SYLLABUS
The study of life saving drugs: Introduction, classification, properties and uses of followings.
Sulfa drugs, Antipyretics and analgesics, Antifungal and Anti-inflammatory drugs.

2.0 INTRODUCTION

Sulfa drugs are the synthetic chemotherapeutic agents which contain sulphonamide (\(-\text{SO}_2\text{NH}_2\)) group in their structure. These were the first chemotherapeutic agents to be widely used for the cure of bacterial infections in human. They have also been found to be active against certain gram +ve and gram –ve cocci, certain gram –ve bacilli and protozoa. They are not only cheap and safe antibacterial but efforts made to determine their mechanism of action have given a tremendous impetus to investigate other anti-metabolites of therapeutic interest. At present sulfa drugs are largely replaced by antibiotics in the treatment of most bacterial disease but they are still used alone or preferably in combination with the one or other antibiotics.

2.1 SULPHA DRUGS

Table 1 lists the commonly used sulpha drugs (also called sulphonamides), together with their structures and names. For naming them, the sulphonamide nitrogen is numbered N\(^1\) and the amino nitrogen is numbered N\(^4\).

Occasionally, there are sulphonamides in which N\(^4\) substituted by acyl group. For example:

Table: 1

<table>
<thead>
<tr>
<th>S.N.</th>
<th>Drug</th>
<th>R</th>
<th>S.N.</th>
<th>Drug</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Sulphanilamide</td>
<td>-H</td>
<td>4.</td>
<td>Sulphoxazole</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Sulphaacetamide</td>
<td>-COOH(_3)</td>
<td>5.</td>
<td>Sulphamerazine</td>
<td></td>
</tr>
</tbody>
</table>
2.2 SYNTHESIS OF SULPHA DRUGS

2.2.1 N¹-Substituted sulphonamides

It can be achieved by the general scheme, involving following steps:

Remember that in step (iii)—CONH group, that is hydrolyzed more readily than —SO2NH group.

The step (ii) in the above scheme requires different RNH₂ for each sulphonamide. The synthesis of important sulphonamides is outlined below.

For sulphanilamide, simple ammonia is needed in step (i).

2.2.2 Sulphacetamide

Which does not require an amine (RNH₂) can be synthesized from sulphanilamide itself by acetylation of both N¹ and N⁴ hydrogen followed by selective alkaline hydrolysis of N⁴ acetyl group.

The 2-aminopyridine required for sulpha pyridine can be prepared from pyridine by reaction with sodamide (chichibabin reaction)

The aminopyrimidine required for sulphadiazine can be prepared as follows:
The aminopyrimidines required for sulphamerazine and sulphadimidine can be synthesized as follows:

\[
\text{Formyl acetate} + \text{Guanidine} \rightarrow \text{2-amino-4-methylpyrimidine (for sulphamethazine)}
\]

\[
\text{Acetylacetone} + \text{Guanidine} \rightarrow \text{2-amino-4,6-dimethylpyrimidine (for sulphadimidine)}
\]

The amine required for sulphathiazole is 2-aminothiazole. It can be synthesized as follows:

\[
\text{vinyl acetate} \xrightarrow{\text{Cl}_2, \text{low temp.}} \text{2-Aminothiazole}
\]

Sulphisoxazole and sulfamethoxazole require 3,4-dimethyl-5-aminoisoxazole and 3-amino-5-methylisoxazole respectively as the coupling amines in step (ii).

**2.2.3 Succinylsulphathiazole and phthalysulphathiazole**

These N'-substituted sulphonamides can be prepared from sulphathiazole as per following scheme.

**2.2.4 Some additional sulphonamides**

Chart 1 lists some additional sulphonamides which have assumed importance in recent years.
2.3 USES

The sulphonamides are the first effective chemotherapeutic agents to have been employed for the prevention and cure of bacterial infections in man. Those derived from pyrimidine (1, 3-diazine) have been most successful in the clinical world. Although sulphonamides have been largely replaced by antibiotics in the treatment of infections, they are still used where patients are intolerant of antibiotics. The individual sulphonamides do not differ much in their activity against specific microorganisms. However, they differ from one another in their degree of absorption; their diffusion to the body tissues and their rate of elimination from the body. Sulphadiazine (pyrimai), sulphadimidine, sulphapyridine, sulphisoxazole, sulphamethiazole and sulphathiazole for example, are readily absorbed.

