ISSN: 2357-0547 (Print)
ISSN: 2357-0539 (Online)

Review Article / JAPR
Mahmoud et al., 2018, 2 (2), 73-88

Journal of Advanced Pharmacy Research

Antiviral Nucleoside and Nucleotide Analogs: A Review

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Submitted on: 14-06-2017; Revised on: 26-11-2017; Accepted on: 26-11-2017

ABSTRACT

Virus infections are an increasing and probably lasting global risk. Nucleoside and nucleotide analogs represent the largest class of antiviral drugs. Early success in the treatment of human immunodeficiency virus infection and the recent approval of sofosbuvir as phosphoramidate nucleoside prodrug for chronic hepatitis C have provided proof of concept for important this class of compounds as an antiviral agent. This review summarizes the antiviral activity of nucleoside and nucleotide analogs and their recent application.

Keywords: *Antiviral; Ebola virus; HCV; Nucleoside; Nucleotide; Zika virus*

Nucleoside analogs are the subunits of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). They are consisting of a sugar moiety linked to a purine or pyrimidine base through a β-N-glycosidic bond through N_9 of the purine and N_1 of the pyrimidine heterocyclic base.[1] Nucleotides are phosphate ester of nucleosides, (**Figure 1**).

The purine bases (adenine and guanine) and the pyrimidine base cytosine are common for both RNA and DNA. However, the pyrimidine base uracil is only found in RNA; whereas thymine, the base-pairing equivalent, is found in DNA.[1] Invariably, in all naturally occurring nucleosides, the configuration at the anomeric center (C-1`) is β.[1] There are two major categories: N-nucleosides and C-nucleosides. N-nucleosides are having a bond between the anomeric carbon of the sugar moiety and the nitrogen of the base moiety, whereas C-nucleosides have a bond between the anomeric carbon of the sugar moiety and the carbon of the base. The nucleoside analogs can be modified in their sugar or nucleobase moieties to develop new drugs with potent biological activity, (**Figure 2**).

The modifications in the sugar moiety of nucleosides include changes of the sugar substituents, replacement of the oxygen with another atom, addition of heteroatom in the sugar ring, modifications in ring size and replacement with acyclic moiety. These alterations may produce remarkable variations in biological activity and degree of selective toxicity, according to their respective chemical and physical properties. **Changes of the sugar substituents:** changes of hydrogen or hydroxyl groups at the 2`-, 3`- and 4`- positions with other groups have produced compounds with a broad range of biological activity. For example, Zidovudine[2] (with azido group at the 3'-position) is used for the treatment of HIV.

Replacement of the oxygen with another atom: Replacement of the 4`-ring oxygen with other heteroatoms affect both the conformation and the biological properties of the nucleoside. Nucleosides whose sugar ring oxygen is replaced by carbon, nitrogen, sulfur, and phosphorus are commonly called carbocyclic nucleosides, azanucleosides, thio-nucleosides, and phosphanucleosides, respectively.

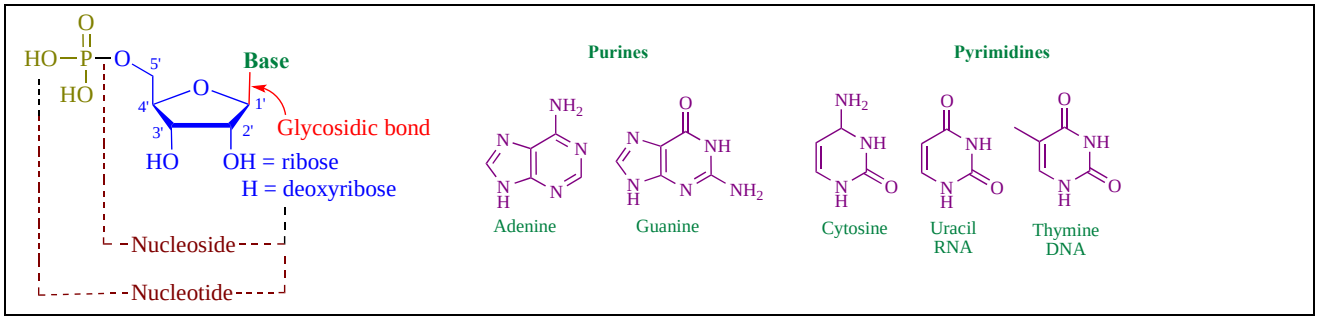


Figure 1. General structure of nucleoside and nucleotide analogs.

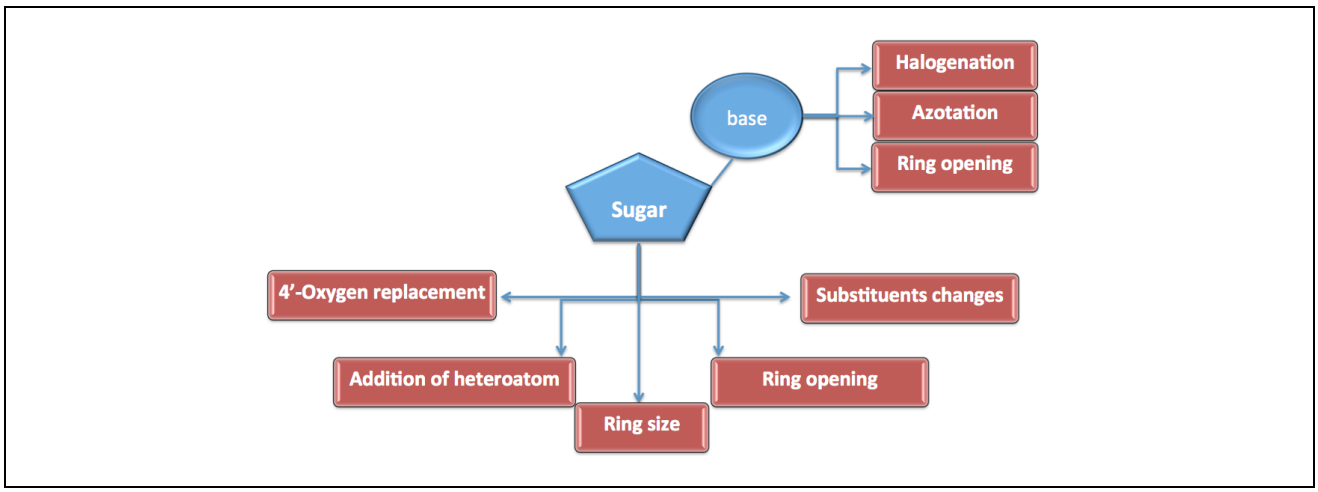


Figure 2. General chemical modifications of nucleoside analogs.

