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Tetrahedron 60 (2004) 441–448
Tetrahedron

Diastereoselective synthesis of homo-*N*,*O*-nucleosides

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Received 29 July 2003; revised 6 November 2003; accepted 6 November 2003

Abstract—A new class of homo-*N*,*O*-nucleosides has been designed, based on the 1,3-dipolar cycloaddition of *C*-substituted nitrones with allyl nucleobases. The *N*-methyl-*C*-ethoxycarbonyl nitrone **1**, and the *C*-α-silyloxymethyl-*N*-methyl nitrone **7** have been exploited: the stereochemical features of the obtained nucleosides are dependent on the nature of the dipole. The results obtained with DFT calculations fully agree with the experimental results and successfully reproduce the experimentally observed reversal of *endo*/*exo* selectivity for nitrones **1** and **7**.

1. Introduction

Structural modifications at the level of the sugar moiety and/or the heterocyclic base in nucleosides have long been recognized to improve their antiviral or anticancer activities: in this context, the synthesis of nucleoside analogues has recently received a great deal of attention.[1]

In natural nucleosides, which possess a *N*-glycosidic linkage, the presence of an anomeric centre is one of the most important factors which contribute to the conformational behaviour of the nucleoside and, hence, to its biological features.[2] The physiological properties, in fact, may change dramatically if the anomeric aminal function is removed from the nucleoside: when replacing, for example, the furanose ring by a carbocyclic five membered ring, the biological activity changes drastically.[3] Another way of removing the anomeric centre is the introduction of a carbon bridge between the base and the carbohydrate part, leading to homo-*N*-nucleosides. In this case, besides an increased resistance to hydrolytic or enzymatic cleavage, compared to the relatively reactive aminal linkage of common nucleosides, more conformational flexibility and rotational freedom is introduced in the molecule.[4] In oligonucleotides composed of these modified nucleosides, the distance between the backbone and base moiety is increased; this feature allows a lowering of the electrostatic repulsion by maintaining the ability to build Watson–Crick base pairs with unnatural DNA or RNA strain, due to a better alignment of complementary nucleobases.[5]

Accordingly, different synthetic approaches towards 1′-homo-*C*- and *N*-nucleosides and the relative biological evaluation as antiviral or antiproliferative agents have been reported in literature. In particular, homo-*N*-nucleosides with a guanine or adenine base moiety exhibit a good antiviral activity against herpes simplex virus[6] (HSV-1 and HSV-2): the analogous uracil homo-*N*-nucleosides have been described as selective inhibitors of viral uracil-DNA glycosylases (UDGs), while having little effect on the human enzyme.[7] Moreover, also the 1′-*C*-azanucleosides have proved very valuable as sequence-specific glycosidase inhibitors and thus as potentially effective anti-HIV drugs.[8]

Recently, we have focused our attention on the synthesis of new classes of modified nucleosides where the sugar moiety has been replaced by an isoxazolidine ring: some of the new *N*,*O*-nucleosides have been shown to possess interesting biological activities.[9]

In this context, as many glycosidases may recognize different glycon moieties and differ only with the type of glycosidic linkage,[10] we have envisaged to synthesize a series of 1′-homo-*N*-nucleosides, in which the sugar unit has been changed into an isoxazolidine ring and the formal insertion of a carbon bridge into the glycosidic bond lengthens the separation between the nucleobase and the heterocyclic system. Thus, we report in this paper the design

Keywords: *N*-methyl-*C*-ethoxycarbonyl nitrone; *C*-α-silyloxymethyl-*N*-methyl nitrone; Nucleobases.
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doi:10.1016/j.tet.2003.11.007

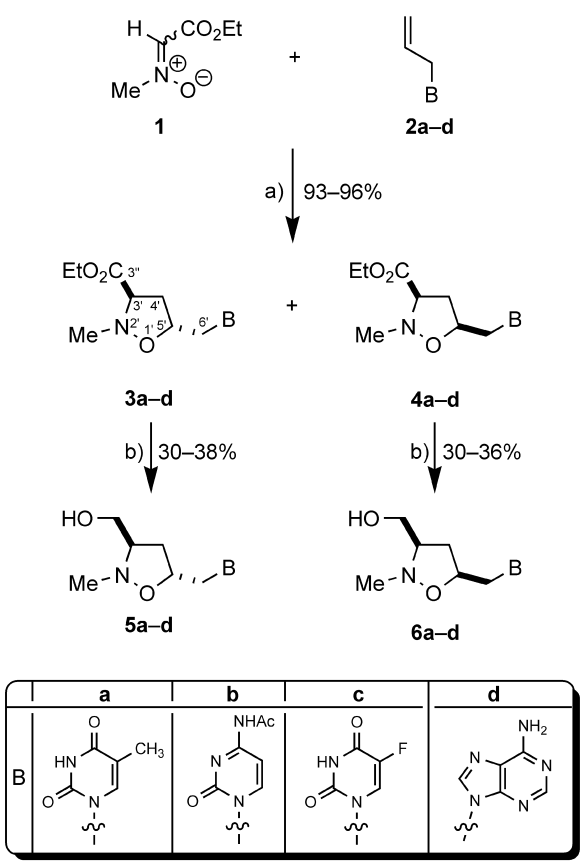
and the synthesis of a new class of {[3-(hydroxymethyl)-2-methylisoxazolidin-5-yl]methyl}-pyrimidine and purine derivatives in an effort to develop specific glycosidase inhibitors.

2. Results and discussion

The cycloaddition reaction between *N*-methyl-*C*-ethoxycarbonyl nitrone **1** (*E*/*Z* ratio 4:1)[9c] and allyl nucleobases **2** proceeded smoothly in anhydrous toluene, at 80 °C for 14 h, to give a mixture of epimeric isoxazolidines **3** and **4** in ca. 2:1 ratio and 93–96% yield (Table 1), which were separated by flash chromatography (Scheme 1, Table 1).

Table 1. Cycloaddition of nitrone **1** and allylbases **2**

Entry	Allylbase	Isoxazolidines	**3**:**4** ratio	Yield (%)
1	**2a**	**3a** and **4a**	2.1:1	96
2	**2b**	**3b** and **4b**	2.2:1	95
3	**2c**	**3c** and **4c**	2.0:1	95
4	**2d**	**3d** and **4d**	1.8:1	93



Scheme 1. (a) Toluene, sealed tube, 80 °C, 1 h; (b) $LiAlH_4$, THF, 0 °C, 1 h.

Structural determinations were performed with the aid of NOE experiments. Thus, for the major 3′,5′-*anti* isomers **3a**–**d**, irradiation of $H_{5'}$ induced a positive NOE effect on $H_{4'b}$, the downfield resonance of methylene protons at $C_{4'}$, while irradiation of $H_{3'}$ gave rise to NOE enhancement for $H_{4'a}$. These results are clearly indicative of a *trans* relationship between $H_{3'}$ and $H_{5'}$ (Fig. 1).

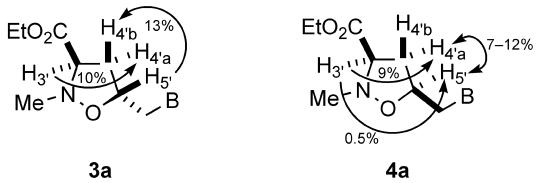


Figure 1. Selected NOEs observed for compounds **3a** and **4a**.

