CHAPTER-1

Section- 1.1 Introduction of Heterocycles
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Section 1.1: Introduction of Heterocycles

The investigations of chemistry of heterocyclic compounds have not only been as essential elements in man's endeavours to unravel the mysteries of 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 chemistry of heterocycles is the result of enormous investigations for many decades. In large measure this is due to many heterocyclic compounds which have created an interest in their structure elucidation of synthetic analogues as potential chemotherapeutics. There is a stream of discovery of heterocyclic substances playing an important role in the metabolism of all living cells and increasing availability of intermediates suitable for large scale production of heterocyclic substances, many of which are finding uses in industries and medicines.

Some heterocyclic compounds are useful in the field of agriculture. The widely used drugs in this field are - pesticides, insecticides, herbicides and plant growth hormones etc. The determination of the structure of a biologically active molecule provides a two fold benefit to organic and medicinal chemists. It make possible research leading to synthesis and modification of changes in structures are accompanied by changes in biological activity and occasionally vast improvement is accomplished.

Heterocyclic compounds are cosmopolitan comprising of carbohydrates, chlorophylls and haem present in the plant and animal kingdom. Similarly various compounds such as vitamins, antibiotics, pigments, dyes, drugs, enzymes and the genetic materials etc. are also
based on heterocyclic rings. Heterocycle, like benzofuran polymerises to give useful plastics and resins. Heteroys like 2-mercaptobenzothiazole, piperidine and phenothiazines are used as antioxidants and vulcanizing accelerators in rubber industry. Some of the heterocyclic compounds are used in azo industry as insecticides and fungicides. 2-phenanthroline, 8-hydroxy quinoline and dipyridyl have their use in analytical chemistry to estimate different metals in solution. A number of heterocycles have also found to be used as agrochemicals and pesticides.

Heterocyclic compounds are essential to life and occupy a key position in the area of drugs and pharmaceuticals. Almost 80% of all the drugs in clinical use are based on heterocyclic constitution. The purine ring system is undoubtedly among the most ubiquitous of all the heterocyclic compounds. The 6-mercaptopurine derivatives are found to be used in the treatment of leukaemia especially in children. The 9-(β-arabino-furanosyl)-adenine which is a powerful antiviral and antitumor agent, is used clinically for these purpose. Acyclovir, a purine based acyclic nucleoside continue to be the only drug for treatment of genital herpese infection. The benzodiazepines for example chlorodiazepoxide, flurazepam, lorazepam, oxazepam etc. play the major pharmacological effects such as antianxiety, sedation, psychostimulant, potent anticonvulsant and many other effects. The recent threat of acquired immunodeficiency syndrome (AIDS) has promoted a broadly based effort to find out a mean of preventing and cures of AIDS. A number of agents from uracil nucleus have been found to inhibit HIV virus in vitro. The compound, 3-azido-2-3-dideoxythymidine has been shown to induce
clinical improvement and prolong survival in patients with fulminant AIDS. This was the first demonstration that an established injection with pathogenic human retro virus was amenable to antiviral therapy. Indole\textsuperscript{13-14} is the basis for diverse group of hallucinogenic agents that may be subdivided into simple indole, harmine and polycyclic derivatives including yohimbine and lysergic acid derivatives. The simplest known compounds for the last decade is N, N-dimethyltryptamine which is a major component of various new world snuffes and psychotropic derivatives and has acquired a unique place in neuropharmacology\textsuperscript{15, 16}.

Heterocycles bearing functional group (NH) are important synthons in organic synthesis. The presence of amino group on biologically active heterocycles would be quite rewarding from synthetic and biological aspects. The recent literature is enriched with progressive findings of the synthesis and pharmacological action of fused heterocycles.

