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# Carbocyclic nucleoside analogues: classification, target enzymes, mechanisms of action and synthesis

E S Matyugina, A L Khandazhinskaya, S N Kochetkov

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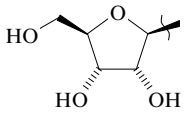

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**Abstract. Key biological targets (*S*-adenosyl-L-homocysteine hydrolase, telomerase, human immunodeficiency virus reverse transcriptase, herpes virus DNA polymerase and hepatitis B virus DNA polymerase) and the mechanisms of action of carbocyclic nucleoside analogues are considered. Structural types of analogues are discussed. Methods of synthesis for the most promising compounds and the spectrum of their biological activities are described. The bibliography includes 126 references.**

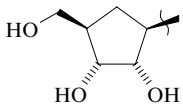
## I. Introduction

Since nucleic acid components and their analogues are involved in all vitally important metabolic processes, they are convenient tools for studying and influencing these processes. This has stimulated extensive studies in various fields, including medicinal chemistry. Data on the antitumour activity of the first synthetic nucleoside analogues, such as 5-fluoro-2′-deoxyuridine (FUDR), arabinofuranosylcytosine (ara-C), 8-azainosine and 7-cyano-7-deazaadenosine (toyocamycin), and the discovery of antiviral properties of arabinofuranosyladenine (ara-A) confirm the value of modified nucleosides as chemotherapeutic agents.[1,2]

Most of nucleoside derivatives are cleaved by cellular enzymes before they exhibit activity. The modification of both the nucleoside base and the carbohydrate moiety can assist in increasing stability. One of the ways to enhance stability is to perform the isosteric replacement of the oxygen atom in the carbohydrate residue by a methylene group.[3] These compounds are referred to as carbocyclic nucleoside analogues.[4]

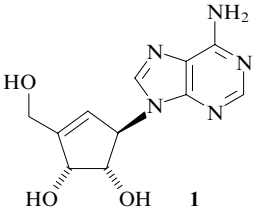


Carbohydrate moiety

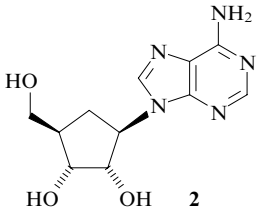


Carbocyclic moiety

Initially, carbocyclic analogues have attracted great interest due to antiviral activity of neplanocin A (**1**)[5] and aristeromycin (**2**)[6] isolated from natural sources.



**1**



**2**

In the last decades, carbocyclic nucleoside analogues have been extensively studied and they were found to exhibit a wide range of biological activities, in particular, antiviral and antitumour properties.[7] It was shown that these nucleoside analogues of are recognized by many enzymes and receptors due to their structural similarity to natural nucleosides, but they have higher resistance to the C – N bond cleavage by phosphorylases and hydrolases. In addition, carbocyclic nucleoside analogues are good cellular kinase substrates.

The activity of carbocyclic nucleoside analogues was tested in numerous biological objects, and some analogues were found to have essential activity. However, many analogues, which exhibited high activity against particular viruses, bacteria or abnormal cells, were not further studied for different reasons and, unfortunately, the mechanisms of their action are unknown.

Several reviews on carbocyclic nucleoside analogues were published. Some of them include the detailed description of the synthesis of numerous compounds of this type, both exhibiting biological activity and inactive.[8–10] Other

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reviews are devoted to inhibitors of particular enzymes.[11,12] The present review combines the 'chemical' and 'biological' views on the problem. Section II covers biological targets of carbocyclic nucleoside analogues and mechanisms of their antiviral action, which were studied in detail. In Section III, structural types and biological activity of carbocyclic nucleoside analogues are considered and the synthetic method for the most promising compounds of this class are described.

## II. Biological targets and mechanisms of antiviral action of carbocyclic nucleoside analogues

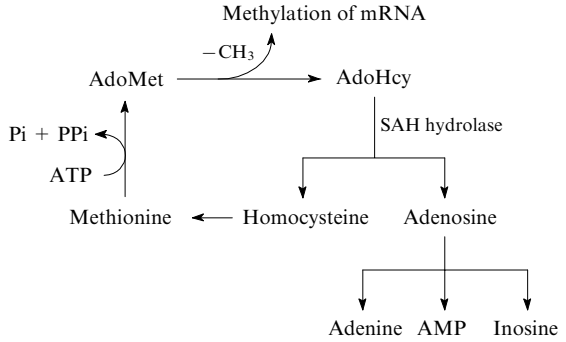
Both cellular and viral enzymes can serve as biological targets for carbocyclic nucleoside analogues.

### 1. *S*-Adenosylhomocysteine hydrolase

*S*-Adenosylhomocysteine hydrolase (SAH hydrolase) belongs to cellular target enzymes. This enzyme in involved in the regulation of cellular methylation processes, in which *S*-adenosyl-L-methionine (AdoMet) acts as a methyl group donor. The conversion of *S*-adenosyl-L-methionine into *S*-adenosyl-L-homocysteine (AdoHcy) is catalyzed by methyltransferases, which transfer a methyl group to viral RNA. The accumulation of *S*-adenosyl-L-homocysteine results in the inhibition of *S*-adenosylmethionine-dependent methylation and the interruption of the transcription of the viral genome.[11] *S*-Adenosylhomocysteine hydrolase catalyzes the breakdown of *S*-adenosyl-L-homocysteine into adenosine and homocysteine, thus preventing its accumulation.[13]

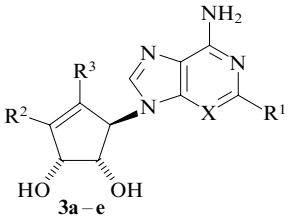
These processes are presented in the general form in Scheme 1.

Scheme 1



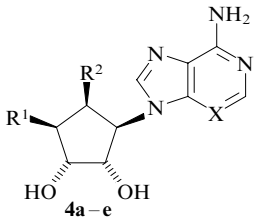

ATP is adenosine 5′-triphosphate, AMP is adenosine 5′-monophosphate, Pi is phosphate, PPi is pyrophosphate

Many carbocyclic nucleoside analogues were found to be SAH hydrolase inhibitors.[14] Along with neplanocin A (**1**) and aristeromycin (**2**), their analogues **3a**–**e** and **4a**–**e**, respectively, are the most active inhibitors.




**3a**–**e**

| Compound **3** | X | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|---|
| **a** | CH | H | $CH_2OH$ | H |
| **b** | N | H | H | H |
| **c** | CH | H | H | H |
| **d** | N | H | $CH_2OH$ | F |
| **e** | N | F | $CH_2OH$ | H |




**4a**–**e**

| Compound **4** | X | $R^1$ | $R^2$ |
|---|---|---|---|
| **a** | CH | $CH_2OH$ | H |
| **b** | N | H | H |
| **c** | N | $CH_2OH$ | F |
| **d** | N | OH | H |
| **e** | CH | OH | H |

The inhibition of this enzyme can occur through two mechanisms. Inhibitors acting by the first mechanism [neplanocin A (**1**) and aristeromycin (**2**)], as well as *S*-adenosyl-L-homocysteine, are oxidized by SAH hydrolase at position 3′. This process leads to a decrease in the content of enzyme-bound $NAD^+$ (NAD is nicotinamide adenine dinucleotide) with the result that SAH hydrolase can no longer initiate the catalysis cycle. This inhibition is reversible and the catalytic activity of SAH hydrolase can be restored by incubation with $NAD^+$ or dialysis. The 4′,5′-unsubstituted analogue of neplanocin A, *viz*., 9-(2′,3′-dihydroxycyclopent-4′-enyl)adenine (**3b**), and the corresponding analogue of aristeromycin, *viz*., 9-(2′,3′-dihydroxycyclopentyl)adenine (**4b**), also belong to inhibitors acting by this mechanism.† Inhibitors acting by the second mechanism are not only oxidized by SAH hydrolase at position 3′ but are also covalently bound to the enzyme. 6′-Fluoroneplanocin A (**3d**) is a typical inhibitor of the second type.[15]

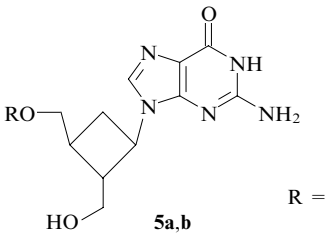
The range of antiviral activity of SAH hydrolase inhibitors is very wide and diverse. These compounds are effective against particular DNA-containing viruses, such as vaccinia virus (VV) and human cytomegalovirus (HCMV). Many (−)-RNA viruses [parainfluenza, measles, Ebola, stomatitis and Varicella–Zoster (VZV) viruses],[16–18] double-stranded RNA viruses (rheo- and rotaviruses) and retroviruses (human immunodeficiency viruses types 1 and 2, HIV-1 and HIV-2) belonging to (+)-RNA viruses are also sensitive to these inhibitors. By contrast, some other (+)-RNA viruses, such as picorna-, toga- and flaviviruses, are insensitive to SAH hydrolase inhibitors.[11] The inhibition of SAH hydrolase is also often used in the design of antiparasitic drugs, because adenosylmethionine-dependent transmethylation is essential for the parasite replication.[19]

### 2. Telomerase

Telomerase is another cellular enzyme sensitive to carbocyclic nucleoside analogues. Telomerase is a ribonucleoprotein complex responsible for the retention of the telomere length at chromosome ends in most of eukaryotes. This enzyme elongates the 3′-end of the chromosome by adding telomeric repeats. The core enzyme consists of telomerase reverse transcriptase (TERT) and telomerase RNA containing a template region for the elongation of DNA.[20,21] Telomerase is active in 85% of cancer cells, whereas its activity is absent in normal somatic tissues. The telomere shortening in tumour cells leads to their death much earlier than in normal cells in the body. Due to these characteristics, telomerase attracts interest as an anticancer therapy target.

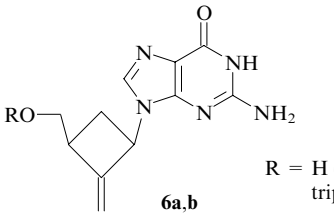
† These names are given according to the nomenclature used in the chemistry of nucleosides. In other cases, the IUPAC nomenclature is used.

Since the catalytic telomerase subunit is reverse transcriptase (RT), the first to be studied were the already known reverse transcriptase inhibitors, in particular, HIV RT inhibitors. It was shown that some nucleoside HIV RT inhibitors (3′-azido-3′-deoxythymidine 5′-triphosphate, 7-deazadeoxyadenosine 5′-triphosphate, 2′,3′-didehydro-2′,3′-dideoxyguanosine 5′-triphosphate and so on) inactivate telomerase. In the presence of nucleoside triphosphates, the telomerase activity is lost and the telomere length decreases.[21,22] The inhibition of telomerase is associated not only with the impossibility of adding the subsequent nucleotide residue but also with the competitive binding of these compounds in the enzyme active site, as it was shown by Takahashi *et al.*,[23] who described the inhibition of vertebrate telomerases by triphosphates of carbocyclic analogues of oxetanocin derivatives **5a** and **6a**. Both compounds appeared to be highly active [competitive with respect to 2′-deoxyguanosine 5′-triphosphate (dGTP)] enzyme inhibitors with the inhibition constants of 2.0 and 4.9 μmol litre$^{-1}$ for C-OXT-GTP (**5b**) and m-C-OXT-GTP (**6b**), respectively (for dGTP, $K_m$ = 11 μmol litre$^{-1}$, where $K_m$ is the Michaelis constant).



**5a**,**b**

R = H (**a**, C-OXT-G),
triphosphate (**b**, C-OXT-GTP)



**6a**,**b**

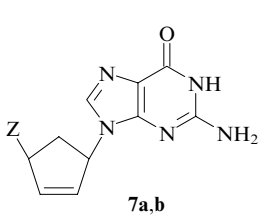
R = H (**a**, m-C-OXT-G),
triphosphate (**b**, m-C-OXT-GTP)

To determine the substrate specificity of telomerase, its interactions with 2′-deoxyguanosine[22] and 2′,3′-dideoxy-2′,3′-didehydroguanosine analogues were investigated.[24] It was shown that racemic‡ 9-[4-(difluoromethyldiphosphonyl)oxyphosphonylmethoxy)cyclopent-2-enyl]guanine (**7a**), carbovir triphosphate (**7b**) and carbocyclic D-2′-deoxyguanosine triphosphate (**8**) have affinity for telomerase comparable with that of the natural substrate dGTP and inhibit telomerase at concentrations of 5, 6 and 11 μmol litre$^{-1}$, respectively.

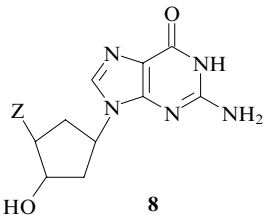
DNA polymerases of some viruses, in particular, of herpes, hepatitis B and human immunodeficiency viruses, are also targets for carbocyclic nucleoside analogues.

