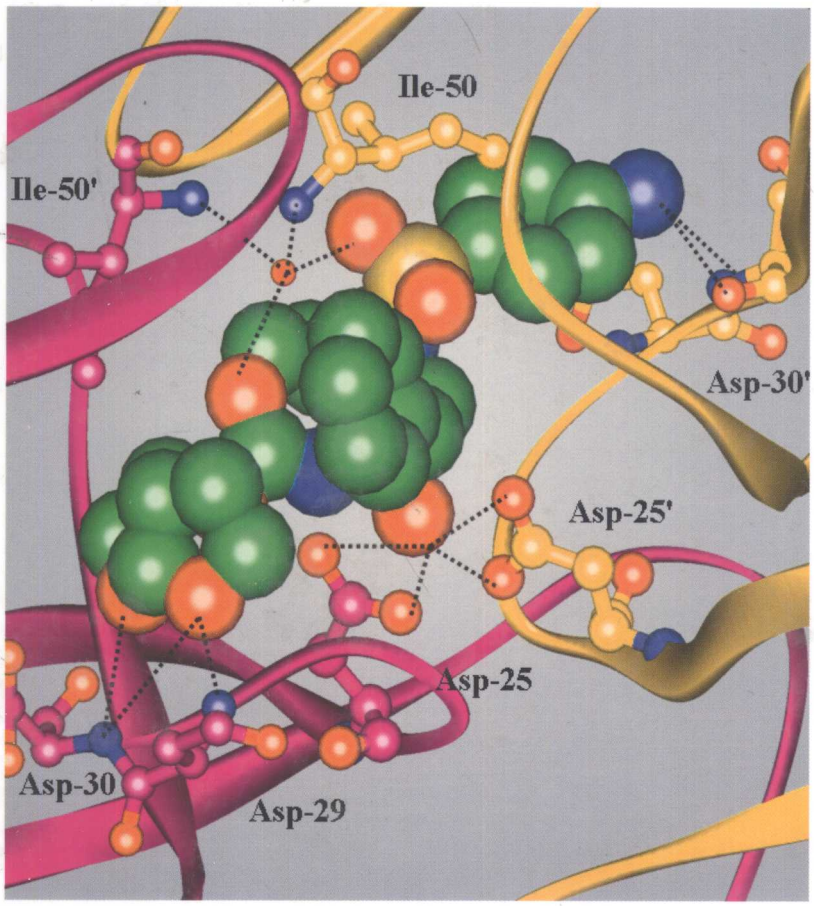
Methods and Principles in Medicinal Chemistry

Edited by Arun K. Ghosh

WILEY-VCH

Aspartic Acid Proteases as Therapeutic Targets



Volume 45

Series Editors:
R. Mannhold,
H. Kubinyi,
G. Folkers

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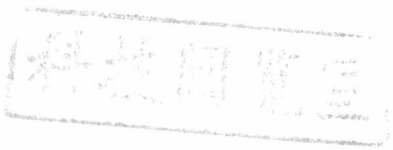

WILEY-VCH Verlag GmbH & Co. KGaA

Series Editors

Prof. Dr. Raimund Mannhold
Molecular Drug Research Group
Heinrich-Heine-Universität
Universitätsstrasse 1
40225 Düsseldorf
Germany
mannhold@uni-duesseldorf.de

Prof. Dr. Hugo Kubinyi
Donnersbergstrasse 9
67256 Weisenheim am Sand
Germany
kubinyi@t-online.de

Prof. Dr. Gerd Folkers
Collegium Helveticum
STW/ETH Zurich
8092 Zurich
Switzerland
folkers@collegium.ethz.ch

Volume Editors

Prof. Dr. Arun K. Ghosh
Purdue University
Dept. of Chemistry
560 Oval Drive
West Lafayette
IN 47907-2084
USA

Cover Description:
X-ray structure of darunavir-bound HIV-1 protease (Tie, Y.; et al. 2004). Darunavir carbons are shown in green. Hydrogen bonds are shown as dotted lines.

