Review Article

The evolution of nucleoside analogue antivirals: A review for chemists and non-chemists. Part 1: Early structural modifications to the nucleoside scaffold

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ABSTRACT

This is the first of two invited articles reviewing the development of nucleoside-analogue antiviral drugs, written for a target audience of virologists and other non-chemists, as well as chemists who may not be familiar with the field. Rather than providing a simple chronological account, we have examined and attempted to explain the thought processes, advances in synthetic chemistry and lessons learned from antiviral testing that led to a few molecules being moved forward to eventual approval for human therapies, while others were discarded. The present paper focuses on early, relatively simplistic changes made to the nucleoside scaffold, beginning with modifications of the nucleoside sugars of Ara-C and other arabinose-derived nucleoside analogues in the 1960's. A future paper will review more recent developments, focusing especially on more complex modifications, particularly those involving multiple changes to the nucleoside scaffold. We hope that these articles will help virologists and others outside the field of medicinal chemistry to understand why certain drugs were successfully developed, while the majority of candidate compounds encountered barriers due to low-yielding synthetic routes, toxicity or other problems that led to their abandonment.

1. Nucleosides and nucleotides

Nucleoside and nucleotide analogues have a long and rich history in the field of medicinal chemistry (Perigaud et al., 1992; De Clercq, 2002; De Clercq, 2005a; De Clercq, 2004; Field and De Clercq, 2004; De Clercq, 2010; De Clercq, 2012). The naturally occurring nucleosides represent a unique starting point for drug design due to their involvement in numerous critical biological processes as well as the fact that they serve as essential building blocks for both DNA and RNA synthesis. Because of this, modifications to their structure can be designed and/or refined, based on the key interactions identified in the binding site of target enzymes. Currently there are 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 currently in clinical and preclinical trials. (Perigaud et al., 1992; De Clercq, 2004; Field and De Clercq, 2004; Jordheim et al., 2013; Niu and Tan, 2015; De Clercq and Li, 2016; Lapponi et al., 2016; Maffioli et al., 2017; Wataya et al., 1984; Isono, 1988; Andriole, 1999).

Nucleosides are composed of a sugar moiety and nucleobase whereas nucleotides are nucleosides that also contain at least one phosphate (or phosphate-like) group. While there are numerous naturally occurring nucleosides found in nature, the five most common in DNA and RNA and other biological processes, include adenosine, guanosine, cytidine, thymidine, and uridine (Fig. 1). As a result, even small changes to their structure can have profound effects. Ideally, nucleoside/tide analogues mimic the structure of a natural nucleoside such that they are recognized by cellular or viral enzymes, however due to modifications to their structure, lead to disruption and/or termination of replication or other biological processes (De Clercq, 2005a, 2005b, 2013a; De Clercq and Neyts, 2009). Since enzyme recognition is dependent on many factors, including shape, electronics, and hydrogen bonding interactions, it is possible to design an analogue that can have activity against a particular biological target, particularly if the mechanism of action is known and information about the binding site is available.

When contemplating potential modifications to the nucleoside scaffold, several different sites can be considered: the sugar moiety, the aromatic heterocyclic base, the glycosidic bond that connects the sugar to the heterocyclic base, and/or the phosphate group of the nucleotide (Fig. 2). (Perigaud et al., 1992; Jordheim et al., 2013) Modifications can be made by simply adding a substituent or group to the heterocyclic base or sugar, by replacing an atom in either group, by moving an atom
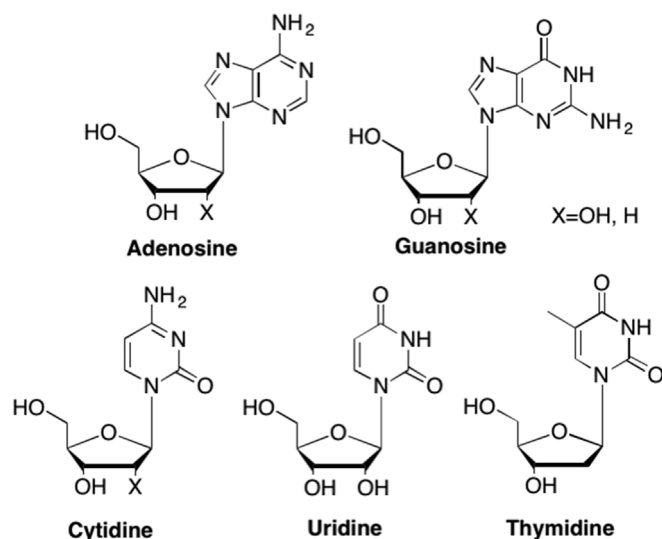

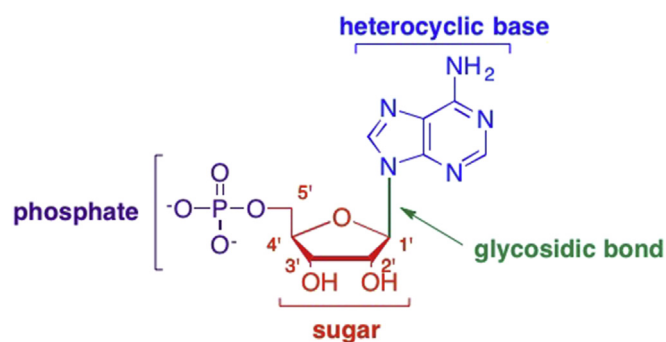Fig. 1. Natural occurring DNA and RNA nucleoside building blocks.

Fig. 2. Sites for potential modifications in nucleoside/tide drug design including changes to the heterocyclic base, the glycosidic bond, the sugar moiety, and the phosphate group.
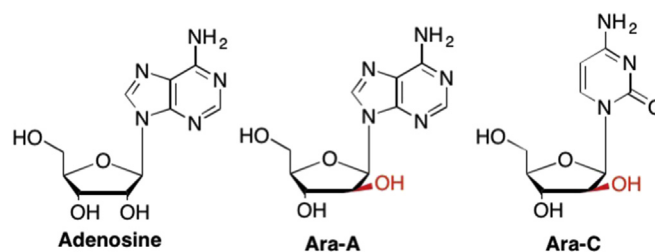

Fig. 3. Examples of "Ara" nucleosides where the 2′-OH is in the "up" configuration found in arabinose sugars rather than the "down" configuration typical of ribose nucleosides.

to a different position, or a combination of these approaches (Perigaud et al., 1992; Jordheim et al., 2013). Similar modifications can also be made to the phosphate groups in nucleotide analogues (Roy et al., 2016; De Clercq, 2007a, 2007b; Pertusati et al., 2012). Even the position of the glycosidic bond can be shifted, for example, to another carbon, however, the latter has traditionally been a less common modification (Agrofoglio et al., 1994; Marquez and Lim, 1986). These modifications can also be done in combination, thereby allowing for a large amount of diversity in nucleoside structure and function.

2. Modifications to the sugar scaffold

Some of the early examples of nucleoside analogues featured modifications to the sugar. These analogues greatly increased our knowledge of normal nucleoside interactions, but also how these interactions could be exploited for medicinal purposes. These modifications include adding or removing substituents on the furanose sugar ring, changing the ring size, or even removing the furanose oxygen to create an entirely new class of nucleosides.

2.1. 2′-OH modifications

Some of the first nucleosides discovered to have medicinal properties were the arabinose or "Ara" analogues, where the conformation of the hydroxyl group at the C2′ position is inverted, or "up" rather than "down" as is found in ribose nucleosides (Fig. 3). (Bergmann and Feeney, 1950, 1951; Bergmann and Burke, 1955) The first two Ara

nucleosides were natural products and included spongothymidine and spongouridine. Both were isolated from the Caribbean sponge *Tethya crypta* in the early 1950's (Bergmann and Feeney, 1950, 1951; Sipkema et al., 2005). While neither spongothymidine nor spongouridine ever became useful drugs, their discovery led to the synthesis of various other arabinose derived nucleoside analogues such as spongoadenosine (Ara-A) and spongocytidine (Ara-C) both of which were synthesized in the 1960's (Fig. 3). (Bergmann and Burke, 1955; Sipkema et al., 2005; Bauer, 1985; Hamann et al., 2007; Walwick et al., 1959; Lee et al., 1960a)

Ara-C, or Cytarabine, was approved for clinical use in 1969 and is considered an essential medicine by the World Health Organization (WHO, 2017) due to its potent activity against many cancers including, non-Hodgkin's Lymphoma, and, most importantly, against many leukemias such as myeloid leukemia, acute lymphatic leukemia, and chronic myelogenous leukemia (Reese and Schiller, 2013; Schilsky et al., 1987; Bodey et al., 1969; Hiddemann, 1991; Momparler, 1974; Rudnick et al., 1979; Herzig et al., 1983). While Ara-C is still currently used primarily for anticancer treatment, its use in antiviral therapy was also explored early on. Unfortunately, there were adverse effects observed for high dose Ara-C during anti-HSV treatments, including myelotoxicity and gastrointestinal toxicities, thus Ara-C was never pursued further as an antiviral drug (Stentoft, 1990; Lauter et al., 1974; Hwang et al., 1985). Ara-A, or Vidarabine, was first approved by the FDA in 1976 and has been used against several viruses including Herpes Simplex Virus 1 and 2 (HSV-1 and HSV-2), as well as Herpes Zoster Virus, which afflicts many AIDS patients (Field and De Clercq, 2004; Bauer, 1985; Hamann et al., 2007; De Clercq, 1982; Suzuki et al., 2006; Lee et al., 1960b). Vidarabine is no longer used due to toxicity issues as well as the discovery of more potent and safer compounds such as Acyclovir, which today is widely prescribed for HSV (Hamann et al., 2007).

In the 70's and 80's, researchers became aware of the unique properties that fluorine imparts to nucleoside analogues (Liu et al., 2008; Pankiewicz and Watanabe, 1993; Pankiewicz, 2000). Fluorine is often used as an isosteric replacement since it is similar in size to a hydrogen, but is also similar in electronegativity to the hydroxyl group found in ribose nucleosides (Liu et al., 2008). Fluorine has found extensive use in both sugar and base modifications (the latter will be discussed later). For example, early studies revealed that fluorine greatly influenced the conformation of the sugar, also known as "sugar pucker" (Saenger, 1984). Because fluorine is the most electronegative element, its presence "locks" the sugar into a specific conformation, which in turn, is one of the factors that affects recognition by different enzymes (Ikeda et al., 1998; Wojtowicz-Rajchel, 2012). For example, some enzymes such as DNA polymerases and reverse transcriptases prefer a "north" conformation, also known as C2′-exo/C3′-endo, while kinases generally prefer a "south" or C2′-endo/C3′-exo conformation (Fig. 4) (Saenger, 1984).

Furthermore, it was found that the presence of fluorine served to increase the stability of neighboring bonds (Liu et al., 2008; Bohm et al., 2004; Kirk, 2006; Park et al., 2001a). This observation also led to
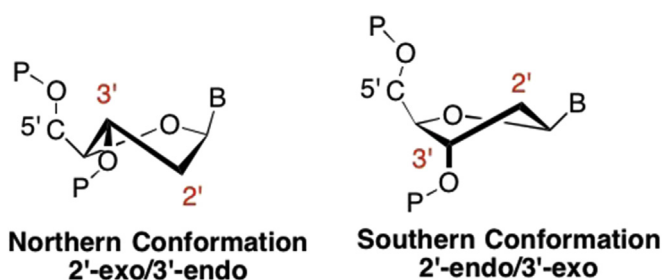
Fig. 4. Standard furanose ring puckering found in ribose and 2′-deoxyribose nucleosides.

the discovery that the presence of a fluorine at the 2′-position of the sugar decreased the nucleoside's susceptibility to enzymatic cleavage of the glycosidic bond – a biological process that can inactivate nucleoside drugs (Wojtowicz-Rajchel, 2012; Park et al., 2001a; Gudmundsson et al., 2000). As a result of these observations, fluorine has become a common modification in drug design.

In one of the first examples exploring the effects of fluorine on the sugar, Watanabe et al. synthesized a series of nucleosides with a fluorine at the 2′-position, including both the "up" and "down" analogues, given the activity previously noted by the Ara nucleosides (Fig. 5). (Liu et al., 2008; Pankiewicz and Watanabe, 1993; Pankiewicz, 2000) The "up" 2′-F proved to be more active than the "down" analogue, however neither analogue proved to be particularly potent and both were fairly toxic (Pankiewicz and Watanabe, 1993; Pankiewicz, 2000). Some years later, Eli Lilly developed the first example of a nucleoside with a geminal substituents – 2′-deoxy-2′,2′-difluorocytidine, which became known as Gemcitabine (Gemzar) (Hertel et al., 1990; de Sousa Cavalcante and Monteiro, 2014; Brown et al., 2014; Brown et al., 2015). This analogue was a groundbreaking discovery - the installation of two identical substituents (other than H) on the same carbon had not previously been tried before in nucleosides (or any molecule for that matter), and many questioned what the result of two fluorines would be on the overall conformation of the sugar. Logic would suggest that the two opposing dipoles would cancel each other out, leading to no change to the sugar pucker, however it was later shown that the two fluorines pulled the ring carbon "out" of the plane, rather than a north or south confirmation. More importantly, the potent activity of Gemcitabine against a number of cancers was striking (Hertel et al., 1990; de Sousa Cavalcante and Monteiro, 2014; Huang et al., 1991; Oettle, 2014; Hernández et al., 2001). Gemcitabine is still used today against breast, ovarian, pancreatic, bladder, and non-small cell lung cancers (de Sousa Cavalcante and Monteiro, 2014; Oettle, 2014; Bergman et al., 2011; Slusarczyk et al., 2014; Bastianich et al., 2017).

