CHAPTER - 1

GENERAL INTRODUCTION
Heterocyclic compounds are those which have a cyclic structure made up of more than one kind of atoms in the ring. This work is devoted to organic heterocyclic compounds in which at least one of the ring atoms is carbon, the others being considered the heteroatoms. Carbon is still by far the most common ring atom in heterocyclic compounds. As the number and variety of heteroatoms in the ring increase, there is a steady transition to the expanding domain of inorganic heterocyclic systems. Since the ring can be of any size from three membered upwards and the heteroatoms can be drawn in almost any combination from a large number of elements (though nitrogen, oxygen and sulphur are the most common), the number of possible heterocyclic systems is almost limitless. An enormous number of heterocyclic compounds is known and this number is increasing very rapidly. The literature of the subject is correspondingly vast and of the three major divisions of organic chemistry; aliphatic, carbocyclic and heterocyclic, the last is much the biggest. Nearly six million compounds are recorded in 'Chemical Abstracts' and approximately half of these are heterocyclic.

Heterocyclic compounds are very widely distributed in nature and are essential to life. They play a vital role in the metabolism of all the living cells. The following are the examples of the heterocyclic compounds:
- The pyrimidine and purine bases of the genetic material DNA;
- The essential amino acids- proline, histidine and tryptophan;
- The vitamins and co-enzyme precursors- thiamine, riboflavin, pyridoxin, folic acid and biotin;
- B₁₂ and E families of vitamins;
- The photosynthesizing pigment- chlorophyll;
- The oxygen transporting pigment- haemoglobin and its breakdown products the bile pigments; and
- The hormones- kinetin, heteroauxin, serotonin and histamine together with most of the sugars.

There are a vast number of pharmacologically active heterocyclic compounds, many of which are in regular clinical use. Some of these are natural products, for example antibiotics such as penicillin and cephalosporin; alkaloids such as vinblastin, ellipticine, morphine, reserpine and cardiac glycosides such as those of digitalis. However, the large majority are synthetic heterocyclics which have found widespread use, for example as anticancer agents, analeptics, analgesics, hypnotics and vasopressor modifiers and as pesticides, insecticides, weedkillers and rodenticides.

There are also a large number of synthetic heterocyclic compounds with other important practical applications such as dyestuffs, co-polymers, solvents, photographic sensitizers and developers, antioxidants and vulcanization accelerators in the rubber industry and many are valuable intermediates in synthesis.

The successful application of the heterocyclic compounds in these and many other ways, their appeal as materials in applied chemistry, in more fundamental and theoretical studies, stems from
their very complexity; this ensures a virtually limitless series of structurally novel compounds with a wide range of physical, chemical and biological properties, spanning a broad spectrum of reactivity and stability. Another consequence of their varied chemical reactivity including the possible distribution of the heterocyclic ring, is their increasing use in the synthesis of specifically functionalized non-heterocyclic structures.

The widespread occurrence of heterocyclic compounds in nature, their vital role in metabolism in the living cells and their economic value as dyes and pharmaceuticals are some of the factors which have directed the attention of organic chemists in this field.

Drugs are substances intended for use in diagnosis, cure, mitigation or prevention of disease in man or in other animals. History of medicinal chemistry shows that more effective analogous are obtained by molecular manipulation, by disjunction or through quantitative structure action relationship studies or group substitution.

Earlier almost all drugs are obtained from natural sources. The isolation, characterization and studies of various physico-chemical parameters of the active compounds of various groups such as hormones, glycosides, alkaloids etc. have provided many important drugs. All natural drugs can not be obtained in all parts of world because of diverse climatic conditions. So, Scientists has to pay their attention towards synthetic alternatives.

