DEPARTMENT OF CHEMISTRY

Udai Pratap Autonomous College

Varanasi -221002

E-content

Subject	:	Organic Chemistry
Class	:	B. Sc. II Semester
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Unit	:	IV
Topic	:	Drugs
Sub-topic	:	Introductory Medicinal Chemistry
Key words	:	Introduction, theories of drug action, soft and hard drug, Uses and functions of antibiotics, antipyretics, analgesic, psychoactive, antiseptic drugs

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B. Sc. II Semester

Unit: IV

Introductory Medicinal Chemistry

The term "drug" is derived from a French word: 'drogue'-a dry herb. Drug is a single active chemical moiety which is present in medicine and used for diagnosis, prevention, treatment and cure of a disease. Drugs which are chemical of low molecular mass interact with macromolecular targets and produce a biological response. According to WHO (1966) "Drug is any substance that can be used to modify or explore physiological systems or pathological states for the benefit of the recipient.

Characteristics of a Drug:

1. The action of an ideal drug should be localized at the site where it is required in body.
2. It should be non-toxic and have minimum side effects.
3. It should not damage host tissues or physiological process.
4. It should not make the host cells resistant to the drug after its use.

Classification of Drugs: On the basis of their therapeutic actions, drugs are classified in two categories.

i. **Chemotherapeutic agents:** These drugs are used in the treatment and cure of specific disease, i.e. disease caused by infection of microorganism like tuberculosis, malaria etc. These include antiseptics, antifungals, antibiotics etc.

ii. **Pharmacodynamic agents:** These drugs have characteristics effects upon the host but are not specific remedies for particular disease. These include antipyretics, analgesics, anaesthetics, antihistamines, anticoagulant etc.

Drugs may be categorized into two:

a. **Essential drugs:** These drugs satisfy the priority healthcare needs of the population.

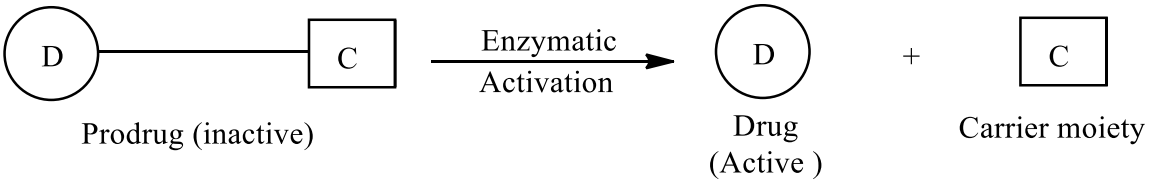
b. **Orphan drugs:** These are the biological products for diagnosis, treatment and prevention of a rare disease.

Prodrugs: The term prodrug was first used by Albert in 1958 for compounds which undergo biotransformation prior to exhibiting their pharmacological effects. They are defined as active drugs which are chemically transformed into inactive derivatives and release the active compound or the parent drug within the body before or after reaching the site of action. Some major objectives of prodrug design are as follows.

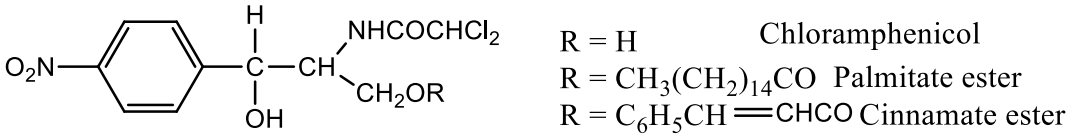
i. Improved chemical stability and bioavailability
ii. Improved organ selectivity
iii. Decreased side effects
iv. Improved patient acceptance and compliance

Based on their structure and mode of activation, prodrugs are of two different types:

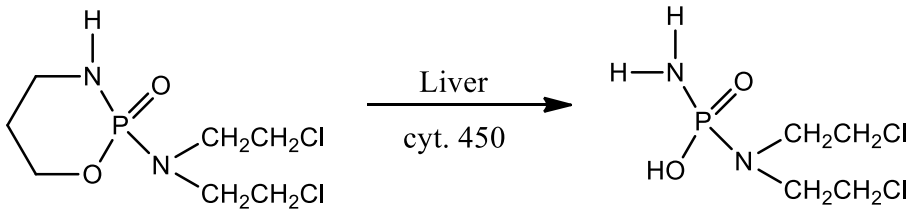
1. **Carrier linked prodrugs:** These are the compounds in which drugs are linked to a carrier moiety by a labile bridge. The carrier moiety is mostly lipophilic in nature. These types of prodrugs are bioactivated by hydrolytic reactions which may be a chemical or enzyme catalysed reaction.



Chloramphenicol has a bitter taste and is used as its palmitate or cinnamate ester (Prodrug). The active parent drug is released from the prodrug by the enzyme esterases present in intestine.

