Chapter-1

INTRODUCTION
There was a time when all our pain relievers and other drugs came from natural sources like plants and animals. But around 1800 AD, scientists began to put around in their laboratories and make new drugs. At first all they did was to re-create natural drugs. This was useful when plant and animal sources are too hard to use and produce enough of the medicine. Once we figured out how to duplicate nature, we began to work on the molecules that are found in the natural world. Some times a plant would give us a medicine that had unpleasant side effects. So, scientists altered the molecular structure of the natural molecule until they had made a drug that worked like the natural drug, but also without side effects. Aspirin was one of the first natural inspired synthetic drug.

Man’s survival on this planet has depended up on his success. Today conflict continues unabated in the laboratory and clinic. The beginning of effective therapy by chemicals has last in anti activity, because it proceed recorded medical history. Early success in the quest for chemicals effective against disease were predominantly found among anti-infective diseases rather than against those usually accompanying the processes.

BACKGROUND OF SYNTHETIC CHEMISTRY

Synthetic organic chemistry is an advanced branch of chemistry. The chemical synthesis of a carbon containing molecule has been a major field of scientific evidence for over a century. Paul Ehrlich (1854-1915) did outstanding work in synthetic medical chemistry and is therefore called "Father of chemotherapy". In 1907 he introduced an organic compound "arsephenamine" which was found active against spirochaete of "Syphilis". Further a large number of drugs such as acrictlavin (an antibacterial) arsenicals such as salvarsan for treatment of syphilis were also produced in his laboratories. Also, plasmoga in (1926) and atebisin (1932) both are antimalarial were also produced in his laboratories.

During that last quarter of the 19th century many noteworthy syntheses were developed. Chloral hydrate was synthesized in 1869, Paraldehyde in 1882, Sulphones in 1888, Phenacetin in 1889, aspir in 1899, etc., Synthesis[1] in the first quarter of the 20th century is further developed, the best examples such as α-terpineol (W.H. Perkin, 1904) camphor (G. Konppa, 1903; W.H. Perkin 1904) and terpinone (R.Robinson, 1917)
During the next quarter of the century, this trend continued with the achievement of such landmark synthesis as estrogenic steroid, equilenin (W. Bachmann, 1939) protoporphrin (hemin) (H. Fischer, 1929); pyridoxin (K. Bolkers, 1939) and quinine (R.B. Wood Ward and W. Von. Doering, 1944).

The last fifty years was an exhilarating period for chemical synthesis. There had occurred more spectacular advances in synthetic medical chemistry, particularly with the discovery of sulpha drugs and antibiotics. The systematic research in pharmaceutical laboratories has led to the introduction of more and more synthetic drugs in the modern times. The synthetic drugs are obtained by simple or more involved modifications of the structure of naturally occurring drugs, or by pure synthesis.


SYNTHETIC ERA

The era of synthetic drugs had to await till the technique of synthetic organic chemistry became well advanced and physiology of human organisms became well known. Most of the earliest efforts of synthetic drugs were concentrated on anaesthetics, hypnotics and analgesics.

The term 'synthetic drug' strictly refers to psychoactive substances that are manufactured through a chemical process in which the essential psychoactive constituents are not derived from naturally occurring substances. The term synthetic drug began to be used synonymously with recreational drug following the emergence of the synthetic drug ecstasy (MDMA) and other ring substituted amphetamines in the recreational dance drug scene, although non-synthetic drugs, such as cannabis, cocaine and magic mushrooms, are also consumed in these settings. Synthetic drugs with long histories of illicit use include amphetamines and lysergic acid diethyl amide (LSD), while
ecstasy (MDMA) and other drugs have much shorter histories of illicit use. There is growing global concern about the potential manufacture of other and newer synthetic drugs sold as an alternative to MDMA, or added to MDMA tablets. Some synthetic drugs, not all have hallucinogenic effects and may be either stimulants or depressants of the central nervous system (CNS), the latter being the case of GHB. There are also synthetic opiates, such as methadone, pethidine (MPPP, MPTP), fentanyl-3-methyl-fentanyl, etc.

