CHAPTER – I

INTRODUCTION

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1.1 INTRODUCTION

Pyrimmidines are six membered N bearing heterocycles.They exist in nature throughout in various forms and these are the building blocks of a large number of naturally occurring substances such as liposaccharides, vitamins, antibiotics, DNA, RNA, etc. The commonly used pyrimidine bases are cytosine, thymine or uracil. The source for the name pyrimidine, since past 1884, which was when the name was coined by Pinner by a amalgamation of the word pyridine and amidine. Since these unique investigations, hundreds of pyrimidine-bearing medicines have been detected in biochemistry. The large number of schemes appeared for this scaffold and its connection to important behaviour made it an inspiring field of investigation.

Heterocyclic chemistry is an integral part of the chemical sciences and it constitutes a considerable part of the modern researches. The study of heterocyclic systems is of great interest from both point of views the theoretical and practical. Heterocycles also play an important role in the design and discovery of new pharmacologically active compounds. Nitrogen-containing heteroaromatic and heterocyclic compounds are indispensable structural units for both chemists as well as biochemists.

Heterocyclic compounds consist of cyclic structures, where one or more of the ring atoms are elements other than carbon. The common hetero atoms are nitrogen, oxygen and sulphur. About one third of known organic compounds are heterocycles. They can be divided into alicyclic and aromatic compounds, which possess five or six membered rings. The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It has seen unparalleled progress due to their wide natural occurrence, specific chemical reactivity and widespread utility in the field of therapeutics. It is equally interesting for its theoretical implications, diversity of its synthetic procedures and physiological industrial significance of heterocyclic compounds. Heterocyclic compounds provide convenient building blocks to which biologically active substitutes can be attached. The interesting biological activities of heterocycles have stimulated considerable research work in recent years including their synthetic utility. Most of the natural products obtained from plants and animal origin contain heterocyclic compounds such as alkaloids-nitrogenous bases and glycosides. They have been used since old age as remedial agents. Reserpine alkaloid from Indian

Rauwolfia, febrifuge from ancient Chinese drug changshan, curare alkaloid from arrow poison, codeine, Ψ-tropine and strychnine are all some well-known examples of heterocyclic compounds.

Acharya et al.[1] showed that structures containing benzimidazole are well-known to have a wide range of biological properties. They have commercial applications in various realms of therapy, including anti ulcerative, antihypertensive, antiviral, antifungal, anti-tumour and antihistaminic agents in veterinary medicine.

Somasundaram et al.[2] reported that compounds with imidazole ring systems have many pharmaceutical activities and play important roles in biochemical processes.

Upadhyay et al.[3] indicated that a number of methods are available for synthesis of these compounds. A traditional method for synthesis of benzimidazoles is the reaction between *o*-phenylenediamine and carboxylic acid under harsh dehydrating reaction conditions, for example, in the presence of HCl, PPA (polyphosphoricacid), H_3BO_3, or *p*-toluenesulfonic acid.

Chidella et al.[4] reported that the benzoxazole derivatives are well-known kind of heterocycles that have considerable importance in the field of materials chemistry, in particular due to their fluorescence properties. These electronic states and behaviour are mainly attributed to the planarity and rigidity of the delocalized electronic system. These types of compounds can find a number of different applications such as electronic devices, sensors for metals, as well as photoluminescent dyes.

Zhang et al.[5] indicated that Heterocyclic quinines containing nitrogen atom are known to possess antibacterial, antifungal and cytotoxic activities. The clinical significance of this class of compounds has stimulated the synthesis of new lead compounds retaining the 'core' quinone chromophore. Quinoxaline derivatives are nitrogen containing heterocyclic compounds and their importance has been reported in the literature. They possess well known biological activities including anti-viral. anti-inflammatory, antiprotozoal, anthelmintic, anticancer.

Alyaninezhad et al.[6] reported that quinoxaline derivatives constitute the basis of many insecticides, fungicides and herbicides, as well as it is important as receptor antagonists. Although rarely described in nature, synthetic quinoxaline moiety is a part of number of antibiotics such as echinomycin levomycin and actinomycin which are

known to inhibit the growth of gram-positive bacteria and also active against various transplantable tumours.

Shan et al.[7] predicted that nitrogen containing heterocycles have always played a major role in the pharmaceutical and agrochemical industries because of their often-potent physiological properties, which have resulted in numerous applications.

Ubale et al.[8] showed that quinazolines and condensed quinazolines are reported to possess interesting pharmacological activities such as antihypertensive, antihistaminic, analgesic and anti-inflammatory, anticancer, and anti-HIV activities.

Sanad et al.[9] reported that quinazolinone possess benzimidazole and triazole unit which are important structural motif in medicinal chemistry and these can be found in a number of biologically active molecules.

Pereira et al.[10] showed preparation and degradation of pyrimidines resulted in ring opening or closing. These reactions are known amidohydrolases and they are fraction of a super family bearing a varied set of enzymes that catalyse mainly hydrolysis procedure and few isomerizations. They have several moieties as nucleic acid, amino acids and ester of organophosphate of recognizable amidohydrolases. This member of biocatalyst has a mono or binuclear metal. At the time of synthesis of the amidohydrolase, dehydratase catalyses the ring formation of carbamoyl-L-aspartate. Organisms that utilizes the reduction way for pyrimidine dilapidation uses dihydopyrimidases to open pyrimidine nucleus while organisms that utilize the oxidative pathway use barbiturates.