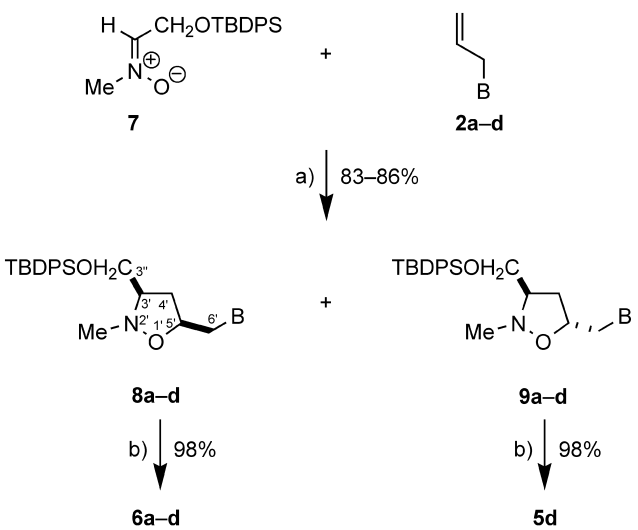
Conversely, in derivatives **4**, the positive NOE correlation between $H_{3'}$ and $H_{5'}$ confirms the *cis* topological arrangement between these protons.

The synthetic scheme was completed by reduction of the ester moiety. A series of different reducing agents have been exploited; the best results have been performed by treatment with $LiAlH_4$ in anhydrous THF to afford the target nucleosides **5** (α) and **6** (β) in moderate yields (~35%) (Scheme 1).

The designed reaction route appears to be versatile and of general application; however, serious limitations are represented by the low yields, due to the difficult reduction of ester groups, and by the obtainment of α isomers as major adducts. We have, however, achieved a successful implementation of the synthetic strategy by the use of nitrone **7**, containing a silyl ether in place of the ester as a masked alcohol functionality.

C-α-silyloxymethyl-*N*-methyl nitrone **7** was prepared in good yields starting from D-mannitol, as previously reported.[10]

The cycloaddition reaction of **7** with allyl nucleobases **2** (Scheme 2), in anhydrous THF at room temperature for 24 h, has been found to proceed with a good stereoselectivity, affording a mixture of epimeric isoxazolidines **8a**–**c** and **9a**–**c** in a relative ratio ca. 7:1 (Table 2, entries 1–3). In the case of allyladenine **2d**, only a moderate stereoselectivity is obtained with the formation of **8d** and **9d** in a 2:1 ratio (Table 2, entry 4).



Scheme 2. (a) Toluene (THF for **2d**), sealed tube, 80 °C, 24 h; (b) TBAF, THF, rt, 1 h

Table 2. Cycloaddition of nitrone **7** and allylbases **2**

Entry	Allylbase	Isoxazolidines	**8**:**9** ratio	Yield (%)
1	**2a**	**8a** and **9a**	7.1:1	85
2	**2b**	**8b** and **9b**	7.0:1	83
3	**2c**	**8c** and **9c**	7.2:1	86
4	**2d**	**8d** and **9d**	2:1	83

The crude mixtures were purified by flash chromatography (chloroform/methanol 95:5 as eluent) and cycloadducts **8a**–**d**, the major products, and **9d** were obtained in pure form.

The structure of the obtained adducts has been assigned on the basis of ^{1}H NMR data and confirmed by NOE experiments. Thus, products **8** show the resonance of $H_{3'}$ as a multiplet in the range 2.77–2.90 ppm; $H_{4'}$ protons give rise to two doublets of doublets centered at 1.75–1.87 and 2.56–2.68 ppm, while $H_{5'}$ resonate as a multiplet at 4.23–4.40 ppm. The methylene group at $C_{5'}$ resonate as two doublets of doublets in the range 3.20–4.10 ppm. In compound **9d**, the resonance of $H_{4'}$ protons appears at 1.98 and 2.76 ppm, respectively, as a doublet of doublets of doublets, whereas $H_{3'}$ appears at 2.88 ppm as a doublet of doublets of doublets of doublets and $H_{5'}$ resonates as a multiplet at 4.20 ppm.

The stereochemistry of the adducts was readily deduced by means of NOE measurements (Fig. 2). In compounds **8a**, chosen as model compound, irradiation of $H_{5'}$ produced strong enhancements for the methylene protons at $C_{5'}$ (2.2%) and $H_{4'b}$ (20%); conversely, when $H_{4'b}$ was irradiated, a positive NOE effect was observed for $H_{5'}$ (8%), $H_{4'a}$ (15%) and $H_{3'}$ (8%). These data support a *cis* relationship between $H_{4'b}$, $H_{3'}$ and $H_{5'}$. In compound **9d**, irradiation of $H_{3'}$ produced a positive NOE effect, together with $H_{4'b}$ (9.3%) and the methylene protons at $C_{3'}$ (6.4%), also with the methylene protons at $C_{6'}$ (1.8%) so indicating a *cis* relationship between $H_{3'}$ and the methylene group at $C_{5'}$.

In the previously reported cycloaddition reaction of *C*-ethoxycarbonyl-*N*-methyl nitrone **1** with the same dipolarophiles **2**, a worse diastereoselectivity had been obtained: isoxazolidines **3** and **4** were obtained in a relative ratio 2:1 (Scheme 1). The stereochemical outcome obtained in the cycloaddition process of nitrone **7** can be explained by considering that **7** has been shown by ^{1}H NMR and NOE data to be the *Z*-isomer;[11] thus, the major products **8a**–**d**

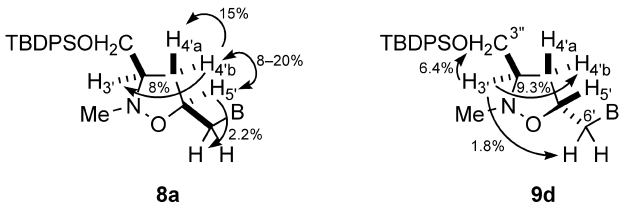


Figure 2. Selected NOEs observed for compounds **8a** and **9d**.

could be formed by the *Z* nitrone reacting in an *exo* mode, according to the results reported for similar α-alkoxy-alkylnitrones.[12]

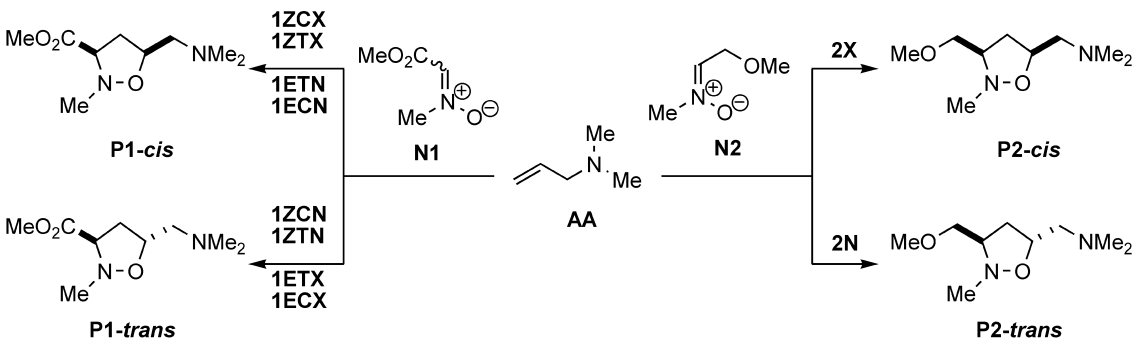
The subsequent removal of the silyl group by treatment of derivatives **8a**–**d** with TBAF afforded β-nucleosides **6a**–**c** in good global yields (71–74%), while the yield for **6d** was 54% (Scheme 2).

3. Theoretical study

In order to assess the importance of electronic and steric effects in the outcome of the cycloaddition reactions of nitrones **1** and **7** with allylbases **2**, we carried out a DFT investigation. We aimed to clarify which is the reactive isomer of nitrone **1** in this reaction[13] and to rationalize the experimentally observed differences in *endo*/*exo* (*cis*/*trans*) selectivities[14] for nitrones **1** and **7**.

