CHAPTER-1

INTRODUCTION
Chapter-1: Introduction

<table>
<thead>
<tr>
<th>S No</th>
<th>Name of the Sub-Title</th>
<th>Page No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Introduction ...........................................................................................................</td>
<td>3-5</td>
</tr>
<tr>
<td>1.2</td>
<td>An over view on heterocyclic compounds and their synthetic approaches........................</td>
<td>5-7</td>
</tr>
<tr>
<td>1.3</td>
<td>An overview on Carbocyclic compounds and their synthetic approaches........................</td>
<td>7-9</td>
</tr>
<tr>
<td>1.4</td>
<td>Importance of 2-substituted 1,3-benzazoles in Organic / Medicinal chemistry...............</td>
<td>9-11</td>
</tr>
<tr>
<td>1.5</td>
<td>Importance of 1,2-disubstituted benzimidazoles in Organic / Medicinal chemistry...........</td>
<td>12-14</td>
</tr>
<tr>
<td>1.6</td>
<td>Importance of polysubstituted pyrroles in Organic / Medicinal chemistry..................</td>
<td>14-16</td>
</tr>
<tr>
<td>1.7</td>
<td>Importance of cascade reactions and functionalized cyclohexanones in Organic / Medicinal chemistry</td>
<td>16-18</td>
</tr>
<tr>
<td>1.8</td>
<td>Conclusion.............................................................................................................</td>
<td>19</td>
</tr>
</tbody>
</table>
1.1 Introduction

Rapid progress in synthetic organic chemistry is connected with searching of new compounds with preferred properties. A gigantic challenge for the pharmaceutical industry is to continue to innovate, to bring clinically differentiated medicines and really make a divergence in patient’s livelihood. For every 5,000-10,000 new compounds that are enter into the research and development pipeline, only one can be capable of getting approval and takes about 10-12 years of clinical development.

Decoding of the human genome has made confident and encouraged the researcher to find out large number of novel drugs into the market. Among 30,000 human genes, at least 1,000 genes involves in the course of syndrome significantly. Since each of these genes have been linked to the function of between five and ten proteins, the conclusion is that there might be 5,000 – 10,000 drug targets for one NCEs.\cite{1,2}

Medicinal chemistry has its roots in several branches of chemistry and biology. However, essentially it concerns with the understanding of mechanisms of action of drugs. It attempts to begin relationship between structure and function and to link biodynamic behavior with chemical reactivity and physical properties. Rightly, therefore, medicinal chemistry is also called pharmaceutical chemistry, therapeutic chemistry, pharmaco chemistry etc., Emphasis is laid on drugs, nevertheless, the interest of the medicinal chemist does not stop at drugs and include bioactive compounds in general. It encompasses discovery, development, identification and interpretation of mode of action at the molecular level. It is also concerned with the study, identification and synthesis of the metabolic products of drugs and related compounds. In addition, medicinal chemistry also involves the isolation, characterization and synthesis of compounds that can be used in medicine for the anticipation, treatment and cure
of diseases. Thus, it provides chemical basis for the interdisciplinary field of therapeutics.

The breakthroughs of the medicinal properties of compounds have always stimulated investigation into the therapeutic chemical reactions and this has led to involve an outlook to develop methods of synthesis of similar substances. Chemists have made possible some of the proudest achievements of human and veterinary medicine as well as animal husbandry. The World Health Organization (WHO) describes drug as “any substance used in a pharmaceutical product that is intended to modify or explore physiological system or pathological states for the benefit of the recipient”.

Compounds having biological activity are extensively used in pharmaceutical industries. Among these, heterocycles and carbocycles are the typical division of organic chemistry and are of immense biological and industrial importance. The greater parts of biologically active compounds are heterocycles also applicative as additives and modifiers used in industries of cosmetics, photography, information storage and plastics. Heterocyclic and carbocyclic compounds are also used in pharmacy and agriculture. Analysis of scientific papers in the last two decades revealed that there is a general trend in research for new drugs are involving amendment of existing biologically active matrices and molecular design of the structures of compounds.

Carbocyclic or heterocyclic ring systems consist of the core of chemical structures of the majority of therapeutic agents. This finding results in the majority of drugs exerting their effect by their actions at receptor or receptor-like sites on cells, enzymes, or related entities. These interactions depend on the receiving site being presented with a molecule that has a well-defined shape, distribution of electron density, and array of ionic or ionizable sites, which harmonize features on the receptor. These requirements are readily met by the relatively
rigid carbocyclic or heterocyclic molecules. A number of important drugs cannot, however, be assigned to one of those structural divisions. Most of these agents act as false substrates for enzymes that handle peptides. The vital structural feature of these compounds is an open-chain sequence that mimics a corresponding feature in the normal peptide. Although these drugs often contain carbocyclic or heterocyclic rings in their structures, these features are peripheral to their mode of action.