2.2. 3′-OH modifications

Due to the initial success with the 2′-modified nucleoside analogues, scientists also explored modifications at the 3′ carbon. Some of the first
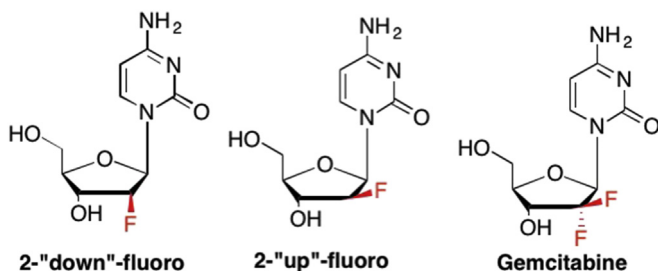

Fig. 5. Examples of 2′-F nucleoside analogues where the fluorine can be in the "down" or "up" configuration, or in both the "up" and "down" configuration as in Gemcitabine.
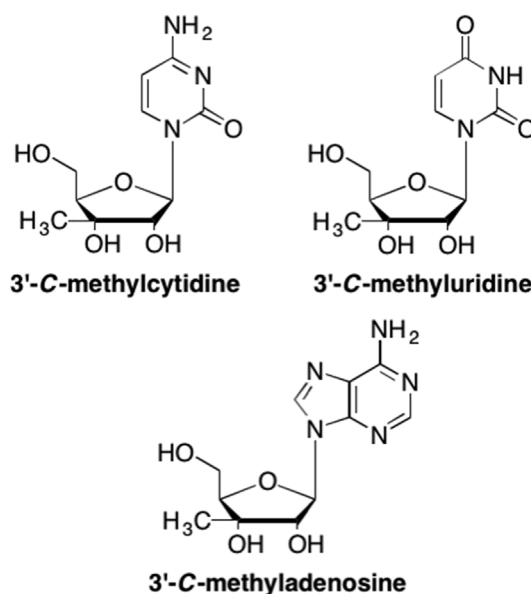

Fig. 6. Examples of 3′-methyl nucleoside analogues where the methyl at the 3′ carbon of the sugar ring is in the "up" configuration and the 3′-OH is in the "down" configuration.

3′ modified nucleosides include 3′-methyl analogues such as 3′-C-methyluridine and 3′-C-methylcytidine (Fig. 6). (Mikhailov et al., 1983) From these initial SAR studies, it was found that 3′-C-methyladenosine served as a potent anticancer agent against numerous human leukemia and carcinoma cell lines, with IC$_{50}$ values of ∼18 μM (Franchetti et al., 2005; Cappellacci et al., 2006). Further analysis found that shifting the methyl from the 3′ position of 3′-C-methyladenosine to another position on the sugar ring was associated with a decrease in activity, thus highlighting the importance of this moiety (Cappellacci et al., 2006). Similarly, this study found that the adenosine nucleobase was the most active analogue against human myelogenous leukemia K562 cells and human colon carcinoma HT-29 and CaCo-2 cell lines, with no antiproliferative activity found with the other nucleobases (Cappellacci et al., 2006). To further test the ability of these 3′-C-methyl analogues as potential therapeutics, the Osolodkin group studied 3′-C-methyluridine and cytidine against Tickborne encephalitis virus, however, none of these analogues demonstrated potent antiviral activity (Orlov et al., 2017). Due to the lack of antiviral activity, as well as the development of more potent anticancer agents, these analogues have not been extensively pursued any further.

2.3. 2′- and 3′-OH modifications

Since it was known that nucleoside analogues are incorporated into the growing nucleic acid chain via the 3′-OH of the template chain and the 5′-position of the incoming nucleotide, researchers speculated that if a nucleotide was missing the 3′-OH, or an alternative functional group was present at this position, then no further incorporation should occur and extension of the growing DNA chain would be halted (De Clercq and Neyts, 2009; Deval et al., 2007; Deval, 2009). This hypothesis led many researchers to pursue these types of modifications, thereby introducing new class of nucleoside analogues designated as "chain terminators", and these analogues signaled the beginning of a new era in nucleoside drug design.

The first examples of the chain terminator approach were the 2′,3′-dideoxy nucleosides dideoxycytidine (ddC, Zalcitabine), and dideoxyinosine (ddI, didanosine), both FDA approved nucleoside reverse transcriptase inhibitors against the Human Immunodeficiency Virus (HIV) (Fig. 7). (De Clercq, 2012; Veal et al., 1995; Mitsuya and Broder, 1986; Horwitz et al., 1967; Plunkett and Cohen, 1975) These analogues
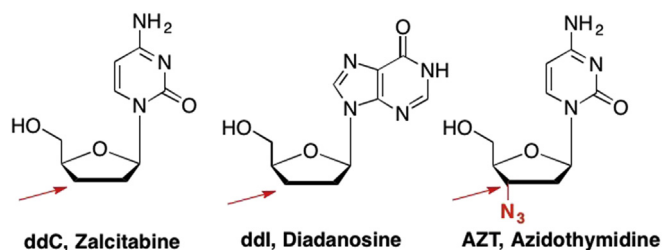
Fig. 7. Examples of 2′,3′-dideoxy nucleosides that act as obligate chain terminators due to the lack of a 3′-OH for the incoming nucleotide to couple to, thus chain elongation is terminated.

were quickly followed by 2′-deoxy,3′-azidothymidine (AZT, Zidovudine), which demonstrated increased activity against HIV compared to the previous dideoxy analogues with an IC_{50} of 0.03 μM as compared to 0.049 μM (ddI) and 0.6 μM (ddC) (Smith et al., 2008; Hostetler et al., 1994; Shirasaka et al., 1995; Horwitz et al., 1964). Interestingly, all three compounds were originally pursued as anticancer agents, however, during the 1980's when HIV quickly rose to the forefront of emerging diseases, researchers found that all three were quite effective against HIV (Martin et al., 2010). In addition, the dideoxynucleosides were also used in Sanger sequencing methods in the mid 1970's as a rapid method to determine DNA sequences with DNA polymerases (Sanger and Coulson, 1975; Sanger et al., 1977).

Unfortunately, a number of problems arose with AZT, ddI, and ddC. For example, it was shown that ddI was acid-labile, thus large buffered tablets were necessary to neutralize stomach pH and ensure effective delivery of the compound (Martin et al., 2010). This led to unwanted side effects including pancreatitis and peripheral neuropathy, as well as overall poor patient compliance (Martin et al., 2010). Fortunately, a few years after its initial approval, an enteric coated small capsule form of ddI was developed, which greatly increased patient compliance as well as decreased the previously described side effects (Martin et al., 2010). Similarly, ddC was also associated with numerous adverse effects; the most serious of which was painful peripheral neuropathy that occurred in all patients treated with ddC for longer than 6 weeks (Martin et al., 2010). For this reason, as well as its poor efficacy, ddC is no longer widely used. AZT also suffered from various side effects and problems with toxicity, but most seriously, the development of viral resistance (Boyer et al., 2006; Kerr and Anderson, 1997; Richman et al., 1994). The most common mechanism for the development of resistance is the mutation of one or more residues in the reverse transcriptase binding site (Larder and Kemp, 1989; Huang et al., 1998; Meyer et al., 1999; Gu et al., 1994; Zhang et al., 1994). This leads to the drug either

not binding at all, or at the very least, less effective binding.

By 1992, the problem of resistance was well-documented for all three therapies, thus researchers considered combination therapy, i.e. use of two nucleosides rather than the standard monotherapy (Richman et al., 1994; Larder and Kemp, 1989; Meng et al., 1992; Larder et al., 1993; St Clair et al., 1991; Collier et al., 1993). Researchers rationalized that if you could target the replication pathway of HIV with two different drugs, then it would increase the chances of stopping the development of resistance since shutting down one step in a pathway by two different mechanisms, or two different steps, or even two different drugs to target the same step, would greatly reduce the chances of mutant strains gaining dominance (Richman et al., 1994; Meng et al., 1992; Larder et al., 1993; Collier et al., 1993). Moreover, if one drug worked against the mutant strains for the other drug or vice versa, then this would exponentially increase the chances of being more effective (Meng et al., 1992; Larder et al., 1993; Collier et al., 1993; Mascolini, 1997). While today combination therapy is considered essential, in those days there was concern that this would lead to the development of even more serious mutations or resistance to the entire class of drugs. Given there were only a limited amount of drugs available for use, the fear was that this would lead to a lack of drugs left to try (Mascolini, 1997, 2010).

Because of the rapid emergence of resistance against AZT and ddC, the field focused on exploring additional modifications at the 2′ and 3′ sugar positions (Boyer et al., 2006; De Clercq, 2009a, 2009b; Sarafianos et al., 2004; Liotta and Painter, 2016). As a result, efforts to find new and better chain terminators were vigorously pursued. This ultimately led to the discovery of numerous analogues still used today including Stavudine (d4T), Lamivudine (3TC), and Emtricitabine (FTC) (Fig. 8). (Martin et al., 2010; Baba et al., 1987; Soudeyns et al., 1991; Schinazi et al., 1992a; Horwitz et al., 1966; Saag, 2006) Like ddI and ddC, Stavudine also lacks the 2′ and 3′-OH moieties, but also introduced unsaturation to the sugar moiety via a double bond between the C2′ and C3′ carbons, which in turn, made the sugar nearly planar due to the increased rigidity of the molecule (Choi et al., 2003). Interestingly, both Lamivudine and Emtricitabine are also examples of "L" nucleosides, the mirror image enantiomers of the naturally occurring "D" nucleosides which will be discussed later in this review. They also feature a sulfur atom instead of a 3′ carbon in the sugar ring (Liotta and Painter, 2016; Vasconcelos et al., 2008). Since the natural nucleosides are "D" nucleosides, it had long been thought that their unnatural enantiomers (non-superimposable mirror images) would not be recognized in biological systems. This proved not to be the case and both were ultimately approved for the use against HIV and Hepatitis B Virus (HBV) after demonstrating low levels of toxicity and diminished side effects
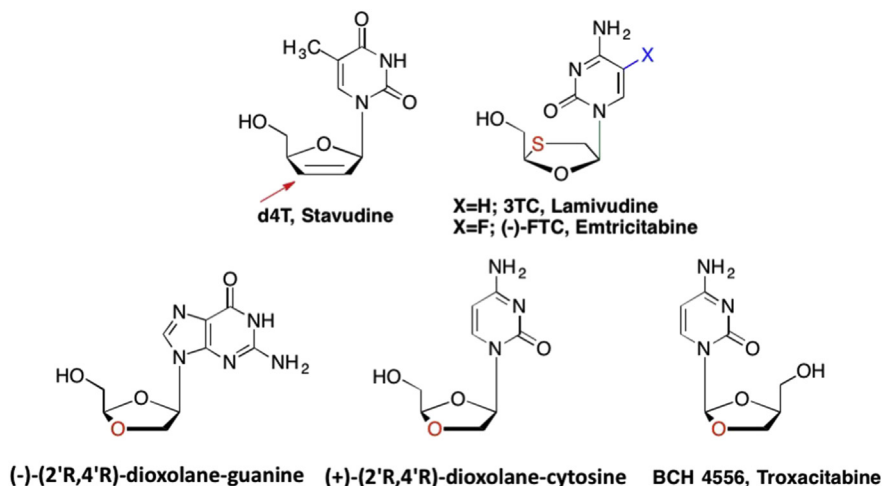

Fig. 8. Examples of second generation 2′,3′-dideoxy obligate nucleoside chain terminators.

compared to the aforementioned chain terminators, including AZT (De Clercq, 2012; Liotta and Painter, 2016; Vasconcelos et al., 2008; Doong et al., 1991).

