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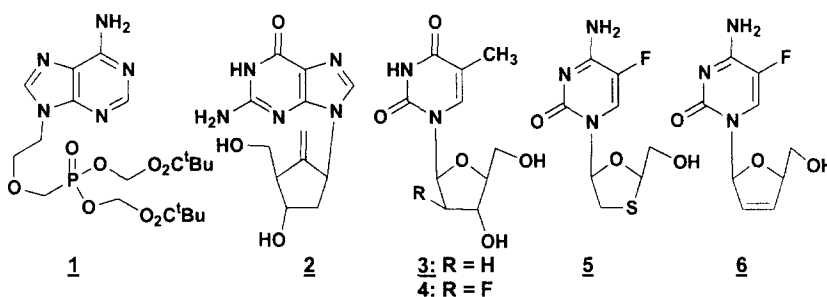
Chapter 22. Non-HIV Antiviral Agents

Nicholas A. Meanwell, Michael H. Serrano-Wu and Lawrence B. Snyder
Department of Chemistry, The Bristol-Myers Squibb Pharmaceutical Research Institute
5 Research Parkway, Wallingford, CT 06492

Introduction – The development of antiviral agents to treat non-HIV infections is largely focussed on therapies for the treatment of the chronic hepatitis infections B and C (1). Nucleoside analogues continue to be the mainstay of HBV therapeutics and clinical development of several continued during 2002. The last year has seen the first small molecule inhibitor of HCV, the NS3 protease inhibitor BILN-2061, enter phase 2 (P2) clinical trials, producing a striking reduction in viral load in treated individuals. The development of the first HCV replicon system in 1998 and its application to screening for antiviral agents is beginning to provide tangible benefit with the disclosure of mechanistically and structurally diverse HCV inhibitors. There remains considerable interest in inhibitors of herpes simplex and human cytomegalovirus viruses, particularly non-nucleoside compounds. Developments in the area of respiratory virus inhibitors have focussed more on respiratory syncytial virus with a description of the first antiviral active in animal models following oral administration. The West Nile virus outbreak in the US, originally confined to the East coast, broadened considerably during the summer of 2002, claiming 230 lives. In the wake of the events of September 11th, 2001, smallpox was a prominent concern as a potential agent of bioterrorism. Developments in each of these areas will be reviewed.

INHIBITORS OF HEPATITIS B AND C VIRUS

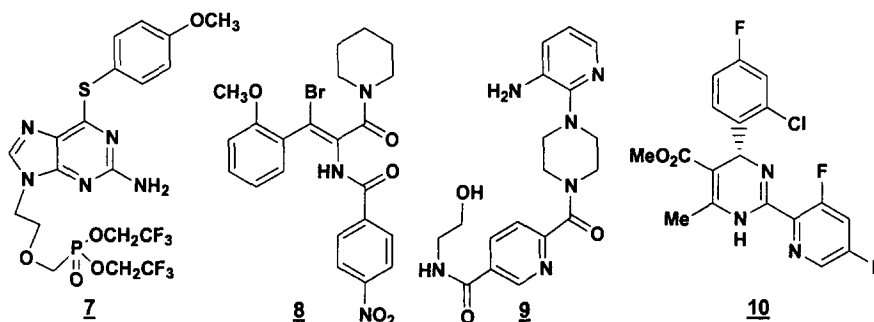
Inhibitors of Hepatitis B Virus (HBV) – Adefovir dipivoxil (Hepsera™) (**1**) was approved in the US for the treatment of HBV on September 20th, 2002 and in the European Union on March 11th, 2003, providing a second small molecule antiviral to add to lamivudine (3TC) and the injectable protein IFN α as the only approved agents for treating HBV infection. Adefovir is an effective inhibitor of 3TC-resistant HBV caused by the rM204I and rL180M + rM204V mutations in the reverse transcriptase (2) and resistance to adefovir has not been seen after 48 weeks of monotherapy (3,4).



A clinical study with entecavir (**2**), currently undergoing P3 trials, compared a dose of 0.1-1 mg/day of **2** to 3TC (100 mg/day) for 48 days in 181 patients previously unresponsive to 3TC treatment (5). Compared to 3TC, treatment with **2** resulted in lower overall viral loads, lower ALT levels and a higher proportion of patients with undetectable HBV DNA levels. Moreover, adverse events for **2** were less than those observed with 3TC. A separate P2 trial of **2** in 177 treatment-naïve patients for 22 weeks at a dose of 0.5 mg/day showed that reduction in viral DNA levels was

independent of baseline ALT levels, with treatment resulting in a 4.7-4.8 log₁₀ reduction in HBV DNA (6).