Organic chemists and pharmaceutical industry used to synthesise large numbers of new compounds every week. The chemists has specific reason for synthesising a particular compound usually based on theoretical consideration, medicinal chemistry, biological mechanism or a combination of all the three. One of the major factors leading to a more rational approach to new drugs has improved the knowledge of biochemical mechanism. The search for chemical structures which exhibit physiological activity, is a difficult goal of organic researcher when advances are made in basic organic chemistry leading to new class of compounds, they must be submitted for screening against all
types of biological and pharmacological actions. The observation of interesting biological activity opens pathway for additional chemical researches in the expansion of the series which often leads to significant new medicinal products. In designing a new drug to have a distinct activity in the treatment of the specifically diseased condition, the most widely used approach is the design of new drug centres by using the drugs of the known structures as a model or prototype from which congeners, homologues or analogues have been designed.

There are also a vast number of biologically active heterocyclic compounds which are in regular clinical practice for example antibiotics: such as penicillin and cephalosporin; alkaloids: vinblastin, morphine and reserpine; antiinflammatory and analgesic agents: flumizole, antipyrine and phenylbutazone; antihistaminic agents: histamine and histidine; hypnotics sedatives: methaqualone and fenadiazole; antimetabolite: azeothiapurine; tranquilizing agent: promazine and chloropromazine; antiehelmintic agent: mebendazole and anticancer agents: razoxane and fluorouracil.

The heterocyclic approach is now firmly established in medicinal and pharmaceutical chemistry and has heightened the scientific stature of their own fields. The successful application of heterocyclic systems in the above mentioned fields and their appeal as material in applied chemistry is more fundamental and theoretical. This ensures virtually limitless series of structurally novel compounds with a wide range of physical, chemical and biological properties, spanning over a broad spectrum of reactivity and stability. Another consequence of heterocyclic system's and their varied chemical reactivity including the possible distributions is now increasing in the synthesis of specially functionalized non-heterocyclic systems.
Penicillins are a class of compounds having a general structure of bicyclic or monocyclic azitidinones (β-lactam). Because of their unique effectiveness in the treatment of bacterial infections in human, these compounds have been investigated intensively from the chemical and clinical point of view since 1940. A large number of penicillins are now in current medical use for example: Penicillin-G, Penicillin-V, Methicillin, Nafcilin Oxacillin, Cloxacillin, Ampicillin, Carbinicillin, Azocillin, Mezlocillin, Piperacillin etc. Penicillins are an important part of Physicians armamentarium against infections diseases and will remain so for a considerable time. There is increasing emphasis on the study and use of fermentable penicillins as starting materials for the productions of other β-lactam antibiotics, leading to a wealth of heterocyclic chemistry.

The barbiturates exert a depressant effect on the cerebrospinal axis. These drugs depress neuronal activity as well as skeletal muscle, smooth muscle and cardiac muscle activity. The barbiturates can produce different degrees of depression, sedation, hypnosis or anaesthesia depending on the compound, dose and route of administration. The first synthetic barbiturate 5, 5-diethylbarbituric acid is still in clinical use and afterwards hundreds of barbiturates have been synthesised and out of them many have turned out to be useful drugs e.g. amobarbital, pantobarbital, phenobarbital, mephobarbital, secobarbital, aprobarbital etc.

Histamine, [4(5) - imidazolyl ethylamine] was first reported by Windaus and Vogt who synthesised this compound because of its chemical resemblance to the naturally occurring alkaloid, pilocarpine.
and to the amino acid, histidine. Histamine was found to be a constituent of many tissues and came to be regarded as a substance liberated in response to injured stimuli. Also it has been shown that histamine stimulates secretion of gastric acid. Therefore first antihistaminic drug arose out of the search for substance to counteract the toxic manifestation of histamine release\textsuperscript{22, 23}. Burimamide was shown to be first and highly specific competitive antagonist of histamine\textsuperscript{24}. Clinically, indications for use of the various antihistaminic drugs vary considerably. The majority of these agents are effective in perennial and seasonal allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis, urticaria and angioedema, allergic reactions to blood and plasma, and as adjuncts to conventional therapy in anaphylactic reactions. Molecular manipulation have led to two other important antihistamine drugs metiamide and cimetidine. Antihistamines should not be given to premature or newborn infants. Some antihistamines viz. bromopheniramine maleate, carbinoxamine maleate, clemastine fumarate, dexchlorpheniramine maleate, dimethindene maleate etc. have also been reported.