Carbocyclic nucleosides, they often display enhanced biostability because of their stability toward hydrolysis by phosphorylases. This replacement improved enzymatic resistance and reduced toxicity of the carbocyclic nucleosides compared with the conventional ones.[3] Aristeromycin and Neplanocin A are examples of carbocyclic natural products (**Figure 3**). Whereas, Abacavir is an example of FDA approved carbocyclic drug for treatment of HIV as shown in **Table 1**. **Azanucleosides,** in their original definition, are nucleoside analogs where the oxygen atom of the furanose ring is replaced by a nitrogen atom. Later on, this concept is extended to compounds where the pyrrolidine core is replaced by piperidine, azetidine or other nitrogen-containing rings, including heterocycles with two heteroatoms, such as morpholino, thiazolidinyl and isoxazolidinyl derivatives. The replacement of the heterocyclic core by an acyclic chain containing a nitrogen atom has also been explored, and these compounds are usually called "acyclic azanucleosides". Many azanucleosides are potent antiviral, anticancer, and antimicrobial agents. For example, forodesine[4] is in advanced clinical trials for the treatment of T-cell leukemia (**Figure 3**). **Thionucleosides,** one of the various replacement options for oxygen in the sugar ring of nucleosides is sulfur, which is the most attractive options. It was hoped that this change in the size and electronegativity might be tolerated in allowing the compounds to retain the activity of their 4`-oxygen analogs in addition to be accompanied by decreased toxicity and increased metabolic stability as a result of decreased susceptibility to the action of nucleoside phosphorylases.[5] For example, Brivudine (BVDU) is known to be a potent and selective inhibitor of herpes simplex virus (HSV) type 1 and varicella zoster virus (VZV). However, BVDU is rapidly metabolized to the inactive E-5-(2-bromovinyl)uracil and 2-deoxyribose-1-phosphate by pyrimidine nucleoside phosphorylase. In contrast, 4`-thio BVDU is resistant to pyrimidine nucleoside phosphorylase and showed a higher chemotherapeutic index than BVDU,[6] (**Figure 3**). **Phosphanucleosides**, in which the oxygen of the sugar moiety is replaced by phosphorus atom. Among these analogs, several compounds with anti-cancer activity have recently been discovered.[7]

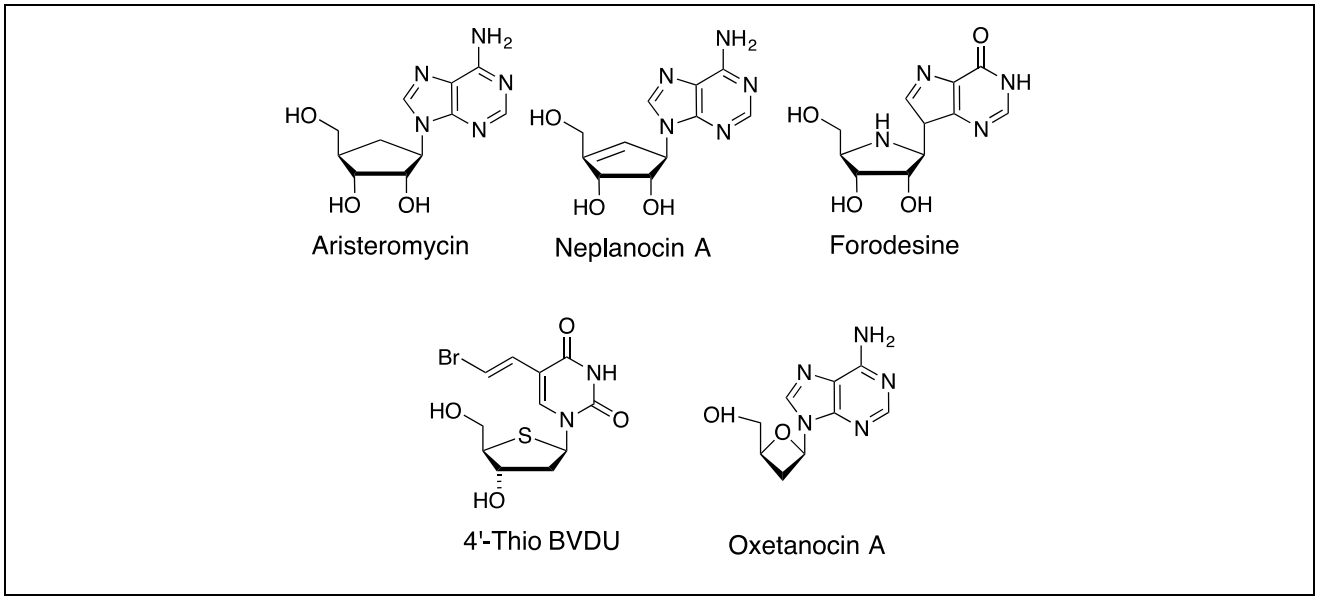


Figure 3. Examples of therapeutically active nucleoside analogs.