Library of Congress Card No.: applied for

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

Bibliographic information published by the Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at http://dnb.d-nb.de.

Cover Design Grafik-Design Schulz, Fußgönheim
Typesetting Thomson Digital, Noida, India
Printing and Binding Strauss GmbH, Mörlenbach

Printed in the Federal Republic of Germany
Printed on acid-free paper

ISBN: 978-3-527-31811-7

List of Contributors

Daniel Bur
Actelion Pharmaceuticals Ltd.
CH-4123 Allschwil
Switzerland

Matthew G. Bursavich
Medical Chemistry
Myriad Pharmaceuticals
305 Chipeta Way
Salt Lake City, UT 84108
USA

Bruno D. Chapsal
Purdue University
Department of Chemistry
560 Oval Drive
West Lafayette, IN 47907-2084
USA

Derek C. Cole
Medical Chemistry Department
Takeda San Diego
10410 Science Center Drive
San Diego, CA 92121-1119
USA

Jon B. Cooper
UCL Department of Medicine
Centre for Amyloidosis and Acute
Phase Proteins
Laboratory for Protein Crystallography
Royal Free Campus
Rowland Hill Street
London NW3 2PF
UK

Jared N. Cumming
Schering-Plough Research Institute
2015 Galloping Hill Road
Kenilworth, NJ 07033
USA

Ben M. Dunn
University of Florida College of
Medicine
Department of Biochemistry &
Molecular Biology
P.O. Box 100245
Gainesville, FL 32610-0245
USA

Ernesto Freire
Johns Hopkins University
Department of Biology
3400 North Charles Street
Baltimore, MD 21218
USA

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ISBN: 978-3-527-31811-7

Sandra Gemma
Università degli Studi di Siena
Dipartimento Farmaco Chimico Tecnologico
via Aldo Moro, No. 2
53100 Siena
Italy

Arun K. Ghosh
Purdue University
Departments of Chemistry and Medicinal Chemistry
560 Oval Drive
West Lafayette, IN 47907-2084
USA

Christopher L. Hamblett
Merck Research Laboratories
33 Avenue Louis Pasteur
Boston, MA 02115
USA

and

Cowen and Company, LCC
Equity Research
2 International Place, 27th Floor
Boston, MA 02100
USA

Richard Heidebrecht, Jr.
The Broad Institute
7 Cambridge Center
Cambridge, MA 02142
USA

Lin Hong
CoMentis, Inc.
865 Research Parkway
Oklahoma City, OK 73104
USA

Ulrich Iserloh
Schering-Plough Research Institute
2015 Galloping Hill Road
Kenilworth, NJ 07033
USA

Olivier Jousson
University of Trento
Centre for Integrative Biology
38100 Trento
Italy

John Kay
Cardiff University
School of Biosciences
Museum Avenue
Cardiff CF10 3US, Wales
UK

Yoshiaki Kiso
Kyoto Pharmaceutical University
Department of Medicinal Chemistry
Center for Frontier Research in Medicinal Science
Yamashina-ku
Kyoto 607-8412
Japan

Urban Lendahl
Medical Nobel Institute
Karolinska Institute
Department of Cell and Molecular Biology
SE 171 77 Stockholm
Sweden

Johan Lundkvist
CNS/PAIN, Astrazeneca R&D
Neuroscience Department
SE 151 85 Södertälje
Sweden

Jürgen Maibaum
Novartis Pharma AG
Institutes for BioMedical Research
Novartis Campus
CH-4056 Basel
Switzerland

Hiroaki Mitsuya
National Cancer Institute
Center for Cancer Research
HIV & AIDS Malignancy Branch
The Experimental Retrovirology Section
Building 10, Room 5A11
9000 Rockville Pike
Bethesda, MD 20892
USA

and

Kumamoto University School of Medicine
Department of Hematology & Infectious Diseases
Kumamoto 860-8556
Japan

