase Stimulants

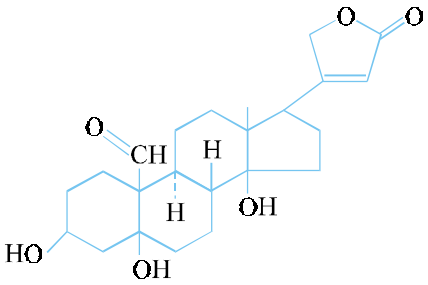
(*d*) Drugs that Enhance the Ca Sensitivity of Myocardial Contractile Proteins.

2.6.1. Cardiac Steroids

The use of the **cardiac glycosides** that act on the heart by causing atrioventricular conduction and vague tone has been discussed earlier. They belong to the class of **cardenolides**. Another cardiac glycoside class, the **bufadienolides**, does not warrant enough therapeutic importance. A typical example of **bufadienolides** is **bufotalin**, the aglycone portion of **bufalin**, a potent **cardiac glycoside** found in poisonous toad—skin secretions. The **glycoside *k*–strophanthoside**, obtained from the seeds of *Strophanthus kombe*, gives rise to the aglycone **strophanthidine** which also exerts cardiac contractions.



Bufalin

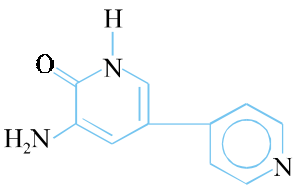


Strophanthidine

2.6.2. Phsophodiesterase Inhibitors

In the recent past a good number of '**nonglycoside inotropic agents**' have emerged as potentially beneficial drugs. This type of agents usually exert their action by the inhibition of a ***c*AMP (cyclic adenosine monophosphate)**-specific phosphodiesterase in the myocardium. The resulting inhibition ultimately leads to increased levels of ***c*AMP**, which through a complicated series of biochemical steps gives rise to an enhancement in intracellular Ca^{2+} and finally an elevation in muscle contractility.

A. *Amrinone* INN, BAN, USAN,

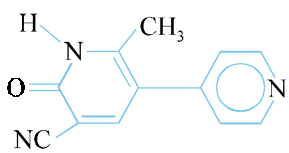


5-Amino [3, 4′-bipyridin]-6 (1H)-one ;

Inocor(R) (Winthrop) ;

It is used for the treatment of heart failure. It has been given by injection and by mouth.

B. *Milrinone* INN, USAN ;



1, 6-Dihydro-2-methyl-6-oxo [3, 4′-bipyridin]-5carbonitrile ;

Primacor(R) ;

It is relatively more potent than **amrinone**. It is found to be tolerated, having least apparent thrombocytopenia or gastrointestinal disturbance.

2.6.2.1. Mechanism of Action

The **mechanism of action** of the medicinal compounds described under Section 2.6.2 shall now be dealt with individually as follows :

2.6.2.1.1. Amrinone

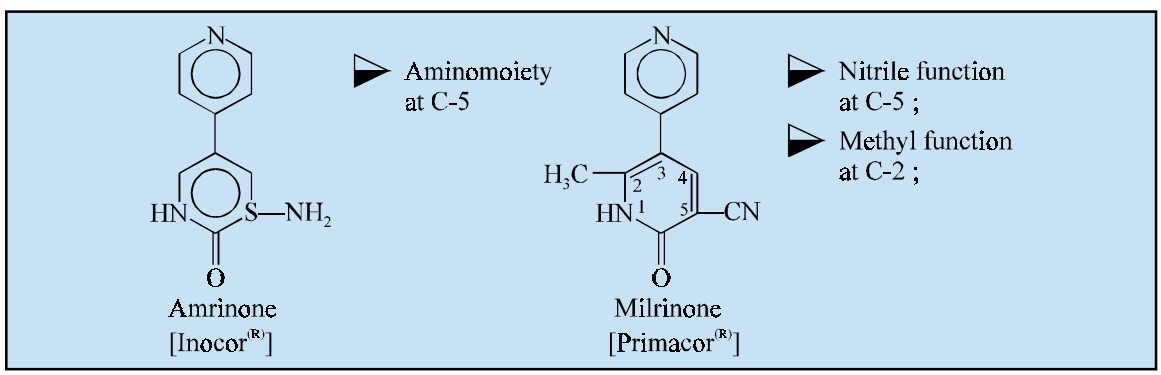
The '**drug**' categorically causes inhibition of the specific enzyme **phosphodiesterase III** and thereby enhances both **intarcellular cAMP** and **calcium** predominantly. Besides, in heart muscle the overall net effect is an apparent enhancement in contractility, whereas in vascular smooth muscle the outcome is relaxation solely. Sumararily, both these ensuing pharmacologic effects in unison contribute to augmentation in cardiac output particularly in **congestive heart failure** ; however, *ventricular unloading* as a result of *arteliolar dilatation* seems to be the more vital characteristic feature.