Two heteroatoms in the sugar ring: nucleosides containing sugar moieties with two heteroatoms have proven to be quite potent antiviral agents, especially the dioxo- and oxothionucleosides,[8] such as Lamivudine (Epivir) which is used for the treatment of HIV. **Ring size:** the isolation of oxetanocin A,[9] a nucleoside which contains an oxetane ring in place of furanose moiety, from *Bacillus megaterium* led to an interest in the synthesis of oxetanocin analogs and other nucleosides containing a 4-ring moiety in place of the normal furanose sugar (**Figure 3**).[10] **Acyclic moiety:** the studies had shown that intact sugar was not necessary to mimic nucleoside binding to the enzyme, leading to the development of acyclic nucleosides. On the other hand, they differ from conventional nucleosides in having an acyclic moiety replacing the sugar ring. The first acyclic nucleoside to show selective inhibition of HSV replication was acyclovir, a guanosine-based nucleoside whose clinical effectiveness as an antiviral agent has stimulated a large interest in acyclic nucleosides.[11]

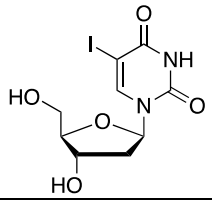
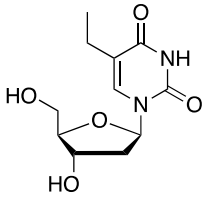
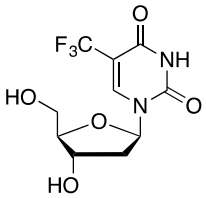
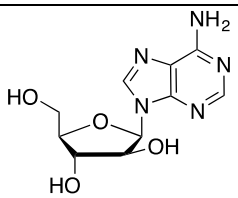
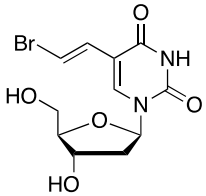
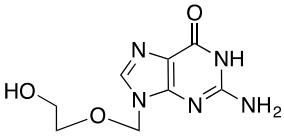
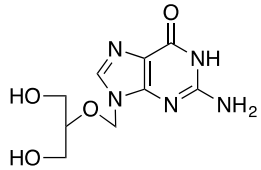
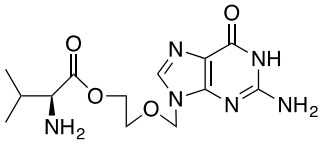
The modifications in the base moiety of nucleoside analogs have resulted in a variety of therapeutic applications. There are different strategies in the modification of the nucleobase such as halogenation like 2`-3`-dideoxy-5-fluoro-3`-thiacytidine (Emtricitabine),[12] or as purine modification like 1,2,4-triazole-3-carboxamide analogue (Ribavirin),[13] which is used to stop viral RNA synthesis (**Table 1**).

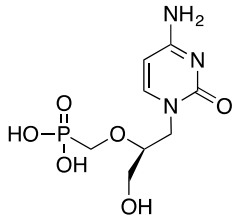
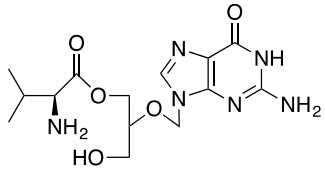
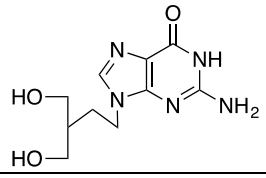
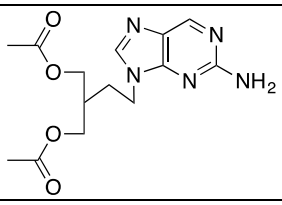
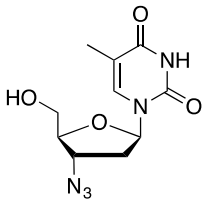
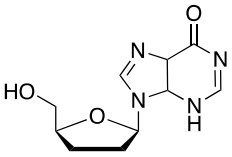
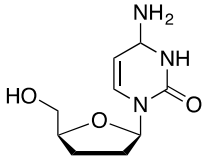
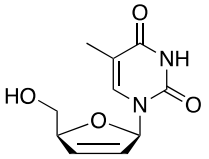
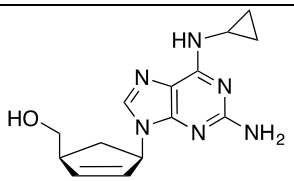
L-nucleosides, for a long time, it was assumed that nucleoside analogs have been only D-configuration and could exhibit biological activity owing to the believed stereospecificity of enzymes in the living system. At the beginning of the 90 s, this assumption was reevaluated, and L-nucleoside enantiomers emerged as a new class of antiviral agents. Although the first synthesis of an L- nucleoside was reported in 1969,[14] little attention was paid to L-nucleoside analogs until the discovery of lamivudine in 1995.[15] The enantiomers of the natural D-nucleosides, are not generally recognized by normal mammalian enzymes, but are recognized by virus-encoded or bacterial enzymes. This results in minimal host toxicity and good antiviral/antibacterial activity. Therefore L-nucleoside analogs have recently become of interest in view of their potential antiviral activity against HBV[12] as Emtricitabine and Telbivudine.

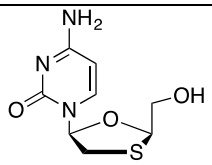
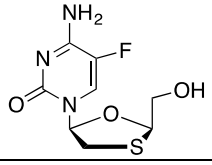
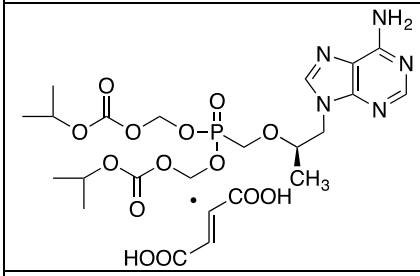
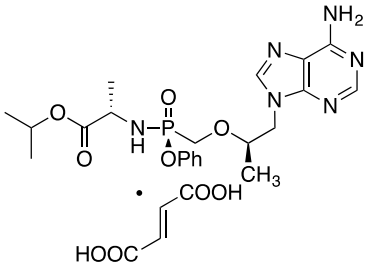
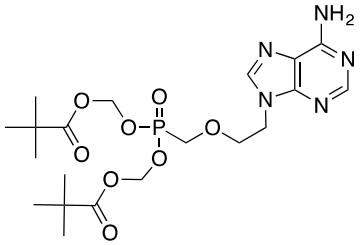
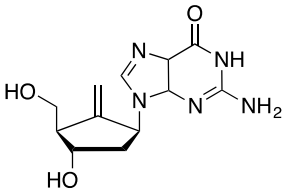
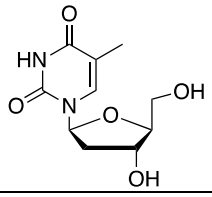
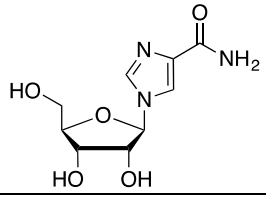
- **Antiviral activity of nucleoside and nucleotide analogs**

