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From cyclopentadiene to isoxazoline-carbocyclic nucleosides: a rapid access to biological molecules through aza-Diels–Alder reactions

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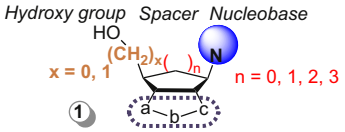
Abstract

A rapid access to carbocyclic nucleosides containing a fused isoxazoline ring is proposed through the Grieco cycloaddition of cyclopentadiene to iminium salts. The prolific elaboration of the isoxazoline cycloadducts allowed preparation of the target aminols through the unmasking of the hydroxymethylene group at the C3 level of the azanorbornene structure. The heterocyclic aminols are readily converted into nucleosides via the linear construction of purine heterocycles.

1. Introduction

Nucleosides are important synthetic targets and the search for analogues containing significantly altered carbohydrate moieties is actively pursued because of their potential antiviral and/or antitumor activities.[1] A variety of modifications of the nucleoside structures have been made and resulted in different derivatives including di-deoxynucleosides where both hydroxy groups on the sugar ring are removed,[2] carbocyclic and heterocyclic nucleosides where the sugar moiety is replaced with a carbocyclic or a heterocyclic ring,[3] acyclic-nucleosides as well as *iso*-nucleosides, where the nucleobases are transposed from the 1′-position to the 2′-position of a furanose ring.[4] New efforts are constantly made to propose attractive synthetic strategies toward new compounds, with potentially increased biological activities and decreased toxicities.[3]

Among the various modifications, carbocyclic nucleosides are extensively investigated because the replacement of the furanose ring oxygen by a methylene group results in the stabilized glycosyl bond under acidic conditions and higher resistance to metabolic enzymes.[3,5] Ring size modifications as well as the mono and polycyclic nature of the spacer between the nucleobases and the hydroxy group affect the conformational bias as well as the activity and function of the nucleoside analogues, as detailed in various structural studies.[6] A variety of synthetic approaches are directed to increase the molecular diversity in nucleosidic compounds, which nevertheless must have the features schematically depicted in **1**.[7]



The carbocyclic moiety is normally constituted by a cyclopentane ring but four-, six-, and seven-membered ring are often proposed as alternatives.[8] The carbocyclic ring is the center of the subsequent structural modifications and can be either saturated or unsaturated and carrying substituents or fused to carbocyclic or heterocyclic rings. A side arm carrying a hydroxy group is always present. This last feature discriminates between the two families of the classical nucleosides (x=1) bearing a hydroxymethylene moiety and the *nor*-nucleosides (x=0) having the hydroxy group directly linked to the

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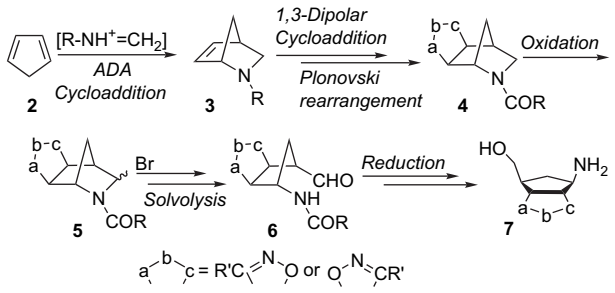
carbocyclic ring.[9] The nucleobases can be of the purine or pyrimidine type and a variety of functionalized structures have been reported, suitable for various functionalizations.

In this context, we have prepared a new class of *nor*-nucleosides containing a fused isoxazoline ring by the linear construction of the desired purine and pyrimidine bases on the aminols obtained from the nitrosocarbonyl adducts with cyclopentadiene.[10] Their activity as potential antiviral agents has been tested against Herpes Simplex virus types 1 and 2.[11] In order to evaluate the effect of the elongation of the hydroxy side chain we have recently proposed a novel approach to useful aminols for the synthesis of carbocyclic nucleosides starting from a convenient source, the 2-azanorborn-5-enes **3**. These are readily available through the Grieco cycloaddition of cyclopentadiene **2** with iminium salts[12] generated in situ under Mannich-like conditions, in a mild and convenient aqueous aza-Diels–Alder (ADA) reaction.[13] They are quite reactive dipolarophiles toward nitrile oxides[14] and afford exclusively the *exo* adducts **4**. This exclusive *exo* selectivity of the norbornene-like dipolarophiles has attracted a great deal of attention and is usually attributed to relief of strain, geometric deformation of the double bond (pyramidalization due to π/σ repulsion), and also favorable staggering effects for the *exo* attack.[10d] The prolific elaboration of the *exo* isoxazoline cycloadducts **4** allowed the preparation of the target aminols **7** through the intermediates **5** and **6** by using NBS oxidation and subsequent solvolysis for the unmasking of the hydroxymethylene group at the C3 level of the azanorbornene structure (Scheme 1).



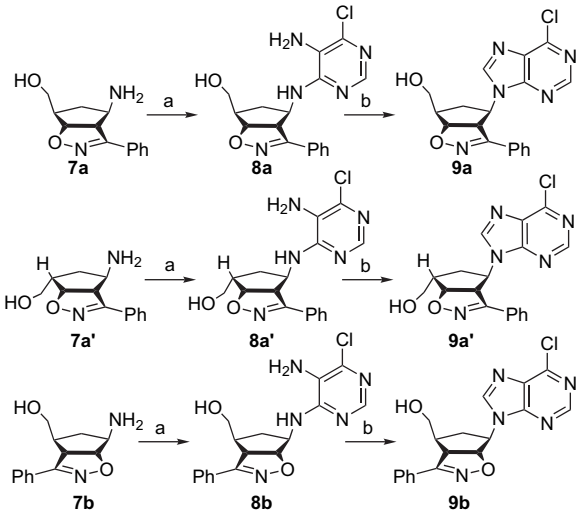
Scheme 1.

