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Mini-review

L-Nucleoside enantiomers as antivirals drugs: A mini-review

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Dedicated to Prof. Erik De Clercq on the occasion of reaching the status of Emeritus-Professor at the Katholieke Universiteit Leuven in September 2006

Abstract

The discovery that some nucleoside analogues endowed with the unnatural L-configuration can possess biological activities has been a significant breakthrough in antiviral chemotherapy. In this regard, lamivudine (3TC) was the first L-nucleoside enantiomer approved against HIV and HBV, and several other L-nucleosides are currently under clinical development as antiviral agents

Keywords: L-Nucleoside enantiomers; Antiviral drugs

Contents

1. Introduction

The current armamentarium for the chemotherapy of viral infections is the result of several decades of research, including syntheses and biological evaluations of nucleoside analogues (De Clercq, 2005a). In the search for antiviral nucleoside analogues, structural modifications of the heterocyclic bases and/or modifications on the sugar moiety of natural nucleosides can be attempted. In the latter, the main modifications involved changes in the (2-deoxy)-D-ribofuranose moiety like, inversion of hydroxyl group configurations, their elimination leading to dideoxy- or dideoxy-didehydro-nucleosides, their substitution/functionalisation by various synthetic groups, or cleavage of the sugar ring leading to acyclic nucleosides. Other structural modifications have also been attempted such as replacement by a methylene group or a sulfur atom of the endocyclic oxygen, transposition of the latter and/or additional insertion of a second heteroatom in the sugar moiety (Mansour and Storer, 1997). Currently, nucleoside analogues are prominent drugs in the management of several viral infections, including HSV, HIV, HBV, HCV and HCMV infections (De Clercq, 2005b). The nucleoside analogues at present formally approved for the treatment of viral infections are shown in Fig. 1.

The mechanism of action of nucleoside analogues is based upon the intracellular phosphorylation to their 5′-triphosphate form which can interact with virus-specific polymerases, acting as a competitive inhibitor or an alternate substrate for these tar-

Abbreviations: HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; HCMV, human cytomegalovirus; EBV, Epstein-Barr virus; VZV, Varicella-Zoster virus; RSV, respiratory syncitial virus

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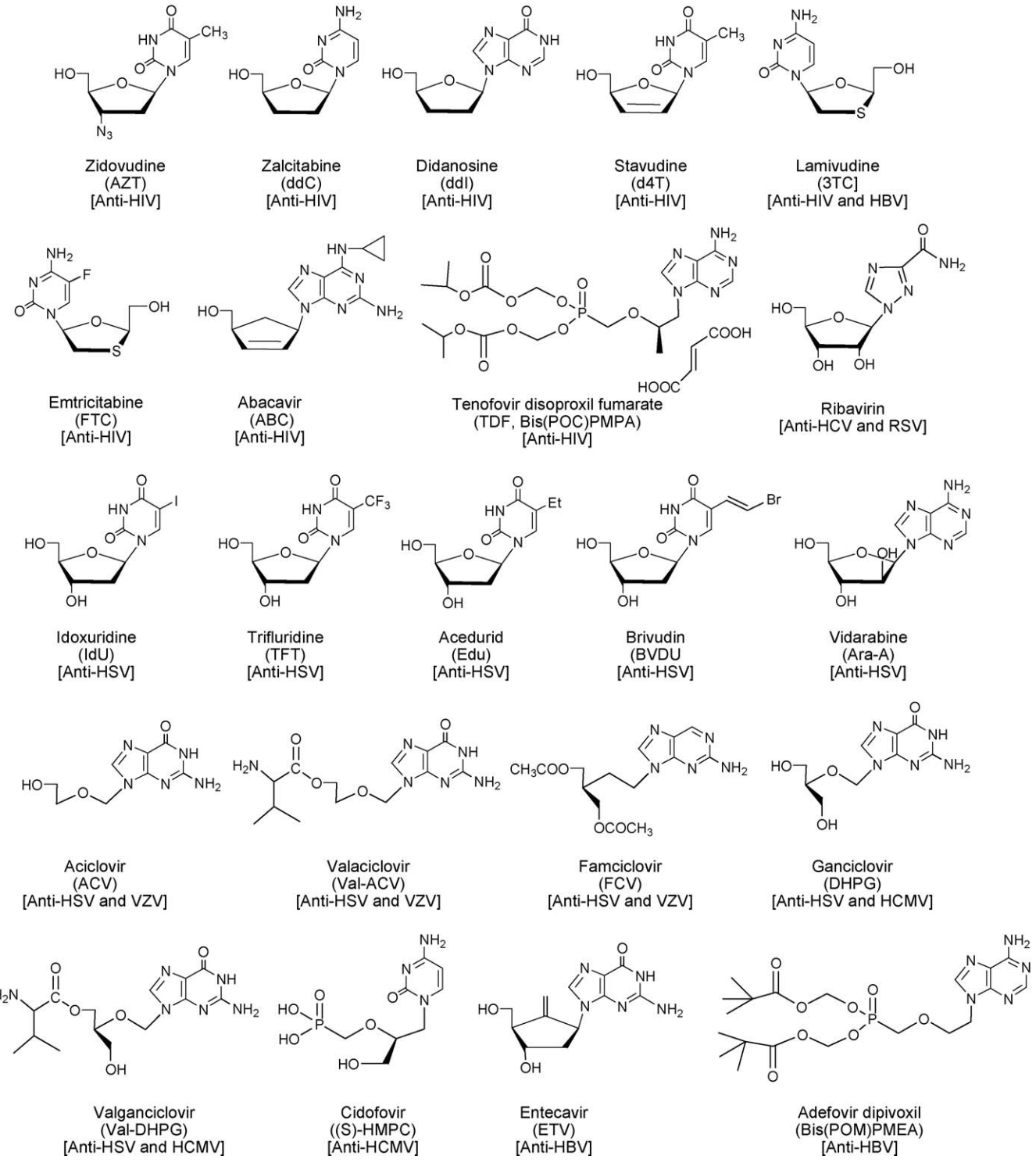