The general mechanism of action of nucleoside DNA polymerase inhibitors is as follows. After the entry into the cell target, analogues are phosphorylated by viral or cellular thymidine kinases (TK) to the corresponding monophosphates and then by cellular kinases to triphosphates. The resulting triphosphates compete to natural nucleoside 5′-triphosphates for the binding to viral DNA polymerases. The incorporation of carbocyclic nucleoside analogues into viral DNA terminates the chain elongation and stops the virus replication.

‡ In the cases when the stereochemistry of the structures of analogues of nucleosides is not specified, we mean racemates, the substituents in four-membered and five-membered carbocycles adopt the 2-*trans*, 3-*cis* and 2′-*trans*, 3′-*trans*, 4′-*cis* configurations, respectively, relative to the nitrogen base (to avoid confusion, the atomic numbering scheme in nucleosides is given).

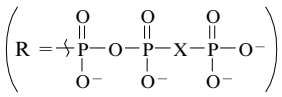


**7a**,**b**



**8**

Z = $OCH_2R$ (X = $CF_2$) (**7a**), $CH_2OR$ (X = O) (**7b**, **8**)



## 3. Herpes virus DNA polymerase

Herpes virus and diseases caused by this virus are the most widespread. The herpes infection is caused by a group of DNA-containing viruses, including about 90 characterized types. Eight of them were isolated from humans: herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), HCMV, VZV, Epstein–Barr virus (EBV) and herpes virus types 6, 7 and 8 (HHV-6, HHV-7 and HHV-8, respectively). Herpes simplex virus type 1 was the first discovered human herpes virus and it was studied in most detail.[25]

Herpes viruses have a similar replication cycle (Fig. 1). The infection starts with the attachment of the virus to cell receptors followed by the fusion of the viral coat with the plasma or endosomal membrane. The naked capsid is transferred to pores in the nuclear membrane *via* which viral DNA is released into the nucleus. Viral DNA is transcribed in the course of the reproduction cycle by cellular RNA polymerase II. Two viral proteins perform

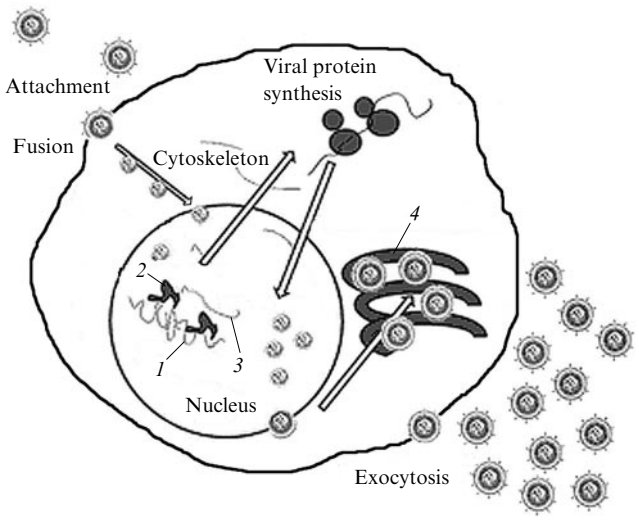
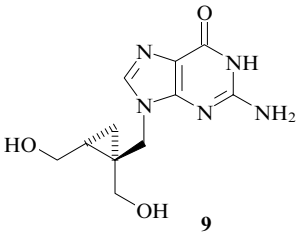


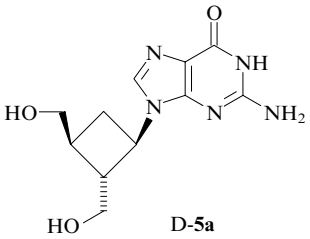

**Figure 1.** Life cycle of herpes simplex virus type 1.
(*1*) Viral DNA, (*2*) RNA polymerase, (*3*) early and late mRNA, (*4*) endoplasmic reticulum (ER).

the synthesis of viral DNA: DNA polymerase and the DNA-binding protein ICP8. The virus assembly consists of the following steps: the packaging of DNA into capsids, the maturing of the virus and the release of the virus from the cell through the plasma membrane.[26]

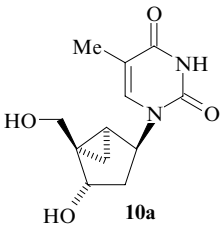
All known effective drugs against herpes virus are nucleoside analogues (acyclovir, pencyclovir, valacyclovir, famcyclovir and so on)[27] inhibiting the viral DNA polymerase, which is a key replication enzyme. Active inhibitors of herpes virus DNA polymerase were found also among carbocyclic nucleoside analogues.




**9**




D-**5a**




**10a**

As an example, refer to (1′*S*,2′*R*)-9-[(1′,2′-bis(hydroxymethyl)-1′-cyclopropylmethyl)]guanine (**9**) (A-5021) (its synthesis is described in Section III). The anti-HSV and anti-VZV properties of compound **9** depend on the efficiency of its phosphorylation by the corresponding viral TK. In experiments using a MRC-5 cell culture infected with HSV-1 and HSV-2, compound **9** proved to be a more effective inhibitor than acyclovir and pencyclovir, as can be seen from their effective concentrations§ ($EC_{50}$, μmol litre$^{-1}$):

| | Compound **9** | Acyclovir | Pencyclovir |
|---|---|---|---|
| $EC_{50}$ (HSV-1) | 0.49 | 0.98 | 3.3 |
| $EC_{50}$ (HSV-2) | 0.56 | 1.3 | 5.9 |

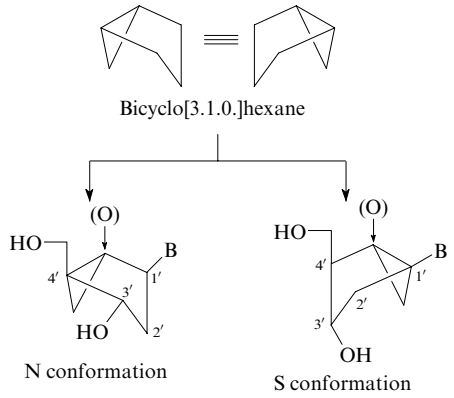
When tested in animals, compound **9** also exhibits much higher therapeutic effect than acyclovir.[28] Such a high activity against the viruses HSV-1, HSV-2 and VZV is associated with high intracellular stability of the corresponding triphosphate. Compared to acyclovir and pencyclovir, compound **9** more effectively treats skin lesions caused by the herpes virus and is more active against herpes encephalitis.[29] This analogue successfully passed the first phase of clinical trials.[30, 31]

Noteworthy also is the active carbocyclic derivative of guanine called cyclobutyl-G (**5a**). Its D enantiomer (Lobucavir®, D-**5a**) is the carbocyclic analogue of oxetanocin-G, which is a promising drug for the treatment of infections caused by cytomegaloviruses and herpes viruses.[32] Oxetanocin-G and acyclovir have synergistic activity against HSV-1 and HSV-2, whereas cyclobutyl-G shows an additive activity (with respect to acyclovir). Cyclobutyl-G is a poor substrate for viral TK, but its phosphorylated form inhibits HSV-1 DNA polymerase competitively with dGTP and also terminates the DNA chain elongation. The clinical testing of cyclobutyl-G in the treatment of corneal ulcers caused by HSV-1 showed the high efficacy and safety of this compound in the local treatment.[33] Lobucavir® is active against HCMV and can play an important role in the prevention and treatment of this infection.[34] It is particularly interesting that Lobucavir® is active against HCMV strains resistant to gancyclovir, foscarnet and cidofovir.[35]

A representative of bicyclic nucleosides, *viz*., 2′-deoxymethanocarbathymidine having the N conformation [(N)-MCT] (**10a**), is also used as an anti-herpes agent.

There is a dynamic equilibrium between the 2′-exo/3′-endo (northern, N) and 2′-endo/3′-exo (southern, S) conformations of the carbohydrate moieties of nucleosides and nucleotides in solution.[36] For the most favourable binding of nucleosides in the active site of the target enzymes, their sugar residues should be in one of these conformations.

The bicyclo[3.1.0.]hexane system has a rigid pseudo-boat conformation (*i.e*., the fixed conformation), and analogues of nucleosides based on this system adopt one of the two conformations (S- or N-like) depending on the type of substitution in the carbocycle.




B is thymine

Carbothymidine derivatives having the N conformation are efficiently phosphorylated by cellular and(or) viral kinases to 5′-mono-, di- and triphosphates.[37] The latter are good substrates for DNA polymerases and act as competitive inhibitors terminating the elongation and cleaving the newly synthesized DNA chain or destabilizing the DNA chain. By contrast, the anti-herpes activity of 2′-deoxymethanocarbathymidine having the S conformation is very low.[37]

It was shown[38] that compound **10a** is selectively phosphorylated by HSV-1 TK, resulting in a high level of the corresponding triphosphate in infected cells. It is interesting that the phosphorylation of bicyclic compound **10a** differs from that of acyclovir and gancyclovir. Thus, HSV-1 TK catalyzes the phosphorylation of monophosphate of (N)-MCT to diphosphate, whereas in the case of acyclovir and gancyclovir, this enzyme catalyzes the formation of the corresponding monophosphates. The affinity of (N)-MCT for HSV-1 TK is ten times higher than for the enzyme of the host cell; therefore, this compound is highly selective.[36]

§ The effective concentration ($EC_{50}$) is the concentration at which the 50% inhibition of the virus is achieved.

## 4. Hepatitis B virus DNA polymerase

Nowadays, 350 million people worldwide are infected with hepatitis B virus (HBV). All individuals infected with HBV are at high risk of developing chronic liver cirrhosis and primary hepatocellular carcinoma (HCC). Despite the existence of the vaccine, HBV is a very dangerous infectious agent causing diseases in humans. The DNA-containing hepatitis B virus belongs to the hepadnavirus family and infects predominantly liver cells.[12]

The life cycle of HBV is shown in Fig. 2.[39] After the binding to the receptor, HBV penetrates into hepatocytes followed by the virus decapsidation and the transport of the capsid content to the nucleus, where DNA polymerase repairs the virion DNA to form covalently closed circular DNA (cccDNA). The latter serves as a template for the synthesis of several types of RNA necessary for the translation of a number of viral proteins, as well as for the formation of the encapsidated RNA-replication pregenome (pgRNA) containing pregenomic RNA and a polymerase. Then the synthesis of the full-length antisense DNA strand catalyzed by virus-specific DNA polymerase takes place on the RNA template in the cytoplasm of the infected hepatocyte followed by the degradation of pregenomic RNA, after which the sense viral DNA is synthesized on the antisense strand. The resulting circular DNA together with the DNA polymerase is incorporated into the nucleocapsid of the virus, whose outer coat is formed by the glycosylated and myristoylated protein HbsAg. Then the newly formed virus particle is released from the hepatocyte and enters the blood.[12]

The main approach to the design of new drugs for the therapy of viral hepatitis B is based on the search for agents suppressing the function of the viral DNA polymerase, because this enzyme plays a key role in the life cycle of the virus. The HBV DNA polymerase has DNA-dependent and RNA-dependent (reverse transcriptase) activities.