While Lamivudine and Emtricitabine featured an oxathiolane sugar, researchers found that they could also replace the sulfur atom with an oxygen atom to yield a dioxolane sugar. This led to the development of anti-HIV analogues such as (+)-(2′R,4′R)-dioxolane cytidine and the corresponding (−)-(2′R,4′R)-dioxolane guanosine (Fig. 8). (Kim et al., 1992a, 1993) Like the oxathiolane sugar analogues, the dioxolane analogues are chain terminators due to the lack of a 3′-OH group. These structurally unique deoxynucleosides demonstrated potent anti-HIV activity, with EC_{50} values of 0.016 µM[110] and 0.003 µM[111] in PBM cells respectively, with the cytidine analogue displaying greater cytotoxicity than the guanosine analogue (Kim et al., 1992a, 1993). Further studies found that the L-enantiomer of the dioxolane cytidine analogue, Troxacitabine (BCH 4556), demonstrated activity against various cancers including renal cell carcinoma, leukemia, and prostate (Fig. 8). (Kadhim et al., 1997; Grove et al., 1995; Giles et al., 2001; Lee et al., 2006; Grove and Cheng, 1996; Siu et al., 1998; Rabbani et al., 1998) Furthermore, Troxacitabine also demonstrated potent activity against HBV and HIV, thus pointing to the importance of these analogues (Kim et al., 1992b).

2.4. Carbocyclic nucleosides

The use of an atom replacement in the sugar moiety as exemplified by Lamivudine and Emtricitabine were not the first examples of this type of modification. In 1966 an unusual nucleoside was synthesized by Shealy and Clayton that featured a cyclopentyl ring in place of the furanose sugar moiety (Fig. 9). (Shealy and Clayton, 1966) This analogue, later named Aristeromycin (Ari), was subsequently isolated from *Streptomyces citrocolour* and found to have potent antiviral properties against viruses such as measles, parainfluenza, vaccinia virus, and vesicular stomatitis (De Clercq, 1985; De Clercq et al., 1989; Rawal et al., 2016). Similarly, a closely related structural analogue was first isolated from *Ampullariella regularis* in 1981 (Hayashi et al., 1981), and later synthesized and named Neplanocin A (NpcA). Similar to Ari, NpcA also featured a cyclopentyl ring in place of the furanose sugar, however, in NcpA the cyclopentyl ring possesses a double bond between the C4′ and C6′ carbons (Fig. 9). (Rawal et al., 2016; Hayashi et al., 1980, 1981) Both NpcA and Ari were highly active, however, they were also quite toxic, as their triphosphate forms closely mimicked ATP, thus leading to misincorporation and disruption of many important biological systems (De Clercq, 1985; De Clercq et al., 1989; Rawal et al., 2016; Hayashi et al., 1980; Wolfe and Borchardt, 1991).

Although the toxicity of the two kept them from being used medicinally, the carbocyclic scaffold was still quite attractive to researchers. Carbocyclic nucleosides possess several advantages such as increased lipophillicity and cell permeability, but most importantly, the glycosidic bond was no longer an unstable hemiaminal ether affected by glycoside hydrolases, thus also led to increased stability (Agrofoglio

et al., 1994; Marquez and Lim, 1986; Stoeckler et al., 1980; Rodríguez and Comin, 2003; Marquez, 1996). Unfortunately, most of the carbocyclic nucleosides, with only a handful of exceptions, were less active than their corresponding ribose nucleosides (Marquez and Lim, 1986; Marquez, 1996; Marquez et al., 1996).

When comparing the sugar puckering of natural nucleosides and carbocyclic nucleosides such as thymidine and *carba*-thymidine, it was found that the loss of the furanose oxygen in the carbocyclic nucleosides not only significantly decreased stereoelectronic effects, it also eliminated the anomeric effect as well as decreased important *gauche* interactions between the furan oxygen and the 3′ hydroxyl groups (Marquez, 1996; Marquez et al., 1996; Boyer et al., 2009; Mahler et al., 2012). As mentioned previously, these interactions typically influence the sugars into either a North or South conformation, or more commonly, an equilibrium of the two (Marquez, 1996; Marquez et al., 1996). The loss of these interactions in the carbocyclic analogues resulted in a 1′-exo sugar confirmation, which differs greatly from the standard 2′-exo/3′-endo (North) or 2′-endo/3′-exo (South) conformations, and thus could explain the decreased activity seen with the carbocyclic derivatives (Marquez, 1996; Marquez et al., 1996; Boyer et al., 2009; Kálmán et al., 1989). Recent studies, however, have shown that alterations such as truncation of the CH_2OH group or addition of an endocyclic double bond to the carbocyclic scaffold (such as that found in Entecavir) could increase the interaction between the 2′ and/or 3′-hydroxyl groups and the nucleoside pharmacophore, thus potentially increasing their biological activity (Marquez, 1996; Marquez et al., 1996). This led to a number of groups pursuing novel carbocyclic analogues to see if this increased stability would indeed improve their overall antiviral properties.

2.5. Second generation carbocyclic nucleosides

As Neplanocin A and Aristeromycin were unable to be used as drugs due to the toxicity of their triphosphate forms, focus turned to the design of carbocyclic analogues that could not be phosphorylated at the 5′ position. One pivotal example was 5′-deoxy-Ari, where replacement of the CH_2OH group with a simple methyl group led to a dramatic increase in activity against both vaccinia virus as well as vesicular stomatitis virus (Fig. 10). (Marquez, 1996; Siddiqi et al., 1992) Another approach that proved advantageous was the development of the 5′-nor analogues by Schneller et al., where the 5′-methylene group was removed resulting in the direct connection of the 5′-OH to the cyclopentyl ring (Patil et al., 1992; Das and Schneller, 2014; Seley et al., 1997a, 1997b, 1997c, 1997d, 1998; Hegde et al., 1999, 2000; Barnard et al., 2001). Surprisingly, despite the presence of a hydroxyl group, phosphorylation did not occur since the shortened bond did not position the hydroxyl group correctly such that it was recognized by cellular and viral kinases (Patil et al., 1992). Taking it one step further, Borchardt, Schneller, Seley-Radtke and others completely removed the 5′-hydroxymethylene group leading to the truncated Ari and NpcA analogues (Hasobe et al., 1987; Zimmermann et al., 2014; Seley et al., 1997e). These truncations
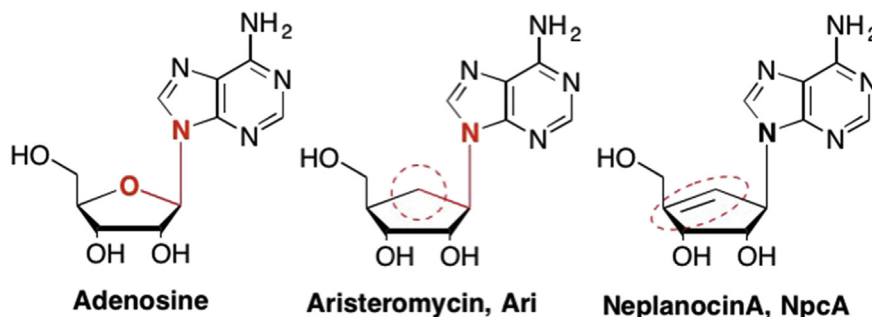

Fig. 9. Early carbocyclic nucleosides that feature a C-C-N glycosidic bond that is more stable compared to the corresponding hemiacetal bond found in the natural sugar nucleosides.
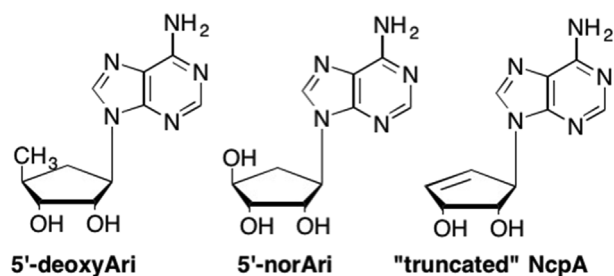
Fig. 10. Examples of second generation carbocyclic nucleosides with the 5′-OH or 4′-substituent removed to generate "truncated" nucleosides.

proved extremely fruitful in that they retained similar activity to the Ari and NpcA analogues, however, the associated toxicity was not observed (Zimmermann et al., 2013, 2014; Seley et al., 1997e).

One of the most important findings for the carbocyclic analogues was that they proved to be some of the most potent inhibitors against S-adenosyl-L-homocysteine hydrolase (SAHase) – an enzyme key to many biological methylations (Marquez and Lim, 1986; De Clercq et al., 1989; Wolfe and Borchardt, 1991; Marquez, 1996; Wang et al., 2011). SAHase was not the only enzymatic target available for the carbocyclic analogues, as many carbocyclic compounds were also found to be effective polymerase inhibitors (Price et al., 1992; Matyugina et al., 2012). One example is (−)-Carbovir, which resembles the d4T sugar structure in that there is a double bond between the 2′ and 3′ carbons, however, (−)-Carbovir possesses a cyclopentyl ring instead of the furanose ring seen in d4T as well as a guanine nucleobase instead of the thymine nucleobase found in d4T (Fig. 11). (Vince et al., 1988; Carter et al., 1990) This was highly strategic in that the unsaturation of the cyclopentyl ring increased the rigidity of the analogue, and the lack of the furanose oxygen lead to increased stabilization of the glycosidic bond of (−)-Carbovir (Vince et al., 1988; Carter et al., 1990; Parker et al., 1993). While (−)-Carbovir has demonstrated its ability to be a potent anti-HIV therapeutic, cytotoxicity, low solubility, and poor oral bioavailability have limited its use in clinical applications (Yeom et al., 1989). In order to alleviate some of these issues, further studies with (−)-Carbovir led to the development of Abacavir, a carbocyclic analogue with a unique modification on the exocyclic amine group at the 6 position of the nucleobase (Fig. 11). (Daluge et al., 1997) The cyclopropyl group acts as a prodrug moiety and, once Abacavir is anabolized to Abacavir 5′-monophosphate, the cyclopropyl group undergoes deamination *in vivo* to yield (−)-Carbovir 5′-monophosphate (Daluge et al., 1997; Faletto et al., 1997; Tisdale et al., 1997; Yuen et al., 2008). From here, (−)-Carbovir 5′-monophpshate is converted into the 5′-diphosphate and subsequently to the 5′-triphosphate by various cellular kinases to give the bioactive (−)-Carbovir 5′-triphosphate (Vince et al., 1988; Daluge et al., 1997; Faletto et al., 1997). Since Abacavir is converted into the active form of (−)-Carbovir *in vivo*, it also acts as a potent HIV-1 therapeutic. Abacavir is typically administered with other
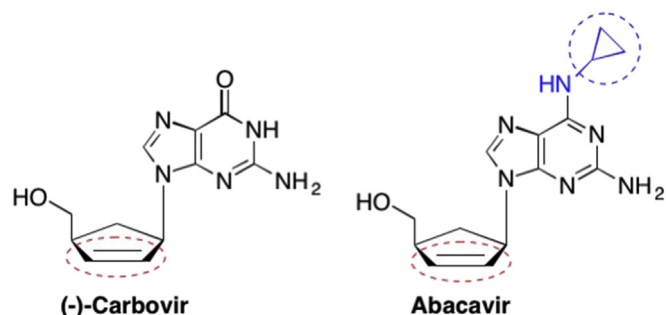

Fig. 11. Structure of the 2′,3′-dideoxy obligate chain terminator Carbovir, a nucleoside that features unsaturation in the sugar ring.
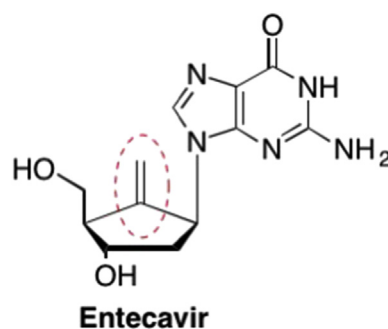

Fig. 12. Structure of the 2′-deoxy non-obligate chain terminator Entecavir that features a unique exocyclic double bond which leads to unfavorable steric interactions resulting in chain termination despite the presence of a 3′-OH.

nucleoside analogues as part of combination therapy, and has demonstrated the ability to overcome some of the bioavailability limitations associated with (−)-Carbovir (Daluge et al., 1997; Tisdale et al., 1997; Harrigan et al., 2000).

One of the most important examples of the carbocyclic nucleosides is Entecavir, which possesses a 3′-OH group but introduced a highly unique exocyclic double bond in place of the furanose oxygen (Fig. 12). (Bisacchi et al., 1997; Wilber et al., 2011) Entecavir is an FDA approved drug for treating both HIV and HBV (Bisacchi et al., 1997; Wilber et al., 2011; Tang et al., 2013). Interestingly, the presence of the exocyclic double bond is critical to the increased binding affinity, as it fits into a hydrophobic pocket of the HBV polymerase, increasing the efficacy of Entecavir against HBV (Tang et al., 2013; Rawal et al., 2015). Initially however, this was not part of the rationale of the overall design - the exocyclic double bond was merely chosen to increase rigidity of the nucleoside and prevent the sugar ring flipping between the North and South conformations, as well as to maximize the distance and orientation between the nucleobase and the 5′-hydroxyl (Tang et al., 2013; Langley et al., 2007).

