CHAPTER - 1

INTRODUCTION

AN OVERVIEW OF HETEROCYCLIC COMPOUNDS AND THEIR BIOLOGICAL SIGNIFICANCE
1.0. INTRODUCTION

1.1. OVERVIEW ON HETEROCYCLIC COMPOUNDS

Two hundred years ago, the chemical science was an undivided field; around 1900 a division into inorganic, organic and physical chemistry became necessary. The increase of factual material enforced a progressive segmentation into sub disciplines. A map shows countries and regions neatly separated; similarly, the uninformed observer may regard chemistry as a side-by-side of numerous disciplines and specialties. The comparison is fallacious, however, because broad overlap is thwarting clear divisions. Chemistry has a lot of fascinating facts, one such is hitherto cyclic compounds. Every first step of life starts with hetero-cyclic compounds.\(^1\)\(^-\)\(^3\) Heterocycles form by far the largest of classical divisions of organic chemistry and are of immense importance biologically and industrially. About one half of over six million compounds recorded in chemical abstracts are heterocyclic.\(^4\)\(^,\)\(^5\) Heterocyclic chemistry is one of the most complex and intriguing branch of organic chemistry and heterocyclic compounds constitute the largest and most varied family of organic compounds. Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance that impinge on almost all aspects of modern organic chemistry, medicinal chemistry and biochemistry.\(^6\) Heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly and economically useful as therapeutic agents.\(^7\)\(^,\)\(^8\) 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 heterocyclic in nature.\(^9\)\(^-\)\(^11\) One striking structural feature inherent to heterocycles, which continue to be exploited to great advantage by the drug industry, lies in their ability to manifest substituents around a core scaffold in defined three dimensional representations.\(^12\)\(^,\)\(^13\) For more than a century,
heterocycles have constituted one the largest areas of research in organic chemistry. They have contributed to the development of society from a biological and industrial point of view as well as to the understanding of life processes and to the efforts 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, sulfur 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 appear.

1.2. IMPORTANCE OF HETEROCYCLIC COMPOUNDS IN LIFE

The nature also prefers to utilize heterocycles during physiological processes occurring in the human body. This is because heterocycles are associated with unique properties to get involved in a wide variety of chemical reactions. Many heterocyclic compounds are biosynthesized by plants and animals and are biologically active. Over millions of years, these organisms have been under intense evolutionary pressure, and their metabolites may be used to advantage; for example, as toxins to ward off predators, or as colouring agents to attract mates or pollinating insects.

Some heterocycles are fundamental to life, such as haem derivatives (1) in blood and the chlorophylls (2) essential for photosynthesis. Similarly, the paired bases found in DNA and RNA are heterocycles (Fig. 1.1), as are the sugars that in combination with phosphates provide the backbones and determine the topology of these nucleic acids. Dyestuffs of plant origin include indigo blue, used to dye jeans. A poison of detective novel fame is strychnine, obtained from the plant resin curare The biological properties of
heterocycles in general make them one of the prime interest of the pharmaceutical and biotechnology industries.\textsuperscript{22-24}

![Chemical structures](image)

**Fig. 1.1**: DNA and RNA
Besides, they play a vital role in the metabolism of all living cells as carbohydrate, proteins and enzyme. In recent years, the marine environment has been recognized as a rich source of novel heterocyclic structures, some of which have valuable biological properties.\textsuperscript{25,26}

The plant kingdom has an abundance of nitrogen compounds, most being heterocyclic, with some of great complexity. Because they are weakly basic and form salts with mineral acids, the compounds from plants became known long ago as alkaloids.\textsuperscript{27} They were among the first natural organic compounds to be isolated and studied and it has been stated that more than 8000 alkaloids are known and that more than 100 are discovered annually in current research, many of which have been structurally characterized. They occur in all parts of plants and they usually have some form of biological activity, which can range from high mammalian toxicity to valuable therapeutic properties of many different kinds.\textsuperscript{28}

![Opium](image.png)

**Fig. 1.2 Opium**

Alkaloid-containing plants have been used by humans since ancient times for therapeutic and recreational purposes. For example, opium (Fig. 1.2) containing drug
which contains approximately 12% morphine (3) is believed to be a gift for bringing oblivion. Extracts from plants containing toxic alkaloids, such as aconitine (4) and tubocurarine (5), were used since antiquity for poisoning arrows.29

![Image 4](image4.png) ![Image 5](image5.png)

A significant contribution to the chemistry of alkaloids in the early years of its development was made by the French researchers, who discovered quinine and dstrychnine. Several other alkaloids were discovered around that time, including xanthine, atropine, caffeine, coinine, nicotine, colchicine, sparteine and cocaine.30