The study of the activity of Lobucavir® (D-**5a**) against HBV showed that its triphosphate acts as a polymerase terminator by inhibiting all three main stages of the viral genome replication: priming, reverse transcription and DNA-dependent DNA synthesis. This inhibition mechanism is typical of other hepadnaviruses as well, in particular, of duck hepatitis B virus (DHBV) and woodchuck hepatitis virus (WHV).[40]

The assessments of the clinical performance of analogues of nucleosides carried out in several laboratories showed that the following compounds exhibit selective inhibition of HBV replication: 9-[4-hydroxy-3-(hydroxymethyl)butyl]guanine (Pencyclovir®), 9-[(1*S*,3*R*,4*S*)-4-hydroxy-3-(hydroxymethyl)-2-methylenecyclopentyl]guanine (entecavir, Baraclude®, **11**), β-L-2′,3′-dideoxy-3′-thiacytidine (3TC), (−)-β-2′,3′-dideoxy-5′-fluoro-3′-thiacytidine (FTC), β-L-2′,3′-dideoxy-2′,3′-didehydro-5-fluorocytidine (L-Fd4C), β-L-dideoxycytidine (L-ddC), β-L-2′-deoxy-5′-fluorocytidine (L-FdC) and β-L-2′-deoxy-5-methyl-2′-fluoroarabinofuranosyluracil (L-FMAU), as well as phosphonates of the acyclic nucleosides (*S*)-9-(3-hydroxy-2-phosphonomethoxypropyl)adenine (HPMPA), (*S*)-9-(2-phosphonomethoxyethyl)adenine (PMEA), (*S*)-9-(2-phosphonomethoxypropyl)adenine (PMPA) and their 2,6-diaminopurine analogues PMEDAP and PMPDAP. It should be emphasized that these medications do not interact with the cellular DNA polymerases and have no effect on the mitochondrial DNA synthesis.[12]

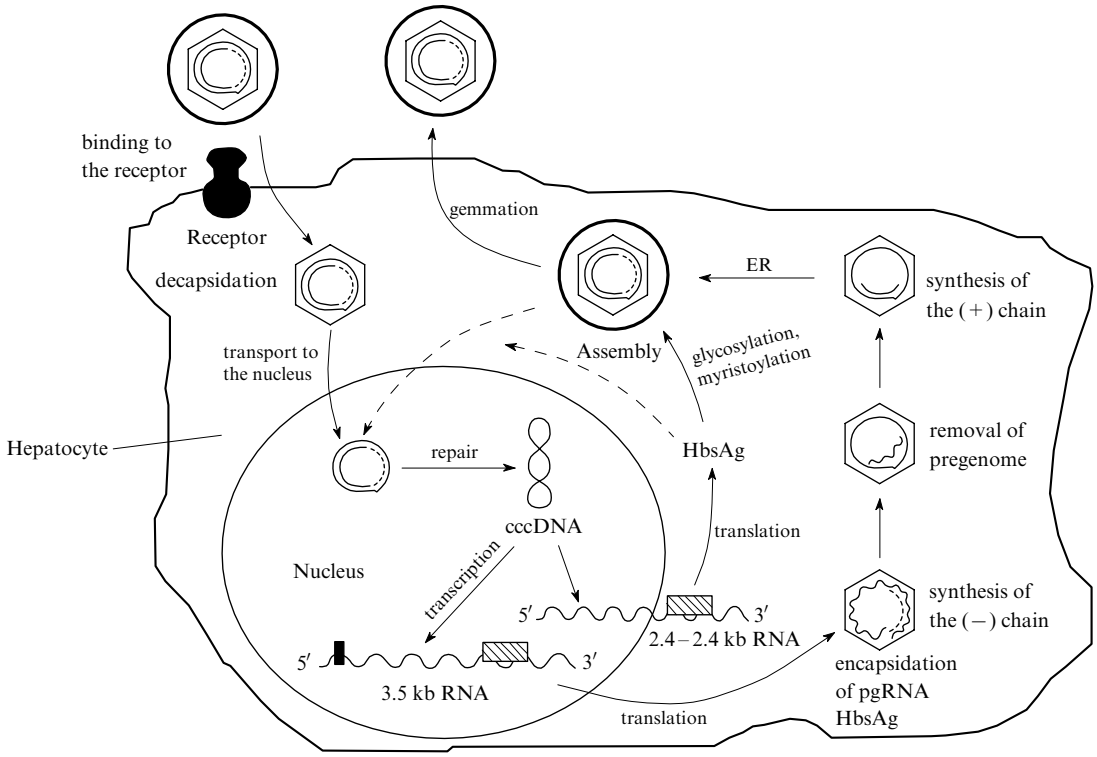
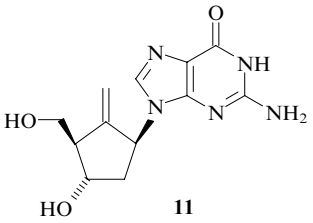



**Figure 2.** Life cycle of hepatitis B virus.
Secondary processes are indicated by arrows, kb stands for 1000 heterocyclic bases.

Entecavir (Baraclude®, **11**), which is a carbocyclic analogue of 2′-deoxyguanosine[41,42] (its synthesis is described in Section III), exhibits exceptionally high anti-hepatitis activity.




**11**

In the Hep G 2 2.2.15 cell line bearing the hepatitis B virus genome, entecavir inhibits HBV replication with $EC_{50} = 3.75$ nmol litre$^{-1}$. Experiments with the isolated enzyme showed that entecavir triphosphate inhibits hepadnavirus DNA polymerase.

The efficacy of entecavir against hepadnavirus infections was confirmed by experiments in woodchucks acquiring chronic WHV infection. This virus is a model for the evaluation of the efficacy of anti-HBV agents because the nucleotide sequence of WHV shares 70% homology with the HBV sequence.[41] The decrease in the viral DNA level in the blood plasma and the decrease in the level of DNA polymerase served as the indicators of the suppression of WBV replication. This was accompanied by a substantial decrease in the level of intracellular DNA, RNA and viral proteins.[43]

After a series of clinical studies, in 2005, the U.S. Food and Drug Administration (FDA) approved entecavir (Baraclude®) as a drug for the treatment of chronic hepatitis B and acute viral HBV infection.[44] It should be emphasized that this drug proved to be effective against the lamivudine-resistant strain of HBV; the development of the resistance to entecavir was not observed even after the long-term drug administration. No toxicity associated with the treatment with entecavir was found so far.

## 5. Human immunodeficiency virus reverse transcriptase

Human immunodeficiency virus causes a disease known as the acquired immunodeficiency syndrome (AIDS). This clinical state is characterized by a substantial decrease in the amount of CD4+ cells in the body and the development of opportunistic infections and malignant tumours. The disease progresses as a result of the permanent HIV replication and propagation in the body.[45] First mass infections with this virus occurred in the late 1970s. Although since that time HIV was investigated more thoroughly than any other virus in the world, patients continue to die from AIDS and millions of individuals are diagnosed with the HIV infection.

The RNA-dependent DNA polymerase or HIV RT is a target for many antiviral agents used in the AIDS therapy.

Human immunodeficiency virus belongs to the retrovirus family (*Retroviridae*), the lentivirus genus (*Lentivirus*). After the penetration of HIV into a cell, particular intracellular processes start up, resulting in the integration of antiviral DNA into host cell chromosomes (Fig. 3). In the early stage, viral genomic RNA is released from the viral capsid and is subjected to the reverse transcription by the RNA-dependent DNA polymerase (reverse transcriptase). This results in the formation of a double-stranded DNA

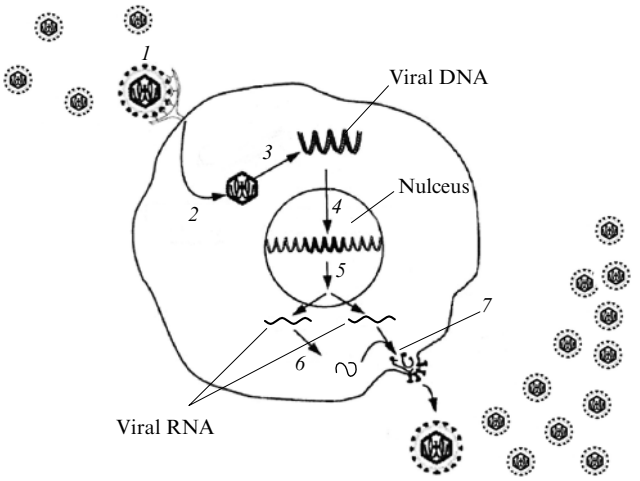


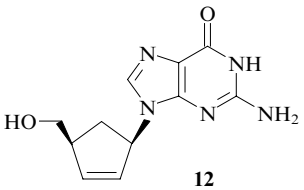

**Figure 3.** Life cycle of human immunodeficiency virus. (*1*) Binding to the receptor, (*2*) penetration and decapsidation, (*3*) reverse transcription, (*4*) integration, (*5*) viral DNA synthesis, (*6*) viral protein synthesis, (*7*) virus assembly and exocytosis.

copy of the viral genome, which is integrated into the host cell genome by the viral integrase. After a particular (often very long) period of time, the synthesis of viral RNA with the participation of cellular enzymes starts up. The viral RNA serves as a template for the protein precursor, which is then specifically processed by the viral protease. After the accumulation of a sufficient amount of viral proteins, the virus assembly takes place followed by the release of the virus from the cell.[45]

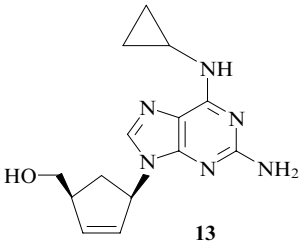
The HIV infection therapy currently remains a challenge. The aim of antiretroviral therapy is to suppress the virus replication to the maximum possible extent for a long period of time in order to create conditions for the recovery of the immune system damaged by HIV.

Nucleoside reverse transcriptase inhibitors (NRTIs) belong to the first and largest class of compounds, which are used in highly active antiretroviral therapy (HAART). They act as terminators of the DNA chain elongation (see above). Nucleoside inhibitors are active in HIV-infected T cells and macrophages and inhibit early stages of the life cycle of the virus.[45] Among the most widely used drugs of this group, note Zidovudine® (AZT), Lamivudine® (3TC), Zalcitabine® (ddC), Emtricitabine® (FTC), Didanosine® (ddI), Ziagen® (ABC) and so on.[46]

Among the most active NRTIs, there are representatives of carbocyclic nucleoside analogues, such as carbovir (**12**) and abacavir (**13**) (their synthesis is described in Section III). Carbovir (carbocyclic mimetic of 2′,3′-didehydro-2′,3′-dideoxyguanosine) and its cyclopropylamine analogue abacavir exhibit high activity in cell cultures infected with HIV. It was shown that abacavir is less toxic, more bioavailable and is characterized by better ability to penetrate into the central nervous system. The intracellular metabolism results in the transformation of abacavir into the active form, *viz*., carbovir 5′-triphosphate (**7b**), which inhibits the reverse transcription. This leads to the termination of the synthesis of viral DNA on the RNA template and stops the HIV replication.[9]



**12**



**13**

The clinical testing of abacavir showed that this drug is effective both in the monotherapy in HIV-infected patients and the treatment in combination with other antiretroviral agents. In 1998, abacavir (Ziagen®) was approved by the FDA as NRTI for the treatment of the HIV-1 infection.[47] The abacavir therapy results in the 99% suppression of the virus activity and a substantial increase in the number of CD4+ cells in HIV-infected patients during 48 weeks.

Therefore, it is evident that the biological activity of carbocyclic nucleoside analogues can be associated with their interactions with both cellular and viral enzymes. Unfortunately, investigations of most compounds were limited only to the activity screening (usually, in cell lines and animal models), whereas targets and mechanisms are currently known for only a few active compounds of this class.

## III. Structural types of carbocyclic nucleoside analogues and methods of synthesis for some representatives

Due to the structural similarity of natural nucleosides and their carbocyclic analogues, there is a wide range of biological targets for the latter. Hence, it is not surprising that the synthesis of various derivatives of carbanucleosides attracts considerable interest. In the last two decades, numerous compounds of this class exhibiting various biological activities were synthesized. Carbocyclic nucleoside analogues are classified into four types according to the size of the carbon ring (a mimetic of the carbohydrate moiety): compounds containing cyclopropane, cyclobutane, cyclopentane and cyclohexane moieties.

Two synthetic strategies for the preparation of carbocyclic analogues of nucleosides are known:

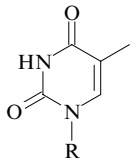
— the direct introduction of a heterocyclic base at position 1′ of the carbocyclic moiety (according to the numbering scheme used in the chemistry of nucleosides); for this purpose, the palladium-catalyzed Trost reaction, the Mitsunobu coupling, *etc*. are used.

— the construction of the heterocyclic base on the 1′-β-amino group of the carbocyclic moiety.

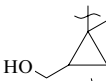
The description of the methods of synthesis for all known carbocyclic nucleoside analogues is beyond the scope of the present review. We are going to demonstrate the diversity of chemical structures and biological properties by considering the most spectacular representative of each type.

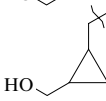
### 1. Carbocyclic nucleoside analogues containing a three-membered ring

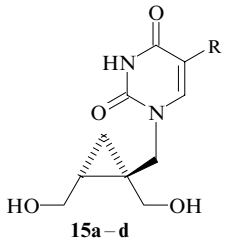
There are only two types of analogues of nucleosides with a three-membered carbocycle. The first type includes cyclopropane derivatives **14a** and **17a** and methylcyclopropane derivatives **9**, **14b**, **15a–d** and **16a**,**b**, which were synthesized as analogues of acyclovir (**17b**) and gancyclovir (**17c**) (the configuration of the substituents in the cyclopropane ring is given with respect to the base fragment).[48]



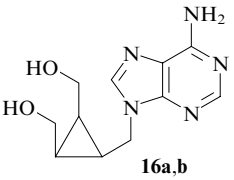
**14a**,**b**

R =  (2-*cis*, **a**),

 (2-*cis*,3-*cis*, **b**)



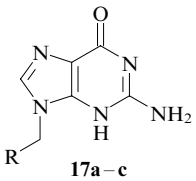
**15a–d**



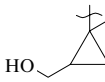
**16a**,**b**

R = (*E*)-CH=CH$_2$X (X = Cl (**a**), Br (**b**), I (**c**)); R = Pr$^n$ (**d**)

**16a**: 2-*cis*,3-*cis*;
**16b**: 2-*trans*,3-*trans*



**17a–c**

R =  (2-*trans*, **a**),

$O(CH_2)_2OH$ (**b**, acyclovir),
$OCH(CH_2OH)_2$ (**c**, gancyclovir)

The cyclopropane ring provides the orientation of the hydroxy groups most favourable for the molecular recognition.[49] These analogues of nucleosides are recognized by thymidine kinases, and the corresponding triphosphates are recognized by viral DNA polymerases, due to which these compounds are promising for the use as antiviral agents.