The approach employed by the modern synthetic chemists in search of better drugs start with the "search of leads". The biological
activity of natural products provide a useful lead for synthesis of newer drugs. It was observed that a cattle fed with improperly stored sweet clover hay suffered from profuse bleeding. The chemical investigation of improperly stored hay leads to the isolation of anti-coagulant compound, bis-hydroxy coumarin. A comparative study of biochemical process involving bacteria, men and animals have also provided leads for the synthesis of newer drugs. Once a suitable leads has been discovered next step involves molecular manipulation. The potency, specificity and various factors affecting physiological activity of the drugs may be governed by such physico-chemical aspects as molecular size and shape, ionization, charge distribution and solubility. The activity of a molecule has been shown to be effected by its lipid-water partition co-efficient, its geometry, distribution of charges and so drug receptor sites. The molecular orbital calculations introduced recently may indicate which atom or groups are the active sites of the molecules including the idea regarding spacing between sites and so the molecular geometry. The isosteric molecules having approximately same size and shape, are likely to exhibit similar biological action. The isoelectric molecules having similar electron density, resonance energy and dipole moment are also likely to behave analogously. These properties are also important in the modification of parent compounds.

The field of study of heterocyclic chemistry is no doubt very wide. But, the present discussion has been confined only the compounds of five and six membered ring system having two hetero atoms as a part of the ring in view of the fact that the present work concerns the
synthesis and pharmacological studies of the compounds having these rings.

A class of five membered heterocyclics which has acquired considerable interest during recent years due to its immense use in pharmaceuticals and dye industries is the 'azoles'.

During the past decade novel approaches have been innovated for the synthesis and pharmacological properties of azoles (viz. pyrazoles, imidazoles, isoxazoles and thiazoles) derivatives with a view to prepare compounds which may enhance the activity and hopefully reduce the side effects.

The use of pyrazole derivatives in medicine is undoubtedly the principal practical application. 3-n-nonylpyrazole was the first naturally occurring pyrazole derivative isolated\(^1\) by Japanese workers from *Houttuynia cordata*, a plant of the 'Piperaceae' family from tropical Asia. This compound was found to inhibit the growth of *Staphylococcus aureus*, *Bacillus subtilis*, *Trichophytons*, *Zygosaccharomycetes salus* and *Aspergillus niger*. The first synthetic compound containing this ring system was 3-methyl-1-phenylpyrazole-5-one\(^2\) which led to the discovery of the drug 'antipyrine' whose antipyretic and analgesic activity was exploited over a long time until the discovery of more potent synthetic drugs. Later on, laevo-\(^\beta\)- (1-pyrazolyl)-alanine, a pyrazole amino acid, was isolated\(^3-5\) from water melon seeds (*Citrullus vulgaris*).

In general, compounds with pyrazole nucleus possess bioantagonistic, antitumor, carcinostatic, antiviral, antimicrobial,
antihistaminic, antigout, enzyme inhibitory, diuretic, cardiovascular, hypocholestermic and hypoglycaemic activities\textsuperscript{6}. Alkyl and aryl pyrazoles produce sedative and soporific effect on the central nervous system along with anticonvulsant and hypothermic effects\textsuperscript{7,8}. There are evidences that 3,5-dimethylpyrazole and its derivatives have a stimulating action on plants and also act as antidiabetic\textsuperscript{9-12} and antineoplastic\textsuperscript{13} agents.

1,3-Dialkyl; 3,5-dialkyl and 1,4,5-trialkylpyrazoles act on the central nervous system to produce tranquilizing and anticonvulsants\textsuperscript{14} effect. Some pyrazoles of the type (1) were also synthesised and used as analgesics, diuretic, sedative and antipyretic\textsuperscript{15} agents.

\[
\begin{align*}
\text{H}_3\text{C} & \begin{array}{c}
\text{N} \\
\text{N}
\end{array} \\
\text{N} - \text{C} = 0 \\
\text{H}_3\text{C} & \begin{array}{c}
\text{N}
\end{array} \\
\text{H}_3\text{C}
\end{align*}
\]

Acyl derivatives of 3,5-diethyl and 3,5-diphenylpyrazoles have also been reported to possess diuretic activity\textsuperscript{16}. Recently, 1-(substituted salicyloyl)-3,5-dimethylpyrazole have been synthesised and found to exhibit hypoglycaemic activity\textsuperscript{17}. Among the aryl substituted pyrazoles those having the amino group such as 3-amine-4-phenylpyrazole and its derivatives, were found to exhibit muscle relaxant activity\textsuperscript{18}. Synthesis of model systems analogous to histamine led to the discovery of pharmacologically active aminoethylpyrazoles. Among a number of aminoalkylpyrazoles, 3-β-aminoethylpyrazole (2) was found to possess unusually high activity\textsuperscript{19}. 

