Broad spectrum antiviral nucleosides—Our best hope for the future

Katherine L. Seley-Radtke*, Joy E. Thames, and Charles D. Waters III
Department of Chemistry & Biochemistry, University of Maryland, Baltimore County, Baltimore, MD, United States
*Corresponding author: e-mail address: kseley@umbc.edu

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1. Introduction

Nucleosides have long served as the primary scaffold for treating many diseases, including those caused by cancers, parasites, bacteria, but most notably, against many different families of viruses.[1–4] Because the naturally occurring nucleosides are the building blocks found in our DNA and RNA, and also play critical roles in numerous biological processes, even small modifications to the nucleoside scaffold can have profound therapeutic effects. This observation provides impetus for designing modified nucleoside analogues. Modifications to their structure can be designed in and/or refined, based on the key interactions identified in the binding site of target enzymes. As the field has progressed and new information has become available about nucleoside structure, enzyme recognition, and biological activity, unique and more complex modifications have been pursued, including multiple modifications on the same scaffold.[2–4] As a result of these modifications,

there are currently more than 30 nucleoside/tide analogues on the market approved for use in treating viruses, cancers, parasites, as well as bacterial and fungal infections, with many more in preclinical and clinical trials.[1–4]

In that regard, we now find ourselves in the middle of a global pandemic caused by the deadly coronavirus, SARS-CoV-2, the zoonotic virus responsible for COVID-19. Never has it been more urgent for researchers to revisit old nucleosides, as well as to explore new and more novel possibilities.[5–7] In addition, given the strong likelihood that this will not be the last pandemic we face, given the number of zoonotic and other diseases circulating globally, it is critical that we find new ways to target future outbreaks.[8] As a result, the current focus for many researchers has turned to the development of therapeutics that have the potential for serving as broad-spectrum inhibitors that can target numerous viruses, both within a particular family, as well as to span across multiple viral families so that we can build an arsenal in preparation for the next outbreak.[9–12] This is not as out of reach as it may seem. As detailed below, many nucleosides have been shown to inhibit multiple viruses due to the conserved nature of many viral enzyme binding sites. Thus, it is somewhat surprising that up until very recently, many researchers focused more on "one bug one drug", rather than trying to target multiple viruses given those similarities.[8] This approach is now changing due to the realization that we need to be proactive rather than reactive to combat emerging and reemerging infectious diseases.[8]

In general, most nucleoside drugs are direct acting antivirals that target the viral polymerases.[1–4,13] Since they resemble the naturally occurring nucleosides, they are taken up by cells, then sequentially phosphorylated by cellular and/or viral kinases to ultimately form the triphosphate, which is typically the active form of the drug.[1–3,13] The triphosphate is recognized by the polymerase and subsequently incorporated in the growing nucleic acid chain, but through one of several different possible mechanisms, the drug acts as a chain terminator, thereby stopping the virus from replicating.[1,13,14] This occurs typically because the nucleoside lacks the necessary 3'-hydroxyl group needed for attachment of the next incoming nucleotide (obligate chain terminator), or if it has a 3'-hydroxyl but also has other substituents that can cause steric issues, the chain either stops immediately (pseudo-obligate chain terminator) or is able to add some additional nucleotides, albeit at an increasingly slower rate until ultimately no more can be added (delayed chain terminator).[1,13,14] There are several other mechanisms that have seen some promise, and those will be discussed further on in this chapter.

2. Early antiviral nucleosides—Obligate chain terminators

The earliest antiviral nucleoside was idoxuridine (Fig. 1), which was approved by the FDA in 1962.[15] It was initially developed as an anticancer drug, but was later approved for use against the ocular form of herpes simplex virus (HSV), HSV keratitis.[15] It works by mimicking thymidine, and once incorporated into viral DNA, leads to inhibition of thymidylate phosphorylase and the polymerase.[15–17] It is not used much anymore, and has been replaced by another nucleoside analogue, trifluridine (Fig. 1).[18] Somewhat related in terms of structure, Brivudine (Fig. 1), another pyrimidine substitute analogue, is widely used in many European countries, but not until recently in the US, for treatment of varicella zoster virus (VZV), which causes herpes zoster, better known as shingles.[14,19,20] It has also been used to treat HSV-1, but not HSV-2.[19] Another older nucleoside that is now being investigated against SARS-CoV-2 is 6-azauridine (Fig. 1). This triazole analogue has shown broad-spectrum activity against a number of different coronaviruses, flaviviruses, including West Nile virus, thus it is not surprising it is now being looked at again.[21–23]