HETEROCYCLIC COMPOUNDS

The heterocyclic compounds occupy key position in the area of drugs and pharmaceuticals. Almost 80% of the drugs in clinical use are based on heterocyclic constitution. Heterocyclic chemistry is a branch in some guise has been inseparable from mankind's origin or history since it fulfills one of our basic need. The cell is generally thought to be the unit of human body and is a marvelous chemical factory. This is surprising because cell or nature has chosen heterocyclic substances for some of the most important functions in the living cell as vitamins, coenzymes and components of nucleic acid. These contents in specific concentration in living cell give the characteristics of life. The investigations of chemistry of heterocyclic compounds have not only been as essential element in man’s endeavours to unravel the mysteries of the living world, but at the same time these studies have constantly stimulating new directions in which the subject may grow in organic, pharmaceutical and medicinal chemistry. The strength of heterocyclic chemistry lies in its rich diversity.

Heterocyclic compounds are those in which there is present one or more rings containing, at least an atom of another element beside carbon. The most commonly found elements in these rings are nitrogen, oxygen and sulphur. The development of heterocyclic chemistry has gone hand in hand with an investigation of great variety of natural products. Many of plant pigments such as catechins and tannins are derived from benzopyran, indigo is derived from indole and stimulated its study, whilst the blood bile pigment and chlorophyll are the complex derivatives of pyrrole. The chemistry of purines and nucleic acids are involved with that of azole chemistry.
SIGNIFICANCE OF HETEROCYCLIC COMPOUNDS

Everything of this creation has its importance and nothing is meaningless. However, some of them have more importance than others. Heterocyclic compounds are such type of important things. Importance of heterocyclics are summarized below.

Heterocycles In Drugs

Heterocyclic compounds exhibit a wide range of biological activities. Quinoline derivatives are well known drugs for the treatment of malaria[3]. Introduction of amino group in the ring of quinolines found to be associated with a number of activities viz. antidepressant[4], hypoglycemic[5], gastric secretion inhibitors[6], antihypertensive[7], gastric ulcer inhibitors[8], psychonaleptic[9], and also active against HIV-I integrate[10]. Sulindac and indomethacin are recent drugs used for the treatment of anti-inflammatory agents in therapy. Both are indole acetic acid derivatives[11], Acridine based antimalarial and antibacterial compounds. (mepacrine, azacrine, proilavine and amincrine) are known[12] 9-(Dimethyl amino propyl) amino 1- nitro acridine has been quite extensively used as antitumor drug in Poland[13]. Ansacrine has a wide spread clinical use as antitumor agent[14]. These compounds are also used for lessening of memory impairment and potent anticonflict activity ex benzothieno pyridines[15]. Besides these, heterocyclic compounds possess various other activities like local anaesthetic[16], antidiabetic[17], diuretic[18], cardiovascular agents[19], antiviral[20], antiparkinsonian[21], african sleeping sickness[22], herbicides, anticonvulsant[23], muscle relaxant[24], antineoplastics[25], antimicrobial[26], antihypertensive[27], antihistamine[28], antispasmodic[29], tranquillizers[30], antiulcer[31], etc., Retinoids[32] are a group of synthetic compounds designed to refine the numerous biological activities of retinoic acid into pharmaceuticals for several diseases, including cancer. Designs that conformationally restricted the rotation of the structures resulted in arotinoids that were biologically active, but with increased toxicity. Incorporation of a heteroatom in one cyclic ring of the arotinoid structures drastically reduced the toxicity, while retaining biological activity.
Heterocycles in nature

