CHAPTER - 1

GENERAL INTRODUCTION
INTRODUCTION AND REVIEW OF LITERATURE

Fighting disease with drugs is the timeless struggle. Its beginnings are echoed out of the primeval jungle. Man's survival on this planet has been depended upon its success. Today the conflict continues unabated in the laboratory and clinic. The scientific approach to this struggle is pharmacology.

The great expansion in medicinal research in past has contributed much to the unparalleled progress of medicine during that period. Improved and basically more meaningful biological test procedures and methods of diagnosis have provided better guidance in drug discovery by pointing out suggestive observations which could be used in the design of new prophylactic and therapeutic agents. The growth of molecular biology with its chemical insight into experimental biology has contributed to more significant pharmacological theories. The elucidation of the structure of many metabolites, and of polypeptides, enzymes, poly nucleotides and other biopolymers has also made possible a more rational study of the chemical mode of action of such compounds, and their interaction with drugs. Medicinal chemistry has taken advantage of these investigations, and the refinement of pertinent chemical theories, to establish itself firmly as an interdisciplinary science. It has become the acknowledged meeting ground of modern organic and physical chemistry, and of biochemistry in the application of these fields to drugs, with its own literature and procedures.

Today a large number of diseases are cured or at least controlled by drug therapy. The fight against bacterial and fungal infections has been largely won and progress has been made in treating disturbed mental, cardiovascular, gastrointestinal condition. To boast, it can be claimed that certain form of cancers can be cured by chemotherapy.

Medicinal Chemistry:

Medicinal chemistry is defined as a field that applies the principles of chemistry and biology to the creation of knowledge leading to the introduction of new therapeutic agents. Hence, the medicinal chemist must not only be a competent organic chemist but he must have a basic background in the biological sciences, especially biochemistry and pharmacology.

The basis of understanding the medicinal chemistry lies in an awareness of the relationships between the chemistry of particular compound or group of compounds
and their inter-action with body, which are known as structure-activity relationships (SAR), and the mechanism by which the compound influences the biological system, which is known as its mode of action. The objective of these studies is to improve the beneficial or therapeutic effect of a drug, whilst at the same time minimizing undesirable side effect.

**Drugs:**

The word ‘drug’ is derived from the French word drogue, which means a dry herb. In general way, a drug may be defined as a substance used in the prevention, diagnosis, treatment or cure of disease in man or other animals. 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 system or pathological states for the benefit of the recipient.

In order to be a useful drug, it must not show toxicity, must show good pharmacokinetic properties, must not be rapidly metabolized and most optimally, must be absorbed after oral administration. Thus, ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) properties of compounds must be investigated early in the drug discovery path to clarify clinical utility of new genes as targets. Very few drugs satisfy all the above conditions. However, the search for ideal drug continues.

There have been three approaches to the problem of finding a drug to combat a particular disease:

1. The method of trial and error. This involves the trial of all kinds of compounds, natural and synthetic.
2. The method of requiring knowledge of cell system, and then synthesizing compounds, which interfere with it.
3. The method in which one starts with a compound known to have some of the required activity (this information has been gained from the previous method), and then to vary the structure of the molecule systematically. This, method has, so far been proved to be the most fruitful.

The drugs are converted into pharmacologically active metabolite by biotransformation. These metabolites are highly active. This activity contributes to pharmacological effect ascribed to parent drugs. In some cases inactive parent drug gets converted to biologically active metabolite. Since all the metabolites are non-
toxic, many toxic side effects like tissue necrosis, carcinogenicity are observed. The formation of water-soluble metabolite enhances elimination and pharmacologically inactive, non-toxic and polar compound formation. Most of the drugs undergo metabolic transformation in the body. The main site of metabolism is liver.

**Pharmacophore:**

The physiological activity of drugs has been found to depend upon the presence of particular functional groups or structural units. Such a part of the drug, which causes the actual physiological effect, is known as pharmacophore.

When a pharmacophore is introduced into biological inactive compound, this makes the compound biologically active many times. Thus, it is possible to make the compounds biologically active but less toxic by introducing various pharmacophores. Some examples of pharmacophores are alkyl, hydroxy, alkoxy, aldehyde or ketone, acidic, nitro, nitrile, effect of unsaturation, effect of isomerism, halogens and unsaturated lipids.

