CHAPTER 1

INTRODUCTION TO HETEROCYCLIC COMPOUNDS
1.1. Overview of heterocycles

Heterocycles form by far the largest of classical divisions of organic chemistry and are of immense importance biologically and industrially. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic while countless additives and modifiers used in industrial applications ranging from cosmetics, reprography, information storage and plastics are also heterocyclic in nature. One striking structural feature inherent to heterocycles, which is exploited to great advantage by the drug industry, lies in their ability to manifest substituents around a core scaffold in defined three dimensional representations. For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry. Heterocycles have contributed to the development of society from a biological and industrial point of view as well as to the understanding of life processes to improve the quality of life. Among the approximately 20 million chemical compounds identified by the end of the second millennium, more than two-thirds are fully or partially aromatic and approximately half are heterocyclic. The presence of heterocycles in all kinds of organic compounds of interest in electronics, biology, optics, pharmacology, material sciences and so on is very well known. Between them, sulphur and nitrogen-containing heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic synthesis. However, heterocycles with other heteroatoms such as oxygen, phosphorus and selenium also occurs. Many natural drugs such as papaverine, theobromine, quinine, emetine, theophylline, atropine, procaine, codeine, reserpine and morphine are all heterocycles. Almost all the compounds, known as synthetic drugs such as diazepam, chlorpromazine, isoniazid, metronidazole, azidothymidine barbiturates, antipyrine, captopril and methotrexate are heterocycles. Some dyes (e.g. mauveine), luminophores, (e.g. acridine orange), pesticides (e.g. diazinon) and herbicides (e.g. paraquat) are also heterocyclic in nature. All these natural and synthetic heterocyclic compounds can and do participate in chemical reactions in the human body. Furthermore, all biological processes are chemical in nature. Such fundamental manifestations of life as the provision of energy, transmission of nerve impulses, sight, metabolism and the transfer of hereditary information are all based on chemical reactions involving the participation of many heterocyclic compounds, such as vitamins, enzymes coenzymes, nucleic acids, ATP and serotonin. Does nature utilize heterocycles? The answer to this question is provided by the fact that heterocycles are able to get involved in an extraordinarily wide range of
reaction types. Depending on the pH of the medium, they may behave as acids or bases, forming anions or cations. Some interact readily with electrophilic reagents, others with nucleophiles, yet others with both. Some are easily oxidized, but resist reduction, while others can be readily hydrogenated but are stable toward the action of oxidizing agents. Certain amphoteric heterocyclic systems simultaneously demonstrate all of the above-mentioned properties. The ability of many heterocycles to produce stable complexes with metal ions has great biochemical significance. The presence of different heteroatoms makes tautomerism ubiquitous in the heterocyclic series. Such versatile reactivity is linked to the electronic distributions in heterocyclic molecules. Evidently, all the natural products and the synthetic drugs mentioned above are good examples of nature’s preference for heterocycles whose biological activity cannot be determined by one or a combination of two or three of the above mentioned properties.

Synthetic heterocycles have widespread therapeutic uses such as antibacterial, antifungal, antimycobacterial, trypanocidal, anti-HIV activity, antileishmanial agents, genotoxic, antitubercular, antimalarial, herbicidal, analgesic, anti-inflammatory, muscle relaxants, anticonvulsant, anticancer and lipid peroxidation inhibitor, hypnotics, antidepressant, antitumoral, anthelmintic and insecticidal agents. There are larger number of synthetic heterocyclic compounds with other important applications such as fungicides, herbicides, anticorrosive agents, photo stabilizers, agrochemicals, dyestuff, copolymer, photographic developers, fluorescent whiteners, sensitizers, booster agent, antioxidant in rubber and flavouring agent. Pyrimidine (cytosine, thymine and uracil) and purine (adenine and guanine) derivatives are monocyclic and bicyclic heterocycles with two and four nitrogen atoms, respectively. They are key components of the deoxyribonucleic acid (DNA) molecules and participate directly in the encoding of genetic information. They also pass information to the related ribonucleic acid (RNA) molecules that control, in protein synthesis, the sequence of amino acids. The need for minute quantities of accessory dietary factors, the vitamins is well-known. Vitamins in the B group thiamine, folic acid, riboflavin, cyanocobalamine, are nitrogen-containing heterocycles and function either as coenzymes or their precursors. Other vitamins such as ascorbic acid (vitamin C) and tocopherol (vitamin E) are oxygen heterocycles.

