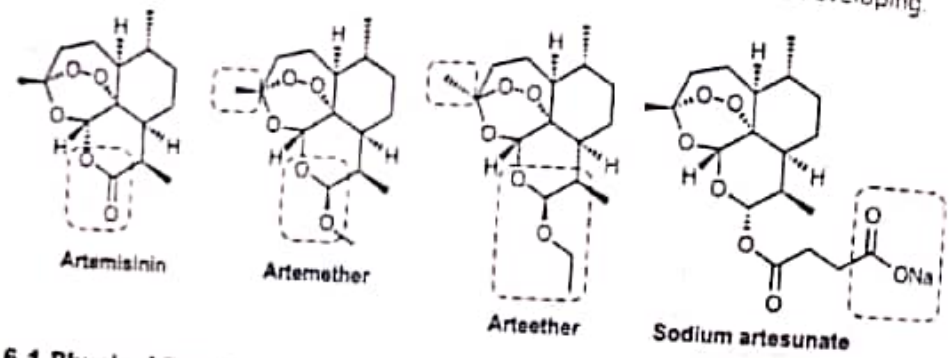
Barbituric acid (pK_a 4.0) 5,5-disubstituted barbituric acid (pK_a 8.0)

3. Artemisinin has proved highly effective in treating malaria, but there are problems related with its use. First of all, it is not water soluble and it has to be administered by intramuscular (IM) injection. It is also found that malaria re-occurs in upto 25% of patients treated after a month or so. The two drugs, artemether and arteether are more hydrophobic than artemisinin and can be administered more easily by injection in oil. They are also more potent. Sodium artesunate salt form is also used clinically. Owing to the ionized carboxylate group, sodium artesunate is water soluble and can be administered by intravenous (IV) injection. Drawbacks for these drugs include a short plasma half-life, which is typically less than an hour, and rapid elimination. This means that the drug is cleared from the system within a day of administration, leaving the longer-lived drugs of the combination therapy to continue the battle alone. This increases the risk of drug-resistant parasites developing.



Artemisinin Artemether Arteether Sodium artesunate

1.6.1 Physical Properties

A physical property of the drug is responsible for its action, such as taste, solubility, surface area, size, lipophilicity, ionization, hydrogen bonding, polarity, aromaticity and shape, polarity etc. It is observed that oral drugs tend to be lighter and have fewer H-bond donors, acceptors, and rotatable bonds than drugs with other routes of administration. Poor solubility in aqueous media is one of the major hurdles in the drug development process. For example, bitter taste drugs increase the flow of hydrochloric acid in the stomach. By increasing the bulk of drug in the intestine produces laxative effect. Certain drugs like kaolin adsorb water on to its surface and thereby reduce gastric motility. The surface area per gram (or per dose) of a solid drug is changed by altering the particle size. For example, a cube that is 1 cm on each side has a surface area of 6 cm^2. If this cube is broken into cubes with sides

integ- increases, the drug will dissolve more rapidly. Therefore, many poorly soluble and slowly dissolving drugs currently are marketed in a micronized or microcrystalline form. Many pharmaceutical solids can exist in two or more crystalline forms called polymorphs. *Polymorphism* is the ability of the same drug molecule to crystallize into more than one different crystal structure that has a different arrangement and/or conformation of molecules in the crystal lattice. The different arrangements of atoms within the crystal unit cell can have a profound effect on physical and chemical properties of the final crystallized compound and on the final drug product. The structurally non-specific drugs include general anesthetics, hypnotics, a few bactericidal compounds and insecticides. However, it is important to note here that the biological characteristic of such drugs is exclusively related to physical properties of molecules rather than chemical properties.

1.6.2 Chemical Properties

A number of compounds that possess significant pharmacological actions are structurally specific drugs. Though physical characteristics of the drug play an important role in the biological activity, yet chemical properties do exert their acceptable influence on the activity. Drugs normally interact with targets such as proteins, enzymes, lipids, or pieces of DNA or RNA, etc. and show their action by simple chemical reactions like neutralization, chelation, oxidation, reduction, hydrolysis, etc.

- **Oxidation :** Mostly carried out by enzyme Cytochrome P450

  Examples : Paracetamol, Ibuprofen etc.
- **Reduction :** Cytochrome P450 working in opposite direction.

  Examples : Chloramphenicol, Warfarin etc.
- **Hydrolysis :** Generally occurs at intestine, blood plasma, and tissues.

  Examples : Aspirin, Procaine etc.
- **Neutralization :** Neutralization of gastric HCl by antacids.

