ADVANCES IN ANTIVIRAL DRUG DESIGN

Editor: E. DE CLERCQ

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PREFACE

This represents the fifth volume of *Advances in Antiviral Drug Design*, continuing the tradition of the preceding volumes published by JAI Press, Inc. in 1993 (volume 1), 1996 (volume 2) and 1999 (volume 3), and Elsevier in 2004 (volume 4). Akin to volume 4, the fifth volume of *Advances in Antiviral Drug Design* is also published by Elsevier.

As has been set from the beginning, *Advances in Antiviral Drug Design* is aimed at keeping up with the progress made in the design and development of new antiviral drugs, thereby overviewing the global area where antiviral agents have started to emerge, where they are targeted at, and how they are likely to evolve into clinically useful antiviral medicines.

The principal aim of this series of treatises is to (try to) form a bridge from the basics (i.e., design and synthesis of new antiviral compounds) to clinics (i.e., therapeutic applications in the therapy and/or prophylaxis of well-defined viral infections). This is a continuously evolving process which is driven by a number of forces, the emergence of new viruses (or re-emergence of old ones), the synthesis of new chemical compounds, the molecular optimization of their potency and/or selectivity, and their eventual (medical) application and usefulness in the clinic.

In previous volumes (volumes 1, 2, 3 and 4), the following topics were dealt with:

(i) uncoating inhibitors for picornavirus infections,
(ii) broad-spectrum antiviral nucleoside analogs (such as ribavirin),
(iii) acyclic nucleoside analogs (such as acyclovir and ganciclovir),
(iv) acyclic nucleoside phosphonates (such as cidofovir and adefovir),
(v) dideoxynucleoside analogs (such as zidovudine, didanosine, zalcitabine, and stavudine),
(vi) antisense oligonucleotides,
(vii) S-adenosylhomocysteine (AdoHcy) hydrolase inhibitors,
(viii) carbocyclic nucleoside analogs,
(ix) nucleotide prodrugs (bypassing the initial phosphorylation step),

(x) HIV protease inhibitors,
(xi) L-nucleoside analogs (such as 3TC, (-)FTC and L-FMAU),
(xii) progress with the acyclic nucleoside phosphonates in clinical trials,
(xiii) emivirine as prototype of the non-nucleoside reverse transcriptase inhibitors (NNRTIs),
(xiv) zanamivir as prototype of the influenza virus neuraminidase inhibitors,
(xv) the bicyclams as inhibitors of the replication of T-lymphotropic X4 HIV-1 strains, acting through a specific antagonization of the CXCR4 receptor,
(xvi) new anti-HIV agents in clinical development,
(xvii) HIV integrase inhibitors,
(xviii) non-peptidic HIV protease inhibitors,
(xix) oseltamivir as prototype of the influenza virus neuraminidase inhibitors,
(xx) six-membered carbocyclic nucleoside analogues as anti-herpesvirus agents,
(xxi) cyclosaligenyl pronucleotides of antiviral agents.

In the present volume, volume 5, of *Advances in Antiviral Drug Design*, six new chapters have been added to the list. *First*, an overview of the *status presens* of the antiviral agents which are active against DNA viruses and retroviruses (the latter, being RNA viruses, replicate *via* a proviral DNA intermediate). *Second*, an overview of the *status presens* of the antiviral agents which are active against RNA viruses except retroviruses. In these overview chapters, I have focussed on three categories of antiviral agents:

(a) those that have been licensed (i.e., approved) for clinical use;
(b) those that are, or have been, under clinical evaluation (i.e., submitted to phase I, II or III clinical trials); and
(c) those that are still in the preclinical development stage.

In Chapter 3 J. Zemlicka has addressed a new class of nucleoside analogues, that of the methylenecyclopropane derivatives which yield great potential as antiviral agents against a wide array of herpesviruses.

Chapter 4 written by K.Y. Hostetler is dealing with the synthesis and antiviral activity of orally bioavailable prodrugs of cidofovir and other acyclic nucleoside phosphonates, with broad antiviral drug potential against virtually all DNA viruses.

The HIV co-receptor antagonists, and, in particular, the CCR5 antagonists have proceeded swiftly through clinical development, and this progress has been highlighted by M. Perros in Chapter 5. The non-nucleoside reverse transcriptase inhibitors (NNRTIs) have remained in the frontline of the treatment of HIV-1 infections, and the development of new highly promising congeners of this series, i.e., DATA and DAPY, has been depicted by J. Heeres and P.J. Lewi (Chapter 6).

Thus, the fifth volume of *Advances in Antiviral Drug Design* aims at continuing with the tradition of the preceding volumes, that is periodically reviewing the recent progress made in the frontline of the design and development of new therapeutic agents for the treatment of DNA virus, retrovirus and RNA virus infections, with, in this volume, particular emphasis on four novel strategies targeted at herpesviruses (i.e., methylenecyclopropane derivatives) and other DNA (*viz.* pox, adeno) viruses (i.e., orally bioavailable prodrugs of acyclic nucleoside phosphonates), and HIV infections (i.e., CCR5 antagonists as well as new highly promising NNRTIs).

E. De Clercq
Editor

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STATUS PRESENS OF ANTIVIRAL DRUGS AND STRATEGIES: PART I: DNA VIRUSES AND RETROVIRUSES

Erik De Clercq

ABSTRACT

More than 40 compounds have been formally licensed for clinical use as antiviral drugs, and half of these are used for the treatment of HIV infections. The others have been approved for the therapy of herpesvirus (HSV, VZV, CMV), hepadnavirus (HBV), hepacivirus (HCV) and myxovirus (influenza, RSV) infections. New compounds are in clinical development or under preclinical evaluation, and, again, half of these are targeting HIV infections. Yet, quite a number of important viral pathogens (i.e. HPV, HCV, hemorrhagic fever viruses) remain in need of effective and/or improved antiviral therapies.

I. INTRODUCTION

There are at present a forty some antiviral drugs that have been formally licensed for clinical in the treatment of viral infections.[44] These are mainly used in the treatment of infections caused by human immunodeficiency virus (HIV), hepatitis B virus (HBV), herpesviruses [herpes simplex virus (HSV), varicella-zoster virus (VZV),

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