CHAPTER-1

THERAPEUTIC SIGNIFICANCE OF SOME NITROGEN CONTAINING
HETEROCYCLIC COMPOUNDS

1.1 INTRODUCTION

Heterocyclic compounds are organic compounds having ring structure containing atoms in addition to carbon such as sulfur, oxygen or nitrogen, as part of the ring [1]. They may be either simple aromatic rings or non-aromatic rings. Heterocyclic chemistry is a very important branch of organic chemistry accounting for nearly one-third of recent publications. The chemistry of heterocyclic compounds is one of the most complex and intriguing branches of organic chemistry, of equal interest for its theoretical implications, for the diversity of its synthetic procedures [2], and for the physiological and industrial significance of heterocycles. Heterocyclic compounds are very widely distributed in nature and are essential to life; they play a vital role in the metabolism of all living cells.

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 pencillin and cephalosporins, alkoloids [3] such as vinblastine, morphine and reserpine, and cardiac glycosides such as those of digitalis. The large majority are synthetic heterocyclics which have found widespread use for pharmaceutical applications for example as anti cancer agents,
analeptics, analgesics, antidepressants [4], hypnotics. A good number of heterocyclic compounds also find applications as pesticides, insecticides, weedicides and rodenticides.

Nitrogen containing heterocyclic compounds [5] are key building blocks used to develop compounds of biological or medicinal interest to chemists. A vast number of nitrogen containing heterocyclic building blocks have applications in pharmaceutical research, agriculture science, and drug discovery. Heterocyclic building blocks also have practical uses as components in dyestuffs, antioxidants, copolymers, bases, and ligands. Most of the organic compounds containing heterocyclic compounds show better biological activity than non-nitrogen compounds.

In the pharmaceutical industry, over 75% of the top two hundred branded drugs have heterocyclic fragments in their structures. Some key biological activities of heterocyclic compounds are discussed below.

1.2 BIOLOGICAL EFFICACY AND THERAPEUTIC UTILITY OF HETEROCYCLIC COMPOUNDS

A) Heterocyclic compounds as antibiotics:

The most commonly prescribed medications in modern medicine are antibiotics. Antibiotics cure disease by killing or injuring bacteria. Antibiotics belong to the broader group of antimicrobial compounds, used to treat the infections caused by microorganisms, including fungi and protozoa. Antibiotics isolated from living organisms, include
aminoglycocides. Some purely synthetic antibacterials are: the sulfonamides [6], the quinolines and the oxazolidinones [7]. Among the antibiotics and anti-bacterial category are betalactams and quinoline derivatives. Betalactams have two different heteroatoms in their structure, eg ampicillin (i), pencillin G [8].

Among the quinoline derivatives ciprofloxacin (ii) [9] is a blockbuster drug.

**B) Heterocyclic compounds as antiemetic agents:**

Several 5-HT₃ receptor antagonists are now in clinical use for the treatment of cancer chemotherapy-induced emesis [10]. Investigations into application of these antagonists for the treatment of various CNS disorders are also being pursued [11].

Substituted imidazoles (ondansetron (iii)), benzamides (zacopride), esters or amides of indazole and related hydrocycles (granisetron (iv)). Conformationally restricted analogues of the third type are potent 5-HT₃ receptor antagonists [12]. Several series of N-(quinuclidin-3-yl) aryl and heteroaryl fused pyridones were synthesized.
and evaluated for 5-HT₃ receptor affinity. The (3S)-quinuclidinyl isomers had > 10 fold higher affinity than (3R) isomers, eg: Palonosetron (v).

![Chemical structures](image)

(iii) (iv) (v)

C) **Heterocyclic compounds as antimigraine agents:**

Natural 5-HT neurotransmitter is called serotonin involved in migraine. Antimigraine drugs mimic the action of serotonin. Two subtypes of serotonin receptors are 5-HT₁B, 5-HT₁D, located in brain blood vessels responsible for constriction. Over the past few years an extensive efforts have been devoted to the development of N,N-dialkyl tryptamines as 5-HT₁D receptor agonists to achieve the desired activity and selectivity for the treatment of migraine. Sumatriptan (vi) is the first of this class of drugs to be approved for this purpose [13]. Other structural variations like replacing of sulfonamide group in sumatriptan with 1,2,4-triazole and oxazolidinone gave rise to rizatriptan (vii) and zolmitriptan (viii) [14,15].
D) 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 [16,17]. Benzimidazoles also are well known for their pharmacological properties [18], in particular they are widely used as antihelminthic agents. It is interesting to note that a series of substituted pyridyl sulfinyl benzimidazole molecules like omeprazole possess gastric antisecretory and consequently antiulcerative activity [19].