The reason for the utilization of heterocycles by nature is based on the fact that heterocycles are able to get involved in an extraordinarily wide range of reaction types.31,32 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.33 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.34 The presence of different heteroatoms makes tautomerism ubiquitous in the heterocyclic series. Such versatile reactivity is linked to the electronic distributions in heterocyclic molecules.35 Furthermore, the reason for the
widespread use of heterocyclic compounds is that their structures can be subtly manipulated to achieve a required modification in function. The water solubility and the transport of the fungicide through the plants are improved by replacing a benzene ring by the more polar heterocycle. Another important feature of the structure of many heterocyclic compounds is that it is possible to incorporate functional groups either as substituents or as part of the ring system itself. For example, basic nitrogen atoms can be incorporated both as amino substituent and as part of a ring. This means that the structures are particularly versatile as a means of providing, or of mimicking, a functional group.\textsuperscript{36}

\textbf{Fig. 1.3: Natural heterocycles}
Based on the above information, many natural drugs such as codeine, ellipticine, emetine, papaverine, procaine, quinine, sangulnarine and theophylline (Fig. 1.3) were discovered which are also heterocycles. Natural products have pharmacological activity that can be of therapeutic benefit in treating diseases. As such, natural products are the active components of many traditional medicines. In fact, natural products are the inspiration for approximately one half of food and drug administration-approved drugs. Natural products may be extracted from tissues of terrestrial fermentation broths, plants, marine organisms or microorganism. A crude extract from any one of these sources typically contains a novel, structurally diverse chemical compounds, which the natural environment is a rich source of. Chemical diversity in nature is based on biological and geographical diversity, so researchers travel around the world obtaining samples to analyze and evaluate in drug discovery screens or bioassays.

1.3. HETEROCYCLIC COMPOUNDS IN DRUG DISCOVERY

Research in the field of pharmaceutical has its most important task in the development of new and better drugs and their successful introduction into clinical practice. The word 'drug' is derived from the French word 'drogue' which means a dry herb. In a general way, a drug may be defined as a substance used in the prevention, diagnosis, treatment or cure of disease in human or animals. Most pharmaceuticals are based on heterocycles. An inspection of the structures of the top-selling brand-name drugs reveals that 8 of the top 10 and 71 of the top 100 drugs contain heterocycles. Heterocycles have dominated medicinal chemistry from the beginning. Consistent with their importance, many patents by pharmaceutical companies involve heterocyclic compounds. There is every reason to expect this trend to continue. All the major pharmaceutical companies have significant research efforts involving heterocycles.
The basis of understanding the medicinal chemistry lies in awareness of the relationships between the chemistry of a particular compound or group of compounds and their interactions with the body, which is known as structure activity relationship, and the mechanism by which the compound influences the biological system, which is known as its mode of action.\textsuperscript{42} We must always continue to search for drugs which exhibit clear advantages over the already existing respective drugs. Such advantages may be: (i) A qualitative or quantitative improvement in activity, (ii) a partial or total absence of undesirable side effects, (iii) a lower toxicity, (iv) more nutritive value, (v) improved stability and (vi) a decrease in production cost. Any drug must ideally have a broad spectrum of activity, with a rapid action. During the period of 1940 to 1960 a large number of important drugs have been introduced and this period is regarded as "Golden Period" of new drug discovery.\textsuperscript{43,44} Heterocycles play in modern drug design, they can serve as useful tools to manipulate lipophilicity, polarity and hydrogen bonding capacity of molecules, which may lead to improved pharmacological pharmacokinetics, toxicological and physicochemical properties of drug candidates and ultimately drugs.\textsuperscript{45-48}

\[
\begin{align*}
&\text{6} \\
&\text{7}
\end{align*}
\]

The first synthetic heterocyclic pharmaceutical seems to be antipyrine (6). It is a pyrazole analgesic and an antipyretic, like aspirin. More recently, antipyrine has been
used in a solution with benzocaine to relieve ear pain and swelling caused by middle ear infections. Several anticancer drugs contain the pyrimidine ring. An early drug, still in use today is methotrexate (7), which acts by inhibiting the formation of folic acid. Methotrexate is also used to treat rheumatoid arthritis. For the synthetic chemist, methotrexate is particularly interesting because it can be prepared in a one-step “shotgun” reaction. Almost all the compounds we know as synthetic drugs such as azidothymidine, barbituric acid, captopril, chloroquinine, chlorpromazine, diazepam, fluconazole, isoniazid and metronidazole (Figure – 1.4) are also heterocycles.
Heterocyclic compounds hold a unique place among pharmaceutical significant natural products and synthetic compounds. The remarkable ability of heterocyclic nuclei to serve both as biomimetics and reactive pharmacophores has largely contributed to their unique value as traditional key elements of drugs. The introduction of heterocyclic group in the drug molecule enhances their bioactivity. This is exemplified by p-aminobenzenesulphonamide moiety, a well-known drug molecule, but the introduction of heterocyclic groups into the original nucleus markedly enhanced their biological activity. The important drugs are sulphathiazole, sulphadiazine, sulphadimethoxine etc., which are highly effective towards several bacterial strains. There is every reason to believe that most newly discovered pharmaceutically active compounds will continue to be based on heterocycles.