Interestingly, Entecavir is one of the rare examples of a rationally (although some might consider it irrationally!) designed nucleoside (Fig. 13). In 1992, another carbocyclic nucleoside, Lobucavir, was garnering much attention, due to its potent antiviral activity against HBV and HSV (Marquez, 1996; Hayashi et al., 1990; Norbeck et al., 1990). Lobucavir possesses a cyclobutyl "sugar", i.e. four-membered ring, and resembles the naturally occurring Oxetanocin G, which was isolated from bacteria in 1986 and later demonstrated antiviral activity against HIV (Fig. 14). (Marquez, 1996)

At the time, researchers at Bristol Myers Squibb, including the lead chemist on the project Robert Zahler, were looking to design something that would occupy the same space as Lobucavir, a unique carbocyclic cyclobutyl nucleoside structurally similar to the naturally occurring Oxetanocins, which also possess a four member sugar ring (Bisacchi et al., 1997; Hayashi et al., 1990). More specifically, they wanted the nucleoside to mimic the orientation of the nucleobase, as well as the distance between the 5′-OH and the guanine base (Fig. 13). (Wilber et al., 2011) Zahler felt strongly that these two factors were the key to Lobucavir's potent activity. Since computational chemistry was only in its early stages, chemists relied on physical models, thus Zahler rationalized that it didn't matter what was in the middle, only that it kept the base and 5′-OH group positioned in the correct distance and the right spatial orientation (Wilber et al., 2011). More specifically, knowing that a sugar ring was prone to flipping conformations, which could subsequently abolish the activity, he knew it would be important to hold the sugar ring rigid enough such that this flip did not occur (Wilber et al., 2011; Tang et al., 2013; Langley et al., 2007). In addition, since ring flipping would impact the orientation of the heterocyclic base into either an anti or syn conformation, which would also impact recognition, mimicking the specific distance between the 5′-OH and the heterocyclic
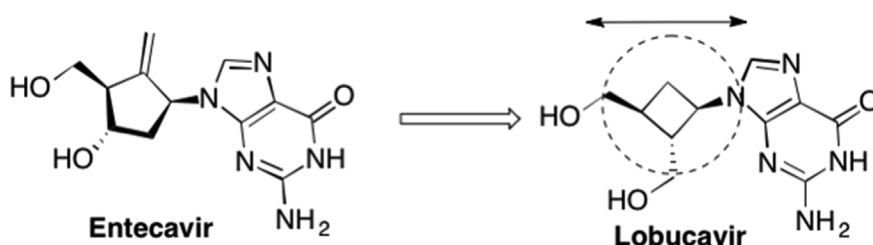
Fig. 13. The spatial and structural similarities between Lobucavir and Entecavir that provided the rationale for Entecavir's unique design.
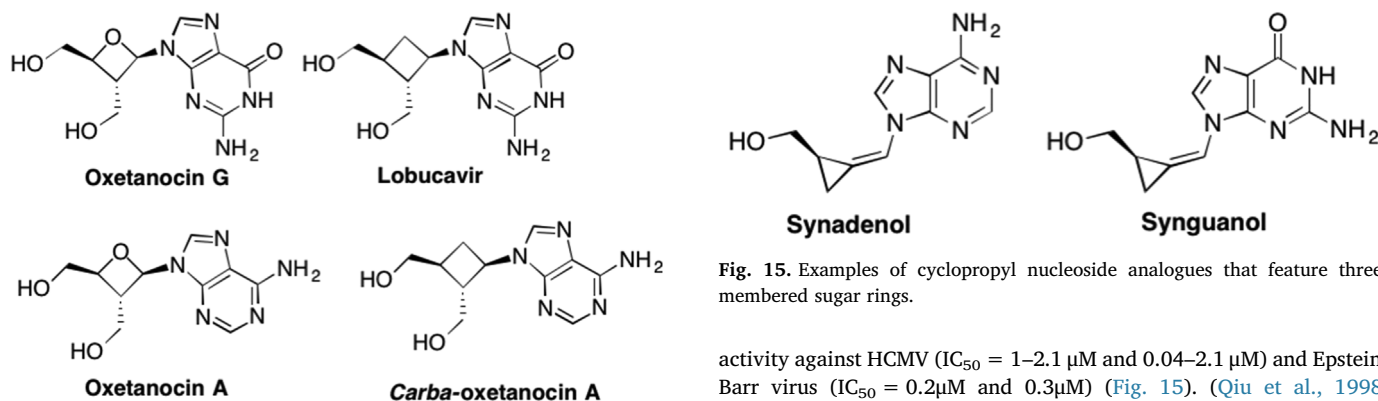

Fig. 14. Examples of nucleosides with four-membered rings including the corresponding carbocyclic ("carba") analogues.

base could potentially be achieved by holding the base in the preferred conformation. Zahler tried a number of approaches but ultimately conceived of a cyclopentyl ring wherein an exocyclic double bond replaced the furanose oxygen (Bisacchi et al., 1997; Wilber et al., 2011; Tang et al., 2013). Not only would this rigidify the ring enough to avoid the ring flip, he also predicted this would hold the nucleobase and OH group in the correct orientation and distance (Bisacchi et al., 1997; Wilber et al., 2011). As it turned out, the overlap with Lobucavir was quite remarkable and Entecavir still represents one of the best and most widely prescribed anti-HBV drugs on the market (Langley et al., 2007). Notably, it has also been shown to be particularly effective against HIV/HBV co-infected patients (McMahon et al., 2007; Pessôa et al., 2008).

2.6. Alternative ring size nucleosides

As introduced briefly above, the naturally occurring oxetanocins possess a four-membered sugar ring. Oxetanocin A is an adenosine mimic that possessed a 4-membered sugar ring and was found to be very active against HIV as well as HSV-1 and HSV-2 (Marquez, 1996; Groaz et al., 2013). Oxetanocin G is the corresponding guanosine mimic which proved effective against HIV (Fig. 14). (Marquez, 1996) Interestingly, the carbocyclic derivatives of both Oxetanocin A (*carba*-oxetanocin A) and Oxetanocin G (*carba*-oxetanocin G; Lobucavir) also displayed high antiviral activity against numerous viruses, including HSV-1, HSV-2, Human Cytomegalovirus (HCMV), and Varicella Zoster Virus (Fig. 14). (Marquez, 1996; Hayashi et al., 1990; Norbeck et al., 1990; De Clercq et al., 2001; Sekiyama et al., 1998)

From these initial studies and the great success of Entecavir, as well as the oxetanocins and Lobucavir, it was clear that ring size could play an important role in recognition and activity. One such ring size were the cyclopropyl nucleosides, which introduced extreme rigidity to the sugar scaffold however exhibited only moderate antiviral activity against HSV and HIV (Sekiyama et al., 1998; Ashton et al., 1988; Qiu et al., 1998; Aihong and Joon, 2007). Later Zemlicka et al. developed the Z-isomers of 2-hydroxymethylcyclopropylidenemethyl purines and pyrimidines (Synadenol and Synguanol) that demonstrated potent

Fig. 15. Examples of cyclopropyl nucleoside analogues that feature three-membered sugar rings.

activity against HCMV (IC_{50} = 1–2.1 μM and 0.04–2.1 μM) and Epstein-Barr virus (IC_{50} = 0.2μM and 0.3μM) (Fig. 15). (Qiu et al., 1998; Baldanti et al., 2002)

In contrast, Herdewijn et al. developed numerous six-membered ring nucleosides including the cyclohexenyl and hexose nucleoside analogues shown in Fig. 16 (Wang et al., 2000). The cyclohexenyl analogues were pursued for two primary reasons – cyclohexene is a bioisostere of a saturated furanose ring, and the cyclohexenyl analogues are more resistant to glycoside hydrolysis due to the change in the glycosidic bond to a hemiaminal ether as previously discussed (Wang et al., 2000; Barral et al., 2005; Herdewijn and De Clercq, 2001; Wang and Herdewijn, 1999). Studies demonstrated that the enantiomers of one particular cyclohexenyl nucleoside, cyclohexenyl guanine, exhibited potent and selective activity against HSV-1, HSV-2, VZV, and HCMV (Wang et al., 2000; Herdewijn and De Clercq, 2001; Wang and Herdewijn, 1999). Unfortunately, due to tedious synthetic procedures, these compounds did not lead to any clinical candidates, however, they did serve to increase our understanding of other aspects of drug design and biological activity.
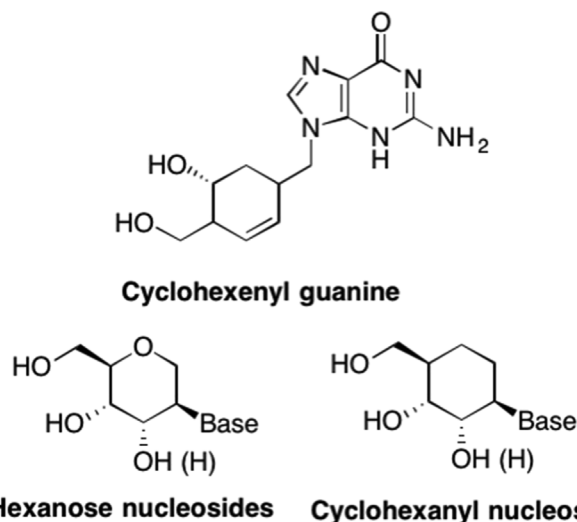

Fig. 16. Examples of nucleoside analogues that feature a six-membered ring instead of the typical five-membered ring found in natural nucleosides.
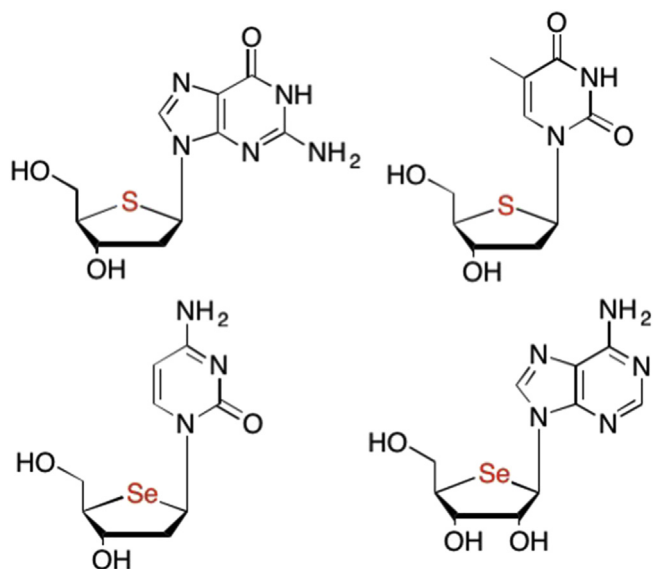
Fig. 17. Examples of non-furanose sugars where the oxygen is replaced with either an isosteric sulfur atom or a selenium atom.

2.7. Replacement of oxygen in the furanose ring by heteroatoms

Given the potent activity exhibited by the carbocyclic nucleosides, researchers next turned to replacing the furanose oxygen with other atoms to see the potential impact on biological activity. One such replacement included that of the isosteric sulfur atom to yield thionucleosides, which have a similar benefit to carbocyclic nucleosides in that they are also unaffected by glycoside hydrolases (Fig. 17). (Messini et al., 1999; Elzagheid et al., 1999; Crnugelj et al., 2002) Sulfur is related to oxygen in several ways, including a similar electronic configuration and the same number of valence electrons, however, sulfur is less electronegative and larger in size than oxygen. In contrast, sulfur does not participate in hydrogen bonding like oxygen, thus this substitution results in the loss of important interactions in enzyme binding pockets (Paulsen, 1966). While numerous analogues were synthesized by Secrist et al. (Messini et al., 1999; Elzagheid et al., 1999) and others (Paulsen, 1966; Inoue et al., 2005; Crnugelj et al., 2002) none led to a marketable drug.

Many years later, Jeong et al. developed the analogous selenonucleosides, however, none showed meaningful anticancer or antiviral activity, most likely due to lack of recognition by cellular kinases, as they were not phosphorylated (Fig. 17). (Sahu et al., 2014; Yu et al., 2013) Extension of the methylene group at the 5′ position of these compounds however, resulted in potent anti-HSV-1 activity with EC_{50} values as low as 2.3 μM since these analogues were able to be phosphorylated by cellular kinases (Sahu et al., 2014; Yu et al., 2013).

Another modification that proved to be highly successful is the use of the nitrogen-containing imino sugar found in the immucillins (Fig. 18) developed by Schramm et al. (Kicska et al., 2001; Schramm and Tyler, 2003), however those will be discussed below in the C-nucleoside section of this review.

