1
An Overview

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1.1
Introduction

The endeavor of this book entitled *Bioactive Natural Products: Chemistry and Biology* is to present details of cutting-edge research in the chemistry and biology of bioactive natural products and it helps the reader understand how natural product research continues to make significant contributions in the discovery and development of new medicinal entities. This is a reference book meant for phytochemists, synthetic chemists, combinatorial chemists, as well as other practitioners and advanced students in related fields. The book, comprising of 16 technical chapters, highlights the chemical and biological aspects of potential natural products with an intention to unravel their pharmaceutical applicability in modern drug discovery processes. The book covers the synthesis, semisynthesis as well as biosynthesis of potentially bioactive natural products. It also features chemical and biological advances in naturally occurring organic compounds, describing their chemical transformations, modes of action, and structure–activity relationships.

This introductory chapter (Chapter 1) presents an overview of the book, and summarizes the contents and subject matter of each chapter so as to offer certain glimpses of the coverage of discussion to the readers before they go for detailed study.

1.2
An Overview of the Book

The present book contains a total of 16 technical chapters – Chapters 2–17; this section summarizes the contents and subject matter of each of these chapters.

Bioactive Natural Products: Chemistry and Biology, First Edition. Edited by Goutam Brahmachari.

1.2.1 Chapter 2

In Chapter 2, Golshani and his group have discussed the use of chemical genomics to investigate the mechanism of action (MOA) for inhibitory bioactive natural compounds. Understanding the specific MOA of small molecules is considered one of the most significant hurdles in developing new drugs. Traditional pathway-specific mechanistic approaches are time consuming and expensive. Global genome-wide single-deletion array (GDA) technology nowadays provides a more feasible alternative to laborious metabolic pathway-specific assays and has the added advantage of working on a global scale. The use of GDA technology to screen natural substances for intriguing inhibitory compounds can help probe the biological complexity of intracellular networks or identify leads for promising novel antimicrobials. GDA technology can both identify direct target and off-target effects of a novel compound or expand our understanding of previously studied compounds. This illuminating and useful chapter offers an extensive overview on the use of GDAs in *Saccharomyces cerevisiae* and *Escherichia coli* as well as combinatorial haploinsufficiency mutant profiling/homozygous mutant profiling (HIP/HOP) as genomic tools to investigate MOA in naturally derived inhibitory compounds. The present chapter offers an impetus to the practitioners deeply engaged in this remarkable field.

1.2.2 Chapter 3

Yang and his group have discussed on the application of high-throughput screening (HTS) of potential natural products based on cancer-signaling strategies including EGFR, P13K, Wnt, and STATs in Chapter 3. With the advances in molecular biology, human genetics, and functional genomics, HTS involves continuous invention and improvement in methods. With the assay of HTS, targeting the cancer-signaling pathways has experienced a more significant impact on drug discovery and development in recent times. More attentions is being focused on the selection of cancer molecular targets between generality and specificity, that is, cell proliferation and survival peculiar to a tumor and anticancer drug research with advanced HTS assays is expected to be a revolutionary technological advance in coming years. The present chapter would surely motivate researchers working in this area of interest.

1.2.3 Chapter 4

Chapter 4, by Demain and his group, is dedicated to potential microbial immunosuppresssants including antifungal peptides and antibiotics cyclosporin,

tacrolimus, sirolimus, mycophenolic acid, and ascomycin. Discovery, fermentation, strain improvement, mode of action, and biosynthesis of the representative immunosuppressants are discussed in detail. The biosynthetic pathway of such microbial products involves a series of complex reactions carried out by multienzyme polypeptides that catalyze reactions in a belt-like manner, first forming a chain, then undergoing elongation and cyclization. Genes encoding these enzymes have been cloned and studied as well. The present chapter highlights the applications of immunosuppressants not only in organ transplantation, but also in the treatment of many other life-threatening diseases such as autoimmune disorders, cancer, AIDS, asthma, skin diseases, respiratory ailments, and malaria. Continuing research offering more insights into the genetics, biosynthesis, and molecular mode of action of these drugs would open new windows for their further applications as effective therapeutics. This illuminating review on immunosuppressants would obviously enrich the readers and would motivate them in undertaking in-depth research in immunosuppressants coupled with medicinal chemistry.

