

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

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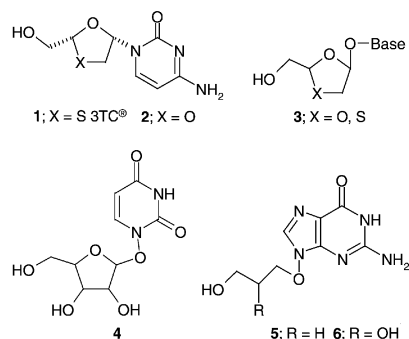
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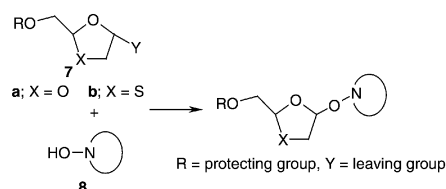
Two series of 1,3-dioxolanes and 1,3-oxathiolane nucleosides containing *N*-1-oxypyrimidine were synthesized as potential antiviral agents.

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 hetero-substitution of these rings has a profound effect on the biological activity of the resulting nucleoside analogue⁵ 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 compounds⁸ 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 (\pm)-1,3-dioxolane and 1,3-oxathiolane nucleoside analogues **3** is based upon reaction of *N*-1-hydroxy-heterocycles **8** with a dioxolane or oxathiolane moiety **7** bearing a suitable leaving group Y (Scheme 1).

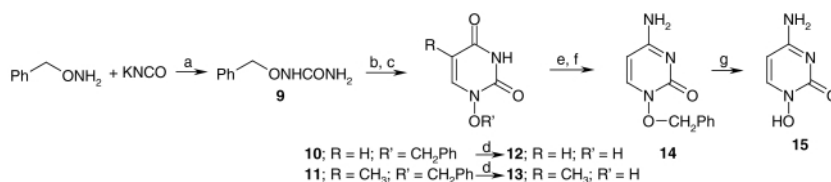


Scheme 1

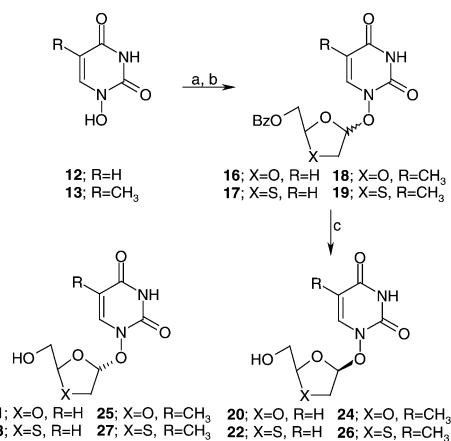
Our strategy was to build stepwise the *N*-1-hydroxypyrimidine base **8** since its direct synthesis by oxidation of the base has not yet been achieved. *N*-1-Hydroxyuracil **12** was selected as the key base in this series.⁹ The preparation of this compound is described in Scheme 2. Treatment of *O*-benzylhydroxylamine 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-benzyl-oxuracil **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-benzyl-oxypyrimidines **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.

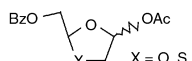
Two approaches were considered for the preparation of pyrimidine and purine nucleosides. The first route was based upon coupling of a suitably functionalised *N*-1-hydroxy base with 1,3-dioxolane or 1,3-oxathiolane sugars under Mitsunobu conditions. Unfortunately, this reaction appeared to be ineffective 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)₂CHCH₂COOEt; (d) 10% Pd/C, cyclohexane, EtOH, 60 °C, 5 h; (e) POCl₃, Et₃N, triazole; (f) NH₃; (g) H₂/Pd-C.

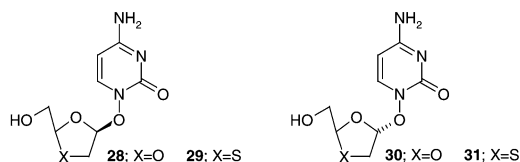


Scheme 3 Reagents and conditions: (a) NaH/THF;

(b) , TMSI or TMSBr, DMF; (c) NH₃/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.

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- The relative stereochemistry of the *cis* and *trans* products was assigned by difference NOE spectra.
- Selected data for **22**: mp 190–191 °C; δ_{H} (DMSO-*d*₆) 11.58 (br, 1H), 7.92 (d, 1H, *J* 4.3), 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 C₈H₁₁N₂O₅S 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 C₈H₁₁N₂O₅S 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⁺).