Antiviral Chemistry & Chemotherapy’s current antiviral agents FactFile (2nd edition): DNA viruses

Hugh J Field1* and Erik De Clercq2

1Department of Veterinary Medicine, University of Cambridge, Cambridge, UK
2Rega Institute for Medical Research, Leuven, Belgium

*Corresponding author: E-mail: AVCCtracker@intmedpress.com

Although most of the recent attempts to develop new antiviral agents have been focussed on RNA viruses (in particular, HIV and hepatitis C virus), a few new compounds are now awaiting their entry into the field of DNA viruses, particularly poxviruses, such as variola virus, because of the bioterrorist context, and herpesviruses, such as herpes simplex virus and cytomegalovirus, where the market scene has for many years been dominated by acyclovir, penciclovir and ganciclovir and their respective orally bioavailable prodrugs: valaciclovir, famciclovir and valganciclovir. Here, we review the current ‘state of the art’ with old compounds ready to rotate off and new compounds eagerly awaiting to appear on the continuously evolving scene of antiviral drug development.

Key to FactFile

Company/Institution

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Systematic/other names
Notes

Compound name
Proprietary name

Structure

Abbreviation list

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<td>Bicyclic nucleoside analogue</td>
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<td>varicella-zoster virus</td>
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### Acyclovir

**Zovirax®**

- **GlaxoSmithKline (GSK)**
- **References:** 1–3

9-(2-Hydroxyethoxymethyl)guanine, acycloguanosine, aciclovir.

**Principal target virus:** HSV-1, HSV-2, VZV.

**Other activities:** HCMV, EBV.

**Compound class:** Acyclic nucleoside analogue.

**Clinical stage:** Licensed. Patent expired.

The compound is used for the treatment of mucosal, cutaneous and systemic HSV-1 and HSV-2 infections (including HSV encephalitis and genital herpes), and in VZV infections (including herpes zoster ophthalmicus). It is also used for the prophylaxis of HSV infections (genital herpes) and VZV infections. Extremely safe compound may be used for long-term suppressive therapy. Rather poor oral availability; the oral prodrug is valaciclovir.

### Adefovir

**Gilead Sciences**

- **References:** 1, 4, 5

9-[(2-(Phosphonylmethoxy)ethyl)adenine, PMEA, GS 393.

**Principal target virus:** HBV.

**Other activities:** HIV-1, HIV-2, HCMV, HSV-1, HSV-2, FIV, SIV.

**Compound class:** NtRTI (acyclic nucleoside phosphonate).

Used as its oral prodrug, adefovir dipivoxil, in the treatment of chronic HBV infections.

### BAY 57-1293

**AiCuris**

- **References:** 6–8

N-[5-aminosulfonyl]-4-methyl-1,3-thiazol-2-yl]-N-methyl-[4-(2-pyridinyl)phenyl]acetamide.

**Principal target virus:** HSV-1, HSV-2.

**Mode of action:** Inhibits HSV helicase-primase complex.

**Compound class:** Thiazolylsulfonamide

Developed originally by Bayer Company. An extremely active and specific inhibitor of HSV-1 and HSV-2, which has been shown efficacious in a variety of infection models.

Resistance mutations found most frequently in helicase and occasionally in primase genes. Mechanism appears to differ slightly from BILS 22BS.
Brivudin is used for the treatment of VZV and HSV-1 infections. The compound has been not been licenced in UK, but has mainly been used in Germany and many other countries.

Cidofovir has a particularly long intracellular half-life and infrequent dosing is possible. The compound is used for the treatment of HCMV retinitis in AIDS patients. Topical gel used ‘off label’ in the treatment of acyclovir-resistant HSV and for treatment of HPV and poxvirus infections. Systemic (intravenous) and ‘off label’ in the treatment of HPV, adenovirus and poxvirus infections.

In contrast to other nucleoside analogues, in clinical trials clevudine demonstrated sustained anti-HBV activity as well as normalization of the alanine aminotransferase level as much as 6 months after the discontinuation of the drug. It has been approved for the treatment of chronic HBV infection in South Korea in November 2006 and is undergoing the Phase III trials in US and Europe.
Factfile: DNA viruses

**Famciclovir**

*Famvir®*

Diacycl 6-deoxy-9-(4-hydroxy-3-hydroxymethyl-but-1-yl)guanine, BRL 42810, FCV.

Principal target virus: HSV-1, HSV-2, VZV.

