Unit VI

Medicinal Chemistry

The word drug is derived from the French word *drogue* meaning a dry herb. *According to WHO, a drug may be defined as any substance or product which is used or intended to be used for modifying or exploring physiological systems or pathological states for the benefit of the recipient.*

Some important terms which are used in chemistry of Drugs- Pharmacy, Pharmacology, Molecular Pharmacology, Pharmacodynamics, Pharmacophore, Pharmacodynamic agents, Antimetabolites, Bacteria, Virus, Fungi, Mutation etc.

Pharmacophore: The physiological activity of drugs has been found to depend upon the presence of particular functional groups or structural units present in a drug. Such a part of drug which causes the actual physiological effect is known as pharmacophore. Biologically active inactive compounds can be converted to active compound by introduction of a pharmacophore. Some important pharmacophore are alkyl, hydroxyl, alkoxy, aldehyde or ketone, halogens and unsaturated lipids.

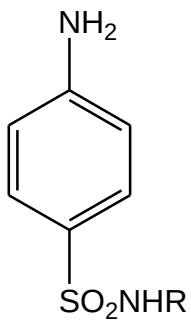
Pharmacodynamic agents: The drugs which stimulate or depress various functions of the body so as to provide relief from symptoms of discomfort are called pharmacodynamic agents. They are generally used in the case of non-infectious diseases to correct abnormal functions. Examples include analgesics, sedatives, anaesthetics etc.

Antimetabolites: The substance which takes part in cellular metabolic reactions is called metabolite. And the chemical agent which blocks the metabolism due to its close structural similarity to the metabolite is called antimetabolite.

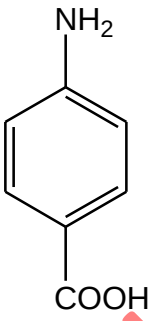
Drug Action

The principle of drug action can be described by the action of sulpha drug as antibacterial activity. We know that *para*-aminobenzoic acid (PABA) is a normal cellular constituent of the bacteria. When a sulphonamide (a structurally similar compound to that of PABA) is

absorbs by bacteria, this sulphonamide can not fulfil the function of PABA, the essential metabolite and hence the growth and reproduction of bacteria would stop.



Sulphonamide

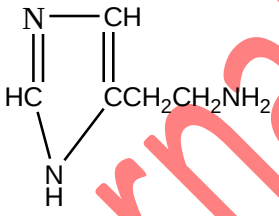


PABA

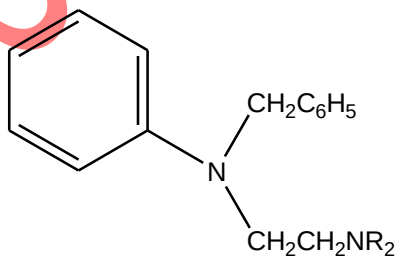
The inhibition or antagonism of the essential metabolite by structurally similar compound is called metabolite-antagonism while the inhibitors are called metabolite-antagonists.

There are some examples of metabolite-antagonists in which antagonists donot resemble the corresponding metabolite structurally. They are

(i) Histamines and anti-histamines: Histamine is an essential amino acid, has been found to be antagonised by all the antihistamines, many of which possess the phenylbenzylalkylamine structure.

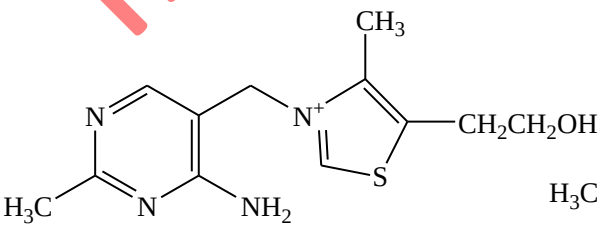


Histamine

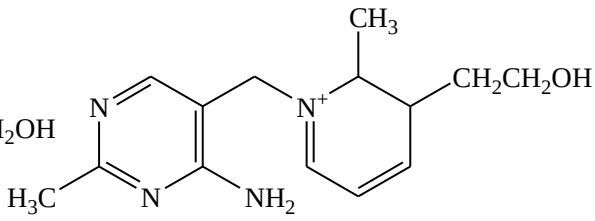


Antihistamines

(ii) Aneurine (Vit- B_1)-pyrithiamine: Aneurine, which is treated as essential growth factor has been antagonised by pyrithiamine.



