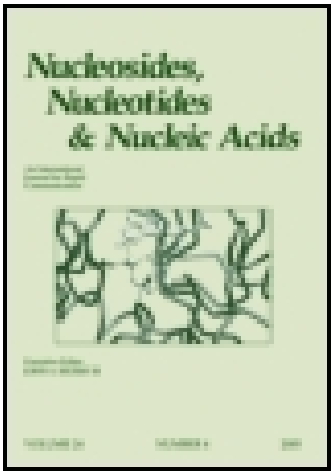

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2-Hydroxyethoxyethylated Bases as Acyclic Analogues of 1,5-Anhydrohexitol Nucleoside Derivatives

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2-HYDROXYETHOXYETHYLATED BASES AS ACYCLIC ANALOGUES OF 1,5-ANHYDROHEXITOL NUCLEOSIDE DERIVATIVES

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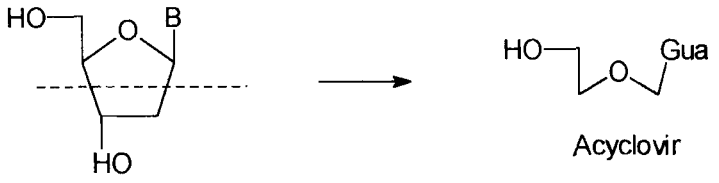
Abstract : *The synthesis and antiviral activity of a new series of acyclic nucleoside analogues containing a (2-hydroxyethoxy)ethyl moiety is discussed.*

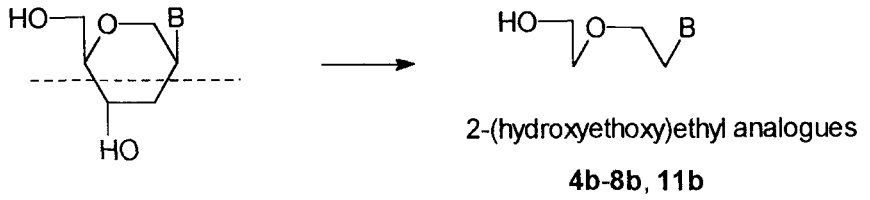
We recently reported the discovery of a new class of nucleoside analogues endowed with interesting antiviral properties and based on a 1,5-anhydrohexitol ring as the carbohydrate fragment[1,2]. Since then several efforts have been undertaken to broaden our knowledge of this new class of antiviral nucleosides and to have a better insight into the structure-activity relationship. As 1,5-anhydrohexitol nucleosides differ from natural 2'-deoxynucleosides by a methylene group inserted between O-4' and C-1' and considering that acyclovir is a non-toxic, biologically active acyclic nucleoside analogue, an obvious approach to modify these anhydrohexitol nucleosides was to cut off the lower part of the tetrahydropyran moiety, leaving only the 2-hydroxyethoxyethyl moiety. This communication deals with the synthesis and activity of these simple acyclic analogues.

Results and discussion

Monotritylation of diethyleneglycol 1 was accomplished with 1 eq of tritylchloride in pyridine in 42 % isolated yield after column chromatography on silica gel (CH_2Cl_2; CH_2Cl_2-MeOH 95:5). Mesylation

+ On leave from Shangai Institute of Planned Parenthood Research, China.





$ROCH_2CH_2OCH_2CH_2OR'$ → $ROCH_2CH_2OCH_2CH_2B$

1. R = R' = H
2. R = Ph_3C, R' = H (42 %)
3. R = Ph_3C, R' = CH_3SO_2 (100 %)

4. B = uracil-1-yl
5. B = cytosin-1-yl
6. B = 5-iodouracil-1-yl
7. B = 5-bromouracil-1-yl
8. B = adenin-9-yl
9. B = 2-amino-6-chloropurin-7-yl
10. B = 2-amino-6-chloropurin-9-yl
11. B = guanin-9-yl

4-11 a,b

a. R = Ph_3C

b. R = H

(1.5 eq) of **2** in CH_2Cl_2 in the presence of 1.6 eq of triethylamine gave quantitative conversion to **3** and after extraction, the crude product was considered to be of sufficient purity to be used directly for the alkylation reactions. Alkylation of uracil, cytosine and adenine proceeded in a straightforward manner under the conditions[3] described in TABLE 1.