1.2 An overview on heterocyclic compounds and their synthetic approaches

A heterocyclic compound, also entitled a heterocycle, as “Any of a dissection of organic compounds whose molecules contain one or more rings of atoms with at least one atom (the heteroatom) being an element other than carbon, most frequently oxygen, nitrogen, or sulfur”. [3]

Although heterocyclic compounds may be inorganic, most have within the ring structure at least one atom of carbon, and one or more elements such as sulfur, oxygen, or nitrogen [4]. Since non-carbons are usually considered to have replaced carbon atoms, they are called heteroatoms. The structures may consist of either aromatic or non-aromatic rings. Heterocyclic chemistry is the branch of chemistry dealing with the synthesis, properties, and applications of heterocycles. Heterocyclic derivatives discriminate as a group; can be divided into two broad areas, aromatic and non-aromatic or aliphatic.
1.2.1 Aliphatic heterocycles:

![Diagram of aliphatic heterocycles]

**Figure-1.1: Aliphatic heterocycles**

In aromatic heterocycles, five-membered and six-membered heterocycles are most significant classification of components in medicinal organic chemistry.

1.2.2 Aromatic five-membered heterocycles:

![Diagram of aromatic five-membered heterocycles]

**Figure-1.2: Aromatic five-membered heterocycles**
1.2.3 Aromatic six-membered heterocycles:

![Chemical structures of various aromatic six-membered heterocycles]

**Figure-1.3**: Aromatic six-membered heterocycles

1.3 An overview on carbocyclic compounds and their synthetic approaches

In chemistry, any of a large class of organic compounds in which three or more atoms of the element carbon are connected together in a ring is called Alicyclic compound. The bonds between pairs of neighboring atoms may all be of the type designated single bonds (involving two electrons), or some of them may be double or triple bonds (with four or six electrons, respectively). A system of alternating single and double bonds may be envisioned in six-membered rings. However, belong to another important class (i.e. aromatic compounds), distinguished from the alicyclic compounds by a characteristically different module of chemical reactivity.

Cyclic organic molecules usually exhibit a certain degree of ring strain that makes them less stable than their linear counterparts. It is because of the angles formed by adjacent covalent bonds are smaller. Bond angles have the preferred value in the larger rings is about 109.5°; as a result, the atoms in the ring do not lie in one plane. Similar limitations on the angles in double and triple bonds influence the stability of alicyclic compounds containing such bonds. Ring strain consequences from angle strain (deviation of bond angles from
109.5°) in small rings and torsional strain. It is largest for 3 and 4
membered rings and tends to be small for medium-sized rings. 
Cyclohexane is the only cycloalkane, which has no ring strain. This is 
because cyclohexane can adopt the chair conformation, which 
completely avoids eclipsing interactions. The chair contains axial and 
equatorial bond positions, which can be interchanged via a chair-chair 
interconversion. Such interconversions go through a less stable boat 
conformation, which contains significant amounts of eclipsing 
interactions. Substituent groups prefer to adopt the equatorial 
positions as there is less steric hindrance from 1,3-diaxial 
interactions. Some groups such as the tert-butyl group are so large 
that they on the whole prevent the chair from flipping into other 
conformations once the groups are in the equatorial positions.

Carbocycles are organic molecules that contain one or more 
rings and chains of atoms. The simplest cyclic molecules are the 
cycloalkanes. Cycloalkanes are named after their corresponding 
linear alkanes with the prefix -cyclo. Cycloalkanes can be drawn as 
regular polygons using line-angle representations.

![Figure-1.4: The cycloalkanes.](image)

1.3.1 Classification of Polycyclic Compounds

The molecules that contain two or more rings that are joined together 
are called Bicyclic or polycyclic compounds. There are three different 
ways that rings can be joined. Where the two atoms and the bond
between them are shared is called fused rings. When more than two atoms are shared, the result is a bridged system, so-called because the shared atoms form a "bridge". Finally, when two rings are joined at a single atom the result is a spiro linkage.