Later several omeprazole (ix) analogues like lansoprazole (x) [20], pantoprazole (xi) [21] have been introduced in the market successfully.

E). Heterocyclic compounds as antidepressants:

Depression is an extremely common and terrible disease that decreases a person’s mood and quality of life [22]. Depression research over the past two decades has shown that people with heart disease are
more likely to suffer from depression than people without heart disease. People with depression are at greater risk of developing heart disease. The understanding of the character and factors behind anxiety and depression has advanced for several centuries, although this awareness is incomplete and has left many facets of depression as the subject of discussion and research [22]. Proposed causes include psychological, psychosocial, and hereditary [22].

Depression in adolescence frequently co-occurs with other disorders such as anxiety, disruptive behavior, eating disorders, or substance abuse. It can also lead to increased risk for suicide [23,24]. There are three specific chemicals that can affect a person’s mood: Serotonin (\text{xii}), Norepinephrine (\text{xiii}) or Dopamine (\text{xiv})

\['
\text{xii} \quad \text{xiii} \quad \text{xiv}
\]

Selective Serotonin Reuptake Inhibitors or Serotonin-Specific Reuptake Inhibitors (SSRIs) [25] are a class of compounds typically used as anti depressants in the treatment of depression, anxiety disorders, and some personality disorders [22].

Selective Serotonin Reuptake Inhibitors (SSRI) are the newest and most popular types of antidepressent medications [22]. SSRIs include
fluoxetine, citalopram, sertraline, and several others. Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) are similar to SSIRs and include venlafaxine and duloxetine [22]. SSRIs and SNRIs are more often prescribed than the older classes of antidepressants, such as tricyclics and Mono Amine Oxidase Inhibitors (MAOIs) because they have been intensively marketed, can be taken once-daily doses, and are less harmful to the heart.

Some of the Antidepressant of the SSRIs are shown in **table 1.1**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Compound structure</th>
<th>Common name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><img src="image1" alt="Citalopram" /></td>
<td>Citalopram [26]</td>
</tr>
<tr>
<td>2.</td>
<td><img src="image2" alt="Dapoxetin" /></td>
<td>Dapoxetin [27]</td>
</tr>
<tr>
<td>3.</td>
<td><img src="image3" alt="Escitalopram" /></td>
<td>Escitalopram [28]</td>
</tr>
<tr>
<td>4.</td>
<td><img src="image4" alt="Fluoxetine" /></td>
<td>Fluoxetine [29]</td>
</tr>
<tr>
<td>No.</td>
<td>Chemical Structure</td>
<td>Name</td>
</tr>
<tr>
<td>-----</td>
<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>5.</td>
<td><img src="image" alt="Fluvoxamine" /></td>
<td>Fluvoxamine [30]</td>
</tr>
<tr>
<td>6.</td>
<td><img src="image" alt="Indalpine" /></td>
<td>Indalpine [31]</td>
</tr>
<tr>
<td>7.</td>
<td><img src="image" alt="Paroxetine" /></td>
<td>Paroxetine [32]</td>
</tr>
<tr>
<td>8.</td>
<td><img src="image" alt="Sertraline" /></td>
<td>Sertraline [33]</td>
</tr>
<tr>
<td>9.</td>
<td><img src="image" alt="Zimelidine" /></td>
<td>Zimelidine [34]</td>
</tr>
</tbody>
</table>

Citalopram hydrobromide is an isobenzofuran derivative, which is a Selective Serotonin Reuptake Inhibitor (SSRI) and used for the treatment of depression.

**F). Therapeutic utility of tetrazoles Compounds**

Nitrogen-containing heterocyclic compounds [35] are key building blocks used to develop compounds of biological or medicinal interest to chemists. A vast number of nitrogen-containing heterocyclic building blocks have applications in pharmaceutical research, agriculture science,
and drug discovery. Heterocyclic building blocks also have practical uses as components in dyestuffs, antioxidants, copolymers, bases, and ligands. Among the heterocyclic compounds, nitrogen containing heterocyclic compounds are most useful compounds. Most of the organic compounds containing heterocyclic compounds show better biological activity than non-nitrogen compounds. One of the important heterocyclic functionality is Tetrazole. Many tetrazole derivatives possess biological activity. The tetrazole function group acts as a metabolically stable isostere for the carboxylic acid [36]. Some of the biologically active tetrazoles have been given in Table 1.2.

