Synthesis of *N*-1-oxypyrimidine 1,3-dioxolane and 1,3-oxathiolane nucleosides

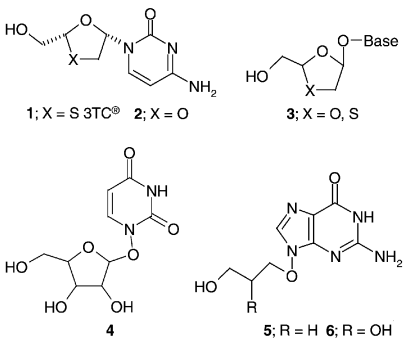
Nghe Nguyen-Ba, Nola Lee, Laval Chan and Boulos Zacharie*

BioChem Pharma Inc. 275 Armand-Frappier Blvd., Laval, Québec, Canada H7V 4A7

Received (in Corvallis, OR, USA) 10th August 2000, Accepted 15th September 2000
First published as an Advance Article on the web 9th November 2000

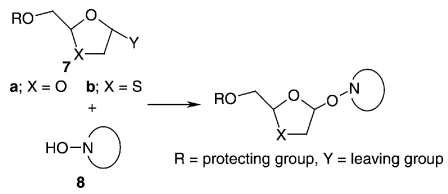
Two series of 1,3-dioxolanes and 1,3-oxathiolane nucleosides containing *N*-1-oxypyrimidine were synthesized as potential antiviral agents.

The potent activity displayed by 3′-azido-3′-deoxythymidine (AZT)[1] against human immuno-deficiency virus (HIV) prompted further design and evaluation of nucleoside analogues.[2] However, the toxicities associated with these compounds as well as the development of resistant viral strains upon prolonged treatment indicates that there is still a need for novel therapeutic agents.[3] One approach is to replace the carbohydrate moiety of 2′,3′-dideoxynucleoside analogues with other five membered rings.[3b,4] It has been demonstrated that heterosubstitution of these rings has a profound effect on the biological activity of the resulting nucleoside analogue[5] as displayed by (−)-2′-deoxy-3′-thiacytidine (3TC®, Epivir) **1**[5c,6] and (+)-2′-deoxy-3′-oxacytidine (Troxacitabine) **2**.[7]



As part of an ongoing search for new antiviral leads, we further explored this class of 3′-heterosubstituted nucleosides. We synthesized a novel class of these compounds where the 1,3-oxathiolane or 1,3-dioxolane ring is linked to the heterocyclic base through a nitrogen–oxygen bond. This is exemplified by the general structure **3**. The structure of these nucleosides are analogous to those of biologically active compounds[8] such as 1-(α-D-ribofuranosyloxy)uracil **4**,[8b] 9-(3-hydroxypropoxy)guanine **5**[8c] and 9-(2,3-dihydroxypropoxy)guanine **6**.[8d] As an example, **6** showed more potent and selective activity than acyclovir against HSV-1, HSV-2 but was less active than acyclovir against VZV.[8c,d]

The synthetic route to (±)-1,3-dioxolane and 1,3-oxathiolane nucleoside analogues **3** is based upon reaction of *N*-1-hydroxyheterocycles **8** with a dioxolane or oxathiolane moiety **7** bearing a suitable leaving group Y (Scheme 1).

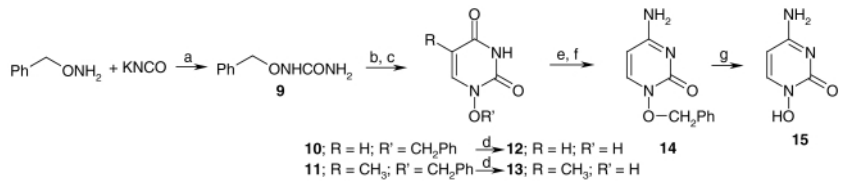


Scheme 1

Our strategy was to build stepwise the *N*-1-hydroxypyrimidine base **8** since its direct synthesis by oxidation of the base has not yet been achieved. *N*-1-Hydroxyuracil **12** was selected as the key base in this series.[9] The preparation of this compound is described in Scheme 2. Treatment of *O*-benzylhydroxylamine with aqueous acidic potassium cyanate afforded urea **9** in 80% yield. This was reacted with sodium hydride followed by ethyl 3,3-dimethoxypropionate to give the protected uracil **10**. This compound was hydrogenated to give *N*-1-hydroxyuracil **12**. Similarly, *N*-1-hydroxythymine **13** was prepared by reacting the urea **9** with ethyl 3,3-diethoxy-2-methylpropionate followed by deprotection of the benzyl group of compound **11**. These pyrimidine bases **12** and **13** were also synthesized by Klötzer using a similar approach.[10] *N*-1-Hydroxycytosine was prepared from its precursor uracil. For example, reaction of *N*-1-benzyloxyuracil **10** with phosphorus oxychloride, triethylamine and triazole gave the triazolo derivative which was treated with ammonia then debenzylated to give *N*-1-hydroxycytosine **15** in 75% yield (Scheme 2).

