

New conformationally locked bicyclic *N,O*-nucleoside analogues of antiviral drugs

Antonio Procopio,^{a,*} Stefano Alcaro,^a Antonio De Nino,^b Loredana Maiuolo,^b
Francesco Ortuso^a and Giovanni Sindona^b

^a*Dipartimento di Scienze Farmaco-Biologiche, Università della Magna Graecia, Complesso Nini Barbieri,
88021 Roccelletta di Borgia (Cz), Italy*

^b*Dipartimento di Chimica, Università della Calabria, Ponte Bucci, cubo 15C, 87036 Arcavacata di Rende (Cs), Italy*

Received 21 October 2004; revised 17 November 2004; accepted 18 November 2004

Available online 23 December 2004

Abstract—In order to obtain rigidity within the sugar moiety of nucleosides, the bicyclic pyrimidine derivatives of *N,O*-isoxazolidines were designed and synthesized by using 1,3-dipolar cycloaddition of Δ^1 -pyrrolidine-1-oxide and the appropriate vinyl-nucleobases.

© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Modified nucleosides containing hydroxyl handles for their enzymatic phosphorylation *in vivo*, such as AZT, ddC, d4T, etc., are currently employed in the multi-drug protocols adopted in therapeutic treatment of HIV infections.¹

A new line of research has been recently opened in this field, which considers the replacement of the modified ribose with an isoxazolidine nucleus.^{2–5}

Preliminary *in vivo* tests have shown a promising biological activity for some of the members of this new family of potential antiviral drugs.⁶ The antiviral activity exhibited by nucleoside analogues has been correlated to some extent to preferred conformations achieved by the drug in the formation of the enzyme–inhibitor complex, which temporarily inhibits the DNA strand proliferation.⁷ Unmodified nucleosides rings, as described by the pseudorotation cycle,⁸ exist in either S-type (2'-*endo*/3'-*exo*) or N-type (2'-*exo*/3'-*endo*) conformations. The observation that reverse transcriptase is able to discriminate between two conformationally locked nucleoside analogues⁹ has prompted the exploitation of strategies aiming at locking the puckering of the furanose ring into one of the two rotamers. Many anti-HIV nucleoside analogues are, in fact, active when their sugar ring conformational equilibria are centered around the (₃E, S-type) C 3'-*exo* conformation. Our original strategy for the formation of isoxazolidinyl nucleosides is based on the 1,3-dipolar cycloaddition of azomethinoxides on vinyl-nucleobases² achievable by a straightforward procedure.^{2,10}

The structural feature of the bicyclic isoxazolidine model (**1**, Fig. 1), obtained from Δ^1 -pyrrolidine-1-oxide and ethene, is represented by the geometric constraints preventing *cis*–*trans* interconversion by nitrogen inversion.¹¹ Moreover, the presence of the second five-membered ring fused to the isoxazolidine moiety induces a restricted conformational mobility. If a nucleobase

The structural feature of the bicyclic isoxazolidine model (**1**, Fig. 1), obtained from Δ^1 -pyrrolidine-1-oxide and ethene, is represented by the geometric constraints preventing *cis*–*trans* interconversion by nitrogen inversion.¹¹ Moreover, the presence of the second five-membered ring fused to the isoxazolidine moiety induces a restricted conformational mobility. If a nucleobase

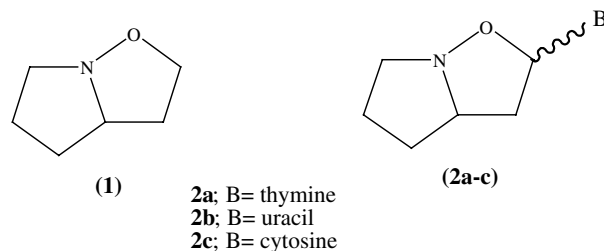


Figure 1.

Keywords: Nucleoside analogues; Vinylpyrimidine nucleobases; *N,O*-isoxazolidines.

*Corresponding author. Fax: +39 0961391143; e-mail: procopio@unicz.it

was inserted in this molecular framework it could be expected that the modified nucleosides **2a–c** show a peculiar structure–function relationship similar to that already experienced with other nucleoside analogues.⁹

The synthesis of the three pyrimidine nucleosides **2a–c** was therefore designed to exploit the effect of the fused ring on the isoxalidine moiety on the conformational mobility of the new compounds compared with the monocyclic analogues.