Amrinone is neither a **β-adrenergic agonist** as **dobutamine**, and nor an **inhibitor of Na^+—K^+–ATPase** as **digitalis**. In the same vein there is no observed α-adrenoreceptor or cholinoreceptor stimulation. Besides, there are no apparent effects on autonomic ganglia. Evidently, the '**drug**' gives rise to enhanced ***c*AMP** levels as being responsible for both observed **vasodilation** and **direct positive inotropy.**

Though the '**drug**' gets absorbed only to a small extent by the oral administration, it fails to show any significant therapeutic effect. Its volume of distribution (v_d^{ss}) stands at 1.2 $L.kg^{-1}$. It is conjugated in the liver upto 70%, while the balance gets excreted through the urine. The half-life of the **'drug'** is about 3.6 hours in normal subjects but extends upto 5–8 hours in patients having heart-failure. The duration of action ranges between 30–120 minutes.

2.6.2.1.1.2. Milrinone Acetate

The '**drug**' is found to be 20—30 folds more potent in comparison to amrinone as a positive inotropic agent, besides being somewhat more potent as an *arteriolar* and *venous dilator* probably due to the *two* basic alteration in functional moieties in it as shown below :



Thus, the '**nitrile**' and '**methyl**' moieties in milirone enhances its therapeutic potency significantly than amrinone. It has been observed that it improves cardiac index by 34% and lowers systemic vascular resistance by almost 31% in subjects having congestive heart failure. It is proved to be much superior to amrinone because it is not only orally active but also fails to cause either fever or *thrombocytopenia**.

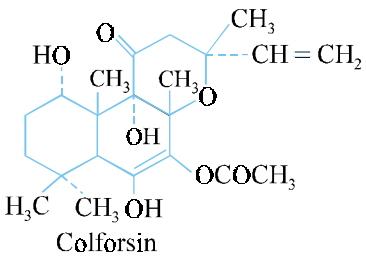
The '**drug**' has a volume of distribution (v_d^{ss}) that stands at 0.4 $L.kg^{-1}$ and a mean half-life varying between 2—3 hours. It, however, gets secreted rapidly in the urine *via* active secretion.

2.6.3. Adenylate Cyclase Stimulants

Colforsin a diterpine directly stimulates adenylate cyclase or a structurally related protein. This causes an elevation of ***c*AMP** levels in the myocardium thereby activating the protein kinases and

*An abnormal decrease in number of the blood platelets (*Syn* : *Thrombopenia*).

enhances the intracellular Ca^{2+}. It also affects vasodilatation. It has been reported that a few physiologic effects caused by **Forskolin** are not mediated by ***c*AMP**.



Colforsin

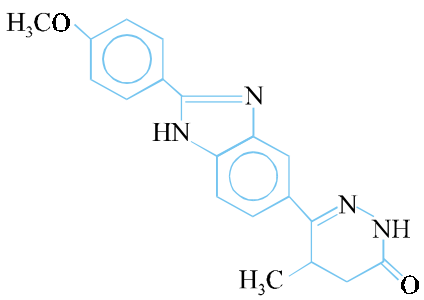
Colforsin [*Syn* : **Boforsin** ; **Forskolin** ; **Forscolin**] exerts its action by causing stimulation of adenylate cyclase. It has been observed that the '**drug**' possesses positive inotropic and bronchodilator effects.

2.6.4. Drugs that Enhance the Ca^{2+} Sensitivity of Myocardial Contractile Proteins

After the spectacular revelation of **amrinone's** inotropic action a vigorous global effort was made in search of other **nonsteroidal inotropic drugs**. These drugs seem to enhance the effect of existing Ca^{2+} levels and subsequently cause an **inotropic effect**.

A few typical examples are discussed here, namely : **Pimobendan** ; **Sulmazole** ;

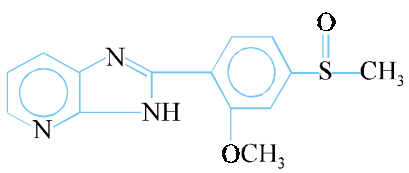
A. *Pimobendan* INN, USAN ;



4, 5-Dihydro-6 [2-(*p*-methoxyphenyl)-5-benzimidazolyl]-5-methyl-3(2H)-pyridazinone ;

It is found to increase the Na^+ sensitivity of myocardial contractile proteins.

B. *Sulmazole* INN, USAN ;



2-[2-Methoxy-4-(methylsulfinyl) phenyl]-3H-imidazo [4, 5-*b*] pyridine ;

Sulmazole, an imidazopyridine derivative also increases Na^+ sensitive of myocardial contractile proteins.

2.6.4.1. Mechanism of Action

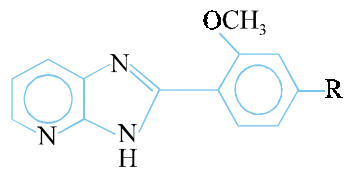
The **mechanism of action** of the medicinal compounds described under Section 2.6.4 shall be treated as below :

2.6.4.1.1. Pimobendan

The '**drug**' is a phosphodiesterase inhibitor having predominant calcium-sensitizing characteristic properties. It also exerts **positive inotropic** and **vasodilatory activity** ; and, therefore, has been tried in the management of heart failure.