On pursuing our studies on nucleoside syntheses, we detail here the first synthesis of a class of racemic purine-carbocyclic nucleosides containing a fused isoxazole ring and having a hydroxymethylene (HO–CH_2) group in the side chain of the carbocyclic unit.

2. Results and discussion

The ADA cycloadduct **3** between cyclopentadiene **2** and the benzyl-iminium salt [$PhCH_2$–NH^+=CH_2] was transformed into the stereodefined regioisomeric *anti* aminols of type **7** (Scheme 1). These syntheses have been performed according to the previously described protocols,[14] which nevertheless required a proper tuning for the scale-up necessary for the synthesis of nucleosides in the due amount for the biological tests.

By adapting the known procedures,[5b,15] the regioisomeric aminols **7a**,**b** have been converted into the pyrimidine derivatives **8a**,**b** through condensation with the 5-amino-4,6-dichloropyrimidine and then into the chloropurines **9a**,**b** with orthoformates under HCl catalysis (Scheme 2). The pyrimidine derivatives **8a**,**b** were obtained in good yields (**8a**, 72%; **8b** 75%) by heating a solution of the aminols **7a**,**b** and 5-amino-4,6-dichloropyrimidine (2 equiv) in *n*-BuOH at reflux (bp 117 °C) in the presence of an excess of *i*-Pr_2NEt (5 equiv) for 48 h. The epimeric aminol **7a′** was also converted into the pyrimidine derivatives **8a′** (79%) and this latter into the chloropurines **9a′** under the same conditions.



Scheme 2. (a) 5-Amino-4,6-dichloropyrimidine (2 equiv), *i*-Pr_2NEt (5 equiv), *n*-BuOH, Δ, 48 h; (b) $HC(OEt)_3$/HCl, rt, 8 days.

The structures of **8a**,**a′**,**b** rely upon the analytical and spectroscopic data. While the IR spectra of pyrimidines **8a**,**a′**,**b** exhibit the expected bands between 3200–3500 cm^{-1} due to the presence of OH, NH, and NH_2 groups, the ^1H NMR spectra were unambiguously consistent for the assigned structures. The spectrum of **8a** in CD_3COCD_3 showed the pyrimidine ring proton as a singlet at δ 8.03, the NH_2 protons as a broad singlet at δ 4.43 and the OH proton as a triplet at δ 4.54 because of the coupling with the methylene at δ 3.89 (AB syst.), while the NH proton is a doublet at δ 7.01 (J=6.9 Hz). The 5- and 4-isoxazolinic protons are found at δ 5.22 (dd, J=9.6, 3 Hz) and 4.29 (dd, J=9.6, 3 Hz), respectively, while the cyclopentane protons are at δ 4.85 (m, CH–N), 2.49 (CH–CH_2–O), and 2.29, 1.77 (m, CH_2).

The spectrum of the regioisomeric **8b** is essentially similar, showing the pyrimidine singlet at δ 7.90, the NH_2 protons as a broad singlet at δ 4.39 and OH proton as a broad singlet at δ 4.77 while the corresponding methylene is at δ 3.87 (AB syst.), the NH at δ 6.85 (d, J=6.4 Hz) and the 5- and 4-isoxazolinic protons at δ 5.11 (d, J=9 Hz) and 4.24 (dd, J=9, 3 Hz). The cyclopentane protons are found at δ 4.77 (m, CH–NH), 2.46 (m, CH), and 2.35, 1.77 (m, CH_2).

Analogously, the spectrum of the stereoisomeric **8a′** shows the pyrimidine singlet at δ 7.93, the NH_2 protons as a broad singlet at δ 4.72, and the NH at δ 6.30 (d, J=5 Hz). The OH

proton appears as a triplet at δ 4.65 (J=6 Hz) while the corresponding methylene is at δ 3.71 (AB syst.). The 5- and 4-isoxazolinic protons are shown at δ 5.27 (dd, J=9, 5 Hz) and 4.43 (d, J=9 Hz) and the cyclopentane protons are found at δ 3.91 (m, CH–NH), 2.88 (m, CH), and 2.02, 1.56 (m, CH_2).

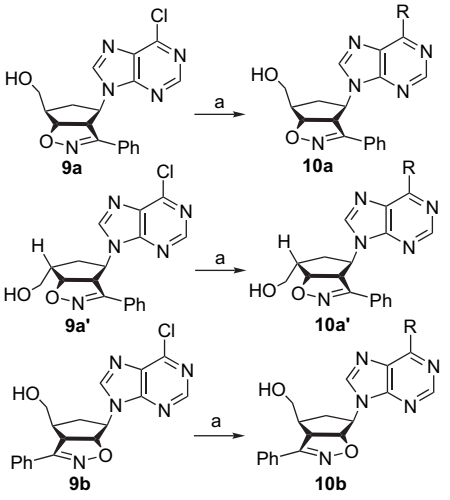
The conversion of the stereoisomeric pyrimidine **8a**,**a′**,**b** into the corresponding chloropurines **9a**,**a′**,**b** was performed using excess triethyl orthoformate in the presence of catalytic 37% HCl by keeping the reactions at rt for 8 days, in accordance with the most frequently reported procedures.[16] The chloropurines **9a**,**a′**,**b** could finally be isolated in good yields (**9a**, 87%, **9a′**, 82% and **9b**, 84%). Contrary to expectations, the reactions performed with the method used for the preparation of the *nor*-nucleosides,[11a] in the presence of excess triethyl orthoformate and catalytic *p*-TsOH, did not take place and the pyrimidine derivatives **8a**,**a′**,**b** were recovered unchanged.

