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Guanine-based Nucleosides: Medicinal Importance and Stratagems for Regioselective Synthesis

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Abstract

Nucleosides and their analogues have been in clinical use since 1950s, and particularly of guanine that have become cornerstone for the treatment of cancer and viral infections. But this rejoice of therapeutic potential is hampered by the intricate glycosylation of guanine, which usually results in a mixture of *N*-7 and *N*-9 guanine nucleosides. The present review is focused on the medicinal importance and different strategies undertaken for regioselective synthesis of guanine nucleosides.

Keywords: *Guanine nucleosides, antiviral nucleosides, locked nucleic acids, transglycosylation.*

1. Introduction

Over six decades, a number of nucleosides have been synthesized that have been the drugs of choice to treat cancer,[1] viral,[1-4] bacterial[5] and fungal infections.[6,7] Among these, the guanine nucleosides and their analogues have continuously reflected their supremacy as therapeutic agents and are first line chemotherapy for the treatment of viral, cancer and fungal infections (**Figure 1**).[8-10]

The approved guanosine analogues include the antiviral drugs Acyclovir,[11, 12] Ganciclovir[13-15] and Penciclovir[16] and their ester analogues as prodrugs, *i.e.* Valaciclovir,[17, 18] Valganciclovir[19] and Famciclovir[20] respectively (**Figure 1**). The prodrugs have been synthesized to increase the oral bioavailability of the drugs. These drugs upon triphosphorylation compete with deoxyguanosine triphosphate (dGTP) and therefore, selectively inhibit viral DNA polymerase (**Figure 2**). In contrast, the triphosphates of anti-retroviral drugs, *i.e.* Abacavir[21, 22] and Entecavir[23-25] targets the reverse transcriptase and may also get incorporated into the newly synthesized viral DNA that offer poor affinity for normal cellular DNA polymerase (**Figure 2**).

The acyclic nucleoside phosphonate, PMEG (9-(2-phosphonylmethoxyethyl)guanine)[26] is an anticancer agent. Whereas, the naturally occuring peptidyl nucleoside analogues containing pyranosyl core, Miharamycin A,[27] Miharamycin B[27] and Amipurimycin[28, 29] (**Figure 1**) possess strong anti-fungal activity against the rice blast disease which is caused by *Pyricularia oryzae*. However, the exact mode of action of these compounds is still uncertain.

1.1. DNA polymerase inhibitors

1.1.1. ***Acyclovir:*** 9-[(2-hydroxyethoxy)-methyl] guanine, Aciclovir, Acyclovir or Acyclo-guanosine (abbreviated as ACV), is a guanosine analogue antiviral drug with an acyclic side chain lacking the 3′-hydroxyl group as compared to natural nucleoside.[30] Approved in 1982 by US Food and Drug Administration (FDA), ACV is marketed under trade names such as *Cyclovir*, *Herpex*, *Acivir*, *Acivirax*, *Zovirax*, *Aciclovir* (Sanofi-Aventis) and *Zovir* (GSK).

Pharmacologist Gertrude B. Elion was awarded the 1988 Nobel Prize in Medicine,[11, 12, 31] partly for the development of acyclovir as it has been a pivotal antiviral drug. Its high specificity for cells infected with herpes simplex virus (HSV)[32] and varicella-zoster virus (VZV)[33] with a favourable toxicity defined acyclovir as one of the safest antiviral drugs.[34] Further it was also used for the treatment of other viral infections like herpes simplex virus type II (HSV-2),[35] Epstein-Barr virus (EBV)[36] and cytomegalovirus (CMV).[37]

After cellular uptake, monophosphorylation of ACV is catalysed by virus-encoded thymidine kinase. Subsequent di- and tri-phosphorylation are catalyzed by host cell enzymes. The concentration of acyclovir triphosphate is found to be 40 to 100 times higher in HSV-infected cells as compared to normal cells.[11, 12, 38]

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