TABLE 1. Reaction conditions for alkylation of the heterocyclic bases and elution solvents (CH_2Cl_2-MeOH) for chromatographic purification on silica gel.

Heterocyclic base	**3**	Additive + reaction conditions	obtained product (elution solvens)	detritylated product (elution solvens)
uracil 1.2 eq	1 eq	K_2CO_3 2.5 eq KI 1.2 eq 20 h 90°C	34 % **4a** (97:3)	89 % **4b** (95:5)
cytosine 1.2 eq	1 eq	$CsCO_3$ 2 eq 20 h 80°C	40 % **5a** (97:3)	90 % **5b** (95:5 → 85:15)
adenine 1.5 eq	1 eq	NaH 1.4 eq 20 h 90°C	28 % **8b** (95:5, losses on purification)	89 % **8b** (95:5 → 85:15)
2-NH_2,6-Cl purine 1.2 eq	1 eq	K_2CO_3 1.3 eq 20 h 90°C	34 % **10a** 13 % **9a** (98:2)	80 % **10b** (95:5 → 80:20)

Assignment of the alkylation site of cytosine was based on NMR and UV data, which were in agreement with the literature[4]. Direct alkylation of the sodium salt of 5-iodouracil[5] gave low yield of the desired product. Therefore **6b** was prepared from the uracil analogue **4a** (45 % yield, elution conditions CH_2Cl_2-MeOH 95:5), after treatment with iodine in the presence of Ce(IV)ammonium nitrate[6,7] which proceeded with concomitant detritylation (FIG. 1). Bromination of **4a** with bromine in pyridine[8], followed by detritylation, afforded 57 % of **7b** (chromatographic purification CH_2Cl_2-MeOH 95:5).

Alkylation of 2-amino-6-chloropurine (1.25 eq) with **3** in the presence of potassium carbonate (1.3 eq) in anhydrous DMF gave 34 % of **10a** and 13 % of the N^7-isomer **9a**, which were distinguished by UV[9] and NMR[10-12]. The compounds **4a-10a** were detritylated with 80 % aqueous HOAc for 1-2 h at 80°C and purified on silica gel. Conversion of **10b** to **11b** was accomplished in 55 % yield by treatment with adenosine deaminase[13] for 40 h at 30°C followed by HPLC purification on a polystyrene divinylbenzene column (RoGel RP 7 nm 10 µM, 250x25 mm, BioRad). A gradient was used of MeOH in water with solvens A containing H_2O-MeOH 98:2 and B containing H_2O-MeOH 15:85. The sample had to be dissolved in MeOH and therefore the chromatography was