Some types of tetrazole derivatives are of explosive in nature and may be used as rocket propellants [37]. Addition of 5-aminotetrazole to nitrocellulose propellant powders rendered them flashes without loss of propellant potential [38,39].
<table>
<thead>
<tr>
<th>S.No</th>
<th>Compound structure</th>
<th>IUPAC name</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>5-(tetrazol-5-yl-methyl)-3-(2’-aminoethyl)indole.</td>
<td>Anti-migraine [40]</td>
</tr>
<tr>
<td>2.</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>2-[5-(3,4-dimethoxyphenyl)-tetrazolidin-2-yl]-N-methyl acetamide</td>
<td>Anti inflammatory [41]</td>
</tr>
<tr>
<td>3.</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>6-aminomethyl-5-tetrazolyl)benzothiazole</td>
<td>Anti-viral [42]</td>
</tr>
<tr>
<td>4.</td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>2,5-bistetrazolylpyridine</td>
<td>Fibrosuppressant [43]</td>
</tr>
<tr>
<td>5.</td>
<td><img src="image5.png" alt="Structure 5" /></td>
<td>3-acetoxymethyl-7-[2-(5-methyl-tetrazol-1-yl)-acetylamino]-8-oxo-5-thia-1-aza-bicyclo[4,2,0] oct-2-ene-2-carboxylic acid.</td>
<td>Anti – microbial [44]</td>
</tr>
<tr>
<td>6.</td>
<td><img src="image6.png" alt="Structure 6" /></td>
<td>Tetrazolylcarboxamide.</td>
<td>Superoxide generation inhibitor [45]</td>
</tr>
<tr>
<td>7.</td>
<td><img src="image7.png" alt="Structure 7" /></td>
<td>1,4-dibutyl-3-[4-(3-tetrazolidin-5-yl-pyridin-2-yl)-benzyl]-1,3-dihydroimidazole-2-one.</td>
<td>Angiotensin-II antagonist [46]</td>
</tr>
</tbody>
</table>
G) Heterocyclic compounds as antineoplastic agents:

Cancer is a second leading cause of deaths by diseases in United States [47]. Cancer is spreading not only across every corner of the globe but also spreading its deadly tentacles to all organs including the skeletal parts and blood cells of the humans. Cancer remains one of the most frightening diseases of the recent times. Combating cancer is most challenging task for every drug maker and researcher in the world. Modern lifestyle, changing food habits, rapidly growing industrial development, increased exposures to oncogenic agents and various forms of radiation, ecological imbalance and polluted environment are leading factors of cancer.

Cancer is not simply one disease but a cluster of several dissimilar diseases. The most important differentiating feature of the cancer is, it disturbs the harmony of good cell division in the human body into irregular and unrestrained growth of diseased cells. Cancerous cells (malignant tumor) infiltrate and destroy normal tissues and may proliferate throughout the body (metastasis) via the lymph system or blood. And it may affect several other tissues and organs.

Oncology is a branch of medicine that deals with the cancer and tumors. It studies their development, prevention, diagnosis, and treatment. Popularly known treating methods in Cancer therapy are
surgery, radiotherapy, chemotherapy and lesser-known immunotherapy in combination or singly.

Kinase inhibitors are being used successfully to treat cancers. A kinase inhibitor is a drug or agent (e.g., anti-sense; small molecules; antibodies; etc), which blocks or reduces the activity of a kinase. This includes tyrosine kinase, serine-threonine kinases, receptor kinases, non-receptor kinases, etc. Generally, a “kinase activity” refers to the ability of a polypeptide to catalyze the transfer of phosphate from one molecule to another.