Probably the most well-known of the early FDA-approved antiviral nucleosides is Zidovudine (AZT) shown in Fig. 2, which was the first nucleoside to be widely used to treat HIV and AIDS.[2,16,24–26] Shortly thereafter, Zalcitibine (ddC), Didanosine (ddI) and stavudine (d4T) were developed (Fig. 2), however ddI and ddC were plagued with various toxicity issues and not used extensively after initial excitement.[26–28] All of these are considered obligate chain terminators and work by inhibiting the HIV reverse transcriptase (RT).[1,13]

Other early nucleoside drugs were the arabinose nucleosides vidarabine (Ara–A) and cytarabine (Ara–C) shown in Fig. 3, both of which are
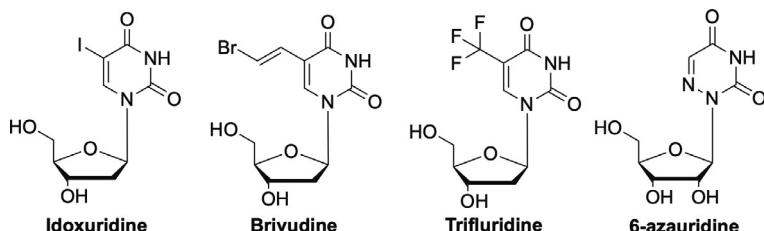

Fig. 1 Early modified nucleoside analogues idoxuridine, brivudine, trifluridine, and 6-azauridine.
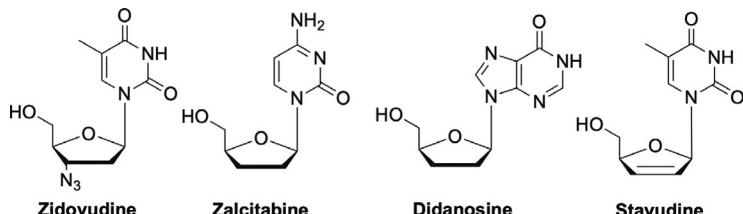
Fig. 2 Other early modified nucleoside analogues zidovudine, zalcitabine, didanosine, and stavudine.
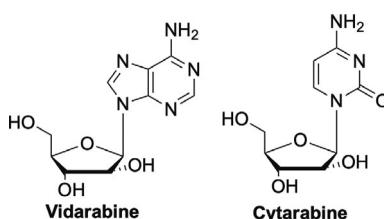
Fig. 3 Vidarabine and cytarabine, competitive inhibitors of DNA polymerases.

competitive inhibitors of DNA polymerases.[1,13] They are incorporated but then due to the steric configuration of the 2'-hydroxyl on the sugar moiety cause chain termination. Ara–A was used clinically for herpes, but both Ara–A and Ara–C were also shown to inhibit vaccinia (VV) and VZV viruses.[15,29] Ara–C went on to be used primarily as an anticancer drug, due to its toxicity.[17,30]

3. Acyclic obligate chain terminator nucleosides

As an extreme approach to obligate chain termination, Professor Antonín Holý developed the acyclic nucleosides and nucleoside phosphonates which lack not only the hydroxyls on the 2'- and 3'-carbons, but also the carbons themselves.[16,31,32] The acyclic nucleosides that are FDA-approved include acyclovir, penciclovir, and ganciclovir, while the phosphonates include adefovir, cidofovir, and tenofovir.[2,16,31] In addition, due to issues with poor oral bioavailability, various prodrugs have been subsequently approved including valacyclovir, valganciclovir, famciclovir, tenofovir disoproxil fumarate (TDF), adefovir dipivoxil, and most recently, tenofovir alafenamide (TAF).[1,2,16] Each will be discussed in more detail below but each work by the same mechanisms – competitive inhibition of the viral polymerases.[16]