Sulphisoxazole (sulphafurazole), sulphamethizole, sulphamethoxazole and sulphaphenazole are used in the treatment of infections of urinary tract.

Sulphapyridine is useful in the treatment of a certain type of dermatitis.

Mixed with trimethoprim (see Chart 1), sulphamethoxazole is used in a wider range of infections, besides urinary tract infections and lower respiratory tract infections.

Sulphadoxine, sulphadimethoxide and sulphamethoxydiazine, stilphamethoxypridazine and sulphalene, commonly called long-acting sulphonamides, are given once a day or even longer in the case of chronic infections. They are particularly effective in urinary tract infections.

Sulphadoxine has been used also in the treatment of leprosy.

Succinylsulphathiazole and phthaltysulphathiazole are relatively poorly absorbed and are used in the treatment of bacillary dysentery and as adjuncts in the treatment of ulcerative colitis. Phthalysulphathiazole is, however, preferred.

Sulphacetamide sodium, in the form of the popular brands Albucid and Loculaq, are applied locally in infections of the eyes.

Sulphaguanidine, which is poorly absorbed by the intestinal mucosa, has been used in the treatment of bacillary dysentery. It can be given in large doses without the development of high blood levels and toxic side effects.

Sulphadiazine is a drug of choice in a number of infections including pneumococcal, meningococcal and H. influenzae. It has fewer toxic reactions.

Sulphathiazole is more potent than sulphapyridine in the treatment of streptococcal, staphylococcal, pneumococcal and gonococcal infections, and is generally the drug of choice in the treatment of these infections.
2.4 ANTIPYRETICS AND ANALGESICS

Drugs used to lower body temperatures in feverish conditions are called antipyretics. Analgesics are the drugs used to relieve pain in various conditions of health without loss of consciousness. The antipyretic action and the analgesic action are usually found together in the same drug. Many synthetic analgesics and antipyretics are known today common being aspirin, phenacetin, paracetamol, phenylbutazone, etc. Some representative analgesics antipyretics are described below:

2.4.1 Aspirin (Aspro, Empirin), acetylsalicylic acid

Among salicylic acid derivatives, this is the most important synthetic analgesic, antipyretic, and anti-inflammatory agent.

2.4.1.1 Synthesis

It consists in acetylating salicylic acid with acetic anhydride or acetyl chloride.

It is a common remedy for the relief of headache, muscular pain and toothache. However, its use in children is not recommended. The toxic-side-effect of 'aspirin-therapy' is gastric irritation leading to ulceration. Therefore, it should not be taken on an empty stomach. It is used orally alone or in conjunction with caffeine or codeine (methyl ether of morphine). It is used widely in the treatment of acute and chronic states of rheumatism gout etc.

The calcium salt of aspirin, which is soluble in water, is better than simple aspirin in that it has fewer undesirable side-effects and inducts analgesia faster than aspirin. A familiar preparation of soluble aspirin is 'Disprin'. Disprin contains calcium carbonate and anhydrous citric acid besides aspirin, and this renders aspirin water soluble. Disprin relieves pain faster than aspirin.

2.4.2 Methyl salicylate (Oil of wintergreen)

It occurs in nature and it can be made synthetically too. It is applied as such or in liniments and ointments, for the relief of pain of lumbago, sciatica and rheumatic conditions. It is also used as a flavouring agent. It is the main constituent of pain reliever 'Iodex'.

2.4.3 Paracetamol (Acetaminophen), p-Acetamido phenol, N-acetyl-p-amino phenol

2.4.3.1 Synthesis

It can be synthesized from p-nitrophenol as outlined below:

2.4.3.2 Uses

It has analgesic and antipyretic activities. It is being used as such under various trade names like Crocin, Metacin etc. It is also marketed in combination with aspirin and caffeine.
2.4.4 Phenacetin, Acetophenetidine

It is the ethyl ether of paracetamol

\[
\text{Phenacetin} \quad \begin{array}{c}
\text{EtO} \\
\text{NHCOCH}_3
\end{array}
\]