Other activities: EBV, HBV.

Mode of action: Phosphorylated by herpes thymidine kinase then inhibits herpes DNA polymerase.

Clinical stage: Licensed.

Marketed by Novartis. The compound is an oral prodrug of penciclovir; an acyclic guanosine derivative used for HSV-1, HSV-2 and VZV infections.

**Fialuridine**

1-2′-Deoxy-2′fluoro-1-β-arabinofuranosyl-5-iodouracil, FIAU, 2′-fluoro-5-iodo-ara-uracil.

Principal target virus: HBV.

Other activities: HSV-1, HSV-2.

Mode of action: Inhibits HBV DNA synthesis.

Compound class: Nucleoside analogue

Clinical stage: Withdrawn after Phase II trial.

Fialuridine results in severe liver toxicity.

**Fomivirsen**

*Vitravene®*

5′-d-[G′C′G′T′T′G′C′T′C′T′C′T′C′T′G′C′G′]-3′

sodium salt

=racemic phosphorothioate

Principal target virus: HCMV.

Mode of action: Antisense oligonucleotide.

Clinical stage: Licensed.

Compound is marketed by Ciba Vision. Phosphorothioate oligonucleotide licensed for intravitreal inoculation in patients with HCMV retinitis. The first antisense compound to receive marketing approval.
**Foscarnet**

**Trisodium carboxyphosphonate, trisodium phosphonoformate hexahydrate, foscarnet sodium, trisodium phosphonoformate, phosphonoformic acid, PFA.**

**Principal target virus:** HCMV.

**Other activities:** HSV-1, HSV-2, VZV, EBV, HHV-6, HIV.

**Mode of action:** Analogue of inorganic pyrophosphate. Targets herpesvirus DNA polymerase at the pyrophosphate-binding site.

**Compound class:** Pyrophosphate analogue.

**Clinical stage:** Licensed.

Foscarnet is often supplied as sodium salt. It is occasionally used for the treatment of HCMV retinitis, pneumonia, gastrointestinal and disseminated infections. Toxicity is well known, but it is among alternative compounds available to treat nucleoside-resistant HSV and VZV infections in immunocompromised patients.

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**Inhibitex**

**References:** 28–30

**3′-(2′-Deoxy-β-D-ribofuranosyl)-6-[4-n-pentylphenyl]-2,3-dihydrofurano[2,3-d]pyrimidin-2-one, 5′-valyl ester hydrochloride.**

**Principal target virus:** VZV.

**Mode of action:** Oral prodrug of nucleoside analogue CI1743.

**Compound class:** BCNA.

**Clinical stage:** Phase I.

FV-100 is a prodrug of CF-1743. Low-nanomolar activity is claimed suggesting it to be very much more potent than acyclovir against VZV.

The BCNAs owe at least part of their antiviral selectivity to a specific activation/phosphorylation by the VZV-encoded thymidine kinase and associated thymidylate kinase (dTMP-K) activity, while being not recognized by the closely related HSV-1-encoded TK/dTMP-K enzyme. In addition, the 5′-monophosphates of BCNAs are neither a substrate nor an inhibitor of the cellular dTMP-K and 5′-deoxynucleotidases.

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**Ganciclovir**

**References:** 1,31,32

**9′-(1,3-dihydroxy-2-propoxymethyl)guanine, 2′NDG, BIOLF-62, BW759U, GCV, DHPG.**

**Principal target virus:** CMV.

**Other activities:** HSV-1, HSV-2, VZV, EBV, HHV-6.

**Mode of action:** Nucleoside analogue phosphorylated by herpesvirus TK; inhibitor of herpesvirus DNA polymerase.

**Compound class:** Acyclic nucleoside analogue.

**Clinical stage:** Licensed.

Ganciclovir is used in therapy and prophylaxis of HCMV disease, including retinitis. Toxicity limits its use against HSV. The compound has poor oral bioavailability; therefore, an oral prodrug has been formulated: valganciclovir.
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**HDP-CDV**

Chimerix Inc

References: 33,34

1-O-hexadecylxoxypropyl-[(S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)cytosine

Principal target virus: CMV.

Other activities: Orthopoxviruses.

Mode of action: Releases cidofovir, which inhibits CMV DNA polymerase.

Compound class: Nucleoside analogue.

Alkoxylalkyl lipid prodrug of cidofovir.