1.4. HETEROCYCLIC COMPOUNDS IN COMMERCIAL FIELDS

Heterocyclic compounds are of great importance in many different fields of commerce. They represent specialized, well-developed areas of technology and an extremely important application of heterocyclic compounds is in the field of dyes and pigments. Extended conjugation is an important ingredient for a compound to be colored, and heterocyclic systems, usually multicyclic, in great numbers have been constructed around this principle. An extremely important application of heterocyclic compounds is in the field of dyes and pigments.
Industrial organic chemistry can trace its beginnings back to the (accidental) discovery of mauveine (8) in 1856. It was the first organic compound to be prepared synthetically at the industrial scale. Another heterocyclic compound, indigo (9), was derived from natural sources and was used for centuries before it was synthesized in 1883 and later made commercially. These two early compounds display the extended conjugation so important in the development of new dye and pigment chemicals.  

Technology in the area of photography is highly developed, making use of heterocyclic compounds in various ways in the several steps of the process. Heterocyclic compounds can participate in polymer technology in several ways. They can be pendants on a polymer chain, as might be formed from the polymerization of vinyl monomers with heterocyclic substituents. There are processes where the polymer is formed by closing heterocyclic rings. Finally, heterocyclic groups can be added to previously formed polymers. Hindered heterocyclic amines are used as light stabilizers in plastic and coating formulations, protecting against degradation by ultraviolet radiation. These agents are known as hindered amine light stabilizers (HALS) and are commonly derivatives of 2,2,6,6-tetramethylpiperidine, an example of a HALS agent is tinuvin (10).

A thriving and highly important field is the construction of coordination complexes from metallic species and heterocycles. These complexes can be useful as reaction catalysts and have other uses as well. To illustrate the catalyst area (which is
large), the zirconium complex formed from the anion of indenylindoyl anion, and zirconium chloride is offered as an example. The complex is an excellent catalyst for the polymerization of olefins.\textsuperscript{64} Also, heterocycles with chirality can form complexes that are useful catalysts for asymmetric synthesis.\textsuperscript{65} This is a field of great contemporary interest. A relatively new and still developing field is the use of heterocyclic compounds in electro-optical applications, which includes light-emitting diodes (LED), thin-film transistors, and photovoltaic cells. To possess these properties, molecules must have extended conjugated unsaturation. This lowers the highest occupied molecular orbital-lowest unoccupied molecular orbital energy gap and causes light absorption at long wavelengths. One type of useful structure has several heterocyclic rings such as pyrrole or thiophene joined in a linear fashion. The phosphole ring system is a new participant in this type of array. This is illustrated by compound (11) in which two thiophene rings are attached to a central phosphole ring (as the sulfide). This compound has LED properties; when deposited as a thin film between a player cathode and anode, the yellow light was emitted by the application of a low voltage. Other related structures are being examined for similar electro-optical activity.\textsuperscript{66} Another new application of heterocyclic compounds is in the field of ionic liquids. These compounds generally are quaternary salts of certain heterocyclic bases, and they are finding use as high-boiling polar solvents for extractions or as reaction media. Common among the ionic liquids known so far are salts of imidazole.\textsuperscript{67}

\textbf{1.5. NITROGEN CONTAINING HETEROCYCLIC COMPOUNDS}

The heteroaromatic ring system is the pivotal part of any biologically active drug molecule. Heteroaromatic rings are essential because they provide similarity with respect to the biologically active compounds within our body. Among many heteroaromatic rings present, nitrogen heterocycles are abundant in nature and are of great significance,
to life because their structural sub-units exist in several natural products such as vitamins, hormones, amino acids, proteins, chlorophyll, haemin, enzymes, antibiotics and alkaloids. They are also major components of biological molecules such as DNA, which is the most important macro-molecule of life.\textsuperscript{68, 69} Nitrogen heterocycles appear in the core structure of several drugs marketed worldwide and these heterocycles comprising around 60\% are covered as a drug substance. Due to the importance of nitrogen heterocycles in medicinal chemistry, pharmaceutical industry, various drug development areas and their importance in the material science enough importance are given for their synthesis and characterization. Based on these observations, researchers interested in the synthesis of the nitrogen containing heterocycles like, oxadiazole, pyrrolidine, piperidine, pyridine, pyrimidone, oxazoline, thiazole etc.\textsuperscript{70, 71}

As per the review about the recent trends in the chemistry of nitrogen containing heterocyclic compounds, it is oxadiazole, a five-membered ring containing two nitrogen and one oxygen atom which has a broad spectrum of biological activities and ubiquitous feature of many pharmaceutical products.\textsuperscript{72, 73} Among the plethora of oxadiazole nucleus discovered, the 1,3,4-oxadiazoles have been explored extensively. The presence of 1,3,4-oxadiazole motifs in diverse types of compounds prove its importance in the field of medicinal chemistry, such as anticancer,\textsuperscript{74} anti-inflammatory,\textsuperscript{75} antiproliferative,\textsuperscript{76} anticonvulsant,\textsuperscript{77} hypoglycemic,\textsuperscript{78} anti- hypertensive,\textsuperscript{79} antimicrobial,\textsuperscript{80-83} antioxidant,\textsuperscript{84} anti-inflammatory and antiviral\textsuperscript{85} properties.