Acyclovir and penciclovir—the carbocyclic version of acyclovir—and their respective prodrugs valacyclovir and famciclovir (Fig. 4), are used primarily to treat various forms of HSV, while ganciclovir and its prodrug valganciclovir are approved for use against human cytomegalovirus (HCMV).[2,16,33–38] Interestingly, HP-083, the fleximer version of acyclovir, and the related fleximer HP-100 (Fig. 5) as well as their prodrugs that were developed in our laboratories some years ago, are not active against HSV or HCMV, but rather are potent inhibitors of Ebola (EBOV), Marburg and Sudan viruses of the filovirus class, as well as SARS-CoV-1, MERS and human coronaviruses, in addition to a number of flaviviruses, including dengue (DENV), yellow fever (YFV) and tickborne encephalitis virus (TBEV).[39–41] Notably, acyclovir is not active against any of those at concentrations up to 1000 μM.[40] Not surprisingly, these compounds have attracted widespread attention for development as potential broad-spectrum inhibitors and are also currently being investigated for activity against SARS-CoV-2.
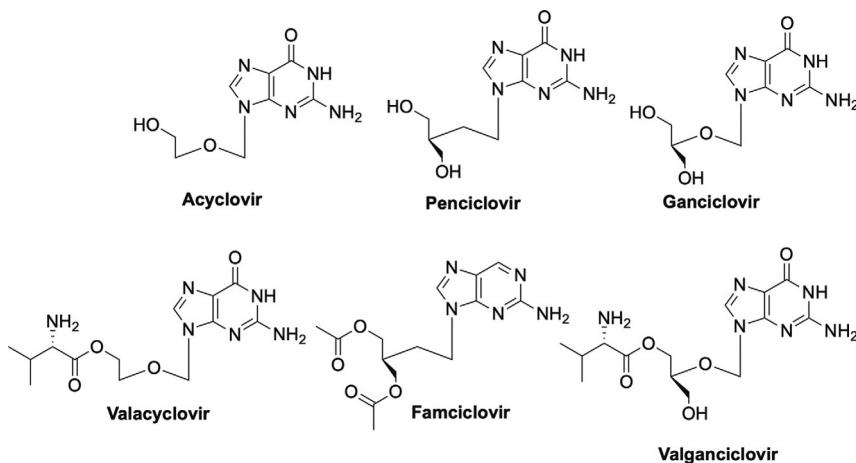
Fig. 4 Approved acyclic nucleosides acyclovir, penciclovir, ganciclovir and their prodrugs valacyclovir, famciclovir, valganciclovir.
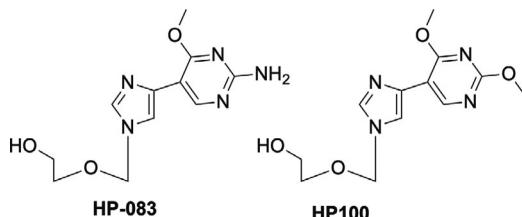
Fig. 5 Fleximer analogues of acyclovir, HP-083 and HP-100.

In terms of the acyclic phosphonates, cidofovir (Fig. 6) has the broadest spectrum of antiviral activity, with inhibition being noted against both DNA and RNA viruses and numerous different families of viruses.[12,32,42–47] Activity exhibited against DNA viruses by cidofovir includes HBV, papillomavirus, polyomavirus, adenovirus, numerous herpes viruses including HSV, HCMV, Epstein Barr virus (EBV) and VZV.[12,32,42–47] In addition, cidofovir has been explored extensively against various poxviruses, such as VV, molluscum contagiosum virus (MCV), variola virus, cowpox, monkeypox, and camelpox.[42,44,45,47] Related to this, brincidofovir (Fig. 6), the lipid prodrug form of cidofovir, was recently stockpiled by the U.S. government for potential outbreaks or terrorist attacks of small-pox.[47–50] As mentioned earlier, not just limited to DNA viruses, cidofovir also works against retroviruses such as HIV, and the corresponding feline and simian forms of HIV, FIV and SIV respectively.[12] As a result, cidofovir and brincidofovir should certainly be revisited for potential use as broad-spectrum antiviral agents.

While cidofovir certainly has the widest range of activities, one of the most important nucleosides for the antiviral field is tenofovir (Fig. 7).[1,2] Like cidofovir, tenofovir is an acyclic phosphonate and lacks the 3'-OH, thus works as an obligate chain terminator.[1,2] Tenofovir was initially
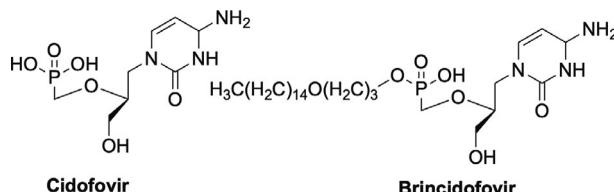