Michel Monod
Centre Hospitalier Universitaire Vaudois
Laboratoire de Mycologie, BT422
Service de Dermatologie
1011 Lausanne
Switzerland

Benito Munoz
Merck Research Laboratories
33 Avenue Louis Pasteur
Boston, MA 02115
USA

and

The Broad Institute
7 Cambridge Center
Cambridge, MA 02142
USA

Utz Reichard
University Hospital of Goettingen
Department of Medical Microbiology and National Reference Center for Systemic Mycoses
37075 Goettingen
Germany

Adam J. Ruben
Sanaria Inc.
Vaccine Stabilization & Logistics
9800 Medical Center Drive
Suite 209A
Rockville, MD 20850
USA

Sanjiv Shah
Merck Research Laboratories
33 Avenue Louis Pasteur
Boston, MA 02115
USA

Suresh B. Singh
Vitae Pharmaceuticals
502 West Office Center Drive
Fort Washington, PA 19034
USA

Sukanto Sinha
ActiveSite Pharmaceuticals, Inc.
1456 Fourth Street, Unit C
Berkeley, CA 94710
USA

Peter Staib
Leibniz Institute for Natural Product Research and Infection Biology – Hans Knoell Institute
Junior Research Group "Fundamental Molecular Biology of Pathogenic Fungi"
D-07745 Jena
Germany

Jordan Tang
Oklahoma Medical Research Foundation and University of Oklahoma
Health Science Center
825 NE 13th Street
Oklahoma City, OK 73104
USA

Colin M. Tice
Vitae Pharmaceuticals
502 West Office Center Drive
Fort Washington, PA 19034
USA

Scott C. Virgil
Director
California Institute of Technology
Department of Chemistry
Caltech Center for Catalysis and Chemical Synthesis
164-30, 1200 East California Blvd.
Pasadena, CA 91125
USA

Yuan-Fang Wang
Georgia State University
Department of Biology
Molecular Basis of Disease Program
P.O. Box 4010
Atlanta, GA 30302-4010
USA

Irene T. Weber
Georgia State University
Department of Biology
Molecular Basis of Disease Program
P.O. Box 4010
Atlanta, GA 30302-4010
USA

Jeanette M. Wood
S*BIO Pte Ltd
1 Science Park Rd, #05-09
The Capricorn, Singapore
Science Park II
Singapore 117528
Singapore

Preface

The digestive enzymes pepsin and chymosin (formerly called rennin), both being known since long, are members of the aspartic protease family. While these enzymes cleave many proteins and peptides in a relatively nonspecific manner, the substrate-specific aspartyic protease renin converts angiotensinogen to angiotensin I, the precursor of the hypertensive peptide angiotensin II. For this purpose, research on renin inhibitors as potential antihypertensive drugs started in the early 1970s, based on Pauling's concept of transition-state mimics as effective enzyme inhibitors. Umezawa's discovery of pepstatin, a picomolar to nanomolar inhibitor of several aspartic proteases, confirmed the importance of a replacement of the scissile amide bond by such a transition state-imitating group. Some early peptide-like renin inhibitors showed nanomolar activities but lacked sufficient bioavailability, a problem that continued for the next decades. In the meantime, the search for aspartic proteases inhibitors was significantly stimulated by the discovery that HIV protease also belongs to the aspartic protease family, like pepsin and renin. Research on this new target was supported by the concept of chemogenomics, that is, by transferring successful design strategies to the new target. Based on the accumulated experience from the search for renin inhibitors, saquinavir, indinavir, and ritonavir resulted as first drugs in the mid-1990s. These peptide-like compounds were followed by some nonpeptidic analogues, all of them bearing a transition state partial structure. Finally, after thousands of man years in research in different companies, the first bioavailable renin inhibitor, aliskiren, was approved and marketed in 2007. Much effort and hope go now into the search for β- and γ-secretase inhibitors as drugs to prevent the development and progression of Alzheimer's disease, as well as plasmepsin inhibitors to treat malaria. This book by Arun K. Ghosh treats all these topics in much detail, starting from the function and physiological role of the corresponding protease, discussing its structural biology, and finally the medicinal chemistry of ligand and drug design.