The synthesis of novel 1,3,4-oxadiazole derivatives, and investigation of their chemical properties and biological behavior, though established about 80 years back it has been accelerated in the last two decades. In recent years the number of scientific studies with these compounds has increased considerably. The literature survey on 1,3,4-oxadiazole, demonstrate its relevance for heterocyclic chemistry. For instance,
oxadiazoles, has attracted an extensive attention of the researchers in the search for the new therapeutics, such as compounds (12) as anticancer\textsuperscript{86} and (13) as HIV-integrase inhibitor\textsuperscript{87} agents.

Besides, 1,3,4-oxadiazoles has attracted an interest in medicinal chemistry as ester and amide bioisosteres for a number of biological targets.\textsuperscript{88} As such their peptidomimetic ability has been explored and reported in the development of Phe-Gly mimetic of dermorphin, a hepta-peptide.\textsuperscript{89} 1,3,4-Oxadiazole molecules are also used as pharmacophores due to their favorable metabolic profile and ability to engage in hydrogen bonding.\textsuperscript{90}

In our efforts towards designing novel nitrogen containing heterocyclic compounds with potential pharmacological activity, a simple and efficient synthesis and anticancer and antimicrobial properties of some novel 2,5-di substituted-1,3,4-oxadiazoles and benzophenone appended 1,3,4-oxadiazoles has been performed and described in chapter- 2 and 4, respectively. Besides, synthesis of benzophenone bearing various nitrogen containing heterocyclic analogues via an amide linkage were also synthesized and evaluated for xanthine oxidase inhibitory activity and represented in chapter-3 of this thesis.
1.6. SYNTHETIC FEATURE OF 1,3,4-OXADIAZOLE ANALOGUES

Taking into account the importance of 1,3,4-oxadiazoles to both heterocyclic and medicinal chemistry, a few of the synthetic approaches reported in the literature for the preparation of substituted 1,3,4-oxadiazoles are outlined in different schemes as mentioned below. There were several routes for the synthesis of 1,3,4-oxadiazoles reported in the literature among which the most important aspects of synthesis were discussed as under.\(^8^5\)

1,3,4-Oxadiazole are generally obtained from acyclic precursors and such reactions are mainly one bond or two bond cyclization. The most widely applicable routes to 2,5-disubstituted-1,3,4-oxadiazole is the thermal or acid catalyzed cyclization of 1,2-diacylhydrazines\(^9^1\) (SCHEME - 1.1) or using diethylaminodifluorosulfinium tetrafluoro borate as a cyclo dehydration reagent.\(^9^2\)

![SCHEME - 1.1](image)

![SCHEME - 1.2](image)
In recent times, 2,5-dibenzophenone-1,3,4-oxadiazole were synthesized starting from acetyl hydrazines with pyridine and triflic anhydride in good yield as shown in (SCHEME - 1.2). Wherein phenyl oxadiazole analogue was synthesized from phenylisoxazoyl N-benzyleinediacetohydrazide in presence of ethanol and chloramine-T (SCHEME - 1.3).

Moreover, 1,3,4-oxadiazole systems have been developed based on microwave assisted synthesis using acetohydrazide as a source of two contiguous nitrogen atoms, and cyanogen bromide (SCHEME - 1.4).

An alternative to cyanogen bromide is phenyl cyanate, which reacted with acetohydrazide to give amino oxadiazole analogue as shown in SCHEME - 1.5.
The synthesis of 1,3,4-oxadiazole analogues was focused on aryl-2-trifluoromethyl-1,8-naphthyridine-3-carbonyl hydrazide as starting material in the presence of acetic anhydride (SCHEME-1.6). 97

![Scheme 1.6](image)

Whereas these types of analogues were also obtained from semicarbazide in the presence of phosphorous oxychloride (SCHEME - 1.7). 98

![Scheme 1.7](image)

In addition, Hansong Chen et al. 99 has synthesized 1,3,4-oxadiazole analogues by the reaction of hydrazide and aromatic acid in the presence of POCl₃ (SCHEME - 1.8).

