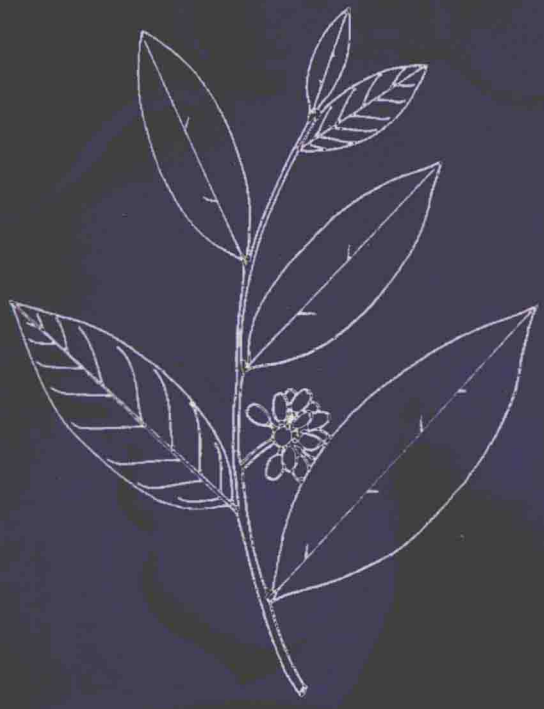
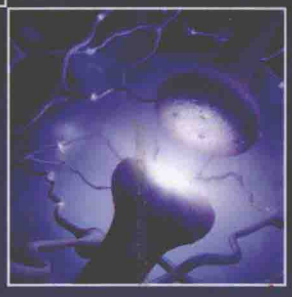
Lead Compounds from Medicinal Plants for the Treatment of Neurodegenerative Diseases

Christophe Wiart





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Christophe Wiart, PharmD, PhD, ACS

Ethnopharmacologist

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Academic Press is an imprint of Elsevier

Academic Press is an imprint of Elsevier
32 Jamestown Road, London NW1 7BY, UK
225 Wyman Street, Waltham, MA 02451, USA
525 B Street, Suite 1800, San Diego, CA 92101-4495, USA

First edition 2014

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

ISBN: 978-0-12-398373-2

Typeset by MPS Limited, Chennai, India www.adi-mps.com

Printed and bound in United States of America

14 15 16 17 10 9 8 7 6 5 4 3 2 1

Lead Compounds from Medicinal Plants for the Treatment of Neurodegenerative Diseases

A volume in the *Pharmaceutical Leads from Medicinal Plants* series

"*Cogito, ergo sum.*"

René Descartes
French mathematician, natural scientist, and philosopher (1596–1650)

Foreword

By Atta-ur-Rahman

The tremendous advances in natural product chemistry in the last few decades have been triggered by spectacular developments in NMR, mass spectroscopy, and various hyphenated techniques that allow rapid separation and identification of the individual compounds in complex mixtures. The development of high throughput screening methods has greatly facilitated the discovery of new bioactive compounds.

Alzheimer's disease (AD) is the most common of neurodegenerative diseases, affecting almost 30 million people globally, and it has been estimated that with growing old-age populations, 1 in 85 people on our planet will be affected by 2050. The medicines developed include acetylcholinesterase inhibitors and an NMDA antagonist. However, they are only of marginal benefit. Parkinson's disease (PD) is another neurodegenerative disorder resulting from the death of dopamine-generating cells in the brain. There is no known cure for PD, although some relief may be provided by levodopa, dopamine agonists, and MAO-B inhibitors. Amyotrophic lateral sclerosis (ALS) is one of five motor neuron diseases that results in muscle weakness and atrophy. In a small percentage (about 5%), the causes have been attributed to genetic defects, but in the majority of cases the causes are not known. Again there is no known cure.

There is an urgent need of finding new compounds that can attack the underlying mechanisms involved in PD, AD, and ALS, not only to block the progression of the disease with age but also offer a cure. Natural products offer a vast reservoir of compounds that present a huge structural diversity. This is accompanied by a corresponding span of biological activities of various types. They can serve as a treasure chest when searching for such novel lead compounds.