1.2.4
Chapter 5

In Chapter 5, Mallik and his group have presented a comprehensive discussion on the activators and inhibitors of ADAM-10 for management of cancer and Alzheimer's disease. A disintegrin and metalloproteinase (ADAM) family of proteolytic enzymes is known for "shedding" of membrane-bound proteins and are unique among cell surface proteins as they possess an adhesion domain and a protease domain. The deviation from normal levels of ADAMs is also observed in various pathological conditions such as cancer and Alzheimer's disease. The enzyme is downregulated in Alzheimer's disease while over-expressed in various cancers. Involvement of ADAM-10 in progression of cancer and Alzheimer's disease is now well established. Compounds from natural and synthetic origins involved in selective activation or inhibition of ADAM-10 possess tremendous potential as therapeutics for treating cancer and Alzheimer's disease. The present chapter offers an up-to-date development in this field.

1.2.5
Chapter 6

Chapter 6, by Huczyński and his group, deals with the structure and biological activity of polyether ionophores and their semisynthetic derivatives. Polyether ionophores, which belong to a large group of antibiotics, are unique natural compounds because they exhibit a broad spectrum of biological activities including antibacterial, antiviral, and anticancer activity. Natural polyether ionophores have been found to exhibit potent activity against those cancer cells that display

multidrug resistance (MDR) and also against cancer stem cells (CSCs). It has been demonstrated that biological potency of such polyether ionophores is related to their unique chemical structure, as well as their ability to form complexes with mono- and divalent metal cations facilitating their transport across lipid membranes. This phenomenon results in a disturbance of the natural cation concentration gradient and intracellular pH change, leading to mitochondrial injury, cell swelling, and vacuolization and, as a consequence, programmed cell death (apoptosis). The authors have discussed all these issues in detail in the present chapter highlighting their structural and chemical properties, semisynthetic derivatives, and the mechanisms of cation transport.

1.2.6 Chapter 7

Désaubry and coauthors have reviewed the synthesis and pharmacology of bioactive flavaglines in Chapter 7. Flavaglines represent a family of cyclopenta[*b*]benzofurans found in medicinal plants of the genus *Aglaia,* and have been reported to display potent anti-inflammatory, neuroprotective, cardioprotective, and anticancer activities. It has been revealed that flavaglines have the ability to kill cancer cells without affecting normal cells. Such a selective cytotoxicity to cancer cells and cytoprotection to normal cells, both of which occur at nanomolar concentrations, is unprecedented. In the present chapter, the authors have offered an excellent overview on the synthetic routes to flavaglines, MOA, and evaluation of biological potency of the target compounds with the objective of discovering certain novel therapeutic agents from this class of bioactive natural products.

1.2.7 Chapter 8

In Chapter 8, Sil and his group have described the beneficial effect of naturally occurring antioxidants against oxidative stress-mediated organ dysfunctions. The metabolism of oxygen by cells generates potentially harmful reactive oxygen species (ROSs). In recent times, oxidative stress or imbalance between pro-oxidants and antioxidants is a comparatively new issue that has extensively troubled research in biomedical sciences. It has now been established that it significantly contributes to the pathophysiology of various prevalent diseases such as hypertension, diabetes, asthma, allergies, autism, lupas, acute renal failure, atherosclerosis, rheumatoid, Alzheimer's, Parkinson's, and cardiovascular diseases. Oxidative stresses in the cells have a considerable impact leading to defective cellular function, aging, or disease. Consequently, a better thoughtful role of ROS-mediated signaling in normal cellular function as well as in disease is necessary for developing therapeutic tools for oxidative stress-related pathogenesis. The present chapter has a detailed discussion on the

multifunctional therapeutic applications and signaling properties of naturally occurring antioxidants, which obviously play a number of beneficial roles in oxidative stress-induced organ dysfunctions. The authors have been successful in unraveling the potential use of naturally occurring antioxidants as novel promising therapeutic strategies.