Some of the kinase inhibitors have been given in **Table 1.3**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Compound structure</th>
<th>Common name (Brand®)</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>Axitinib</td>
<td>Inhibit growth of breast cancer in xenograft models [48].</td>
</tr>
<tr>
<td>2.</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>Bosutinib</td>
<td>Tyrosine kinase inhibitor undergoing research for use in the treatment of cancer [49].</td>
</tr>
<tr>
<td>3.</td>
<td><img src="image" alt="Cediranib" /></td>
<td>Cediranib</td>
<td>Potent inhibitor of vascular endothelial growth factor receptor tyrosine kinases [50,51,52].</td>
</tr>
<tr>
<td>4.</td>
<td><img src="image" alt="Dasatinib" /></td>
<td>Dasatinib (Sprycel®)</td>
<td>Dasatinib is an oral dual BCR/ABL and Src family tyrosine kinases inhibitor</td>
</tr>
<tr>
<td>5.</td>
<td><img src="image" alt="Erlotinib" /></td>
<td>Erlotinib (Tarceva®)</td>
<td>Epidermal growth factor receptor (EGFR) [53].</td>
</tr>
<tr>
<td>6.</td>
<td><img src="image" alt="Gefitinib" /></td>
<td>Gefitinib (Iressa®)</td>
<td>First selective inhibitor of EGFR tyrosine kinase domain [54,55].</td>
</tr>
<tr>
<td>7.</td>
<td><img src="image" alt="Imatinib" /></td>
<td>Imatinib (Gleevec®)</td>
<td>US FDA has approved imatinib as first-line treatment for CML [56].</td>
</tr>
</tbody>
</table>
8. Lapatinib (Tykerb®)

Lapatinib is an active drug for breast cancer and other solid tumours. It is a dual tyrosine kinase inhibitor which interrupts the HER2 growth receptor pathway [57,58].

9. Linifanib

Linifanib is used for advanced renal cell cancer.

10. Sorafenib (Nexavar®)

Sorafenib is unique in targeting the Raf/Mek/Erk pathway (MAP Kinase pathway) [59].

11. Sunitinib (Sutent®)

Sunitinib is a multi-targeted receptor tyrosine kinase (RTK) inhibitor. Sunitinib also inhibits KIT [60].

12. Tivozanib

Tivozanib is an oral VEGF receptor tyrosine kinase inhibitor.
Sorafenib is a small molecular inhibitor of several tyrosine protein kinases [59]. Sorafenib is unique in targeting the Raf/Mek/Erk pathway (MAP kinase pathway). Sorafenib inhibits VEGFR and PDGFRB signalling pathways and reduces angiogenesis in human tumor xenografts [61,62]. In orthotopic anaplastic thyroid carcinoma xenografts, sorafenib induces an endothelial apoptosis [63]. This anti-angiogenic effect results in reduced tumor growth and improved survival of mice. Sorafenib also seems to decrease proliferation and survival of tumour cells by blocking the RAF/MEK/ERK pathway [61,62]. These combined actions explain anti-tumoral activity of sorafenib. Sorafenib could also interact with TSH-signalling pathways. Indeed, the TSH signal transduction cascade has been reported to involve the RAF pathway, a target of sorafenib [64,65].

H). Heterocyclic compounds as anti-resorptive agents:

Osteoporosis has become one of the important health care issues in the current industrial countries. It is estimated that there are about 200 million women suffering from osteoporosis worldwide, especially older women.

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture.

The bones in our skeleton are made of a thick outer shell and a strong inner mesh filled with collagen (protein), calcium salts and other minerals. The inside looks like honeycomb, with blood vessels and bone
marrow in the spaces between bone. Normal and osteoporosis bones are shown in Fig: 1.1 and Fig: 1.2.

The three main mechanisms of osteoporosis are 1) inadequate peak bone mass (the skeleton develops insufficient mass and strength during growth). 2) excessive bone resorption and 3) inadequate formation of new bone during remodeling.

Osteoporosis can be prevented with lifestyle changes and sometimes medication; treatment may involve both in some cases. Lifestyle change includes preventing falls and exercise; medication includes calcium, vitamin D, **bisphosphonates** and several others.

Bisphosphonates are the main pharmacological measures for treatment. However, newer drugs have appeared in the 1990s, such as teriparatide and strontium ranelate.
Bisphosphonates are pyrophosphates analogues in which the oxygen atom in P-O-P moiety has been replaced by a carbon, resulting in a metabolically stable P-C-P structure [66]. The first bisphosphonates were synthesized in the 19th century. They were initially used mainly as antiscaling, anticorrosive agents and also as complexing agents in the textiles, fertilizers, and oil industries [67]. However, it was not until the late 1960s that their potential for the treatment of various diseases of bone mineral metabolism became evident. In contrast to pyrophosphate, Bisphosphonates are also orally active, although their low bioavailability often limits the usefulness of oral administration. Pamidronate (xv), a second generation bisphosphonate was the starting point for extensive SAR (Structure Activity Relationship) Studies. Small changes of the structure of xv led to marked improvements of the inhibition of osteoclastic resorption potency.