L-nucleosides represent a promising area of antiviral research (7). LdT (telbivudine, **3**) is currently in P3 clinical trials designed to evaluate 1200 patients for safety and efficacy compared with standard treatment in HBeAg+ and HBeAg- patients (8). Recent P2b data was released from a trial involving 104 adults randomized to receive 3TC plus **3** or 3TC monotherapy once daily for 1 year. Viral load reductions of greater than 6 log₁₀ were seen for all patients in the study arms containing **3** and no treatment-limiting or dose-related adverse events were reported. The mechanism of action of L-FMAU (clevudine) (**4**), currently in P1/P2 trials, is not firmly understood but recent molecular dynamics simulation experiments have suggested that the triphosphate derivative of **4** may act as a competitive inhibitor rather than as a substrate of HBV polymerase (9,10). Emtricitabine (Coviracil™) (**5**) is also currently in P3 clinical trials for the treatment of HBV. An NDA seeking approval to market **5** for the treatment of HIV was filed in September 2002 (9). Results from a P1/P2 clinical trial with ACH-126443 (elvucitabine, **6**) have been released (11-13). In 36 HBV treatment-naïve patients receiving single daily doses of 1-100 mg of **6**, mean declines in plasma HBV DNA of up to 2.5 log₁₀ were observed after 14 days of treatment. Furthermore, plasma levels in excess of the IC₅₀ values for wild type and YMDD mutants were achieved in the low dose arms. It is therefore anticipated that **6** will be efficacious against 3TC resistant infections in an ongoing P2 trial.



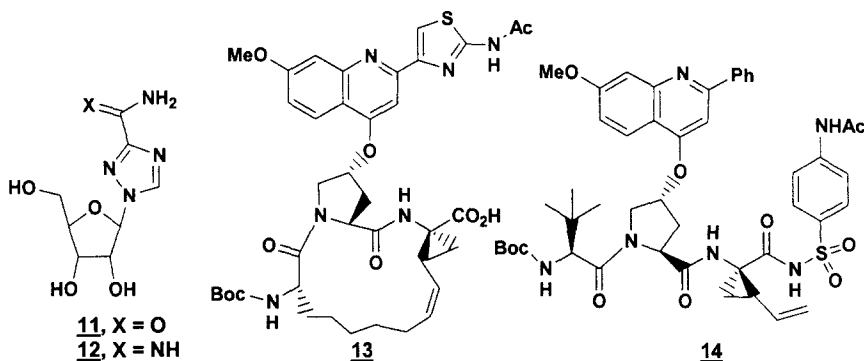
LY-582563 (MCC-478, **7**) is more potent than 3TC in HB611 cells, EC₅₀ = 27 nM and 2.2 μM, respectively, and retains activity towards HBV carrying the recently identified G1896A mutation (14-16). This mutation, which arises in response to 3TC therapy, is found in the precore region and confers HBeAg negativity. The major metabolite of **7** formed in rat or human serum is the mono-ester, which is a more potent HBV inhibitor, EC₅₀ = 70 nM, than 3TC. It is postulated that the arylthio moiety is responsible for the specificity towards HBV and lower cytotoxicity than PMEA, the active component of adefovir dipivoxil. Additional analogs in this structural class have been prepared with the phenylthio- and 3-methoxyphenylthio ethers showing the most promise whilst other aromatic thioethers exhibited higher cytotoxicity (14,15).

Non-nucleoside inhibitors of HBV are beginning to emerge that are anticipated to show reduced cross-resistance with nucleoside analogues. AT130 (**8**) and its close analog AT61 are active against wild type HBV and the rL180M, rM204I, and rL180M+rL204V mutants (EC₅₀ = 2-5 μM) in HepG2-derived cells (17,18). It has been postulated that **8** interferes with the packaging of pregenomic viral RNA resulting in inhibition of viral reverse transcription. Pyridinedicarboxamide **9** represents the first report of a non-nucleoside inhibitor of HBV reverse transcriptase (19). The unique mechanism of action of Bay 41-4109 (**10**), a potent HBV inhibitor *in vitro*, EC₅₀ in HepG2.2.15 cells = 50 nM, has recently been elucidated (20,21). Only the (*R*)-

enantiomer of **10** is active in cell culture and appears to prevent proper formation of the viral nucleocapsid.

