DOI: 10.1002/ejoc.200700569

A Straightforward Synthesis of Isoxazoline-Based Carbocyclic Nucleosides from 1,3-Cyclohexadiene through Nitrosocarbonyl Chemistry

Paolo Quadrelli,*[a] Mariella Mella,[a] Serena Carosso,[a] Bruna Bovio,[b] and Pierluigi Caramella[a]

Keywords: Carbocyclic nucleosides / Nitroso compounds / Nitrile oxides / 1,3-Dipolar cycloadditions / Cieplak effect

3-Benzoyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene undergoes cycloaddition with benzonitrile oxide to afford a mixture of *syn* and *anti* regioisomeric cycloadducts. The *anti* cycloadducts were easily elaborated to stereodefined isoxazoline-based carbocyclic aminols that serve as synthons for the linear construction of purine nucleosides.

Introduction

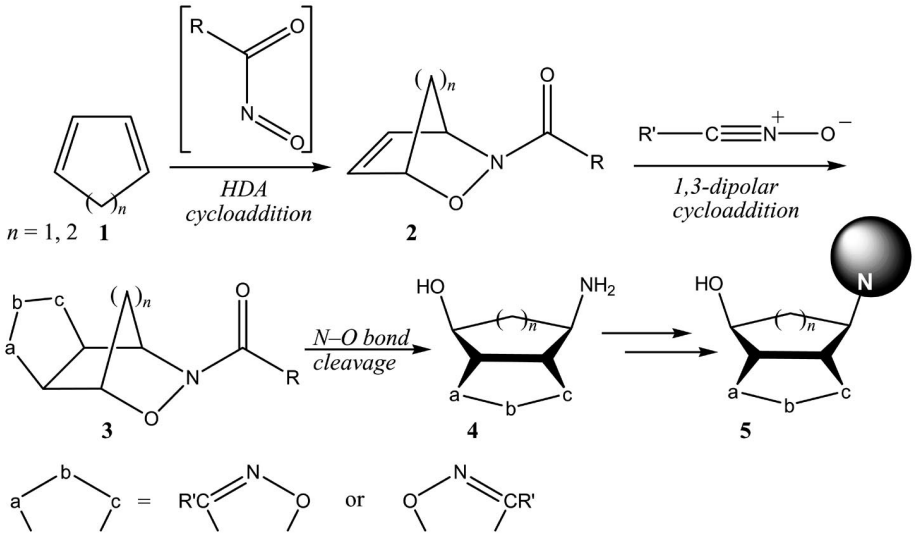
The development of new modified nucleosides as antiviral agents has remained a very active field of research.[1] Recently, we have developed the synthesis of the isoxazoline-based carbocyclic nucleosides **5** by the linear construction of the desired purine and pyrimidine bases on the regioisomeric aminols **4** (Scheme 1) obtained through elaboration of the hetero-Diels–Alder (HDA) cycloadducts **2** of cyclopentadiene (**1**, $n = 1$) with nitrosocarbonyl intermediates (RCONO).[2] These fleeting intermediates are traditionally generated by periodate oxidation of hydroxamic acids[3] or by oxidation of nitrile oxides with *N*-methylmorpholine *N*-oxide (NMO),[4] and are promptly trapped with dienes to afford HDA cycloadducts in high yields. The HDA cyclopentadiene cycloadducts **2** have proved to be highly reactive dipolarophiles towards nitrile oxides, affording regioisomeric 1,3-dipolar cycloadducts of type **3**, which are converted quantitatively by detachment of the acyl moiety and reductive cleavage of the N–O bond into the stereodefined *anti* aminols **4**.[5] Starting from these, through the linear construction of the heterobases, we have detailed the first synthesis of a class of racemic purine- and pyrimidine-carbocyclic nucleosides **5** containing a fused isoxazoline ring and lacking a methylene group in the side chain in the carbocyclic unit.[2]

Despite the fact that carbocyclic nucleosides have been extensively studied, few examples of six-membered carbocyclic analogues have been reported in the literature.[6] The major factors that highlight the importance of six-membered carbocyclic nucleosides are their resistance to hydrolysis[7] and their (bio)isoster nature with the furanose ring.[7,8] In particular, the conformational behaviour of cyclohexene derivatives proved to be relevant in determining the antiviral activity, being similar to that of a saturated five-membered ring.[9] The presence of two sp^2-hybridized carbon atoms in the cyclohexene ring limits the accessible conformational space, which is no longer describable as the cyclohexane globe, but as a plane (i.e., the conformational space occupied by a furanose ring).[8] Conformational analyses[10] of cyclohexenyl nucleosides led to the conclusion that these sugar-modified nucleosides best mimic natural furanose derivatives, as the antiviral evaluations confirmed. Traditionally, cyclohexenyl nucleosides are prepared through Mitsunobu reactions with cyclohexenyl alcohols[7a,11] or through palladium-catalysed reactions from cyclohexenyl acetates.[12] Few examples of syntheses starting from cyclohexenyl aminols have been reported.[13]

When a second carbocyclic or heterocyclic ring is fused to the main carbocyclic moiety of a nucleoside derivative, the conformational flexibility is somewhat further decreased. A few examples of cases of cyclopentane-nucleoside derivatives fused with three-[14] and four-membered[15] carbocyclic rings have been reported in the literature, as well as five-membered heterocyclic rings such as pyrazole[16] or isoxazoline systems.[2,17] Nucleosides lacking a methylene group in the side chain belong to the so-called "nor" class and in some cases display reduced cytotoxicity.[18]

In pursuit of our studies on the synthetic potential of the nitrosocarbonyl HDA cycloadducts, we detail here the

[a] Dipartimento di Chimica Organica, Università degli Studi di Pavia,
Viale Taramelli 10, 27100 Pavia, Italy
[b] Dipartimento di Chimica Generale, Università degli Studi di Pavia,
Viale Taramelli 12, 27100 Pavia, Italy
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.



Scheme 1. In the 1,3-dipolar cycloadducts, the moieties deriving from the nitrile oxides have been abbreviated as "a–b–c", to depict the two possible regioisomers concisely, as reported previously.[2]

synthesis of a class of racemic purine six-membered carbocyclic ($n = 2$) nucleosides, each containing a fused isoxazole ring and lacking a methylene group in the side chain of the six-membered carbocyclic unit.

Results

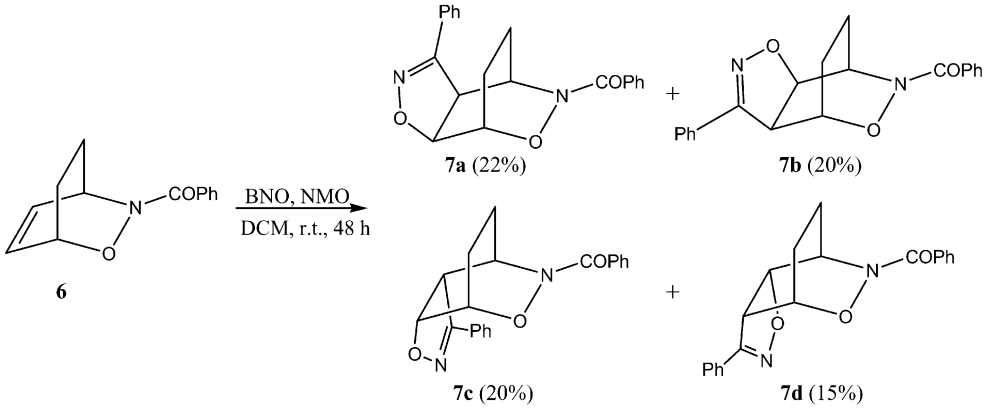
Cycloaddition of Benzonitrile Oxide to 3-Benzoyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene and Conversion of the *anti* Cycloadducts into Aminols

We obtained 3-benzoyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (**6**; Scheme 2) in quantitative yields by the mild oxidation of benzonitrile oxide (BNO) with NMO (1.3 equiv.) in dioxane in the presence of an excess of 1,3-cyclohexadiene (2.5 equiv.) according to the published procedure.[4]

The HDA adduct **6** displays only moderate dipolarophilic activity towards nitrile oxides, as is to be expected for bicyclo[2.2.2]oct-5-ene derivatives.[19] Cycloaddition between excess BNO (1.5 equiv.) and **6**, however, afforded a mixture of all the four 1,3-dipolar cycloadducts **7a**–**d** in a fair yield (77%), and these were isolated by column chromatography in comparable amounts (Scheme 2).

Table 1 gives the relevant ^{1}H and ^{13}C NMR spectroscopic data, which are in the ranges expected for isoxazolinic ^{1}H and ^{13}C signals.[20] The spectra, however, show the extensive line broadenings typical of *O*,*N*-dialkyl hydroxamic acids,[21] which mask spin–spin splittings useful for structural assignments. A first and important contribution to the solution of this structural problem was provided by single-crystal X-ray analyses conducted on the *syn* cycloadducts **7c** and **7d**, which allowed for the unequivocal attribution of the stereo- and regioisomeric structures. ORTEP views of the cycloadducts **7c** and **7d** are provided in Figure 1, while the associated crystallographic data are given in the Supporting Information.

The NMR spectra of the remaining *anti* adducts **7a** and **7b** do not allow any firm regiochemical attribution because of the line broadenings and peak overlapping. As already noted in the related case of the *exo* adducts of BNO and *N*-benzoyl-2-oxa-3-aza-norborn-5-ene,[5a] the bridgehead protons adjacent to the *N*-benzoyl substituents are remark-

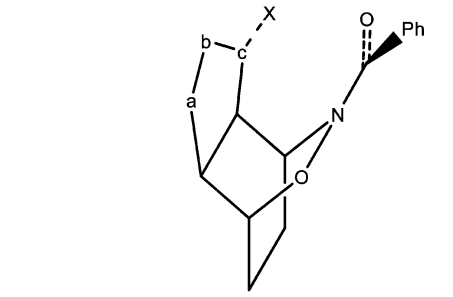


Scheme 2.

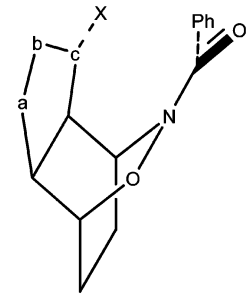
Table 1. Relevant NMR spectroscopic data for cycloadducts **7a**–**d**.

7	NMR ($CDCl_3$): ^1H, δ				NMR ($CDCl_3$): ^{13}C, δ			
	H-5 isox.	H-4 isox.	CH–O	CH–N	5-C isox.	4-C isox.	CH–O	CH–N
a	5.20 (br.)	4.43 (br.)	4.46 (br.)	5.07 (br.)	77.4	50.1	71.8	45.1 (br.)
b	5.25 (br.)	4.44 (br.)	4.65 (br.)	5.10 (br.)	78.4	50.9	71.6	46.5 (br.)
c	4.89 (br.)	4.14, d; 3.98, d[a]	4.40 (br.)	5.10 (br.)	74.5	46.4	68.3	39.7 (br.)
d	5.10, d; 4.92, d[b]	4.00, d (J = 11.5)	4.44 (br.)	5.10 (br.); 4.67 (br.)	79.1, 78.6	51.6	70.1	46.4 (br.)