2. Results and discussions

The design of isoxazolidine nucleosides **2a–c** as novel heterocyclic nucleoside analogues was based on the following considerations: (1) the use of rigid isoxazolidine pyrrolidine bicyclic heterocycles as surrogates for conformationally restricted deoxyribose; (2) the basicity of the hydroxylamino nitrogen atom should confer enhanced stability to glycosidic linkage in acid media.

In a comparative structural study performed on hexahydropyrrolo[1,2-*b*]isoxazolidine¹¹ it was concluded that a fused pyrrolidine ring can impart significant rigidity to the isoxazolidine portion on the molecule to the extent that the resulting nucleoside analogues indeed show identical conformations in the solid state and in solution. For this reason, we have conducted a conformational analysis for evaluating the reverse transcriptase (RT) potential binding properties starting with conformationally locked nucleoside probes whose structural features in the solid state and in solution are virtually identical.

We have designed the bicyclic nucleoside analogues **2a–c**, which are promising precursors for novel types of therapeutic nucleoside derivatives. The sugar moiety in **2a–c** consists of a hexahydropyrrolo[1,2-*b*]isoxazolidine ring system, with the isoxazolidine part conformationally restricted by the fused pyrrolidine ring. With the aim to identify most stable conformations, the structural properties of bicyclic pyrimidine derivatives **2a–c** were investigated by means of molecular modeling studies.

All molecules have been built using the Maestro¹² Linux graphical user interface and submitted to 2000 steps of Monte Carlo conformational search taking into account the nucleobase rotation and the interconversion of the

glycoside moiety. Solvent effects have been considered using the GB/SA¹³ water method for all calculations as implemented in MacroModel ver. 7.2.¹⁴ Each Monte Carlo generated conformer has been energy minimized with the force field MMFFs¹⁵ by means of 5000 iterations of the Polak Ribiere conjugate gradient algorithm adopting a convergence criterion equal to 0.01 kcal/Å mol. In order to consider in the following analysis only the most representative conformations, each generated structure has been compared to the others including both geometric and energetic criteria. Conformers with an internal energy difference lower than 0.1 kcal/mol and with a root mean square deviation, computed on the heavy atomic coordinates, lower than 0.25 Å have been considered identical. The large average number of duplicate structures, in all cases higher than 147, allowed us to estimate the conformational space of all compounds widely explored founding both south (C2' *endo*–C3' *exo*) and north (C3' *endo*–C2' *exo*) conformers. A structural comparison between them is reported in Figures 2 and 3, respectively, as global minimum energy south and high energy north conformations of **2a–c** compounds.

The conformer population has been evaluated by means of the Boltzmann analysis by using the MOLINE thermodynamic module.¹⁶ With the purpose to validate our conformational model, the **2a–c** global minimum energy conformers have been submitted to molecular dynamic simulations. We performed two runs, respectively, at 300 K (MD300) and at 500 K (MD500), computed for 5 ns using a time step equal to 1.5 fs. During these two calculations, χ and $\nu 0$ –4 torsions, as defined in Scheme 1, have been monitored.

The average value of χ has been used to locate the position of the base with respect to the glycoside moiety while $\nu 0$ –4 to compute the phase angle of pseudorotation *P*.⁸ In Table 1 are summarized the conformational properties of **2a–c** compounds, glycoside moieties expressed, in the Monte Carlo case, as sum of the Boltzmann population for each north (N) and south (S) conformer and, in the molecular dynamics cases, as *P*. The geometric properties of compounds **2a–c** have been evaluated considering these two descriptors that showed a very low variability indicating, for all molecules, one highly constrained conformation. Base rotamers, controlled by the χ torsion, have been widely explored during molecular dynamics simulation of both (see Fig. 4).

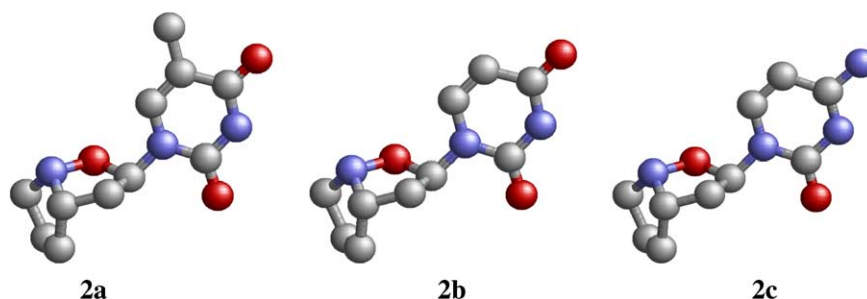


Figure 2. Global minimum energy south conformers of **2a–c** structures.