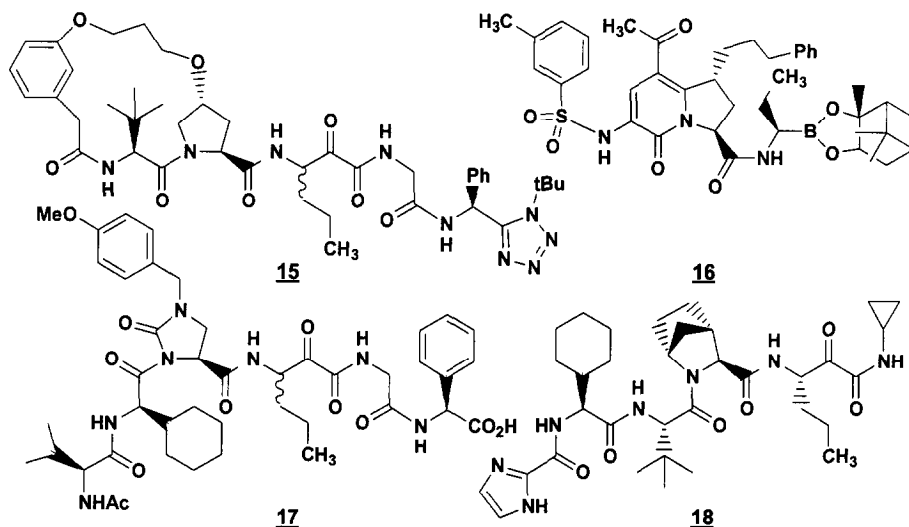
Inhibitors of Hepatitis C Virus (HCV) – Nearly 170 million individuals are infected with hepatitis C virus (HCV) worldwide and HCV infection is responsible for 8,000-10,000 deaths annually in the United States, a burden expected to increase significantly (22,23). A second pegylated interferon- α (IFN), Roche's Pegasys, was approved in 2003, both as mono therapy and in conjunction with ribavirin (**11**) (Copegus™) (24). However, safety concerns with combination therapy remain, as the accumulation of **11** in erythrocytes can lead to hemolytic anemia. This has prompted a search for safer interferon co-therapies which include the active enantiomer of **11**, levovirin, and the prodrug viramidine (**12**), which improves liver at the expense of erythrocyte exposure (25,26).

The development of safe, efficacious, and HCV-specific antiviral agents remains an important goal and the development of subgenomic HCV replicons has dramatically enhanced the potential to identify inhibitors (27,28). A significant advance towards establishing a correlation between replicon inhibition and clinical efficacy was recently accomplished with the disclosure of preliminary clinical data for BILN-2061, a selective inhibitor of the NS3 serine protease of HCV that is structurally related to **13**. This highly modified macrocyclic tripeptide derivative is extremely potent *in vitro*, with K_i values of 0.3 nM and 0.66 nM towards HCV-1a and HCV-1b NS3 proteases, respectively (29). These figures are similar to the potency observed in cell culture in the cognate HCV replicons, $EC_{50} = 4$ nM and 3 nM, respectively (29). Antiviral efficacy was established in a study conducted with 10 patients with chronic HCV and significant liver fibrosis, where all patients treated with BILN-2061 (200 mg p.o. b.i.d.) displayed a decrease in serum HCV RNA levels of at least 2.0 \log_{10} copies/mL after two days of treatment (30). Four of these patients recorded a reduction in viral load of more than 3 orders of magnitude and viral titers returned to baseline following cessation of therapy, with no drug-related safety issues identified (31).

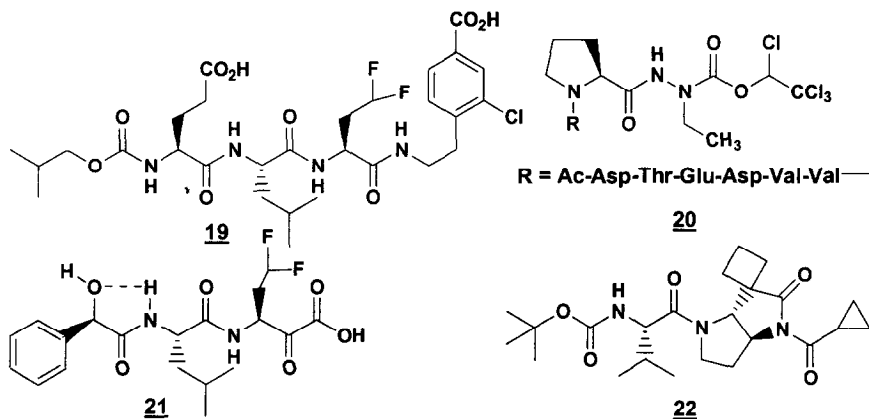


The intensity of effort devoted towards the discovery of inhibitors of HCV NS3 has continued, with the focus largely on peptide-based molecules that are required to effectively complement the active site and proximal regions of the protease (32-34). The crystal structure of a macrocyclic inhibitor related to **13** bound to HCV protease has been disclosed and an acyclic tripeptidic inhibitor has been used to generate resistant subgenomic replicons in which mutations mapped to the protease (35,36). Amongst several strategies disclosed, the C-terminal carboxylate of peptide inhibitors may be replaced with an N-acyl sulfonamide moiety, as exemplified by **14** (37). Novel approaches to constrain or mimic the peptidic backbone are represented by macrocycle **15**, the tetrahydroindolizine **16** ($IC_{50} = 0.12$ μ M), the imidazolone **17** and