2.8. Acyclic nucleosides

While 2′ and 3′-OH modified analogues such as AZT, ddI, and ddC were effective antiviral analogues, researchers concurrently speculated as to just how much of the sugar scaffold they could remove and still retain the activity of the nucleoside. Studies found that not only could the 2′ and 3′-OH moieties be removed, but the 2′ and 3′-carbons could also be excised to yield what was dubbed an acyclic nucleoside (Fig. 19). (Deval, 2009; De Clercq et al., 2001; Sekiyama et al., 1998; King, 1988; Elion, 1993; Kimberlin, 2001; Freeman and Gardiner,
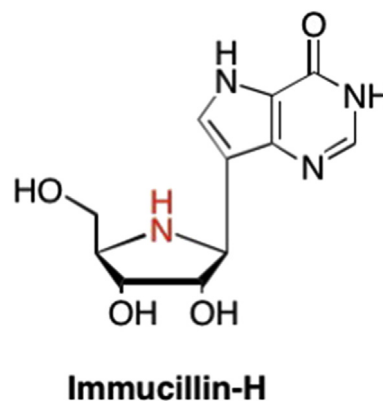

Immucillin-H

Fig. 18. Structure of the imino sugar modified nucleoside Immucillin-H, where the furanose oxygen is replaced with a nitrogen.
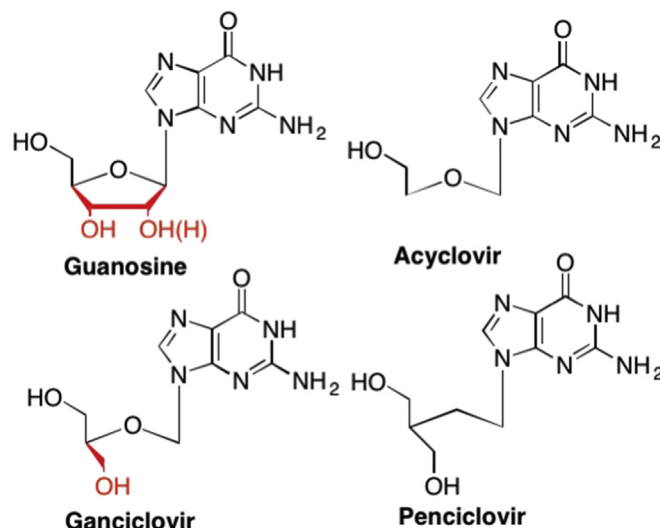

Fig. 19. Comparison of the structure of guanosine with the acyclic nucleosides Ganciclovir, which is missing a 2′ carbon and corresponding 2′-OH, Acyclovir, which is missing both the 2′ and 3′ hydroxyl groups, and Penciclovir, the analogous carbocyclic version of Ganciclovir.

1996)

One of the most medically important acyclic nucleosides is Acyclovir, an acyclic guanosine mimic that has displayed high specificity and activity towards HSV-1 and HSV-2 (Fig. 19). (King, 1988; Elion, 1993; Kimberlin, 2001; Freeman and Gardiner, 1996; Reardon and Spector, 1989; McMahon et al., 2008) This high specificity and activity is due to many factors. For example, Acyclovir is more readily recognized and phosphorylated by viral thymidine kinases than the corresponding cellular thymidine kinases (King, 1988; Reardon and Spector, 1989) at a rate of > 3000 fold higher, thus leading to higher concentrations of monophosphorylated Acyclovir in infected cells as opposed to uninfected cells (Elion, 1993; McMahon et al., 2008). In addition, the triphosphorylated Acyclovir is recognized and incorporated 100 fold more efficiently by the viral DNA polymerase as compared to the cellular polymerase (King, 1988; Reardon and Spector, 1989). It has also been shown that Acyclovir's inherent flexibility allows for optimized interactions in target enzyme binding sites (Alvarez-Ros and Palafox, 2014; Tuttle and Krenitsky, 1984; Wesołowski et al., 1987).

Unfortunately, like most nucleoside analogues, Acyclovir suffers from poor water solubility and thus a low oral bioavailability (de Miranda and Blum, 1983; Elion et al., 1977). One way to alleviate this issue is to add prodrug moieties to the nucleoside analogues to increase
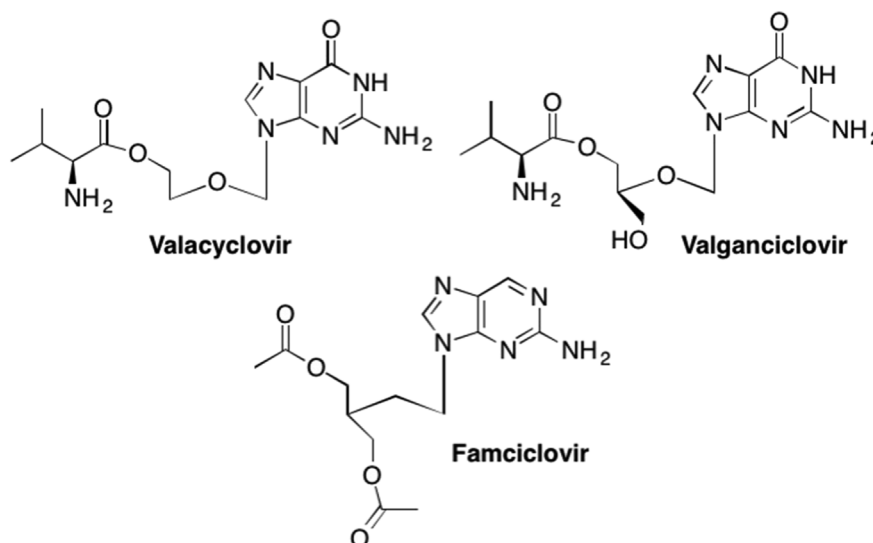
Fig. 20. Examples of the prodrug analogues of Acyclovir, Ganciclovir, and Pencyclovir that increase lipophillicity and subsequent bioavailability.

lipophillicity and ultimately increase the delivery of the active analogue to the active site. In the case of Acyclovir, various amino acid esters of Acyclovir were synthesized including the valine ester prodrug of Acyclovir, (Valacyclovir), which served to increase oral bioavailability 3-to-5 fold in humans (Fig. 20). (Colla et al., 1983; Bras et al., 2001; Weller et al., 1993; Steingrimsdottir et al., 2000; Perry and Faulds, 1996; Soul-Lawton et al., 1995; Smiley et al., 1996) This increase in bioavailability also resulted in an improved efficacy against herpesviruses such as varicella-zoster virus and cytomegalovirus infections, that had previously shown less susceptibility to Acyclovir (Weller et al., 1993; Perry and Faulds, 1996; Soul-Lawton et al., 1995; Smiley et al., 1996; Burnette et al., 1995; Beutner, 1995). Moreover, Valacyclovir could be administered in the form of eye drops to treat herpetic keratitis, in contrast to Acyclovir, which had to be administered as an ointment (Maudgal et al., 1984). The increased absorption of Valacyclovir is attributed to the facilitated transport of Valacyclovir across the intestinal membrane by human oligopeptide transporter 1 (hPepT1), as compared to simple diffusion utilized by Acyclovir (de Vrueh et al., 1998; Balimane et al., 1998). Valacyclovir has also been utilized for treatment against HSV-1 and HSV-2 (Perry and Faulds, 1996; Smiley et al., 1996; Beutner, 1995).

The initial discovery of Acyclovir led many researchers to pursue additional nucleoside analogues utilizing the acyclic sugar scaffold. One example is Ganciclovir, also an acyclic guanosine mimic, however, unlike Acyclovir, Ganciclovir retains the 3′-hydroxyl group (Fig. 19). (Kimberlin, 2001; Freeman and Gardiner, 1996; Hewlett et al., 2004; Fan-Havard et al., 1989) Ganciclovir is most commonly used to treat HCMV in immunocompromised patients, and, like Acyclovir, HCMV infected cells have a higher affinity for Ganciclovir than non-infected cells (Kimberlin, 2001; Fan-Havard et al., 1989). Unfortunately, since HCMV treatment is usually long term, instances of resistance to Ganciclovir have been reported (Kimberlin, 2001; Hewlett et al., 2004; Komatsu et al., 2014). Like Acyclovir, Gancyclovir also demonstrates low bioavailability which can be increased with the addition of a valine ester to yield the prodrug Valganciclovir (Fig. 20). (Curran and Noble, 2001; Martin et al., 1987) Valganciclovir is currently utilized for both treatment of CMV retinitis in patients with HIV as well as a prophylactic treatment for the prevention of CMV in transplant patients (Reischig et al., 2008; Paya et al., 2004; Martin et al., 2002; Piketty et al., 2000; De Clercq and Field, 2006; Chamberlain et al., 2008).

Another example is Penciclovir, a carbocyclic guanosine analogue similar in structure to both Acyclovir and Ganciclovir, however, Penciclovir has a methylene group instead of the oxygen in the acyclic

sugar moiety (Fig. 19). (Boyd et al., 1987, 1993; Harnden and Jarvest, 1985) Like Acyclovir, Penciclovir is also a potent therapeutic against both HSV-1 and HSV-2, however, surprisingly Penciclovir demonstrated a lower bioavailability than Acyclovir, thus researchers attempted to find a suitable prodrug (De Clercq and Field, 2006; Harnden and Jarvest, 1985; Vere Hodge et al., 1989). These studies ultimately led to the development of Famciclovir, a prodrug analogue that utilizes a typical acetate prodrug for the hydroxyl moieties, but also features the removal of the carbonyl group on the guanosine nucleobase (Fig. 20). (Vere Hodge et al., 1989; Harnden et al., 1989) After enzymatic oxidation *in vivo* of the nucleobase to add the carbonyl to the purine ring and hydrolysis of the acetate groups, Famciclovir yields Penciclovir (Vere Hodge et al., 1989; Harnden et al., 1989; Vere Hodge, 1993). Due to the increased bioavailability associated with Famciclovir, this analogue has been utilized for years as a treatment against both HSV-1 and HSV-2 as well as against herpes zoster infections as it can be administered less frequently and at lower doses as compared to Acyclovir treatment (De Clercq and Field, 2006; Degreef and Group, 1994; Tyring et al., 1995; Sacks et al., 1996; Mertz et al., 1997).

2.9. Acyclic nucleoside phosphonates

During DNA/RNA replication, nucleosides are phosphorylated by various host cell kinases into their active triphosphate form, then are taken up by polymerases and incorporated into the growing chain (De Clercq and Neyts, 2009; Deval, 2009). The same process is required for modified nucleosides, however, one of the major limitations to utilizing nucleosides as drugs is the specificity of the kinases involved in the various phosphorylation steps. These steps then become rate limiting for the overall conversion to the active triphosphate form. Since nucleoside analogues are not always recognized efficiently and thus may initially appear inactive, it became important to design analogues that could overcome this issue (De Clercq, 2007a, 2007b; Pertusati et al., 2012; De Clercq and Holý, 2005; De Clercq et al., 2005). In that regard, researchers attempted to utilize monophosphate analogues, however, the phosphate group renders the nucleotides extremely polar, therefore making it difficult for the compounds to cross the cellular membrane. Moreover, this also increases the susceptibility of these compounds towards degradation by cellular enzymes, particularly phosphatases, thus was not a viable solution (Pertusati et al., 2012; De Clercq and Holý, 2005; Macchi et al., 2015).

In the late 1980's, Antonín Hóly and his team circumvented this issue by adding a phosphonate, rather than a phosphate, group to the
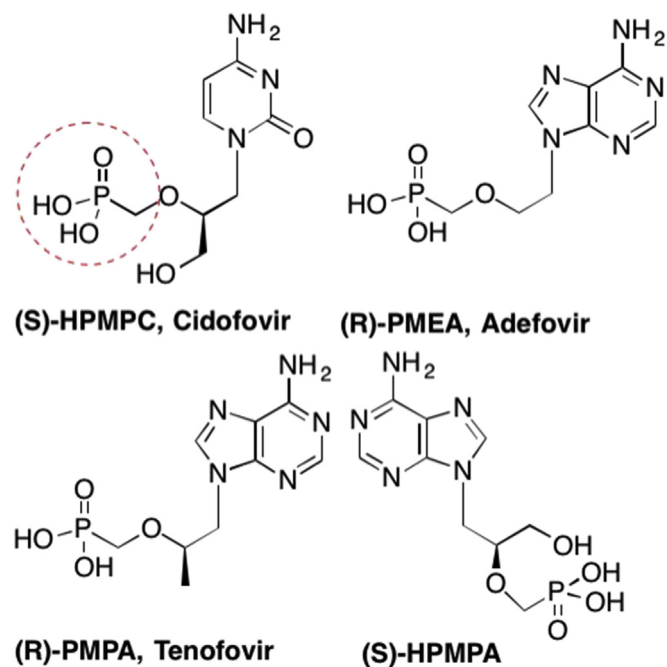
Fig. 21. Examples of acyclic nucleoside phosphonates such as Cidofovir, Adefovir, and Tenofovir, where the phosphate group is replaced by the more stable phosphonate group.

acyclic nucleoside scaffold. This not only increased the stability of the phosphate bond, but also successfully delivered a monophosphate mimic into the cell, thereby overcoming that first rate-limiting phosphorylation step, as well as overcoming issues with delivery (De Clercq, 2007a, 2007b; De Clercq and Holý, 2005; Macchi et al., 2015; Hóly and Rosenberg, 1987; Holý, 2006). The corresponding acyclic nucleoside phosphonates (ANPs) were associated with prolonged antiviral activity due to the fact that these compounds were no longer susceptible to cellular phosphatases that would cleave the phosphorester bond, reverting it back to the parent nucleoside (De Clercq, 2007a, 2007b; Pertusati et al., 2012; Macchi et al., 2015; Engel, 1977). The addition of the phosphonate moiety also increased the scope of the antiviral activities as seen with ANPs such as Cidofovir, Adefovir, and Tenofovir (Fig. 21). (De Clercq, 2003, 2007a, 2007b)

Cidofovir (S-HPMPC) (Fig. 21) is a cytosine derivative that retains the 2′-carbon and corresponding 2′-hydroxyl group and has demonstrated activity against most DNA viruses including: polyoma-, papilloma-, adeno-, pox-virus, HSV-1, HSV-2, VZV, HCMV, and Epstein-Barr virus (De Clercq, 2003, 2007a, 2007b, 2013b; De Clercq and Holý, 2005; Lalezari et al., 1997). While the primary use of Cidofovir is for the treatment of HCMV retinitis in AIDS patients, Cidofovir is currently one of the only licensed antiviral drugs that has been stockpiled for the possible use as short term prophylaxis against smallpox in the event of a biological weapons attack (De Clercq, 2003, 2007a, 2007b; De Clercq and Holý, 2005; Holý, 2006). Unfortunately Cidofovir, like almost all of the acyclic nucleoside phosphonates, is associated with severe side effects, including nephrotoxicity, impaired renal function, and other side effects due to the presence of the phosphonate moiety. Thus, Cidofovir contains a black box warning, which limits its use to short term therapies (De Clercq, 2003; Lalezari et al., 1997; Smee et al., 2002).