  Examples : Aluminium hydroxide gel, Calcium carbonate etc.
- **Chelation :** When metals like lead, mercury, iron, and arsenic build up in your body, they can be toxic. Chelation therapy is a treatment that uses medicine to remove these metals so they don't make you sick.

Toxic heavy metals can be eliminated by chelating agents like EDTA, Penicillamine etc. Some drugs produce effects without altering cellular function and without binding to a receptor. For example, most antacids decrease gastric acidity through simple chemical reactions; antacids are bases that chemically interact with acids to produce neutral salts e.g. Aluminium hydroxide neutralizes acid in stomach.

introduce such drugs is to inject, but they cannot be used against intracellular targets as they are unable to cross cell membranes.

Very hydrophobic drugs if administered orally, they are likely to be dissolved in fat globules in the gut and will be poorly absorbed. If they are injected, they are poorly soluble in blood and are likely to be taken up by fat tissue, resulting in low circulating levels. In order to be absorbed efficiently from the GIT, a drug must have accurate balance of water against fat solubility. For example amines are weak bases and it is observed that most of the effective drugs contain amine groups having pK_a value in the range 6 to 8. Hence, they are partially ionized at slightly acidic pH and alkaline pH present in the intestine and blood, respectively, and can easily equilibrate between their ionized and non-ionized forms. This allows them to cross cell membranes in the non-ionized form, while the presence of the ionized form gives drug good water solubility and permits good binding interactions with its target binding site.

2.6 LIPINSKI RULE OF FIVE

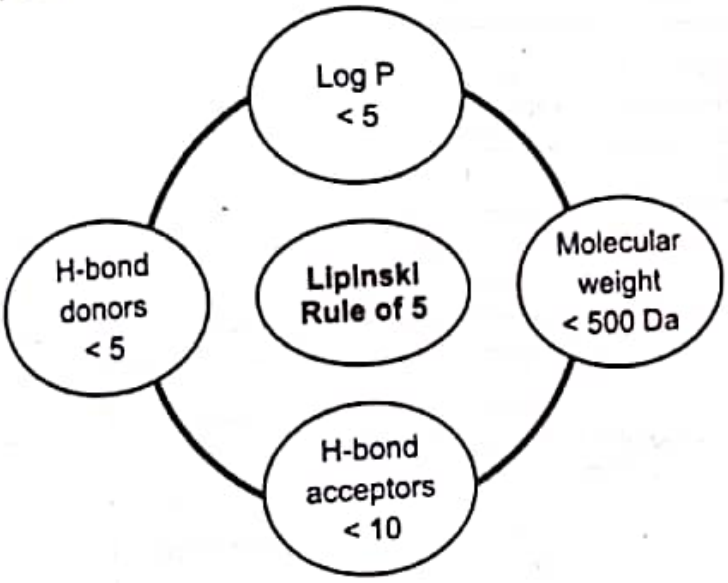
The rule of five was derived from an analysis of compounds from the World Drugs Index database aimed at identifying features that were important in making a drug orally active. It was found that the factors concerned involved numbers that are multiples of five :

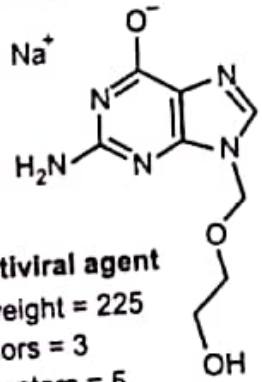
(i) *Molecular weight less than 500;*

(ii) Not more than *5 hydrogen bond donor (HBD)* groups;

(iii) Not more than *10 hydrogen bond acceptor* groups;

(iv) log P *value less than +5* (log P is a measure of a drug's hydrophobicity).





Acyclovir : Antiviral agent

- Molecular weight = 225
- H-bond donors = 3
- H-bond acceptors = 5
- Log P = 1

The rule of five has been extremely useful rule of thumb for many years. It has also been verified that a high molecular weight causes poor oral bioavailability. One of the reasons that the molecular weight appears to be important is that larger molecules always have too many functional groups capable of forming hydrogen bonds. Lipinski himself stated that a

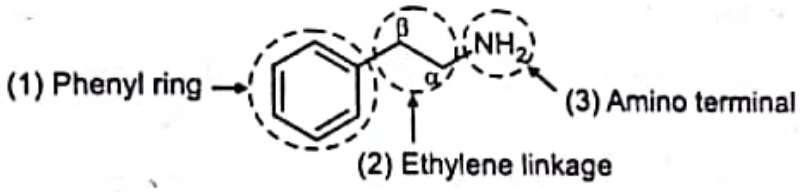
effects to treatments, rational drug design begins with a hypothesis that modulation of a specific biological target may have therapeutic value.

