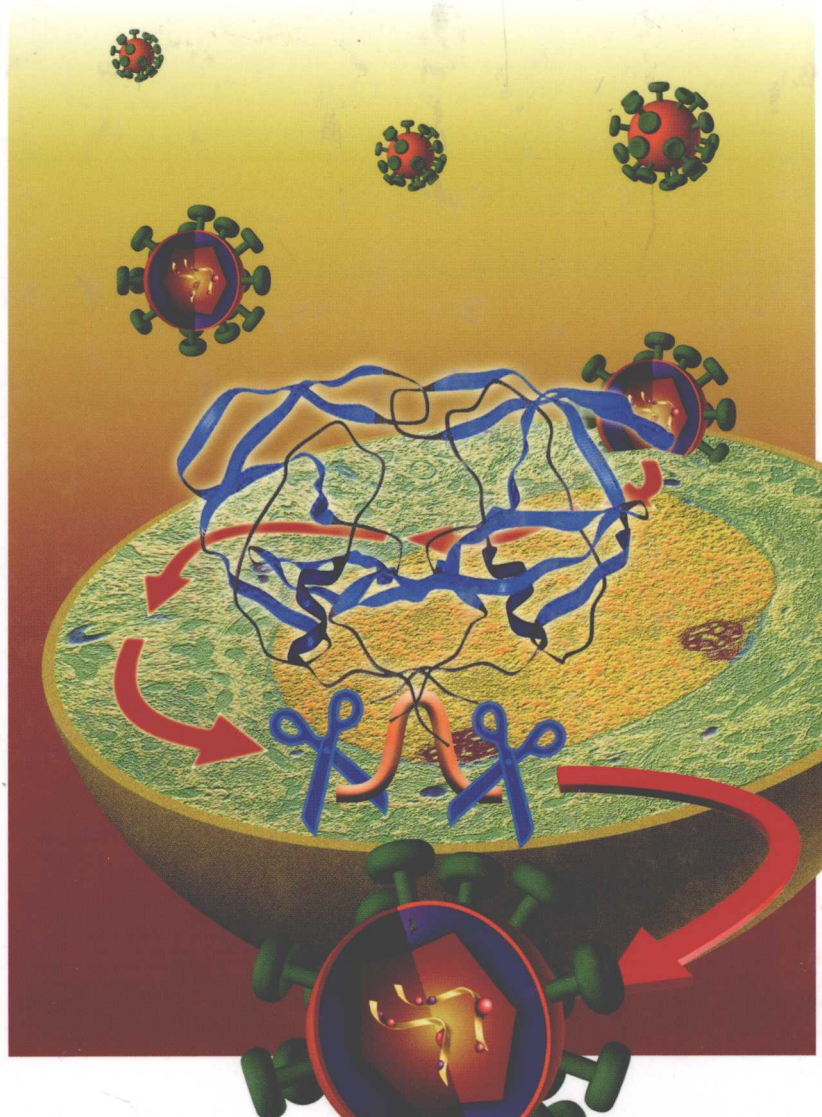
Methods and Principles in Medicinal Chemistry

Edited by Erik De Clercq

WILEY-VCH

Antiviral Drug Strategies



Volume 50

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Antiviral Drug Strategies

WILEY-VCH Verlag GmbH & Co. KGaA

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Cover Description
Recent approaches on how to combat virus infections, i.e. HIV, HCV, HSV, HCMV and influenza virus.
HIV-Protease, PDB code 3k4v (F. M. Olajuyigbe et al., ACS Med. Chem. Lett. 2010 asap, DOI: 10.1021/ml100046d); protein backbone generated with LigandScout 3.0, inte:ligand

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.

Typesetting Thomson Digital, Noida, India
Printing and Binding betz-druck GmbH, Darmstadt
Cover Design Schulz Grafik-Design, Fußgönheim

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

ISBN Print: 978-3-527-32696-9
ISBN oBook: 978-3-527-63595-5
ISBN ePDF: 978-3-527-63597-9
ISBN ePub: 978-3-527-63596-2
ISBN Mobi: 978-3-527-63598-6

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Antiviral Drug Strategies

Methods and Principles in Medicinal Chemistry

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Preface

The World Community Grid, an association connecting numerous individual computers to generate massive computational power for ligand docking, has recently focused on antiviral drug research. Whether this strategy will succeed or not, the mission signifies a large public and scientific interest and medical need in the development of new antiviral drugs. The naïve dream of eradicating and providing a sustained cure to infectious diseases is over. Viruses are active and fast drivers of evolution and the human body as a habitat is one of their favorable playgrounds to achieve adaptations, which unfortunately turn out to be pathogenic for our species in many cases.

Hence, we face the same situation as in the field of antibiotics, a situation that has been described metaphorically as the race of the Red Queen. In Lewis Carroll's classic, *Through the Looking-Glass*, the Red Queen, a living chess piece that Alice meets, has to run in place as quickly as she can to simply stay in the same place. In order to get anywhere else, she says, you must run twice as fast. Continuous effort has to be made to compete with viral evolutionary strategy. Stagnation in viral research results in a loss of terrain.

