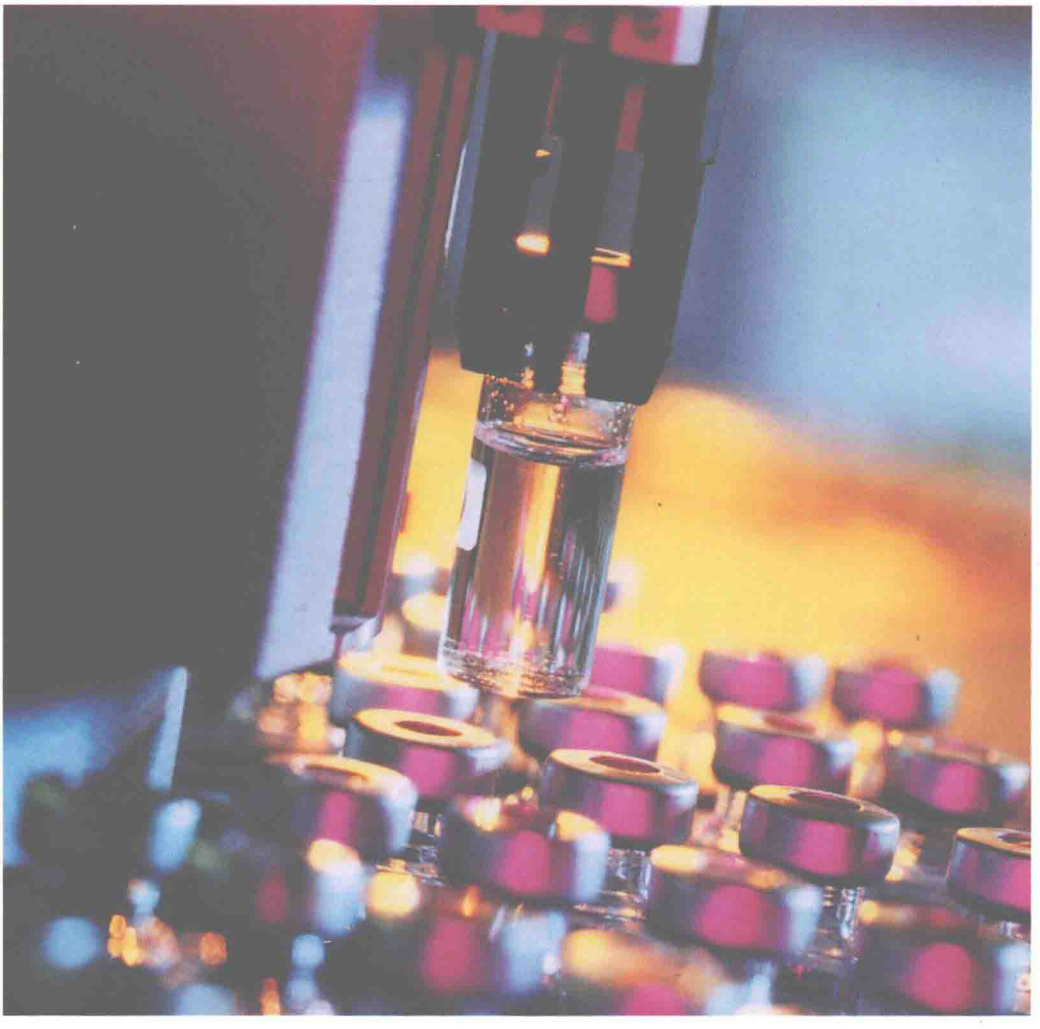
RSC Drug Discovery

Edited by Manoj C. Desai and Nicholas A. Meanwell

Successful Strategies for the Discovery of Antiviral Drugs



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RSC Publishing

RSC Drug Discovery Series No. 32

ISBN: 978-1-84973-657-2
ISSN: 2041-3203

A catalogue record for this book is available from the British Library

Published by The Royal Society of Chemistry,
Thomas Graham House, Science Park, Milton Road,
Cambridge CB4 0WF, UK

Registered Charity Number 207890

For further information see our web site at www.rsc.org

Printed in the United Kingdom by CPI Group (UK) Ltd, Croydon, CR0 4YY

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Preface

Viruses are obligate parasites that enter and reproduce within the cells of their host, so their life cycle relies upon forming an intimate partnership and dependency. For many viruses, such as influenza and respiratory syncytial virus (RSV), this relationship is temporary in nature and self-limiting. However, some viruses, including human immunodeficiency virus (HIV, >35 million people infected worldwide), hepatitis B virus (HBV, >400 million people infected) and hepatitis C virus (HCV, >150 million people infected), cause persistent infections and the virus never leaves the host. Such a long-term association is detrimental to the wellbeing of infected cells, the functions of the organ they infect and, ultimately, the overall health of the host.