**Quantitative Structure - Activity Relationships (QSAR):**

Why QSAR is necessary?

1. Prediction of biological activity.
2. Understand mechanism of action.
3. Classification of compounds.
5. Lead search.
7. Economize new drug development.

Quantitative structure-activity relationships (QSAR) have become a widely used tool to get a better understanding of the molecular mechanism of many chemical processes, and to propose simple and practical mathematical expression for property prediction. Application to toxicology has evident scientific interest, especially as an alternative to animal testing. Many studies on this subject have been reported.
Chemotherapy:

The treatment of infectious disease by using a chemical agent is called chemotherapy. The substance so employed is referred to as chemotherapeutic agent. These agents are designed in such a way that they kill or destroy the disease-producing organisms without any harmful effect on the cells in which organisms are present.

Paul Ehrlich (1854-1915) did outstanding work in medicinal chemistry and therefore called 'Father of Chemotherapy'. He gave original ideas about the models of action of drugs. According to him, there are some cellular constituents in mammalian cells, which were earlier called receptors by Langley (1878). Ehrlich defined chemotherapy as the use of drugs to injure an invading organism without causing injury to the host.

Chemotherapeutic drugs:

According to Ehrlich chemotherapeutic agents are chemical substances with high parasitotropism and low or no organotropism, in other words, they are selectively toxic, being harmful to as much as possible to the invading organism but innocuous to the host.

Chemotherapeutic agents are drugs used in the treatment of infectious diseases. These diseases are caused by certain species of metazoa, protozoa, fungi, bacteria, ricketiest and viruses. Drugs active on these pathogenic agents divided into the following type according to their therapeutic activity.

1. Anthelmintic Agents
2. Antimalarial Agents
3. Antiprotozoal Agents
4. Antifungal Agents
5. Antibacterial Agents
6. Antiseptic Agents.
7. Anti tuberculosis and Anti lepral Agent
8. Antibiotics
9. Anti neoplastic Agents
10. Antiviral Agents
Pharmacodynamic agents:
The drugs, which stimulate or depress various functions of body so as to provide relief from symptoms of discomfort, are known as pharmacodynamic agents. Although these agents have a characteristic effect on the animal, they have no specific remedies for particular diseases. These agents are mainly used in the case of non-infectious diseases, to correct abnormal functions. However, they have no action on infective organism, which causes the disease. Examples of pharmacodynamic agents are analgesics, sedatives, anesthetics, antihistamines, etc.

Some differences may be pointed out between chemotherapeutic agents and pharmacodynamic agents; among them are the following:

1. Chemotherapeutic agents find use in the treatment and cure of infectious disease; pharmacodynamic agents are used for relief and correction of abnormal functions.

2. Chemotherapeutic agents usually exert an irreversible action, by attaching strongly, sometimes through a covalent bond, to special moieties of macromolecules of invading organism; pharmacodynamic agents should preferably produce reversible results, by forming weak bonds with pharmacological receptors.

3. In chemotherapeutic agents the all-or-nothing effect has been unobjectionable, whereas pharmacodynamic agents are expected to give a graded response, according to the doses administered.

4. Potential chemotherapeutic agents are often easily screened, because in many cases it is very simple to isolate the invading organism and study it separately; pharmacodynamic agents have been found to be more difficult to test, because it is not possible to isolate receptor molecules.

Some therapeutic agents may have one or both of the following effects:

a) Static, when they inhibit further growth or multiplication of invading organism or cell;

b) Cidal; when they kill or destroy it.

For instance, we have both bacteriostatic and bactericidal agents. Static or cidal effects depend on several factors, such as concentration of drug, pH, temperature, duration of action, metabolic phase of the invader, and presence of interfering substance. Thus drug with static effects may exert cidal effects if the doses are increased.
The relative efficiency and safety of chemotherapeutic agents has been indicated by the so-called chemotherapeutic index, which may be expressed by the relationship:
Chemotherapeutic index = Maximal tolerated dose by the host / minimal curative dose

The greater this index, consider better chemotherapeutic agent because of its greater safety to the patient.

