Pergamon

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Tetrahedron 59 (2003) 2177–2184

TETRAHEDRON

Rapid access to acyclic nucleosides via conjugate addition

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Received 21 June 2002; revised 16 December 2002; accepted 10 January 2003

Abstract—The synthesis of several acyclic nucleosides **5** and **6**, analogs of penciclovir, was achieved by Michael addition as the key step. This reaction worked not only for the protected natural bases but even for the less nucleophilic deaza purine and deaza pyrimidine.

1. Introduction

Interest in acyclic nucleosides[1] started in 1970 when acyclovir **1** (ACV, 'Zovirax') was reported as a potent anti-viral agent.[2] Acyclovir showed a selective activity against HSV-1 and HSV-2. Ganciclovir **2**, structurally different from acyclovir, was also active against herpes virus and particularly efficient against cytomegalovirus infections.[3] Due to the lack of selectivity of ganciclovir, its clinical use was restricted. On the other hand, the carba-analogue of ganciclovir, penciclovir **3** and its regioisomer **4b**, showed similar biological properties than acyclovir (Fig. 1).[4]

In the course of the preparation of nucleosides, bases are generally introduced by substitution or construction. Few acyclic nucleosides have been synthesized by Michael addition of purine and pyrimidine.[4c,5] We envisaged to test this strategy to prepare several analogs of penciclovir **4** and **5** (Scheme 1). It was also interesting to check if this strategy could work with deaza purines and deaza pyrimidines, which are weakly nucleophilic. Indeed, these bases have usually been introduced by construction.[6]

2. Results and discussion

In a previous work, we obtained good results for the conjugate nucleophilic addition of alcohols, thiophenol and phenylselenol to diethyl methylenemalonate **6**.[7] We tried to extend the possibility to purine and pyrimidine bases. In the case of 6-*N*-benzoyladenine,[8] we could thus obtain the expected product **9a**, which was reduced by $LiAlH_4$ to afford the acyclic nucleoside **5a** in a 30% overall yield. However, the reaction of the protected guanine[9] with **6** led to a mixture of products resulting from mono and double condensation, **9b** and **10b**, respectively. They could be separated by chromatography on silica gel. In the case of

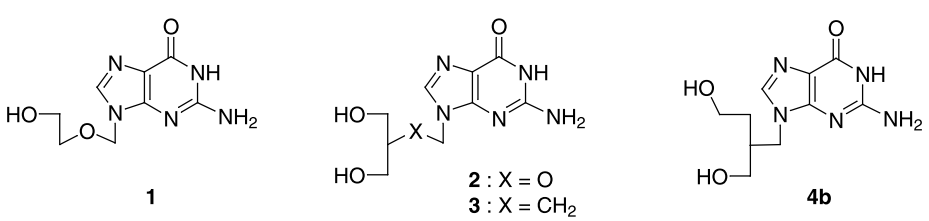

Figure 1.

Keywords: Michael addition; acyclic nucleosides; deaza purine and deaza pyrimidine; analogs of penciclovir.

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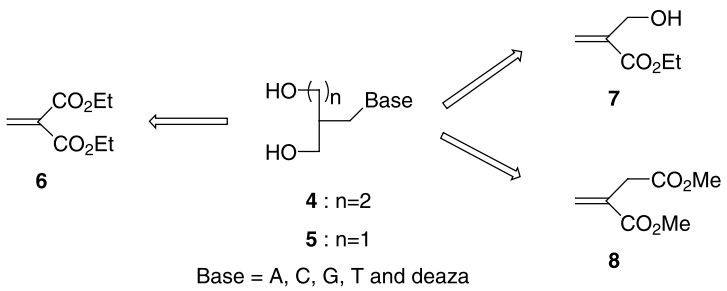
0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00190-X



Scheme 1.

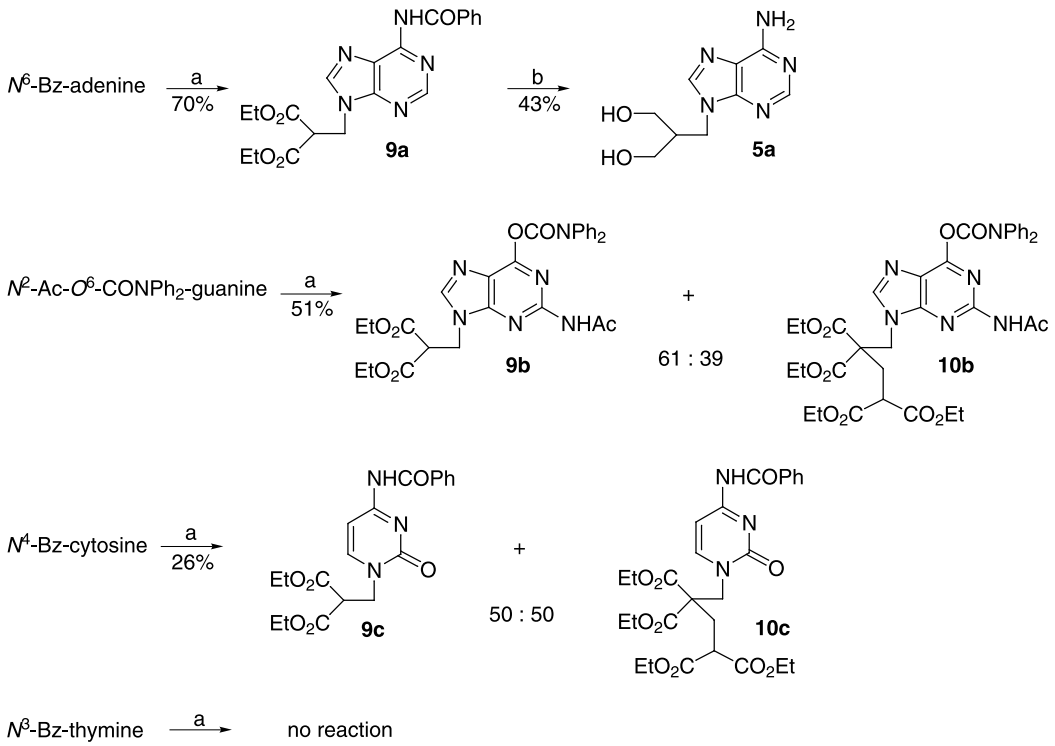
4-*N*-benzoylcytosine, we also obtained a mixture of products (**9c** and **10c**), which could not be separated, in a low yield of 26%. The formation of the compounds **10** was not surprising as we had already observed such double condensations with alcohols and phenylselenol as the nucleophilic reagents.[7,10] With protected thymine,[11] no reaction occurred (Scheme 2).

The low yield from 4-*N*-benzoylcytosine and the lack of reaction with thymine were probably due to the low nucleophilicity of these bases. When the reaction of thymine was run under basic condition (NaOMe), Michael reaction occurred, but the major product was the one resulting from the double condensation. We then decided to use another Michael acceptor, ethyl 2-hydroxymethyl acrylate **7**,[12] adduct of Baylis–Hillman to prepare the acyclic nucleosides **5b–d**.