Geometry optimizations of the stationery points (reactants, transition structures and products) were carried out by using the B3LYP[15] functional with the 6-31G(d) basis set.[16] All transition structures were found to have only one negative eigenvalue with the corresponding eigenvector involving the formation of the newly created C–C and C–O bonds. Vibrational frequencies were calculated (1 atm, 298.15 K) for all B3LYP/6-31G(d) optimized structures and used unscaled, to compute ZPVE and activation energies. All calculations were performed using the Gaussian 03 revision B.01 suite of programs.[17]

Simplified models were defined to avoid excessively lengthy calculations. Nitrones **N1** and **N2** were considered suitable models for nitrones **1** and **7**, respectively, and *N*,*N*-dimethyl allylamine (**AA**) was chosen to represent the allylbase. Due to its configurational instability the nitrone **N1** could, in principle, react as the corresponding *E*- or *Z*-isomers. In addition, *cisoid* and *transoid* conformations



Scheme 3.

should be considered because of their close values in energy.[13] So, we have evaluated, for the cycloaddition between **N1** and **AA**, a total of eight transition states (*E*/*Z* isomers, *cisoid*/*transoid* conformers and *endo*/*exo* approaches) leading to the 3,5-disubstituted isoxazolidines **P1**-*cis* and **P1**-*trans* (Scheme 3).

For the cycloaddition between **N2** and **AA** the *endo* and *exo* approaches leading to the 3,5-disubstituted isoxazolidines **P2**-*trans* and **P2**-*cis* were studied. The transition states are named as follows: the number indicates the nitrone, i.e. **1** for **N1** and **2** for **N2**, the first letter indicates the nitrone isomer (*Z* or *E*). Then it is added C for a *cisoid* conformation and T for a *transoid* conformation; finally we used N and X for *endo* and *exo* approaches, respectively. For instance, **1ETN** corresponds to the transition state of the reaction between the *E*-isomer in a *transoid* conformation of **N1** and **AA** through an *endo* approach leading to **P1**-*cis*. For the transition states corresponding to the reactions of **N2**, **2N** correspond to the *endo* transition state and **2X** to the *exo* one.

The optimized geometries and the lengths of forming bonds of the more stable transition states for each cycloaddition are displayed in Figure 3. The values of total and relative energies for the different stationary points are given in Table 3. All reactions showed to be exothermic (in terms of enthalpy) in the range of −19.2 to −23.5 kcal/mol, the most stable products being the *trans* isomers.

For the reaction between **N1** and **AA**, clearly the most favoured approach is the *E*-*exo* one.[18] The lowest energy value correspond to transition structure **1ECX**, predicting the preferential formation of **P1**-*trans*. These results are in agreement with the experimental observations described in Table 1.

For the reaction between **N2** and **AA**, the calculated activation energies predict the formation of the *cis* adduct **P2**-*cis* as the major product. The differences in energy

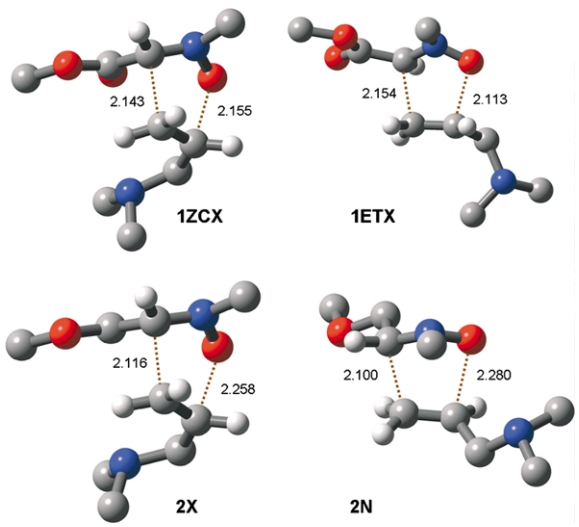


Figure 3. Optimized geometries at B3LYP/6-31G(d) level for the most favoured transition structures leading to **P1**-*cis*, **P1**-*trans*, **P2**-*cis* and **P2**-*trans*. Some hydrogen atoms have been omitted for clarity. Distances of forming bonds are given in angstroms.

Table 3. B3LYP/6-31G(d) electronic energies (*G*), free energies (*E*) and relative values (ΔE and ΔG) for the stationary points of the reactions between **AA** and nitrones **N1** and **N2**

	E[a]	ΔE[b]	G[a]	ΔG[b]
s-cis (E)-**N1**	−436.875858		−436.909646	
s-trans (E)-**N1**	−436.870147		−436.904864	
s-cis (Z)-**N1**	−436.869533		−436.903599	
s-trans (Z)-**N1**	−436.869637		−436.903709	
N2	−362.811582		−362.844905	
AA	−251.711773		−251.742859	
1ZCN	−688.550731	23.16[c]	−688.594505	36.40[c]
1ZCX	−688.556165	19.75[c]	−688.599393	33.33[c]
1ECN	−688.556064	19.81[c]	−688.600376	32.71[c]
1ECX	−688.562154	15.99[c]	−688.606713	28.73[c]
1ZTN	−688.550634	23.22[c]	−688.594788	36.22[c]
1ZTX	−688.554816	20.59[c]	−688.599180	33.46[c]
1ETN	−688.552037	22.34[c]	−688.596081	35.41[c]
1ETX	−688.557936	18.63[c]	−688.602782	31.20[c]
2N	−614.490789	20.44[d]	−614.533699	33.93[d]
2X	−614.494573	18.06[d]	−614.537473	31.56[d]
P1-*cis*	−688.616775	−18.29[c]	−688.661713	−5.78[c]
P1-*trans*	−688.617209	−18.56[c]	−688.661822	−5.85[c]
P2-*cis*	−614.558353	−21.96[d]	−614.601821	−8.32[d]
P2-*trans*	−614.558528	−22.07[d]	−614.601015	−8.82[d]

[a] Hartrees.
[b] kcal/mol.
[c] Referred to *s-cis (E)*-**N1**+**AA**.
[d] Referred to **N2**+**AA**.

barriers between *endo* and *exo* approaches for these reaction agree very well with the experimentally observed ratio reported in Table 2. Also, for this reaction the *trans* product is the most stable. So, it can be assumed that the reaction is kinetically controlled, although the differences between energies of **P2**-*cis* and **P2**-*trans*, not differing enough from the calculation errors, are not decisive. The higher inverse barriers when compared with the direct one makes that the reaction cannot be considered as a reversible process.

According to the calculations, the *cis*/*trans* selectivity observed for the reaction of **AA** with nitrone **N1** is due to the equilibrium between *E*- and *Z*-isomers, since in all cases the *exo* approach is favoured with respect to the *endo* one. The preferential formation of the *trans* isomer is caused by the higher reactivity of the *E*-isomer as inferred from the energy differences between optimized transition structures. With nitrone **N2**, which exists only as the *Z*-isomer, also the *exo* approach is clearly favoured and, in consequence, the reaction is more selective giving rise preferentially to the *cis* isomer.

4. Conclusions

In conclusion, a versatile approach towards a new class of homo-*N*,*O*-nucleosides has been designed, based on the 1,3-dipolar cycloaddition of *C*-substituted nitrones with allyl nucleobases. Two different nitrones have been exploited: the stereochemical features of the obtained nucleosides are dependent on the nature of the dipole. While the configurationally unstable nitrone **1** affords 2:1 mixtures in which the α isomer is predominant, the *Z* nitrone **7** leads preferentially to β-isomers with a good level of selectivity, 7:1. Only in the case of the allylbase **2d** a lower 2:1 selectivity was observed. The results obtained with DFT

calculations fully agree with the experimental results and successfully reproduce the experimentally observed reversal of *endo*/*exo* selectivity for nitrones **1** and **7**. In the case of nitrone **1** the *E*-isomer is showed to be more reactive than the *Z*-isomer.