![Scheme 1.8](image)

Conveniently 2,5-disubstituted 1,3,4-oxadiazole was accomplished by cyclodehydration of 1,2-diacylhydrazine either by using chlorosulphonic acid 100 or phenyl dichorophosphite in dimethylformamide (SCHEME - 1.9). 101

![Scheme 1.9](image)

In a related reaction, 1,1,2-triacetylhydrazine with trimethylsilylchloride/triethyl amine gave oxadiazolinyl silylether 102 (SCHEME - 1.10).
 Nevertheless cyclodehydration of hydrazinyl diester using PCl₅/POCl₃ gave the diphenyloxyoxadiazole¹⁰³ (SCHEME-1.11). Oxidation of acylhydrazones derived from aldehydes has been developed into a useful route to disubstituted oxadiazoles (SCHEME - 1.11). The use of potassium permanganate with acetone as a solvent was claimed to give better yields than the use of other oxidizing agents like halogens.¹⁰⁴,¹⁰⁵

A series of 2,5-disubstituted 1,3,4-oxadiazoles were synthesized starting from 1-aryloyl-2-arylidine hydrazides with potassium permanganate as an oxidizing agent on the surface of silica gel. Nevertheless the same reaction was also performed in a mixture of acetone and water under microwave irradiation¹⁰⁶ (SCHEME - 1.13).

Recently, a mild, convenient, and efficient one-pot synthesis of amino-1,3,4-oxadiazoles was described by Guda et al. (SCHEME - 1.14).¹⁰⁷ Wherein, in
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situ preparation of various thiosemicarbazides by the reaction of different carboxylic acid hydrazides with trimethylsilyl isothiocyanate, followed by cyclodesulphurization of thiosemicarbazides under basic conditions in the presence of I$_2$/KI resulted in 2-amino-1,3,4-oxadiazoles in high yield.

![Scheme 1.14]

Nevertheless, a one pot synthesis of 2-amino-1,3,4-oxadiazoles mediated by tosylimino phenyl iodane has been described by Prabhu et al. In this protocol acylthiosemicarbazides obtained from corresponding acyldrazides undergo efficient cyclodesulphurization (Scheme 1.15).\textsuperscript{108}

1.7. IMPORTANCE OF OXADIAZOLS IN PHARMACOLOGICALLY

1,3,4-Oxadiazole is a versatile lead compound for designing potent bioactive agents\textsuperscript{109} and it has become an important construction motif for the development of new drugs.\textsuperscript{110, 111} In recent years the number of scientific studies with these compounds has increased considerably. Taking into account the importance of these compounds to both heterocyclic and medicinal chemistry, the researcher has described the main synthesis approaches used for obtaining the heterocyclic nucleus, as well as the broad spectrum of pharmacological activities.\textsuperscript{87, 112, 113} as mentioned below.
1.7.1. ANTICANCER AGENTS

Cancer, the second cause of mortality in the world, after cardiovascular disease,\textsuperscript{114} is continuing to be a major health hazard in developing as well as in undeveloped countries.\textsuperscript{115} Design and development of anticancer drugs with fewer or no side effects are important for the treatment of cancer. The search for such potential anticancer drugs has led to the discovery of synthetic molecules with anticarcinogenic activity. Therefore, cancer has become a major challenge to mankind,\textsuperscript{116} and it has opened up myriad new avenues for advance drug design and discoveries. Cancer may affect people at all ages, even fetuses,\textsuperscript{117} but the risk of different types of cancer varies with age. In the present-day, there are three main methods of cancer treatments are surgery, radiation therapy and chemotherapy. With the development of molecular biology, chemotherapy is becoming a more important therapeutic method. Therefore, designing new anti-cancer drugs with high competence and wide spectrum activity is an extensive study platform today.

![Chemical structures](image)

Based on these observations, researchers synthesized and investigated 1,3,4-oxadiazole analogues as anticancer agents. For instance, our group\textsuperscript{86} has synthesized benzophenones bearing oxadiazoles and structural activity relationship suggests that the position and the type of substituent on the aromatic ring are important for anticancer activity. Compound (14) with chloro and bromo group play a dominant role in inhibiting
the leukemic cell proliferation. Whereas, benzimidazoles bearing oxadiazole nucleus (15) exhibited remarkable anticancer activity against most of the tested cell lines.118

Furthermore, in search of a new agent for the treatment of cancer benzimidazole bearing 1,3,4-oxadiazole (15) was synthesized as a lead compound with a broad spectrum of anticancer activities.119 1,3,4-Oxadiazoles present ample opportunities for scientists in drug discovery. The widespread use of them as a scaffold in medicinal chemistry establishes this moiety as a member of the privileged structures class.

