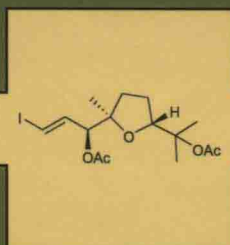
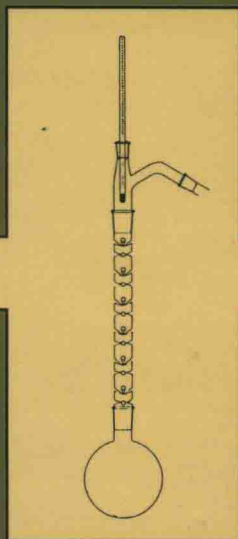
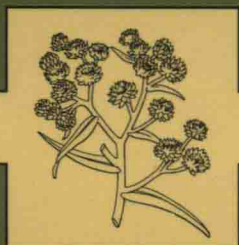




# Studies in Natural Products Chemistry

Atta-ur-Rahman, FRS

Editor



Volume 45

# Studies in Natural Products Chemistry

Volume 45

---

*Edited by*

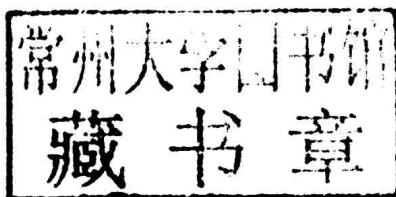
**Atta-ur-Rahman, FRS**

International Center for Chemical and Biological Sciences

H.E.J. Research Institute of Chemistry

University of Karachi

Karachi, Pakistan



ELSEVIER

AMSTERDAM • BOSTON • HEIDELBERG • LONDON  
NEW YORK • OXFORD • PARIS • SAN DIEGO  
SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO

Elsevier

Radarweg 29, PO Box 211, 1000 AE Amsterdam, Netherlands  
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK  
225 Wyman Street, Waltham, MA 02451, USA

Copyright © 2015 Elsevier B.V. All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: [www.elsevier.com/permissions](http://www.elsevier.com/permissions).

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

### Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

ISBN: 978-0-444-63473-3

ISSN: 1572-5995

For information on all Elsevier publications  
visit our website at <http://store.elsevier.com>



Working together  
to grow libraries in  
developing countries

[www.elsevier.com](http://www.elsevier.com) • [www.bookaid.org](http://www.bookaid.org)

Printed in the United States of America

# **Studies in Natural Products Chemistry**

**Volume 45**



# Contributors

**Rohaya Ahmad** Atta-ur-Rahman Institute for Natural Product Discovery, and Faculty of Applied Sciences, Universiti Teknologi MARA, Selangor, Malaysia

**Andrzej Bajguz** Department of Plant Biochemistry and Toxicology, Institute of Biology, University of Białystok, Białystok, Poland

**Iwona Bąkała** Department of Plant Biochemistry and Toxicology, Institute of Biology, University of Białystok, Białystok, Poland

**Leandro Machado de Carvalho** Universidade Federal de Santa Maria – UFSM, Campus universitário, Santa Maria, Rio Grande do Sul, Brazil

**Gerardo Cebrián-Torrejón** Department de Química Analítica, Universitat de València, Burjassot (Valencia), Spain; Departamento de Química Fundamental, Instituto de Química, Universidade de São Paulo – USP, São Paulo, Brazil

**Angela Chambery** Department of Environmental Biological and Pharmaceutical Sciences and Technologies, Second University of Naples, Caserta, Italy

**Łukasz Cieśla** Department of Inorganic Chemistry, Faculty of Pharmacy, Medical University of Lublin, Chodźki, Lublin, Poland

**Massimo Curini** Department of Pharmaceutical Science, University of Perugia, Perugia, Italy

**Brigida D’Abrosca** Department of Environmental Biological and Pharmaceutical Sciences and Technologies, Second University of Naples, Caserta, Italy

**Antonio Doménech-Carbó** Department de Química Analítica, Universitat de València, Burjassot (Valencia), Spain

**Mehmet Emin Duru** Department of Chemistry, Faculty of Science, Muğla Sıtkı Koçman University, Kötekli, Muğla, Turkey

**Antonio Fiorentino** Department of Environmental Biological and Pharmaceutical Sciences and Technologies, Second University of Naples, Caserta, Italy