5. Experimental

5.1. General information

Melting points were measured on a Kofler apparatus and are uncorrected. ^{1}H NMR spectra were measured on a 500 MHz Varian Unity Inova instrument in $CDCl_3$ as solvent. Chemical shifts are in ppm (δ) from TMS as internal standard. NOE difference spectra were obtained by subtracting alternatively right-off-resonance free induction decays (FIDS) from right-on-resonance-induced FIDS. IR spectra were recorded using an FTIR-8300 (Shimadzu) spectrophotometer. MS spectra were measured with a JEOL JMS-D 300 spectrometer. Elemental analyses were performed on a Perkin–Elmer 240B microanalyzer. Merck silica gel 60H was used for preparative short-column chromatography. Allyl nucleobases **2**–**5** have been prepared as reported in literature.[19]

5.2. Preparation of *N*,*O*-nucleosides 3 and 4

General procedure. A solution of nitrone **1** (1.31 g, 10 mmol) and allylnucleobase (10 mmol) in anhydrous toluene (20 mL) in sealed tube was heated at 80 °C for 14 h. The reaction mixture was evaporated and the residue purified by flash chromatography (chloroform/methanol 98:2) to give isoxazolidines **3** and **4**.

5.2.1. Reaction of nitrone 1 with allylthymine 2a. First eluted product was ethyl (3*RS*,5*RS*)-2-methyl-5-[(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl]isoxazolidine-3-carboxylate **3a**. (65.0%, 1.93 g), colourless sticky oil; δ_H (500 MHz, $CDCl_3$) 1.26 (t, 3H, *J*=6.6 Hz), 1.89 (d, 3H, *J*=0.9 Hz), 2.30 (m, 1H, $H_{4'a}$), 2.65 (m, 1H, $H_{4'b}$), 2.77 (s, 3H, *N*–CH_3), 3.40 (m, 1H, $H_{3'}$), 3.80 (dd, 1H, $H_{6'a}$, *J*=5.7, 14.5 Hz), 4.06 (dd, 1H, $H_{6'b}$, *J*=5.9, 14.5 Hz), 4.20 (q, 2H, *J*=6.6 Hz), 4.40 (m, 1H, $H_{5'}$), 7.16 (q, 1H, H_6, *J*=0.9 Hz), 10.10 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 12.1, 18.8, 35.6, 42.5, 49.4, 61.4, 69.5, 76.1, 94.4, 110.3, 141.2, 151.2, 179.5. Anal. calcd for $C_{13}H_{19}N_3O_5$: C, 52.52; H, 6.44; N, 14.13. Found: C, 52.44; H, 6.42; N, 14.15. Exact mass calculated for $C_{13}H_{19}N_3O_5$: 297.1325. Found: 297.1323.

Second eluted compound was ethyl (3*RS*,5*SR*)-2-methyl-5-[(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl]isoxazolidine-3-carboxylate **4a**. (31.0%, 920 mg), colourless sticky oil; δ_H (500 MHz, $CDCl_3$) 1.28 (t, 3H, *J*=6.6 Hz), 1.87 (d, 3H, *J*=1.0 Hz), 2.30 (m, 1H, $H_{4'a}$), 2.75 (m, 1H, $H_{4'b}$), 2.74 (s, 3H, *N*–CH_3), 3.45 (m, 1H, $H_{3'}$), 4.12 (dd, 1H, $H_{6'a}$, *J*=3.5, 15.0 Hz), 4.19 (dd, 1H, $H_{6'b}$, *J*=2.5, 15.0 Hz), 4.22 (q, 2H, *J*=6.6 Hz), 4.45 (m, 1H, $H_{5'}$), 7.24 (q, 1H, H_6, *J*=1.0 Hz), 9.95 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 13.9, 19.1, 35.4, 44.4, 50.3, 61.5, 68.8, 76.9, 101.3, 109.8, 142.1, 151.3, 170.2. Anal. calcd for $C_{13}H_{19}N_3O_5$: C, 52.52; H, 6.44; N, 14.13. Found: C, 52.39; H, 6.46; N, 14.17. Exact mass calculated for $C_{13}H_{19}N_3O_5$: 297.1325. Found: 297.1322.

5.2.2. Reaction of nitrone 1 with allyl-*N*-acetylcytosine 2b. First eluted product was ethyl (3*RS*,5*RS*)-5-{[4-(acetylamino)-2-oxopyrimidin-1(2*H*)-yl]methyl}-2-methylisoxazolidine-3-carboxylate **3b**. (65.3%, 2.11 g), light yellow sticky oil; δ_H (500 MHz, $CDCl_3$) 1.20 (t, 3H, *J*=7.1 Hz), 2.20 (ddd, 1H, $H_{4'a}$, *J*=7.7, 8.7, 13.1 Hz), 2.22 (s, 3H, CH_3), 2.59 (ddd, 1H, $H_{4'b}$, *J*=6.1, 7.6, 13.1 Hz), 2.70 (s, 3H, *N*–CH_3), 3.25 (dd, 1H, $H_{3'}$, *J*=6.1, 8.7 Hz), 3.88 (dd, 1H, $H_{6'a}$, *J*=5.5, 14.0 Hz), 4.13 (q, 2H, *J*=7.1 Hz), 4.20 (dd, 1H, $H_{6'b}$, *J*=2.8, 14.0 Hz), 4.38 (dddd, 1H, $H_{5'}$, *J*=2.8, 5.5, 7.6 and 7.7 Hz), 7.36 (d, 1H, H_5, *J*=7.2 Hz), 7.64 (d, 1H, H_6, *J*=7.2 Hz), 10.42 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 13.9, 24.6, 35.4, 44.5, 51.4, 61.3, 68.5, 74.8, 96.6, 149.8, 156.0, 163.0, 169.5, 171.3. Anal. calcd for $C_{14}H_{20}N_4O_5$: C, 51.85; H, 6.22; N, 17.27. Found: C, 52.05; H, 6.23; N, 17.21. Exact mass calculated for $C_{14}H_{20}N_4O_5$: 324.1433. Found: 324.1430.

Second eluted compound was ethyl (3*RS*,5*SR*)-5-{[4-(acetylamino)-2-oxopyrimidin-1(2*H*)-yl]methyl}-2-methylisoxazolidine-3-carboxylate **4b**. (29.7%, 962 mg), colourless sticky oil; δ_H (500 MHz, $CDCl_3$) 1.22 (t, 3H, *J*=7.1 Hz), 2.21 (ddd, 1H, $H_{4'a}$, *J*=6.3, 8.5, 13.2 Hz), 2.28 (s, 3H, CH_3), 2.78 (s, 3H, *N*–CH_3), 2.79 (ddd, 1H, $H_{4'b}$, *J*=5.0, 7.5, 13.2 Hz), 3.33 (dd, 1H, $H_{3'}$, *J*=5.0, 6.3 Hz), 3.95 (dd, 1H, $H_{6'a}$, *J*=5.0, 11.3 Hz), 4.20 (q, 2H, *J*=7.1 Hz), 4.30 (dd, 1H, $H_{6'b}$, *J*=1.5, 11.3 Hz), 4.45 (dddd, 1H, $H_{5'}$, *J*=1.5, 5.0, 7.5, 8.5 Hz), 7.38 (d, 1H, H_5, *J*=7.2 Hz), 7.45 (d, 1H, H_6, *J*=7.1 Hz), 10.10 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 12.9, 25.0, 36.4, 44.5, 52.1, 61.5, 67.8, 74.8, 96.7, 150.0, 156.1, 162.9, 170.5, 171.8. Anal. calcd for $C_{14}H_{20}N_4O_5$: C, 51.85; H, 6.22; N, 17.27. Found: C, 51.71; H, 6.19; N, 17.31. Exact mass calculated for $C_{14}H_{20}N_4O_5$: 324.1433. Found: 324.1435.

