

# Drug Design and Discovery in Alzheimer's Disease



Edited by  
Atta-ur-Rahman and Muhammad Iqbal Choudhary

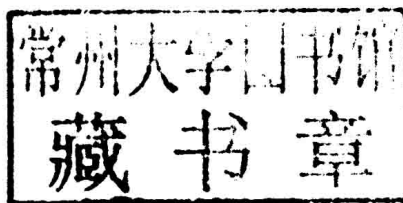
# Drug Design and Discovery in Alzheimer's Disease

Edited by

Atta-ur-Rahman, FRS  
Honorary Life Fellow, Kings College, University of  
Cambridge, UK

And

Muhammad Iqbal Choudhary  
H.E.J. Research Institute of Chemistry, International  
Center for  
Chemical and Biological Sciences, University of  
Karachi, Pakistan



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 © 2014 Bentham Science Publishers Ltd. Published by Elsevier Inc. 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: 978-0-12-803959-5

#### **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

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)

## Drug Design and Discovery in Alzheimer's Disease



## PREFACE

Alzheimer's disease (AD) is one of the most common neurological disorders, affecting a large portion of the human population in both the developed and the developing world. The demographic changes in the next few decades are likely to increase the prevalence of AD to epidemic proportions. Unfortunately, despite major advances in molecular and structural biology, neurochemistry, disease genomics and cell physiology, the etiology of the disease is only marginally understood. AD has been the focus of major research efforts, both in the pharmaceutical industry and in academia. The literature is continuously enriched by exciting discoveries on various aspects of AD and its prevention and treatment. It is nearly impossible for any researcher to remain on top of the most recent developments in this dynamic field without access to comprehensive reviews on various aspects.

This volume of the book series "*Frontiers in Drug Discovery and Development*" is focused on key developments in the understanding of the disease at molecular levels, identification and validation of molecular targets, as well as innovative approaches towards drug discovery, development and delivery. The volume comprises 16 scholarly written review articles by leading researchers in the field, covering a broad range of topics.

The review contributed by Korabecny *et al* sets the stage for the subsequent chapters by detailing the main symptomatic strategies available for the treatment of AD and for the improvement of quality of life of AD patients. This review summarizes various classes of current and future therapies of AD.

Rashid and Ansari focus on the major challenges faced in the discovery and development of anti-AD drugs. They provide examples of several blockbuster AD drugs, obtained through various approaches. Revadigar and his team have contributed a chapter reviewing the literature about the identification of various enzymes involved in the on-set and progression of Alzheimer's diseases. They have included numerous examples of inhibitors of these enzymes which has either already developed as drugs or are in various stages of drug development.

Aziz *et al* focus on the significance of small molecules, both natural and synthetic, as possible drug candidates for the treatment of neurodegenerative diseases, including AD.

The four review articles (chapters 5-8), contributed by Joubert *et al*, Grieg *et al*, Saify and Sultana, and Alcolea-Palafox *et al*, specifically focus on the role of cholinesterases in the on-set and progression of AD and their inhibition, which has potential as an effective treatment. It is important to note that most of the current therapies of AD are based on cholinesterase modulation and the field remains active.

Beta-site APP clearing enzyme-1 (BACE-1) plays an important role in the production of  $\beta$ -amyloid proteins, one of the key reasons of the progression of AD. BACE-1 has been identified as the key target for the development of anti-AD therapies. Klaver and Tesco, Decourt *et al*, and Henary *et al* have contributed three excellent reviews (chapter 9-11) on the modulation of BACE-1 activity, as a strategy towards new drug discovery and development. Along with the small molecular inhibitors of BACE-1, the role of metal chelating agents has also been reviewed.

Along with two key targets, cholinesterase and BACE-1, a number of other targets have also been identified for drug discovery. Sandoval *et al* contributed a comprehensive review on various chemical compounds which serve as agonist of somatostatin subtype-4 receptor as a possible treatment regimen for AD.

Neprilysin, a key target in the etiology of AD, has been the focus of recent research. Neprilysin catalyzes the degradation of amyloid beta peptides ( $A\beta$ ), which are neurotoxins and contribute in the pathophysiology of AD. Pope and Cascio have reviewed the recent work on the inhibition of neprilysin and the prospects of their development as treatment for AD.