In particular, 1,3,4-oxadiazole analogue (21) has been found to exhibit excellent anticancer activity. The in vitro anticancer activity of this compound was evaluated against three cancer cell lines by the MTT method, which has shown activity superior to the positive control.120

1.7.2. XANTHINE OXIDASE INHIBITORY AGENTS

An increasing number of researchers during the past decade have suggested that xanthine oxidase (XO) plays an important role in various forms of ischemic and other types of tissue and vascular injuries, inflammatory diseases, and chronic heart failure.121 XO is a complex metalloflavoprotein that catalyzes the conversion of hypoxanthine to xanthine and xanthine to uric acid with concomitant production of hydrogen peroxide and superoxide anions.122 Increase in uric acid level in serum eventually leads to the
deposition of microand macroscopic deposits of sodium hydrogen urate monohydrate crystals in the joints of humans that leads to the hyperuricemic condition called gout.\textsuperscript{123}

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

Gout is a common disease with a higher prevalence in men older than 30 years and in women older than 50 years.\textsuperscript{124} These findings highlight the need for emerging treatments to effectively lower urate levels.\textsuperscript{125, 126} These observations and researcher interest in the pharmaceutical chemistry of heterocyclic compounds promoted them to synthesize a series of different derivatives of 1,3,4-oxadiazole and investigated them in the reduction of swelling and pain. In this connection, compounds (18)\textsuperscript{127} exhibited potential inhibition response towards the reduction of pain with lower IC\textsubscript{50} value. Correspondingly compound (19)\textsuperscript{128} shown strong inhibition towards the enzyme compared to the standard drug allopurinol.

1.7.3. ANTIMICROBIAL AGENTS

Infections diseases represent a critical issue for health and the major cause of morbidity and mortality worldwide. Despite significant progress in human medicine, infections diseases caused by microorganisms are still a serious threat to public health.\textsuperscript{129} The impact is even greater in developing countries due to unavailability of medicine in all the locations, the practice of self-medication and the emergence of microorganism drug resistance.\textsuperscript{130} The development of resistance to current antibacterial therapy continues to drive the search for more effective agents. In addition, primary and opportunistic fungal infections continue to increase the number of immune compromised patients, those suffering from such as AIDS or cancer or who have undergone organ transplantation.\textsuperscript{131} In recent years, the incidence of fungal and bacterial infections has increased
The widespread use of antibacterial and antifungal drugs resulted in resistance to drug therapy against bacterial and fungal infections, which led to serious health hazards. The resistance of the wide spectrum antibacterial and antifungal agents has initiated discovery and modification of the new antibacterial and antifungal drugs.

The literature study reveals that oxadiazoles are an important pharmacophore and exhibits outstanding microbial activity. For example, oxadiazole analogue \(20\) was synthesized and evaluated for antifungal activity. Interestingly, it has shown almost equivalent antibacterial activity to standard drug.

Moreover, 2,5-di substituted oxadiazole bearing aryl moiety were synthesized and screened in vitro for their efficacy as antimicrobial agents against bacterial and fungal strains by broth dilution method. Among the series, compound \(21\) showed potent antimicrobial activity against candida albicans and aspergillus flavus screened strains.

1.8. COMMERCIAL APPLICATIONS

The analogues of 1,3,4-oxadiazole, have a wide number of commercial applications. For instance, they are commercially used for modification and/or regulation of plant growth to provide beneficial effects which are appreciated by the agricultural art. Among the most well recognized classes of plant growth regulatory chemicals are plant growth stimulants. Thus, oxadiazole analogues have been applied to fruits such as pears, lemons, grapes and cherries to increase the size and/or amount of fruit developed; to vegetables such as asparagus, celery and lettuce to promote vegetative growth; to seeds of
crops such as oats, peas, cotton, rye, soybeans and wheat to promote the rapid emergence and to ornamentals to produce earlier blooming or more profuse or larger flowering.  

During the past decade, organic electronics have attracted a great deal of interest due to its applicability in a wide range of applications and high potential for commercial success. These applications, notably range from organic light emitting diodes to organic photovoltaics and sensors. Organic diodes undoubtedly have the potential to redefine many present day lighting solutions if the performances and device stability are significantly improved. Over the years, several basic structures have received the attention of researchers for the design of these appealing materials, namely triphenylamines and oxadiazoles that can respectively act as the hole-transporting and electron-transporting moieties in these ambipolar materials.  

Furthermore, 1,3,4-oxadiazole analogues have been used as a pi-conjugation relay to prepare a number of donor-acceptor molecules carrying a pi-electron rich aromatic ring. Therefore, these compounds may be a good candidate for optical material or biologically active chemicals. 1,3,4-Oxadiazoles have proved to be useful in material science as a probe for their fluorescence and scintillation properties. In addition, 1,3,4-oxadiazole derivatives have been widely used as electron conducting and hole blocking material in molecules based as well as polymeric light emitting devices.  