The search for new, effective and safe drugs have become an increasingly sophisticated and costly process. This is true because of a growing awareness of the potential dangers engendered by foreign agents in the body. It is necessary to demonstrate that a drug will perform the pharmacologic role for which it is recommended. The architects of drug design, the planners in the pharmaceutical industry, and the drug scientists in academia must utilize research and development approaches that will yield a maximum amount of information about molecules
under study as drugs with a minimum outlay of resources. The key step in the iterative process of synthesis-testing-synthesis-testing is an intermediate one, in which information is derived relating molecular structure to changes in the experimental test results.

The development of a useful structure-activity relationship from a body of chemical and biologic experimental work is an intellectual exercise. No experiments are performed. The drugs are of major importance to human health and nutrition on account of their action on biological and pathological process. The use of drugs has shown considerable world-wide increase in recent years and this tendency is likely to be maintained in near future. The chemist plays an important role in discovery and development of new drugs. The point of departure in the search of a new drug usually lies in a consideration of the structure and pharmacologic response of a natural product. The chance of the discovering a new drug has diminished to 1 in 15,000 and will decrease even further, whereas development costs have risen to million dollars per new drug. Thus it is small wonder that any rationalization of activity which will reduce the number of compounds to be tested is attractive not only from scientific point of view but also commercially. The range of chemical compound is virtually boundless, and it will never be possible to explore it fully. This is particularly true in the search for new therapeutics, because the multitude of biological systems and the tests they require have added a new dimension. Therefore any procedure is unavoidably bound to consist of the selection of subsystem from a large group of compounds. A subsystem is in general understood to represent a number of chemical compounds formed substantial variations in a given parent structure, referred to as the lead compound.
Section 1.2: Literature Survey on Azoles

Azoles, a class of five membered ring with heteroatom have acquired considerable interest during recent years due to its immense use in pharmaceuticals and dye industries while planning this treatise the scope of the subject matter and how best to organise it, has kept very much in mind. The organisational problem has been resolved by considering the potential "azoles".

During the last several years novel approaches have been innovated for the synthesis and pharmacological properties of azoles. Azole chemistry is currently undergoing a period of transition in which the chemical knowledge is progressively integrated with the more classical knowledge of pharmacological, biochemical as well as a higher texa, open new disciplines of the Pharmacologist and Biologist and offer new points in considering problems of structures and functions.

Interest in many of azoles has been estiamated because of their application in industrial, agriculture and pharmaceuticals. The pyrazole nucleus is found in naturally occurring compounds such as histamine, histidine and allantoin. Histidine is implicated in the development of allergies and the consequence has generated interest in antihistaminic drugs. A number of nitro and chloro derivatives of pyrazole has found to be of medicinal application as bacteriostatic. Azole has been shown to be part of Vitamine $B_{12}$. Several azoles such as imidazole, pyrazole, benzotriazole, carbazole, benzimidazole, oxazole and its derivatives are commercially available as pharmaceuticals. In recent years 1, 3, 4-triazole have provided valuable sources as light stabilizers, optical brightening agent and precursors of azopurine which are potential
carcinostatic agents. Pentamethyl triazole is a powerful central nervous system stimulant used to counteract barbiturate overdoses.