GSK3 $\beta$ / $\beta$ -catenin signaling has been identified as a possible contributor to the on-set and progressive degeneration of neuron in AD. GSK-3 controls proteosomal degradation of catenin, thus slowdown, the neurodegeneration. Zeidán-Chuliá and

Moreira have critically analyzed its validity as a target for anti-AD drug discovery.

Seneci covers the important aspects of AD treatment and inhibition of phosphorylation of tau-proteins, collectively called taupathy. The focus has been to understand the expression of such proteins at the genetic level and to identify the structural characteristics which makes them aggregatory in nature. Another aim is to use small molecules as effective inhibitors of these processes.

Last but not least, the article contributed by Ahmed *et al* comprehensively reviews the applications of nanotechnology in the development of effective drug delivery vehicles for AD drugs. Nanomedicines can serve as novel carrier of cholinesterase inhibitors effectively crossing the anatomical and biochemical barriers.

We wish to express our profound thanks to all the contributors of reviews in this volume for their hard, and scholarly work and critical commentary. We are confident that their scholarly contributions will make this volume of great interest to many researches. We are also grateful to Mr. Mahmood Alam (Director Publication) and Ms. Sara Yaser (Manager Publications) of Bentham Science Publishers for their excellent management skills and secretarial support.

**Atta-ur-Rahman, *FRS***

Honorary Life Fellow, Kings College,  
University of Cambridge,  
UK

**Muhammad Iqbal Choudhary**

H.E.J. Research Institute of Chemistry,  
International Center for Chemical and Biological Sciences,  
University of Karachi,  
Pakistan



## **List of Contributors**

### **A. Michael Crider**

*United Arab Emirates University, Faculty of Medicine and Health Sciences,  
Department Pharmacology and Therapeutics, Al Ain, UAE*

### **Abdu Adem**

*Department of Pharmacology and Therapeutics, Faculty of Medicine and Health  
Sciences, United Arab Emirates University, Al-Ain, UAE*

### **Adel M. Abuzenadah**

*King Fahd Medical Research Center, King Abdulaziz University, P. O. Box  
80216, Jeddah 21589, Saudi Arabia*

### **Ali Jawad**

*Department of Applied Physics, Zakir Husain College of Engineering and  
Technology, Aligarh Muslim University, Aligarh UP, India*

### **Benjamin P. Repsold**

*Pharmaceutical Chemistry, North-West University, Private Bag X6001,  
Potchefstroom, 2520, South Africa*

### **Boris Decourt**

*Banner Sun Health Research Institute, Sun City, AZ, USA*

### **Carmen Martínez-Rincón**

*Nursing Department, Complutense University of Madrid, Spain*

### **Daniel Jun**

*University Hospital Hradec Kralove, Sokolska 581, 500 05 Hradec Kralove,  
Czech Republic*

### **Darrick Pope**

*Department of Chemistry and Biochemistry, Duquesne University, Pittsburgh, PA  
15282, USA*

**David F. Fischer**

*BioFocus; Leiden, The Netherlands*

**David William Klaver**

*Alzheimer's Disease Research Laboratory, Department of Neuroscience, Tufts University School of Medicine, Boston, MA, USA*

**Dolores Rodríguez-Martínez**

*Nursing Department, Complutense University of Madrid, Spain*

**Eric A. Owens**

*Department of Chemistry, Center for Diagnostics and Therapeutics, Georgia State University, Atlanta, Georgia, 30303, USA*

**Eugenie Nepovimova**

*Department of Toxicology, Faculty of Military Health Sciences, Trebesska 1575, 500 01 Hradec Kralove, Czech Republic*

**Faizul H. Nasim**

*Department of Chemistry, BJ Campus, The Islamia University of Bahawalpur, Bahawalpur, Pakistan*

**Fares Zeidán-Chuliá**

*Center of Oxidative Stress Research, Department of Biochemistry, Postgraduate Program in Biological Sciences: Biochemistry, Institute of Basic Health Sciences, Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil*

**Farhan Jalees Ahmad**

*Nanomedicine Research Lab, Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard, New Delhi 110062, India*

**Farzana L. Ansari**

*Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan*

**Filip Zemek**

*Department of Toxicology, Faculty of Military Health Sciences, Trebesska 1575,  
500 01 Hradec Kralove, Czech Republic*

**Giuseppina Tesco**

*Alzheimer's Disease Research Laboratory, Department of Neuroscience, Tufts  
University School of Medicine, Boston, MA, USA*

**Gjumrakch Aliev**

*Department of Health Science and Healthcare Administration, University of  
Atlanta, Atlanta, GA, USA, and GALLY International Biomedical Research  
Consulting LLC, San Antonio, TX, USA*

