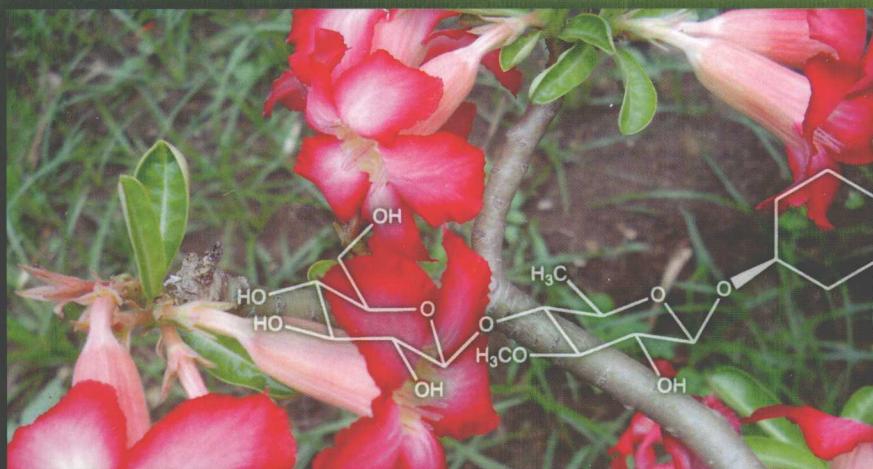
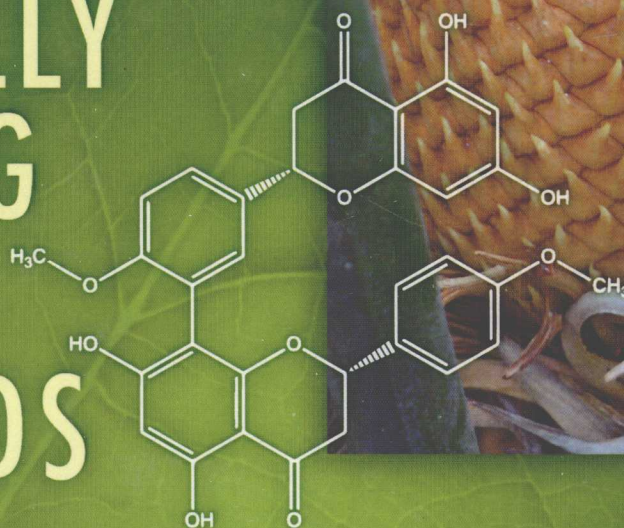




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CHEMISTRY and PHARMACOLOGY of NATURALLY OCCURRING BIOACTIVE COMPOUNDS

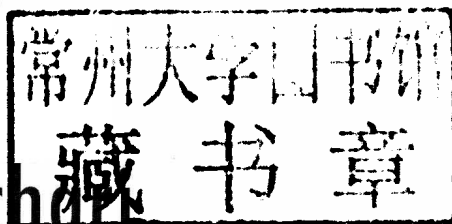
Edited by
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Dedication

*To all those who are working globally with bioactive
natural products for the cause of human welfare*

Forewords

Natural Products as Drugs—The Road Ahead

For millennia, natural products, mostly plants, were the only source of drugs. Some of the original knowledge has undoubtedly been lost. We know very little about the ancient use of plants in North and South America, most of Europe, Africa, and Australia. But some of the advanced ancient civilizations have left us amazing pharmacopeias. Many of the plants described in them have yet to be explored. The Assyrians (about the second millennium BC to the sixth century BC) have left us hundreds of tablets and plant lists, which were used by Campbell Thomson (1949) to compile a detailed Assyrian herbal. The Chinese classic medical pharmacopeia Ben Ts'ao, originally compiled around the first century AD and finalized in the sixteenth century AD, details thousands of prescriptions (Needham, 1978). The plant drugs used in Ancient Egypt (summarized by Von Deines and Grapow, 1959) are mentioned in many of the papyri. The outstanding herbal by Dioscorides (died circa AD 90) was one of the most influential drug books over 18 centuries. It summarizes in detail the existing knowledge on plant drugs in the Middle East and was widely copied by medieval herbalists (Dioscorides, 1934). Apparently, the well-established herbal use in India was first compiled and published by Da Orta (1563)—a Portuguese-Jewish physician who was on the run from the Inquisition. One can find in these herbals most of the medicinal plants that have been evaluated over the last century and from which many of the modern drugs have been developed—be they either the molecules as found in the plant or their synthetic derivatives. And we continue to find new natural medicinal agents in them. Artemisinin, the very valuable antimalarial drug from a Chinese plant, is just one of them.

