Foreword

'Non-Conventional Synthesis–Bioactive Heterocycles', edited by Dr. Bubun Banerjee and Professor (Dr.) György Keglevich is an admirable compilation of seventeen chapters showcasing developments inthe nonconventional synthesis of bioactive heterocyclic compounds and related drug design and discovery. The narrative of the book is built on sustainable chemistry leading to efficient synthesis of a wide range of heterocyclic systems. All the chapters are written with a lot of acumen and with a global perspective based on the contributions made by a number of researchersinvolved in developing alternate ways for the synthesis of bioactive heterocyclic compounds. This book is indeed a pleasure to read, in part because it gives a concise but clear description of various nonconventional recent strategies and methodologies for the synthesis of a variety of bioactive heterocycles together with other aspects germane to the development of drug design and development.

Historically, the synthesis of heterocyclic compounds is of critical importance in thedevelopment of bioactive molecules, materials and a variety of industries. Further, the ever increasing presence of different types of heterocyclic units in drugs and pharmaceuticals has given much impetus to synthetic chemists for discovering and designing more and more efficient ways of synthesizing heterocyclic compounds, and for which numerous synthetic strategies and protocols have been developed over the years. In recent years, however, considering the detrimental effects on the Earth's environment due to excessive use of chemicals and release of chemical wastes from various chemical operations,feverish attempts have been made by the chemists, resulting into numerous successful endeavours of discovering, developing and promoting alternate ways of synthesizing chemical compounds, also including the heterocycles.The focus has been on replacing the conventional synthetic methods with alternate, efficient and environment-safe chemical reactions and processes, and technologies for scale-up production of chemical compounds for various needs.It is in these contexts, this book bears much significance.

This book comprises seventeen chapters. The first three chapters of the book showcase synthesis of various types of heterocycles under microwave irradiation conditions. In the 1st Chapter entitled 'Microwave-Assisted Catalyst-Free Synthesis of Bioactive Heterocycles', Ali Bodaghi, Ali Ramazani, and Zeinab Rafiee, review microwave-assisted synthesis of several five-, six- and seven-membered bioactive heterocycles in the absence of any catalyst under various reaction conditions. The chapter begins with an introductory remark highlighting some drugs and bioactive compounds containing heterocyclic rings. Subsequently the authors describe synthesis of a variety of heterocyclic compounds containing nitrogen, oxygen and sulfur atoms, combined heterocycles, and further other heterocycles such as 3-hydroxy-2-oxidoles, and 3-functionalized 4-hydroxycoumarins, etc.

In Chapter 2 entitled 'Microwave-Assisted Synthesis of *N*-Heterocycles", Chetna Ameta, Dharmendra, Yogeshwari Vyas, Purnima Chaubisa, Abhilasha Jain, and Suresh C. Ameta summarize recent developments in the microwave-assisted synthesis of bio-

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logically promising nitrogen-containing heterocycles using one-pot, multi-component techniques. The chapter uncovers synthesis of different types of five and six-membered heterocycles with one and two N-atoms, synthesis of triazole and tetrazole derivatives, and a few fused heterocyclic compounds containing N-atoms, *etc*.

In Chapter 3 entitled 'Microwave-Assisted Synthesis of *O,S*-Heterocycles', Rajib Sarkar and Chhanda Mukhopadhyay address several aspects of the synthesis of *O,S*-heterocyclic molecules under microwave irradiation. Presented in three parts, the first part uncovers the microwave protocols by using metal catalysts, the second part emphasizes the synthetic protocols utilizing non-metal catalysts, while the third part includes the catalyst-free microwave assisted protocols.

The contents of the above mentioned three chapters are adequate enough not only inproviding a good understanding of required reaction conditions under microwave irradiation for the synthesis of different types of heterocycles, but arealso useful in providing information needed for further development ofmicrowave-assisted synthetic protocols for the synthesis of bioactive heterocycles.

The next three chapters are about the ultrasound-assisted synthesis of heterocycles. Thus, in Chapter 4, Yadavalli Venkata Durga Nageswar, Katla Ramesh and Katla Rakhi in the article entitled 'Ultrasound-Assisted Synthesis of *N*-Heterocycles'highlight recent research findings in the application of ultrasonic irradiation in thesynthesis of a broad range of nitrogen-containing heterocyclic systems.

In chapter 5,GarimaAmetaa, Rakshit Ametab, Seema Kothari and Suresh C. Ameta in their article entitled "Ultrasound-Assisted Synthesis of *O,S*-Heterocycles' catalogue sonochemical synthesis of oxygen- and sulfur-atoms containing heterocycles, also including the chromenes, flavones, and a variety of other heterocyclic compounds comprising both the oxygen and sulfur atoms.

In the next chapter 6 concerning ultrasound-assisted synthesis, Bubun Banerjee, Aditi Sharma, Anu Priya, Manmeet Kaur and Arvind Singh in their article entitled 'Ultrasound-Assisted Synthesis of Bioactive 1,2,3-Triazoles *via* Click Reactions'summarize some of the recent advances inultrasound-assisted synthesis of structurally diverse and biologically promising 1,2,3-triazoles *via* the click chemistry between various azides and alkynes.

