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Synthesis and biological activity of some 4-substituted 1-[1-(2,3-dihydroxy-1-propoxy)methyl-1,2,3-triazol-(4 & 5)-ylmethyl]-1*H*-pyrazolo[3,4-*d*]pyrimidines

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Abstract

Cycloaddition of **7a**, **b** with **6** gave, after separation and deprotection, two regioisomers **10a**, **b** and **11a**, **b**. The deprotected acyclic nucleoside **10a** used as the precursor for the preparation of 4-amino (**12**), 4-methylamino (**13**), 4-benzylamino (**14**), 4-methoxy (**15**) and 4-hydroxy (**16**) analogues. All acyclic nucleosides were evaluated for their inhibitory effects against HIV-1(IIIB), HIV-2(ROD) in MT-4 cells, for their anti-tumor activity and for their inhibitory effects against *Mycobacterium tuberculosis*. No marked activity was found.

Keywords: Acyclic nucleosides; Pyrazolo[3,4-*d*]pyrimidine; 1,2,3-Triazole; Biological evaluation

1. Introduction

Nucleoside analogues display a wide range of biological activities and have attracted considerable attention as anti-viral and anti-tumor agents [1]. Amongst these, nucleosides with an acyclic carbohydrate moiety have been shown to possess anti-viral activity [2–6]. Acyclovir **1** (ACV) and ganciclovir (DHPG) **2** (Fig. 1) have been approved for clinical use against herpes simplex virus type 1 and human cytomegalovirus infections, respectively. In spite of their potent anti-viral activity each compound suffers from a different problems regarding clinical utility [7–10]. Consequently, the search for new molecules which exhibit high therapeutic indexes is today of great interest for anti-viral research. In this respect, we recently reported the synthesis of some acyclic pyrazolo[3,4-*d*]pyrimidine nucleosides [11] **3a**–**h** (Fig. 1). Their anti-viral evaluation showed that non significant activity was found.

In connection with this work, and based on our interest in the insertion of 1,2,3-triazol-(4 or 5)-ylmethyl between heterocyclic rings and acyclic chains [12–15] or between nucleosides [16,17], we present the synthesis of some acyclic nucleosides **10a**, **b**, **11a**, **b** and **12**–**16** (Scheme 2) in order to determine the influence on biological evaluation of the 1,2,3-triazol-(4 or 5)-ylmethyl moiety as a spacer between the 4-substituted

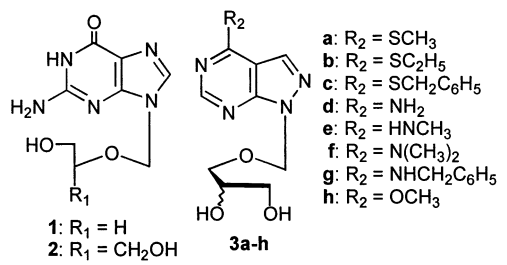

Fig. 1.

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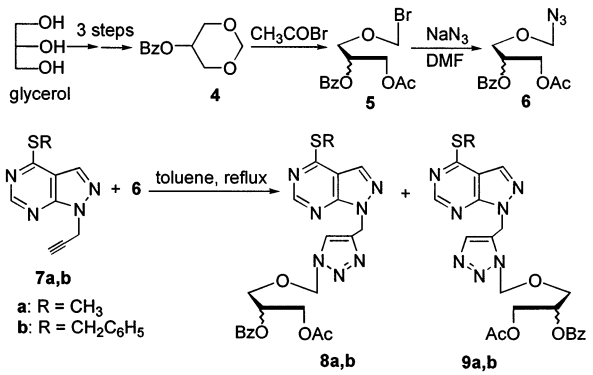
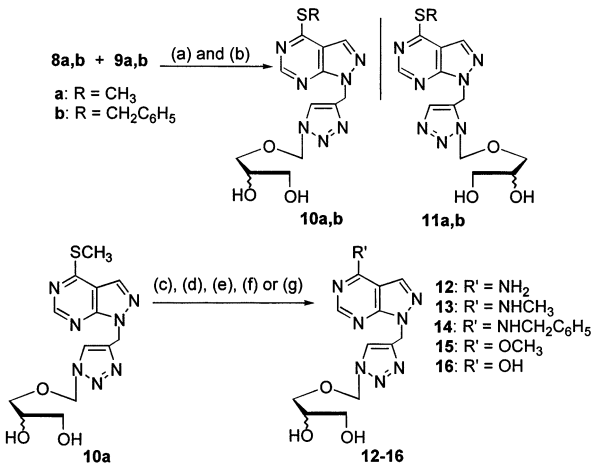


Scheme 1.