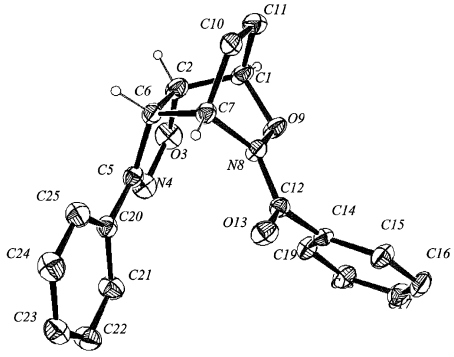
[a] In a 4:1 ratio, J = 11 Hz. [b] In a 1:1 ratio, J = 11.5 Hz; the signal at δ = 5.10 ppm overlaps with one of the CHN signals.



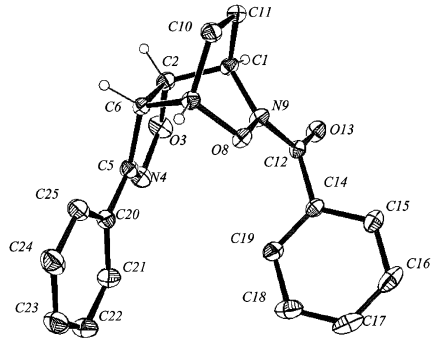
(*E*)-**8**



(*Z*)-**8**



7c



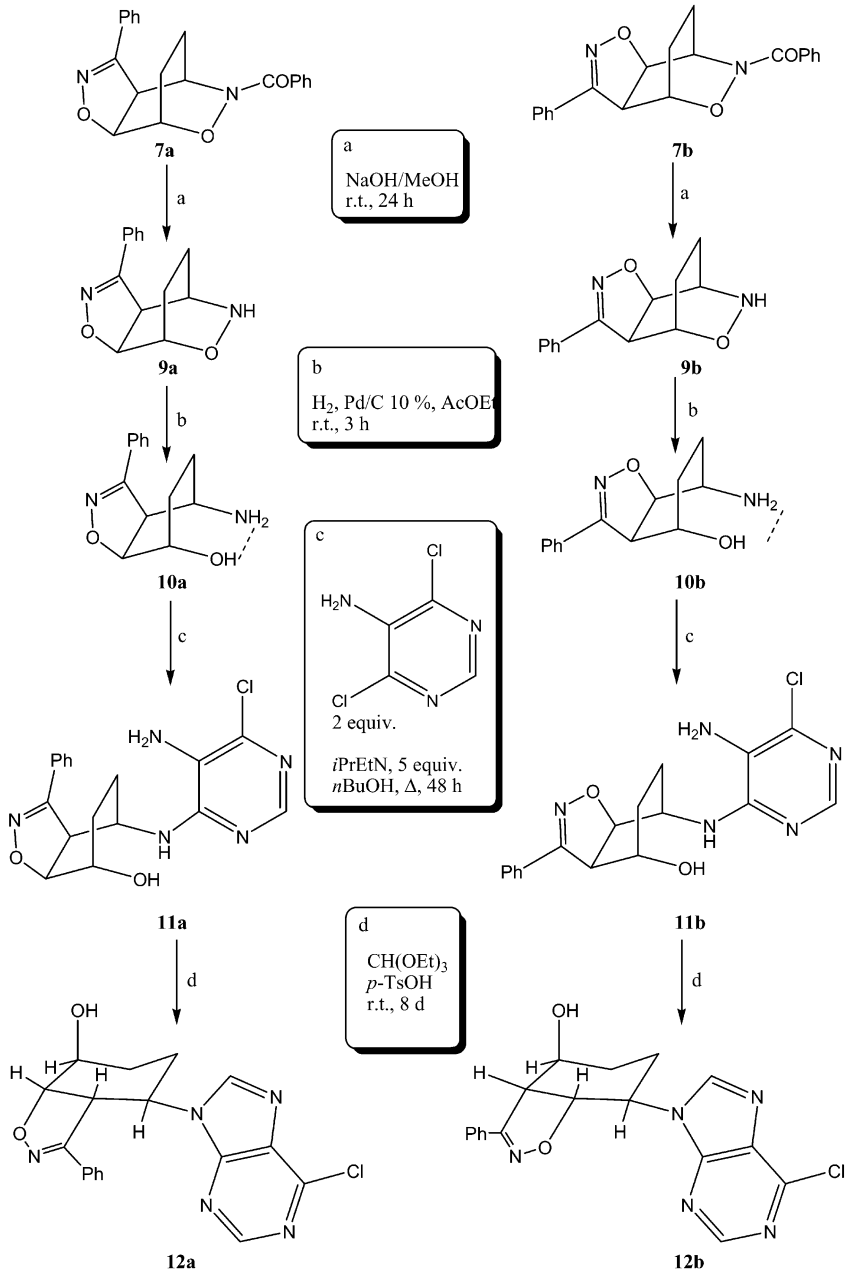
7d

Figure 1. ORTEP plots of cycloadducts **7c** and **7d** with atom labelling (ellipsoid at 25% probability). Hydrogen atoms are omitted for clarity, except for those at C1, C2, C6 and C7.

ably deshielded because of the sizeable anisotropic effects of the amide group[22] and appear at lower field than the bridgehead protons adjacent to the oxygen and close to the 5-isoxazolinic protons. The assignments were established with the aid of ^{13}C-^1H COSY (HSQC) experiments,[23] which show the ^{13}CH–O signals in the expected range (δ = 68–72 ppm) while the ^{13}CH–N signals are well separated and appear at δ = 39–47 ppm. Moreover, the regiochemical attribution could be firmly established after detachment of the benzoyl substituent, thus also removing the line broadening (vide infra).

Rather unexpectedly, the NMR spectra of the *syn* adducts **7c** and **7d** instead each show two sets of signals, which are clearly discernible in the case of the isoxazolinic protons proximal to the *N*-benzoyl moiety and can be ascribed to the presence of the two rotamers (*E*)-**8** and (*Z*)-**8** (Figure 1) in a slow equilibrium. In the *syn* adduct **7c** the two rotamers are present in a 4:1 ratio, while in the regioisomeric adduct **7d** they are present in approximately equal amounts. The observation of the two rotamers implies an increase in the barrier to rotation in the *syn* adducts, which can be ascribed to the shielding of the *syn* heterocyclic ring, which hinders the *N*-benzoyl rotation. The different rotameric populations can be accounted for on steric grounds. The two rotamers thus exhibit similar energies in the *syn* adducts **7d**, while in the *syn* adduct **7c** the (*E*) rotamer prevails, since the presence of a phenyl group in the position marked with an X causes steric hindrance in the (*Z*) rotamers.

Analogously with the case of the *exo* norbornene cycloadducts,[5] the *anti* cycloadducts **7a** and **7b** were almost



Scheme 3.

quantitatively converted into aminols with the aid of the transformations shown in Scheme 3. Alkaline hydrolysis of the cycloadducts **7a** and **7b** takes place easily at room temp. and quantitatively affords the cyclic hydroxylamines **9a** and **9b**, whose NMR spectra no longer show line broadenings. The bridgehead protons appear in the regular range ($\delta_{CHO} > \delta_{CHN}$), and the spectra display small but reliable coupling constants between the isoxazoline protons and the adjacent bridgehead protons, allowing for their regiochemical assignment (Table 2). Hydroxylamines **9a** and **9b** were also converted into the aminols **10a** and **10b** in excellent yields by catalytic hydrogenolysis.

Table 2. Relevant ^{1}H NMR spectroscopic data for hydroxylamines **9a** and **9b** and aminols **10a** and **10b**.

	^{1}H NMR, $CDCl_3$: δ, ppm; J, Hz				
	H-5 isox.	H-4 isox.	CH–O	CH–N	CH_2–CH_2
9a	5.15, dd (10.5, 5.2)	4.25, dd (10.5, 2.0)	4.16, m (5.2)[a]	3.47, m (2.0)[a]	1.5–2.1, m
9b	5.15, dd (9.7, 3.5)	4.33, dd (11, 2)	4.28, d (2)	3.37, m (3.5)[a]	1.5–2.1, m
10a	4.90, dd (10, 3)	3.71, dd (10, 2)	4.18, m	3.33, m	1.6–2.1, m
10b	4.76, dd (10, 3)	4.03, dt (10, 2)	3.96, m	3.67, m	1.6–2.0, m

[a] COSY experiments.

The NMR spectra show only small (2–3 Hz) coupling constants between the isoxazolinic protons and the adjacent bridgehead protons. The small couplings and the absence of typical axial coupling constants[24] in the other cyclohexane couplings support the presence of a twist-boat (TB) conformation for the cyclohexane ring. The near planarity of the isoxazoline rings tends to destabilize the staggered cyclohexane chair, while the intramolecular hydrogen bond between the alcoholic and amino moieties should favour the adoption of this otherwise uncommon conformation.[25] Bulky noncyclic substituents can also destabilize the cyclohexane chair.[26]

Conversion of the Aminols into Purine Nucleosides

By adapting known procedures for the construction of the purine nucleus,[27] we have converted the stereodefined aminols **10a** and **10b** into the pyrimidine derivatives **11a** and **11b** by substitution of 5-amino-4,6-dichloropyrimidine and then into the chloropurines **12a** and **12b** by condensation with orthoformates (Scheme 3). The pyrimidine derivatives **11a** and **11b** were obtained in good yields (**11a**, 88%; **11b**, 97%) by heating of a solution of the aminols **10a** and **10b** and 5-amino-4,6-dichloropyrimidine (2 equiv.) in *n*BuOH (b.p. 117 °C) at reflux in the presence of an excess of $i\text{Pr}_2\text{NEt}$ (5 equiv.) for 48 h.

The structures of **11a** and **11b** are based upon analytical and spectroscopic data. While the IR spectra of pyrimidines **11a** and **11b** exhibit complex series of bands between 3190–3450 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 conversion of the stereoisomeric pyrimidines **11a** and **11b** into the chloropurines **12a** and **12b** was finally achieved in excellent yield (88 and 90%, respectively) by treatment with triethyl orthoformate in the presence of catalytic *p*TsOH by keeping the reactions at room temp. for 8 d and in accordance with a previously reported protocol.[2] Isolation and purification of **12a** and **12b** were achieved by hydrolysis of triethyl orthoformate, evaporation of the organic solvent and extraction of the water solution with DCM, followed by crystallization of the final products.

The chloropurines **12a** and **12b** were fully characterized spectroscopically. Infrared spectra each show a single, broad band at 3351 cm^{-1} (**12a**) or 3517 cm^{-1} (**12b**) corresponding to the OH absorptions. In the ^1H NMR spectra the two N=*CH* protons of the purine rings occur as singlets at δ = 7.93 and 8.57 ppm in the case of **12a** and at δ = 8.28 and 8.82 ppm in that of **12b**, while the 5- and 4-isoxazolinic protons appear at δ = 4.62 and 4.23 ppm in the case of **12a** and at δ = 5.38 and 4.20 ppm in that of **12b**, with J = 10 and 9 Hz, respectively, between them. The coupling constants between the isoxazolinic protons and the adjacent bridgehead H atoms increase sizeably (J = 6–7 Hz) in **12a** and **12b**, indicating a change in the conformations of the cyclohexane rings attributable to the absence of the intramolecular H-bonds in **12a** and **12b**. A single crystal of **12a** was subjected to X-ray analysis, and the ORTEP view (Figure 2) indeed shows that the large purine ring has been displaced in the expected equatorial position for a chair conformation.

