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Chapter 12. Antiviral Agents

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The previous review of antiviral agents in Annual Reports in Medicinal Chemistry emphasized compounds with activity against DNA viruses.[1] The focus of this year's chapter is on agents with activity primarily against RNA viruses. A brief update of this year's advances in anti-DNA virus agents is provided. Antiviral agents with activity against RNA viruses were previously reviewed in the 1981 volume.[2] Neither interferons nor interferon inducers are included in this review as they were covered in the 1981 and 1982 volumes, respectively. Several reviews have been published that give an overview of the most promising clinical and experimental antiviral agents[3-5] or provide background on viral diseases.[6-8] More comprehensive reviews dealing with specific drugs are cited in the sections where these compounds are discussed.
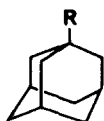
VIRAL RESPIRATORY DISEASE

RNA viruses are the major causative factors of the various forms of acute respiratory disease.[8] The communicable diseases of the respiratory tract are probably the most common cause of symptomatic human infections. Among both children and adults, acute respiratory tract illness results in significant morbidity, lost time from work, physician visits, and death. It has been calculated that throughout the world over two million deaths occur annually from acute respiratory disease.[9] The viruses that are causative agents for human respiratory disease comprise the five taxonomically distinct families Orthomyxoviridae, Paramyxoviridae, Picornaviridae, Coronaviridae and Adenoviridae.[9] The influenza viruses, which are comprised of types A, B and C, belong to the family Orthomyxoviridae. Types A and B have been associated with significant increases in mortality during epidemics. The disease may be asymptomatic or cause symptoms ranging from the common cold to fatal pneumonia. Immunization against influenza has been recommended for high-risk groups, and antiviral chemotherapy (amantadine) is available for the treatment and prophylaxis of all influenza A infections. The family Paramyxoviridae includes respiratory syncytial virus (RSV) and parainfluenza virus which are a major cause of lower respiratory tract infections. RSV is a factor in severe bronchiolitis and pneumonia in infants and young children. Efforts to develop a vaccine for RSV have been ineffectual, but recent clinical trials with ribavirin as a small particle aerosol have been promising. The parainfluenza viruses, of which there are four human serotypes, are second only to RSV as a cause of lower respiratory tract illness. There is both a great need for and interest in developing a chemo-therapeutic agent for treatment of these two viral, respiratory tract pathogens. The family Picornaviridae contains the genus Rhinovirus, which is composed of over a hundred distinct serotypes. The rhinoviruses are recognized as the most important causative agents of the

common cold. The development of a vaccine has been precluded due to
the many rhinovirus serotypes. Although a number of different chemical
agents have been tested in man, none has shown much clinical efficacy.
Coronaviruse (family Coronaviridae) also has an appreciable role in
upper respiratory tract illness although technical difficulties appear
to have hindered studies on vaccines and antiviral agents. The adeno-
viruses (family Adenoviridae) are a ubiquitous group of doublestranded
DNA viruses which are responsible for a wide variety of respiratory
illnesses. These infections are most common among children, although
acute respiratory disease and pneumonia are also common among military
recruits. Two comprehensive reviews of viral respiratory diseases and
measures for their control and treatment have been recently
published.[8,9]

AGENTS ACTIVE PRIMARILY AGAINST RNA VIRUSES

Amantadine (1-adamantanamine) and rimantadine (α-methyl-1-adamantanemethyl-
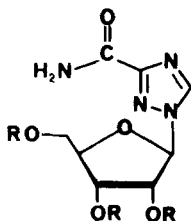amine) - Amantadine (1) and rimantadine (2) are specifically active
against influenza A virus infections. In 1966
amantadine was licensed for general use against