Scheme 2.

pyrazolo[3,4-*d*]pyrimidines and the (2,3-dihydroxy-1-propoxy)methyl chain. The synthesis and biological activity are described herein.

2. Results and discussion

For the synthesis of (3-acetoxy-2-*O*-benzoyl-1-propoxy)methylazide (**6**) (Scheme 1), we started from the 5-*O*-benzoyl-1,3-dioxane (**4**), which was prepared in three steps from the glycerol as previously described [11]. The cleavage of compound **4** with acetyl bromide gave (3-acetoxy-2-*O*-benzoyl-1-propoxy)methylbromide (**5**), as a clear oil, in 97% yield. Treatment of product **5** with sodium azide in anhydrous *N*,*N*-dimethylformamide (DMF) afforded compound **6** in 93% yield.

The 4-(methyl and benzyl)thio-1-propargyl-1*H*-pyrazolo[3,4-*d*]pyrimidines (**7a**, **b**) (Scheme 1) which have been described before [12] served as starting materials. The latter were reacted with azido-compound **6** via 1,3-dipolar cycloaddition reaction, in anhydrous toluene under reflux, to afford a mixture of two possible regioisomers (**8a** + **9a**) and (**8b** + **9b**) in 78 and 84% overall yield, respectively (Scheme 1). It is well known from the literature [18] that the addition of azides to unsymmetrical acetylenes is determined by steric and electronic factors. In general, such addition tends to give mainly the isomers with electron withdrawing groups at the 4-position and electron releasing groups at 5-position. Thus, after separation of protected acyclic nucleosides **8a**, **b** and **9a**, **b** on silica gel column chromatography, compounds **8a**, **b** were obtained as the major regioisomers in 59 and 64% yield, respectively. The structures of the two regioisomers **8a**, **b** and **9a**, **b** were established by comparison of the chemical shift values for the triazole ring protons with those available from a known pair 4- and 5-substituted 1,2,3-triazole derivatives [12,13,18]. The 1,4-regioisomers **8a**, **b** showed an H-5 resonance at lower field (8.21 and 8.20 ppm, respectively). For 1,5-regioisomers **9a**, **b**, the H-4 resonance is at higher field (7.70 and 7.59 ppm, respectively). The differences in the chemical shifts between regioisomers are in agreement with literature data [12,13,18].

The benzoyl and acetyl groups were subsequently removed from the protected acyclic nucleosides **8a**, **b** and **9a**, **b** by treatment with a solution of methanol saturated with ammonia at 25 °C, affording the required acyclic nucleosides **10a**, **b** and **11a**, **b** in quantitative yield (Scheme 2).

When compound **10a** was treated with methanol saturated with ammonia in a sealed reacting vessel at 100 °C, the acyclic nucleoside **12** was obtained in 85% yield. Condensation of compound **10a** with primary amines in aqueous or alcohol solution afforded compounds **13** and **14** in 90 and 85% yield, respectively. The acyclic nucleosides **15** and **16** were synthesized in 84 and 78% yield, respectively, via treatment of **10a** with CH_3ONa/CH_3OH and NaOH solutions at room temperature (Scheme 2).

Structure identification of the synthetic products was done by ^1H NMR, mass spectra and elemental analysis.

2.1. Biological activity

Compounds **10a**, **b**, **11a**, **b** and **12**–**16** were evaluated for their cytotoxicity and their inhibitory effects on HIV-1(IIIB) and HIV-2(ROD) replication in MT-4 cells. No significant activity was found against the replication of HIV-1(IIIB) and HIV-2(ROD) at subtoxic concentration.

These compounds were also evaluated for their antitumor activity using a series of tumor-cell lines (leukemia, colon cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, breast cancer, brain cancer, non-small cell lung cancer). However, none of the compounds showed appreciable anti-tumor activity at compound concentrations lower than 10^{-4} M.

All above mentioned acyclic nucleosides were also evaluated for their inhibitory effect against *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294) in BACTEC 12B medium. No anti-tuberculosis activity was noted at concentrations up to 12.5 μg/ml. However, compound **7b** [14] had potent activity (90% of inhibition at a concentration of 12.5 μg/ml).

3. Conclusions

We showed that the 1,3 dipolar cycloaddition reaction is an efficient method to obtain the acyclic 1,2,3-triazol-(4 and 5)-ylmethyl-1*H*-pyrazolo[3,4-*d*]pyrimidine nucleosides with the same acyclic chain as in the anti-herpetic *iso*-DHPG, in good yield, from easily accessible starting materials. Unfortunately, the biological evaluation of these compounds has not shown significant anti-HIV, anti-tumor and anti-tuberculosis activities. Their anti-herpetic evaluations are in progress.

