Introduction:

Organic chemists synthesize hundreds of new heterocyclic compounds every week. In most cases the chemist has specific reasons for synthesizing a particular compound, usually based on theoretical considerations, medicinal chemistry, biological mechanisms or a combination of all three. Heterocyclic compounds have known held center stage in the development of molecules to enhance quality of human life. For example, around seventy percent of drugs used today are heterocyclic compounds. The heterocyclic compounds are very widely distributed in nature and are very essential to living organisms. They play a vital role in the metabolism of all the living cells. Among large number of heterocycles found in nature, nitrogen heterocycles are the most abundant specially those containing oxygen or sulphur due to their wide distribution in nucleic acid illustration and their involvement in almost every physiological process of plants and animals. Heterocyclic compounds possess great applicability in industry as well as in our life in various ways. For example most of the sugars including vitamin C and their derivatives are exits in the form of five (Furanosied structure) or six (Pyranosied structure) membered ring containing one oxygen atom. Further, most members of the vitamin B group possess heterocyclic rings containing nitrogen, e.g, vitamin B6 (Pyridoxine) which is a derivative of the pyridine essential in amino acid metabolism. The heterocyclic compounds also occupy key position in the area of drugs and pharmaceuticals. Almost 80% of the drugs in clinical use are based on heterocyclic constitution because they have specific chemical reactivity. Majority of the drugs being introduced in pharmacopeias in recent year are heterocyclic compounds. A wide variety of drugs such as guanethidine (antihypertensive), indapamide (diuretic and antihypertensive), chlor Diazepoxide (tranquillizer), imipromine (antidepressant), etc. The non-steroidal drugs such as
fenoprofen and flurbiprofen\textsuperscript{11} ketoprofen,\textsuperscript{12} are well known anti-inflammatory agents; these derivatives are found to more potent and with fewer side effects. Many antibiotics including streptomycin\textsuperscript{13, 14} norfloxacin,\textsuperscript{15} penicillin,\textsuperscript{16} cephalosporin,\textsuperscript{17} etc, also all these contain heterocyclic ring. Many veterinary products like morantel and pyrantel are the drug of choice as broad spectrum anthelmintics.\textsuperscript{18} The atrazine and simazine are the herbicides is well known example of heterocyclic agrochemical.\textsuperscript{19, 20} Plant pigments such as chlorophyll,\textsuperscript{21} hemoglobin,\textsuperscript{22} indigo,\textsuperscript{23} and anthocyanins,\textsuperscript{24} has contributed to colour chemistry and all these contain heterocyclic ring. Today, most of the heterocyclic drugs are not extracted from natural sources but are synthesized from readily available fine chemicals.

Taking in view of the applicability of heterocyclic compounds, the present work was undertaken to synthesize some new heterocycles bearing Pyrrole, oxadiazole and oxadiazepine nucleus.
The importance of pyrrole and oxadiazole derivatives.

The existence of pyrrole in coal tar, bone oil. It was first summarized in 1843 by Runge \(^{25}\) when he observed that bone oil and coal tar contain a substance that dyes pine splinters red. Runge called this unidentified substance pyrrole (derived from greek red) meaning fiery oil. Although he did not actually isolate the compound, he did not know its chemical constitution and supposed it to be a gas. Pyrrole obtained from bone tar was first purified and analysed by Anderson in 1857 \(^{26}\). The actual structure of pyrrole \([1]\) was established in 1870 (Scheme 1).

![Scheme 1. Shows the structure of pyrrole.](image)

Pyrrole is one of a class of organic heterocyclic compounds of five membered unsaturated ring structure composed of four carbon atoms and one nitrogen atom. It is a colorless to pale yellow, toxic oil with pungent taste. It is susceptible to air oxidation and readily polymerizes under acidic condition. Pyrroles are five membered aromatic systems with lone pair on nitrogen delocalized through the ring. This gives the ring a total of six \(\pi\) electrons obey Huckel’s rules for the aromaticity. As such the pyrrole ring displays reactivity identical to that of an aromatic molecule.\(^{27}\) Pyrrole undergoes electrophilic substitution, which is faster than that of the benzene and substitution occurs preferentially at two positions. This is due to the fact that a cationic intermediate at 3 positions has increased resonance stability that a cation at the two position \([2]\) (Scheme 2).
Scheme 2. Resonance structures of the two possible cationic intermediates during electrophilic aromatic substitution.