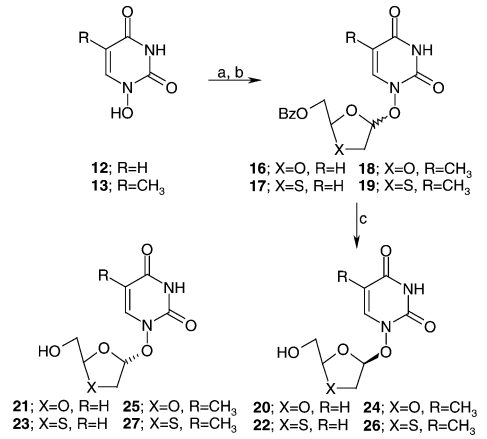
Unlike 1-(benzyloxy)imidazole which is unstable under alkaline conditions,[8a] the *N*-1-benzyloxypyrimidines **10**, **11**, **14** are stable under a variety of conditions. These include acidic and basic conditions, as well as temperatures (< 90 °C) and catalytic hydrogenation. In addition, the final free *N*-1-hydroxy compounds **12**, **13**, **15** can be stored for months at 0 °C without decomposition.

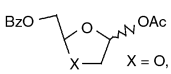
Two approaches were considered for the preparation of pyrimidine and purine nucleosides. The first route was based upon coupling of a suitably functionalised *N*-1-hydroxy base with 1,3-dioxolane or 1,3-oxathiolane sugars under Mitsunobu conditions. Unfortunately, this reaction appeared to be ineffective and resulted in low yield. In fact, the Mitsunobu reaction between acylated furanose and 1-hydroxybenzotriazole gave similar results.[11] The second approach offers a more general route for the synthesis of these nucleosides. Scheme 3 illustrates a representative example where the sugar moieties of 1,3-dioxolane or 1,3-oxathiolane were reacted with iodo- or bromotrimethylsilane then the solution was treated with a mixture of sodium hydride and *N*-1-hydroxyuracil **12** or



Scheme 2 *Reagents and conditions:* (a) 10% aq. acetic acid; (b) NaH, DMSO, 70 °C, 22 h; (c) Na, EtOH, $(MeO)_2CHCH_2COOEt$; (d)10% Pd/C, cyclohexane, EtOH, 60 °C, 5 h; (e) $POCl_3$, Et_3N, triazole; (f) NH_3; (g) H_2/Pd-C.

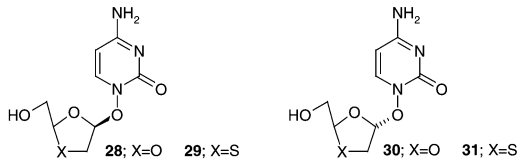
DOI: 10.1039/b006600l



Scheme 3 *Reagents and conditions*: (a) NaH/THF; (b)  , TMSI or TMSBr, DMF; (c) NH_3/MeOH.

thymidine **13** in DMF. This gave the desired nucleoside **16** and **17** or **18** and **19**, respectively, as a 1 : 1 mixture of *cis* and *trans* isomers in 72 and 66% yields, respectively.[12] Replacement of halotrimethylsilane with trimethylsilyl triflate or the base sodium hydride with triethylamine did not alter the ratio of isomers but reduced the yield. Separation of the isomers **16**–**19** by chromatography followed by deprotection with methanolic ammonia gave the expected nucleosides **20**–**27** in high yields.[13]

Similarly, cytosine derivatives **28**–**31** were produced in a 1 : 1



mixture of *cis* and *trans* isomers under the same conditions starting from *N*-1-hydroxycytosine **15**. Direct conversion of uracil nucleoside **16** or **17** to the corresponding cytosine using the triazolo–phosphorus oxychloride–ammonia procedure was not successful and gave low yield of the expected product **28**–**31**.

