Goutam Brahmachari

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Handbook of Pharmaceutical Natural Products

Volume 2

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Dedicated To My Little Asanjan

Preface

Nature stands as an inexhaustible source of novel chemotypes and pharmacophores. There has been a history of success in developing drugs from natural sources, particularly in tropical countries such as India, China, Japan, Nepal, Mexico, and South Africa. Nature has been a source of medicinal agents for thousands of years, and an impressive number of modern drugs find their origin in nature. Although the use of bioactive natural products or herbal drug preparations dates back a long time ago, their application as isolated and characterized compounds to modern drug discovery and development started only in the nineteenth century, the dawn of the chemotherapy era. Natural product chemistry has now experienced an explosive and diversified growth, making natural products the subject of much interest and promise in the present-day research directed toward drug design and drug discovery. Natural products and their derivatives from plant, microbial, and marine sources are at various advanced stages of clinical development.

Owing to multidirectional promising aspects, the interest in natural products continues to this very day. The last decade has seen a greater use of botanical products among members of the general public through self-medication than ever before. The use of herbal drugs is once more escalating in the form of complementary and alternative medicine (CAM). This phenomenon has been mirrored by an increasing attention to phytomedicines as a form of alterative therapy by the health professionals; in many developing countries, there is still a major reliance on crude drug preparation of plants used in traditional medicines for their primary health care. The World Health Organization (WHO) estimates that approximately 80% of the world's population relies mainly on traditional medicine, predominantly originated from plants, for their primary health care. The worldwide economic impact of herbal remedies is noteworthy; in the United States alone, in 1997 it was estimated that 12.1% of the population spent $5.1 billion on herbal remedies. In the United Kingdom, sales of herbal remedies were worth of £75 million in 2002, an increase of 57% over the previous 5 years. Studies carried out in other countries, such as Australia and Italy, also suggest an increasing prevalence of the use of herbal medicines among the adult population. In India and China, respectively, the Ayurvedic and Chinese traditional medicine systems are particularly well developed, and

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both have provided potentials for the development of Western medicine. Pharmacognosists employed in different institutions are aware of the changing trends of herbal medications and a number of useful texts on the analysis, uses, and potential toxicities of herbal remedies have appeared recently, which serve as useful guides in pharmacy practice.

Medicinal chemistry of bioactive natural products spans a wide range of fields, including isolation and characterization of bioactive compounds 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 relationship (SAR). It has been well documented that natural products played crucial roles in modern drug development, especially for antibacterial and antitumor agents; however, their use in the treatment of other epidemics such as AIDS, cardiovascular, cancerous, neurodegradative, infective, and metabolic diseases has 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. The development of separation techniques and spectroscopic methods allows the isolation of complex mixtures and the characterization of a diversity of complex structures, contributing to the importance of the investigation of terrestrial and marine sources in order to obtain novel bioactive organic compounds coming from nature. Such diversified structural architectures of the isolated molecules presented scientists with unique chemical structures, which are beyond human imagination most of the time, inspired scientists to pursue new chemical entities with completely different structures from known drugs.

The most striking feature of natural products in connection to their long-lasting importance in drug discovery is, thus, their structural diversity that is still largely untapped. Most natural products not only are sterically more complex than synthetic compounds but also differ in regard to the statistical distribution of functionalities. They occupy a much larger volume of the chemical space and display a broader dispersion of structural and physicochemical properties than compounds issued from combinatorial synthesis. It needs to be mentioned that in spite of massive endeavors adopted in recent times for synthesizing complex structures following "diversity-oriented synthesis" (DOS) strategy, about 40% of the chemical scaffolds found in natural products are still absent in today's medicinal chemistry. The chemical diversity and unique biological activities of a wide variety of natural products have propelled many discoveries in chemical and biological sciences, and provided therapeutic agents to treat various diseases as well as offered leads for the development of valuable medicines. Analysis of the properties of synthetic and natural compounds compared to drugs revealed the distinctiveness of natural compounds, especially concerning the diversity of scaffolds and the large number of chiral centers. This may be one reason why approximately 50% of the drugs introduced to the market during the past 20 years are directly or indirectly derived from natural compounds.