The chloropurine **9a** has been fully characterized spectroscopically. Infrared spectra showed a single broad band at 3320 cm^{-1} corresponding to the OH absorptions. In the ^1H NMR spectra ($CDCl_3$) the two N=*CH* protons of the purine rings occur as singlets at δ 8.76 and 8.02 while the 5- and 4-isoxazolinic protons appear as double doublets at δ 5.47 and 4.82 (J_{H4H5}=10 Hz). Similarly, the regioisomeric chloropurine **9b** shows a single broad band at 3373 cm^{-1} corresponding to the OH absorptions in the infrared spectrum and in the ^1H NMR spectra the two N=*CH* protons of the purine rings occur as singlets at δ 8.80 and 8.27. The 5- and 4-isoxazolinic protons appear as double doublets at δ 5.74 and 4.47 (J_{H4H5}=10 Hz).

The stereoisomeric chloropurine **9a′** shows a single broad band at 3353 cm^{-1} corresponding to the OH absorptions in the infrared spectrum and in the ^1H NMR spectra the two N=*CH* protons of the purine rings occur as singlets at δ 8.80 and 8.13. The 5- and 4-isoxazolinic protons appear at δ 5.67 (dd, J=9, 5 Hz) and 4.93 (d, J=9 Hz).

From the chloro-substituted nucleosides **9a**,**a′**,**b** a variety of derivatives can be obtained by nucleophilic substitution.[17] On heating MeOH solutions of **9a**,**a′**,**b** at 50 °C in the presence of an excess of NH_3 or other differently substituted amines, the amino derivatives **10a**,**a′**,**b**(**A**–**C**) could easily be obtained (Scheme 3). Ethoxy derivatives **10a**,**a′**,**bD** were directly obtained from pyrimidine derivatives **9a**,**a′**,**b** when orthoformate/H^+ treatment is prolonged for 14 days.

Table 1 reports the chemical yields and physical constants of nucleosides **10a**,**a′**,**b**(**A**–**D**), which have been fully characterized through their analytical and spectroscopic data. The IR spectra of the adenine derivatives **10aA**, **10a′A**, and **10bA** showed neat and distinctive OH bands (3551, 3399, and 3359 cm^{-1}, respectively) and NH_2 bands (3311, 3143; 3426, 3329, and 3314, 3114 cm^{-1}, respectively). The ^1H NMR spectra showed the characteristic signals of adenine (CH= singlets at δ 8.16, 8.06; 8.28, 8.15 and 8.22, 8.19 respectively). The isoxazolinic protons occur as double doublets, because of an additional coupling with the adjacent cyclopentane methines, thus indicating the same conformation in the cyclopentane ring of the chloro-nucleosides **9a**,**a′**,**b**. The major coupling constant (J=10 Hz in **10a**,**bA** and J=8.5 Hz in **10a′A**) is between the H4- and H5-isoxazolinic protons while those between the isoxazolinic protons and the adjacent methines differ in the two regioisomers (**10aA**, J=5 Hz, **10a′A**, J=5 Hz, and **10bA**, J=6 Hz).



Scheme 3. (a) RNH_2/MeOH, 50 °C, 24 h; R: see Table 1.

Table 1
Yields and physical constants of purine derivatives

	R	Mp (°C) (Solvent)	Yield (%)
9a	Cl	>200 dec (Diisopropyl ether)	87
10aA	NH_2	224 dec (Diisopropyl ether)	89
10aB	NHMe	186–188 (Diisopropyl ether)	92
10aC	NHcPr	Oil	90
10aD	OEt	130–132 (*n*-Hexane/benzene)	84
9a′	Cl	>200 dec (*n*-Hexane/benzene)	82
10a′A	NH_2	>200 dec (Diisopropyl ether)	88
10a′B	NHMe	191–193 (Diisopropyl ether)	95
10a′C	NHcPr	170–175 dec (Diisopropyl ether)	80
10a′D	OEt	171–173 (Benzene)	77
9b	Cl	>200 dec (Diisopropyl ether)	84
10bA	NH_2	>220 dec (*n*-Hexane/benzene)	72
10bB	NHMe	>200 dec (*n*-Hexane/benzene)	87
10bC	NHcPr	>220 dec (*n*-Hexane/benzene)	80
10bD	OEt	180–182 (Benzene)	80

In the amine derivatives **10a**,**a′**,**b**(**B**,**C**) the IR spectra showed the NH bands in the range 3257–3394 cm^{-1}. The ^1H NMR spectra showed the characteristic NH signals as broad singlets at δ 6.87, 6.91 for **10aB**,**C**, δ 6.83, 6.90 for **10a′B**,**C**, and δ 6.82, 6.92 for **10bB**,**C**. In ethoxy derivatives **10a**,**a′**,**bD** the ^1H NMR spectra showed the OCH_2CH_3 signals, the methylenes as quartets at δ 4.72, 4.71, 4.71 and the methyls as triplets at δ 1.57, 1.55, 1.55, respectively.

These compounds, as well as the pyrimidine derivatives whose synthesis is actually in progress, have been taken as candidates for the biological evaluation against the same viruses in order to have a comparison at the SAR level.