The essential amino acid proline, histidine and tryptophan, photosynthesizing pigment chlorophyll, the oxygen transporting pigment haemoglobin, the hormones
kinetin, heteroauxin, cytokinins, neurotransmitter serotonin, histamine respectively are successful applications of heterocyclic compounds. The introduction of a heteroatom into a cyclic compound imparts new properties. Heterocycles are chemically more flexible and better able to respond to the many demands of biochemical systems. The constantly accelerating rate of research and development in heterocyclic chemistry has added enormous numbers of heterocyclic systems that are now well known and this number is increasing very rapidly.

1.2. Importance of heterocycles in medicine

Most pharmaceuticals are based on heterocycles. An inspection of the structures of the top selling brand name drugs in 2007 reveals that 8 of the top 10 and 71 of the top 100 drugs contain heterocycles. This is not surprising as heterocycles have dominated medicinal chemistry from the beginning. Consistent with their importance, many U.S. patents by pharmaceutical companies involve heterocyclic compounds. For example, a search of the patent literature from 1976 to September 2008 revealed that 1729 patents issued to Pfizer, as a representative company, contain the word “pyridine.” Merck has 3504 U.S. patents containing the word pyridine. This is not peculiar to pyridine, other heterocycles in medicine; include examples of indoles, quinolines, azepines, and pyrimidine in many pharmaceutically active ingredients. Selection of these five groups is arbitrary and ignores several other types of heterocycles, but it is meant to give examples of the use of heterocycles in medicine. This classification is also an oversimplification. Many pharmaceutical compounds contain more than one type of ring system. For example, the exemplified pyridine compounds used as proton pump inhibitors also contain a benzimidazole structure. Dimebon is discussed in the section on pyridines, but it also contains the indole ring. This, too, is arbitrary and not meant to imply that the pyridine structure is more important for Alzheimer’s treatment than the indole structure. The United States Adopted Names Council serves health professionals by selecting non proprietary names for new drugs based on pharmacological and/or chemical relationships. One monograph organizes these new drugs by chemical structure, and much of the text involves heterocycles. There are 5-membered heterocycles, 6-membered heterocycles, 5-membered heterocycles fused to one benzene ring, 6-membered heterocycles fused to one benzene ring, bicyclic-fused heterocycles, and polycyclic-fused heterocycles.
1.2.1. Brief history

Heterocycles have been used medicinally since the beginning of written records. Shen Nung, a Chinese scholar-emperor who lived in 2735 B.C. wrote of the herb Ch’ang Shan, as being helpful in treating fevers. Ch’ang Shan was later found to contain dichroins, for example, β–dichroine.

Another example of ancient usage of a heterocyclic compound is opium. Opium contains several alkaloids including morphine and was imported from Greece by the Egyptians before the war of Troy, which was waged in approximately 1200 B.C. Even before the ancient Greeks; the Sumerians (Babylonians) carved tablets with pictures of the opium poppy. Some of the first animal studies of drugs were done with opium. For example, in the 1700s, Robert Whytt used frogs to study the effect of opium on the heart.

The first synthetic heterocyclic pharmaceutical seems to be antipyrine. Antipyrine is a pyrazole analgesic and an antipyretic, like aspirin. Ludwig Knorr used Emil Fischer’s discovery of phenyl hydrazine to synthesize antipyrine, and in 1883, Knorr was granted a patent on the synthesis. In 1885, one year after market introduction, almost 6 metric tons were sold, and in 1899, sales had grown to almost 800 metric tons. More recently, antipyrine has been used in a solution with benzocaine to relieve ear pain and swelling. Another class of early drugs is based on malonylurea, which was discovered in 1864 by Von Baeyer. Knorr’s synthesis is shown in Scheme 1.1. Compound from urea and malonic acid, Von Baeyer gave malonylurea the name barbituric acid.
There are many derivatives of barbituric acid. The first of them to be marketed was diethylbarbituric acid, which is also known as barbital, malonal or gardenal. Phenobarbital was introduced by Bayer Pharmaceuticals in 1912 and is currently used for the treatment of epilepsy. In 1926 the effect of phenobarbital on cerebral circulation was studied. During the twentieth century, more than 2500 barbiturates were synthesized, 50 of which were eventually employed clinically.