For several years, it has been our goal to include monographs on therapeutically relevant targets and their modulators in our book series "Methods and Principles in Medicinal Chemistry." After volumes on G protein-coupled receptors (volume 24), voltage-gated ion channels (volume 29), ligand design for GPCRs (volume 30),

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ISBN: 978-3-527-31811-7

antitargets (volume 38), nuclear receptors (volume 39), epigenetic targets (volume 42), and drug transporters (volume 44), this monograph is the first one in an important family of therapeutically relevant enzymes, the aspartic proteases.

We would like to express our appreciation for Arun Ghosh for his enthusiasm and perseverance in bringing this project to fruition. We wish to thank Joseph Vacca for his initial efforts toward this goal. A team of leading scientists discusses the above-mentioned aspartic proteases, as well as some others, and their inhibitors. We are very grateful to all these authors for their excellent contributions, as well as to Frank Weinreich and Nicola Oberbeckmann-Winter for their ongoing engagement in our series "Methods and Principles in Medicinal Chemistry," in which this book will surely be as well accepted as all previous volumes.

April 2010

Raimund Mannhold, Düsseldorf
Hugo Kubinyi, Weisenheim am Sand
Gerd Folkers, Zürich

A Personal Foreword

The human genome features a family of 15 active aspartic acid proteases that play a central role in the pathogenesis of many human diseases. The therapeutic inhibition of these aspartic acid proteases could conceivably provide a basis for novel treatment of human diseases. The disease targets include renin for hypertension, pepsin for gastric ulcers, HIV protease for AIDS, β- and γ-secretases for Alzheimer's disease, plasmepsins for malaria, cathepsin D and E for neoplastic diseases, and candida proteases for fungal infections. The catalytic aspartic acids in the active site motif are responsible for polarizing a bound water molecule that affects the proteolysis of the scissile bond of the substrate through a tetrahedral transition-state intermediate. Subsequently, mechanism-based design of nonhydrolysable dipeptide isosteres, mimicking the transition-state cleavage the scissile bond led to the evolution of potent substrate-derived inhibitors. Early studies on X-ray structures of fungal aspartic proteases bound to inhibitors, especially pepstatin-related structures, provided important molecular insights into the ligand-binding site interactions. This, in turn, provided important impetus for medicinal chemistry efforts toward the design and synthesis of a variety of transition-state isostere-derived peptidomimetic aspartyl protease inhibitors. Early efforts in the development of aspartic protease inhibitor drugs focused on the design of renin inhibitors for the treatment of hypertension. However, first-generation inhibitors were peptide-like, and due to their unfavorable pharmacological properties, early renin inhibitors never made it to clinical development. With the advent of AIDS and the discovery of human immunodeficiency virus (HIV) as the etiological agent, HIV-protease was recognized to play a critical role in the HIV life cycle. This led to massive research efforts in both academic and industrial laboratories in the quest for orally bioavailable protease inhibitor (PI) drugs as effective chemotherapeutics for AIDS. By the mid-1990s, the first aspartic acid protease inhibitor drug, saquinavir, received regulatory approval for the treatment of HIV/AIDS in combination with reverse transcriptase inhibitors. Soon after, a number of other first-generation HIV protease inhibitors were approved for use in highly active antiretroviral therapy (HAART). This was indeed a turning point in the management of HIV/AIDS. HAART treatment regimens significantly reduced mortality and improved the quality of life for HIV/AIDS

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patients. However, the emergence of multidrug-resistant HIV strains required the search for a better long-term treatment with novel drugs. New-generation PIs have been developed to address the issue of drug resistance.

