New viruses can arise very quickly and, if unchecked, result in major pandemics. Obvious examples being the AIDS and SARS virus. In order to deal with such imminent threats, drug development times need to be cut short. This is only possible by relying on proven strategies and adapting them to the specific features of any new virus or virus variant.

By focusing on general molecular mechanisms of antiviral drugs rather than therapies for individual viruses, this ready reference provides the critical knowledge needed to develop entirely novel therapeutics and to target new viruses. It is edited by Erik de Clercq, a world authority on antiviral drug discovery.

The volume covers a general discussion of antiviral strategies, followed by a broad survey of known viral targets, such as reverse transcriptases, proteases, neuraminidases, RNA polymerases, helicases, and primases, as well as their known inhibitors. The book also contains several case studies of recent successful antiviral drug development.

As a result, medicinal and pharmaceutical chemists, as well as virologists will be able to pinpoint strategies for combating future viral pandemics.

Erik De Clercq, M.D., PhD, is currently President of the Rega Foundation, a member of the Belgian (Flemish) Royal Academy of Medicine and of the Academia Europaea, and a Fellow of the American Association for the Advancement of Science. He is an active Emeritus Professor of the Katholieke Universiteit Leuven (K.U. Leuven), Belgium. He is honorary doctor of the Universities of Ghent, Belgium, Athens, Greece, Fano, Italy, Finner (Stanford), China, Charles (Prague), Czech Republic, and Jihoceska (Ceske Budejovice), Czech Republic, and Tours, France.

For his pioneering efforts in antiviral research, Professor De Clercq received in 1996 the Aventis award from the American Society for Microbiology, and in 2000 the Maxine Price for Biomedical Sciences from the Belgian National Science Foundation. In 2008 he was elected Inventor of the Year by the European Union, jointly with Dr. Anthony Fauci. Prof. De Clercq received the Dr. Paul Janssen Award for Biomedical Research in 2010.

He is the (co)inventor of a number of antiviral drugs, used for the treatment of HSV (valaciclovir, Valtrex®, Zelitrex®), VZV (brivudin, Zostex®, Brivirac®, Zerpex®), CMV (cidofovir, Vistide®), HBV (adefovir dipivoxil, Hepsera®), and HIV infections (AIDS) (tenofovir disoproxil fumarate, Viread®).
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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 Clercq 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
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
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
1

Outlook of the Antiviral Drug Era, Now More Than 50 Years After Description of the First Antiviral Drug

Erik De Clercq

1.1

Introduction: The Prehistory

More than 50 years ago, the synthesis of IDU (iododeoxyuridine), a thymidine analogue, was described by Prusoff [1]. This compound would later become the first antiviral drug to be licensed for (topical) use in the treatment of herpes simplex virus (HSV) infections of the eye. In this sense, the advent of IDU marked the birth of the antiviral drug era. There are now about 50 licensed antiviral compounds, half of them are used for the treatment of AIDS, of which the viral origin was first recognized 27 years ago [2, 3] (2008 Nobel Prize for Medicine or Physiology was awarded to Françoise Barré-Sinoussi and Luc Montagnier for their discovery of human immunodeficiency virus and to Harald zur Hausen for demonstrating the link between human papilloma virus (HPV) and cervical cancer).

Was IDU truly the first antiviral? In retrospect, the antiviral chemotherapy era had a rather slow and unremarkable start. The first compounds quoted to have antiviral activity (against vaccinia virus) were the thiosemicarbazones [4, 5]. These compounds were also found effective against vaccinia virus infection in mice and rabbits [6–8], and one of the thiosemicarbazones, that is, N-methylisatin-β-thiosemicarbazone, even entered clinical studies for the prophylaxis of smallpox [9] just when the smallpox vaccination took over and made any further attempts to develop an antipoxvirus drug apparently superfluous.

Then came the benzimidazole derivatives as inhibitors of influenza virus multiplication [10, 11], but despite the reported effectiveness of the 5,6-dichloro-1-β-D-ribofuranosyl benzimidazole (DRB) [10, 11] against influenza virus multiplication, it was not pursued further as a potential anti-influenza virus agent. Another benzimidazole derivative, 2-(1-hydroxybenzyl)benzimidazole (HBB), was found active against the multiplication of poliovirus (and other enteroviruses) [12–14], but with the successful implementation of the poliovirus vaccine, just as we had witnessed for smallpox, interest in developing an antiviral drug for poliovirus infections vanished.