Addition of protected guanine, cytosine and thymine to **7**, in basic conditions, led to the expected adducts **11b–d** as single isomers. Regiochemistries for the nucleosides **11b** and **11c** were elucidated by HMBC experiments (Fig. 2). In the case of **11b**, H-8 was correlated only with C-4 and C-5. As the signal of C-5, which is between C and N, appears at a higher field than for C-4, which is between two N, they were both assigned. The long-range correlations between H-1′ and C-8 and C-4 proved that **11b** was the *N*-9 regioisomer. In the case of **11c**, correlations between H-1′ and C-2 and C-6 proved the *N*-1 regiochemistry.

Reduction of the adducts **11b** and **11d** followed by removal of the protecting group by ammonia afforded the analogs of penciclovir **5b**[13] and **5d** in 52 and 58% yield, respectively (Scheme 3).

For the synthesis of the acyclic nucleosides **4**, the dimethyl itaconate **8** was used as Michael acceptor. Addition of protected adenine, cytosine, thymine and guanine to **8**, in basic conditions, led to the expected compounds **12a–d** in a satisfactory yield. From the protected adenine, the reaction at 25°C provided a mixture of two regioisomers **12a** and **12a′**, in a 1/1 ratio, which could be separated by



Scheme 2. (a) **6**, CH_3OH or DMF; (b) $LiAlH_4$, THF.

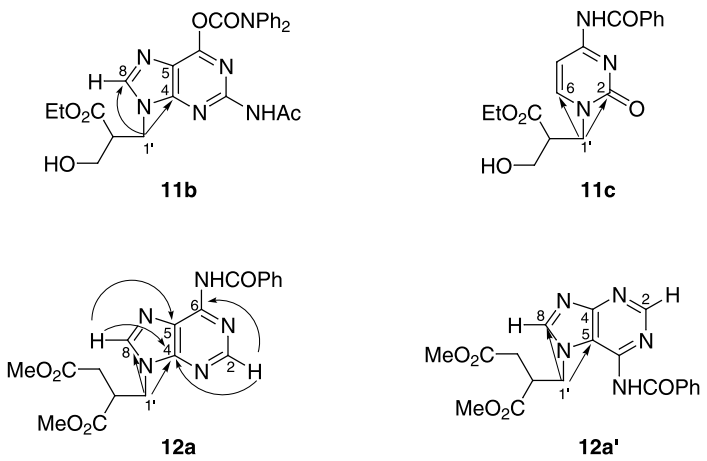


Figure 2. Relevant HMBC correlations.

chromatography. The reaction run at 80°C afforded the same mixture but in an 87/13 ratio. Therefore, **12a** seems to be the thermodynamic product (Scheme 4).

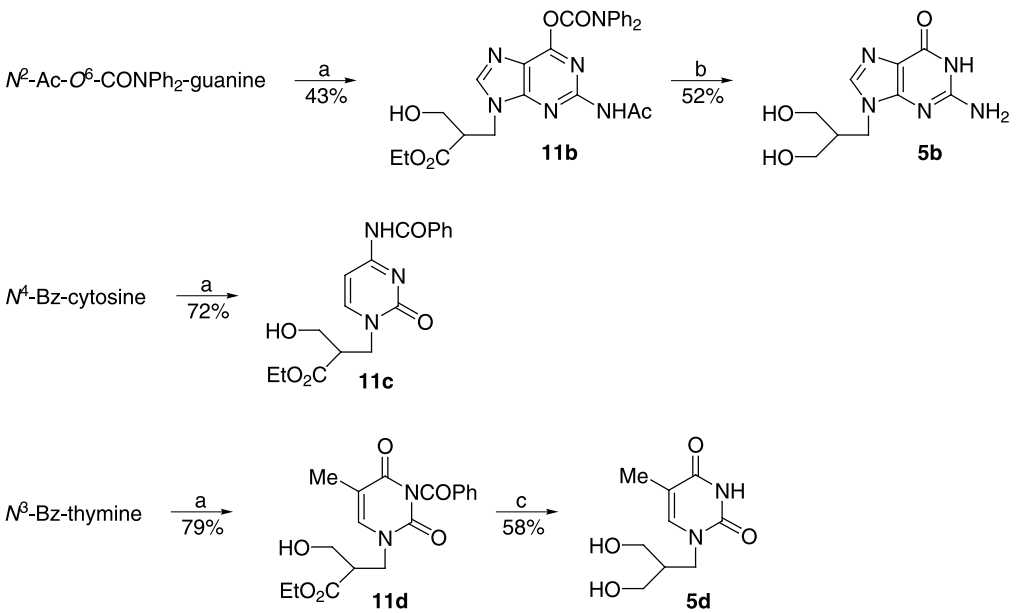
To assign regiochemistry for the isomers **12a** and **12a′**, HMBC experiments have been carried out (Fig. 2). As it is pointed out above, in purine derivatives, signal of C-5 is always at higher field than the ones of other quaternary C of the base moiety. The long-range couplings (^3J) between C-5 and H-8, but not with H-2, in the HMBC spectrum, easily led to assignment of these two protons. Afterwards the ^1J $^1H/^{13}C$ correlation led to the assignments of the corresponding carbons, C-2 and C-8. As C-6 was correlated only with H-2, and C-4 with H-2 and H-8, they also could be assessed. Finally, for **12a**, correlation (^3J) between H-1′ and C-8 and C-4 proved the *N*-9 regiochemistry. For **12a′**, correlation (^3J) between H-1′ and C-8 and C-5 proved the *N*-7 regiochemistry.

Reduction and removal of the protecting groups, for compounds **12a–d**, gave the nucleosides **4a–d** in 51, 49, 17 and 53% yield, respectively (Scheme 4).