\[
\begin{align*}
(xv) & : \quad \begin{array}{c}
\text{H}_2\text{N} \quad \text{O=POH} \\
\text{O=POH} \\
\text{OH}
\end{array} \\
(xvi) & : \quad \begin{array}{c}
\text{H}_2\text{N} \quad \text{O=POH} \\
\text{O=POH} \\
\text{OH}
\end{array} \\
(xvii) & : \quad \begin{array}{c}
\text{H}_3\text{C} \quad \text{N} \quad \text{O=POH} \\
\text{O=POH} \\
\text{OH}
\end{array}
\end{align*}
\]

Alendronate (xvi), with two extra methylene groups in the N-alkyl chain, and OLPadronate (xvii), the N,N-dimethyl analogue are about 10 times more potent than Pamidronate [68]. Further SAR studies involves the replacement of one of the N-methyl groups of (xvii) with n-pentyl
moleity leads to Ibandronate (xviii) [69], which is the most potent for the
treatment of osteoporosis.

The search for more potent bisphosphonates by many
pharmaceutical companies has resulted in a number of novel, highly
potent derivatives [70,71].

Most of the highly potent third generation bisphosphonates
contain heteroaromatic moieties with one or more ring nitrogen atoms as
components of their side chains. Risedronate (xix) [72], Zoledronate (xx)
[73] are some of them belonging to such class of compounds.

\[
\begin{align*}
\text{(xviii)} & \quad \begin{array}{c}
\text{CH}_3 \\
\text{OH} \\
\text{O=POH} \\
\text{O=POH} \\
\text{OH} \\
\end{array} \\
\text{(xix)} & \quad \begin{array}{c}
\text{N} \\
\text{OH} \\
\text{O=POH} \\
\text{O=POH} \\
\text{OH} \\
\end{array} \\
\text{(xx)} & \quad \begin{array}{c}
\text{N} \\
\text{OH} \\
\text{O=POH} \\
\text{O=POH} \\
\text{OH} \\
\end{array}
\end{align*}
\]

1.3 PRESENT WORK

The above discussion is a concise review highlighting the
importance of heterocyclic compounds that are endowed with potential
biological activity. Many people in the society are suffering from various
types of cancer diseases and depression. Osteoporosis is observed in
women. We have taken up the synthesis of urea derivatives of sorafenib
analogues as anti-proliferative activity, citalopram analogues containing
tetrazoles as anti depressants and zoledronic acid, ibandronicacid
analogues as anti resorptive agents as a part of our research programme to develop new analogues and NCEs for pharmaceutical applications.

Observations from the cancer literature and our continued interest in the synthesis of urea derivatives of sorafenib analogues have prompted us to prepare various urea derivatives and investigate biological activities.

Because of the therapeutic importance of bisphosphonic acids of compounds, it became essential to study and develop simple and improved process and preparation of various bisphosphonic acids.

Among the above described antidepressant compounds, citalopram being an isobenzofuran derivative and having huge market value was selected in the present study with a view to develop new efficient, simple and economically viable process through new intermediates and citalopram analogues containing tetrazoles is aimed at.

The total work carried out in the present research programme is being presented in the following chapters.

**Chapter-2:** The synthesis of novel diaryl urea derivatives derived from aryl amine 36 and aryl isocyanates 38 have been discussed in this chapter. The synthesized compounds are analogues of sorafenib [4-\{4-\[[4-chloro-3-(trifluromethyl)phenyl]amino\]carbonyl\]amino\]phenox\}]-N-methylpyridine-2-carboxamide].

**Chapter-3:** This chapter is divided into two sections. Section-A deals with the novel and improved process for the preparation of
Citalopram and Section-B describes the synthesis & characterization of citalopram analogues containing tetrazoles as novel structural variants.

**Chapter-4:** The synthesis of some novel bisphosphonates from the phosphorylation of carboxylic acid have been discussed in this chapter.

**Chapter-5:** This chapter is divided into two sections. Section-A deals with a novel commercial process for the preparation of ibandronate sodium and studies on the polymorphism of ibandronate sodium have been discussed in Section-B.

The results of the above studies involving new derivatives and analogues have advantages and applications in developing industrially feasible methods in many of the process developed during the course of the above studies have resulted in novel patent-noninfringing routes.