1, R = NH₂   Asian (H2N2) influenza in the United States and
2, R = CHCH₃NH₂ since 1976 has had FDA approval for the
prophylaxis and therapy of all influenza A
infections.[10,11] Rimantadine is a closely related analog that has been
widely used in the U.S.S.R. A review of the results of experimental and
clinical studies performed in the U.S.S.R. with rimantadine has been
published.[12] Several placebo-controlled, double-blind clinical trials of
amantadine and rimantadine in the treatment of influenza A infections
have been recently completed.[13-15] In a large-scale trial, both drugs
were highly effective with no significant differences between the rates
of illness or infection in the two drug-treated groups.[13] The amantadine
recipients reported a higher incidence of side effects largely attributed
to central nervous system (CNS) symptoms.[13,14] This difference in side
effects may be a pharmacokinetic phenomenon which results in higher
plasma concentrations of amantadine.[16] A controlled study of healthy,
adult volunteers found 1 and 2 to have minor side effects comparable to
those of a common antihistamine.[17] However, an open study involving
hospital employees receiving amantadine showed a high incidence of CNS
symptoms.[18] Guidelines for the use of amantadine in patients with
impaired renal function have been formulated from the results of
pharmacokinetic studies on amantadine in patients with normal and impaired
renal function.[19,20] Since approximately 90% of an oral dose of
amantadine is excreted unchanged in the urine, patients with renal
insufficiency can accumulate the drug, resulting in toxic manifestations.
The mechanism by which 1 and 2 inhibit influenza A virus replication had
previously been narrowed to a virus-specific event after virus penetration
but prior to primary transcription. A recent study with virus labeled
with radioactive precursors seems to show that uncoating is a multistep
process.[21] Rimantadine prevents the second step of uncoating, the
release of matrix (M) protein from ribonucleoproteins (RNP).[22] This
blocks the penetration of RNP into the nucleus and prevents the nuclear
phase of virus reproduction. Amantadine produces the same effect on
uncoating as rimantadine.[21] These adamantyl amines may also have utility
in the treatment of other types of viral infections. Rimantadine has
been shown to be an effective inhibitor of dengue virus replication in
vitro.[23] The amelioration of post-herpetic neuralgia due to recurrent
herpes simplex sciatica[24] and from acute herpes zoster[25] has been
reported with early administration of amantadine.

Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) - This
nucleoside has activity against a broad range of DNA and RNA viruses in
tissue culture and in animal model systems.[2]   An
analysis of the status of ribavirin (3) as an
antiviral agent has been published.[26] Its mechanism
is still unresolved but may involve guanosine
nucleotides and inhibition of inosine monophosphate
dehydrogenase.[26] In a clinical trial against
influenza A, oral ribavirin failed to alter clinical
signs and symptoms of the disease.[2] However, it
has recently been reported to have a therapeutic
effect against both influenza A and influenza B
virus infections when administered to patients by
inhalation of small-particle aerosol through a face
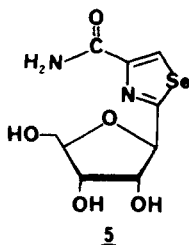mask.[27,28] This method of treatment may
find utility in those patients at high risk such as the elderly and the
chronically ill. Ribavirin has also been shown to inhibit respiratory
syncytial virus (RSV) infection in an animal model when administered
i.p. or by aerosol treatment.[29] This in vivo activity has now been
substantiated in two controlled, double-blind clinical trials.[30,31]
Administration of a continuous aerosol of ribavirin to infants
hospitalized with lower respiratory tract disease from RSV resulted in
significant clinical improvement.[31] In a study of the effects of
several antiviral agents against Colorado tick fever virus (CTFV),
ribavirin inhibited CTFV in vitro.[32] Ribavirin did not protect mice
inoculated intracerebrally with CTFV. However, the 2',3',5'-triacetate
derivative 4 significantly increased the number of survivors when
administered i.p., which suggests that this lipophilic prodrug of
ribavirin is able to cross the blood-brain barrier.[32] Intraperitoneal
administration of 4 was also found to protect mice inoculated intra-
cerebrally with dengue virus, under conditions where ribavirin had no
significant protective effect.[33] In another study, ribavirin reduced
the growth of four types of dengue virus in vitro, but it had no effect
on virus replication in human peripheral blood leukocytes (PBL) which
have been implicated in the pathogenesis of dengue virus in vivo.[34]
However, a combination of ribavirin with 6-mercapto-9-(tetrahydro-2-
furyl)purine, an inhibitor of hypoxanthine-guanine phosphoribosyl
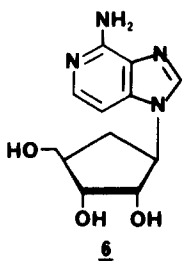transferase, resulted in a marked suppression of dengue virus replication
in human PBL.[34]