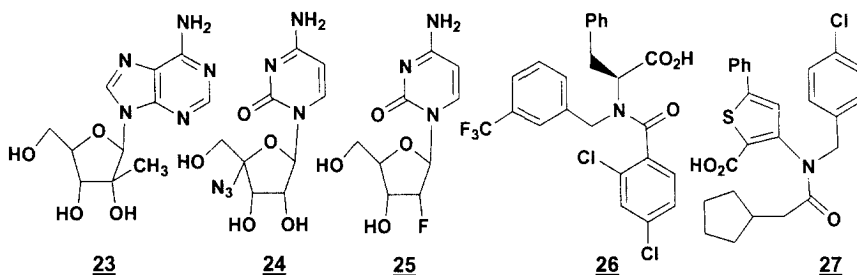
the bicyclic proline derivative **18** ($K_i = 0.042 \mu\text{M}$, $\text{IC}_{50} = 0.251 \mu\text{M}$) (38-46). These inhibitors are constructed around either an α -keto amide or a boronic acid moiety, well-precedented as serine protease inhibitor motifs that engage the catalytic serine residue in a covalent but reversible interaction.



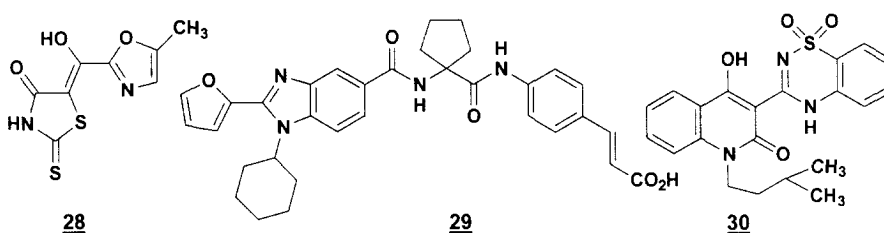
However, chemical reactivity is not a prerequisite for potent inhibition in a peptidic background since phenethylamide **19** and the azapeptide **20** inhibit HCV NS3 with K_i values of 0.6 and 0.2 μM , respectively (47,48). The more active diastereomer of the α -hydroxy amide P3 element explored in the context of **21** was found to possess the (*R*)-configuration, unanticipated and explained by the presence of an intramolecular hydrogen bond that orients the lipophilic moiety of this isomer into S3, as depicted (49). Non-peptidic inhibitors of NS3/NS4A protease are much less common but some progress has been made in this direction. The bicyclic lactam **22** is a mechanism-based inhibitor of HCV NS3 whilst additional examples of bis-benzimidazole derivatives that rely upon Zn^{2+} to consolidate the enzyme-inhibitor complex have been described (50,51).



The NS5B RNA polymerase is another structurally-characterized viral protein that is an attractive target for therapeutic intervention (52-55). Inhibitors of HCV polymerase can be broadly divided into nucleoside and non-nucleoside derivatives. The nucleoside analog ribavirin (**11**) has been suggested to interfere with both the initiation and elongation steps of HCV RNA replication (52). Several HCV NS5b inhibitors incorporate modified D-ribose elements and include the 2'-Me derivative **23**, $EC_{50} = 0.25 \mu\text{M}$, the 4'-azido analog **24**, $EC_{50} = 1.2 \mu\text{M}$, and the 2'-deoxy-2'-fluoro cytidine derivative **25**, $EC_{50} = 0.74 \mu\text{M}$ (56-59).



Several non-nucleoside inhibitors of HCV NS5B have been reported, including a series of phenylalanine derivatives of which compound **26**, $K_i = 2.2 \mu\text{M}$, is representative (60,61). This compound has been co-crystallized with NS5B and appears to bind to the inactive, open conformation of the polymerase almost 35 Å from the active site (62). Other scaffolds with which HCV polymerase inhibitors have been discovered include an amino thiophene, represented by **27**, the enolic rhodanine **28** ($IC_{50} = 1.0 \mu\text{M}$), and structural variations of previously disclosed benzimidazole derivatives **29** ($IC_{50} < 0.5 \mu\text{M}$) claimed to be active in replicons (61,63-67). Mechanistic studies with the benzo[1,2,4]thiadiazine polymerase inhibitor **30** suggest interference with the initiation step of viral RNA synthesis, allowing for a potential synergy with existing elongation inhibitors (68).