1.9. IMPORTANCE OF AMIDE LINKAGE  

The amide formation reaction being a key reaction in organic chemistry and the amide bond is widely prevalent in both naturally occurring and synthetic compounds. It is increasingly important in pharmaceutical chemistry, being present in 25% of available drugs, with amidation reactions being among the most commonly used reactions in medicinal chemistry. There is considerable interest in the development of new approaches
to direct amidation and amide bond formation is one of the most important reactions used in the industry for which better reagents are required.¹⁴⁰

The amide functionality is a common feature in small or complex synthetic or natural molecules. For example, it is ubiquitous in life, as proteins play a crucial role in virtually all biological processes. Amides also play a key role for medicinal chemists.¹⁴¹ This can be expected, since carboxamides are neutral, are stable and have both hydrogen-bond accepting and donating properties. Amide linkages¹⁴² are not only the key chemical connections of proteins, but they are also the basis for some of the most versatile and widely used synthetic heterocyclic compounds, materials and polymers. Chemical reactions for their formation are among the most executed transformations in organic chemistry. In living systems, most amide bonds are formed by the complex factors that are ribosomes. Long, complex proteins are assembled amino acid by amino acid, using a templated amidation of amines and the active esters of amino acid monomers and RNA. In addition, the amide bond is commonly found as a key structural element in agrochemicals and in products from the fine chemicals industry.

1.10. SYNTHETIC FEATURE OF AMIDE LINKAGE

Amide bond formation is a fundamentally important reaction in organic synthesis, and is typically mediated by one of a myriad of so-called coupling reagents (SCHEME - 1.16).

\[
\begin{align*}
\text{R}_1 & \quad \text{OH} \\
\text{O} + \text{Coupling reagents} & \quad \text{Base} \\
\text{Solvent} & \quad \text{R}_1 \\
\text{N} & \quad \text{O} \\
\text{R}_2
\end{align*}
\]

\[\text{R}_1 \& \text{R}_2 = \text{Alkyl/Aryl}\]

SCHEME - 1.16
The various coupling reagents used for the formation of amide linkage are N-hydroxysuccinimide, N-hydroxy-5-norbornene-2,3-dicarboximide, 1-hydroxy benzotriazole, 6-chloro-1-hydroxy benzotriazole, 1-hydroxy-7-azabenzotriazole, dicyclohexyl-carbodiimide and more recently 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine and its aza derivative.\textsuperscript{143, 144}

Formally, the amide bond is formed through the condensation of a carboxylic acid and an amine with the release of one equivalent of water. This reaction has been considered challenging due to the competing acid–base reaction. Although there are a large range of reagents and strategies for amide bond formation available, few can really be considered ideal. Currently there is a focus on the development of novel, atom-economical, benign methods for amidation, and there have been many recent developments in this field. An important consideration here is the ease with which the reagent or catalyst can be separated from the resulting product. Alternatively, a number of metal-based catalytic systems have also been reported, under strictly anhydrous dehydrating conditions.\textsuperscript{145, 146} Nevertheless, 3,4,5-trifluorobenzeneboronic acid as a catalyst was found to be the most active and for the reaction of benzylamine with 4-phenylbutyric acid, to afford amide in 96% yield as shown in SCHEME-1.17.\textsuperscript{147}

3,4,5-Trifluorobenzeneboronic acid is also an effective catalyst for the polycondensation of carboxylic acids and amines.\textsuperscript{148} Direct polycondensation is desirable both environmentally and industrially. The direct polycondensation of adipic acid and
hexamethylenediame was examined for the formation of nylon-6,6 with a yield of 89%. This amidation procedure has been employed in the synthesis of several active pharmaceutical ingredients. 149,150

Formation of amide linkage was also focused on the thermal amidation151 as depicted in SCHEME-1.18.

In recent years, it has been reported that simple borate esters are effective reagents for the direct synthesis of amides from carboxylic acids or primary amides.152 Boron mediated amidation reactions have attracted considerable attention, and in most cases, the amide products can be purified by a simple filtration procedure using commercially available resins, with no need for aqueous workup or chromatography (SCHEME-1.19).

The use of microwave irradiation has been reported to simplify and improve a number of organic reactions, often leading to higher conversions and shorter reaction times.153 Preparation of amides by the heating of carboxylate ammonium salts obtained
from the mixture of an amine and carboxylic acid has been examined under microwave irradiation conditions in the absence of a catalyst and of solvent (SCHEME-1.20).

\[ \text{SCHEME - 1.20} \]

For example, benzylamine reacted with benzoic acid affording the corresponding amide in high yield (80%). However, when the same reaction was heated using an oil bath, only 8% yield of the amide was isolated.

1.11. PHARMACOLOGICAL IMPORTANCE OF AMIDE LINKAGE IN HETEROCYCLIC COMPOUNDS

Amides are versatile organic compounds since all the three atoms in the O-C-N chain are potentially reactive. This result partly due to the delocalization of the π-electrons along the O-C-N chain. The partial double-bond character in the CO-NH bond generates a 1,3-dipole, with nitrogen bearing the partial positive charge and oxygen the partial negative charge. The consequences of partial double bond character are the planar nature of the amide group and the existence of configurational isomers, whereas donor-acceptor properties of the amide moiety manifest in acid base and complexing interactions and a tendency to self associate are a consequence of its dipolar structure. The versatility of the amide group in forming partial bonds with itself and many other functional groups is partly responsible for the structural subtleties of the biologically important proton derivatives. The SAR also indicated that the major interactions of RT enzyme are through the amide group.