Another acyclic nucleoside phosphonate that initially garnered much attention was Adefovir (R-PMEA, Fig. 21), an adenosine analogue that was first utilized in the treatment of HIV, however, the high dosage needed was associated with toxicity and numerous adverse side effects (De Clercq, 2005b, 2007a; De Clercq and Holý, 2005; Holý, 2006; Hadziyannis et al., 2003; Dando and Plosker, 2003; Angus et al., 2003). Adefovir is still used in some countries, however at a much lower dosage, as it was subsequently proven to be a very effective and inexpensive treatment for chronic Hepatitis B infections (De Clercq, 2003, 2005b, 2007a, 2007b; De Clercq and Holý, 2005; Holý, 2006).

In contrast, one of the most widely used phosphonate nucleoside drugs is Tenofovir (R-PMPA). Tenofovir (Fig. 22) is an adenosine analogue that is utilized to treat HIV as well as chronic Hepatitis B infections (De Clercq, 2003, 2005b, 2007a, 2007b, 2009a, 2009b; De Clercq and Holý, 2005; Holý, 2006). Unfortunately, like most acyclic nucleoside phosphonates, Tenofovir is associated with a very low bioavailability, however, this was greatly increased with the addition of a prodrug moiety (De Clercq, 2003; Fung et al., 2002; Porche, 2002; Chapman et al., 2003). Tenofovir disoproxil fumarate (TDF) was initially marketed in 2001, and demonstrated a higher potency and greater efficacy than the parent Tenofovir (Fig. 22). (Fung et al., 2002; Porche, 2002; Chapman et al., 2003) Most recently however, Tenofovir Alafenamide (TAF) has largely replaced TDF in HIV treatments, primarily due to the significant difference in dosage – only 30 mgs vs 300 mgs, as well as greatly increased levels of the nucleotide inside the virally infected cell (De Clercq, 2016a; Ray et al., 2016). Recently
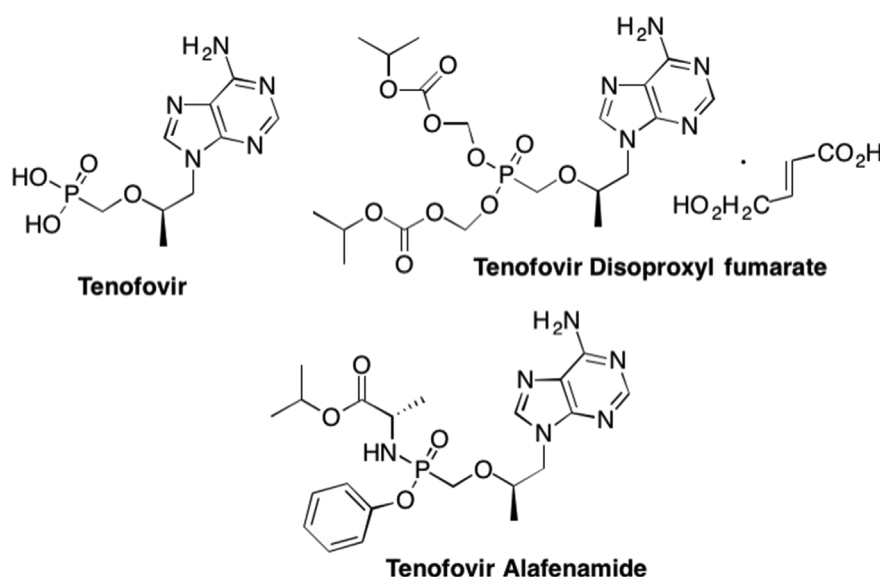

Fig. 22. Structure of the acyclic nucleoside phosphonate Tenofovir and its prodrug analogues Tenofovir disoproxil fumarate and Tenofovir alafenamide.

growing concerns over increasing incidents of nephrotoxicity and other renal issues related to TDF have arisen, similar other phosphonates, although these side effects took years to arise (Rawal et al., 2015; De Clercq, 2016a; Ray et al., 2016; Birkus et al., 2015). Importantly, almost no reports of resistance against TAF have been reported, thereby rendering TAF a much more effective and safe drug (De Clercq, 2016a; Ray et al., 2016; Stray et al., 2017).

Not just limited to antiviral uses, several other acyclic nucleoside phosphonates, including the 9-(3-hydroxy-2-phosphonylmethoxypropyl) derivatives, have demonstrated potent activity against different members of the *Trypanosoma* genus that cause lethal African sleeping sickness (Fig. 21). (Kaminsky et al., 1994, 1996) The adenosine analogues were the most effective of the 9-(3-hydroxy-2-phosphonylmethoxypropyl) derivatives, especially the *S* enantiomer, which demonstrated potent activity against *T.b. rhodesiense* with an EC$_{50}$ of 0.028 μg/mL (Kaminsky et al., 1994, 1996). These potent analogues are still under investigation as potential therapeutics and have yet to reach clinical trials.

3. Modifications to the nucleobase

Concurrently to the aforementioned approaches to modify the sugar moiety, numerous modifications were also being made to both the purine and the pyrimidine heterocyclic bases of the nucleosides. Analogous to various interactions involved in recognition and binding for the sugar of the nucleoside, enzyme-ligand recognition and binding also involves many different types of interactions with the base. Thus changing the sterics, electronics, or hydrogen bonding interactions can also significantly impact recognition, and subsequently, biological activity (Jordheim et al., 2013; De Clercq and Neyts, 2009; Deval, 2009). Modifications to the heterobase have primarily focused on adding substituents onto the base, removing or adding atoms to the rings themselves, or changing positions of the atoms. These types of changes have served to create many new classes of nucleoside analogues over the years.

3.1. Modifications at the 5 position of pyrimidines

Although various modifications can be made to the pyrimidine ring, one of the most common early modifications in nucleoside drug design involved adding substituents to the C5 position of the pyrimidine ring. This modification can potentially alter the sterics, the electronic environment, and even the hydrogen bonding interactions between the enzyme binding site and the nucleoside analogue (De Clercq, 2010; Prusoff, 1959; Kaufman and Heidelberger, 1964; Whitley, 1996). One early nucleoside that utilized this modification was Idoxuridine, a 2′-deoxyuridine analogue with an iodine at the C5 position on the uridine ring (Fig. 23). (De Clercq, 2010, 2013b; Prusoff, 1959) Idoxuridine was one of the first examples of a pyrimidine analogue and was originally developed as an anticancer agent, however, subsequent studies later determined that treatment with Idoxuridine was also associated with profound antiviral activity, most notably against DNA viruses such as HSV (Prusoff, 1959). Other noteworthy C5 modified analogues that were developed early on included 5-trifluorothymidine (Trifluridine), which was primarily used for ocular herpes infections, and 5-bromo-vinyl deoxyuridine (Brivudine), which was utilized for treating VZV (Fig. 23). (De Clercq, 2010, 2013b; Bauer, 1985; Kaufman and Heidelberger, 1964; Whitley, 1996; De Clercq et al., 1979)

As mentioned previously, use of a fluorine in the sugars of the nucleosides was known to be advantageous. This also proved true for the nucleobases. The anticancer drug 5-fluorouracil (5-FU), and the corresponding 2-deoxyribonucleoside floxuridine are important examples of a bioisosteric replacement of fluorine for hydrogen (Fig. 23). In a series of biologically mediated reactions, 5-FU is first converted to a nucleoside and then to its monophosphate, which subsequently becomes part of a ternary complex between thymidylate synthase and its
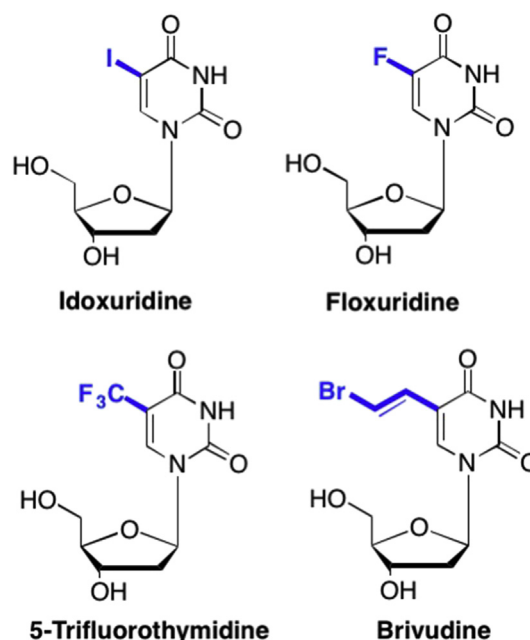
Fig. 23. Examples of typical heterocyclic modifications at the 5-position of the pyrimidine moiety.

cofactor 5,10-methylenetetrahydrofolate (Longley et al., 2003; Santi et al., 1987). Because the hydrogen normally present at C5 is subsequently abstracted by thymidylate synthase, thereby causing the complex to disassemble, which ultimately leads to thymidine (and tetrahydrofolate), replacement of the hydrogen with the fluorine results in a dead-end complex that cannot come apart and therefore does not lead to the production of thymidine (Longley et al., 2003; Santi et al., 1987). Since this process is a critical source of thymidine, and cancer cells need elevated levels of thymidine to replicate, use of 5-FU is highly effective (Longley et al., 2003; Santi et al., 1987). Notably, addition of fluorine at the C5 position also renders cytosine nucleosides stable to deaminases, enzymes that are known to inactivate many nucleosides with amine groups on their bases, further highlighting the importance of this particular structural modification (Secrist et al., 1985; Montgomery et al., 1983; Park et al., 2001b).

Another commonly pursued modification at the C5 position involved addition of various alkyl groups, which were systematically pursued by systematically increasing the length of the alkyl chain one methylene group (Fig. 24). These types of homologous modifications were pursued for two main reasons – one, to increase the drug's lipophillicity to aid in delivery, and two, to potentially increase the fit of the drug into a hydrophobic pocket in an enzyme binding site (Silverman and Holladay, 2014; Dohme et al., 1926). Initial studies revealed that while increasing the chain length often led to an increase in activity, at a certain point this trend reversed and the nucleoside lost activity (Dohme et al., 1926). This is most likely due to the nucleoside becoming too lipophilic, which can lead to aggregation and accumulation in fatty tissues (Silverman and Holladay, 2014; Dohme et al.,
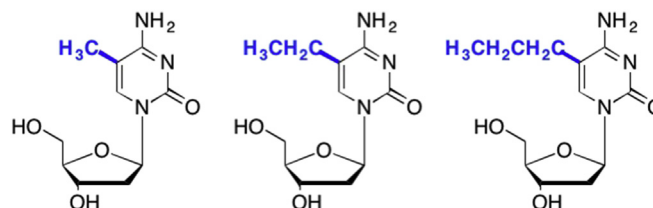
Fig. 24. Example of a homologous series of modifications that increase lipophillicity up to a certain threshold.
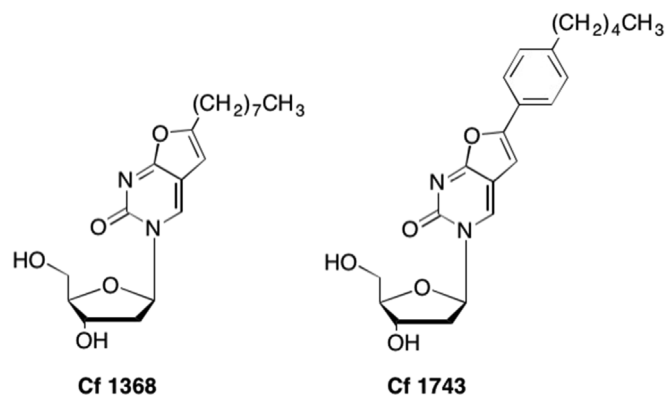
Fig. 25. Examples of bicyclic pyrimidine nucleoside analogues (BCNAs) with potent anti-VZV activity.