2.6.4.1.2. Sulmazole

The cardiotonic agent (*a*) was shown to produce **'bright visions'** in some patients, which suggested that it was entering the CNS. It was indeed supported by the fact that the log P value of (*a*) was 2.5 g. In order to check the '**drug**' from entering the CNS directly, the 4-OCH_3 moiety was duly replaced with a 4-S(O) CH_3 group. This specific moiety is approximately of the same size and magnitude as that of the methoxy moiety, but certainly more hydrophilic in nature. **Sulmazole** has a log P value of 1.17 (about 50% less).



(*a*) R = OCH_3
(*b*) R = S(O)CH_3
Sulmazole

Thus, this '**drug**' turned out to be too hydrophilic in status so as to enter the CNS ; and, therefore, was devoid of CNS- side-effects.

2.7. Heparin

Heparin is a **mucopolysaccharide**, having a molecular weight ranging from 6,000 to 20,000, made up of several repeating units of **glucuronic acid** and **sulphated glucosamine**. It is comparatively a strong acid that forms water–soluble salts, for instance heparin sodium. The presence of a number of ionizable sulphate moieties renders the molecule a strong electronegative charge.

***A. Heparin* INN ; *Heparin Sodium* USAN ;**

Heparin B.P. ; Int. P. ; Heparin Sodium USP ;

Heparin Lock Flush$^{(R)}$ (Abbott) ; Lipo–Hepin$^{(R)}$ (Riker) ; Liquaemin Sodium$^{(R)}$ (Organon) ; Liquemin$^{(R)}$ (Roche) ;

It is prepared in large–scale from liver and lung by adopting the procedure advocated by Kuizenga and Spaulding and purifying the isolated heparin by suitable means.

Heparin may be administered intravenously by any of the two following methods, namely ;

(*a*) the continuous infusion method or by deep subcutaneous injection, and

(*b*) the intermittent injection method.

However, the continuous infusion method is generally performed as it affords a more constant anticoagulating activity besides offering lower incidence of bleeding complications. Nowadays, a constant–rate infusion pump is mostly recommended.

Dose : *Usual, full-dose, parentral, the following amounts, as indicated by prothrombin–time determinations : IV, 10,000 USP heparin units initially, then 5,000 to 10,000 U every 4 to 6 hours ; infusion ; 20,000-40,000 U/L at a rate of 1000 U/ hour over a 24-hour duration ; subcutaneous ; 10,000 to 20,000 U initially, then 8,000 to 10,000 U every 8 hours or 15,000 to 20,000 U every 12 hours ; Usual, pediatric dose ; IV injection ; 50 U/kg of body weight initially, then 50-100 U/kg of body wight every 4 hours ; 50 U/kg of body weight intiially, followed by 100 U/kg, added and observed every 4 hours.*

Mechanism of Action. The '**drug**' combines with **AT III***. The resulting complex then interacts with certain activating clotting factors, such as : Factors IX, X, XI and XII, in order to prevent the conversion of **prothrombin to thrombin**. It has been observed that in high concentrations the complex invariably interacts with thrombin and thereby inhibits its effects to promote conversion of **fibrinogen** into **fibrin**. In short, it inhibits the aggregation of platelets. It is indeed a fast acting drug substance which has the overwhelming plus point of being a naturally occurring substance.

2.8. Radiosensitizer

The value and importance of radioisotopes for the imaging and killing of cancerous tumours has gained cognizance for more than three decades. A significant leap forward was duly accomplished with the incorporation of monoclonal antibodies that may be employed to direct imaging or cytotoxic agents to cancer sites with abundant selectively. The most effective and successful treatment of cancer with the aid of radionucleotides is critically dependent on the attainment of a **high target** (*i.e.,* the tumour and secondary metastases) to **non-target** (*i.e.,* healthy tissue and organs) ratio. In fact, the two most important and specifically radiosenitive tissues in humans are identical as the intestinal mucosa and the bone marrow, for which the target to non-target ratios of the order of 20 : 1 must be maintained so as to avoid the lethal consequences of high radiation doses.

Very high degree of selectivity in targeting the tumour cells can only be accomplished with the aid of an antibody that binds promptly and strongly to the **tumour–associated compounds (antigens)** that clears swiftly from the normal tissue and which has been irreversibly radiolabelled with the appropriate radioisotoppe. Molecular biologists are effectively tackling the first two issues to constantly devising antibodies, both whole and fragments, whose rates of catabolism, clearance and uptake besides half-life in the tumour relative to other tissues may be mentioned for the desired *in vivo* duration. However, the latter problem is solely addresed by the practising chemist, who in turn is required to design, synthesize and link to the antibody an appropriate **functionalized ligand** whose structure is determined by the choice of radioisotopoe.