**Jyotirmoy Ghosh** Natural Product Chemistry Division, CSIR-North East Institute of Science and Technology, Jorhat, Assam, India

**Zbigniew Janeczko** Chair and Department of Pharmacognosy, Collegium Medicum, Jagiellonian University, Medyczna, Cracow, Poland

**Takaomi Kobayashi** Department of Materials Science and Technology, Nagaoka University of Technology, Nagaoka, Niigata, Japan

**Lie-Feng Ma** College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou, Zhejiang, P. R China

- Elsebai Mahmoud Fahmi** Nice Institute of Chemistry, Bioactive Molecules Team, UMR 7272 CNRS, Nice Sophia Antipolis University, Nice, France; Department of Pharmacognosy, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt
- M. Carla Marcotullio** Department of Pharmaceutical Science, University of Perugia, Perugia, Italy
- Mariele Martini** Universidade Federal de Santa Maria – UFSM, Campus universitário, Santa Maria, Rio Grande do Sul, Brazil
- Federica Messina** Department of Pharmaceutical Science, University of Perugia, Perugia, Italy
- Mehiri Mohamed** Nice Institute of Chemistry, Bioactive Molecules Team, UMR 7272 CNRS, Nice Sophia Antipolis University, Nice, France
- Akhtar Muhammad** Department of Chemistry, Faculty of Science, Muğla Sıtkı Koçman University, Kötekli, Muğla, Turkey
- Legrave Nathalie** Nice Institute of Chemistry, Bioactive Molecules Team, UMR 7272 CNRS, Nice Sophia Antipolis University, Nice, France
- Mehmet Öztürk** Department of Chemistry, Faculty of Science, Muğla Sıtkı Koçman University, Kötekli, Muğla, Turkey
- Amade Philippe** Nice Institute of Chemistry, Bioactive Molecules Team, UMR 7272 CNRS, Nice Sophia Antipolis University, Nice, France
- Ornelio Rosati** Department of Pharmaceutical Science, University of Perugia, Perugia, Italy
- Muhammahd Saleem** Department of Chemistry, The Islamia University of Bahawalpur, Bahawalpur, Pakistan
- Fatimah Salim** Atta-ur-Rahman Institute for Natural Product Discovery, Universiti Teknologi MARA, Selangor, Malaysia
- Monica Scognamiglio** Department of Environmental Biological and Pharmaceutical Sciences and Technologies, Second University of Naples, Caserta, Italy
- Valeria Severino** Department of Environmental Biological and Pharmaceutical Sciences and Technologies, Second University of Naples, Caserta, Italy
- Wei-Guang Shan** College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou, Zhejiang, P. R China
- Parames C. Sil** Division of Molecular Medicine, Bose Institute, Kolkata, India
- Marta Talarek** Department of Plant Biochemistry and Toxicology, Institute of Biology, University of Białystok, Białystok, Poland
- Gülsen Tel-Çayan** Department of Chemistry, Faculty of Science, Muğla Sıtkı Koçman University, Kötekli, Muğla, Turkey
- Pınar Terzioğlu** Department of Chemistry, Faculty of Science, Muğla Sıtkı Koçman University, Kötekli, Muğla, Turkey
- Drochss P. Valencia** Departamento de Química Fundamental, Instituto de Química, Universidade de São Paulo – USP, São Paulo, Brazil

**You-Min Ying** College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou, Zhejiang, P. R China

**Daniel Załuski** Chair and Department of Pharmacognosy, Collegium Medicum, Jagiellonian University, Medyczna, Cracow, and Faculty of Health Sciences, Almamater University, Wolska, Warsaw, Poland

**Zha-Jun Zhan** College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou, Zhejiang, P. R China





# Preface

The present book represents the 45th volume of this long-standing series that has become the most comprehensive encyclopedic treatise in the field of natural products.