The anti HIV, HBV, HSV-1 and HSV-2 activities of (±)-1,3-dioxolane and 1,3-oxathiolane nucleoside analogues **20**–**27**, **28**–**31**, were evaluated and compared with 3TC® (Epivir) and AZT. All of them were found to be inactive and non-toxic, except the cytosine derivative **29** which displayed weak inhibition of extracellular HBV.

In summary, described herein is a novel class of (±)-1,3-dioxolane and 1,3-oxathiolane nucleoside analogues. The biological results demonstrate that linking the sugar to the heterocyclic base through an oxygen causes dramatic reduction in antiviral activity in this series of compounds.

We thank Drs R. Storer and T. Bowlin for reading the manuscript, Mrs L. Bernier and J. Dugas for technical assistance with HPLC purification, and Mrs L. Marcil for secretarial and technical assistance.

Notes and references

1 H. Mitsuya, J. K. Weinhold, P. A. Furman, M. H. St-Clair, S. Nusinoff-Lehrman, R. C. Gallo, D. Bolognesi, D. W. Barry and S. Broder, *Proc. Natl. Acad. Sci. U.S.A.*, 1985, **82**, 7096.

2 (*a*) H. Mitsuya and S. Broder, *Proc. Natl. Acad. Sci. U.S.A.*, 1986, **83**, 1911; (*b*) R. Yarchoan, H. Mitsuya, R. V. Thomas, J. M. Pluda, N. R. Hartman, C.-F. Perno, K. S. Marczyk, J.-P. Allain, D. G. Johns and S. Broder, *Science*, 1989, **245**, 412; (*c*) T.-S. Lin, R. F. Schinazi and W. H. Prusoff, *Biochem. Pharmacol.*, 1987, **36**, 2713.

3 (*a*) For a recent review, see: E. De Clerq, *J. Med. Chem.*, 1995, **38**, 2491; (*b*) M. L. Peterson and R. Vince, *J. Med. Chem.*, 1991, **34**, 2787 and references cited therein.

4 (*a*) B. Belleau, L. Brasili, L. Chan, M. DiMarco, B. Zacharie, N. Nguyen-Ba, H. J. Jenkinson, J. A. V. Coates and J. M. Cameron, *Bioorg Med. Chem. Lett.*, 1993, **3**, 1723; (*b*) M. J. Bamford, D. C. Humber and R. Storer, *Tetrahedron Lett.*, 1991, **32**, 271 and references cited therein; (*c*) J. Branalt, I. Kvarnstrom, B. Classon and B. Samuelsson, *J. Org. Chem.*, 1996, **61**, 3604 and references cited therein.

5 (*a*) N. Nguyen-Ba, W. L. Brown, L. Chan, N. Lee, L. Brasili, D. Lafleur and B. Zacharie, *Chem. Commun.*, 1999, 1245; (*b*) N. Nguyen-Ba, W. Brown, N. Lee and B. Zacharie, *Synthesis*, 1998, 759; (*c*) J. A. V. Coates, N. Cammack, H. J. Jenkinson, I. M. Mutton, B. A. Pearson, R. Storer, J. M. Cameron and C. R. Penn, *Antimicrob. Agents Chemother.*, 1992, **36**, 202; (*d*) M. W. Chun, D. H. Shin,.H. R. Moon, J. Lee, H. Park and L. S. Jeong, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1475.

6 J. M. Camaron, P. Collis, M. Daniel, R. Storer and P. Wilcox, *Drugs of the Future*, 1993, **18**, 319 and references cited therin.

7 K. L. Grove, X. Guo, S.-H. Liu, M. Kukhanova, C. K. Chu and Y.-C. Cheng, *Nucleosides Nucleotides*, 1997, **16**, 1229.

8 (*a*) M. R. Harnden, EP 0319 228 A3; (*b*) E. Grochowski, H. Stepowska, P. Salanski and J. Jurczak, *Carbohydr. Res.*, 1988, **177**, 244; (*c*) S. Bailey, M. R. Harnden, R. L. Jarvest, A. Parkin and M. R. Boyd, *J. Med. Chem.*, 1991, **34**, 57; (*d*) M. R. Harnden, P. G. Wyatt, M. R. Boyd and D. Sutton, *J. Med. Chem.*, 1990, **33**, 187.