Fig. 1. Nucleoside analogues currently used in antiviral therapy.

get enzymes, usually preventing further viral nucleic acid chain elongation. For a long period, it was assumed that nucleoside analogues having only a natural D-configuration, by analogy with the natural ones, could exhibit biological activity, owing to the believed stereospecificity of enzymes in living systems (Focher et al., 2003; Maury, 2000). In the beginning of the 90 s, this assumption was reevaluated, and L-nucleoside enantiomers (which are non-superimposable mirror images of the natural D-nucleosides, like the right and left hands) emerged as a new class of antiviral agents. Although the first synthesis of a L-nucleoside was reported in 1964 (Smejkal and Sorm, 1964), little attention was paid to L-nucleoside analogues until the discovery of lamivudine (3TC, Fig. 1) (Cameron et al., 1993; Jarvis and Faulds, 1999). Since then, a large number of L-nucleoside ana-

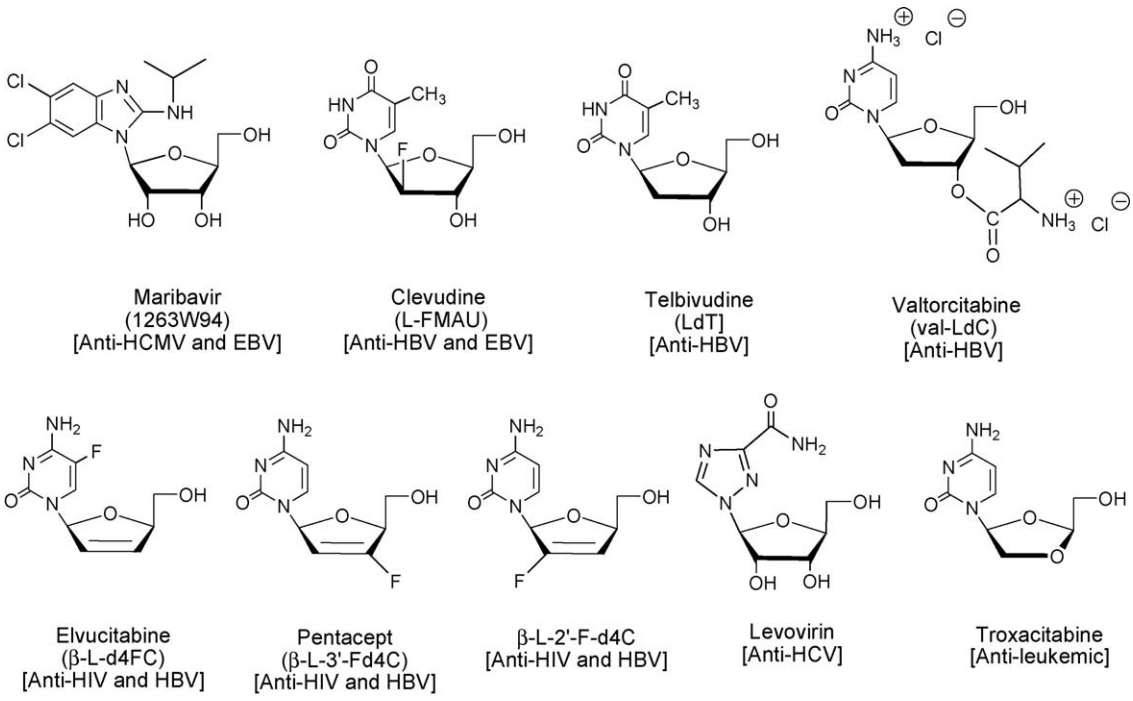

Fig. 2. L-Nucleoside analogues currently in clinical trials.

logues have been synthesized and their antiviral activities evaluated (Furman and Painter, 1995; Nair and Jahnke, 1995; Wang et al., 1998; Graciet and Schinazi, 1999; Zemlicka, 2000; Cheng, 2001; Gumina et al., 2001, 2002). From this tremendous work, it appears that favorable features of L-nucleoside analogues may include an antiviral activity comparable and sometimes greater than their D-counterparts, more favorable toxicological profiles and a greater metabolic stability. In this mini-review, we will summarize briefly biological features and the current status of the L-nucleosides currently undergoing clinical trials and/or preclinical studies as antiviral agents.

2. L-Nucleoside analogues as anti-HCMV agents