- In order for a biomolecule to be selected as a drug target, two essential pieces of information are required. The first is evidence that modulation of the target will be disease modifying. This knowledge may come from, for example, disease linkage studies that show an association between mutations in the biological target and certain disease states. The second is that the target is "druggable". This means that it is capable of binding to a small molecule and that its activity can be modulated by the small molecule. A drug design that relies on the knowledge of the three-dimensional structure of the bio molecular target is known as structure-based drug design.

2.7.9 Structure-Activity Relationship (SAR)

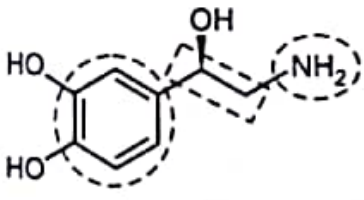
Medicinal chemistry is the study of how novel drugs can be designed and developed. *Structure-Activity Relationship (SAR) is the most important concept in drug development.* The process of drug design and development is greatly influenced by a detailed understanding of the structure and function of molecular targets that are present in the body. Structure-activity relationships (SARs) and quantitative structure-activity relationships (QSARs) are theoretical models that can be used to predict the physicochemical, biological (e.g., a toxicological endpoint), and environmental properties of substances.

A SAR is an (qualitative) association between a chemical substructure and the potential of a chemical containing the substructure to exhibit a certain biological property or effect. The major drug targets are normally large molecules (macromolecules), such as proteins and nucleic acids. Knowing structures, properties, and functions of these macromolecules is critical if we think to design new drugs. Knowing the target structure and its functional groups will allow the medicinal chemist to design a drug that contains complementary functional groups that will bind the drug to the target.