This book is concerned with the medicinal chemistry of those natural products that have been found to have potential for the treatment of these neurodegenerative disorders. I would like to compliment Dr. Christophe Wiart for writing an excellent book that comprehensively covers various classes of natural products that can be potentially employed directly or that can offer interesting pharmacophores for the treatment of these diseases.

The book should be of great interest to a large community of medicinal chemists working in this challenging area.

Atta-ur-Rahman, FRS
International Center for Chemical & Biological Sciences
University of Karachi
Karachi, Pakistan

Professor Atta-ur-Rahman obtained his PhD in organic chemistry from Cambridge University (1968). He has 910 publications in several fields of organic chemistry including 701 research publications, 27 international patents, 117 books and 65 chapters in books published largely by major U.S. and European presses. He is the Editor-in-Chief of 12 European Chemistry journals and the Editor of *Studies in Natural Product Chemistry*—37 volumes of which have been published by Elsevier (The Netherlands) under his editorship during the last two decades. Seventy-six students have completed their PhD degrees under his supervision.

Professor Rahman is the first scientist from the Muslim world to have won the prestigious UNESCO Science Prize (1999) in the 35-year-old history of the Prize. He was elected as Fellow of the Royal Society (London) in July 2006. He has been awarded honorary doctorate degrees by many universities including the degree of Doctor of Science (ScD) by Cambridge University (UK) (1987), Honorary degree of Doctor of Education by Coventry University (UK) (2007), Honorary DSc degree by Bradford University (UK) (2010), Honorary PhD by the Asian Institute of Technology (2010) and Honorary Doctorate by the University of Technology, Mara, (2011) (bestowed by the King of Malaysia). He was elected Honorary Life Fellow of King's College, Cambridge University, UK in 2007. Professor Atta-ur-Rahman was awarded the TWAS Prize for Institution Building in Durban, South Africa in October 2009 in recognition of his contributions for bringing about revolutionary changes in the higher education sector in Pakistan. The Austrian government also honored him with its highest civil award (Grosse Goldene Ehrenzeischen am Bande) (2007) in recognition of his eminent contributions. Successive Governments of Pakistan have conferred on him four civil awards, Tamgha-i-Imtiaz (1983, President General Ziaul Haq), Sitara-i-Imtiaz (1991, Prime Minister Mohtarma Benazeer Bhutto), Hilal-i-Imtiaz (1998, Prime Minister Nawaz Sharif), and the highest national civil award Nishan-i-Imtiaz (2002, President General Musharraf).

He is President of the Network of Academies of Sciences of Islamic Countries (NASIC) and the Vice-President (Central & South Asia) of the Academy of Sciences for the Developing World (TWAS) Council, Foreign Fellow of Korean Academy of Sciences, and Foreign Fellow of the Chinese Chemical Society. Professor Atta-ur-Rahman was the President of the Pakistan Academy of Sciences (2003–2006). He was again elected as the President of the Academy from 1st January 2011 and continues in that capacity.

Professor Atta-ur-Rahman was the Federal Minister for Science and Technology (14th March, 2000—20th November, 2002), Federal Minister of Education (2002), and Chairman of the Higher Education Commission with the status of a Federal Minister from 2002 to 2008.

Professor Atta-ur-Rahman was the Coordinator General of COMSTECH, an OIC Ministerial Committee comprising the 57 Ministers of Science & Technology from 57 OIC member countries, from 1996 to 2012. He is Distinguished National Professor as well as Professor Emeritus at Karachi University. He is also the Patron-in-Chief of the International Center of Chemical and Biological Sciences (which comprises a number of institutes, including the Husein Ebrahim Jamal Research Institute of Chemistry and the Dr. Panjwani Center of Molecular Medicine and Drug Development) at Karachi University.

Foreword

By Derek J. McPhee

As Editor-in-Chief of the MDPI journals *Molecules* and *Pharmaceuticals*, I came to know Dr. Wiart as a result of a letter he had sent to the *Molecules* Editorial Office alerting us of a misidentified plant species in one of our published papers. During the subsequent email exchanges, I became aware of his profound knowledge of all matters related to plant pharmacognosy, so it is with great pleasure that I learn he has now chosen to follow up his numerous other well-received books in this area with one dedicated entirely to the topic of Lead Compounds from Medicinal Plants for the Treatment of Neurodegenerative Diseases.