Aueurine



Pyrithiamine

Absorption of Drugs

The performance of a drug is based on its ability to reach the site where it is required. The drug action can be achieved by the process of absorption. Drugs are generally weak acids or weak bases. Thus absorption of drugs in the gastrointestinal tract has been found to depend upon their acid or basic strength. The weakly acidic drugs have been absorbed more readily in the stomach because in the acidic environment they are almost undissociated. On the weakly basic drugs have been readily absorbed in the intestine because due to the intestine alkalinity they are slightly dissociated there.

The lowest pk_a value of an acid drug for absorption in the stomach has been found to be about 3 whereas the highest pk_a value of a basic drug for rapid absorption in the intestine has been found to be about 7.8.

Quantitative structure-activity and relationships (QSAR)

Quantitative structure-activity and relationships, often simply known as QSAR, is an analytical application that can be used to interpret the quantitative relationship between the biological activities of a particular molecule and its structure. It is considered a major method of chemical researching all over the world today and is frequently used in agricultural, biological, environmental, medicinal, and physical organic studies.

The main objective of QSAR is to observe the biological responses of a set of molecules, measure it, and statistically relate the measured activity to some molecular structure on their surface. The product of QSAR will then produce useful equations, images or models in either 2D or 3D form that would relate their biological responses or physical properties to their molecular structure.

Applications

1. One of the first historical QSAR applications was to predict boiling points.
2. The biological activity of molecules is usually measured in assays to establish the level of inhibition of particular signal transduction or metabolic pathways. Drug delivery often involves the use of QSAR to identify chemical structures that could have good inhibitory effects on specific target and have low toxicity (non-specific activity).
3. While many quantitative structure activity relationship analyses involve the interactions of a family of molecules with an enzyme or receptor binding site, QSAR can also be used to study the interactions between the structural domains of proteins. Protein-protein interactions

can be quantitatively analyzed for structural variations resulted from site-directed mutagenesis.

4. (Q)SAR models have been used for risk management.

Lead compounds

A lead compound is a representative of a compound series with sufficient potential (as measured by potency, selectivity, pharmacokinetics, physicochemical properties, absence of toxicity and novelty) to progress to a full drug development programme. Or it can be said that a lead compound is a compound from a series of related compounds that has some of a desired biological activity. A lead compound is a first foothold on the drug discovery ladder. It takes much more effort to make a lead compound into a drug candidate. Identification of a lead compound may arise from a variety of different routes and in modern drug discovery this is likely to be very different in the past.

The identification of a new lead compound can fall into to two categories, depending on whether a biological target relevant to the disease/condition in question is known or unknown. Below is the example of how lead compound has been discovered in the past.

Penicillin

Fleming discovered that mould from one culture caused bacteria in its vicinity to undergo analysis. Penicillin G and V isolated; antibiotic activity discovered; new β-lactams discovered and made through modification to give antibiotics with improved activity. Chlordiazepoxide (Librium) Sternbach, searching for new drugs to treat anxiety, revisited some quinazoline oxides which were first made 20 years ago and thought to have the benzheptoxadiazinone structure.

Elementary idea of molecular modelling of drugs

Molecular modelling has become an integrated part of investigating, explaining, and predicting the properties of small organic molecules as potential drug candidates. Modelling techniques are applied in the fields of compound synthesis (conformational analysis and reaction planning), drug discovery (virtual screening), activity rationalization (docking and molecular dynamics simulations), and lead optimization including the prediction of antitarget effects.

To be successfully incorporated into the drug discovery and development process, all these methodologies require constant experimental feedback from medicinal chemistry and biological experiments to validate the results obtained by modelling to further improve these

methods. This close interplay of disciplines is vital; however, it can be challenging to establish a vivid and cooperative communication between modellers, chemists, and biologists.