Radioisotopes may be conveniently divided into *two* categories, namely ;

(*a*) Therapeutic Radioisotopes

(*b*) Imaging Radioisotopes

2.8.1. Therapeutic Radioisotopes

The **radioisotopes** that are used exclusively for the treatment of various diseases are generally known as therapeutic **radioisotopes**. The following Table contains the different ranges of **therapeutic radioisotopes** :

*Antithrombin III.

Isotope	Half-life/h	Dose Rate/ radh^{-1} per Gg^{-1}	Total electron dose/rad from 1 Gg^{-1} at t_{∞}	Mean range in tissue/mm
^{90}Y	64	1.96	180	3.9
^{67}Cu	62	0.58	30	0.2
^{111}Ag	170	0.82	198	1.1
^{131}I	193	1.22	115	0.4
^{161}Tb	166	0.50	101	0.3
^{188}Re	17	1.91	44	3.3
^{199}Au	75	0.53	47	0.1

In **radioimmunotherapy** it is pertinent to select a specific type of isotope that should be suitable for the tumour morphology. This fact may be substantiated with the help of the following two examples :

Example-1 : **Long-range emitters** :

The densely packed lymphomas or hepatacellular carcinoma when crossfixed from the long-range emitters like ^{90}**Y**—it registers an appreciable contribution to the dose to the tumour. This particular aspect is very important because the radiolabelled antibody may not be in a position to penetrate densely packed tumours efficiently or may not bind uniformly to tumours where the level of surface antigen is modest.

Example-2 : Short-range emitters :

Interestingly the smaller tumours such as the leukemias can be more effectively treated with the short-range emitters like ^{199}**Au**.

2.8.2. Imaging Radioisotopes

The ideal **radionucleotides** or **radiopharmaceuticals** for **organ imaging** should possess the following characteristic features, namely :

(*a*) decay by γ-radiation alone and having an energy of about 200 keV ;

(*b*) possess half-life in ranging between 6 to 12 hours ;

(*c*) must be readily available ;

(*d*) should be chemically versatile *i.e.*, be easily incorporated into carrier molecules ;

(*e*) produce radiopharmaceuticals that are fairly stable both *in vitro* and *in vivo*.

Ironically enough, not a single **radionucleotide** is known till date which compiles all the five above mentioned criteria. There are in all about **2000 imaging radioisotopes** that are used today for organ imaging purposes.

The following table contains a few important ranges of **imaging radiopharmaceuticals** :

Imaging Radioisotopes :

Isotope	Half-life/h	Photon energy/keV
^{111}In	68	171
^{99m}Tc	6.02	141
^{67}Ga	80	184
^{131}I	193	364
^{123}I	13.2	159
^{64}Cu*	12.8	511

*For use in positron emission tomography (PET)

Two typical examples are described here :

2.8.2.1. Technetium-99m (^{99m}Tc)

Because it has a short-life and can be administered in relatively large doses, and because the energy of its γ-emission is readily detected, **Technetium-99m** is very widely employed, either as the pertechnetate or in the form of various labelled compounds, particles and colloids for scanning bone and organs such as the brain, liver, lung, spleen and thyroid. **^{99}Tc** is used in over 80% of imaging procedures.

Dose : *Usual, 37 to 185 MBq (1 to 5 millicuries) in the investigation of the liver and spleen and upto 740 MBq (20 millicuries) for bone marrow).* **[mCi = Millicuries]**

2.8.2.2. Gallium-67 (^{67}Ga)

This **imaging radiopharmaceutical**, in the form of its citrate, is concentrated in some tumours of the lymphatic system and other soft tissues. Localization has been reported in inflammatory lesions and **Gallium-67** has been employed effectively for the diagnosis of infection.

Dose : *For tumours of lymphatic system and soft tissues : 55.5 to 92.5 MBq (1.5 to 2.5 millicuries) to visualize tumour by scanning techniques.*

2.9. Cromakalim

Cardiovascular diseases is still responsible as the cardinal cause of death in the technologically advanced and developed countries and also supported by the fact that hypertension places a person on a high risk of heart attacks and strokes. About 1/5th of the population suffers from hypertension, the causes of which are not yet fully understood, but various factors for instance : genetic history, age, diet, stress and strain and smoking may be involved either fully or partially. While mild hypertension can be arrested by altering the patient's lifestyle, but non-treatment of acute hypertension may ultimately lead to enhanced risk of stroke, kidney failure and impaired vision.