The development of methods for the isolation and structure elucidation of natural products during the late nineteenth and over the twentieth century slowly decreased traditional herbal use. Many naturally occurring bioactive compounds and/or their derivatives have become drugs of central importance and represent a high percentage of the drugs used today. Antibiotics, hormones, and statins are well-known examples. Today, treatments that involve the use of plants or plant extracts are part of “alternative medicine.” However, still a large part of the population in third world countries relies on herbal products and, surprisingly, in the rest of the world their use is coming back.

Several decades ago, an isolated natural product with proven therapeutic activity could be introduced in the clinic shortly after its isolation. Thus, in the 1920s insulin became a drug within months after its identification. Various naturally occurring steroids became drugs within a few years after their discovery in the 1930s and 1940s. The picture has changed. For example, anandamide, a lipid brain constituent, with a wide spectrum of therapeutic properties as shown by animal trials, has never been administered to a human being nearly 20 years after its discovery (Devane et al., 1992). Due to lack of patent protection of most identified molecules of natural origin, few pharmaceutical companies can afford to spend hundreds of millions on the toxicology and clinical evaluations needed to get approval. Many useful natural products are lost for medicine.

Treatments with herbal drugs have positive as well as negative aspects. The positive side is associated with the accumulated knowledge over centuries, or even millennia, of their therapeutic action. Our knowledge on the activities of these drugs comes from their human use in diseases, many of which do not have good animal models, and hence modern drugs are difficult to develop. In some plants, or mixtures of plants, the therapeutic effect may be due to synergism or an “entourage effect” of several constituents. Again, such plants are mostly lost to medicine. The use of herbal products as drugs also has its negative aspects. In most countries, the content of the active constituents of plant drugs sold to the public is unknown. The secondary metabolites, which are the active

constituents of plant drugs, are notorious in their variability, which depends on the soil, the climate, the plant pathogens, etc. Hence, a patient can never be sure of the level of the active drug consumed.

Few herbal products have been investigated for their chronic effects. While some medicinal plants or extracts are used on an acute basis and hence their long-term effects are presumably mostly negligible, many are consumed on a daily basis for long periods of time and may lead to various pathologies. This is not the case with most drugs, of either natural or synthetic origin, introduced over the last few decades, whose effects are followed for years after market introduction by the companies that have developed them.

Some of the “modern” trends of herbal plant use are not based on traditional use but on premises, which are unacceptable. Thus, one of the basic rules of homeopathy, a nineteenth-century-invented method of medicinal plant use, is that dilution of a drug solution leads to better results. When extreme dilution actually leads to the disappearance of the active molecule in the formulation, the answer by homeopathic dispensers is that “water retains drug memory”—a statement of questionable value.

In the United States, the Food and Drug Administration (FDA) has to approve all new drugs sold to the public. This approval is based on thorough evaluations of pharmacological and clinical data. An FDA approval is generally accepted in most countries. However, U.S. law does not allow the FDA to use its criteria for “alternative medicine”—hence in the United States, as well as in many other countries, regulations as regards herbal drugs are lax.

How do we balance the positive with the negative aspects? There are some obvious steps that have to be taken to close the gap between plant drugs and extracts and approved drugs based on detailed pharmacological and clinical investigations:

1. Every batch of a herbal drug on the market should indicate the concentrations of the active molecule and any possible side effects.
2. Drug regulatory bodies should be given wider responsibility over herbal plant drugs.
3. Therapeutic claims should be based on scientific data.

But the best way to apply the knowledge gathered over millennia is to evaluate and develop it by modern methods—chemical, pharmacological, and clinical—and thus help to introduce novel, single molecule drugs based both on ancient practice and on contemporary science.

This volume, edited by Dr. Brahmachari, presents not only an extensive spectrum of chemical and pharmacological aspects on bioactive natural products and their derivatives, written by leading researchers in the field, but also a significant amount of what might best be covered under the rubric of alternative medicine or even functional foodstuffs. The book contains excellent chapters on the chemistry and the methodologies of production of natural products that could be drug molecules in their own right. Besides, there are chapters by well-known experts on not only classical fermentation processes using microorganisms but also on methodologies involved in plant tissue culture and biosynthetic pathway modulations directed toward the enhancement of natural product production. Natural products clearly are an important source for future therapeutic options for an array of acute and chronic diseases, but more research is needed on efficacy, standardization, toxicity, and long-term effects. This book, by providing state-of-the-art evidence on bioactive natural products, will obviously help to fill this gap. I am very happy to recommend this volume to academics, researchers, and students interested in understanding the chemistry and pharmacology of bioactive natural products and their enormous role in the modern drug discovery processes.