The reason for the lack of lead compounds from synthetic libraries in some therapeutic areas such as anti-infectives, immunosuppression, oncology, and metabolic diseases may, thus, be attributed to the different chemical space occupied by

natural products and synthetic compounds. This difference in chemical space makes natural products an attractive alternative to synthetic libraries, especially in therapeutic areas that have a dearth of lead compounds. Natural products have also been used as starting templates in the synthesis of combinatorial libraries. Natural product pharmacophores are well represented in lists of "privileged structures," which makes them ideal candidates for building blocks for biologically relevant chemical libraries. Natural products still constitute a prolific source of novel lead compounds or pharmacophores for medicinal chemistry, and hence, they should be incorporated into a well-balanced drug discovery program. Besides their potential as lead structures in drug discovery, natural products also provide attractive scaffolds for combinatorial synthesis and act as indispensable tools for validation of new drug targets. The diversity of three-dimensional shapes of natural molecules still surpasses that of synthetic compounds, and this ensures that natural products will continue to be important for drug discovery.

The wide range of nature virtually remains unexplored; it is estimated that only 5–15% of the approximately 2 50 000 species of higher plants (terrestrial flora) have been investigated chemically and pharmacologically so far. The marine environment has become an important source of new structures with new activities; hence, marine kingdom stands as an enormous resource for the discovery of potential chemotherapeutics and is waiting to be explored. Another vast untapped area is the microbial world – less than 1% of bacterial species and less than 5% of fungal species are known – and recent evidence indicates that millions of microbial species remain undiscovered. Microbial sources are making an increasingly important contribution to bioactive natural products, and the complex structures of such microbial natural products have fascinated chemists for decades. The future of natural products in drug development thus appears to be a tale of justifiable hope. Faithful drives are needed in more intensified fashion to explore nature as a source of novel and active agents that may serve as the leads and scaffolds for elaboration into urgently needed efficacious drugs for a multitude of disease indications.

The *Handbook of Pharmaceutical Natural Products* provides a much needed and comprehensive survey of bioactive natural products and their potentials as "drug candidates" for prospective use of such significant molecules in the pharmaceutical world; more than 1500 such individual molecules have been selected and discussed under a total of 950 entries distributed in two volumes of this book. Systematic and trivial names, physical data, source(s), structure, natural derivative(s), and pharmaceutical potentials with an emphasis on the structure–activity relationship of each bioactive molecule are presented in this book; hence, the book would serve as a key reference for recent developments in the frontier research on natural products and would also find much utility to the scientists working in this area. The book serves as a valuable resource for researchers in their own fields to predict promising leads for developing pharmaceuticals to treat various ailments and disease manifestations.

I would like to express my deep sense of appreciation to all of the editorial and publishing staff members of Wiley-VCH, Weinheim, Germany, for their all-round help so as to ensure that the highest standards of publication are maintained in bringing out this book. My effort will be successful only when it is found helpful to

the readers at large. Every step has been taken to make the manuscript error-free; in spite of that, some errors might have crept in. Any remaining error is, of course, of my own. Constructive comments on the contents and approach of the book from the readers will be highly appreciated.

Finally, I should thank my wife and my son for their well understanding and allowing me enough time throughout the entire period of writing; without their support, this work would not have been possible.

Santiniketan, September 2009 *Goutam Brahmachari*

Further Reading

Balandrin, M.F., Kinghorn, A.D., and Farnsworth, N.R. (1993) Plant-derived natural products in drug discovery and development: an overview, in *Human Medicinal Agents from Plants, American Chemical Society Symposium Series, No. 534* (eds A.D. Kinghorn and M.F. Balandrin), American Chemical Society, Washington, DC, pp. 2–12.