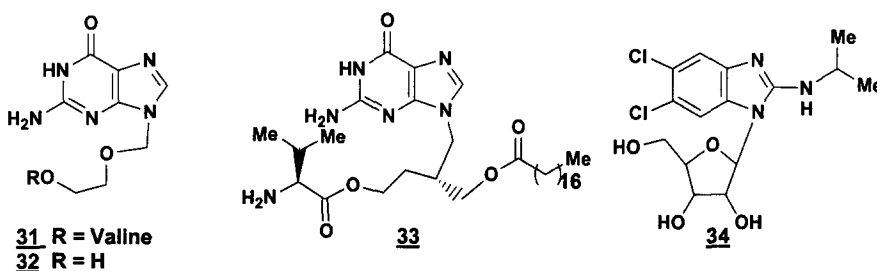
Novel approaches to HCV therapy include blocking the viral RNA internal ribosomal entry site (IRES), binding of the viral E2 envelope glycoprotein or attachment (69-72). The highly conserved IRES has been targeted by oligonucleotides and artificial ribozymes, but little progress has been made in the development of small molecule inhibitors (70,71). P2 clinical evaluation of the antisense 20-mer oligonucleotide ISIS-14803 revealed a 1-2 \log_{10} reduction in plasma HCV RNA levels in approximately 30% of the patients after 4 weeks of treatment (73). Another approach, which may prove complementary to virus-specific HCV therapy, is the induction of interferon production in host cells. Small molecules that act *via* toll-like receptor activation have been identified as activators of an immune response (74). RNA interference (RNAi) is a rapidly emerging technology that has proven to be a powerful means of selectively controlling protein production in cell culture. Inhibition of HCV replication in replicons has been accomplished using this procedure whilst the

demonstration of selective targeting of the liver protein Fas *in vivo* using RNAi holds promise for the treatment of HCV (75-78).

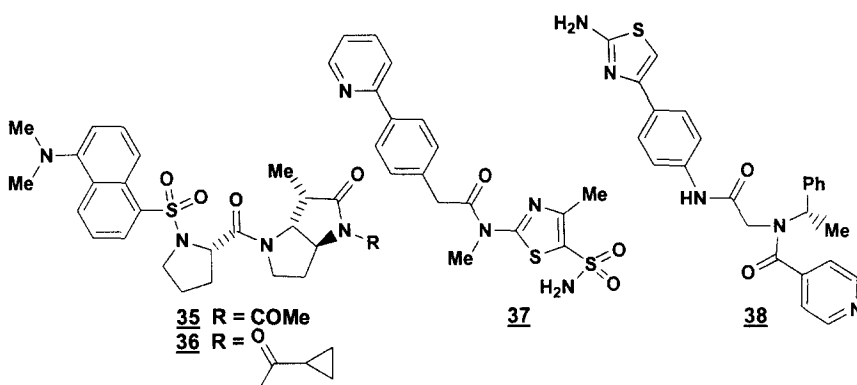
INHIBITORS OF HERPES SIMPLEX VIRUS AND HUMAN CYTOMEGALOVIRUS

The eight human herpes viruses cause a variety of pathophysiological conditions ranging in severity from mild cold sores to life threatening illnesses in immunocompromised patients. While herpes simplex virus (HSV) types 1 and 2 typically cause localized cold sores and genital herpes, other members of the herpesviridae family can be more problematic. Varicella zoster virus (VZV) is the causative agent in chicken pox whilst human cytomegalovirus (HCMV) is particularly difficult for the immunocompromised population, including AIDS patients where clinical manifestations include retinitis, colitis, oesophagitis, and pneumonia (78). Epstein-Barr virus (EBV) is responsible for mononucleosis in immunocompetent patients and lymphoma in immunocompromised individuals. Finally, HHV-6, HHV-7 and HHV-8 are the remaining known pathogenic herpes viruses of which HHV-8 is responsible for the debilitating effects of Kaposi's sarcoma. Nine antiviral agents are licensed to treat infections caused by the herpes virus family, all but one of which, fomiversen, terminate viral DNA synthesis by inhibiting the viral DNA polymerase (80,81). Resistance to current antiherpetics is modulated primarily by the thymidine kinase (TK), the UL97 phosphotransferase in HCMV and the DNA polymerase (82-86).

Valacyclovir hydrochloride (Valtrex™) **31** was approved in September 2002 for the treatment of cold sores in healthy adults and acyclovir (Zovirax™) **32** cream was approved for the treatment of recurrent herpes labialis or cold sores (87). Valomaciclovir stearate (MIV-606, **33**) has shown promise in P2 clinical trials for the treatment of herpes zoster with P3 trials planned (88). Maribavir (1263W94, **34**), an inhibitor of the HCMV UL97 protein kinase ($IC_{50} = 3$ nM), has been dropped from P2 clinical development for the treatment of HCMV infection (89-91). Data from a P1 clinical trial in HIV-1 infected men with asymptomatic HCMV shedding has been released (92,93). Maribavir demonstrated *in vivo* anti-HCMV activity in all of the dosage regimens tested (100, 200, and 400 mg tid, and 600 mg bid), with mean reductions in semen HCMV titers of 2.9 to 3.7 log₁₀ PFU/mL (92).