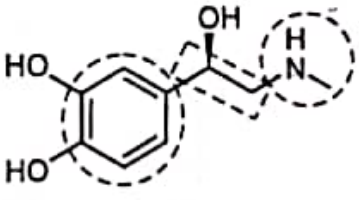


β-Phenylethylamine

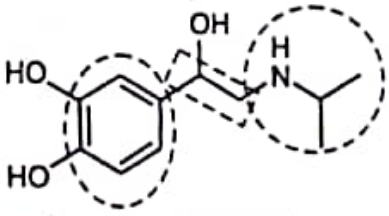
Structure - Activity relationship



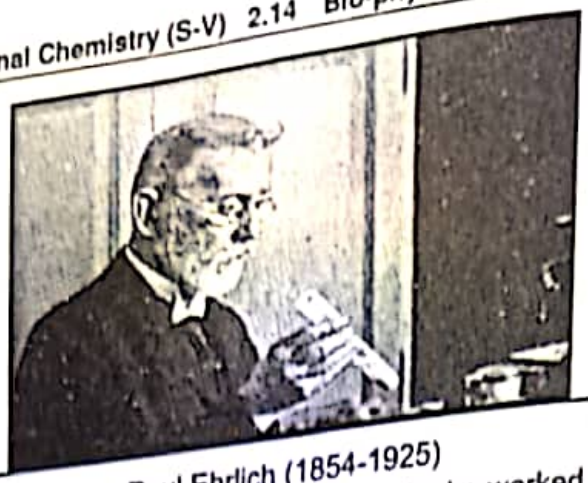
Norepinephrine



Epinephrine

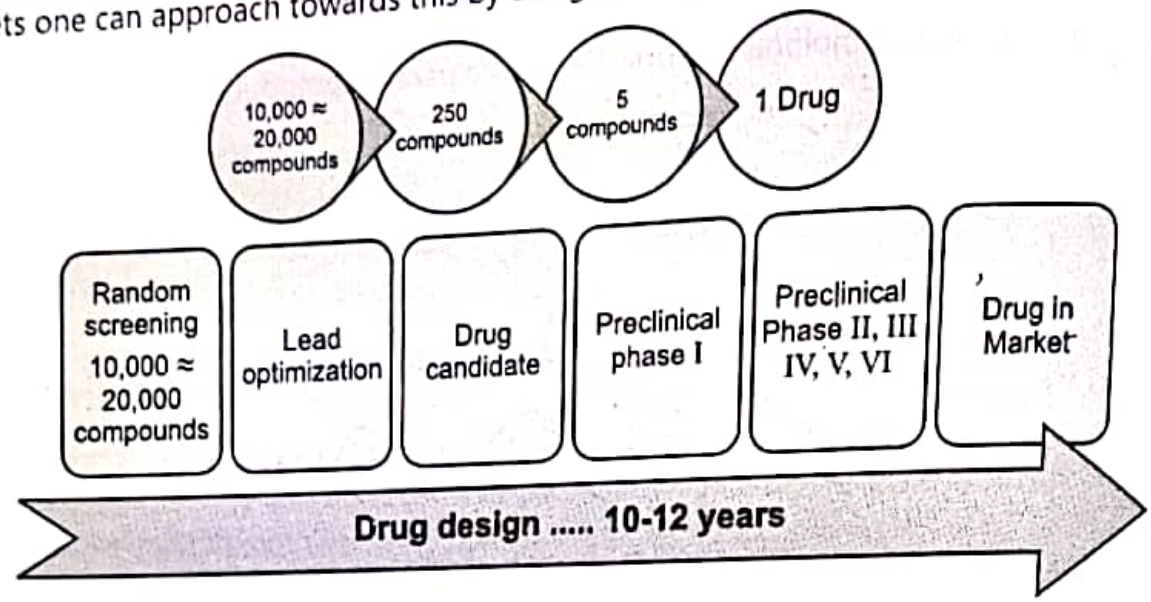


Isoproterenol



Paul Ehrlich (1854-1925)
A Nobel Prize-winning German scientist, who worked in the fields of immunonogy and antimicrobial chemotherapy

Thus the concept of magic bullet was introduced by Paul Ehrlich and what he said wa we image an organism as infected by certain species of a bacterium, then it would be e to cure it if we can discover a substance that would have specific affinity for these bacte and only this bacteria and they should have not affinity for normal constituents of the bo and such substances which he defined them as magic bullet. In reality there are no ma bullets one can approach towards this by using rational techniques.



- Drug design, frequently referred to as rational drug design, is the innovative process of finding new drugs based on the knowledge of a biological target.
- The first step in the discovery process of a new drug is the identification of the lead compound. It should have some desirable properties that are likely to be therapeutically useful.
- Changing the structure of lead compound is known as *molecular modification*. The modern research tendency is to *avoid the synthesis of new molecules based on chemical perception*, which is time and cost consuming.
- In contrast to *traditional methods of drug discovery, which depend on trial-and-error testing of chemical substances* on cells or animals, and matching the superficial

Sir Alexander Fleming (1881-1955) : Scottish bacteriologist best known for discovery of Penicillin.

In 1928, while working on influenza virus, he observed that mould had develop accidently on a staphylococcus culture plate and the mould had created a bacteria-fr circle around itself.

He was inspired to further experiment and found that a mould culture prevente growth of staphylococci. He named the active substance as a penicillin. Fleming w awarded **Nobel Prize** in the year 1945.

(A) Antimicrobial Agents

3.1 INTRODUCTION

Disease : The term disease refers to abnormal functioning of a body. Usually disease are described as medical conditions that are characterized by specific signs and symptoms The causative agents can be external (pathogen) or internal *(dysfunctioning of interna organs)*. In humans, diseases are associated with pain, distress, dysfunctioning of bod systems, social problems and even death also. Diseases can affect a person physically as wel as mentally.

Diseases are classified usually on the basis of cause i.e. pathogenesis or symptoms. The diseases are broadly divided into following two categories.

(a) Infectious Diseases :

These are diseases that are caused by pathogenic microorganisms, including bacteria fungi, parasites and viruses. They are also known as communicable diseases or transmissible diseases. Transmission of these agents can occur in several ways, including direct physical contact with an infectious person, consuming contaminated foods, contact with contaminated body fluids, contaminated inanimate objects, airborne (inhalation), or by insect or tick bite. Some disease agents can be transmitted from animals to humans, and some of these agents can be transmitted in more than one way. Examples of common infectious diseases are hepatitis, COVID-19, malaria, influenza, anthrax, aspergillosis bacterial meningitis, cholera, chickenpox, diphtheria, tuberculosis, leprosy, yellow fever etc.

In 1929, Alexander Fleming discovered the first β-lactam antibiotic, penicillin G from a rare fungal variant of *Penicillium notatum* (*Penicillium chrysogenum*) but he was unable to isolate it in pure form. Later in 1938 Florey and Chain successfully isolated and purified penicillin. It was the first antibiotic to be used clinically in 1941. Initially Penicillin-G was associated with some shortcomings; let us discuss some of them.

