Bioactive Fused Heterocycles: Nucleoside Analogues with an Additional Ring

ARTICLE *in* EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY · JANUARY 2015

Impact Factor: 3.45 · DOI: 10.1016/j.ejmech.2014.12.026 · Source: PubMed

4 AUTHORS, INCLUDING:

Jerzy Boryski
Institute of Bioorganic Chemistry Polish Ac…
60 PUBLICATIONS **442** CITATIONS

SEE PROFILE

European Journal of Medicinal Chemistry 97 (2015) 388–396

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Review article

Bioactive fused heterocycles: Nucleoside analogs with an additional ring

Zofia Jahnz-Wechmann, Grzegorz Framski, Piotr Januszczyk, Jerzy Boryski*

Institute of Bioorganic Chemistry, Polish Academy of Science, Z. Noskowskiego 12/14, PL-61704, Poland

ARTICLE INFO

Article history:
Received 1 September 2014
Received in revised form
5 December 2014
Accepted 17 December 2014
Available online 3 January 2015

Keywords:
Fused heterocycles
Bioactive nucleosides
Ethenonucleosides
Furano[2,3-*d*]pyrimidine nucleosides
Pyrrolo[2,3-*d*]pyrimidine nucleosides
Antiviral activity

ABSTRACT

The following mini-review summarizes the basic literature data regarding synthesis, biological activity, structure–activity relationship, and discussion of the mechanisms of action of two major classes of nucleoside analogs with fused heterocyclic rings: (i) the ethenonucleosides and their related derivatives of the 5,9-dihydro-3-glycosyl-6-alkyl-9-oxo-5*H*-imidazo[1,2-*a*]purine type; (ii) the bicyclic nucleosides of 6-alkyl-2,3-dihydrofurano[2,3-*d*]-pyrimidin-2(3H)-one and 6-alkyl-2,3-dihydropyrrolo[2,3-*d*]-pyrimidin-2(3*H*,7*H*)-one.

1. Introduction

A number of fused heterocyclic compounds indicate a variety of biological properties, and many of them have found application as chemotherapeutic agents. However, this subject is broad that it would be difficult to condense it into a short review. Therefore, this paper is limited mainly to nucleoside analogs modified with a fused heterocyclic ring in their aglycone portion.

The naturally occurring nucleosides are basic constituents of nucleic acids, and are composed of an aglycone moiety – a pyrimidine- or purine-derived base, and a sugar portion: β-D-ribofuranose in the RNA series (**1**–**4**) or 2′-deoxy-β-D-ribofuranose in the DNA series (**5**–**8**) (Fig. 1). Modification of heterocyclic base moiety of nucleosides with an additional ring often results in new interesting physicochemical (*e.g.* enhanced lipophilicity, fluorescence) or biological properties. In general, bioactive nucleoside analogs possessing an additional ring exhibit selective and potent activity acting as inhibitors of crucial viral enzymes, or showing a noticeable anticancer activity. Some of them may act as β-D-ribofuranosyl or 2′-deoxy-β-D-ribofuranosyl nucleosides, while others require further modifications of the sugar portion to achieve their biological activity.

In the present paper we have focused our attention on the following classes of compounds:

A. 1,N^6-ethenoadenosine, 3,N^4-ethenocytidine, as well as 1,N^2-ethenoguanosine and its derivatives of the 5,9-dihydro-3-glycosyl-6-alkyl-9-oxo-5*H*-imidazo[1,2-*a*]purine type;
B. bicyclic nucleosides of 6-alkyl-2,3-dihydrofurano[2,3-*d*]-pyrimidin-2(3H)-one and 6-alkyl-2,3-dihydropyrrolo[2,3-*d*]-pyrimidin-2(3*H*,7*H*)-one (BCNAs).

2. Ethenonucleosides

It has been shown that among the eight basic ribo- and 2′-deoxyribonucleosides (**1**–**8**, Fig. 1), only cytidine and adenine derivatives can readily react with chloroacetaldehyde in aqueous solution producing new fluorescent compounds – the so-called ethenonucleosides: 3,N^4-ethenocytidine (**9, 10**) or 1,N^6-ethenoadenosine (**11, 12**), respectively [1–5] (Scheme 1). Due to their high fluorescence, the reaction has been used as a probe to study enzymatic mechanisms and three-dimensional structure of nucleic acids [3–9].

Unlike adenosine and cytidine, guanosine (**4**) is practically inactive in the reaction with chloroacetaldhyde under physiological

* Corresponding author.
E-mail address: jboryski@ibch.poznan.pl (J. Boryski).

http://dx.doi.org/10.1016/j.ejmech.2014.12.026
0223-5234/

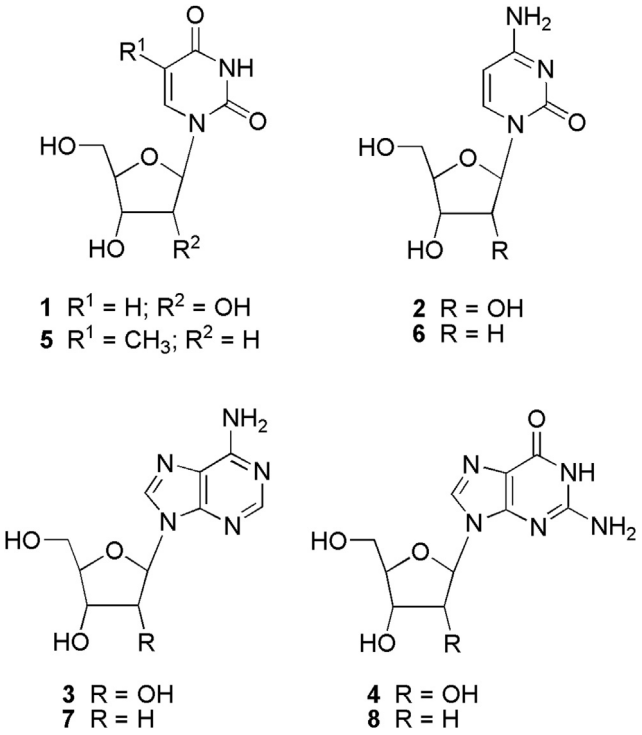


Fig. 1. Naturally occurring nucleosides, constituents of RNA and DNA: uridine (**1**), cytidine (**2**), adenosine (**3**), guanosine (**4**), thymidine (**5**), 2′-deoxycytidine (**6**), 2′-deoxyadenosine (**7**), 2′- deoxyguanosine (**8**).

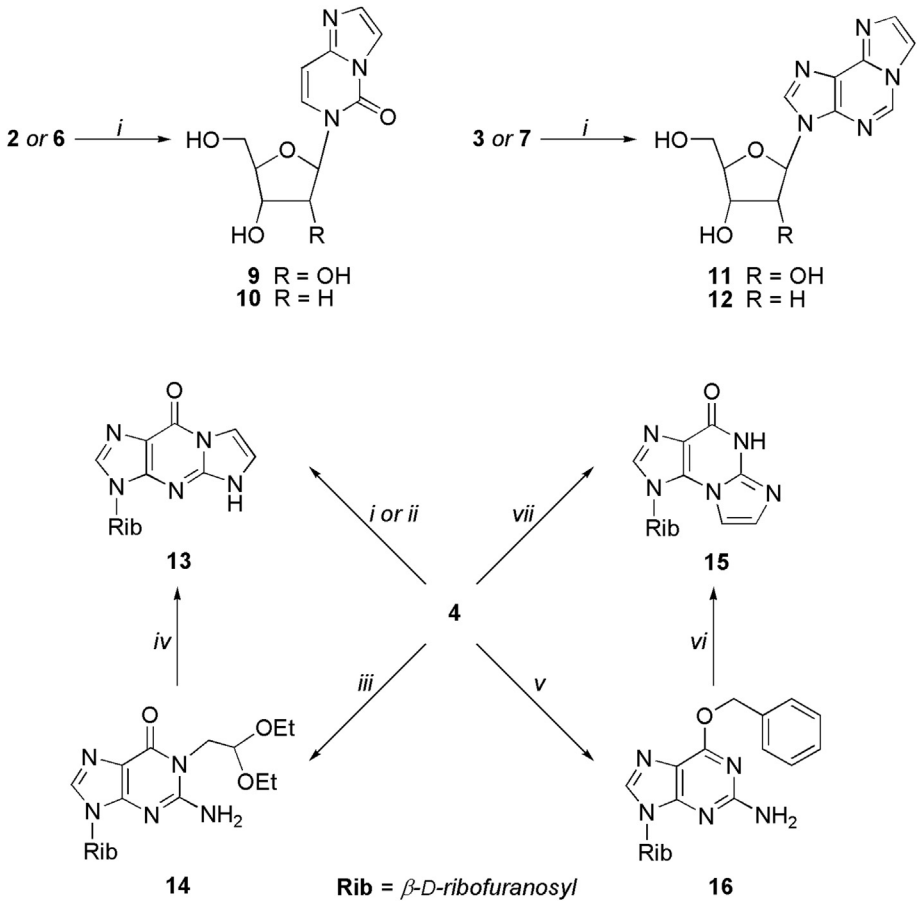
conditions. For instance, the treatment of guanosine with an excess of chloroacetaldehyde in aqueous solution at pH 6.4 for 7 days affords 1,N^2-ethenoguanosine (**13**) in a poor yield 7.5% [10] (Scheme 1). 1,N^2-Ethenoguanosine is a non-fluorescent tricyclic nucleoside, one of the two possible isomers which, due to the ring composition, has been called the "linear" form [10]. The yield of its synthesis can be slightly improved when the reaction is carried out at higher pH values (9–10; 13%), or in the case of the reaction of guanosine N-1 sodium salt under anhydrous conditions (24%) [11]. Some better results have been obtained in a two-step approach: i) alkylation of **4** with bromoacetaldehyde diethylacetal to form a 1-substituted nucleoside (**14**); ii) acidic hydrolysis of **14** to an aldehyde on the nucleoside level, followed by spontaneous intramolecular cyclization to **13** (overall yield 50%) [11]. More recently, the efficient transformation of a guanosine analog into its 1,N^2-etheno derivative in the reaction with chloroacetaldehyde, proceeding at 70 °C, has been reported [12]. 1,N^2-Ethenoguanosine (**13**) and its 2′-deoxy congener have also been found in chloroacetaldehyde-treated polinucleotides and DNA [13].

