SECTION A

Introduction
Nature of Selected Heterocycles
Pyrazoline Derivatives
Quinoline Derivatives
Indole Derivatives
Carbazole Derivatives
Complex Compounds
CHAPTER-1

Introduction
History:

There was a time when all our pain relievers and other drugs came from natural sources like plants and animals. But around 1800 scientists began to put around in their laboratories and made new drugs. At first all did was to re-create natural drugs. This was useful when plant and animal sources are too hard to use or don't produce enough of the medicine. Once man figured out how to duplicate nature, he began to tweak 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 would alter the molecular structure of the natural molecule until they had made a drug that worked like the natural drug, but without the side effects. Asprin was one of the first natural inspired synthetic drugs.

The vegetable drugs have obvious limitation like non availability throughout the year and hard work involved in their cultivation, collection, extraction, purification and characterization. Therefore scientists have been inspired to find synthetic alternatives. Francois Megendie laid down the foundation of pharmacology (i.e.). The science dealing with the action of drugs, by introducing the scientific method of studying the effect of drugs on guinea pig. Fighting disease with drug is the timeless struggle. Its beginning echoed out of the primitive jungle.

Man's survival on this planet is dependent upon his success. Today the conflict continues unabated in the laboratory and clinic.
The beginning of effective therapy by chemicals has lost in antiquity, because it preceded recorded medical history. Early success in the quest for chemicals effective against disease were predominantly found among anti-infective disease rather than against those usually accompanying the ageing process, such as hypertension and cancer. Since chemical processes were largely underdeveloped nature initially provided the more sophisticated and promising agent.

Synthetic Era:

The era of synthetic drugs had to await till the technique of synthetic organic chemistry become well advanced and physiology of human organisms become well known. Most of the earliest efforts to find synthetic drugs were concentrated on anaesthetics, hypnotics and analgesics. Chloralhydrate was synthesized in 1869, paraldehyde in 1882, sulpharous is 1888, phenacetin in 1889, asprin in 1899, sulphadrugs in 1933 known as first antibacterial drug and penicillin in 1940 antibiotic drug etc.

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 dance as recreational drugs 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\textsuperscript{1} have much shorter histories of illicit use. There are growing global concern about the potential manufacture of other and newer synthetic drugs sold as an alternatives 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 for (GHB). There are also synthetic opiates such as methadone, pethidine (MPPP, MPTP), pertainyl-s-methyl fentanyl etc.

**Heterocyclic Compounds**:

The heterocyclic compounds occupy key position in the area of drugs and pharmaceuticals. Almost 85% of the drugs in clinical use are based on heterocyclic constitution. Heterocyclic chemistry in a branch in some quise has been inseparable from mankind origin or history, since it fulfills one of our basic need. The cell is generally thought a to be the unit of human body and is a marvellous chemical factory. This is surprising because cell or nature has chosen heterocyclic substances for some of the most important function in the living cell as vitamins, co-enzymes and *pigment, chlorophyll* and component of genetic materials. These contents in specific concentration in living cells give the characteristics of life. The investigation on chemistry of heterocyclic compounds have not only
been as essential elements in man’s endeavours to unravel the mysteries of the living world but at the same time those studies have constantly stimulating new direction 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 an atom or atoms 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 to hand with an investigation of great variety of natural products. Many of plant pigments such as catecins 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 azoles chemistry.

**Significance of Heterocyclic compounds:**

Most of the heterocyclic compounds which are nitrogenous bases occurring in plants and many antibiotics including penicillin and streptomycin also contain heterocyclic ring system. Many natural pigments such as indigo, haemoglobin and anthocynin are heterocycles. Most of the sugars, their derivatives including vitamin for instance, exist largely in the form of five membered or six membered ring containing nitrogen. Life saving drugs, poison and medicines (both natural and synthetic) such a sulphathiazole,
pyrathrin, rafenone, strychnine, reserprine, the ergot alkaloids
caffeine, cocaine, barbiturates etc. heterocyclic natures. Some typical
areas where heterocycles signify a large importance have been
summarized:

**Heterocyclic in drugs:**

The 'golden period' of new drug discovery was 1930 to 1970,
chemical sciences contributed extensively new discoveries leading to
useful drugs since 1930. The modern concept of drug discovery
started in 1933 by **Gerhard Dogma**k with his finding of 'protonilred'
a compound responsible for the antibacterial activity. A very large
number of important drugs had been introduced during that period,
such as:

