Preface

The work presented in this thesis concerns with the synthesis and biological evaluation of a variety of new nitrogen, sulphur and oxygen containing heterocycles. The thesis is divided into two sections, consisting of seven chapters in all. Section A, comprising of chapters 1-5 describes the general introduction, applications, synthesis, characterization and biological testing results of some sulphur and/or nitrogen containing heterocycles of potential medicinal interest. The work reported in Section B on 5-substituted benzyloxy-2-arylbenzofuran-3-carboxylic acids has partly been carried out in the laboratories of Late Dr. Aaron D. Mills at Department of Chemistry, University of Idaho, Moscow, USA. This section, comprising of chapters 6 and 7, presents a brief overview of ion channels with special emphasis on calcium activated chloride channels (CaCCs) and TMEM16A protein as well as synthesis, characterization and biological evaluation of novel 5-substituted benzyloxy-2-arylbenzofuran-3-carboxylic acids as CaCC inhibitors. Each of the chapters 2, 3, 4, 5 and 7 begins with a brief introduction highlighting the rationale of undertaking the present work. This is followed by a detailed discussion of the synthetic methodology used, and elucidation of the structures of the compounds thus synthesized through rigorous analysis of their IR, NMR, and Mass spectral data analysis. Biological testing results, conclusions and experimental details follow the discussion while adequate bibliography has been appended at the end of the each chapter.

Chapter 1 provides an overview of the applications, synthetic strategies, characterization and biological applications of various nitrogen and/or sulphur containing heterocycles that have been synthesized during the course of the work. Because of the space restrictions in these introductory pages, the literature citation has been illustrative rather than exhaustive.

Chapter 2 begins with motivation for undertaking the present work followed by synthetic discussion as well as biological evaluation of newly synthesized bipyrazole derivatives. This chapter is extension of the M. Phil work undertaken by me whereby a series of pyrazolylpyrazolines were synthesized. During the course of M. Phil work, we attempted a few methods to oxidize pyrazolylpyrazolines into bipyrazoles but could not succeed. In the course of Ph.D. work, we have successfully oxidized pyrazolylpyrazolines into bipyrazoles by utilising oxone/DMF/H$_2$O system.
Vilsmeier-Haack reaction was utilized for synthesis of formylpyrazole from hydrazones, Claisen-Schmidt condensation of formylpyrazoles with appropriately substituted acetophenones yielded chalcones. Chalcones and appropriate hydrazine were refluxed in ethanol in the presence of catalytic amount of glacial acetic acid to afford pyrazolylpyrazolines which in turn, were oxidized to corresponding bipyrazoles by oxone in refluxing DMF-H₂O system. Target compounds were evaluated for their in-vivo anti-inflammatory (AI) and in-vitro antimicrobial activity and many of the compounds exhibited good activity.

Chapter 3 starts with a brief description about the motivation for the present work which is followed by synthetic discussion as well as biological evaluation of newly synthesized pyrazolines as antimicrobial, antioxidants, and anti-inflammatory agents. In the present study, a series of pyrazolines, bearing sulphonamide moiety, methoxy and free hydroxyl groups has been synthesized by condensation of substituted chalcones and appropriate hydrazine. Newly synthesized compounds were evaluated for their AI and antimicrobial activity. Four compounds bearing free hydroxy groups were evaluated for their antioxidant activity. Some of the target compounds exhibited good antimicrobial, antioxidant and anti-inflammatory activity.

Chapter 4 deals with the synthesis of pyrazolylthiazole derivatives and presents the rationale for undertaking the present work, synthetic discussion as well as evaluation of newly synthesized pyrazolylthiazole derivatives as potential antimicrobial agents. To achieve the synthesis of target compounds, 4-cyanopyrazoles were prepared from 4-formylpyrazoles using I₂/aq.NH₃/THF. Cyano group was further transformed into carbothiomides by passing H₂S gas through a solution of 4-cyanopyrazoles in pyridine in the presence of triethylamine. Four of the newly synthesized pyrazolylthiazoles exhibited excellent AI activity comparable to the reference drug indomethacin while a few of them were identified as potent antimicrobial agents.

Chapter 5 describes in detail the synthesis and biological evaluation of some newly synthesized benzimidazole derivatives of potential medicinal interest. In this study, we have combined two heterocyclic rings, pyrazole and benzimidazole in a single pharmacophore in search of more potent drug candidates. Both of these heterocyclic rings individually are of much medicinal interest as evident from their
broad spectrum of bioactivities e.g., anti-cancer, antibacterial, antifungal, anti-inflammatory, etc. After a few failed attempts, target compounds were synthesized by refluxing 4-formylpyrazoles with o-phenylenediamine in oxone/DMF/H$_2$O system. The 4-formylpyrazoles in turn were synthesized from appropriate hydrazones exploiting the Vilsmeier-Haack reaction. The target compounds synthesized in this series are being evaluated for their antimicrobial as well as anti-inflammatory activity.

Chapter 6 provides a brief description about the significance of anion channels with special emphasis on calcium activated chloride channels (CaCCs) in biological systems. Structure and function of TMEM16A as well as physiological roles of CaCCs have been discussed in brief along with the mechanism of activation of these channels.

Chapter 7 details the work carried out on novel 5-substituted benzylxoxy-2-arylbenzofuran-3-carboxylic acids as CaCC inhibitors. Synthesis of novel target compounds was achieved starting from ethyl 3-aryl-3-oxopropanoates which were obtained by carbethoxylation of the commercially available appropriately substituted acetophenones with diethyl carbonate using sodium hydride. Condensation of the ethyl 3-aryl-3-oxopropanoates with p-benzoquinone-ZnCl$_2$ in DCM in microwave reactor resulted in the formation of substituted ethyl 5-hydroxybenzofuran-3-carboxylates. Ethyl 5-hydroxybenzofuran-3-carboxylates were in turn condensed with substituted benzylbromides in acetone in the presence of anhydrous potassium carbonate to yield ethyl 5-aryloxy-2-arylbenzofuran-3-carboxylate which on base hydrolysis afforded the target compounds. The target compounds were evaluated for their selective calcium activated chloride channel/TMEM16A inhibition. Some of the compounds exhibited excellent TMEM16A inhibition. Anti-asthma investigations are underway for 2y and four other compounds (2m, 2u, 2aa and 2ab) in the laboratories of our collaborator Prof. Charles Emala, Department of Anesthesiology, Columbia University, New York, USA.

All the final compounds as well as novel intermediates synthesized as a part of the thesis work have been characterized by a rigorous analysis of their IR, $^1$H NMR, $^{13}$C NMR and Mass spectral data.