Barnes, J. (2003) Pharmacovigilance: a UK perspective. *Drug Safety*, **26**, 829.

Brahmachari, G. (2006) Prospects of natural products research in the 21st century: a sketch, in *Chemistry of Natural Products: Recent Trends & Developments* (ed. G. Brahmachari), Research Signpost, Kerala, India, pp. 1–22.

Brahmachari, G. (2009) Mother Nature: an inexhaustible source of drugs and lead molecules, in *Natural Products: Chemistry, Biochemistry and Pharmacology* (ed. G. Brahmachari), Alpha Science International, Oxford, UK, pp. 1–20.

Burke, M.D., Berger, E.M., and Schreiber, S.L. (2003) Generating diverse skeletons of small molecules combinatorially. *Science*, **302**, 613.

Buss, A.D. and Waigh, R.D. (1995) Natural products as leads for new pharmaceuticals, in *Burger's Medicinal Chemistry and Drug Discovery*, 5th edn, vol. 1 (ed. M.E. Wolff), John Wiley & Sons, Inc., New York, pp. 983–1033.

Butler, M.S. (2004) The role of natural product chemistry in drug discovery. *J. Nat. Prod.*, **67**, 2141.

Carte, B.K. (1996) Biomedical potential of marine natural products. *Bioscience*, **46**, 271.

Cragg, G.M. and Newman, D.J. (2001) Medicinals for the millennia: the historical record. *Ann. N.Y. Acad. Sci.*, **953**, 3.

Cragg, G.M., Newman, D.J., and Snader, K.M. (1997) Natural products in drug discovery and development. *J. Nat. Prod.*, **60**, 52.

Donia, M. and Hamann, M.T. (2003) Marine natural products and their potential applications as anti-infective agents. *Lancet Infect. Dis.*, **3**, 338.

Haefner, B. (2003) Drugs from the deep: marine natural products as drug candidates. *Drug Discov. Today*, **8**, 536.

Horton, D.A., Bourne, G.T., and Smythe, M.L. (2003) The combinatorial synthesis of bicyclic privileged structures or privileged substructures. *Chem. Rev.*, **103**, 893.

Kaul, P.N. and Joshi, B.S. (2001) Alternative medicine: herbal drugs and

their critical appraisal – part II. *Prog. Drug Res.*, **57**, 1.

Kingston, D.G.I. and Newman, D.J. (2002) Mother nature's combinatorial libraries: their influence on the synthesis of drugs. *Curr. Opin. Drug Discov. Dev.*, **5**, 304.

Lee, M.-L. and Schneider, G.J. (2001) Scaffold architecture and pharmacophoric properties of natural products and trade drugs: application in the design of natural product-based combinatorial libraries. *Combin. Chem.*, **3**, 284.

Newman, D.J., Cragg, G.M., and Snader, K.M. (2000) The influence of natural products upon drug discovery. *Nat. Prod. Rep.*, **17**, 215.

Newman, D.J. and Cragg, G.M. (2004) Advanced preclinical and clinical trials of natural products and related compounds from marine sources. *Curr. Med. Chem.*, **11**, 1693.

Newman, D.J., Cragg, G.M., and Snader, K.M. (1997) Natural products in drug discovery and development. *J. Nat. Prod.*, **60**, 52.

Newman, D.J., Cragg, G.M., and Snader, K.M. (2000) The influence of natural products on drug discovery. *Nat. Prod. Rep.*, **17**, 215.

Newman, D.J., Cragg, G.M., and Snader, K.M. (2003) Natural products as sources of new drugs over the period 1981–2002. *J. Nat. Prod.*, **66**, 1022.

Shu, Y.-Z. (1998) Recent natural products based drug development: a pharmaceutical industry perspective. *J. Nat. Prod.*, **61** 1053.