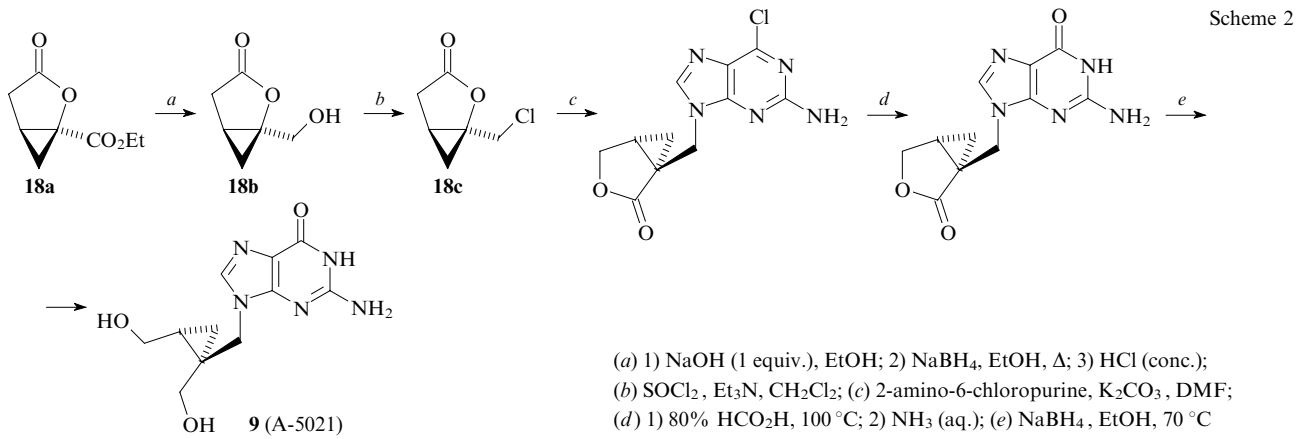
A series of 5-substituted uracil derivatives **15a–d** containing the (1′*S*,2′*R*)-[1′,2′-bis(hydroxymethyl)cyclopropyl]-methyl group were synthesized by Tsuji and co-workers.[50] Compound **15b** exhibited high activity (40–60 times higher than that of acyclovir) against VZV, good bioavailability in rats (68.5%) and the absence of cytotoxicity up to the concentration of 1.5 μmol litre$^{-1}$ (Ref. 50).

Guanine derivative **9** proved to be very effective against the viruses HSV-1, HSV-2 and VZV. Its therapeutic effect is much higher than that of acyclovir.[49] The synthesis of compound **9** is shown in Scheme 2.[51, 52]

In the first step, bicyclic ester **18a**, which was synthesized from epichlorohydrin and diethyl malonate,[53] was selectively reduced with sodium borohydride to alcohol **18b**. The latter was treated with thionyl chloride followed by the condensation of chloro derivative **18c** with 2-amino-6-chloropurine. The reaction with aqueous ammonia and the subsequent reduction with $NaBH_4$ afforded the target product **9**. The mechanism of its antiviral action is described in detail in Section II.

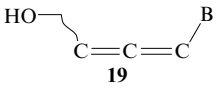
The structures of cyclopropane analogues of the second type are characterized by the presence of the double bond between the purine base and the cyclopropane ring. This class of compounds, which can be considered as analogues of adenallene (**19**) effectively inhibiting the HIV replication,[54] was described for the first time by Zemlicka and coworkers[55, 56] in 1998. The design of these compounds was based on the suggestion that the introduction of a rigid

Scheme 2



(*a*) 1) NaOH (1 equiv.), EtOH; 2) $NaBH_4$, EtOH, Δ; 3) HCl (conc.); (*b*) $SOCl_2$, $Et_3N$, $CH_2Cl_2$; (*c*) 2-amino-6-chloropurine, $K_2CO_3$, DMF; (*d*) 1) 80% $HCO_2H$, 100 °C; 2) $NH_3$ (aq.); (*e*) $NaBH_4$, EtOH, 70 °C

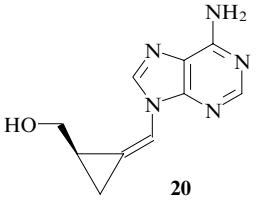
structural group into nucleosides or their carbocyclic analogues can increase the antiviral activity.



**19**

B is adenine

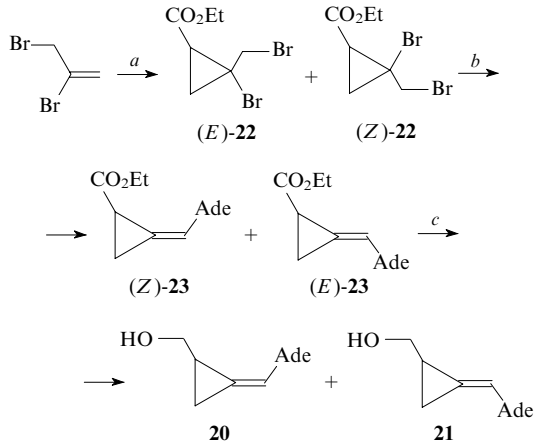
The antiviral activity of the adenine derivative, synadenol (**20**), based on the methylenecyclopropane structure was tested against eight viruses: HCMV, mouse cytomegalovirus (MCMV), HSV-1, HSV-2, EBV, HIV-1, HBV and VZV.



**20**

Synadenol [**20**, the (−)-enantiomer is given] proved to be an inhibitor of EBV ($EC_{50}$ = 0.06–0.09 μmol litre$^{-1}$), HCMV ($EC_{50}$ = 2.4–2.9 μmol litre$^{-1}$) and VZV ($EC_{50}$ = 2.5 μmol litre$^{-1}$). In all cases, *Z* isomer **20** was more effective than *E* isomer **21**. The synthesis of synadenol is shown in Scheme 3.[55]

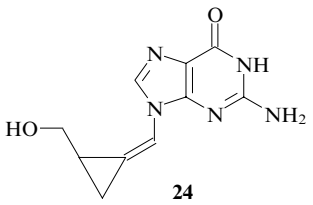
Scheme 3



(*a*) $N_2CHCO_2Et$, $Rh_2(OAc)_4$, $CH_2Cl$; (*b*) adenine, $K_2CO_3$, DMF; (*c*) diisobutylaluminium hydride (DIBAL-H), THF

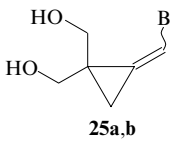
A mixture of 2-bromo-2-(bromomethyl)cyclopropane-1-carboxylates **22** (*Z* : *E* = 3 : 2) was prepared by the reaction of ethyl diazoacetate with 2,3-dibromopropene in the presence of a rhodium catalyst (yield 91%). The alkylation of adenine with carboxylates **22** in the presence of potassium carbonate afforded a mixture of the *Z* and *E* isomers of compound **23** (2 : 1) in 39% yield. The reduction of esters **23** gave a mixture of synadenol **20** and its *E* isomer **21**; the yield was 75%. However, attempts to separate compounds **20** and **21** by chromatography failed. The transformation of isomers **20** and **21** into the corresponding $N^6$-(dimethylamino)-methylene derivatives resulted in their successful separation, and the treatment of these compounds with ammonia in methanol produced target isomers **20** and **21** in 85% and 86% yields, respectively.[55] The separation of enantiomers of synadenol (**20**) was performed with the use of adenosine deaminase.[54]

The similar guanosine derivative, synguanol [(±)-**24**], exhibited activity against HCMV ($EC_{50}$ = 0.04–2.0 μmol litre$^{-1}$) and EBV ($EC_{50}$ = 0.3–5.6 μmol litre$^{-1}$). As in the case of synadenol, the *Z* isomer of synguanol proved to be much more effective.[55] The scheme of the synthesis of compound (±)-**24** is similar to that developed for synadenol.[55]



**24**

The research group headed by Zemlicka synthesized the *E* and *Z* isomers of methylenecyclopropane analogues of 2′-deoxyguanosine and 2′-deoxyadenosine **25a**,**b** containing the geminal hydroxymethyl groups and studied their biological properties.[57]



**25a**,**b**

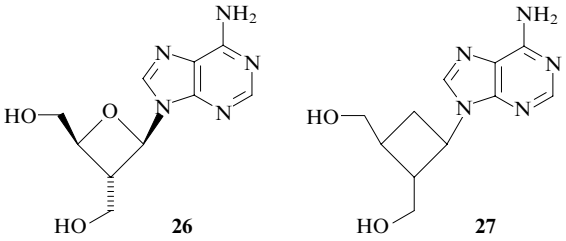
B is guanine (**a**), adenine (**b**)

In the EBV-infected Akata cell culture, $EC_{50}$ for the *Z* isomer of compound **25a** is 8 μmol litre$^{-1}$. The Z isomer is

non-toxic in this culture but its activity is lower than that of gancyclovir.[58] It also proved to be active against HCMV ($EC_{50} = 1.2 \pm 0.8$ μmol litre$^{-1}$) and MCMV ($EC_{50} = 0.3$ μ mol litre$^{-1}$), but was less active against HCMV containing the UL97 mutant gene. Evidently, the carbocyclic nucleoside analogue **25a** is phosphorylated by HCMV-encoded phosphotransferase ppUL97. The preclinical testing of compound (*Z*)-**25a** (cyclopropavir) as a potential medication for the treatment of the HCMV infection is underway.[58] The *E* isomers of derivatives **25a**,**b** did not exhibit antiviral properties.

## 2. Carbocyclic nucleoside analogues containing a four-membered ring

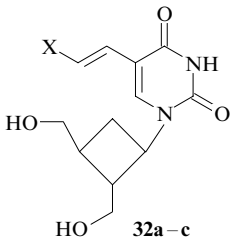
Oxetanocin A (**26**) was isolated for the first time in 1986 from *Bacillus megaterium*. The considerable antiviral, antitumour and antibacterial activities of this compound have prompted interest in the synthesis of its analogues.[59, 60] The carbocyclic analogue of oxetanocin A, cyclobutyl-A [(±)-**27**], showed activity against a series of viruses, including HIV-1, HSV-1, HSV-2, HCMV, EBV and HBV.[61] Cyclobutyl-A is more active against VZV than acyclovir ($EC_{50} = 1.5$ *vesrus* 3 μmol litre$^{-1}$) but is less effective against HSV-1 and HSV-2.[62, 63] The activity of compound (±)-**27** against EBV (0.2 μmol litre$^{-1}$) proved to be an order of magnitude higher than that of gancyclovir.[62]




A racemic mixture of the guanine-containing derivative of cyclobutyl-G (**5a**) acts as an inhibitor of HCMV,[61] HIV-1 (Ref. 63) and VZV,[64] and its D enantiomer (D-**5a**, Lobucavir®) is very active against HSV-1 and HSV-2 (the mechanism of action is considered in Section II).[65] Compound D-**5a** exhibits also activity against HBV ($EC_{50} = 2.5 \pm 0.85$ μmol litre$^{-1}$).[41] The testing of Lobucavir® as an anti-HBV agent was performed in animals by the Bristol-Myers Squibb Co.; however, the studies were stopped because of its the oncogenic effect.[62]

The synthesis of Lobucavir® is shown in Scheme 4.[66] Optically pure (1*S*,2*S*)-cyclobutanone **28** was synthesized by the diastereoselective [2 + 2]-cycloaddition of dimenthyl fumarate (**29**) and ketene dimethyl acetal (**30**) followed by the reduction, benzylation and hydrolysis of the adduct. The reduction of *trans*-di(benzoyloxymethyl)cyclobutanone (**28**) with diisobutylaluminium chloride (DIBAC) at −35 °C gave alcohol **31a**, which was transformed into triflate **31b** by the reaction with trifluoromethanesulfonic anhydride. Then 2-amino-6-iodopurine was added to compound **31b** followed by the deprotection. The yield of Lobucavir® was 35%, the stereoselectivity of the method was 99%.

Derivatives of 5-substituted uracil **32** containing the cyclobutane ring were synthesized and their biological properties were studied.