In Chapter 1, Kobayashi reviews the use of cellulose from bagasse wastes to fabricate hydrogel films with flexible and bioactive properties that can be used in tissue engineering. Different applications of cellulose fiber nanostructures of the hydrogel films are discussed. Marcotullio et al. discuss the important biological activities of *Cannabis* and the efforts aimed to the discovery of natural and nonnatural selective cannabinoids in Chapter 2. In the next chapter, the new applications of electrochemistry that provide information about the pharmacological activity of natural products are reviewed by Doménech-Carbó et al. These include the electrochemical testing of specific pharmacological activity by electrochemical screening, in situ evaluation of drug–substrate interactions, and electrochemical mimicry of selected biological redox processes to observe correlations between molecular structure, redox properties, and pharmacological activity. In Chapter 4, recent advances in structural elucidation of saponins by NMR and MS are discussed by Scognamiglio et al.

Phytoecdysteroids belong to a large family of ecdysteroids that comprises more than 250 representatives. The pharmacological effects of these compounds in vertebrates and humans are discussed by Bajguz et al. in Chapter 5. Drimane-related merosesquiterpenoids are complex natural products that occur frequently in lower organisms and rarely in higher plants. The classification, biosynthesis, and bioactivity of these compounds are discussed by Zhan et al. in Chapter 6. In Chapter 7, the recent advances in researches on the structure–activity relationships of secondary plant metabolites with antimicrobial, free radical-scavenging activities and inhibitory properties against selected enzymes are presented by Załuski et al. Marine polyacetylenic compounds exhibit a variety of biological activities including antimicrobial, antifouling, cytotoxic, antiviral, and anti-inflammatory activities. They therefore offer interesting molecular models for the development of new pharmaceuticals. This area is reviewed in the next chapter by Nathalie et al.

In Chapter 9, Saleem has presented the isolation, characterization, and biological studies of more than 500 natural products from marine-derived fungi, published during 2006–2012. In the next chapter, Ozturk et al. review the polysaccharides, terpenoids, steroids, phenolics, and alkaloids isolated from

mushroom species along with their biological activities. In Chapter 11, Sil et al. assess the potential of natural products in the field of organ pathophysiology. In the final chapter, Ahmad and Salim present the chemical, biological, and pharmacological properties of oxindole alkaloids from *Uncaria* species along with their potential for drug development.

I am confident that the readers will find the present volume of great interest.

I would like to thank Ms Taqdees Malik and Ms Humaira Hashmi for their assistance in the preparation of this volume. I am also grateful to Mr Mahmood Alam for editorial assistance.

**Atta-ur-Rahman, FRS**

International Center for Chemical and Biological Sciences

H.E.J. Research Institute of Chemistry

University of Karachi, Karachi, Pakistan

# Contents

|              |    |
|--------------|----|
| Contributors | xi |
| Preface      | xv |

## 1. Fabrication of Cellulose Hydrogels and Characterization of Their Biocompatible Films

*Takaomi Kobayashi*

|   |    |
|---|----|
| Introduction  | 1  |
| Fabrication of Cellulose Films and Their Properties                           | 3  |
| Phase Inversion Processes for Fabricating Hydrogel Films from Plant Cellulose | 4  |
| Characterization of Hydrogel Films  | 5  |
| Cellulose Hydrogel Bioactivity  | 8  |
| Cellulose Scaffold Biocompatibility and Cytotoxicity                          | 8  |
| Concluding Remarks  | 12 |
| List of Abbreviations   | 13 |
| Acknowledgments   | 13 |
| References  | 13 |