The examples of synthetic reactions uncovered in the abovementioned three chapters on ultrasound-assisted methods highlight the efficiency of the sonochemical methods for the synthesis of bioactive heterocyclic molecules of medicinal importance, and useful as scaffolds in different pharmaceuticals. The information provided in these chapters will be quite useful in enhancing the applications of sonochemical methods for the synthesis of bioactive heterocycles, which is expected to grow in the coming days.

In Chapter 7 entitled 'Photoirradiated Synthesis of Bioactive Heterocycles', Prabhakar Chettia, Vipin Kumar and V. Jayathirtha Rao present an informative account of UV-Vis light-mediated synthesis of different heterocycles containing N/O/S/O,N/N,S atoms. Also are included select named reactions useful in building heterocyclic frame-

works. The light-mediated synthetic routes are quite promising inproviding relatively more greener and sustainable ways of synthesizing bioactive heterocycles. However, theseprocesses need more attention, in particular with regard to achieving light-induced transformations as cleanly and in as high chemical yield as is the case in ground-state chemistry, and further developing a clear understanding of the light-mediated functional group manipulations and, more importantly, of mechanisms of such processes. This chapter can serve as a basis and reference guide for researchers interested in designing and developing light-induced synthesis of bioactive heterocycles endowed with various useful properties.

In Chapter 8 entitled 'Synthesis of Heterocycles through Electrolysis', Poulami Hota, Prasenjit Das, Rajjakfur Rahaman, and Dilip K. Maiti provide an assessment of the recent reports on the electrochemical synthesis of heterocycles.The authors showcase several electrochemical syntheses of a diverse group of heterocyclic compounds achieved through intra- and inter-molecular cyclizations involving oxidative / reductive formation of >C-C<, >C-O / >C-N< bonds, utilizing various electronically appropriate functional groups and reactive species. The chapter provides a good understanding of electrochemical synthesis of heterocyclic compounds, and will be helpful in designing and developing electrochemical routes to various bioactive heterocyclic systems.

In Chapter 9 entitled 'Flow Synthesis of Oxygen and Nitrogen Heterocycles', Moumita Saha, and Asish. R. Das discuss the merits and applications of continuous flow technique for synthesis. This emergent methodology allows sequential combinative-synthesis through which a diverse class of compounds can be obtained serially *via* application of single flow reactor containing flow switch, and is of much interest in industrial sectors, as well as in pharmaceutical research field, especially in the area of active pharmaceutical molecules. Besides giving a brief introduction of the Flow technique, the authors describe several examples of the synthesis of different kinds of bioactive heterocyclic compounds.The utility, versatility and productivity of flow technique for synthesis is expected to only further grow with the accessibility of novel microprocessor control chips.

Sabir Ahammed, Sandipan Ghosal and Brindaban C. Ranu in Chapter 10 entitled 'Ball-Milling Promoted Synthesis of Bioactive Heterocycles' present an accomplished and useful overview of the mechanochemically-induced synthesis of a range of heterocyclic molecules of much pharmaceutical importance. Under ball-milling condition, the reactions can be achieved at ambient temperature, and desirably avoiding toxic organic solvents and ligands. Attributes like solvent-free reaction, easy workup, and purification by crystallization avoiding chromatography, fast reaction and high yields of the products in mechanochemically-induced reactions make this approach quite useful for efficient synthesis of bioactive heterocycles.

Authors Sabbasani Rajasekhara Reddy, Neelima D. Tangellamudi, Bhulakshmi Sathi, Sridhar P, and Adinarayana Doddi, in Chapter 11 entitled 'Synthesis of Bioactive Heterocycles *via* click Reaction'explore the efficacy of the well-known click chemistry towards synthesis of various scaffolds of bioactive heterocyclic compounds. Among

several other aspects of heterocyclic compounds, the chapter provides a brief but adequate account of the applications of click reactions for diversity-oriented synthesisof various groups of bioactive heterocyclic systems, also including modifications of alkaloids.Indeed, the click chemistry has made significant progress in recent years. It offers a high potential reaction for identifying and optimizing the lead candidates in drug discovery and development and generating compound libraries, and further developing novel bioactive scaffolds for use in medicinal chemistry.

Prasenjit Das, PoulamiHota, Rajjakfur Rahaman and Dilip K. Maiti in Chapter 12 entitled 'Synthesis of Bioactive Heterocycles by Nanocatalysis' review the use and merits of nanocatalysts in the synthesis of heterocyclic compounds. Desirably, the chapter begins by outlining the basic aspects of nanocatalysts and nanocatalysis, which is followed by a brief survey of nanocatalysts in the synthesis of bioactive heterocycles. Several examples of nanocatalysts-mediated synthesis of heterocyclic systems containing N/O/S atoms in four, five, six and seven membered ring frameworks are presented. In the coming days, the nanocatalysis-mediated synthesis of bioactive heterocyclic compounds is expected to increase in research laboratories,industries and businesses.