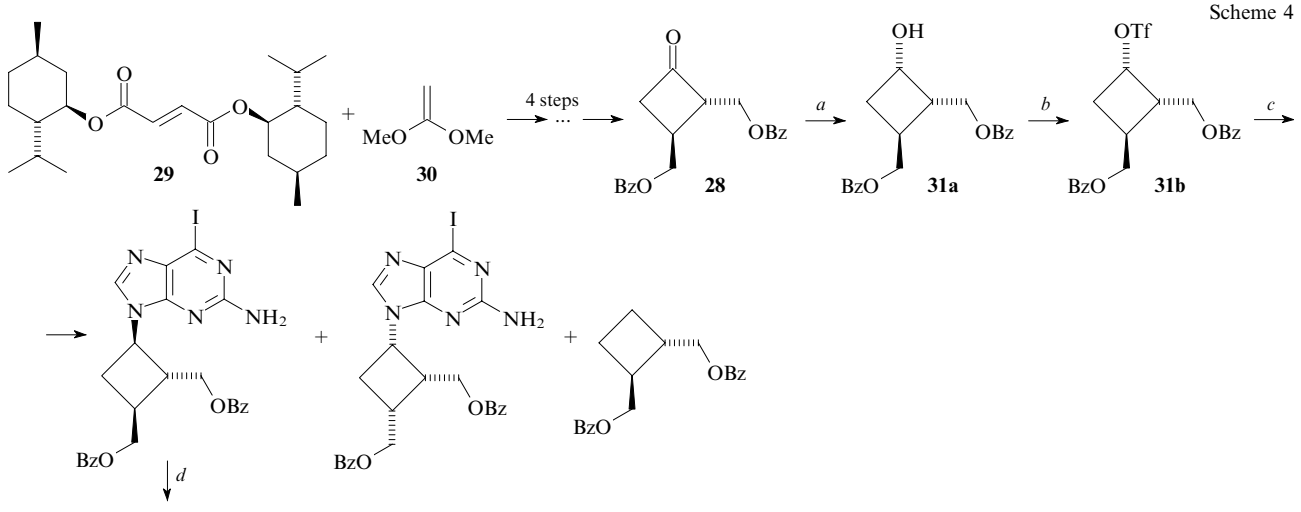



X = Br (**a**), I (**b**), Cl (**c**)

In particular, analogues of 5-(2-bromovinyl)uracil (±)-**32a**–**c** synthesized by Slusarchyk *et al.*[67] proved to be effective inhibitors of VZV ($EC_{50} = 0.001 - 0.4$ μmol litre$^{-1}$ *versus* 0.4–4 μmol litre$^{-1}$ for acyclovir), but they did not show activity in TK-deficient (TK$^-$) cells. Compounds **32a**–**c** are much less effective inhibitors of HSV-1 ($EC_{50} = 1.5 - 13$ μmol litre$^{-1}$ *versus* 0.2–0.4 μmol litre$^{-1}$ for acyclovir), and they are inactive against HSV-2 and HCMV.[67]

Cyclobutyl derivatives of adenine and its analogues **33a**–**e** were synthesized by construction of the purine base on the amino group of 2-{(1*R*)-*cis*-3-amino-2,2-dimethylcy-

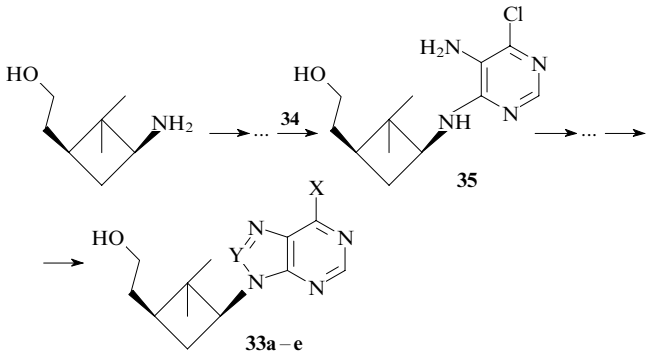
Scheme 4




(*a*) DIBAC, $CH_2Cl_2$, −35 °C; (*b*) $Tf_2O$, pyridine, $CH_2Cl_2$;
(*c*) 2-amino-6-iodopurine, DMF; (*d*) 1) NaOMe, MeOH; 2) HCl (conc.)

clobutyl}ethanol (Scheme 5).[68] 5-Amino-4,6-dichloropyrimidine (**34**) served as the precursor of the heterocyclic base. The cyclization of the reaction product of **34** with alcohol (compound **35**) in the presence of triethyl orthoformate produced 6-chloropurine derivative **33a**. Refluxing of the latter with NaOH gave analogue of inosine **33b**, and the heating with liquid ammonia under high pressure afforded adenine derivative **33c**. To synthesize compounds **33d**,**e** containing 8-azapurine bases, diamine **35** was treated with sodium nitrite in hydrochloric acid. The subsequent heating gave the analogue of 8-azainosine **33d**, and the treatment with aqueous ammonia afforded 8-azaadenine derivative **33e**.

Scheme 5



Y = CH: X = Cl (**a**), OH (**b**), $NH_2$ (**c**); Y = N: X = OH (**d**), $NH_2$ (**e**)

The activity of compounds **33a**–**e** was studied against HIV-1, HIV-2, HSV-1, HSV-2, HCMV, VV, VZV, parainfluenza virus and reovirus type 1.[69] Most of compounds of this series did not exhibit antiviral properties even at high concentrations. Only derivative **33e** showed considerable selective activity against the $TK^+$ and $TK^-$ strains of the VZV virus; thus, it was proved that the inhibition of VZV replication proceeds without the participation of thymidine kinase.[69]

## 3. Carbocyclic nucleoside analogues containing a five-membered ring

This group of carbocyclic nucleoside analogues is the largest one. This is attributed, on the one hand, to the fact that they are most structurally similar to natural nucleosides and, on the other hand, to a wide range of their biological activities. Due to the conformational similarity between the cyclopentane moiety and the ribose, these analogues can act as either inhibitors or substrates for enzymes catalyzing the conversions of natural nucleosides and nucleotides.

### a. Analogues containing the C–N bond between a heterocyclic base and a carbocyclic moiety

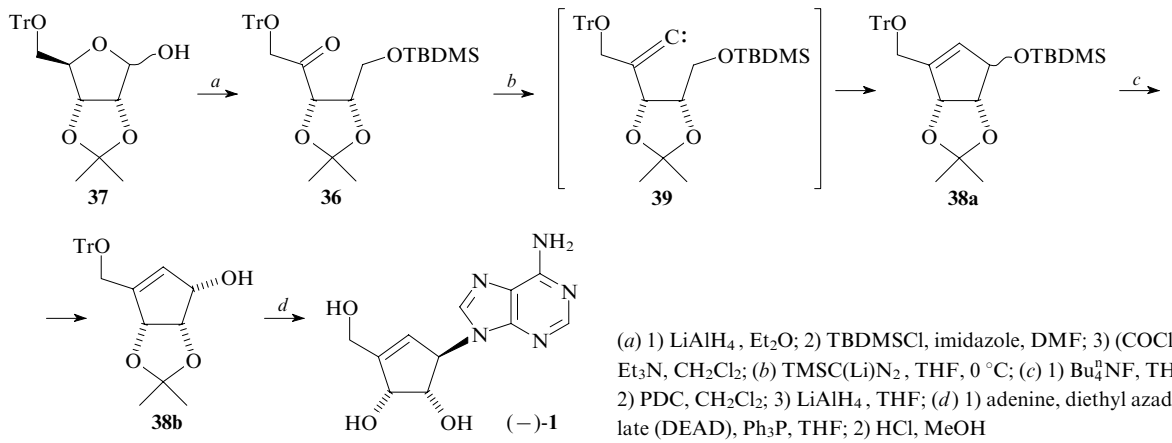
Two most well known members of this class of compounds, *viz*., neplanocin A (**1**) and aristeromycin (**2**), were isolated from natural sources: aristeromycin from *Streptomyces citricol* in 1969[4,70] and neplanocin A from *Ampullariella regularis* in 1979.[71–73]

The efficient chemical synthesis of (–)-neplanocin A starting from D-ribose was described by Yamato and co-workers (Scheme 6).[74] Ketone **36** was synthesized by the reduction of 2,3-*O*-isopropylidene-D-ribose triphenylmethyl ether (**37**) followed by protection of the hydroxy group with *tert*-butyldimethylsylil chloride (TBDMSCl). Cyclopentene derivative **38a** was prepared in 55%–65% yield through the intermediate formation of alkylidene carbene **39**. Compound **38a** was transformed into alcohol **38b** by removing the protecting group with tetrabutylammonium fluoride followed by the oxidation with pyridinium dichromate (PDC) and reduction with lithium aluminium hydride. The Mitsunobu coupling and subsequent deprotection afforded (–)-neplanocin A (**1**) in quantitative yield.[75]

Kobayashi and co-workers[76] improved the stereoselective synthesis of aristeromycin (**2**) with the use of 4-aryl-1-azidocyclopent-2-enes **40a**–**c** as new synthons for the synthesis of carbocyclic nucleosides (Scheme 7).[77] This approach is an example of construction of the purine base on the 1′-β-amino group of the carbocyclic moiety. Azides **40a**–**c** were oxidized with osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide (NMMO), and then the hydroxy groups were protected with the isopropylidene residue in the presence of *p*-toluenesulfonic acid pyridine salt (PPTS). The aryl group of acetonides **41a**–**c** was transformed into the methoxycarbonyl group by oxidation with $NaIO_4$ in the presence of the catalyst $RuCl_3$ followed by the reaction with diazomethane. The ester and azido groups in compound **42** were reduced with $LiAlH_4$. Amino alcohol **43** is a versatile precursor for the synthesis of carbocyclic nucleoside analogues with a five-membered ring.[77–79] Subsequent transformations gave aristeromycin (**2**); the total yield of **2** was 17%.[76]

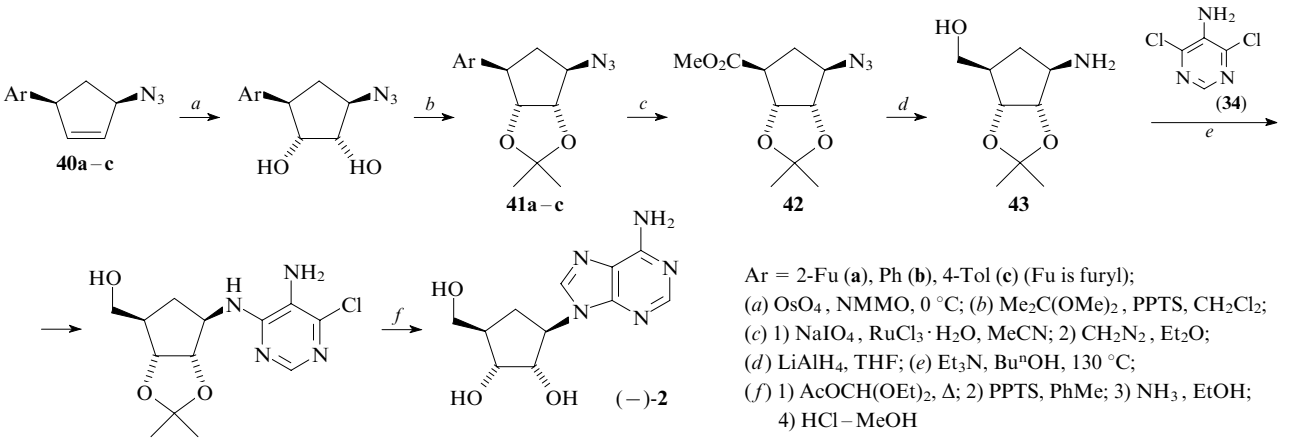
Neplanocin A (**1**) and aristeromycin (**2**) showed a broad spectrum of biological activities, and demonstrated good prospects of the design of new analogues of nucleosides with a five-membered carbocycle and the search for new poten-

Scheme 6



(*a*) 1) $LiAlH_4$, $Et_2O$; 2) TBDMSCl, imidazole, DMF; 3) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$; (*b*) TMSC(Li)$N_2$, THF, 0 °C; (*c*) 1) $Bu^n_4NF$, THF; 2) PDC, $CH_2Cl_2$; 3) $LiAlH_4$, THF; (*d*) 1) adenine, diethyl azadicarboxylate (DEAD), $Ph_3P$, THF; 2) HCl, MeOH

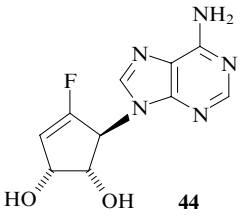
Scheme 7




tial therapeutic agents.[72] Cellular *S*-adenosylhomocysteine hydrolase (see section II) is the target enzyme for these compounds.[14,80] In addition to SAH hydrolase, compounds **1** and **2** are also substrates for cellular kinases. These compounds, like adenosine, are phosphorylated to mono-, di- and triphosphates. Since aristeromycin and neplanocin A triphosphates are structurally similar to adenosine 5′-triphosphate, these compounds are involved in important cellular processes, which is responsible for their high toxicity.[14,81–83]

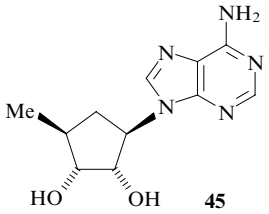
During many years, researchers synthesized various neplanocin A and aristeromycin derivatives and other compounds of this series in order to reduce the toxicity. One of approaches is based on the modification of the 4′-hydroxymethyl group. In this case, analogues of neplanocin A and aristeromycin lose their substrate properties toward cellular adenosine kinase and adenosine deaminase and, consequently, they are less toxic.[81]