Fig. 6 Phosphonate nucleoside cidofovir and its lipid prodrug brincidofovir.
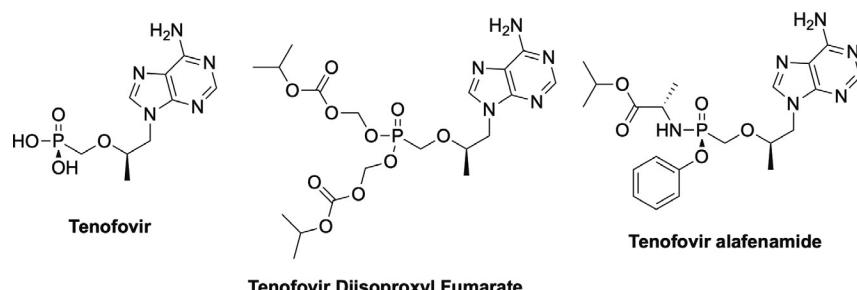

Fig. 7 Phosphonate nucleoside tenofovir and its two prodrug forms, tenofovir disoproxil fumarate and tenofovir alafenamide.

approved as a treatment for HIV, but was later also approved for treatment of HBV, and represents the nucleoside backbone in nearly every combination drug cocktail that has been developed in the past two decades.[27,51–53] Due to issues with bioavailability, tenofovir was developed as a prodrug, with the first form being tenofovir disoproxil fumarate (TDF, Fig. 7).[1,27,53] Recently however, a newer form was introduced, which possesses a McGuigan ProTide moiety, tenofovir alafenamide (TAF, Fig. 7).[1,2,7,54] This change in prodrug drastically lowered the required dose from 300 mgs/kg to 25 mgs//kg with far less side effects due to more rapid absorption into cells, which lessens the amount of phosphonate in the plasma.[55]

Perhaps it is important at this point, to deviate and explain a bit about the impact that the discovery and development of the McGuigan ProTides has had on medicinal chemistry, particularly on nucleoside drugs.[56–59] There are two inherent problems with nucleoside drugs—one, delivery across the cell membrane and two, phosphorylation once inside the cell.[56–59] In terms of delivery, nucleosides as a class are typically polar, so it leads to issues with poor permeability.[56–59] By masking the polar hydroxyl group at the 5'-position with a non-polar moiety, it allows the drug to cross more readily.[56–59] As mentioned previously, typically the active form of the nucleoside is the triphosphate, however you cannot directly administer the triphosphate due to the extreme polarity.[56–59] Moreover, the first phosphorylation step is typically rate limiting due to the acute selectivity of most kinases.[56,58,59] Once the first phosphorylation has occurred, the second and third tend to be more facile, although not always. As a solution to both problems, a number of years ago the late Professor Chris McGuigan and his team developed what they dubbed the McGuigan ProTide (Fig. 8).[56–59]

As shown in Fig. 8, there are 3 basic components to the ProTide—the ester, the aromatic moiety, and the amino acid. The ProTide renders the nucleoside less polar, thus it is able to cross the cell membrane.[56–59]

McGuigan ProTide scaffold
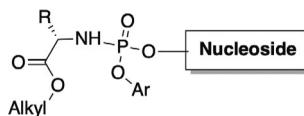
R = amino acid residue
Ar can be substituted
Alkyl can be straight, branched or cyclic

Fig. 8 General structure of the McGuigan ProTide.
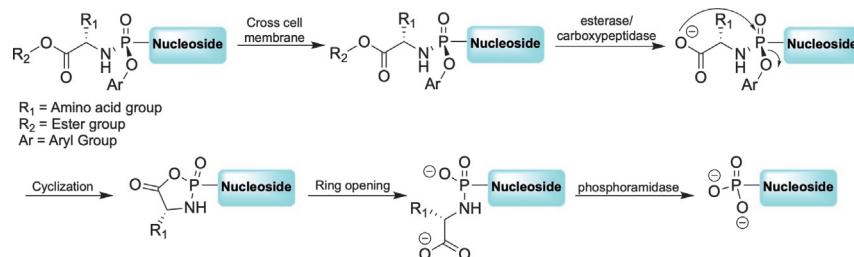
Fig. 9 Mechanism of McGuigan ProTide metabolism.
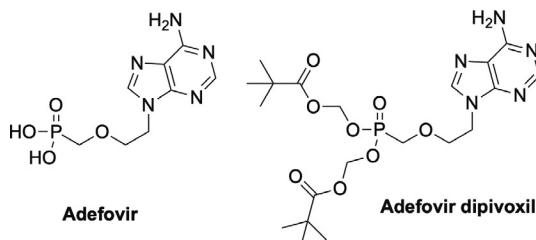
Fig. 10 Other approved phosphonate nucleosides, adefovir and its prodrug adefovir dipivoxil.