3. Conclusions

The first synthesis of isoxazoline-carbocyclic nucleosides having a hydroxymethylene side chain and a variety of

analogues was attained starting from the stereodefined heterocyclic aminols **7a**,**a′**,**b**, which are readily available through *exo* selective 1,3-dipolar cycloadditions of benzonitrile oxide to 2-azanorborn-5-enes **3** (R=CH_2–Ph) and elaboration of the cycloadducts. The stereodefined heterocyclic aminols **7a**,**a′**,**b** afford the carbocyclic skeleton for the linear construction of the purine rings. Functionalization of the chloropurines **9a**,**a′**,**b** with a variety of amines extended the synthetic potential of this strategy allowing for a fine tuning of their biological and antiviral activity as well as comparison with the corresponding *nor*-nucleosides.

Biological evaluation of the newly obtained compounds **10a**,**a′**,**b** is actually in progress.

4. Experimental

4.1. General

All melting points are uncorrected. Elemental analyses were done on a C. Erba 1106 elemental analyzer. IR spectra (Nujol mulls) were recorded on an FT-IR Perkin–Elmer RX-1. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 300 in the specified deuterated solvents. Chemical shifts are expressed in parts per million from internal tetramethylsilane (δ). UV–vis spectra were recorded on a UV Perkin–Elmer LAMBDA 16 spectrophotometer using acetonitrile as solvent. HPLC analyses were carried out by means of a WATERS 1525 instrument equipped with an UV 2487 detector (λ=266 nm) both controlled by Breeze™ software and a RP C-18 Intersil ODS-2 column; a mixture of H_2O/CH_3CN 50:50 was used as eluant. Column chromatography and TLC: silica gel 60 (0.063–0.200 mm) (Merck); eluant chloroform. The identification of samples from different experiments was secured by mixed mps and superimposable IR spectra.

4.2. Materials

ADA cycloadduct **3** has been prepared according to Grieco′s procedure.[12] Benzhydroximoyl chloride was prepared according to the reported method.[18] The cycloaddition of BNO to ADA cycloaddutct **3** was performed according to the procedure described in the previous study, as well as the oxidation of the regioisomeric 1,3-dipolar cycloadducts with *m*-CPBA and the Polonovski rearrangement of the *N*-oxides with acetic anhydride.[14]

The *N*-acetyl derivatives **4** were then dissolved in CCl_4 (40 mL/g) and 1.5 equiv NBS was added along with 15 mol % of AIBN. The mixtures were refluxed at reflux monitoring the reaction by TLC until the starting materials have disappeared (2–3 h). The solutions were cooled down to ambient and then to lower temperature in an ice-bath to ensure the maximum separation of succinimide. From the filtrate organic phases the solvent was removed upon evaporation and the crude residues were submitted to chromatographic separation on silica gel by eluting initially with $CHCl_3$ and $CHCl_3$/MeOH 9:1 afterward. The bromo-cycloadducts **5** were collected along with the products of their solvolysis, the acetals, and the corresponding aldehydes. The 3-bromine derivatives **5** were treated with excess $NaHCO_3$ in refluxing EtOH for several days to promote their solvolysis to the aldehydes of type **6**. Reduction of these latters and deprotection of the amino group afforded the desired aminols **7**.[14]

4.3. Synthesis of the pyrimidine derivatives *8a*,*a′*,*b*

To aminols **7a**,**a′**,**b** (1.70 g, 7.32 mmol) dissolved in *n*-BuOH (75 mL), 5-amino-4,6-dichloropyrimidine (2.55 g, 15.5 mmol) and *i*-Pr_2NEt (4.02 g, 31.1 mmol) were added. The mixtures were heated at 117 °C with stirring for 48 h. The cooled solutions were evaporated to dryness, taken up in CH_2Cl_2, washed with brine, and dried over anhydrous Na_2SO_4. The crude residues were then submitted to column chromatography to separate the excess of amino-pyrimidine from adducts **8a**–**c**, which were isolated in 72, 79, and 75% yields, respectively.

4.3.1. Compound *8a*

Yield: 1.90 g, 72% as white crystals from ethanol, mp 175–180 °C; [Found C, 56.6; H, 5.0; N, 19.3. $C_{17}H_{18}N_5O_2Cl$ (MW=359.82) requires C, 56.75; H, 5.04; N, 19.46%]; ν_{max} (Nujol) 3411, 3348, 3303, 3257, 1658 cm^{-1}; δ_H (300 MHz, CD_3COCD_3) 8.03 (1H, s, CH=N), 7.91 (2H, m, Ph), 7.39 (3H, m, Ph), 7.01 (1H, d, *J* 6.9 Hz, NH), 5.22 (1H, dd, *J* 9.6, 3 Hz, H5-isoxaz.), 4.85 (1H, m, C*H*–NH), 4.54 (1H, t, *J* 4.5 Hz, CH_2–O*H*), 4.43 (2H, br s, NH_2), 4.29 (1H, dd, *J* 9.6, 3 Hz, H4-isoxaz.), 3.89 (2H, m, CH_2–OH), 1.59 (1H, m, CH), 2.29 (1H, m, H–CH), 1.77 (1H, dt, *J* 13, 5 Hz, H–CH); δ_C (75 MHz, CD_3COCD_3) 158.6, 153.7, 148.3, 140.9, 130.9, 130.7, 129.8, 128.5, 124.7, 90.6, 64.3, 61.0, 57.7, 50.7, 36.3.