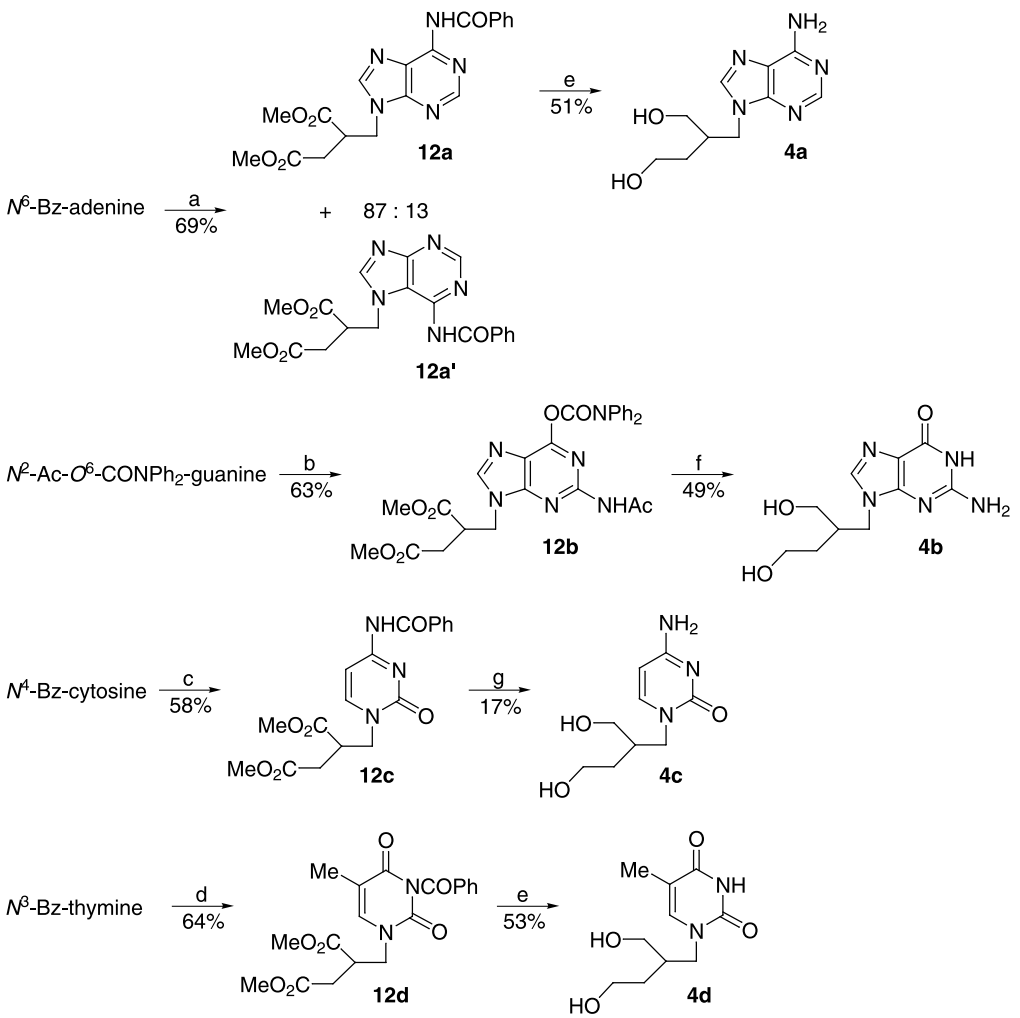
We then tried to extend the method to synthesize acyclic nucleosides with deaza bases that could affect the processivity of telomerase.[14] We were pleased to observe that these weakly nucleophilic bases reacted with **8** to afford the desired acyclic nucleosides **13** and **14** in 49 and 60% yield, respectively. To the best of our knowledge, it is the first time that deaza purine and pyrimidine have been introduced by Michael alkylation. Reduction of **13** and **14** gave the new acyclic nucleosides **4e** and **f** (Scheme 5).

3. Conclusion

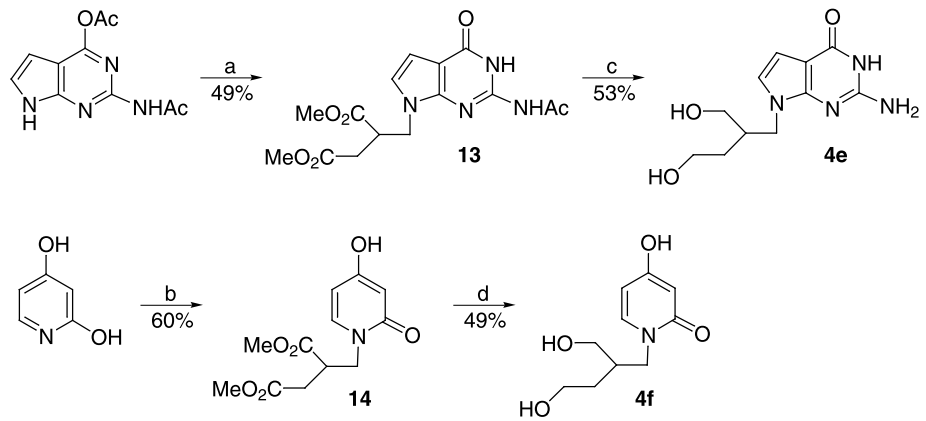
In summary, several acyclic nucleosides were synthesized by a short route involving a Michael addition as the key step. This method is efficient even for condensation of deaza purine and deaza pyrimidine. Biological tests showed that



Scheme 3. (a) **7**, DBU, DMF or CH_3CN; (b) (1) $LiBH_4$, EtOH, (2) NH_3/MeOH; (c) (1) $Ca(BH_4)_2$, THF, (2) NH_3/MeOH.



Scheme 4. (a) **8**, K_2CO_3, DMF, 80°C; (b) **8**, K_2CO_3, DMF; (c) **8**, DBU, DMF; (d) **8**, DBU, CH_3CN; (e) (1) $Ca(BH_4)_2$, THF, (2) NH_3/MeOH; (f) (1) $LiBH_4$, EtOH, (2) NH_3/MeOH; (g) (1) $LiAlH_4$, THF, (2) NH_3/MeOH.



Scheme 5. (a) **8**, DBU, DMF, 60°C; (b) **8**, DBU, DMF, room temperature; (c) (1) $Ca(BH_4)_2$, THF, (2) NH_3/MeOH; (d) $LiAlH_4$, THF.

these nucleosides **4** and **5** did not have anti-HIV properties. Antiviral and cytotoxicity assays for compounds **4** and **5** against HSV-1 in Vero (African Green Monkey) cells were performed. Only **5b** has shown a significant activity. For the compound **4b**, prepared in this work directly from protected guanine, the activity against herpes[4c] has been confirmed. Their evaluation as antitumor agents is in progress.

4. Experimental

4.1. General

All the moisture-sensitive reactions were carried out in oven-dried glassware (100°C) and under nitrogen atmosphere. Commercially available reagents and solvents were

purified and dried, when necessary, by standard methods just prior to use. All melting points were uncorrected. IR spectra were scanned on a FT infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100.6 MHz, respectively. Chemical shifts are reported in ppm downfield from TMS which was used as an internal reference. Elemental analyses were obtained from the Service de Microanalyse, CNRS ICSN, Gif-sur-Yvette. High-resolution mass measurements were performed at the CRMPO, Rennes.

4.1.1. Diethyl 2-(6-*N*-benzoyladenin-9-ylmethyl) malonate 9a. To a suspension of 6-*N*-benzoyladenine (278 mg, 1.16 mmol) in MeOH (2 mL) was added a solution of diethyl methylenemalonate **6** (200 mg, 1.16 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred for 3 h at room temperature and solvents were then removed under reduced pressure. The residue was taken up with CH_2Cl_2 and the precipitate was filtered. The filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/EtOAc: 6/4→3/7) affording **9a** (334 mg, 0.812 mmol, 70%) as a colorless oil: IR (neat, cm^{-1}) 1729, 1660, 1614, 1583, 1552; ^{1}H NMR ($CDCl_3$) δ 9.19 (br s, 1H, NH), 8.80 (s, 1H, CH), 8.10 (s, 1H, CH), 8.02 (d, 2H, arom, J=7.0 Hz), 7.61 (m, 1H, arom), 7.51 (m, 2H, arom), 4.79 (d, 2H, CH_2–N, J=7.0 Hz), 4.25–4.10 (m, 5H, CH and CH_2–O), 1.21 (t, 6H, CH_3, J=7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 166.7 (C═O), 164.6 (C_6H_5CO), 152.7 (CH), 151.9 (quat C), 149.4 (quat C), 143.7 (CH), 133.5 (quat C), 132.7 (CH), 128.8 (CH), 127.8 (CH), 122.7 (quat C), 62.3 (CH_2–O), 51.1 (CH), 42.1 (CH_2–N), 13.8 (CH_3); HRMS (CI) calcd for $C_{20}H_{22}N_5O_5$ (M+H)$^+$: 412.1621. Found: 412.1623.