5.2.3. Reaction of nitrone 1 with allyl-5-fluorouracil 2c. First eluted product was ethyl (3*RS*,5*RS*)-5-[(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl]-2-methylisoxazolidine-3-carboxylate **3c**. (63.4%, 1.91 g), light yellow sticky oil; δ_H (500 MHz, $CDCl_3$) 1.32 (t, 3H, *J*=7.1 Hz), 2.29 (m, 1H, $H_{4'a}$), 2.75 (m, 1H, $H_{4'b}$), 2.77 (s, 3H, *N*–CH_3), 3.49 (dd, 1H, $H_{3'}$, *J*=8.7, 9.3 Hz), 3.68 (dd, 1H, $H_{6'a}$, *J*=9.3, 14.2 Hz), 4.13 (dd, 1H, $H_{6'b}$, *J*=2.5, 14.2 Hz), 4.23 (q, 2H, *J*=7.1 Hz), 4.43 (m, 1H, $H_{5'}$), 7.43 (d, 1H, H_6, *J*=5.8 Hz), 10.45 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 14.4, 35.7, 44.5, 50.7, 62.1, 69.2, 74.7, 101.7, 130.9, 141.9, 150.1, 170.5. Anal. calcd for $C_{12}H_{16}N_3O_5F$: C, 47.84; H, 5.35; N, 13.95. Found: C, 48.01; H, 5.36; N, 13.93. Exact mass calculated for $C_{12}H_{16}N_3O_5F$: 301.1074. Found: 301.1072.

Second eluted compound was ethyl (3*RS*,5*SR*)-5-[(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)methyl]-2-methylisoxazolidine-3-carboxylate **4c**. (31.6%, 952 mg), light yellow sticky oil; δ_H (500 MHz, $CDCl_3$) 1.36 (t, 3H, *J*=7.1 Hz), 2.33 (m, 1H, $H_{4'a}$), 2.78 (m, 1H, $H_{4'b}$), 2.84 (s, 3H, *N*–CH_3), 3.40 (m, 1H, $H_{3'}$), 3.70 (dd, 1H, $H_{6'a}$, *J*=7.1, 15.1 Hz), 4.18 (dd, 1H, $H_{6'b}$, *J*=2.5, 15.1 Hz), 4.26 (q, 2H, *J*=7.1 Hz), 4.45 (m, 1H, $H_{5'}$), 7.45 (d, 1H, H_6, *J*=5.8 Hz), 10.50 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 18.2, 35.9, 46.5,

47.2, 62.1, 69.5, 74.7, 101.3, 129.0, 141.9, 150.1, 170.5. Anal. calcd for $C_{12}H_{16}N_3O_5F$: C, 47.84; H, 5.35; N, 13.95. Found: C, 47.90; H, 5.36; N, 13.91. Exact mass calculated for $C_{12}H_{16}N_3O_5F$: 301.1074. Found: 301.1073.

5.2.4. Reaction of nitrone 1 with allyladenine 2d. First eluted product was ethyl (3*RS*,5*RS*)-5-[(6-amino-9*H*-purin-9-yl)methyl]-2-methylisoxazolidine-3-carboxylate **3d**. (59.8%, 1.83 g), light yellow sticky oil; δ_H (500 MHz, $CDCl_3$) 1.30 (t, 3H, *J*=7.1 Hz), 2.18 (ddd, 1H, $H_{4'a}$, *J*=7.2, 9.1, 15.0 Hz), 2.73 (ddd, 1H, $H_{4'b}$, *J*=7.1, 8.1, 15.0 Hz), 2.76 (s, 3H, *N*–CH_3), 3.15 (dd, 1H, $H_{3'}$, *J*=8.1, 9.1 Hz), 4.18 (q, 2H, *J*=7.1 Hz), 4.40 (m, 2H, $H_{6'}$), 4.48 (m, 1H, $H_{5'}$), 6.42 (bs, 2H, NH_2), 7.96 (s, 1H, H_3), 8.35 (s, 1H, H_8); δ_C (125 MHz, $CDCl_3$) 13.9, 35.5, 44.5, 46.0, 61.5, 74.6, 76.6, 118.9, 135.3, 153.0, 155.7, 156.0, 169.5. Anal. calcd for $C_{13}H_{18}N_6O_3$: C, 50.97; H, 5.92; N, 27.43. Found: C, 50.80; H, 5.91; N, 27.47. Exact mass calculated for $C_{13}H_{18}N_6O_3$: 306.1440. Found: 306.1443.

Second eluted compound was ethyl (3*RS*,5*SR*)-5-[(6-amino-9*H*-purin-9-yl)methyl]-2-methylisoxazolidine-3-carboxylate **4d**. (33.2%, 1.01 g), light yellow sticky oil; δ_H (500 MHz, $CDCl_3$) 1.25 (t, 3H, *J*=7.1 Hz), 2.35 (ddd, 1H, $H_{4'a}$, *J*=5.8, 9.10, 15.2 Hz), 2.77 (s, 3H, *N*–CH_3), 2.78 (m, 1H, $H_{4'b}$), 3.42 (dd, 1H, $H_{3'}$, *J*=6.5, 9.1 Hz), 4.21 (q, 2H, *J*=7.1 Hz), 4.19 (m, 2H, $H_{6'}$), 4.55 (m, 1H, $H_{5'}$), 6.42 (bs, 2H, NH_2), 7.94 (s, 1H, H_3), 8.33 (s, 1H, H_8); δ_C (125 MHz, $CDCl_3$) 13.9, 35.4, 45.0, 44.9, 61.5, 69.0, 75.3, 118.9, 135.5, 152.9, 155.7, 156.0, 169.5. Anal. calcd for $C_{13}H_{18}N_6O_3$: C, 50.97; H, 5.92; N, 27.43. Found: C, 50.79; H, 5.94; N, 27.46. Exact mass calculated for $C_{13}H_{18}N_6O_3$: 306.1440. Found: 306.1444.

5.3. Preparation of *N*,*O*-nucleosides 5 and 6 from 3 and 4

General procedure. To a solution of nucleosides **3** and **4** (1 mmol) in anhydrous THF (20 mL), at 0 °C, $LiAlH_4$ (60.0 mg, 1.5 mmol) was added and the mixture was stirred for 1 h. At the end of this time, the solvent was removed and the residue was subjected to column chromatography on neutral alumina (chloroform/methanol 95:5).

5.3.1. Reaction of 3a with $LiAlH_4$. 1-{[(3*RS*,5*RS*)-3-(Hydroxymethyl)-2-methylisoxazolidin-5-yl]methyl}-5-methylpyrimidine-2,4(1*H*,3*H*)-dione **5a**. (38.0%, 57 mg), colourless sticky oil; δ_H (500 MHz, $CDCl_3$) 1.92 (d, 3H, *J*=1.3 Hz), 2.09 (ddd, 1H, $H_{4'a}$, *J*=8.4, 8.6, 12.6 Hz), 2.35 (ddd, 1H, $H_{4'b}$, *J*=5.5, 7.5, 12.6 Hz), 2.76 (s, 3H, *N*–CH_3), 2.83 (dddd, 1H, $H_{3'}$, *J*=3.7, 5.2, 5.5, 8.4 Hz), 3.57 (dd, 1H, $H_{3'a}$, *J*=5.5, 11.5 Hz), 3.65 (dd, 1H, $H_{3'b}$, *J*=3.7, 11.5 Hz), 3.68 (dd, 1H, $H_{6'a}$, *J*=6.9, 14.5 Hz), 4.11 (dd, 1H, $H_{6'b}$, *J*=3.0, 14.5 Hz), 4.25 (dddd, 1H, $H_{5'}$, *J*=3.0, 3.7, 7.5, 8.6 Hz), 7.13 (q, 1H, H_6, *J*=1.3 Hz), 8.80 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 12.3, 34.2, 45.8, 50.2, 61.8, 68.7, 76.1, 110.3, 141.3, 151.0, 164.1. IR (neat) 3550, 3440, 3090, 2950, 2870, 1680, 1645, 1475, 1290, 1020, 865, 740 cm^{-1}. Anal. calcd for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46. Found: C, 51.60; H, 6.72; N, 16.49. Exact mass calculated for $C_{11}H_{17}N_3O_4$: 255.1219. Found: 255.1216.