1-substituted amino-4-dimethylpyrazoles were also reported to possess antipyretic, analgesic and anti-inflammatory properties. 5-(n-dimethylaminoacetamide)-1,3-diphenylpyrazole has been found to possess analgesic activity and such compounds also enhanced the analgesic activity of aminopyrine.

5-amino-3-(N,N-dialkylaminophenyl)-4-cyanopyrazoles have been synthesised which exhibited antiviral activity against mengovirus in FL cell cultures. The compound 1-N, N-dimethylcarboxamido-3, 5-dimethylpyrazole was found useful as a hydraulic fluid denaturant and also found to possess analgesic, diuretic, sedative and antipyretic properties. Further, 5-methyl-3-pyrazolecarboxamides were reported to exhibit hypoglycaemic activity.

Later, 1-substituted-3-aminoalkoxy-4,5-cycloalkylpyrazoles with central nervous system depressant activity have been synthesised. Some aminopyrazole sulphides of the type (3) containing an alkyl side chain are reported to exhibit antifungal activity against strains of Candida albicans and Trichophyton mentagrophytes and antimicotic activity. Remarkable antimycosis was shown by those substances in which the alkyl group attached to sulphur containing at least three carbon atoms whereas a very low antifungal activity appears when an aryl group takes the place of an alkyl group.
5-methylpyrazole-3-carboxylic acid has been found to exhibit high hypoglycaemic activity\(^2\) which was neither altered by adrenalectomy nor potentiated by tolbutamide, oxalic acid or insulin. Pyrazole acetic acids are inflammatory inhibitors and 5-chloro-1,3-diphenylpyrazole-4-acetic acid was found to be ten times as effective as phenylbutazone in the carrageenan oedema test\(^2\). The methyl ester of 1-methyl-4- (p-methoxybenzoyl) -pyrazole-5-carboxylic acid has been found to be therapeutically active\(^2\) against adenocarcinone H.K. in mice. 3-methyl-4-carboxamidopyrazoles have been found to be a long lasting inhibitor of lipolysis\(^3\). 4-pyrazole acetic acid derivatives have been reported to exhibit anti-inflammatory and analgesic activities\(^4\).

Some pyrazole derivatives, such as 3-(substituted triazino)-pyrazole-4-carboxylic acid esters and 3-(substituted triazino)-pyrazole-4-carboxamides were found to possess good antileukemic activity\(^2\),\(^3\) against leukemia L-1210 system in primary screening of cancer chemotherapy. Some substituted pyrazolylthioacetic acids and their esters are found to be useful as trichomonicides\(^4\). Pyrazole derivatives of the type (4) have been prepared and found to be histamine antagonistics\(^5\).

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{N} \\
\text{O(CH}_2)\text{N} & \quad \text{CH}_3 \\
\text{R} & \quad \text{O(CH}_2)\text{N} \\
\text{R} = \text{C}_6\text{H}_5, \text{CH}_2\text{-C}_6\text{H}_5
\end{align*}
\]

(4)
The antihistaminic activity is improved when the phenyl group at position-1 is replaced by a benzyl group and out of the many compounds, 1-benzyl-3-methyl-5-(2-dimethylamino ethoxy) pyrazole exhibited a very high histamine antagonistic potency. 3-methyl-5-phenoxyethylpyrazole has been synthesised and reported as an orally active antidiabetic agent\textsuperscript{36}. Very recently, 4-(aryloxy) alkyl pyrazoles were reported to have antiherpetic activity\textsuperscript{37} against \textit{Herpes simplex} and antibacterial activity\textsuperscript{38} against \textit{Staphylococcus albus}, \textit{Shigella sonnei} and \textit{Salmonella paratyphi}.