4.1.2. Diethyl 2-(2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)-guanin-9-ylmethyl) malonate 9b and 2-(2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)guanin-9-ylmethyl)-2,4-diethoxycarbonyl-pentanedioic acid diethyl ester 10b. To a suspension of 2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)guanine (71 mg, 0.183 mmol) in DMF (0.5 mL) was added a solution of diethyl methylenemalonate **6** (31.4 mg, 0.183 mmol) in DMF (0.5 mL). The mixture was stirred at room temperature for 15 h. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2. The precipitate was filtered and the filtrate was evaporated under reduced pressure. Both compounds were separated by column chromatography (silica gel, CH_2Cl_2/EtOAc: 9/1) to give successively **10b** as a colorless oil (26.1 mg, 0.036 mmol, 20%) then **9b** as a colorless oil (31.2 mg, 0.056 mmol, 31%).

Compound **9b**. IR (neat, cm^{-1}) 1733, 1621, 1580, 1495; ^{1}H NMR ($CDCl_3$) δ 8.08 (br s, 1H, NH), 7.99 (s, 1H, CH), 7.45–7.25 (m, 10H, H arom), 4.66 (d, 2H, CH_2–N, J=7.0 Hz), 4.2 (q, 4H, CH_2–O, J=7.4 Hz), 4.06 (t, 1H, CH, J=7.0 Hz), 2.58 (s, 3H, CH_3), 1.23 (t, 6H, CH_3, J=7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 166.7 (C═O), 156.2 (quat C), 155.0 (quat C), 152.3 (C═O), 150.3 (C═O), 144.7 (CH), 141.7 (quat C), 129.2 (CH), 127.2–127.0 (CH), 120.6 (quat C), 62.4 (CH_2–O), 51.1 (CH), 42.3 (CH_2–N), 25.2 (CH_3), 13.9 (CH_3); HRMS (CI) calcd for $C_{28}H_{29}N_6O_7$ (M+H)$^+$: 561.2098. Found: 561.2095.

Compound **10b**. IR (neat, cm^{-1}) 1735, 1618, 1575, 1492; ^{1}H NMR ($CDCl_3$) δ 8.09 (br s, 1H, NH), 8.04 (s, 1H, CH), 7.45–7.22 (m, 10H, H arom), 4.66 (s, 2H, CH_2–N), 4.18 (q, 4H, CH_2–O, J=7.1 Hz), 4.07 (q, 4H, CH_2–O, J=6.9 Hz), 3.87 (t, 1H, CH, J=5.9 Hz), 2.59 (s, 3H, CH_3), 2.56 (d, 2H, CH_2, J=5.9 Hz), 1.25 (t, 6H, CH_3, J=6.9 Hz), 1.14 (t, 6H, CH_3, J=7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 168.7 (C═O) (2 signals overlap), 156.3 (quat C), 155.9 (quat C), 152.3 (C═O), 150.3 (C═O), 144.8 (CH), 141.7 (quat C), 129.2 (CH), 127.2–127.1 (CH), 120.0 (quat C), 62.6 (CH_2–O), 62.0 (CH_2–O), 57.6 (CH), 48.3 (CH_2–N), 45.8 (quat C), 30.6 (CH_2), 25.2 (CH_3), 14.0 (CH_3), 13.6 (CH_3); HMRS (CI) calcd for $C_{36}H_{41}N_6O_{11}$ (M+H)$^+$: 733.2833. Found: 733.2826.

4.1.3. Ethyl 3-(2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)guanin-9-yl)-2-hydroxymethyl propanoate 11b. DBU (15.2 mg, 0.1 mmol) and ethyl-2-hydroxymethyl acrylate **7** (195 mg, 1.5 mmol) were added to a suspension of 2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)guanine (390 mg, 1 mmol) in DMF (6 mL). After 84 h stirring at room temperature, the solvent was removed under reduced pressure. Purification of the residue by column chromatography (silica gel, CH_2Cl_2/EtOAc: 1/9) gave **11b** (222 mg, 0.428 mmol, 43%) as a white powder: mp 68–69°C; IR (KBr, cm^{-1}) 3419, 1733, 1621, 1590, 1492, 1187; ^{1}H NMR ($CDCl_3$) δ 8.55 (br s, 1H, NH), 8.09 (s, 1H, CH), 7.47–7.33 (m, 10H, H arom), 4.70 (dd, 1H, CH_2–N, J=3.7, 14.5 Hz), 4.59 (dd, 1H, CH_2–N, J=4.7, 14.5 Hz), 4.15 (m, 2H, CH_2–O), 3.90 (dd, 1H, CH_2–O, J=4.5, 12.3 Hz), 3.59 (dd, 1H, CH_2–O, J=9.8, 12.3 Hz), 2.26 (s, 3H, CH_3), 1.24 (t, 3H, CH_3, J=7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 171.0 (C═O), 156.1 (quat C), 155.8 (quat C), 151.7 (C═O), 150.4 (C═O), 145.9 (CH), 141.6 (quat C), 129.2–127.4 (CH), 120.6 (quat C), 61.3 (CH_2–O), 58.2 (CH_2–OH), 48.1 (CH), 40.7 (CH_2–N), 24.9 (CH_3), 14.1 (CH_3). Anal. calcd for $C_{26}H_{26}N_6O_6$, 0.21H_2O: C, 59.79; H, 5.10; N, 16.09. Found: C, 59.54; H, 5.15; N, 15.98.

4.1.4. Ethyl 3-(4-*N*-benzoylcytosin-1-yl)-2-hydroxymethyl propanoate 11c. To a suspension of 4-*N*-benzoylcytosine (250 mg, 1.16 mmol) in DMF (7 mL) were added DBU (195 mg, 1.28 mmol) and **7** (166 mg, 1.28 mmol). The mixture was stirred for 12 h at room temperature and solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2 /EtOAc: 6/4→0/1) to give **11c** (255 mg, 0.738 mmol, 64%) as a white solid: mp 127–128°C; IR (KBr, cm^{-1}) 3357, 3156, 1714, 1668, 1560, 1488; ^{1}H NMR ($CDCl_3$) δ 8.92 (br s, 1H, NH), 7.90 (m, 2H, arom), 7.87 (d, 1H, CH, J=7.4 Hz), 7.62 (m, 1H, arom), 7.52 (m, 2H, arom), 7.51 (d, 1H, CH, J=7.4 Hz), 4.31 (dd, 2H, CH_2–N, J=6.3, 12.5 Hz), 4.19 (q, 2H, CH_2–O, J=7.1 Hz), 3.92 (dd, 1H, CH_2–O, J=5.4, 11.9 Hz), 3.81 (dd, 1H, CH_2–O, J=6.3, 11.9 Hz), 3.4 (br s, 1H, OH), 3.17 (m, 1H, CH), 1.27 (t, 3H, CH_3, J=7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 171.9 (C═O), 166.4 (C_6H_5CO), 162.8 (C═O), 156.0 (quat C), 150.5 (CH), 133.1 (quat C), 132.8 (CH), 128.8 (CH), 127.7 (CH), 96.9 (CH), 61.3 (CH_2–O), 60.0 (CH_2–O), 48.9 (CH_2–N), 46.1 (CH), 14.0 (CH_3). Anal. calcd for $C_{17}H_{19}N_3O_5$: C, 59.12; H, 5.55; N, 12.17. Found: C, 58.96; H, 5.44; N, 11.96.