5.3.2. Reaction of 4a with $LiAlH_4$. 1-{[(3*RS*,5*SR*)-3-(Hydroxymethyl)-2-methylisoxazolidin-5-yl]methyl}-5-methylpyrimidine-2,4(1*H*,3*H*)-dione **6a**. (35.0%, 89 mg), white foam; δ_H (500 MHz, $CDCl_3$) 1.79 (ddd, 1H, $H_{4'a}$, *J*=6.0, 6.1, 12.7 Hz), 1.91 (d, 3H, *J*=1.2 Hz), 2.59 (ddd, 1H, $H_{4'b}$, *J*=8.3, 8.5, 12.7 Hz), 2.72 (s, 3H, *N*–CH_3), 2.99 (dddd, 1H, $H_{3'}$, *J*=3.8, 6.0, 6.4, 8.3 Hz), 3.50 (dd, 1H, $H_{3'a}$, *J*=6.4, 11.6 Hz), 3.57 (dd, 1H, $H_{6'a}$, *J*=8.5, 14.3 Hz), 3.60 (dd, 1H, $H_{3'b}$, *J*=3.8, 11.6 Hz), 4.12 (dd, 1H, $H_{6'b}$, *J*=2.7, 14.3 Hz), 4.46 (dddd, 1H, $H_{5'}$, *J*=2.7, 6.1, 8.5, 8.5 Hz), 7.55 (q, 1H, H_6, *J*=1.2 Hz), 8.95 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 12.3, 33.8, 44.3, 50.6, 62.3, 69.0, 74.7, 110.2, 141.8, 150.8, 163.9. IR (KBr) 3580, 3420, 3095, 2930, 2910, 1655, 1625, 1485, 1302, 1035, 855, 749 cm^{-1}. Anal. calcd for $C_{11}H_{17}N_3O_4$: C, 51.76; H, 6.71; N, 16.46. Found: C, 51.70; H, 6.69; N, 16.48. Exact mass calculated for $C_{11}H_{17}N_3O_4$: 255.1219. Found: 255.1215.

5.3.3. Reaction of 3b with $LiAlH_4$. *N*-(1-{[(3*RS*,5*RS*)-3-(Hydroxymethyl)-2-methylisoxazolidin-5-yl]methyl}-2-oxo-1,2-dihydropyrimidin-4-yl)acetamide **5b**. (32.0%, 90 mg), colourless sticky oil; δ_H (500 MHz, $CDCl_3$) 2.02 (s, 3H, CH_3), 2.10 (ddd, 1H, $H_{4'a}$, *J*=6.0, 9.5, 12.5 Hz), 2.42 (ddd, 1H, $H_{4'b}$, *J*=6.5, 7.2, 12.5 Hz), 2.82 (s, 3H, *N*–CH_3), 2.90 (m, 1H, $H_{3'}$), 3.58 (dd, 1H, $H_{3'a}$, *J*=4.8, 11.3 Hz), 3.64 (dd, 1H, $H_{3'b}$, *J*=4.5, 11.3 Hz), 3.75 (dd, 1H, H $H_{6'a}$, *J*=6.2, 13.8 Hz), 4.15 (dd, 1H, $H_{6'b}$, *J*=3.2, 13.8 Hz), 4.22 (m, 1H, $H_{5'}$), 7.28 (d, 1H, H_5, *J*=7.5 Hz), 7.68 (d, 1H, H_6, *J*=7.5 Hz), 10.50 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 18.8, 37.6, 38.5, 53.6, 64.0, 68.7, 81.2, 98.0, 130.0, 156.2, 168.2, 179.4. IR (neat) 3520, 3480, 3070, 2925, 2870, 1675, 1660, 1655, 1430, 1285, 1080, 830, 780 cm^{-1}. Anal. calcd for $C_{12}H_{18}N_4O_4$: C, 51.05; H, 6.43; N, 19.85. Found: C, 50.95; H, 6.41; N, 19.92. Exact mass calculated for $C_{12}H_{18}N_4O_4$: 282.1328. Found: 282.1330.

5.3.4. Reaction of 4b with $LiAlH_4$. *N*-(1-{[(3*RS*,5*SR*)-3-(Hydroxymethyl)-2-methylisoxazolidin-5-yl]methyl}-2-oxo-1,2-dihydropyrimidin-4-yl)acetamide **6b**. (30.0%, 85 mg), white foam; δ_H (500 MHz, $CDCl_3$) 1.98 (s, 3H, CH_3), 2.20 (ddd, 1H, $H_{4'a}$, *J*=5.8, 8.5 and 12.8 Hz), 2.43 (ddd, 1H, $H_{4'b}$, *J*=6.7, 8.2, 12.8 Hz), 2.78 (s, 3H, *N*–CH_3), 2.98 (m, 1H, $H_{3'}$), 3.60 (dd, 1H, $H_{3'a}$, *J*=4.5, 10.8 Hz), 3.64 (dd, 1H, $H_{3'b}$, *J*=3.9, 10.8 Hz), 3.68 (dd, 1H, H $H_{6'a}$, *J*=6.5, 13.5 Hz), 4.18 (dd, 1H, $H_{6'b}$, *J*=3.2, 13.5 Hz), 4.35 (m, 1H, $H_{5'}$), 7.32 (d, 1H, H_5, *J*=7.5 Hz), 7.58 (d, 1H, H_6, *J*=7.5 Hz), 10.25 (bs, 1H, NH); δ_C (125 MHz, $CDCl_3$) 18.5, 37.8, 39.5, 54.6, 62.0, 67.7, 83.1, 99.5, 131.0, 155.2, 162.8, 180.7. IR (KBr) 3570, 3490, 3080, 2930, 2875, 1690, 1670, 1660, 1430, 1290, 1080, 840, 775 cm^{-1}. Anal. calcd for $C_{12}H_{18}N_4O_4$: C, 51.05; H, 6.43; N, 19.85. Found: C, 51.20; H, 6.41; N, 19.89. Exact mass calculated for $C_{12}H_{18}N_4O_4$: 282.1328. Found: 282.1325.

5.3.5. Reaction of 3c with $LiAlH_4$. 5-Fluoro-1-{[(3*RS*,5*RS*)-3-(hydroxymethyl)-2-methylisoxazolidin-5-yl]methyl}pyrimidine-2,4(1*H*,3*H*)-dione **5c**. (38.0%, 98 mg), white foam; δ_H (500 MHz, $CDCl_3$) 2.01 (ddd, 1H, $H_{4'a}$, *J*=5.3, 10.6, 12.6 Hz), 2.39 (ddd, 1H, $H_{4'b}$, *J*=6.0, 7.2, 12.6 Hz), 2.79 (s, 3H, *N*–CH_3), 2.91 (m, 1H, $H_{3'}$), 3.37 (dd, 1H, $H_{3'a}$, *J*=7.7, 14.8 Hz), 3.68 (m, 2H, $H_{6'}$), 4.27 (dd, 1H, $H_{3'b}$, *J*=2.9, 14.8 Hz), 4.28 (m, 1H, $H_{5'}$), 7.47 (d, 1H, H_6, *J*=5.7 Hz); δ_C (125 MHz, $CDCl_3$) 34.6, 37.6, 46.9, 50.6, 61.8, 75.7, 102.1, 130.5, 149.7, 157.4. IR (KBr) 3490, 3430, 3120, 2940, 2890, 1670, 1654, 1510, 1350, 1280, 1120, 970,

850 cm^{-1}. Anal. calcd for $C_{10}H_{14}N_3O_4F$: C, 46.33; H, 5.44; N, 16.21. Found: C, 46.48; H, 5.43; N, 16.26. Exact mass calculated for $C_{10}H_{14}N_3O_4F$: 259.0968. Found: 259.0971.

