PREFACE

The study of heterocycles is an evergreen field in the branch of organic chemistry and always attracts the attention of scientists working not only in the area of natural products but also in the synthetic organic chemistry. Heterocyclic compounds are very widely distributed in nature and are essential to life in various ways due to their wide variety of physiological activities. Heterocycles play a vital role in pharmacological, agricultural and synthetic fields. Amongst different heterocyclic systems, the chemistry of 5-membered heterocycles with more than one heteroatom such as isoxazolines, pyrazolines and oxadiazoles have gained significance because of their pronounced bioactive nature.

Heterocycles containing an oxygen and nitrogen heteroatoms are considered as an important class of compounds in medicinal chemistry because of their diversified biological applications. The exploitation of a simple molecule with different functionalities for the synthesis of heterocycles is a worthwhile contribution in the chemistry of heterocycles. Isoxazoles have been demonstrated to be very versatile building blocks in organic synthesis, which are largely used in the synthesis of pharmaceutically important molecules.

Pyrazoles and its derivatives are well known nitrogen heterocycles that occupy a prime position in medicinal and pesticide chemistry for their broad spectrum of biological activities. They have been known to exhibit antimicrobial, analgesic, anticancer, anti-tubercular, anti-inflammatory, antidepressant, anticonvulsant, antihyperglycemic, antipyretic, antihelmintic, antioxidant and herbicidal properties.

1,3,4-oxadiazoles are biologically versatile compounds displaying a variety of biological effects, which include anti-inflammatory, antifungal, antiparasitic, CNS
depressant, insecticidal, antitubercular, anti-HIV, herbicidal, anticonvulsant and antimicrobial activities. They have also known to exhibit antimalarial, muscle relaxants, antitumour, lipid peroxidation inhibitor, diuretic, hypnotic and sedative properties.

In view of the above facts, we have planned to synthesize heterocyclic compounds having above said moieties with a hope of getting the new molecules with enhanced biological activities.

The thesis entitled “Synthesis, Characterization and Biological Studies of Five Membered Nitrogen Heterocycles” comprises of five chapters, which are further divided into subsections. The contents of the thesis are highlighted in the following paragraphs.

Chapter-1 of the thesis is an introductory chapter. It has three parts. Part-I deals with the general background, mechanistic considerations, stereochemical aspects and applications of 1, 3-dipolar cycloaddition reactions. Part-II comprises of introduction, literature survey pertaining to the generation, cycloaddition reactions and uses of nitrile oxides in the synthesis of biologically active molecules. Part-III comprises of introduction, literature survey pertaining to the generation and applications of nitrile imines in cycloaddition reactions.

Chapter-2 comprises of general introduction, literature survey pertaining to the synthesis, reactions and applications of isoxazolines. Following the introductory part, this chapter discusses the synthesis of isomeric mixture of 3-aryl-5-(4-methoxyphenyl)-4, 5-dihydroisoxazole-4-carbonitriles (61) (major) and 3-aryl-4-(4-methoxyphenyl)-4, 5-dihydroisoxazole-5-carbonitriles (62) (minor) products utilizing 4-methoxy cinnamonicnitrile (60) as precursor (Scheme-64). Various aromatic
aldoximes (59) were prepared from aromatic aldehydes by reacting with hydroxylamine hydrochloride in the presence of sodium acetate in ethanol as a solvent (Scheme-62). The 1, 3-dipolar cycloaddition reactions of nitrile oxide generated in situ by the catalytic dehydrogenation of aldoximes with 4-methoxy cinnaminitrile using chloramine-T and magtrieve (CrO₂) as reagents gave a series of isomeric mixture (61 and 62) of new isoxazolines.

All the synthesized new isoxazoline derivatives (61) and few of isomeric forms (62) were characterized by spectral and elemental analysis and were tested for their antimicrobial susceptibility activity against Gram-negative bacteria species *Escherichia coli* and *Salmonella typhimurium*, Gram-positive bacteria species *Bacillus subtilis* and *Staphylococcus aureus*. They were also tested against the fungi species *Aspergillus niger*, *Aspergillus flavus* and *Candida albicans*. The antibiotics ciprofloxacin and griseofulvin were used as standard drugs against bacteria and fungi species respectively. The antioxidant activity of the synthesized compounds was evaluated by DPPH radical scavenging method.

Probable mechanisms for the generation of nitrile oxide using chloramine-T and magtrieve (CrO₂) and 1, 3-dipolar cycloaddition reaction of nitrile oxide with 4-methoxy cinnaminitrile (60) to give isoxazolines (61) and (62) were discussed. The present method is concise and efficient. The main advantage of this process is easy work up process and good yields are observed. The spectral studies, antimicrobial and antioxidant activity results of the synthesized compounds are discussed.