## 2. *Cannabis* and Bioactive Cannabinoids

*Federica Messina, Ornelio Rosati, Massimo Curini and M. Carla Marcotullio*

|   |    |
|---|----|
| Cannabis  | 18 |
| Cannabis in History   | 19 |
| The Endocannabinoid System  | 22 |
| Endocannabinoids  | 23 |
| Cannabinoids  | 26 |
| Natural Cannabinoids or Phytocannabinoids                                 | 26 |
| Phytocannabinoids from <i>Cannabis sativa</i>                             | 27 |
| Classes of Cannabinoids and Biosynthesis                                  | 27 |
| Phytocannabinoids beyond the <i>Cannabis</i>                              | 30 |
| Synthetic Cannabinoids  | 33 |
| First Generation of Synthetic Cannabinoids: Nonselective CB1/CB2 Agonists | 34 |

|   |     |
|---|-----|
| Second Generation of Synthetic Cannabinoids: Selective CB1/CB2 Agonists/Antagonists/Inverse Agonists                          | 36  |
| New Emerging Classes of Cannabinoid Heterocycles  | 45  |
| Allosteric Modulators of Cannabinoid Receptors  | 48  |
| The Therapeutic Potential of Cannabinoids   | 49  |
| Concluding Remarks  | 50  |
| List of Abbreviations   | 51  |
| References  | 52  |
| <br><b>3. Electrochemical Monitoring of the Pharmacological Activity of Natural Products</b>                                  |     |
| <i>Antonio Doménech-Carbó, Leandro Machado de Carvalho, Mariele Martini, Drochss P. Valencia and Gerardo Cebrían-Torrejón</i> |     |
| Introduction  | 59  |
| General Aspects   | 60  |
| Materials and Techniques  | 62  |
| Correlation between Electrochemical Data and Activity   | 64  |
| Thermochemical and Mechanistic Information  | 64  |
| Electrochemical Screening   | 69  |
| Electrochemical Monitoring of Activity  | 71  |
| Antioxidant Assays  | 74  |
| Studies Dealing with ROS  | 77  |
| Final Considerations  | 79  |
| List of Abbreviations   | 80  |
| Acknowledgments   | 80  |
| References  | 81  |
| <br><b>4. Structural Elucidation of Saponins: A Combined Approach Based on High-Resolution Spectroscopic Techniques</b>       |     |
| <i>Monica Scognamiglio, Valeria Severino, Brigida D'Abrosca, Angela Chambery and Antonio Fiorentino</i>                       |     |
| Introduction  | 85  |
| Saponin Classification  | 86  |
| Saponin Structural Elucidation  | 88  |
| Nuclear Magnetic Resonance Spectroscopy   | 89  |
| Structural Elucidation of the Aglycone Portion  | 93  |
| Structural Elucidation of the Sugar Portion   | 94  |
| Glycosylation Site and Sugar Chain Branching  | 95  |
| Further Structural Features   | 96  |
| Advances in Structural Elucidation of Saponins Using MS   | 96  |
| Tandem MS   | 103 |
| NMR and MS at Work in Saponin Structural Elucidation  | 104 |
| List of Abbreviations   | 116 |
| References  | 116 |

## **5. Ecdysteroids in Plants and their Pharmacological Effects in Vertebrates and Humans**

*Andrzej Bajguz, Iwona Bąkała and Marta Talarek*

|   |     |
|---|-----|
| <b>Introduction</b>                                     | 121 |
| <b>Chemical Structure of Phytoecdysteroids</b>          | 122 |
| <b>Occurrence of Ecdysteroids in Plants</b>             | 128 |
| <b>Biosynthesis and Metabolism of Phytoecdysteroids</b> | 130 |
| <b>Function of Ecdysteroids in Plants</b>               | 132 |
| <b>Pharmacological Effects of Phytoecdysteroids</b>     | 134 |
| Adaptogenic Effects                                     | 135 |
| Anabolic Effects  | 135 |
| Antidiabetic Effects                                    | 137 |
| Antitumor Effects                                       | 138 |
| Antiosteoporosis Agents                                 | 139 |
| Immunoprotective/Immunostimulant Effects                | 139 |
| Hepatoprotective Effects                                | 139 |
| Effect on the Urea Balance and the Renal Dysfunction    | 140 |
| Effect on Skin  | 140 |
| Synergism with Vitamin D                                | 141 |
| Endocrine Disruption                                    | 141 |
| Brain Protection  | 141 |
| <b>Concluding Remarks</b>                               | 142 |
| <b>List of Abbreviations</b>                            | 142 |
| <b>Acknowledgments</b>                                  | 143 |
| <b>References</b>                                       | 143 |