The amide linkage highlight how this chemical bond factor in the design of enzyme inhibitors, cyclic peptides, antibacterial agents, and emerging nanotechnology applications. Because of the broad functions exhibited by the various members of the
fatty acid amide family, a wide range of indications could benefit from a fatty acid amide-targeted drug, including cancer, cardiovascular disease, inflammation, pain, drug addition, eating disorders, anxiety and depression.\textsuperscript{156, 157} Looking to the importance of amide linked compounds, research in this area is stimulated with methods of synthesis, and pharmacology of amide linked heterocyclic compounds as briefed below.

\textbf{1.11.1. ANTICANCER AGENTS}

In the current scenario, development of anticancer drugs with specific targets is of prime importance in modern chemical biology. Observing the importance of amide linked heterocyclic analogues, it would be worthwhile to design and synthesize novel compounds as potent anticancer agent. In this connection, our research group has synthesized and investigated compound (22) in vitro against the Michigan Cancer Foundation-7 and Ehrlich’s ascites tumor cell lines.\textsuperscript{158} Further, investigation resulted in the achievement of compound (23) endowed with excellent antiproliferative potency with significant IC\textsubscript{50} value and in vivo antitumor effect of the same compound against murine EAC and solid DL tumor model system was evident by the extended survivality.\textsuperscript{159}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fatty_acid_amide_family.png}
\caption{Example of fatty acid amide family compounds}
\end{figure}

\textbf{1.11.2. XANTHINE OXIDASE INHIBITORY AGENTS}

The increasing prevalence of gout has been accompanied by a growing number of patients intolerant to or with disease refractory to the available urate-lowering therapies. This metabolic disease is a common disease with a higher prevalence in men older than
30 years and in women older than 50 years. These findings highlight the need for emerging treatments to effectively lower urate levels.

In this view, amide linked pyrimidone (24) \(^{160}\) was synthesized and investigated as XO which exhibited good inhibitory activity. Also, amide linked thiazolidone (25) with methoxy substituent was demonstrated as potent inhibitors of XO. \(^{161}\)

1.11.3. ANTIMICROBIAL AGENTS

There is an increasing demand for the development of compounds having improved properties and which can be used against several different diseases, such as the treatment of an infection caused by a microorganism. Concerning microbial diseases, antibiotic research at the industrial level has been focused on the identification of more refined variants of already existing drugs. \(^{162}\)
Despite the rapidity with which new chemotherapeutic agents are introduced, microbes have shown a remarkable ability to develop resistance to these agents and the search for new drugs, such as amide linked heterocyclic compounds, is in progress. These drugs have a different mode of action compared to the commonly used commercial drugs. For instance, the compound (26)$^{163}$ was recognized as persuasive compounds towards both the bacterial and fungal strains. Moreover compound (27)$^{164}$ containing amide linkage with benzthiazole, oxadiazole and coumarin heterocyclic ring exhibited good antimicrobial activity.

1.12. AIMS AND OBJECTIVES:

In the pharmaceutical field, there has always been and will continue to be a need for new and novel chemical entities with diverse biological activities. Our efforts focus on the introduction of chemical diversity in the molecular framework in order to synthesize pharmacologically interesting compounds of widely different composition. During the course of research work, several entities have been designed, generated and characterized using spectral studies. Besides, biological activities of the generated entities were carried out. The details are as under.

- Overview of literature survey of the biological activity of heterocyclic compounds in particular, nitrogen containing heterocycles.

- Synthesized several analogues like various heterocyclic ring appended benzophene analogues via amide linkage, benzophenones bearing oxadiazole nucleus analogues, substituted nicotinic acid based 4-arylloyl aryloxyacet hydrazides and 2,5-diphenyl alkoxy 1,3,4-oxadiazoles.

- Characterized all the synthesized compounds for structure elucidation using spectroscopic techniques like IR, $^1$H NMR, $^{13}$C NMR and mass spectral studies.
Heterocyclic ring appended benzopheone analogues via an amide linkage were screened for xanthine oxidase inhibition.

Evaluated benzophenones bearing oxadiazole nucleus for the better drug’s potential against different strains of bacteria and fungi.

Substituted nicotinic acid based 4-aryloyl aryloxyacythydrazides were screened for antiproliferative and apoptogenic properties against Dalton’s lymphoma by both in vitro and in vivo analysis.

Evaluated anticancer activity of the 2,5-diphenyl alkoxy 1,3,4-oxadiazoles.

1.13. REFERENCES


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