El-Messery et al.[11] observed that all enzymes share a seemingly common mechanism, using a metal hydroxide as an acid/base. These reactions are generally reversible. One of the best studied enzymes is dihydroorotase from *Escherichia coli*. Recently a less studied pyrimidine utilizing-amidohydrolase is barbiturate.

Poojari et al.[12] prepared that enzyme carries out a function similar to that of the dihydropyrimidases. Preliminary biochemical studies of this enzyme show that the enzyme carried out the conversion of barbiturate to uredo malonic acid, a necessary step in the oxidative catabolism of pyrimidines. This enzyme show that it has relatively low homology to the dihydropyrimidases and dihydroorotases. Barbiturate has been shown to be a tetramer with 4.4 mols of zinc per enzyme, likely a mononuclear zinc amino

hydrolase. This property indicates a slight difference between the mechanism of this amidohydrolase and those of dihydroorotates and dihydropyrimidases, both of which use a binuclear metal centre. Lower metal content for dihydropyrimidase led early researchers to also conclude that it was a mononuclear zinc enzyme. This phenomenon is due to fact that pH playing an important part in the metal binding to amidohydrolases. Both dihydroorotases and dihydropyrimidases require a post-translational carboxylation of an active site lysine to function properly and bind the second metal effectively. This modification and the increase in metal affinity are highly dependent upon pH. Further structural studies or pH-dependent metal titrations of this enzyme provide better insight as to whether this new amidohydrolase family does indeed use a different mechanism than was found for the dihydroorotases and dihydropyrimidase. The ring opening of pyrimidines is also seen in nature without the aid of enzymes. At high temperatures, pyrimidine dihydrouridine, found in modified t-RNA, has been shown to undergo ring opening through hydrolysis. This reaction is accelerated by both heat as well as basic pH, dihydrouracil is thought to be absent in the RNA of thermophiles.

Procedure of drug plan is at length driven by the nature and knowledge of pharmaceutical research scientists. It is often informative to attempt to “imprison” these experiences by analysing the past record in victorious drug design projects of the past. From this analysis, the inferences are haggard which play significant role in shaping our present and future projects. Towards this region, one would like to analyse the structures of a large number of drugs as final product of a victorious drug design attempt. Our objective for this is to begin to deco volute this information in order to be relevant it to design of novel drugs. Nitrogen containing heterocyclic ring such as pyrimidine is a promising structural moiety for drug design. Pyrimidine derivative form a component in different practical drugs and are associated with many biological activities. Pyrimidines have an extended and distinguished history extending from the days of their discovery as significant constituents of more than a few biological molecules such as nucleic acids, cofactors, a variety of toxins, to their present use in the chemotherapy of AIDS. These compounds provide huge assurance for the treatment of retro virus infections in humans.

Chavan et al.[13] showed that first study into the synthesis of pyrimidine nucleus appeared more than a hundred years ago and then more than a few methods for the synthesis of dihydropyridine were reported and their physicochemical properties has been studied.

Ighodaro et al.[14] reported that alloxan is known for its diabetogenic action in a number of animals. Uracil, thymine and cytosine are the three important constituents of nucleic acids. Mahdavi et al.[15] observed that diseases of the arterial tree cause more premature deaths than all other diseases such as cancer. Among the major risk factors for arterial diseases, high blood pressure is the most important one.

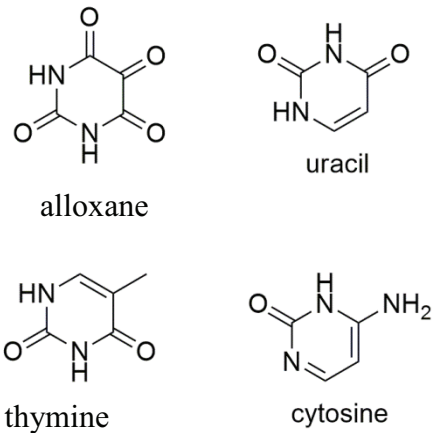

Fig. 1.1: Examples of nucleic acids

The pyrimidine ring is found in vitamins like riboflavin and folic acid.