The biological importance of pyrrole derivatives can be listed in the following basic concept the first one which exists in the structure of many natural products possessing biological activity. Secondly, they are versatile building blocks in organic synthesis. Moreover, they are important starting materials for various synthetic transformations. Finally, they are widely used in material science. These properties of pyrrole derivatives are crucial in the synthesis of many drugs, particularly anticancer drugs.

The most relevant examples of pyrrole containing natural compounds are Lamellarins and Ningalins which belong to the marine natural products. The common feature of many compounds of these groups has potential multidrug resistance (MDR) reversal property by means of showing cytotoxicity activity. MDR is a persistent problem limiting the effectiveness of a wide variety of antibiotic, anticancer drugs, and protease inhibitor. The Lamellarins are the class of marine natural products which were first isolated from the prosobranch mollusc *Lamellaria sp.*, and important members of this class have been disclosed by Faulkner, Bowden,
Fenical, Scheuer and Capon.\textsuperscript{31, 32} Recent analysis of several lamellarins demonstrated their cytotoxic activity, revealed equally effective cytotoxic activity against multidrug-resistant (MDR) cell lines, and revealed MDR reversal even at noncytotoxic concentrations by inhibition of P-glycoprotein (P-gp)-mediated drug efflux.\textsuperscript{32} Lamellarins K [3] and L [4] (Scheme 3) possess biological activities which include cytotoxicity, HIV-1 integrase inhibition, and multidrug-resistance reversal.\textsuperscript{33, 34}

\textbf{3 and 4}

\textbf{Scheme 3. Lamellarin.}

<table>
<thead>
<tr>
<th>Lamellarin</th>
<th>R\textsubscript{1}</th>
<th>R\textsubscript{2}</th>
<th>R\textsubscript{3}</th>
<th>R\textsubscript{4}</th>
<th>R\textsubscript{5}</th>
<th>R\textsubscript{6}</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>K [3]</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>OH</td>
</tr>
<tr>
<td>L [4]</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
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Ningalin B [5] (Scheme 4) is the second member of recently identified ningalin class of marine natural products possessing a 3,4-diaryl-substituted pyrrole nucleus bearing a 2-carboxylate. It was isolated by Fenical (1997) from an ascidian of the \textit{Genus didemnum} collected in Western Australia.\textsuperscript{35} It shows MDR reversal activity against HCT116 and L1210 cell lines.\textsuperscript{36}
Another important natural product containing pyrrole nucleus is roseophilin [6] (Scheme 5). The structure of roseophilin was disclosed Seto et al in 1992, a novel antibiotic isolated from Streptomyces griseo Viridis.37 These alkaloids exhibits very promising cytotoxicity in vitro against human erythroid leukemia (K562) and human epidermoid carcinoma (KB) cell lines in the sub-micromolar range.

Pyrrole nucleus not only exits in the structure of many naturally accruing biologically active compounds, but also in the structure of some biologically active compounds with no natural source. From this point of view, pyrroles are very important building blocks in organic synthesis so in the drug industry. A good example for this case is atorvastatin calcium, the active material of famous drug named as “Atorvastatin” 7] (produced by Pfizer drug company) (Scheme 6).
This drug has the blood cholesterol lowering activity. Pyrrole being useful building blocks in organic synthesis makes them efficient starting materials for many kinds of synthetic transformations. Pyrroles play important role in the synthesis of porphyrin [8] systems. Porphyrins and other closely related tetra pyrrolic pigments occur widely in nature, and they play very important roles in various biological processes. Heme [9] [the iron(II) protoporphyrin-IX complex] is the prosthetic group in hemoglobins and myoglobins, which are responsible for oxygen transport and storage in living tissues (Scheme 7).

Reduction of one of the pyrrole units on the porphyrin ring leads to a class of porphyrin derivatives called chlorins [10]. Chlorophylls [11] (e.g. chlorophyll-a), found abundantly in green plants, belong to this category. They play very important roles in the process of photosynthesis (Scheme 8).