1.2.8 Chapter 9

Chapter 9, by Gopinatha Suresh Kumar, deals with the nucleic acid and protein-binding aspects of isoquinoline alkaloids and their analogs, and their therapeutic potential for drug design. Isoquinoline alkaloids and analogs represent an important class of molecules that have attracted attention for their various potential pharmacological activities. Specific binding to cellular biomacromolecules such as DNA and RNA has been thought to be one of the most important routes for their therapeutic action. In this chapter, an up-to-date knowledge on the binding aspects of some of the most important isoquinoline alkaloids and their analogs are presented. Elucidation of the recognition mechanism and accumulation of a large volume of recent research outcomes have been covered in the present chapter, which serves as a useful guide to researchers working in the development of potential therapeutic agents.

1.2.9 Chapter 10

Jean Fotie has presented an exhaustive discussion on the potential of peptides and depsipeptides from terrestrial and marine organisms in the fight against human protozoan diseases such as malaria, trypanosomiasis, leishmaniasis, amebiasis, toxoplasmosis, cryptosporidiosis, sarcocystis, coccidiosis, babesiosis, and giardiasis in Chapter 10. Peptides and depsipeptides are a widely distributed family of naturally occurring molecules, usually found in fungi, actinomycetes, cyanobacteria, higher plants, and marine organisms, with a broad window of biological and pharmacological activities ranging from antibacterial to anticancer, some of which are currently in clinical use or have entered human clinical trials as antibiotic or anticancer agents. This family of compounds should be given a serious and careful consideration for their antiprotozoan activity. The present chapter would act as a stimulus in this direction.

1.2.10 Chapter 11

Chapter 11, by Chaturvedi and his group, is devoted to naturally occurring sesquiterpene lactones and their semisynthetic analogs as potential anticancer agents. Wide structural diversity coupled with potential biological

activities of sesquiterpene lactones has attracted a great deal of attention from medicinal chemists around the world. Although, the exact MOA of SLs is not well known, it has been documented through various published reports that the biological activity displayed by majority of sesquiterpene lactones is due to the presence of α-methylene-γ-lactones and the α,β-unsaturated cyclopentenone ring. In the present chapter, the authors have focused on an up-to-date and comprehensive account on the sesquiterpenes lactones as anticancer agents.

1.2.11 Chapter 12

Brahmachari has focused on the chemistry and biology of naturally occurring calanolides in Chapter 12. Natural calanolides occupy a significant position in the pyranocoumarin class of compounds, and are well known for their anti-HIV potential. In addition, these pyrnocoumarins have also been found to exhibit anti-tuberculosis activity as well. Such promising pharmaceutical activity coupled with low availability of natural calanolides has evoked tremendous interest among the organic chemists to undertake systematic chemical studies toward the total synthesis of this class of compounds. Preclinical and clinical results of both natural and synthetic calanolides have been found to be quite encouraging, and consequently they are being regarded as potential "leads" in the development of future anti-HIV and antituberculosis drugs. The present chapter covers up-to-date literature of naturally occurring calanolides in view of their anti-HIV and antituberculosis potential, their chemical analogs, and total syntheses.

1.2.12 Chapter 13

Chapter 13, by Lakshmanan and Sadasivan, deals with certain plant-derived selective estrogen receptor modulators (SERMs). Phytoestrogens are markedly similar in chemical structure to the mammalian estrogen and estradiol; they and bind to estrogen receptors, with a preference for ERβ. Different physiological functions of the body such as reproduction, behavior, and neuroendocrine function are regulated by estrogen through estrogen receptor subtypes. These receptors have tissue-specific functions with respect to each other. For example, ERα induces cell proliferation, whereas ERβ antagonizes this action. Thus, their differential expression and activation in a balanced manner is necessary for normal functioning of the body and any imbalance in this expression leads to oncogenesis and several autoimmune diseases. Hence, phytoestrogens which mimic the function of endogenous estrogen can be judiciously exploited for regulating this imbalance and reverting back the normal functions of the body. SERMs may, thus be considered as potential lead compounds for the development of drugs in the treatment of estrogen-mediated cancers and autoimmune diseases.