4.3.2. Compound *8a′*

Yield: 1.98 g, 75% as white crystals from ethanol, mp>210 °C (dec); [Found C, 56.7; H, 5.0; N, 19.5. $C_{17}H_{18}N_5O_2Cl$ (MW=359.82) requires C, 56.75; H, 5.04; N, 19.46%]; ν_{max} (Nujol) 3412, 3368, 3300, 3157, 1646 cm^{-1}; δ_H (300 MHz, CD_3COCD_3) 8.09 (2H, m, Ph), 7.93 (1H, s, CH=N), 7.46 (3H, m, Ph), 6.30 (1H, d, *J* 5 Hz, NH), 5.27 (1H, dd, *J* 9, 5 Hz, H5-isoxaz.), 4.72 (2H, br s, NH_2), 4.65 (1H, t, *J* 6 Hz, CH_2–O*H*), 4.43 (1H, d, *J* 9 Hz, H4-isoxaz.), 3.91 (1H, m, C*H*–NH), 3.71 (2H, AB syst., *J* 13 Hz, CH_2–OH), 2.88 (1H, m, CH), 2.02 (1H, m, H–CH), 1.56 (1H, m, H–CH); δ_C (75 MHz, CD_3COCD_3) 157.9, 153.1, 147.7, 139.9, 130.9, 130.7, 129.9, 128.6, 125.0, 87.8, 62.1, 60.7, 57.6, 49.2, 34.3.

4.3.3. Compound *8b*

Yield: 2.08 g, 79% as white crystals from ethanol, mp 118–120 °C; [Found C, 56.7; H, 5.1; N, 19.5. $C_{17}H_{18}N_5O_2Cl$ (MW=359.82) requires C, 56.75; H, 5.04; N, 19.46%]; ν_{max} (Nujol) 3391, 3327, 3283, 3233, 1654 cm^{-1}; δ_H (300 MHz, CD_3COCD_3) 7.90 (1H, s, CH=N), 7.83 (2H, m, Ph), 7.46 (3H, m, Ph), 6.85 (1H, d, *J* 6.4 Hz, NH), 5.11 (1H, d, *J* 9 Hz, H5-isoxaz.), 4.77 (1H+1H, m, C*H*–NH+OH), 4.39 (2H, br s, NH_2), 4.24 (1H, dd, *J* 9, 3 Hz, H4-isoxaz.), 3.87 (2H, m, CH_2–OH), 2.46 (1H, m, CH), 2.35 (1H, m, H–CH),

1.77 (1H, m, H–CH); δ_C (75 MHz, CD_3COCD_3) 154.3, 147.1, 141.3, 130.9, 124.3, 123.6, 123.2, 121.6, 118.0, 87.6, 58.4, 53.2, 47.9, 41.0, 27.9.

4.4. Construction of the purine nucleosides *9a,a′,b*

To a solution of pyrimidine derivatives **8a**,**a′**,**b** (0.532 g, 1.48 mmol) in triethyl orthoformate (25 mL), a catalytic amount of HCl was added. The reaction was stirred at rt for 8 days. After this period of time, the excess orthoformate was hydrolyzed and the water phase extracted with CH_2Cl_2 and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was taken up with diisopropyl ether and the chloropurine derivatives **9a**,**a′**,**b** crystallized.

4.4.1. Compound *9a*

Yield: 0.48 g, 87% as white crystals from diisopropyl ether, mp>200 °C (dec); [Found C, 58.4; H, 4.4; N, 19.0. $C_{18}H_{16}N_5O_2Cl$ (MW=369.82) requires C, 58.46; H, 4.36; N, 18.94%]; ν_{max} (Nujol) 3320, 1654, 1560 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.76 (1H, s, CH=N), 8.02 (1H, s, CH=N), 7.29 (5H, m, Ph), 5.47 (1H, dd, *J* 10, 6 Hz, H5-isoxaz.), 4.97 (1H, m, CH–N), 4.82 (1H, dd, *J* 10, 7 Hz, H4-isoxaz.), 4.01 (2H, m, CH_2–OH), 2.58 (2H, m, CH_2), 2.43 (1H, m, CH); δ_C (75 MHz, $CDCl_3$) 159.3, 156.6, 151.8, 144.5, 144.3, 129.0, 128.5, 127.6, 126.7, 122.3, 88.0, 62.9, 61.0, 57.9, 48.0, 34.3.

4.4.2. Compound *9a′*

Yield: 0.45 g, 82% as white crystals from benzene/*n*-hexane, mp>200 °C (dec); [Found C, 58.5; H, 4.3; N, 18.9. $C_{18}H_{16}N_5O_2Cl$ (MW=369.82) requires C, 58.46; H, 4.36; N, 18.94%]; ν_{max} (Nujol) 3353, 1655, 1580 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.80 (1H, s, CH=N), 8.13 (1H, s, CH=N), 7.68 (2H, m, Ph), 7.43 (3H, m, Ph), 5.67 (1H, dd, *J* 9, 5 Hz, H5-isoxaz.), 5.15 (1H, d, *J* 6 Hz, CH–N), 4.93 (1H, d, *J* 9 Hz, H4-isoxaz.), 4.00 (2H, m, CH_2–OH), 3.13 (1H, m, CH), 2.24 (2H, m, CH_2); δ_C (75 MHz, $CDCl_3$) 156.5, 151.9, 151.3, 144.0, 134.0, 130.7, 129.1, 127.5, 126.9, 88.3, 61.2, 61.0, 58.9, 47.6, 34.0.