Raphael Mechoulam
Hebrew University, Jerusalem, Israel

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Mankind has been utilizing natural products, mostly from plants, for ages as traditional medicines, fragrances, spices, and colorants. Naturally occurring bioactive compounds are still the major source of lead molecules in modern drug discovery and development. In the last decade, natural products have gained a renewed interest in the pharmaceutical industry, and as a consequence a new drive toward the study of bioactive compounds, both directly derived from natural sources or derived/inspired from those obtained from natural products, has been initiated worldwide. It is also interesting to recall that human bodies and health are composed of natural products and supported by everyday intake of natural products, in spite of remarkable renovations occurring in the individual natural medicinal products and the ways of utilizing them.

The content of this book, well organized by Dr. Brahmachari, comprises wide areas in the natural resources, their production, bioactive compounds produced by them, and new facts that could lead to novel methods of creating new medicines. Many readers will find various buried jewels based on their own specialties. Summarized contents of all chapters are very precisely documented in the overview in Chapter 1, where the readers will easily find how to reach the chapters of most to interest them. I am very happy to recommend this book without any reservation to graduate and PhD students of medicinal chemistry as well as to scientists and professionals working in the domain of bioactive natural products to explore their potential as prospective molecules of medicinal interests.

Takuo Okuda
Okayama University, Japan

Preface

This single volume entitled *Chemistry and Pharmacology of Naturally Occurring Bioactive Compounds* is an endeavor to focus on the recent cutting-edge research advances in the field of bioactive natural products and their significant contributions in the domain of discovery and development of new medicinal agents. This book consists of a total of 22 chapters contributed by eminent researchers from several countries in response to my personal invitation. I am most grateful to the contributors for their generous and timely response in spite of their busy and tight schedules with academics, research, and other responsibilities.

Natural products have played a crucial role in modern drug development and still constitute a prolific source of novel lead compounds, or pharmacophores, for ongoing drug discovery programs. Natural products present in the plant and animal kingdom offer a huge diversity of chemical structures, which are the result of biosynthetic processes that have been modulated over the millennia through genetic effects, and hence the search for bioactive molecules from nature (plants, animals, microflora) continues to play an important role in fashioning new medicinal entities. With the advent of modern techniques, particularly the rapid improvements in spectroscopic as well as accompanying advances in high-throughput screening techniques, it has become possible to have an enormous repository of bioactive natural compounds, thus opening up exciting new opportunities in the field of new drug development to the pharmaceutical industry. Medicinal chemistry of such bioactive compounds encompasses a vast area that includes their isolation and characterization from natural sources, structure modification for optimization of their activity and other physical properties, and also total and semisynthesis for a thorough scrutiny of structure–activity relationships. It has been well documented that natural products played a crucial role in modern drug development, especially for antibacterial and antitumor agents; however, their uses in the treatment of other epidemics such as AIDS and cardiovascular, cancerous, neurodegradative, infective, and metabolic diseases have also been extensively explored. The need for leads to solve such health problems threatening the world population makes all natural sources important for the search of novel molecules, diversified and unique structural architectures of which inspired scientists to pursue new chemical entities with completely different structures from known drugs. Researchers around the globe are deeply engaged in exploring the detailed chemistry and pharmacology of such potent and efficacious naturally occurring bioactive compounds.

This book, which comprises a variety of 22 chapters written by active researchers and leading experts working in the field of chemistry of biologically active natural products, brings together an overview of current discoveries and trends in this remarkable field. Chapter 1 presents an overview of the book and summarizes the contents of the other chapters so as to offer glimpses of the subject matter covered to the readers before they go in for a detailed study. Chapters 2 through 22 are devoted to exploring the ongoing chemical and pharmacological advances in naturally occurring organic compounds and describe their spectral and x-ray properties, chemical transformations, and structure–activity relationships, including mode of action, toxicology, pharmacokinetics, and metabolism of certain bioactive molecules of medicinal interest.

This timely volume encourages interdisciplinary work among chemists, pharmacologists, biologists, botanists, and agronomists with an interest in bioactive natural products. It is also an outstanding source of information with regard to the industrial application of natural products for medicinal purposes. The broad interdisciplinary approach dealt with in this book would surely make the work much more interesting for scientists deeply engaged in the research and/or use of bioactive natural products. It will serve not only as a valuable resource for researchers in their own fields to predict

promising leads for developing pharmaceuticals to treat various ailments and disease manifestations but also to motivate young scientists to the dynamic field of bioactive natural products research.