The removal of the 4′-hydroxymethyl group of neplanocin A (**1**) affords 9-(*trans*-2′-*trans*-3′-dihydroxycyclopent-4′-enyl)adenine (DHCeA, **3b**). Compound **3b** showed activity against vaccinia virus in the cell culture of L929 mouse fibroblasts comparable to that of neplanocin A ($EC_{50}$ = 0.28 and 0.08 μmol litre$^{-1}$, respectively) and was >30 times less toxic [the toxic concentration ($CC_{50}$) was 17 and 0.5 μmol litre$^{-1}$ for DHCeA and neplanocin A, respectively].[84] More recently, halogen derivatives of DHCeA have been synthesized, among which 5′-F-DHCeA (**44**) proved to be the most effective inhibitor of SAH hydrolase ($EC_{50}$ = 7.67 μmol litre$^{-1}$).[85,86]




**44**

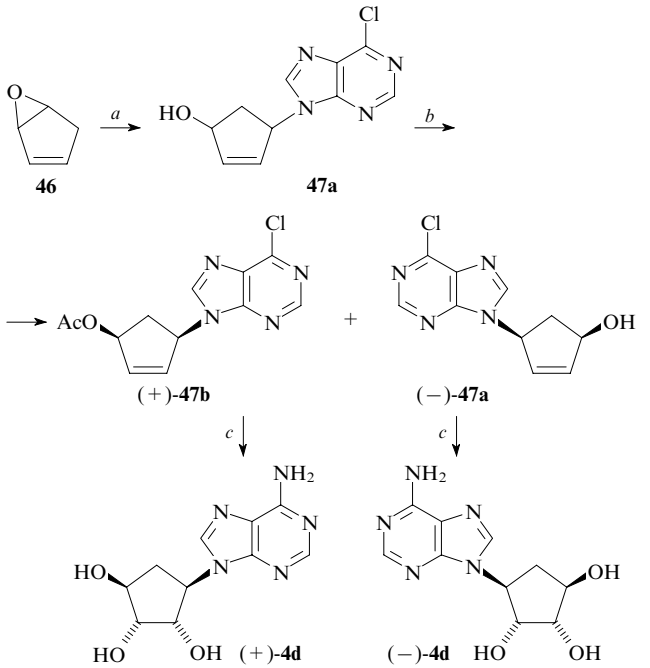
Analogues of aristeromycin, *viz.*, 5′-noraristeromycin (**4d**) and 5′-deoxyaristeromycin (**45**), were synthesized in the laboratory headed by Schneller.[87,88] Compound **45** exhibits moderate activity and is non-toxic because it cannot form the triphosphate form, whereas analogue **4d** shows higher activity against VV, HCMV, HBV, and measles and influenza viruses.[89,90]




**45**

The synthesis of individual enantiomers of 5′-noraristeromycin (**4d**) is shown in Scheme 8.

Scheme 8



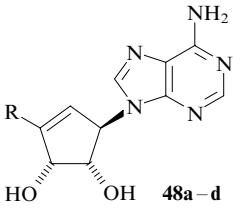

(*a*) 6-Chloropurine, $Pd(PPh_3)_4$, DMSO–THF, 0 °C; (*b*) lipase from *Ps. cepacia*, AcOCH=$CH_2$; (*c*) 1) $K_3Fe(CN)_6$, $OsO_4$; 2) $NH_3$–MeOH, 100–120 °C

The condensation of epoxide (±)-**46** with 6-chloropurine was performed in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) to prepare compound **47a** as a mixture of enantiomers (yield 80%), which were separated using lipase from *Pseudomonas cepacia* into acetate (+)-**47b** with optical purity of >95% and alcohol (−)-**47a** with optical purity of >95%. Enantiomers of

5′-noraristeromycin (+)-**4d** and (−)-**4d** can be synthesized from these carbocyclic analogues of 2′,3′-dideoxy-2′,3′-didehydro nucleosides by oxidation with osmium tetroxide in the presence of potassium ferricyanide followed by the treatment with a saturated solution of ammonia in methanol.[91] The total yields were 29% and 32% for enantiomers (+)-**4d** and (−)-**4d**, respectively.

Substituted *N*(1)-oxides belong to another group of 5′-noraristeromycin derivatives.[92,93] Being depot forms, these compounds are less toxic than the starting noraristeromycin (**4d**), but they did not exhibit higher activity against smallpox viruses.

A series of active and non-toxic analogues **48a–d** were prepared by modifying the 4′-hydroxymethyl group of neplanocin A (**1**).[53,94,95]



**48a–d**

R = $(CH_2)_2OH$ (**a**), $CO_2H$ (**b**), $C(O)NH_2$ (**c**), $CH(OH)CH{=}CH_2$ (**d**)

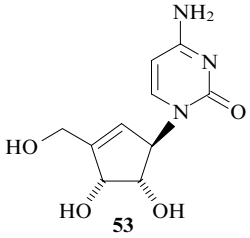
Homoneplanocin A (**48a**) is highly active against VZV ($EC_{50}$ = 3.6 μmol litre$^{-1}$) without cytotoxicity up to 1.8 μmol litre$^{-1}$ (the toxic concentration of neplanocin A is 0.65 mmol litre$^{-1}$).

Homoneplanocin A (**48a**) was synthesized starting from cyclopentenone **49**, which is widely used as a precursor in the synthesis of carbocyclic analogues (Scheme 9).[94] The addition of the product, which was obtained by deprotonation of EtOAc with $LiN(TMS)_2$, to carbocyclic synthon **49** derived from D-ribose gave compound **50**, whose ester group was reduced with $LiBH_4$. The hydroxy groups of cyclopentenediol **51** were protected by *tert*-butyldimethylsilyl (TBDMS) and acetyl residues. Then the allylic rearrangement with the use of $Pd^{2+}$ afforded compound **52a**, which was transformed into the corresponding mesylate **52b**. The condensation of the latter with adenine proceeded by the $S_N2$ mechanism in the presence of crown ether. The final step involved the removal of protecting groups to form the target homoneplanocin A (**48a**).

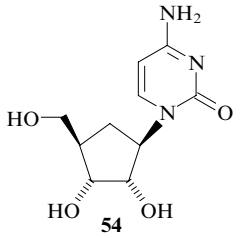
Carboxy derivative **48b** and amide **48c** synthesized from neplanocin A (**1**) inhibit SAH hydrolase ($EC_{50}$ = 1.4 and 9 μmol litre$^{-1}$, respectively).[95] Amide **48c** exhibited activity against RNA-containing viruses, such as parainfluenza 3, measles and epidemic parotitis viruses, at effective concentrations from 0.14 to 4.88 μmol litre$^{-1}$ (Ref. 95).

Vaccinia virus proved to be very sensitive to 5′-*C*-vinylneplanocin A (**48d**). The latter compound was also synthesized starting from neplanocin A (**1**); the effective concentration was 0.2 μmol litre$^{-1}$, which is 10 times lower than that for neplanocin A (2.6 μmol litre$^{-1}$).[96,97]

Cyclopentenylcytosine (**53**, CPE-C) and carbodine (**54**) are examples of cytosine analogues of neplanocin A (**1**) and aristeromycin (**2**), respectively. These compounds have considerable anticancer activity, which was studied in different cell lines. In addition, CPE-C and carbodine showed good activity against HSV-1, HSV-2 and influenza virus.[98,99]



**53**

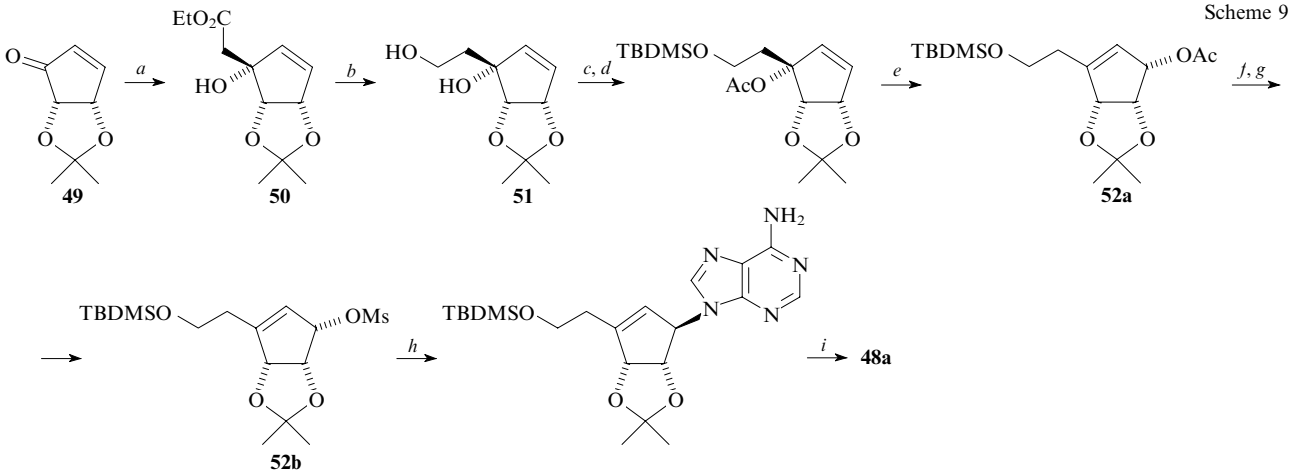


**54**

It was found the high cytotoxicity of compounds **53** and **54** is associated with the inhibition of the conversion of uridine 5′-triphosphate into cytidine 5′-triphosphate (CTP) in the reaction catalyzed by CTP synthase, resulting in the complete exhaustion of the CTP pool in the treated cells.

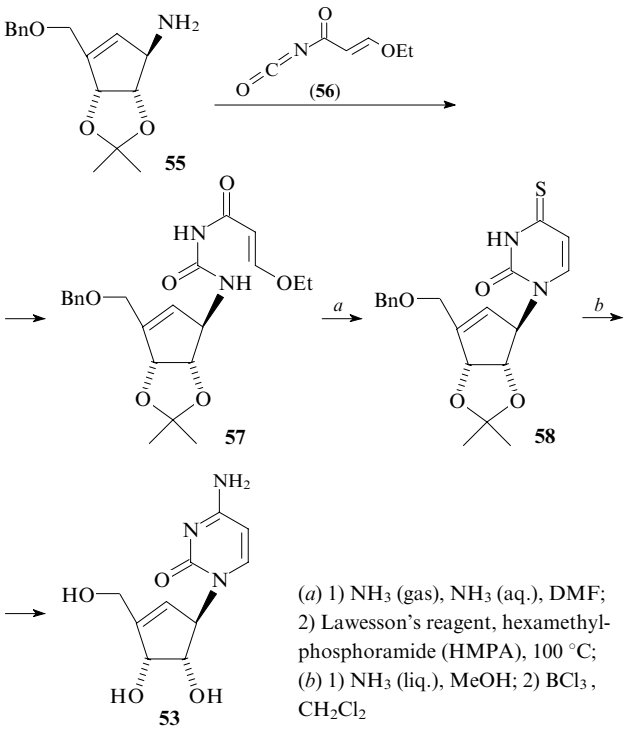
Compounds **53** and **54** were synthesized by construction of the heterocyclic base.[98,99] The synthesis of cyclopentenylcytosine **53** is presented in Scheme 10.[98] Carbodine (**54**) was synthesized in a similar way.[100]

Scheme 9



(*a*) $(TMS)_2NH$, $Bu^nLi$, EtOAc, THF; (*b*) $LiBH_4$, THF; (*c*) TBDMSCl, imidazole, THF; (*d*) $Ac_2O$, DMAP, $Et_3N$, THF; (*e*) $PdCl_2(MeCN)_2$, *p*-benzoquinone, THF; (*f*) $K_2CO_3$, MeOH; (*g*) MsCl, dimethylaminopyridine (DMAP), $CH_2Cl_2$; (*h*) adenine, NaH, 15-crown-5, DMF; (*i*) HCl, MeOH (aq.)

Scheme 10




Cyclopentylamine **55**, which is a versatile precursor in the synthesis of carbocyclic nucleoside analogues, was synthesized from D-ribose, as was described[75] for the synthesis of neplanocin A. Isocyanate **56** was synthesized from 3-ethoxyprop-2-enoyl chloride and silver isocyanate and was then immediately introduced into the reaction with amine **55**. The cyclization of compound **57** under mild conditions and subsequent transformation of the carbonyl group into the thiocarbonyl group with the use of Lawesson's reagent (2,4-bis(4-methoxyphenyl-1,2,3,4-dithiadiphosphetane 2,4-disulfide) gave thiouracil derivative **58**. The treatment of the latter with ammonia in methanol and the removal of the protecting group with boron trichloride afforded the target product CPE-C (**53**).