4. Experimental procedures

4.1. General

Melting points (m.p.) were determined in a Electrothermal digital melting point apparatus and are uncorrected. The ^{1}H NMR spectra were obtained in a Bruker AC-250 spectrometer operating at 250 MHz. The chemical shifts were reported as parts per million (δ ppm) from $(CH_3)_4Si$ (TMS) as an internal standard. Key: s (singlet), d (doublet), t (triplet), m (multiplet) and br (broad). Mass spectra were obtained with a JEOL JMS DX 300 instrument using fast atomic bombardment (FAB positive), matrix: 3-nitrobenzyl alcohol (3-NBA) or glycerol–triglycerol (G/T) 1:1. A Perkin–Elmer 580 instrument was used to determine IR spectra. Thin-layer chromatography (TLC) was performed on plates of Merck Kieselgel 60 F_{254} and short wavelength UV light (254 nm) was used to detect the UV-absorbing spots. Solvent A: chloroform–MeOH, 90:10, solvent B: chloroform–MeOH, 80:20. R_f^2 is R_f after two migrations in hexane–ethyl acetate, 70:30. Column chromatography separations were obtained on silica gel 60 (70-230 mesh, Merck). Elemental analyses were determined by a French microanalytical central service.

4.2. (3-Acetoxy-2-O-benzoyl-1-propoxy)methylbromide (5)

Freshly distilled acetyl bromide (4.70 g, 38.21 mmol) was stirred magnetically with cooling in an ice bath while 7.92 g (38.07 mmol) of compound **4** was added slowly. A rapid exothermic reaction occurred providing quantitative conversion to **5**. Vacuum distillation of this material gave 12.22 g (97%) of **5**. IR (CCl_4): $\nu = 1741$, 1725 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 2.02$ (s, 3H, CH_3), 3.92 (d, $J = 4.90$ Hz, 2H, OCH_2CH), 4.32 (distorted d, 2H, CH_2OAc), 5.41 (m, 1H, $CHOBz$), 5.46 (s, 2H, OCH_2Br), 7.50 and 8.05 (2m, 5H, C_6H_5). $^+$FAB MS (3-NBA); m/z: 322 $(M+H)^+$.

4.3. (3-Acetoxy-2-O-benzoyl-1-propoxy)methylazide (6)

To a solution of finely ground NaN_3 (3.57 g, 55 mmol) in 300 ml of anhydrous DMF was added 12.14 g (36.67 mmol) of freshly distilled compound **5** and the resulting mixture was heated at 90 °C under stirring for 4 h. The solid was removed and washed with DMF (3×30 ml). To a combined filtrate and washings was added 100 ml of water and the mixture was extracted with ether (4×60 ml). The extracts were combined, dried ($MgSO_4$) and then evaporated in vacuo to leave a pale yellow oil. The oil was purified on a column of silica gel, using hexane as eluent, to give compound **6** (10 g, 93%) as a clear oil. IR (CCl_4): $\nu = 2120$, 1741, 1725 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 2.02$ (s, 3H, CH_3), 3.92 (d, $J = 4.90$ Hz, 2H, OCH_2CH), 4.32 (distorted d, 2H, CH_2OAc), 5.41 (m, 1H, $CHOBz$), 5.50 (s, 2H, OCH_2N_3), 7.50 and 8.05 (2m, 5H, C_6H_5). $^+$FAB MS (3-NBA); m/z: 294 $(M+H)^+$. *Anal.* Calc. for $C_{13}H_{15}N_3O_5$ (293.27): C, 53.24; H, 5.15; N, 14.23. Found: C, 53.47; H, 5.19; N, 14.48%.

4.4. General procedure for the preparation of 8a, b and 9a, b

A mixture of propargylated heterocycle **7a** or **7b** (10 mmol) and the azide derivative **6** (15 mmol) in anhydrous toluene (100 ml) was refluxed for 38 h. The reaction was monitored by TLC and was shown to be completed at this time with formation of two isomers. The solution was evaporated to dryness. The mixture of regioisomers was separated in a silica gel column, using hexane–ethyl acetate (70:30) mixture as eluent, to give: from the fastest moving band 0.94 g (19%) of **9a** or 1.15 g (20%) of **9b** (as a white foam) and from the slowest moving band 2.94 g (59%) of **8a** (as an amorphous solid) or 3.67 g (64%) of **8b** (as a white foam).