3, R = H

4, R = COCH$_3$

Selenazole (2-β-D-ribofuranosylselenazole-4-carboxamide) - The novel
selenazole carboxamide nucleoside 5 was recently synthesized[35], and it
has been reported to have in vitro antiviral activity superior to that
of ribavirin.[36] Selenazole (5) has broad-spectrum antiviral activity
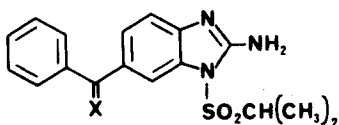against both RNA and DNA viruses, but it was most
active against representative RNA viruses.[36] The
virus families Paramyxoviridae, Reoviridae,
Togaviridae, Bunyaviridae and Arenaviridae were
particularly sensitive with ED$_{50}$ values typically
ranging from 1 to 8 µg/ml, although yellow fever
virus was especially sensitive with an ED$_{50}$ =
0.005 µg/ml. Although selenazole was relatively
nontoxic for Vero and HeLa cells,[36] it was
found to be cytotoxic towards P388 and L1210 cells
in culture and exhibited marked activity against
Lewis lung carcinoma in mice.[35]

5

Carbocyclic 3-deazaadenosine (C-c^{3}Ado) - The carbocyclic nucleoside 6 has been reported to inhibit the in vitro replication of DNA and RNA viruses[1,37]. C-c^{3}Ado was active against vaccinia, reo, measles, parainfluenza and vesicular stomatitis viruses (VSV) at concentrations from 0.2 to 1 µg/ml but exhibited no toxicity for the host cells at 400 µg/ml. In vivo, 6 protected newborn mice against a lethal infection of VSV when administered i.p. Its spectrum of antiviral activity was suggested to be compatible with an impairment of viral mRNA transcription and/or processing.[37]

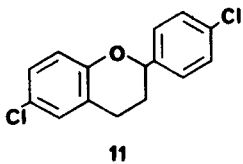Enviroxime (LY 122772) - Enviroxime (7) is a potent inhibitor of rhino-virus replication in cell culture with a uniform level of activity against over sixty rhinovirus serotypes.[2] In clinical trials in England, intranasal and oral enviroxime had some beneficial effect on rhinovirus infections although the oral form was poorly tolerated.[38,39] In two U.S.A. based clinical trials, prophylactic administration of intranasal enviroxime failed to prevent infection or to reduce the frequency of colds after experimental rhinovirus challenge.[40,41] Enviroxime, as its syn-anti mixture, and the propenyl analog 8 (LY 127123) have been reported to be highly active against thirteen enteroviruses in vitro.[42] When injected s.c. into infant mice, both compounds significantly reduced the mortality caused by Echo and coxsackie viruses.[42] A number of analogs of the olefin 8 in which X was equal to groups as diverse as CHCH$_2$CH$_3$, CHC≡N, CHCONH$_2$, CHCOOCH$_3$ and CHCl were reported to have potent in vitro activity against poliovirus with IC$_{50}$'s ranging from 0.01 to 0.04 µg/ml.[43] Activity is highly specific for the E-isomer, a trend that parallels earlier findings in the enviroxime series.[44]

7, X = NOH—anti

8, X = CHCH$_3$—trans

The recent literature on 2-(α-hydroxybenzyl)benzimidazole (HBB) (9) and several analogs has been reviewed.[45] The in vitro antiviral activity of 9 against thirteen enteroviruses in comparison with enviroxime and in combination with guanidine has been published.[42] The mutual synergistic activity of the combination of 9 and guanidine was confirmed against Echo and coxsackie viruses in infant mice.[42,46]