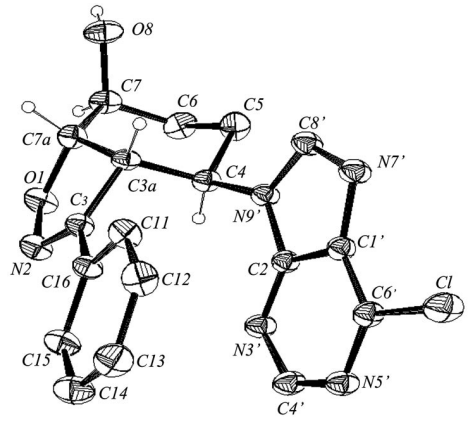
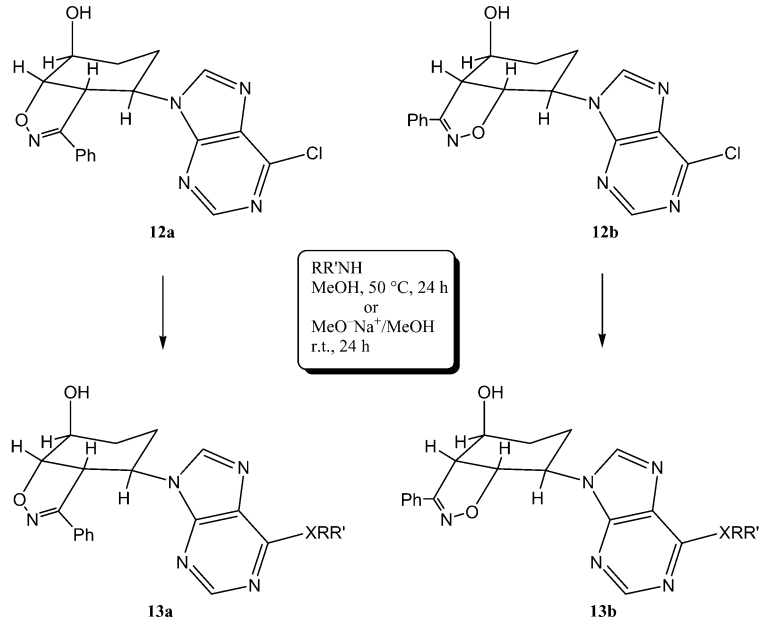


Figure 2. ORTEP plot of cycloadduct **12a** with atom labelling (ellipsoids at 25% probability). Hydrogen atoms are omitted for clarity, except for those at C3a, C4, C7 and C7a.

Some derivatives of the chloro-substituted nucleosides **12a** and **12b** were obtained by the ready nucleophilic substitution of the chlorine atoms.[27a,27c,28] On heating of MeOH solutions of **12a** and **12b** at 50 °C in the presence of excess NH_3 or other differently substituted primary and secondary amines, the amino derivatives **13a(A–E)** and **13b(A–E)** were easily obtained (Scheme 4). Table 3 reports the chemical yields and physical constants of nucleosides **13a(A–E)** and **13b(A–E)**, which have been fully characterized through their analytical and spectroscopic data.

The IR spectra of the adenine derivatives **13aA** and **13bA** showed neat and distinctive OH bands (3345 and 3425 cm^{-1}, respectively) and NH_2 bands (3335, 3185 and 3324, 3160 cm^{-1}, respectively). The ^1H NMR spectra (DMSO) showed the characteristic signals of adenine (CH= singlets at δ = 7.92, 8.01 ppm and δ = 8.17, 8.27 ppm, respectively). The functionalization on the purine ring does not cause any noteworthy changes in the NMR signals either of the isoxazolinic or of the carbocyclic moieties. The IR spectra of nucleosides **13a(B–D)** and **13b(B–D)** obtained with primary amines showed broad and distinctive OH bands and NH absorptions in the 3185–3411 cm^{-1} range. The ^1H NMR spectra display the signals of the amino moieties, together with the almost unchanged signals of the chloro derivative backbone. Nucleosides **13aB** and **13bB** showed the CH_3–NH methyls at δ = 2.06 and 2.10 ppm, respectively, while the signals of the cyclopropyl-NH substituents in compounds **13aC** and **13bC** are found at δ = 0.66, 0.80 and 2.82 ppm for **13aC** and at δ = 0.71, 0.82, 0.88 and 2.69 ppm for compound **13bC**. The benzylamino-substituted nucleosides **13aD** and **13bD** prominently showed the methylene protons at δ = 4.87 and 4.43 ppm, respectively. The diethylamino derivatives **13aE** and **13bE** showed broad OH bands at 3538 and 3382 cm^{-1}, respectively, in their IR spectra, while in their ^1H NMR spectra



Scheme 4.

Table 3. Yields and physical constants of purine derivatives **13a(A–F)** and **13b(A–F)**.

Entry		X	R	R′	m.p. [°C][a]	% Yield
	13a					
1	**A**	N	H	H	170–172	64
2	**B**	N	CH_3	H	134–137	82
3	**C**	N	C_3H_5	H	176–177	68
4	**D**	N	$PhCH_2$	H	198–200	57
5	**E**	N	CH_3–CH_2	CH_3–CH_2	thick oil	50
6	**F**	O	CH_3	/	>200 (dec.)	80
	13b					
7	**A**	N	H	H	>200 (dec.)	52
8	**B**	N	CH_3	H	137–139	82
9	**C**	N	C_3H_5	H	>200 (dec.)	81
10	**D**	N	$PhCH_2$	H	80–82	75
11	**E**	N	CH_3–CH_2	CH_3–CH_2	125–127	87
12	**F**	O	CH_3	/	>200 (dec.)	91

[a] Solvent: diisopropyl ether, except **13bA** (from methanol).

the diethyl groups were in the expected regions [δ = 1.22 (CH_3), 3.94 ppm (CH_2–N) and 1.28, 1.39 ppm (CH_3); 2.84, 3.07 ppm (CH_2–N), respectively].

In particular, nucleoside **13aE** is the only oily product and in its ^{1}H NMR spectrum the methylene of the diethyl groups give rise to broad signals due to hindered rotation and the signals of the isoxazolinic protons are no longer neat doublets but merge with those of the CH–N and CH–O protons in a single group of signals, thus indicating a conformational change in the cyclohexane ring.

From the chloro-substituted nucleosides **12a** and **12b** the methoxy derivatives **13aF** and **13bF** were also easily obtained upon treatment with MeO^-Na^+/MeOH solution (4.5 M) at room temperature for 24 h. Nucleosides **13aF** and **13bF** showed broad OH bands at 3276 and 3359 cm^{-1}, respectively, in their IR spectra, while in their ^{1}H NMR spectra the methoxy groups were found at δ = 4.08 and 4.16 ppm, respectively.

Mechanistic Considerations

The lack of any noteworthy regiochemical and stereochemical selectivity in the cycloaddition of BNO to 3-benzoyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (**6**) is at first sight surprising. The lack of sizeable regiochemical control had already been observed in the exclusive *exo* addition to 3-benzoyl-2-oxa-3-azanorborn-5-ene (**2a**, n = 1) and can be related to the comparable electron-withdrawing abilities of the alkoxy and acylamino allylic substituents, which have similar σ_I substituent constants.[29] The two different heteroatoms of the dihetero bridge of **6** would then be expected to display comparable inductive and hyperconjugative influences on the dipolarophilic activity of the two ends of the C=C double bond of **6**, which consequently undergoes unregioselective additions.

The influences of the two different bridges, the hetero and the dimethylene bridge, on the two faces of the double bond of **6** are different, however, because of the widely differing π/σ and π/σ^* interactions acting on the two faces and leading eventually to a deformation of the double bond, which pyramidalizes in the unsymmetrical environment.[30] Figure 3 outlines the shapes of the (symmetrical) bicyclo[2.2.2]oct-5-ene (***A***), the more stable (*E*)-conformer of 3-formyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (***B***) and the related 2,3-dioxabicyclo[2.2.2]oct-5-ene[31] (***C***) along with those of norbornene[30b,32] (***D***), 3-formyl-2,3-oxazanorbornene (***E***) and 5,6-dioxanorbornene (***F***) as obtained by B3LYP/6-31G*[33] geometry optimization. The numbers in parentheses near the hydrogen atoms specify the out-of-

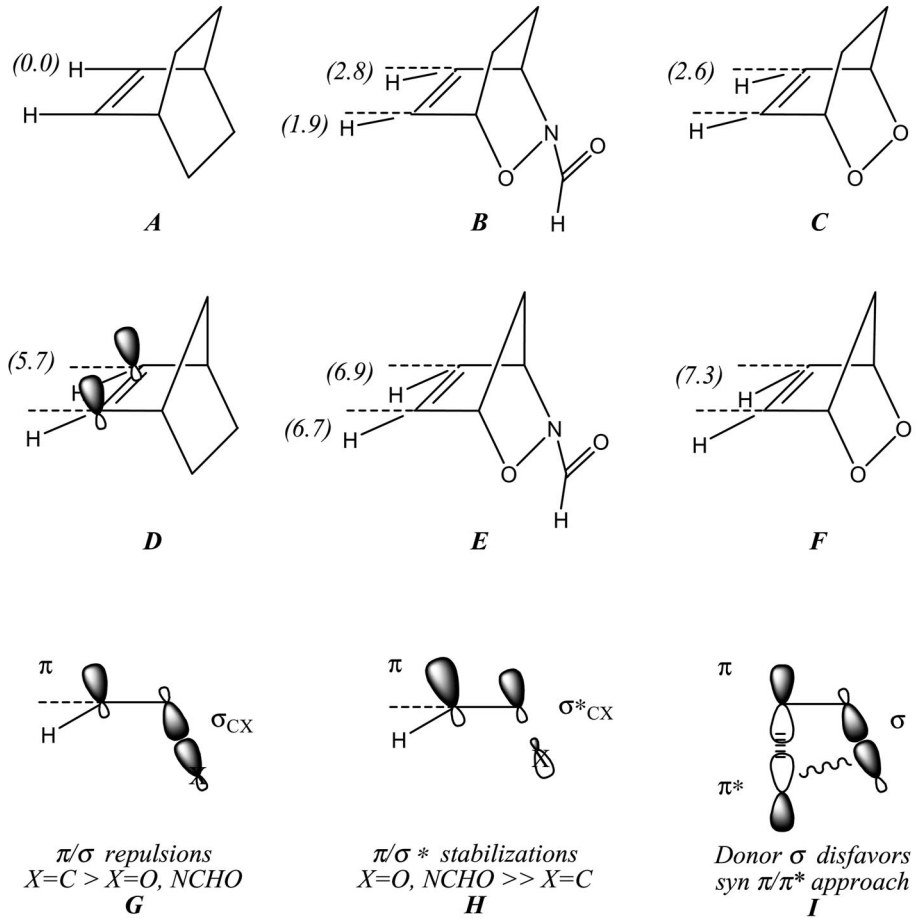


Figure 3. Pyramidalization of the double bond in 2-oxa-3-azabicyclo[2.2.2]oct-5-ene derivatives ***A***–***C*** and 2,3-oxazanorbornene derivatives ***D***–***F***. Effects of π/σ repulsions (***G***) and π/σ* stabilization (***H***) in the interaction of π and C–X fragments and expected changes upon variation of the X component. In the HOMO, π mixes in an allylic donor substituent σ in an antibonding fashion, disfavouring the *syn* approach of an incoming LUMO π* (***I***); the wavy line indicates unfavourable overlap between the addends.

plane tilting angles of the corresponding hydrogen atoms in degrees and gauge the pyramidalization of the double bonds of these dipolarophiles. For the sake of clarity orbital extensions of the π bond are shown only in the classical case of norbornene ***D***.