![Fused, Bridged, and Spiro bicyclic molecules](image)

**Figure-1.5:** *Fused, bridged, and spiro bicyclic molecules*

### 1.4 Importance of 2-substituted 1,3-benzazoles in Organic / Medicinal chemistry

Heterocyclic compounds have occupied a prominent place amongst various classes of organic compounds by virtue of their diverse biological activities. Hence the design, synthesis and production of new molecules to bring in health and human welfare have taken center stage in recent years. Compounds having benzimidazole and benzothiazole nucleus are reported to elicit certain biological activities such as anti-inflammatory, anti-malarial, anti-tumor, anti-viral, bronchodilatory, anti-helminthic, anti-amoebic, analgesic, selective inhibition of the platelet-derived growth factor receptor etc.,

Due to their important pharmaceutical efficacy, the synthesis of 1,3-benzazoles (A, Figure 1.6) i.e. benzimidazole and benzothiazole (B, Figure 1.6) are considered as privileged structures in the area of medicinal chemistry[^4].
Figure 1.6: Basic skeleton of 1,3-benzimidazole and benzothiazole

Benzazole nucleus facilitates to make a large number of therapeutic agents. During recent years there have been some remarkable developments in the biological activities of benzazole. These compounds have special significance in the field of medicinal chemistry due to their incredible pharmacological potentialities. This is exemplified by a range of commonly used drugs such as Albendazole (A, Figure 1.7), Fenbendazole (B, Figure 1.7), Tiabendazole (C, Figure 1.7), Mebendazole (D, Figure 1.7), Fproton-pump inhibitor Omeprazole (E, Figure 1.7), Lansoprazole (F, Figure 1.7), TTX-sensitive sodium channels blocker Riluzole (A, Figure 1.8), Inhibitors of p38a MAP kinase (B, Figure 1.8) and direct thrombin inhibitor Dabigatran.
Examples of 1,3-benzimidazole based drugs:

Albendazole (A)

Fenbendazole (B)

Tiabendazole (C)

Mebendazole (D)

Omeprazole (E)

Lansoprazole (F)

Figure-1.7

Examples of 1,3-benzothiazole based drugs:

Riluzole (A)

Inhibitors of p38a MAP kinase (B)

Figure-1.8
1.5 Importance of 1,2-disubstituted benzimidazoles in Organic / Medicinal chemistry

1,2-disubstituted benzimidazoles were also depicted as intermediates for dyes and polymers,[5] and have frequently been used as ligands.[6] In addition, there have also been reports of their use as possible precursors for aminoboronic acids with an interest as bifunctional organic catalysts.[7] Certainly, benzimidazoles are important scaffolds, thus substantial efforts have been made to the search for new synthetic strategies to assemble this structure, both in solid [8-14] and in solution the phase.[15] Solid-phase synthesis is extremely useful for combinatorial approaches towards novel benzimidazole libraries with increased structural complexity. While methods to prepare 1- or 2-substituted benzimidazoles have highly increased during the last years,[16,17] the assembly of 1,2-disubstituted benzimidazoles remains a complicated task (Scheme-1.1).[18]

![Scheme-1.1](image-url)
The classical and most common methods to make benzimidazoles involve the condensation of O-phenylene diamine with aldehydes, carboxylic acids, or their derivatives (nitriles, amidates, orthoesters).\textsuperscript{[19-21]} N-Alkyltion and N-arylation of benzimidazoles is frequent alternatives.\textsuperscript{[22]} However, these methods are typically not suitable for the regioselective synthesis of the 1,2-disubstitutued benzimidazoles and are limited to the accessible starting materials. Consequently, improvements were made towards the development of new strategies, such as the metal-catalyzed arylamination chemistry\textsuperscript{[8]} and the cascade arylamination/condensation method.\textsuperscript{[9,10]} The development of solid phase synthesis,\textsuperscript{[15]} allied with the optimization of microwave conditions\textsuperscript{[19-21]} allowed a more rapid, efficient and sustainable route to achieve this relevant class of benzimidazoles. The pursuant of simple and regioselective synthetic methods for these compounds remains an emerging research area.

**Examples of 1,2-disubstituted benzimidazole based drugs:**

![Atacand](image1.png)  
**Atacand**

![Telmisartan](image2.png)  
**Telmisartan**

![Blistine](image3.png)  
**Blistine**
1.6 Importance of polysubstituted pyrroles in Organic / Medicinal chemistry

Pyrrole is one of the classes of organic heterocyclic compounds of five-membered diunsaturated ring structure composed of four carbon atoms and one nitrogen atom. Pyrrole itself is the simplest member of pyrrole family. Pyrrole ring system is involved in colored products (green pigment, chlorophyll; red, hemoglobin; blue, indigo) in nature. Pyrrolidine, the saturated tetrahydropyrrole, is part of the structures of amino acids (proline, hydroxyproline and hygrine). Pyrrolidine is a pyrrole in which one of the two solid bonds has been hydrogenated.