Once inside, each piece of the ProTide is sequentially removed by two cellular enzymes as well as spontaneous mechanistic steps (Fig. 9). This in turn, reveals the monophosphate form of the nucleoside, thus bypassing that first phosphorylation step and overcoming the rate limiting barrier to activation for the drug.[56–59] After extensive structure activity relationship (SAR) studies on the various components of this clever system, many nucleoside analogues are now being pursued and even marketed, for example, the aforementioned TAF as the McGuigan ProTide form.[55,56]

Prior to the development of TDF and TAF, the other FDA approved nucleoside phosphonate was adefovir and its prodrug adefovir dipivoxil (Fig. 10), which are used to treat chronic HBV.[60–62] Like tenofovir, adefovir works by competitive inhibition of the viral reverse transcriptase and subsequent chain termination.[1,16] In general, these inhibitors are known as nucleoside reverse transcriptase inhibitors or NRTIs.[1,16,63]

4. Other obligate chain terminator antivirals

Returning to antivirals possessing a cyclic sugar moiety, other important antiviral NRTIs of note that target HBV are entecavir, and three L-nucleoside analogues—telbivudine, lamivudine (3TC), and its closely
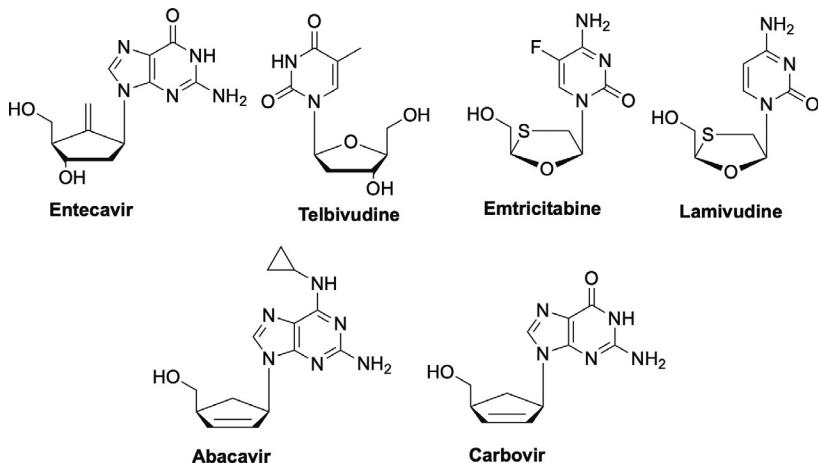
Fig. 11 Nucleoside reverse transcriptase inhibitors entecavir, telbuvidine, emtricitabine, and lamuvidine (L-nucleosides), as well as abacavir and carbovir.

related analogue emtricitabine (FTC) (Fig. 11).[1,2,43,64,65] Interestingly, entecavir introduced the idea of rigidifying the sugar of the nucleoside with the exocyclic double bond, something that still remains quite novel in terms of scaffold modifications.[2] Also of note, the discovery that L–nucleosides could be active was an important finding, as many believed that enzymes would not recognize the unnatural form of the drug.[2,62,66–73] Two other FDA–approved NRTIs, abacavir and carbovir (Fig. 11), are carbocyclic nucleosides used to treat HIV.[24,74–76] Notably, abacavir is one of the few drugs available for use in children with HIV.[76]

5. Antivirals that act by lethal mutagenesis

All of the nucleosides discussed to this point have been NRTIs or polymerase inhibitors that act by chain termination, however another mechanism of action has been explored that doesn't involve chain termination. Lethal mutagenesis is a type of antiviral therapy that essentially increases the viral mutation rate by incorporating nucleosides that act as mutagens, to the point of destroying the viability of the virus.[10,77]