Guanosine (**4**) can also form an isomeric compound of the etheno type – an "angular", fluorescent N^2,3-ethenoguanosine (**15**), in the reaction of 6-O-benzylguanosine (**16**) with chloroacetaldehyde followed by removal of benzyl group [10,14]. In turn, it has been shown that N^2,3-ethenoguanosine is formed *in vivo* by the human carcinogen, vinyl chloride [15]. It should also be mentioned that ethenoguanine compounds and some related tricyclic nucleosides may be obtained upon reactions with other bifunctional alkylating reagents, like glyoxal [16], glycidaldehyde [17,18], epoxy carbonyl compounds [19] or 1-halooxiranes [20], and malonaldehyde (additional six-membered ring) [21].

However, the most common reagents, applied for the transformation of guanine nucleosides into their tricyclic derivatives, are α-bromoketones. There are several reasons for that. Firstly, it is worth mentioning of the discovery of the so called Y-nucleosides, fluorescent tricyclic compounds occurring in phenylalanine transfer ribonucleic acids (tRNA^{Phe}) [22,23], which have aroused a great interest for their synthesis through which it is possible to evaluate their unusual physicochemical and biological properties. Thus, wyosine (**17**, Scheme 2; systematic name: 4,9-dihydro-4,6-dimethyl-3-β-D-ribofuranosyl-9-oxoimidazo[1,2-*a*]purine), the simplest representative of the Y-nucleosides family, can be considered as a dimethyl derivative of 1,N^2-ethenoguanosine (**13**), or as 3-methyl-1,N^2-isopropenoguanosine. A desmethyl analog of wyosine, the so-called 4-desmethylwyosine (**18**; systematic name: 5,9-dihydro-3-β-D-ribofuranosyl-6-methyl-9-oxo-5*H*-imidazo[1,2-*a*]purine) may easily be synthesized in the reaction of guanosine N-1 sodium salt and bromoacetone followed by alkaline hydrolysis [24]. Its transformation to wyosine, however, has been a challenge for chemists for many years. Methylation of desmethylwyosine (**18**), using common methylating reagents like methyl iodide in the presence of potassium carbonate or diazomethane, leads mainly to the isomeric 5-methyl nucleoside (**19**) instead of wyosine, which can be obtained just as a side product (yield 3% for the reaction CH_2N_2/CH_2Cl_2)) [24]. Finally, the yield of methylation in the 4-position has satisfactorily been enhanced to about 70% by applying the Simmons–Smith organozinc reagent (Scheme 2) [25]. An alternative route to wyosine (**17**) involves the reaction of 3-methylguanosine (**20**) with bromoacetone [26]. This approach, however, requires a laborious, multistep synthesis of 3-methylguanosine itself. On the other hand, since the synthesis of wyosine (**17**) and its 5-methylisomer (**19**) *via* methylation of **18** has successfully been explored, both compounds may serve as useful synthons for the preparation of either 3-methylguanosine (**20**) [27] or N-2-methylguanosine (**21**) [28], which cannot be obtained by direct methylation of guanosine (**4**) (see Scheme 2).

Considering the biological activity of etheno ribo- or 2′-deoxyribonucleosides, one may notice there are no literature reports on it. On the other hand, the incorporation of etheno units into a polynucleotide chain of DNA or RNA may seriously disturb the biological function of nucleic acids. The presence of an appended etheno ring changes the base pairing properties of nucleotides and therefore, may cause mutagenic transitions and initiate malignant transformation [5,15,29–32]. Interestingly, in some situations the addition of etheno ring can bring a beneficial biological effect. Wyosine (**17**) and its structurally more complex congeners, the only naturally occurring ethenonucleosides, are located in the position adjacent to the 3′-end of anticodon in tRNAs, and probably prevent from the miscoding in the codon – anticodon recognition.

As it has been stated above, on the nucleoside level, the etheno ribo- and 2′-deoxyribonucleosides do not demonstrate any biological activity which could be of use for designing new chemotherapeutics. However, the exchange of sugar portion for an acyclic substituent gives rise to a series of novel nucleoside analogs of pronounced and selective antiviral activity (Fig. 2). For instance, modification of acyclovir (ACV; Zovirax; systematic name: 9-(2-hydroxyethoxymethyl)guanine), a potent antiviral drug [33], in the reaction with bromoacetone as in the case of the synthesis of desmethylwyosine (**18**), allows to obtain a tricyclic derivative of acyclovir (**22**; TACV; 1,N^2-isopropenoacyclovir; systematic name: 3-(2-hydroxyethoxymethyl)-3,9-dihydro-6-methyl-9-oxo-5*H*-imidazo[1,2-*a*]purine) [34]. TACV demonstrates an inhibitory effect on herpes simplex virus type 1 and 2 (HSV-1 & –2) replication *in vitro* at concentrations of one order of magnitude higher (0.7–2.0 μg/mL) than that of acyclovir, but is more selective in its anti-HSV action than the parent acyclonucleoside. In contrast to acyclovir, the tricylic compound (**22**) has not been active against other herpes viruses, and has no cytostatic effect on a number of tumor cells [34]. Its crystal structure has recently been reinvestigated [35].



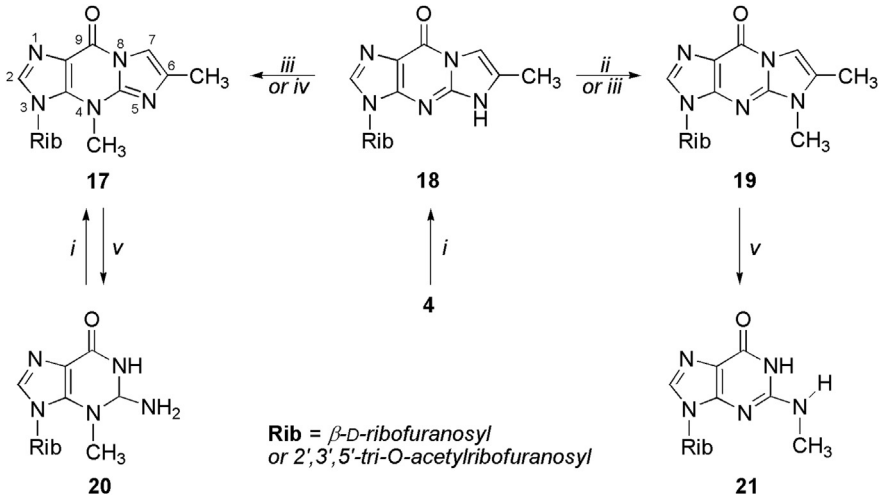
Scheme 1. Ethenonucleosides and their synthesis. *Reagents:* (i) aq. chloroacetaldehyde; (ii) NaH, then anhydr. chloroacetaldehyde; (iii) K_2CO_3, bromoacetaldehyde diethylacetal; (iv) 1 N HCl; (v) benzyl bromide; (vi) chloroacetaldehyde, then H_2 Pd/C; (vii) vinyl chloride.

1,N^2-Isopropenoacyclovir (**22**) has become a leading structure for design and synthesis of novel tricyclic congeners, and more than 80 nucleoside analogs of this type have been obtained and evaluated for their biological properties [12,36–47]. The most representative structures of the series are presented in Fig. 2. 1,N^2-Etheno compound (**23**) shows considerably lower antiherpes activity. In turn, replacing the sugar moiety with another pseudosugar substituent, 3-(1,3-dihydroxy-2-propoxymethyl) chain of the ganciclovir type (**24**), causes a substantial increase in the antiherpes activity (MIC_{50} in the range of 0.015–0.2 μg/mL for HSV-1 and HSV-2); the compound also inhibits other viruses, e.g. varicella-zoster virus (VZV) and cytomegalovirus (CMV) [37,38]. Further substitutions in the 6- or/and 7-positions have resulted in the most active compounds in the series of tricyclic analogs of acyclovir and ganciclovir [38–40,42,43]. It has been found that the presence of 6-aryl substituents give the best antiviral results. For instance, 6-(4-methoxy)phenyl derivative of ganciclovir (**25**) demonstrates the level of activity comparable to that of a parent drug. Moreover, the 6-aryl derivatives exhibit fluorescence, which according to the authors, would be of use in the noninvasive diagnosis of herpes virus infections [39–42]. The antiherpes properties of tricyclic nucleosides structurally related to acyclovir and ganciclovir have been summarized in the review articles by Golankiewicz and Ostrowski [48] and De Clercq [49].