Vitamin B12 contains a porphyrin-like unit called corrin [13], a reduced form of corrole [12] (Scheme 9).


There are two general approaches to obtain a desired porphyrin: by modification of a naturally occurring porphyrin (e.g. heme), or by total synthesis. Although it is convenient, modification of naturally occurring porphyrins possess great limitations on the choice of peripheral substituents because certain substituents cannot be modified easily. In most cases, such limitations can be overcome by total synthesis, which involves the synthesis of the pyrrole subunits having the required substituents. Tetramerization of pyrrole [14] and aldehyde [15] is commonly used.
method in porphyrin [16] total synthesis (Scheme 10). In addition to this method, condensation of dipyrrolic intermediates is another convenient and frequently applied synthetic route being used in recent publications.\(^{37}\)

![Scheme 10. Synthesis of porphyrin.](image)

One more important application of pyrrole derivatives are the frequent use of them in material science. An example to this is the use of pyrroles in oligoaryl systems. It is an important class of compounds which exhibit a variety of fascinating properties for optoelectronic interests, incorporation of five-membered heteroaromatic moieties into these conjugated molecules will occasionally increase fluorescence quantum yields and the optoelectronic properties of the oligomers can be tuned.\(^{38}\) For this purpose, desired substituted pyrroles or furans are synthesized in order to incorporate them into the oligoaryls.\(^{39}\)

Pyrroles display a wide variety of physiological activities,\(^{40}\) particularly, tetrassubstituted pyrrole derivatives\(^{41}\) are biologically active and have been found to show antibacterial,\(^{42}\) antiinflammatory,\(^{43}\) antiviral,\(^{44}\) and antioxidant activities and to inhibit cytokine-mediated diseases.\(^{45}\) Additionally, they have been proven to potent inhibiting platelet aggregation\(^{46}\) and hypertensive activities.\(^{47}\) Said bayomi\(^{48}\) found that 2-amino-3-cyno-4-(substituted phenyl)-pyrroles (Scheme 11) [17] acts as an antimicrobial agents.
Scheme 11. Examples of pyrrole based antimicrobial agents.

Pyrrole derivatives (Scheme 12) [18] and their salts having structure type, shown below are useful as inhibitors of the human immunodeficiency virus (reverse transcriptase) enzyme which is involved in viral replication and consequently may be advantageously used as therapeutics agents for HIV mediated process.49

Scheme 12. Examples of pyrrole based antimicrobial and therapeutics agents.

Reduced pyrrole derivatives such as pyrrolidine-2-carboxilic acid hydrazide [19] (Scheme 13) derivatives for use as metallopeptide inhibitors.50

Scheme 13. Examples of pyrrole based metallopeptide inhibitors.
Febrizio and group have synthesized 2,4-dicarboxy-pyrroles [20] (Scheme 14) and tested as selective non-competitive mGluR1 antagonists.$^{51}$

![Scheme 14. Examples of pyrrole based mGluR1 antagonists.](image)

Various reduce pyrrole derivatives such as pyrroline [21] (Scheme 15), pyrrolidine are active on the cardiovascular apparatus and useful for preparation of structurally modified bioactive peptides.$^{52}$

![Scheme 15. Examples of pyrrole based bioactive aminoacids.](image)

Wijngaarden$^{53}$ and et al have synthesized a series of 2-phenylpyrrole using Mannich bases and screened in pharmacological models for antipsychotic activity and extrapyramidal effects. They made structure modification of 5-(4- flourophenyl)-2-[4-(2-methoxyphenyl)-I-piperazinyl] methyl pyrrole, the prototype of new class of sodium independent atypical dopamine D-2 anganosits. They found excellent oral activity in the apomorphine induced climbing behavior and the conditioned avoidance response tests and the absence of catalepsy make this compound particularly promising as a potential antipsychotic [22] (Scheme 16) with low propensity to induce acute extrapyramidal side effect.
Demetri\textsuperscript{54} has suggest, GIST is the most common mesenchymal cancer of the gastrointestinal tract. Activating mutations in KIT are common in GIST, and imatinib, which also inhibits KIT, was found to be the first RTK inhibitors \[23\] (Scheme 17) to show efficacy in this cancer, dramatically improving disease outcome. However, resistance to imatinib resulting from subsequent mutations in KIT has emerged.