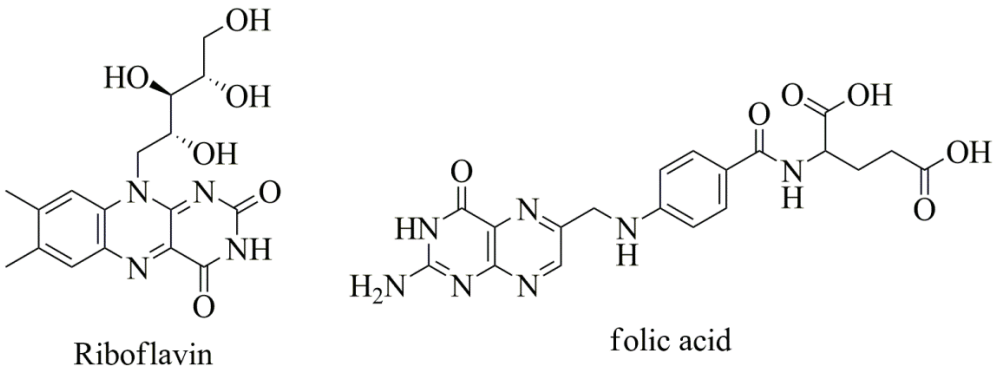

Fig. 1.2: Examples of Vitamines

You et al.[16] reported that sulfadimethoxine was introduced with a half-life of approximately 40 h. The sulfamethoxydiazine also possess good half-life. A new broad-spectrum sulfonamide, sulfamethomidine is comparatively non-toxic and patients do not need extra fluid intake or alkalization. Sulfacytine has been reported to be 3–10 times more potent than sulfaisoxazole and sulfisodimidine**.**

Aggarwal et al.[17] have synthesized 2,7-diamino-3-phenylazo-6-phenylpyrazolo [1,5-a] pyrimidine (PPD) as a new hetero-cyclic ligand, act as a selective Hg^{2+} ion chemosensor.

Finger et al.[18] reported that Pyrimidine represent the valuable scaffold in the discovery of antitubercular agents.

Tabarsaei et al.[19] reported for the synthesis of $Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs as a new heterogeneous organometallic catalyst. XRD, FESEM, EDX and TEM analysis were used for confirming the structure of synthesized nanocatalyst.

Rejinthala et al.[20], a series of new pyrimidine-piperazine hybrid molecules were designed and synthesized as possible antimicrobial agents. The synthesized compounds were characterized using ^{1}H NMR, ^{13}C NMR, MS and elemental analysis and then the activity of the new compounds were compared with that of antibiotics.

Ibrahim et al.[21] showed suitable approach to construct a new annulated systems namely chromeno [3′,2′:5,6] pyrido [2,3-*d*] pyrido [2′,3′:4,5] [1,3] thiazolo [3,2-*a*] pyrimidines.

Badigar et al.[22] described one-pot synthesis of pyrano [2,3-*d*] pyrimidine derivatives using aromatic aldehyde, ethyl cyanoacetate and barbituric or thiobarbituric acid accelerated by microwave irradiation in the presence of agro-waste extract solvent medium with few drops of ethanol as a co-solvent presented. The reaction was optimized by various methods such as magnetic stirring, ultrasound, mechanochemical and microwave irradiation, but the microwave irradiation method excelled product formation faster rate with high yield and purity. The advantages of the present approach are the metal-free, chemical-less, and hazardous solvent-less employed and considered as an eco-friendly protocol for the synthesis of pyrano [2,3-*d*] pyrimidine derivatives developed.

Adel and Abouzid.[23] sought to develop more potent pyrrolopyrimidine surrogates through introduction of fluorine atom at the phenyl moiety near to the urea moiety mimicking regorafenib. They hypothesized that this would improve the compounds potency. Surprisingly, Compound 9e possessed better VEGFR2 inhibitory activity (IC50 = 52.4 nM) compared to standard drug sorafenib, whereas compounds (9b,d and f) showed moderate inhibitory activity. The newly synthesized compounds were tested on 60 human cancer cell lines.

Zarenezhad et al.[24] showed that heterocyclic derivatives as a major group of organic compounds are enormously used for a wide range of pharmaceutical and

industrial applications. They are known for their biological and pharmacological properties including anti-inflammatory, antimicrobial, anticancer, antitumor, and anti-viral activities. The pyrimidine and pyrimidine containing ring have attracted much attention as they are available in the substructures of therapeutic imperative products. The potential therapeutic properties of these heterocycles have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents.

Bansal et al.[25] reported that Fusion of pyrimidine with different heterocyclics yields a variety of pyrimidine-based scaffolds, which represent a class of privileged structures in chemistry due to their presence in various bioactive agents. Fused-pyrimidine scaffolds are used as templates to develop a diversity of compounds having applications as antiviral, anti-tumor, anti-allergic, antihypertensive, anticancer, antioxidant and hepatoprotective agents.

Ansari and Joshi.[26] summarized the progress of eight-membered heterocycles fused with a pyrimidine ring and their biological properties. Among this fusion class, pyrimidine-fused eight-membered hetero-aromatic ring fused pyrimidines derivatives have not been sufficiently investigated. Despite bioactivity being reported in a handful of studies so far, it has not been explored much. The major reason highlighted for this gap again includes entropic factors, along with transannular interactions and unsatisfactory synthetic procedures. So, it becomes very important to disclose the biological and medicinal properties of eight-membered fused-pyrimidine heterocycles.

1.2 HETEROCYCLIC COMPOUNDS

Heterocyclic compounds are the largest and most diverse group of organic chemicals. After all, any carbocyclic compound, regardless of structure or usefulness, can theoretically be transformed into a collection of heterocyclic analogues by substituting a different element for one or more of the carbon atoms in the ring. Even if we limit ourselves to the most frequent heterocyclic constituents of oxygen, nitrogen, and sulphur, the permutations and combinations of such a replacement are vast. Heterocyclic compounds can be used in a variety of ways. They are the most common sorts of compounds used as medications, agrochemicals, veterinary products, antioxidants, corrosion inhibitors, and other forms of additives. Heterocyclic structures can be found in a variety of dyes and pigments.