5.3.6. Reaction of 4c with $LiAlH_4$. 5-Fluoro-1-{[(3*RS*,5*SR*)-3-(hydroxymethyl)-2-methylisoxazolidin-5-yl]methyl}pyrimidine-2,4(1*H*,3*H*)-dione **6c**. (36.0%, 93 mg), white foam; δ_H (500 MHz, $CDCl_3$) 1.84 (ddd, 1H, $H_{4'a}$, *J*=6.3, 6.4, 12.7 Hz), 2.58 (ddd, 1H, $H_{4'b}$, *J*=8.3, 8.4, 12.7 Hz), 2.74 (s, 3H, *N*–CH_3), 2.96 (dddd, 1H, $H_{3'}$, *J*=3.5, 5.7, 6.4, 8.3 Hz), 3.56 (dd, 1H, $H_{3'a}$, *J*=5.7, 11.7 Hz), 3.59 (dd, 1H, $H_{6'a}$, *J*=8.8, 14.2 Hz), 3.66 (dd, 1H, $H_{3'b}$, *J*=3.5, 11.7 Hz), 4.13 (dd, 1H, $H_{6'b}$, *J*=2.6, 14.2 Hz), 4.44 (dddd, 1H, $H_{5'}$, *J*=2.6, 6.3, 8.4, 8.8 Hz), 7.51 (d, 1H, H_6, *J*=5.7 Hz); δ_C (125 MHz, $CDCl_3$) 34.1, 44.3, 50.8, 62.2, 69.0, 74.2, 130.4, 139.1, 141.0, 149.7. IR (KBr) 3520, 3440, 3100, 2920, 2895, 1690, 1640, 1500, 1360, 1270, 1180, 920, 860 cm^{-1}. Anal. calcd for $C_{10}H_{14}N_3O_4F$: C, 46.33; H, 5.44; N, 16.21. Found: C, 46.49; H, 5.46; N, 16.17. Exact mass calculated for $C_{10}H_{14}N_3O_4F$: 259.0968. Found: 259.0971.

5.3.7. Reaction of 3d with $LiAlH_4$. {(3*RS*,5*RS*)-5-[(6-Amino-9*H*-purin-9-yl)methyl]-2-methylisoxazolidin-3-yl}-methanol **5d**. (30.2%, 78 mg), white foam; δ_H (500 MHz, $CDCl_3$) 1.85 (ddd, 1H, $H_{4'a}$, *J*=5.5, 7.6, 13.2 Hz), 2.25 (ddd, 1H, $H_{4'b}$, *J*=4.8, 6.5, 13.2 Hz), 2.82 (s, 3H, *N*–CH_3), 2.92 (m, 1H, $H_{3'}$), 3.52 (dd, 1H, $H_{3'a}$, *J*=5.5, 11.8 Hz), 3.68 (dd, 1H, $H_{6'a}$, *J*=4.2, 14.0 Hz), 3.70 (dd, 1H, $H_{3'b}$, *J*=3.5, 11.8 Hz), 4.10 (dd, 1H, $H_{6'b}$, *J*=3.2, 14.0 Hz), 4.54 (m, 1H, $H_{5'}$), 8.15 (s, 1H, H_3), 8.35 (s, 1H, H_8); δ_C (125 MHz, $CDCl_3$) 36.8, 38.5, 56.2, 62.3, 68.7, 82.3, 127.0, 143.0, 146.9, 151.8, 155.0. IR (KBr) 3538, 3495, 3110, 2890, 2885, 1690, 1640, 1580, 1420, 1290, 1035, 985, 820, 750 cm^{-1}. Anal. calcd for $C_{11}H_{16}N_6O_2$: C, 50.00; H, 6.10; N, 31.80. Found: C, 49.84; H, 6.12; N, 31.87. Exact mass calculated for $C_{11}H_{16}N_6O_2$: 264.1335. Found: 264.1333.

5.3.8. Reaction of 4d with $LiAlH_4$. {(3*RS*,5*SR*)-5-[(6-Amino-9*H*-purin-9-yl)methyl]-2-methylisoxazolidin-3-yl}-methanol **6d**. (30.4%, 80 mg), colourless sticky oil; δ_H (500 MHz, $CDCl_3$) 2.07 (ddd, 1H, $H_{4'a}$, *J*=4.8, 6.7, 13.8 Hz), 2.35 (ddd, 1H, $H_{4'b}$, *J*=5.2, 6.5, 13.8 Hz), 2.78 (s, 3H, *N*–CH_3), 2.95 (m, 1H, $H_{3'}$), 3.60 (dd, 1H, $H_{3'a}$, *J*=6.5, 12.7 Hz), 3.78 (dd, 1H, $H_{6'a}$, *J*=4.9, 13.8 Hz), 3.80 (dd, 1H, $H_{3'b}$, *J*=3.5, 12.7 Hz), 4.07 (dd, 1H, $H_{6'b}$, *J*=4.2, 13.8 Hz), 4.62 (m, 1H, $H_{5'}$), 8.10 (s, 1H, H_3), 8.32 (s, 1H, H_8); δ_C (125 MHz, $CDCl_3$) 34.8, 37.5, 57.6, 60.9, 69.7, 84.0, 126.0, 145.6, 147.9, 151.6, 156.0. IR (neat) 3600, 3510, 3120, 2860, 2855, 1700, 1670, 1560, 1420, 1295, 1020, 990, 830, 760 cm^{-1}. Anal. calcd for $C_{11}H_{16}N_6O_2$: C, 50.00; H, 6.10; N, 31.80. Found: C, 50.08; H, 6.08; N, 31.90. Exact mass calculated for $C_{11}H_{16}N_6O_2$: 264.1335. Found: 264.1337.

5.4. Preparation of *N,O*-nucleosides 8a–d and 9d

General procedure. A solution of nitrone **7** (5.73 g, 17.5 mmol) and allyl nucleobases (18 mmol) in anhydrous toluene (THF, in the case of allyladenine **2d**), was stirred at 80 °C, in a sealed tube, for 24 h. At the end of this time, the solvent was removed and the residue was subjected to silica gel column chromatography (chloroform/methanol 95:5) to give compounds **8a–d** and **9d**.

5.4.1. 1-{[(3*RS*,5*SR*)-3-({[*tert*-Butyl(diphenyl)silyl]oxy}-methyl)-2-methylisoxazolidin-5-yl]methyl}-5-methylpyrimidine-2,4(1*H*,3*H*)-dione 8a. (74.5%, 6.43 g), light yellow sticky oil; δ_H (500 MHz, $CDCl_3$) 1.06 (s, 9H), 1.75 (ddd, $H_{4'a}$, *J*=5.8, 6.5, 13.1 Hz), 1.94 (d, 3H, *J*=1.2 Hz), 2.58 (ddd, 1H, $H_{4'b}$, *J*=8.3, 8.4, 13.1 Hz), 2.77 (s, 3H, *N*–CH_3), 2.90 (dddd, 1H, $H_{3'}$, *J*=3.5, 5.8, 6.5, 8.3 Hz), 3.20 (dd, 1H, $H_{6'a}$, *J*=8.0, 15.5 Hz), 3.65 (dd, 2H, $H_{3'}$, *J*=5.8, 14.1 Hz), 4.02 (dd, 1H, $H_{6'b}$, *J*=1.5, 15.5 Hz), 4.35 (dddd, 1H, $H_{5'}$, *J*=1.5, 5.8, 8.0, 8.4 Hz), 7.05 (q, 1H, H_6, *J*=1.2 Hz), 7.40–7.60 (m, 10H), 8.70 (bs, 1H, NH). δ_C (125 MHz, $CDCl_3$) 13.8, 19.1, 27.2, 35.6, 45.1, 51.0, 65.0, 79.1, 74.3, 110.3, 128.0, 130.2, 133.4, 135.9, 141.3, 151.0, 164.0. Anal. calcd for $C_{27}H_{35}SiN_3O_4$: C, 65.69; H, 7.15; N, 8.51. Found: C, 65.87; H, 7.13; N, 8.53. Exact mass calculated for $C_{27}H_{35}SiN_3O_4$: 493.2397. Found: 493.2394.

