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Farheen
Preface

The synthesis of heterocyclic compounds has always drawn the attention of researchers over the years mainly because these compounds have played vital roles in biological processes, agrochemicals, pharmaceuticals and also in human life. Therefore, the development of simple, facile, efficient and environmentally benign chemical processes or methodologies to synthesize novel heterocycles and their derivatives is one of the major aspects in organic synthesis.

The work embodied in this thesis entitled “Studies in Chemistry of Oxygen and Nitrogen heterocycles” deals with the design and development of simple and efficient protocol to synthesize new biologically important heterocyclic derivatives from cheap and readily available starting materials such as 4-hydroxycoumarin, 3-formylchromone, 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde and 3-formyldindle. To discuss systematically, thesis is divided into five chapters, which are as follows:

Chapter 1

Pyrazoles, Pyridines, Coumarins, Chromones and Indoles are well known nitrogen and oxygen heterocyclic compounds which are employed as important skeletons in organic synthesis, medicinal chemistry and pharmacology. Therefore, various applications associated with these molecules motivated us to select them as potential candidates for the synthesis of novel heterocycles. This chapter contains scope of present work and depicts a comprehensive survey of literature on the synthesis and reactions of starting materials namely, 4-hydroxycoumarin, 3-formylchromone, 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde, 3-formyldindle, which were taken throughout the thesis and for their applications in the synthesis of different five and six membered heterocycles such as β-enaminones, pyrazoles, pyridines, dicoumarols, chromanones, indolyl chalcone, indolyl pyrazolines etc.
Chapter 2

β-Enaminones are important synthetic intermediates for the synthesis of various biologically active heterocyclic compounds due to presence of an amino group linked through a C=C to a carbonyl group. Thus, due to their importance in pharmaceuticals and in organic synthesis as intermediates, in this section, we have described a simpler and clean method for the synthesis of heterocyclic β-enaminones (176a-d) by condensation of heterocyclic methyl ketones (174a-d) with DMF-DMA (175) by thermal heating under solvent- and catalyst-free condition at lower temperature in excellent yields. Attempts were made to synthesize pyrazole (178a-h) and pyranyl pyridine derivatives (180a-h) by the reaction of β-enaminone (176a) with different hydrazines (177a-b) and active methylene compounds (179a-h) respectively under thermal solvent-free condition in the presence of NaHSO₄-SiO₂. As expected reactions proceeded efficiently and the desired products were obtained in excellent yields. The catalytic system, NaHSO₄-SiO₂ and products were characterized by powder XRD, SEM and EDX and spectral analysis respectively.

Chapter 3

Dicoumarol is a naturally occurring anticoagulant drug that functions as a vitamin K antagonist and possesses various other pharmacological activities such as insecticidal, anthelmintic, hypnotic, antifungal, phytoalexin, HIV proteases inhibition, antimicrobial and antioxidant etc. In clinical trials, such compounds have also demonstrated to have some activity against prostate cancer, malignant melanoma and metastatic renal cell carcinoma. Homogeneous catalysis play a key role in the development of greener, more sustainable chemical processes, and are powerful tools for the synthesis of fine chemicals, pharmaceuticals and materials. This chapter is divided into two sections and describes the synthesis of dicoumarols and 2-hydroxy-4-chromanones in the presence of Zn[(L)proline]₂ as an efficient, environmentally benign, water-tolerant, Lewis acid catalyst in green solvent, “water” as the reaction medium.
Initially, attempts were made to synthesize dicoumarol derivatives (182a–j) by the reaction of 4-hydroxycoumarin (29) with a variety of aromatic/heteroaromatic aldehydes (181a–j) in the presence of 5 mol % Zn[(L)proline]₂ in reflux water. The products were obtained in excellent yield in a short time period. In order to show the superiority of Zn[(L)proline]₂:water catalytic system, a model reaction of 4-hydroxycoumarin and 4-hydroxybenzaldehyde was carried out in different catalysts, solvents and with different amount of catalysts. And it was observed that Zn[(L)proline]₂ exhibited the highest catalytic activity over other catalyst and water as the best solvent for the formation of dicoumarols in terms of reduced reaction time and the maximum yield of the products. The catalyst was successfully recovered and recycled without significant loss in yield and selectivity. All the synthesized compounds were characterized by spectroscopic data.