The pyrazoles of the type (5) having an amino group at position-5 have been used as xanthine oxidase inhibitors, antilipemics, antiphlogistics and anti-arrhythmics\textsuperscript{39}.

\begin{center}
\begin{tikzpicture}
    \draw (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle;
    \draw (0.5,0.5) -- (0.5,1.5);
    \draw (0,0.5) -- (0.5,0.5);
    \draw (0.5,0) -- (1,0.5);
    \draw (0,1.5) -- (0.5,1);
    \draw (0.5,2) -- (1,1.5);
    \draw (0,0) -- (0,1.5);
    \draw (1,0) -- (1,1.5);
    \draw (0.5,0) -- (0.5,1.5);
    \draw (0.5,1.5) -- (0.5,2);
    \node at (0.5,0) {H};
    \node at (0.5,1) {NH\textsubscript{2}};
    \node at (1,0) {\textbackslash C-\textbackslash NH-\textbackslash CHO};
    \node at (0,1.5) {O};
\end{tikzpicture}
\end{center}

\textit{(5)}

Further, some of the pyrazoles have been claimed to be effective in influenza\textsuperscript{40}, germicides\textsuperscript{41}, antactinics\textsuperscript{42} and as herbicides\textsuperscript{43,44}.

4-nitropyrazole derivatives have been found to possess psychosedative effect on mice and were also useful as analgesics and muscle relaxants\textsuperscript{45,46}. 4-nitrosopyrazole derivatives when synthesised and tested for their biological properties, were found to be active\textsuperscript{47,48} against virulent strains of \textit{Mycobacterium tuberculosis} and were useful for combating the fungal and bacterial infections. It was
also observed that the presence of pyridine at position-1 of these compounds made them useful in the treatment of ring worms\textsuperscript{49} in cattle.

Halopyrazoles have attracted the attention of chemists for their hypolipidemic, herbicidal and insecticidal properties\textsuperscript{50-53}. Using a new approach to the concept of altering the structure activity relationship in anabolic steroids, several types of steroidal pyrazoles have been synthesised which possess psychopharmacological properties and are reported to produce changes in the endocrinological activity\textsuperscript{54-57}.

Pyrimidinopyrazoles are being studied\textsuperscript{58-61} in the fight against cancer. 1-pyrimidinopyrazoles of the type (6) were synthesised and reported as anti-inflammatory\textsuperscript{62} agents.

\[
\begin{array}{c}
\text{H}_2\text{N-C-H}_2\text{C} \\
\text{N} \\
\text{OCH}_3 \\
\text{H}_3\text{C} \\
\text{CH}_3 \\
\end{array}
\]

1-substituted-4, 6-diaminopyrazolo (3,4-d)-pyrimidines are reported to be effective antibacterial agents\textsuperscript{63}. Very recently, some pyrazolylamino imidazolines have been found to exhibit antihypertensive activity\textsuperscript{64}.

3-\{1-pyrazolyl\}-pyridazines of the type (7) have been synthesised from hydrazinopyridazines and were found to possess antihypertensive activity\textsuperscript{65}. Pyrazolyl-thiazoles have been reported
good herbicides and have control on Chenopodium album.

\[
\begin{align*}
R & = H, \text{alkyl}, \\
R_1 & = \text{CN, NO}_2, \text{NH}_2, \text{CONH}_2, H, Cl, Br, \text{alkyl}. \\
R_2 & = \text{NH}_2, \text{Cl, alkyl}. \\
R_3 & = H, \text{Cl, NH}_2, \text{CONH}_2.
\end{align*}
\]

8-chloropyrazolo-(1,5-c)-quinazoline derivatives have hypotensive, psychomotor depressant and bacteriostatic activities. Further, pyrazoles having a furan ring attached to it were found to be active against Staphylococcus aureus, Shigella sonnei, Staphylococcus flexneri, Escherichi coil, Candida albicans and Pseudomonas aeruginosa. Later, these pyrazoles were also tested for their bactericidal and fungicidal actions and positive results were obtained.