A series of fluorescent tricyclic compounds derived from acyclovir and ganciclovir, substituted with aromatic groups in the 6-position (e.g. structure **25**), has also been tested for their cytostatic activity in HSV thymidine kinase gene transduced tumor cell lines. Some of them have proven to be potent inhibitors of human osteosarcoma (OST TK$^-$) and murine mammary carcinoma (FM3A) cells proliferation. The cytostatic potency of tested compounds is in a proper correlation with their antiherpes activity [41].

Acyclovir and ganciclovir are not the only drugs that may form biologically active compounds of the etheno type. It has been demonstrated that other active guanine nucleoside analogs retain their biological properties when transformed to the respective 1,N^2-ethenoguanine derivatives. For instance, the 1,N^2-etheno derivative (**26**) of PMEG (9-[(2-phosphonomethoxy)ethyl]guanine) [50], a phosphonic acid derivative of acyclovir, exhibits marked activity against both VZV and CMV [12]. However, on the basis of the structure–activity analysis in the case of tricyclic derivatives of acyclovir and ganciclovir [34,36–43], we could anticipate much higher antiviral potency of 6-aryl 1,N^2-ethenoguanine analogs of PMEG, nevertheless, their synthesis has not yet been reported. Similarly, the 6-aryl-1,N^2-ethenoguanine compounds (e.g. **27**) derived from a potent antiviral agent 9-{[cis-1′,2′-bis(hydroxymethyl)cycloprop-1′-yl]methyl}guanine (A-5021), show a significant inhibitory activity against HSV-1, HSV-2, and VZV, while the respective 6-alkyl compounds tend to be less active [44,45].

Besides acyclic ethenonucleosides, some other etheno analogs possessing five-membered modified sugar portions have been synthesized and evaluated for their biological properties [46]. For example, 6-(4-diethylamino)phenyl-1,N^2-etheno derivative (**28**) of 9-(4-hydroxymethyl)cyclopentenyl guanine (CBV) inhibits human



Scheme 2. Wyosine (**17**) and related tricyclic nucleosides: synthesis and synthetic application. *Reagents*: (i) NaH, then bromoacetone and alkaline hydrolysis; (ii) K_2CO_3, methyl iodide (iii) CH_2N_2/CH_2Cl_2; (iv) CH_2N_2/ZnI_2; (v) N-bromosuccinimide, then alkaline hydrolysis.

immunodeficiency virus (HIV) replication at EC_{50} 0.13 μM. In turn, an analogous compound of a 3-dioxolanyl structure (**29**) exhibits *in vitro* anti-HIV activity at EC_{50} 0.25 μM, while the most active derivative (**30**) of -3′-azido-2′,3′-dideoxyguanosine (AZG) acts at a meaningful concentration EC_{50} 0.04 μM. Another 1,N^2-ethenoguanine compound (**31**), derived from 2′-C-β-methylguanosine, is an inhibitor of HCV replication (EC_{50} 0.13 μM). In all four cases the antiviral spectra reflect those of parent nucleoside analogs and, interestingly, the reported activity of two ethenonucleosides (**29, 30**) is even higher than that of their guanine substrates.

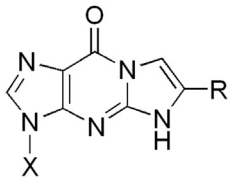
Acyclovir in its antiherpes action depends on virus-encoded deoxythymidine kinase (TK), which transforms it into a monophosphate, in the infected cells. The mononucleotide is further phosphorylated by cellular kinases to a nucleoside diphosphate, and finally to the respective triphosphate, which is an active form of the drug. The acyclovir triphosphate acts as a chain terminator during the synthesis of viral DNA, because the lack of 3′-hydroxy group does not allow for chain elongation [33,51]. We may assume that similar mechanism of action takes place in the case of tricyclic derivatives of acyclovir, although a new question arises here: are they intrinsically active, or are they decomposed to acyclovir prior to inhibition? The former possibility has been presented in some papers [34,39,48], and that notion has been supported by some rational arguments, mainly by an experimental evidence that TACV (**22**) is phosphorylated by herpes TK [41,52]. On the other hand, it has been known for years that the additional etheno ring can easily be removed under oxidizing conditions, such as the treatment with N-bromosuccinimide (NBS) [27,28,53] or with I_2/MeOH [54]. More recently, degradation of tricyclic nucleosides to the parent active compounds has been proved experimentally [46]. The authors have shown a correlation between the antiviral activity and the electron effects of the 6-aryl substituents in tricyclic compounds: the less stable the additional ring is, the highest activity is exhibited. Furthermore, they have demonstrated that 6-(4-dialkylamino) phenyletheno analogs (**28**–**31**), the most active compounds in the tested series, are extremely unstable in water (e.g. half-time of hydrolysis for **30** is 25 min). If it so, the synthesis of fluorescent tricyclic compounds of this type makes no sense, since the fluorophore is degradated before the inhibition of viral replication starts.

The latter finding [46] means that the discussed tricyclic derivatives act as prodrugs of acyclovir (or other biologically active nucleoside analogs) with enhanced lipophilicity, facilitating their transport into the cells. This is in line with a general observation that all 1,N^2-ethenoguanine nucleosides demonstrate similar biological activity spectra as the parent nucleoside analogs. There is also a third possibility in the case of the more stable ethenonucleosides where the observed antiviral effect could be the sum of actions of the tricyclic monophosphate and the parent nucleoside monophosphate both of which could be present in the infected cell as a mixture, but this would be difficult to prove experimentally.

3. Bicyclic nucleosides of the furano[2,3-*d*]pyrimidine and pyrrolo[2,3-*d*]pyrimidine type

The furano[2,3-*d*]pyrimidine (general structure **32** in Scheme 3) and pyrrolo[2,3-*d*]pyrimidine (**33**) nucleosides constitute another major and relatively new class of analogs with fused heterocyclic rings which to date exhibit pronounced antiviral activity *in vitro* and *in vivo*. While ethenonucleosides act as prodrugs of other biologically active nucleoside analogs, the furano- and pyrrolopyrimidine compounds derive from the respective naturally occurring uracil or cytosine compounds (**1, 2, 5,** and **6**) which are not intrinsically active. The furano[2,3-*d*]pyrimidine and pyrrolo [2,3-*d*]pyrimidine nucleosides are called bicyclic pyrimidine nucleoside analogs (BCNAs).

The discovery of antiviral activity of the bicyclic furano[2,3-*d*] pyrimidine nucleosides has been reported by McGuigan et al. [55]. However, compounds of this type, has previously been known as fluorescent side-products in the Pd-catalyzed coupling of 5-substituted pyrimidines with 1-alkynes. The furano compounds may easily be transformed into their pyrrolo[2,3-*d*]pyrimidine analogs [56]. The synthesis of both types of bicyclic nucleosides is relatively simple, and a typical synthetic route is depicted in Scheme 3. Furano- and pyrrolo[2,3-*d*]pyrimidine nucleosides may efficiently be prepared from the respective 5-iodouracil substrates (**34**) and 1-alkynes under the Sonogashira coupling conditions. The course of coupling reaction depends on the temperature and the choice of palladium catalyst. Thus, the use of tetrakis(-triphenylphosphine)palladium(0) [$Pd(Ph_3P)_4$] at room temperature allows for obtaining of the 5-(alkyn-1-yl)uracil derivatives (**35**) [57,58]. The choice of an appropriate solvent seems to be of importance, e.g. the use of DMF helps to stop the reaction at the 5-alkynyl stage. The latter compounds can then smoothly be converted to cyclic furanopyrimidine nucleosides (**32**) under heating (ca. 60 °C), and in the presence of triethylamine and CuI [55]. In



22 X = A R = CH_3
23 X = A R = H
24 X = B R = CH_3
25 X = B R = *p*-$CH_3OC_6H_4$
26 X = C R = H
27 X = D R = C_6H_5
28 X = E R = 4-$N(CH_2CH_3)_2C_6H_4$
29 X = F R = 4-$N(CH_2CH_3)_2C_6H_4$
30 X = G R = 4-$N(CH_2CH_3)_2C_6H_4$
31 X = H R = 4-$N(CH_3)_2C_6H_4$