Another heterocyclic drug of historical significance is quinine. South American natives used the bark of cinchona evergreen trees before the arrival of the Spanish, but it was the Jesuits who are credited with the introduction of cinchona bark into medical use in Europe around 1640. The bark was widely used as an antimalarial drug, but it was not until 1820 that French scientists, Pelletier and Caventou, isolated quinine as the active ingredient. Pelletier and Caventou are regarded as the founders of alkaloid chemistry. A factory that they established in Paris for the extraction of quinine can be considered as the beginning of the modern pharmaceutical industry. The synthesis of
quinine remained elusive for more than 100 years after its isolation. In 1856 Perkin synthesized mauveine, which is an indigo dye. This was the first synthetic dye and was an offshoot of his unsuccessful efforts to synthesize quinine. Today, the Perkin Medal is widely acknowledged as the highest honor in American industrial chemistry. The cinchona bark was in scarce supply in World War II. The plantations had been captured by Germany and Japan, which caused thousands of allied soldiers fighting in Africa and the Pacific to die after contracting malaria. This prompted the need for a synthetic source.\(^{45}\) In 1944 Woodward and Doering reported the total synthesis of quinine, which is an alkaloid that was later claimed to be “the drug to have relieved more human suffering than any other in history.”

Despite the advances, malaria remains a problem. There were an estimated 247 million malaria cases among 3.3 billion people at risk in 2006 which caused nearly a million deaths, mostly of children under 5 years. In 2008, 109 countries were endemic for malaria, and 45 countries were within the World Health Organization (WHO) African region.\(^{46}\) Quinine is still used as are the structurally simpler chloroquine and primaquine. Chloroquine is a purely synthetic drug discovered to solve the problem of quinine shortage during the war. Also prescribed today are the artemisinin-based combination therapies (ACTs).\(^{47}\)
In 1932 Gerhard Domagk, who was working for I.G. Farbenindustrie, tested a red dye, 4-[(2,4-diaminophenyl)azo] benzenesulfonamide hydrochloride on mice that had been injected with streptococci. All the controls died and all the treated mice survived. The dye was later found to have curative powers in humans and went on the market in 1935 as Prontosil.

In 1939 the Nobel Prize in physiology or medicine was awarded to Domagk for his work with Prontosil. By 1939 Prontosil was recognized as the first of a new class of antibacterial drugs called the sulfa drugs. The discovery of the antibacterial action of prontosil prompted a flurry of research activity. At the Pasteur Institute, between July and November 1935 Jacques and Therese Trefouel synthesized 44 azo compounds, of which 18 were sulfonamides; Daniel Bovet and Frederic Nitti conducted animal studies on 80 compounds. In 1935 Bovet and Nitti tried p-aminobenzenesulfonamide, which contained the similar functionality present in the other molecules, found the white compound to be active, which resulted in a breakthrough in the research that had previously been focused on dyes. In 1937 p-amino benzenesulfonamide, by then called sulfanilamide in the United States, went on the market.

During the next decade, thousands of sulfonamides were synthesized and tested as antibacterial agents. These were the first structure–activity studies that provided new lead compounds for other diseases. Many sulfonamides are still in use. More than a dozen antibiotics are listed in the U.S. Pharmacopeia, some of them shown below, with varying substituents on the sulfonamide nitrogen.
Another common drug based on sulfonamide chemistry is hydrochlorothiazide, which is sometimes abbreviated HCT or HCTZ. Hydrochlorothiazide is a diuretic that inhibits the kidney’s ability to retain water. This reduces sodium levels and hydrochlorothiazide is used for hypertension and other treatment such as the prevention of kidney stones. Hydrochlorothiazide is used in combination with various angiotension II antagonists in brand name drugs such as DIOVAN HCT (Novartis Pharmaceuticals Corporation), HYZAAR (Merck & Co. Inc.), BENICAR HCT (Daiichi Sankyo Inc.), AVALIDE (Bristol Myers Squibb Sanofi-Synthelabo Partnership) and MICARDIS HCT (Boehringer Ingelheim Pharmaceuticals, Inc.). Hydrochlorothiazide is one of several sulfonamide nonantibiotic drugs. Other examples are dorzolamide and brinzolamide which are used for the treatment of glaucoma.