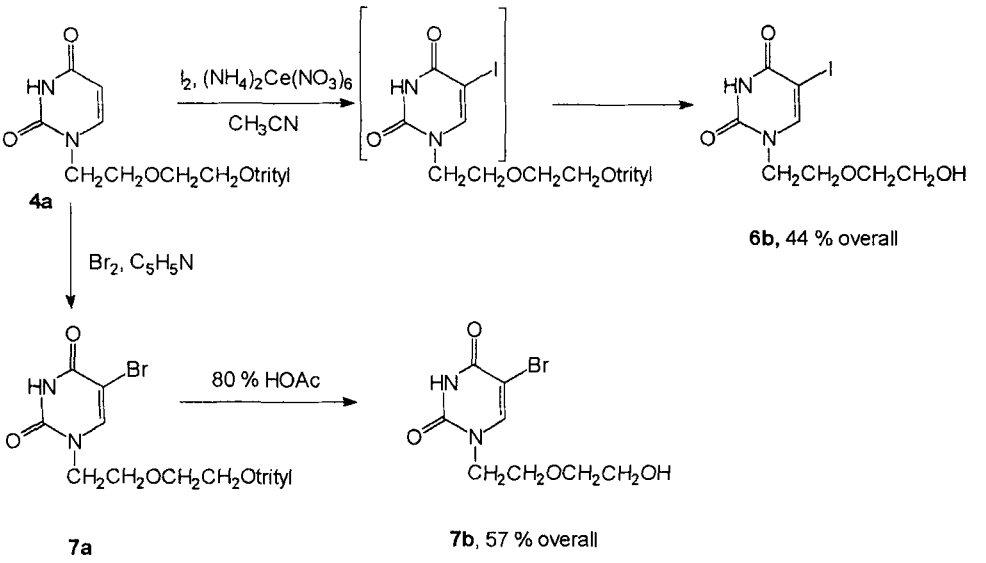


FIG. 1.

TABLE 2. Characteristic analytical data of final compounds.

	mp	UV (MeOH) λ_{max} (ε)	HRMS (M + H)
4b	100°C	266 (10.200)	calcd. for $C_8H_{13}N_2O_4$ 201.0875 Found 201.0856
5b	150°C	275 (9400)	Calcd. for $C_8H_{14}N_3O_3$ 200.1036 Found 200.1018
6b	92°C	287 (7650)	Calcd. for $C_8H_{12}IN_2O_4$ 326.9842 Found 326.9830
7b	130-131°C	282 (8900)	Calcd. for $C_8H_{12}BrN_2O_4$ 278.9980 Found 278.9977
8b	162°C	261 (13.900)	Calcd. for $C_9H_{14}N_5O_2$ 224.1147 Found 224.1137
11b	218°C	254 (13.100) 271 (sh, 9000)	Calcd. for $C_9H_{14}N_5O_3$ 240.1097 Found 240.1097

started at very low MeOH concentration with a gradient from 0 to 40 % B in 25 min followed by 40 to 100 % B in 25 min at 8 mL/min. Elution was obtained at approximately 65 % B[14].

The 2-(hydroxyethoxy)ethyl analogues **4b-8b** and **4b** were evaluated for their activity against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), vaccinia virus, vesicular stomatitis virus, Coxsackie virus B4, polio virus-1, parainfluenza-3 virus, reovirus-1, Sindbis virus and Semliki forest virus.

Only the guanine derivative **11b** displayed marginal activity, without any apparant cytotoxicity, against HSV-1 (minimal effective concentration : 20 μg/mL, which equals 80 μM) in embryonic skin-muscle cells (E_6SM). This marginal activity (50 μM in Vero cells) likewise was reported by the Wellcome Research Laboratories when studying acyclic analogues of acyclovir[15]. However, neither analytical details nor synthetic strategies were described in the Wellcome report. The remaining acyclic derivatives described in this manuscript, have not been reported anywhere else before.

Acknowledgements

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SUPPLEMENTARY PAGES

N^1-[2-(Trityloxyethoxy)ethyl]uracil (4a)

UV (MeOH) λ_{max} 235 and 267 nm

^1H NMR ($CHCl_3$) δ 3.15 (t, 2H), 3.44-3.68 (m, 4H), 3.82 (dd, 2H), 5.45 (d, J=7.7 Hz, 1H), 7.10-7.42 (m, 17 H)

^{13}C NMR ($CDCl_3$) δ 48.1, 62.8, 68.7, 70.5, 86.4, 101.0, 126.8, 127.5, 128.4, 143.6, 145.9, 150.8, 164.2 ppm.

MS-LSIMS (thioglycerol + NaCl) 465 (M + Na), 243 (Trityl), 221 (M-trityl).

N^1-[2-(hydroxyethoxy)ethyl]uracil (4b)

mp (MeOH - Et_2O) 100°C
UV (MeOH) λ_{max} 266 (10.200) nm
^1H NMR (DMSO-d_6) δ 3.43 (m, 4H), 3.60 (t, J=4.8 Hz, 2H), 3.80 (t, J=4.8 Hz, 2H), 4.57 (t, J=4.4 Hz, 1H, 4'-OH), 5.51 (d, J=7.5 Hz, 1H), 7.57 (d, J=7.8 Hz, 1H), 11.2 (br s, 1H) ppm.
^{13}C NMR (DMSO-d_6) δ 47.2, 60.2, 67.9, 72.2, 100.4, 146.3, 151.0, 163.8 ppm.
HRMS - CI(iC_4H_{10}) calculated for $C_8H_{13}N_2O_4$ 201.0875, found 201.0856.