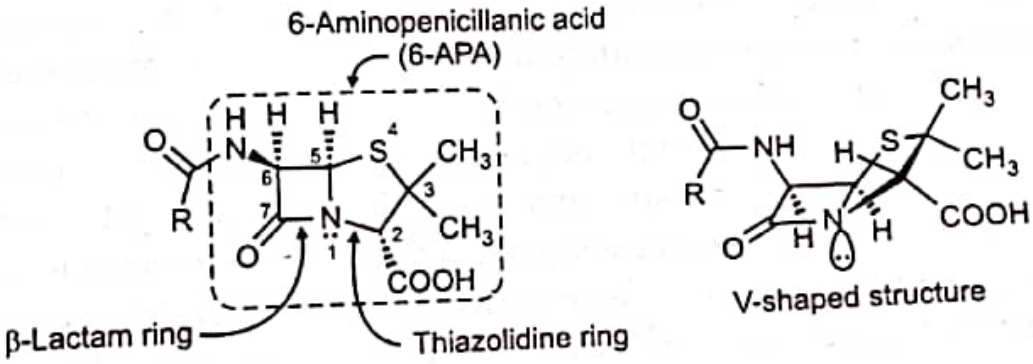
Shortcomings of Penicillin G :

- **Acid sensitivity :** Inactivation of β-lactam ring due to opening under acidic conditions was the major drawback of Penicillin G. This was due to highly strained and reactive lactam ring and neighbouring group participation by acyl side chain. If it is given orally it is inactivated under acidic condition in stomach, hence it is injected.
- **Inactivation by an enzyme β-lactamase :** Many bacterial strains develop an enzyme β-lactamase which trigger lactam ring to open, resulting in inactivation of penicillin G.
- **Narrow spectrum of activity :** Penicillin G was active against only non-β-lactamase producing gram positive bacilli and several gram negative cocci. In order to overcome these problems, various structural modifications were carried out.

As a result, currently many potential penicillin derivatives are in therapeutic use e.g. Ampicillin (stable towards acid), naficillin (stable towards β-lactamase). Ampicillin and amoxicillin are examples of broad spectrum penicillin derivatives.

Structure of Penicillin :

The penicillin nucleus consists of 6-aminopenicillanic (6-APA) acid which is composed of fused thiazolidine and β-lactam rings and a side chain consisting of an amide linkage.



The structure of Penicillin

The overall structure of the molecule is "V" shaped or like a half-open book. Due to this, planarity of lactam bond is lost and the resonance of amide nitrogen with its carbonyl group is inhibited. Consequently, the β-lactam ring is much more reactive and becomes more sensitive towards nucleophilic attack as compared with normal planar amides.

Structure-Activity Relationship (SAR) :

The conclusions of SAR studies are as follows :

- The strained β-lactam ring is essential for the activity.

(b) Non-infectious Diseases :

Non-infectious diseases are diseases that are not caused by pathogenic microorganisms and are not transmissible directly from one person to another. These include diseases like cancer, diabetes, heart diseases, arthritic diseases, alzheimer, depression, kidney diseases, respiratory diseases etc.

In this chapter, we will discuss drugs used to treat infectious diseases.

3.1.1 Antimicrobial Agents

The word antimicrobial was derived from the Greek words anti (against), micro (little) and bios (life) and refers to all agents that act against microbial organisms. *Antimicrobial agent* can be defined as a chemical that kills or inhibits the growth of microorganisms. These can act against microbial infections either by killing microorganism or by arresting their growth. They do this by different mechanisms including inhibition of cell metabolism, inhibition of bacterial cell wall synthesis, interactions with the plasma membrane, protein synthesis and inhibition of nucleic acid transcription and replication. Most of them are selectively toxic to microorganisms without affecting host cells. The basis of selective microbial toxicity is the action of the drug on a component of the microbe (e.g. bacterial cell wall) or metabolic processes (e.g. folate synthesis) that is not found in the host, or high affinity for certain microbial biomolecules.

3.1.2 Classification of Antimicrobial Agents

Antimicrobial agents can be broadly classified depending on types of organisms against which the drug is primarily active. These are as follows.

(a) **Antibacterial agents :** Examples : Penicillins, aminoglycosides, fluoroquinolones, erythromycin, sulfa drugs, etc.

(b) **Antifungal agents :** Examples : Griseofulvin, amphotericin B, ketoconazole, fluconazole etc.

(c) **Antiviral agents :** Examples : Acyclovir, zidoyudine, amantadine, ribavirin.