4.5. 1-[1-(3-Acetoxy-2-O-benzoyl-1-propoxy)methyl-1,2,3-triazol-4-ylmethyl]-4-methylthio-1H-pyrazolo-[3,4-d]pyrimidine (8a)

$R_f^2 = 0.40$. M.p. 77–78 °C ($CHCl_3$–hexane). ^{1}H NMR (DMSO-d_6): $\delta = 1.92$ (s, 3H, CH_3), 2.68 (s, 3H, SCH_3), 3.76 (d, $J = 4.99$ Hz, 2H, OCH_2CH), 4.20 (m, 2H, CH_2OAc), 5.29 (m, 1H, CHOBz), 5.65 (s, 2H, CCH_2N), 5.70 (s, 2H, OCH_2N), 7.47–7.88 (m, 5H, C_6H_5), 8.21 (s, 1H, aromatic proton of triazole group),

8.31 and 8.77 (2s, 2H, H-3 and H-6). $^+$FAB MS (3-NBA); m/z: 498 $(M+H)^+$. *Anal.* Calc. for $C_{22}H_{23}N_7O_5S$ (497.52): C, 53.11; H, 4.65; N, 19.70. Found: C, 53.46; H, 4.91; N, 19.85%.

4.6. 1-[1-(3-Acetoxy-2-O-benzoyl-1-propoxy)methyl-1,2,3-triazol-5-ylmethyl]-4-methylthio-1H-pyrazolo-[3,4-d]pyrimidine (**9a**)

$R_f^2 = 0.46$. ^{1}H NMR (DMSO-d_6): $\delta = 1.91$ (s, 3H, CH_3), 2.66 (s, 3H, SCH_3), 3.66 (d, $J = 4.96$ Hz, 2H, OCH_2CH), 4.10 (m, 2H, CH_2OAc), 5.14 (m, 1H, CHOBz), 5.79 (s, 2H, CCH_2N), 6.85 (s, 2H, OCH_2N), 7.44–7.85 (m, 5H, C_6H_5), 7.70 (s, 1H, aromatic proton of triazole group), 8.29 and 8.74 (2s, 2H, H-3 and H-6). $^+$FAB MS (3-NBA); m/z: 498 $(M+H)^+$. *Anal.* Calc. for $C_{22}H_{23}N_7O_5S$ (497.52): C, 53.11; H, 4.65; N, 19.70. Found: C, 53.49; H, 4.93; N, 19.89%.

4.7. 1-[1-(3-Acetoxy-2-O-benzoyl-1-propoxy)methyl-1,2,3-triazol-4-ylmethyl]-4-benzylthio-1H-pyrazolo-[3,4-d]pyrimidine (**8b**)

$R_f^2 = 0.48$. ^{1}H NMR (DMSO-d_6): $\delta = 1.90$ (s, 3H, CH_3), 3.75 (d, $J = 4.97$ Hz, 2H, OCH_2CH), 4.18 (m, 2H, CH_2OAc), 4.65 (s, 2H, SCH_2), 5.25 (m, 1H, CHOBz), 5.64 (s, 2H, CCH_2N), 5.69 (s, 2H, OCH_2N), 7.22–7.65 (m, 10H, 2 C_6H_5), 8.20 (s, 1H, aromatic proton of triazole group), 8.28 and 8.81 (2s, 2H, H-3 and H-6). $^+$FAB MS (3-NBA); m/z: 574 $(M+H)^+$. *Anal.* Calc. for $C_{28}H_{27}N_7O_5S$ (573.62): C, 58.62; H, 4.74; N, 17.09. Found: C, 58.90; H, 4.81; N, 17.21%.

4.8. 1-[1-(3-Acetoxy-2-O-benzoyl-1-propoxy)-methyl-1,2,3-triazol-5-ylmethyl]-4-benzylthio-1H-pyrazolo-[3,4-d]pyrimidine (**9b**)

$R_f^2 = 0.55$. ^{1}H NMR (DMSO-d_6): $\delta = 1.90$ (s, 3H, CH_3), 3.60 (d, $J = 4.97$ Hz, 2H, OCH_2CH), 4.18 (m, 2H, CH_2OAc), 4.68 (s, 2H, SCH_2), 5.19 (m, 1H, CHOBz), 5.80 (s, 2H, CCH_2N), 6.90 (s, 2H, OCH_2N), 7.22–7.65 (m, 10H, 2 C_6H_5), 7.59 (s, 1H, aromatic proton of triazole group), 8.30 and 8.80 (2s, 2H, H-3 and H-6). $^+$FAB MS (3-NBA); m/z: 574 $(M+H)^+$. *Anal.* Calc. for $C_{28}H_{27}N_7O_5S$ (573.62): C, 58.62; H, 4.74; N, 17.09. Found: C, 58.96; H, 4.83; N, 17.28%.