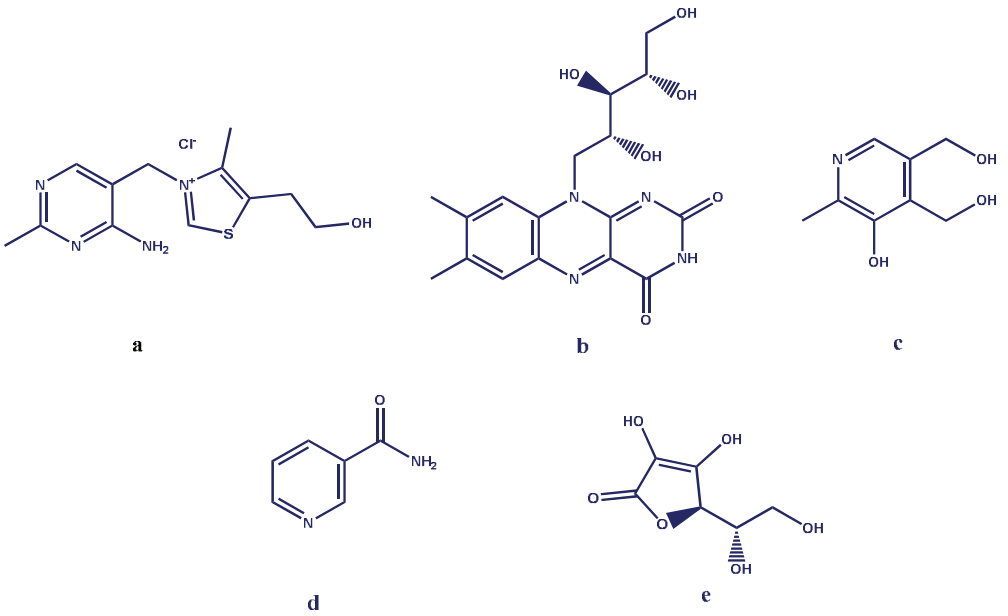

Fig. 1.3: Heterocyclic Compounds

Most biologically active chemicals are heterocyclic organic molecules, which have a ring structure that includes some other atoms than carbon, such as sulphur, oxygen, or nitrogen. Many synthetic heterocyclic compounds have major practical applications, such as dyestuffs, copolymers, solvents, photographic sensitizers, developers, antioxidants, vulcanization accelerators in the rubber sector, and many are useful synthesis intermediates. There are also many pharmacologically active heterocyclic compounds, which are used in clinical practice on a regular basis.

Some heterocyclic compounds, such as pyridines and imidazole have long been employed as metal ligands, but their structure is increasingly being tuned to a specific orientation. Heterocyclic compounds, for example, are now commonly utilised as chiral ligands for transition metals, and the resultant complexes serve as catalysts in a range of asymmetric synthetic reactions. Heterocyclic compounds can be found in abundance in nature. These are important parts of biological processes. Nucleic acid bases, for example, are derivatives of the pyrimidine and purine ring systems and are fundamental to the replication mechanism. The components required for photosynthesis and oxygen transport in higher plants and animals, respectively, are chlorophyll and haeme, both of which are derivatives of the porphyrin ring system. Heterocyclic compounds include thiamine (vitamin B_1), riboflavin (vitamin B_2), pyridoxol (vitamin B_6), nicotinamide (vitamin B_3), and ascorbic acid (vitamin C), which are all found in essential dietary elements.

Over the last few years, medicinal chemistry has introduced various novel strategies to speed up the drug development process, including combinatorial chemistry, microwave-assisted organic synthesis, and high throughput purification. Triazoles, thiazoles, oxadiazoles, pyrimidines, and isoxazoles are nitrogen and sulfur-containing heterocyclic molecules with essential biological activity. As a result, in recent years, the development of novel compounds containing these moieties and known pharmacological characteristics has gained traction. Piperazine has been classed as a favored structure since its nucleus can bind many receptors with high affinity. Some examples of heterocyclic compounds are :