Vuorelaa, P., Leinonenb, M., Saikkuc, P., Tammelaa, P., Rauhad, J.P., Wennberge, T., and Vuorela, H. (2004) Natural products in the process of finding new drug candidates. *Curr. Med. Chem.*, **11**, 1375.

Abbreviations

A-549	human lung carcinoma
AA	arachidonic acid
$ABTS^{\bullet+}$	2,2′-azinobis(3-ethylbenzothiozoline-6-sulfonate) radical cation
ACAT	acetyl-CoA:cholesterol acyltransferase
AChE	acetylcholinesterase
ACV	acyclovir
AD	Alzheimer's disease
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
AP-1	activator protein
Apr	acyclovir/phosphonoacetic acid-resistant
AST	serum aspartate aminotransferase
ATP	adenosine triphosphate
AZT	3′-azido-3′-deoxythymidine
BChE	butyrylcholinesterase
BCS	bovine calf serum
BHA	2,6-di-*tert*-butyl-4-hydroxyanisol
BHT	2,6-di-*tert*-butyl-4-methoxyphenol
BSO	buthionine sulfoximine
Caco-2	human colon carcinoma
Caspase	cysteine proteases
CC_{50}	50% cytotoxic concentration
Cdk	cyclin-dependent kinase
CL	chemoluminescence
Col-2	human colon carcinoma
COX	cyclooxygenase
COX-1	cyclooxygenase-1
COX-2	cyclooxygenase-2
CPE	cytopathic effect
DHF	dihydroxyfumaric acid
DNA	deoxyribose nucleic acid
DOPA	2-amino-3-(3′, 4′-dihydroxyphenyl)propionic acid
DPPH	1,1-diphenyl-2-picrylhydrazyl radical

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EC_{50}	effective concentration (50%)
ED_{50}	effective dose (50%)
EGP-R PTK	epidermal growth factor receptor protein tyrosine kinase
Egr-1	early growth response gene-1
EMSA	electrophoretic mobility shift
FAS	fungal fatty acid synthase
fMLP	formyl-methionyl-leucyl-phenylalanine
5-FU	5-fluorouracil
GalN	D-galactosamine
GGTase I	geranylgeranyltransferase type I
GI_{50}	concentration inhibiting cell growth by 50%
GSK-3	glycogen synthase kinase-3
GST	glutathione *S*-transferase
HBeAg	hepatitis B virus e antigen
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
hCMV	human cytomegalovirus
HCT-8	human ileocecal carcinoma
HCT-116	human colon tumor cells
HCV	hepatitis C virus
HDAC	histone deacetylase
HDM	house dust mite
HEMn	human epidermal melanocytes
Hep-G2	human hepatocellular carcinoma
β-HEX	β-hexosaminidase
12-HHTrE	12-hydroxyheptadecatrienoic acid
HIF-1	hypoxia-inducible factor-1
HIV	human immunodeficiency virus
HIV-1/2-RT	human immunodeficiency virus type-1/2 reverse transcriptase
HLE	human leucocyte elastase
HNE	human neutrophil elastase
HPC	human prostate cancer
HPLF	human periodontal ligament fibroblasts
HPV	human papilloma virus
HSV	herpes simplex virus
HSV-1	herpes simplex virus type 1
HSV-2	herpes simplex virus type 2
HUVEC	human umbilical vein endothelial cell
HUVEC	human umbilical venous endothelial cell
IBMX	3-isobutyl-1-methylxanthine
IC_{50}	inhibitory concentration (50%)
ICE	interleukin-1β converting enzyme