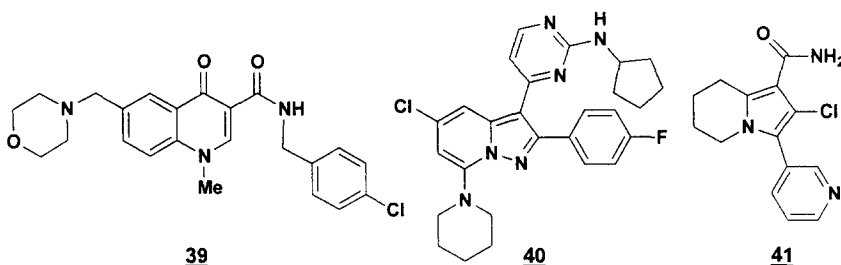


The HCMV serine protease has been perceived as an attractive antiviral target. Recent crystal structure data demonstrated significant conformational flexibility in the S3 binding pocket of protein complexed with two peptidomimetic inhibitors (94). A series of *trans*-lactams, represented by **35** and **36**, $IC_{50} = 0.54$ and 0.34 μ M, respectively, are derived from the same structural platform as the HCV NS3 inhibitor **22** but inhibit the HCMV serine protease with excellent selectivity (95-97). Mechanistic studies are consistent with acylation of the active site Ser₁₃₂ of HCMV protease in a reversible and time-dependent manner.

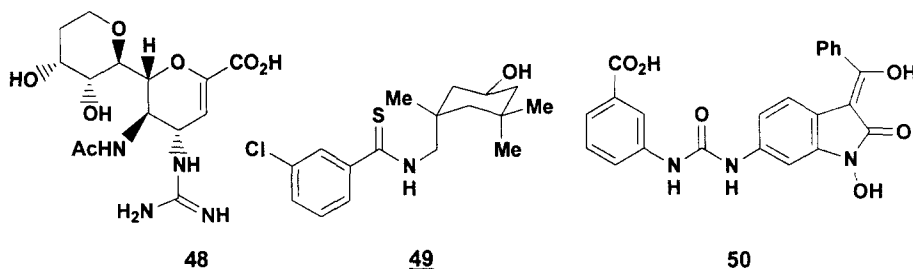


All but one of the currently licensed drugs available to treat HSV act by inhibiting the viral DNA polymerase, providing a suitable backdrop for the emergence of resistant virus and a rationale for identifying inhibitors of other viral proteins (98,99). Two groups have reported novel thiazole-containing inhibitors of the HSV helicase-primase. BAY 57-1293 (**37**) is a leading pre-clinical candidate that is more potent ($EC_{50} = 12$ nM) than any anti-herpetic currently used to treat HSV infections (100,101). In a murine lethal challenge model of HSV-1 and HSV-2, **37** was protective with an ED_{50} value of 0.5 mg/kg, which compares with the much higher doses of 22 and 16 mg/kg for HSV-1 and HSV-2, respectively, required for acyclovir to show efficacy. Additional patent applications that extend this promising chemotype have appeared (102,103). A second series of HSV helicase-primase inhibitors, of which BILS-179 BS (**38**) is representative, has been disclosed (104). BILS 179 BS inhibits viral growth with an EC_{50} of 27 nM, displays an excellent therapeutic index of >2000 and reduces cutaneous HSV-1 and genital HSV-2 disease in a murine model when treatment is initiated 3 hours post-infection. Interestingly, when treatment was initiated 65 hours after infection, **38** reduced HSV-1 pathology by 75% and HSV-2 mortality by 75% (200 mg/Kg/day) when compared to acyclovir or untreated animals (104).

A series of 4-oxo-dihydroquinolone derivatives that are potent and broad spectrum non-nucleoside inhibitors of DNA polymerases of the herpesvirus family, including HCMV, HSV-1, HHV-8 and VZV, have been the subject of a number of recent disclosures (105). These compounds exhibit no significant inhibitory activity towards human α -, γ -, or δ -polymerases. PNU-183792 (**39**) is an effective antiviral in cell culture, potently inhibiting HCMV ($EC_{50} = 0.69$ μ M), VZV ($EC_{50} = 0.37$ μ M) and HSV ($EC_{50} = 0.58$ μ M), that is active towards ganciclovir- and cidofovir-resistant HCMV and acyclovir-resistant HSV (106). Excellent oral bioavailability and a protective effect in a murine CMV animal model were also reported. A series of related analogs have been reported in the recent patent literature (107,108).