N^1-[2-(Trityloxyethoxy)ethyl]cytosine (5a)

UV (MeOH) λ_{max} 234, 274 nm
^1H NMR (DMSO-d_6) δ 3.13 (t, 2H), 3.57 (t, 2H), 3.71 (m, 2H), 3.90 (m, 2H), 5.65 (d, J=7.3 Hz, 1H), 7.10-7.53 (m, 17H) ppm.
^{13}C NMR (DMSO-d_6) δ 48.7, 62.6, 68.5, 69.9, 85.8, 92.9, 126.5, 127.3, 128.1, 143.6, 146.1, 153.0, 165.8 ppm.
MS-LSIMS (thioglycerol + NaCl) 464 (M + Na), 243 (trityl), 220 (M-trityl)

N^1-[2-(hydroxyethoxy)ethyl]cytosine (5b)

mp (MeOH) 150°C
UV (MeOH) λ_{max} 275 (9400), λ_{min} 253 nm
^1H NMR (DMSO-d_6) δ 3.44 (m, 4H), 3.60 (t, J=4.4 Hz, 2H), 3.77 (t, J=4.7 Hz, 2H), 5.64 (d, J=7.3 Hz, 1H), 7.00 (br s, NH_2), 7.51 (d, J=7.3 Hz, 1H) ppm.
^{13}C NMR (DMSO-d_6) δ 48.4, 60.2, 68.3, 72.2, 92.9, 146.8, 155.9, 166.1 ppm.
MS-LSIMS (glycerol) 491 (M_2H + glycerol), 399 (2M + H), 292 (MH + glycerol), 200 (100 %, M+H)
HRMS calculated for $C_8H_{14}N_3O_3$ 200.1036, found 200.1018.

N^1-[2-(hydroxyethoxy)ethyl]-5-iodouracil (6b)

mp (MeOH - Et_2O) 92°C
UV (MeOH) λ_{max} 287 (br, 7650), λ_{min} 246 nm
^1H NMR (DMSO-d_6) δ 3.45 (s, 4H), 3.58 (t, J=5 Hz, 2H), 3.84 (t, J=5 Hz, 2H), 4.55 (br s, 1H), 8.10 (s, 1H, H-6) ppm.
^{13}C NMR (DMSO-d_6) δ 47.2, 60.1, 67.4, 67.7, 72.1, 150.5, 150.6, 161.0 ppm.
HRMS-CI (iC_4H_{10}) calculated for $C_8H_{12}IN_2O_4$ (M + H) 326.9842, found 326.9830.

N^1-[2-(hydroxyethoxy)ethyl]-5-bromouracil (7b)

mp (MeOH-toluene) 130-131°C
UV (MeOH) λ_{max} 282 (8900), λ_{min} 243 nm.
^1H NMR (DMSO-d_6) δ 3.43 (br s, 4H), 3.62 (t, J=4.8 Hz, 2H), 3.82 (t, J=4.8 Hz, 2H), 4.60 (br s, 1H), 8.12 (s, 1H) ppm.
^{13}C NMR (DMSO-d_6) δ 48.0, 60.5, 68.1, 72.4, 94.6, 146.4, 150.7, 158.6 ppm.
MS-LSIMS (thioglycerol) 279 (M + H), 199 (M - Br).
HRMS calculated for $C_8H_{12}BrN_2O_4$ 278.9980, found 278.9977.