Treatment of cancer

There are many types of cancer treatment. The types of treatment that you have will depend on the type of cancer you have and how advanced it is. Some people with cancer will have only one treatment. But most people have a combination of treatments, such as surgery with chemotherapy and/or radiation therapy. You may also have immunotherapy, targeted therapy or hormone therapy.

Types of Treatment

There are many types of cancer treatment. The types of treatment that you receive will depend on the type of cancer you have and how advanced it is.

The main types of cancer treatment include:

Surgery

Describes how surgery is used to treat cancer. Includes information about what you can expect before, during, and after surgery.

Radiation therapy

Describes how radiation therapy is used to treat cancer. Includes information about the types of radiation, side effects, and what you can expect from treatment.

Chemotherapy

Describes how chemotherapy is used to treat cancer. Includes information about what to expect during treatment and tips for managing diet needs and working during treatment.

Immunotherapy

Describes how immunotherapy helps your immune system fight cancer. Includes information about the types of immunotherapy and what you can expect during treatment.

Targeted therapy

Information about the role that targeted therapies play in cancer treatment. Includes how targeted therapies work against cancer, who receives targeted therapies, common side effects, and what to expect when having targeted therapies.

Hormone Therapy

Describes how hormone therapy slows or stops the growth of breast and prostate cancers that use hormones to grow. Includes information about the types of hormone therapy and side effects that may happen.

Stem Cell Transplant

Describes how stem cell transplants are used in cancer treatment. Includes information about the types of transplants and what to expect when receiving a transplant.

Precision Medicine

Information about the role that precision medicine plays in cancer treatment. Includes how genetic changes in a person's cancer are identified and may be used to select treatments that are most likely to help them.

Some people with cancer will have only one treatment. But most people have a combination of treatments, such as surgery with chemotherapy and/or radiation therapy. When you need treatment for cancer, you have a lot to learn and think about. It is normal to feel overwhelmed and confused. But, talking with your doctor and learning about the types of treatment you may have can help you feel more in control.

Treatment of HIVS

HIV is treated using a combination of medicines to fight HIV infection. This is called antiretroviral therapy (ART). ART isn't a cure, but it can control the virus so that you can live a longer, healthier life and reduce the risk of transmitting HIV to others.

ART involves taking a combination of HIV medicines (called an HIV regimen) every day, exactly as prescribed.

These HIV medicines prevent HIV from multiplying (making copies of itself), which reduces the amount of HIV in your body. Having less HIV in your body gives your immune system a chance to recover and fight off infections and cancers. Even though there is still some HIV in the body, the immune system is strong enough to fight off infections and cancers.

By reducing the amount of HIV in your body, HIV medicines also reduce the risk of transmitting the virus to others.

ART is recommended for all people with HIV, regardless of how long they've had the virus or how healthy they are. If left untreated, HIV will attack the immune system and eventually progress to AIDS.

HIV medicines are grouped into six drug classes according to how they fight HIV. The six drug classes are:

- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Protease inhibitors (PIs)
- Fusion inhibitors
- CCR5 antagonists (CCR5s) (also called entry inhibitors)
- Integrase strand transfer inhibitors (INSTIs)

The six drug classes include more than 25 HIV medicines that are approved to treat HIV infection. Some HIV medicines are available in combination (in other words, two or more different HIV medicines are combined in one pill.)

Side effects

Short term side effects

Almost all medicines have side effects, including HIV medicines. While your HIV meds are controlling the virus in your body, they may also cause:

- Anemia (abnormality in red blood cells)
- Diarrhea
- Dizziness
- Fatigue
- Headaches
- Nausea and vomiting
- Pain and nerve problems
- Rash

Long term side effects

HIV medications can have some significant long-term side effects. Many of these side effects are treatable, some can be long-term. HIV infected patients should aware the nature of side effect and need to consult with healthcare about any side effects, so that he or she can decide the best course of treatment for both your HIV disease and the side effects. Some of the most common long-term side effects of HIV treatment are:

- **Lipodystrophy**–A problem in the way your body produces, uses, and stores fat. (Also called "fat redistribution"). These changes can include losing fat in the face and extremities, and gaining fat in the abdomen and back of the neck.
- **Insulin Resistance**–A condition that can lead to abnormalities in blood sugar levels and which may start diabetes.