The present chapter would be very useful to readers whose interests lie in the study of potential phytoestrogens.

1.2.13
Chapter 14

Modolo and her group have discussed biosynthesis and biological activities of phenylpropanoids in Chapter 13. Phenylpropanoids compounds, which bear a C_6-C_3 phenolic scaffold, have received particular attention not only because of their function in plants but also because of their wide spectrum of biological activities. Flavonoids, coumarins, and stilbenes have been considered as the main subclass of phenylpropanoids in the present discussion. This illuminating overview provides valuable information about the biosynthesis and pharmacological potential of such medicinally important phenylpropanoid compounds.

1.2.14
Chapter 15

Chapter 15 by Serafini and his group is devoted to neuropeptides which are the active neuromodulators involved in the pathophysiology of suicidal behavior and major affective disorders. Neuropeptidergic circuits seem to act as fundamental mediators of human behavior. These molecules may represent interesting mediators of stress-related disorders, major affective conditions, and suicidal behavior. From their detailed literature survey, it has been demonstrated that there remains an association between suicidality and corticotrophin-releasing factor (CRF), nerve growth factor (VGF), cholecystokinin (CCK), orexin, substance P, and Neuropeptide Y (NPY); these molecules play a key role in many biological functions and act as important neuromodulators of emotional processing. Although many studies identified a positive association between neuropeptide alterations and major depressive disorders/suicidal behavior, it is, however, unlikely that neuropeptides may currently represent definitive biomarkers of suicidality/depression. Further studies are needed in order to elucidate the complex nature of neuropeptidergic abnormalities underlying suicidal behavior and major affective conditions. The authors of this present chapter have performed the job in this direction to offer an insight into the cause and the search for possible remedies.

1.2.15
Chapter 16

Chapter 16 by Miller and his group is devoted to the discussion on some innovative techniques to identify and characterize novel compounds from marine organisms

as potential drug molecules. Marine organisms are a rich source of natural products, having potential as lead compounds in drug discovery. The path from discovery of a novel compound to clinical use, however, is a long and complex one in which many lead structures drop out along the way. In the present chapter, the authors have focused on the approach used in their chemistry and biology laboratories to find new biologically active compounds (NMR-based screening) along with providing clues on their mode of action (chemical genetics and proteomics), and validation of their effects in mammalian cells (biochemical analysis of target responses). This chapter would provide useful information to researchers deeply involved in the drug discovery process.

1.2.16 Chapter 17

Chapter 17, by Leal and Calado, deals with the biodiscovery, biodiversity, and bioproduction of marine natural products (MNPs). MNPs are acknowledged as the "blue gold," as they hold a vast reservoir of promising leads for drug development. Critical survey of literature on the biodiscovery, biodiversity, and bioproduction of MNPs reveals that although new technologies have promoted significant advances in the collection, screening, and identification of a whole new range of molecules, marine chemical ecology is still several decades behind its terrestrial counterpart; there is still a vast fraction of marine biodiversity yet to be screened, as well as regions in the world's oceans that remain poorly explored. In this chapter, the authors have overviewed past and current trends of MNP biodiscovery, both taxonomically and geographically, and discuss them in view of marine biodiversity and biogeography. In addition, they have also discussed the bioproduction of secondary metabolites of marine organisms, particularly through *in toto* aquaculture.

1.3 Concluding Remarks

This introductory chapter summarizes the technical chapters of this book, each of which is exhaustive in its representation of facts and with discussions that are authoritative and deeply informative. The readers will find discussions that provoke interest in each of the chapters, which practically cover wide area of bioactive natural product research, particularly on their chemical and biological aspects. The references encourage interdisciplinary work among chemists, pharmacologists, biologists, botanists, and agronomists with an interest in bioactive natural products. Hence, the present book should definitely serve as a key reference for recent developments in frontier research on bioactive natural products, and also would find much utility for the scientists working in this area.