IDU, soon to be followed by TFT (trifluorothymidine), could be considered as the third, and successful, attempt to herald the antiviral chemotherapy era. IDU was first
considered as a potential antitumor agent [15] before it was shown by Herrmann to be active against HSV and vaccinia virus [16]. That IDU and TFT finally became antiviral drugs for the topical treatment of HSV eye infections, in particular HSV keratitis, is due to the pioneering work of Kaufman [17, 18].

1.2 Key Events in Antiviral Drug Development

Table 1.1 presents the key events in antiviral drug discovery, 1959 being the year when IDU was first described [1]. Ribavirin was the first low molecular weight compound described as a broad-spectrum antiviral agent (in 1972) by Sidwell et al. [19]. The combination of ribavirin with (pegylated) interferon-α has now become a standard treatment [20] for patients with chronic hepatitis C. That virus infections could be specifically tackled, without harm to the host cell, was heralded by the advent (in 1977) of acyclovir [21, 22], which is today still considered as the gold standard for the treatment of HSV infections. Two years after the discovery of HIV, in 1985, the first antiretrovirus agent (to become a drug 2 years later), AZT (zidovudine) was described [23], and this opened the search for, and development of, a wealth of new 2',3'-dideoxynucleoside analogues, now collectively referred to as nucleoside reverse transcriptase inhibitors (NRTIs).

In 1986, we described the first of a new class of broad-spectrum anti-DNA virus agents [24], namely, acyclic nucleoside phosphonates, several of which are active against the HIV and HBV reverse transcriptase and, therefore, referred to as nucleotide reverse transcriptase inhibitors (NtRTIs). Then followed in December 1989 and 1990 the description of a new concept for inhibiting the HIV-1 reverse transcriptase by nonnucleoside analogues (i.e., HEPT [25, 26] and TIBO [27]), giving rise to a still growing class of antiviral drugs, the nonnucleoside reverse transcriptase inhibitors (NNRTIs). With saquinavir, the year 1990 marked the birth of the rational design of HIV protease inhibitors (HIV PIs), which, in the mean time, has yielded 10 licensed drugs.

In 1992, we described an unusual class of compounds, the bicyclams as HIV inhibitors interacting with a viral uncoating event [28]. These compounds (prototype: AMD3100) would be, later on, shown to act as CXCR4 antagonists. Together with the CCR5 antagonists (the only licensed anti-HIV drug of this class of compounds being maraviroc), CXCR4 and CCR5 antagonists can be considered coreceptor inhibitors (CRIs), targeted at the coreceptor usage of X4 and R5 HIV strains, respectively. The year 1993 marked the description of two totally different strategic options: (i) that of DP-178, which later on would become known as enfuvirtide as an HIV fusion inhibitor (FI) [29] and (ii) that of 4-guanidino-Neu5Ac2en, which later on would become known as zanamivir as a neuraminidase-based inhibitor (NAI) of influenza virus replication [30]. Then followed in 1998 the seminal observation that HSV replication could be inhibited at the DNA helicase–primase level by a 2-aminothiazole (T157602) [31] that would later give impetus to the development of helicase–primase inhibitors (HPIs) as potential anti-HSV drugs.
### Table 1.1 Milestones in antiviral drug discovery: year when key compounds were first described.

<table>
<thead>
<tr>
<th>Year</th>
<th>(NRTIs)</th>
<th>(NtRTIs)</th>
<th>(HIV PIs)</th>
<th>(NAIs)</th>
<th>(INIs)</th>
<th>(HCV PIs)</th>
<th>(Poxviruses inhibitors)</th>
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<tr>
<td>1959</td>
<td>IDU</td>
<td>TMT01</td>
<td>AZT</td>
<td></td>
<td>T157602</td>
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<td>BIL-179S</td>
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<td>1969</td>
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<td>Acyclovir</td>
<td>ddT</td>
<td></td>
<td>Enfuvirtide</td>
<td></td>
<td>BAY 57-1293</td>
</tr>
<tr>
<td>1985</td>
<td>Acyclovir</td>
<td>ddC</td>
<td>ddC</td>
<td></td>
<td>4'-Azidocytidine</td>
<td></td>
<td>(NRRIs)</td>
</tr>
<tr>
<td>1992</td>
<td>Bicyclams</td>
<td>AZT</td>
<td>d4T</td>
<td></td>
<td>GS-327073</td>
<td></td>
<td>GS-327073</td>
</tr>
<tr>
<td>1993</td>
<td>2'-C-methyl nucleosides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>2003</td>
<td></td>
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</tr>
</tbody>
</table>