A study on allergic reactions to sulfa-based drugs lists 38 sulfonamide nonantibiotic drugs. Based on the rich history of heterocycles in medicine, it is not surprising that sulfonamides dominate to this day.

1.2.3. Pyridines

The pyridine ring is found in many current pharmaceuticals. It is present in some proton pump inhibitors used for reducing the amount of acid produced by the stomach. These drugs can be used to treat reflux disease, ulcers or heartburn. Omeprazole, lansoprazole, pantoprazole and rabeprazole are some of the examples.
Two thiazolidinedione compounds that contain the pyridine ring and are used for diabetes are pioglitazone and rosiglitazone.

Pfizer Inc. and Medivation Inc. are co-developing dimebon, which contains both a pyridine ring and an indole ring. Dimebon is in Phase III clinical trials for Alzheimer’s disease.\textsuperscript{52}
1.2.4. Indoles

Serotonin, which is an indole, occurs naturally in the body. In most cases of migraines and serotonin levels decrease. Many migraine medications are based on the indole structure.

The indol-2-one is also present in ropinirole, which is a dopamine agonist used for Parkinson’s disease.

1.2.5. Quinoline

One class of drugs containing the quinoline ring is the quinolone antibiotics, especially the fluoro quinolone antibiotics. The first quinolone antibacterial was discovered serendipitously in the early 1960s. Chemists at the Sterling-Winthrop laboratories in Rensselaer, NY, isolated a by-product in their synthesis of chloroquine. The fluoro quinolones are second-generation antibacterials. Ciprofloxacin and moxifloxacin kills sensitive bacteria by stopping the production of essential proteins needed by the bacteria to survive. Moxifloxacin is used in a sterile ophthalmic solution. PF-2545920 is a quinoline-based compound that as of 2008, Pfizer had entered into phase II clinical trials for treatment of schizophrenia.
1.2.6. Azepines

Perhaps the most common drugs based on 7-membered rings are the benzodiazepines. Different benzodiazepines have been used for the treatment of seizures, insomnia, depression and anxiety.

Olanzapine is a psychotropic agent that belongs to the thienobenzodiazepine class. Olanzapine (ZYPREXA; Eli Lilly and Company) is approved by the U.S. Food and Drug Administration (FDA) for treating the symptoms of schizophrenia and acute mixed, manic episodes and maintenance treatment of bipolar disorder. Quetiapine a dibenzothiazepine is a mood-stabilizing medication approved by the FDA to treat both the highs and lows of bipolar disorder. Oxcarbazepine (TRILEPTAL, Novartis Pharmaceuticals Corporation) is used for the treatment of partial seizures in people with epilepsy. Varenicline (used as the tartrate salt as CHANTIX, Pfizer Inc.) is a smoking cessation drug containing a benzazepine ring structure. Azelastine (hydrochloride salt is
ASTELIN, Meda Pharmaceuticals Inc.) is an antihistamine that is used as a nasal spray and provides relief for seasonal allergies.

1.2.7. Pyrimidines

Nucleic acid bases cytosine, thymine and uracil contain a pyrimidine ring while adenine and guanine have purine ring. Because the five nucleic acid bases contain the pyrimidine/purine ring, perhaps it is surprising that pyrimidines are prominent in the pharmaceutically active ingredients used in a variety of therapies including antipsychotic, cholesterol reduction, cancer, erectile dysfunction, antivirals and human immunodeficiency virus (HIV).

1.2.8. Imidazole

The substituted imidazole derivatives are valuable in treatment of many systemic fungal infections. Imidazoles belong to the class of azole antifungals, which includes ketoconazole, miconazole, voriconazole and fluconazole.⁵⁶
1.2.9. Quinazoline containing drugs:

Prazosin is chemically 2-[4-(2-furoyl)piperazin-1-yl]-6,7-dimethoxy quinazoline-4-amine. It is a sympatholytic drug used to treat high blood pressure. It belongs to the class of α-adrenergic blockers, which lower blood pressure by relaxing blood vessels. Specifically, prazosin is selective for the α-1 receptors on vascular smooth muscle. These receptors are responsible for the vasoconstrictive action of norepinephrine, which would normally raise blood pressure. By blocking these receptors, prazosin reduces blood pressure. It is also known as minipress, vasoflex, pressin and hypovase.