<table>
<thead>
<tr>
<th>Name of drugs</th>
<th>Year</th>
<th>Usages</th>
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<tbody>
<tr>
<td>Sulfa drugs</td>
<td>1933</td>
<td>First antibacterial drug</td>
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<tr>
<td>Penicillin</td>
<td>1940</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>1945</td>
<td>Antimalarial</td>
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<td>Methyl dopa</td>
<td>1950</td>
<td>Antihypertensive</td>
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<tr>
<td>Chlorthiazide</td>
<td>1957</td>
<td>Diuretic</td>
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<tr>
<td>Adrinergic beta blocker</td>
<td>1958</td>
<td>Coronary vasodilatory</td>
</tr>
<tr>
<td>Somi synthetic penicillin</td>
<td>1960</td>
<td>Antibacterial</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>1965</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td>Disodium chromoglycoate</td>
<td>1970</td>
<td>Antiallergic</td>
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In case of heterocyclic compounds exhibit wide range of
biological activities. Quinoline derivatives are well known drugs for the
treatment of malaria. Introduction of amino group in the ring of
quinolines found to be associated with a number of activities viz.
antidepressant, hypoglycemic, gastric secretion inhibitory, antiherpetic, gastric ulcer inhibitors, psychonnaleptic, and inhibit DNA topo isomerase and display cytotoxic and antitumour activities, chemotherapeutic activities and also active against HIV-I integrate. Sulindac and indomethacin are recent drugs used for the treatment of anti-inflammatory agents in therapy. Both are indole acetic acid derivatives. Acridine based antimalarial and antibacterial compounds (Mepacrine, azacrine, prolatvine and aminocrine) are known. 9-(Dimethyl amino propyl) amino-1-nitro acridine has been quite extensively used as antitumour drug in Poland. Ansacrine has wide spread clinical use as antitumour agent. The compounds are also used for lessening of memory inapirment and potent anticonflict ex. benzothieno pyridines. Besides these, heterocyclic compounds possess various other activities like local anaesthetic, antidiabetic, diuretic, cardiovascular agents, antiviral, antiparkinsonin African sleeping sickness herbicides, anticovulsant, muscle relaxant, antineoplastics, antimicrobial, antihypertensive, antihistamine, antispasmodic, tranquillizers, antiulcer, etc. Retinoids are 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 stucture resulted in arotinaide that were biologically active but with increased toxicity. Incorporation of a hetero atom in one cyclic ring of the arotinoid structure drastically reduced the toxicity, while retaining biological activity.
Heterocyclics in nature:

Heterocyclic compounds are widely distributed in nature. The plants are green and blood is red due to their presence as chlorophyll and haemin and also, the life of plants and animals are restored in them. Carbohydrates, turning and amino acid are derived from hetrocyclic origin. The physiologically active substances of heterocyclic origin are co-enzymes, metabolically active substances like heteroauxin, serotonin and adenine, biotin, vitamin B-12 family, tocopherol, histamine, vitamins like thiamine, riboflavin, nicotine acid, pyridoxin, thiocitic acid etc. purine, and pyrimidines base like adenine, guanine, cytocene, thiamine, break down products of metabolism like uric acid, alloxane and allantoin, essential amino acids like histidine, tryptophan and proline, alkaloids such as strychnine, reserpine and morphine, antibiotics like penicillin, energy storing units like A.D.P. and A.T.P. electron transport system like cytocrome 'a' and 'b' etc.

Heterocyclics in Dyes:

Some of the dyes bounded is heterocyclic ring system enjoy their unique importance in the field of dyes. This is because of their height lincctorial power and excellent fastness properties towards certain agencies. Azo dyes prepared from amino heterocyclic compounds have proved to be commercially useful because of their ability to provide whole range of shade, tailor made preparation and better fastness properties compared to other class of dyes. In dye-stuff industry, heterocyclic compounds are encountered in all the
established class of coloring matters. Azodyes for example contain heterocyclics such as quinoline, pyrazolones, thiazoles, indoles, imidazoles, carbazole and triazole. The azole components include carbazole dibenzofuran or benzothiazole unites besides these, heterocyclic system such as azine, oxaine, xanthaine, thiazine, quinoline, aminothiazole\textsuperscript{35}, aminobenzothiazole\textsuperscript{36}, aminothiophene\textsuperscript{37}, 3-Amino-1,2,4-triazole\textsuperscript{38} and aminobenzoisothiazole\textsuperscript{39} constitute individual class of synthetic coloring matters. The heterocyclic phthalocyanine and quinacridine are important pigments.