Helene Pellissierin Chapter 13 entitled 'Enantioselective Metal-Catalyzed Domino Reactions in the Total Synthesis of Bioactive Heterocycles' highlight developments in the total synthesis of a variety bioactive chiral heterocycles based on asymmetric metal-catalyzed domino reactions as the key step. The chapter comprises four parts, dealing successively with the syntheses employing bisphosphine ligands, bisoxazoline ligands, P,N-ligands and a few other ligands. Such one-pot catalytic processes mediated by palladium and copper coordinated with different types of chiral ligands allow much complex bioactive heterocyclic architectures to be achieved from simple starting reagents. The asymmetric metal-promoted domino processes are expected to continue to attract attention of synthetic chemists for the total synthesis of bioactive heterocyclic molecules.

In Chapter 14, entitled 'Synthesis of Pharmacologically Significant Pentathiepins: A Journey from Harsh to Mild Conditions', Lukas M. Jacobsen, Roberto Tallarita, Siva S. M. Bandaru, and Carola Schulzke present a rich account of the synthesis of a special class of cyclic polysulfides – the Pentathiepins, which bear interesting pharmacological significance. The authors showcase synthesis of various pentathiepins achieved *via* metal-free approaches, and also *via*approaches utilizing metals like Tin, Titanium, and Molybdenum. Further, different reactions of pentathiepins, including thermal decomposition, reduction, oxidation, nucleophilic behaviour, ring contraction, and many other heterocyclic systems are also uncovered. Structural and physical characteristics of pentathiepins as seen under X-ray crystallography and various spectroscopic measurements, some recent DFT calculations results, and a brief discussion of biological activity and applications of different pentathiepinsand their analogues are also described.

The focus of Chapter 15 is on the synthesis of ring phosphine oxides, wherein in the article entitled 'Development in the Synthesis of Ring Phosphine Oxides', György

Keglevich presents a nice survey of results published in the last 5 years. The author records newer developments in the synthetic strategies for the cyclic phosphine oxides, such as 5- and 6-ring P-heterocycles, as well as large P-ring compounds and bridged derivatives. Among several other aspects, the new developments of phosphole oxides, phospholene oxides, oxaphospholenes, dihydrophosphinine oxides, tetrahydrophosphinine oxides, hexahydrophosphinine oxides, along with oxaphosphinine and azaphosphinine derivatives are discussed.

In Chapter 16, SabbasaniRajasekhara Reddy, Sathi Bhulakshmi and Sanjivani Pal in the article entitled 'Total Synthesis of Bioactive Heterocyclic Scaffolds *via* Pauson Khand Reaction' nicely uncover the efficiency of Pauson Khand Reaction (PKR), well-known for its ability to incorporate so much of molecular complexity in a single step. The chapter begins with an introduction to the PKR, which is followed by several examples of itsapplications in the construction of different types of terpenoids, alkaloids, and steroids, which in their cyclic structure contain N/O as hetero-atoms. Further highlighted are the possibilities of advancements in developing PKR-based sustainable synthetic methodologies using photocatalytic, aqueous mediated reactions, metal catalysts- based on cost effective and naturally abundant metals, etc.

The penultimate Chapter 17 entitled 'Nonconventional Approaches in Drug Discovery' is devoted to various aspects of rational drug discovery. Authors Shashi Kiran Misra and Kamla Pathak present an informative account of how nonconventional approaches for drug discovery drive parallel data generation, low volume bioassay and virtual screening in a cost effective manner.The authors rightly point out that these approaches enable researchers to design chemical libraries and facilitate more refined processes in reduced timelines. Due to minimum reagent and chemical consumption in nonconventional approaches, lead compound optimization and validation steps are economically chased. Further on, the authors underline the need for studies of phenotypic screening, predictive validation, biochemical interactions, suitable animal models and other bioassays for opting non-conventional approaches.

The learned authors have compiled recent developments in nonconventional synthesis of bioactive heterocycles and aspects of drug discovery together with an insightful analysis and thoughts regarding present-day scenarios and future prospects. In doing so, the authors have discussed ideas and observations of many researchers. Moreover, the book is written and presented in an easy and reader-friendly manner. The authors have discussed the matter in reasonable detail and various aspects of the subject are illustrated by suitable examples of reactions and synthetic transformations together with figures and mechanisms, where appropriate and necessary. At the end of each chapter, authors have included pertinent references on the scientific matters discussed. This will facilitate easy access to a lot of relevant recent references and will prove to be of considerable value to students, teachers and researchers alike.

Surely, the topics discussed in the book will sensitize and promote new thinking among researchers with interest in designing and developing environment-safe and sustainable chemical synthesis and technologies for bioactive heterocycles and re-

lated drug-worthy molecules. With the kind of research advancements made in recent years as evident from the material discussed in this book, it can be safely said that the coming years are destined to witness further development of this area with much greater stride and novelty. More and more new imperatives for the synthesis of bioactive heterocyclic compounds are expected to be discovered and developed, which is pivotal to further develop drugs, pharmaceuticals and many other chemical products.

For this, the editors and the authors deserve the heartfelt thanks of the community of students, teachers and researchers in chemical- and allied-sciences, for their commendable efforts of making available this volume on a subject of much interest. I congratulate the editors and the authors and convey my best wishes to them and all the readers.

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