9

10
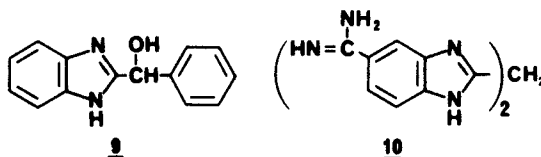
Mono- and diamidinobenzimidazoles such as bis(5-amidino-2-benzimidazolyl)methane (BABIM) (10) possess significant suppressive effects on the cytopathology and yield of respiratory syncytial virus (RSV).[47] The mechanism of action of BABIM may be related to its inhibition of certain trypsin-like proteases,[47] but a study of twenty-four amidine derivatives showed no correlation between RSV-induced cell fusion and inhibition of four protease enzymes.[48]
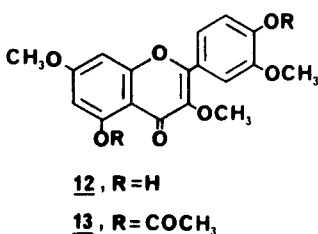
4',6-Dichloroflavan (BW683C) - BW683C (11) is a potent inhibitor of the in vitro replication of several serotypes of rhinovirus.[49] The IC$_{50}$ value for 11 against serotype 1B is 7 nM. However, the sensitivity of the nineteen serotypes against which 11 was tested was highly variable. BW683C was found to be most active when added to the cell culture simultaneously with the virus.[50] The compound does not interfere with virus adsorption to cells nor with uncoating of the viral RNA. It appears to bind directly to rhinovirus 1B and may prevent virus replication immediately following uncoating of the viral RNA.[50] The compound is relatively nontoxic as no untoward effects were evident with HeLa cells at concentrations up to 3.6 μM. In rats, no ill effects were observed after oral administration of up to 1000 mg/kg or i.p. administration of up to 700 mg/kg.[49] In a double-blind, placebo-controlled volunteer trial, oral BW683C failed to produce a consistent reduction in any of the quantitative indices of rhinovirus infection.[51] Administration of this antiviral agent by inhalation may prove to be more efficacious.[52]
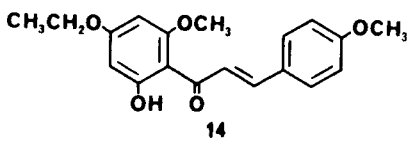
4',5-Dihydroxy-3,3',7-trimethoxyflavone (Ro 09-0179) - Ro 09-0179 (12), which was originally isolated from a Chinese medicinal herb, is a selective inhibitor of the replication of human picornaviruses.[53] Its IC$_{50}$ against twenty serotypes of rhinovirus was 0.1 μg/ml in HeLa or WI-38 cells, and its 50% cytotoxic dose was about 15 μg/ml. The compound does not directly inactivate the virus, but it was most effective when present in the early stages of virus replication. Although 12 was not active in vivo, its diacetyl derivative 13 (Ro 09-0298) was orally effective in protecting mice from lethal infections with coxsackievirus B1.[53] The closely related natural product, quercetin, has antiviral activity both in vitro and in vivo.[54] Additional studies with quercetin against Mengo M virus infected mice have confirmed previous reports of its oral efficacy.[54,55]

12, R=H

13, R=COCH$_3$

4'-Ethoxy-2'-hydroxy-4,6'-dimethoxychalcone (Ro 09-0410) - An agent active exclusively against rhinoviruses has emerged from a synthesis program on analogs of the flavone Ro 09-0179 (12). Ro 09-0410 (14), a chalcone, has activity against 46 of the 53 serotypes tested with IC$_{50}$s ranging from 3 μg/ml to less than 0.003 μg/ml.[56] In contrast, 14 was inactive against nine other DNA and RNA viruses at concentrations up to 3 μg/ml. Toxicological studies in rodents produced no adverse effects at a daily oral dose of 1000 mg/kg for two weeks. A phosphate ester (Ro 09-0415) of 14 has been evaluated in humans at the MRC Common Cold Unit in Salsbury, England.[57]

14

2-(3,4-Dichlorophenoxy)-5-nitrobenzonitrile (MDL-860) - MDL-860 (15) is a selective inhibitor of picornavirus replication in vitro.[58] At a concentration of 1.0 μg/ml, 15 caused a reduction in virus yield of at

15
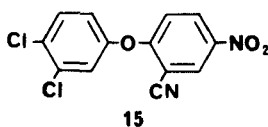
least ten fold in eight of ten entero-
viruses and seventy-two of ninty
rhinovirus serotypes, but it had no effect
on six other types of viruses.[58] MDL-860
does not directly inactivate the virus nor
does it inhibit virus uncoating.[59] Although **15** had no adverse effects
on RNA or protein synthesis of uninfected HeLa cells, it was found to
inhibit viral RNA synthesis when added shortly after virus absorption.