\textbf{Scheme 16.} Examples of pyrrole based antipsychotic agent.

\textbf{Scheme 17.} Examples of pyrrole based RTK inhibitors.

\textbf{1,2,4-Oxadiazoles}

Oxadiazoles are five-membered heteroaromatic compounds containing two nitrogen atoms and one oxygen atom on the ring. In fact, there are four isomeric structures for oxadiazoles; 1,2,3-oxadiazoles \[24\], 1,2,4-oxadiazoles \[25\], 1,2,5-oxadiazoles \[26\], 1,3,4-oxadiazoles \[27\] [ (Scheme 18).\textsuperscript{55} In particular, 1,2,4-oxadiazoles constitute an important class of heterocyclic compounds due to the wide range of biological activities they exhibit.
Tremann and Kruger were synthesized first oxadiazole derivatives in 125 years ago. Since many articles have been published for the application of 1,2,4-oxadiazole in material science (ionic liquids, liquid crystals, OLED) and medicine. Structure-metabolism relationship studies often reveal that incorporation of one or more heteroatoms in an aromatic ring influences the chemical and biochemical reactivity of these compounds and therefore alter their metabolism.

1,2,4,-oxadiazoles have been described as good bioisosters of amide. Furthermore, they have been reported to have agonist for cortical muscarinic receptors, 5-HT\textsubscript{1D} (5-hydroxytryptamine) benzodiazepine 5-HT\textsubscript{3}, histemic H3 and sphingosine-1-phosphate-1 (S1P1) receptors. They also display activity as anti-inflammatory, anti-tumor agent and antiparasitic, anti diabetic, anti-asthamatics, cell adhesion, monomine oxidase and tryptase inhibitor properties, and also, they show activity against several breast and cancer cell lines human nueterophilelastase antagonist of the integrin α\textsubscript{v}β\textsubscript{3}, and DNA topoisomerases.
Scheme 19. Examples of 1,2,4-oxadiazole-containing anticancer 28, anti-diabetics 29, and anti-asthmatics 30 agents.

Recent studies have proved anti-inflammatory properties of 3,5 diaryl 1,2,4-oxadiazole with long chain at C-5 have been found to possess not only anti-inflammatory but also possess antitumor activities [31 and 32] (Scheme 20)\textsuperscript{81} interestingly these compounds exhibit similar activity as compared with aspirin and ibuprofen.

Scheme 20. Examples of 1,2,4-oxadiazole based anti inflammatory agents.

In addition to anti-microbial activity, 1,2,4-oxadiazole derivatives [33] were found to have the best bioisosteric replacement of methyl ester groups, which maintained of anti-HIV with submicromolar EC\textsubscript{50} values.\textsuperscript{82} 1,2,4-oxadiazole
derivatives also used as neuroprotective agents for the therapy of Alzheimer’s and Parkinsons diseases. 1,2,4-oxadiazole derivative [34] have been designed to be Neuroprotective agents (Scheme 21), particularly the derivatives of 1,2-dithiolane-3-pentanoic acid (α-lipoic acid) are neuroprotective antioxidants. For this purpose, a different 3,5-dialkyl/aryl-1,2,4-oxadiazole containing lipoic acid have been prepared to find neuroprotective agents.83

5-thiocyno-substitued oxadiazoles displayed anti-bacterial properties, particularly, 3-aryl-5-thiocynomethyl-1,2,4-oxadiazole derivatives [35] were found to drugs for the treatment of Lesihmaniasis (Scheme 21).84

![Chemical structures](image)

**Scheme 21.** Examples of 1,2,4-oxadiazole based anti-microbial and neuroprotecting agents.

Polymers containing oxadizole units such as [36] and [37] are known to have good thermal and hydrolytic stability in material science applications since they are thermally degraded in 300-400 °C range (Scheme 22),85 and they are soluble in strong acids like sulfuric acid and trifluoroacetic acid.
Scheme 22. Examples of 1,2,4-oxadiazole-bearing polymers.