ICM-1	intercellular adhesion molecule-1
IFN-γ	interferon-γ
IKK	IκB kinase
IL-6	interleukin-6
iNOS	inducible nitric oxide synthase
IκB	inhibitory subunit of NF-κB
JNK	c-Jun NH_2-terminal kinase
K-562	human chronic myelogenous leukaemia cell
KB	human oral epidermoid carcinoma cell
L1210	lymphocytic murine leukaemia cell
L5178	mouse lymphoma
LD_{50}	lethal dose (50%) concentration
L-NAMA	N^{ω}-monomethyl-L-arginine
LoVo/Dx	human colon adenocarcinoma
LOX	lipoxygenase
LPS	lipopolysaccharide
LRSA	linezolid-resistant methicillin-resistant *Staphylococcus aureus*
LTB_4	leukotriene B_4
Lu-1	human lung carcinoma
MAPK	mitogen-activated protein kinase
MCF-7	human breast adenocarcinoma
MDA	malondialdehyde
MDR	multiple-drug resistant
MIC	minimum inhibitory concentration
MLC	minimum lethal concentration
MLCR	mixed lymphocyte culture reaction
MMP	matrix metalloproteinase
MRSA	methicillin-resistant *Staphylococcus aureus*
MRSE	methicillin-resistant *Staphylococcus epidermidis*
MSSA	methicillin-susceptible *Staphylococcus aureus*
MSSE	methicillin-susceptible *Staphylococcus epidermidis*
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium
NAC	*N*-acetyl-L-cysteine
NADPH	nicotinamide adenine dinucleotide phosphate (reduced)
NBT	nitroblue tetrazolium
NCI	National Cancer Institute
NCI-H187	human lung cancer cells
NFAT	nuclear factor of activated T-cells
NF-κB	nuclear factor kappaB
NGF	nerve growth factor
NIDDM	noninsulin-dependent diabetes mellitus
NIK	NF-κB-inducing kinase
NO	nitric oxide
NQO1	NAD(P)H:quinine oxidoreductase

NSCLC	non-small-cell lung cancer
6-OHDA	6-hydroxydopamine
OVCAR-8	ovarian cell line
P-388	lymphoid murine leukaemia cell
PA	phosphatidic acid
PAA	phosphonoacetic acid
PAF	platelet-activity factor
PARP-1	poly(ADP-ribose)polymerase-1
PC-3	human prostrate cancer cell
PDF	peptide deformylase
PEP	prolyl endopeptidase
PGE_2	prostaglandin E_2
PKC	protein kinase C
PLC	phospholipase C
PMA	phorbol 12-myristate 13-acetate
PP-1	protein phosphatase 1
PP-2A	protein phosphatase 2A
PRSP	penicillin-resistant *Streptococcus pneumoniae*
PSSP	penicillin-susceptible *Streptococcus pneumoniae*
PTK	protein tyrosin kinase
PTPase	protein tyrosine phosphatase
QRSA	quinolone-resistant *Staphylococcus aureus*
Quin-R	quinolone-resistant *Streptococcus pneumoniae*
REV	regulation of virion expression
RocB	didesmethyl-rocaglamide B
ROS	reactive oxygen species
RSV	respiratory syncytial virus
SAR	structural activity relationships
SI	selectivity index
SK-MEL-5	human malignant melanoma cell line
SPA	scintillation proximity assay
$sPLA_2$	secretory phospholipase A_2
SSAR	succinic semialdehyde reductase
STZ	streptozotocin
SV40	transformed fibroblast cells
TEAC	trolox equivalent antioxidant capacity
TI	therapeutic index
TMV	tobacco mosaic virus
TNF-α	tumor necrosis factor-alpha
TPA	12-*O*-tetradecanoylphorbol-13-acetate
TRAF	tumor necrosis factor (TNF) receptor-associated factor
TRAIL	TNF-related apoptosis-inducing ligand
Trolox	6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid
TRP-2	tyrosinase-related protein-2
TSP-1	throbospondin-1

TXB_2	thromboxane B_2
U46619	9,11-dideoxy-11α,9α-epoxymethanoprostagrandin
VCAM-1	vascular cell adhesion molecule-1
VEGF	vascular endothelial growth factor
VISA	vancomycin-intermediate *Staphylococcus aureus*
VRE	vancomycin-resistant *Enterococcus*

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