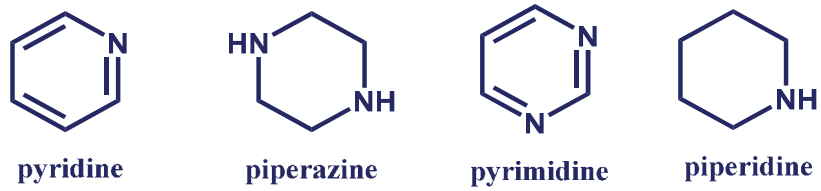

Fig. 1.4: Drug Development Process

Heterocyclic chemistry is a major branch of organic chemistry that accounts for roughly one-third of all recent publications. Heterocyclic compounds make up two-thirds of all organic substances. The carbocyclic compound is a cyclic organic compound with all carbon atoms arranged in a ring configuration. A heterocyclic compound is one in which at least one atom other than carbon is present in the ring structure. Heterocyclic compounds play a vital function in medicinal chemistry, and they are attracting a lot of attention due to their vast scope for synthesizing and processing a wide range of pharmacological activities. Apart from their widespread presence in natural goods, heterocyclic compounds are also important components of biological molecules such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Indeed, DNA is the most significant macromolecule in life, and the monomer of RNA and DNA, i.e. nucleotides. The building blocks of our genes are purine and pyrimidine bases derivatives. Chlorophyll, a green pigment that aids in the creation of oxygen by absorbing carbon dioxide in plants, and heme, the non-protein portion of hemoglobin, which is derived from giant porphyrin rings, is the oxygen carrier in animals. On the other hand, synthetic heterocyclic compounds have a wide range of therapeutic applications, including antibacterial, antifungal, analgesic, anti-inflammatory, antimycobacterial, antitubercular, antimalarial, trypanocidal, anti-HIV activity, anticonvulsant, anti-tumoral,

antileishmanial agents, genotoxic etc. They have also been found in a variety of synthetic medications and agro-based chemicals as a significant structural ingredient. Most heterocyclic compounds have essential material science applications, such as fluorescent sensors & dyes, brightening agents, polymers, information storage, and analytical reagents. Many heterocyclic compounds can also be employed in the production of organic conductors, semiconductors, photovoltaic cells, molecular wires, organic light-emitting diodes (LED), light-harvesting systems, optical data carriers, chemically programmable switches, and liquid crystalline compounds. The synthetic value of heterocyclic compounds as synthetic intermediates, chiral auxiliaries, protecting groups, and metal ligands in asymmetric catalysts in organic synthesis is also of great interest. Because of the huge applicability throughout the range of utility, more emphasis has been placed on developing efficient novel methods for synthesizing heterocyclic molecules.

1.3 OXYGEN-BASED HETEROCYCLES

They serve a variety of modulatory and cytoprotective purposes as polyphenolic compounds, which are primarily found in plants. As such, they offer a potential route for the development of novel compounds with a desirable combination of anticancer properties and superior pharmaceutical characteristics for clinical use.

Because they can be used in a wide range of processes, such as the creation of cosmetics, pharmaceuticals, and fragrances, coumarin compounds and their derivatives are crucial in organic chemistry. The benzopyrone family, which includes substances with a benzene ring linked to a pyrone ring, includes coumarin. Manufacturers of pharmaceuticals, cosmetics, and fragrances are just a few industries that employ them. Optical brightening agents, distributed fluorescent dyes, and laser dyes are examples of special applications. The heterocyclic moiety of coumarin (2-oxo-2H-1-benzopyran) is widely regarded as a "privileged" structural motif in a number of natural products and synthetic chemical compounds having pharmacological activity. Insecticides, scents and perfumes, agrochemicals, and food & cosmetic additives all use coumarin derivatives. Optical examples of unique applications include optical brightening agents, distributed fluorescent dyes, fluorescence sensors and laser dyes. Widely regarded as a "privileged" structural motif in many natural products and synthetic chemical compounds with pharmacological activity is the heterocyclic moiety of coumarin (2-oxo-2H-1-

benzopyran). Such molecules include, but are not limited to, fluorescent transthyretin folding sensors, optical brighteners, fluorescent sensors, and molecular photonic devices.

Flavanones, a naturally occurring substance has a wide range of biological properties including potent anticancer activity against human colon, breast, and kidney adenocarcinoma as well as analgesic, antioxidant, and antibacterial properties and minimal toxicity. Surprisingly, the furan rings (oxygen-based rings) derivatives outperformed all other derivatives in terms of anticancer activity across all cell lines. Despite the fact that the exact mechanism of action of this particular derivative is still unknown, furfuraldehyde, a heterocycle flavanone derivative with a furan ring, demonstrated preclinical evidence of being a moderately effective anticancer drug. Like coumarins, flavones could serve as a long-term building block for new and improved anticancer medications.

Similar to coumarins, benzofurans are oxygen-based heterocycle type that can be found in nature and have a variety of biological activities. Recent studies have demonstrated that compounds based on benzofuran are cytotoxic to cancer cell lines.

One with a ring structure that contains both; oxygen and nitrogen is another intriguing heterocycle. The 23 different mefloquine-oxazolidine derivatives, which are cyclic molecules with oxygen and nitrogen, have antiproliferative effects. To better understand the potential therapeutic impact of oxazolidine rings as building blocks for the development of cancer therapies, a number of oxazolidine derivatives have been developed. Surprisingly, it was discovered that substituent groups at the 3 or 4 positions are essential for action, whereas ortho-substituted compounds were ineffective at killing cancer cells. The S isomer exhibited the highest activity, frequently ten times that of the enantiomers.

Additionally, studies focus on the anticancer properties of oxazolidine compounds, suggesting that this class of oxygen-based and nitrogen-based heterocycles is a new area of study. These findings demonstrate that the toxicities of many of the oxygen-based heterocycles are currently being investigated in preclinical trials which differ significantly depending on the type of oxygen-based heterocycle, its general structure, ligands, ring size, and aromaticity. Despite this, it is still not clear exactly, how many of these novel heterocycle drugs and scaffolds are effective in treatment of various diseases.