One approved nucleoside that has been shown to work by this mechanism is ribavirin, although ribavirin has also been shown to work by other mechanisms and in general, its mechanism of action is not well understood.[6] Ribavirin (Fig. 12) was originally approved for the treatment of severe respiratory syncytial virus (RSV) infection, it has also been used for treatment of
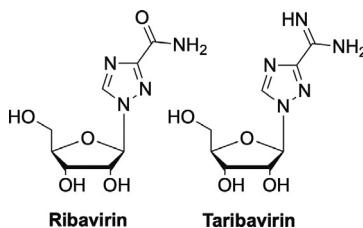
Fig. 12 Two nucleosides that work by lethal mutagenesis ribavirin and taribavirin.
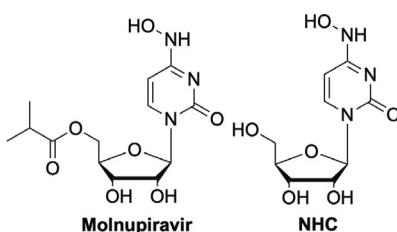
Fig. 13 NHC and its prodrug molnupiravir, another nucleoside that works by lethal mutagenesis.

Lassa fever virus infection, as well as influenza A and B.[78–80] Most recently it has been approved for use against HBV and HCV but has been tested against many other viruses including coronaviruses, however without much success in the latter case.[6,81,82] More recently a prodrug of ribavirin, taribavirin (also known as viramidine) has entered Phase III human trials (Fig. 12). Notably, taribavirin has been reported to target the liver better than ribavirin, which is important because as previously mentioned, both ribavirin and taribavirin have been shown to be highly effective against HCV and HBV.[83–86]

Another nucleoside analogue that also works by lethal mutagenesis that has recently gained significant attention against SARS-CoV-2 is molnupiravir (Fig. 13).[10] Molnupiravir is a prodrug of N-hydroxycytidine (NHC, Fig. 13) and is reported to increase mutations of G to A and C to U in replicating coronaviruses.[77] So far it is showing great promise and is currently in Phase II/III clinical trials. Interestingly, the U.S. Department of Health and Human Services has committed to purchasing $1.2B worth of molnupiravir should it ultimately be approved by the FDA.[87]

Similarly, the heterocyclic base favipiravir (Fig. 14) also works by lethal mutagenesis. Although favipiravir is administered as the base, it is subsequently converted to the nucleoside following ribosylation, and then undergoes normal phosphorylation by the various kinases, thus providing the triphosphate active form.[6,88,89]
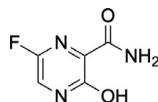
Favipiravir

Fig. 14 Favipiravir.

6. Newer antiviral therapeutics—And new mechanisms of action

As more and more information has become known about emerging and reemerging viruses due to increased access to crystal structures and various enzymes involved in viral replication, multiple modifications to the nucleoside scaffold have become quite standard.[2,3] Examples of these complex nucleoside scaffolds include such drugs such as sofosbuvir and the closely related uprifosbuvir, remdesivir and the parent nucleoside GS-441524, EFdA (also known as Islatravir), NITD008, AT-527, and galidesivir, an immunocillin analogue.[1–3]

Sofosbuvir is a nucleoside analogue that features an alanine McGuigan ProTide moiety as well as a di-substitution at the C-2 position (Fig. 15).[90–92] Sofosbuvir is used to treat HCV, and what makes sofosbuvir stand out among nucleoside analogues is that it is not just a treatment, but rather, a cure.[91,92] For example, HIV patients must take their drug cocktails for their lifetime in order to maintain undetectable levels of viral load, but Sofosbuvir clears the virus completely in 8-12 weeks.[91] This was a remarkable breakthrough in antiviral therapy and has set a new standard for researchers to achieve that same effect in other viruses with their nucleoside analogues. Sofosbuvir, and the closely related uprifosbuvir (Fig. 15), are both delayed chain terminators.[1,93] Uprifosbuvir differs from Sofosbuvir at the C-2 position, featuring a chlorine atom instead of the fluorine, as well as

Sofosbuvir   **Uprifosbuvir**
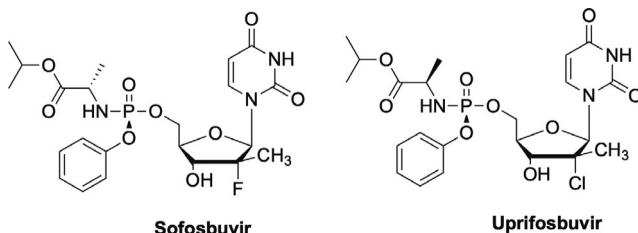
Fig. 15 Delayed chain terminators, sofosbuvir and uprifosbuvir.