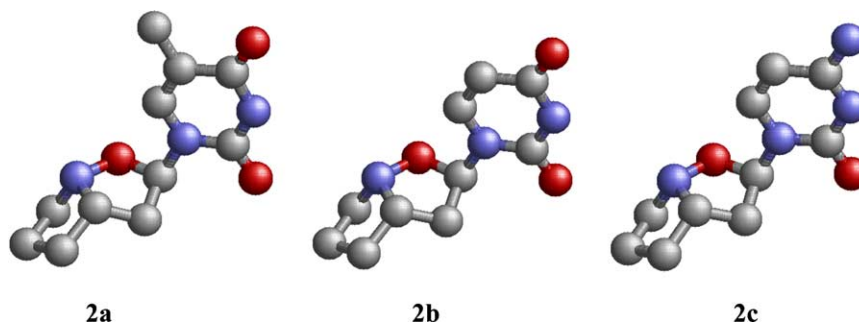
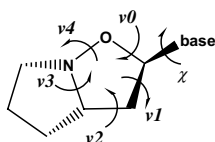


Figure 3. Energy minimized north conformers of **2a–c** compounds. Relative energies, in kJ/mol, of these structures are: **2a** 10.85, **2b** 14.86 and **2c** 10.77.



Scheme 1. Notation of the rotatable bonds used for conformational analysis.

Table 1. Boltzmann probability in percent at room temperature for N and S conformers and the average *P* values

Compd	Monte Carlo		MD300	MD500
	N	S	<i>P</i>	<i>P</i>
2a	5.44	94.56	178.89°	180.10°
2b	5.53	94.47	180.27°	178.83°
2c	4.10	95.90	179.00°	184.49°

The *syn* conformation was energetically less stable than the *anti* one, likely due to the electrostatic and Van der Waals repulsion between the sp^2 oxygen in position 2

onto the pyrimidine ring and that of the isoxazolidine moiety.

Taking into account the bicyclic structure of the glycoside moiety, the analysis of *P* clearly indicated the dependence of this parameter on the C4' stereochemistry, which, in our compounds, was related to the anomeric carbon C2' configuration due to synthetic pathway. The puckering interconversion was observed only for not populated high energy conformations.

In conclusion, compounds **2a–c** showed quite similar structural properties. The molecular complication of the glycoside locked this moiety in a S conformation widely reducing the probability of puckering interconversion also in extreme conditions (i.e., molecular dynamics simulation at 500 K). This observation indicates that these molecules have a strongly conserved DNA-like shape and therefore they could be considered for further optimization studies with the aim to design new or more potent HIV reverse transcriptase inhibitors.