4.1.5. Ethyl 3-(3-*N*-benzoylthymin-1-yl)-2-hydroxymethyl propanoate 11d. Reaction from 3-*N*-benzoylthymine (400 mg, 1.74 mmol), **7** (339 mg, 2.61 mmol) and

DBU (26.5 mg, 0.174 mmol) in acetonitrile (7 mL), in the same experimental conditions as for **11c**, led to **11d** (495 mg, 1.37 mmol, 79%) as a yellow oil after column chromatography (silica gel, CH_2Cl_2/EtOAc: 8/2→6/4): IR (neat, cm^{-1}) 3490, 1747, 1697, 1660, 1250, 1180; ^1H NMR ($CDCl_3$) δ 7.92 (m, 2H, arom), 7.65 (m, 1H, arom), 7.50 (m, 2H, arom), 7.26 (q, 1H, CH, J=1.2 Hz), 4.2 (q, 2H, CH_2–O, J=7.1 Hz), 4.09 (dd, 2H, CH_2–N, J=3.9, 6.7 Hz), 3.92 (dt, 1H, CH_2–O, J=5.4, 11.5 Hz), 3.79 (ddd, 1H, CH_2–O, J=4.2, 7.4, 11.5 Hz), 3.01 (m, 1H, CH), 2.67 (br s, 1H, OH), 1.95 (d, 3H, CH_3, J=1.2 Hz), 1.29 (t, 3H, CH_3, J=7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 171.9 (C═O), 168.7 (C_6H_5CO), 163.0 (C═O), 150.5 (C═O), 141.2 (CH), 135.1 (quat C), 131.4 (CH), 130.4 (CH), 129.9 (CH), 110.8 (quat C), 61.5 (CH_2–O), 60.1 (CH_2–O), 47.2 (CH_2–N), 46.2 (CH), 14.1 (CH_3), 12.4 (CH_3). Anal. calcd for $C_{18}H_{20}N_2O_6$, $0.2H_2O$: C, 59.40; H, 5.65; N, 7.70. Found: C, 59.42; H, 5.73; N, 7.95.

4.1.6. Dimethyl 2-(6-*N*-benzoyladenin-9-ylmethyl) succinate 12a and dimethyl 2-(6-*N*-benzoyladenin-7-ylmethyl) succinate 12a′. A solution of 6-*N*-benzoyladenine (235 mg, 0.983 mmol), dimethyl itaconate **8** (233 mg, 1.475 mmol) and K_2CO_3 (11.5 mg, 0.098 mmol) in DMF (4 mL) was heated at 80°C for 24 h. The mixture was evaporated under reduced pressure and both compounds were separated by column chromatography (silica gel, CH_2Cl_2/EtOAc: 1/9→0/1) to give successively isomer **12a′** (36.9 mg, 0.093 mmol, 9%) as a white solid then isomer **12a** (231.7 mg, 0.583 mmol, 59%) as a white solid.

Compound **12a**. Mp 109–111°C; IR (KBr, cm^{-1}) 3440, 3158, 3100, 1734, 1660; ^1H NMR ($CDCl_3$) δ 9.09 (br s, 1H, NH), 8.80 (s, 1H, CH), 8.07 (s, 1H, CH), 8.05 (d, 2H, arom, J=7.0 Hz), 7.62 (m, 1H, arom), 7.53 (m, 2H, arom), 4.70 (dd, 1H, CH_2–N, J=7.1, 14.1 Hz), 4.53 (dd, 1H, CH_2–N, J=5.6, 14.1 Hz), 3.71 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.51 (m, 1H, CH), 2.74 (dd, 1H, CH_2, J=6.4, 17.0 Hz), 2.69 (dd, 1H, CH_2, J=6.4, 17.0 Hz); ^{13}C NMR ($CDCl_3$) δ 172.3 (C═O), 171.3 (C═O), 164.8 (C_6H_5CO), 152.8 (CH), 152.3 (quat C), 150.0 (quat C), 147.7 (CH), 133.7 (quat C), 132.9 (CH), 129.0 (CH), 128.0 (CH), 122.8 (quat C), 52.7 (CH_3), 52.3 (CH_3), 44.2 (CH_2–N), 41.5 (CH), 33.4 (CH_2). Anal. calcd for $C_{19}H_{19}N_5O_5$: C, 57.43; H, 4.82; N, 17.62. Found: C, 57.17; H, 4.83; N, 17.33.

Compound **12a′**. Mp 61–62°C; IR (KBr, cm^{-1}) 3446, 3060, 3012, 1733, 1637; ^1H NMR ($CDCl_3$) δ 15.5 (br s, 1H, NH), 8.34 (s, 1H, CH), 8.23 (d, 2H, arom), 8.12 (s, 1H, CH), 7.54 (m, 1H, arom), 7.49 (m, 2H, arom), 5.15 (dd, 1H, CH_2–N, J=7.1, 13.7 Hz), 4.91 (dd, 1H, CH_2–N, J=7.3, 13.7 Hz), 3.78 (m, 1H, CH), 3.72 (s, 3H, CH_3), 3.62 (s, 3H, CH_3), 2.78 (dd, 1H, CH_2, J=4.3, 17.1 Hz), 2.60 (dd, 1H, CH_2, J=6.9, 17.1 Hz); ^{13}C NMR ($CDCl_3$) δ 179.0 (C_6H_5CO), 171.6 (C═O), 170.7 (C═O), 158.1 (quat C), 149.9 (quat C), 146.6 (CH), 141.6 (CH), 136.5 (quat C), 131.8 (CH), 128.8 (CH), 127.7 (CH), 114.6 (quat C), 52.0 (CH_3), 51.6 (CH_3), 47.4 (CH_2–N), 42.0 (CH), 32.2 (CH_2). Anal. calcd for $C_{19}H_{19}N_5O_5$: C, 57.43; H, 4.82; N, 17.62. Found: C, 57.73; H, 4.84; N, 17.46.

4.1.7. Dimethyl 2-(2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)-guanin-9-ylmethyl) succinate 12b. A solution of 2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)guanine (307 mg, 0.790 mmol), dimethyl itaconate **8** (187 mg, 1.18 mmol) and K_2CO_3 (9.1 mg, 0.077 mmol) in DMF (3 mL) was stirred for 60 h at room temperature. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel, CH_2Cl_2/EtOAc: 2/8→1/9) to afford **12b** (270 mg, 0.494 mmol, 63%) as a white solid: mp 68–70°C; IR (KBr, cm^{-1}) 3502, 3264, 1741, 1621, 1590, 1550, 1492; ^1H NMR ($CDCl_3$) δ 8.01 (br s, 1H, NH), 7.96 (s, 1H, CH), 7.46–7.24 (m, 10H, arom), 4.58 (dd, 1H, CH_2–N, J=7.4, 14.3 Hz), 4.45 (dd, 1H, CH_2–N, J=5.4, 14.3 Hz), 3.69 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 3.45 (m, 1H, CH), 2.68 (d, 2H, CH_2, J=6.1 Hz), 2.56 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 172.1 (C═O), 171.1 (C═O), 156.2 (quat C), 155.2 (quat C), 152.2 (C═O), 150.4 (C═O), 144.5 (CH), 141.7 (quat C), 129.2–126.3 (CH), 120.5 (quat C), 52.6 (CH_3), 52.1 (CH_3), 44.3 (CH_2–N), 41.3 (CH), 33.3 (CH_2), 25.1 (CH_3). Anal. calcd for $C_{27}H_{26}N_6O_7$: C, 59.34; H, 4.80; N, 15.38. Found: C, 59.01; H, 4.82; N, 15.15.