Representation of facts and their discussions in each chapter are exhaustive, authoritative, and deeply informative; hence, the book would serve as a key reference for recent developments in the frontier research on bioactive natural products and would also be of much utility to scientists working in this area. I would like to express my sincere thanks once again to all the contributors for the excellent reviews on the chemistry and pharmacology of bioactive natural products. It is their participation that makes my effort to organize such a book possible. Their masterly accounts will surely provide the readers with a strong awareness of current cutting-edge research approaches being followed in some of the promising fields of biologically active natural products.

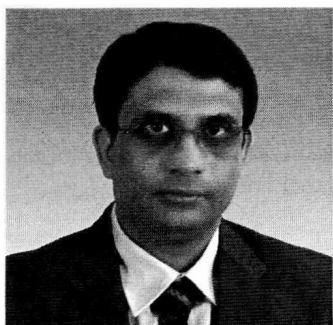
I would like to express my sincere thanks and deep sense of gratitude to Professor Raphael Mechoulam, Institute for Drug Research, Medical Faculty, Hebrew University, Israel, and Professor Takuo Okuda, Okayama University, Japan, for their keen interests in the manuscript and for writing forewords to the book.

I would also like to express my deep sense of appreciation to all of the editorial and publishing staff members associated with Taylor & Francis Group/CRC Press, United States, for their keen interest in publishing the works as well as their all-round help so as to ensure that the highest standards of publication have been maintained in bringing out this book.

Goutam Brahmachari

*Chemistry Department, Visva-Bharati University
Santiniketan, India*

Editor



Dr. Goutam Brahmachari received his high school degree in scientific studies in 1986 at Barala R. D. Sen High School under the West Bengal Council of Higher Secondary Education (WBCHSE). He then moved to Visva-Bharati (a central university founded by Rabindranath Tagore at Santiniketan, West Bengal, India) to study chemistry at the undergraduate level. After graduating from this university in 1990, Dr. Brahmachari completed his master's in 1992 with specialization in organic chemistry and thereafter received his PhD in 1997 in natural products chemistry from the same university. He was appointed as assistant professor of organic chemistry at Visva-Bharati University, Department of

Chemistry, in 1998. In 2008, he became an associate professor of organic chemistry in the same faculty. At present, he is responsible for teaching courses in organic chemistry, natural products chemistry, and physical methods in organic chemistry. Several students have received their PhDs under his supervision during this period, and a dozen of research fellows are presently working with him both in the fields of natural products and synthetic organic chemistry. Dr. Brahmachari also serves as a member of the Indian Association for the Cultivation of Science (IACS), Kolkata, and as an editor in chief for *Signpost Open Access Journal of Organic and Biomolecular Chemistry*.

Dr. Brahmachari's research interests include (1) isolation, structural determination, and/or detailed NMR study of new natural products from medicinal plants; (2) evaluation of biological activities and pharmacological potential of such phytochemicals; (3) semisynthetic studies with natural products; and (4) synthetic organic chemistry. With more than 15 years of teaching experience, he has produced so far about 70 publications, including original research papers, review articles, and invited book chapters in edited books in the field of natural products and organic synthesis from internationally reputed presses. Dr. Brahmachari has authored/edited a number of text and reference books that include *Organic Name Reactions: A Unified Approach* (Narosa Publishing House, New Delhi; copublished by Alpha Science International, Oxford, 2006), *Chemistry of Natural Products: Recent Trends and Developments* (Research Signpost, 2006), *Organic Chemistry Through Solved Problems* (Narosa Publishing House, New Delhi; copublished by Alpha Science International, Oxford, 2007), *Natural Products: Chemistry, Biochemistry and Pharmacology* (Alpha Science International, Oxford, 2009), *Handbook of Pharmaceutical Natural Products*—two-volume set (Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2010), and *Bioactive Natural Products: Opportunities and Challenges in Medicinal Chemistry* (World Scientific Publishing Co. Pte. Ltd., Singapore, 2011). He is regularly consulted as a referee by *RSC Advances*; *Tetrahedron Letters*; *Journal of Molecular Catalysis A: Chemical*; *Spectroscopy Letters*; *Journal of Heterocyclic Chemistry*; *Phosphorus, Sulfur, and Silicon and the Related Elements*; *Archives der Pharmazie*; *Current Organic Chemistry*; *Natural Product Communications*; *Journal of Antimicrobial Chemotherapy*; *Mini Reviews in Medicinal Chemistry*; *Phytochemistry Reviews*; *Pharmaceutical Biology*; *Indian Journal of Chemistry: Sec B*, *Journal of the Indian Chemical Society*; *Annals of the Brazilian Academy of Sciences*; *Journal of Medicinal Plants Research*; *International Journal of Green Pharmacy*; *Journal of Essential Oil Bearing Plants*, and some other international journals and financial commissions.