- **Lipid abnormalities**–A problem which may lead to increase in cholesterol or triglycerides.
- **Decrease in bone density**–Decrease in bone density is a significant issue, especially for older adults with HIV. This can lead to an increase risk of injury and fractures.
- **Lactic acidosis**–Lactic acidosis can cause problems ranging from muscle aches to liver failure.

Sulpha Drugs

The synthetic chemotherapeutic agents which contains sulphonamide, SO_2NH_2 group in their structure are called sulpha drugs. These drugs are widely used for the treatment of bacterial infections. They are also used against certain gram positive and gram negative cocci, gram negative bacilli and protozoa. Presently, sulphonamides have been largely replaced by most antibiotics used for the treatment of many bacterial diseases.

The first synthetic sulphanilamide (*p*-aminobenzene sulphonamide) was successfully prepared by Glemo in 1908. Sulphanilamides are now replaced by the more broadly effective chemical antibiotics.

Classification

From the therapeutic point of view, the sulphanilamides have been classified as

1. Compounds which are readily absorbed and readily excreted. Eg: Sulphamethazine, sulphadiazine, sulphacetamide etc.
2. Compounds which are readily absorbed and slowly excreted. Eg: Sulphaphenazole, sulphamethoxypyridazine etc.
3. Compounds which are poorly absorbed. Eg: succinylsulphathiazole, sulphaguanidine etc
4. Compounds with special indication. Eg: Marfanil, sulphapyridine etc.
5. Absolute Compounds. Eg: Sulphanilamide, sulphathiazole etc.

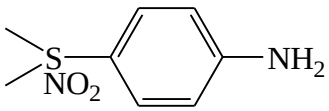
Sometimes they have also been classified according to their therapeutic utility as follows

1. Sulphoamides used for the treatment of systematic infection. Eg: Sulphacetamide, sulphamethizole (short acting), sulphamethoxazole, sulphasymazine (intermediate acting), sulphamethoxypyridazine (long acting).
2. Sulphoamides used for the treatment of local gastrointestinal infections. Eg: Sulphaguanidine, succinyl sulphathiazole, salicylazosulphapyridine etc.

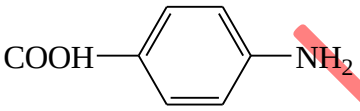
Mechanism of Action of Sulpha Drugs

Sulpha drugs don't kill the bacteria directly at the concentrations in which they are used but they prevent the growth and multiplication of bacteria.

Woods, in 1940, found that the bacteriostatic properties of sulphonamides have been due to their similarity in structure with that *p*-aminobenzoic acid (PABA). The later compound (PABA) is an important for the normal functioning of some of the vital process in bacteria.

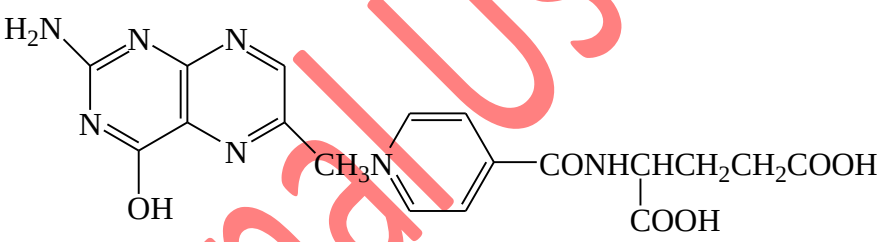


Sulphonamide



PABA

PABA is required for the synthesis of folic acid which is essential for the growth and multiplication of microorganisms. Folic acid is not single substance but is composed of a group of closely related substances, the most important of which is pteroylglutamic acid.



pterin glutamic acid

Due to similar structure with that of PABA, the sulphonamides compete with it for the attachment to the enzyme which converts PABA into folic acid. The enzyme is thus blocked and the synthesis of folic acid stops. Consequently organism becomes unable to grow and multiply.