4.9. General procedure for the preparation of **10a**, **b** and **11a**, **b**

To 45 ml of anhydrous methanol saturated with NH_3 at -5 °C was added 1 mmol of the protected product **8a**, **b** or **9a**, **b**. The flask was stoppered tightly and the solution was stirred for 20 h at room temperature (r.t.). TLC evaluation indicated that complete deprotection of the protected product had occurred. Volatile materials were evaporated in vacuo and the resulting solid was recrystallized or, if necessary, purified on a column of silica gel, using chloroform–methanol (96:4) mixture as eluent, to obtain the expected acyclic nucleoside.

4.10. 1-[1-(2,3-Dihydroxy-1-propoxy)methyl-1,2,3-triazol-4-ylmethyl]-4-methylthio-1H-pyrazolo-[3,4-d]pyrimidine (**10a**)

Yield: 0.33 g (94%). $R_f = 0.52$ (solvent A). M.p. 106–107 °C (ethanol). ^{1}H NMR (DMSO-d_6): $\delta = 2.66$ (s, 3H, SCH_3), 3.20–3.47 (m, 5H, OCH_2CHCH_2), 4.50 (t, $J = 5.64$ Hz, 1H, $HOCH_2$, D_2O exchangeable), 4.74 (d, $J = 5.00$ Hz, 1H, CHO*H*, D_2O exchangeable), 5.62 (s, 2H, CCH_2N), 5.67 (s, 2H, OCH_2N), 8.16 (s, 1H, aromatic proton of triazole group), 8.31 and 8.76 (2s, 2H, H-3 and H-6). $^+$FAB MS (GT); m/z: 352 $(M+H)^+$. *Anal.* Calc. for $C_{13}H_{17}N_7O_3S$ (351.37): C, 44.43; H, 4.87; N, 27.90. Found: C, 44.41; H, 4.99; N, 27.88%.

4.11. 1-[1-(2,3-Dihydroxy-1-propoxy)methyl-1,2,3-triazol-5-ylmethyl]-4-methylthio-1H-pyrazolo-[3,4-d]pyrimidine (**11a**)

Yield: 0.33 g (94%). $R_f = 0.59$ (solvent A). M.p. 92–93 °C (ethanol). ^{1}H NMR (DMSO-d_6): $\delta = 2.73$ (s, 3H, SCH_3), 3.21–3.47 (m, 5H, OCH_2CHCH_2), 4.54 (t, $J = 5.64$ Hz, 1H, $HOCH_2$, D_2O exchangeable), 4.78 (d, $J = 4.98$ Hz, 1H, CHO*H*, D_2O exchangeable), 5.85 (s, 2H, CCH_2N), 5.89 (s, 2H, OCH_2N), 7.67 (s, 1H, aromatic proton of triazole group), 8.42 and 8.84 (2s, 2H, H-3 and H-6). $^+$FAB MS (GT); m/z: 352 $(M+H)^+$. *Anal.* Calc. for $C_{13}H_{17}N_7O_3S$ (351.37): C, 44.43; H, 4.87; N, 27.90. Found: C, 44.39; H, 4.98; N, 27.83%.

4.12. 4-Benzylthio-1-[1-(2,3-dihydroxy-1-propoxy)-methyl-1,2,3-triazol-4-ylmethyl]-1H-pyrazolo[3,4-d]-pyrimidine (**10b**)

Yield: 0.40 g (93%). $R_f = 0.45$ (solvent A). M.p. 100–100 °C (ethanol). ^{1}H NMR (DMSO-d_6): $\delta =$ 3.21–3.48 (m, 5H, OCH_2CHCH_2), 4.08 (s, 2H, SCH_2), 4.53 (t, $J = 5.64$ Hz, 1H, $HOCH_2$, D_2O exchangeable), 4.77 (d, $J = 5.03$ Hz, 1H, CHO*H*, D_2O exchangeable), 5.65 (s, 2H, CCH_2N), 5.69 (s, 2H, OCH_2N), 7.26 (m, 5H, C_6H_5), 8.18 (s, 1H, aromatic proton of triazole group), 8.24 and 8.62 (2s, 2H, H-3 and H-6). $^+$FAB MS (GT); m/z: 428 $(M+H)^+$. *Anal.* Calc. for $C_{19}H_{21}N_7O_3S$ (427.47): C, 53.38; H, 4.95; N, 22.93. Found: C, 53.27; H, 4.97; N, 22.85%.