Heterocyclic compounds are widely distributed in nature. The plants are green and blood is red due to the presence of chlorophyll and haemin respectively and also, the life of plants and animals is restored in them. Carbohydrates, tannins and aminoacids are derived from heterocyclic origin. The physiologically active substances of heterocyclic active origin are co-enzymes and metabolically active substances like heteroauxin, serotonin and histamine, vitamins like thiamine, riboflavin, nicotinic acid, pyridoxin, biotim, vitamin B_{12} family, toopherol family etc., Purine and pyrimidine bases like adenine, guanine, cytosine and thiamine, break down products of metabolism like uric acid, alloxane and allantoin, like histidine, morphine, antibiotics like penicillin; energy strong units like A.T.P. and A.D.P., electron transport system like cytochrome “a” and “b” etc.,

Heterocycles in dyes

In dye-stuff industry, heterocyclic compounds are encountered in all the established classes of colouring matters. Azodyes for example contain heterocycles such as pyrazolones, thiazoles, indoles, imidazoles and triazoles. The azoic components include carbazole, dibenzofuran or benzothiazole units. Besides these heterocyclic systems such as azine, oxazine, acridine, thazine, quinoline and thiazole constitute industrial classes of synthetic colouring matters. The heterocyclic phthalocyanine and quinacridine are important pigments.

Heterocycles in agrochemicals

1,2, 4–triazoles have found broad application as herbicides, fungicides and antibacterial agents. Triazole and their derivatives have been detected only in the last decade to possess significant biological activity which makes them of interest in the area of agrochemicals.

Heterocycles in photostabilizers

Benzotriazoles have successfully applied as photostabilizers for fibers, plastics or dyestuffs and also used for the protection of human skin from harmful UV radiation.
METHODS OF CHEMICAL ANALYSIS

During the last few years, enormous development in the filed of synthetic organic chemistry has taken place due to the availability of powerful analytical techniques. The spectral methods have been of immense help in collection of valuable information about individual compounds. Ultraviolet, infrared, nuclear magnetic resonance spectroscopy and mass spectrometry are among the most impartment spectroscopic techniques that the organic chemists now use routinely to gain information about a particular substance\textsuperscript{[33,34]}. In the present study IR and \textsuperscript{1}H-NMR techniques are used to characterize the synthesised compounds.

Infrared spectroscopy

In the structure elucidation of various organic compounds especially for the presence of functional groups, IR spectral technique is very reliable. This technique depends on the vibration and rotation of atoms of molecules. Bellamy\textsuperscript{[35]} and Rao\textsuperscript{[36]} have reviewed the applications of I.R. spectroscopy. This technique is most widely used for the identification of all kinds of organic compounds\textsuperscript{[37,38]}.

The infrared absorption spectroscopy is based on the absorption of infrared radiation by molecules. It has been observed that all chemical compounds show marked selective absorption in the infrared. The infrared absorption spectrum of an organic compound represents one of its truly unique physical property. I.R. spectrum of a chemical substance is a finger print for its identification. Organic applications on infrared spectroscopy are almost entirely concerned with the range 650-4000 cm\textsuperscript{-1}.

Many scientists have applied I.R. spectroscopy for the structural interpretation of terpenes, glycosides, carbohydrates and all kinds of natural and synthetic compounds. Dhar and Singh\textsuperscript{[39]} have studied the I.R. spectra of some new Chalcones. Advance studies have been done in this filed and are illustrated by many workers\textsuperscript{[40]}.

Nuclear magnetic resonance spectroscopy

Nuclear magnetic resonance spectroscopy serve as a powerful tool for the structural elucidation of organic compounds. (\textsuperscript{1}H-NMR and \textsuperscript{13}C-N.M.R techniques configurationally and conformational nature of compound). This technique is helpful in
observing each and every proton and carbon atom separately in the compounds. A large number of synthesis\cite{41-44} as well as natural compounds\cite{45,46} have been studied by NMR spectroscopy. The method of NMR was first developed by E.M. Purcell and Felix Bloch (1946). The subject has developed very rapidly in recent years and today it has extended so much that it is of equal importance with the older established vibrational and electronic branches of spectroscopy.