Pyrrole and its derivatives are widely used as an intermediate in synthesis of pharmaceuticals, medicines, agrochemicals, dyes, photographic chemicals, perfumes and other organic compounds. For example, chlorophyll and heme are the derivatives which are made by four pyrrole ring formation of porphyrin ring system. They are used as catalysts for polymerization process, corrosion inhibitors, preservatives, and as solvents for resins and terpenes. They are used as the standard of chromatographic analysis. At last, they are also used in organic synthesis and the pharmaceutical industry. For illustration, polymers made from pyrrole-containing monomers are
generally sold on the basis of their unique physical properties and function, rather than for any bioactivity. Pyrroles can be classified as specialty chemicals because of a relatively lower sales volume than commodity chemicals. They are most often sold in the marketplace as chemical intermediates used to manufacture final consumer products.

**Examples of pyrrole based new inhibitors:**

![Atorvastatin](image1)

![Tolmetine](image2)

![Roseophilin](image3)

![Tumor Necrosis factor inhibitors](image4)

![Pyrrole-based histone deacetylase inhibitor](image5)
1.7 Importance of cascade reactions and functionalized cyclohexanones in Organic / Medicinal chemistry

A cascade reaction or tandem reaction or domino reaction is a successive series of intramolecular organic reactions which frequently proceed via highly reactive intermediates. It allows the organic synthesis of complex multinuclear molecules from a single acyclic precursor. The substrate contains many functional groups that take part in chemical transformations one at the time. Often a functional group is generated in situ from the previous chemical transformation. The definition includes the prerequisite intramolecular in order to distinguish this reaction type from a multi-component reaction. In this sense it differs from the classification of a biochemical cascade. The main advantages of a cascade reaction in organic synthesis are that the reaction is often fast due to its intramolecular nature. The
reaction is also clean, displays high atom economy, and does not involve workup and isolation of many intermediates. It adds much complexity effectively in one step.

The cyclohexanone or cyclohexane framework has also been explored in the discovery and development of phosphodiesterase 4 (PDE4) inhibitors e.g. Cilomilast.\textsuperscript{[23]} PDE4 inhibitors are known to be useful for the treatment of COPD (Chronic Obstructive Pulmonary Disease) and asthma and have potential in the treatment of CNS related diseases.\textsuperscript{[23,24]} Only one drug i.e. Roflamilast (Daxas\textsuperscript{®}, Nycomed) has been launched so far and side effects including nausea and emesis\textsuperscript{[25,26]} have delayed the market launch of Cilomilast. Thus, discovery of novel PDE4 inhibitors having fewer side effects is desirable. In pursuance of our research on identification of PDE-4 inhibitors\textsuperscript{[27-30]} based on cyclohexane framework\textsuperscript{[31]} (I) we became interested in assessing library of compounds II against PDE4 (Fig. 1.11).

![Figure-1.11: Basic skeleton of potential inhibitors](image-url)

**Examples of cyclohexanone based new inhibitors:**
Cycloalkane derivatives are an important class of carbocyclic compounds which displays a wide variety of biological activities. Some of the biological active compounds are presented below.
**Figure 1.12**

Methoxetamine

Ketamine

Cannabinoids (Nabilone)

NMDA Receptor modulator
1.8 Conclusion:

Heterocyclic and carbocyclic structures will continue to attract considerable interest of organic, medicinal and natural product chemists because of natural occurrence and a vast range of pharmacological activities. Compounds containing these moieties will continue to play a key role in many areas of drug discovery and pharmaceutical research. It is evident from the previous sections that, several diverse and elegant methodologies have been developed so far for the construction and functionalization of heterocyclic and carbocyclic structures. Synthetic chemists have demonstrated their exceptional imagination, strategies and skill in developing these synthetic methodologies. These efforts eventually helped both medicinal and natural product chemists in synthesizing their target molecules. An increasing number of reports are now appearing not only on the design and identification of biologically active small molecules based on heterocyclic and carbocyclic frameworks but also on the preparation of heterocycle / carbocycle -based natural products. While extensive research work have been carried out to develop more straight forward, efficient, shorter and greener methodologies for accessing library of compounds containing heterocyclic and carbocyclic structures, synthetic routes to highly substituted or polysubstituted heterocycles and carbocycles still remained less explored. Further research effort is therefore clearly required to address this problem. No doubt that the newly developed cutting-edge technologies in other areas of organic synthesis would help in inventing novel methodologies to find better solutions.