Photochemical reactivity of 1,2,4-oxadiazole [38] was examined in detail and it was shown in (Scheme 23). These heterocycles can be used as synthon for the construction of other heterocycles systems including different 1,2,4-oxadiazoles [39], 1,2,4-triazoles [40], 1,2,4-triazines [41], 1,3,4-oxadiazoles [42], N-benzylbenzamidines [43], indazoles [44], N-imidoylziridines [45], quinazolinones [46] (Scheme 23). Some other heterocycles such as photochemical rearrangement of benoxazole [94] benzimidazoles [95] and quinolones [96] were also obtained after photochemical rearrangement of 1,2,4-oxadiazoles. The rearrangement of 1,2,4-oxadiazoles under photochemical conditions generally started with the cleavage of N-O bond, followed by different reaction pattern depending on the nature of the substituents on the ring.
1,2,4-oxadiazole are generally prepared by two methods first method was 1,3-dipolar cycloaddition of nitrile oxides with nitrile and second method was cyclocondensation of amidoximes with carbonyl containing reactants; such as activated acids, acid chlorides and fluorides, esters, acid anhydrides and β-ketoesters.

Scheme 23. Photo chemical rearrangement of 1,2,4-oxadiazoles.
1,2,4-Oxadiazepines

1,2,4-oxadiazepines are seven-membered ring heterocycles containing two nitrogen and one oxygen atoms on the ring. In fact, there are nine isomers are possible in oxadiazepines [47-58] (Scheme 24). 1,2,3-[47], 1,2,4-[48], 1,2,5-[49], 1,2,6-[50], and 1,2,7-[51] Oxadiazepines are not known but few derivatives of their fused or benzo-fused few analogues are known.\(^9^7\)

\[ \text{Scheme 24. Isomers of oxadiazepines.} \]

Compound containing the oxadiazepine skeleton\(^9^8-1^0^2\) have attracted interest in bio-organic, natural products and medicinal chemistry.

Lim [56] (Scheme 25) has isolated a natural product containingg fused oxadiazepinete trihydrofuran group from *Malayan Tabernaemontana corymbosa*\(^1^0^3\)
Scheme 25. Structure of a naturally occurring fused oxadiazepine.

They are an important class of heterocyclic compounds that have found in several drugs. Diazepam [57], Chlorodizepoxide [58], Oxazepam [59] belongs to Benzodiazepines class of drugs (Scheme 26) that produce central nervous system (CNS) depression and that are most commonly used to treat insomnia and anxiety. Among them biological activities including antimicrobial, antifungal, and anticancer. A few methods have been reported in the literature for the synthesis of oxadiazpine heterocycles which are multi-step in nature. Based on our literature survey, reports on the synthesis of oxadiazpine heterocycle are few few.

Scheme 26. Benzodiazepines class of drugs.

1.4 Aim of the Work

Now-a-days small libraries molecules become an important source for the discovery of new drug molecules. In particular, heterocycles with pyrrole and
oxadiazole ring which exist in the structure of many natural products possessing biological activity beside their valuable feature of being versatile building blocks in organic synthesis and important starting materials for various synthetic transformations, there exist a constant demand for the development of new methods for the synthesis of pyrrole and oxadiazole. Synthesis of pyrroles in high yields with minimum number of steps through metal-free catalytic reaction has become an attractive goal for many synthetic organic chemistry research groups. Being aware of the importance of pyrrole, oxadiazole derivatives and the importance of development of new and efficient synthetic method for them.

In the first part of this study we aimed to develop an efficient method for the synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives through acid catalyzed cyclization reaction and evaluated for their antiproliferative activity against different human leukemic cell lines [K562, HeLa] at lower concentration.

And we aimed to develop an efficient method for the synthesis of novel 3,5-diaryl 1,2,4-oxadiazole derivatives. All the synthesized compounds were evaluated for their antimicrobial activity against two bacteria in the second part of this study.

We aimed to develop an efficient method for the synthesis of novel oxadiazepine derivatives through trifluoro propionoic acid as shown in the in the third part of this study.

And finally crystal and molecular structure studies of pyrrole derivatives were studied in this thesis.
REFERENCES


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