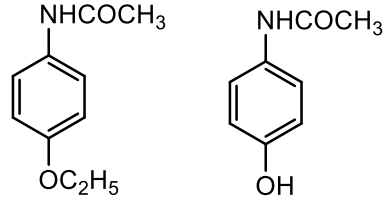


2. **Bioprecusors:** These are prodrugs which do not have a carrier group. They are bioactivated to the parent drug by enzyme catalysed hydroxylation, N-alkylation, O-dealkylation, oxidation or reduction reactions. Example: Cyclophosphamide is converted to active phosphoramide mustard in the liver.



Cyclophosphamide
(Prodrug)

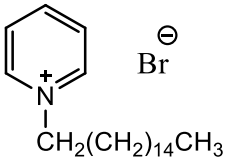
Active drug



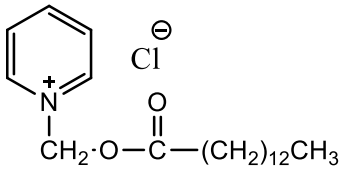
Phenacetin
Prodrug

Paracetamol
Active drug

Soft and hard drugs: Soft drugs are the drugs which are easily metabolized whereas hard drugs are either non-metabolisable or are hard to metabolise. Example: Cetyl pyridinium bromide (A) is an antimicrobial agent but it is difficult to metabolise. However, introduction of an ester linkage (B) in the structure of compound makes its metabolism easier.



Cetyl pyridinium bromide
A



B

Theories of Drug activity: A number of theories have been given to explain the activity of the drug but no single theory explains the activity of all types of drugs.

Occupancy theory: This theory was given by Clark and Gaddum (1926). It is also known as template theory. It states that the intensity of pharmacological effect of a drug is directly proportional to the number of receptors occupied.

$$\text{Drug (D)} + \text{Receptor (R)} \rightleftharpoons \text{Drug-receptor complex (DR)} \Longrightarrow \text{Response effect (E)}$$

The intensity of the response at any time will be proportional to the number of receptors occupied by the drugs

$$E \propto [DR]$$

If R_T is the total number of receptors, the maximum response E_{max} is given as

$$E_{max} \propto [R_T]$$

Assuming that all receptors are occupied by the drug, then fraction of maximum response (E/E_{max}) is given by the relationship as:

$$\frac{E}{E_{max}} = \frac{[DR]}{[R_T]}$$

$$\because DR \rightleftharpoons D + R$$

And if K_D is the dissociation constant, then

$$K_D = \frac{[D][R]}{[DR]}$$

$$\because [R_T] = [R] + [DR]$$

$$\therefore K_D = \frac{[D]([R_T] - [DR])}{[DR]}$$

$$= \frac{[D][R_T]}{[DR]} - [D]$$

$$\frac{K_D + [D]}{[D]} = \frac{[R_T]}{[DR]}$$

Or

$$\frac{E}{E_{max}} = \frac{[DR]}{[R_T]} = \frac{[D]}{K_D + [D]}$$

Or

$$E = \frac{E_{max}[D]}{K_D + [D]}$$

This theory is most applicable when all the drugs considered in the series have same type of drug receptor interactions and they produce the same maximal response irrespective of the dose.

Induced Fit Theory: This theory is based on the hypothesis that there occurs an induced conformational change in enzymes. It was originally proposed to explain enzyme substrate interactions. Koshland extended the theory to explain the mode of drug action. However, with drugs as substrates, biopolymers other than enzymes must also be considered as receptors. Koshland postulated that the active site of an isolated, crystalline enzyme does not necessarily need to have a morphology which is complementary to that of the substrate, but that it acquires such morphology only after interacting with the substrate which induces the conformational change.

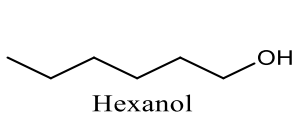
According to the induced fit theory, the biological effects produced by drugs arise due to the activation or deactivation of the enzymes. However, for non-catalytic proteins it may occur through a reversible change in the tertiary structure of enzymes or proteins. Drugs having flexible structures can also undergo conformational changes as they approach the receptor sites. Therefore, the drug-receptor interaction is dynamic and in most cases, the reversible morphological and electronic changes are responsible for the biological effects.

Rate Theory: This theory was given by Paton in 1961. According to rate theory it is not only the number of receptors occupied by a ligand that determines the response but it also controlled by the rate of formation of receptor ligand complex. Rate of association of a drug and receptor is proportional to the total number of encounters that drug has with the receptor per unit of time. The response effect of a drug is a function only of the rate of association and dissociation of the drug and receptor. If the rate of association and dissociation is high, the drug will be an agonist and if the rate of dissociation is slow, response gets reduced and the drug will be an antagonist.