**Heterocycles in Industry:**

Heterocycles like benzofuran polymerises to give useful plastics and resins. Heterocyclics like 2-mercapto benzothiazoles, piperidine and phenothiazines are used as antioxidants and vulcanizing accelerators in rubber industry. Some of the heterocyclic compounds are used in agro industry as insecticides and fungicides. 2-phenathroline, 8-hydroxy quinoline and dipyridyl have their use in analytical chemistry to estimate different metals in solution.

**Heterocycles in Agrochemicals:**

1,2,4-trizoles have found broad applications as herbicides, fungicides and antibacterial agents. Triazoles 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:

1,2,4-Tiazoles and benzotriazoles have successfully applied as photostabilisers for fibers, plastics or dyestuffs and also used for the protection of human skin from harmful UV radiations.

Methods of chemical analysis:

During last thirty years enormous development in the field of synthetic organic chemistry has taken place due to the availability of powerful analytical techniques. The spectral methods have been of immense help in the collection of valuable information about individual compounds. Ultraviolet, infrared, nuclear magnetic resonance spectroscopy and mass spectrometry are among the most important spectroscopic techniques that the organic chemists now use routinely to gain information about a particular substance. In the present study IR and \(H^1\)NMR techniques have been used to characterise the synthesized compounds. Thin layer chromatography has been used to check the purity of the synthesized compounds.

Infra red 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 at atom of molecules. Bellamy and Rao reviewed the applications of IR spectroscopy this technique is most widely used for the identification of all kinds of organic compounds.
The infrared absorption spectroscopy is based on the absorption of infrared radiations by molecules. It has been observed that all chemical compounds show marked selective absorption in the infrared region.

However, infrared spectroscopy is most widely used for the identification of organic compounds. The infrared absorption spectrum of an organic compound represents one of its truly unique physical property. IR spectrum of chemical substance is a finger print for its identification. The organic applications of infrared spectroscopy are almost entirely concerned with range 650-4000 cm\(^{-1}\). The region of frequencies lower than 650 cm\(^{-1}\) is called the far infrared and that of frequencies higher than 4000 cm\(^{-1}\) is called near infrared.

This method can solve many problems in organic chemistry and co-ordination chemistry, while in some other problems infrared data advantageously complement the results obtained by other methods. In structure determination the infrared spectra can at once indicate the presence of various atomic groupings and can give some information about the size of the ring. This technique is useful for identification of functional groups, study of chemical reaction, study of tautomerism and for finding out hydrogen bonding in the molecules. Many scientists have applied IR spectroscopy for the structural interpretation of terpenes, glycosides, carbohydrates and all kinds of natural and synthetic compounds. Dhar and Singh\(^{45}\) have studied the IR spectra of some new chalcones. Advanced studies have been done in this field and are illustrated by many workers\(^{46}\).
Nuclear magnetic resonance spectroscopy:

Nuclear magnetic resonance spectroscopy serves as a powerful tool for the structural elucidation of organic compounds. H’NMR and $^{13}$C-NMR techniques gave configurational and conformational nature of the compounds. This technique is helpful in observing each and every proton and carbon atom separately in the compounds. A large number of synthesis$^{47-50}$ as well as natural compounds$^{51-55}$ have been studied by NMR spectroscopy. The method of NMR was first developed by E.M. Purcell and Felix Bloch in 1946. This subject has developed very rapidly in recent years and today it has extended so much that it is of equal importance with that of older established vibrational and electronic branches of spectroscopy. Nuclear magnetic resonance involves the interaction between an oscillating magnetic field of electromagnetic radiation and the magnetic energy of the hydrogen nucleus or some other type of nuclei when these are placed in an external static magnetic field. The sample absorbs electronic radiation in radiowave region at different frequencies, since absorption depends upon the type of proton or certain nuclei contain in the sample. Radio waves are regarded as the lowest energy form of electromagnetic radiations that find valid application 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. Nowadays the structure of a number of natural products as well as other organic compounds are confirmed by their NMR spectra. It is extensively used
in pharmaceutical and polymer industry. The applications have been extensively reviewed in standard works\textsuperscript{56}.