2.4.4.1 Synthesis

It can be synthesized by either of the following schemes:

\[\text{a)}\]

\[
\begin{array}{c}
\text{HO} \\
\text{p-Acetamidophenol (paracetamol)}
\end{array} \xrightarrow{\text{NaOH}} \begin{array}{c}
\text{NaO} \\
\text{NHCOCH}_3
\end{array}
\]

\[\text{Phenacetin} \quad \begin{array}{c}
\text{EtO} \\
\text{NHCOCH}_3
\end{array}
\]

\[\text{b)}\]

\[
\begin{array}{c}
\text{HO} \\
\text{NO}_2
\end{array} \xrightarrow{\text{1. NaOH}} \begin{array}{c}
\text{EtO} \\
\text{NHCOCH}_3
\end{array}
\]

\[\text{Phenacetin} \quad \begin{array}{c}
\text{EtO} \\
\text{NHCOCH}_3
\end{array}
\]

2.4.4.2 Uses

It has been widely used as an analgesic and an antipyretic, usually in combination with aspirin, caffeine and codeine. In recent years, it has been found to be somewhat toxic in nature. It may damage kidneys if used over long periods.

2.4.5 Phenylbutazone (Butazolidine), 4-n-Butyl-1, 2-diphenyl-3, 5-pyrazolidinedione

It is commonly used as an anti-arthritis and anti-inflammatory agent. Since it has many undesirable side-effects also, it should be used under strict supervision of a doctor.

2.4.5.1 Synthesis

It can be synthesized from malonic ester as outlined below:
2.4.6 Analgin (Metamezole) Sodium 2,3-dimethyl-1-phenyl-5-pyrazolone-4-yl-N-methyl amino methane sulphonate

2.4.6.1 Synthesis

It can be prepared from ethyl acetoacetate as outlined below.

$$
\begin{align*}
\text{Ethyl acetoacetate} & \quad + \quad \text{Phenyl hydrazine} \\
\text{Amino antipyrine} & \quad + \quad \text{Phenyl methyl pyrazolone}
\end{align*}
$$

$$
\begin{align*}
\text{(CH}_3\text{)}_2\text{SO}_4 & \quad \text{HCHO/NaHSO}_3 \\
\text{Analgin}
\end{align*}
$$

2.4.6.2 Uses

It is widely used for its analgesic and antipyretic properties.

2.4.7 Some additional antipyretics and analgesics

Aminopyrine is used as an antipyretic and analgesic, but is slower in action. However, it seems to be much more effective in rheumatic fever.

Oxyphenyl butazone, sold under the trade name Tendril is a metabolite of phenylbutazone, commonly used as an antiarthritic and anti-inflammatory agent.

2.5 ANTIPYRETICS AND ANALGESICS

An antipyretic is a drug which is responsible for lowering the temperature of a feverish organism to normal but has no effect on normal temperature states. On the other hand, an analgesic is a drug which relieves pain without the loss of consciousness. The diminutions of pain may be a consequence of febrifuge effect.

In the earlier days, the antipyretic compounds studied and synthesized were also found to have analgesic properties. Therefore, these two types of drugs are studied together. However, some compounds have only the antipyretic property without any analgesic action.

Analgesics are the drugs which by virtue of their action on the central nervous system decrease the sensation of pain.
2.5.1 Classification of analgesics
It can readily be made on the basis of narcosis. Thus, analgesics can be classified into the following two groups

2.5.1.1 Narcotics
They produce analgesia and sleep and in high doses cause unconsciousness. They are mainly the opium alkaloids or their synthetic and semi-synthetic derivatives e.g., morphine, codeine, pethidine, etc. They are very potent drugs and their chronic use leads to addiction.

2.5.1.2 Non-narcotics
These are the drugs which are not so potent and do not cause addiction. They usually produce an antipyretic effect also. Examples of non-narcotics analgesics are aspirin, analgin, etc.

2.5.2 Mode of Action of Antipyretics
In order to regulate body temperature, there should exist balance between heat production and heat loss. The central nervous system, especially the hypothalamus, plays an important role in maintaining the balance between the two. That is why the hypothalamus is known as the 'thermostat' of the body. In cases of fever, there still exists the balance between heat loss and heat production but the thermostat is only set at a higher level. The antipyretic drug helps to reset the 'thermostat' for normal temperature. Heat production is not inhibited but heat loss is increased by increased peripheral blood flow, which increases the rate of perspiration. This in turn causes the body to lose heat and subsequently lowers the body temperature. Antipyretics do not have any effect on body temperature when it is in the normal range.