Infections by herpes viruses are among the most common and easily transmitted viral diseases in man. Numerous distinct herpes viruses have been identified and the treatment by therapeutic agents of diseases caused by some of them has produced clinical benefits. Human cytomegalovirus (HCMV) is one of the eight human herpes viruses that cause widespread infections. Currently, in the United States, more than 40% of the population is infected with HCMV (Sia and Patel, 2000). Normally, in healthy individuals HCMV infections are asymptomatic, while in immunocompromised patients, such as AIDS patients (McKenzie et al., 1991), bone marrow recipients (Wingard et al., 1990), organ transplant recipients (Grattan et al., 1989), they are life threatening. Currently, there are five drugs which have been approved in the US for treatment of HCMV infection, including ganciclovir (Fig. 1), valganciclovir (Fig. 1), cidofovir (Fig. 1), foscarnet and formivirsen. However, there are several drawbacks associated with the use of these drugs including poor oral bioavailability, toxicity and/or resistance development. Therefore, there is a need for new compounds having better oral bioavailability and safer pharmacological profiles. An L-ribofuranosyl benzimidazole, namely 1-(β-L-ribofuranosyl)-2-isopropylamino-5,6-dichlorobenzimidazole (maribavir, Fig. 2) is a potent and selective inhibitor of HCMV (Biron et al., 2002). HCMV strains resistant to ganciclovir and foscarnet are sensitive to maribavir. Phase I clinical trials, which have been completed, have proved that maribavir shows a good tolerance, good oral bioavailability and low toxicity compared to currently available anti-HCMV drugs (Lalezari et al., 2002) and phase II trials were initiated in July 2004 (Lu and Thomas, 2004). Maribavir, which is currently developed by Viropharma (http://www.viropharma.com), is also active against EBV, and its effects on both EBV and HCMV seem to involve direct or indirect inhibition of viral protein kinases, as well as possible interference with nuclear egress of virions during viral maturation (Gershburg and Pagano, 2005).