(d) **Antiprotozoal agents :** Examples : Chloroquin, pyrimethamine, metronidazole.

(e) **Anthelmintic :** Examples : Mebendazole, albendazole, diethyl carbamazine.

The drugs from each of these classes are further subdivided into different groups or classes on the basis of different factors e.g. type of antimicrobial action, source, chemical structure, spectrum of activity and mechanism of action.

Types of Antimicrobial Actions :

(a) **Microbiocidal agent :** Antimicrobial agent that kills the microorganism is called as microbiocidal agent. These can be of following types.

Bactericidal agents : (These kill bacteria) e.g. Cephalosporins, penicillins, aminoglycosides, etc.

Fungicidal agents : (These kill fungi) e.g. Terbinafine, itraconazole (in high

4.2.3 Cancer

In cancer, some of the body's abnormal cells grow uncontrollably and spread to other parts of the body, and destroy body tissue. These cells may form lumps of tissue, known as tumors, which can be cancerous or non-cancerous (benign). The prominent types of cancer are breast cancer, prostate cancer, skin cancer (melanoma), colon cancer, lung cancer, basal cell cancer, leukemia (Blood cancer), lymphoma, etc.

4.2.4 Diabetes

When the sugar level goes up, pancreas releases insulin to control it. Diabetes is a condition of the body that affects the conversion of food into energy. It is usually a long-lasting or a chronic health condition, where it results in too much sugar in the blood. This is known as diabetes mellitus. Other types of diabetes are Type 1 diabetes (where the pancreas produces little or no insulin); Type 2 diabetes (which affects the way the body processes blood sugar), Prediabetes (in which blood sugar is high, but not high enough to be type-2 diabetes) and Gestational diabetes (a form of high blood sugar affecting pregnant women).

4.2.5 Mental Health Disorders

Mental health disorders also called mental illness, including a wide range of mental health conditions like dementia, schizophrenia, developmental disorders like autism, and other psychoses, etc. There are some anxiety disorders like depression, bipolar disorder, attention deficit hyperactivity disorder, borderline personality disorder also come under these disorders.

4.3 CHARACTERISTICS OF NON-INFECTIOUS DISEASES

- Non-infectious diseases are also called non-contagious or non-communicable diseases.
- These diseases are not caused by infectious agents like bacteria and viruses, and thus these do not spread from an infected person to a healthy individual.
- Most non-infectious diseases are caused due to an unhealthy diet and lifestyle, mutations, heredity, and environmental changes.
- Non-infectious diseases, unlike infectious diseases, are not seasonal and might occur at any time of the year.
- Diseases like cancer and diabetes might even be hereditary, which are inherited from parents to the offspring.
- These diseases are also more chronic as the symptoms appear gradually and thus are difficult to diagnose. Most non-communicable diseases give severe and long-lasting health effects on patients.
- These diseases are also found to be more severe and responsible for about 70% of all deaths worldwide.

They are commonly used :

1. To reduce high temperature and fever (antipyretic activity) e.g. Paracetamol.
2. To relieve moderate to mild pain in conditions such as headache, backache, myalgia, migraine, toothache joint pains, muscle pains, etc. (analgesic activity)
3. In the treatment of rheumatoid arthritis, osteoarthritis, juvenile rheumatoid arthritis (anti-inflammation activity). e.g. Indomethacin, Ibuprofen.
4. For the treatment and prevention of myocardial infarction, transient ischemic attack, and embolic strokes. e.g. Aspirin.
5. In the treatment of gout, rheumatic fever.

Side effects of NSAIDs :

- Gastrointestinal tract disturbances
- Nausea and vomiting
- Epigastric discomfort
- Peptic ulcer
- Gastrointestinal hemorrhage
- Anemia

4.5 ANALGESIC AGENTS (PAIN KILLLERS)

To understand pain killers we should know what pain is. So let us start with what it means.

Pain : Pain is defined as an unpleasant sensory and emotional experience due to actual or potential tissue damage or injury. Pain is one of the body's most important communication tools. Imagine what would happen if you felt nothing when put your hand on a hot plate. So, to some extent pain is beneficial as it is a warning signal about the threat and prevent further damage. There are different types of pains such as acute pain occurs immediately, chronic pain lasts for longer time, nociceptive pain (due to tissue damage), neuropathic pain (nerve damage) and psychogenic pain due to physiological factors.