Dr. Brahmachari enjoys songs of Rabindranath Tagore and finds interests in literature as well!

Contributors

Bimal K. Banik

Department of Chemistry
The University of Texas—Pan American
Edinburg, Texas

Vagner A. Benedito

Plant and Soil Sciences Division
Genetics and Developmental Biology Program
West Virginia University
Morgantown, West Virginia

Ira Bhatnagar

Marine Biochemistry Laboratory
Department of Chemistry
Pukyong National University
Busan, Korea

and

Laboratory of Infectious Diseases
Centre for Cellular and Molecular Biology
Hyderabad, India

Goutam Brahmachari

Laboratory of Natural Products and Organic
Synthesis
Department of Chemistry
Visva-Bharati University
West Bengal, India

Philip C. Calder

Faculty of Medicine
Human Development and Health Academic Unit
Southampton General Hospital
University of Southampton
Southampton, United Kingdom

Devdutt Chaturvedi

Laboratory of Medicinal Chemistry
Amity Institute of Pharmacy
Amity University Lucknow Campus
Uttar Pradesh, India

Ana M. Damas

Instituto de Biologia Molecular e Celular
and
Instituto de Ciências Biomédicas Abel Salazar
Universidade do Porto
Porto, Portugal

Danilo Davyt

Facultad de Química
Cátedra de Química Farmacéutica
Universidad de la República
Montevideo, Uruguay

Arnold L. Demain

Research Institute for Scientists Emeriti
Drew University
Madison, New Jersey

Zelalem Y. Desta

Department of Chemistry
University of Botswana
Gaborone, Botswana

Anna Dzierżęga-Lęcznar

Faculty of Pharmacy
Department of Instrumental Analysis
Medical University of Silesia in Katowice
Sosnowiec, Poland

Francesco Epifano

Dipartimento di Farmacia
Università “G. D’Annunzio” of Chieti-Pescara
Chieti Scalo, Italy

Raquel O. Faria

Grupo de Estudos em Bioquímica de Plantas
Departamento de Botânica
Instituto de Ciências Biológicas
Universidade Federal de Minas Gerais
Belo Horizonte, Brazil

Ângelo de Fátima

Grupo de Estudos em Química Orgânica e
Biológica
Departamento de Química
Instituto de Ciências Exatas
Universidade Federal de Minas Gerais
Minas Gerais, Brazil

Luís Gales

Instituto de Biologia Molecular e Celular
and
Instituto de Ciências Biomédicas Abel Salazar
Universidade do Porto
Porto, Portugal

Salvatore Genovese

Dipartimento di Farmacia
Università "G. D'Annunzio" of Chieti-Pescara
Chieti Scalo, Italy

Paolo Girardi

Mental Health and Sensory Organs
Department of Neurosciences
Sant'Andrea Hospital
Sapienza University of Rome
Rome, Italy

Francisco V. González

Facultad de Farmacia
Departamento de Biología Vegetal
Universidad de La Laguna
Grupo de Biología Vegetal Aplicada
España, Spain

Maria Y. González-Padrón

Facultad de Farmacia
Departamento de Biología Vegetal
Universidad de La Laguna
Grupo de Biología Vegetal Aplicada
España, Spain

Vincent Gullo

Research Institute for Scientists Emeriti
Drew University
Madison, New Jersey

Vivek K. Gupta

Post-Graduate Department of Physics and
Electronics
University of Jammu
Jammu Tawi, India

S.W.A. Himaya

Marine Biochemistry Laboratory
Department of Chemistry
Pukyong National University
Busan, Republic of Korea

Se-Kwon Kim

Marine Biochemistry Laboratory
Department of Chemistry
and
Marine Bioprocess Research Center
Pukyong National University
Busan, Republic of Korea

Vladimir V. Kouznetsov

Laboratorio de Química Orgánica y
Biomolecular
Escuela de Química
Universidad Industrial de Santander
Bucaramanga, Colombia