3. L-Nucleosides as anti-HBV agents

According to the World Health Organization, over 350 millions people (≈5% of the world population) are chronically infected with hepatitis B virus (HBV). HBV infection induces a spectrum of disease ranging from mild, asymptomatic infection to severe chronic liver diseases, including cirrhosis and hepatocellular carcinoma. Although safe and effective vaccination for HBV is available for developing countries, there is still a need for effective treatment for the millions of chronically infected individuals. Currently, three drugs (lamivudine, entecavir and adefovir dipivoxil, Fig. 1) have been approved for the treatment of HBV infection, and several L-nucleosides are in clinical trials. Among them, a 2′-fluorinated nucleoside

analogue, namely 1-(β-L-2-fluoro-2-deoxyarabinofuranosyl)-5-methyluracil (clevudine, Fig. 2) showed promising anti-HBV and anti-EBV activity without associated toxicity (Chu et al., 1995). Clevudine, which is currently developed by Pharmasset (http://www.pharmasset.com), inhibits HBV replication by acting on the viral polymerase, reducing its ability to incorporate nucleosides into a new viral DNA chain. This mechanism of action is different from nucleoside inhibitors currently used for the treatment of HBV infection, which act after incorporation, into the new viral DNA chain, as chain terminators. Furthermore, clevudine is not incorporated into normal human cellular DNA, and does not interfere with the mitochondrial γ DNA polymerase. In woodchucks, clevudine produced profound and sustained viral suppression, accompanied by significant reduction of cccDNA which is responsible for the persistence of chronic HBV infection and the reactivation of hepatitis B after stopping therapy. A phase II dose-escalating trial of clevudine in patients with chronic hepatitis B (Marcellin et al., 2004) has shown that clevudine was well tolerated with no dose-limiting toxicities. A transient increase in alanine aminotransferase was observed in six patients in the 100-mg cohort, without sign of liver failure. These increases were associated with improved viral suppression, and the pharmacokinetic profile of clevudine was proportional to the dose. Clevudine has been undergoing multicenter and randomised phase III clinical trials, and the results demonstrated its tolerability and potent activity in HBV-infected patients (Yoo et al., 2005a,b).

Two others L-nucleoside analogues, namely telbivudine (Fig. 2) (Kim et al., 2006) and valtorcitabine (Fig. 2), both developed by Idenix (http://www.idenix.com), have proven to be extremely specific and selective anti-HBV agents and have exhibited an exceptional safety profile (Gosselin et al., 2004). The basic chemical structure of these compounds is very simple, since they are the mirror images of thymidine (dT) and deoxycytidine (dC), two naturally occurring nucleoside building blocks of DNA. Telbivudine and valtorcitabine have demonstrated no activity against HIV and other viruses that cause human diseases. This specificity may permit the treatment of co-infected persons with other viruses like HIV, without an increased risk of resistance development for these other viruses. Additionally, both telbivudine and valtorcitabine target the positive strand of HBV DNA, in contrast to lamivudine, which targets the negative strand. The targeting of the positive strand may be associated with a slower development of resistance mutations (Nelson, 2003). In a recently completed phase IIb clinical trial, 1 year of telbivudine treatment reduced HBV in the blood to undetectable levels (i.e. less than 200 particles/mL) in 61% of patients, significantly more than the 32% of patients who achieved this result with lamivudine, the current standard of care (Lai et al., 2005). The high degree of viral suppression provided by telbivudine is among the most significant of anti-HBV therapeutic agents in development. Additionally, in this clinical trial, serum alanine aminotransferase (ALT), a marker of HBV-related liver inflammation, normalized in 86% of telbivudine-treated patients, significantly greater than the 63% in the lamivudine group. This clinical trial also demonstrated the importance of early viral suppression for improving clinical outcome. In all treatment groups, patients with the greatest degree of viral suppression early in the course of therapy (24 weeks) had the highest rates of seroconversion, ALT normalization and the lowest rate of drug resistance. Telbivudine appears to be well tolerated in clinical trials, and to date, there has been no pattern of patient discontinuations due to serious adverse events. An international phase III clinical trial for telbivudine, known as "the GLOBE study", is ongoing and fully enrolled, including more than 1350 patients and approximately 135 clinical centers. The initial phase of this clinical trial has been completed at the end of 2005, showing that, after 1 year, telbivudine provided superior response on all evaluated virologic markers compared to lamivudine. Idenix is also conducting clinical trials of valtorcitabine (Fig. 2), another drug candidate for the treatment of HBV, which is being developed as a fixed dose combination with telbivudine. In laboratory studies and predictive animal models of HBV disease, telbivudine and valtorcitabine each demonstrate profound and highly specific antiviral activity against HBV. In these preclinical studies, the combination of the two agents has demonstrated even greater antiviral activity than either drug alone. Idenix is developing telbivudine and valtorcitabine in collaboration with Novartis (http://www.novartis.com) under a development and commercialization agreement. In the beginning of 2006, Idenix and Novartis announced the submissions of a New Drug Application (NDA) and a Marketing Autorization Application (MAA), respectively to the FDA and the European Medicine Agency (EMEA) seeking marketing approval for a 600 mg dose of telbivudine as an oral, once-daily drug for the treatment of chronic hepatitis B.