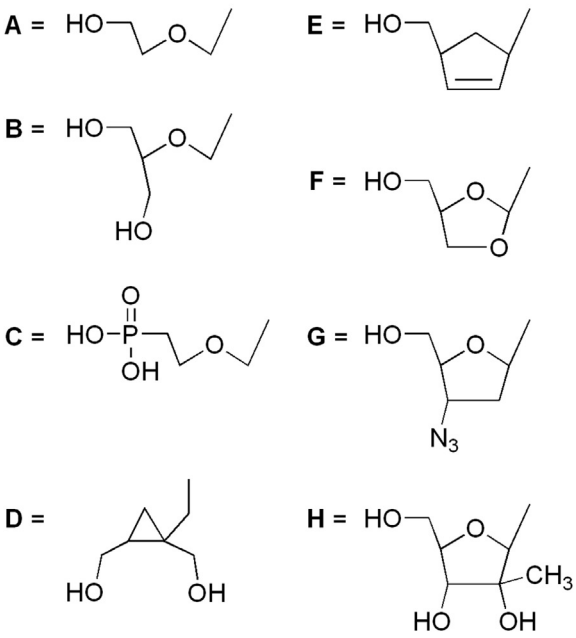
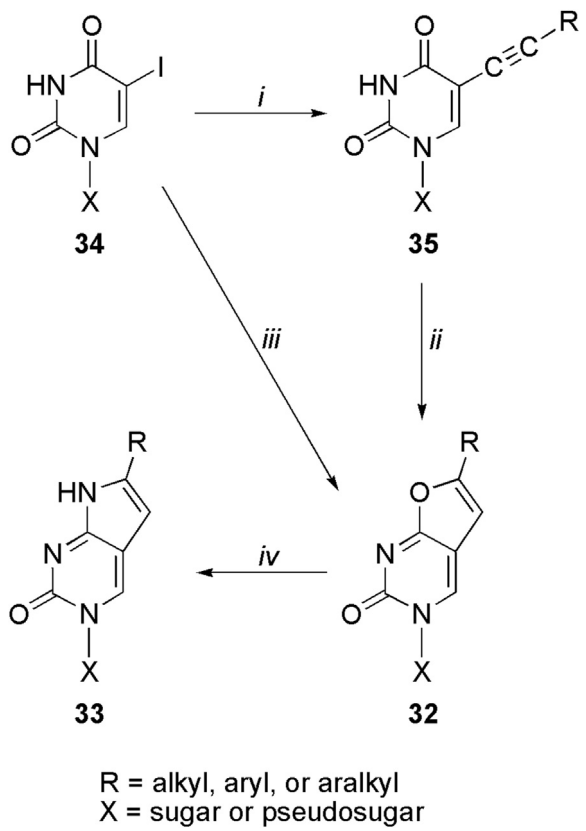


Fig. 2. Selected examples of biologically active derivatives of 1,N^2-ethenoguanine.

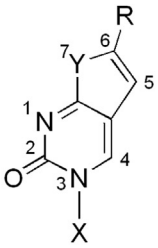
turn, the application of Pd/C catalyst at elevated temperature in the range between 70 and 80 °C in acetonitrile leads directly to cyclic fluorescent products (**32**) [59,60]. The furanopyrimidine nucleosides can then be converted to the respective pyrrolo derivatives (**33**) under treatment with methanolic ammonia at 50 °C. All the reactions may be performed without any protection of the sugar or pseudosugar portion. In some cases, however, O-acetyl or O-benzoyl protecting groups have been applied for the coupling and/or cyclization reactions.

A number of the furano[2,3-*d*]pyrimidine and pyrrolo[2,3-*d*]pyrimidine nucleosides along with their analogs have been synthesized, and some selected examples are presented in Fig. 3. It has been found that furano[2,3-*d*]pyrimidine 2′-deoxyribonucleosides are the most potent and selective inhibitors of varicella-zoster virus (VZV) when equipped with C_8 to C_{10} alkyl chains in the 6-position (e.g. **36**) [55,61,62] For instance, nucleoside **36** acts at EC_{50} values in the range of 0.008–0.024 μM (VZV OKA and YS strains), being of two orders of magnitude more potent than acyclovir. Because compound **36** is not cytotoxic, it displays a very high selectivity index, i.e. the ratio of minimum cytotoxic concentration to EC_{50} value (>5000) [55,63]. Its analogs of shorter alkyl chains are only moderately active, while those of longer chains are poorly soluble in water. The most anti-VZV active compounds (C_8–C_{10} 6-alkyl substituents) are not active against thymidine kinase-deficient strains (VZV TK^-), and this clearly shows that the furanopyrimidine nucleosides must be 5′-phosphorylated to demonstrate their potent anti-VZV activity [55,64]. What is even more interesting, the anti-VZV active nucleosides have not been active against other herpes viruses, like HSV-1, HSV-2, CMV or vaccinia virus (VV), which is rather unusual for biologically active nucleoside analogs. Therefore, furano[2,3-*d*]pyrimidine 2′-deoxyribonucleosides are entirely VZV-specific [55,63–65].

As stated above, the furanopyrimidine compounds can smoothly be converted to the respective pyrrolopyrimidine nucleosides (e.g. **37**). However, this transformation results in the reduction of the antiviral activity by one order of magnitude, in comparison to the furano analog (**36**). Nevertheless, pyrrolopyrimidine nucleosides are still potent and selective inhibitor of VZV replication (EC_{50} in the range 0.15–0.38 μM), even though they remain inactive against other herpes viruses [56]. In turn, the replacement of furano by thieno ring increases the anti-VZV activity as compared to the parent nucleoside (**36**). The thieno[2,3-*d*]pyrimidine analog (**38**) exhibits a high antiviral potency (EC_{50} 0.002–0.005 μM), however, its chemical synthesis requires taking 5 steps from a 5-iodouridine substrate [66]. Therefore, the anti-VZV potency of bicyclic nucleoside analogs (**36**–**38**) depends on the kind of heteroatom in the 7-position (Y in Fig. 3), and the activity of BCNAs can be ranked in the following order: Y=S > Y=O > Y=NH.



Scheme 3. General protocol for synthesis of furano- and pyrrolo[2,3-*d*]pyrimidine nucleosides. *Reagents*: (i) 1-alkyne, $Pd(Ph_3P)_4$, CuI, Et_3N, RT; (ii) CuI, Et_3N, Δ; (iii) 1-alkyne, 10% Pd/C or $Pd(Ph_3P)_4$; CuI, Et_3N, Δ; (iv) NH_3/MeOH, Δ.



36	X = A	Y = O	R = C_8H_{17}
37	X = A	Y = NH	R = C_8H_{17}
38	X = A	Y = S	R = C_8H_{17}
39	X = B	Y = O	R = C_9H_{19}
40	X = C	Y = O	R = C_8H_{17}
41	X = C	Y = NH	R = C_8H_{17}
42	X = D	Y = O	R = C_8H_{17}
43	X = D	Y = NH	R = C_8H_{17}
44	X = E	Y = O	R = $C_{10}H_{21}$
45	X = F	Y = O	R = C_8H_{17}
46	X = G	Y = O	R = 4-$CH_3(CH_2)_4C_6H_4$
47	X = H	Y = O	R = C_8H_{17}
48	X = A	Y = O	R = $CH_3(CH_2)_4O(CH_2)_4$
49	X = A	Y = O	R = $Cl(CH_2)_9CH_2$
50	X = A	Y = O	R = 4-$CH_3(CH_2)_4C_6H_4$
51	X = I	Y = O	R = 4-$CH_3(CH_2)_4C_6H_4$

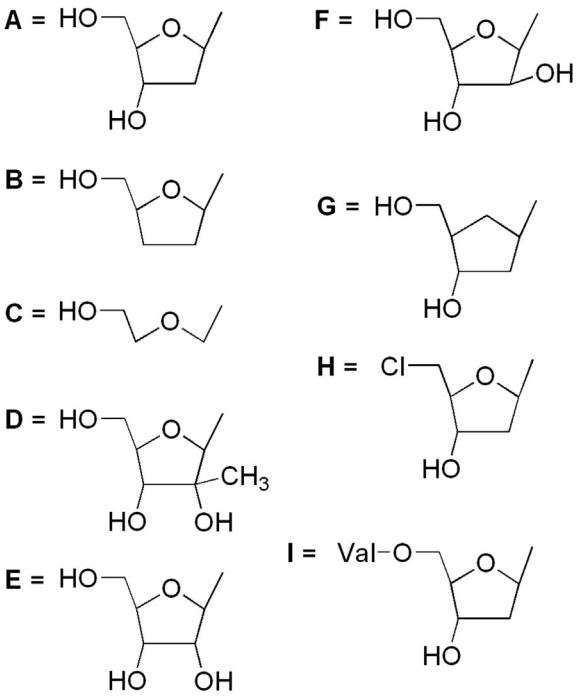


Fig. 3. Selected examples of the furano[2,3-*d*]pyrimidine and pyrrolo[2,3-*d*]pyrimidine nucleosides and their analogs (BCNAs).

To increase antiviral activity and to widen or change its spectrum, the bicyclic nucleoside analogs have been modified in their glycon portion as well. For example, in the 6-alkylfurano series, the 2′-deoxyfuranosyl moiety has been exchanged for 2′,3′-dideoxyribosyl substituent (e.g. **39**) [67]. Surprisingly, the dideoxy compounds have been totally inactive against the tested varicella zoster viruses. Therefore, the presence of 3′-hydroxyl group seems to be essential for anti-VZV activity. Instead of this, the new bicyclic nucleosides have proven to be selective inhibitors of human cytomegalovirus (HCMV) with EC_{50} 1.2 μM (for compound **39**), i.e. they are twice as active as ganciclovir. Analyzing the SAR dependence in the inhibition of HCMV, McGuigan et al. have postulated a hypothetic non-nucleosidic mechanism of their action [67]. More recently, a series of the bicyclic 2′,3-dideoxy-L-nucleosides have been synthesized and evaluated for their activity. Again, the compounds have not been active against varicella zoster virus, but they demonstrated an appreciable inhibitory effect upon vaccinia virus (VV) and, to some extent, upon wild type measles virus [68].

