CHAPTER-I

AN OVERVIEW OF HETEROCYCLIC COMPOUNDS AND THEIR BIOLOGICAL SIGNIFICANCE
An Overview of Heterocyclic compounds and their biological significance

Introduction

Heterocyclic chemistry is a very important branch of organic chemistry accounting for nearly one-third of modern publications. In fact two thirds of organic compounds are heterocyclic compounds. A cyclic organic compound containing all carbon atoms in ring formation is referred to as a *carbocyclic compound*. If at least one atom other than carbon forms a part of the ring system then it is designated as a *heterocyclic compound*. Nitrogen, oxygen and sulfur are the most common heteroatoms but heterocyclic rings containing other heteroatoms are also widely known. An enormous number of heterocyclic compounds are known and this number is increasing rapidly. Accordingly the literature on the subject is very vast. Heterocyclic compounds may be classified into *aliphatic* and *aromatic*. The aliphatic heterocyclics are the cyclic analogues of amines, ethers, thio ethers, amides, etc. Their properties are particularly influenced by the presence of strain in the ring. These compounds generally consist of small (3- and 4-membered) and common (5 to 7 membered) ring systems. The aromatic heterocyclic compounds, in contrast, are those which have a heteroatom in the ring and behave in a manner similar to benzene in some of their properties. Furthermore, these compounds also comply with the general rule proposed by Huckel. Besides the vast distribution of heterocycles in natural products, they are also the major components of biological molecules such as DNA and RNA. DNA is without doubt the most important macromolecule of life. Nucleotides, the
building blocks of our genes are derivatives of pyrimidine and purine ring structures. Chlorophyll and heme, the oxygen carriers in plants and animals respectively are derivatives of large porphyrin rings.

Heterocycles are an important class of compounds, making up more than half of all known organic compounds. Heterocycles are present in a wide variety of drugs, most vitamins, many natural products, biomolecules, and biologically active compounds, including antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and insecticidal agents. Also, they have been frequently found as a key structural unit in synthetic pharmaceuticals and agrochemicals. Some of these compounds exhibit a significant solvatochromic, photochromic, and biochemical luminescence properties. Most of the heterocycles possess important applications in materials science such as dyestuff, fluorescent sensor, brightening agents, information storage, plastics, and analytical reagents. In addition, they have applications in supramolecular and polymer chemistry, especially in conjugated polymers. Moreover, they act as organic conductors, semiconductors, molecular wires, photovoltaic cells, and organic light-emitting diodes (OLEDs), light harvesting systems, optical data carriers, chemically controllable switches, and liquid crystalline compounds. Heterocycles are also of considerable interest because of their synthetic utility as synthetic intermediates, protecting groups, chiral auxiliaries, organ catalysts, and metal ligands in asymmetric catalysts inorganic synthesis. Therefore, substantial attention has been paid to develop efficient new methods to synthesize heterocycles.
The alkaloids form a major group of naturally occurring heterocyclic compounds having varied biological activity. Most alkaloids contain basic nitrogen atoms. Ergotamine, the indole based alkaloid exhibits antimigraine activity\textsuperscript{2}. Cinchonine, a quinolone class of alkaloid shows antimalarial activity\textsuperscript{3}.

![Ergotamine](image1)

![Cinchonine](image2)

Posaconazole is a triazole antifungal drug\textsuperscript{4}. It is active against the following microorganism *candida, asperigillus, Zygomycetes*.

![Posaconazole](image3)
Anastrozole is an aromatase-inhibiting drug approved for the treatment of breast cancer after surgery, as well as for metastasis in both pre and post-menopausal women. The severity of breast cancer is increased by estrogen, as sex hormones cause hyperplasia, and differentiation at estrogen receptor sites\textsuperscript{5,6}. Anastrozole works by inhibiting the synthesis of estrogen.

\begin{center}
\textbf{Anastrozole}
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Three out of twenty natural amino acids are heterocyclic, as are many essential vitamins. The range of application of heterocyclic compounds is very wide. They are of specific importance as they are associated with a wide variety of physiological activities.

Significant number of compounds synthesized in the industrial sector is heterocyclic in nature. A large number of synthetic heterocyclic compounds are predominant among all types of pharmaceuticals, agrochemicals veterinary products. Some of the synthetic heterocyclics are used in photography and as rocket propellants.