4.4.3. Compound *9b*

Yield: 0.46 g, 84% as white crystals from diisopropyl ether, mp>200 °C (dec); [Found C, 58.5; H, 4.5; N, 19.1. $C_{18}H_{16}N_5O_2Cl$ (MW=369.82) requires C, 58.46; H, 4.36; N, 18.94%]; ν_{max} (Nujol) 3373, 1597, 1561 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.80 (1H, s, CH=N), 8.27 (1H, s, CH=N), 7.78 (2H, m, Ph), 7.48 (3H, m, Ph), 5.74 (1H, dd, *J* 10, 6 Hz, H5-isoxaz.), 4.99 (1H, m, CH–N), 4.47 (1H, dd, *J* 10, 5 Hz, H4-isoxaz.), 3.91 (2H, m, CH_2–OH), 2.64 (2H, m, CH_2), 2.47 (1H, m, CH); δ_C (75 MHz, $CDCl_3$) 159.9, 151.6, 151.4, 144.6, 132.4, 130.5, 128.9, 128.0, 127.3, 89.1, 64.3, 63.9, 53.1, 43.9, 32.9.

4.5. Syntheses of the amino derivatives *10a,a′,b*

General method: Solutions of chloro-nucleosides **9a**,**a′**,**b** (30 mg, 0.08 mmol) in MeOH (2 mL) were saturated with ammonia or other gaseous amines and kept in a sealed tube at 50 °C for 24 h. In the case of liquid amines, an excess (50 equiv) was added to the solutions. The solutions are then cooled and concentration of the solutions afforded oily residues from which the amino derivatives were crystallized from the proper solvent. Table 1 reports the physical constants (solvent of crystallization) and yields (determined by HPLC analyses) of the amino nucleosides **10a**,**a′**,**b**(**A–C**). Ethoxy derivatives **10a**,**a′**,**bD** were obtained upon extended reaction with ethyl orthoformate up to 14 days and further addition of drops of 37% HCl and usual work-up.

4.5.1. Compound *10aA*

Yield: 25 mg, 89% as white crystals from diisopropyl ether, mp 224 °C (dec); [Found C, 61.3; H, 5.1; N, 23.7. $C_{18}H_{18}N_6O_2$ (MW=350.37) requires C, 61.70; H, 5.18; N, 23.99%]; ν_{max} (Nujol) 3551, 3311, 3143, 1666 cm^{-1}; δ_H (300 MHz, CD_3COCD_3) 8.16 (1H, s, CH=N), 8.06 (1H, s, CH=N), 7.25 (5H, m, Ph), 6.63 (2H, br s, NH_2), 5.36 (1H, dd, *J* 10, 5 Hz, H5-isoxaz.), 5.02 (2H, m, CH–N and H4-isoxaz.), 4.07 (1H, br s, OH), 3.84 (2H, m, CH_2–OH), 2.42 (3H, m, CH_2 and CH); δ_C (75 MHz, CD_3COCD_3) 165.2, 159.2, 153.6, 148.6, 141.4, 138.4, 131.0, 129.9, 129.8, 128.0, 89.4, 63.4, 61.2, 58.3, 50.0, 36.4.

4.5.2. Compound *10aB*

Yield: 27 mg, 92% as white crystals from diisopropyl ether, mp 186–188 °C; [Found C, 62.3; H, 5.5; N, 23.0. $C_{19}H_{20}N_6O_2$ (MW=364.40) requires C, 62.62; H, 5.53; N, 23.06%]; ν_{max} (Nujol) 3402, 3257, 1625 cm^{-1}; δ_H (300 MHz, CD_3COCD_3) 8.23 (1H, s, CH=N), 8.01 (1H, s, CH=N), 7.31 (5H, m, Ph), 6.87 (1H, br s, NH), 5.36 (1H, dd, *J* 10, 5 Hz, H5-isoxaz.), 5.03 (2H, m, CH–N and H4-isoxaz.), 4.11 (1H, br s, OH), 3.83 (2H, m, CH_2–OH), 2.40 (3H, m, CH_2 and CH), 2.06 (3H, d, *J* 7 Hz, CH_3); δ_C (75 MHz, CD_3COCD_3) 159.0, 153.8, 140.8, 131.0, 130.2, 129.8, 128.5, 128.0, 89.5, 63.3, 61.2, 58.3, 49.9, 36.5, 27.7.

4.5.3. Compound *10aC*

Yield: 28 mg, 90% as yellowish oil; [Found C, 64.5; H, 5.6; N, 21.5. $C_{21}H_{22}N_6O_2$ (MW=390.43) requires C, 64.60; H, 5.68; N, 21.53%]; ν_{max} (Nujol) 3297, 1622, 1572 cm^{-1}; δ_H (300 MHz, CD_3COCD_3) 8.24 (1H, s, CH=N), 8.02 (1H, s, CH=N), 7.23 (5H, m, Ph), 6.91 (1H, br s, NH), 5.32 (1H, dd, *J* 10, 5 Hz, H5-isoxaz.), 5.03 (2H, m, CH–N and H4-isoxaz.), 3.83 (2H, m, CH–NH and CH), 3.73 (2H, m, O–CH_2), 2.70 (2H, m, CH_2), 0.89 (2H, m, CH_2), 0.63 (2H, m, CH_2); δ_C (75 MHz, CD_3COCD_3) 162.0, 152.3, 139.6, 129.6 129.5, 128.4, 126.6, 122.3, 88.1, 62.0, 59.8, 57.0, 48.6, 35.0, 22.0, 6.2, 5.3.