1926). While these modifications helped increase our knowledge of the parameters of enzyme binding sites and the importance of lipophilicity, most of these analogues proved to be clinically relevant, and led to the oft quoted phrase, "methyl, ethyl, propyl, butyl, futile"!

These original C5 alkyl modifications led to the discovery of other long chain substituted analogues such as the bicyclic pyrimidine nucleoside analogues (BCNAs) originally discovered by Balzarini and McGuigan (Fig. 25). (Balzarini and McGuigan, 2002; McGuigan et al., 1999) Through structure activity relationship studies, even more potent BCNAs were discovered with high specificity towards VZV treatment (Balzarini and McGuigan, 2002). Analogues CF-1368 and CF-1743 were especially potent, with EC$_{50}$ values of 0.027 ± 0.013 and 0.0002 ± 0.00017 μM compared to Brivudine and Acyclovir (EC$_{50}$ = 0.009 ± 0.004 μM and 3.4 ± 0.67 μM respectively), two analogues already used in the clinic to treat VZV infections (Balzarini and McGuigan, 2002; Andrei et al., 2005). Not only were these analogues extremely potent against VZV, they also demonstrated low cytotoxicity at levels up to 50 μM (Balzarini and McGuigan, 2002; McGuigan et al., 1999). As with the C5 alkyl study, increased branching of the BCNAs was associated with a decrease in antiviral activity, with the optimum length proving to be C8-C10 (McGuigan et al., 1999; Luoni et al., 2005).

3.2. Nitrogen substitutions and rearrangements

As mentioned earlier, adding substituents was not the only type of modification that was routinely tried in an effort to find activity or temper side effects. Other common modifications included removing or relocating various atoms from the nucleobase. For example, removal of a nitrogen from the purine or pyrimidine ring system (referred to as a "deaza" analogues) could be utilized to explore the effect of hydrogen bonding interactions in enzyme binding sites. Given that removal or addition of a strong hydrogen bond donor or acceptor affects reactivity as well as properties at other positions on the bases, this approach can have a profound affect. One important example is 3-deaza-

deoxyguanosine, where the N3 is replaced by a CH (Fig. 26). (Mian and Khwaja, 1983; Liu et al., 2001) Not only did this modification result in broad spectrum antiviral activity against both DNA and RNA viruses, potent antitumor properties against leukemia L1210 and P388 cell lines were also observed (Mian and Khwaja, 1983; Revankar et al., 1984). Other medically relevant deaza analogues are 7-deazaadenosine analogues, such as Tubercidin, where the N7 was replaced by a CH group (Fig. 26). (Olsen et al., 2004; Acs et al., 1964; Itoh et al., 1972) Tubercidin was originally isolated from the bacteria *Streptomyces tubercidicus*, and has demonstrated potent activity as an antibiotic against *Streptococcus faecalis* (Olsen et al., 2004; Acs et al., 1964; Bloch et al., 1967). While many early deaza compounds were purines, others similarly used a deaza approach in pyrimidine analogues, such as 3-deazauridine, where the N3 of the pyrimidine ring was replaced by a CH (Fig. 26). (Ebrahimi et al., 2001; Patching et al., 2005) While the 3-deazauridine analogues did not display meaningful biological activity, these analogues often helped to identify the specific requirements of the various amino acids involved in binding within enzyme binding sites (Patching et al., 2005).

Another common nitrogen modification was the addition of a nitrogen to the purine ring system (referred to as "aza" analogues). This type of modification can introduce new hydrogen bonding donors or acceptors, and depending upon their position in the ring system, can direct the reactivity of the aromatic ring itself towards nucleophilic and electrophilic substitutions. One example of this type of modification is present in 5-azacytidine, an antibiotic analogue originally isolated from *Streptoverticillium ladakanus* (Fig. 27). (Winkley and Robins, 1970) The addition of the extra nitrogen also endowed 5-azacytidine with profound anticancer properties, specifically against acute myelogenous leukemia and MCF07 human breast cancers, as well as in the treatment of myelodysplastic syndrome (Winkley and Robins, 1970; Chang et al., 2014; Gryn et al., 2002; Raj and Mufti, 2006).

While nitrogens can be removed or added to the pyrimidine or purine scaffold, nitrogens can also be repositioned in the ring, thus retaining the same number of nitrogens as the parent nucleoside, but also introducing alternative hydrogen bond donors or acceptors to that can therefore interact with new areas of the enzyme binding site. This is especially true for the adenosine mimic 8-aza-7-deazapyrazole pyrimidine (Fig. 27). Due to the antiparasitic activity associated with this analogue, numerous researchers subsequently attempted to add various substituents to the pyrazole moiety in order to increase the activity, however, to date this approach has not proven particularly fruitful (Petrie et al., 1985; Bhat et al., 1981; Montgomery et al., 1974; Rideout et al., 1982).

3.3. Expanded purine nucleobases

Since changing the size of the sugar ring led to clinically relevant results for some nucleoside analogues, researchers also pursued increasing the size of the nucleobase. In that regard, Nelson Leonard was an early pioneer in the development of base modified nucleosides. He first introduced the nucleoside field to this concept with his benzyl-
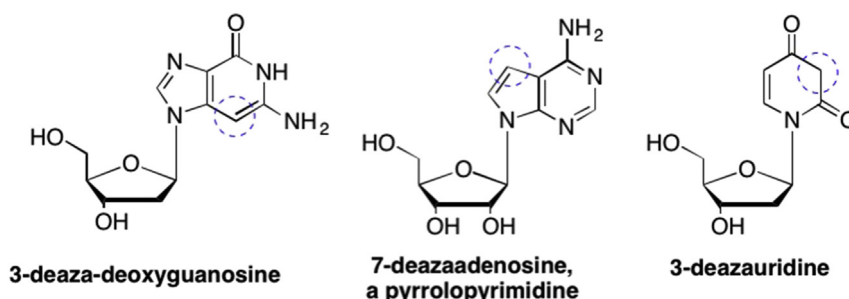

Fig. 26. Examples of "deaza" modifications to the heterobase scaffold where a nitrogen is removed from either the purine or the pyrimidine ring.
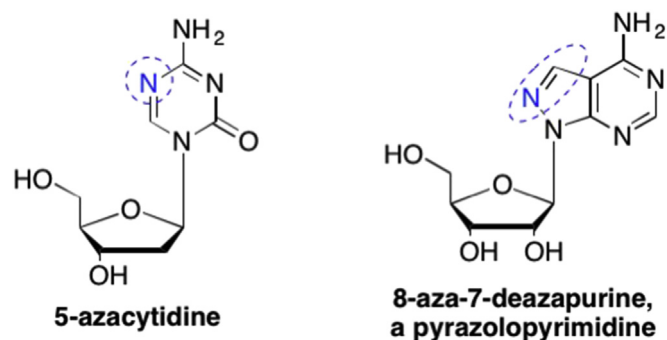
Fig. 27. Examples of "aza" modifications to the heterobase scaffold where a nitrogen is added to either the purine or pyrimidine ring.

Fig. 29. Structures of the "thieno-expanded" purine nucleosides developed by Seley-Radtke based on Leonard's original benzyl-expanded derivatives, where a 5 membered thiophene ring separates the imidazole and pyrimidine components of the nucleobase scaffold.

expanded purines including *lin*-benzoadenosine, as well as the corresponding proximal and distal analogues (Fig. 28). (Leonard et al., 1975, 1976, 1978; Leonard, 1982) These analogues were originally developed in order to probe adenosine metabolizing enzyme binding sites to determine the upper limits of enzyme-substrate recognition (Leonard et al., 1978; Leonard, 1982). Through numerous studies, it was determined that this modification served to not only increase the aromaticity and polarizability of the heterocyclic base, but also increased π-π stacking, an important element of recognition in enzyme binding sites (Leonard et al., 1975, 1976; Lee and Kool, 2006; Lynch et al., 2006; Krueger et al., 2007). Unfortunately, while some of these compounds demonstrated interesting biological activity, none proved to be potent enough to continue on to the clinic.

Many years later, Seley-Radtke took Leonard's shape modifications one step further, and replaced Leonard's benzene spacer ring with various five-membered heteroaromatic rings, most notably, a series of thieno-expanded purines (Fig. 29). The tricyclic thieno analogues were associated with numerous benefits while still retaining the essential recognition elements of the parent nucleoside, including increased aromaticity and polarizability of the base (Seley-Radtke et al., 2008; Zhang et al., 2008; Wauchope et al., 2012; Chen et al., 2015). These analogues are also smaller than Leonard's benzyl spacer derivatives, thus can base pair more readily (Seley-Radtke et al., 2008; Zhang et al., 2008; Wauchope et al., 2012). These shape modified nucleosides showed some interesting biological activity in several areas including HCV and cancer (Wallace et al., 2004; Seley et al., 2000), as well as to serve as probes in various enzyme binding sites (Quirk and Seley, 2005), however, the synthesis of these analogues was excessively tedious and plagued with overall unacceptably low yields, thus have not been pursued extensively since the initial studies.

4. Other structural modifications

While numerous analogues with either a sugar or a nucleobase modification were employed, researchers have of course, not been limited to one or two modifications per analogue, and, as such, many analogues feature multiple modifications to the nucleobase and/or
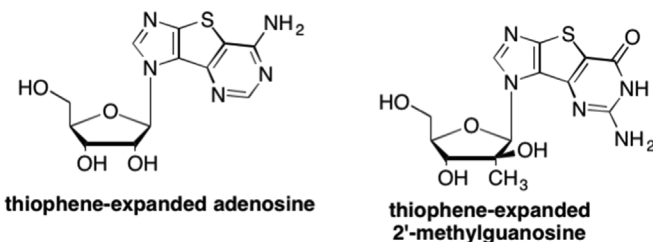
sugar, including double modifications to the same position on the sugar, as well as to the glycosidic bond. Although the more complex nucleoside/tide analogues will be reviewed more extensively in the second paper of this series, there are several additional classes of nucleosides that will be briefly covered below as they fall into some of the categories already discussed above.

4.1. C-nucleosides

As mentioned previously, one of the limiting factors in the development of nucleoside analogues is stability of the glycosidic bond to cleavage by various glycoside hydrolases. While some researchers opted to remove the furanose oxygen and create carbocyclic analogues to overcome issues with the glycosidic bond instability, others attempted to remove the N3 nitrogen in the purine ring to create C-nucleosides (Fig. 30). (De Clercq, 2016b; Stambaský et al., 2009; Temburnikar and Seley-Radtke, 2018)

One of the first C-nucleosides discovered was pseudouridine, a naturally derived nucleoside analogue, where the pyrimidine ring is attached to the ribose moiety at C5 instead of C6 (Fig. 31). (De Clercq, 2016b; Stambaský et al., 2009; Srinivasan and Borek, 1964; Charette and Gray, 2000) Pseudouridine is most commonly found in both transfer RNA and ribosomal RNA and is the most abundant naturally occurring C-nucleoside (Stambaský et al., 2009; Charette and Gray, 2000). While no significant biological activity has been associated with pseudouridine, its discovery aided in the discovery and identification of other medically relevant C-nucleosides (Stambaský et al., 2009). One such analogue is Showdomycin, which is a naturally occurring 5-membered uridine mimic first isolated in 1964 from *Streptomyces showdonesis* by Nishimura et al. (Fig. 31). (Nishimura et al., 1964) Showdomycin proved to be an effective antibiotic against several Gram-positive and Gram-negative bacteria, particularly against *Streptococcus haemolyticus* and *Streptococcus pyogenes* (Roy-Burman et al., 1968; Darnall et al., 1967). Furthermore, this analogue has also demonstrated potent antitumor activity against Ehrlich mouse ascites as well as HeLa cells *in vitro* (Stambaský et al., 2009; Roy-Burman et al., 1968; Darnall et al., 1967).