4.1.8. Dimethyl 2-(4-*N*-benzoylcytosin-1-ylmethyl) succinate 12c. A solution of 4-*N*-benzoylcytosine (250 mg, 1.16 mmol), dimethyl itaconate **8** (275 mg, 1.73 mmol) and DBU (212 mg, 1.39 mmol) in DMF (3.5 mL) was stirred for 40 h at room temperature. The mixture was evaporated under reduced pressure and the crude product was purified by column chromatography (silica gel, CH_2Cl_2/EtOAc: 75/25→4/6) to give **12c** (370 mg, 0.991 mmol, 58%) as a white solid: mp 132–133°C; IR (KBr, cm^{-1}) 3479, 1727, 1660, 1625, 1554, 1486, 1251; ^1H NMR ($CDCl_3$) δ 8.69 (br s, 1H, NH), 7.89 (m, 2H, arom), 7.79 (d, 1H, CH, J=7.9 Hz), 7.63 (m, 1H, arom), 7.53 (d, 1H, CH, J=7.9 Hz), 7.48 (m, 2H, arom), 4.19 (d, 2H, CH_2–N, J=5.5 Hz), 3.71 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.44 (m, 1H, CH), 2.85 (dd, 1H, CH_2, J=5.3, 17.1 Hz), 2.72 (dd, 1H, CH_2, J=6.3, 17.1 Hz); ^{13}C NMR ($CDCl_3$) δ 173.2 (C═O) (2 signal overlap), 172.0 (C═O), 163.1 (C_6H_5CO), 150.5 (CH), 133.6 (quat C), 133.5 (CH), 129.4 (CH), 128.1 (CH), 97.0 (CH), 52.9 (CH_3), 52.5 (CH_3), 52.1 (CH_2–N), 40.2 (CH), 34.1 (CH_2). Anal. calcd for $C_{18}H_{19}N_3O_6$: C, 57.90; H, 5.13; N, 11.26. Found: C, 57.75; H, 5.12; N, 11.13.

4.1.9. Dimethyl 2-(3-*N*-benzoylthymin-1-ylmethyl) succinate 12d. Reaction from 3-*N*-benzoylthymine (92 mg, 0.4 mmol), dimethyl itaconate **8** (63.3 mg, 0.4 mmol) and DBU (6.1 mg, 0.04 mmol) in acetonitrile (2 mL), in the same experimental conditions as for **11d**, led to **12d** (99 mg, 0.255 mmol, 64%) as a yellow oil after column chromatography (silica gel, CH_2Cl_2/EtOAc: 9/1): IR (neat, cm^{-1}) 3068, 3006, 1753, 1699, 1654, 1253, 1176; ^1H NMR ($CDCl_3$) δ 7.93 (m, 2H, arom), 7.65 (m, 1H, arom), 7.50 (m, 2H, arom), 7.21 (s, 1H, CH), 4.04 (dd, 1H, CH_2–N, J=8.0, 14.0 Hz), 3.97 (dd, 1H, CH_2–N, J=7.4, 14.0 Hz), 3.71 (s, 3H, CH_3), 3.69 (s, 3H, CH_3), 3.26 (m, 1H, CH), 2.76 (dd, 1H, CH_2, J=6.6, 17.0 Hz), 2.70 (dd, 1H, CH_2, J=6.3, 17.0 Hz), 1.96 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 172.6 (C═O), 171.8 (C═O), 168.8 (C═O), 163.0 (C_6H_5CO), 160.0 (C═O), 140.6 (CH), 135.0 (quat C), 131.5 (CH), 130.5 (CH), 129.1 (CH), 110.7 (quat C), 52.6 (CH_3), 52.1 (CH_3), 49.7 (CH_2–N), 40.5 (CH), 33.5 (CH_2), 12.4 (CH_3). Anal. calcd for $C_{19}H_{20}N_2O_7$: C, 58.76; H, 5.19; N, 7.21. Found: C, 58.37; H, 5.17; N, 7.01.

4.1.10. Dimethyl 2-(2-*N*-acetyl-7-deazaguanin-9-ylmethyl) succinate 13. A solution of 2-*N*-acetyl-6-*O*-acetyl-7-deazaguanine (57.6 mg, 0.246 mmol), dimethyl itaconate **8** (78.7 mg, 0.498 mmol) and DBU (41.7 mg, 0.274 mmol) in DMF (1 mL) was heated at 60°C for 60 h. The mixture was evaporated under reduced pressure and **13** (43 mg, 0.123 mmol, 49%) was obtained, after column chromatography (silica gel, CH_2Cl_2/MeOH: 97/3), as a brown powder: mp 71–72°C; IR (KBr, cm^{-1}) 3446, 3197, 1733, 1660; ^1H NMR ($CDCl_3$) δ 11.69 (br s, 1H, NH), 9.36 (br s, 1H, NH), 6.60 (d, 1H, CH, J=3.5 Hz), 6.53 (d, 1H, CH, J=3.5 Hz), 4.25 (dd, 1H, CH_2–N, J=6.8, 14.1 Hz), 4.12 (dd, 1H, CH_2–N, J=7.3, 14.1 Hz), 3.57 (s, 6H, CH_3), 3.26 (m, 1H, CH), 2.65 (dd, 1H, CH_2, J=7.1, 17.1 Hz), 2.45 (dd, 1H, CH_2, J=5.6, 17.1 Hz), 2.21 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 173.1 (C=O), 172.2 (C=O), 172.0 (C=O), 158.3 (C=O), 148.0 (quat C), 146.3 (quat C), 123.0 (CH), 105.3 (quat C), 103.7 (CH), 52.8 (CH_3), 52.4 (CH_3), 45.8 (CH_2–N), 42.8 (CH), 33.4 (CH_2), 24.7 (CH_3); HRMS (EI) calcd for $C_{15}H_{18}N_4O_6$: 350.1226. Found: 350.1230.