**Iqbal Ahmad**

*Nanomedicine Research Lab, Department of Pharmaceutics, Faculty of  
Pharmacy, Jamia Hamdard, New Delhi 110062, India*

**Ismael Ortuño- Soriano**

*Institute for Health Research at the San Carlos Clinical Hospital (IdISSC),  
Madrid, Spain; Nursing Department, Complutense University of Madrid, Spain*

**Jacobus P. Petzer**

*Pharmaceutical Chemistry, North-West University, Private Bag X6001,  
Potchefstroom, 2520, South Africa*

**Jacques Joubert**

*School of Pharmacy, University of the Western Cape, Private Bag X17, Bellville  
7535, South Africa*

**Jan Korabecny**

*Department of Toxicology, Faculty of Military Health Sciences, Trebesska 1575,  
500 01 Hradec Kralove, Czech Republic*

**Javed Ahmad**

*Nanomedicine Research Lab, Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard, New Delhi 110062, India*

**José Cláudio Fonseca Moreira**

*Center of Oxidative Stress Research, Department of Biochemistry, Postgraduate Program in Biological Sciences: Biochemistry, Institute of Basic Health Sciences, Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil*

**José L. Pacheco-del-Cerro**

*Nursing Department, Complutense University of Madrid, Spain*

**Julie Frearson**

*BioFocus; Chesterford Research Park, Saffron Walden, Essex, CB10 1XL, UK*

**Kamil Kuca**

*University Hospital Hradec Kralove, Sokolska 581, 500 05 Hradec Kralove, Czech Republic*

**Kamil Musilek**

*University Hospital Hradec Kralove, Sokolska 581, 500 05 Hradec Kralove, Czech Republic*

**Karin E. Sandoval**

*Department of Pharmaceutical Sciences, Southern Illinois University Edwardsville, Edwardsville, Illinois 62026, USA*

**Katarina Spilovska**

*Department of Toxicology, Faculty of Military Health Sciences, Trebesska 1575, 500 01 Hradec Kralove, Czech Republic*

**Kenneth A. Witt**

*Department of Pharmaceutical Sciences, Southern Illinois University Edwardsville, Edwardsville, Illinois 62026, USA*

**Lara Pacheco-Cuevas**

*Nursing Department, Complutense University of Madrid, Spain*

**Louis H.A. Prins**

*Department of Pharmacy, University of Namibia, Windhoek, Namibia*

**Maged M. Henary**

*Department of Chemistry, Center for Diagnostics and Therapeutics, Center for Biotechnology and Drug Design, Georgia State University, Atlanta, Georgia, 30303, USA*

**Maria Kontoyianni**

*Department of Pharmaceutical Sciences, Southern Illinois University Edwardsville, Edwardsville, Illinois 62026, USA*

**Marwan Sabbagh**

*Banner Sun Health Research Institute, Sun City, AZ, USA*

**Mauricio Alcolea-Palafox**

*Chemical-Physics Department, Chemistry Faculty, Complutense University of Madrid, Spain*

**Michael Cascio**

*Department of Chemistry and Biochemistry, Duquesne University, Pittsburgh, PA 15282, USA*

**Michael D. Wall**

*BioFocus; Chesterford Research Park, Saffron Walden, Essex, CB10 1XL, UK*

**MiMi Macias**

*Banner Sun Health Research Institute, Sun City, AZ, USA*

**Mohamed A. Embaby**

*Department of Chemistry, Faculty of Sciences & Arts Khulais, King Abdulaziz University, Jeddah, KSA*

**Mohammad A. Kamal**

*King Fahd Medical Research Center, King Abdulaziz University, P. O. Box 80216, Jeddah 21589, Saudi Arabia*

**Mohammad Zaki Ahmad**

*Department of Pharmaceutics, College of Pharmacy, Najran University, Saudi Arabia*

**Nasimudeen R. Jabir**

*King Fahd Medical Research Center, King Abdulaziz University, P. O. Box 80216, Jeddah 21589, Saudi Arabia*

**Nigel H. Grieg**

*Drug Design & Development Section, Laboratory of Neurosciences, Intramural Research Program, National Institute on Aging, National Institutes of Health, Baltimore, MD 21224, USA*

**Nighat Sultana**

*Pharmaceutical Research Center, PCSIR Laboratories Complex, Shahrah-e-Dr. Salimuzzaman Siddiqui, Karachi 75280, Pakistan*