2.5.3 Mode of action of analgesics
Main function of analgesics is to relieve or decrease the sensation of pain. They act by increasing the threshold of pain which may be defined as the lowest perceptible intensity of pain. The pain is induced by a stimulus and the amount of stimulus may be regarded, as a measure of the threshold of pain. If more stimuli are required, the threshold of pain is increased and if fewer stimuli are required, the threshold of pain is decreased. When analgesics are used, the pain is not decreased but only the threshold of pain is increased. Therefore, the patient does not feel the pain.

The most commonly used antipyretics-analgesics belong to the following groups.
- Pyrazolone and pyrazolidones
- Aniline derivatives
- Derivatives of p-aminophenol
- Quinoline derivatives
- Salicylic acid and its derivatives and
- Morphine and related compounds

2.6 ANTIFUNGAL AGENTS
Previously fungal infection was regarded as an uncommon disease. Now in recent years fungal infections are worldwide in nature and are systemic as well as local among individuals of all ages. Many remedies have been used against fungus infections, and research still continues which would lead one to conclude that the ideal topical antifungal agent has not yet been found. However, now practically the whole spectrum of fungus diseases can be successful treated.

The antifungal agents used now-a-days have been divided into the following two groups:
- Those used for local infections
- Those used for systemic infections
Each group in turn is divided in those, obtained chemical synthesis and antibiotics.

2.6.1 Acids and their Salts
Previously it was postulated that it was the pH of perspiration which was responsible for its fungicidal and fungistatic effect. However, Peck in 1939 showed that the presence of fatty acids and their salts was responsible for this property of perspiration. Chemical analysis
of sweat reveals that it possesses about 0.0081 per cent of propionic acid. Later on, it was found that the propionic acid and its sodium, ammonium, calcium, zinc, and potassium salts are active fungicides. Further the salts have been found to be active as the free acid. Other acids like caprylic and undecylenic acids also exhibit similar fungicidal properties. Many other fatty acids are known which also possess antifungal properties. However, the above acids are used because they are readily available.

\[
\begin{align*}
\text{Propionic acid} & \quad \text{Caprylic acid} & \quad \text{Undecylenic acid} \\
\text{CH}_3\text{CH}_2\text{COOH} & \quad \text{CH}_3\text{(CH}_2)_2\text{CH}_2\text{COOH} & \quad \text{H}_3\text{C}==\text{CHCH}_2\text{(CH}_2)_2\text{COOH}
\end{align*}
\]

Of these undecylenic acid is best fatty acid which is used as topical fungicidal agent. **Benzoic acid** and **salicylic acid** have also antifungal properties. Salicylic acid is a comparatively mild antifungal agent but possesses keratolytic properties.

### 2.6.2 Other topical agents

These are as follows

#### 2.6.2.1 Salicylanilide (Salinidol)

It is the anilide of salicylic acid. It is an antifungal agent useful in the treatment of tinea capitis. Due to its irritant action on the skin, the concentration used should be 5 per cent or less.

#### 2.6.2.2 Tolnaftate

This compound, which is essentially an ester of β-naphthol; is a potent antifungal agent. Only one or two drops of 1 percent solution in a polyethylene glycol is adequate for areas as large as the hand.

Some other topical fungicidal agents such as **chlordantoin (Sporostacin)**, **clotrimazole (Lobrim and BAYL 5097)** and **miconazole nitrate (Monistat)** are also known.

**Chlordantoin** has been found to be a non-staining fungicide which does not cause skin irritation or sensitization. Clotrimazol has been found to be effective against tinea infection and for candidiasis.

Many polyene antibiotics having a conjugated system of double bonds show similar antifungal activity. They are macrocyclic lactones but are different from the macrolide antibiotics of the erythromycin type having a larger lactone ring in which conjugated polyene system is present.

Three important macrocyclic antibiotics which are used as antifungal agents are **Nystain (Mycostanin)**, **Amphotericin B (Fungizone)** and **Candicidin (Candeptin)**

### 2.7 ANTI–INFLAMMATORY DRUGS

Inflammation may be defined as series of changes that take place in the living tissues following injury. This injury may be caused by variety of conditions like physical agents the mechanical, trauma, ultraviolet or ionizing radiation, chemical agents like organic or inorganic compounds, the toxins of various bacteria, intracellular replication of viruses, hypersensitivity reactions like reaction due to sensitized bacteria etc. Inflammation however is a
normal, essential, protective response to any noxious stimulus that may threaten the host and may vary from localized reaction to a complex response involving the whole organism.