The tilting angles of the norbornene family ***D***–***F*** are the largest, and are larger by far than those of the bicyclo[2.2.2]-oct-5-ene family ***A***–***C***. Within the families, however, tilting angles increase similarly on going from the all-carbon species ***A*** and ***D*** to the heterosubstituted derivatives. The trend is consistent with the expected decrease in π/σ repulsion and a more effective increase in the π/σ* stabilization upon replacement of the dimethylene bridge with an hetero bridge.[30b]

The π bond pyramidalizes *anti* with respect to the allylic bond, to minimize π/σ repulsions and to maximize π/σ* stabilizations as shown in (***G***) and (***H***) of Figure 3. In the case of the bicyclo[2.2.2] family, the tilting effects of the two bridges are in opposition and only a modest pyramidalization ensues in ***B*** and ***D***, due to the larger influence of π/σ* interactions. In the norbornene family the allylic bonds of the methylene bridge are not properly aligned for interaction with the π bond and do not compensate the pyramidalization effects due to the two-membered bridges, giving rise to larger pyramidalizations due to the combined π/σ and π/σ* effects.

The pyramidalization of a double bond indicates the direction of the easier facial distortion of a dipolarophile in attaining the transition structure (TS) geometry.[30] In spite of the relatively small ground state pyramidalization, the energetic differences between the competing distortions become sizeable (1–2 kcal mol^{-1}) in TS geometries.[30b,30d] At variance with the classical norbornene case, however, the pyramidalization of the hetero-disubstituted bicyclo[2.2.2]-oct-5-enes ***B*** and ***C*** are quite small, and the effect on the facial distortion can readily be counteracted by effects due to intermolecular interactions (TS effects) as well as by electrostatic interaction and/or steric effects between the addends.

Among TS effects, the Cieplak effect[34] states that addition takes place *anti* to the best donor. In the case of the 2,3-dihetero bicyclo[2.2.2]oct-5-enes ***B*** and ***C***, the Cieplak effect thus predicts *syn* addition, which is opposite to what would be expected on the basis of pyramidalization.

Note that in frontier orbital terms the Cieplak effect corresponds to the disfavouring of the addition *syn* to the best donor, owing to the unfavourable overlap in the $HOMO_{(dipolarophile)}$–$LUMO_{(dipole)}$ interaction as shown in (**I**) in Figure 3. Thus, although the allylic donor substituent would appear to be less effective than the allylic acceptor substituent in determining the ground state geometry of the dipolarophile, the role of the allylic donor substituent increases in the TSs according to the Cieplak effect and may compensate for opposite facial ground state effects.

Electrostatic and steric interactions are also in opposition in these reactions. Electrostatic repulsion between the 1,3-dipole ends and the dipolarophile oxygen should favour *anti* attack, while the larger hindrance of the dimethylene bridge should favour *syn* attack. Apparently the various effects compensate remarkably in the case at hand. The cycloadditions take place both on the *exo* and *endo* faces and afford rather unselectively mixtures of the two regioisomeric cycloadducts **7a** and **7b** or **7c** and **7d**. Similar rather unselective cycloadditions have been reported for 2,3-dioxabicyclo[2.2.2]oct-5-ene.[31]

In analogy with the reactivity patterns of Diels–Alder (DA) reactions (normal, neutral and inverse),[35] the 1,3-dipolar cycloadditions of BNO belong to the "neutral" type, in which both of the two Frontier Orbital (FO) interactions are influential, giving rise to the characteristic U-shaped plots of the logarithms of the relative rates vs. the ionization potentials of the dipolarophiles.[19,36] In the cycloadditions between BNO and the *N*-formyl-2-oxa-3-azabicyclo derivatives ***B*** and ***E*** the two FO gaps between the addends are almost identical, as are the global electrophilicities ω (Table 4). The global electrophilicity index (ω)[37] has recently been shown to be a valuable descriptor for the assessment of the reactivity of DA[38] and 1,3-dipolar[39] cycloadditions, and the difference in the global electrophilicity index ($\Delta\omega$) of the diene/dienophiles or 1,3-dipole/dipolarophile interacting pairs is related to the polar character of the mechanism. The modest differences in $\Delta\omega$ in the cases at hand strongly support the occurrence of nonpolar cycloadditions.[39]

Table 4. B3LYP/6-31G* FO energies [eV], global electrophilicities ω [eV] and local Fukui functions[a] (in parentheses) in the cycloadditions between BNO and the 2-oxa-3-azabicyclo derivatives ***B*** and ***E***.

	E_{HOMO}	E_{LUMO}	ω
B	–7.45	–0.35	1.07
	(0.406, 0.403)[b]	(0.360, 0.341)[c]	
E	–7.45	–0.54	1.01
	(0.384, 0.362)[b]	(0.349, 0.337)[c]	
BNO	–6.34	–1.32	1.46

[a] C5 is the olefinic carbon proximal to N, and C6 is the distal one. [b] f_5^- and f_6^-. [c] f_5^+ and f_6^+.

Also given in Table 4 are the local Fukui functions[40] (f^- and f^+) for the C5 and C6 olefinic carbons of the 2-oxa-3-azabicyclo dipolarophiles. The local Fukui functions f^- allow identification of the most nucleophilic sites in electrophilic attacks, just like the HOMO coefficients, while functions f^+ indicate the most electrophilic sites, analogously to the LUMO coefficients.[37b] The local Fukui functions f_5^- and f_6^- for the two olefinic carbons are almost identical, and the same applies to the f_5^+ and f_6^+ values. The close values of the local Fukui functions of the dipolarophiles are highly consistent with the observed lack of regioselectivity in the reported cycloadditions.

Conclusions

We have clarified the complex course of 1,3-dipolar cycloaddition between benzonitrile oxide and the cyclohexadiene adduct **6** of (nitrosocarbonyl)benzene, which affords regioisomeric mixtures of *exo* and *endo* cycloadducts. The *exo* cycloadducts **7a** and **7b** are suitable starting materials for isoxazoline-cyclohexane nucleoside synthesis. Detachment of the benzoyl group and reductive cleavage of the N–O bond provided the stereodefined aminols **10a** and **10b**, which were used for the linear construction of purine nucleosides by well established synthetic protocols.[2] Substitution with 5-amino-4,6-dichloropyrimidine and subsequent condensation with orthoformates afford the chloropurines **12a** and **12b**. These were further derivatized by replacement of the chlorine with amines and alkoxides to give suitable samples for antiviral tests in very good yields.

Experimental Section

General: All melting points are uncorrected. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. IR spectra (Nujol mulls) were recorded on a Perkin–Elmer RX-1 FT-IR. ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 300 in the specified deuterated solvents. Chemical shifts are expressed in ppm from internal tetramethylsilane (δ). UV/Vis spectra were recorded on a Perkin–Elmer LAMBDA 16 UV spectrophotometer in acetonitrile as solvent. HPLC analyses were carried out with a WATERS 1525 instrument fitted with a UV 2487 detector (λ = 266 nm), both controlled by Breeze TM software, and a RP C-18 Intersil ODS-2 column; a mixture of H_2O/CH_3CN (60:40) was used as eluent. Column chromatography and tlc: silica gel 60 (0.063–0.200 mm, Merck); eluent cyclohexane/ethyl acetate from 9:1 to 5:5. The identification of samples from different experiments was confirmed by mixed mps and superimposable IR spectra.

Materials: Benzhydroximoyl chloride, the precursor of BNO,[41] was obtained by treatment of benzaldoxime with sodium hypochlorite.[42] 5-Amino-4,6-dichloropyrimidine was purchased from Sigma-Aldrich.

Cycloaddition between BNO and 3-Benzoyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (6): Benzonitrile oxide was generated in situ by dehydrohalogenation of benzhydroximoyl chloride with triethylamine.[41] A solution of benzhydroximoyl chloride (5 g, 32 mmol) in anhydrous DCM (20 mL) and triethylamine (5 mL, 1.1 equiv.) was added whilst stirring at 0 °C over a 0.5 h period to a stirred solution of the dipolarophile **6** (25 mmol) in the same solvent (100 mL). After the reaction mixture had been kept for 2 d at room

temp., the organic phase was washed twice with water and dried with Na_2SO_4. The filtrate was concentrated under reduced pressure, leaving a residue that was separated by column chromatography.

Cycloadduct 7a: 1.84 g (22%), m.p. 137–138 °C from benzene/*n*-hexane. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.66 and 2.17 (m, 1 H + 3 H, CH_2–CH_2), 4.43 (br., J = 11 Hz, 1 H, H4 isox.), 4.46 (br., 1 H, CH–O), 5.07 (br., 1 H, CH–N), 5.20 (br., J = 11, 5 Hz, 1 H, H5 isox.), 7.46 (m, 6 H, arom.), 7.74 (m, 4 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 18.7, 19.4, 45.1, 50.1, 71.8, 77.4, 126.7, 127.8, 127.9, 129.1, 129.4, 129.5, 130.7, 131.3, 133.0, 156.0 ppm. IR: $\tilde{\nu}$ = 1634 (C=O), 1580 (C=N) cm^{-1}. $C_{20}H_{18}O_3N_2$ (334.36): calcd. C 71.84, H 5.43, N 8.38; found C 74.8, H 5.4, N 8.4.

Cycloadduct 7b: 1.67 g (20%), m.p. 159–161 °C from benzene/*n*-hexane. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.61 and 2.19 (m, 1 H + 3 H, CH_2–CH_2), 4.44 (br., 1 H, H4 isox.), 4.65 (br., 1 H, CH–O), 5.10 (br., 1 H, CH–N), 5.25 (br., 1 H, H5 isox.), 7.46 (s, 6 H, arom.), 7.66 (m, 4 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 17.1, 21.3, 46.5, 50.9, 71.6, 78.4, 126.5, 128.0, 129.1, 130.7, 131.1, 155.8 ppm. IR: $\tilde{\nu}$ = 1635 (C=O), 1575 (C=N) cm^{-1}. $C_{20}H_{18}O_3N_2$ (334.36): calcd. C 71.84, H 5.43, N 8.38; found C 71.7, H 5.4, N 8.3.