N^9-[2-(trityloxyethoxy)ethyl]adenine (8a)

UV (MeOH) λ_{max} 232, 261 nm.
^1H NMR (DMSO-d_6) δ 3.01 (t, J=4 Hz, 2H), 3.57 (t, J=4 Hz, 2H), 3.85 (t, J=4.7 Hz, 2H), 4.37 (t, J=4.7 Hz, 2H), 7.14-7.42 (m, 15H), 8.13, 8.15 (2 x s, 2H) ppm.
^{13}C NMR (DMSO-d_6) δ 43.0, 63.0, 68.6, 69.6, 85.9, 118.7, 126.9, 128.2, 141.8, 143.8, 149.6, 152.4, 156.0 ppm.
MS-CI (iC_4H_{10}) 466 (M + H), 243 (trityl)

N^9-[2-(hydroxyethoxy)ethyl]adenine (8b)

mp (MeOH-Et_2O) 162°C

UV (MeOH) λ_{max} 261 (13.900) nm.
^{1}H NMR (DMSO-d_6) δ 3.46 (m, 4H), 3.78 (t, J=5.3 Hz, 2H), 4.30 (t, J=5.2 Hz, 2H), 4.63 (t, 4'-OH, 1H), 7.19 (br s, 2H), 8.12, 8.15 (2 x s, 2H) (H2, H8) ppm.
^{13}C NMR (DMSO-d_6) δ 43.5, 60.6, 68.8, 72.4, 118.8, 142.2, 149.9, 152.9, 156.1 ppm.
MS-LSIMS (glycerol) 316 (M + H + glycerol), 224 (100 %, M + H), 136 (B + 2H).
HRMS calculated for $C_9H_{14}N_5O_2$ 224.1147, found 224.1137.

N^9-[2-(trityloxyethoxy)ethyl]-2-amino-6-chloropurine (10a)

UV (MeOH) λ_{max} 309 nm.
^{1}H NMR ($CDCl_3$) δ 3.20 (t, J=6 Hz, 2H), 3.60 (t, J=6 Hz, 2H), 3.81 (t, J=5 Hz, 2H), 4.26 (t, J=5.4 Hz, 2H), 5.30 (br s, NH_2), 7.15-7.50 (m, 15H), 7.90 (s, 1H, H-8) ppm.
^{13}C NMR ($CDCl_3$) δ 43.6, 63.1, 68.8, 70.7, 86.5, 125.5, 126.8, 127.6, 128.4, 143.3, 143.7, 150.9, 153.5, 158.9 ppm.
MS-CI (iC_4H_{10}) 500 (M + H), 256 (M - trityl), 243 (trityl).

N^7-[2-(trityloxyethoxy)ethyl]-2-amino-6-chloropurine (9a)

UV (MeOH) λ_{max} 319 nm, λ_{min} 275 nm.
^{1}H NMR (DMSO-d_6) δ 3.00 (t, 2H), 3.56 (t, 2H), 3.82 (t, 2H), 4.52 (t, 2H), 6.60 (s, 2H, NH_2), 7.15-7.45 (m, 15H), 8.33 (s, 1H) ppm.
^{13}C NMR (DMSO-d_6) δ 46.3, 63.0, 69.3, 69.7, 85.9 (Ph_3C), 114.8, 126.9, 127.8, 128.2, 143.5, 143.7, 150.0, 159.9 ppm.
MS-CI (iC_4H_{10}) 500 (M + H), 256 (M-trityl), 243 (trityl).

N^9-[2-(hydroxyethoxy)ethyl]guanine (11b)

mp (H_2O-MeOH) 218°C
UV (MeOH) λ_{max} 254 (13.100), 271 (sh, 9000) nm.
^{1}H NMR (DMSO-d_6) δ 3.46 (br s, 4H), 3.72 (t, J=5.2 Hz, 2H), 4.11 (t,

J=5.0 Hz, 2H), 6.63 (br s, 2H, NH_2), 7.69 (s, 1H, H8) ppm.

^{13}C NMR (DMSO-d_6) δ 43.2, 60.6, 69.0, 72.5, 116.8, 138.9, 151.9, 154.3, 158.3 ppm.

MS-LSIMS (thioglycerol) 240 (M + H), 152 (B + 2H)

HRMS calculated for $C_9H_{14}N_5O_3$ 240.1097, found 240.1097.

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