Further Zn[(L)proline]₂ was explored for the synthesis of new series of chromanaone derivatives (185a–j) by the reaction of 3-formylchromone (64) with various amines (183a–j) in refluxing water. All the reactions were found to be completed within 10-15 min and afforded chromanone derivatives (185a–j) in excellent yields. The method was advantageous in terms of mild reaction conditions, use of water as solvent, cleaner reaction profiles, simplicity in operation, excellent yields of the products, faster reaction rates and reusability of the catalyst with no loss in its activity.

CHAPTER 4

Due to the widespread applications associated with pyrazole and their derivatives from pharmacological, agrochemicals and industrial point of view, this chapter is divided into two sections. Section A, deals with the synthesis of novel halopyrazole derivatives (187) and (189) in good yields by using 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde (105) as starting material. The structures of the compounds isolated were characterized by elemental and spectral analysis.
The infections caused by various microorganisms pose a serious challenge to the medical community and need for an effective therapy led to a search for novel antimicrobial agents. Therefore, all the newly synthesized compounds were evaluated for their in vitro antimicrobial activity against *Streptococcus pyogenes*, Methicillin resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Bacillus subtilis*, *Salmonella typhimurium* and *Escherichia coli* bacterial strains and fungal cultures of *Candida albicans*, *Aspergillus fumigatus*, *Aspergillus niger*, *Trichophyton mentagrophytes* and *Penicillium marneffei* by disk diffusion assay. The investigation of antibacterial and antifungal screening data revealed that all the tested compounds (187) and (189) showed moderate to good bactericidal and fungicidal activities. MIC of compounds was in the range of 12.5–50 µg/mL. The MBC of compounds was found to be two or four folds higher than the corresponding MIC results.

**Chapter 5**

This section divided into two sections

Microwave-assisted organic reaction enhancement is well-established technique for rapid and efficient synthesis of variety of heterocycles particularly from the viewpoint of green chemistry. In the microwave environment chemical reactions usually proceed faster and give higher yields with less by-products and allows fast optimization of chemical reactions compared to conventional heating.

Chalcones (1,3-diaryl-2-propene-1-ones) are natural substances found in fruits, vegetables, spices, tea and soy based foodstuff and has been subject of great interest for possessing interesting pharmacological activities. On the other hand pyrazoline nucleus is a ubiquitous feature of various compounds possessing many pharmacological and physiological activities.
Keeping in view the potential biological activities of indole, chalcones and pyrazolines as well as the utility of microwave irradiation in organic synthesis, this section of the chapter deals with the synthesis of indolyl chalcones (192a-c) and their substituted pyrazoline derivatives (193a-f) under microwave irradiation. As visualized, the reaction proceeded smoothly under solvent-free condition and the products were obtained in excellent yield in shorter time period. The work also describes the superiority of green synthetic methods over conventional heating procedure. All the newly synthesized compounds were characterized by elemental and spectral analysis.

In recent years, there is a considerable therapeutic interest in novel anti-inflammatory drugs with a mode of action different from that of the classical acidic nonsteroidal anti-inflammatory drugs (NSAIDs), mainly for use in patients with arthritis of varying degree of severity. The classical NSAIDs do not prevent progression of such a disease and are subject to irritant side effects. The most prevalent side effect of the use of NSAIDs is the occurrence of gastrointestinal damage with gastric upset, bleeding, nephrotoxicity, intolerance and renal toxicity and irritation being the major problems. Therefore, the discovery of new and safer anti-inflammatory drugs represents a challenging goal for such a research area. A literature survey reveals that the compounds with the backbone of chalcone and pyrazolines attached to an indole nucleus may show improved anti-inflammatory activity in carrageenan induced inflammation model. Thus, keeping this in view, in this section the present study was undertaken to investigate the anti-inflammatory activity of the synthesised compounds (indolyl chalcones and pyrazolines) (192a-c and 193a-f) in experimental models using carrageenan induced paw edema assay model of inflammation on Wistar rats, using aspirin as reference drug.