Sodium 5-aminosulfonyl-2,4-dichlorobenzoate (M12325) - A broad spectrum

16

of activity against RNA viruses in vitro and in vivo
has been reported for M12325 (**16**).[60] The MICs
against several strains of influenza virus were
comparable to the activity of amantadine, but **16** was
less cytotoxic and had a higher LD_{50}. Oral doses of
16 were reported to be effective in reducing
influenza induced mortality in mice.[60]
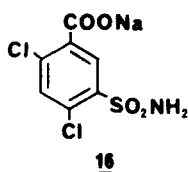
Arildone (WIN 38020) - Arildone (**17**) is a β-diketone which has broad-
spectrum activity against several important DNA
and RNA viral pathogens.[1,2] An isoxazole
analog, WIN 49321 (**18**), has recently been
reported to have antipicornavirus activity.[61]
The isoxazole **18** inhibited plaque formation
by 24 of 27 human rhinovirus serotypes,
poliovirus and Echovirus by 50% at concentra-
tions ranging from 0.03 to 15 μM. It was
orally effective in protecting mice against
poliovirus-induced death in a dose-dependent
manner. Mechanism studies show that **18** prevents viral replication by
inhibiting the virion uncoating process.[61]

17, R = CH(ĊCH$_2$CH$_3$)$_2$

18, R =
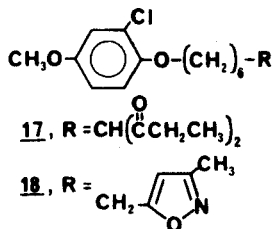
1-(5-Tetradecyloxy-2-furanyl)ethanone (RMI 15,731) - RMI 15,731 (**19**) has
been reported to be a rhinovirus specific
antiviral that directly inactivates virus in
vitro.[2] In a recent clinical trial, intranasal
19 failed to show significant prophylactic
activity in experimental human rhinovirus type
39 infections.[62]

19
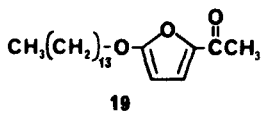
DNA VIRUSES

Significant progress continues to be made in the clinical use and
development of agents active against DNA viruses. Acyclovir
(9-(2-hydroxyethoxymethyl)guanine) has been the subject of several
reviews[63-68] and of a symposium[69] during the past year. Clinical trial
results have been published that attest to the efficacy of oral acyclovir
in the treatment of primary[70] and recurrent[71] genital herpes simplex
virus (HSV) infections and in the protection of bone marrow transplant
patients from herpes infections.[72] Chronic, oral acyclovir treatment
was highly effective in suppressing recurrent herpes simplex genitalis
in a group of patients with unusually frequent episodes.[73] Topical
acyclovir cream was effective for treatment of recurrent herpes
labialis.[74] Considerable progress has been made in evaluating the
clinical promise of acyclovir; however, there remains much to be learned
concerning the best use of this drug in clinical practice.[75] Some
studies on candidate prodrug forms of acyclovir have recently been
published. Several esters of acyclovir were reported to have improved

