Antiviral Drug Strategies

The process of discovery and development of antiviral drugs, which commenced only a little more than 50 years ago, has faced unique challenges relative to longer standing approaches to more conventional medicinal agents. Viruses do not replicate outside the host cell, so drugs that inhibit viral replication must exploit subtle biological differences between virus-infected cells and normal, uninfected cells. Certain proteins and processes native to the host cell can enable virion entry, replication of viral constituents, or budding of nascent virus particles; hence, they are included as potential targets for antiviral drugs. In order to avoid toxicity and various side effects, the drug industry has traditionally tried to achieve high potency and selectivity toward proteins that are characteristic of the virus, not of the host cell. New drug leads are typically discovered by screening compounds for inhibition of specific viral proteins in vitro, or by screening compounds for inhibition of viral replication in cells. The latter method is broader than specifically targeted screens because compounds that inhibit replication by any mechanism can be discovered, including inhibitors of viral entry or budding of nascent virions (for screens conducted in cell cultures).

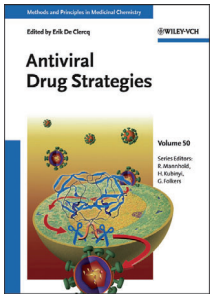
The book, *Antiviral Drug Strategies*, is currently the most complete compilation of accounts of antiviral drug development studies. This is volume 50 in the series, *Methods and Principles in Medicinal Chemistry*, edited by Mannhold, Kubinyi, and Folkers. The editor of the current volume is Erik De Clercq, a well known co-developer of many antiviral compounds and an early investigator of drugs against the causative agent of AIDS, the human immunodeficiency virus (HIV).

De Clercq provides a very good historical introduction to the era of antiviral drugs in Chapter 1 and concludes the volume with a personal account of the discovery of a specific HIV non-nucleoside reverse transcriptase inhibitor (rilpivirine) in Chapter 15. He has been able to solicit and assemble chapters on many types of drugs effective against many viruses and operating by several different general mechanisms of action. While the book is not a comprehensive source of information on all antiviral drugs, it presents several detailed case studies on development of some commercial antiviral drugs and some good reviews of experimental findings on compounds inhibiting certain viruses or operating by certain general mechanisms.

While the chapters of *Antiviral Drug Strategies* are not in a particular topical order, they fall into several categories. Four of the fifteen chapters deal with anti-HIV drugs operating by certain mechanisms: Chapter 2 on HIV entry inhibitors, Chapter 3 on inhibitors of HIV integrase, Chapter 4 on inhibitors of HIV protease, and Chapter 11 on lethal mutagenesis as an unconventional approach to combat HIV. Chapter 2 contains an excellent and very detailed description of the processes of HIV attachment, fusion and entry into the host cell. Most of the entry inhibitor approaches are thoroughly covered, though the ambiguous stereochemistry of the CXCR5 antagonist maraviroc in Figure 2.2 is a minor flaw. Chapter 3 provides a good description of the structure of HIV integrase (IN) and the mechanism by which it catalyzes integration of nascent HIV DNA into the host cell's genome. Inhibitors of HIV replication operating by binding IN, binding DNA, inhibiting IN dimerization, and blocking IN-cofactor interaction are all covered, the last three mechanisms being relatively novel and not yet leading to commercial drugs.

Chapter 4 chronicles an important advance in medicinal chemistry: the development of inhibitors of HIV protease. This enzyme post-translationally modifies a protein that is essential for production of functional virus particles. Drugs inhibiting HIV protease prevent HIV replication and to a large extent enable chemotherapy with combinations of drugs operating by different mechanisms, avoiding viral resistance to individual drugs and making long-term treatment of HIV infection practical. From a chemist's point of view, this chapter contains significant flaws. The importance of the X-ray crystal structure of HIV protease on early studies is not emphasized, while this discovery made it possible for chemists to design drugs in silico. Figure 4.2 nicely displays the structures of various approved protease inhibitors oriented in the active site, but Figure 4.4 does not show the correct structures of three of the four substituent groups (R^1–R^4) of darunavir, and the associated synthetic scheme is very unclear. On the other hand, there is a good discussion of drug development studies involving structure–activity relationships and binding of darunavir analogs in the active site of HIV protease.

A number of chapters describe certain methods for inhibiting replication of various viruses. Chapter 5 deals with inhibitors of RNA and DNA polymerase, Chapter 6 with helicase/primase inhibitors for herpes simplex virus (HSV) and hepatitis C virus (HCV), Chapter 8 with prodrugs of antiviral nucleoside phosphates and phosphonates, Chapter 12 with HCV protease inhibitors, and Chapter 13 with antiviral approaches involving RNA interference (RNAi). There are two chapters on drugs for treatment of infection by the human



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cytomegalovirus (HCMV): Chapter 9 detailing the development of a specific drug, maribavir; and Chapter 10, an extensive, general review of commercial and experimental anti-HCMV compounds. The remaining Chapter 14 is the only one on anti-influenza compounds. This is focused only on neuraminidase inhibitors, but this is another landmark story in medicinal chemistry as it has produced the currently most effective tool for fighting influenza pandemics, Tamiflu.

As stated previously, this book is not a comprehensive source of information on antiviral drugs, but it is currently the most complete compilation of case studies and reviews. The references appear up-to-date at the time of publication and there is a useful index at the back of the book. This volume would certainly be a useful addition to the libraries of academic chemists, biochemists, and microbiologists, as well as to those of pharmaceutical research groups.

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