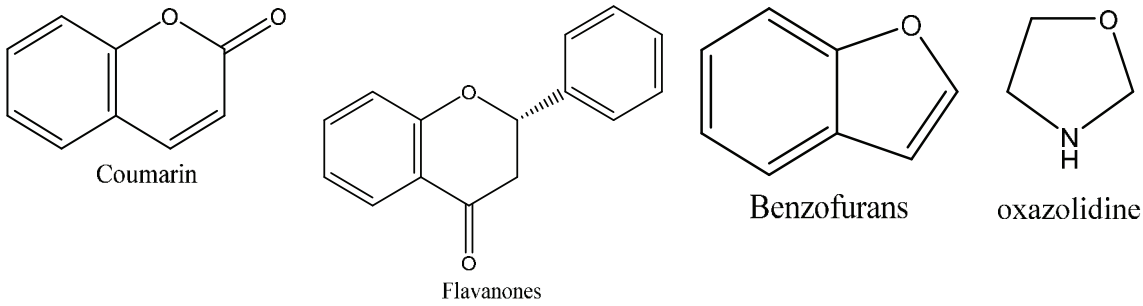

Fig. 1.5: Oxygen Based Heterocycles

1.4 NITROGEN-BASED HETEROCYCLES

In medicinal chemistry, analogues of nitrogen-based heterocycles occupy a special position as a valuable source of pharmaceuticals. More than 75% of drugs that have been FDA-approved and are currently on the market contain heterocyclic moieties with nitrogen as heteroatom. New pharmaceuticals with nitrogen as an active ingredient are likely to make up a much larger portion of the market in the following decades. There have been numerous new nitrogen-based heterocycles synthesized. There are increasingly more novel N-heterocyclic molecules with important physiological traits and potential medicinal chemistry uses. Use of nitrogen-based moieties in drug design and the creation of a number of effective and capable candidates against a variety of diseases have been discussed[27].

The most prevalent pharmacophore system among nitrogen-based compounds is the 1,2,3-triazole moiety, and it is essential for the creation of new biological targets[28]. These three nitrogen heteroatoms can be used to easily assemble these five-membered heterocyclic motives, thanks to "click" chemistry. These substances can interact with a range of biological targets through hydrogen bonding, noncovalent and van der Waals interactions, as well as dipole-dipole bonding interactions[29-32]. Triazoles are weakly acidic and basic, making them more vulnerable to reducing agents. Additionally, the 1,2,3-triazole-based compound carboxyamidotriazole has been successfully used in clinical studies to treat cancer[33]. The triazole unit's strong dipole properties have also increased its value in medicinal chemistry because they allow for highly specific binding to biological targets[34].

One of the most adaptable and frequently used nitrogen-based heterocyclic similar fragments in the preparation of drugs for typical clinical disorders are indoles and

their derivatives[35]. There has been an emphasis on the synthesis of indole derivatives recently because there are practically endless possibilities for architectural design of polycyclic structures by incorporating multiple fused heterocyclic scaffolds in an effort to achieve promising new heterocycles with chemical and biomedical relevance. Due to physicochemical characteristics like hydrogen bond donor-acceptor capability, stacking interactions, coordination bonds with metals as a ligand, van der Waals forces, polarisation, and hydrophobic forces, these fragments are gaining more and more attention. Derivatives can readily bind to a variety of biomolecules, including enzymes and nucleic acids, due to the properties that cause their reactivity[36-39].

Pyrimidines and pyrimidinones have drawn a lot of attention in organic synthesis due to the variety of biological activities[40]. The pyrimidine nucleus is a six-membered 1,3-diazine ring with a ketone unit. Natural products and nucleic acids, among other biologically active substances, contain pyrimidine analogues. Additionally, this type of heterocyclic molecule has several therapeutic uses in medicinal chemistry as a crucial building block of a wide range of drug candidates and nucleic acids due to its structural resemblance to purines. pyrimidine and pyrimidinone derivative-based anticancer medications (ibrutinib, capecitabine, folinic acid, and monastrol). These pyrimidines and their scaffolds are frequently used in drug development studies because of the wide range of bioactivity they exhibit[41-43].

Piperidine and pyridine complexes are two of the heterocyclic elements that are most frequently present in pharmaceuticals. Several N-(piperidine-4-yl) benzamide derivatives were found to have anticancer properties. The structure N-(1-(2, 6-difluorob-benzyl)-piperidine-4-yl)-4-phenoxybenzamide was discovered to be the most effective against a hepatocarcinoma cell line. Other major nitrogen-based scaffolds, their diversity in structure, patterns of substitution, and significance as essential elements are piperidines, pyridines, piperazines, cephems, pyrolidines, pyrazoles, purines, pyrimidines, and others[44].

1.5 SULFUR-BASED HETEROCYCLES

Thiirane, also referred to as ethylene sulphide, is a three-membered heterocycle that contains sulphur. Heterocycles with three atoms are typically very reactive due to ring tension. It has been proved that thiirane and its derivatives have antibacterial, antimicrobial, and anticancer properties. Among the biological effects of steroidal drugs

with the thiirane moiety are peptidase inhibitors, carboxypeptidase A inhibitors, aromatase inhibitors, and metalloproteinase inhibitors. Examples of compounds containing thiirane include natural hydrocarbons, cyclic and acyclic alcohols, natural or semi-synthetic steroids, peptides, and polyethers. Thiirane can be used to synthesise a variety of polymers, drugs, insecticides, herbicides, liquid crystals, and adhesives, according to various publications in the literature.