Cycloadduct 7c: 1.67 g (20%), m.p. 178–180 °C from ethanol/acetone. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.78 (m, 2 H, CH_2), 2.28 (m, 2 H, CH_2), 3.98 and 4.14 (d, J = 11 Hz, 1 H, H4 isox.), 4.40 (br., 1 H, CH–O), 4.89 (br., J = 11 Hz, 1 H, H5 isox.), 5.10 (br., 1 H, CH–N), 7.37 (m, 6 H, arom.), 7.63 (m, 4 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 15.3, 16.9, 18.1, 26.2, 39.7, 46.4, 68.3, 74.5, 121.9, 123.2, 123.7, 124.0, 124.2, 124.3, 125.3, 125.6, 125.8, 128.4, 151.1, 163.1 ppm. IR: $\tilde{\nu}$ = 1623 (C=O), 1565 (C=N) cm^{-1}. $C_{20}H_{18}O_3N_2$ (334.36): calcd. C 71.84, H 5.43, N 8.38; found C 71.9, H 5.4, N 8.5.

Cycloadduct 7d: 1.25 g (15%), m.p. >215 °C (dec.) from ethanol/acetone. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.77 (m, 2 H, CH_2), 2.19 (m, 2 H, CH_2), 4.00 (d, J = 11.5 Hz, 1 H, H4 isox.), 4.44 (br., 1 H, CH–O), 4.67 and 5.10 (br., 1 H, CH–N), 4.92 and 5.10 (d, J = 11.5 Hz, 1 H, H5 isox.), 7.42 (m, 6 H, arom.), 7.64 (m, 4 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 19.0, 20.0, 23.0, 46.4, 51.6, 70.1, 78.6, 79.1, 126.8, 128.2, 128.9, 130.0, 130.2, 130.4, 155.6, 166.0 ppm. IR: $\tilde{\nu}$ = 1630 (C=O), 1601 (C=N) cm^{-1}. $C_{20}H_{18}O_3N_2$ (334.36): calcd. C 71.84, H 5.43, N 8.38; found C 71.7, H 5.3, N 8.3.

Alkaline Hydrolysis of the *N*-Benzoyl Adducts 7a and 7b: The *N*-benzoyl adducts **7a** and **7b** were deacylated by adding each adduct (6 mmol) to a stirred solution of NaOH (9 mmol) in methanol (80 mL). After storage overnight at room temp. the solutions were concentrated under reduced pressure and taken up with DCM, and the organic phases were washed three times with water and finally dried with Na_2SO_4. Evaporation of the solvent afforded oily residues of compounds **9a** and **9b**, which were crystallized from diisopropyl ether/ethanol.

Compound 9a: 1.38 g (100%), m.p. 150–151 °C from diisopropyl ether. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.61, 1.78 and 2.14 (m, 1 H + 1 H + 2 H, CH_2–CH_2), 3.47 (d, J = 2.0 Hz, 1 H, CH–N), 4.16 (m, J = 5.2 Hz, 1 H, CH–O), 4.25 (dd, J = 10.5, 2.0 Hz, 1 H, H4 isox.), 5.15 (dd, J = 10.5, 5.2 Hz, 1 H, H5 isox.), 7.44 (m, 3 H, arom.), 7.71 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 18.9, 21.1, 47.5, 50.6, 66.4, 78.1, 126.6, 128.5, 129.0, 130.3, 156.5 ppm. IR: $\tilde{\nu}$ = 3218 (NH) cm^{-1}. $C_{13}H_{14}O_2N_2$ (230.26): C 67.81, H 6.13, N 12.17; found C 67.7, H 6.1, N 12.0.

Compound 9b: 1.37 g (99%), m.p. 115–117 °C from diisopropyl ether. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.54, 1.98 and 2.16 (m, 1 H + 2 H + 1 H, CH_2–CH_2), 3.37 (m, J = 3.5 Hz, 1 H, CH–N), 4.28 (d, J = 2 Hz, 1 H, CH–O), 4.33 (dd, J = 11, 2 Hz, 1 H, H4 isox.), 5.15 (dd, J = 9.7, 3.5 Hz, 1 H, H5 isox.), 7.43 (m, 3 H, arom.), 7.68 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 18.1, 21.6, 48.5, 51.0, 66.1, 78.9, 126.6, 128.6, 128.9, 130.3, 156.4 ppm. IR: $\tilde{\nu}$ = 3203 (NH) cm^{-1}. $C_{13}H_{14}O_2N_2$ (230.26): C 67.81, H 6.13, N 12.17; found C 67.8, H 6.1, N 12.2.

Hydrogenolytic Cleavage of the Cyclic Hydroxylamines 9a and 9b: A solution of **9a** or **9b** (4 mmol) and Pd/C (10%, 0.3 g) in ethyl acetate (60 mL) absorbed 1 equiv. of hydrogen in 3 h. The catalyst was filtered off and the filtrate was evaporated under reduced pressure. Crystallization from ethanol afforded the aminol **10a** or **10b**.

Compound 10a: 0.85 g (92%), m.p. >200 °C from ethanol. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.62, 1.95 and 2.10 (m, 2 H + 1 H + 1 H, CH_2–CH_2), 3.33 (m, 1 H, CH–N), 3.71 (dd, J = 10.2 Hz, 1 H, H4 isox.), 4.18 (m, 1 H, CH–O), 4.90 (dd, J = 10, 3 Hz, 1 H, H5 isox.), 7.45 (m, 3 H, arom.), 7.70 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 23.1, 24.1, 45.5, 51.4, 63.9, 83.3, 126.9, 128.8, 129.0, 130.1, 159.0 ppm. IR: $\tilde{\nu}$ = 3345, 3257 (NH_2), 3108 (OH) cm^{-1}. $C_{13}H_{16}O_2N_2$ (232.27): C 67.22, H 6.94, N 12.06; found C 67.2, H 7.0, N 12.1.

Compound 10b: 0.92 g (99%), m.p. 106–109 °C from ethanol. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.64, 1.84 and 2.03 (m, 2 H + 1 H + 1 H, CH_2–CH_2), 3.67 (m, 1 H, CH–N), 3.96 (m, 1 H, CH–O), 4.03 (dt, J = 10, 2 Hz, 1 H, H4 isox.), 4.76 (dd, J = 10, 3 Hz, 1 H, H5 isox.), 7.44 (m, 3 H, arom.), 7.77 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 22.0, 23.7, 44.6, 52.4, 64.8, 83.0, 126.7, 128.4, 129.7, 158.6 ppm. IR: $\tilde{\nu}$ = 3322, 3264 (NH_2), 3176 (OH) cm^{-1}. $C_{13}H_{16}O_2N_2$ (232.27): C 67.22, H 6.94, N 12.06; found C 67.3, H 7.1, N 12.0.

Synthesis of the Pyrimidine Derivatives 11a and 11b: 5-Amino-4,6-dichloropyrimidine (8 mmol) and iPr$_2$NEt (20 mmol) were added to aminol **10a** or **10b** (4 mmol) dissolved in *n*BuOH (40 mL). The mixtures were heated at reflux at 117 °C with stirring for 48 h. The cooled solutions were evaporated to dryness, taken up in CH_2Cl_2, washed with water and dried with anhydrous Na_2SO_4. The crude residues were then subjected to column chromatography to separate the excess of amino-pyrimidine from adduct **11a** or **11b**.

Compound 11a: 1.27 g (88%), m.p. 143–145 °C from diisopropyl ether. ^{1}H NMR (300 MHz, CD_3COCD_3, 25 °C): δ = 1.61, 1.90 and 2.07 (m, 1 H + 2 H + 1 H, CH_2–CH_2), 3.90 (t, J = 8 Hz, 1 H, H4 isox.), 4.19 (d, J = 3 Hz, 1 H, CH–O), 4.35 (br. s, 1 H, OH), 4.46 (m, 1 H, CH–N), 4.52 (dd, J = 8, 5 Hz, 1 H, H5 isox.), 6.24 (d, J = 8 Hz, 1 H, NH), 7.30 (m, 3 H, arom.), 7.65 (s, 1 H, CH), 7.81 (m, 2 H, arom.) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3, 25 °C): δ = 25.1, 28.2, 50.1, 50.8, 65.4, 86.5, 124.2, 128.7, 129.4, 130.8, 131.2, 148.0, 153.5, 163.9 ppm. IR: $\tilde{\nu}$ = 3446, 3322 (NH_2), 3338 (NH), 3248 (OH), 1647 (C=N) cm^{-1}. $C_{17}H_{18}ClO_2N_5$ (359.80): C 56.75, H 5.04, N 19.47; found C 56.7, H 5.0, N 19.5.

Compound 11b: 1.40 g (97%), m.p. 155–157 °C from diisopropyl ether. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.78, 1.89 and 2.20 (m, 1 H + 1 H + 2 H, CH_2–CH_2), 3.40 (br. s, 1 H, OH), 3.81 (dd, J = 9, 4 Hz, 1 H, H4 isox.), 4.31 (dd, J = 10, 2 Hz, 1 H, CH–O), 4.76 (m, 1 H, CH–N), 4.83 (dd, J = 9, 4 Hz, 1 H, H5 isox.), 5.80 (d, J = 8 Hz, 1 H, NH), 7.47 (m, 3 H, arom.), 7.78 (m, 2 H, arom.), 8.12 (s, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 22.1, 25.7, 45.2, 51.8, 67.0, 78.7, 82.1, 121.8, 127.2, 128.2, 128.7, 128.8, 130.3, 149.6, 154.2, 159.9 ppm. IR: $\tilde{\nu}$ = 3403, 3100 (NH_2),

3304 (NH), 3192 (OH), 1642 (C=N) cm^{-1}. $C_{17}H_{18}ClO_2N_5$ (359.80): C 56.75, H 5.04, N 19.47; found C 56.8, H 5.0, N 19.4.

Construction of the Purine Nucleosides 12a and 12b: A catalytic amount of *p*TsOH was added to a solution of pyrimidine derivative **11a** or **11b** (1.50 mmol) in triethyl orthoformate (25 mL). The reaction mixture was stirred at room temp. for 8 d. After this period of time, the excess orthoformate was hydrolysed and the water phase was extracted with DCM. The dried organic phase was evaporated and the residue afforded the chloro-purine derivative **12a** or **12b**, which was recrystallized or possibly purified by column chromatography on silica gel by elution with $CHCl_3$.

Compound 12a: 0.49 g (88%), m.p. 199–201 °C from diisopropyl ether/ethanol. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.84, 2.15 and 2.79 (m, 2 H + 1 H + 1 H, CH_2–CH_2), 4.23 (dd, J = 10, 7 Hz, 1 H, H4 isox.), 4.46 (m, 1 H, CH–N), 4.56 (m, 1 H, CH–O), 4.62 (m, 1 H, H5 isox.), 7.01 (m, 3 H, arom.), 7.15 (m, 1 H, arom.), 7.44 (m, 1 H, arom.), 7.93 (s, 1 H, CH), 8.57 (s, 1 H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 24.6, 29.6, 49.7, 57.6, 64.2, 86.3, 127.6, 128.7, 129.1, 132.0, 132.7, 144.9, 152.3, 152.6, 153.0, 164.0 ppm. IR: $\tilde{\nu}$ = 3351 (OH), 1679 (C=N) cm^{-1}. $C_{18}H_{16}ClO_2N_5$ (369.80): C 58.46, H 4.36, N 18.94; found C 58.3, H 4.3, N 18.8.