4.5.4. Compound *10aD*

Yield: 25 mg, 84% as white crystals from *n*-hexane/benzene, mp 130–132 °C; [Found C, 63.2; H, 5.6; N, 18.5. $C_{20}H_{21}N_5O_3$ (MW=379.41) requires C, 63.31; H, 5.58; N, 18.46%]; ν_{max} (Nujol) 3292, 1598, 1575 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.52 (1H, s, CH=N), 7.75 (1H, s,

CH=N), 7.36 (2H, m, Ph), 7.25 (3H, m, Ph), 5.46 (1H, dd, *J* 10, 5 Hz, H5-isoxaz.), 4.88 (1H, m, CH–N), 4.81 (2H, dd, *J* 10, 3 Hz, H4-isoxaz.), 4.72 (2H, q, *J* 7 Hz, O–CH_2), 4.00 (2H, br s, CH_2–OH), 2.63 (2H, m, CH_2), 2.48 (1H, m, CH), 1.57 (3H, t, *J* 7 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 161.1, 158.2, 151.9, 151.1, 141.6, 130.4 128.9, 128.2, 127.8, 126.8, 88.9, 63.4, 63.3, 61.3, 57.8, 47.9, 34.6, 14.4.

4.5.5. Compound ***10a′A***

Yield: 25 mg, 88% as white crystals from diisopropyl ether, mp>200 °C (dec); [Found C, 61.5; H, 5.2; N, 23.8. $C_{18}H_{18}N_6O_2$ (MW=350.37) requires C, 61.70; H, 5.18; N, 23.99%]; ν_{max} (Nujol) 3426, 3399, 3329, 1654 cm^{-1}; δ_H (300 MHz, DMSO) 8.28 (1H, s, CH=N), 8.15 (1H, s, CH=N), 7.70 (2H, m, Ph), 7.42 (3H, m, Ph), 5.45 (1H, dd, *J* 8.5, 5 Hz, H5-isoxaz.), 4.95 (2H, m, CH–N and H4-isoxaz.), 4.68 (2H, br, NH_2), 3.70 and 3.51 (2H, AB syst., CH_2–OH), 2.81 (1H, m, CH), 1.98 and 1.72 (2H, m, CH_2); δ_C (75 MHz, DMSO) 156.5, 155.9, 152.2, 149.2, 139.6, 130.1, 129.0, 128.2, 126.9, 119.1, 87.2, 59.8, 58.5, 57.8, 47.7, 34.6.

4.5.6. Compound ***10a′B***

Yield: 28 mg, 95% as white crystals from diisopropyl ether, mp 191–193 °C; [Found C, 62.4; H, 5.4; N, 23.1. $C_{19}H_{20}N_6O_2$ (MW=364.40) requires C, 62.62; H, 5.53; N, 23.06%]; ν_{max} (Nujol) 3318, 1630 cm^{-1}; δ_H (300 MHz, CD_3COCD_3) 8.29 (1H, s, CH=N), 8.11 (1H, s, CH=N), 7.84 (2H, m, Ph), 7.44 (3H, m, Ph), 6.83 (1H, br, NH), 5.57 (1H, dd, *J* 9, 5 Hz, H5-isoxaz.), 5.13 (1H, d, *J* 6 Hz, CH–N), 5.03 (1H, dt, *J* 9, 1 Hz, H4-isoxaz.), 3.94 and 3.74 (1H+1H, AB syst., CH_2–OH), 3.16 (1H, br s, OH), 3.05 (1H, m, CH), 2.82 (3H, d, *J* 8 Hz, N–CH_3), 2.25 and 1.95 (1H+1H, m, CH_2); δ_C (75 MHz, CD_3COCD_3) 157.9, 153.9, 140.2, 131.2, 130.1, 128.3, 89.1, 62.0, 61.9, 60.7, 59.7, 49.6, 35.9.

4.5.7. Compound ***10a′C***

Yield: 25 mg, 80% as white crystals from diisopropyl ether, mp 170–175 °C (dec); [Found C, 64.4; H, 5.5; N, 21.4. $C_{21}H_{22}N_6O_2$ (MW=390.43) requires C, 64.60; H, 5.68; N, 21.53%]; ν_{max} (Nujol) 3328, 1655, 1618 cm^{-1}; δ_H (300 MHz, CD_3COCD_3) 8.30 (1H, s, CH=N), 8.13 (1H, s, CH=N), 7.84 (2H, m, Ph), 7.43 (3H, m, Ph), 6.90 (1H, br s, NH), 5.57 (1H, dd, *J* 9, 5 Hz, H5-isoxaz.), 5.13 (1H, d, *J* 6.6 Hz, CH–N), 5.03 (1H, d, *J* 9 Hz, H4-isoxaz.), 3.95 (1H, m, *CH*–NH), 3.73 (2H, m, O–CH_2), 3.16 (1H, br s, OH), 3.07 (1H, m, CH), 2.08 and 1.92 (2H, m, CH_2), 0.83 (2H, m, CH_2), 0.72 (2H, m, CH_2); δ_C (75 MHz, CD_3COCD_3) 153.8, 152.5, 151.2, 140.4, 134.6, 131.2 130.1, 128.4, 89.1, 62.0, 60.7, 59.7, 49.6, 35.9, 25.0, 7.6, 7.3.

4.5.8. Compound ***10a′D***

Yield: 23 mg, 77% as white crystals from benzene, mp 171–173 °C; [Found C, 63.1; H, 5.5; N, 18.4. $C_{20}H_{21}N_5O_3$ (MW=379.41) requires C, 63.31; H, 5.58; N, 18.46%]; ν_{max} (Nujol) 3348, 1596 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.55 (1H, s, CH=N), 7.88 (1H, s, CH=N), 7.72 (2H, m, Ph), 7.44 (3H, m, Ph), 5.66 (1H, dd, *J* 9, 5 Hz, H5-isoxaz.), 5.11 (1H, d, *J* 6 Hz, CH–N), 4.93 (1H, d, *J* 9 Hz, H4-isoxaz.), 4.71 (2H, q, *J* 7 Hz, O–CH_2), 4.00 (2H, m, CH_2–OH), 3.15 (1H, m, CH), 2.18 (2H, m, CH_2), 1.55 (3H, t, *J* 7 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 161.0, 156.8, 152.1, 151.6, 140.7, 130.5 129.1, 127.7, 127.0, 122.2, 88.6, 63.2, 61.4, 60.4, 59.0, 47.5, 34.0, 14.4.