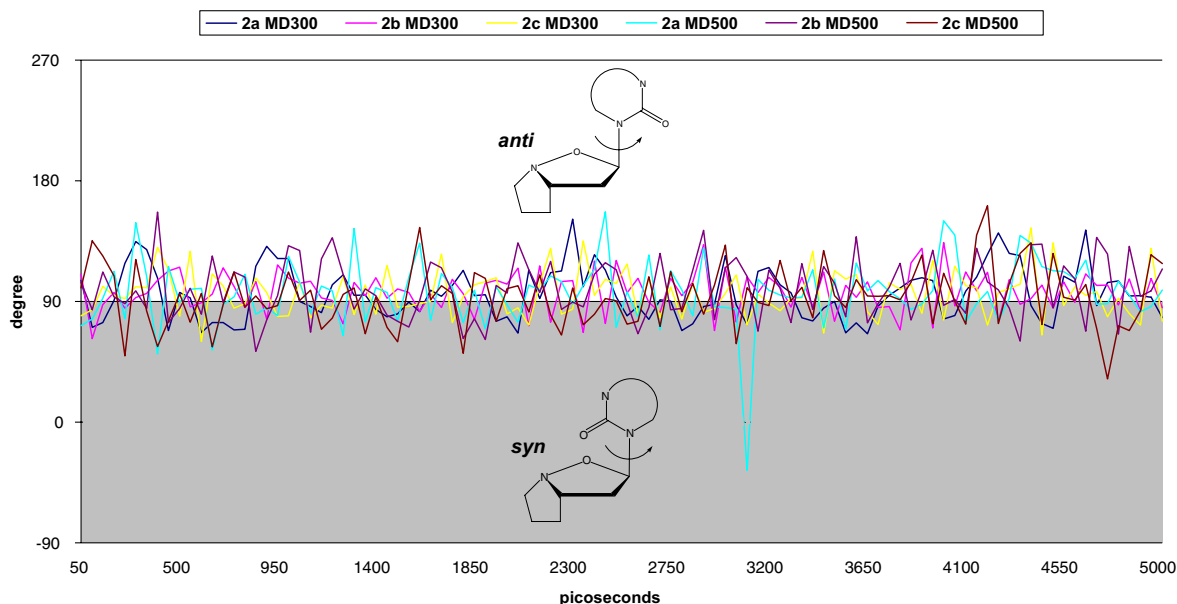
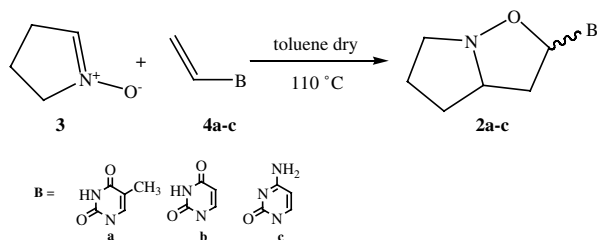


Figure 4. χ rotation during MD300 and MD500 simulations. *anti*- and *syn*-conformations are, respectively, depicted as white and grey areas.

Scheme 2. Synthetic route to **2a–c**.

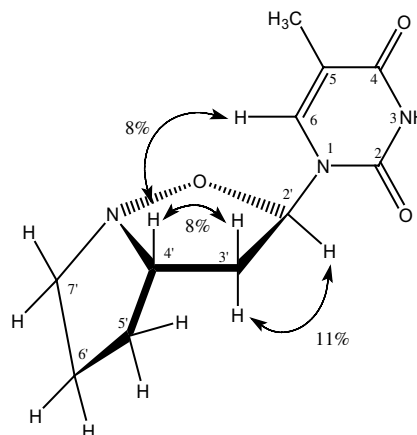
Based on molecular modeling the compounds **2a–c** were predicted to exist in a S-type conformation (corresponding to 3E , C3'-*exo* in the ribo nucleoside analogues). In order to confirm the assumed rigidity the modeled molecules were synthesized and a possible equilibrium between different conformational states were investigated by analysis of proton NMR spectra.

Here we describe a convenient first synthesis of **2a–c** and also discuss their conformation. The 1,3-cycloaddition reaction of Δ^1 -pyrrolidine-1-oxide **3** with N1-vinyl pyrimidine derivatives **4a–c** gave the bicyclic adducts **2a–c** in good yields (Scheme 2).

The configuration and conformation of the bicyclic nucleosides **2a** was evaluated by ^1H NMR and NOE experiments. The spectrum evidenced the presence of a NOE effect between the H-6 of the thymine moiety and H-4' (8%/8%) indicating an *anti* conformation of the thymidine ring and C4'-*exo* conformation of the isoxazolidine ring, which resemble the 3E (C3'-*exo*) conformation in the β -D-ribo configured nucleoside analogues. In addition, mutual NOEs between H-4' and H-3'a, one of two hydrogen nuclei in 3', (8%/8%) and H-2', and H-3'b, the other hydrogen nucleus in 3', (11%/11%) supported the assigned structure and conformation.

The absence of any coupling constant between H-4' of the isoxazolidine ring and H-2' also indicates the conformation of the isoxazolidine ring to be exclusively S-type. So **2a** was assigned as derived from an *exo* approach of the dipolarophile to the nitrone furnishing almost exclusively the 2'*RS*, 4'*SR* enantiomer where H-2' and H-4' are *anti* each other (Fig. 5). The constant reproducibility of the 1,3-dipolar process and the homogeneity of the ^1H NMR data permit us to consider the extension of these conclusions to the other two cycloadducts **2b** and **2c**.