The replacement of the 2′-deoxyribose by acyclovir-type 3-[(2-hydroxyethoxy)methyl] chain (**40**), is another modification of the sugar portion, that has caused a substantial decrease of the anti-VZV activity (EC_{50} 11 μM for compound **40**) [69], while the pyrrolo analog (**41**) has remained inactive. A series of furano- and pyrrolo acyclonucleosides has been tested for their inhibitory effect on replication of other viruses (HIV-1, HIV-2, HCMV, HSV-1, HSV-2, VV, VSV), but they have proven to be generally inactive. Only the C8 furano compound (**40**) has demonstrated some moderate anti-HCMV properties (EC_{50} 10–31 μM) [69]. On the other hand, it has been shown that some analogous acyclonucleosides exhibit the activity against HIV and HSV at micromolar concentrations [70]. In turn, 3-[2-(phosphonomethoxy)ethyl derivatives of furanopyrimidine nucleosides have been evaluated for their *in vitro* activity against a variety of DNA- and RNA viruses, but the tested compounds have not indicated any appreciable inhibitory activity [71].

Similarly, the presence of another modified sugar, 3-(2′-C-β-methyl)-β-D-ribofuranose, has not resulted in the inhibition of hepatitis C virus (HCV) [60]. Thus, the respective furano and pyrrolo [2,3-*d*]pyrimidine compounds (**42, 43**) show merely slight anti-HCV activity in the HCV subgenomic replicon system Huh-5-2-cells (EC_{50} in the range of 31–85 μM). While the bicyclic nucleoside analogs have intensively been studied in the 2′-deoxy series, relatively low attention has been paid to their ribofuranosyl congeners. For instance, it has been shown that the respective ribosides and arabinonucleosides (**44, 45**) of furano compounds are almost inactive against VZV and HCMV strains [72]. In a similar study, 6-decyl-3-(β-D-ribofuranosyl)-2,3-dihydrofurano[2,3-*d*]pyrimidin-2-on (**44**) efficiently inhibits bovine viral diarrhea virus (BVDA) and shows some moderate anti-HCV activity in HCV replicon system cells [73,74], being also quite cytotoxic. Following this study, a series of related bicyclic ribonucleoside 5′-O-triphosphates have been synthesized and tested for their substrate properties towards some DNA and RNA polymerases. Only 6-hexyl-furano[2,3-*d*]pyrimidine trinucleotide has been recognized by calf thymus terminal deoxynucleotydyl transferase (TDT) and HIV reverse transcriptase (HIV-RT) [73,74]. Another example of the sugar-modified BCNAs involves replacement of the 2′-deoxyfuranosyl moiety with a carbocyclic substituent (**46**). Again, the structural change of the lead 2′-deoxy compound has resulted in a substantial reduction of the anti-VZV activities [75]. Similar result has been noted when 5′- or 3′-hydroxyl groups have been substituted by chlorine (**47**), emphasizing the presence of both hydroxyl groups is mandatory to obtain potent and selective anti-VZV activity [76]. Concluding this part, we can state that all attempted efforts to obtain more active compounds by modification of the sugar portion have been fruitless, except for the dideoxy modification which changed the antiviral spectrum of BCNAs.

Taking into account the discussion so far, we may notice that the optimal structure for highly active BCNAs should contain the following elements: (i) the appended 2,3-dihydrofurano ring; (ii) the presence of 3-(2′-deoxy)ribofuranosyl sugar (at least for the anti-VZV activity); (iii) a C_8 to C_{10} alkyl chain in the 6-position. Due

to the latter requirement, however, the bicyclic nucleosides equipped with lipophilic side-chain are poorly soluble in water and therefore, the required inhibitory concentration may be difficult to achieve in some cases. To overcome this serious limitation, a series of novel BCNAs bearing ether or glycol type side-chain (e.g. **48**) have been synthesized. Indeed, the newly obtained compounds have been much better soluble than their 6-alkyl analogs, but their anti-VZV potency is significantly reduced [77]. More recently, the problem of solubility of BCNAs has successfully been overcome by application of the dipeptidyl peptidase IV derived nucleosidic prodrugs [78]. In this approach, the tripeptidyl derivatives (e.g. 5′-Val-Prol-Val-BCNA) may serve as water-soluble prodrugs, which are hydrolyzed in the presence of the dipeptidyl peptidase IV (DPPIV/CD26). The peptidyl prodrugs markedly enhanced oral bioavailability of BCNAs *in vivo*.

In continuation of the SAR study regarding the nature of 6-substituents, a series of the bicyclic 2′-deoxynucleosides possessing a terminal halogen atom (F, Cl, Br, I) in the side-chain have been obtained and evaluated for their inhibitory activity against VZV (e.g. compound **49**). Interestingly, the halogenated compounds have retained their high and selective activity (EC_{50} for **49** in the range of 0.007–0.012 μM) [79]. One of the most promising modification of the 6-substituent structure involves the introduction of the benzene ring between the furano portion and the *n*-alkyl chain [80–84]. The 6-pentylphenyl analog (**50**; designed Cf1743) appears to be the most potent anti-varicella zoster virus agent in the bicyclic nucleoside analogs series (EC_{50} in the range of 0.0001–0.0003 μM). Moreover, due to its low cytotoxicity (MMC > 200 μM), Cf1743 is the drug candidate exhibiting extraordinary selectivity towards VZV (SI > 100,000), and being perhaps the most selective nucleoside-analog agent reported to date. The valyl ester pro-drug of Cf1743 (**51**; FV-100) is the lead clinical candidate indicating enhanced solubility in water among highly lipophilic BCNAs. In addition, due to its strong fluorescence, Cf1743 may be traced by fluorescence microscopy in the living cells.

A possible mechanism of action of the anti-VZV furano[2,3-*d*]pyrimidine and pyrrolo[2,3-*d*]pyrimidine nucleosides has been discussed in several original papers [55,61–65,67,81–84]. What is known for sure? At the first glimpse, we may notice that the BCNAs cannot act the same way as it has been described for the etheno-nucleosides, i.e. the decomposition of the additional etheno ring with the regeneration of a parent active compound. In such a case, the removal of the furano or pyrollo rings (for instance, in compounds **36** and **37**) would just generate the natural 2′-deoxy-nucleosides, dU or dC. On the other hand, the 2′-C-methyl derivative (**43**) would be transformed into 2′-C-β-methylcytidine, which is a well-known and potent inhibitor of hepatitis C virus (HCV) – nevertheless compound **43** itself shows only marginal anti-HCV activity.

Another possibility is a partial degradation of the appended furano or pyrollo rings, leading to some 5-substituted pyrimidine deoxynucleosides, which could resemble the structure of known antivirals, like 5-bromovinyluridine (BVDU) or its 5-alkynyl congeners. However, the mechanism of the BCNAs seems to be quite different than that of BVDU. Firstly, the bicyclic deoxynucleosides are phosphorylated exclusively by the VZV-specific deoxy-thymidine kinase (VZV TK), while BVDU (and related antivirals) are recognized by other virus-encoded TK, specific for a variety of herpes viruses, e.g. HSV-1 TK. Secondly, they have turned out to be resistant to catabolic enzymes like uridine phosphorylase (Upase), while BVDU and its analogs undergo the catabolic cleavage. Furthermore, the respective bicyclic furano or pyrrolo bases have not exhibit any appreciable antiviral activity.

Consequently, the mechanism of action for BCNAs is still unclear. It depends on the VZV TK activity, which transforms 2′-deoxynucleosides into the corresponding monophosphates. However, there is no experimental evidence, whether or not the mononucleotides are phosphorylated further to di- and triphosphates, which is a usual way of activation in the case of other antivirally active nucleoside analogs. Presumably, BCNAs may be phosphorylated to diphosphates, due to the monophosphate kinase activity of the VZV TK. Nevertheless, the mechanism of the antiviral activity of BCNAs seems to be substantially different from that of other nucleoside analogs. Moreover, the concluding discussion of this mechanism requires prior identification of the BCNAs' molecular target.

4. Conclusion

The ethenonucleosides and the bicyclic nucleosides of the furano- or pyrrolo[2,3-*d*]pyrimidine constitute two major classes of fused heterocyclic ring analogs which demonstrate potent antiviral activity. A great number of the related compounds have first been designed and synthesized, then evaluated in a variety of biological assays, and finally analyzed in a structure–activity relationship study or in a computer simulation. The arsenal of possible further structural modifications seems to be almost depleted.

To our best knowledge, none of the ethenucleosides has advanced into clinical study and it does not seem likely that any of them will became a promising antiviral drug in the nearest future. There might be several reasons for this, including policies of pharmaceutical companies. In our opinion, however, the main setback is the lower activity of ethenonucleosides in comparison with that of their parent nucleosides, like acyclovir, ganciclovir or AZT. Furthermore, it has not been demonstrated whether the enhanced lipophilicity and lower cytotoxicity of etheno derivatives may compensate their lower activity in search for new antivirals. In turn, the furanopyrimidine nucleosides seem to be more promising candidates for novel antiviral drugs. As mentioned above, the valyl ester FV-100 (**51**) has successfully been tested as a clinical BCNA candidate for treatment of varicella zoster virus infection [83]. The Phase II clinical trial has been performed by Inhibitex, and the results were presented by Andrei and Snoeck [65].