Cyclohexane and androstane substituted pyrazoles are of considerable interest as pharmaceutical and antitumor drugs. Some alkyl derivatives of tetrahydropyrrolo-(3,4-c)-pyrazoles were found to possess anti-inflammatory activity. Imidazolopyrazoles were found to protect mice against 20 hours Pasteurella multocida culture.

Some of the substituted napthoxypyrazoles (8) have been synthesised and were found to inhibit fertility at 100 mg S.C. twice a day.
Pyrazolenaphthridines (9) prepared from pyrazole-(3, 4-b)-pyridine exhibited bactericidal activity\textsuperscript{74}.

(9)

"IMIDAZOLE" derivatives are very well known to possess a wide range of pharmaceutical properties like hypnotic\textsuperscript{75}, potent CNS depressant\textsuperscript{76,77} etc. Many of the imidazolines are potent antihypertensive agents. A series of 2-amino-4-aryl-2-imidazolines have been synthesised and reported as antihypertensive\textsuperscript{78}.

Recently, the acute toxicity and antifungal, analgesic and anti-inflammatory activities of several benzimidazoles of the type (10) have been studied\textsuperscript{79}.

(10)

(a) : $R_1 = \text{NO}_2; \ R_2 = R_3 = R_4 = \text{H}$.
(b) : $R_3 = \text{Br}; \ R_1 = R_2 = R_4 = \text{H}$.
(c) : $R_1 = R_3 = \text{Br}; \ R_2 = R_4 = \text{H}$.

Methyl 5-(6)-butyl-2-benzimidazole carbamate (perbendazole) of the type (11) is a potent anthelmintic agent\textsuperscript{80}.

(11)
A series of 1- (substituted cinnamamido) - 2, 4 - imidazolinediones of the type (12) has been prepared and these compounds possess a significant degree of anthelmintic activity against the mouse pin worm, Syphacia obvelata. However, the most active compounds are those substituted with halogen or cyano groups.

\begin{align*}
\text{(12)} \\
R_1 & = Cl ; R_2 = Cl. \\
R_1 & = H ; R_2 = H. \\
R_1 & = CH_3 ; R_2 = Cl. \\
R_1 & = Cl ; R_2 = H. \\
R_1 & = Cl ; R_2 = CF_3. \\
R_1 & = F ; R_2 = H. \\
R_1 & = H ; R_2 = F. \\
R_1 & = F ; R_2 = Cl. \\
R_1 & = C_2H_5 ; R_2 = Cl. \\
R_1 & = Br ; R_2 = CH_3.
\end{align*}

Several benzimidazoles possessing a broad spectrum anthelmintic activity against the intestinal nematodes of sheep have been reported. Benzothiazoles with 1- and 2- carbamoyl substituents are also reported to have broad spectrum anthelmintic activity.

A series of imidazolyl amino alcohols of the type (13) have been synthesised and two of them (a and b) were found to produce tachycardia and a very modest dilation of the coronary vessels in the isolated perfused rabbit heart.

\begin{align*}

\text{(13)} \\
R_1 & = H; R_2 = CHOH-CH_2-NH_2. \\
R_1 & = H; R_2 = CHOH-CH_2-NH-CH_3.
\end{align*}
The benzimidazo [2, 1-b] -quinazolin-12-ones constitute a novel group of compounds. They were prepared as a part of a series for new immunosuppressive agents and have proven markedly active in the sheep erythrocyte antibody in mice (SEA M) assay.