Heterocyclics are able to get involved in an extraordinarily wide range of reaction types. Depending upon pH of the medium, they may behave as acids or bases, forming anions or cations. Some interact readily with electrophilic reagents,
other with nucleophiles, yet others with both. Some are readily oxidized, but resist reduction, while others can be readily hydrogenated but are stable toward the action of oxidizing agents. The ability of many heterocyclics to produce stable complexes with metal ions has great biochemical significance.

Sumatriptan, a heterocyclic compound is the first antimigrain drug, replacement of sulfonamide moiety in sumatriptan with 1, 2,4-triazole (A), which is also a potent 5-HT\textsubscript{1D} receptor agonist.

![Sumatriptan](image)

The practical application of indole and pyrroles are heavily centered in the pharmaceutical area. Many analogues of indole derivatives have been synthesized in an effort to find substances with useful central nervous systems (CNS) activity. The furan ring is common in many naturally occurring terpenoid compounds. The cardiac active steroidal lactones are important class of naturally occurring 2(5H)-furanones and because of their pharmaceutical importance and many synthetic routes for the 2(5H)-furanones have been developed. A number of relatively simple pyridine is used in the treatment of muscular rheumatism. Compounds which have unsaturated \(\delta\)-lactone rings are reported to have carcinogenic and
antitumor activity as well as other biological property\textsuperscript{12}. The fusions of a five
membered rings with six membered heterocyclic rings are interesting and
pharmacologically active.

The rich activity of heterocyclic compounds in biological systems is
important for pharmaceuticals, agricultural, and natural products.

Heterocyclic compounds have provided a platform for the rapid exchange
of research in the areas of organic, pharmaceutical, analytical, and medicinal
chemistry. In the pharmaceutical industry over 75\% of the top two hundred
branded drugs have heterocyclic fragments in their structures.

**Biological efficacy and Therapeutic utility of Heterocyclic Compounds:**

Isoxazole is an azole with an oxygen atom next to the nitrogen. It is also the
class of compounds containing this ring. Isoxazolyl is the univalent radical derived
from isoxazole.

Isoxazole derivatives have served as versatile building blocks in organic
synthesis\textsuperscript{13}. The isoxazole nucleus is a prominent structural motif found in
numerous natural products and synthetic compounds with vital medicinal value\textsuperscript{14}.
Also, isoxazoles have applications in functional materials\textsuperscript{15}, such as liquid
crystalline compounds\textsuperscript{16} and exhibit GABAA antagonist\textsuperscript{17}, analgesic\textsuperscript{18},
antibacterial\textsuperscript{19}, anti-inflammatory\textsuperscript{20}, hypoglycemic\textsuperscript{21}, COX-2 inhibitory\textsuperscript{22},
antinociceptive\textsuperscript{23} and anticancer activity\textsuperscript{24}.

Isoxazole rings are found in some natural products, such as ibotenic acid.
Isoxazoles also form the basis for a number of drugs, including the COX-2
inhibitor viz; veldecoxib (Bextra). A derivative, furoxan, is a nitric oxide donor. An isoxazolyl group is found in many betalactamase-resistant antibiotics, such as cloxacillin, dicloxacillin and flucloxacillin. The synthetic androgenic steroid danazol also possess an isoxazole ring²⁵.

**Quinoxaline 1-4-di-N-Oxide derivatives:**

Quinoxalines display a broad spectrum of biological²⁶ and pharmacological²⁷ activities such as insecticides, fungicides, herbicides, anthelmintics, antibacterial²⁸, antitycobacterial, antiprotozoal, anticancer and antibiotic properties²⁹. Quinoxaline derivatives have found applications in dyes³⁰ electron luminescent materials³¹ and chemically controllable switches³² as building blocks for the synthesis of anion receptors³³, cavitands³⁴, dehydro annulenes³⁵ and organic semiconductors³⁶ and as electron transport materials in multilayer OLEDs³⁷. A number of synthetic strategies have been developed for the preparation of substituted quinoxalines, including condensation of aryl-1,2-diamines with α-functionalized ketones, usually dicarbonyl compounds or their equivalents³⁸,³⁹.
Chapter I; Introduction

Heterocyclic compounds as antimalarial:

Malaria is one of the most serious, complex and refractory malady facing humanity this century. Some 300-500 million of world’s population are infected by the disease, presenting 120 million clinical cases annually.