**Idoxuridine**

*Herpid®, Stoxil®*

Bioglan Laboratories, Ferring Pharmaceuticals, GlaxoSmithKline (GSK)

References: 1,35,36

5-Iodo-2’-deoxyuridine, IDU, iodouracil deoxyribose, IdUrd, 5-IUdR.

Principal target virus: HSV-1.

Other activities: HSV-2, VZV.

Compound class: Nucleoside analogue. Phosphorylated by cellular and herpesvirus thymidine kinase with only modest selectivity for virus thymidine kinase. Inhibitor of herpes DNA polymerase.


Idoxuridine is too toxic for systemic administration. Regarded as a ‘first generation’ nucleoside of great historical importance, but now of limited use (mainly to topically treat HSV keratoconjunctivitis and ophthalmic zoster). The compound has been administered in DMSO for herpes zoster to improve skin penetration with questionable efficacy. Largely replaced by ‘second generation’ nucleosides.

**Imiquimod**

*Aldara®*

3M Pharmaceuticals

References: 37–39

1-(2-Methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine, S-26308, R-837.

Principal target virus: HPV.

Other activities: Skin cancers.

Compound class: Immunomodulator.

Clinical stage: Licensed.

Imiquimod is now owned and marketed in the USA by Graceway Pharmaceuticals and in Europe by Meda, AB (Sweden). The compound induces cytokines including interferons via a toll-like receptor 7 activation. Topical application is licensed for the treatment of genital and perianal warts caused by HPV and also for the skin cancer conditions superficial basal cell carcinoma and actinic keratosis.
GlaxoSmithKline (GSK), ViroPharma Inc.

References: 40–42

1-β-1(Ribosyl)-2-isopropylamino-5,6-dichlorobenzimidazole, 1263W94, benzimidavir.

Principal target virus: CMV.
Other activities: EBV.
Mode of action: A benzimidazole that is not phosphorylated, but strongly inhibits CMV UL97 protein kinase (which is involved in DNA synthesis and nucleocapsid egress). Does not inhibit DNA polymerase or DNA synthesis directly. Appears to inhibit CMV replication by effecting DNA maturation and processing.
Clinical stage: Phase II/III.

A potent (submicromolar) inhibitor of CMV replication. Used for prevention of CMV disease in transplant recipients. A Phase II study in stem cell transplant patients demonstrated that maribavir significantly reduced CMV reactivation. Resistance mutations map to CMV UL97 and UL27 genes.

Beecham Research Laboratories Ltd.

References: 43–45

9-(4-Hydroxy-3-hydroxymethyl-but-1-yl)guanine, PCV, BRL 39123.

Principal target virus: HSV-1, HSV-2.
Other activities: VZV, EBV, HBV.
Mode of action: Similar to acyclovir, but higher affinity for HSV thymidine kinase and lower affinity for HSV DNA polymerase.
Compound class: Acyclic nucleoside analogue.
Clinical stage: Licensed.

Marketed by Novartis. Similar to acyclovir with similar resistance profile, but appears to have longer intracellular half-life than acyclovir. A 1% cream (Vectavit®) is licensed for topical therapy for cutaneous HSV-1 infections (herpes labialis). The oral bioavailability is very low and the prodrug form, famciclovir, is among the first of the successful antiviral prodrugs. As famciclovir, it is used for VZV infections.

Procept

References: 46–48

Naphthalene sulfonate polymer.

Principal target virus: HIV-1, HIV-2.
Other activities: HSV-1, HSV-2.
Compound class: Sulfonated polyamide.
Clinical stage: Phase II/III.

Microbicide (virucide) vaginal gel.
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**Sorivudine**
*Usevir®, Brovavir®*

Yamasa Corporation, Bristol-Myers Squibb
References: 49–51

1-β-D-Arabinofuranosyl-(E)-5-(2-bromovinyl)uracil, BVaraU, YN-72.

**Principal target virus:** VZV.
**Other activities:** HSV-1.
**Mode of action:** Phosphorylated by VZV thymidine kinase inhibits VZV DNA polymerase.
**Compound class:** Nucleoside analogue.
**Clinical stage:** Withdrawn from Phase III clinical trials.

License withdrawn following unexpected toxic interaction with 5-fluorouracil resulting from the formation of the metabolite bromovinyluracil, which inhibits dihydrothymine dehydrogenase (dihydrothymine dehydrogenase normally degrades 5-fluorouracil).

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**ST-246**

SIGA Technologies
References: 52–54

{4-Trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide}.