Gefitinib also known as Iressa marketed by Astra Zeneca and Teva is a drug used in the treatment of certain types of cancer. Gefitinib is an EGFR inhibitor (epidermal growth factor receptor) which interrupts signaling through the epidermal growth factor receptor in target cells. Gefitinib has yet to be proven to be effective in other cancers, there is potential for its use in the treatment of other cancers where EGFR over expression is involved. Applications to expand its label as a first line treatment in patients harbouring EGFR mutations is currently in process based on the latest scientific evidence. Chemically it is N-(3-chloro-4-fluoro-phenyl)-7- methoxy-6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine.
The trade name of Erlotinib is Tarceva and its chemically known as N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine.\(^5^9\) It is a drug used to treat non-small cell lung cancer, pancreatic cancer and several other types of cancers. It is a tyrosine kinase inhibitor, which acts on the epidermal growth factor receptor (EGFR). Erlotinib is an EGFR inhibitor. The drug follows Iressa gefitinib which was the first drug of this type. Erlotinib specifically targets the epidermal growth factor receptor (EGFR) tyrosine kinase, which is highly expressed and occasionally mutated in various forms of cancer. It binds in a reversible fashion to the adenosine triphosphate (ATP) binding site of the receptor. It is an inhibitor of epidermal growth factor receptor tyrosine kinase.

The trade name of alfuzosin are uroXatral, urion, xatral, alfetim, chemically known as N- [3-[(4-amino-6,7-dimethoxy-quinazolin-2-yl)-methyl-amino]propyl] tetrahydrofuran-2-carboxamide.\(^6^0\) It is a $\alpha$-1 receptor antagonist used to treat benign prostatic hyperplasia (BPH). It works by relaxing the muscles in the prostate and bladder neck, making it easier to urinate. Alfuzosin has to be used with caution in patients with severe renal insufficiency, and should not be prescribed to patients with a known history of QT prolongation who are on medications known to prolong the QT interval.

Nolatrexed has chemical name 2-Amino-6-methyl-5-(4-pyridylthio)-1H-quinazolin-4-one.\(^6^1\) Nolatrexed is a thymidylate synthase inhibitor. Its brand name is Hydromox chemically known as 7-chloro-2-ethyl-4-oxo-1,2,3,4-tetrahydro quinazoline-6-sulfonamide.\(^6^2\) Quinathazone is a thiazide diuretic used to treat hypertension. Common side effects include dizziness, dry mouth, nausea and low potassium levels.
1.2.10. Benzoxazole and benzothiazole

Flunoxaprofen, also known as priaxim, is a chiral non-steroidal anti-inflammatory drug. Riluzole is a drug used to treat amyotrophic lateral sclerosis.

1.2.11. Oxadiazole

Raltegravir is antiretroviral drug used to treat HIV infection. Butalamine is a vasodilator, Fasiplon is a nonbenzodiazepine anxiolytic drug from the imidazo pyrimidine family of drugs. "2-(oxadiazolyl)- and 2-(thiazolyl)imidazo[1,2-a] pyrimidines as agonists and inverse agonists at benzodiazepine receptors."

The heterocyclic nucleus is one of the most important integral features of a variety of natural products and medicinal agents. Heterocyclic nucleus is present as a core structural component in an array of drug categories such as antimicrobial, anti-inflammatory, analgesic, antiepileptic, antiviral, antineoplastic, antihypertensive
antimalarial, local anaesthetic, antianxiety, antidepressant antihistaminic, antioxidant, antitubercular, anti Parkinson's, antidiabetic, antiobesity and immunomodulatory agents, etc.

This chapter reflects the contribution of heterocycles to the development of society from a biological point of view as well as to the understanding of life processes and to the efforts to improve the quality of life. Sulphur, oxygen and nitrogen-containing heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic synthesis. The grounds of this interest were their biological activities and unique structures that led to several applications in different areas of pharmaceutical, agrochemical research and more recently in material sciences. The thesis is an attempt to synthesize new heterocyclic compounds for screening their biological activity and is presented in chapter 2, while an attempt is made to develop simple efficient methods for synthesis of these heterocyclic compounds which is presented in chapter 3, 4 and 5.
1.3. References


42. Lancini, G. C.; Lazari, E. Experentia 1965, 21, 83.
56. Arduengo, A. J. US patent 6,177,575.