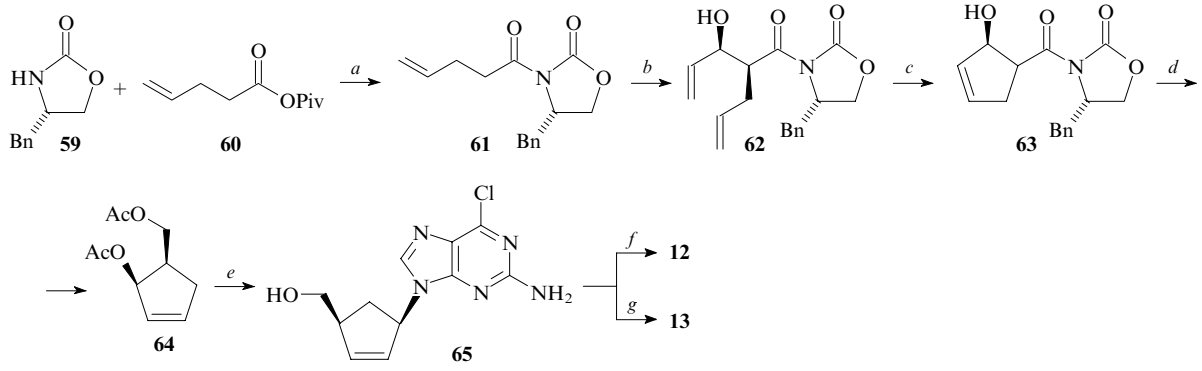
Although many available analogues of nucleosides containing a five-membered ring have antiviral activity, only some of them have found use as medications. A more thorough study of the potential therapeutic agents revealed the properties interfering with their further development. Only a few agents successfully passed tests and were approved as drugs. Carbovir (**12**) and its cyclopropylamine analogue abacavir (**13**) can be mentioned as good examples. Carbovir showed high activity in HIV-infected cell cultures, but it displayed low solubility and bioavailability and, as a consequence, it poorly penetrated cells of the central nervous system.[9] For the purpose of improving the properties of carbovir, a series of prodrugs, including 6-cyclopropyl-substituted analogue **13**, were synthesized. Based on the results of further investigations, abacavir was approved by the FDA as a medication for the treatment of the HIV infection under the trade name Ziagen® (Ref. 9).

Although several methods were developed for the synthesis of abacavir, attempts to optimize its synthesis are still made. The synthesis of carbovir and abacavir proposed by Crimmins is presented below (Scheme 11).[100, 101]

The synthesis begins with the acylation of oxazolidinone **59** with mixed anhydride **60**. The reaction of compound **61** with acrolein in the presence of the complex of the alkaloid (−)-sparteine with $TiCl_4$ gives *syn* isomer **62**, which is transformed into cyclopentenol **63** in the presence of the Grubbs catalyst. The reduction of **63** with lithium borohydride followed by the acetylation of diol affords diacetate **64**. The Trost reaction[102] of the latter with 6-amino-2-chloropurine in the presence of the Pd complex produces compound **65**. The treatment of intermediate **65** with alkali yields carbovir (**12**), and the reaction of intermediate **65** with cyclopropylamine and NaOH produces abacavir (**13**).

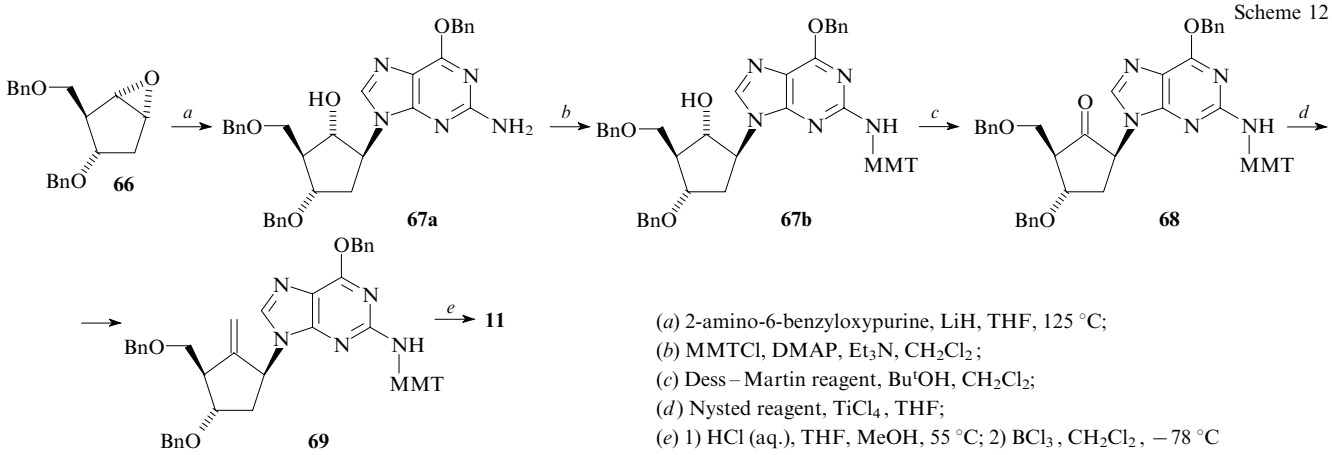
Note also the carbocyclic analogue of 2′-deoxyguanosine, entecavir (**11**), which is successfully used in the therapy of hepatitis B virus.[44] The synthesis of **11** proposed by Bisacchi and co-workers[103] is shown in Scheme 12.[9] Chiral epoxide **66** is a convenient precursor of entecavir. The reaction of **66** with 2-amino-6-benzyloxypurine gave adduct **67a**, which was treated with 4-monomethoxytrityl chloride (MMTCl) to protect the amino group of the base; intermediate **67b** was obtained in 82% yield. The subsequent oxidation of **67b** with the Dess–Martin reagent [1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one] and methylenation of compound **68** with the complex of $C_6H_{12}Br_2OZn_3$ (Nysted reagent) with $TiCl_4$ in THF gave the analogue of 2′-deoxyguanosine **69**, and its deprotection resulted in entecavir with optical purity >99%.

Scheme 11




(*a*) Bu$^n$Li, THF, −78 °C; (*b*) 1) $TiCl_4$, (−)-sparteine, $CH_2Cl_2$; 2) acrolein; (*c*) $(cHex_3P)_2Cl_2Ru{=}CHPh$, $CH_2Cl_2$; (*d*) 1) $LiBH_4$, THF–MeOH; 2) $Ac_2O$, $Et_3N$, DMAP, $CH_2Cl_2$; (*e*) 6-amino-2-chloropurine, NaH, $Pd(PPh_3)_4$, THF–DMSO; (*f*) — NaOH; (*g*) — $NH_2C_3H_5$-cyclo, NaOH; Piv is pivaloyl, cHex is cyclohexyl

Scheme 12

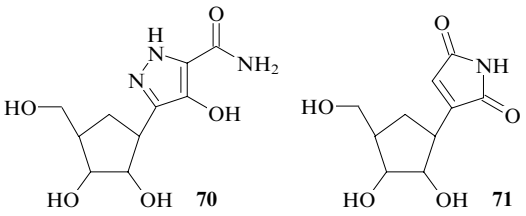


(*a*) 2-amino-6-benzyloxypurine, LiH, THF, 125 °C;
(*b*) MMTCl, DMAP, $Et_3N$, $CH_2Cl_2$;
(*c*) Dess–Martin reagent, $Bu^tOH$, $CH_2Cl_2$;
(*d*) Nysted reagent, $TiCl_4$, THF;
(*e*) 1) HCl (aq.), THF, MeOH, 55 °C; 2) $BCl_3$, $CH_2Cl_2$, −78 °C

**b. Carbocyclic analogues of C-nucleosides**

C-Nucleosides are nucleosides, in which the ribofuranose moiety is linked to the heterocyclic base by the C−C bond instead of the C−N bond. As a result of this replacement, compounds are more resistant to chemical and enzymatic hydrolysis. Due to stability and biological properties, C-nucleosides attract considerable attention.[104] Some naturally occurring C-nucleosides, such as oxazinomycin, pyrazomycin, showdomycin and formycin A, exhibit antibacterial, antitumour and(or) antiviral activities.[105, 106]

First carbocyclic analogues of C-nucleosides were described in the 1960s.[107] However, only a few compounds of this type have been synthesized due to the complexity of their synthesis.

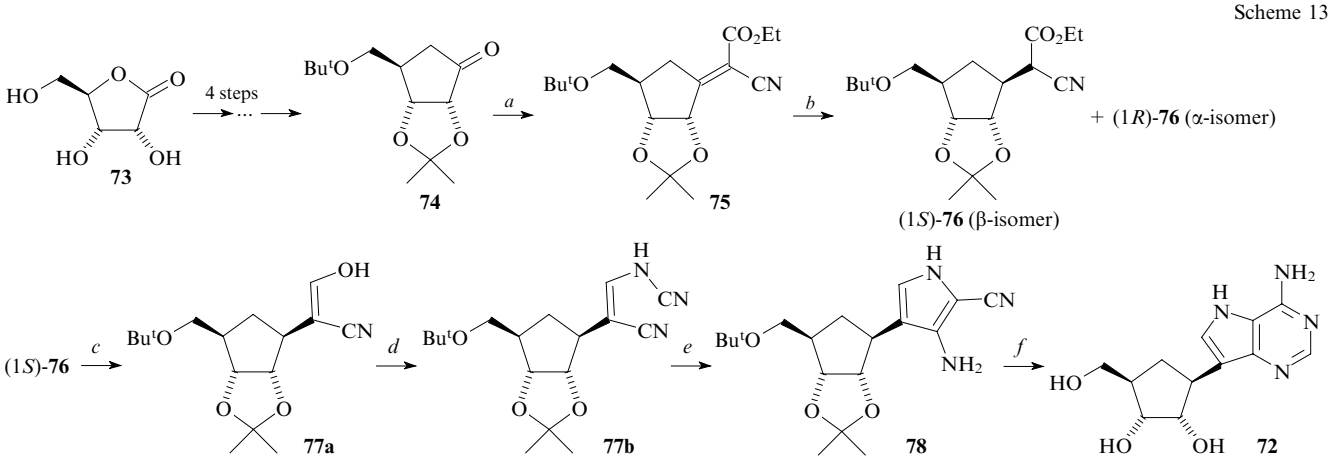


Carbocyclic derivatives of pyrazofurine (**70**) and showdomycin (**71**) were the first analogues of natural biologically active C-nucleosides. These compounds were synthesized as racemic mixtures and did not exhibit significant biological activity.[108, 109]

(−)-9-Deazaaristeromycin (**72**) (the carbocyclic analogue of formycin A) was synthesized from D-γ-ribolactone **73** in 70% yield (Scheme 13).[110, 111] This synthesis is an example of the strategy of construction of the heterocyclic base. Ketone **74** was treated with ethyl cyanoacetate and potassium *tert*-butoxide in ethanol. Intermediate **75** was reduced with $Bu^n_3SnH$ in the presence of azobis(isobutyronitrile) (AIBN) in boiling benzene. The reaction is highly stereoselective (for product **76**, the ratio of isomers $\beta:\alpha = 7:1$) and gives products in moderate yield (62%). The reaction of β-isomer **76** with diisobutylaluminium hydride in diethyl ether at −78 °C produced compound **77a**, which was treated with $H_2NCH_2CN \cdot H_2SO_4$ in methanol. The reaction of intermediate **77b** with $ClCO_2Et$ in methanol and subsequent cyclization in the presence of 1,5-diazobicyclo[4.3.0]non-5-ene (DBN) gave pyrrole derivative **78**. (−)-9-Deazaaristeromycin (**72**) was synthesized by heating compound **78** with formamidine acetate in ethanol followed by the removal of protecting groups with an aqueous solution of thrifluoroacetic acid.

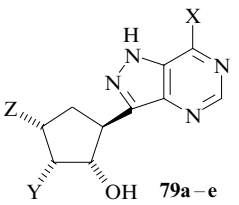
More recently, a series of carbocyclic analogues of formycin **79a**–**e** were synthesized, and wide screening for these compounds was carried out; however, they did not exhibit significant antiviral activity.[112–114] Nevertheless,

Scheme 13



(*a*) $NCCH_2CO_2Et$, $KOBu^t$, EtOH; (*b*) $Bu^n_3SnH$, AIBN, PhH, 80 °C; (*c*) DIBAL-H, $Et_2O$, −78 °C; (*d*) $H_2NCH_2CN \cdot H_2SO_4$, MeOH;
(*e*) 1) $ClCO_2Et$, $CH_2Cl_2$; 2) DBN; 3) $Na_2CO_3$, MeOH; (*f*) $H_2NCH{=}NH \cdot HOAc$, EtOH; 2) $CF_3CO_2H$, $H_2O$, 50 °C

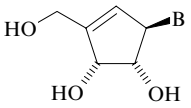
studies on the optimization of the methods for the synthesis of this class of compounds are underway.[115]



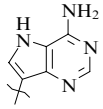
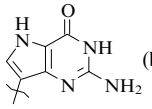
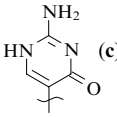
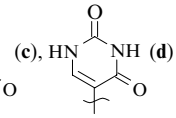
**79a–e**

| Compound **79** | X | Y | Z |
|---|---|---|---|
| **a** | $NH_2$ | H | H |
| **b** | OH | H | H |
| **c** | $NH_2$ | OH | H |
| **d** | OH | OH | H |
| **e** | $NH_2$ | OH | $CH_2OH$ |

Chu and co-workers[116] obtained interesting results when studying the antiviral activity of purine and pyrimidine C-nucleoside analogues of neplanocin A, *viz*., compounds **80a–d**.