**Chromatographic techniques:**

Chromatography is the most useful technique for the separating and identifying a mixture of substances into its components. This technique is based upon the differences in the rate of mobility of various constituents of substances through a porous medium (called stationary phase) under the influence of some solvent or gas (called moving phase) based on the nature of stationary or moving phase. There are different types of chromatographic technique like paper, thin layer, column and gas chromatography in the present research work thin layer chromatography has been used to check the purity of the compounds. Thin layer chromatography also serves as a great tool for separation of various complex organic mixtures. In this technique, stationary phase is made by coating a slurry of adsorbent on a glass plate as a thin and uniform layer. It is a rapid technique and separation is very sharp. Its sensitivity of detection is very high. This technique successfully separates the heterocyclic compounds, alkaloids, flavonoids and amino acids.

**Biological assay studies:**

For the development in the field of chemotherapy, it is necessary to test new chemicals for their curative properties against various diseases. So it was thought worthwhile to study pyrazoline, quinoline,
indole, carbazole for their (1) anitimicrobial (Chapter.No.8) and (2) insecticidal (ChapterNo.9) 3-anthelmintic (Chapter No.10) properties.

**Antimicrobial activity**

The invention of microscope in the 17th century gave vision to the hitherto unknown world of micro-organism. These organisms are closely associated with the health and welfare of human beings and plants. Some are beneficial and others cause disease 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 implication in related field of study.

In 1878 Barrill 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. Agastino Bassi in early 1800, proved that muscardin is a fungal disease which is common in silkworms. The common disease of human and animal which are caused by fungi include antinomycosis, sporotrichosis and epidemophytosis.

Joseph Hinston in 1878 was the first scientist who developed pure culture technique to the germ out side the body and proved by experiments that the germs can grow outside the body are also susceptible to produce same symptoms, when it is inoculated in to
body as the same pattern. 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 vitro in order to determine.

(1) The potency of antimicrobial agent.

(2) Sensitivity of the germ microorganism to the known concentration of the drug.

**Anthelmintic activity:**

The anthelmintics are the drugs, which are used to kill or expel the parasitic worms known as helminths from the infected host. These drugs are of the great importance because helminthiasis is the most common disease in the world. Sollmann reported that all the clinical anthelmintic are toxic to earthworm. Therefore, earthworms can be used to have an idea, whether the test substance has anthelmintic activity and to compare its relative activity with the standard like piperazine hydrochloride, etc. A number of workers have used earthworms for the preliminary in vitro evaluation of anthelmintic activity of new substances.

**Insecticidal activity:**

Without doubt insects occupy a dominant position in the animal world, out numbering all other inhabitants and they are very successful animals. Of the estimated 1.35 million living species of animal, more than 9,00,000 are insects. Their tenacity for life is
amazing and their capacity for multiplication and their wonderful adaptation has made them a serious threat to human existence. They eat human crops and some of his other possessions and transmit disease such as malaria, trypanosomiasis, onchocerciasis and other disease of his animals. The above losses result in the economic and wealth damages and that is the reason why from 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{62}.

The ultimate practical objective of insects control is to lessen the extract of insect damage to human possessions or prevention of insect out break. The earlier insecticides\textsuperscript{63,64}, were sulphur, arsenic and paris green. Synthetic organic compounds dominate the field of insecticidal control today. Important examples of such type are dinitro cresol, DDT, BHC, TEEP, Schradan etc.

Elliot\textsuperscript{65} in 1977 suggested that the synthetic insecticides should have low mammalian toxicity and controlled environmental stability.

**Aims and objectives**:

In the pharmaceutical field, these have always been and will continue to be a need for new and novel chemical inhibitors of biological function. Our efforts are focussed on the introduction of chemical diversity in the molecular frame work in order to synthesize pharmacologically interesting compounds of wildly different composition.
During the course of research work looking to the application of heterocyclic compounds, several entities of heterocyclic compounds have been designed, generated and characterised using spectral studies. The details are summarized as under:

1. To generate several derivatives like chalcones, pyrazoline and quinoline.

2. To synthesise indole and carbazole derivatives.

3. To synthesize the above said group derivatives their complex with Co and Cu metals.

4. To characterise these compounds for structure elucidation using spectroscopic techniques like IR and NMR spectral studies.

5. To check the purity of all compounds by using thin layer chromatography.

6. To evaluate these new compounds for better drug potential against different stains of bacteria and fungi.

7. To evaluate these compounds for better drug potential insecticidal and anthelmintic activity against cockroaches and earthworms.

Keeping in view, the applicability of heterocyclic compounds, the construction of new heterocycles of therapeutic importance, bearing quinoline, pyrazoline, indole and carbazole nucleus have been investigated in the following parts.
REFERENCES