What is the future of research in this area? It is unlikely that many new biologically active compounds of these two classes could

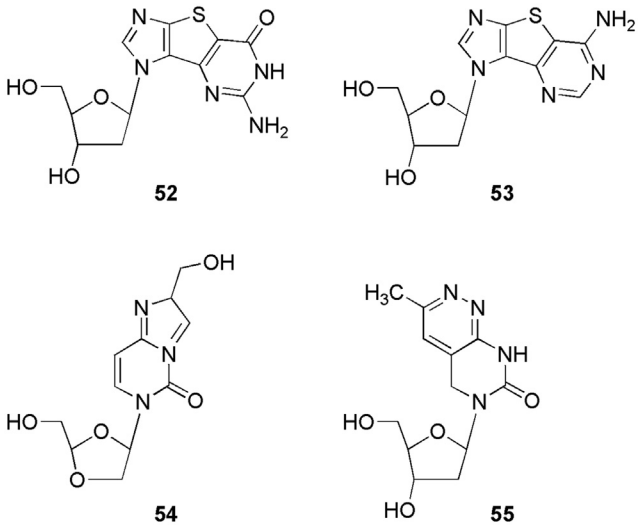


Fig. 4. Examples of other nucleoside derivatives with the fused heterocyclic ring: thieno-expanded analogs of guanosine (**52**) and adenosine (**53**) [85,86]; an imidazo[1,2-*c*]pyrimidin-5(6H)-one nucleoside (**54**) [87]; a pyrimido[4,5-*c*]pyridazine nucleoside (**55**) [88,89].

be obtained in the future. We rather expect further derivatization of the known active analogs in order to improve their pharmacological characteristics, perhaps mainly by application of the pro-nucleoside or pro-nucleotide approaches. Nevertheless, there are still some possibilities to discover and exploit new classes of bioactive nucleoside analogs possessing additional rings. Therefore, concluding this mini-review, we would like to present some examples (Fig. 4) of other fused heterocyclic nucleosides which will hopefully give rise to novel, promising chemotherapeutics.

Acknowledgments

The financial support from the Polish Ministry of Science and Higher Education (statutory financing) is gratefully acknowledged.

References

[1] N.K. Kochetkov, V.N. Shibaev, A.A. Kost, New reaction of adenine and cytosine derivatives, potentially useful for nucleic acids modifications, Tetrahedron Lett. (1971) 1993.
[2] J.R. Barrio, J.A. Secrist III, N.J. Leonard, Fluorescent derivatives of adenosine and cytidine, Biochem.. Biophys. Res. Commun. 46 (1972) 597–604.
[3] J.A. Secrist III, J.R. Bario, N.J. Leonard, G. Weber, Fluorescent modification of adenosine-containing coenzymes – biological activities and spectroscopic properties, Biochemistry 11 (1972) 3499–3506.
[4] J. Biernat, J. Ciesiolka, P. Gornicki, R.W. Adamiak, W.J. Krzyzosiak, M. Wiewiorowski, New observations concerning chloroacetaldehyde reaction with some transfer-RNA constituents – stable intermediates, kinetics and selectivity of reaction, Nucleic Acids Res. 5 (1978) 789–804.
[5] J.T. Kusmierek, B. Singer, 1, N^2-Ethenodeoxyguanosine: preparation, properties and formation in chloroacetaldehyde-treated polinucleotides and DNA, Chem. Res. Toxicol. 5 (1992) 634–638.
[6] N.J. Leonard, J.R. Barrio, J.A. Secrist III, Spray reagent for adenine-containing residues – detection by fluorescence, Biochim. Biophys. Acta 269 (1972) 531–532.
[7] R.F. Steiner, W. Kinner, A. Lunasin, J. Delac, Fluorescent derivatives of polyribonucleotides containing epsilon-adenosine, Biochem. Biophys. Acta 294 (1973) 24–37.
[8] L.H. Schulman, H. Pelka, Locations of accessible bases in *Escherichia-coli* formylmethionine transfer-RNA as determined by chemical modification, Biochemistry 15 (1976) 5769–5775.
[9] N.J. Leonard, Etheno-substituted nucleotides and coenzymes – fluorescence and biological activity, CRC Crit. Rev. Biochem. 15 (1984) 125–199 (and references cited therein).
[10] P.D. Sattsangi, N.J. Leonard, C.R. Frihart, 1, N2-ethenoguanine and N2,3-ethenoguanine. Synthesis and comparison of the electronic spectral properties of these linear and angular triheterocycles related to the Y bases, J. Org. Chem. 42 (1977) 3292–3296.
[11] J. Boryski, 1,N^2-Ethenoguanosine: three methods of synthesis, Nucleosides Nucleotides 9 (1990) 803–813.
[12] K. Horejsi, G. Andrei, E. De Clercq, R. Snoeck, R. Pohl, A. Holy, Tricyclic etheno analogs of PMEG and PMEDAP: synthesis and biological activity, Bioorg. Med. Chem. 14 (2006) 8057–8063.
[13] J.T. Kusmierek, B. Singer, 1, N^2-Ethenodeoxyguanosine: preparation, properties and formation in chloroacetaldehyde-treated polinucleotides and DNA, Chem. Res. Toxicol. 5 (1992) 634–638.
[14] J.T. Kusmierek, D.E. Jensen, S.J. Spengler, R. Stolarski, B. Singer, Synthesis and properties of N^2,3-ethenoguanosine and N^2,3-ethenoguanosine 5'diphosphate, J. Org. Chem. 52 (1987) 2374–2378.
[15] B. Singer, S.J. Spengler, F. Chavez, J.T. Kusmierek, The vinyl chloride-derived nucleosides, N2,3-ethenoguanosine, is a highly efficient mutagen in transcription, Carcinogenesis 8 (1987) 745–747.
[16] R. Shapiro, J. Hachmann, The reaction of guanine derivatives with 1,2-dicarbonyl compounds, Biochemistry 5 (1966) 2799–2807.
[17] V. Nair, G.A. Turner, Determination of the structure of the adduct from guanosine and glycidaldehyde, Tetrahedron Lett. 25 (1984) 247–250.
[18] B.T. Golding, P.K. Slaich, G. Kennedy, Ch Bleasdale, W.P. Wattson, Mechanism of formation of adducts from reactions of glycidaldehyde with 2′-deoxyguanosine and/or guanosine, Chem. Res. Toxicol. 9 (1996) 147–157.
[19] V. Nair, R.J. Offerman, Ring-extended products from the reaction of epoxy carbonyl compounds and nucleic acid bases, J. Org. Chem. 50 (1985) 5627–5631.
[20] F.P. Guengerich, V.R. Raney, Formation of etheno adducts of adenosine and cytidine from 1-halooxiranes. Evidence for a mechanism involving initial reaction with the endocyclic nitrogen atoms, J. Am. Chem. Soc. 114 (1992) 1074–1080.
[21] H. Seto, T. Takesue, T. Ikemura, Reaction of malonaldehyde with nucleic acids. II. Formation of fluorescent pyrimido[1,2-*a*]purin-10(3*H*)-one mononucleotide, Bull. Chem. Soc. Jpn. 58 (1985) 3431–3435.
[22] S.H. Blobstein, R. Gebert, D. Grunberger, K. Nakanishi, I.B. Weinstein, Structure of the fluorescent nucleoside of yeast phenylalanine transfer ribonucleic acid, Arch. Biochem.. Biophys. 167 (1975) 668–673 (and references cited therein).
