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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
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Keywords: L-Nucleoside enantiomers; Antiviral drugs

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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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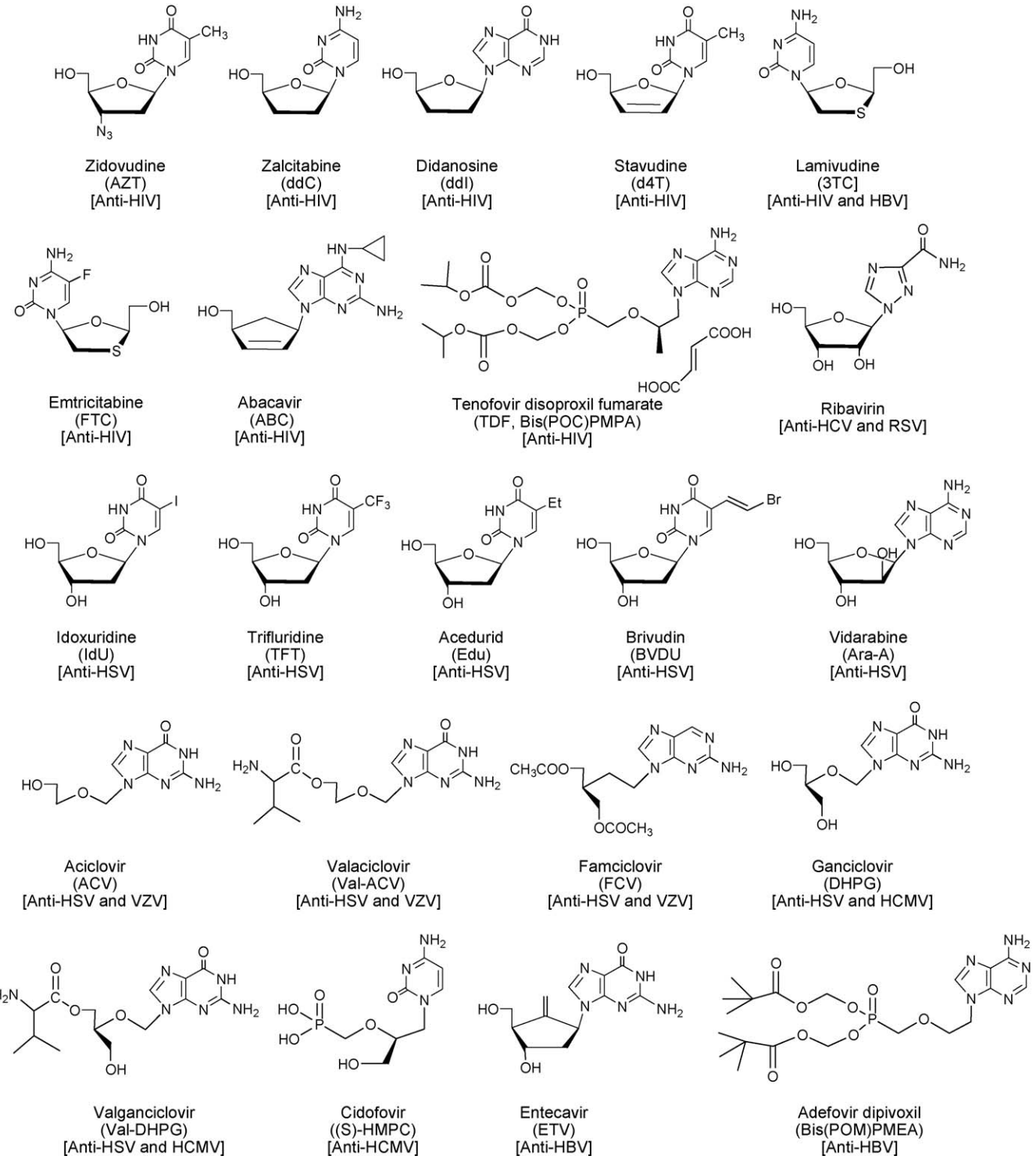

Fig. 1. Nucleoside analogues currently used in antiviral therapy.

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-

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