Chapter-3 comprises of general introduction, the literature survey pertaining to the synthesis, reactions and applications of pyrazolines. Following the introductory part, in the chapter efforts have been made for the synthesis of isomeric mixture of 3-aryl-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole-5-carbonitriles (91,
Major) and 3-aryl-5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole-4-carbonitriles (92, Minor) products. The targeted compounds were synthesized by 1, 3-dipolar cycloaddition reaction of \textit{in situ} generated nitrile imines with 4-methoxy cinnamonicitrile (60) (Scheme-99). Various aromatic aldehyde phenyl hydrazones (90) were prepared from aromatic aldehydes by reacting with phenyl hydrazine hydrochloride in the presence of sodium acetate in ethanol as a solvent (Scheme-98).

The synthesized new pyrazolines derivatives were characterized by IR, $^1$H NMR, $^{13}$C NMR, MS studies and elemental analysis. The synthesized compounds were tested for their antimicrobial susceptibility activity against bacteria species \textit{Escherichia coli}, \textit{Salmonella typhimurium}, \textit{Bacillus subtilis}, \textit{Staphylococcus aureus} and against the fungi species \textit{Aspergillus niger}, \textit{Aspergillus flavus}, \textit{Candida albicans} and \textit{Fusarium oxysporium}. The antibiotics streptomycin and griseofulvin were used as standard drugs against bacteria and fungi species respectively. The antioxidant activity of the synthesized compounds was evaluated by DPPH radical scavenging method.

Probable mechanisms for the generation of nitrile imine using chloramine-T and 1, 3-dipolar cycloaddition reaction of nitrile imine with 4-methoxy cinnamonicitrile (60) to give pyrazolines (91) and (92) were discussed. The main advantage of the reaction is it involves a simple procedure, mild conditions and produces good yields. The spectral studies, antimicrobial and antioxidant activity results of the synthesized compounds are discussed.

Chapter-4 deals with synthesis of trisubstituted 4, 5-dihydro pyrazole derivatives (121) using 4-phenylbut-3-en-2-one (119) as the precursor. 4-phenylbut-3-en-2-one (119) reacts with substituted phenyl hydrazines (120) in the presence of sodium acetate to form trisubstituted 4, 5-dihydropyrazoles (121) in good yield.
The intermediate phenyl-hydrazones could very rarely be isolated with 4-phenylbut-3-en-2-one (119). It might be expected that the reaction of α, β-unsaturated compounds with phenyl hydrazine or other substituted hydrazines would proceed through ring closure in a straightforward way to give pyrazolines. We have demonstrated the crystal and molecular structure of 3-methyl-1,5-diphenyl-4,5-dihydro-1H-pyrazole by the single crystal X-ray diffraction technique.

The synthesized new pyrazolines derivatives were characterized by spectral, X-ray diffraction and elemental analysis and were tested for their antimicrobial susceptibility activity against fungal species C. albicans, A. niger, A. flavus and bacteria species E. coli, S. typhimurium, B. subtilis. The antibiotics amphotericin B and ciprofloxacin were used as standard drugs against fungi and bacteria species respectively. Probable mechanism for the formation of pyrazoline is discussed. The main advantage of this process is, it is an easy accessible method and appreciable yields are observed. The spectral studies and antimicrobial activity results are discussed.

Chapter-5 comprises of general introduction, the literature survey pertaining to the synthesis, reactions and applications of 1, 3, 4-oxadiazoles. Following the introductory part, the present work deals with the synthesis of 2, 5-disubstituted 1, 3, 4-oxadiazoles (140) using ethyl oleate (137) as the precursor. In order to synthesize the target molecules, initially stearic acid hydrazide (138) was synthesized by refluxing ethyl oleate with hydrazine hydrate in absolute alcohol on a water bath for 3 h. Ethyl oleate (137) reacts with hydrazine hydrate to form stearic acid hydrazide (138), the reaction proceeds with the simultaneous reduction of 9, 10 C=C bond of ethyl oleate. The stearic acid hydrazide formed on intermolecular cyclization with different aliphatic acids or aromatic acids (139) or ethyl oleate (137) in the presence
of phosphorus oxychloride gives 2, 5-disubstituted 1, 3, 4-oxadiazoles (140) in good yield (Scheme-131).

The synthesized new compounds were characterized by spectral and elemental analysis. The synthesized compounds were subjected to antibacterial and antifungal activity assay by cup diffusion and poisoned food technique against *Escherichia coli*, *Staphylococcus aureus* and three strains of seed borne toxigenic *Fusarium verticilloides* isolated from maize (*Zea mays* L.) and paddy (*Oryza sativa* L.). *F. verticilloides* was confirmed by species specific primers VERT 1 and VERT 2 and fumonisin producing ability was confirmed by VERTF-1 and VERTF-2 using polymerase chain reaction. The antibiotics gentamicin and streptomycin were used as standard drugs against bacteria species.

Probable mechanism for the formation of 2, 5-disubstituted 1, 3, 4-oxadiazoles was discussed. The main advantage of this process is, a new class of symmetrical and unsymmetrical 1, 3, 4-oxadiazoles were prepared adopting simple and versatile methodology. The characterization of the compounds by spectral studies, elemental analysis and the antimicrobial activity results of the new 1, 3, 4-oxadiazoles are discussed.

At the end of the 5 chapters, complete list of references cited in all the five chapters is given in a separate section in cumulative order.