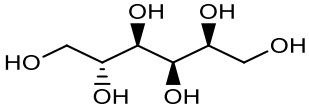
Structure Activity Relationship of Drug Molecule: The structure activity relationship (SAR) is the relationship between the chemical structure of a molecule and its biological activity. This allows modification of the effect or the potency of a bioactive compound by changing its chemical structure. The important groups along with their physiological effects are explained as below.

Binding role of –OH group: The binding role of hydroxyl group into aliphatic compounds generally decreases their biological and physiological activity which is almost proportional to the number of the hydroxyl groups. Examples:

1. Hexanol is more physiologically active than sorbitol.

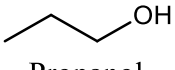


Hexanol

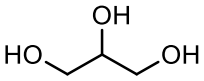


Sorbitol

2. Propanol is much more active than glycerol.

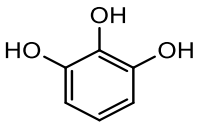


Propanol

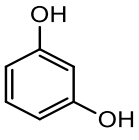


Glycerol

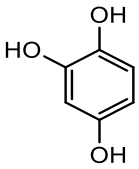
3. Polyphenols are more toxic in nature than phenol.



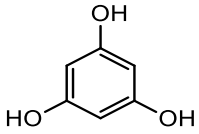
Pyrogallol



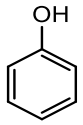
Resorcinol



Phloroglucinol

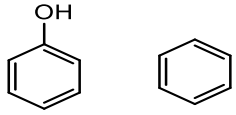


benzene-1,3,5-triol



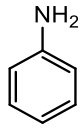
Phenol

4. Phenol is an antiseptic compound and contains strong toxicity more than benzene.

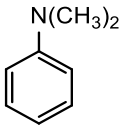


Phenol Benzene

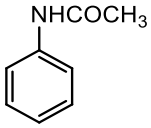
Binding role of –NH_2 group: The binding role of amino group in drug molecules is toxic in nature. Alkylation reduces their toxicity. Acylation also decreases the physiological action of parent compound. Example: Aniline is physiologically toxic while acetylated derivative, Sulphonation and carboxylation may also reduce the activity of amino compounds.



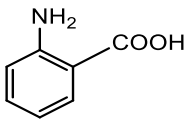
aniline



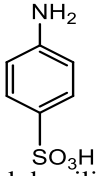
N,N-dimethylaniline



N-phenylacetamide



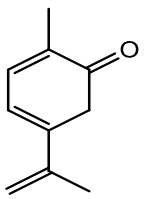
2-aminobenzoic acid
Anthranilic acid



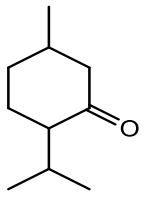
Sulphanilic acid

Binding role of double bond and aromatic ring: Double bonds are also electron rich, which make them potentially more reactive in the presence of strong electron acceptor. Example:

Aromatic compounds serve as the basis for many drugs, antiseptics, explosive, solvents and plastics (e.g. polyesters and polystyrene). The two simplest unsaturated compounds ethylene and acetylene were once used as anesthetics and were introduced to the medical field in 1924.



Carvone
(More toxic)



Menthone
(Less toxic)

Quantitative Analysis of Structure Activity Relationship (QSAR):

The quantitative structure activity relationship is a mathematical relationship in the form of an equation between the biological activity and measurable physiochemical parameters such as lipophilicity, shape and

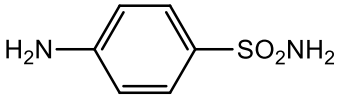
electronic distribution which have a measurable influence on the drug activity. Crum-Brown and Fraser published equation in 1868 which is considered to the first formulation of a quantitative structure activity relationship.

$$\phi = f(c)$$

The physiological activity (ϕ) was expressed as a function of the chemical structure (c). Richet, Meyer and Overton independently found that the biological activity of hypnotic and narcotic agents have a linear relationship with lipophilicity. Lipophilicity was expressed as oil-water distribution coefficient (partition coefficient) which measures the distribution of the compound between aqueous and lipid phases of the tissue.

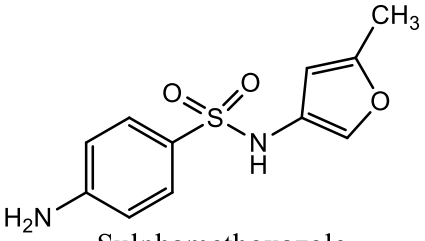
Uses and functions of antibacterial and antifungal agents:

Sulphonamides: Sulphonamide is a Sulphanilamide anti-infective used to treat vulvovaginal candidiasis caused by candida albicans. It is a competitive inhibitor of bacterial enzyme dihydropteroate synthetase.



