PREFACE

Heterocycles constitute the largest diversity of organic molecules of chemical, biomedical, and industrial significance. They widely exist in numerous natural products, such as vitamins, hormones, antibiotics, alkaloids, herbicides, and dyes. They are also among the most frequently encountered scaffolds in numerous drugs and pharmaceutically relevant substances. In the past several decades, a significant number of efforts have been made on the discovery and development of more efficient pharmaceuticals, pesticides, insecticides, rodenticides, weed killers by following well studied natural models and biochemical pathways in living cells. In addition, a series of libraries consisting of heterocycles have been successfully established for the structure activity-relationship studies (SAR) for drug design and synthesis. Meanwhile, the diversity-oriented synthesis (DOS) continues to be an area of importance at the interface of organic synthesis and chemical biology. While DOS plays an important role in searching for new bioactive small molecules with functional and stereochemical diversity, more efficient multicomponent domino reactions (MDRs) for the synthesis of a series of heterocycles, particularly functionalized multitargeted drugs, have been in high demand.

Multi-component reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product. By nature, MCRs are by no means restricted to a particular application, but rather they can be used advantageously in any area of modern chemistry-based technology.

Today, a large number of MCRs are known and many of them have been successfully applied in the synthesis of diverse heterocyclic scaffolds. The work embodied in this thesis is an attempt to Synthesize Novel Heterocycles with Potential for Drug Development.

The thesis entitled “Design and Synthesis of Novel Heterocycles with Potential for Drug Development.” describes our endeavors leading to the accomplishment of newer anti-hyperglycemic and anti-parasitic agents. The thesis has been organized under five main chapters as summarized below:

The first chapter presents a concise review on multi-component reaction derived synthesis of diverse heterocyclic scaffolds. A large number MCRs are known and they have been utilized in synthesis of almost all classes of heterocycles. As illustrated in this review, a wide variety of heterocycles of different sizes and ring systems can be readily synthesized through MCR strategies that often result in a broad scope of applications. More novel and efficient multicomponent
Domino reactions need to be developed for the synthesis of leading structures, particularly, of those complex products existing in nature. Solid-phase MCRs and enantioand diastereoselective MCRs have not been paid enough attention and will be interesting and challenging topics in modern organic chemistry. The review has been classified according to the number and type of heteroatoms in the ring systems.

The second chapter describes the “2,4-Disubstituted Hexahydroquinolines as New Agents Against Diabetes and Dyslipidemia.” 2,4-Disubstituted hexahydroquinolines (3d, 3l, 5b and 5d) have shown potent anti-hyperglycemic activity comparable to standard drugs along with significant lipid lowering activity in SLM, STZ and db/db mice models. Interestingly, in-vitro anti-hyperglycemic activity evaluation exhibited that compounds 3d (diaryl substituted) (IC\textsubscript{50} = 2.9 \mu M) and 4r (IC\textsubscript{50} = 4.7 \mu M) are potential PTP-1B inhibitors thereby revealing their possible mechanism of anti-diabetic action. Further study raveled that series of compound 3c, 3d, and 5b were showing promising anti-dyslipidemic activity in triton induced rat model. Thus, 2,4-disubsituted polyhydroquinoline show remarkable promise for further study as antidiabetic candidates.

The third chapter of the thesis illustrates the “Synthesis of Highly Functionalized 1,4-Dihydropyridines via a Domino Multicomponent Reaction and Their Antihyperglycemic Activity”. Encouraged by the results of previous chapter (Chapter 2) and our lab work on the synthesis and promising anti hyperglycemic activity of novel polyhydroquinoline derivatives prompted us to take some new dihydropyridines as a molecular template and an active pharmacophore for further diversification. Domino multicomponent reaction for the synthesis of dihydropyridines has been developed in solvent-free as well as catalyst free condition. The features of this procedure are mild reaction conditions, high yields, operational simplicity, and the environmentally friendly procedure. These synthesized dihydropyridine ring system were efficiently converted in to polyhydronaphthyridine in water. The synthesized compounds have been submitted for \textit{in-vivo} anti-hyperglycemic activity and results are awaited.

The fourth chapter of the thesis depicts the “Design and Synthesis of 3-Substituted Indole Derivatives as Anti- Diabetic Agents.” Inspired by the previous chapter based on the synthesis of antidiabetic agents, herein, we have developed a general, highly chemoselective, and novel three-component reaction of indoles, formaldehyde and tertiary aromatic amines using silica supported perchloric acid as catalyst for their anti-diabetic activity. The synthesis is operationally simple and offers high yields of the 3-alkylated indoles. however compounds did not show significant anti-diabetic activity in SLM as well as STZ-S model.
The fifth chapter of the thesis has been divided in two parts, first part (Chapter 5a) describes the synthesis "Natural Product Inspired Design and Synthesis of Chloroquine-Febrifugine Hybrids and Anti-Malarial Potential." Several synthesized compounds exhibited potent antimalarial activity in-vitro, and few of them were superior to chloroquine with exceptionally high selectivity index. 15 out of 25 synthesized compounds were more active than standard drug chloroquine against the CQ-R K1 strain and most active "in-vitro" compound (5g) showed IC$_{50}$ of 0.03 µg/ml with exceptionally high selectivity index (SI) of 2208.67. Further, in-vivo results on selected compounds revealed that these compounds also showed significant antimalarial activity in MDR plasmodium yoelii in Swiss mice and P.berghei (CQ-S) mice by oral route. The present findings are sufficient to establish the direction to overcome P. falciparum resistance to CQ both in-vitro and in-vivo via hybridization of drug (chloroquine) and natural product (febrifugine). Second part (Chapter 5b) involves the "Design and synthesis of Pentamidine Fused Quinazolinone Hybrids and Their Anti-Leishmanial Potential." The synthesized compounds have shown promising antilieshmanial activity. Two compounds (8e and 8f) having IC$_{50}$ values of 1.57µM and 4.18µM respectively were most promising compound, when compared to the standard drugs like Pentamidine (IC$_{50}$ = 20.43µM, SI = 2.58) and SSG (IC$_{50}$ = 71.90µM, SI = 5.53).

The sixth chapter of the thesis has been divided in two parts, first part (Chapter 6a), involves "Copper-catalyzed cascade heterocoupling of amides: efficient synthesis of biologically important quinazolinones". Herein we have investigated the first CuI mediated cascade heterocoupling of two amidic components for the synthesis of quinazolinone. This methodology was utilized for the total synthesis of sclerotigenin via coupling cascade approach. In addition, this methodology could be useful for the synthesis of several other quinazolinones related natural products and bioactive molecules. Second part (Chapter 6b) depicts the "Palladium assisted C-S activation and highly chemoselective N-H insertion: unprecedented synthesis of 2-aminopyrimidines". 2-Aminopyrimidines is ubiquitous substructures in variety of natural products, pharmaceuticals and display a wide range of biological properties. Therefore our interest has been towards the desulfitative synthesis of amino functionalized heterocycles. Herein we sought to uncover a first palladium assiated C-S activation of heteroaromatic thiols, via direct amination with ammonia and in-situ aerobic oxidation, which provides a versatile method for the synthesis of highly substituted 2-aminopyrimidine and their cytotoxicity evaluation.