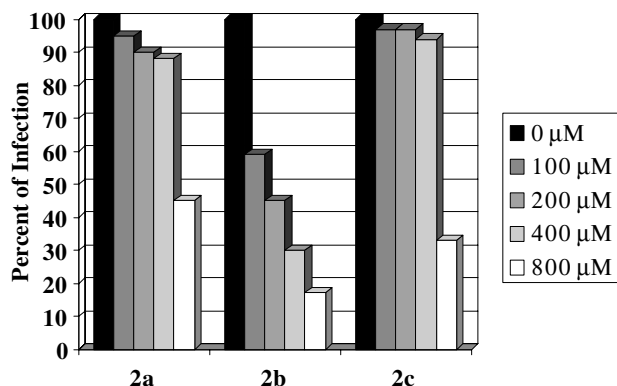
For the purpose of detecting a possible equilibrium between different conformational states, proton NMR spectra of thymine derivative **2a** was recorded in DMSO- d_6 over the temperature range of 20–80 °C.

Figure 5. (2'*RS*,4'*SR*)-1-(Hexahydropyrrolo[1,2-*b*]isoxazolyl) 5-methyl-1H-pyrimidine-2,4-dione (**2a**).

Any changes was observed for the relevant coupling constants or chemical shifts between the low and high temperature spectra indicating that the isoxazole ring in these compounds does not appears to be involved in a conformational N $\leftrightarrow$ S equilibrium in solution as is the case for conventional nucleosides.

The synthesized three modified nucleosides were preliminarily screened in a cell-based system (VERO cells) for their ability to inhibit HSV-1 replication (Fig. 6). In addition, cytotoxicity was evaluated in parallel in an MTS [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium]-based assay (Table 2).

One of these nucleosides (**2b**) displayed an interesting inhibition of HSV-1 replication in the concentration

Figure 6. Antiviral efficacy of **2a–c** in VERO cells infected with HSV-1 in the presence of indicated concentration of the three compounds. The results are expressed as mean values along with those of three independent experiments.Table 2. Percent growth of a VERO cell line exposed at four increasing concentrations (100, 200, 400, 800 μM)

Cell line	2a				2b				2c			
HSV-1 in VERO cells ^a	100	200	400	800	100	200	400	800	100	200	400	800
	−5	−10	−12	−55	−41	−55	−70	−83	−3	−3	−6	−67

^a The negative value indicate the percent of cells killed.

range 100 μ M (41% of cells killed) to 500 μ M (83% of cells killed) (Table 2) and for the three compounds no significant toxicity was detected in the treatment in the MOLT-3 (human lymphoblastoid) and VERO (African Green Monkey) cell lines assayed ($CC_{50} > 1000$ in every case). Moreover, no apoptosis was detected.

3. Conclusions

Conformational analysis of nucleoside analogues **2a–c** by molecular modeling and NOE spectroscopy supported the assumption of rigid bicyclic structure in which the isoxazolidine ring was locked in S-type conformation.

The bicyclic *N,O*-nucleoside analogues **2a–c** can be considered valuable structural probes for the evaluation of RT binding affinity as well as useful templates for further drug design investigations.

Furthermore, preliminary biological assays seem to reveal interesting chances to develop new potential antiviral drugs starting from a locked nucleoside structures resembling molecules **2a–c**.

4. Experimental

Solvents and reagents were purified by standard procedures and were distilled prior to use. ^1H NMR spectra were recorded at 300 MHz in $\text{DMSO}-d_6$ using a tetramethylsilane (TMS) as internal standard (Bruker ACP 300 MHz). Chemical shifts are given in ppm from TMS and coupling constants in Hz. Microanalyses were carried out with a Perkin–Elmer 240 analyzer.