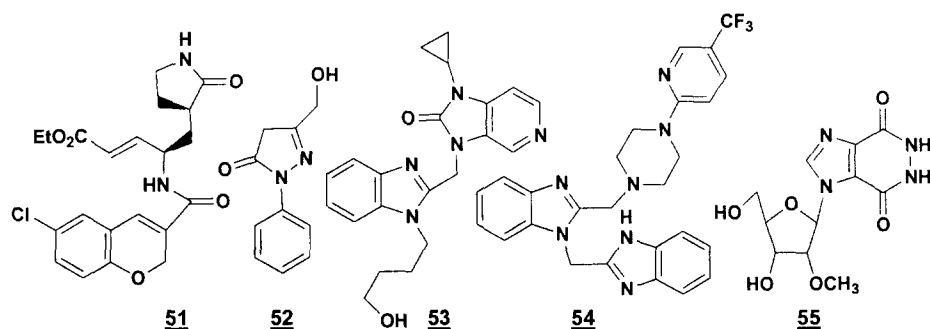
The O-methyl analogue of zanamivir is claimed to protect mice against a lethal influenza infection following oral administration of the prodrug **47** whilst the bicyclic ether **48** is the first zanamivir derivative to demonstrate oral efficacy in the mouse model (127,128). The optimization of a screening lead into potent, cyclopentane-based inhibitors of neuraminidase using a combination of structure-based design and combinatorial chemistry has been described in detail (129).



The thioamide **49** was the most potent of a series of influenza fusion inhibitors whilst the tetramic acid **50** was the most potent of a new class of influenza endonuclease inhibitors, $IC_{50} = 6.6 \mu\text{M}$ (130,131).

Inhibitors of Human Rhinovirus (HRV) – The NDA for the HRV uncoating inhibitor pleconaril (Picovir™) was rejected by the FDA on May 31st with the agency requesting additional drug interactions studies.

Mechanism-based inhibitors of the HRV 3C cysteine protease have been probed using a combination of structure-based design principles and parallel synthesis methods in an effort to find less peptidic inhibitors (132). The chroman **51** emerged as an inhibitor of HRV-14 replication in cell culture, $EC_{50} = 160 \text{ nM}$; however, the serotype coverage of this compound was poor with much reduced potency against other subtypes, an observation rationalized in the context of structural data (132). The HRV 2A cysteine protease releases itself from the viral P2 polyprotein, cleaves the P2 in both a *cis* and *trans* fashion to release the 2B and 2C proteins and also proteolyzes the host cap binding complex in order to compromise host cell transcription. A series of *N*-phenylated pyrazole derivatives have been claimed as inhibitors of this essential enzyme with **52** an effective antiviral agent in cell culture, $EC_{50} = 1.8 \mu\text{M}$, $CC_{50} = 388 \mu\text{M}$ (133). The HRV RNA-dependent RNA polymerase from HRV-16, a potential drug discovery target, has been cloned, expressed and purified from *E. coli* and shown to be enzymatically active (134).



Inhibitors of Respiratory Syncytial Virus (RSV) – The role of RSV in morbidity and mortality continues to be a focus of research designed to provide a more accurate perspective of this virus as a mediator of significant disease burden. (115,116,135,136). The enhanced awareness of RSV has stimulated interest in this virus as a therapeutic target with the recent emergence of new structural classes of inhibitor. However, clinical proof-of-principle remains to be established for RSV antivirals. Viropharma has suspended development of VP-14637, an RSV fusion inhibitor under examination as a topically administered agent. The benzimidazole BMS-433771 (**53**) has been described as the first RSV inhibitor to demonstrate antiviral activity in animal models following oral administration (137,138). Mechanism of action studies indicate that **53** is an inhibitor of the fusion of viral and host cell membranes and targets the RSV F (fusion) protein (137). Analogues of **53** form the basis of proprietary claims (139,140) whilst Trimeris has disclosed a series of benzimidazole-based inhibitors of RSV fusion (141). Representative of this series is **54**, which is active in cell culture, $EC_{50} = 10 \text{ ng/mL}$.