Antibiotics

Chemical substances which are produced by or derived from living cells, capable of inhibiting the life processes in small concentrations or even destroying the micro-organisms are called antibiotics.

All chemical substances produced or derived from living cells are not treated as antibiotics. The chemicals which satisfy certain conditions are called antibiotics. They are

(a) Antibiotic must have been a product of metabolism although it might have been synthesized.

(b) If the antibiotic is a synthetic product, then it should be a structural analogue of naturally occurring antibiotic.

(c) The antibiotic must be effective at low concentrations.

(d) The antibiotic must antagonise the growth and/or survival of one or more species of the micro-organisms.

If antibiotic is use as therapeutic agent then following condition has to be satisfied:

(a) It must be effective against a pathogen.

(b) It must not cause significant toxic side-effects.

(c) Its stability must be appreciably high.

(d) It could be stored for a long time period without appreciable loss of activity.

(e) The antibiotic should be completely eliminated from the body soon after its administration has been stopped.

Classification of Antibiotics

Antibiotics have been classified into a number of ways

1. **First classification:** The broad based classification of antibiotics divides them into the following two types:

(a) Broad spectrum antibiotics: This includes such antibiotics which may be used as curative agents against several ailments. Examples of this type are penicillin, chloramphenicol, tetracyclines etc.

(b) Narrow spectrum antibiotics: These include such antibiotics which are highly specific in their action. Examples are bacitracin, nystatin etc.

2. **Second classification:** This classification is based on the type of bacteria (Gram +ve or gram -ve) the antibiotic can destroy.

In the gram stain method, the fixed bacterial smear is made to treat with a solution of crystal violet followed by the treatment with iodine. The smear is then washed with alcohol. The bacteria which retain the colour of the crystal violet and appear deep violet in colour are called **Gram positive bacteria**. On the other hand, bacteria which loss the violet colour and get counter stained by safranin ad appear red in colour are called **Gram negative bacteria.** Some example of Gram positive and Gram negative bacteria are:

Gram positive bacteria	Gram negative bacteria
Diphtheria bacillus	Coli and typhoid bacillus
Leprocy bacillus	Gonococcus
Streptococcus	Vibrios
Stapphylococcus	Plague bacillus

3. **Third classification:** This classification is based on their chemical structures. The different classes are:

   (a) Penicillins: These are derived from amino acids.

   (b) *Aminoglycosides:* These contain a sugar molecule glycosidically linked to an amino compound.

   (c) Chloramphenical and synthetic analogues

   (d) Macrolides: These contain a large lactone ring

   (e) *Lincomycins:* These are sulphur containing antibioticsbut sulphur atom is not present in ring.

   (f) Polypeptides: These contain polypeptide chain

   (g) *Polyenes:* These have conjugated polyene system.

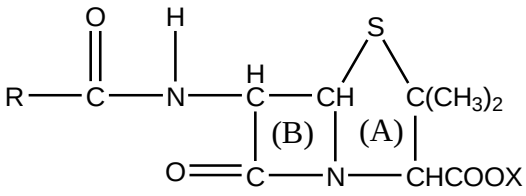
   (h) *Antitubercular antibiotics:* These have antitubercular action.

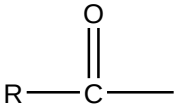
   (i) *Antineoplastic antibiotics:* These have active for controlling of cancer.

   (j) *Unclassified antibiotics:* These include a nuber of antibiotics which are not related to any one of the class described. Examples: griseofulvin, vancomycin hydrochloride etc.

Penicillins

Penicillin is a chemical whose chemical formula is $C_9H_{11}N_2O_4SR$ and differs only in the nature of R. The general structure of penicillin is



Here the thiazolidine ring nucleus (A) is fused to a β-lactam ring (B) which is attached to a side chain (

). In the above structure, X is sodium, potassium, aluminium, peocaine, benzathine or free acid.