4.1. Δ^1 -Pyrrolidine-1-oxide (**3**)

$\text{NH}_2\text{OH}\cdot\text{HCl}$ (8.83 g, 127.0 mmol) was added to a solution of 1,4-dibromobutane (10.0 g, 46.3 mmol) in dry Et_3N (70 mL). The stirred solution was maintained under reflux for 1.5 h. The reaction mixture was then cooled to room temperature and the solution separated from the insoluble salts was diluted with ethylic ether and filtered on Celite. The collected organic phases were dried over Na_2SO_4 , filtered and concentrated to give a crude mixture, which afforded the 1-hydroxypyrrolidine in quantitative yield as a yellow oil pure enough to be used in the oxidation step as shown by comparison of its spectral data with those reported in literature.¹⁷

A 0.6 M solution of 1-hydroxypyrrolidine in CH_2Cl_2 was cooled at 0 $^\circ\text{C}$ and yellow HgO (9.0 g, 41.5 mmol) was added slowly. After 0.5 h, the mixture was warmed to room temperature and reacted for 4 h as indicated by TLC [$\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH} = 9:1$]. The crude mixture was then diluted with CH_2Cl_2 and filtered on Celite. The collected organic phases were dried over Na_2SO_4 , filtered and concentrated. The obtained crude products were purified on silica gel by flash-chromatography [$\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH} = 9:1$]. The product **3** was obtained as pure compound with 89% yield and was identified

by comparison of its spectral data with those reported in literature.¹⁷

4.2. General procedure **2a–c**

A suspension of *N*1-vinyl pyrimidine derivatives **4a–c**⁶ in dry toluene (20 mM) was added to Δ^1 -pyrrolidine-1-oxide **3** (3.0 equiv) (prepared from its corresponding hydroxylamine by HgO oxidation) and some grains of hydroquinone as polymerization inhibitor. The reaction mixture was stirred under reflux for 6–20 h (Table 3), then the solution was concentrated under vacuum and the crude mixture purified by flash-chromatography (ethyl acetate/methanol = 9:1).

4.3. (2'*RS*,4'*SR*)-1-(Hexahydropyrrolo[1,2-*b*]isoxazoly) 5-methyl-1*H*-pyrimidine-2,4-dione (**2a**)

^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ (ppm) 11.30 (s, 1H, NH); 7.64 (s, 1H, H_6); 6.16 (dd, 1H, $\text{H}_{2'}$, $J_{\text{H}2'/\text{H}3'a} = 5.5$, $J_{\text{H}2'/\text{H}3'b} = 4.4$); 3.84–3.73 (m, 1H, H_4'); 3.02–2.87 (m, 1H, $\text{H}_{7'a}$); 2.70–2.53 (m, 2H, $\text{H}_{3'}$); 2.02–1.53 (m, 8H, $\text{H}_{5'}$, $\text{H}_{6'}$, $\text{H}_{7'b}$, CH_3). ^{13}C NMR (300 MHz, $\text{DMSO}-d_6$): δ (ppm) 164.36; 150.95; 136.88; 109.29; 83.64; 64.95; 56.95; 43.31; 31.41; 24.13; 12.79. ESI/MS m/z 260 (44) $[\text{M}+\text{Na}]^+$, 238 (100) $[\text{M}+\text{H}]^+$, 123 (50), 112 (26) $[\text{M}-\text{Thy}]^+$. Anal. Calcd for $\text{C}_{11}\text{H}_{15}\text{N}_3\text{O}_3$: C, 55.69; H, 6.37; N, 17.71. Found: C, 55.78; H, 6.32; N, 17.66.

4.4. (2'*RS*,4'*SR*)-1-(Hexahydropyrrolo[1,2-*b*]isoxazoly) 1*H*-pyrimidine-2,4-dione (**2b**)

^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ (ppm) 11.43 (s, 1H, NH); 8.02 (d, 1H, H_6 , $J_{\text{H}6\text{H}5} = 8.00$); 6.33 (dd, 1H, $\text{H}_{2'}$, $J_{\text{H}2'/\text{H}3'a} = 6.72$, $J_{\text{H}2'/\text{H}3'b} = 3.66$); 5.82 (d, 1H, H_5 , $J_{\text{H}5\text{H}6} = 8.00$); 4.00–3.89 (m, 1H, H_4'); 3.20–3.06 (m, 1H, $\text{H}_{7'a}$); 2.91–2.73 (m, 2H, $\text{H}_{3'}$); 2.20–1.97 (m, 5H, $\text{H}_{5'}$, $\text{H}_{6'}$, $\text{H}_{7'b}$). ^{13}C NMR (300 MHz, $\text{DMSO}-d_6$): δ (ppm) 163.82; 150.97; 141.34; 101.58; 84.09; 64.80; 56.94; 43.70; 31.50; 24.15. ESI/MS m/z 224 (62) $[\text{M}+\text{H}]^+$, 112 (67) $[\text{M}-\text{Ura}]^+$, 84 (100), 68 (10), 56 (3). Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_3$: C, 53.80; H, 5.87; N, 18.82. Found: C, 53.68; H, 5.94; N, 18.88.