Other important examples of C-nucleosides include the aforementioned Immucillin-H (Forodesine) and BCX-4430 (Fig. 32). (Warren

Fig. 28. Structures of the "benzene-expanded" purine nucleosides originally developed by Leonard, in which there is a benzene spacer ring separating the imidazole and the pyrimidine components of the purine nucleobase scaffold.
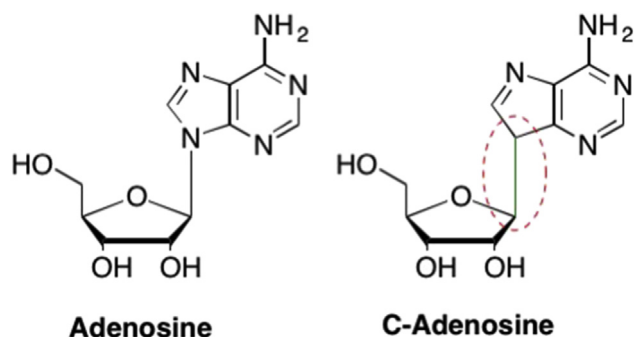
Fig. 30. Comparison of the structure of adenosine and the corresponding C-adenosine analogue where the glycosidic bond is removed due to removal of the N1 nitrogen in the purine ring.
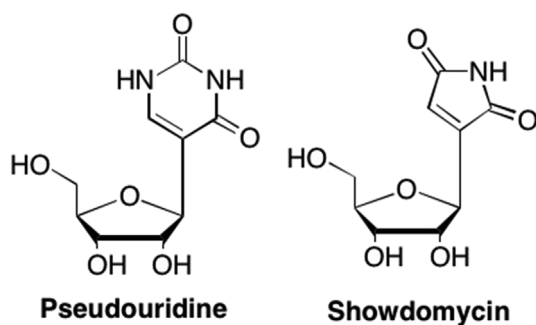

Fig. 31. Examples of early naturally occurring C-nucleosides Pseudouridine and Showdomycin.
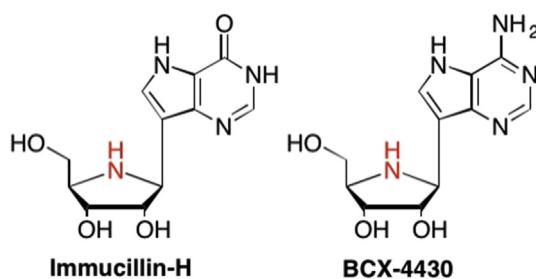

Fig. 32. Structure of C-nucleosides with an imino sugar.

et al., 2014; Bergeron-Brlek et al., 2015; Korycka et al., 2007) While both Immucillin-H and BCX-4430 feature an imino sugar, where the furanose oxygen has been replaced with a secondary amine, not all C-nucleosides feature this type of sugar (De Clercq, 2016b; Stambaský et al., 2009; Korycka et al., 2007; Boutureira et al., 2013). The addition of the NH in the imino sugar imparts a significant benefit over corresponding carbocyclic sugars in that the nitrogen is a hydrogen bond donor (whereas the furanose oxygen was simply a hydrogen bond acceptor), thus expanding the potential interactions of imino sugars in enzyme binding sites (Schramm and Tyler, 2003; Bergeron-Brlek et al., 2015). This benefit is especially seen in Immucillin-H, a transition state analogue that inhibits purine nucleoside phosphorylase (PNP), which in turn inhibits the growth of malignant T cells in human leukemia (Kicska et al., 2001; Korycka et al., 2007; Bantia et al., 2001). Similarly, BCX-4430 has demonstrated the ability to be a broad spectrum antiviral agent, with micromolar activity against numerous viruses including Ebola, Zika, Yellow Fever, and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), just to name a few (Warren et al., 2014; Julander et al., 2014, 2017; Taylor et al., 2016; Eyer et al., 2017).
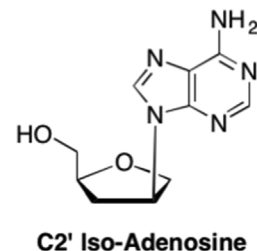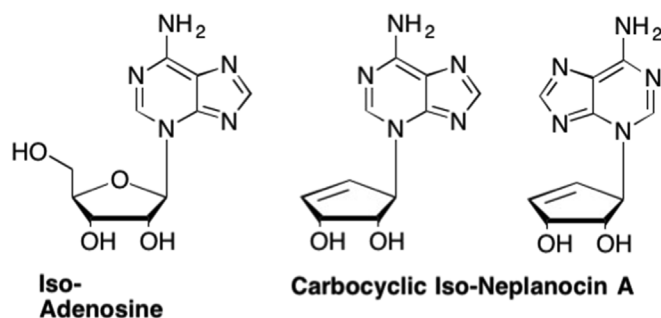

Fig. 33. Examples of Iso-adenosine analogues where the sugar moiety is now attached to the N3 instead of the N7 as in natural nucleosides. Iso-analogues can also be formed with attachment of the nucleobase at the 2′-carbon instead of the 1′-carbon.

4.2. Iso-nucleosides

Other nucleosides that feature an altered glycosidic bond are the iso-nucleosides, which were also developed by Nelson Leonard and are represented by Iso-adenosine (Iso-A), wherein the adenine base is connected to the sugar at N3 instead of N9 (Fig. 33). (Leonard and Laursen, 1963, 1965; Kumar et al., 1988; Leonard et al., 1986) This modification was associated with various biological activities, most notably against lymphoblastic leukemia cells *in vitro* (Gerzon et al., 1966). Unfortunately, Iso-A is not particularly stable since it is hyperconjugated and has a tendency to rearrange in an effort to restore the aromaticity, thus resulting in re-forming adenosine (Seley et al., 2003). Furthermore, Iso-A was also unstable due to the presence of a glycosidic bond, rendering the analogue susceptible to cleavage by both acids, bases, and glycosidic hydrolases (Seley et al., 2003). This led to further investigation by Seley-Radtke et al., wherein a carbocyclic Iso-Neplanocin A was synthesized (Fig. 33). (Seley et al., 2003) This analogue overcame the instability of the glycosidic bond, with the N3 product preferably formed (Seley et al., 2003). Unfortunately none of these analogues exhibited any clinically useful levels of antiviral or anticancer activity.

More recent examples of iso-nucleosides were introduced by Nair et al., and featured the glycosidic bond relocated to C2′ on the sugar (Fig. 33). (Nair and Nuesca, 1992; Nair et al., 1995; Nair and Jahnke, 1995) These analogues proved to exhibit much greater stability in acidic conditions compared to other dideoxy analogues, where the half-life of C2′-iso-adenosine was greater than 16 days at pH 1 compared to a half-life of dideoxyadenosine of 0.5 h at pH 3 (Nair and Nuesca, 1992; Nair et al., 1995; Nair and Jahnke, 1995). Moreover, this analogue demonstrated potent micromolar anti-HIV activity *in vitro* with no apparent cytotoxicity (Nair and Nuesca, 1992; Nair et al., 1995; Nair and Jahnke, 1995). While these analogues possessed potent activity against HIV integrase, they have not been extensively pursued for other purposes (Nair et al., 1995; Nair and Jahnke, 1995).

4.3. L-nucleosides

Most of the examples of modified nucleosides discussed thus far were initially synthesized as racemic mixtures of the D and L
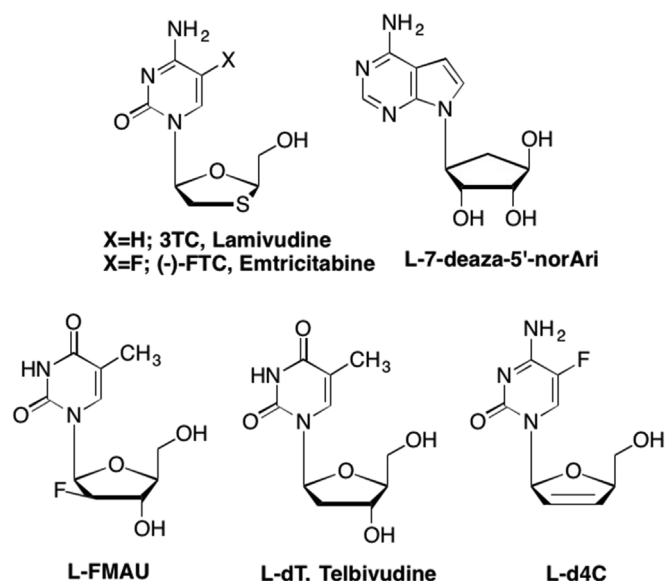
Fig. 34. Examples of the L-enantiomer of nucleoside analogues that were assumed to be inactive since naturally occurring nucleosides are the D-enantiomers. Later it was shown that the L-nucleosides exhibit potent biological activity against a variety of pathogens.

nucleosides, however, in the 1980s it became apparent that, in general, only one of the enantiomers in a racemic mixture was responsible for the activity. In addition, it was also found that in some cases the L-enantiomer could prove to be the cause of toxicity, or to interfere with or lower the activity of the more active enantiomer, although this wasn't always true. For example in some cases, the L-enantiomer showed different activities or even synergistic activities. Indeed, some L nucleosides have exhibited quite potent antiviral activities when the corresponding D nucleosides did not, particularly against HBV (Gumina et al., 2001, 2007).

The most notable examples of biologically relevant L nucleosides were FTC and 3TC, identified earlier in Fig. 6 and again below in Fig. 34. Resolution of the two enantiomers of (±)-BCH-189 to give the L-enantiomer (dubbed 3TC) proved to quite important, as 3TC was found to be exponentially more active against both HIV-1 and HBV (EC$_{50}$ 0.002 μM and 0.01 μM) compared to its D-counterpart (EC$_{50}$ 0.2 μM and 0.5 μM) (Schinazi et al., 1992a, 1992b; Gumina et al., 2001; Jarvis and Faulds, 1999). Moreover, not only was 3TC more potent than the D-enantiomer or the racemic mixture (±)-BCH-189, 3TC also displayed less toxicity, likely due to the fact that it was quite resistant to deamination (Gumina et al., 2001; Chang et al., 1992). The potent activity against both HIV-1 and HBV also makes 3TC one of the leading treatments of coinfections of hepatitis B and HIV in patients (Gumina et al., 2001; Mathé and Gosselin, 2006).

Another L-nucleoside that garnered much attention early on was telbivudine (L-dT) for its potent effect in the treatment of chronic Hepatitis B infections (Fig. 34). (Han, 2005; Kim et al., 2006) L-dT is the L-enantiomer of naturally occurring thymidine, and once transformed into the active triphosphate form, is incorporated by viral DNA polymerase and induces chain termination (Han, 2005; Kim et al., 2006). In comparison to other nucleoside analogues used to treat HBV infections such as 3TC, treatment with L-dT elicits higher therapeutic and biochemical responses in patients (Lai et al., 2005, 2007). Moreover, L-dT is specific for HBV polymerase, and is not recognized by human polymerases, making treatment with L-dT safe and effective (Kim et al., 2006; Semizarov et al., 1997; Bryant et al., 2001a).

Another early L-nucleoside was 1-(2-deoxy-2-fluoro-β-L-arabino-furanosyl)-5-methyluracil (L-FMAU), a thymidine analogue that displayed potent antiviral activity against HBV (EC$_{50}$ = 0.1 μM in Hep-G2/

2.2.15 cells) with no toxicity reported up to 100 μM *in vitro* (Fig. 34). (Chu et al., 1995; Du et al., 1999) Initially there was hope that L-FMAU could be utilized in treatment of chronic HBV infections, however ultimately more potent drugs were discovered and it was no longer used clinically (Chu et al., 1995; Du et al., 1999; Wright et al., 1995; Peek et al., 2001). Another example of a promising L-nucleoside was L-7-deaza-5′-noraristeromycin, which not only featured an L-nucleoside, but also utilized the 5′-nor carbocyclic sugar scaffold as well as a deazapurine heterobase (Fig. 34). (Seley et al., 1997a, 1998; Siddiqi et al., 1995) Initial studies found potent activity for this analogue against several pathogens including HBV and four strains of African trypanosomes, one of which is known to cause east African sleeping sickness (Seley et al., 1997a, 1998). Finally, Elvucitabine, or L-d4FC, was a cytidine dideoxynucleoside reverse transcriptase inhibitor that also demonstrated micromolar activity against HBV (Fig. 34). (Mathé and Gosselin, 2006; Bryant et al., 2001a, 2001b; Li et al., 1998) The potent activities demonstrated by some of these analogues, particularly against HBV, has led to continued interest in pursuing L-nucleosides.

5. Conclusions

Nucleoside analogues continue to play an essential role in the treatment of diseases, thus the pursuit of new nucleoside analogues is critical to solving global health issues such as emerging and reemerging infectious diseases and other pathogens. The examples covered in this review are by no means meant to be exhaustive. It would be impossible to show all of the various nucleoside modifications that have been synthesized in each of these broad categories, however, it was our intention to provide a flavor of the historical progression of nucleoside development and the various types of structural modifications that have been pursued to date. As the field has progressed and new information has become available about nucleoside structure, enzyme recognition, and biological activity, new and more complex modifications have been pursued, including multiple modifications to the same scaffold. Those and other types of approaches will be reviewed in the second paper in this series.

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