A wide variety of azoles and their derivatives have been proved to various biological activity. Azoles and their various derivatives have been reported to display as antimicrobial\textsuperscript{25-28}, antiinflammatory\textsuperscript{29-31}, herbicidal\textsuperscript{32}, central nervous system depressant\textsuperscript{33-35}, anthelmintic\textsuperscript{36, 38}, anticancer\textsuperscript{39, 40}, antitumour agent\textsuperscript{41}, antiparasitic activity\textsuperscript{42}, anticonvulsant\textsuperscript{43, 44}, analgesic\textsuperscript{45, 46} and antihypertensive activity\textsuperscript{47}.

Substituted triphenyl imidazole(1) showed analgesic, antiinflammatory, antipyretic and antithrombic activity while 2, 4, 5-trichloroimidazole was found to be effective biocidal against nymphs, *Amblyomma americanum*. 2-(4-chloro-1-naphthylmethyl)-imidazole(2) showed vasoconstrictive activity\textsuperscript{48}.
Several substituted 2-(amino methyl)-imidazoles (3) have shown to display potent adrenergic activity⁴⁹.

(3) : \( R_1=4-\text{CH}_3\text{C}_6\text{H}_4/\text{H}/2-\text{ClC}_6\text{H}_4/4-\text{ClC}_6\text{H}_4/2-\text{OHC}_6\text{H}_5/\text{C}_6\text{H}_5 \)

\( R_2=\text{C}_6\text{H}_5/\text{2-OHC}_6\text{H}_5/\text{H}/\text{CH}_3/\text{C}_2\text{H}_5/\text{C}_6\text{H}_{10} \)

5-Acylamino-1H-benzimidazoles (4) were synthesized and found to be active against both the male and female adult worms of *Litomosodes carini*⁵⁰.

(4) : \( R_1=\text{CH}_3/\text{C}_2\text{H}_5/2\text{-furyl} \)

The antifungal activity of 1-(β-cyanoethyl) benzimidazole(5) is comparable with that of the standard drug in cases of *Curvularia hunata*⁵¹.
2-Nitro substituted analogous of benzimidazoles (6) have been reported to possess effective radiosensitizing activity\textsuperscript{52}.

\[
(6) : \begin{align*}
R_1 &= \text{H/CH}_2\text{COOC}_2\text{H}_5 \\
R_2 &= \text{NO}_2 \\
R_3 &= R_4 = \text{H/NO}_2
\end{align*}
\]

5-(3, 5-diphenyl pyrazol-4-yl-oxymethyl)-1, 3, 4-oxadiazole/thiadiazoles (7) have been found to be antifungal agent\textsuperscript{53}. 1, 3, 4-oxadiazoles (8) have been synthesised and found to be potential antimicrobial agent\textsuperscript{54}.

\[
(7) : R_1 = \text{OCH}_3/\text{H} \\
X = \text{O/S}
\]

\[
(8) : R_1 = \text{alkyl/aryl/sub.aryl}
\]
4-Benzyldiene-5-imidazolone derivative (9) has been synthesised and reported CNS depressant and anticonvulsant activity\textsuperscript{55}.

\[
\begin{align*}
\text{C}_6\text{H}_5-\text{HC} & \quad \text{SO} \\
\text{CH}_3 & \quad \text{OCH}_3 \\
\end{align*}
\]

(9)

Benzotriazole derivatives (10) and (11) have been reported to exhibit antimicrobial activity and showed pronounced activity against \textit{Staphylococcus aureus} and \textit{Candida albicans}\textsuperscript{56}.