Quinine may be claimed, without exaggeration, as the drug to have relieved more human suffering than any other inhibitors\(^\text{40}\). Chloroquinine, the main drug among the 4-aminoquinoline class, is one of the most successful antimalarial agents ever produced.

Primaquinine is the drug of 8-aminoquinoline class, which is connected to amino acids by forming peptide bond to the amino group. These amino acid derivatives are known for higher activity and lower toxicity\(^\text{41}\).
Heterocyclic compounds as Diuretic agents:

Diuretics are medicines that help reduce the amount of water in the body. Acetazolamide is a potent carbonic anhydrase inhibitor, effect in the control of fluid secretion in the treatment of certain Convulsive disorders and in the promotion of diuresis in instances of abnormal fluid retention. Acetazolamide is not a mercurial diuretic. Rather, it is non-bacteriostatic sulfonamide possessing a chemical structure and pharmacological activity distinctly different from the bacteriostatic sulfonamides. The anticonvulsant activity of acetazolamide may depend on a direct inhibition of carbonic anhydrase in the CNS, which decreases carbon dioxide tension in the pulmonary alveoli, thus increasing arterial oxygen tension. The diuretic effect depends on the inhibition of carbonic anhydrase, causing a reduction in the availability of hydrogen ions for active transport in the renal tubule lumen\(^{42-44}\). This leads to alkaline urine and increase in the excretion of bicarbonate, sodium, potassium, and water.

Heterocyclic compounds as anthelmintic:

Helminthes are parasitic worms, which infect an estimated two billion people worldwide, nearly all in poor developing tropical or semitropical countries. Helminthic infections contribute to malnutrition, anemia, stunted growth, cognitive impairment, and increased susceptibility to other diseases.

![Acetazolamide](image_url)
Benzimidazole, pyrazine, isoquinoline, tetrahydropyrimidine, tetrahydroquinolone, piperidine, piperazine, triazoles, indoleisoxazole derivatives are the different types of heterocyclic used as anthelmintics. Albendazole is the most active benzamidazole anthelminitic drug\textsuperscript{45}.

![Albendazole](image)

**Heterocyclic compounds as antineoplastic agents:**

Cancer is a major human health problem worldwide and is the second leading cause of death in United States\textsuperscript{46}. Systematic chemotherapy began in the 1940’s and 1950’s with nitrogen mustards developed from war gases and with antimetabolites developed from early knowledge of DNA metabolism. Compounds that alkylated DNA have long been of interest as anticancer drugs. Different types of antineoplastic agents are developed, which include nitrogen mustards (Bendamustine), tyrosine kinase inhibitors, 26S proteasome inhibitors etc.

![Bendamustine](image)
Quinazoline and pyrimidine derivatives are used as tyrosine kinase inhibitors. A series of substituted 2-(aminopyridyl)- and 2-(aminopyrimidinyl) thiazole-5-carboxamides was identified as potent Src/Abl kinase inhibitors with excellent antiproliferative activity against hematological and solid tumor cell lines\textsuperscript{47}. Chronic Myelogenous Leukemia (CML) is a myeloproliferative disorder that is characterized by hyper proliferation of stem cells, followed by their subsequent differentiation into peripheral white blood cells. Imatinib, is the blockbuster drug used for the treatment of Chronic Myelogenous Leukemia (CML)\textsuperscript{48}. Imatinibmysilate is marketed under brand name Gleevec. The quinazoline derivative drugs like erlotinib, and lapatinib are also important tyrosine kinase inhibitors.
Heterocyclic compounds as antidepressants:

An antidepressant is a psychiatric medication used to alleviate mood disorders, such as major depression, and dysthymia. Drugs including the monoamine oxidase inhibitors (MAOIS), tricyclic antidepressants (TCAs), tetracyclic antidepressants (TeCAs), selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are most commonly associated with them.