Hypertension the quite and dreadful disease has been treated effectively over the past two decades with the aid of different classes of drugs, for instance ;

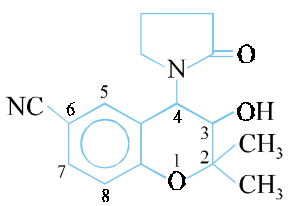
(*a*) β-Blockers (or β-adrenoreceptor antagonist)

(*b*) Calcium channel blockers and

(*c*) Angiotensin converting enzyme (ACE) inhibitors

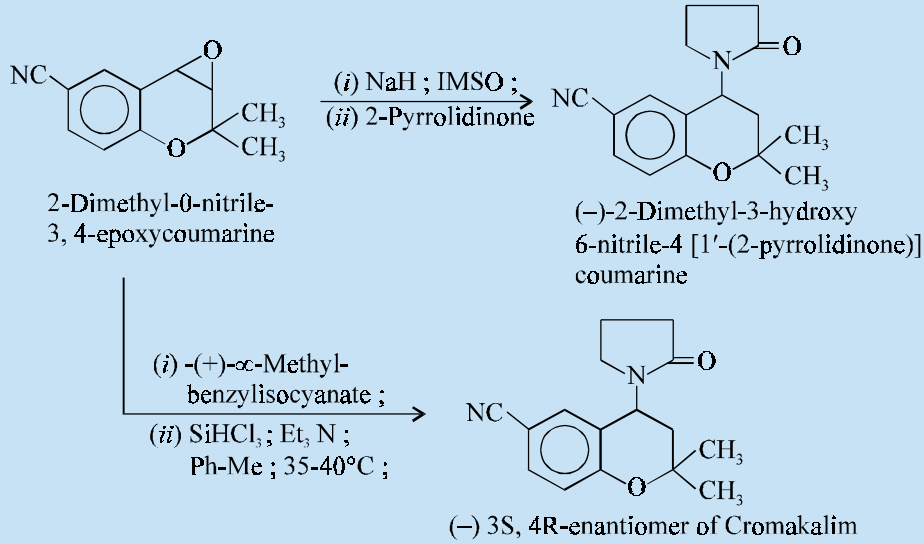
More recently a new class of drugs for treating hypertension has been discovered that relaxes smooth muscle by activating potassium channels. Precisely this novel mechanism involves an enhancement in the outward movement of potassium ions through channels in the membranes of vascular smooth muscle cells, ultimately leading to relaxation of the smooth muscle. Hence, these compounds may be termed as **potassium channel activators**.

A. *Cromakalim*



2-Dimethyl-3-hydroxy-6-nitrile-4 [1′-(2-pyrrolidone)] coumarine ;

Synthesis



It is prepared by treating 2-dimethyl-6-nitrile-3, 4-epoxy coumarine *first* with sodium hydride in dimethylsulphoxide and *secondly* with 2-pyrrolidinone to obtain 2-dimethyl-3-hydroxy-6-nitrile-4 [1′ (2-pyrrolidinone)] coumarine. The resolution of the resulting **cromakalim** is achieved *via* the S-α-methylbenzyl carbamate to get the (-)-3S, 4R enantiomer.

It is used as an antihypertensive agent. It has also shown the ability to relax human bronchial tissue. It is an **effective inhibitor of histamine-induced bronchoconstriction**. The long plasma half-life of cromakalim suggests that it would be specifically beneficial in the treatment of patients suffering from nocturnal asthama.

Dose : *Hypertension : oral, 1.5 mg ; Asthma ; oral, 0.5 mg at night (at the low oral dose employed, no reduction in blood pressure is observed.*

Future Prospects

The future perhaps lies in the design and synthesis of selective potassium channel modulators for treating the various ailments associated with smooth muscle function. It is, however, quite evident that potassium ion channels showing diverse characteristics exist in plethora of cells in the human body and because these channels are particularly responsible in modulating cellular activity, it is very much likely that drugs which are able to influence different categories of these channels may be developed in the near future for treating many other diseases effectively. In short, **cromakalim** has shown to be a versatile drug having potential usage in a number of diseases. It is further anticipated that this potential will be meaningfully exploited with its active enantiomer **(-) 3S, 4R cromakalim**.

2.10. Drugs to Combat AIDS

The **acquired immunodeficiency syndrome (AIDS)** is a condition characterized by the development of life-threatening opportunistic infection or malignancies with severe depression of the T-cell mediated immune system caused by infection with **human immunodeficiency virus (HIV)**.

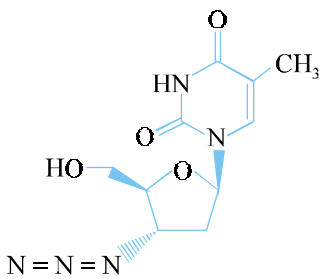
AIDS was first and foremost described as a specific entity in the US in 1981, and its frequency and mortality since have increased tremendously in geometrical proportion. In the US alone by 1991, approximately 1,20,000 cases were reported in adults and adolescents and nearly 2000 cases in children.

There is a global epidemic of **AIDS** perdominantly in the US, Europe, South America, Canada, Africa and South East Asea. These **HIV centres** rare broadly responsible for transmission of the virus to others. Unless and until serious and prompt corrective measures are not taken immediately by the respective governments in terms of sex-education, dreadfulness of this disease and meaningful precautionary measures to contain the spreading of **AIDS**, there is every possibility that it may even penetrate into relatively healthier countries of the world.