9 A similar approach for the synthesis of 1-(hydroxyalkoxy)pyrimidines has been reported by M. R. Harnden, L. J. Jenning and A. Parkin, *Tetrahedron Lett.*, 1988, **29**, 4013.

10 (*a*) W. Klötzer, *Monatsh. Chem.*, 1964, **95**, 1729; (*b*) W. Klötzer and M. Herberz, *Monatsh. Chem.*, 1965, **96**, 1721.

11 E. Grochowski and H. Stepowska, *Synthesis*, 1988, 795.

12 The relative stereochemistry of the *cis* and *trans* products was assigned by difference NOE spectra.

13 Selected data for **22**: mp 190–191 °C; δ_H (DMSO-d_6) 11.58 (br, 1H), 7.92 (d, 1H, *J* 5.4), 6.07 (d, 1H, *J* 4.3), 5.63 (t, 1H, *J* 5), 5.50 (d, 1H, *J* 7.5), 5.23 (t, 1H), 3.67 (m, 1H), 3.63 (m, 1H), 3.54 (m, 2H); δ_C (DMSO-d_6) 163.2, 148.5, 145.1, 109.5, 99.7, 86.8, 64.0, 34.7; HRMS (FAB): M^+ calcd for $C_8H_{11}N_2O_5S$ 247.038868, found 247.038107. For **23**: mp 180-182 °C; δ_H (DMSO-d_6) 11.59 (br, 1H), 7.99 (d, 1H, *J* 3.9), 5.97 (t, 1H, *J* 3.4), 5.52 (d, 1H, *J* 3.6), 5.49 (t, 1H, *J* 6), 5.44 (t, 1H), 3.74 (m, 1H), 3.71 (m, 1H), 3.18 (m, 1H), 3.34 (m, 1H); δ_C (DMSO-d_6) 163.71, 148.61, 145.05, 110.87, 99.62, 88.74, 64.99, 35.56; HRMS (FAB): M^+ calcd for $C_8H_{11}N_2O_5S$ 247.038868, found 247.039700. For **26**: mp 188–189 °C; δ_H (DMSO-d_6) 11.55 (s, 1H), 7.86 (s, 1H), 5.93 (dd, 1H, *J* 1.2, 5.0), 5.38 (m, 2H), 3.73 (m, 1H), 3.63 (m, 1H), 3.44 (dd, 1H, *J* 5.2, 12.6), 3.31 (d, 1H, *J* 12.4), 1.74 (s, 3H); δ_C (DMSO-d_6) 163.35, 148.12, 140.39, 110.53, 107.23, 88.40, 64.90, 35.49, 11.67; LRMS (FAB) *m/z* = 261 (MH^+). For **27**: mp 146–147 °C; δ_H (DMSO-d_6) 11.54 (s, 1H), 7.77 (d, 1H, *J* 1.2), 6.04 (d, 1H, *J* 4.4), 5.62 (t, 1H, *J* 5.0), 5.19 (br s, 1H), 3.64 (m, 1H), 3.52 (m, 1H), 3.35 (dd, 1H, *J* 4.6, 12.3), 3.21 (d, 1H, *J* 12.4), 1.75 (d, 3H, *J* 1.0); δ_C (DMSO-d_6) 163.36, 148.14, 140.22, 108.96, 107.53, 86.46, 63.84, 34.67, 11.73; LRMS (FAB) *m/z* = 261 (MH^+). For **29** mp 210-212 °C; δ_H (DMSO-d_6) 7.83 (d, 1H, *J* 7.5), 7.27 (br d, 2H), 5.92 (dd, 1H), 5.60 (d, 1H, *J* 7.5), 5.43 (t, 1H), 5.37 (t, 1H, *J* 5.0), 3.75 (m, 1H), 3.61 (m, 1H), 3.42 (m, 1H); δ_C (DMSO-d_6) 165.00, 152.07, 144.82, 109.89, 93.07, 88.72, 65.44, 35.81; LRMS (FAB) *m/z* = 246 (MH^+). For **31** mp 183–185 °C; δ_H (DMSO-d_6) 7.78 (d, 1H, *J* 7.4), 7.47 (br d, 2H), 6.08 (dd, 1H), 5.62 (d, 1H, *J* 7.6), 5.59 (t, 1H, *J* 5.0), 5.20 (br s, 1H), 3.67 (m, 1H), 3.55 (m, 1H), 3.48 (m, 2H); LRMS (FAB) *m/z* = 246 (MH^+).