water solubility.[76] A diaminopurine analog A134U (2,6-diamino-9-(2-hydroxyethoxymethyl)purine), which is metabolically deaminated to acyclovir by adenosine deaminase,[77] has been reported to be better absorbed from the gut, resulting in higher plasma levels of acyclovir.[78] Several new reports have further documented the potent antiherpetic activity of 9-(2-hydroxy-1-(hydroxymethyl)ethoxymethyl)guanine. This compound has been reported to be highly effective in reducing the severity of both primary and recurrent lesions of HSV-2 in animal models.[79,80] It also appears to hold substantial promise in the treatment of human cytomegalovirus (HCMV) based on its specific anti-HCMV activity in vitro.[80,81] In an animal model, 9-(2-hydroxy-1-(hydroxymethyl)-ethoxymethyl)guanine was shown to be a potent, orally active, chemo-therapeutic agent against Equid herpesvirus.[82] FIAC (2'-fluoro-5-iodo-1-β-D-arabinofuranosylcytosine) has been reported to stabilize cutaneous lesions in immunosuppressed patients suffering from acute herpesvirus infection.[84] A minor metabolite of FIAC, 2'-fluoro-5-methyl-1-β-D-arabinofuranosyluracil (FMAU), is also antiherpetic, but, in addition, it has i.p. and p.o. activity against murine leukemias resistant to 1-β-D- arabinofuranosylcytosine. Pharmacokinetic studies on FIAC and FMAU have been published,[85] and the synthesis and in vitro anti-HSV activities of a series of analogs have been reported.[86] A review of the antiviral activity of BVDU ((E)-5-(2-bromovinyl)-2'-deoxyuridine) and other 5-substituted pyrimidine nucleoside analogs has been published.[87] Several 2',3'-diester and 5'-monoester prodrug forms of ara-A (9-(1-β-D-arabinofuranosyl)adenine) have been evaluated with favorable results in HSV-2 induced genital infections in female guinea pigs.[88] The 5'-monophosphate of ara-A was found to be as effective as ara-A in the treatment of immunosuppressed patients suffering from varicella-zoster.[89] A carbocyclic analog of ara-A, cyclaradine, and its 5'-methoxyacetate ester have been reported to have activity in an HSV-1 encephalitis animal model that was comparable to the activity demonstrated by ara-A.[90] These two compounds may possess some clinical advantage over ara-A due to their low systemic toxicity. The antiviral effects of phosphonoformic acid (PFA, foscarnet sodium), which is presently in Phase III clinical trials in Europe,[83] have been discussed in a recent review.[91] The synthesis and structural requirements for antiherpes activity of a series of PFA esters have also been reported.[92]

APPROACHES TO THE DESIGN OF ANTIVIRAL AGENTS

Significant strides have been made in the development of clinically useful antiviral agents, especially against the DNA viruses of the herpes family. Most of these agents are directed against viral nucleic acid synthesis and require activation by a virus-induced thymidine kinase. Researchers are beginning to focus on other strategies which may produce broader spectrum antiviral agents with different mechanisms of action. Inhibition of polyamine biosynthesis may serve as a suitable target for antiviral drug design. The polyamine antimetabolite methylglyoxal bis(guanylhydrazone) and α-difluoromethylornithine, an inhibitor of polyamine biosynthesis, have recently been reported to inhibit replication of human CMV in vitro.[93] Another target is the inhibition of essential methylation reactions. For some viruses, efficient replication is dependent on viral mRNA that has been methylated at its 5'-terminal guanosine residue. Ribavirin 5'-triphosphate has been reported to be an effective inhibitor of this capping reaction which is catalyzed by a mRNA(guanine-7-)methyltransferase.[94] Another permutation of this theme is preservation of cellular S-adenosylhomocysteine (SAH) by inhibition of SAH hydrolase. SAH is an endogenous inhibitor of transmethylation

reactions in which S-adenosylmethionine is the methyl donor.[95] The 2-5A system is one of the mechanisms by which interferon exerts its antiviral effect.[96,97] There has been substantial interest in exploiting this system as an approach to antiviral drug development. These efforts have primarily been aimed at the synthesis of 2-5A core analogs that are permeable to cells and stable to degradative enzymes. During the process of infection some viruses change the permeability of infected cells. This allows cellular penetration by compounds that are normally excluded. The selective antiviral activity of hygromycin B supports the suggestion that screening for agents which are selectively permeable to virus infected cells could result in broad-spectrum antiviral agents.[98] A review of the concept of selective delivery of antiviral agents by conjugation with protein carriers has been published.[99] These experiments suggest that the chemotherapeutic index of ara-A for the treatment of chronic hepatitis B could be improved by coupling the agent to lactosaminated albumin. A number of lipophilic amines of diverse structure have in vitro antiviral activity against enveloped viruses including Semliki Forest virus, Sendai virus, vesicular stomatitis virus, and influenza A and B viruses.[100-103] This activity appears to be mediated by an obligatory lysosomal step in the uncoating of enveloped viruses. Amines such as chloroquine may prevent uncoating by increasing the lysosomal pH above a value required for release of the virus nucleocapsid into the cytoplasm. A better understanding of this process could lead to the development of broad-spectrum antiviral agents.

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