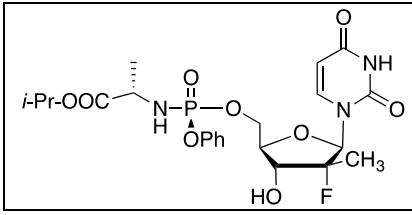
Recently, we are facing an outburst of new and emerging viral diseases, as new strains of hepatitis and herpes viruses, West-Nile virus, Zika virus, and some exotic viruses that have the potential for a pandemic outbreak. Nucleoside analogs have been the drugs of choice in the treatment of several diseases caused by herpes simplex virus (HSV), human cytomegalovirus (HCMV), varicella zoster virus (VZV), human immunodeficiency virus type 1 (HIV-1) and human hepatitis B (HBV) and C (HCV) virus[16]. Currently, there are over twenty FDA approved nucleoside and nucleotide analogs that are used as antiviral agents for several infections such as different types of viral hepatitis, human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) and herpes virus infections,[16] (**Table 1**).

Table 1. FDA approved nucleos(t)ide analogs as antiviral drugs

Structure	Compound	Virus	Company
	Idoxuridine, IDU, Herplex	HSV, VZV	GSK, 80s, no FDA label
	Edoxudine, EDU, Aedurid	HSV	Upjohn, 1969
	Trifluridine, TFT, Viroptic	HSV	King Pharmaceutical 1980
	Vidarabine, Ara-A, Vira-A	HSV, VZV	Parkedale pharmaceuticals, no FDA label
	Brivudine, BVDU, Helpin	HSV, VZV	Berlin Chemie, 80s, no FDA label
	Acyclovir, ACV, Aciclovir	HSV, VZV	GSK, 1982
	Ganciclovir, GCV, Cytovene	CMV	Hoffmann-La Roche, 1989
	Valaciclovir, VACV, V altrex	HSV, VZV, CMV	GSK, 1996

	Cidofovir, CDV, Vistide	CMV in AIDS	Gilead Sciences and Pfizer, 1996
	Valganciclovir, VGCV, Valcyte	CMV	Hoffmann-La Roche, 2001
	Penciclovir, PCV, Denavir	HSV	Novartis, 2002
	Famciclovir, FCV, Famvir	HSV	Novartis, 2007
	Zidovudine, AZT, Retrovir	HIV	GSK, 1987
	Didanosine, ddI, Videx	HIV	BMS, 1991
	Zalcitabine, ddC, Hivid	HIV	Hoffmann-La Roche, 1992
	Stavudine, d4T, Zerit	HIV	BMS, 1994
	Abacavir, ABV, Ziagen	HIV	GSK, 1998

	Lamivudine, 3TC, Epivir	HIV then HBV	GSK, 1995
	Emtricitabine, FTC, Emtriva	HIV, then HBV	Gilead Sciences, 2003
	Tenofovir disoproxil fumarate, TDF, Viread	HIV, then HBV	Gilead Sciences, 2008
	Tenofovir alafenamide fumarate, TAF, vemlidy	HIV, HBV	Gilead Sciences, 2015
	Adefovir dipivoxil, ADV, Hepsera	HBV	Gilead Sciences, 2003
	Entecavir, ETV, Baraclude	HBV	MS, 2004
	Telbivudine, LdT, Tyzeka	HBV	Novartis, 2006
	Ribavirin, RBV, Virazole	HCV, Influenza, Flaviviruses, hemorrhagic viruses, RSV	First developed by ICN Pharmaceuticals, 1980, no FDA label

	Sofosbuvir, Sovaldi	HCV	Gilead Sciences, 2013

The era of antiviral drug therapy started with Idoxuridine (IDU). In 1959, it was synthesized by Prusoff as a potential anticancer drug.[17] Furthermore, it was shown in 1961 to possess activity against HSV by Herrmann.[18] IDU is still used in the topical treatment of herpetic eye infections. After that, a variety of biologically interesting and promising nucleosides have been discovered, some of them are being used clinically or are undergoing preclinical or clinical development. The 2`-deoxynucleosides as Idoxuridne (IDU),[18] Trifluridine (TFT),[19] Edoxudine (EDU),[20] Vidarabine and Brivudine[21] (BVDU) have been used for the treatment of herpes viruses as DNA polymerase inhibitors. Acyclic nucleosides as Acyclovir (ACV), Ganciclovir (GCV), Valaciclovir (VACV), Cidofovir (CDV), Valganciclovir (VGCV), Penciclovir (PCV) and Famciclovir (FCV) have been used for the treatment of herpes viruses (**Table 1**).[22]

The 2`,3`-dideoxynucleosides (ddNs) have proved to be the most effective therapeutic agents against HIV because the absence of 3`-hydroxyl group can be lead to the termination of DNA sequence such as Zidovudine (AZT), Didanosine (ddI), Zalcitabine (ddC), Stazudine (d4T)[23] and Abacavir[24] (ABV). L-nucleosides as Lamivudine (3TC) and Emtricitabine (FTC) and acyclic nucleoside prodrugs as Tenofovir disoproxil fumarate (TDF), Tenofovir alafenamide (TAF)[25] have been used for the treatment of HIV and HBV as reverse transcriptase inhibitors. Adefovir dipivoxil (ADV), Entecavir (ETV) and Telbivudine (LdT)[26] have been approved for treatment of HBV as reverse transcriptase inhibitors. Ribavirin[13] (RBV) was approved for medical use in 1986 and used to treat hepatitis C and viral hemorrhagic fever. Currently, Sofosbuvir (SOF) [27] has been approved for the treatment of HCV as non-structural 5B (NS5B) polymerase inhibitor.