4.5.9. Compound ***10bA***

Yield: (20 mg, 72%) as white crystals from *n*-hexane/benzene, mp>220 °C (dec); [Found C, 61.5; H, 5.2; N, 23.7. $C_{18}H_{18}N_6O_2$ (MW=350.37) requires C, 61.70; H, 5.18; N, 23.99%]; ν_{max} (Nujol) 3359, 3314, 3114, 1673, 1603 cm^{-1}; δ_H (300 MHz, CD_3COCD_3) 8.22 (1H, s, CH=N), 8.19 (1H, s, CH=N), 7.86 (2H, m, Ph), 7.50 (3H, m, Ph), 6.52 (2, br s, NH_2), 5.84 (1H, dd, *J* 10, 6 Hz, H5-isoxaz.), 4.98 (1H, m, CH–N), 4.45 (1H, dd, *J* 10, 6 Hz, H4-isoxaz.), 4.26 (1H, t, *J* 5 Hz, OH), 3.79 (2H, m, CH_2–OH), 2.53 (2H, m, CH_2), 2.36 (1H, m, CH); δ_C (75 MHz, CD_3COCD_3) 161.5, 158.9, 157.6, 153.8, 147.6, 141.2, 136.7, 131.2, 130.0, 128.7, 90.3, 64.7, 54.1, 49.3, 34.9, 20.0.

4.5.10. Compound ***10bB***

Yield: 25 mg, 87% as white crystals from *n*-hexane/benzene, mp>200 °C (dec); [Found C, 62.5; H, 5.4; N, 23.2. $C_{19}H_{20}N_6O_2$ (MW=364.40) requires C, 62.62; H, 5.53; N, 23.06%]; ν_{max} (Nujol) 3387, 1634, 1576 cm^{-1}; δ_H (300 MHz, CD_3COCD_3) 8.29 (1H, s, CH=N), 8.14 (1H, s, CH=N), 7.87 (2H, m, Ph), 7.49 (3H, m, Ph), 6.82 (1H, br, NH), 5.84 (1H, dd, *J* 10, 6 Hz, H5-isoxaz.), 4.99 (1H, m, CH–N), 4.46 (1H, dd, *J* 10, 4 Hz, H4-isoxaz.), 4.30 (1H, br, OH), 3.78 (2H, m, CH_2–OH), 2.81 (3H, d, *J* 7 Hz, *CH_3*–NH), 2.51 (2H, m, CH_2), 2.37 (1H, m, CH); δ_C (75 MHz, CD_3COCD_3) 161.0, 153.8, 140.7, 131.2, 130.5, 130.0, 128.7, 90.4, 64.7, 64.1, 54.1, 45.8, 35.0, 27.5.

4.5.11. Compound ***10bC***

Yield: 25 mg, 80% as white crystals from *n*-hexane/benzene, mp>220 °C (dec); [Found C, 64.5; H, 5.6; N, 21.5. $C_{21}H_{22}N_6O_2$ (MW=390.43) requires C, 64.60; H, 5.68; N, 21.53%]; ν_{max} (Nujol) 3394, 1619, 1572 cm^{-1}; δ_H (300 MHz, CD_3COCD_3) 8.30 (1H, s, CH=N), 8.16 (1H, s, CH=N), 7.86 (2H, m, Ph), 7.47 (3H, m, Ph), 6.92 (1H, br s, NH), 5.83 (1H, dd, *J* 10, 6 Hz, H5-isoxaz.), 4.98 (1H, m, CH–N), 4.45 (1H, dd, *J* 10, 6 Hz, H4-isoxaz.), 4.29 (1H, br, OH), 3.77 (2H, m, CH_2–OH), 2.51 (2H, m, CH_2), 2.33 (1H, m, CH), 2.10 (1H, m, C*H*–NH), 0.83 (2H, m, CH_2), 0.73 (2H, m, CH_2); δ_C (75 MHz, CD_3COCD_3) 161.0, 153.7, 140.9, 131.2, 130.5, 130.0, 128.7, 90.3, 64.8, 64.1, 54.1, 45.8, 34.9, 23.6, 7.6, 6.7.

4.5.12. Compound ***10bD***

Yield: 24 mg, 80% as white crystals from benzene, mp 180–182 °C; [Found C, 63.2; H, 5.6; N, 18.5. $C_{20}H_{21}N_5O_3$ (MW=379.41) requires C, 63.31; H, 5.58; N, 18.46%]; ν_{max} (Nujol) 3294, 1597, 1575 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.55 (1H, s, CH=N), 8.01 (1H, s, CH=N), 7.77 (2H, m, Ph), 7.48 (3H, m, Ph), 5.71 (1H, dd, *J* 10, 5 Hz, H5-isoxaz.),

4.96 (1H, m, CH–N), 4.71 (2H, q, J 7 Hz, O–CH_2), 4.47 (1H, dd, J 10, 5 Hz, H4-isoxaz.), 3.90 (2H, m, CH_2–OH), 2.94 (1H, br, OH), 2.67 (2H, m, CH_2), 2.49 (1H, m, CH), 1.55 (3H, t, J 7 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 160.0, 151.7, 141.6, 130.3, 128.8, 128.2, 127.3, 89.8, 64.6, 63.2, 53.5, 44.2, 33.1, 30.8, 14.4.

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