**Metabolites**
- AZT: azidothymidine
- ddC: 2',3'-didehydro-2',3'-dideoxythymidine
- d4T: 2',3'-dideoxy-3'-thiacytidine
- ddI: 2',3'-dideoxyinosine
- ddC: 2',3'-dideoxycytidine
- d4T: 2',3'-dideoxythymidine
- dT: deoxythymidine
- ABC: 2',3'-dideoxy-3'-thiacytidine
- TIBO: 2',3'-dideoxyinosine
- HEPT: 2',3'-dideoxycytidine
- NFV: nevirapine
- EFV: efavirenz
- DRV: darunavir
- ATV: atazanavir
- TMC: tipranavir
- LPV: lopinavir
- NVP: nelfinavir
- Ritonavir
- BVDU: 2-bromo-2-deoxyuridine
- BCNAs: 2-bromo-2'-deoxy-5-nitroarabinofuranoside
- IDU: intravenous idoxuridine
- TMT01: thymidine 5'-triphosphate
ddI: 2',3'-dideoxyinosine
- ddC: 2',3'-dideoxycytidine
- d4T: 2',3'-dideoxythymidine

**Drug Classes**
- NRTIs: nucleoside reverse transcriptase inhibitors
- NtRTIs: nucleotide reverse transcriptase inhibitors
- NNRTIs: nonnucleoside reverse transcriptase inhibitors
- NINs: integrase inhibitors
- HIV PIs: HIV protease inhibitors
- CRIs: coreceptor inhibitors
- NAs: neuraminidase inhibitors
- HPIs: helicase–primase inhibitors
- HCV PIs: HCV protease inhibitors
- NNRRIs: nonnucleoside RNA replicase inhibitors
- NRRIs: nucleoside RNA replicate inhibitors
- FIs: fusion inhibitors
- RIs: RNA replicase inhibitors
- FIIs: RNA polymerase inhibitors
- NHIs: nuclease inhibitors
- TNIs: tyrosine kinase inhibitors
- VAs: viral entry inhibitors
- PIs: proteinase inhibitors
- SIs: serum protease inhibitors
- CRIs: coreceptor inhibitors
- (--)FTC: emtricitabine
Although considered an attractive target for two decades or so, the HIV integrase became a realistic target only when Hazuda et al. [32] demonstrated in 2000 it to be inhibited by the so-called diketo acids, which have yielded one integrase inhibitor (INI) that has already been formally approved (raltegravir) and another one under development (elvitegravir). Also described in 2000 was a pestivirus inhibitor (VP32947) [33] that hallmarkd the search for inhibitors targeted at the RNA-dependent RNA polymerase (RdRp) of not only pestiviruses but also hepaciviruses (nonnucleoside RNA replicase inhibitors (NNRRIs)). In 2003, Lamarre et al. published their pioneering observation that hepatitis C virus (HCV) replication could be inhibited by ciluprevir [34], which (although the compound itself was not further developed) generated the search for other HCV PIs. Also in 2003, Migliaccio et al. [35] reported that 2’-C-methyl-substituted ribonucleosides were inhibitory to the replication of HCV and other flaviviruses by acting as nonobligate chain terminators, thus inciting the search for nucleoside RNA replicase inhibitors (NRRIs).

While, since the days of methisazone, interest in developing antivirals for poxvirus infections (i.e., smallpox) died, the advent in 2005 of ST-246 testifies to the renewed interest in this area [36], and this is further demonstrated by the observations that poxvirus infections can be successfully suppressed through inhibitors of tyrosine kinases (Gleevec [37] and CI-1033 [38]).

1.3 Antiviral Drugs: Current State of the Art

Most of the antiviral agents that have been approved, and are used in the treatment of virus infections, are targeted at HIV, HBV, HCV, influenza virus, HSV, and other herpesviruses such as varicella zoster virus (VZV) and cytomegalovirus (CMV). More compounds for the treatment of HIV, HBV, HCV, HSV, VZV, CMV, and influenza virus and several other viral infections, for example, poxvirus (e.g., variola, vaccinia, and monkeypox), respiratory syncytial virus, hemorrhagic fever virus (e.g., Lassa, Rift Valley, Ebola, yellow fever, and dengue), and enterovirus (e.g., polio, Coxsackie, and Echo), either are in clinical or preclinical development or still have to be developed. The antiviral compounds that have been approved by the US FDA (Food and Drug Administration) are listed in Table 1.2.

1.4 Antiviral Drugs Active against Herpesviruses (i.e., HSV, VZV, and so on)

Starting from IDU and TFT, many more 5-substituted 2’-deoxyuridines were synthesized [39], the most prominent antiviral drug of this class of compounds being (E)-5-(2-bromovinyl)-2’-deoxyuridine (BVDU) [40]. Although selectively active against both HSV-1 and VZV, BVDU has been developed specifically for the treatment of VZV infections (i.e., herpes zoster) [41].
### Table 1.2 Antiviral drugs approved by the US FDA.