Mechanism of action of nucleoside analogs

Therapeutic nucleoside and nucleotide analogs have the same metabolic pathways as endogenous nucleosides and nucleotides (**Figure 4**). Nucleoside and nucleotide analogs enter cells through specific nucleoside transporters.[28] Inside the cell, the nucleoside analog undergoes an initial rate-limiting phosphorylation step by a nucleoside kinase, which leads to the production of a monophosphate metabolite. A second phosphorylation step is then performed by nucleoside monophosphate kinase, and the third phosphorylation step is performed by nucleoside diphosphate kinase. Triphosphorylated nucleosides are the active forms of these drugs and they act as inhibitors for intracellular essential enzymes, such as viral polymerases or act as a substrate for the viral enzyme and incorporated into newly synthesized nucleic acid by competition with their normal counterparts. The incorporation of nucleoside or nucleotide analogs into DNA or RNA may induce either the termination of chain elongation or the accumulation of mutations in the viral progeny.[16]

In addition to participation in RNA transcription as the substrates, nucleoside 5`-triphosphates (NTPs) are involved in many biological regulations and pathways. To transcribe RNAs and investigate the biological systems, many native and modified NTPs are synthesized either chemically or enzymatically. Since the first chemical synthesis of NTPs was accomplished six decades ago,[29] a large number of chemical strategies have been developed to effectively synthesize nucleoside triphosphates in the past decades. Because of the drawbacks of enzymatic synthesis, such as the substrate specificity, yield and cost, chemical synthesis is still a better choice for preparing a large quantity of nucleoside triphosphates, especially those with modifications.[30] In spite of many synthetic strategies developed including one-pot synthesis such as Yoshikawa protocol,[31-33] Ludwig and Eckstein protocol[34,35] and Borch protocol, [36] a convenient synthesis of the 5`-triphosphates directly from unprotected nucleosides with high regioselectivity still remains a challenge. [30]

Nucleoside monophosphate prodrugs

These nucleoside analogs depend on cellular kinases to undergo addition of phosphate groups to form the corresponding active nucleoside triphosphate to express their therapeutic effects.[37] However, nucleoside triphosphates cannot be considered as a viable drugs as they usually have poor chemical stability with a high polarity that prevent them from transporting across cell membranes. During the nucleoside analog phosphate activation process, the first

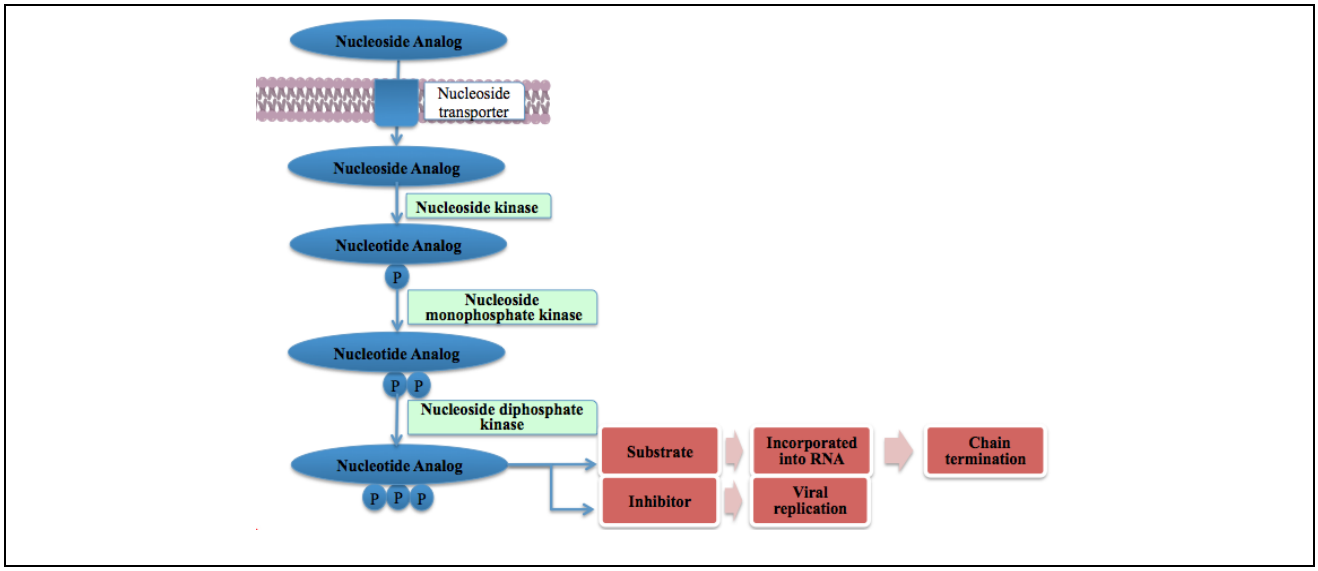


Figure 4. Mechanism of action of nucleoside analogs[16].

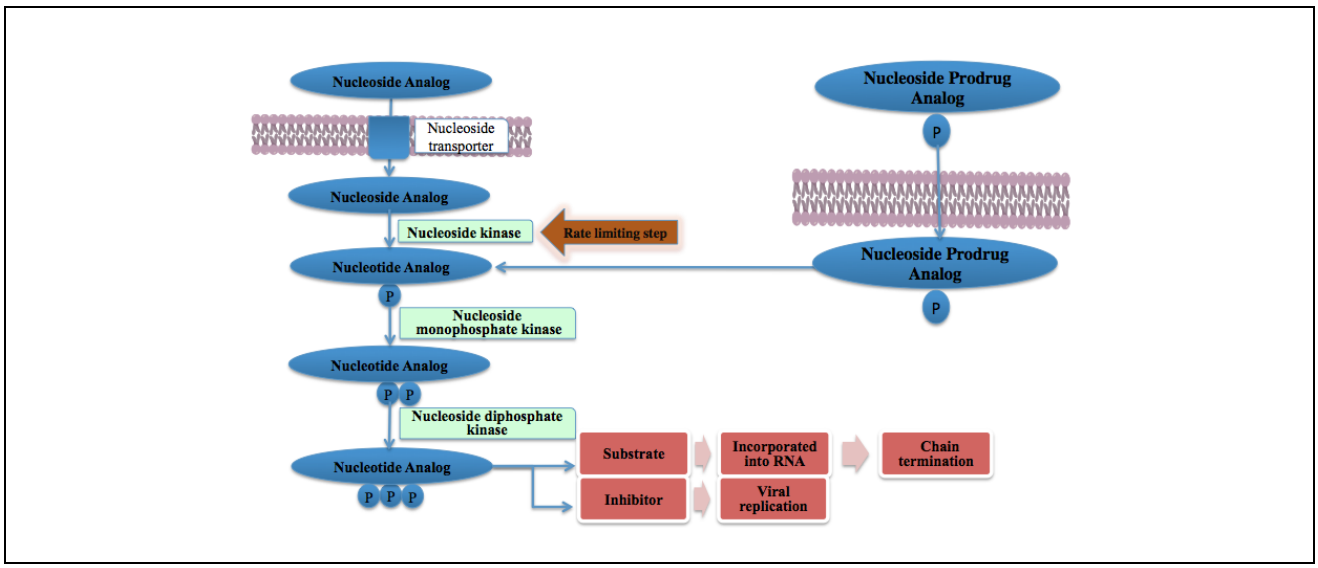


Figure 5. General strategy for nucleoside prodrug[16].