**Principal target virus:** Smallpox virus.
**Other activities:** Monkeypox, camelpox, vaccinia, ectromelia and many other Orthopoxviridae.
**Mode of action:** Small molecule inhibitor of envelopment, maturation and virion release.
**Clinical stage:** US Food and Drug Administration registration currently in process.

Orally bioavailable. Highly efficacious in animal infection models. Targets cowpox V061 and vaccinia F13L gene products. These are membrane proteins required for release of infectious virions.

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**Telbivudine**
*Tyzeka™*

Idenix/Novartis
References: 1,55,56

1-((2S,4R,5S)-4-hydroxy-5-hydroxymethyltetrahydrofurano-2-yl)-5-methyl-1H-pyrimidine-2,4-dione 1-(2-deoxy-β-D-ribofuranosyl)-5-methyluracil, β-D-thymidine, β-D-2′-deoxythymidine, 1-dT.

**Principal target virus:** HBV.
**Other activities:** HSV-1, HSV-2.
**Compound class:** β-D-Nucleoside analogue.
**Clinical stage:** Licensed.

The compound is used for the treatment of chronic hepatitis B infections.
GlaxoSmithKline (GSK)
References: 1, 57, 58
5-Trifluoromethyl-2′-deoxyuridine, TFT, trifluorothymidine, F3dThd.

Principal target virus: HSV-1.
Other activities: HSV-2, VZV.
Mode of action: 'First generation' nucleoside analogue; phosphorylated by herpesvirus thymidine kinase, but without selectivity and inhibits herpes DNA polymerase.
Compound class: Deoxythymidine analogue
Clinical stage: Licensed, patent expired.

One of the original antiviral agents with clinical utility first described in 1964. Extremely toxic and may only be used topically. However, it is very soluble and has a use in ophthalmic herpes infections. The ophthalmic solution is sold under the brand name of Viroptic®, which is distributed by Monarch Pharmaceuticals.

GlaxoSmithKline (GSK)
References: 59–61
l-Valine ester of 9-(2-hydroxyethoxymethyl)guanine, l-valyl ester of acyclovir, BW256U87, VACV.

Principal target virus: HSV-1, HSV-2, VZV.
Other activities: HCMV, EBV.
Mode of action: Oral prodrug of acyclovir.
Clinical stage: Licensed.

The most successful of several compounds formulated to overcome the poor oral bioavailability of acyclovir. After oral administration is cleaved in gut and liver to yield acyclovir and the natural amino acid l-valine. Used for the treatment of mucosal, cutaneous and systemic HSV-1 and HSV-2 infections and VZV. It is also used for the long-term suppression of recurrent HSV infections.

Roche
References: 33, 62, 63
l-valine ester of 9-(1,3-dihydroxy-2-propoxymethyl)guanine.

Principal target virus: CMV.
Mode of action: Polymerase inhibitor.
Compound class: Nucleoside analogue.
Clinical stage: Licensed.

Valganciclovir is a prodrug of ganciclovir. The compound is rapidly converted to ganciclovir – by intestinal and hepatic esterases – increasing its oral bioavailability to approximately 60%.
**Valomaciclovir stearate**

Medivir, Epiphany Bioscience

References: 64–66


Principal target virus: VZV.
Other activities: HHV-6, HSV-1, HSV-2, EBV, HIV-1, HIV-2.
Mode of action: Polymerase inhibitor.
Compound class: Nucleoside analogue.
Clinical stage: Phase IIb.

Valomaciclovir stearate is a prodrug of H2G; it is rapidly converted to H2G.

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**Vidarabine**

Vira-A®

Parke-Davis

References: 67,68

9-β-D-Arabinofuranosyladenine monohydrate, Ara-A, adenine arabinoside.

Principal target virus: HSV-1, HSV-2.
Other activities: VZV.
Compound class: Adenosine analogue.
Clinical stage: No longer used.

An early nucleoside analogue and the first to be considered safe for systemic administration. Vidarabine was the first antiviral drug used in the therapy of herpes encephalitis until it was superseded by acyclovir. No longer commercially available.
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Disclosure statement

EDC is coinventor of adeovir, brivudin, cidofovir, FV-100 and valaciclovir. HJF has a current research collaboration with AiCuris, Germany.

Disclaimer

The authors declare that the second edition of the current antiviral agent FactFile is accurate and up-to-date to the best of their knowledge. The authors are happy to receive any comments or any information about new compounds for inclusion in future editions.

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