*4.13. 4-Benzylthio-1-[1-(2,3-dihydroxy-1-propoxy)-methyl-1,2,3-triazol-5-ylmethyl]-1H-pyrazolo[3,4-d]-pyrimidine (**11b**)*

Yield: 0.40 g (93%). $R_f = 0.52$ (solvent A). M.p. 86–87 °C (ethanol). ^{1}H NMR (DMSO-d_6): $\delta = 3.20$–3.50 (m, 5H, OCH_2CHCH_2), 4.08 (s, 2H, SCH_2), 4.49 (t, $J = 5.64$ Hz, 1 H, $HOCH_2$, D_2O exchangeable), 4.73 (d, $J = 5.01$ Hz, 1H, CHO*H*, D_2O exchangeable), 5.80 (s, 2H, CCH_2N), 5.83 (s, 2H, OCH_2N), 7.26 (m, 5H, C_6H_5), 7.60 (s, 1H, aromatic proton of triazole group), 8.27 and 8.62 (2s, 2H, H-3 and H-6). $^+$FAB MS (GT); m/z: 428 $(M+H)^+$. *Anal.* Calc. for $C_{19}H_{21}N_7O_3S$ (427.47): C, 53.38; H, 4.95; N, 22.93. Found: C, 53.22; H, 5.00; N, 22.80%.

*4.14. 4-Amino-1-[1-(2,3-dihydroxy-1-propoxy)-methyl-1,2,3-triazol-4-ylmethyl]-1H-pyrazolo[3,4-d]pyrimidine (**12**)*

Solution of **10a** (0.18 g, 0.51 mmol) in 30 ml of methanol saturated with ammonia (previously saturated at −5 °C) was heated at 100 °C for 20 h in a sealed reacting vessel. After removal of the solvent, the resulting solid was recrystallized from 95% ethanol to provide pure compound **12** (0.14 g, 85%). $R_f =$ 0.32 (solvent B). M.p. 178–179 °C (ethanol). ^{1}H NMR (DMSO-d_6): $\delta = 3.18$–3.50 (m, 5H, OCH_2CHCH_2), 4.50 (t, $J = 5.64$ Hz, 1H, $HOCH_2$, D_2O exchangeable), 4.74 (d, $J = 5.02$ Hz, 1H, CHO*H*, D_2O exchangeable), 5.51 (s, 2H, CCH_2N), 5.62 (s, 2H, OCH_2N), 7.70 (br s, 2H, NH_2, D_2O exchangeable), 8.06 (s, 1H, aromatic proton of triazole group), 8.09 and 8.17 (2s, 2H, H-3 and H-6). $^+$FAB MS (GT); m/z: 321 $(M+H)^+$. *Anal.* Calc. for $C_{12}H_{16}N_8O_3$ (320.30): C, 44.99; H, 5.03; N, 34.98. Found: C, 44.57; H, 5.01; N, 34.90%.

*4.15. 1-[1-(2,3-Dihydroxy-1-propoxy)methyl-1,2,3-triazol-4-ylmethyl]-4-methylamino-1H-pyrazolo-[3,4-d]pyrimidine (**13**)*

A solution of 0.21 g (0.60 mmol) of **10a** in 40% aqueous methylamine (6.3 ml) was refluxed for 10 min. The reaction was monitored by TLC, and was complete at this time. After cooling, the residue was coevaporated with benzene (5 × 4 ml) and the resulting solid was recrystallized from ethanol to provide crystalline **13** (0.18 g, 90%). $R_f = 0.13$ (solvent A). M.p. 136–137 °C (ethanol). ^{1}H NMR (DMSO-d_6): $\delta = 2.93$ (d, $J = 4.56$ Hz, 3H, CH_3), 3.20–3.50 (m, 5H, OCH_2CHCH_2), 4.50 (t, $J = 5.64$ Hz, 1H, $HOCH_2$, D_2O exchangeable), 4.74 (d, $J = 4.96$ Hz, 1H, CHO*H*, D_2O exchangeable), 5.52 (s, 2H, CCH_2N), 5.62 (s, 2H, OCH_2N), 8.03 (s, 1H, aromatic proton of triazole group), 8.07 and 8.25 (2s, 2H, H-3 and H-6), 8.23 (m, 1H, HN, D_2O exchangeable). $^+$FAB MS (3-NBA); m/z: 335 $(M+H)^+$. *Anal.* Calc. for $C_{13}H_{18}N_8O_3$ (334.33): C, 46.70; H, 5.42; N, 33.51. Found: C, 46.60; H, 5.44; N, 33.43%.