Various therapeutic agents in the form of specific drugs, **immunoglobulins**, **vaccines** and **photochemical procedures** are known to the world to combat the ever-increasing menace of AIDS. They will be discussed briefly in this chapter.

For instance : Zidovudine, **Carbovir**, **AIDS-immunoglobulins**, **AIDS-vaccines**, and **HIV-drug** under the spotlight.

A. *Zidovudine*



Thymidine, 3′-azido-3′-deoxy ; Azidothymidine ; AZT ;

Retrevir(R) (Burroughs Wellcome) ;

Zidovudine has shown activity against human immunodeficiency virus (HIV) ; consequently, it is used for the treatment of **AIDS** and **AIDS-related complex (ARC)**. It positively enhances the survival and improves the quality of life of patients with complications such as severe weight loss, fever, pneumocystosis, herpes zoster, herpes or thrush. Because it crosses the **blood-brain-barrier (BBB)**, it has a favourable response on the neurological symptoms of **AIDS**.

Zidovudine is a nucleoside analogue structurally similar to thymidine and hence it is also known as **azidothymidine**.

It may be given to symptomatic patients with HIV-infection (with blood CD_4 counts of less than 200 per mm^3 or 200 to 500 per mm^3 and rapidly falling).

Its oral bioavailability ranges between 52 to 75%. The plasma-protein binding is 34 to 38%. The drug is mostly metabolized in the liver with a half-life ranging between 0.8 to 1.9 hours. Only 14% of the drug is eliminated as such through the urine.

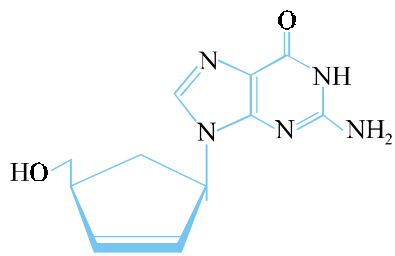
Dose : *Adult, oral, asymptomatic HIV-infection, initially 100 mg every 4 hour, while awake (500 mg a day), after 1 month dose may be reduced to 100 mg every 4 hour ;* intravenous infusion, *1 to 2 mg/kg infused over 1 hr. every 4 hr. around the clock (6 times a day).*

Mechanism of Action. The '**drug**' exerts its action by creeping into the **retroviral DNA** *via* **reverse transcriptase** to render a more or less nonsense sequence which essentially breaks the ensuing DNA chain synthesis. However, it has been established that the *reverse transcriptase* is nearly 100 folds more susceptible to the '**drug**' in comparison to the **mammalian DNA polymerase.** Zidovudine exhibits its therapeutic activity specifically against the human immuno deficiency virus. Consequntly, it is employed for the treatment of **AIDS** and **AIDS-related complex (ARC)**. As it happens to cross the **blood-chain barrier (BBB)**, it demonstrated a rather favourable effect on the prevailing **neurological symptoms of AIDS.** However, in the course of prolonged therapy resistance may also take place gradually.

Another school of thought suggests that **zidovudine** gains its entry into the host cells by means of diffusion, and in turn gets *phosphorylated* by the **cellular thymidine kinase.** Thus, the enzyme **thymidylate kinase** eventually helps in the conversion of the *monophosphate* into the *diphosphate* and the *triphosphates* respectively. It is, however, pertinent to state here that the rate determining step is actually **'the conversion to the diphosphate'** ; and, therefore, perhaps very high levels of **monophosphorylated AZT** invariably get accumulated into the cell. Besides, relatively low levels of diphoshpate and triphosphate are also present. Importantly, **AZT-triphosphate** affords competitive inhibition of **reverse transcriptase** specifically with regard to **thymidine triphosphate.**

Furthermore, the 3′-azido functional moiety [—N = $\overset{\oplus}{N}$ = $\overset{\ominus}{N}$] predominantly prevents the formation of a **5′, 3′-phosphodiester bond** ; and, therefore, **AZT** gives rise to DNA-chain termination effectively, thereby producing an **incomplete proviral DNA** substantially.* Besides, **AZT-monophosphate** also executes competitive inhibition of the specific **cellular thymidylate kinase**, thereby lowering the **intracellular levels of thymidine triphosphate**. It has been reported that the '**point mutations**' at multiple sites prevailing in the reverse transcriptase invariably causes resistance that may ultimately lead to a rather lower degree of affinity for **AZT**.**