4.5.1 Definition

Analgesic drugs are drugs that relieve or eliminate pain in the body without loss of consciousness. They decrease the sensitivity of pain by depressing CNS (central nervous system) or act on peripheral pain mechanisms without significantly altering consciousness. Analgesics are also called pain killers. These medicines are commonly used to treat pain due to surgery, toothache, arthritis, headache, or other causes. e.g. Aspirin, Paracetmol.

4.5.2 Types of Analgesic Agents

Analgesics are classified into two types :

(A) Narcotics or Opioid or True Analgesics :

Narcotic analgesics are a class of medicines that are used to provide relief from moderate to severe acute or chronic pain. These are the derivatives of opium, which are

ucture :

The chemical name of Aspirin is Acetyl Salicylic Acid (ASA).

perties :

- Aspirin occurs as colourless crystals or powder.
- It is slightly soluble in water and soluble in alcohol, chloroform, ether, and glycerine.
- Aspirin is stable in dry air but in the presence of moisture, it hydrolyses slowly into salicylic acid and acetic acid.
- Aspirin is acidic and produces effervescence with carbonates and bicarbonates.
- The salicylates have potent anti-inflammatory activity with mild analgesic and antipyretic activities.
- It is readily absorbed from stomach and small intestine.
- It is metabolized by tissue/plasma esterase.

ode of Action :

- Aspirin and nonselective NSAIDs are acted by blocking prostaglandin synthesis which are mediators of the inflammatory process. They inhibit the activity of the cyclooxygenase (COX) enzyme by binding covalently and irreversibly with COX-1 and COX-2 by acylating serine-530 in the active site.
- Acetylation of COX-1 creates a steric block that prevents the binding of arachidonic acid at the cyclooxygenase active site.

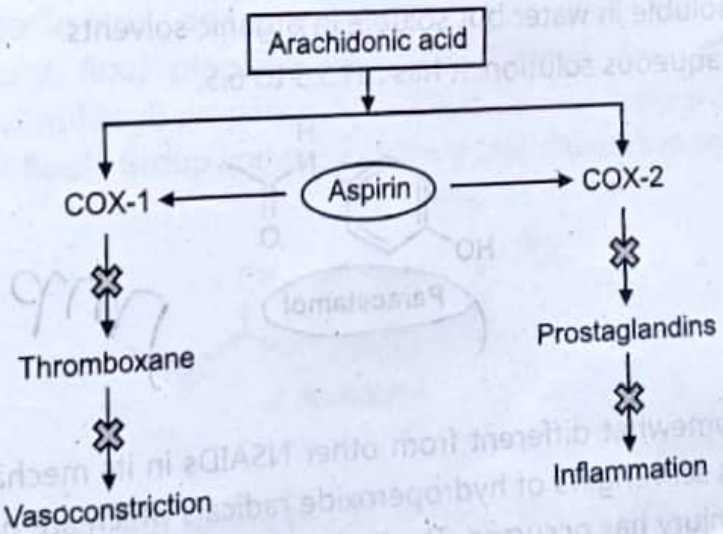


Fig. 4.6 : Mode of action of Aspirin

cyclooxygenase. In areas of high leukocyte activity (significant injury and inflammation) high concentration of hydroperoxides can overcome anilides and prostaglandins are duced. Therefore, anilides have no anti-inflammatory action. They are only capable of ppressing cyclooxygenase activity in areas that are not inflammed. The lack of acidic nctionality and weak COX inhibitory activity in anilides imparts several advantages to these gents including limited gastric irritation, ulceration.

Paracetamol also reduces fever by affecting chemical messengers in an area of brain that egulates body temperature.

ses :

1. It is one of the most common and effective medicine in reducing high temperature.
2. It is used to relieve mild to moderate pain such as joint, headache, migraine, body ache, toothache.
3. It is also used to treat arthritis pain of knee, hand, or hips.

ide Effects :

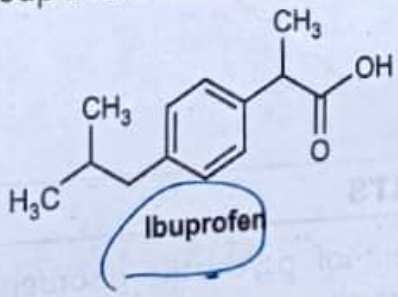
1. Nausea.
2. Stomach pain.
3. Loss of appetite.
4. Skin rashes.
5. Yellow eyes or skin.
6. Bloody or black stool.

4.6.3 Ibuprofen (Advil, Nuprin, etc.)

Ibuprofen was the first member of the propionic acid class of NSAIDs to come into general use. It is a traditional non-steroidal anti-inflammatory drug (NSAID) widely used in the treatment of mild to moderate pain and inflammation.