*4.16. 4-Benzylamino-1-[1-(2,3-dihydroxy-1-propoxy)-methyl-1,2,3-triazol-4-ylmethyl]-1H-pyrazolo[3,4-d]-pyrimidine (**14**)*

To a solution of **10a** (0.21 g, 0.60 mmol) in absolute ethanol (7 ml) was added 2.43 ml of freshly distilled benzylamine and the mixture was heated at reflux temperature with stirring overnight. The solvent was removed in vacuo, the residue was purified on a column of silica gel, using chloroform–methanol (98:2) mixture as eluent, and then recrystallized from ethanol to give compound **14** (0.21 g, 85%). $R_f = 0.31$ (solvent A). M.p. 115–116 °C (ethanol). ^{1}H NMR (DMSO-d_6): $\delta = 3.27$–3.57 (m, 5H, OCH_2CHCH_2), 4.58 (t, $J = 5.64$ Hz, 1H, $HOCH_2$, D_2O exchangeable), 4.77 (d, $J = 5.00$ Hz, 1H, CHO*H*, D_2O exchangeable), 4.82 (d, $J = 5.00$ Hz, 2H, $HNCH_2$), 5.62 (s, 2H, CCH_2N), 5.70 (s, 2H, OCH_2N), 7.27–7.40 (m, 5H, C_6H_5), 8.15 (s, 1H, aromatic proton of triazole group), 8.19 and 8.35 (2s, 2H, H-3 and H-6), 8.85 (t, $J = 5.00$ Hz, 1H, HN, D_2O exchangeable). $^+$FAB MS (3-NBA); m/z: 411 $(M+H)^+$. *Anal.* Calc. for $C_{19}H_{22}N_8O_3$ (410.43): C, 55.60; H, 5.40; N, 27.30. Found: C, 55.50; H, 5.42; N, 27.22%.

*4.17. 1-[1-(2,3-Dihydroxy-1-propoxy)methyl-1,2,3-triazol-4-ylmethyl]-4-methoxy-1H-pyrazolo[3,4-d]-pyrimidine (**15**)*

A solution of 0.20 g (8.60 mmol) of sodium was dissolved in 50 ml of anhydrous methanol. To this solution 2 g (5.69 mmol) of compound **10a** was added. The mixture was stirred at r.t. for 5 h. The resulting clear solution was neutralized with Amberlite IRN77. The resin was removed by filtration and washed with hot methanol (3 × 50 ml). The filtrate and washings were combined and evaporated under reduced pressure to provide a colorless solid. This solid was recrystallized from ethanol to furnish acyclic nucleoside **15** (1.60 g, 84%); $R_f = 0.40$ (solvent A). M.p. 108–109 °C (ethanol). ^{1}H NMR (DMSO-d_6): $\delta = 3.24$–3.50 (m, 5H, OCH_2CHCH_2), 4.10 (s, 3H, CH_3), 4.53 (t, $J = 5.64$ Hz, 1H, $HOCH_2$, D_2O exchangeable), 4.77 (d, $J = 4.96$ Hz, 1H, CHO*H*, D_2O exchangeable), 5.67 (s, 2H, CCH_2N), 5.71 (s, 2H, OCH_2N), 8.20 (s, 1H, aromatic proton of triazole group), 8.25 and 8.63 (2s, 2H, H-3 and H-6). $^+$FAB MS (3-NBA); m/z: 336 $(M+H)^+$. *Anal.* Calc. for $C_{13}H_{17}N_7O_4$ (335.31): C, 46.56; H, 5.11; N, 29.23. Found: C, 46.31; H, 5.11; N, 29.23%.

4.18. 1-[1-(2,3-Dihydroxy-1-propoxy)methyl-1,2,3-triazol-4-ylmethyl]-4-hydroxy-1H-pyrazolo[3,4-d]-pyrimidine (**16**)

Compound **10a** (0.21 g, 0.60 mmol) was stirred in 2 N NaOH (50 ml) at r.t. for 3 h. The reaction was monitored by TLC and was shown to be complete at this time. After neutralization using a 2 N HCl solution and filtration, the solvent was removed in vacuo. The residue was coevaporated with benzene (5 × 4 ml) and the resulting solid was purified on a column of silica gel, using chloroform–methanol (96:4) as eluent, to give crystalline **16** (0.15 g, 78%). $R_f = 0.11$ (solvent A). M.p. 172–173 °C (ethanol). ^{1}H NMR (DMSO-d_6): δ = 3.27–3.56 (m, 5H, OCH_2CHCH_2), 4.59 (t, $J = 5.53$ Hz, 1H, $HOCH_2$, D_2O exchangeable), 4.83 (d, $J = 4.77$ Hz, 1H, CHO*H*, D_2O exchangeable), 5.61 (s, 2H, CCH_2N), 5.71 (s, 2H, OCH_2N), 8.11 (s, 1H, aromatic proton of triazole group), 8.15 and 8.22 (2s, 2H, H-3 and H-6), 12.22 (br s, 1H, OH, D_2O exchangeable). $^+$FAB MS (3-NBA); *m*/*z*: 322 $(M + H)^+$. *Anal.* Calc. for $C_{12}H_{15}N_7O_4$ (321.29): C, 44.86; H, 4.70; N, 30.51; Found: C, 44.75; H, 4.72; N, 30.69%.

