Preface

The thesis delineates the synthesis of fused triazoles and 4-functionalized pyrazoles as carbonic anhydrase inhibitors and development of elegant methodologies for synthesis of some heterocyclic compounds and their precursors. The work manifested in thesis is organized in the form of two sections spanning over six chapters in all. Section A, comprising of chapters 1-3, describes the general introduction to carbonic anhydrases (CAs) and their inhibitors, synthesis, characterization and biological testing results of fused 1,2,4-triazoles and 4-functionalized pyrazoles. Section B, comprising of chapters 5-6, presents facile and efficient synthetic methodologies for 3-chloroacrylonitriles, propynenitriles and triazolothiones.

A brief introduction to carbonic anhydrases, their mechanism of action as well as inhibition is given in chapter 1. This chapter also provides a brief review on selective inhibitors of tumor associated hCA IX and XII isoforms of CAs over hCA I and II as a promising strategy in cancer therapy.

The second chapter describes the synthesis and biological evaluation of two series of benzenesulfonamide bearing fused triazoles namely triazolothiadiazines and triazolothiadiazoles. All the newly synthesized compounds were evaluated as CA inhibitors against hCA I, II, IX and XII, as well as for anti-inflammatory–antimicrobial activity profiles. Many of the tested compounds exhibited excellent CA inhibition profile showing low nanomolar potency ($K_i < 10$ nM) against the tumor associated isoforms hCA IX and XII as well as good anti-inflammatory–antimicrobial activity profiles.

Chapter 3 describes the synthesis of two different series of 4-functionalized pyrazoles. In the first series, 1,3-diarylpyrazole-4-carboxamides bearing benzenesulfonamide moiety at position-1 of pyrazole ring are synthesized and evaluated as CA inhibitors as well as antimicrobial agents. The second series describes 4-functionalized pyrazoles containing 6-aminosulfonylbenzothiazole moiety at position-1 of the pyrazole ring which were evaluated for CA inhibition as well as anti-inflammatory – antimicrobial activity profile. In the second series, benzothiazole ring was introduced with the purpose to provide a space linker between sulfonamide group and the pyrazole motif. Pyrazole-4-carboxamides bearing benzenesulfonamide at position-1 of pyrazole ring were the most potent compounds exhibiting excellent inhibitory potential against all of the four hCA isoforms. Many compounds of this series were better inhibitors against all the tested hCA isoforms as compared to the standard drug AZA. Pyrazoles containing 6-aminosulfonylbenzothiazole moiety were
comparatively weaker inhibitors of hCA isoforms as compared to pyrazole-4-carboxamides but have shown high degree of selectivity for hCA IX and XII over hCA I.

Chapter 4 opens up with a brief description of synthetic importance of 3-chloropropenenitriles as precursors for heterocyclic compounds as well as the methods available for their preparation and limitations associated with them. Further, this chapter reports a novel and efficient approach for the straightforward synthesis of 3-chloropropenenitriles from 3-chloropropenals under mild aqueous reaction conditions. The methodology reported here is clearly better as the transformation from chloropropenals to chloropropenenitriles is directly achieved in excellent yields under milder aqueous conditions using equimolar molecular iodine without involving a harsh dehydration step. Furthermore, the β-chlorocinnamionitriles obtained after simple work-up are sufficiently pure thus negating the need for flash chromatography.

Fifth chapter reports an efficient one pot procedure for the preparation of alkynenitriles starting from readily available chloropropenals. In line with chapter 4, this chapter also begins with a description of the synthetic importance of alkynenitriles, methods available for their preparation and associated limitations. The newly developed protocol uses economically benign aqueous reaction conditions and non-toxic reagents thus overcoming the limitations associated with reported procedures. Optimization of the protocol is discussed in detail in the subsequent section – results and discussion. It is noteworthy that no side products are formed in the reaction and yield of reaction is excellent while products formed do not need further purification.

Chapter 6 concerns with the development of a simple and facile one pot approach for the synthesis of triazolothiones from readily available aromatic amines and aryl acid hydrazides using carbon disulfide and sodium hydroxide. Aromatic amines were first converted to their corresponding dithiocarbamate salts using carbon disulfide as a reagent as well as solvent in presence of triethylamine. The in situ generated salts were treated as such in the next step with aromatic acid hydrazides in the same pot. The methodology developed is of practical significance and requires simple and easily available starting materials.

It is pertinent to mention here that CA assay for the compounds synthesized in chapter 2 and 3 has been performed in the laboratories of our collaborator Prof. Claudiu T. Supuran at Laboratorio di Chimica Bioinorganica, at University of Florence, Italy.