Structure :

Ibuprofen is propionic acid derivative (Profen). The structure of Ibuprofen has three parts, isobutyl, propionic acid, and phenyl; hence the name was derived from these components as isobutyl (ibu) propionic acid (pro) phenyl (fen). The IUPAC name of ibuprofen is 2-(4-isobutylphenyl) propanoic acid. It was derived from propionic acid in 1960s by the research arm of Boots Group and is considered safe alternative to aspirin.



Properties :

1. It is a strong organic acid having pK_a 3.0 to 5.0.
2. It forms water-soluble salts with an alkaline reagent.

Uses of Aspirin :

1. Aspirin is used as an analgesic drug (Dose 300 to 600 mg/day). Aspirin is used to relieve mild to moderate pain, swelling associated with many health conditions such as headache, flu, sprains migraine, etc.
2. It is used as an anti-inflammatory agent in the treatment of Rheumatoid arthritis.
3. It is used as an antipyretic drug
4. It is also used to treat or prevent heart attack, strokes, and chest pain.

Side Effects of Aspirin :

Most of side effects of aspirin are related to stomach and intestine. The side effects are mild and do not continue after the body uses up and eliminates. Occasionally there are some severe side effects. Common side effects of aspirin include :

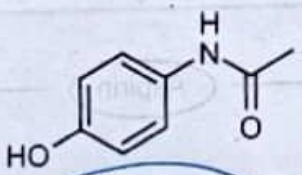
1. Difficulty in breathing.
2. Swelling of face, lips, tongue, or throat.
3. Severe nausea, vomiting, or stomach pain.
4. Sneezing and blurriness in the eye.
5. Hypersensitivity.
6. Ringing in ears.

4.6.2 Paracetamol [(N-4-hydroxyphenyl) Acetamide]

Acetaminophen is a p-aminophenol derivative. Paracetamol is the abbreviation of **para**-**acet**yl-**am**ino-phen**ol**, another name of the compound N-acetyl-para-aminophenol (or APAP). It is also known as acetaminophen in the USA. It is sold by many brand names like Crocin, Calpol, Tylenol, Panadol, etc. Paracetamol relieves mild-to-moderate pain, headache, and fever. It was first made in 1878 by Harmon Northrop Morse.

Properties :

1. It is a white crystalline solid, melts at 169-171°C.
2. It is odourless and has a slightly bitter taste.
3. It is slightly soluble in water but soluble in organic solvents.
4. In saturated aqueous solution, it has pH 5.5 to 6.5.



Paracetamol

Mode of Action :

Paracetamol is somewhat different from other NSAIDs in its mechanism of action. They are believed to act as scavengers of hydroperoxide radicals which are generated by invading leukocytes after the injury has occurred. The hydroperoxide radicals have a stimulating effect

(ii) Barbiturates e.g. Phenobarbitone, Secobarbital.

(iii) Non-barbiturate sedatives e.g. Chloral hydrate, Meprobamate.

4.8 HYPNOTICS AND SEDATIVES

Hypnotics and sedatives are sometimes called antidepressants and anxiolytic drugs. In general, sedative-hypnotics are a class of drugs used to slow down mental and physical functions of the body. These are central nervous system depressants that reduce anxiety and emotional tension. Sedatives are chemical agents that tend to produce a calming effect, relax muscles, and relieve feelings of tension, anxiety, and irritability without producing sleep. At higher doses, most of these sedative drugs will also produce drowsiness and cause sleep. Drugs that have such a sleep-inducing effect are called hypnotic drugs or hypnotics and are to be used in the treatment of insomnia (sleeplessness) or for surgical anesthesia. There is no sharp distinction line between sedatives and hypnotics and the same drug shows both the activities depending upon the dose used.

Ideal characteristics of Sedatives - Hypnotics :

1. They produce a sleep state identical to natural sleep.
2. Should not cause undesired daytime sedation.
3. Does not produce addiction and dependence.
4. No potential for decreasing or arresting respiration even at a relatively high dose.

Based on chemical structure, sedatives and hypnotics are classified as follows :

1. **Barbiturates :** e.g. Phenobarbitone, Pentobarbitone, Amobarbitone etc.
2. **Non-barbiturates :** They are further classified as follows :
   - **(a) Aldehydes and their derivatives :** Chloral hydrate, paraldehyde.
   - **(b) Piperidine derivatives :** Glutethimide, methyprylone.
   - **(c) Quinazoline derivatives :** Methaqualone.