This is indeed a timely subject, for neurodegenerative diseases constitute an area of pressing interest given the expectation that the number of people afflicted worldwide by these diseases will rapidly expand with the increasing aging population, while it remains a therapeutic area where there is currently a dearth of approved drugs. As several of these approved drugs are plant-derived natural products or close analogs, the expectation that plants will provide additional leads for such drugs seems entirely reasonable. Confirming my view on the timeliness of the topic, only a few days before I received the publisher's kind invitation to pen this foreword, I had seen a May 2013 conference announcement for a New York Academy of Sciences sponsored meeting on the topic of Translating Natural Products into Drugs for Alzheimer's and Neurodegenerative Diseases, and I was already aware of several journal reviews and some chapters in the *Springer Handbook of Natural Compounds* that have appeared in the past few years and cover different aspects of this field.

To this body of literature we can now add Dr. Wiart's most recent tome, where every major chemical class is covered in one of its three chapters (Chapter 1: Alkaloids, further divided according to skeleton into Amide, Piperine, and Pyridine Alkaloids; Indole Alkaloids; Isoquinoline Alkaloids and Derivatives; and Terpenoid Alkaloids; Chapter 2: Terpenes, with subchapters dedicated to Monoterpenes, Sesquiterpenes, Diterpenes, and Triterpenes; and Chapter 3: Phenolics, with headings covering Benzopyrones, Quinones, and Lignans). Within each chapter all the medical plant species containing these chemical entities are listed, with extensive critically evaluated coverage of chemical structures, detailed structure–activity relationship information, biological activity targets, and mechanisms of action. All this is complemented by an exhaustive listing of the primary literature sources and valuable cross-referenced indexes by Natural Product, Pharmacological Terms, and Plants.

I have no doubt that this book's readers, which will include both the experienced scientist and the novice in the field seeking background to guide a search for novel entities with biological

activity in this therapeutic area, will soon come to consider this the definitive "go-to" book for comprehensive information in this area for many years to come, and Dr. Wiart is to be congratulated for another success in his lengthy and distinguished publishing history.

Derek J. McPhee
Senior Director of Technology Strategy
Amyris Inc.
Emeryville, California, USA

Derek J. McPhee is currently the Senior Director of Technology Strategy at Amyris Inc., a publicly traded biotechnology company based in Emeryville (California, USA) focused on the production of renewable alternatives to petroleum-based fuels and specialty chemicals. A native of Scotland, he has a LicC degree in Applied Chemistry from the Universidad de Málaga (Spain) and a PhD in Organic Chemistry from the University of Calgary (Canada). After pursuing a NSERC Postdoctoral Research Associateship at the Division of Chemistry of the Canadian National Research Council in Ottawa, the remainder of his career has been in industry.

Following a period of 14 years with Uniroyal Chemical (now part of Chemtura Corporation) working on the discovery, process development, and manufacture of agricultural, rubber, and specialty chemicals, he has worked in the generic pharmaceutical industry as a Senior Scientist at Brantford Chemicals (now Apotex Pharmachem), and as Director of Chemistry and Vice President of a U.S./Canada-based custom synthesis company. Before joining Amyris in March 2005, he was a self-employed consultant to several chemical and pharmaceutical startups.

In addition to his current position at Amyris, he has been that company's Director and Senior Director of Chemistry, leading a team that, with funding from the Bill and Melinda Gates Foundation, developed a novel low-cost route to the antimalarial drug precursor artemisinin using a raw material produced by fermentation of genetically engineered yeast. The launch by Sanofi of an ACT drug made using this technology was officially announced a few days prior to World Malaria Day in March 2013.