4. Other L-nucleoside analogues of interest as potential antiviral agents

Emtricitabine (Fig. 1), which is marketed by Gilead (http://www.gilead.com) as Emtriva® in combination with other antiretroviral agents for the treatment of HIV infection in adults, is currently in clinical trials in order to evaluate its potency for the treatment of chronic hepatitis B (Saag, 2006).

Another 5-fluoro-L-cytosine nucleoside analogue (elvucitabine, 2′,3′-didehydro-2′,3′-dideoxy-β-L-5-fluorocytidine, Fig. 2), has also shown potent in vitro activity against HIV and HBV (Chen, 2002). Elvucitabine is currently developed by Achillion (http://www.achillion.com), and clinical and preclinical data collected to date indicates that this compound can be dosed as one pill once a day and may be used in combination therapy for the treatment of HIV.

Two nucleoside analogues fluorinated in the sugar moiety, namely, 2′,3′-didehydro-2′,3′-dideoxy-3′-fluoro-β-L-cytidine (β-L-3′-F-d4C, Fig. 2) and 2′,3′-didehydro-2′,3′-dideoxy-2′-fluoro-β-L-cytidine (β-L-2′-F-d4C, Fig. 2) are currently under preclinical studies. β-L-3′-F-d4C (pentacept), which is currently developed by Pharmasset (http://www.pharmasset.com), is a potent and selective antiretroviral nucleoside with activity against lamivudine-resistant HIV-1 and HBV (Asif et al., 2005). β-L-2′-F-d4C also exhibits both anti-HIV and anti-HBV activity with no toxicity, favorable pharmacokinetic profile and acceptable oral bioavailability (Chen et al., 2003; Pai et al.,

2005). This class of 2′- or 3′-vinylic fluorinated nucleosides warrant further development and could be useful candidates for individuals co-infected with HIV and HBV.

Finally, 1-β-L-ribofuranosyl-1,2,4-triazole-3-carboxamide (levovirin, Fig. 2), which is the L-enantiomer of ribavirin (Fig. 1) was investigated as a new potential anti-HCV agent in order to improve the safety profile of ribavirin (Walker et al., 2003). Levovirin, which was discovered by Valeant Pharmaceuticals International (http://www.valeant.com) has no direct antiviral effect against HCV, but shows immunomodulatory properties similar to or greater than ribavirin. Roche (http://www.roche.com) had been investigating levovirin in early phase studies, but discontinuated its development based on unfavorable results from phase I/II trials. Roche also conducted phase I studies of R1518, a valine ester prodrug of levovirin (Huang et al., 2005).

5. Conclusion

Drug discovery in antiviral chemotherapy has provided effective treatments for various viral infections. In particular, nucleoside analogues have been the cornerstone of antiviral treatments for several decades. In the search for new, safe and effective agents within this class, L-nucleoside enantiomers represent an immense breakthrough. As a general feature, those compounds with an unnatural configuration confer in most cases lower toxicity and higher metabolic stability compared to the natural D-counterparts. As a result, several L-nucleoside analogues are currently under development as antiviral agents, and some of them are likely to be introduced into antiviral treatments in the next years. It is noteworthy that the chemotherapeutic potential of L-nucleoside analogues is not limited to the antiviral field. For instance, unnatural L-nucleosides, like L-adenosine and L-ribothymidine, could find utility in new malaria chemotherapy (Gero et al., 2003). Additionally, (2*S*,3*S*)-1-[2-(hydroxymethyl)1,3-dioxolan-4-yl]cytosine (troxacitabine, Fig. 2), which was discovered by BioChem Pharma and further developed by Shire BioChem Inc. (http://www.shire.com), is currently licensed by SGX Pharmaceuticals (http://www.sgx.com) under the name of Troxatyl™ for the indication of pancreatic cancer and myeloid leukemia (Gourdeau et al., 2004).

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