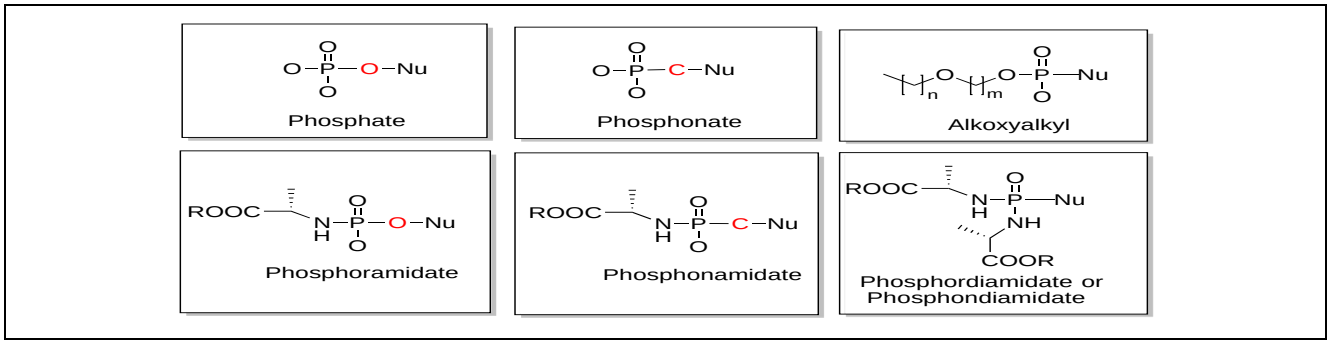


Figure 6. Functional group names of P (V) moieties.

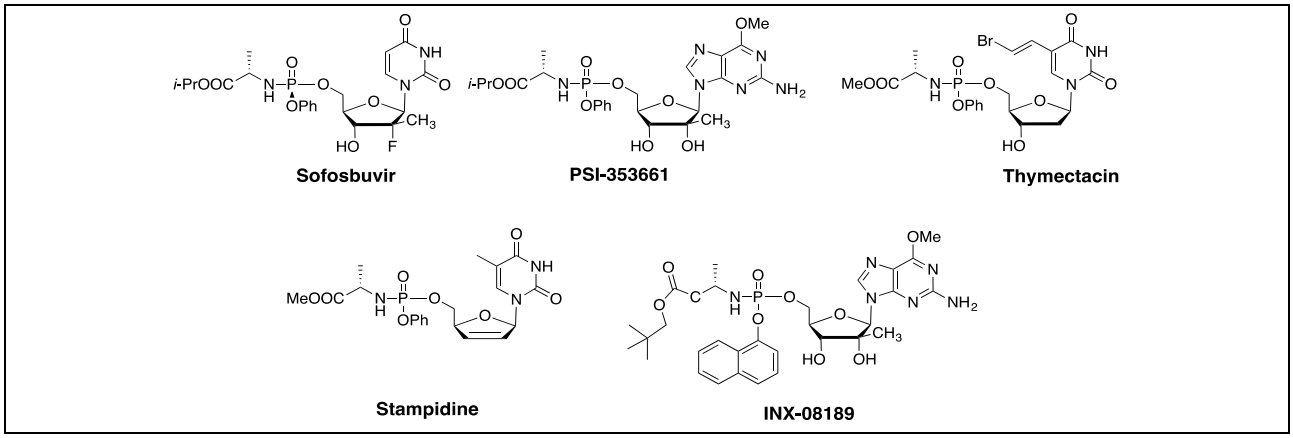


Figure 7. Phosphoramidate prodrugs in clinical trials or FDA approved.

