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Topics in Heterocyclic Chemistry

Series Editor: R. R. Gupta

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Volume Editor: Satya Prakash Gupta

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The series *Topics in Heterocyclic Chemistry* presents critical reviews on "Heterocyclic Compounds" within topic-related volumes dealing with all aspects such as synthesis, reaction mechanisms, structure complexity, properties, reactivity, stability, fundamental and theoretical studies, biology, biomedical studies, pharmacological aspects, applications in material sciences, etc. Metabolism will be also included which will provide information useful in designing pharmacologically active agents. Pathways involving destruction of heterocyclic rings will also be dealt with so that synthesis of specifically functionalized non-heterocyclic molecules can be designed.
The overall scope is to cover topics dealing with most of the areas of current trends in heterocyclic chemistry which will suit to a larger heterocyclic community.
As a rule contributions are specially commissioned. The editors and publishers will, however, always be pleased to receive suggestions and supplementary information. Papers are accepted for *Topics in Heterocyclic Chemistry* in English.
In references *Topics in Heterocyclic Chemistry* is abbreviated *Top Heterocycl Chem* and is cited as a journal.

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Preface to the Series

Topics in Heterocyclic Chemistry presents critical accounts of heterocyclic compounds (cyclic compounds containing at least one heteroatom other than carbon in the ring) ranging from three members to supramolecules. More than 50% of billions of compounds listed in *Chemical Abstracts* are heterocyclic compounds. The branch of chemistry dealing with these heterocyclic compounds is called heterocyclic chemistry, which is the largest branch of chemistry and as such the chemical literature appearing every year as research papers and review articles is vast and can not be covered in a single volume.

This series in heterocyclic chemistry is being introduced to collectively make available critically and comprehensively reviewed literature scattered in various journals as papers and review articles. All sorts of heterocyclic compounds originating from synthesis, natural products, marine products, insects, etc. will be covered. Several heterocyclic compounds play a significant role in maintaining life. Blood constituent hemoglobin and purines as well as pyrimidines, the constituents of nucleic acid (DNA and RNA) are also heterocyclic compounds. Several amino acids, carbohydrates, vitamins, alkaloids, antibiotics, etc. are also heterocyclic compounds that are essential for life. Heterocyclic compounds are widely used in clinical practice as drugs, but all applications of heterocyclic medicines can not be discussed in detail. In addition to such applications, heterocyclic compounds also find several applications in the plastics industry, in photography as sensitizers and developers, and in dye industry as dyes, etc.

Each volume will be thematic, dealing with a specific and related subject that will cover fundamental, basic aspects including synthesis, isolation, purification, physical and chemical properties, stability and reactivity, reactions involving mechanisms, intra- and intermolecular transformations, intra- and intermolecular rearrangements, applications as medicinal agents, biological and biomedical studies, pharmacological aspects, applications in material science, and industrial and structural applications.

The synthesis of heterocyclic compounds using transition metals and using heterocyclic compounds as intermediates in the synthesis of other organic compounds will be an additional feature of each volume. Pathways involving the destruction of heterocyclic rings will also be dealt with so that the synthesis of specifically functionalized non-heterocyclic molecules can be designed. Each

volume in this series will provide an overall picture of heterocyclic compounds critically and comprehensively evaluated based on five to ten years of literature. Graduates, research students and scientists in the fields of chemistry, pharmaceutical chemistry, medicinal chemistry, dyestuff chemistry, agrochemistry, etc. in universities, industry, and research organizations will find this series useful.

I express my sincere thanks to the Springer staff, especially to Dr. Marion Hertel, executive editor, chemistry, and Birgit Kollmar-Thoni, desk editor, chemistry, for their excellent collaboration during the establishment of this series and preparation of the volumes. I also thank my colleague Dr. Mahendra Kumar for providing valuable suggestions. I am also thankful to my wife Mrs. Vimla Gupta for her multifaceted cooperation.

Jaipur, 31 January 2006 R.R. Gupta

Preface

The series *Topics in Heterocyclic Chemistry* now devotes its two volumes, Vols. 3 and 4, to today's most fascinating area of medicinal chemistry: quantitative structure-activity relationships (QSAR) and molecular modeling, which has revolutionalized drug discovery in the present era. These two volumes together present some very timely and important reviews on QSAR and molecular modeling studies in heterocyclic drugs and are titled *QSAR and Molecular Modeling Studies in Heterocyclic Drugs I* and *QSAR and Molecular Modeling Studies in Heterocyclic Drugs II*. Since the pioneering work of Corwin Hansch from 1962–1964 that laid the foundations of QSAR by means of three important contributions: the combination of several physicochemical parameters in one equation, the definition of the lipophilicity parameter π, and the formulation of the parabolic model for nonlinear lipophilicity–activity relationships, the area of computer-aided drug design with the development of computer technology went through a revolutionary change from two-dimensional to three-dimensional and now to multi-dimensional QSAR. The QSAR and molecular modeling studies have drastically reduced the cost and the time involved in the drug design and development. With the objective that some timely in-depth reviews on such studies in heterocyclic drugs may be of great value to those involved in drug discovery, some leaders in the field were invited to contribute and the overwhelming response led to devote two volumes on the topic. Both volumes cover the excellent and novel articles of varied interest.