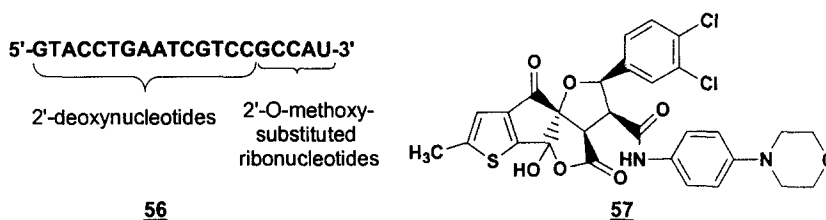
Coronaviruses – Coronaviruses are enveloped, single-strand, positive-sense RNA viruses most commonly associated with respiratory infections in man (142). Two coronaviruses are the underlying cause of approximately 30% of upper respiratory tract infections, usually mild to moderate in severity and generally recognized as the common cold, although in the immunocompromised population coronavirus infections can lead to pneumonia. However, in March, 2003 an outbreak of severe acute respiratory syndrome (SARS) emerged in Southeast Asia that very quickly spread to 27 countries, carried largely by air travelers (143-145). More than 6500 SARS infections were documented worldwide within the following 2 months that were associated with substantial morbidity, including fever, non-productive cough, malaise, chills, headache and dyspnea, and significant mortality, with over 460 deaths reported (146). Whilst SARS appears to have originated in Southern China in November, 2002, reports of major outbreaks in Hong Kong and Toronto, Canada in March 2003 brought the disease to world prominence (143-145). The attributes of modern technology, communication and international teamwork led to the rapid isolation and sequencing of the virus causing SARS, identified as a novel coronavirus with little similarity to previously known human coronaviruses (147-153). Final confirmation came with the demonstration that infection of monkeys with SARS produced a syndrome identical to that seen in man and that virus could subsequently recovered (154). These experiments were rapidly followed by the development of diagnostic assays based on a real-time quantitative PCR method and a TaqMan protocol (148, 155). Transmission of SARS appears to be via person-person contact with infected droplets rather than airborne and, possibly, a fecal-oral route. Inhibitors of coronaviruses are largely unknown although treatment with ribavirin (**11**) and oseltamivir have been examined in an empirical fashion (143, 156).

INHIBITORS OF WEST NILE VIRUS AND PAPILLOMA VIRUS

Inhibitors of West Nile Virus (WNV) – The geographical scope of the mosquito-borne West Nile virus outbreak in the US broadened considerably in the summer of 2003 extending to almost all states and causing over 2,500 cases of encephalitis and 230 deaths (157,158). The virus presents several conventional proteins as targets suitable for intervention including the NS3 protein, which expresses serine protease, helicase and nucleoside triphosphatase activities, and the NS5 RNA-dependent RNA polymerase (159). Moreover, screening using a cell culture assay provides a panoply of less well understood targets. However, few potent and selective WNV inhibitors have been described to date. Ribavirin (**11**) inhibits WNV RNA production in oligodendroglial cells, a human neural cell line, with an EC_{50} of $\sim 60 \mu\text{M}$ (160). The nucleoside analogue HMC-HO4 (**55**) interferes with the helicase activity of WNV NS3 with an IC_{50} of $30 \mu\text{M}$ and is a similarly potent antiviral in cell culture (161).

Inhibitors of Vaccinia Virus (Smallpox) – Smallpox has aroused considerable concern with discussion prominently focussed on its potential as an agent of bioterrorism (162-167). Many inhibitors of vaccinia virus replication interfere with host cell pathways and include **11** (inosine monophosphate dehydrogenase), the cyclopentenyl nucleoside analogue neplanocin A (S-adenosylhomocysteine hydrolase) and pyrazofurin (OMP decarboxylase) (168, 169). The cytidine and 5-F cytidine analogues of neplanocin A are equally potent inhibitors of several orthopox viruses, including smallpox (170). The nucleoside phosphonate cidofovir (HPMPC), licensed in 1996 for the treatment of HCMV retinitis in HIV patients, inhibits vaccinia virus *in vitro* ($EC_{50} = 18 \mu\text{g/mL}$) and protects mice from a lethal vaccinia infection following a single systemic (intraperitoneal) or intranasal (aerosolized) dose (171). 5-Iodo-2'-deoxyuridine, an inhibitor of vaccinia virus DNA synthesis *in vitro*, delays the effects of a lethal vaccinia infection, following subcutaneous dosing, by 15 days (172).

Inhibitors of Papilloma Virus – The contribution of HPV-16 and HPV-18 to the etiology of cervical cancer was discussed as part of a broader review of the role of viruses in the development of cancer (173). ORI-1001 (**56**), a 20-mer phosphorothioate hybrid oligonucleotide, is being developed as a topical agent for the treatment of genital warts (174). ORI-1001, which complements the E1 mRNA start codon of HPV and has demonstrated efficacy in two animal models, is currently undergoing P1/2 clinical evaluation. The fused tetracyclic amide **57** is claimed to inhibit the E2-dependent binding of papilloma virus E1 to DNA, a critical step in viral replication, with an IC_{50} of $<500 \text{ nM}$ (175). A vaccine derived from an HPV-16 virus-like particle, completely prevented the incidence of cervical neoplasias in HPV-16-naïve young women (176). This impressive result provides strong encouragement to the development of a vaccine with a spectrum that, in addition, encompasses the broader range of HPVs (18, 31, 33 and 35) responsible for the majority of cervical cancers (177). A combined, multivalent vaccine based on self-assembling virus-like particles and directed towards HPV-16 and HPV-18, recognized as MEDI-517, is entering P2 trials (178).



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