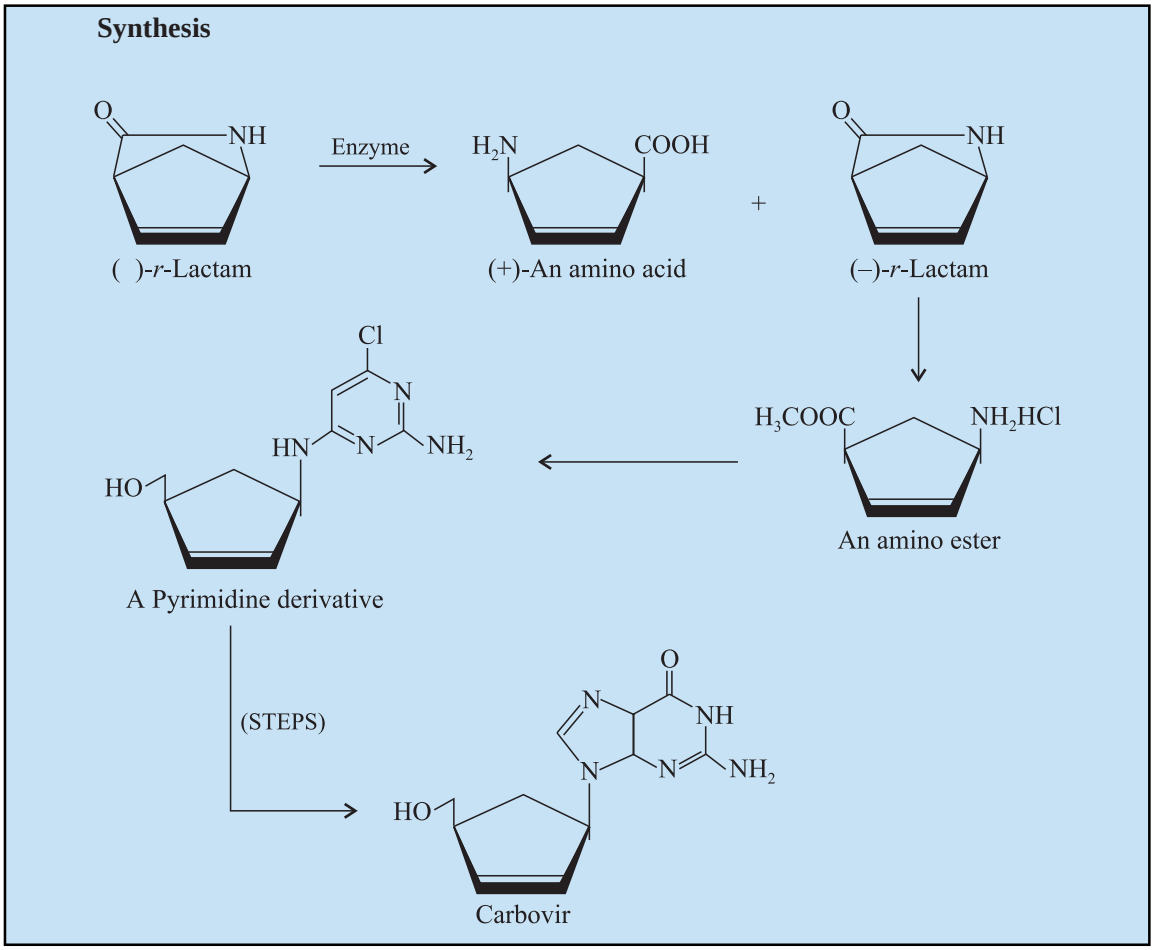
B. Carbovir



Carbovir

*Furman PA *et al.* Proc. Nale. Aead. Sci. USA., *873* : 8333, 1996.

Richman DD *et al. J. Infect. Dis.*, **164, 1075, 1991.



The racemic mixture of the γ-lactam is hydrolyzed enantioselectively to give the corresponding amino acid in tis *dextro*-form and the lactam, (-)-γ-lactam by an enzyme from a *Pseudomonas* microorganisms. The optically pure lactam, **(-)-γ-lactam** is ring-opened chemically to give the corresopnding amino ester. This compound is converted *via* the pyrimidine derivative into the desired **guanosine analogue** *i.e.*, **carbovir**.

It is a **cyclopentane derivative** that has been prepared in optically active form by employing a chemoenzymatic total azymmetric synthesis.

Carbovir has attracted a lot of interest as a potent inhibitor of the **AIDS** virus *in vivo.*

Mechanism of Action. The '**drug**' is a nucleoside analogue structurally related to guanosine having distinct antiviral activity against **HIV-1**. Its acts as an inhibitor of viral reverse transcryptase and is under investigation in the treatment of **AIDS**.

C. *AIDS-Immunoglobulins* :

AIDS-immunoglobulins are also known as **HIV-immunoglobulins**. More recently, **AIDS immunoglobulin preparations** containing **HIV-neutarlizing antibodies** have been prepared from the plasma of asymptomatic HIV-positive subject. They are being tried for passive immunization in patients with **AIDS** or **AIDS-related complex (ARC)**.

D. ***AIDS-Vaccines :***

These are also referred to as **HIV-vaccines**. In fact, a large number of prototype vaccines against the **AIDS** have been tested in human subjects for their critical studies.