<table>
<thead>
<tr>
<th>Registered brand name</th>
<th>Generic name</th>
<th>Manufacturer</th>
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</thead>
<tbody>
<tr>
<td><strong>Anti-HIV compounds</strong></td>
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<td></td>
</tr>
<tr>
<td>Nucleoside reverse transcriptase inhibitors</td>
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<td>Zerit®</td>
<td>Stavudine (d4T)</td>
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<td>Lamivudine (3TC)</td>
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<td>Abacavir (ABC)</td>
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<td>Nucleotide reverse transcriptase inhibitors</td>
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<td>Truvada®</td>
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Table 1.2 (Continued)

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<td>Antitherpesvirus compounds</td>
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<tr>
<td>HSV and VZV inhibitors</td>
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<tr>
<td>Zovirax®</td>
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<td>Valaciclovir (VACV)</td>
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<td>Trifluridine (TFT)</td>
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<td>Brivudin (BVDU)</td>
<td>Berlin Chemie/Menarini</td>
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<td>CMV inhibitors</td>
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<td>Ganciclovir (GCV)</td>
<td>Roche</td>
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<td>Valganciclovir (VGCV)</td>
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<td>Foscarnet</td>
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<td>Cidofovir (CDV)</td>
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<td>Fomivirsen</td>
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<td>Anti-influenza virus compounds</td>
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<td>Anti-HCV compounds</td>
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<td>Rebetol®</td>
<td>Ribavirin</td>
<td>Schering-Plough</td>
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<td>Copegus®</td>
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<td>Interferon-α-2b</td>
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<td>Rebetron®</td>
<td>Interferon-α-2b + ribavirin</td>
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a) Not formally approved by the US FDA.
BVDU owes its antiviral selectivity to a specific phosphorylation by the HSV-1- and VZV-encoded thymidine kinase, just as acyclovir does, but compared to acyclovir, BVDU is a much more potent inhibitor of VZV replication. If BVDU is further converted to a bicyclic furano[2,3-d]pyrimidine nucleoside analogue (BCNA) carrying an aliphatic side chain interrupted by a phenyl moiety [42, 43], as in Cf 1743, the compound becomes exquisitely and exclusively active against VZV.

Although BVDU and acyclovir belong, respectively, to the pyrimidine and purine nucleoside analogues, they share, structurally, the same carboxamide pharmacophore (Figure 1.1), which may explain why they are both specifically recognized as substrate by the HSV- and VZV-encoded thymidine kinases. The same pharmacophore is found in other acyclic guanosine analogues such as ganciclovir and penciclovir and

![Figure 1.1 Pharmacophores in antiviral agents.](image-url)
penciclovir, again explaining the specificity of these compounds against HSV and VZV. Remarkably, the same pharmacophore is also found in ribavirin, which was described as a broad-spectrum antiviral agent, 5 years before acyclovir was reported (see Table 1.1), but in the case of ribavirin, the presence of the ribofuranosyl moiety primarily directs its antiviral activity spectrum toward RNA viruses due to an inhibitory action at the level of the IMP dehydrogenase [44–46].

While BVDU and acyclovir interact in their active triphosphate form with the viral DNA polymerase, the first phosphorylation step by the viral thymidine kinase required only to initiate the activation process, the HPIs seem to be directly targeted at the HSV helicase–primase UL5–UL8–UL52 complex [47]. The first HPI reported to inhibit HSV replication via interaction with the helicase component of this complex [31] was the 2-aminothiazole T-157602. The HPIs that were subsequently described and also found to be more effective than acyclovir and famciclovir against HSV infections in murine models of HSV-1 and HSV-2 infection [48–51], namely, BILS 179BS and BAY 57-1293, are also built upon the 2-aminothiazole scaffold (Figure 1.1). HPIs represent an exciting new avenue in the development of antivirals active against herpesviruses [47], but whether they represent an alternative (or additional) strategy to acyclovir (and acyclic guanosine analogues in general) will depend on their exact spectrum of antiviral activity, whether or not encompassing VZV (an issue that presently can only be speculated upon), and the readiness by which they elicit resistance mutations [52, 53] (an issue that needs continued vigilance).

1.5 Antiviral Drugs Active against Retroviruses (HIV)

The best known class of the antiretroviral agents is that of the nucleoside reverse transcriptase inhibitors, now containing seven members – zidovudine, didanosine,