the configuration of the methyl group on the ProTide moiety.[93,94] Both have shown broad-spectrum activity against a number of viruses including ZIKV, YFV and chikungunya viruses, as well as more recently, SARS-CoV-2. Uprifosbuvir is currently in Phase III clinical trials.[90,93–96]

Similarly, remdesivir (RDV, Fig. 16), currently the only drug approved for emergency use against SARS-CoV-2 is also a broad-spectrum inhibitor and also contains a McGuigan ProTide moiety like sofosbuvir, uprifosbuvir and TAF, however RDV's ester moiety differs than TAF and sofosbuvir's.[3,97] RDV was first under development for Ebola, including five compassionate cases, but was later pushed aside due to the development of two monoclonal antibodies that showed significant activity compared to RDV.[6,98,99] RDV is not ideal as it has to be administered in a hospital setting, which limits its widespread usage and effectiveness. RDV was later shown to have activity against SARS-1 and MERS, thus it wasn't surprising that it was immediately investigated for SARS-2.[6,98]

Interestingly, the parent nucleoside of remdesivir, GS-441524 (Fig. 16), has been used for some time for coronaviruses in cats.[98] Current efforts involve development a nasal spray as well as an oral form of RDV, both of which would have a major impact on making this drug more accessible globally.[6,98,100] Regardless, RDV has shown significant broad-spectrum activity against a number of other viruses, therefore certainly has promise for future use in fighting other emerging RNA viruses.[9] Remdesivir is also a delayed chain terminator that appears to involve incorporation, followed by pausing and then restarting.[6,9,98] More recently, RDV has been shown to also work by a second mechanism, as a translocation RT inhibitor, which is currently being studied more in depth.[101]

A new nucleoside analogue that has recently emerged on the scene due to its excellent activity against SARS-CoV-2 is AT-527 (Fig. 17).[102] AT-527 is a guanosine analogue being developed by Atea Pharmaceuticals and was recently licensed by Merck to take through clinical trials.[103] AT-527 has
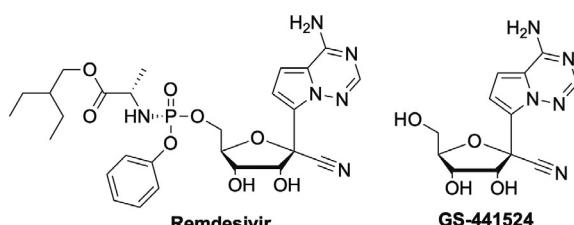
Fig. 16 Delayed chain terminators, GS-441524 and its prodrug Remdesivir.
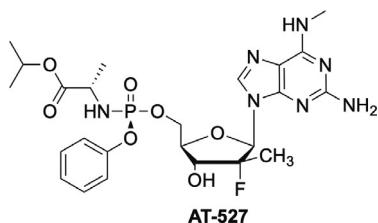
Fig. 17 Double prodrug AT-527.

the C-2' modification found in sofosbuvir as well as the same McGuigan alanine moiety, but is a double prodrug due to the N-methyl group on the heterocyclic base.[102,104,105]

AT-527 has shown significant promise and has numerous advantages over RDV, including being orally bioavailable and safe, thus representing a direct acting antiviral suitable for easy and early administration, as well as for pre- or post-exposure prophylaxis.[102–105] Additionally, AT-527 has exhibited no inhibition of human polymerases, no mitochondrial toxicity in vivo, no toxicity, cardiotoxicity, or neurological effects in rats or monkeys at doses up to 1000 mg/kg, a 10 fold safety profile over RDV for the 550 mg BID dose in humans, a 7 fold higher concentrations in human nasal and lung cells at 72 h, and a much longer half-life.[102–105]

Like other nucleoside analogues, AT-527 contains a McGuigan ProTide moiety, which delivers the monophosphate.[102,104,105] In contrast to other ProTides such as RDV, sofosbuvir and tenofovir, AT-527 exhibits much greater concentrations of the triphosphate, the active form of the drug, in the lungs.[102,105] Most notably however, AT-527 inhibits SARS-CoV-2 in a very unique manner—one molecule of AT-527 is incorporated into the growing strand, while another gets stuck in the active site, both of which lead to chain termination, while a third molecule inhibits the Nidovirus RdRp-Associated Nucleotidyltransferase (NiRAN) binding site, which is adjacent to the RdRp binding site.[102] This unique dual mechanism of action is highly synergistic and is likely what is responsible for its superior potency.[102]