Paroxetine, reboxetine, are some of most useful antidepressants containing heterocyclic moiety in their structure. Some piperidine and pyrimidine derivatives also possess antidepressant activity. A variety of small molecule nano-peptide antagonist heterocyclics have been discovered and shown to possess antidepressant activity in animal behavioral tests\textsuperscript{49,50}.

\[ \text{Paroxetine} \]

\[ \text{Reboxetine} \]

Heterocyclic compounds as antiulcer agents:

Pyridine ring plays an important role in human metabolism due to its interaction with amino acids. Many of the active drugs in the market contain pyridine moiety\textsuperscript{51,52}. Benzamidazoles also are well known for their
pharmacological properties in particular, they are widely used as anthelmintic agents. It is interesting to note that a series of substituted pyridylsulfinylbenzimidazole molecules like omeprazole possess gastric antisecretary and consequently anti-ulcerative activity\textsuperscript{53}.

Later several omprazole analogues like lanoprazole\textsuperscript{54}, pantoprazole\textsuperscript{55} have been introduced in the market successfully.

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**Omperazole**

**Lanoprazole**

**Pantoprazole**
Heterocyclic compounds as antipsychotic agents:

Antipsychotic agents constitute a diverse class of heterocyclic drugs that are effective in the treatment of major psychosis, including those associated with schizophrenia. Which is a severe, life-long, idiopathic psychiatric disorder with a polygenic component. Schizophrenia is a disorder afflicting approximately 1% of human of most population.

Benzisoxazole derivatives are found to have antipsychotic properties and are more potent. 3-(piperidin-4-yl)-1,2-benzisoxazole possess anti-psychotic properties and helpful in the treatment of variety of disorders in which serotonin release is of predominant importance\textsuperscript{56}.

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\includegraphics[width=0.5\textwidth]{image.png}
\end{center}

3-(Piperidin-4-yl)-1,2-benzisoxazole

Apart from the above significant classes of heterocyclic compounds useful as therapeutic agents, some indole derivatives as antiosteoporotic agents\textsuperscript{57}, and triazole compounds (fluconazole, Isavuconazole, Hexaconazole, epoxiconazole, difenoconazole, tebuconazole etc.,) are used as a fungicides\textsuperscript{58}, Indole derivatives are used as antimigraines; Quinoline/Isoquinoline drugs are used as antimalarial, and drugs for asthma & allergies, hypertension\textsuperscript{59}.
Chapter I; Introduction

**Bazedoxifene**
(antiosteoporotic agent)

**Fluconazole**
antifungal

**Hexaconazole**

**Isavuconazole**
Triazoles

1,2,3-Triazole has become one of the most important heterocycles in current chemistry research, due to its important industrial, agrochemical, and pharmaceutical applications, especially in biological science, material chemistry, and medicinal chemistry. One of the most attractive ways to prepare these compounds involves thermal 1,3-dipolar cyclo addition of azides with alkynes. Additionally, the chemistry of the tetrazole ring is gaining increasing attention due to its importance in a variety of synthetic and industrial processes and excellent properties as a metabolically stable isosteric replacement for the carboxylic acid moiety and as a cis-peptide bond mimetic. Tetrazoles have also been used as precursors to other heterocycles and in high energy compounds.

The synthesis of tetrazoles from a cycloaddition reaction between a nitrile and an azide is well documented.

Heterocyclic chemistry is vastly expanding, because of the enormous amount of research work being done in this area. The majority of known molecules are heterocyclics. Heterocyclic compounds dominate the field of biochemistry, medicinal chemistry, dyestuff, photographic sciences and are of increasing importance in many other areas including polymers, adhesives and molecular engineering. Among the heterocyclic compounds, Quinoxalines, Oxoindolines, Triazoles and Isooxazoles are important chemotherapeutic agents and have found wide clinical applications as antimicrobial, anticancer, antiviral and anti-AIDS, antitubercular, sedative/hypnotic/antiepileptic, cardiac agents, as well as analgetics, diuretics, antibiotics and metabolic electrolytes etc.
On continuation of our interest to synthesis the heterocyclic compounds, the present work is focused on synthesis of some novel Quinoxaline 1-4-di-N-Oxide derivatives, Oxoindoline derivatives, triazole derivatives and isooxazoles derivatives and to evaluate for their antimicrobial, anticancer and anti-inflammatory activities.
References