One sulphate and three carbon atoms make up the four-membered ring saturated chemical known as thietane. Thietane received less attention from researchers than other S and O heterocycles because of ring strain. On the other hand, it has been claimed that oxidized thietane compounds have anticoccidial, anticancer, antidepressant, insecticide, and herbicidal properties. Thietanes have been demonstrated to take part in ring expansion to produce five to seven membered, sulfur-containing heterocyclic compounds using lithium diisopropylamide (LDA) as a catalyst. In addition, they undergo insertions, intramolecular cyclization, ring opening, and isomerization.

Thiophene is a sulfated, five-membered aromatic heterocycle that is present in a variety of natural products, biologically active chemicals, and potential medications. In the field of material sciences, such as the creation of polymer semiconductors and the light-emitting diode, these are also used as building blocks. Thiophenes are colourless liquids with a boiling point that is similar to that of benzene. They also produce an azeotrope when combined with ethanol, just like benzene does. The ability of thiophene and its derivatives, such as benzothiophene and dibenzothiophene to form coordination bonds with metals via sulphur increases with the number of electron-donating substituents in the thiophene. Thiophene and its derivatives have a variety of pharmacological properties, including antibacterial, photoactivated insecticidal, anticancer, anti-inflammatory, anti-leishmanial, antimicrotubule, antioxidant, anti-HIV, and antifungal.

Sulphur heteroatoms replace the ring carbon atom in homocyclic hydrocarbons. There are significant changes in the cyclic molecular structure caused by different electron configurations, unshared pairs of electrons, and ultimately, the electronegativity between heteroatoms and carbon. These changes are give homocyclic hydrocarbons their significance. The physicochemical characteristics and reactivity of heterocycles containing sulphur are strongly influenced by the overall electron configuration as well

as the adaptable chemistry of the sulphur atom itself. The main protein building blocks cysteine and methionine hold sulphur as a key for the overall tertiary structure. Sulfur is a determinant in many biological processes and is known to form metal complexes with metal ions. Other regulatory roles in biological systems include playing significant roles in regulating translation through sulfuration of transfer RNA, as well as being an essential component in many vitamin cofactors, sugars, and nucleic acids.

It is obvious why sulfur-based heterocycle medications should be given importance in biological systems and how well-liked, it is as a regulatory agent. Due to their biological reactivity, thiadiazole and thiazole complexes are also important in the context of sulfur-based heterocycles. The development of medications to treat a wide range of diseases, including cancer, allergies, infectious diseases, neurological disorders, chronic pain, and fungus-related issues, among others, has led to the discovery of these chemicals. Recently, several novel thiazole-based nitrogen mustards significantly inhibit a panel of human cancer cell lines.

Derivatives of benzothiophene acrylonitrile, which resemble natural combretastatins in terms of structure, have also shown promise as scaffolds for the creation of fresh anticancer medications with improved pharmacological profiles.

One of the components of thiopyran, a six-membered heterocyclic compound, has a sulphur heteroatom. Depending on where the double bond is located, the compound thiopyran can be found in two isomeric forms: 2H-thiopyran and 4H-thiopyran. Due to different substitutions on the thiopyran nucleus, this class of S heterocycles has a broad range of pharmacological effects, including antibacterial, anticancer, anti-hyperplasia, anti-inflammatory, anti-viral, anti-bacterial, and anti-glaucoma properties. Additionally, it has been found that the S-oxides and S, S-dioxide thiopyran oxide forms increase the biological activity of the core thiopyran. Thiopyrans have been used in both; synthetic and medicinal chemistry and can be found in a number of natural compounds, including thromoboxanes, serricornin, tetrahydrodicranenone, and cyclopentanoids.

1.6 DIHETEROATOM CONTAINING COMPOUNDS

Heterocyclic compounds based on nitrogen had good properties. Phenazines are a type of heterocylic compound. A wide variety of bacteria produce phenazines, a sizable group of nitrogen-containing heterocyclic compounds. The effects of phenazine derivatives on bacterial interactions and biotechnological procedures are being studied

for both, natural and synthetic forms. Phenazines act as cell signals that control patterns of gene expression, shuttle electrons to different terminal acceptors, alter cellular redox states, support the formation and structure of biofilms, and improve bacterial survival. Phenazines affect eukaryotic hosts and host tissues in a variety of ways, altering a variety of host cellular responses in the process.