**Rheumatic diseases** are considered to be the most important inflammatory conditions that affect more people and cause more crippling than any other chronic illness. Rheumatic diseases can be classified as **connective tissue diseases**. They belong to complex group of auto immune condition. They include rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, gout, rheumatic fever, psoriasis etc.

These have been chronic, disabling inflammatory conditions which may affect single or multiple organ systems of the body.

**Anti-inflammatory drugs** are said to modify the inflammatory response to diseases but are not curative and do no remove the underlying cause of the diseases. An ideal anti-inflammatory drug should affect only aberrant, uncontrolled inflammation and not interfere with the normal inflammatory response, which forms a part of the body’s vital defense mechanism.

Earlier, **steroids**, namely, prednisolone, dexamethasone, betamethasone and **hydrocortisone** were regarded to be the drug of choice as anti-inflammatory drugs. But due to their several adverse effects, they have been more or less replaced by much safer and better tolerated non-steroidal anti-inflammatory drugs (NSAID).

On the basis of their basic chemical structure anti-inflammatory drugs could be classified into following classes:

- Salicylic acid derivatives
- N-aryl anthranilic acid derivatives
- Aryl acetic acid derivatives
- Aryl propionic acid derivatives.
- Naphthalene acetic acid derivatives
- Gold Compounds
- Pyrazolones and pyrazolodiones
- Miscellaneous anti-inflammatory drugs

Among the anti-inflammatory drugs aryl acetic acid derivatives, N-aryl anthranilic acid derivatives and naphthalene acetic acid derivatives are important. They are described as follows:

### 2.7.1 Aryl acetic-acid derivatives

A few potent drugs belonging to this class of compounds include ibuprofen, ibufenac and diclofenac sodium.

![Ibuprofen structure](image)

**Ibuprofen**

[2-(p-isobutylphenyl) propionic acid]

#### 2.7.1.1 Ibuprofen

It is also known as brufen. It is an anti-inflammatory drug which is having antipyretic as well as analgesic properties. It is indicated for the treatment of rheumatoid arthritis and osteoarthritis. It has been also recommended to arrest acute flares and in the long term management of these diseases.

**Manufacture**

Benzene on treatment with isobutyl chloride in presence of anhydrous aluminum chloride or aluminum shavings gives isobutyl benzene, which is further treated with triethoxy acetyl chloride. Product obtained is reduced to give p-isobutyl benylic acid. It is treated with sodium ethoxide. Sodium derivative obtained is heated with diethyl carbonate. Product is again converted into sodium derivative with sodium ethoxide and then treated with methyl iodide. Methyl derivative thus formed is subjected to acid hydrolysis and then to decarboxylation to give Ibuprofen.
It is used as an analgesic, anti-inflammatory drug.

**Dose**
For analgesia (dysmenorrhea) 200-400 mgs, 4-6 times per day—orally. For rheumatic arthritis and osteoarthritis 300-400 mgs, 3-4 times per day orally.

2.7.2 N-aryl anthranilic acid derivatives
The structural analogues of N-aryl anthranilic acid is having analgesic, anti-pyretic and anti-inflammatory properties. The few potent drugs belonging to this class of compounds include mefenamic acid, flufenamic acid and meclofenamic acid.

It is having analgesic, antipyretic and anti-inflammatory properties; it is normally used in the treatment of rheumatic or mauculoskeletal disorders, rheumatoid arthritis, dysmenorrhea and acute gout. Its sodium salt finds use as an analgesic for many varieties of painful conditions.

**Dose**
For rheumatic arthritis—250 to 375 mg as initial dose 2 times per day. In acute gout, 750 mg as loading dose followed by 250 mg 3 times a day until relieved.
It has been a potent analgesic and an anti-inflammatory agent. It has been 5 times more effective than codeine and 3 times more effective than aspirin in relieving chronic pain. It is usually indicated for the relief of mild to moderate pain especially that following dental extraction. It also finds use in the treatment of primary dysmenorrhea. 500 mg followed by 250 mg 4 times daily —orally. (It must not be used for more than 7—days).

**Side effects**
Side effects are diarrhea, nausea, gastrointestinal ulceration, headache and drowsiness.

### 2.7.3 Naphthalene acetic acid derivatives
Naphthalene acetic acid compounds are considered to be the leading compounds of an extensive series of promising clinical agents, for example, Naproxen.

![Naproxen](image-url)