[23] H. Kasai, M. Goto, K. Ikeda, M. Zama, Y. Mizuno, S. Takemura, S. Matsuura, T. Sugimoto, T Goto, Structure of wye (Yt base) and wyosine (Yt) from *Torulopsisi utilis* phenylalanine transfer ribonucleic acid, Biochemistry 15 (1976) 898–904 (and references cited therein).
[24] B. Golankiewicz, W. Folkman, Methylation of desmethyl analogue of Y nucleosides. Wyosine from guanosine, Nucl. Acids Res. 11 (1983) 5243–5255.
[25] H. Bazin, X.X. Zhou, C. Glemarec, J. Chattopadhyaya, En efficient synthesis of Y-nucleoside (wyosine) by regiospecific methylation of N4-desmethylwyosine using organozinc reagent, Tetrahedron Lett. 28 (1987) 3275–3278.
[26] T. Itaya, T. Watanabe, H. Matsumoto, A simple synthesis of 3-β-D-ribofuranosylwye and the stability of its glycosidic bond, JCS Chem. Comm. (1980) 1158–1159.
[27] J. Boryski, W. Folkman, B. Golankiewicz, A novel route to 3-methylguanosine by chemical degradation of wyosine, Tetrahedron Lett. 29 (1988) 4163–4164.
[28] J. Boryski, T. Ueda, A new simple synthesis of N-2-metylguanosine and its analogues via derivatives of 4-desmetylwyosine, Nucleosides Nucleotides 4 (1985) 595–606.
[29] R. Gómez-Bombarelli, M. González-Pérez, J. Arenas-Valgañón, I.F. Céspedes-Camacho, E. Calle, DNA-damaging disinfection byproducts: alkylation mechanism of mutagenic mucohalic acids, Environ. Sci. Technol. 45 (2011) 9009–9016.
[30] M. Ogawa, T. Matsuda, A. Ogata, T. Hamasaki, A. Kumanogoh, T. Toyofuku, T. Tanaka, DNA damage in rheumatoid arthritis: an age-dependent increase in the lipid peroxidation-derived DNA adduct, heptanone-etheno-2′-deoxycytidine, Autoimmune Dis. (2013), http://dx.doi.org/10.1155/2013/183487.
[31] A. Calabretta, C.J. Leumann, Base pairing and miscoding properties of 1,N^6-ethenoadenine- and 3,N^4-ethenocytosine-containing RNA oligonucleotides, Biochemistry 52 (2013) 1990–1997.
[32] L.F. Bonnac, L.M. Mansky, S.E. Patterson, Structure–activity relationships and design of viral mutagens and application to lethal mutagenesis, J. Med. Chem. 56 (2013) 9403–9414.
[33] G.B. Elion, P.A. Furman, J.A. Fyfe, P. de Miranda, L. Beauchamp, H.J. Schaeffer, Selectivity of action of an anti-herpetic agent, 9-(2-hydroxyethoxymethyl) guanine, Proc. Natl. Acad. Sci. USA 74 (1977) 5716–5720.
[34] J. Boryski, B. Golankiewicz, E. De Clercq, Synthesis and antiviral activity of novel n-substituted derivatives of acyclovir, J. Med. Chem. 31 (1988) 1351–1355.
[35] M. Meepripruk, K.J. Haller, Reinvestgation of tricyclic acyclovir: characterization of a 'proton-wire' model, Acta Cryst. C69 (2013) 1077–1080 (and references cited therein).
[36] B. Golankiewicz, T. Ostrowski, J. Boryski, E. De Clercq, Synthesis of acyclowyosine and acyclo-3-methylguanosine, as probes for some chemical and biological properties resulting from the N-3-substitution of guanosine and its analogues, J. Chem. Soc. Perkin Trans. 1 (1991) 589–593.
[37] J. Boryski, B. Golankiewicz, E. De Clercq, Synthesis and antiviral activity of 3-substitued derivatives of 3,9-dihydro-9-oxo-5*H*-imidazol[1,2-*a*]purines, tricyclic analogues of acyclovir and ganciclovir, J. Med. Chem. 34 (1991) 2380–2383.
[38] B. Golankiewicz, T. Ostrowski, G. Andrei, R. Snoeck, E. De Clercq, Tricyclic analogues of acyclovir and ganciclovir. Influence of substituents in the heterocyclic moiety on the antiviral activity, J. Med. Chem. 37 (1994) 3187–3190.
[39] B. Golankiewicz, T. Ostrowski, T. Goslinski, P. Januszczyk, J. Zeidler, D. Baranowski, E. De Clercq, Fluorescent tricyclic analogues of acyclovir and ganciclovir. A structure-antiviral activity study, J. Med. Chem. 44 (2001) 4284–4287.
[40] T. Goslinski, B. Golankiewicz, E. De Clercq, J. Balzarini, Synthesis and biological activity of strongly fluorescent tricyclic analogues of acyclovir and ganciclovir, J. Med. Chem. 45 (2002) 5052–5057.
[41] J. Balzarini, T. Ostrowski, T. Goslinski, E. De Clercq, B. Golankiewicz, Pronounced cytostatic activity and bystander effect of a novel series of fluorescent tricyclic acyclovir and ganciclovir derivatives in herpes simplex virus thymidine kinase gene-transduced tumor cell lines, Gene Ther. 9 (2002) 1173–1182.
[42] T. Goslinski, G. Wenska, B. Golankiewicz, J. Balzarini, E. De Clercq, Synthesis and fluorescent properties of 6-(4-biphenylyl)-3,9-dihydro-9-oxo-5*H*-imidazol[1,2-*a*]purine analogues of acyclovir and ganciclovir, Nucl. Nucl. Nucleic Acids 22 (2003) 911–914.
[43] T. Ostrowski, B. Golankiewicz, E. De Clercq, J. Balzarini, Fluorosubstitution and 7-alkylation as prospective modifications of biologically active 6-aryl derivatives of tricyclic acyclovir and ganciclovir analogues, Bioorg. Med. Chem. 13 (2005) 2089–2096.
[44] T. Ostrowski, B. Golankiewicz, E. De Clercq, J. Balzarini, Synthesis and biological activity of tricyclic analogues of 9-{[cis-1′,2′-bis(hydroxymethyl) cycloprop-1'-yl]methyl}guanine, Bioorg. Med. Chem. 14 (2006) 3535–3542.
[45] T. Ostrowski, B. Golankiewicz, E. De Clercq, G. Andrei, R. Snoeck, Synthesis and anti-VZV activity of 6-heteroaryl derivatives of tricyclic acyclovir and 9-{[cis-1′,2′-bis(hydroxymethyl)cycloprop-1′-yl]methyl}guanine analogues, Eur. J. Med. Chem. 44 (2009) 3313–3317.
[46] F. Amblard, E. Fromentin, M. Detorio, A. Obikhod, K.L. Rapp, T.R. McBrayer, T. Whitaker, S.J. Coats, R.F. Schinazi, Synthesis, antiviral activity, and stability of nucleoside analogs containing tricyclic bases, Eur. J. Med. Chem. 44 (2009) 3845–3851.
[47] M.A. Lesniewska, T. Ostrowski, J. Zeidler, I. Muszalska, Ester groups as carriers