(10) \text{: R}_1 = \text{C}_6\text{H}_2\text{C}_2\text{H}_5/\text{CH}_3

(11) \text{: R}_1 = \text{CH}_2\text{C}_6\text{H}_5/\text{C}_6\text{H}_5/\text{CH}_3\text{C}_6\text{H}_5/\text{BrC}_6\text{H}_4
Some 2-substituted phenyl-3-alkyl/aryl-5, 6-dihydro-s-thiazolo[1, 3, 4]-thiadiazol-6-yl indoles (12) have been synthesised and found to exhibit antibacterial, antifungal and antiinflammatory activities\textsuperscript{57}. Some metal substituted N-phenyl-3-methyl-4-(4'-sulphonamoyl)-phenylhydrazo pyrazolin-5-one derivatives (13) have been synthesised and shown antibacterial activity\textsuperscript{58}.

\begin{align*}
(12): & R_1=\text{CH}_3/\text{C}_2\text{H}_5/\text{C}_6\text{H}_5/\text{CH}_2\text{C}_6\text{H}_5 \\
& R_2=\text{H}/\text{CH}_3/\text{C}_2\text{H}_5/\text{Cl}
\end{align*}

\begin{align*}
(13): & R_1=\text{H}/2-\text{NO}_2\text{C}_6\text{H}_4/2-\text{ClC}_6\text{H}_5
\end{align*}
some 3-methyl/ethyl (α-methyl) - ethyl - morpholine / piperidino - 4-amino-5-mercapto-4(H)-1, 2, 4-triazoles (14) have been synthesised and found to exhibit antimicrobial activity. Pyrazole-1-carboxyl-1,8-naphthyridine derivatives (15) have been found to be good antimicrobial agent.

2-Chloro-9-(dimethyl aminopropyl)-7-methoxy carbazole (16) was found to be anticonvulsant and diuretic.

A number of substituted 6-H-pyrido carbazole (17) and the corresponding octahydro compound (18) were also synthesised and found to exhibit anticancerous activity.
The analgesic and anti-inflammatory properties\textsuperscript{53} of 2-carbazole propionic acid (19) received wide spread attention and its derivatives are also comparable of those to indomethacin with a greater safety margin.

Few novel phenyl ester of carbazol-9-acetic/propionic acid (20) have been prepared and showed diuretic, anticonvulsant and antimicrobial activities\textsuperscript{64}. Some N-substituted mono and biheterocycles (21) have been synthesised and found to exhibit anti-inflammatory, anticonvulsant and anthelmintic activities\textsuperscript{65}.
Cis-3a, 4, 5, 6, 7a-hexahydro-3-(1-methyl-5-nitro-1H-imidazol-2-yl)-1,2-benzoiso-oxazole (22) have been found to produce urinary metabolites of antiprotozoal activity in rats\(^66\).

6-Tetra-butyl-2-sulphamoylimidazo-(2,1-b) -1,3,4-thiadiazole (23) exhibits anticonvulsant activity\(^67\).

Pyrrol-2-acetic acid (24) has been synthesised and found to exhibit effective analgesic activity\(^68\). Some indole (25) and indazole (26) derivatives have been synthesised and found to display antiinflammatory activity\(^69\).
Some new amino acyl carbazole derivatives (27) have been synthesized and found to display antibacterial activity\textsuperscript{70}.

\[
\begin{array}{c}
\text{(27)}: R_1 = R_2 = H/NO_2, \\
R_3 = \text{phthaly} \\
X = \text{glycine}
\end{array}
\]

N-[2-phenoxy/chloro/bromo/nitro/methyl phenoxy]-acetyl/propionyl]-carbazoles (28) have been prepared and showed antimicrobial, anti-inflammatory and anticonvulsant activities\textsuperscript{71}. 
4-Amino-5-carboxamines 1, 2, 3-triazole (29) was synthesised and found to be effective anticancer agent. 1-methoxy-4-nitro-1, 2, 3-benzotriazole (30) was found to be herbicide.