Compound 12b: 0.50 g (90%), m.p. 193–194 °C from diisopropyl ether/ethanol. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.71, 1.98 and 2.77 (m, 4 H, CH_2–CH_2), 2.62 (s, 1 H, OH), 4.20 (dd, J = 9, 6 Hz, 1 H, H4 isox.), 4.52 (br. s, 1 H, CH–N), 4.64 (m, 1 H, CH–O), 5.38 (dd, J = 9, 7 Hz, H5 isox.), 7.50 (m, 3 H, arom.), 7.71 (m, 2 H, arom.), 8.28 (s, 1 H, CH–N), 8.82 (s, 1 H, CH–N) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.8, 28.7, 54.3, 56.5, 65.2, 80.8, 127.1, 127.3, 128.1, 128.9, 130.6, 133.5, 144.9, 151.4, 151.6, 159.5 ppm. IR: $\tilde{\nu}$ = 3517 (OH), 1662 (C=N) cm^{-1}. $C_{18}H_{16}ClO_2N_5$ (369.80): C 58.46, H 4.36, N 18.94; found C 58.4, H 4.3, N 19.9.

Syntheses of the Amino Derivatives 13a and 13b. General Method: Solutions of chloro-nucleosides **12a** or **12b** (0.08 mmol) in MeOH (2 mL) were saturated with the gaseous primary amines of choice and kept in sealed tubes at 50 °C for 24 h. In the case of liquid amines, an excess (50 equiv.) was added to the solutions. The solvent was evaporated and the residues were taken up with diisopropyl ether to crystallize the nucleoside derivatives **13a(A–E)** and **13b(A–E)**. Table 2 reports the physical constants and yields (determined by hplc analyses) of the products.

Compound 13aA: 18 mg (64%), m.p. 170–172 °C from diisopropyl ether. ^{1}H NMR (300 MHz, DMSO, 25 °C): δ = 1.53, 1.87 and 2.55 (m, 1 H + 2 H + 1 H, CH_2–CH_2), 4.19 (br., 1 H, H4 isox.), 4.30 (m, 1 H, CH–N), 4.44 (br., 2 H, NH_2), 4.47 (m, 1 H, CH–O), 5.37 (d, J = 3.6 Hz, 1 H, H5 isox.), 7.05 (m, 5 H, arom.), 7.92 (s, 1 H, CH–N), 8.01 (s, 1 H, CH–N) ppm. ^{13}C NMR (75 MHz, DMSO, 25 °C): δ = 23.6, 28.4, 46.7, 54.8, 61.7, 85.5, 118.9, 126.2, 127.9, 128.5, 129.8, 139.5, 149.0, 152.0, 155.8, 163.2 ppm. IR: $\tilde{\nu}$ = 3345 (OH), 3335 and 3185 (NH_2), 1646 (C=N) cm^{-1}. $C_{18}H_{18}O_2N_6$ (350.37): C 61.70, H 5.18, N 23.99; found C 61.6, H 5.2, N 24.0.

Compound 13aB: 24 mg (82%), m.p. 134–137 °C from diisopropyl ether. ^{1}H NMR (CD_3COCD_3): δ = 2.06 (d, J = 6 Hz, 3 H, CH_3–NH), 1.67, 2.01 and 2.80 (m, 1 H + 2 H + 1 H, CH_2–CH_2), 4.38 (m, 1 H + 1 H, CH-N and H4 isox.), 4.57 (m, 1 H + 1 H, CH–O and H5 isox.), 6.99 (m, 3 H, arom.), 7.14 (m, 2 H, arom.), 7.85 (s, 1 H, CH–N), 8.15 (s, 1 H, CH–N) ppm. ^{13}C NMR (CD_3COCD_3): δ = 23.6, 25.0, 30.7, 48.5, 57.1, 63.7, 87.1, 127.7, 129.2, 130.4, 130.9, 140.4, 153.5, 164.5 ppm. IR: $\tilde{\nu}$ = 3221 (OH), 1629 (C=N) cm^{-1}. $C_{19}H_{20}O_2N_6$ (364.40): C 62.62, H 5.53, N 23.06; found C 62.6, H 5.5, N 23.0.

Compound 13aC: 21 mg (68%), m.p. 176–177 °C from diisopropyl ether. ^{1}H NMR (CD_3COCD_3): δ = 0.66 (m, 2 H, cPr), 0.80 (m, 2 H, cPr), 1.68 and 2.09 (m, 4 H, CH_2–CH_2), 2.82 (m, 1 H, CH–N, cPr), 3.11 (br. s, 1 H, OH), 4.37 (m, 2 H, CH–N and H4 isox.), 4.54 (m, 2 H, H5 isox. and CHO), 6.69 (br. s, 1 H, NH), 6.98 (m, 3 H, arom.), 7.12 (m, 2 H, arom.), 7.79 (s, 1 H, CH), 8.17 (s, 1 H, CH) ppm. ^{13}C NMR (CD_3COCD_3): δ = 7.7, 24.9, 30.5, 48.5, 57.1, 63.9, 87.1, 127.7, 129.2, 134.0, 139.0, 145.0, 153.4, 164.5 ppm. IR: $\tilde{\nu}$ = 3217 (OH), 1618 (C=N) cm^{-1}. $C_{21}H_{22}O_2N_6$ (390.43): C 64.60, H 5.68, N 21.53; found C 64.6, H 5.7, N 21.5.

Compound 13aD: 20 mg (57%), m.p. 198–200 °C from diisopropyl ether. H NMR (CD_3COCD_3): δ = 1.68, 1.97 and 2.80 (m, 1 H + 2 H + 1 H, CH_2–CH_2), 4.37 (m, 1 H + 1 H, CH–N and H4 isox.), 4.50 (m, 1 H + 1 H, CH–O and H5 isox.), 4.87 (br. s, 2 H, CH_2Ph), 6.9–7.6 (m, 10 H, arom.), 7.92 (s, 1 H, CH–N), 8.11 (s, 1 H, CH–N) ppm. ^{13}C NMR (CD_3COCD_3): δ = 24.9, 44.3, 48.7, 51.3, 56.9, 63.7, 87.1, 127.6, 128.0, 128.6, 129.1, 129.3, 129.5, 129.7, 129.8, 129.9, 130.0, 130.1, 130.4, 130.7, 130.9, 131.6, 140.6, 141.6, 153.4, 164.5 ppm. IR: $\tilde{\nu}$ = 3185 (OH), 1623 (C=N) cm^{-1}. $C_{25}H_{24}O_2N_6$ (440.49): C 68.16, H 5.49, N 19.08; found C 68.2, H 5.5, N 19.1.

Compound 13aE: 16 mg (50%), thick oil. ^{1}H NMR (300 MHz, CD_3COCD_3, 25 °C): δ = 1.22 (t, J = 7 Hz, 6 H, CH_3), 1.70, 2.02 and 2.75 (m, 1 H + 2 H + 1 H, CH_2–CH_2), 3.94 (br., 4 H, CH_2–N), 4.36 (br., 1 H, H4 isox.), 4.40–4.52 (m, 3 H, CH–N + CH–O + H5 isox.), 6.98 (m, 2 H, arom.), 7.12 (m, 3 H, arom.), 7.81 (s, 1 H, CH–N), 8.09 (s, 1 H, CH–N) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3, 25 °C): δ = 14.4, 24.9, 30.0, 43.9, 48.9, 56.9, 64.1, 87.2, 127.8, 129.2, 130.6, 130.8, 139.3, 153.0, 164.6 ppm. IR: $\tilde{\nu}$ = 3538 (OH), 1705 (C=N) cm^{-1}. $C_{22}H_{26}O_2N_6$ (406.48): C 65.00, H 6.45, N 20.68; found C 65.2, H 6.5, N 21.0.

Compound 13bA: 15 mg (52%), m.p. > 200 °C (dec.) from methanol. ^{1}H NMR (300 MHz, DMSO, 25 °C): δ = 1.45, 1.66 and 2.35 (m, 1 H + 2 H + 1 H, CH_2–CH_2), 4.13 (m, 2 H, OH and H4 isox.), 4.49 (m, 1 H, CH–N), 5.25 (d, J = 4 Hz, 1 H, CH–O), 5.44 (t, J = 8.5 Hz, 1 H, H5 isox.), 7.25 (s, 2 H, NH_2), 7.52 (m, 3 H, arom.), 7.69 (m, 2 H, arom.), 8.17 (s, 1 H, CH–N), 8.27 (s, 1 H, CH–N) ppm. ^{13}C NMR (75 MHz, DMSO, 25 °C): δ = 22.2, 28.5, 53.9, 54.4, 63.8, 80.0, 127.0, 128.3, 128.6, 129.7, 139.9, 148.8, 148.9, 151.9, 155.7, 159.7 ppm. IR: $\tilde{\nu}$ = 3425 (OH), 3324 and 3160 (NH_2), 1669 (C=N) cm^{-1}. $C_{18}H_{18}O_2N_6$ (350.37): C 61.70, H 5.18, N 23.99; found C 62.0, H 5.2, N 23.7.

Compound 13bB: 24 mg (82%), m.p. 137–139 °C from diisopropyl ether. ^{1}H NMR (CD_3COCD_3): δ = 1.58, 1.83 and 2.66 (m, 1 H + 2 H + 1 H, CH_2–CH_2), 2.10 (d, J = 6 Hz, 3 H, CH_3NH), 4.24 (dd, J = 9, 3 Hz, 1 H, H4 isox.), 4.37 (m, 1 H, CH–N), 4.64 (m, 1 H, CH–O), 5.53 (dd, J = 9, 8 Hz, 1 H, H5 isox.), 7.51 (m, 3 H, arom.), 7.78 (m, 2 H, arom.), 8.14 (s, 1 H, CH–N), 8.29 (s, 1 H, CH–N) ppm. ^{13}C NMR (CD_3COCD_3): δ = 23.9, 28.7, 30.2, 55.8, 56.7, 66.2, 82.3, 128.8, 129.9, 130.9, 131.2, 142.2, 153.7, 161.4 ppm. IR: $\tilde{\nu}$ = 3411 (OH), 1652 (C=N) cm^{-1}. $C_{19}H_{20}O_2N_6$ (364.40): C 62.62, H 5.53, N 23.06; found C 62.6, H 5.5, N 23.1.

Compound 13bC: 25 mg (81%), m.p. >200 °C from diisopropyl ether. ^{1}H NMR (CD_3COCD_3): δ = 0.71, 0.82 and 0.88 (m, 1 H + 2 H + 1 H, cPr), 1.55, 1.83 and 2.40 (m, 1 H + 2 H + 1 H, CH_2–CH_2), 2.69 (m, 1 H, CH–N, cPr), 4.27 (dd, J = 9, 2 Hz, 1 H, H4 isox.), 4.37 (m, 1 H, CH–N), 4.64 (m, 1 H, CH–O), 5.53 (dd, J = 9, 8 Hz, 1 H, H5 isox.), 7.51 (m, 3 H, arom.), 7.79 (m, 2 H, arom.), 8.18 (s, 1 H, CH–N), 8.31 (s, 1 H, CH–N) ppm. ^{13}C NMR (CD_3COCD_3): δ = 6.1, 6.2, 22.6, 54.4, 55.4, 64.8, 80.9, 119.8, 127.5, 128.5, 129.5, 129.8, 140.0, 152.2, 155.2, 160.0 ppm. IR: $\tilde{\nu}$ = 3375 (OH), 1628 (C=N) cm^{-1}. $C_{21}H_{22}O_2N_6$ (390.43): C 64.60, H 5.68, N 21.53; found C 64.5, H 5.6, N 21.5.