Here, the book by Erik De Clercq provides an evaluation of the situation. Historical aspects of half a century of antiviral research pave the way for the most recent strategies ranging from new small-molecule inhibitors to complex gene therapeutic interferences with viral replication.

There are few who would be more qualified to provide a synopsis of ups and downs, successes and pitfalls of viral research. Erik has been awarded the Descartes Prize for anti-HIV strategies, published a well-praised book on viral biological warfare and made the Rega Institute and the University of Leuven a renowned hot spot of antiviral research. From the 1980s, a long list of important scientific contributions stands witness to his research in the fields of chemotherapy of virus infections and malignant diseases, molecular mechanism of action of antiviral and antitumor agents, enzyme targets for antiviral and antitumor agents, nucleoside and nucleotide analogues for various targets in viral replication, gene therapy strategies using virus-encoded thymidine kinase, and tumor cell differentiation inducers.

Erik De Clerq has gathered leading experts from industry and academia to report on their views and their achieved innovations in the field of antiviral drug strategies.

The 15 chapters cover a broad range of efforts to cope with viral pathogenic effects by using the arsenal within the realm of medicinal chemistry. The book may also provide a certain basis for self-reflection about the gains and losses and how to learn from the conceptually related fields of antibiotic and antitumor research.

The series editors are indebted to the authors and the editor who made this comprehensive book possible. We are convinced that the book represents an important contribution to the body of knowledge in the field of antiviral research.

We also want to express our gratitude to Nicola Oberbeckmann-Winter, Heike Nöthe and Frank Weinreich of Wiley-VCH for their invaluable support to this project.

November 2010
Düsseldorf
Weisenheim am Sand
Zurich

Raimund Mannhold
Hugo Kubinyi
Gerd Folkers

A Personal Foreword

When my good friend Hugo Kubinyi asked me to put together this book, I was very reluctant for several reasons: why should I, a retired professor, undertake this initiative and knock as I had done so many times before, often in vain, at the doors of young(er) and (more) active colleagues who had much more in mind and at hand than contributing to an old colleague's book... but Hugo was so persuasive and persistent I could not refuse to engage myself in putting together one more book. Here are the fruits of this endeavor. I do not know whether I will (be able or willing to) ever repeat the exercise, but I was pleased to note that most of those whom I contacted instantly replied they would help. I am immensely grateful to all those who contributed to this volume. In present times, with increasing demands on the goodwill of capable scientists, this is not obvious. This explains why I am so thankful to all of you who did contribute.

This book is not a comprehensive coverage on antiviral drugs, rather a snapshot on the current state of the art; even so, it brings a flavor of present-day research on antiviral drug strategies, and it does not afford the final solution to the antiviral drugs, not even the beginning thereof, but, hopefully, the end of the beginning. Antivirals are today where antibiotics stood exactly 30 years ago. The first antiviral (idoxuridine) dates back to 50 years and the first antibiotic (penicillin) to 80 years ago. In our further conquest of antivirals, we should learn from the successes and failures of antibiotics research. This book is just meant to add a small contribution to the continuously evolving conquest of science in the field of antiviral research that has since its conception always been in the shadow of its big brother, antibiotics, but I trust one day antivirals will be in the same limelight as antibiotics were 30 years before them, and hopefully researchers in the antiviral field will in the meantime have learned from both the successes and the failures of the antibiotic experts.

Quo vadis, antivirals? Fifty years after idoxuridine and, shortly thereafter, trifluridine, were recognized as antiviral agents specifically active against herpes simplex virus (HSV), and twenty-five years after the first antiretroviral drug azidothymidine was described, the antiviral drug area has come of age. Old viruses have remained, new ones have emerged, but the ingenuity and perseverance in creating and developing new approaches have continued unabatedly. With this book, my colleagues, contributors to this endeavor, want to pay tribute to the field of antiviral

research and leave an enduring stamp on the never vanishing hope of finding the ideal antiviral(s).

The chapters presented in this volume on antiviral drug strategies are as follows:

1. Outlook of the antiviral drug era, now more than 50 years after description of the first antiviral drug
2. Inhibition of HIV entry
3. Targeting integration beyond strand transfer: Development of second-generation HIV integrase inhibitors.
4. From saquinavir to darunavir: The impact of 10 years of medicinal chemistry on a lethal disease
5. Acyclic and cyclic nucleoside phosphonates
6. Helicase–primase inhibitors: A new approach to combat herpes simplex and varicella zoster virus
7. Cyclophilin inhibitors
8. Alkoxyalkyl ester prodrugs of antiviral nucleoside phosphates and phosphonates
9. Maribavir: A novel benzimidazole ribonucleoside for the prevention and treatment of cytomegalovirus diseases
10. Anti-HCMV compounds
11. Lethal mutagenesis as an unconventional approach to combat HIV
12. Recent progress in the development of HCV protease inhibitors
13. Antiviral RNAi: How to silence viruses
14. Neuraminidase inhibitors as anti-influenza agents
15. From TIBO to rilpivirine: The chronicle of the discovery of the ideal nonnucleoside reverse transcriptase inhibitor

July 2010
Leuven

Erik De Clercq

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