Some triazole derivatives (31) and (32) from ibuprofen have found to be more potent antiinflammatory, analgesic and antipyretic than ibuprofen itself.
N-substituted phenylimidazoles (33) have been shown to display potent *in vitro* and *in vivo* antifungal properties\textsuperscript{75, 76}.

\[ \text{(33): } R_1 = R_2 = 2,4-	ext{Cl}_2C_6H_3/2-	ext{ClC}_6H_4/C_6H_5/OCH}_3C_6H_4/(CH}_3)_2NC_6H_4 \]

Some 3-substituted benzoxazole-[3, 2-C]-[1, 2, 4]-triazoles (34) have been synthesised and found to exhibit pesticidal activity such as herbicidal and fungicidal\textsuperscript{77}. Probenzimidazole, benzimidazole and pyrimido-[1, 2-a]-benzimidazoles (35) have been synthesised and shown an anthelmintics\textsuperscript{78}.

\[ \text{(34): } R_1 = \text{OH/Cl/CH}_3/H \]
Some organophosphorous compounds containing substituted \( s\)-triazole and fused ring heterocycles (36) have been synthesised and found to be insecticidal agent\(^7\).

\[
\text{\( (36) : R_1 = R_2 = \text{CH}_3/\text{C}_2\text{H}_5/\text{CH(CH}_3)_2 \)}
\]

3-Indole fatty acid derivative (37) produced anti-inflammatory, analgesic and antipyretic activities\(^8\).

\[
\text{\( (37) \)}
\]

3-[2-(Methyl propyloxy)-pyrrolidinopropyl phenyl] - indoline (38) was found to be a cardiovascular agent\(^9\).
A number of 1-(3-chloro-2-hydroxypropyl)-substituted nitroimidazoles and related compounds (39) and 4, 5-diphenyl-2-substituted imidazole (40) have been synthesised and exhibited antiprotozoal and antiinflammatory activity.\(^{82,83}\)

\[(39): R_1=\text{CH}_3/\text{CH} (\text{CH}_3)_2\quad (40): R_2=R_1=\text{C}_6\text{H}_5/\text{CH}_3/\text{CF}_3\]

1H-triazole [4, 5-b]-quinol-4-one (41) is found to inhibit Passive Cutaneous anaphylaxis in rats and in treatment of human asthma.\(^{84}\) 5-nitro benzotriazole (42) was found to exhibit muscle relaxant properties.\(^{85}\)
2, 4, 6-Trichlorophenoxy acetyl benzotriazole (43) and naphthoxy acetyl N'-benzotriazole (44) found to display good antiinflammatory activity\textsuperscript{85, 87}.

![Chemical Structure](43)

4-Aryl-2-substituted aminothiazoles (45) and (46) have been reported anthelmintic activity against \textit{Accylostoma ceylanicum}, \textit{Nippostrongylus brasiliensis} and \textit{Hymenolepis nana} in rodents which showed positive results\textsuperscript{88}.

![Chemical Structure](45) ![Chemical Structure](46)
A series of 1-(substituted cinnamamido)-2, 4-imidazolidines (47) have been prepared and reported anthelmintic activity against the mouse pinworm, *Syphacia obvelata*.

![Chemical structure of 1-(substituted cinnamamido)-2, 4-imidazolidines](image)

Some new 2-thio-3-(substituted-amino-methyl)-5-(3,5-dinitrophenyl)-1, 3, 4-oxadiazoles (48) have been synthesised and reported anti-inflammatory and CNS activity.

![Chemical structure of 2-thio-3-(substituted-amino-methyl)-5-(3,5-dinitrophenyl)-1, 3, 4-oxadiazoles](image)

(48) : \( R_1 = \text{N-methyl/Piperazino/Diethylamino/Diethanol-amino/N-methylanilinol/N-phenyl piperizino} \)

Some new substituted 2-amino-4-arylthiazoles (49) were reported as antimicrobial activity against the test organisms *A. flavus*, *A. Higer*, *C. lunata* and *F. moniligormac* as the fungi and *S. aureus* and *E. coli* as the bacteria.

![Chemical structure of 2-amino-4-arylthiazoles](image)

(49) : \( R_1 = R_2 = R_3 = R_4 = R_5 = \text{F/H/C}_2\text{H}_4/\text{Cl}/\text{Br} \)