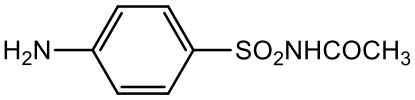
Sulphonamide

Sulphanethoxazol: Sulphamethoxazole is an oral Sulphonamide antibiotic. It is given in combination with trimethoprim to treat a variety of urinary tract, respiratory system and gastrointestinal tract disorders.



Sulphamethoxazole

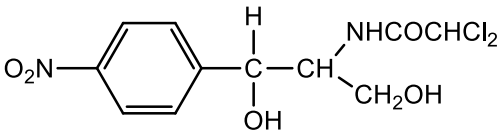
Sulphacetamide: Sulphacetamide is an anti-infective agent that is typically used to treat skin infections and urinary tract infections. It is indicated for the treatment of bacterial vaginitis, keratitis, acute conjunctivitis and blepharitis.



Sulphacetamide

Uses and functions of antibiotics:

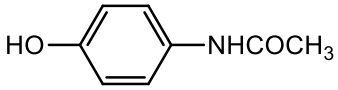
Chloramphenicol: Chloramphenicol is a laevorotatory broad spectrum antibiotic produced from streptomycetes. It is especially used for the treatment of typhus and typhoid fever. It is effective against viral disease as well as those due to bacterial invasion.



Chloramphenicol

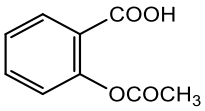
Uses and functions of antipyretics and analgesics: Drugs used to lower body temperature in feverish conditions are called antipyretics. Analgesics are the drugs used to relieve pain in various condition of health without loss of consciousness.

Paracetamol: It has analgesic and antipyretic activities. It is effective in a wide variety of arthritic and rheumatic condition involving musculoskeletal pain as well as the pain of headache etc.



Paracetamol

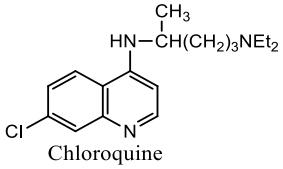
Aspirin: Aspirin is used as antipyretic, anti-inflammatory and an analgesic in headache, discomfort and fever due to common cold, muscular pain and aches.



Aspirin

Uses and functions of antimalarial agents: The drug used for suppression and treatment of the tropical disease malaria are called antimalarials.

Chloroquine: It is a much more effective than quinine.

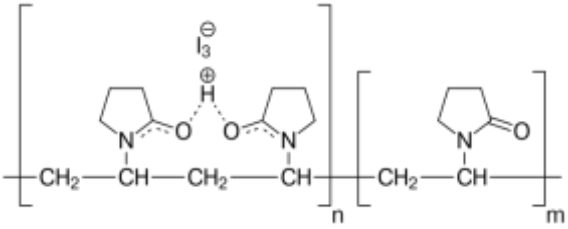


Chloroquine

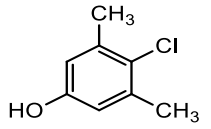
Uses and functions of antiseptics:

Povidone-iodine:

Povidone-iodine is a chemical complex of the polymer povidone (polyvinylpyrrolidone) and triiodide (I_3^-). It is soluble in cold and mild-warm water, ethyl alcohol, isopropyl alcohol, polyethylene glycol, and glycerol.

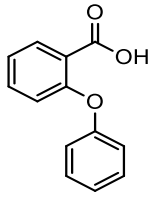


Dettol: Alcoholic solution known as Dettol. It is widely used as an antiseptic for skin cuts and in dressing wounds.



Chloro-m-xylenol
(Dettol)

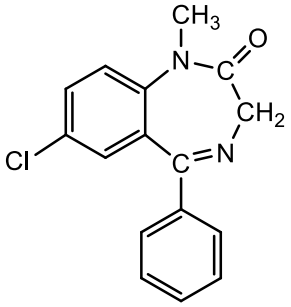
Salol: It is power full external and internal antiseptic.



Phenylsalicylate
Salol

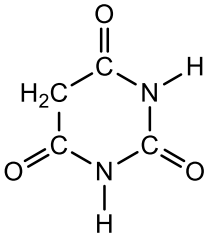
Uses and functions of Tranquilizers:

Diazepam: It is commonly used to treat a range of conditions including anxiety, seizures, alcohol withdrawal syndrome, muscle spam, and restless legs syndrome.



Diazepam

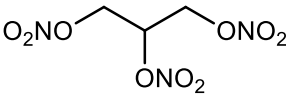
Barbiturates: Barbiturates are widely used as hypnotics (sleep inducers) and sedative to relieve tension caused by the complexities and pressures of modern life.



Barbituric acid

Uses and functions of psychoactive drugs:

Glyceryl nitrate: Nitroglycerin is a vasodilator used as antianginal drug. It is used as a medicine to treat cardiovascular disease. It is more explosive in liquid state as compared to solid state.



Nitroglycerin