**Omar Aziz**

*BioFocus; Chesterford Research Park, Saffron Walden, Essex, CB10 1XL, UK*

**Ondrej Soukup**

*University Hospital Hradec Kralove, Sokolska 581, 500 05 Hradec Kralove, Czech Republic*

**Othman Sulaiman**

*School of Industrial Technology, Universiti Sains Malaysia, Minden-11800, Pulau Pinang, Malaysia*

**Paloma Posada-Moreno**

*Institute for Health Research at the San Carlos Clinical Hospital (IdISSC), Madrid, Spain; Nursing Department, Complutense University of Madrid, Spain*

**Pierfausto Seneci**

*Department of Chemistry, University of Milan, Via Golgi 19, I-20133 Milan, Italy*

**Raza Murad Ghalib**

*Department of Chemistry, Faculty of Sciences & Arts Khulais, King Abdulaziz University, Jeddah, KSA*

**Rokiah Hashim**

*School of Industrial Technology, Universiti Sains Malaysia, Minden–11800, Pulau Pinang, Malaysia*

**Roland W. Bürli**

*BioFocus; Chesterford Research Park, Saffron Walden, Essex, CB10 1XL, UK*

**Sarel F. Malan**

*School of Pharmacy, University of the Western Cape, Private Bag X17, Bellville 7535, South Africa*

**Sayed Hasan Mehdi**

*Department of Chemistry, SPG College, UP, Lucknow, India*

**Shams Tabrez**

*King Fahd Medical Research Center, King Abdulaziz University, P. O. Box 80216, Jeddah 21589, Saudi Arabia*

**Sohail Akhter**

*Nanomedicine Research Lab, Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard, New Delhi 110062, India*

**Surendra Reddy Punganuru**

*Department of Chemistry, Georgia State University, Atlanta, Georgia, 30303, USA*

**Tyler L. Dost**

*Department of Chemistry, Georgia State University, Atlanta, Georgia, 30303, USA*

**Umer Rashid**

*Department of Chemistry, Hazara University, Mansehra 21120, Pakistan*

**Vageesh Revadigar**

*Discipline of Pharmacology, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Minden–11800, Pulau Pinang, Malaysia*

**Vikneswaran Murugaiyah**

*Discipline of Pharmacology, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Minden–11800, Pulau Pinang, Malaysia*

**Zafar Saied Saify**

*International Center for Chemical Sciences, H. E. J. Research Institute of Chemistry, University of Karachi, Karachi 75270, Pakistan*

**Ziyaaur Rahman**

*Irma Lerma Rangel College of Pharmacy, Texas A&M Health Science Center, Kingsville, Texas, USA*



# CONTENTS

<i>Preface</i>	<i>viii</i>
----------------	-------------

<i>List of Contributors</i>	<i>xi</i>
-----------------------------	-----------

## CHAPTERS

<b>1. Pharmacotherapy of Alzheimer's Disease: Current State and Future Perspectives</b>	<b>3</b>
<i>Jan Korabecny, Filip Zemek, Ondrej Soukup, Katarina Spilovska, Kamil Musilek, Daniel Jun, Eugenie Nepovimova and Kamil Kuca</i>	
<b>2. Challenges in Designing Therapeutic Agents for Treating Alzheimer's Disease-from Serendipity to Rationality</b>	<b>40</b>
<i>Umer Rashid and Farzana L. Ansari</i>	
<b>3. Enzyme Inhibitors Involved in the Treatment of Alzheimer's Disease</b>	<b>142</b>
<i>Vageesh Revadigar, Raza Murad Ghalib, Vikneswaran Murugaiyah, Mohamed A. Embaby, Ali Jawad, Sayed Hasan Mehdi, Rokiah Hashim and Othman Sulaiman</i>	
<b>4. Towards Small Molecules as Therapies for Alzheimer's Disease and Other Neurodegenerative Disorders</b>	<b>199</b>
<i>Omar Aziz, Roland W. Bürli, David F. Fischer, Julie Frearson and Michael D. Wall</i>	
<b>5. Multifunctional Enzyme Inhibition for Neuroprotection - A Focus on MAO, NOS, and AChE Inhibitors</b>	<b>291</b>
<i>Jacques Joubert, Jacobus P. Petzer, Louis H.A. Prins, Benjamin P. Repsold and Sarel F. Malan</i>	

*Contd....*