The clinical success in the realm of HIV protease inhibitor drugs stimulated an intense effort to find new inhibitor drugs for other aspartic protease targets. The search for a renin inhibitor drug was reinvigorated. The design, development, and approval of the first orally bioavailable renin inhibitor, aliskiren, marked the beginning of a new treatment for hypertension. This development has intensified further design and development of novel classes of renin inhibitors. The design of γ-secretase and β-secretase inhibitors for the treatment of Alzheimer's disease (AD) has also been a very active area of research in academic and pharmaceutical laboratories and several inhibitors are now in clinical development. Furthermore, drug design efforts against plasmepsins for malaria treatment are being actively made in many laboratories.

The X-ray crystal structures of numerous human aspartic acid proteases have now been determined at high resolution. In addition, detailed kinetic and subsite specificity studies provided in-depth knowledge of their catalytic mechanisms. These studies immensely contributed to the structure-based design and synthesis of a broad range of aspartic acid protease inhibitors for the treatment of many human diseases. Today, aspartic acid protease enzymes, as well as medicinal chemistry in the quest of novel inhibitor drugs, have become one of the most prolific areas of research.

This book is a comprehensive collection aimed at providing a thorough overview of the field of medically important aspartic acid proteases. It covers broad research areas with particular emphasis on the chemical and biological relevance of the targets, design of molecular probes, and problems and resolutions related to selectivity, toxicity, and oral bioavailability. Furthermore, it encompasses structure–activity studies, critical molecular insights from protein-ligand X-ray structures, and the development of various design tools. The first four chapters provide a general overview of aspartic acid proteases and their relevance to various disease targets. Chapters 5–9 describe the design, synthesis, X-ray structures, and clinical development of the first- and second-generation HIV-1 protease inhibitors for the treatment of HIV/AIDS. Chapter 9 provides a clinical perspective on protease inhibitors and their use in the treatment of HIV infection and AIDS. Chapters 10 and 11 cover the design and development of aliskiren as a first-in-class treatment of hypertension and current drug design efforts in renin inhibitors. The chemistry and biology of γ-secretase and inhibitors of γ-secretase for the treatment of AD are described in Chapters 12 and 13. The next four chapters address the emergence of β-secretase as a possible target for Alzheimer's disease intervention, drug design efforts, development of tools for selectivity, issues of blood–brain barrier penetration, and the design of extensive structural classes of inhibitors. The plasmepsins as antimalarial targets and related inhibitor design efforts are described in Chapters 18 and 19. The last chapter provides an overview of fungal aspartic acid proteases and their relevance as targets for antifungal agents.

This book is written by the foremost experts in the field of aspartic acid proteases. Each chapter is well illustrated and provides an up-to-date account of the subject materials. This book will be an excellent resource to medicinal chemists, biochemists, pharmacologists, and to those working in related fields. I am very grateful to all authors for their insightful contribution to this work. I hope that their efforts and research expertise will pave the way for further advancement in the aspartic acid protease research field. I very much enjoyed working with Dr. Frank Weinreich, Dr. Nicola Oberbeckmann-Winter, and the Wiley-VCH editorial team. I personally want to express my sincere appreciation for their help, support, toward the completion of this work. I would like to thank Dr. Joseph Vacca for his initial efforts and help on this book. I am grateful to Dr. Jordan Tang, my friend and collaborator, for help and suggestions. I would also like to thank my research colleagues, Dr. Bruno Chapsal, Dr. Sean Fyvie, Mr. Zach Dawson, and Mr. David Anderson for their help with proofreading of chapters and Ms. Heather Miller for her help with manuscript preparation and organization. Finally, I wish to thank my family, my wife Jody, and my three children for their love, support, and inspiration. They are my spirit.

January 2010

Arun K. Ghosh, Purdue University

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ISBN: 978-3-527-31811-7