Compound 13bD: 26 mg (75%), m.p. 80–82 °C from diisopropyl ether. ^{1}H NMR (CD_3COCD_3): δ = 1.60, 1.85 and 2.70 (m, 1 H + 2 H + 1 H, CH_2–CH_2), 4.21 (dd, 1 H, J = 9, 4 Hz, H4 isox.), 4.37 (m, 1 H, CH–N), 4.43 (s, 2 H, CH_2Ph), 4.65 (m, 1 H, CH–O), 5.52 (dd, 1 H, J = 9, 8 Hz, H5 isox.), 7.34 (m, 4 H, arom.), 7.51 (m, 4 H, arom.), 7.76 (m, 2 H, arom.), 8.15 (s, 1 H, CH–N), 8.28 (s, 1 H, CH–N) ppm. ^{13}C NMR (CD_3COCD_3): δ = 23.9, 44.5, 55.8, 55.9, 56.8, 66.2, 82.2, 127.3, 128.0, 128.7, 128.8, 128.9, 129.3, 129.5, 129.9, 130.9, 131.2, 141.5, 142.6, 153.6, 167.8 ppm. IR: $\tilde{\nu}$ = 3300 (OH), 1618 (C=N) cm^{-1}. $C_{25}H_{24}O_2N_6$ (440.49): C 68.16, H 5.49, N 19.08; found C 68.2, H 5.5, N 19.1.

Compound 13bE: 28 mg (87%), m.p. 125–127 °C from diisopropyl ether. ^{1}H NMR (300 MHz, CD_3COCD_3, 25 °C): δ = 1.28 (t, J = 7 Hz, 3 H, CH_3), 1.39 (t, J = 7 Hz, 3 H, CH_3), 1.61, 1.84 and 2.67 (m, 1 H + 2 H + 1 H, CH_2–CH_2), 2.84 (s, 2 H, CH_2–N), 3.07 (q, J = 7 Hz, 2 H, CH_2–N), 4.05 (br. s, 1 H, OH), 4.23 (dd, J = 9, 4 Hz, 1 H, H4 isox.), 4.37 (m, 1 H, CH–N), 4.67 (m, 1 H, CH–O), 5.54 (dd, J = 9, 8 Hz, 1 H, H5 isox.), 7.51 (m, 3 H, arom.), 7.78 (m, 2 H, arom.), 8.16 (s, 1 H, CH–N), 8.24 (s, 1 H, CH–N) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3, 25 °C): δ = 11.8, 14.3, 23.9, 43.1, 43.8, 55.8, 56.4, 66.4, 82.3, 121.2, 128.8, 129.9, 130.9, 131.2, 140.1, 151.9, 153.1, 155.0, 161.4 ppm. IR: $\tilde{\nu}$ = 3382 (OH), 1584 (C=N) cm^{-1}. $C_{22}H_{26}O_2N_6$ (406.48): C 65.00, H 6.45, N 20.68; found C 65.1, H 6.4, N 21.1.

Syntheses of the Methoxy Derivatives 13aF and 13bF. General Method: A MeO^-Na^+/MeOH solution (4.5 M, 5 equiv.) was added with stirring to a solution of chloro-nucleosides **12a** or **12b** (0.03 mmol) in MeOH (5 mL) and the mixture was left at room temperature for 36 h. After this period of time, the reaction was quenched by addition of an equiv. volume of water. The methanol was evaporated at reduced pressure and the water phase was extracted twice with DCM and the organic phase was dried with Na_2SO_4. On evaporation of the DCM a solid residue was obtained and was recrystallized from diisopropyl ether to afford the methoxy derivative **13aF** or **13bF**. Table 2 reports the physical constants and yields of the products.

Compound 13aF: 9 mg (80%), m.p. > 200 °C (dec.) from diisopropyl ether. ^{1}H NMR (300 MHz, CD_3COCD_3, 25 °C): δ = 1.74 and 2.07 (m, 1 H + 3 H, CH_2–CH_2), 4.08 (s, 3 H, OCH_3), 2.77 (br., 1 H, H4 isox.), 4.38 (m, 1 H, CH–N), 4.50 (m, 1 H + 1 H, CH–O and OH), 4.55 (m, 1 H, H5 isox.), 6.96 (m, 2 H, arom.), 7.11 (m, 3 H, arom.), 8.11 (s, 1 H, CH–N), 8.33 (s, 1 H, CH–N) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3, 25 °C): δ = 24.9, 49.0, 54.6, 57.2, 63.8, 87.1, 127.7, 129.3, 130.4, 131.0, 143.0, 152.4, 164.4 ppm. IR: $\tilde{\nu}$ = 3276 (OH), 1606 (C=N) cm^{-1}. $C_{19}H_{19}O_3N_5$ (365.38): C 62.45, H 5.24, N 19.17; found C 62.3, H 5.2, N 19.1.

Compound 13bF: 10 mg (91%), m.p. > 200 °C (dec.) from diisopropyl ether. ^{1}H NMR (300 MHz, CD_3COCD_3, 25 °C): δ = 1.64, 1.85 and 2.80 (m, 1 H + 2 H + 1 H, CH_2–CH_2), 4.16 (s, 3 H, CH_3–O), 4.58 (dd, J = 8, 3 Hz, 1 H, H4 isox.), 4.42 (m, 1 H, CH–N), 4.73 (m, 1 H, CH–O), 5.54 (dd, J = 8, 7 Hz, 1 H, H5 isox.), 7.52 (m, 3 H, arom.), 7.77 (m, 2 H, arom.), 8.36 (s, 1 H, CH–N), 8.53 (s, 1 H, CH–N) ppm. ^{13}C NMR (75 MHz, CD_3COCD_3, 25 °C): δ = 23.8, 54.6, 55.9, 62.8, 65.5, 82.2, 98.8, 121.6, 128.8, 129.9, 130.9, 131.3, 144.0, 145.5, 152.6, 158.4, 179.2 ppm. IR: $\tilde{\nu}$ = 3359 (OH), 1598 (C=N) cm^{-1}. $C_{19}H_{19}O_3N_5$ (365.38): C 62.45, H 5.24, N 19.17; found C 62.4, H 5.3, N 19.1.

Crystal Structure Determinations: The crystals of the compounds **7c**, **7d** and **12a**, utilized for the X-ray studies, were colourless prisms obtained by crystallization from the reported solvents. Accurate unit dimensions for both structures were obtained by least-squares treatment of 2θ values for 25 reflections measured on a single-crystal Enraf Nonius CAD4 computer-controlled diffractometer with graphite-monochromated Mo-K_α radiation at the Centro Grandi Strumenti at the University of Pavia. Lorentz polarization and absorption correction[43] were applied. The approximate thermal factors[44] were 3.32, 2.58 and 3.065 Å^2 for compounds **7c**, **7d** and **12a**, respectively. Non-hydrogen atoms were found by direct methods SIR–92[45] and difference Fourier syntheses. The structures were refined by block-matrix least-squares with use of SHELXL–93.[45] The positions of hydrogen atoms were determined from a final difference Fourier map. and refined isotropically.

CCDC-650553 (for **7c**), -650554 (for **7d**) and -650555 (for **12a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): Crystallographic data and bond lengths, angles and torsion angles of cycloadducts **7c**, **7d** and **12a**. Conformational analyses of crystal structures.

Acknowledgments

Financial support by the University of Pavia (Fondo d'Ateneo per la Ricerca, FAR) and the Ministero dell'Università e Ricerca (MiUR, PRIN 2005) is gratefully acknowledged. Thanks are due to Dr. Massimo Boiocchi (Centro Grandi Strumenti, CGS) for the X-ray data collection.

[1] a) W. Hnang, M. J. Miller, E. De Clercq, J. Balzarini, *Org. Biomol. Chem.* **2007**, *5*, 1164–1166; b) A. Piperno, M. A. Chiacchio, D. Iannazzo, R. Romeo, *Curr. Med. Chem.* **2006**, *13*, 3675–3695; c) C. McGuigan, A. Hassan-Abdallah, S. Srinivasan, Y. Wang, A. Siddiqui, S. M. Daluge, K. S. Gudmundsson, H. Zhou, E. W. McLean, J. P. Peckham, T. C. Burnette, H. Marr, R. Hazen, L. D. Condreay, L. Johnson, J. Balzarini, *J. Med. Chem.* **2006**, *49*, 7215–7226; d) M. X.-W. Jiang, B. Jin, J. L. Gage, A. Priour, G. Savela, M. J. Miller, *J. Org. Chem.* **2006**, *71*, 4164–4169; e) L. S. Jeong, J. A. Lee, *Antiviral Chem. Chemother.* **2004**, *15*, 235–250; f) P. Merino, *Curr. Med. Chem.* **2002**, *1*, 389–411; g) J. N. Martin, R. C. F. Jones, *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Eds.: A. Padwa, W. H. Pearson), John Wiley & Sons, Hoboken, NJ, **2003**, pp. 1–81; h) Y. Mizuno, *The Organic Chemistry of Nucleic Acids*, Kadansha LTD, Tokyo, **1986**; i) T. Ueda, *Chemistry of Nucleosides and Nucleotides* (Ed.: L. B. Townsend), Plenum Press, New York, **1988**, vol. 1, chapter 1; j) P. C. Srivasta, R. K. Robins, R. B. Meyer Jr, *Chemistry of Nucleosides and Nucleotides* (Ed.: L. B. Townsend), Plenum Press, New York, **1988**, vol. 1, chapter 2; k) G. R. Revenkar, R. K. Robins, *Chemistry of Nucleosides and Nucleotides* (Ed.: L. B. Townsend), Plenum Press, New York, **1988**, vol. 2, chapter 4.

[2] P. Quadrelli, R. Scrocchi, P. Caramella, A. Rescifina, A. Piperno, *Tetrahedron* **2004**, *60*, 3643–3651.

[3] a) G. W. Kirby, *Chem. Soc. Rev.* **1977**, *6*, 1–24; b) P. F. Vogt, M. J. Miller, *Tetrahedron* **1998**, *54*, 1317–1348; c) L. Boger, S. M. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic Press, San Diego, CA, U.S.A., **1987**.

[4] a) P. Quadrelli, A. Gamba Invernizzi, P. Caramella, *Tetrahedron Lett.* **1996**, *37*, 1909–1996; b) P. Quadrelli, M. Mella, A. Gamba Invernizzi, P. Caramella, *Tetrahedron* **1999**, *55*, 10497–10510.

[5] a) P. Quadrelli, M. Mella, P. Paganoni, P. Caramella, *Eur. J. Org. Chem.* **2000**, 2613–2620; b) P. Quadrelli, V. Fassardi, A.