Nitroimidazoles are chemotherapeutically important as antiprotozoal and antibacterial agents. Metronidazole, [1-(2-hydroxyethyl-2-methyl-5-nitroimidazole] is both, an amoebicide and trichomonacide while azomycin, (2-nitroimidazole) exhibits antibiotic properties. Other compounds of this type are effective against a variety of protozoan infections. A partial list includes dimetridazole, (1, 2-dimethyl-5-nitroimidazole) which is used against trichomonas in cows and Hymenolepis meleagris infections in fowl. Ronidazole, (1-methyl-1-carbamylmethyl-5-nitroimidazole) is a potent histomonastat. Ipronidazole, (1-methyl-2-isopropyl-5-nitroimidazole) (14) is a potent antitrichomonial agent.

![Chemical Structure](image)

Some 2-styryl-5-nitroimidazoles which are effective against trichomonas, have been synthesised. Fluonidazole, [1-(2-hydroxyethyl)-2-(p-fluorophenyl)-5-nitroimidazole] is a trichomonacide which is also an active local and oral amoebicide against various animals. A number of 1-(3-chloro-2-hydroxypropyl)-substituted nitroimidazoles and related compounds of the type (15) have been synthesised having significant antiprotozoal activity.
Recently, thirteen new 1-(2'-methoxy-4'-nitrophenyl)-2-methyl-4-substituted benzylidene-5-imidazolones of the type (16) have been synthesised and tested for CNS depression and anticonvulsant activity. They have been found appreciable CNS depression properties as is evident by antimetrazole test and presence of alaxia decrease SMA and righting reflex in albino mice.\(^9^3\)

A variety of imidazole derivatives of the type (17) were synthesised and found to possess potent inhibitors of cyclic nucleotide phosphodiesterases (PD).\(^9^4\)

(a) : \(R_1 = CH_3; R_2 = H\).  
(b) : \(R_2 = CH_3; R_2 = CH_3\).

Certain 4, 5-diphenyl-2-substituted imidazoles of the type (18) exhibited anti-inflammatory activity comparable to phenylbutazone.
in the carrageenan rat paw oedema test\textsuperscript{95}.

\[ R = \text{C}_6\text{H}_5 \quad \text{or} \quad \text{CH}_3 \quad \text{or} \quad \text{CF}_3 \]

A series of thioacetals and hydrazones of 2-(4-formylstyryl)-5-nitro-1-vinylimidazole of the type (19) were prepared and displayed good activity against \textit{Trypanosoma rhodesiense} \textsuperscript{96}.

\[ R = \text{COOH} \quad \text{or} \quad \text{CHO} \quad \text{or} \quad \text{CH}_0 \]

\textit{N}-substituted phenethylimidazoles have been shown to display potent \textit{in vitro} and \textit{iv vivo} antifungal properties\textsuperscript{97,98}. One of these, namely 'MICONAZOLE' (20) is currently finding use in human medicine as an antimycotic agent\textsuperscript{99}.

\[ \text{Ar} = \text{Ar}' = 2,4-\text{C}_2\text{H}_5\text{H}_3 \]
'MORPHOLINE' and its various derivatives have attracted the attention of chemists for their wide range of biological properties. 3-phenyloctahydroxypyrdo-2, 1-c 1,4 oxazine hydrochloride (21) has been synthesised which was shown to possess a depressant action on the central nervous system\textsuperscript{100}.

![Chemical Structure](21)

Phenmetrazine and phendimetrazine of the type (22) (a and b respectively) are the morpholine derivatives that are claimed to possess fewer peripheral adrenergic effects as compared to amphetamine in relation to their central anorexic actions\textsuperscript{101-103}.

![Chemical Structure](22)

(a) : $R = H$

(b) : $R = CH_3$

Recently, some N-2-(phenoxy/chlorophenoxy) acetyl morpholines (23) have been synthesised and found to possess anti-inflammatory, CNS depressant, antiallergic and plant growth promoting properties\textsuperscript{104}. 

(a) : R₁, R₂, R₃ = H.
(b) : R₁, R₂, R₃ = Cl.
(c) : R₁, R₂ = Cl; R₃ = H.
(d) : R₁, R₃ = Cl; R₂ = H.
(e) : R₁ = Cl; R₂, R₃ = H.
(f) : R₂ = Cl; R₁, R₃ = H.