4.5. (2'*RS*,4'*SR*)-1-(Hexahydropyrrolo[1,2-*b*]isoxazoly) 5-methyl-1*H*-4-amino-pyrimidine-2-one (**2c**)

^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ (ppm) 7.78 (d, 1H, H_6 , $J_{\text{H}6\text{H}5} = 7.70$); 7.08 (d, 2H, NH_2 , $J_{\text{gem}} = 21.99$); 6.09 (dd, 1H, $\text{H}_{2'}$, $J_{\text{H}2'/\text{H}3'a} = 7.14$, $J_{\text{H}2'/\text{H}3'b} = 2.75$); 5.72 (d, 1H, H_5 , $J_{\text{H}5\text{H}6} = 7.70$); 3.74–3.61 (m, 1H, H_4'); 3.05–2.85 (m, 1H, $\text{H}_{7'a}$); 2.72–2.54 (m, 1H, $\text{H}_{3'a}$); 2.52–2.36 (m, 1H, $\text{H}_{3'b}$); 2.02–1.53 (m, 5H, $\text{H}_{5'}$, $\text{H}_{6'}$, $\text{H}_{7'b}$). ^{13}C NMR (300 MHz, $\text{DMSO}-d_6$): δ (ppm) 166.25;

Table 3. Cycloaddition reaction for **2a–c** preparation

Nucleobase	Reaction time (h)	Yield (%)	Epimeric ratio (%)
Thymine (2a)	6	95	98:2
Uracil (2b)	17	65	90:10
Cytosine (2c)	20	80	98:2

155.74; 141.57; 93.95; 84.65; 64.66; 56.98; 44.37; 31.47; 24.98. ESI/MS m/z 445 (12) $[2M-H]^+$, 223 (93) $[M+H]^+$, 112 (100) $[M-Cyt]^+$. Anal. Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 53.91; H, 6.42; N, 25.29.

Acknowledgements

We thank MIUR (Ministero per l'Università e Ricerca) for financial support (COFIN 2002).