Cardarelli, P. Caramella, *Eur. J. Org. Chem.* **2002**, 2058–2065.
[6] J. Wang, M. Froeyen, P. Herdewijn, *Adv. Antiviral Drug Des.* **2004**, *4*, 119–145.
[7] a) K. Barral, P. Halfon, G. Pepe, M. Camplo, *Tetrahedron Lett.* **2002**, *43*, 81–84; b) V. Nair, G. S. Buenger, *J. Org. Chem.* **1990**, *55*, 3695–3697.
[8] a) P. Herdewijn, E. De Clercq, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1591–1597; b) J. Wang, M. Froeyen, C. Hendrix, G. Andrei, R. Snoeck, E. De Clercq, P. Herdewijn, *J. Med. Chem.* **2000**, *43*, 736–745.
[9] J. Wang, M. Froeyen, C. Hendrix, G. Andrei, R. Snoeck, E. De Clercq, P. Herdeweijn, *J. Med. Chem.* **2000**, *43*, 736–745.
[10] D. Cremer, K. J. Szabo, *Conformational Behaviour of Six-Membered Rings*, VCH Publishers, New York, **1995**, pp. 59–135.
[11] a) K. Barral, J. Courcambeck, G. Pépe, J. Balzarini, J. Neyts, E. De Clercq, M. Camplo, *J. Med. Chem.* **2005**, *48*, 450–456; b) J. Wang, J. Morral, C. Hendrix, P. Herdewijn, *J. Org. Chem.* **2001**, *66*, 8478–8482; c) M. J. Pérez-Pérez, J. Rozenski, R. Busson, P. Herdewijn, *J. Org. Chem.* **1995**, *60*, 1531–1537.
[12] a) Å. Rosenquist, I. Kvarnström, B. Classon, B. Samuelsson, *J. Org. Chem.* **1996**, *61*, 6282–6288; b) M. J. Konkel, R. Vince, *Tetrahedron* **1996**, *52*, 799–808; c) M. J. Konkel, R. Vince, *Tetrahedron* **1996**, *52*, 8969–8978; d) K. Ramesh, M. S. Wolfe, Y. Lee, D. Vander Velde, R. T. Borchardt, *J. Org. Chem.* **1992**, *57*, 5861–5868; e) M. J. Konkel, R. Vince, *Nucleosides Nucleotides* **1995**, *14*, 2061–2077; f) J. H. Arango, A. Geer, P. E. Rodriguez, P. E. Young, P. Scheiner, *Nucleosides Nucleotides* **1993**, *12*, 773–784.
[13] N. Katagiri, Y. Ito, T. Shiraishi, T. Maruyama, Y. Sato, C. Kaneko, *Nucleosides Nucleotides* **1996**, *15*, 631–647.
[14] a) B. V. Joshi, H. R. Moon, J. C. Fettinger, V. E. Marquez, K. A. Jacobson, *J. Org. Chem.* **2005**, *70*, 439–447; b) B. K. Chun, S. Olgen, J. H. Hong, M. G. Newton, C. K. Chu, *J. Org. Chem.* **2000**, *65*, 685–693; c) V. E. Marquez, P. Russ, R. Alonso, M. A. Siddiqui, S. Hernandez, C. George, M. C. Nicklaus, F. Dai, H. Ford Jr, *Helv. Chim. Acta* **1999**, *82*, 2119–2129; d) J. H. Hong, B. K. Chun, C. K. Chu, *Tetrahedron Lett.* **1998**, *39*, 225–228.
[15] R. Alibes, A. Alvarez-Larena, P. de March, M. Figueredo, J. Font, T. Parella, A. Rustullet, *Org. Lett.* **2006**, *8*, 491–494.
[16] M. D. Garcia, O. Caamaño, F. Fernandez, X. Garcia-Mera, I. Perez-Castro, *Synthesis* **2006**, 3967–3972.
[17] P. Quadrelli, N. Vazquez Martinez, B. Bovio, M. Mella, A. Piccanello, P. Caramella, *Tetrahedron* **2006**, *62*, 7370–7379.
[18] a) Y. Kitade, H. Kojima, F. Zulfiqur, H. S. Kim, Y. Wataya, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3963–3965; b) N. G. Ramesh, A. J. H. Klunder, B. Zwanenburg, *J. Org. Chem.* **1999**, *64*, 3635–3641; c) J. Wu, S. W. Schneller, K. L. Seley, E. De Clerq, *Heterocycles* **1998**, *47*, 757–763; d) S. M. Siddiqui, M. Raissian, E. Schneller, S. Ikeda, R. Snoeck, G. Andrei, J. Balzarini, E. De Clerq, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 663–666; e) A. D. Da Silva, E. S. Coimbra, J. L. Fourrey, A. S. Machado, M. Robert-Gero, *Tetrahedron Lett.* **1993**, *34*, 6745–6748; f) M. Koga, S. W. Schneller, *Tetrahedron Lett.* **1990**, *31*, 5861–5864.
[19] P. Caramella, P. Grünanger, *1,3-Dipolar Cycloaddition Chemistry* (Eds.: A. Padwa), John Wiley & Sons, New York, **1984**, vol. 1, 291–392.
[20] P. Grünanger, P. Vita Finzi, *Isoxazoles*, John Wiley & Sons, New York, **1999**, vol. 2, pp. 739–827.
[21] D. A. Brown, W. K. Glass, R. Mageswaran, S. A. Mohammed, *Magn. Reson. Chem.* **1991**, *29*, 40–45.
[22] W. E. Stewart, T. H. Siddal, *Chem. Rev.* **1970**, *70*, 517–551.
[23] A. G. Palmer III, J. Cavanagh, P. E. Wright, M. Rance, *J. Magn. Reson.* **1991**, *93*, 151–170.
[24] H. Friebolin *Basic One- and Two-Dimensional NMR Spectroscopy*, Wiley-VCH, Weinheim, 3rd ed., pp. 89–93, **1998**.
[25] a) B. Bovio, P. Caramella, P. Quadrelli, *J. Mol. Struct.* **2005**, *743*, 135–143; b) B. Bovio, P. Caramella, P. Quadrelli, *J. Mol. Struct.* **2005**, *743*, 135–143.
[26] J. Weiser, O. Golan, L. Fitjer, S. E. Biali, *J. Org. Chem.* **1996**, *61*, 8277–8284.
[27] a) M. Ishikura, A. Murakami, N. Katagiri, *Org. Biomol. Chem.* **2003**, *1*, 452–453; b) S. Daluge, R. Vince, *J. Org. Chem.* **1978**, *43*, 2311–2320; c) N. Katagiri, Y. Yamatoya, M. Ishikura, *Tetrahedron Lett.* **1999**, *40*, 9069–9072; d) C. T. Evans, S. M. Roberts, K. A. Shoben, A. G. Sutherland, *J. Chem. Soc. Perkin Trans. 1* **1992**, 589–592.
[28] D. Salvatori, R. Volpini, S. Vicenzetti, A. Vita, S. Costanzi, C. Lambertucci, G. Cristalli, S. Vittori, *Bioorg. Med. Chem.* **2002**, *10*, 2973–2980.
[29] O. Exner, *Correlation Analysis in Chemistry* (Eds.: N. B. Chapman, J. Shorter), Plenum, London, **1978**, chapter 10.
[30] a) G. Mehta, J. Chandrasekhar, *Chem. Rev.* **1999**, *99*, 1437–1467; b) N. G. Rondan, M. N. Paddon-Row, P. Caramella, K. N. Houk, *J. Am. Chem. Soc.* **1981**, *103*, 2436–2438; c) P. Caramella, N. G. Rondan, M. N. Paddon-Row, K. N. Houk, N. G. Rondan, F. K. Brown, W. L. Jorgensen, J. D. Madura, D. C. Spellmeyer, *J. Am. Chem. Soc.* **1983**, *105*, 5980–5988; d) J. Spanget-Larsen, R. Gleiter, *Tetrahedron* **1983**, *39*, 3345–3350; e) D. Seebach, T. Maetzke, W. Petter, B. Klötzer, D. A. Plattner, *J. Am. Chem. Soc.* **1991**, *113*, 1781–1786.
[31] a) R. Gandolfi, G. Tonoletti, A. Rastelli, M. Bagatti, *J. Org. Chem.* **1993**, *58*, 6038–6048; b) A. Rastelli, M. Burdisso, R. Gandolfi, *J. Phys. Org. Chem.* **1990**, *3*, 159–173.
[32] M. C. Holthausen, W. Koch, *J. Phys. Chem.* **1993**, *97*, 10021–10027.
[33] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, Revision B.02, Gaussian, Inc., Pittsburgh PA, **2003**.
[34] a) A. S. Cieplak, B. D. Tait, C. R. Johnson, *J. Am. Chem. Soc.* **1989**, *111*, 8447–8462; b) H. Li, W. J. le Noble, *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 199–210; c) A. S. Cieplak, *Chem. Rev.* **1999**, *99*, 1265–1336; d) M. Kaselj, W.-S. Chung, W. J. le Noble, *Chem. Rev.* **1999**, *99*, 1387–1413; e) K. Ohkata, Y. Tamura, B. B. Shetuni, R. Takagi, W. Miyanaga, S. Kojima, L. A. Paquette, *J. Am. Chem. Soc.* **2004**, *126*, 16783–16792 and references cited therein.
[35] a) J. Sauer, R. Sustmann, *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 779–807; b) W. Oppolzer, in *Comprehensive Organic Synthesis* (Eds.: L. A. Paquette), Pergamon Press, Oxford, **1991**, vol. 5, pp. 315–399.
[36] K. Bast, M. Christl, R. Huisgen, W. Mack, *Chem. Ber.* **1973**, *106*, 3312–3320.
[37] a) P. K. Chattaraj, U. Sarkar, D. R. Roy, *Chem. Rev.* **2006**, *106*, 2065–2091; b) D. H. Ess, G. O. Jones, K. N. Houk, *Adv. Synth. Catal.* **2006**, *348*, 2337–2361.
[38] L. R. Domingo, M. J. Aurell, P. Perez, R. Contreras, *Tetrahedron* **2002**, *58*, 4417–4423.
[39] a) P. Perez, L. R. Domingo, M. J. Aurell, R. Contreras, *Tetrahedron* **2003**, *59*, 3117–3125; b) M. J. Aurell, L. R. Domingo, P. Perez, R. Contreras, *Tetrahedron* **2004**, *60*, 11503–11509.

[40] a) R. Contreras, P. Fuentealba, M. Galvan, P. Perez, *Chem. Phys. Lett.* **1999**, *304*, 405–413; b) P. Fuentealba, P. Perez, R. Contreras, *J. Chem. Phys.* **2000**, *113*, 2544–2551.
[41] C. Grundmann, P. Grünanger, *The Nitrile Oxides* Springer-Verlag, Heidelberg, **1971**.
[42] A. Corsico Coda, G. Tacconi, *Gazz. Chim. Ital.* **1984**, *114*, 131–132.
[43] A. C. T. North, D. C. Phillips, F. C. Scott-Mathews, *Acta Crystallogr., Sect. A* **1968**, *24*, 351–359.
[44] A. J. C. Wilson, *Nature* **1942**, *150*, 151–152.
[45] G. M. Sheldrick, *SHELXL–93*. Program for the refinement of crystal structures, Germany, University of Göttingen.

Received: June 20, 2007
Published Online: October 25, 2007