Another nucleoside that is not as well-known as sofosbuvir or RDV, is Islatravir or EFdA (Fig. 18). EFdA is an adenosine analogue that has also been shown to work by multiple mechanisms.[106,107] EFdA has shown remarkable activity against HIV, including resistant strains.[106–108] What is even more remarkable, is that unlike other nucleoside analogues that typically work by a single mechanism, EFdA has been shown to work by a number of mechanisms. Similar to RDV, EFdA can function as a delayed chain
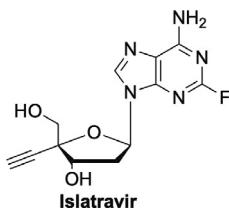
Fig. 18 Adenosine analogue islatravir.
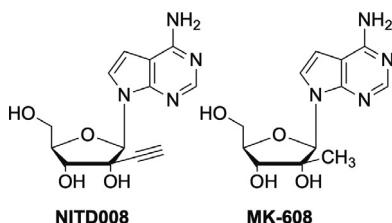
Fig. 19 Modified C2′ nucleosides NITD008 and MK-608.

terminator due to the presence of the 4'-triple bond, which causes steric issues.[106,107] Also like RDV, EFdA can act as a translocation RT inhibitor that essentially slows DNA synthesis, thereby acting as a de facto immediate, or pseudo obligate chain terminator.[106,107] Finally, EFdA-MP can also be misincorporated by RT, leading to mismatched primers that are extremely hard to extend, and are protected from excision by proofreading enzymes.[106,107] This multifaceted mechanism of action is likely to be important for combating the development of viral resistance, something that has plagued medicinal chemists for decades.[106,107]

Similar to EFdA, another nucleoside analogue that features a triple bond, albeit at the C2′-position, that initially showed promise is NITD008 (Fig. 19).[109–112] NITD008 and the closely related MK-608 (Fig. 19), have both exhibit broad-spectrum inhibition against a number of viruses.[109–115] NITD008 has shown potent activity against flaviviruses such as HCV, DENV, TBEV, ZIKV, West Nile virus, and YFV, as well as more exotic viruses such as Powassan virus, Kyasanur forest disease, which is a tickborne virus, and Omsk hemorrhagic fever virus.[110–115] In contrast, MK-608 appears to have only shown activity against DENV, TBEV, ZIKV and poliovirus. Both are delayed chain terminators, both are 7-deaza analogues and both are di-substituted at the C-2'-position, however NITD008 possesses the aforementioned triple bond in the "up" configuration, while MK-608 has a methyl group.[3] Unfortunately neither have been pursued
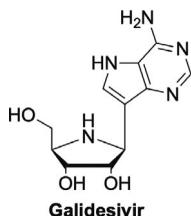
Fig. 20 Galidesivir, one of the immucillin nucleosides.

extensively after NITD008 proved too toxic in preclinical trials and MK-608 failed in early human clinical trials.[116,117]

Finally, this brings us to galidesivir, also known as Immucillin A or BX-4430. Galidesivir is interesting structurally due to the presence of a nitrogen in the sugar ring, rather than the typical furanose oxygen found in most nucleoside analogues, or the methylene group found in carbocyclic nucleosides.[2] This class of nucleosides are known as immucillins and they have shown potent activity against a number of viruses. Galidesivir is an adenosine analogue that has been investigated for use against numerous viruses from various different families.[118–122] It has shown activity against filoviruses including Ebola and Marburg, against flaviviruses such as YFV and ZIKV, as well as broad spectrum activity against various negative- and positive-sense RNA viruses, including coronaviruses and arenaviruses.[11] Because of this broad-spectrum activity, it is now being investigated against SARS-CoV-2, and like many of the nucleosides revisited herein, is an excellent example of how nucleosides can be effective against many viruses[123] (Fig. 20).

In summary, while this review is by no means comprehensive, rest assured, there are many other nucleoside analogues out there that are being investigated not only as treatments against one virus, but now against multiple viruses. The stark realization brought about by the SARS-CoV-2 pandemic and the over 4.55 M deaths as of September 2021 shows us just how unprepared we were to fight emerging viruses.[124] It has never been clear that we must be able to develop and stockpile small molecule broad-spectrum inhibitors to fight emerging and reemerging infectious diseases, particularly zoonotic ones given the vast number of viruses circulating in animals. In that regard, nucleoside inhibitors will indoubtedly remain our best hope just as they have for decades.

Acknowledgments

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