## **6. Drimane-Related Merosesquiterpenoids, a Promising Library of Metabolites for Drug Development**

*Wei-Guang Shan, You-Min Ying, Lie-Feng Ma and Zha-Jun Zhan*

|   |     |
|---|-----|
| <b>Introduction</b>   | 148 |
| <b>Occurrence, Classification, and Biosynthesis of Polyketide-MSRDs</b> | 150 |
| Triketide-MSRDs   | 150 |
| Tetraketide-MSRDs   | 152 |
| Miscellaneous Polyketide-MSRDs  | 166 |
| <b>Occurrence, Classification, and Biosynthesis of Shikimate-MSRDs</b>  | 167 |
| Normal Drimane SHQs and SQs   | 169 |
| 4,9-Friedodrimane SHQs and SQs  | 173 |
| 9-Friedodrimane SHQs and SQs  | 174 |
| Ring-Enlarged Drimane SHQs and SQs                                      | 176 |
| Nordrimane SHQs and SQs   | 180 |
| Other Abnormal Drimane SHQs and SQs                                     | 182 |
| Dimeric MSRDs Derived from Shikimate                                    | 185 |

|  |     |
|--|-----|
| Occurrence, Classification, and Biosynthesis of Amino Acid-MSRDs   | 185 |
| Biological Activities  | 188 |
| Cardiovascular and Metabolic Disease Area  | 188 |
| Neurological Disease Area  | 193 |
| Oncological Disease Area   | 194 |
| Infectious Disease Area  | 196 |
| Inflammatory, Immunological, and Related Disease Areas   | 198 |
| Ecological, Agricultural, and Other Roles  | 199 |
| Conclusions  | 199 |
| Structural Abbreviations Used in the Chapter   | 200 |
| References   | 200 |
| <br>7. The Structure–Activity Relationships of Plant Secondary Metabolites with Antimicrobial, Free Radical Scavenging and Inhibitory Activity toward Selected Enzymes |     |
| <i>Daniel Załuski, Łukasz Cieřła and Zbigniew Janeczko</i>   |     |
| Introduction   | 218 |
| SARs for Compounds with Inhibitory Activity Against Selected Enzymes   | 219 |
| Hyal Inhibitors  | 219 |
| AChE and BuChE Inhibitors  | 223 |
| Alkaloids as Inhibitors of AChE and BuChE  | 224 |
| Terpenoids as Inhibitors of AChE and BuChE   | 229 |
| Inhibitors of MMPs   | 232 |
| Antibacterial and Antifungal Mechanism of Action of Selected Secondary Plant Metabolites   | 235 |
| Structure–Free Radical Scavenging Activity Relationships for Selected Secondary Plant Metabolites  | 239 |
| Antioxidant–Activity Relationship for Polyphenols  | 240 |
| Antioxidant–Activity Relationship for Non-Phenolics  | 242 |
| Mono- Di- and Sesquiterpenes   | 242 |
| Carotenoids  | 245 |
| Concluding Remarks   | 246 |
| List of Abbreviations  | 247 |
| References   | 247 |
| <br>8. Marine Polyacetylenes: Distribution, Biological Properties, and Synthesis   |     |
| <i>Legrave Nathalie, Elsebai Mahmoud Fahmi, Mehiri Mohamed and Amade Philippe</i>  |     |
| Introduction   | 251 |
| Marine Organisms as Source of Polyacetylenes   | 252 |
| Polyacetylenes from Sponges  | 254 |
| Polyacetylenes from Cnidarians   | 280 |
| Polyacetylenes from Tunicates  | 280 |
| Polyacetylenes from Algae and Microorganisms   | 280 |
| Synthesis of Polyacetylenes  | 284 |