- **Antibacterial Chemotherapy:**
  The development of resistance to current antibacterial therapy continues to drive the search for more effective agents. Bacteria are commonly responsible for many diseases, which were considered until recently to be resistant to chemotherapy.

- **Bacteria:**
  These are a group of microorganisms, which are unicellular and surrounded by rigid, complex, protein cell wall. These may be free living, saprophytic or parasitic; some are pathogenic to man, animals and plants.

  Bacteria are classified into two types, i.e. Gram-positive and Gram-negative according to method developed by Christian Gram, which is as follows:

  In this method, the fixed bacterial smear is first treated with a solution of crystal violet and then with iodine solution, which reacts with the dye and the cell constituents. The smear is then washed with alcohol (decolourizing agent) and safranine or some other counter stain is added.

  The bacteria that retain the colour of crystal violet and appear deep violet (in colour) are called Gram-positive bacteria, whereas those, which lose the violet colour and get counterstained by safranine and appear red in colour, are called Gram-negative bacteria. The following are some of the disease causing bacteria classified in this manner:

<table>
<thead>
<tr>
<th>Gram-positive bacteria</th>
<th>Gram-negative bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Diphtheria bacillus</em></td>
<td><em>Coli and Typhoid bacillus</em></td>
</tr>
<tr>
<td><em>Leprosy bacillus</em></td>
<td><em>Gonococcus</em></td>
</tr>
<tr>
<td><em>Pneumococcos</em></td>
<td><em>Meningococcus</em></td>
</tr>
<tr>
<td><em>Staphylococcus</em></td>
<td><em>Plague bacillus</em></td>
</tr>
<tr>
<td><em>Streptococcus</em></td>
<td><em>Spirochaetes</em></td>
</tr>
<tr>
<td><em>Tubercle bacillus</em></td>
<td><em>Vibrios (V. Cholerae)</em></td>
</tr>
</tbody>
</table>
Antibacterial agents:

The history of antibacterial has been dynamic, characterized by the constant emergence of new challenges followed by investigation, discovery and the production of new drugs. A complete review of the various agents employed as antibacterial would be beyond the scope of this work and hence is not attempted. A brief summary of the important classes of antibacterial compounds are given below.

Synthetic antibacterial agents:

The synthetic antibacterial agents are comprised of two major classes of compounds; those effective systematically and those used topically.

[A] Topical antibacterial agents:

Antibacterial agents that are employed topically are commonly termed antiseptics, disinfectants or preservatives depending on how they are employed. Since there is a considerable degree of overlap in usage among these three groups, the more convenient method of classifying them, i.e., according to structural types.

The antiseptics and disinfectants are a large, diverse group of chemical compounds that play an important role in the maintenance of human and animal health. Although they are often improperly utilized and overrated in their effectiveness by both lay and medical personnel, they are invaluable when properly employed\(^1\). The hexachlorophene tragedy has shown that extensive toxicological studies are just as important for topical agents as for systematic, and older agents should be employed with due care.

Topical synthetic antibacterials are classified as follows:

1. Halogens and Halophors [1]
2. Phenols [2-5]
3. Alcohols
5. Quaternary Ammonium compounds [7-8]
6. Dyes [9-11]
8. Heavy Metal Compounds [16-17]
9. Miscellaneous [18]
Systematically antibacterial agents:

The systematically active antibacterial has been divided into three groups, two of which, are sulfonamides and the antimycobacterial agents. The remaining compounds principally agents for the treatment of urinary tract infections. Except for the sulfonamides and antimycobacterial drugs, only a few systemically active synthetic antibacterials are commercially important today. The multitudes of highly effective relatively nontoxic antibiotics available for the treatment of bacterial infections have provided stiff competition for the medicinal chemist attempting to synthesize new antibacterial agents.

Systematic synthetic antibacterials are classified as follows:

1. Anti mycobacterial agents [19-20]
2. β-lactum antibiotics [20-21]
3. Trimethoprim, Cotrimoxazole, Methanamines[27]
4. Nitrofurans [28]
5. Quinolones [29]

According to the effect produced, antibacterial drugs can be bacteriostatic (inhibit growth of bacteria) or bactericidal (kill the bacteria). Commonly used bacteriostatic and bactericidal drugs are given below.