References and notes

- (a) Larder, B. A.; Kellam, P.; Kemp, S. D. *Nature* **1993**, 365, 451; (b) Collier, A. C.; Coombs, R. W.; Shoenfeld, D. A.; Basset, R. L.; Timponi, J.; Baruch, A.; Jones, M.; Facey, K.; Whitacre, C.; McAuliffe, V. J.; Friedman, H. M.; Merigan, T. C.; Reichman, R. C.; Hooper, C.; Corey, L. N. *Engl. J. Med.* **1996**, 334, 1011; (c) Reijers, M. H. E.; Weverling, G. J.; Jurriaans, S.; Wit, F. W. N. M.; Weigel, H. M.; Kate, R. W. T.; Mulder, J. W.; Frissen, P. H. J.; van Leeuwen, R.; Reiss, P.; Schuitemaker, H.; de Wolf, F.; Lange, J. M. A. *Lancet* **1998**, 352, 185; (d) Montaner, J. S. G.; Hogg, R.; Raboud, J.; Harrigan, R.; O'Shaughnessy, M. *Lancet* **1998**, 352, 1919; (e) van Praag, R. M.; Wit, F. W.; Jurriaans, S.; de Wolf, F.; Prins, J. M.; Lange, J. M. *AIDS* **2002**, 16, 719.
- (a) Leggio, A.; Liguori, A.; Procopio, A.; Siciliano, C.; Sindona, G. *Tetrahedron Lett.* **1996**, 37, 1277; (b) Leggio, A.; Liguori, A.; Procopio, A.; Siciliano, C.; Sindona, G. *Nucleos. Nucleot.* **1997**, 16, 1515; (c) Leggio, A.; Liguori, A.; Maiuolo, L.; Napoli, A.; Procopio, A.; Siciliano, C.; Sindona, G. *J. Chem. Soc., Perkin Trans. I* **1997**, 3097; (d) Colacino, E.; Converso, A.; De Nino, A.; Leggio, A.; Liguori, A.; Maiuolo, L.; Napoli, A.; Procopio, A.; Siciliano, C.; Sindona, G. *Nucleos. Nucleot.* **1999**, 18(4–5), 581.
- (a) Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Piperno, A.; Rescifina, A.; Romeo, R.; Romeo, G. *Tetrahedron Lett.* **2001**, 42, 1777; (b) Richichi, B.; Cicchi, S.; Chiacchio, U.; Romeo, G.; Brandi, A. *Tetrahedron* **2003**, 59, 5231.
- Merino, P. *Curr. Med. Chem.-Anti. Infective Agents* **2002**, 1, 389.
- (a) Pan, S.; Amankulor, N. M.; Zhao, K. *Tetrahedron* **1998**, 54, 6587; (b) Gi, H. J.; Xiang, Y.; Schinazi, R. F.; Zhao, K. *J. Org. Chem.* **1997**, 62, 88.
- Chiacchio, U.; Corsaro, A.; Iannazzo, D.; Piperno, A.; Pistara, V.; Rescifina, A.; Romeo, R.; Valveri, V.; Mastino, A.; Romeo, G. *J. Med. Chem.* **2003**, 46, 3696.
- Van Roey, P.; Salerno, J. M.; Chu, C. K.; Schinazi, R. F. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, 86, 3929.
- (a) Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1972**, 94, 8205; (b) Altona, C.; Sundaralingam, M. *J. Am. Chem. Soc.* **1973**, 95, 2333.
- (a) Björnsne, M.; Szabó, T.; Samuelsson, B.; Classon, B. *Bioorg. Med. Chem.* **1995**, 3, 397; (b) Marquez, V. E.; Ezzitouni, A.; Russ, P.; Siddiqui, M. A.; Ford, H., Jr.; Feldman, R. J.; Mitsuya, H.; George, C.; Barchi, J. J., Jr. *J. Med. Chem.* **1998**, 120, 2780; (c) Olsen, A. G.; Rajwanshi, V. K.; Nielsen, C.; Wengel, J. *J. Chem. Soc., Perkin Trans. I* **2000**, 3610; (d) Bhushan, R. G.; Vince, R. *Bioorg. Med. Chem.* **2002**, 10, 2325; (e) Kim, M. J.; Kim, H. O.; Kim, H. D.; Kim, J. H.; Jeong, L. S.; Chun, M. W. *Bioorg. Med. Chem. Lett.* **2003**, 13, 3299; (f) Obika, S.; Nanbu, D.; Hari, Y.; Morio, K. I.; In, Y.; Ispida, T.; Imanishi, T. *Tetrahedron Lett.* **1997**, 50, 8735; (g) Kværnø, L.; Kumar, R.; Dahl, B. M.; Olsen, C. R.; Wengel, J. *J. Org. Chem.* **2000**, 65, 5161; (h) Håkansson, A. E.; Koshkin, A. A.; Sørensen, M. D.; Wengel, J. *J. Org. Chem.* **2000**, 65, 5167; (i) Shin, K. J.; Moon, H. R.; George, C.; Marquez, V. E. *J. Org. Chem.* **2000**, 65, 2172.
- (a) Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Procopio, A.; De Munno, G.; Sindona, G. *Tetrahedron* **2001**, 57, 4035; (b) Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Procopio, A.; Romeo, R.; Sindona, G. *Synthesis* **2002**, 172.
- Perzanowski, H. P.; Al-Jaroudi, S. S.; Wazeer, I. M.; Ali, Sk. A. *Tetrahedron* **1997**, 53, 11869.
- Schrödinger Inc., 1500 S.W. First Avenue, Suite 1180, Portland, OR 97201-5815.
- Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, 112, 6127.
- Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, 11, 440.
- Halgren, T. A. *J. Comput. Chem.* **1996**, 17, 490.
- Alcaro, S.; Gasparrini, F.; Incani, O.; Mecucci, S.; Misiti, D.; Pierini, M.; Villani, C. *J. Comput. Chem.* **2000**, 21, 515.
- (a) Cordero, F. M.; Machetti, F.; DeCarlo, F.; Brandi, A. *Gazz. Chim. Ital.* **1997**, 127, 25; (b) Cicchi, S.; Corsi, M.; Goti, A. *J. Org. Chem.* **1999**, 64, 7243; (c) Murahashi, S. I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, 55, 1736.