|  |     |
|--|-----|
| General Methodologies  | 284 |
| Synthesis of Lembehynes A from <i>Haliclona</i> sp.  | 286 |
| Synthesis of a C-20 Bisacetylenic Alcohol from <i>Callyspongia</i> sp.                                     | 288 |
| Synthesis of Strongylodiol A   | 289 |
| Synthesis of Petrosyne Ia and Ib   | 291 |
| Conclusion   | 291 |
| List of Abbreviations  | 292 |
| References   | 292 |
| <br><b>9. Bioactive Natural Products from Marine-Derived Fungi: An Update</b>                              |     |
| <i>Muhammahd Saleem</i>  |     |
| Alkaloids Isolated from Marine-Derived Fungi   | 298 |
| Polypeptides Isolated from Marine-Derived Fungi  | 309 |
| Polyketides and Polyketide Derivative Compounds Isolated from Marine-Derived Fungi                         | 317 |
| Lactones and Macrolides-Based Polyketides Isolated from Marine-Derived Fungi                               | 332 |
| Steroids Isolated from Marine-Derived Fungi  | 340 |
| Terpenoids Isolated from Marine-Derived Fungi  | 343 |
| Miscellaneous Metabolites Isolated from Marine-Derived Fungi   | 350 |
| References   | 355 |
| <br><b>10. Mushrooms: A Source of Exciting Bioactive Compounds</b>   |     |
| <i>Mehmet Öztürk, Gülsen Tel-Çayan, Akhtar Muhammad, Pınar Terzioğlu and Mehmet Emin Duru</i>              |     |
| Introduction   | 363 |
| Isolated Bioactive Compounds   | 365 |
| The Polysaccharides  | 365 |
| The Terpenoids   | 372 |
| The Steroids   | 404 |
| The Phenolic Compounds   | 409 |
| The Alkaloids  | 416 |
| Other Miscellaneous Bioactive Compounds  | 420 |
| Conclusion   | 421 |
| List of Abbreviations  | 450 |
| Acknowledgments  | 451 |
| References   | 451 |
| <br><b>11. Natural Bioactive Molecules: Mechanism of Actions and Perspectives in Organ Pathophysiology</b> |     |
| <i>Jyotirmoy Ghosh and Parames C. Sil</i>  |     |
| Introduction   | 458 |
| Role of Small Bioactive Molecules in Organ Pathophysiology   | 459 |



|  |     |
|--|-----|
| Arjunolic Acid: Its Extraction and Characterization  | 459 |
| Quercetin  | 466 |
| Role of Kombucha Tea in Cellular Oxidative Stress  | 468 |
| Mangiferin: Basics and Extraction  | 469 |
| Beneficial Role of Taurine   | 470 |
| <b>Beneficial Role of Macromolecules in Organ Pathophysiology</b>  | 473 |
| Basics of <i>C. indicus</i> L. and the Active Constituent of the Leaves of<br><i>C. indicus</i>  | 473 |
| Basics of <i>P. niruri</i> and PNP   | 476 |
| <b>Conclusion</b>  | 477 |
| <b>List of Abbreviations</b>   | 478 |
| <b>References</b>  | 479 |
| <br><b>12. Oxindole Alkaloids of <i>Uncaria</i> (Rubiaceae, Subfamily Cinchonoideae): A Review on Its Structure, Properties, and Bioactivities</b> |     |
| <i>Rohaya Ahmad and Fatimah Salim</i>  |     |
| <b>Background</b>  | 486 |
| <b>Phytochemistry of <i>Uncaria</i>: Oxindole Alkaloids</b>  | 487 |
| Oxindole Alkaloids   | 488 |
| Tetracyclic Oxindole Alkaloids   | 488 |
| Pentacyclic Oxindole Alkaloids   | 491 |
| Miscellaneous Oxindole Alkaloids   | 494 |
| Absolute Configuration of Oxindole Alkaloids   | 496 |
| <b>Biogenesis of Oxindole Alkaloids in <i>Uncaria</i></b>  | 497 |
| Biological and Pharmacological Studies on Oxindoles of <i>Uncaria</i>  | 498 |
| Alkaloid Extracts/Fractions  | 500 |
| Tetracyclic Oxindole Alkaloids   | 516 |
| Pentacyclic Oxindole Alkaloids   | 518 |
| Structure–Activity Relationships   | 520 |
| <b>Conclusion</b>  | 522 |
| <b>References</b>  | 522 |
| <br><b>Index</b>   | 527 |