of antivirally active tricyclic analogue acyclovir in prodrugs designing: synthesis, lipophilicity – comparative statistical study of the chromatographic and theoretical methods, validation of the HPLC method, Comb. Chem. High. Throughput Screen 17 (2014) 639–650.
[48] B. Golankiewicz, T. Ostrowski, Tricyclic nucleoside analogues as antiherpes agents, Antiviral. Res. 71 (2006) 134–140.
[49] E. De Clercq, The next ten stories on antiviral drug discovery (Part E): advents, advances and adventures, Med. Res. Rev. 31 (2010) 118–160.
[50] A. Holy, J. Günter, H. Dvorakova, M. Masojidkova, G. Andrei, R. Snoeck, J. Balzarini, E. De Clercq, Structure – antiviral activity relationship in the series of pyrimidine and purine N[2-(2-phosphonomethoxyethyl] nucleotide analogues. 1. Derivatives substituted at the carbon atoms of the base, J. Med. Chem. 42 (1999) 2064–2086.
[51] J.E. Reardon, T. Spector, Herpes-simplex virus type-1 DNA-polymerase – mechanism of inhibition by acyclovir triphosphate, J. Biol. Chem. 264 (1989) 7405–7411.
[52] J. Czaplicki, T. Bohner, A.K. Habermann, G. Folkers, A. Milon, A transferred NOE study of a tricyclic analog of acyclovir bound to thymidine kinase, J. Biomol. NMR 8 (1996) 261–272.
[53] N. Yamaji, K. Suda, Y. Onoue, M. Kato, Studies on the syntheses of compounds related to adenosine 3′,5′-cyclic phosphate. Removal of etheno group of 2-substituted 1,N^6-etheno-adenosine 3′,5′-cyclic phosphates, Chem. Pharm. Bull. 25 (1977) 3239–3246.
[54] J. Boryski, T. Ostrowski, D. Baranowski, T. Goslinski, B. Golankiewicz, Oxidative cleavage of the tricyclic derivatives of 9-Substituted guanines, Collect. Czech. Chem. Commun. 61 (1996) S38–S41.
[55] C. McGuigan, C.J. Yarnold, G. Jones, S. Velazquez, H. Barucki, A. Brancale, G. Andrei, R. Snoeck, E. De Clercq, J. Balzarini, Potent and selective inhibition of varicella-zoster virus (VZV) by nucleoside analogues with unusual bicyclic base, J. Med. Chem. 42 (1999) 4479–4484.
[56] C. McGuigan, R. Pathirana, G. Jones, G. Andrei, R. Snoeck, E. De Clercq, J. Balzarini, Anti-varicella-zoster virus bicyclic nucleosides: replacement of furo by pyrro base reduces antiviral potency, Antivir. Chem. Chemother. 11 (2000) 343–348 (and references cited therein).
[57] M.J. Robins, P.J. Barr, Nucleic acid related-compounds. 31. Smooth and efficient palladium copper catalyzed coupling of terminal alkynes with 5-iodouracil nucleosides, Tetrahedron Lett. 22 (1981) 421–424.
[58] M.J. Robins, P.J. Barr, Nucleic acid related-compounds. 39. Efficient conversion of 5-iodo to 5-alkynyl and derived 5-substituted uracil bases and nucleosides, J. Org. Chem. 48 (1983) 1854–1862.
[59] G.A. Tolstikov, A.G. Mustafin, R.R. Gataullin, L.V. Spirikhin, V.S. Sultanova, I.B. Abdrakhmasnov, A new interaction type of 5-iodopyrimidinic nucleosides with alkynes, Russ. Chem. Bull. (1993) 596–597.
[60] P. Januszczyk, J. Fogt, J. Boryski, K. Izawa, T. Onishi, J. Neyts, E. De Clercq, Synthesis and antiviral evaluation of 2′-C-methyl analogues of 5-alkynyl- and 6-alkylfurano- and pyrrolo[2,3-*d*]pyrimidine ribonucleosides, Nucl. Nucl. Nucleic Acids 28 (2009) 713–723.
[61] E. De Clercq, Nucleoside analogues exerting antiviral activity through a non-nucleosidic mechanism, Nucl. Nucl. Nucleic Acids 23 (2004) 457–470.
[62] G. Andrei, R. Sienaert, Ch McGuigan, E. De Clercq, J. Balzarini, R. Snoeck, Susceptibilities of several clinical varicella-zoster virus (VZV) isolates and drug-resistant VZV strains to bicyclic furano pyrimidine nucleosides, Antimicrob. Agents Chemother. (2005) 1081–1086.
[63] C. McGuigan, A. Brancale, H. Barucki, S. Srinivasan, G. Jones, R. Pathirana, A. Carangio, S. Blewett, G. Luoni, O. Bidet, A. Jukes, C. Jarvis, G. Andrei, R. Snoeck, E. De Clercq, J. Balzarini, Furano pyrimidines as novel potent and selective anti-VZV agents, Antivir. Chem. Chemother. 12 (2001) 77–89.
[64] R. Sienaert, L. Naesens, A. Brancale, E. De Clercq, C. McGuigan, J. Balzarini, Specific recognition of the bicyclic pyrimidine nucleoside analogs, a new highly potent and selective inhibitors of varicella-zoster virus (VZV), by the VZV-encoded thymidine kinase, Mol. Pharmacol. 61 (2002) 249–254.
[65] G. Andrei, R. Snoeck, Advances in the treatment varicella-zoster virus infection, in: E. De Clercq (Ed.), Advances in Pharmacology, Antiviral Agents, vol. 67, Elsevier Inc., Amsterdam, Boston, Heidelberg, London, New York, Oxford, Paris, San Diego, San Francisco, Sydney, Tokyo, 2013, pp. 107–168.
[66] A. Brancale, C. McGuigan, B. Algain, P. Savy, R. Benhida, J.L. Fourrey, G. Andrei, R. Snoeck, E. De Clercq, J. Balzarini, Bicyclic anti-VZV nucleosides: thieno analogues retain full antiviral activity, Bioorg. Med. Chem. Lett. 11 (2001) 2507–2510.
[67] C. McGuigan, R. Pathirana, R. Snoeck, G. Andrei, E. De Clercq, J. Balzarini, Discovery of a new family of inhibitors of human cytomegalovirus (HCMV) based upon lipophilic alkyl furano pyrimidine dideoxy nucleosides: action via a novel non-nucleosidic mechanism, J. Med. Chem. 47 (2004) 1847–1851.
[68] C. McGuigan, K. Hinsinger, L. Farleigh, R. Pathirana, J.J. Bugert, Novel antiviral activity of l-dideoxy bicyclic nucleoside analogues versus vaccinia and measles viruses in vitro, J. Med. Chem. 56 (2013) 1311–1322.
[69] Z. Janeba, J. Balzarini, G. Andrei, R. Snoeck, E. De Clercq, M.J. Robins, Synthesis and biological evaluation of acyclic 3-[(2-hydroxyethoxy)methyl] analogues of antiviral furo- and pyrrolo[2,3-*d*]pyrimidine nucleosides, J. Med. Chem. 48 (2005) 4690–4696.
[70] F. Amblard, V. Aucagne, P. Guenot, R.F. Schinazi, L.A. Agrofoglio, Synthesis and antiviral activity of novel acyclic nucleosides in the 5-alkynyl- and 6-alkylfuro [2,3-*d*]pyrimidine series, Bioorg. Med. Chem. 13 (2005) 1239–1248.
[71] Z. Janeba, A. Holy, R. Pohl, R. Snoeck, G. Andrei, E. De Clercq, J. Balzarini, Synthesis and biological evaluation of acyclic nucleotide analogues with a furo [2,3-*d*]pyrimidin-2(3H)-one base, Can. J. Chem. 88 (2010) 628–638.
[72] M.J. Robins, K. Miranda, V.K. Rajwanshi, M.A. Peterson, G. Andrei, R. Snoeck, E. De Clercq, J. Balzarini, Synthesis and biological evaluation of 6-(alkyn-1-yl) furano[2,3-d]pyrimidin-2(3H)-one base and nucleoside derivatives, J. Med. Chem. 49 (2006) 391–398.
[73] L.A. Alexandrova, M.A. Ivanov, L.S. Victorova, M.K. Kukhanova, Furano- and pyrrolo[2,3-*d*]pyrimidine nucleosides and their 5′-O-triphosphates: synthesis and enzymatic activity, Nucl. Nucl. Nucleic Acids 26 (2007) 1083–1086.
[74] M.A. Ivanov, A.V. Ivanov, I.A. Krasnitskaya, O.A. Smirnova, I.L. Karpenko, E.F. Belanov, V.S. Prasolov, V.L. Tunitskaya, L.A. Alexandrova, New furano- and pyrrolo[2,3-*d*]pyrimidine nucleosides and their 5′-O-triphosphates: synthesis and biological properties, Russ. J. Bioorg. Chem. 34 (2008) 593–601.
[75] M.D. Migliore, N. Zonta, Ch McGuigan, G. Henson, G. Andrei, R. Snoeck, J. Balzarini, Synthesis and antiviral activity of the carbocyclic analogue of the highly potent and selective anti-VZV bicyclo furano pyrimidines, J. Med. Chem. 50 (2007) 6485–6492.
[76] G.M. Luoni, C. McGuigan, G. Andrei, R. Snoeck, E. De Clercq, J. Balzarini, Bicyclic nucleoside inhibitors of varicella–zoster virus modified on the sugar moiety: 3′ and 5′ derivatives, Antivir. Chem. Chemother. 15 (2004) 333–341.
[77] A. Brancale, S. Srinivasan, C. McGuigan, G. Andrei, R. Snoeck, E. De Clercq, J. Balzarini, Synthesis and anti-varicella-zoster virus activity of some novel bicyclic nucleoside inhibitors: effect of enhanced aqueous solubility, Antivir. Chem. Chemother. 11 (2000) 383–393.
[78] A. Diez-Torrubia, J. Balzarini, G. Andrei, R. Snoeck, I. De Meester, M.-J. Camarasa, S. Velazquez, Dipeptidyl peptidase IV dependent water-soluble prodrugs of highly lipophilic bicyclic nucleoside analogues, J. Med. Chem. 54 (2011) 1927–1942.
[79] A. Brancale, C. McGuigan, G. Andrei, R. Snoeck, E. De Clercq, J. Balzarini, Bicyclic nucleoside inhibitors of varicella-zoster virus (VZV): the effect of a terminal halogen substitution in the side-chain, Bioorg. Med. Chem. Lett. 10 (2000) 1215–1217.
[80] C. McGuigan, H. Barucki, S. Blewett, A. Carangio, J.T. Erichsen, G. Andrei, R. Snoeck, E. De Clercq, J. Balzarini, Highly potent and selective inhibition of varicella-zoster virus by bicyclic furopyrimidine nucleosides bearing an aryl side chain, J. Med. Chem. 43 (2000) 4993–4997.
[81] J. Balzarini, C. McGuigan, Chemotherapy of varicella-zoster virus by a novel class of highly specific anti-VZV bicyclic pyrimidine nucleosides, Biochim. Biophys. Acta 1587 (2002) 287–295.
[82] C. McGuigan, J. Balzarini, Aryl furano pyrimidines: the most potent and selective anti-VZV agents reported to date, Antivir. Res. 71 (2006) 149–153.
[83] C. McGuigan, R.N. Pathirana, M. Migliore, R. Adak, G. Luoni, A.T. Jones, A. Diez-Torrubia, M.-J. Camarasa, S. Velazquez, G. Henson, E. Verbeken, R. Sienaert, L. Naesens, G. Andrei, R. Snoeck, J. Balzarini, Preclinical development of bicyclic nucleoside analogues as potent and selective inhibitors of varicella zoster virus, J. Antimicrob. Chemother. 60 (2007) 1316–1330.
[84] M. Migliore, FV-100: the most potent and selective anti-varicella zoster virus agent reported to date, Antivir. Chem. Chemother. 20 (2010) 107–115.
[85] O.R. Wauchope, M.J. Tomney, J.L. Pepper, B.E. Korba, K.L. Seley-Radtke, 2′-C-Modified tricyclic nucleosides as potential anti-HCV therapeutics, Org. Lett. 12 (2010) 4466–4469.
[86] O.R. Wauchope, C. Johnson, P. Krishnamurthy, G. Andrei, R. Snoeck, J. Balzarini, K.L. Seley-Radtke, Synthesis and biological evaluation of a series thieno-expanded purine 2′-deoxy nucleoside analogues, Bioorg. Med. Chem. 20 (2012) 3009–3015 (and references cited therein).
[87] T.S. Mansour, C.A. Evans, M. Charron, B.E. Korba, Discovery of imidazo[1,2-c] pyrimidin-5(6H)-one heterosubstituted nucleoside analogues with potent activity against human hepatitis B virus in vitro, Bioorg. Med. Chem. Lett. 7 (1997) 303–308.
[88] D. Loakes, D.N. Brown, S.A. Salisbury, M.G. McDougall, C. Neagu, S. Nampalli, S. Kumar, Synthesis and some biological properties of a novel 5,6,7,8-tetrahydropyrimido[4,5-*c*]pyridazine nucleoside, Helv. Chim. Acta 86 (2003) 1193–1204.
[89] D. Loakes, D.N. Brown, S.A. Salisbury, M.G. McDougall, C. Neagu, S. Nampalli, S. Kumar, Synthesis and enzymatic incorporation of a novel, bicyclic pyrimidine nucleoside: thymidine mimic, Tetrahedron Lett. (2003) 3387–3389.