4.1.11. Dimethyl 2-(3-deazauracil-1-ylmethyl) succinate 14. Reaction from 2,4-dihydroxypyridine (104.3 mg, 0.939 mmol), dimethyl itaconate **8** (223 mg, 1.41 mmol) and DBU (157.2 mg, 1.03 mmol) in DMF (1 mL), in the same experimental conditions as for **12b**, gave **14** (148.5 mg, 0.551 mmol, 60%) as a yellow solid, after purification by column chromatography (silica gel, CH_2Cl_2/MeOH: 98/2→96/4): mp 190–192°C; IR (KBr, cm^{-1}) 3459, 1733, 1621, 1556, 1498; ^1H NMR (CD_3OD) δ 7.40 (d, 1H, CH, J=7.4 Hz), 6.02 (dd, 1H, CH, J=2.5, 7.4 Hz), 5.78 (d, 1H, CH, J=2.5 Hz), 4.84 (br s, 1H, OH), 4.12 (dd, 2H CH_2–N, J=1.7, 7.4 Hz), 3.65 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 3.29 (m, 1H, CH), 2.69 (dd, 1H, CH_2, J=8.4, 17.0 Hz), 2.60 (dd, 1H, CH_2, J=5.4, 17.0 Hz); ^{13}C NMR (CD_3OD) δ 177.3 (C=O), 176.1 (C=O), 169.4 (C=O), 143.6 (CH), 105.7 (CH), 102.5 (CH), 55.5 (CH_3), 55.2 (CH_3), 53.8 (CH_2–N), 44.9 (CH), 37.0 (CH_2); HRMS (EI) calcd for $C_{12}H_{15}NO_6$: 269.0899. Found: 269.0861.

4.1.12. 2-(Adenin-9-ylmethyl)-propane-1,3-diol 5a. To a suspension of $LiAlH_4$ (29.5 mg, 0.778 mmol) in anhydrous THF (1 mL), a solution of **9a** (100 mg, 0.243 mmol) in anhydrous THF (1 mL) was added at 0°C. The mixture was stirred at room temperature overnight. After cooling to 0°C, H_2O (0.1 mL) was added and the precipitate was removed by filtration and washed with EtOAc. Solvents were removed under reduced pressure and purification of the crude product by column chromatography (silica gel, CH_2Cl_2/MeOH: 95/5→9/1) afforded **5a** (24.2 mg, 0.108 mmol, 43%) as a white solid: mp 39.5–41°C; IR (KBr, cm^{-1}) 3446, 1643; ^1H NMR (CD_3OD) δ 8.22 (s, 1H, CH), 8.11 (s, 1H, CH), 4.34 (d, 2H, CH_2–N, J=5.6 Hz), 3.57 (dd, 2H, CH_2–O, J=5.6, 11.3 Hz), 3.53 (dd, 2H, CH_2–O, J=5.6, 11.3 Hz), 2.25 (m, 1H, CH); ^{13}C NMR (CD_3OD) δ 157.3 (quat C), 153.7 (CH), 151.0 (quat C), 143.4 (CH), 119.9 (quat C), 61.0 (CH_2–O), 45.2 (CH_2–N), 43.2 (CH); HRMS (CI) calcd for $C_9H_{12}N_5O_2$ $(M+H)^+$: 224.1147. Found: 224.1151.

4.1.13. 2-(Guanin-9-ylmethyl)-propane-1,3-diol 5b. To a solution of **11b** (450 mg, 0.869 mmol) in anhydrous ethanol, $LiBH_4$ (58 mg, 2.66 mmol) was added at 0°C. After stirring for 7 h at room temperature, acetone (4 mL) and 1 M HCl (4 mL) were added and the mixture was neutralized with 1 M NaOH. Solvents were evaporated under reduced pressure, the residue was taken up with a mixture CH_2Cl_2 (8)/MeOH (2) and was filtered on silica gel (2.5 g). After removal of solvents under reduced pressure, the residue was dissolved in MeOH (4 mL) and a saturated solution of NH_3 in MeOH (4 mL) was added at 0°C. The mixture was stirred at room temperature for 12 h and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH: 85/15→8/2) to lead to **5b** (107 mg, 0.448 mmol, 52%) as a white powder: mp >300°C; IR (KBr, cm^{-1}) 3432, 1693, 1648; ^1H NMR (CD_3OD) δ 10.57 (br s, 1H, NH), 7.62 (s, 1H, CH), 6.48 (br s, 2H, NH_2), 4.62 (t, 2H, OH, J=5.2 Hz), 3.94 (d, 2H, CH_2–N, J=7.2 Hz), 3.38 (dd, 2H,CH_2–O, J=5.7, 10.8 Hz), 3.31 (dd, 2H, CH_2–O, J=5.2, 10.8 Hz), 2.01 (m, 1H, CH); ^{13}C NMR (CD_3OD) δ 157.6 (C=O), 154.1 (quat C), 151.4 (quat C), 137.9 (CH), 116.4 (quat C), 58.9 (CH_2–O), 43.7 (CH_2–N), 41.4 (CH). Anal. calcd for $C_9H_{13}N_5O_3$: C, 45.18; H, 5.48; N, 29.27. Found: C, 45.19; H, 5.55; N, 29.31.

4.1.14. 2-(Thymin-1-ylmethyl)-propane-1,3-diol 5d. $CaCl_2$ (235 mg, 2.11 mmol) and $NaBH_4$ (164.1 mg, 4.23 mmol) were stirred in anhydrous THF (5 mL) for 1 h. Compound **11d** (507 mg, 1.41 mmol) in solution in anhydrous THF (5 mL) was added and the resulting mixture was stirred at room temperature for 12 h. After adding H_2O (0.6 mL), the solvent was evaporated under reduced pressure. The residue was dissolved in MeOH (4 mL) and a saturated solution of NH_3 in MeOH (4 mL) was added at 0°C. The mixture was stirred at room temperature for 12 h. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH: 95/5→9/1) to yield **5d** (175 mg, 0.818 mmol, 58%) as a white powder: mp 133–134°C; IR (KBr, cm^{-1}) 3428, 1679, 1489, 1224; ^1H NMR (CD_3OD) δ 7.44 (q, 1H, CH, J=1.2 Hz), 3.80 (d, 2H, CH_2–N, J=7.2 Hz), 3.59 (d, 4H, CH_2–O, J=5.7 Hz), 2.06 (m, 1H, CH), 1.87 (d, 3H, CH_3, J=1.2 Hz); ^{13}C NMR (CD_3OD) δ 168.1 (C=O), 154.7 (C=O), 145.1 (CH), 112.3 (quat C), 62.8 (CH_2–O), 49.5 (CH_2–N), 45.6 (CH),13.5 (CH_3); HRMS (EI) calcd for $C_{10}H_{14}N_2O_4$: 214.0954. Found: 214.0957.

4.1.15. 2-(Adenin-9-ylmethyl)-butane-1,4-diol 4a. Following the same procedure as for **5d**, compound **12a** (115 mg, 0.290 mmol) led, after column chromatography (silica gel, CH_2Cl_2/MeOH: 85/15→8/2), to **4a** (35 mg, 0.148 mmol, 51%) as a white powder: mp 36–37°C; IR (KBr, cm^{-1}) 3405, 1648, 1604; ^1H NMR (CD_3OD) δ 8.21 (s, 1H, CH), 8.15 (s, 1H, CH), 4.39 (dd, 1H, CH_2–N, J=7.1, 14.2 Hz), 4.27 (dd, 1H, CH_2–N, J=6.1, 14.2 Hz), 3.65 (m, 2H, CH_2–O), 3.46 (d, 2H, CH_2–O, J=5.7 Hz), 2.26 (m, 1H, CH), 1.65–1.57 (m, 2H, CH_2); ^{13}C NMR (CD_3OD) δ 159.1 (quat C), 155.5 (CH), 152.8 (quat C), 145.2 (CH), 121.7 (quat C), 64.3 (CH_2–O), 62.3 (CH_2–O), 47.8 (CH_2–N), 41.4 (CH), 34.6 (CH_2); HRMS (EI) calcd for $C_{10}H_{15}N_5O_2$: 237.1226. Found: 237.1228.