5.4.2. *N*-(1-{[(3*RS*,5*SR*)-3-({[*tert*-Butyl(diphenyl)silyl]-oxy}methyl)-2-methylisoxazolidin-5-yl]methyl}-2-oxo-1,2-dihydropyrimidin-4-yl)acetamide 8b. (72.6%, 6.61 g), colorless sticky oil; δ_H (500 MHz, $CDCl_3$) 1.08 (s, 9H), 1.89 (ddd, 1H, $H_{4'a}$, *J*=5.9, 6.8, 12.0 Hz), 2.58 (ddd, 1H, $H_{4'b}$, *J*=7.8, 8.0, 12.0 Hz), 2.63 (s, 3H, *N*–CH_3), 2.89 (m, 1H, $H_{3'}$), 3.58 (dd, 2H, $H_{3'}$, *J*=4.2, 12.3 Hz), 4.08 (dd, 2H, $H_{6'}$, *J*=2.2, 14.8 Hz), 4.38 (m, 1H, $H_{5'}$), 7.30 (d, 1H, H_5, *J*=7.0 Hz), 7.40–7.60 (m, 10H), 7.64 (d, 1H, H_6, *J*=7.0 Hz); δ_C (125 MHz, $CDCl_3$) 18.5, 24.6, 25.1, 34.6, 45.1, 52.6, 63.3, 69.8, 75.4, 92.3, 127.1, 129.8, 133.0, 134.9, 136.5, 158.1, 160.2, 169.8. Anal. calcd for $C_{28}H_{36}SiN_4O_4$: C, 64.59; H, 6.97; N, 10.76. Found: C, 64.84; H, 6.95; N, 10.74. Exact mass calculated for $C_{28}H_{36}SiN_4O_4$: 520.2506. Found: 520.2508.

5.4.3. 1-{[(3*RS*,5*SR*)-3-({[*tert*-Butyl(diphenyl)silyl]oxy}-methyl)-2-methylisoxazolidin-5-yl]methyl}-5-fluoropyrimidine-2,4(1*H*,3*H*)-dione 8c. (75.5%, 6.32 g), white foam; δ_H (500 MHz, $CDCl_3$) 1.10 (s, 9H), 1.87 (ddd, 1H, $H_{4'a}$, *J*=6.3, 6.4, 12.8 Hz), 2.68 (ddd, 1H, $H_{4'b}$, *J*=8.3, 8.4, 12.8 Hz), 2.74 (s, 3H, *N*–CH_3), 2.77 (dddd, 1H, $H_{3'}$, *J*=3.5, 5.7, 6.4, 8.3 Hz), 3.50 (dd, 1H, $H_{6'a}$, *J*=8.8, 14.1 Hz), 3.70 (dd, 2H, $H_{3'}$, *J*=3.5, 11.8 Hz), 4.05 (dd, 1H, $H_{6'b}$, *J*=1.5, 14.1 Hz), 4.40 (dddd, 1H, $H_{5'}$, *J*=1.5, 6.3, 8.3, 8.8 Hz), 7.20–7.60 (m, 11H, H_6 and ArH), 9.40 (bs, 1H, NH). δ_C (125 MHz, $CDCl_3$) 19.5, 27.1, 35.5, 44.1, 51.5, 64.3, 68.9, 74.0, 128.1, 130.2, 131.0, 135.3, 135.5, 159.7. Anal. calcd for $C_{26}H_{32}SiN_3O_4$: C, 65.24; H, 6.74; N, 8.78. Found: C, 65.02; H, 6.73; N, 8.79. Exact mass calculated for $C_{26}H_{32}SiN_3O_4$: 478.2162. Found: 478.2159.

5.4.4. 9-{[(3*RS*,5*SR*)-3-({[*tert*-Butyl(diphenyl)silyl]oxy}-methyl)-2-methylisoxazolidin-5-yl]methyl}-9*H*-purin-6-amine 8d. (55.3%, 4.86 g), white foam; δ_H (500 MHz, $CDCl_3$) 1.05 (s, 9H), 1.85 (ddd, 1H, $H_{4'a}$, *J*=6.0, 6.8, 12.0 Hz), 2.56 (ddd, 1H, $H_{4'b}$, *J*=8.3, 8.4, 12.0 Hz), 2.72 (s, 3H, *N*–CH_3), 2.83 (dddd, 1H, $H_{3'}$, *J*=3.5, 5.7, 6.8, 8.3 Hz), 3.60 (m, 2H, $H_{3'}$), 4.10 (m, 2H, $H_{6'}$), 4.23 (m, 1H, $H_{5'}$), 5.88 (bs, 2H, NH_2), 7.37–7.46 (m, 10H, ArH), 7.92 (s, 1H, H_8), 8.29 (s, 1H, H_2). δ_C (125 MHz, $CDCl_3$) 16.8, 22.1, 37.8, 41.2, 56.7, 67.5, 70.0, 82.3, 128.0, 130.2, 135.0, 137.3, 139.4, 142.0, 158.7, 160.0. Anal. calcd for $C_{27}H_{34}SiN_6O_2$: C, 64.51; H, 6.82; N, 16.72. Found: C, 64.61; H, 6.80; N, 16.68. Exact mass calculated for $C_{27}H_{34}SiN_6O_2$: 502.2512. Found: 502.2515.

5.4.5. 9-{[(3*RS*,5*RS*)-3-({[*tert*-Butyl(diphenyl)silyl]oxy}-methyl)-2-methylisoxazolidin-5-yl]methyl}-9*H*-purin-6-amine 9d. (27.7%, 2.43 g), white foam; δ_H (500 MHz, $CDCl_3$) 1.10 (s, 9H), 1.98 (ddd, 1H, $H_{4'a}$, J=5.5, 6.7, 11.5 Hz), 2.76 (ddd, 1H, $H_{4'b}$, J=7.3, 8.2, 11.5 Hz), 2.86 (s, 3H, $N-CH_3$), 2.88 (dddd, 1H, $H_{3'}$, J=3.9, 6.2, 7.8, 9.2 Hz), 3.72 (m, 2H, $H_{3'}$), 3.95 (m, 2H, $H_{6'}$), 4.20 (m, 1H, $H_{5'}$), 6.18 (bs, 2H, NH_2), 7.30–7.58 (m, 10H, ArH), 7.90 (s, 1H, H_8), 8.32 (s, 1H, H_2). δ_C (125 MHz, $CDCl_3$) 18.8, 24.2, 38.2, 45.2, 58.6, 69.7, 72.0, 84.8, 109.4, 130.0, 131.2, 136.0, 138.2, 141.8, 144.0, 158.5, 162.0. Anal. calcd for $C_{27}H_{34}SiN_6O_2$: C, 64.51; H, 6.82; N, 16.72. Found: C, 64.33; H, 6.79; N, 16.77. Exact mass calculated for $C_{27}H_{34}SiN_6O_2$: 502.2512. Found: 502.2515.

5.5. Preparation of *N*,*O*-nucleosides 5d and 6a–d from 8a–d and 9d

General procedure. To a solution of isoxazolidine **8a–d** and **9d** (1 mmol) in dry THF, 1 M TBAF in THF (1.1 mmol, 1.1 mL) wad added and the solution was stirred at rt for 1 h. After evaporation of the solvent in vacuo, the residue was purified by flash chromatography, using chloroform/methanol (95:5) as eluent, to gave nucleosides **5d** and **6a–d** in 98% yields.

Acknowledgements

This work was partially supported by M.I.U.R. (progetto P.R.I.N. 2002 and F.I.R.B.). We also thank for their support the Spanish Ministry of Science and Technology (MCYT), FEDER Program (Project CASANDRA, BQU2001-2428) and the Government of Aragon in Spain (Project P116-2001).

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