The central hypothesis to medical intervention for the treatment of viral diseases is to prevent the spread of a virus to uninfected cells by blocking viral replication, helping the host to control infection. The approval of the nucleoside analog acyclovir for the treatment of herpes simplex virus (HSV) infection in 1978 was a key event in the history of antiviral drug discovery and development, setting the standard for a selective and effective therapeutic that is now available over-the-counter. Oral antiviral agents of this type offer a practical, convenient and rapid means of intervening with virus replication, and over the last 30 years over 50 drugs have been licensed for marketing. In addition, in 2012 alone there were >100 industry-sponsored Phase 3 trials currently registered at ClinicalTrials.gov (www.clinicaltrials.gov).

The demand for antiviral agents has been driven by the HIV-1 epidemic, a virus that continues to present a significant challenge, and the large number of worldwide HBV and HCV infections, all of which contribute to an ever-increasing morbidity and mortality in those unfortunate enough to host these infectious agents. Although HIV-1 and HBV infections have proven extremely difficult to cure, the RNA-based life cycle of HCV is currently susceptible to curative intervention with combinations of pegylated interferon-α, ribavirin

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Published by the Royal Society of Chemistry, www.rsc.org

and a protease inhibitor. However, recent clinical studies have clearly indicated the potential for combinations of small-molecule, direct-acting antiviral agents that selectively and effectively target viral proteins to effect cures with as little as 12 weeks of therapy. Consequently, there is a growing belief that HCV infection will be the first chronic viral infection to be cured by small molecules. For HIV-1 infection, the launch of Atripla®, a combination of the nucleoside phosphonate prodrug tenofovir disoproxil, the nucleoside analog emtricitabine and the non-nucleoside reverse transcriptase inhibitor efavirenz, by the collaborative effort of Gilead Sciences and Bristol-Myers Squibb, represented a watershed in the treatment of this disease by providing a convenient, fixed-dose combination taken once a day that effectively controls viral replication.

The focus of this book is to summarize successful strategies for the discovery and development of antiviral agents into clinically relevant therapeutic agents. The book is organized according to the strategies deployed both to discover and to optimize lead compounds. Section I provides an overview of drug discovery programs that span HCV, RSV, dengue virus and pox viruses and that owe their origin to a robust *in vitro* cell culture system used both to identify lead inhibitors using high-throughput screens and to optimize molecules for potency and selectivity. This kind of chemical genomics screening paradigm has proven to be a highly successful strategy for the discovery of mechanistically interesting antiviral agents, many of which could not be discovered using biochemical assays. By applying selective pressure to viruses grown in cell culture with repeated rounds of replication (passaging) in the presence of increasing concentrations of lead inhibitors, resistant viruses can be isolated and their genomes sequenced for mutations that usually afford insight into the mode of action of a lead inhibitor.

Biochemical screens are an equally important source of leads, a strategy of particular importance in the early days of HCV drug discovery where the enzymatic activities of the NS3 protease and NS5B polymerase could be recapitulated *in vitro* and used to assay compound collections using high-throughput screening methodology. Lead optimization campaigns were subsequently facilitated by structure-based drug design since these proteins were crystallized with inhibitors bound. Section II provides examples of the application of these contemporary technologies that rely upon biochemical screening and structure-based optimization strategies for the discovery of potent and selective antiviral agents for the treatment of HIV-1 and HCV and nicely illustrate the evolution of modern medicinal chemistry technology. Section III includes some of the recent mechanistic approaches that take advantage of host–viral interactions for the treatment of HCV that could be complementary to direct-acting oral antivirals. Finally, the delivery of antiviral agents can present significant challenges and Section IV highlights the development and application of strategies that can be deployed to facilitate oral absorption of nucleosides or the systemic delivery of an entire therapeutic regimen that improves compliance.

The objective of this book is to capture tactical aspects of problem solving in antiviral drug design and development, an approach that not only holds special

appeal for those engaged in the antiviral research, but will also be instructive to the broader medicinal chemistry community.

As we compose this Preface in January 2013, we note the passing in 2012 of two chemists who made seminal contributions to antiviral drug discovery. Professor Antonín Holý, a pioneer of the nucleoside phosphonate chemotype that led to the discovery of cidofovir, adefovir and tenofovir, passed away on 16 July 2012 in his native Prague. Jerome P. Horwitz, who synthesized azidothymidine, the first drug approved to treat HIV-1 infection and whose research led to the development of dideoxycytidine, passed away on 6 September 2012 in West Bloomfield, Michigan, close to his native Detroit. We recognize the critically important contributions that these scientists made to the therapy of HIV-1 infection.

We would like to thank the authors of the chapters in this volume for their hard work, patience, dedication and scholarship in the lengthy process of writing, editing and making last-minute revisions to their contributions.

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