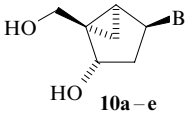
**80a–d**

B =  (**a**),  (**b**),  (**c**),  (**d**)

9-Deazaneplanocin A (**80a**) exhibited moderate anti-HIV activity ($EC_{50}$ = 2.0 μmol litre$^{-1}$). Compounds **80b** and **80c** showed some activity against Punto Toro virus (the phlebovirus family) without substantial cytotoxicity. Compound **80c** was active against West Nile fever virus ($EC_{50}$ = 11 μmol litre$^{-1}$. Compound **80d** displayed insignificant activity against coronavirus causing acute respiratory syndrome.[116]

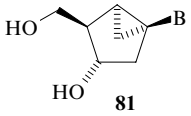
**c. Bicyclic analogues of nucleosides**

Marquez and co-workers[37,117,118] synthesized carbocyclic nucleoside analogues **10a–e** and **81** containing the bicyclo[3.1.0.]hexane system corresponding to both the N and S conformations as the carbocyclic moiety.



**10a–e**

B is thymidine [**a**, (N)-2′-deoxymethane carba-T], cytosine [**b**, (N)-2′-deoxymethane carba-C], guanine [**c**, (N)-2′-deoxymethane carba-G], adenine [**d**, (N)-2′-deoxymethane carba-A], uracil [**e**, (N)-2′-deoxymethane carba-U]

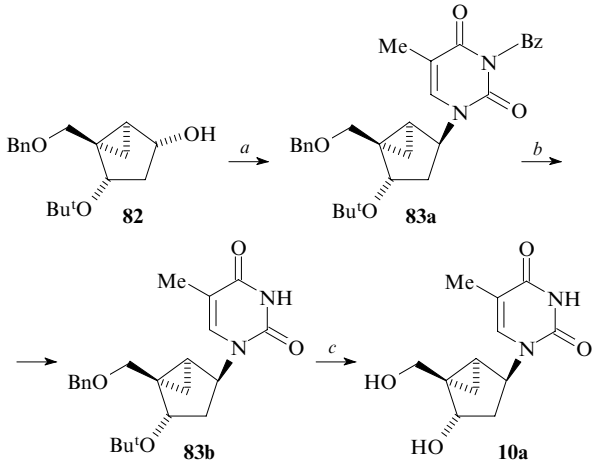


**81**

B is thymidine [(S)-2′-deoxymethane carba-T]

The antiherpes virus activity of derivatives **10a–e** tested in cell cultures infected with HSV-1 and HSV-2 decreases, depending on the nature of the heterocyclic base, in the series T > C > G > A > U. The $EC_{50}$ value for (N)-2′-deoxymethane carba thymidine [(N)-MCT, **10a**] is 0.1 (HSV-1) and 0.3 μmol litre$^{-1}$ (HSV-2) *versus* 1.7 (HSV-1) and 0.3 μmol litre$^{-1}$ (HSV-2) for acyclovir [the mechanism of antiviral action of (N)-MCT is described in Section II]. The synthesis of (N)-MCT (**10a**) is presented in Scheme 14.[36]

Scheme 14



(*a*) 3-Benzoylthymine, $Ph_3P$, DEAD, −45 °C, THF; (*b*) $NH_4OH$, MeOH; (*c*) $BCl_3$, $CH_2Cl_2$, −78 °C

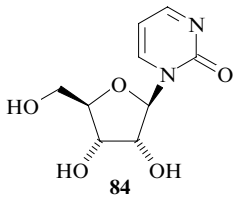
The coupling of chiral carbocyclic alcohol **82** (Ref. 119) with 3-benzoylthymine was performed under the Mitsunobu reaction conditions.[120] The removal of the benzoyl protecting group of compound **83a** under alkaline conditions followed by the deprotection of compound **83b** gave (N)-MCT (**10a**).

More recently, it was shown that (N)-MCT (**10a**) exhibits also high activity against orthopoxviruses (vaccinia and cowpox viruses).[38] It was found that the inhibitory activity of compound **10a** toward the viral DNA synthesis is comparable to that of Cidofovir®:

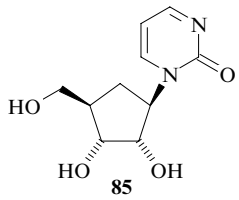
| | $EC_{50}$/ μmol litre$^{-1}$ | |
|---|---|---|
| | (N)-MCT | Cidofovir® |
| Vaccinia virus | 3.9 | 5 |
| Cowpox virus | 11 | 14 |

Taking into account the specific mechanism of antiviral action (see Section II) of (N)-MCT (**10a**), the latter can be considered as the dual-action agent against the herpes and orthopoxvirus infections.

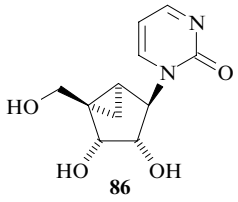
Marquez's research group also synthesized compounds **85** and **86**, which are carbocyclic analogues of Zebularine (**84**) acting as the cytidine deaminase inhibitor.



**84**



**85**



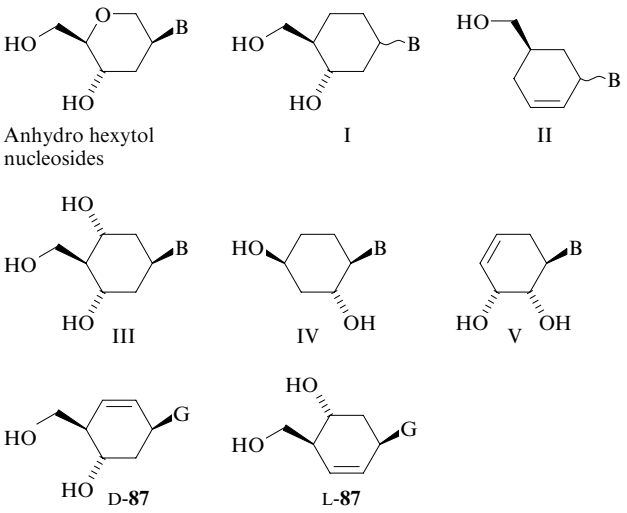
**86**

Zebularine was suggested for the use in cancer therapy in combination with cytosine arabinoside or 5-aza-2′-deoxycytidine. However, zebularine proved to be very labile, which decreases the biological activity of the complex as a whole.[121] With the aim of preparing more stable structures of this type, carbocyclic analogues of zebularine were synthesized; however, unfortunately, they exhibited no activity.[122, 123]

Further investigations showed that the replacement of the oxygen atom by a less electronegative carbon atom reduces the ability of the pyrimidin-2(1*H*)-one ring to form a covalent hydrate necessary for inhibition of the transition state of cytidine deaminase.[52, 121]

### 4. Carbocyclic nucleoside analogues containing a six-membered ring

In the late 1990s, quite numerous carbanucleosides containing a six-membered carbocyclic moiety instead of a carbohydrate moiety (for example, compounds I–V) were synthesized.[124] However, most of them did not exhibit substantial antiviral activity. Apparently, the conformation of the nucleoside is a key factor responsible for the activity of the compound. In most cases, the replacement of the oxygen atom in anhydro hexytol nucleosides by a methylene group leads to the loss of antiviral activity.[124, 125] However, in a series of such compounds (see formulas I–V), the D and L enantiomers of 9-(5′-hydroxycyclohex-2-enyl)guanine (cyclohexenyl-G, D-**87** and L-**87**) showed high selectivity and activity against the viruses HSV-1 ($EC_{50}$ = 0.007 and 0.01 μmol litre$^{-1}$, respectively), HSV-2 ($EC_{50}$ = 0.2 and 0.25 μmol litre$^{-1}$, respectively) and VZV ($EC_{50}$ = 1.7 and 4 μmol litre$^{-1}$, respectively) comparable to the activity of acyclovir and gancyclovir.[125]



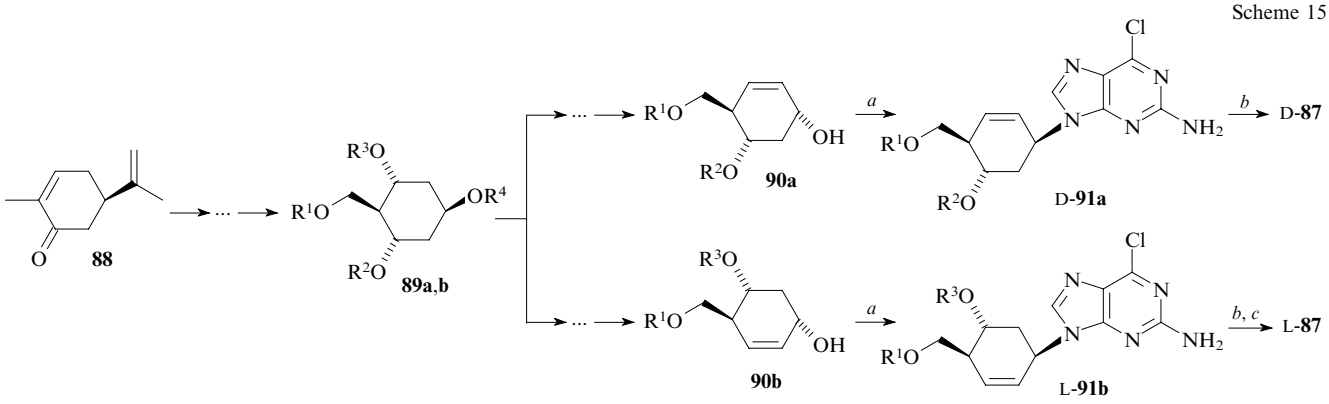

The synthesis of enantiomers of cyclohexenyl-G is shown in Scheme 15.[125, 126] Commercially available (−)-carvone (**88**) was used as the starting compound. A series of transformations afford intermediates **89a**,**b** containing four chiral centres. Depending on the nature of the substituents $R^1-R^4$ in compounds **89a**,**b**, D and L enantiomers of cyclohexenyl-G were obtained. The coupling of 2-amino-6-chloropurine with compounds **90a**,**b** was performed under the Mitsunobu reaction conditions.[120] Then the reaction mixture was treated with a $CF_3CO_2H-H_2O$ mixture (3 : 1). Under these conditions, the *tert*-butyldimethylsilyl groups in compound **91a** were simultaneously removed, resulting in the formation of the target product D-**87**. In the case of compound L-**87**, 2-amino-6-chloropurine was transformed into guanine with a $CF_3CO_2H-H_2O$ mixture and subsequent deprotonation of the adduct with a saturated $NH_3$ solution in methanol gave product L-**87**. Therefore, this strategy made it possible to synthesize the target D and L enantiomers of guanine derivative **87** in total yields of 46% and 75%, respectively.

## IV. Conclusion

Although the first carbocyclic nucleoside analogues were characterized more than 40 years ago and since that time many laboratories have been engaged in the development of methods for their synthesis and investigation of the spectrum of biological activities, these compounds still attract attention. In our opinion, this interest can be attributed to several factors. First, carbocyclic analogues are structurally similar to natural nucleosides and, in addition, are highly stable. Due to a combination of these properties, carbocyclic analogues provide valuable tools for the fundamental study of biochemical processes in the cell. On the other hand, three members of this class of compounds (abacavir, lobucavir and entecavir) are used in medicine as drugs, which clearly shows the practical significance of these compounds.

Noteworthy is the diversity of carbocyclic nucleoside analogues and synthetic strategies for their preparation. Although the targets of action and the mechanisms of biological activity were established for particular com-

Scheme 15




**89**: $R^1 = R^2$ = TBDMS, $R^3$ = H, $R^4$ = Bn (**a**); $R^1 = R^3$ = H, $R^2 = R^4$ = TBDMS (**b**); **90**, **91**: $R^1 = R^2$ = TBDMS (**a**), $R^1 = R^3$ = Bz (**b**); (*a*) 2-amino-6-chloropurine, DEAD, $Ph_3P$; (*b*) $CF_3CO_2H-H_2O$ (3 : 1), 2 days; (*c*) $NH_3$, MeOH, 80 °C

pounds, there are many carbocyclic analogues for which these characteristics are to be found.

Therefore, this class of compounds is of interest from the point of view of both the design of new molecules and investigation of their biological activity.

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