E. ***HIV-Drug Under the Spotlight :***

Photodynamic therapy (PDT), the photochemical procedure now being used for cancer treatment, was successfully adapted to help in the fight against **AIDS**. A dye has been identified that can latch onto HIV and related viruses and knock them out when a light is shown on them.

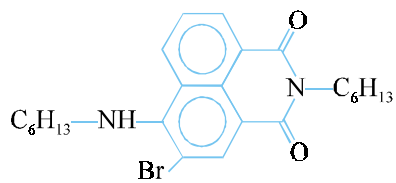
The collaborative research of **David Lewis**-an organic chemist and **Ron Utecht**-a biochemist, led to the development of a series of hydrophobic compounds which get among the lipids of the viruse's envelopes and finally link to trytophan molecules. The **loose dye-trytophan linkage** upon irradiation gets converted to a strong chemical bond. It is an established fact that trytophan is responsible for the transport of proteins across the biological membrane, it ultimately makes the viral envelope impermeable and its DNA cannot migrate out and thus the virus is rendered non-ineffective.

Later on, Lewis and Utecht, tried to **improve the single oxygen production of the dye** by introduction heavy atoms onto the molecule, such as bromine. In this way, they succeeded in turning the soft-virus envelope into a concrete jacket. It revealed that the new dyes prepared with bromine atom were 1000 times more potent and effective than the earlier compounds prepared by them.

The heavy-atom containing dyes are based on 3-bromo-4-alkylamino-N-alkyl-1, 8-naphthalimide. These are yellow dyes that absorb blue light, and are similar to the optical brighteners used in washing powders.

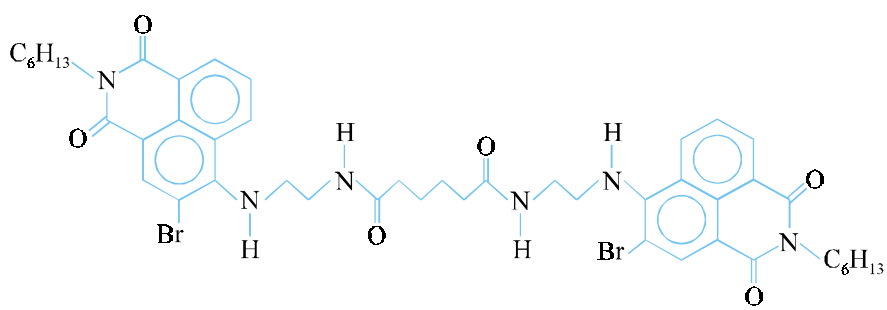
The **bromine-containing dyes** were prepared by Lewis and Utecht which are described here :

A. ***3-Bromo-4 (hexylamino)-N-hexyl-1, 8-naphthalimide***



It is a monomeric naphthalimide. It acts against **herpes simplex virus (HSV)** at concentrations around 250 nM.

B. ***Bis-amide of 3-Bromo-4 (hexylamino)-N-hexyl-1, 8-naphthalimide***



A Bis-Amide

It is a **dimeric naphthalimide**. It is effetive against **HSV** at concentrations below 100 nM.

In short, it may prove to be a good news for the potential therapy, because **HSV** is rather more difficult to kill than **HIV**.

Probable Questions for B. Pharm. Examinations

1. Discuss the role of **Prostaglandins** and **Eicosanoids** to combat the following diseases :

(*a*) Gastric ulceration

(*b*) Management of congenital heart disease

(*c*) Haemolytic-uramic syndrome and anticoagulant in the dialysis procedure.

2. (*a*) What is the role of **antilipedmic drugs** ?

(*b*) Enumerate the various factors causing **atherosclerosis.**

(*c*) Give the structure, chemical name and uses of **three** potent **antilipedemic drugs.**

3. How would you classify **Hormonal Antagonists.** Give the structure, chemical name and uses of at least **one** potent drug from each category.

4. Write a brief note on the following :

(*a*) Probucol

(*b*) Nitromifene citrate

(*c*) Flutamide

(*d*) Chlormadinone

(*e*) Spironolactone

(*f*) Gestrinone.

5. Discuss the synthesis of the following :

(*a*) Propylthiouracil from 3-oxo-caproate

(*b*) Isoniazid

(*c*) Cromakalim

(*d*) Ethambutol hydrochloride.

6. Give a comprhensive account of the **antimycobacterial drugs.** Support your answer with suitable examples.

7. Describe any **two** of the following **cardiac steroids and inotropic drugs :**

(*a*) cardiac drugs

(*b*) phosphodiesterase inhibitors

(*c*) adenylate cyclase stimulants

(*d*) drugs that emulate the Ca^{2+} sensitivity of myocardial contractile proteins.

8. What are **biosensitizers ?** Classify them by citing a few appropriate examples in support of your answer.

9. Discuss **cromakalim** as an important potassium channel activator. Give its synthesis and future prospects.

10. (*a*) Give a brief account on the **global epidemic of AIDS.**

(*b*) Discuss the synthesis of **carbovir.**

(*c*) **HIV-drug** under the spotlight.

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