During the period 2000–2005 he was the Managing Editor of MDPI's online chemistry journal *Molecules*, and since 2005 he has served as its Editor-in-Chief. He has also been the Editor-in-Chief of the MDPI journal *Pharmaceuticals* since its launch in 2004. He is the sole author/coauthor of 23 patents, 19 papers in peer-reviewed scientific journals, and two book chapters.

Foreword

By Cornelis J. Van der Schyf

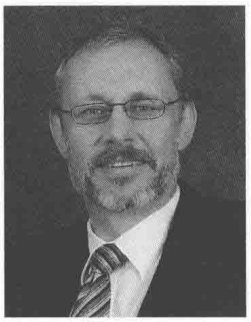
Neurodegenerative diseases are a group of disorders with complex pathoetiological pathways leading to neuronal cell death. These disorders constitute an emerging epidemic as the aging cohort of the world population expands and their burden on society grows inexorably, with enormous economic and human costs. Of note—and of great concern—is the fact that neurodegenerative diseases lack effective treatment options for patients. Although some *de novo* "designed" agents show significant promise in preclinical studies as neuroprotective and disease-modifying agents, the need to discover unique organic molecules to serve as design leads for drug discovery programs is a growing concern. In this regard, natural products have served exquisitely as design templates for several complex drug design studies. Plant-derived secondary metabolites have long served as an important resource for the development of small-molecule therapeutics due primarily to their combination of unique chemical features and potent bioactivities. Accumulating evidence suggests that phytochemicals themselves may potentially mitigate neurodegeneration, and improve memory and cognitive and neuromotor function. Ironically, nutraceutical products (most of which are derived directly from plants) may offer a viable short-term option for many patients suffering from neurodegenerative disorders since these products are subject to fewer regulations than traditional pharmaceuticals and therefore could be made available to patients much more expeditiously than newly developed prescription drugs.

It is in these contexts that the value of Christophe Wiart's second volume in the series *Pharmaceutical Leads from Medicinal Plants* can be truly appreciated. This volume, titled *Lead Compounds from Medicinal Plants for the Treatment of Neurodegenerative Diseases*, collates data from the peer-reviewed literature that present pharmacological evidence, structure-activity relationships, cellular targets, and mechanisms of action in a very compelling way.

Chapters follow a primary arrangement using chemical structure types rather than plant species or specific pharmacological mechanism of action as indexing mechanisms. This makes perfect sense in view of the target audience, which would draw extensively from the drug development and drug discovery community. For example, listed under the title of Chapter 1, "Alkaloids," detailed descriptions follow that describe the amide, piperine, pyridine, indole, isoquinoline, and terpenoid subclass alkaloids. The same pattern is used for Chapters 2, "Terpenes," and 3, "Phenolics." Sublisted below these descriptors, the individual plant species that actually produce the chemical classes and subclasses are described individually. The elegance of this approach can be exemplified by the stilbene scaffold that has become popular in particular due to the neuroprotective effects of the non-flavonoid natural product resveratrol, and compounds derived from the xanthine scaffold that afford neuroprotection in Parkinson's disease through mechanisms that include dual adenosine A_{2A} receptor antagonism and MAO-B inhibition. Both the stilbene and xanthene scaffolds are present in a number of related and unrelated plant species, and it is extremely useful to have these species listed after the primary desired chemical scaffold has been identified in the index.

Natural products derived from medicinal plants in particular are widely anticipated to play a significant and increasing role in the development of new therapeutic leads for neurodegenerative disease. It is my contention that this volume by Dr. Wiart will play a core role in this evolving era, and that every discovery in this arena will prove to have been inspired, at least in part, by the monumental work of this author.

Cornelis J. (Neels) Van der Schyf
Dean of the Graduate School & Professor of Biomedical and Pharmaceutical Sciences
Idaho State University
Pocatello, Idaho, USA



Dr. Van der Schyf is Dean of the Graduate School and Professor of Biomedical and Pharmaceutical Sciences at Idaho State University (ISU). Before joining ISU, Van der Schyf was Associate Dean for Research and Graduate studies in the College of Pharmacy and Professor of Neurobiology in the College of Medicine at Northeast Ohio Medical University. He earned his BPharm, MSc, DSc (PhD), and DTE degrees from Potchefstroom University (now North-West University) in South Africa and completed a postdoctoral fellowship in the Department of Medicinal Chemistry at the University of Connecticut, during which time he did research at the Francis Bitter National Magnet Lab at MIT in Cambridge, Massachusetts.