<table>
<thead>
<tr>
<th>Bactericidal Drugs</th>
<th>Bacteriostatic Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Amino glycosides</td>
<td>Nitro furans</td>
</tr>
<tr>
<td>Polymyxin, Colistin</td>
<td>Erythromycins</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>Lincomycin</td>
</tr>
</tbody>
</table>
Table-1: Properties of Some Common Antibacterial Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Primary Effect</th>
<th>Spectrum</th>
<th>Side Effects *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>Cidal</td>
<td>Broad (Gram +, some-)</td>
<td>Allergic responses (diarrhea, anemia)</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>Cidal</td>
<td>Narrow (Gram +)</td>
<td>Renal injury if injected</td>
</tr>
<tr>
<td>Carbenicillin</td>
<td>Cidal</td>
<td>Broad (Gram +, many-)</td>
<td>Allergic responses (nausea, anemia)</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Cidal</td>
<td>Broad (Gram +, some -)</td>
<td>(Allergic responses, thrombophlebitis, renal injury)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Static</td>
<td>Broad (Gram +, -; rickettsia and chlamydia)</td>
<td>Depressed bone marrow function, allergic reactions</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Cidal</td>
<td>Broad (Gram +, -)</td>
<td>Gastrointestinal upset, allergic Responses</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Static</td>
<td>Narrow (Gram +, anaerobes)</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Static</td>
<td>Narrow (mycobacteria)</td>
<td>(anemia, allergic responses)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Static</td>
<td>Narrow (Gram +, mycobacteria)</td>
<td>(Gastrointestinal upset, hepatic injury)</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>Cidal</td>
<td>Narrow (Gram-)</td>
<td>(Allergic responses, nausea, loss of hearing, renal damage)</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Static or Cidal</td>
<td>Narrow (mycobacteria)</td>
<td>(Allergic reactions, gastrointestinal upset, hepatic injury)</td>
</tr>
<tr>
<td>Methicillin</td>
<td>Cidal</td>
<td>Narrow (Gram +)</td>
<td>Allergic responses (renal toxicity, anemia)</td>
</tr>
<tr>
<td>Penicillin</td>
<td>Cidal</td>
<td>Narrow (Gram +)</td>
<td>Allergic responses (nausea, anemia)</td>
</tr>
</tbody>
</table>

# Occasional side effects are in parentheses. Other side effects not listed may also arise.

Drugs vary considerably in their range of effectiveness. Many are narrow spectrum drugs—that is, they are effective only against a limited variety of pathogens (table-1). Others are broad spectrum drugs and attack many different kinds of pathogens. Drugs may also be classified based on the general microbial group they act against: antibacterial, antifungal, anti protozoal and antiviral. Some agents can be used against more than one group; for example, sulfonamides are active against bacteria and some protozoa.

Chemotherapeutic agents can be synthesized by microorganism or manufactured by chemical procedures independent of microbial activity. A number of
the most commonly employed antibiotics are natural—that is, totally synthesized by one of the few bacteria or fungi. In contrast, several important chemotherapeutic agents are completely synthetic. The synthetic antibacterial drugs in table-1 are the sulfonamides, trimethoprim, chloramphenicol, ciprofloxacin, isoniazid and dapsone. Many antiviral and antiprotozoal drugs are synthetic. An increasing number of antibiotics are semi synthetic. Semi synthetic antibiotics are natural antibiotics that have been chemically modified by the addition of extra chemical groups to make them less susceptible to inactivation by pathogens. Ampicillin, carbenicillin and methicillin (table-1) are good examples.

- **Mechanism of action of antimicrobial agents:**

  The mechanisms of action of specific chemotherapeutic agents are taken up in more detail when individual drugs and groups of drugs are discussed later in this chapter. A few general observations are offered at this point. It is important to know something about the mechanisms of drug action because such knowledge helps in explaining the nature and degree of selective toxicity of individual drugs and sometimes aids in the design of new chemotherapeutic agents.

  Antimicrobial drugs can damage pathogens in several ways. As can be seen in table-2, which summarizes the mechanisms of the antibacterial drugs listed in table-1. The most selective antibiotics are those that interfere with the synthesis of bacterial cell walls (e.g., penicillins, cephalosporins, vancomycin, and bacitracin). These drugs have a high therapeutic index because bacterial cell walls have a unique structure not found in eukaryotic cells.