Volume 3 contains five articles. The first article by Castro et al. describes the application of flexible molecular descriptors in the QSAR study of heterocyclic drugs. In this article, the various formulations of optimal descriptors introduced by different authors during the last ten years are discussed for the special case of heterocyclic drugs. The second article by Basak et al. is on predicting pharmacological and toxicological activity of heterocyclic compounds using QSAR and molecular modeling. Heterocyclic compounds are important as drugs, toxicants, and agrochemicals. In this article, the authors report the QSAR modeling of pharmacological activity, insect repellency, and environmental toxicity for a few classes of heterocyclic compounds from their structure. Pharmacological activity of drugs depends mainly on the interaction with their biological targets, which have complex three-dimensional structure, and their molecular recognitions are guided by the nature of in-

termolecular interactions. In the third article, therefore, Ponnuswamy et al. present conformational aspects and interaction studies of different heterocyclic drugs. In the next article, Khanna et al. describe, in detail, *in silico* studies on PPARγ agonistic heterocyclic systems. Several heterocyclic derivatives like oxazolidinedione, thiazolidinedione, tetrazole, phenoxazine, etc., are being developed for the treatment of insulin resistance and type 2 diabetes mellitus. The heterocyclic head group in these systems binds to and activates peroxisome proliferator activated receptor γ (PPARγ), a nuclear receptor that regulates the expression of several genes involved in the metabolism. In this article, therefore, various molecular modeling studies have been described that are important in understanding the drug–receptor interactions, analyzing the important pharmacophore features, identifying new scaffolds, and understanding the electronic structure and reactivity of these heterocyclic systems. The final article in this volume, written by Garg and Bhhatarai, is on QSAR and molecular modeling studies of HIV protease inhibitors. HIV protease is one of the major viral targets for the development of new chemotherapeutics against AIDS. In this article, therefore, Garg and Bhhatarai have presented a detailed study on structure–activity relationship studies on many groups of HIV protease inhibitors, providing the excellent rationale to design potent and pharmaceutically important protease inhibitors.

There are six fascinating articles in Vol. 4. These six articles present QSAR and molecular modeling on six different classes of heterocyclic drugs. The first article by Hadjipavlou-Litina is related to thrombin and factor FXa inhibitors. Both thrombin and factor FXa are bound to and are enzymatically active in blood clots. Thus a QSAR study on them may be of great use to investigate potent antithrombotics or antocoagulants. Similarly, the second article by Hannongbua has reviewed structural information and drug–enzyme interaction of the non-nucleoside reverse transcriptase inhibitors based on quantum chemical approaches, providing the valuable guidelines to design and develop potent anti-HIV drugs. Reverse transcriptase is an important enzymatic target to inhibit the growth of human immunodeficiency virus of type 1 (HIV-1), which is the causative agent of AIDS. In the next article, Vračko has described a QSAR approach in study of mutagenicity of aromatic and heteroaromatic amines. These compounds are highly hazardous to the environment and can be carcinogenic and thus are the subject of both theoretical and experimental studies.

Cocaine is a widely abused heterocyclic drug and there is no available anti-cocaine therapeutic, but in the fourth article Zhan describes the state of the art of molecular modeling of the reaction mechanism for the hydrolysis of cocaine and the mechanism-based design of anti-cocaine therapeutics. Amongst the heterocyclic systems, thiazolidine is a biologically important scaffold known to be associated with several biological activities. Some of the prominent biological responses attributed to this skeleton are antiviral, antibacterial, antifungal, antihistaminic, hypoglycemic, and anti-inflammatory activities. In the fifth

article, therefore, Prabhakar et al. have presented a very comprehensive review on the QSAR studies of diverse biological activities of the thiazolidines published during the past decade. This study may be of importance to explore the possibility if thiazolidine nucleus can be exploited to design the drugs for some other diseases. In the final article, however, Gupta has reviewed the QSAR studies on calcium channel blockers (CCBs). CCBs have potential therapeutic uses against several cardiovascular and non-cardiovascular diseases and the article throws light on how to design more effective CCBs that may be therapeutically useful.

Thus both these volumes of *Topics in Heterocyclic Chemistry* are unique and make interesting readings for all those involved, theoretically or experimentally, in design and development of drugs. As an editor of these volumes, I have greatly enjoyed reading the articles and hope all readers will too.

Pilani, March 2006 Satya Prakash Gupta

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