4.19. Biological assays

The anti-viral experiments using MT-4 cell cultures and HIV(IIIB) and HIV-2(ROD) were performed following procedures that have been previously described [19,20].

The anti-tumor experiments were realized in the National Cancer Institute using the procedure published in *Seminars in Oncology* [21].

The anti-tuberculosis assay is as described previously [22].

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References

[1] (a) C.K. Chu, D.C. Baker, Plenum Press, New York, 1993;
(b) J.B. Hobbs, in: C. Hansch, P.G. Sammes, J.B. Taylor (Eds.), Comprehensive Medicinal Chemistry, vol. 2, Pergamon press, Oxford, 1990, pp. 306–322.
[2] H.J. Schaeffer, L. Beauchamp, P. De miranda, G.B. Elion, D.J. Bauer, P. Collins, Nature (London) 272 (1978) 583–585.
[3] A. Larsson, S. Alenius, N.G. Johansson, B. Öberg, Antivir. Res. 3 (1983) 77–86.
[4] T.S. Lin, M.C. Liu, Tetrahedron Lett. 25 (1984) 905–906.
[5] H.H. Balfour, Rev. Infect. Dis. 12 (1990) 849–860.
[6] (a) E.S.H. El Ashry, Y. El Kilany, Adv. Heterocycl. Chem. 67 (1996) 391–438;
(b) E.S.H. El Ashry, Y. El Kilany, Adv. Heterocycl. Chem. 68 (1997) 1–88;
(c) E.S.H. El Ashry, Y. El Kilany, Adv. Heterocycl. Chem. 69 (1998) 129–215.
[7] P. Collins, M.N. Ellis, J. Med. Virol. 1 (1993) 58–66.
[8] J.D. Meyers, Annu. Rev. Med. 42 (1991) 179–187.
[9] P. De Miranda, T. Burnette, D. Cederberg, M.R. Blum, H.R. Brodie, J. Millis, Program Abstr. 26th Interscience Conference on Antimicrobial Agents and Chemotherapy, 1986, Abstr. No. 566.
[10] J.C. Drach, in: E. De Clercq, R.T. Walker (Eds.), Target for the Design of Antiviral Agents. In: Life Sciences, vol. 73, Plenum Press, New York, 1983, pp. 231–257.
[11] M.L. Taha, H.B. Lazrek, Bull. Soc. Chim. Belg. 106 (1997) 163–168.
[12] O. Moukha-chafiq, M.L. Taha, H.B. Lazrek, C. Pannecouque, M. Witvrouw, E. De Clercq, J.L. Barascut, J.L. Imbach, Nucleosides Nucleotides 20 (2001), in press.
[13] O. Moukha-chafiq, M.L. Taha, H.B. Lazrek, J.J. Vasseur, C. Pannecouque, M. Witvrouw, E. De Clercq, Nucleosides Nucleotides 20 (2001), in press.
[14] O. Moukha-Chafiq, M.L. Taha, H.B. Lazrek, J.L. Barascut, J.L. Imbach, C. R. Acad. Sci., Paris, t. 321, Série IIc 3 (2000) 639–641.
[15] H.B. Lazrek, M. Taourirte, T. Oulih, M. Lebtoumi, J.L. Barascut, J.L. Imbach, Nucleosides Nucleotides 16 (1997) 1115–1118.
[16] H.B. Lazrek, A. Rochdi, J.W. Engels, Nucleosides Nucleotides 18 (1999) 1257–1259.
[17] H.B. Lazrek, J.W. Engels, W. Pfleiderer, Nucleosides Nucleotides 17 (1998) 1851–1856.
[18] R. Alvarez, S. Velasquez, A. San-félix, S. Aquaro, E. De Clercq, C.F. Perno, A. Karlsson, J. Balzarini, M.J. Camarasa, J. Med. Chem. 37 (1994) 4185–4194 (and references therein).
[19] R. Pauwels, J. Balzarini, M. Baba, R. Sneock, D. Schols, P. Herdewijn, J. Desmyter, E. De Clercq, J. Virol. Methods 20 (1988) 309–321.
[20] M. Witvrouw, J. Balzarini, C. Pannecouque, C. Jhaumar-Laullo, J. Esté, D. Schols, P. Cherepanov, J.-C. Schmit, Z. Debyser, A.-M. Vandamme, J. Desmyter, R. Ramadas, E. De Clercq, Antimicrob. Agents Chemother. 41 (1997) 262–268.
[21] M.R. Grever, S.A. Schepartz, B.A. Chabner, Semin. Oncol. 19 (1992) 622–653.
[22] L. Collins, S.G. Franzblau, Antimicrob. Agents Chemother. 41 (1997) 1004–1009.