Phenazines may also affect plant growth and induce systemic resistance in plants. Phenazines have multiple functions for producing organism and affect behaviour and ecological fitness. The large class of heterocyclic nitrogen-containing compounds known as phenazines has different chemical and physical characteristics depending on the type and location of the functional groups. Over 6,000 compounds with phenazine as a central moiety have been synthesised, and more than 100 different phenazine structural derivatives have been found in nature[44]. The only known source of naturally occurring phenazines is bacteria. However, due to their potential influence on bacterial interactions and biotechnological procedures, natural and synthetic phenazines are of considerable interest. These secondary metabolites are produced by a variety of bacteria, particularly pseudomonads, and have undergone extensive research due to their roles in virulence and broad spectrum antibiotic properties. Physicochemical characteristics of phenazines, such as their oxidation-reduction (redox) properties, bright pigmentation, and capacity to change colour with pH and redox state, are largely responsible for their ongoing biotechnological interest. The use of phenazines is still widespread and includes uses as electron acceptors and donors, building blocks for fuel cells, environmental and biological sensors, and essential parts of antitumor drugs. Phenazines affect cellular redox state, act as electron shuttles that change electron flow patterns, support the formation and architecture of biofilms, act as cell signals that control gene expression patterns, and support producer survival. Phenazines alter a variety of host cellular responses in eukaryotic hosts and host tissues. Phenazines have an impact on plant growth and induce systemic resistance. The observations that bacterial species may produce various and frequently multiple phenazine derivatives, that these derivatives are produced in various proportions, and the question of whether the quantity or proportion of each derivative produced changes during growth or in response to environmental factors are of particular interest in defining their functional impact.

A five-membered aromatic ring called, isothiazole is also called a 1,2-thiazole, containing three carbon atoms, one nitrogen atom, and one sulphur atom. Isothiazoles

interact with other heteroaromatic chemicals exhibiting aromatic properties. Particular focus is placed on isothiazole ring opening and modifications that lead to functionalized alkenes or other heterocyclic compounds. Particularly appealing isothiazole addition processes produce novel bisheterocyclic compounds with an isothiazole fragment. Reactive dioxides, which are of great interest, are also produced, when the sulphate atom of the isothiazole ring is oxidised. The preferred heterocyclic frameworks are isothiazole (1,2-thiazole) and its benzo counterparts, which can be found in a variety of chemicals with various biological profiles.

Antibacterial drug sulfamethyzole and neuroleptics are ziprasidone and perospirone. In the presence of adogen, it is simple to produce the pale greenish solid dithiazole from chloroacetonitrile and sulphur monochloride. An important class of molecules in medicine chemistry are nitrogen-containing heterocycles with sulphur atoms, such as 1,2,3-dithiazole, a five-membered sulfur-nitrogen heterocycle. It is viewed as a potential scaffold for medicinal chemistry because of its biological activity, unexpected chemical changes, and intriguing physical properties. The design and synthesis of stable neutral and negatively charged radicals, can be used as actual or potential building blocks for molecules-based conductive and/or magnetic functional materials, have been successfully accomplished using the 1,2,3-dithiazole scaffold. The intriguing properties of neutral 1,2,3-dithiazoles have been studied against bacteria, fungi, and herbs.

The five-membered ring of thiazolidine, the sulphur counterpart of oxazolidine, has S and N at positions 1 and 3, respectively. Thiazolidine-2,4-diones have anti-tubercular, antibacterial, anti-diabetic, anti-inflammatory, anti-oxidant, anticonvulsant, antifungal, and anticancer properties.

Thiazole is a sulphur and nitrogen-containing five-membered heterocyclic molecule with the chemical formula C_3H_3NS. It is also known as 1, 3-thiazole because nitrogen and sulphur are located in the first and third positions, respectively. Thiazole is a flexible nucleus that is present in many bioactive molecules, including natural chemicals, and has pharmacological effects that include anti-cancer, anti-microbial, anti-inflammatory, anticonvulsant, antiviral, and anti-tubercular. An important class of S heterocycles with a large number of commercially available drugs are thiazoles. New

biologically active compounds have been developed by combining the thiazole moiety with various heterocyclic rings.

The seven-membered heterocyclic ring structure is thiazepine, which contains nitrogen and sulphur atoms. Depending on where the nitrogen and sulphur atoms are located in the ring, these are either 1,3-thiazepine or 1,4-thiazepine. Thiazepines come in two reduced forms: Thiazapanes, which are completely reduced, and dihydrothiazepines, tetrahydrothiazepines, which are only partially reduced. The 1,4-thiazepine isomer is the more significant one, because it has structural characteristics that make it possible to design and synthesise new bioactive compounds with significant pharmacological activity. Additionally, the benzo- and dibenzo-fused derivatives of these compounds are an important class of scaffolds for numerous drugs and medications.

S-Heterocycles are more in demand in the pharmaceutical industry due to their greater therapeutic potential. In addition, the accessibility of S-heterocycles has increased as a result of recent advancements in their synthesis feasibility. They are a well-known group of heterocyclic chemicals that have a variety of biological effects, such as antiviral, anticancer, antidiabetic, antibacterial, antifungal, anti-inflammatory, and antiviral properties. There is still a need to research new S heterocycles to address various failures and obstacles, such as the increased risk of toxicity via S-heterocycles containing pharmaceuticals, against various pathogenic targets, despite many advancements and diverse techniques in the field of sulphur chemistry. Sulfur-containing pharmaceutically active molecules have been synthesized using more environmentally friendly techniques. Molecules based on S-heterocycles, can serve as a guiding reservoir for researchers in almost every pathological condition, aiding them in the creation of new drugs.

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