  Streptomycin, gentamicin, chloramphenicol, tetracycline, erythromycin and many other antibiotics inhibit protein synthesis by binding with the prokaryotic ribosome. Because these drugs discriminate between prokaryotic and eukaryotic ribosomes, their therapeutic index is fairly high, but not as favorable as that of cell wall synthesis inhibitors. Some drugs bind to the 30S (small) subunit, while others attach to the 50S (large) ribosomal subunit. Several different steps in the protein synthesis mechanism can be affected: aminoacyl-t-RNA binding, peptide bond formation, m-RNA reading, and translocation. For example, fusidic acid binds to EF-G and blocks translocation, whereas mucopirocin inhibits isoleucyl-t-RNA synthetase.

  The antibacterial drugs that inhibit nucleic acid synthesis or damage cell
membranes often are not as selectively toxic as other antibiotics. This is because prokaryotes and eukaryotes do not differ as greatly with respect to nucleic acid synthetic mechanisms or cell membrane structure. Good examples of drugs that affect nucleic acid synthesis or membrane structure are quinolones and polymyxins. Quinolones inhibit the DNA gyrase and thus interfere with DNA replication, repair and transcription. Polymyxins act as detergents or surfactants and disrupt the bacterial plasma membrane.

### Table-2: Mechanism of Antibacterial Drug Action

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell Wall Synthesis Inhibition</strong></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>Inhibit transpeptidation enzymes involved in</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>The cross-linking of the polysaccharide chains of the bacterial cell wall peptidoglycan.</td>
</tr>
<tr>
<td>Carbenicillin</td>
<td>Activate cell wall lytic enzymes,</td>
</tr>
<tr>
<td>Methicillin</td>
<td></td>
</tr>
<tr>
<td>Cephalosporin</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Binds directly to the D-Ala-D-Ala terminus and inhibits transpeptidation</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>Inhibits cell wall synthesis by interfering with action of the lipid carrier that transports wall precursors across the plasma membrane.</td>
</tr>
<tr>
<td><strong>Protein Synthesis Inhibition</strong></td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Binds with the 30S subunit of the bacterial ribosome to inhibit protein synthesis and causes misreading of mRNA.</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>Bind to the 50S ribosomal subunit and blocks peptide bond formation through inhibition of peptidyl transferase.</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Bind to the 30S ribosomal subunit and interfere with aminoacyl-tRNA binding.</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td></td>
</tr>
</tbody>
</table>
SYNTHESIS AND CHARACTERISATION OF SOME NEW SULPHUR BASED HETEROCYCLES

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin and Clindamycin</td>
<td>Bind to the 30S ribosomal subunit and inhibit peptide chain elongation.</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>Bind to EF-G and blocks translocation.</td>
</tr>
<tr>
<td><strong>Nucleic Acid Synthesis Inhibition</strong></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin and other quinolones</td>
<td>Inhibit bacterial DNA gyrase and thus interfere with DNA replication, transcription and other activities involving DNA</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Blocks RNA synthesis by binding to and inhibiting the DNA-dependent RNA polymerase.</td>
</tr>
<tr>
<td><strong>Cell Membrane Disruption</strong></td>
<td></td>
</tr>
<tr>
<td>Polymyxin B</td>
<td>Binds to the plasma membrane and disrupts its structure and permeability properties.</td>
</tr>
<tr>
<td><strong>Metabolic Antagonism</strong></td>
<td></td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Inhibit folic acid synthesis by competition with p-aminobenzoic acid.</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Blocks tetrahydrofolate synthesis through inhibition of the enzyme dihydrofolate reductase.</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Interferes with folic acid synthesis.</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>May disrupt pyridoxal or NAD metabolism and functioning. Inhibits the synthesis of the mycolic acid &quot;cord factor&quot;.</td>
</tr>
</tbody>
</table>
SYNTHESIS AND CHARACTERISATION OF SOME NEW SULPHUR BASED HETEROCYCLES

References:

11) Browning C. H. & Gilmour W., J. Pathol. Bacterid., 1913, 18, 144.
SYNTHESIS AND CHARACTERISATION OF SOME NEW SULPHUR BASED HETEROCYCLES