Cornelis J. Van der Schyf is considered as one of the leading contributors to the concept of designed multiple ligands in the treatment of neurodegenerative diseases, and has published more than 110 peer-reviewed research and review articles, more than 200 abstracts and presentations—many of these as invited keynote speaker, seven book chapters, several reports to industry, and journal editorials. He holds 14 patents. He is the Editor-in-Chief of the *Journal of Biophysical Chemistry* and is or has been a member of the editorial advisory boards for *BMC Pharmacology and Toxicology, Expert Opinion on Drug Discovery, Molecules, International Journal of Brain and Cognitive Sciences, Medicinal Chemistry Research, The Open Medicinal Chemistry Journal, Open Medicinal Chemistry Letters, Neurotoxicity Research*, and *Pharmaceutics & Novel Drug Delivery Systems: Current Research*, and serves on the International Advisory Board of the *South African Journal of Chemistry*. He was an invited guest editor for the January 2009 issue of the journal *Neurotherapeutics*. As visiting professor in Australia (University of Queensland, Brisbane), Belgium (FUNDP, Namur), USA (Virginia Tech), and currently as Emeritus Extraordinary Professor at North-West University (South Africa), he remains active internationally.

Besides serving or having served *ad hoc* and as a chartered member on several NIH Study Sections and many other national and international granting agencies, he is a member of the Phi Beta Delta Honor Society, Sigma Xi, and The Scientific Research Society, and has received several honors, including "Most Cited Paper" awards, the APSSA Upjohn Achievement Award and South Africa's highest honor in drug discovery research, the FARMOVS Prize for Pharmacology and Drug Development.

Preface

During the Tertiary period, some little apes gained optical, olfactory, and locomotor abilities which allowed feeding not only on seeds, fruits, and leaves from trees but also herbs, mosses, and mushrooms, the phytonutrients of which may have in fact possibly contributed to the subsequent birth of humanity. This possibility raises interesting questions regarding how plant natural products may have induced or facilitated the constitution of the bewildering web of neuronal connections required to form the human brain. This question is yet unanswered, but acetylcholine, dopamine, and serotonin, which account for neurotransmission, occur in plants which indeed appeared in the Tertiary period.

Today, the accelerating speed of aging comes with an increased number of patients diagnosed with neurodegenerative diseases for which there is no robust treatment despite intensive research. In effect, the progression of Alzheimer's disease and Parkinson's disease can be slowed down but not stopped or reversed. Besides this, other critical conditions such as amyotrophic lateral sclerosis and spinal cord injuries remain completely untreatable. In this light, we present in this volume evidence that natural products are not only able to protect neurons and to boost their activities, but also to induce neuritogenesis, raising the captivating possibility that the flowering plants that helped to lead apes to evolve into *Homo sapiens* may in the near future allow not only complete victory over neurodegenerative diseases and neuronal injuries but also the boosting of human intelligence.

Christophe Wiart, PharmD, PhD, ACS

About the Author

Dr. Christophe Wiart was born August 12, 1967 in Saint Malo, France. He obtained a Doctorate of Pharmacy from the University of Rennes in 1996 and was a pupil of the pharmacognosist Professor Loic Girre and the botanist Lucile Allorge from the Botanical section of the Museum of Natural History in Paris. Dr. Wiart has been studying the medicinal plants of India, Southeast Asia, China, Korea, Japan, Australia, and the Pacific Islands for the last 20 years. He has collected, identified, classified, and made botanical plates of about 2000 medicinal plants. Dr. Wiart is regarded as the most prominent living authority in the field of Asian ethnopharmacology, chemotaxonomy, and ethnobotany. His research team currently works on the identification and pharmacological evaluation of Asian medicinal plants at the University of Nottingham. He has authored numerous bestselling books devoted to the medicinal plants of Asia and their pharmacological and cosmetological potentials.

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