Nuclear magnetic resonance involves the interaction between oscillating magnetic field of electric radiation and the magnetic energy at the hydrogen nucleus or some other type of nuclei when these are placed in an external static magnetic field. The sample absorbs electromagnetic radiations in radio wave region at different frequencies, since absorption depends upon the type of protons or certain nuclei contained in the sample. Radio waves are regarded as the lowest energy form of electromagnetic radiation that find valid applications in analytical chemistry. It is a powerful tool for investigating nuclear structure. It has been used to determine the molar ratio of the components in a mixture. Now-a-days the structure of natural products as well as other organic compounds are confirmed by their NMR spectra. It is extensively used in pharmaceutical and polymer industry. Its application have been extensively reviewed in standard works\cite{47}.

**BIOLOGICAL ASSAY STUDIES**

For the development in the field of chemotherapy, it is necessary to test new chemicals for their curative properties against various disease causing organisms. So it was thought worth while to study 1,4-dihydro pyridines, pyrimidines, pyrazines, 2-pyrazolenes and 4-thiazolidinones for their (1) antimicrobial\cite{chapter -vii} (2) anthelmintic\cite{chapter-viii} and (3) insecticidal\cite{chapter-ix} properties.

**Antimicrobial activity**\cite{48}

The investigation of the microscope in the 17\textsuperscript{th} century gave vision to the hitherto unknown world of microorganisms. These organisms are closely associated with the health and welfare of human being and plants. Some are beneficial and others cause diseases to human and plants. The theory of the spontaneous generation of disease was finally buried by Pasteur and Koch in 1876 when they convinced one and all that the anthrax disease was incited by a bacterium. This had wide implications in related fields
of study. In 1878 Burrill of Illinois, reported that the fire blight disease of peas and apple was caused by bacterium. Arthur (1885) proved that the disease could be incited by the bacterium obtained from a pure culture. By 1900 E.F. Smith firmly established the study of bacterial disease by bringing in the best method of study in animal bacteriology. Joseph Heinsten, in 1878 was the first scientist who developed pure culture technique to the germs outside the body and proved that the germs can grow outside the body are also susceptible to produce same symptoms, when it is inoculated into the body. Fungi and bacteria are grown using the suitable culture media and a number of chemicals can be tested, in vitro for their activity on microbes.

The microbial activity is measured in order to determine.

(i) The potency of antimicrobial agents.

(ii) Sensitively of the germ microorganism to the known concentration of drug.

**Anthelmintic activity**

The anthelmintics are the drugs, which are used to kill or remove the parasitic worms, known as helminthes from the infected host. These drugs are of great importance because helminthiasis is the most common disease in the world.

Solaman reported that all the clinical anthelmintics are toxic to earth worm. Therefore earthworms can be used to have an idea, whether the test substance has any anthelmintic activity and to compare its relative activity with the standard like piperazine hydrochloride etc., A number of workers have used earth worms for the preliminary in vitro evaluation of anthelmintic activity of new substances.

**Insecticidal activity**

Without doubt insect occupy a dominant position in the animal world, out numbering all other inhabitants, and they are very successful animals. Of the estimated living species of animals (1.35 million) there was more than 9,00,000 insects. Their tenacity for life is amazing and their capacity for multiplication and their wonderful adaptability has made them a serious threat to human existence. They ate human crop and some of his other possessions and transmit diseases such as malaria, trypanosomiasis onchocerociasis and other diseases. The above losses result in the enormous wealth damages, and that is the reason why, form age old days a number of chemicals have been
introduced for insect control. The chemicals used for control of insects are termed as insecticides\textsuperscript{[54]}.  

The ultimate practical objective of insect control is to lessen the extent of insect damage to human possessions or prevention of insect out break. The earlier insecticides\textsuperscript{[55,56]} were sulphur, arsena and paris green. Synthetic organic compounds dominate the field of insecticidal control today. Important examples of such type are dimierocresot, DDT, BHC, TEEP, shradan etc.,  

Elliot\textsuperscript{[57]} in 1977, suggested that the synthetic insecticides should have low mammalian toxicity and controlled environmental stability.
REFERENCES