Dhananjay Kumar

Department of Chemistry
Centre of Advanced Study
Banaras Hindu University
Varanasi, India

Slawomir Kurkiewicz

Faculty of Pharmacy
Department of Instrumental Analysis
Medical University of Silesia in Katowice
Sosnowiec, Poland

Divya Kushwaha

Department of Chemistry
Centre of Advanced Study
Banaras Hindu University
Varanasi, India

Debomoy K. Lahiri

Department of Psychiatry
Institute of Psychiatric Research
and
Department of Medical and Molecular
Genetics
Indiana University School of Medicine
Indianapolis, Indiana

Juan C. Luis

Facultad de Farmacia
Departamento de Biología Vegetal
Universidad de La Laguna
Grupo de Biología Vegetal Aplicada
España, Spain

Diego R. Merchan Arenas

Laboratorio de Química Orgánica y
Biomolecular
Escuela de Química
Universidad Industrial de Santander
Bucaramanga, Colombia

Bhuwan B. Mishra

Department of Chemistry
Centre of Advanced Study
Banaras Hindu University
Varanasi, India

Luzia V. Modolo

Grupo de Estudos em Bioquímica de Plantas
Departamento de Botânica
Instituto de Ciências Biológicas
Universidade Federal de Minas Gerais
Belo Horizonte, Brazil

Dandara R. Muniz

Grupo de Estudos em Bioquímica de Plantas
Departamento de Botânica
Instituto de Ciências Biológicas
Universidade Federal de Minas Gerais
Belo Horizonte, Brazil

Kanakapura K. Namitha

Fruit and Vegetable Technology Department
Central Food Technological Research Institute
Council of Scientific and Industrial Research
Mysore, India

Pradeep S. Negi

Fruit and Vegetable Technology Department
Central Food Technological Research Institute
Council of Scientific and Industrial Research
Mysore, India

Raquel M. Pérez

Facultad de Farmacia
Departamento de Biología Vegetal
Universidad de La Laguna
Grupo de Biología Vegetal Aplicada
España, Spain

Marina P. Polovinka

Laboratory of Natural and Bioactive
Compounds
The Novosibirsk Institute of Organic
Chemistry SB RAS
Novosibirsk, Russia

Maurizio Pompili

Mental Health and Sensory Organs
Department of Neurosciences
Sant'Andrea Hospital
Sapienza University of Rome
Rome, Italy

Balmiki Ray

Department of Psychiatry
Institute of Psychiatric Research
Indiana University School of Medicine
Indianapolis, Indiana

Fernando A. Rojas Ruiz

Laboratorio de Química Orgánica y
Biomolecular
Escuela de Química
Universidad Industrial de Santander
Bucaramanga, Colombia

Nariman F. Salakhutdinov

Laboratory of Natural and Bioactive
Compounds
The Novosibirsk Institute of Organic
Chemistry SB RAS
Novosibirsk, Russia

Sumit Sarkar

Division of Neurotoxicology
National Center for Toxicological Research/the
Food and Drug Administration
Jefferson, Arkansas

Larry Schmued

Division of Neurotoxicology
National Center for Toxicological Research/the
Food and Drug Administration
Jefferson, Arkansas

Gianluca Serafini

Mental Health and Sensory Organs
Department of Neurosciences
Sant'Andrea Hospital
"Sapienza" University of Rome
Rome, Italy

Gloria Serra

Facultad de Química
Cátedra de Química Farmacéutica
Universidad de la República
Montevideo, Uruguay

Jay Sharma

Department of Pharmacology
Celprogen Inc.
San Pedro, California

Girija S. Singh

Chemistry Department
University of Botswana
Gaborone, Botswana

Krystyna Stepień

Faculty of Pharmacy
Department of Instrumental Analysis
Medical University of Silesia in Katowice
Sosnowiec, Poland

Irena Tam

Faculty of Pharmacy
Department of Instrumental Analysis
Medical University of Silesia in Katowice
Sosnowiec, Poland

Vinod K. Tiwari

Department of Chemistry
Centre of Advanced Study
Banaras Hindu University
Varanasi, India

Leonor Y. Vargas Méndez

Laboratorio de Química Orgánica y
Biomolecular
Escuela de Química
Universidad Industrial de Santander
Bucaramanga, Colombia

Ignacio F. Viera

Facultad de Farmacia
Departamento de Biología Vegetal
Universidad de La Laguna
Grupo de Biología Vegetal Aplicada
España, Spain

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