4.1.16. 2-(Guanin-9-ylmethyl)-butane-1,4-diol 4b. Following the same procedure as for **5b**, compound **12b** (280 mg, 0.513 mmol) led, after column chromatography (silica gel, CH_2Cl_2/MeOH: 85/15→8/2), to **4b** (64 mg,

0.253 mmol, 49%) as a white powder: mp 218–220°C; IR (KBr, cm^{-1}) 3446, 3135, 1691, 1608; ^1H NMR (CD_3OD) δ 7.76 (s, 1H, CH), 4.11 (d, 2H, CH_2–N, J=6.9 Hz), 3.65 (m, 2H, CH_2–O), 3.44 (m, 2H, CH_2–O), 2.18 (m, 1H, CH), 1.54 (m, 2H, CH_2); ^{13}C NMR (CD_3OD) δ 159.8 (C=O), 156.7 (quat C), 155.1 (quat C), 141.9 (CH), 118.4 (quat C), 64.1 (CH_2–O), 62.1 (CH_2–O), 47.1 (CH_2–N), 41.2 (CH), 34.3 (CH_2); HRMS (EI) calcd for $C_{10}H_{15}N_5O_3$: 253.1175. Found: 253.1151.

4.1.17. 2-(Cytosin-1-ylmethyl)-butane-1,4-diol 4c. Following the same procedure as for **5a**, compound **12c** (250 mg, 0.804 mmol) led, after column chromatography (silica gel, CH_2Cl_2/MeOH: 9/1→85/15), to **4c** (27.9 mg, 0.131 mmol, 17%) as a white powder: mp 142–143°C; IR (KBr, cm^{-1}) 3400, 3215, 1655, 1624, 1498; ^1H NMR (CD_3OD) δ 7.57 (d, 1H, CH, J=7.1 Hz), 5.86 (d, 1H, CH, J=7.1 Hz), 3.81 (dd, 1H, CH_2–O, J=6.4, 13.5 Hz), 3.77 (dd, 1H, CH_2–O, J=7.8, 13.5 Hz), 3.70–3.62 (m, 2H, CH_2–O), 3.50 (dd, 1H, CH_2–N, J=4.8, 11.8 Hz), 3.46 (dd, 1H, CH_2–N, J=4.6, 11.8 Hz), 2.08 (m, 1H, CH), 1.68–1.49 (m, 1H, CH_2); ^{13}C NMR (CD_3OD) δ 169.6 (C=O), 161.2 (quat C), 149.8 (CH), 97.3 (CH), 63.9 (CH_2–O), 62.3 (CH_2–O), 53.6 (CH_2–N), 40.5 (CH), 34.5 (CH_2); HRMS (EI) calcd for $C_9H_{15}N_3O_3$: 213.1113. Found: 213.1102.

4.1.18. 2-(Thymin-1-ylmethyl)-butane-1,4-diol 4d. Following the same procedure as for **5d**, compound **12d** (233 mg, 0.6 mmol) led, after column chromatography (silica gel, CH_2Cl_2/MeOH: 95/5→9/1), to **4d** (72 mg, 0.315 mmol, 53%) as a white solid: mp 108–109°C; IR (KBr, cm^{-1}) 3463, 3126, 3043, 1687, 1473; ^1H NMR (CD_3OD) δ 7.43 (q, 1H, CH, J=1.2 Hz), 3.75 (dd, 2H, CH_2–O, J=7.1, 13.8 Hz), 3.66 (m, 2H, CH_2–O), 3.51 (d, 2H, CH_2–N, J=4.7 Hz), 2.07 (m, 1H, CH), 1.87 (d, 3H, CH_3, J=1.2 Hz), 1.57 (m, 2H, CH_2); ^{13}C NMR (CD_3OD) δ 169.6 (C=O), 156.1 (C=O), 146.5 (CH), 113.7 (quat C), 65.2 (CH_2–O), 63.3 (CH_2–O), 53.4 (CH_2–N), 41.4 (CH), 35.4 (CH_2). Anal. calcd for $C_{10}H_{16}N_2O_4$, $0.25H_2O$: C, 51.60; H, 7.14; N, 12.01. Found: C, 51.82; H, 7.08; N, 11.68.

4.1.19. 2-(7-Deazaguanin-9-ylmethyl)-butane-1,4-diol 4e. Following the same procedure as for **5d**, compound **13** (70 mg, 0.200 mmol) led, after column chromatography (silica gel, CH_2Cl_2/MeOH: 9/1→85/15), to **4e** (27.1 mg, 0.107 mmol, 53%) as a pale yellow solid: mp 181–183°C; IR (KBr, cm^{-1}) 3400, 1635; ^1H NMR (CD_3OD) δ 6.72 (d, 1H, CH, J=3.6 Hz), 6.40 (d, 1H, CH, J=3.6 Hz), 4.67 (br s, 2H, OH), 4.03 (dd, 2H, CH_2–N, J=6.9, 6.4 Hz), 3.61 (m, 2H, CH_2–O), 3.40 (d, 2H, CH_2–O, J=4.9 Hz), 2.10 (m, 1H, CH), 1.52 (m, 2H, CH_2); ^{13}C NMR (CD_3OD) δ 163.8 (C=O), 155.5 (quat C), 154.2 (quat C), 125.1 (CH), 104.2 (CH), 102.8 (quat C), 64.4 (CH_2–O), 62.5 (CH_2–O), 48.1 (CH_2–N), 41.2 (CH), 34.5 (CH_2); HRMS (EI) calcd for $C_{11}H_{16}N_4O_3$: 252.1222. Found: 252.1217.

4.1.20. 2-(3-Deazauracil-1-ylmethyl)-butane-1,4-diol 4f. Following the same procedure as for **5a**, compound **14** (160 mg, 0.595 mmol) led, after column chromatography (silica gel, CH_2Cl_2/MeOH: 9/1), to **4f** (62.8 mg, 0.295 mmol, 49%) as a white solid: mp 94–96°C; IR (KBr, cm^{-1}) 3454, 3251, 1647, 1551, 1225; ^1H NMR (CD_3OD) δ 7.49 (d, 1H, CH, J=7.4 Hz), 6.06 (dd, 1H, CH, J=2.5, 7.4 Hz), 5.83 (d, 1H, CH, J=2.5 Hz), 3.94 (d, 2H, CH_2–N, J=7.6 Hz), 3.65 (m, 2H, CH_2–O), 3.47 (dd, 1H, CH_2–O, J=5.7, 11.8 Hz), 3.43 (dd, 1H, CH_2–O, J=4.2, 11.8 Hz), 2.07 (m, 1H, CH); ^{13}C NMR (CD_3OD) δ 171.6 (quat C), 168.6 (C=O), 149.9 (CH), 104.9 (CH), 101.8 (CH), 63.9 (CH_2–O), 62.5 (CH_2–O), 52.8 (CH_2–N), 41.0 (CH), 34.6 (CH_2); HRMS calcd for $C_{10}H_{15}NO_4$: 213.1001. Found: 213.0977.

Acknowledgements

We thank the local section of Sarthe of the Ligue Nationale contre le Cancer for a fellowship to S. G.

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