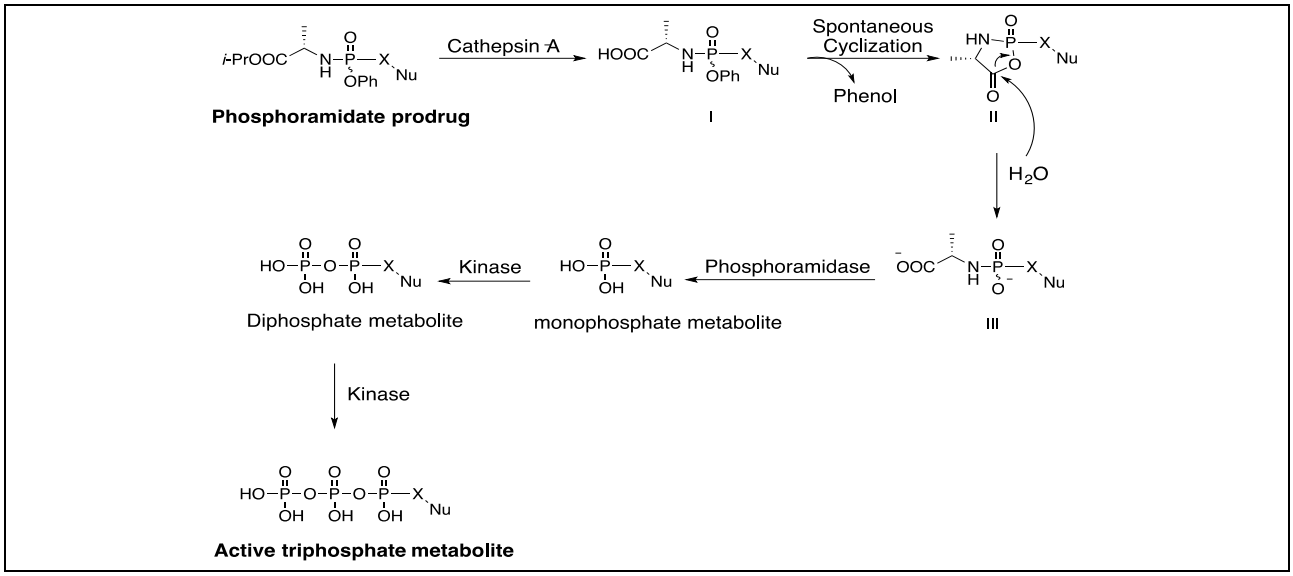
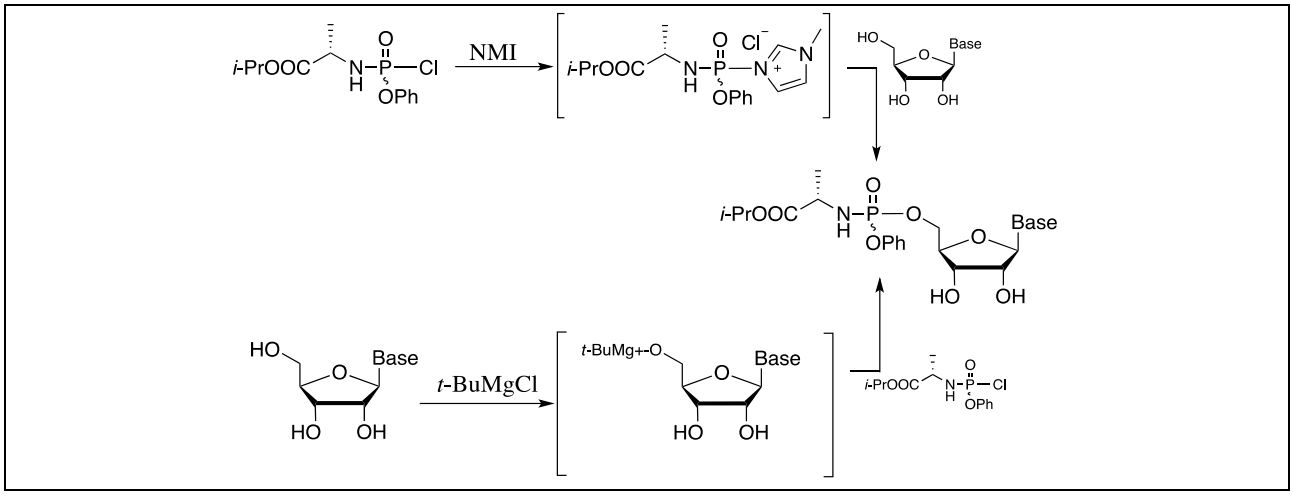
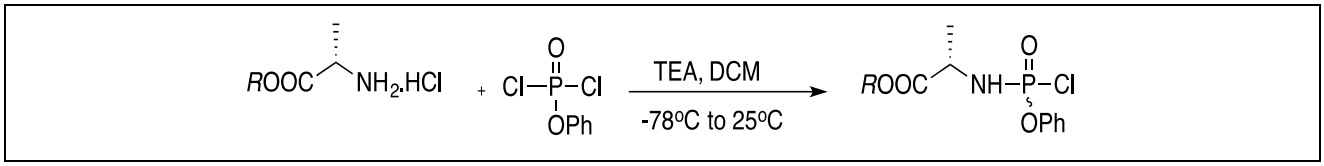


Figure 8. Metabolism of phosphoramidate prodrugs.



Scheme 1. Mechanism of synthesis of phosphoramidates nucleosides.



Scheme 2. Synthesis of phosphorylating reagents.

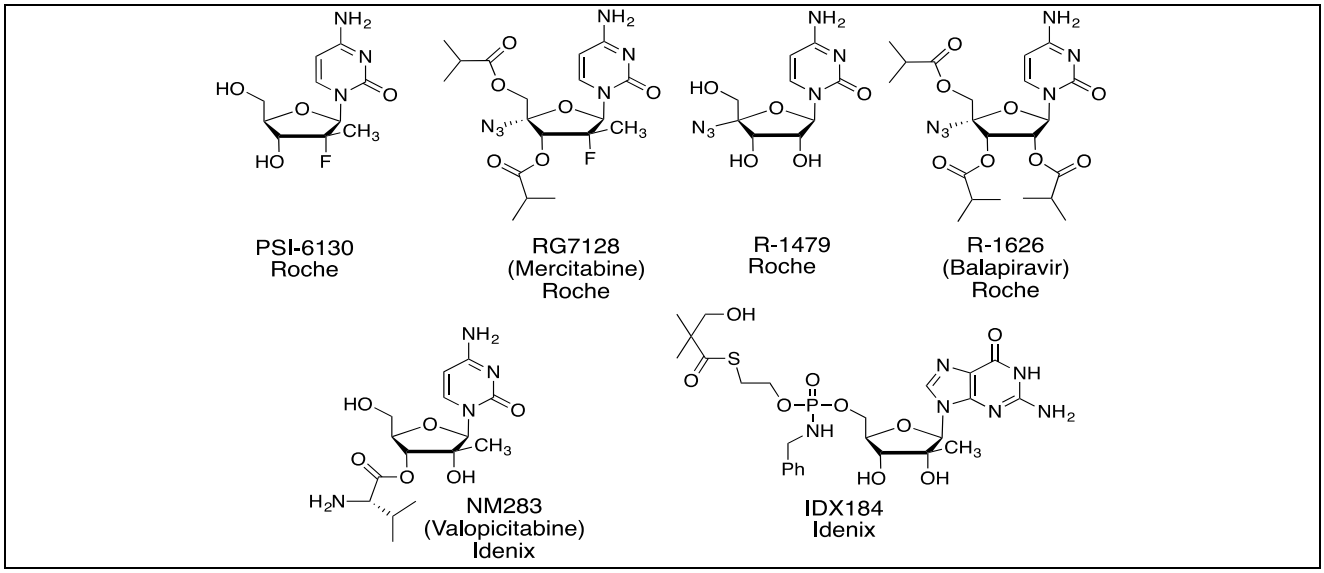


Figure 9. Examples of nucleos(t)ide HCV NS5B polymerase inhibitors.

phosphorylation has been identified as the rate-limiting step, which led medicinal chemists to prepare stable protected monophosphate nucleosides able of delivering nucleoside monophosphates intracellularly. These nucleoside monophosphate prodrugs are designed to pass the biological barriers and reach the targeted cells or tissues. Once inside the cell, the protecting groups are then degraded enzymatically and/or chemically, releasing the nucleoside analog in the monophosphate form, which can efficiently express its therapeutical potency by intracellular conversion to the corresponding nucleoside triphosphate (**Figure 5**).

Several strategies allowing intracellular delivery of nucleotide analogs were developed over the past 20 years based on the design of many different types of nucleoside monophosphate prodrugs including: nucleoside phosphates and phosphonates, phosphoramidate and phosphonamidate, alkoxy alkyl monoester and phosphorodiamidates and phosphonodiamidates (**Figure 6**).[37] Currently, phosphoramidate prodrugs are the most important approach after the FDA approval of Sofosbuvir.

Phosphoramidate Prodrugs

Aryloxyphosphoramidate prodrugs, also called "ProTides", contain a phosphorus atom linked to an amino acid alkyl ester and an aryloxy group. In the early 1990s by McGuigan[38] and co-workers, this prodrug approach was development as a result of several years of SAR studies during which several types of masked phosphate moieties were evaluated as bis(alkyloxy) and haloalkyloxyphosphates, bis(aryloxyphosphate), cyclic and noncyclic alkyloxyphosphoramidates.

Phosphoramidate prodrugs approach has the ability to increase the activity of nucleosides, and also they are relatively easy to prepare. After the approval of sofosbuvir, the development of several phosphoramidate prodrugs has now advanced to clinical trials for HCV treatment as (INX-08189 and PSI-353661), HIV treatment (as stampidine) and cancer (as thymectacin) as shown in **Figure 7**.

The metabolism of these phosphoramidate prodrugs,[37] leading to the intracellular delivery of active nucleoside monophosphates, has been studied in detail over the years. After crossing the cell membrane, the monophosphate deprotection is initiated by an esterase or cathepsin A producing carboxylate I. The intermediate I is exposed to spontaneous intramolecular cyclized to form a five-member ring II, followed by

releasing a molecule of phenol. Cyclic intermediate II undergoes chemical opening in the presence of water leading to phosphoramidate diester III. Finally, cleavage of intermediate III by intracellular phosphoramidase frees the nucleoside monophosphate. Then, consecutively phosphorylated to diphosphate and to active triphosphate metabolite by kinase enzyme, (**Figure 8**).

General mechanism of synthesis of phosphoramidate nucleoside prodrugs has been reported by coupling of nucleosides with phosphorochloridate by either activation of the imidazolium intermediate with NMI (N-methyl imidazole) [39] or by 5′- deprotonation of the nucleoside with *t*-BuMgCl [40] and subsequent substitution with the chlorophosphoramidate (**Scheme 1**).

Over the past twenty years, substitutions of the phosphorochloridate reagents have been explored by modifying:

1. The nature of the aryloxy portion (substituted phenols or naphthols).
2. The amino acid. (commonly L-alanine)
3. The amino acid ester. (*i*-propyl ester or ethyl ester)

Phosphorochloridate is the term used to refer to the phosphorylating reagents used for the coupling with the nucleosides. According to the procedure of Curly *et al*.,[41] these were obtained from the low temperature (-78 ºC) coupling of aminoacid ester hydrochloride salts with phenyl dichlorophosophate in the presence of TEA in anhydrous DCM (Scheme 2). Phosphorochloridates are generally obtained as a 1:1 mixture of R_p and S_p diastereoisomers. From all of the natural amino acids, L-alanine is commonly used, whereas the nature of the aryl group and carboxyl ester portion is dependent on the nucleoside and/or its application.

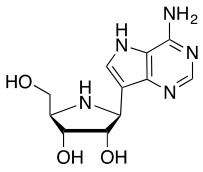
- **Recent FDA approved and clinical trials antiviral nucleoside and nucleotide analogs**

Nucleos(t)ides against HCV

Sofosbuvir[27] has highly potent clinical anti-HCV activity across all genotypes. Sofosbuvir is a phosphoramidate prodrug that initially yields a monophosphate metabolite following intracellular hydrolysis, which is further converted to its diphosphate then to its active triphosphate form that binds to the active site of NS5B. Sofosbuvir contains the 2′-fluoro-*C*-methyl sugar moiety; is currently the only one received FDA approval in December 2013 as nucleotide polymerase inhibitors. Sofosbuvir containing regimens with other direct acting agents (DAAs) can be achieved very high-sustained virologic response and shorter in duration e.g., with ledipasvir (Harvoni) or with velpatasvir (Epclusa). Modeling studies suggest that the 2`-*C*-methyl group of the incorporated nucleotide inhibitor might cause a steric conflict with the endogenous nucleotide substrate.[42] Therefore, Sofosbuvir and related 2`-*C*-methylated derivatives with a hydroxyl group or fluorine atom at the 2`-position act as potent chain terminators, such as PSI-6130,[43-51] Mercitabine,[52-61] IDX184[62,68], Valopicitabine,[69-72] R-1479 and its prodrug Balapiravir R-1626[73-79] as shown in **Figure 9**.

Nucleosides against Ebola

The imino-C-nucleoside BCX4430 is used as a potential therapeutic for the treatment of Ebola virus infections, it showed a promising result *in vitro* studies and it is in phase 1 trial. It is designed by Biocrst Pharma. The BXC 4430's mechanism of action is that it is taken up by viral RNA polymers and halts the RNA replication. In vitro studies it showed promising results against Ebola Virus.[80-82]



BCX4430

Nucleosides against dengue and zika

A lot of nucleoside analogs have been tested against dengue virus, but it was found that the inhibitory effects of valganciclovir and stavudine against dengue suggest that they may be explored further as antiviral agents aganist dengue infection and lead in the development of new analogs in targeting dengue infections.[83] It was reported that 2`-*C*-methylated nucleosides exerted activity against ZIKV under in vitro conditions. These compounds provide a basis for structure-based optimization and rational design of effective prodrugs, which will be further tested in rodent models for therapy of ZIKV infection.[84]

Conflict of Interest

The authors declare that they don't have any conflict of interest.

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